3.06
Furans and Their Benzo Derivatives: Reactivity

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3.06.1 Introduction

The chemistry of furans, their benzologs, and their derivatives was covered in CHEC(1984) <1984CHEC(3)599> and in CHEC-II(1996) <1996CHEC-II(2)297>. This chapter is intended to update the previous work concentrating on major new reactions published in 1996–2006. Attention is placed on the more interesting reactivities of these compounds, instead of executing an exhaustive literature search of all relevant articles that were recorded in 1996–2006. A number of books <B-2000MI319, B-2000MI297>, book chapters <1997PHC117, 1998PHC129, 1999PHC144, 2000PHC134, 2001PHC130, 2002PHC139, 2003PHC167, 2004PHC156, 2005PHC142>, and reviews <B-1997RCC3061, 2006AHC1> were published which are concerned with the chemistry of furans, benzofurans, and their derivatives.

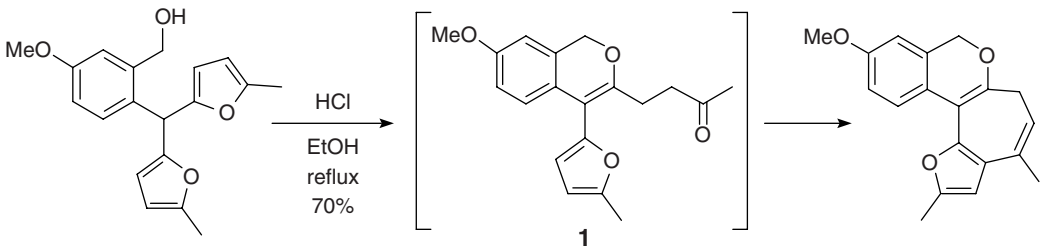
3.06.2 Reactivity of Fully Conjugated Rings

3.06.2.1 Reactivities of Furans

3.06.2.1.1 Reactions with electrophiles

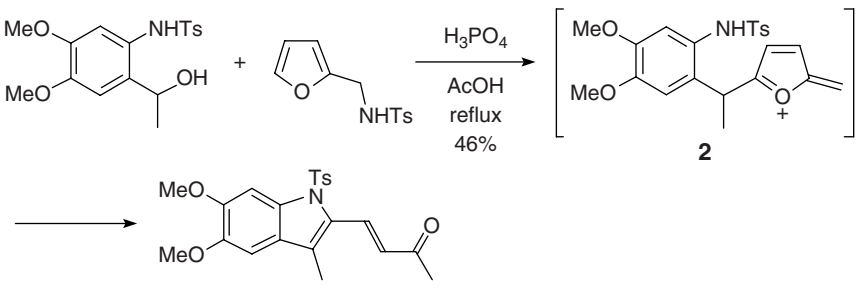
3.06.2.1.1(i) Protonation

Interesting intra- and intermolecular transformations involving oxonium ions formed by protonation of furan rings were shown to lead to elaborated ring systems. As shown in **Scheme 1**, interception of a transient cation by the pendant hydroxyl group led to the ketone intermediate **1**, which further cyclized to provide the tetracyclic isochromene product <2005TL8439>.



Scheme 1

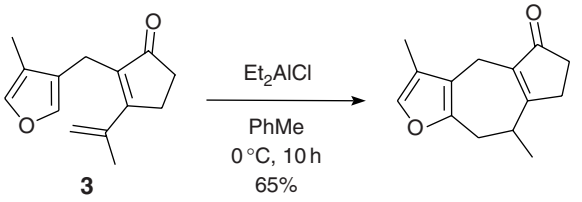
As exemplified in **Scheme 2**, a one-pot C-5-benzylation/eliminative cyclization of *N*-tosylfurfurylamine with electron-rich benzyl alcohols in strong acids under refluxing conditions provided indole derivatives in modest yield <2005TL8443>. Presumably, the indole ring was formed via trapping of the cation **2**, generated by the loss of the furan *N*-tosyl group in the benzylated intermediate, by the aniline nitrogen.



Scheme 2

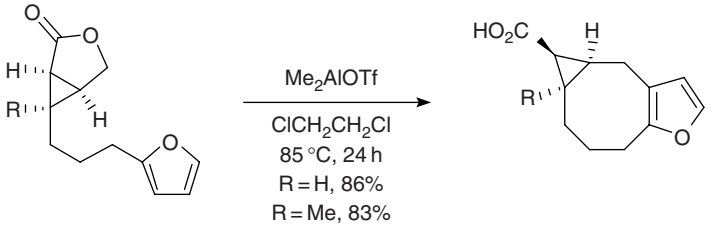
3.06.2.1.1(ii) Alkylation

As illustrated in Equation (1), a Lewis acid-promoted intramolecular conjugate addition of a furan to a dienone was used to generate the seven-membered ring of the fused tricyclic framework of sesquiterpene echinofuran <2003T1877>. The use of Et_2AlCl provided the best result, minimizing undesired polymerization of the furan substrate **3**.



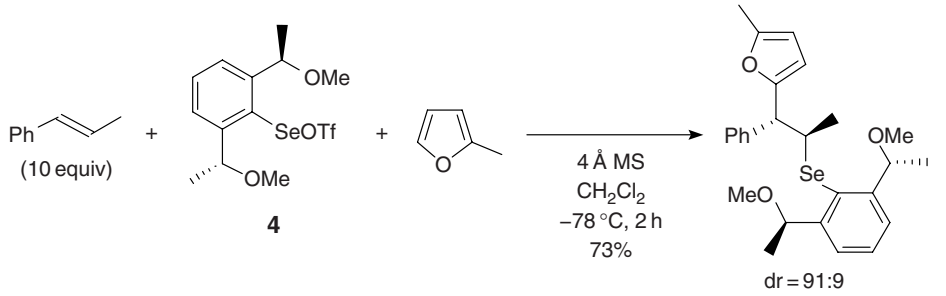
(1)

An intramolecular Friedel–Crafts alkylation of a furan was employed to construct the unusual bicyclo[6.1.0]nonane skeleton of the crenulide diterpenoids. As shown in Equation (2), the formation of the eight-membered ring under the Lewis-acidic conditions proceeded in high yield and without resorting to high dilution <2003JOC9487>.



(2)

Asymmetric carboselenenylation of furans was achieved by using the C_2-symmetric selenenyl triflate **4**, as shown in Equation (3). The reaction was only effective for styrene derivatives <2005AGE3588>.

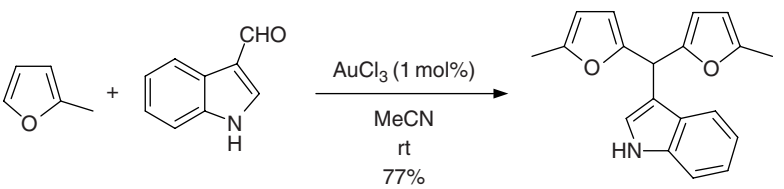


(3)

Kinetic investigations of the electrophilic substitution of 2-(trialkylsilyl)furans <2001OL1629> and 2-(tri-*n*-butylstannyl)furan <2001OL1633> with benzhydryl cations suggested that 2-organometallic groups activate the 5-position to a much greater extent than the 2-position. Therefore, the apparent electrophilic *ipso*-substitution was the net result of electrophilic substitution at the 5-position followed by protodemetallation.

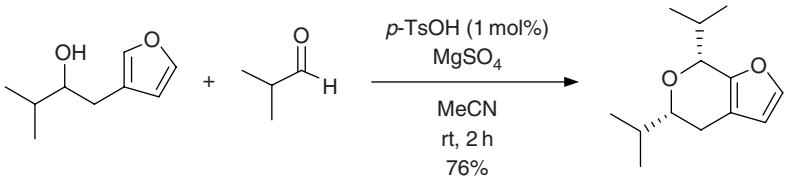
3.06.2.1.1(iii) Reactions with aldehydes and ketones

Electron-rich furans were found to condense with aryl aldehydes under mild $AuCl_3$-catalyzed conditions, forming triheteroarylmethanes as exemplified in Equation (4) <2005OL5857>. This reaction was applied to the synthesis of dendritic structures.



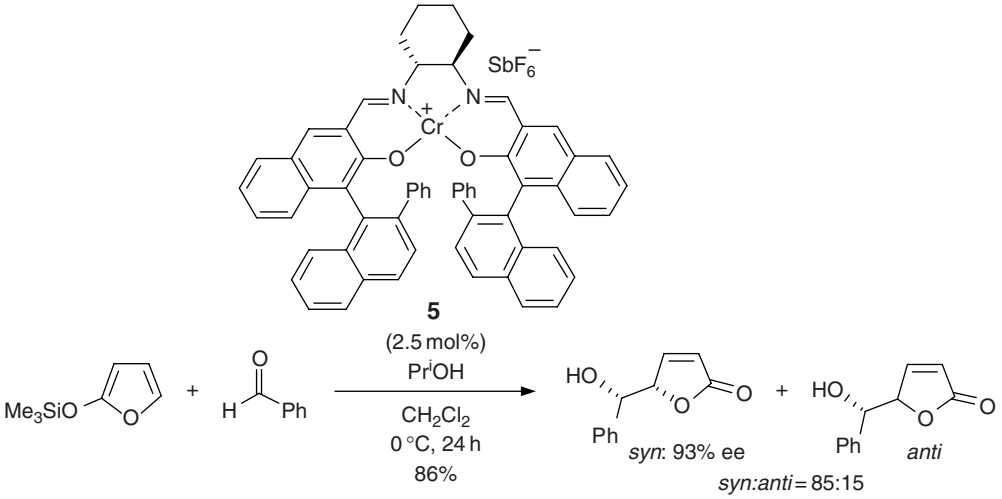
(4)

1-(3-Furanyl)ethanol derivatives participated in acid-catalyzed oxa-Pictet–Spengler reaction with aldehydes to give *cis*-5,7-disubstituted 4,5-dihydro-7*H*-furano[2,3-*c*]pyrans under kinetic control, as illustrated in Equation (5) <2002S1541>.

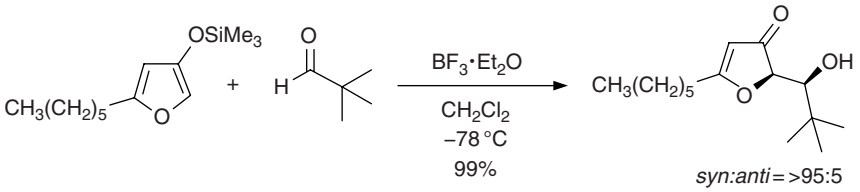


(5)

The *syn*-selective vinylogous Mukaiyama aldol addition of 2-trimethylsilyloxyfuran to aldehydes, and the corresponding *anti*-selective addition to aldimines as well as their synthetic applications were extensively reviewed <1999SL1333, 2000CSR109, 2000CRV1929>. The aldol addition of 2-trimethylsilyloxyfuran to achiral aldehydes in the presence of a catalytic amount of BINOL–titanium complex was discovered to undergo asymmetric autoinduction by the δ-hydroxy-γ-butenolide products formed, leading to higher yields and better enantioselectivity (BINOL = 1,1′-bi-2-naphthol) <2000AGE1799>. This reaction, when catalyzed by the C_2-symmetric chromium(salen) complex **5**, produced an enantiomeric excess (ee) of up to 97% for the major *syn*-isomer in the presence of isopropanol (salen = *N*,*N*′-bis(salicylaldehydo) ethylenediamine) <2003CL974>. A typical example of this process is shown in Equation (6). However, these catalytic systems for the enantioselective addition to aldehydes have not been shown to be generally applicable, and the *syn*/*anti*-diastereoselectivity would require further improvement. The less well studied 3-trimethylsilyloxyfurans were also shown to react with aldehydes at the 2-position in an aldol addition manner under Lewis-acidic conditions. High *syn*-diastereoselectivity was obtained with bulky aldehydes as shown in Equation (7) <2005OL387>.

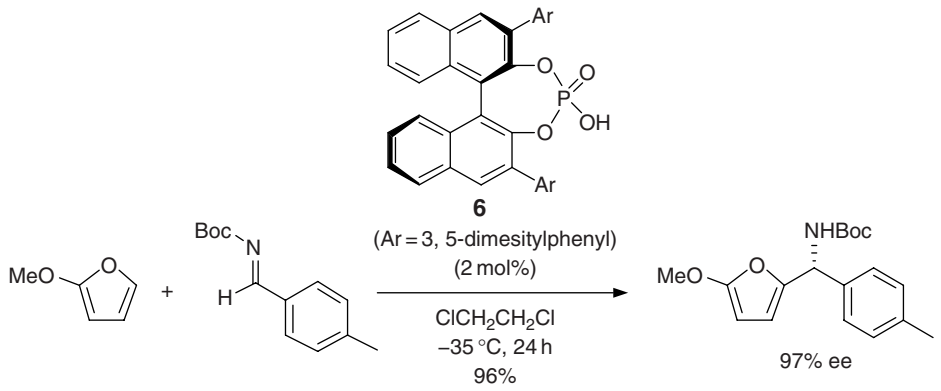


(6)



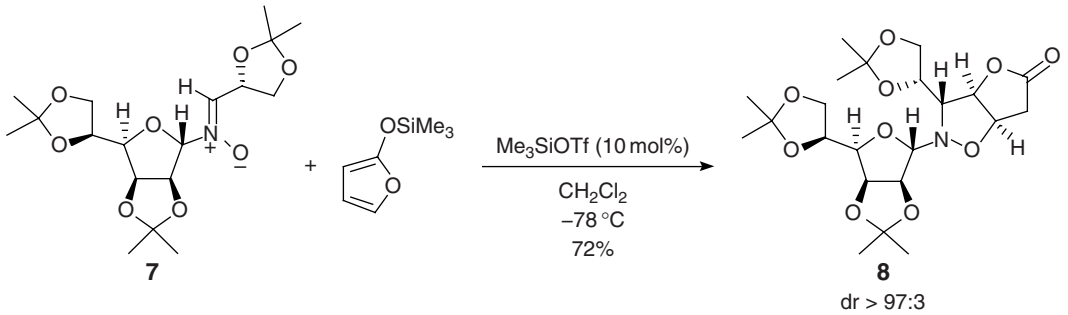
(7)

Furfurylamine derivatives could be prepared, via an *in situ*-generated aldimine intermediate, by treatment of an aldehyde and *N*-sulfinyl-*p*-toluenesulfonamide with furan in the presence of $ZnCl_2$ <2003T4939>. As shown in Equation (8), enantioselective addition of 2-methoxyfuran to aldimines was achieved using the chiral C_2-symmetric phosphoric acid **6** as an organocatalyst <2004JA11804>. This reaction uniformly provided ≥94% ee irrespective of the substitution pattern on the aldimine phenyl ring.



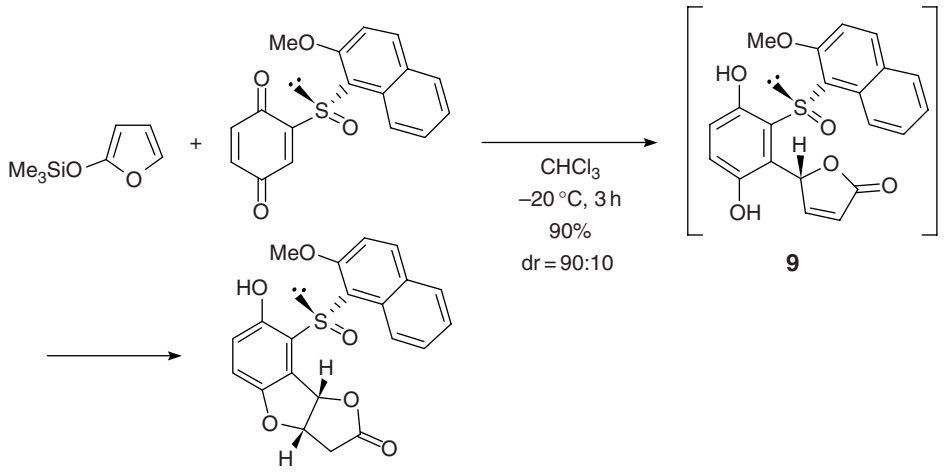
(8)

The Lewis acid-catalyzed addition of 2-trimethylsilyloxyfuran to *N*-gulosylnitrones was shown to be diasteroeselective <2002OL1111, 1997T11721>. In particular, the reaction with the D-glyceraldehyde-derived gulosylnitrone **7**, shown in Equation (9), provided tetrahydrofuro[2,3-*d*]isoxazol-5(2*H*)one **8** as the predominant product, which was converted into a ribofuranosylglycine precursor to polyocin C <2002OL1111>.



(9)

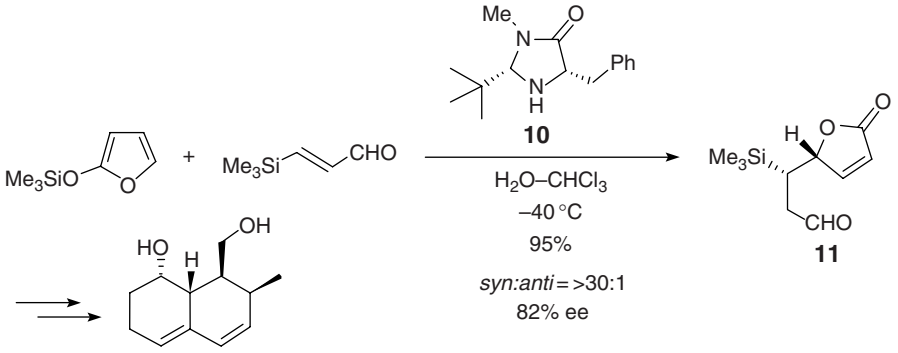
Structural characterizations of reaction intermediates and products of the addition of 2-trimethylsilyloxyfuran to naphthoquinones <1998TA1257> and benzoquinones <1999TA4357> to form furanofuranones indicated that the reaction proceeded via Michael addition, rather than Diels–Alder cycloaddition, in which the type of intermediate **9** shown in **Scheme 3** was observed by proton nuclear magnetic resonance (NMR) spectroscopy.



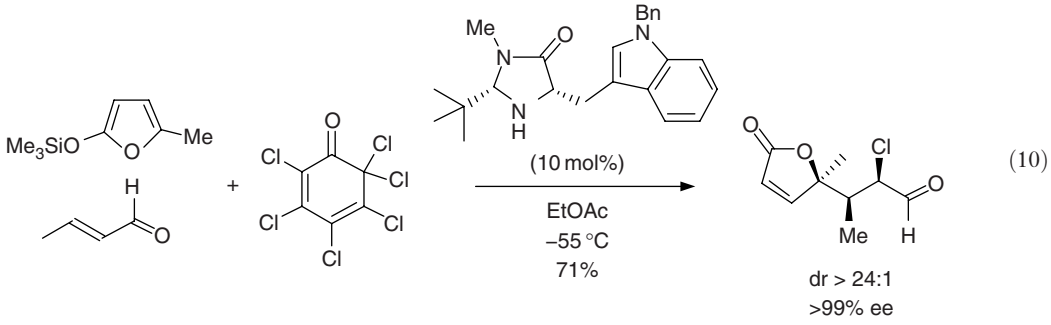
Scheme 3

A *syn*-selective, organocatalytic, enantioselective vinylogous Mukaiyama–Michael addition of 2-trimethylsilyloxyfuran to α,β-unsaturated aldehydes to produce γ-butenolides was achieved by using a chiral amine catalyst

<2003JA1192>. The methodology was adopted to prepare the key intermediate **11** using the catalyst **10** in a formal total synthesis of campactin <2006OL597>, as depicted in **Scheme 4**. This type of reaction was extended to incorporate a chlorination reaction of the enamine intermediate in the reaction cycle as shown in Equation (10). Furans also function as effective nucleophiles in such catalytic organocascade reactions <2005JA15051>.



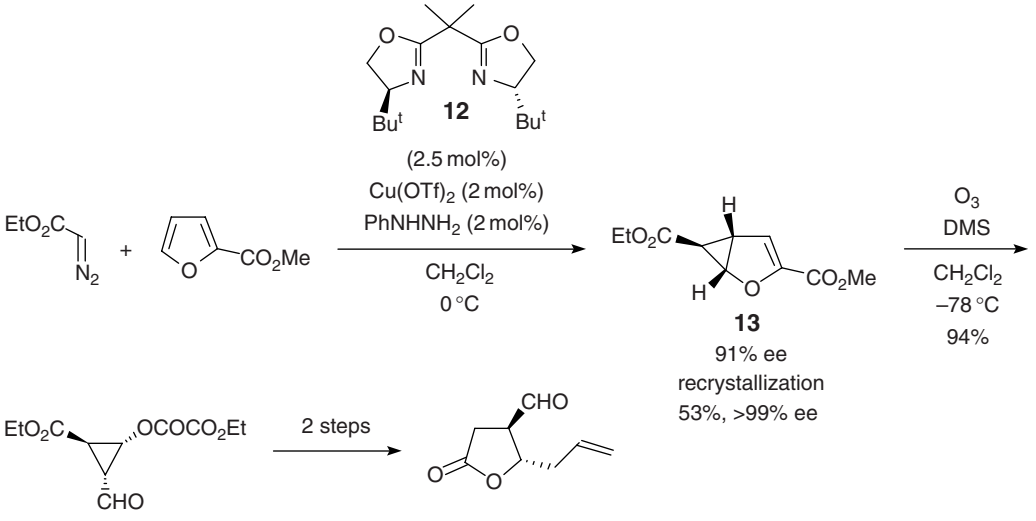
Scheme 4



(10)

3.06.2.1.1(iv) Reactions with diazonium salts and diazo compounds

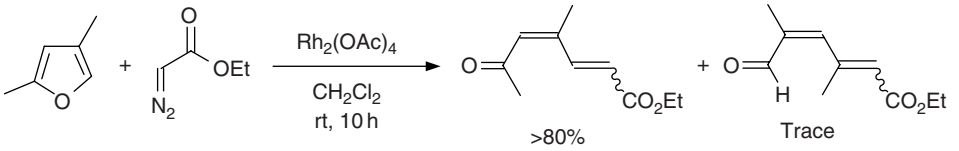
The copper(I)-catalyzed asymmetric cyclopropanation of methyl furan-2-carboxylate with ethyl diazoacetate was achieved by the use of the bisoxazoline ligand **12** to provide the *exo*-isomer of 2-oxa[3.0.1]bicyclohexene **13**, as shown in **Scheme 5** <2003CEJ260>. The product was transformed into 1,2,3-trisubstituted cyclopropane by ozonolysis



Scheme 5

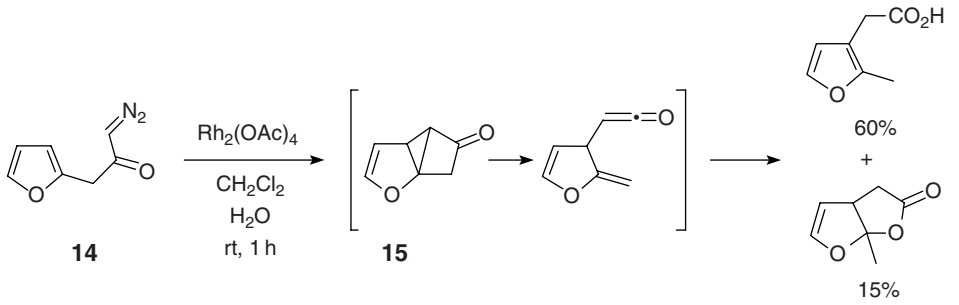
<2000EJO2955>, and then elaborated to γ-butyrolactones by a two-step sequence comprising of allylsilane addition and retro-aldol lactonization <2003CEJ260>. This methodology was applied to the asymmetric synthesis of paraconic acids <2003CEJ260>, (–)-roccellaric acid <2001OL1315>, the fused cyclic ring systems of xanthanolides, guaianolides, and eudesmanolides <2003OL941>, and the *cis*-fused 5-oxofuro[2,3-*b*]furan core of spongiane diterpenoids <2005OL5353>.

$Rh_2(OAc)_4$-catalyzed intermolecular addition of ethyl diazoacetate to 2-methylfuran proceeded on the 4,5-double bond of the furan ring, leading to ethyl 6-oxo-2,4-heptadienoate, with a 19:1 regioselectivity. The corresponding reaction with 3-methylfuran gave a low 2:1 regioselectivity, although still favoring the unsubstituted side. Consistently, reaction with 2,4-dimethylfuran predominantly occurred at the 4-methyl side of the furan nucleus, as shown in Equation (11) <1999TL5171>. These results are in accord with a mechanism involving nucleophilic attack on the carbenoid carbon by the more nucleophilic furan C-2-position. The reactions of other 2-methyl analogs of furan also exhibited similar regioselectivity <1999TL5439>. These types of reactions were also performed on 2-methoxy- and 2-trimethylsilyloxyfurans using aryl diazoketones to give 6-aryl-6-oxo-(*2Z*,*4E*)-hexadienoates and 6-aryl-6-oxo-(*2Z*,*4E*)-hexadienoic acids, respectively, using $Rh_2(OAc)_4$ as catalyst <2001T7303>, as well as with diazoarylacetates using pentacarbonyl(η^2-*cis*-cyclooctene)chromium(0) as a catalyst <2004JOM2662>.

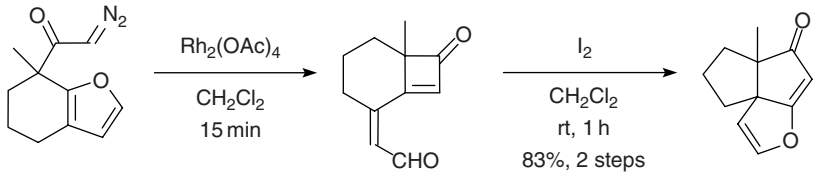


(11)

1-Diazo-3-(3-furanyl)-2-propanone underwent intramolecular metal carbenoid addition and, subsequently, the typical rearrangement to provide a 1,6-dicarbonyl product. However, as shown in **Scheme 6**, the cyclopropane intermediate **15** formed during the reaction of the isomeric 1-diazo-3-(2-furanyl)-2-propanone **14** underwent a Wolff-type rearrangement to give 2-(2-methylfuranyl)acetic acid as the major product in the presence of water <1998JOC9828>. When the tether was constrained by the introduction of a fused ring, the usual rearrangement occurred and was exploited for the synthesis of [6,6], [6,5], and even [6,4]-fused ring systems, as exemplified in **Scheme 7** <2005HCA330>.



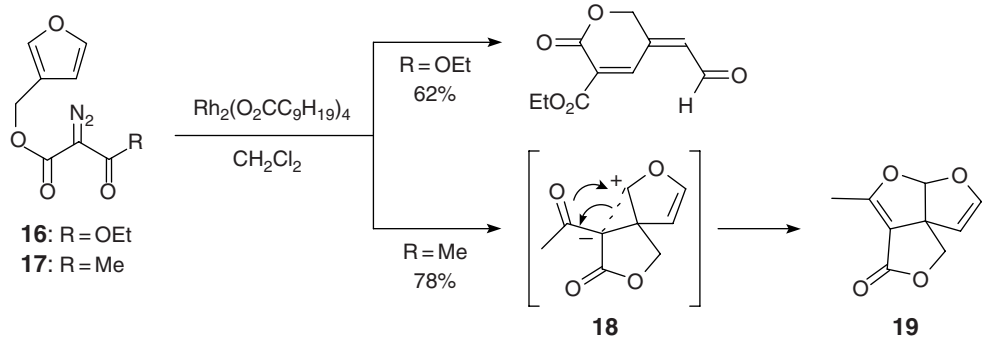
Scheme 6



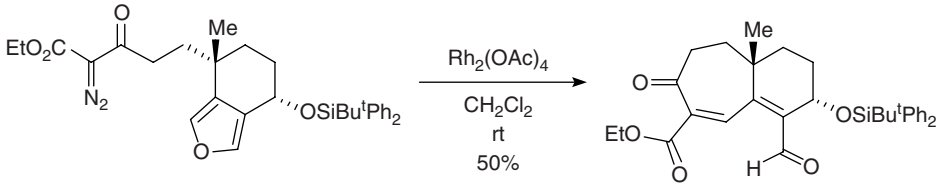
Scheme 7

Intramolecular addition of more elaborated diazoacetates and diazoketones to a pendant furan moiety are more complex <1997TL5623>. 2-Substituted substrates uniformly provided the 2,4-diene-1,6-dicarbonyl products. Products of 3-substituted substrates depended on the structure of the diazocarbonyl and the rhodium catalyst used. For example,

in contrast to the reaction of diazomalonate **16** (**Scheme 8**), reaction of the diazoacetoacetate **17** produced the fused tricycle **19**, presumably as a result of [3+2] annulation of the intermediate **18**. This type of transformation was exploited in the construction of the [6,7]-fused ring system of guanacastepenes, as shown in Equation (12) <2003OL4113>. Furans tethered with diazocarbonyl moieties to the 2-position were also used for generating macrocyclic rings <1999OL1327>. Regioselectivity with respect to addition to furan 2,3-double bond was dependent on the metal catalyst, as well as the inherent selectivity differences between diazoacetates and diazoketones used.

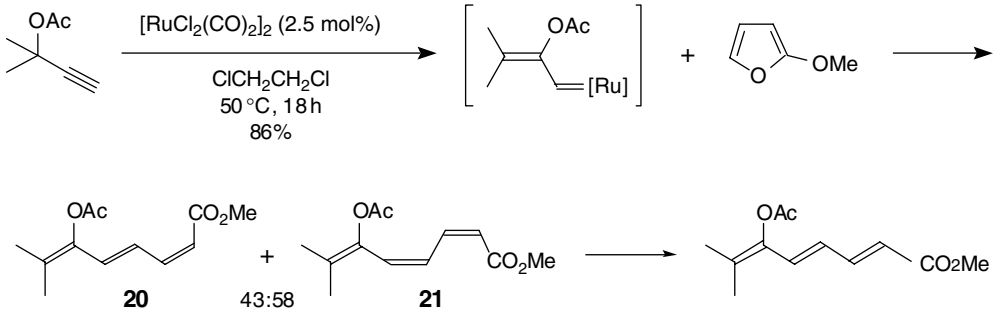


Scheme 8



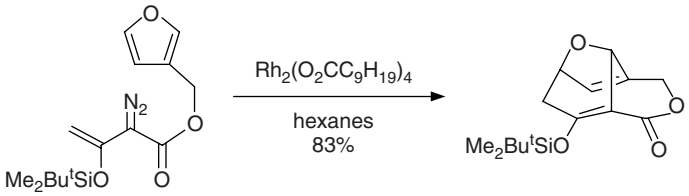
(12)

Ruthenium and platinum carbenoids, derived from tertiary propargyl carboxylates, also reacted with furans in a similar manner, leading to triene systems (as represented in **Scheme 9**) <2006OL1741>. The initially formed mixture of (*2Z,4E*) and (*2Z,4Z*) isomers **20** and **21**, respectively, could be isomerized completely to a single (*2E,4E*) isomer.



Scheme 9

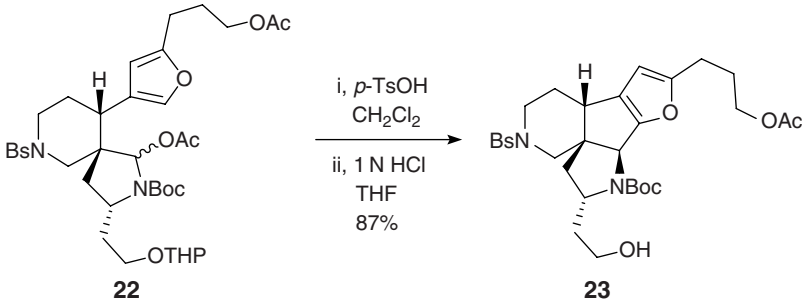
The feasibility of intramolecular type II annulations between furans and vinylcarbenoids to give highly strained molecular frameworks that contained *anti*-Bredt alkenes is depicted in Equation (13) <1997TL1737>.



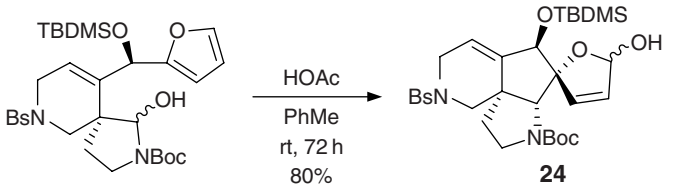
(13)

3.06.2.1.1(v) Reactions with other electrophiles

An intramolecular Mannich-type cyclization of the functionalized furan **22**, shown in Equation (14), to the cyclic iminium cation that was generated from the aminal was the key step in the construction of the strained ABCD ring system during the total synthesis of nakadomarin A. The fused tetracyclic advanced intermediate **23** was obtained as a single isomer <2003JA7484>. As illustrated in Equation (15), when the furan was tethered at the 2-position, a novel spirocyclization occurred, giving the spiro-2,5-dihydrofuran derivative **24** as the sole diastereoisomer. This spirocyclization proceeded irrespective of the length of the carbon linker <2006OL27>.

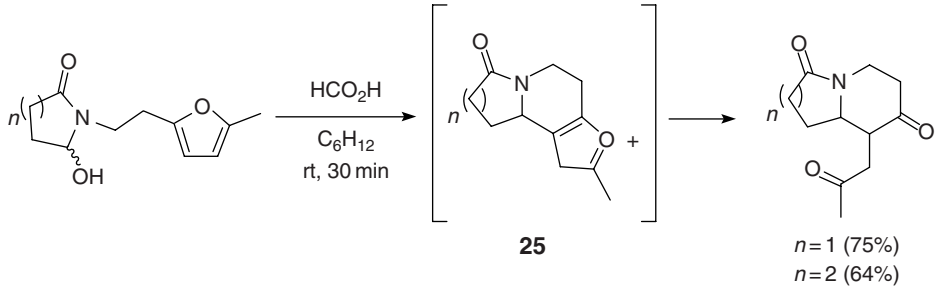


(14)



(15)

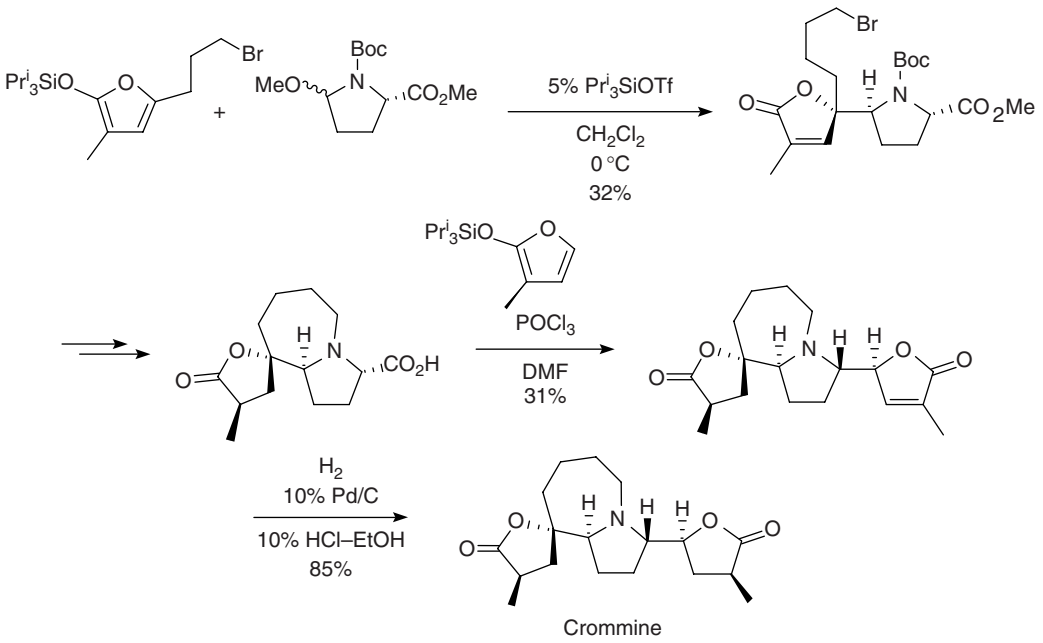
An interesting example concerning hydrolytic cleavage of furan rings that occurred following the addition to *N*-acyliminium ions to give dicarbonyl compounds is shown in **Scheme 10**. This reaction presumably occurred via the oxonium ion intermediates **25** that were generated from a 1,5-proton shift of the initially formed oxonium ions <1998JOC6914>.



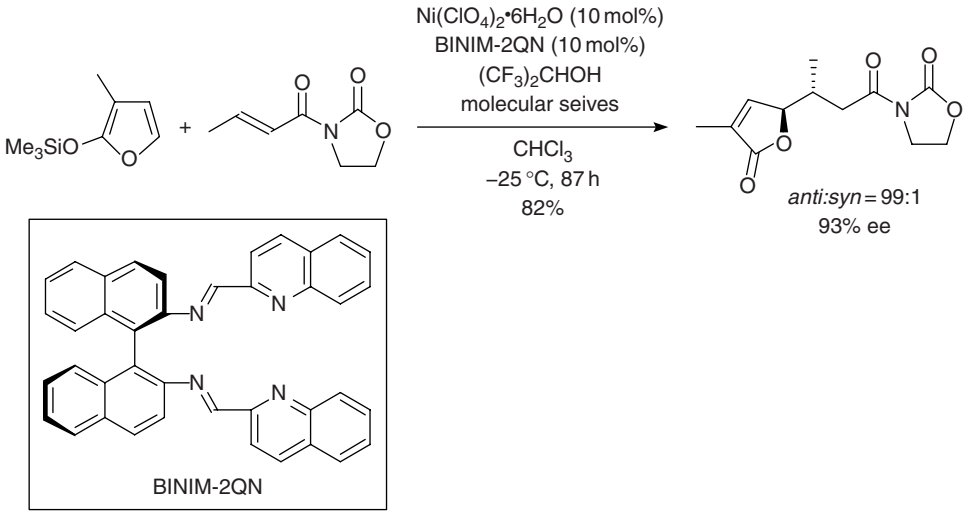
Scheme 10

The synthetic utility of vinylogous Mannich additions of 2-silyloxyfurans to cyclic iminum ions <2001T3221> that provided *threo*-products predominantly was demonstrated by the assembly of the complete carbon framework during the total synthesis of the plant alkaloid, crommine, as shown in **Scheme 11** <1996JA3299, 1999JA6990>.

Vinylogous Mukaiyama–Michael additions of 2-trimethylsilyloxyfuran to 3-alkenoyl-2-oxazolidinones to provide γ-butenolides were shown to be *anti*-selective. The reaction could be rendered enantioselective in the presence of a C_2-symmetric copper–bisoxazoline complex <1997T17015, 1997SL568> or a 1,1′-binaphthyl-2,2′-diamine-nickel(II) complex as catalyst, as depicted in Equation (16) <2004CC1414>.

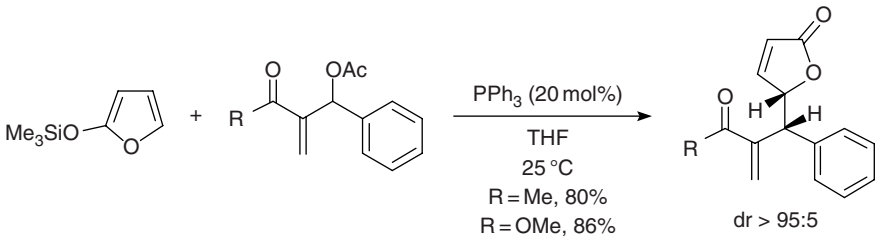


Scheme 11



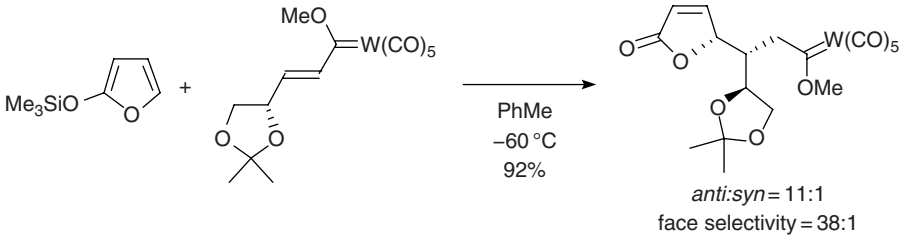
(16)

As shown in Equation (17), 2-trimethylsilyloxyfuran also participated in a triphenylphosphine-catalyzed substitution reaction with Morita–Baylis–Hillman acetates to provide interesting γ-butenolides regio- and diastereoselectively <2004AGE6689>. However, the reaction mechanism (vinylogous Michael vs. Diels–Alder) has not been distinguished.



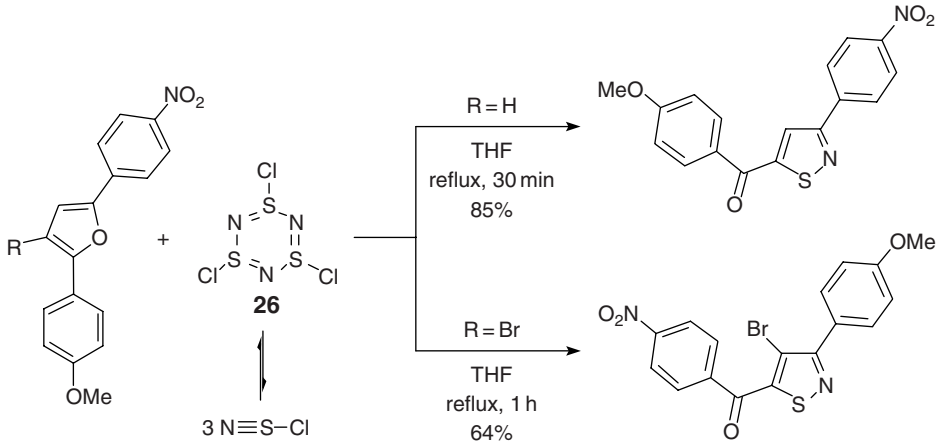
(17)

2-Trimethylsilyloxyfuran reacted stereoselectively with chiral tungsten carbene complexes in a Mukaiyama–Michael addition fashion to provide *anti*-products, as shown in Equation (18) <2005AGE6583>. The metal carbene in the butenolide product serves as a useful functional group for further transformations.



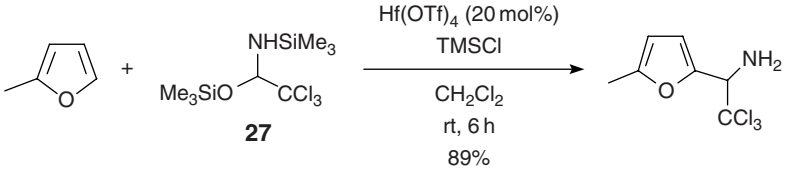
(18)

Reaction of 2,5-disubstituted and 2,3,5-trisubstituted furans with the cyclic trithiazyl trichloride **26**, which was in thermal equilibrium with the monomeric thiazyl chloride, in boiling solvents resulted in the regiospecific formation of isothiazoles, as shown in **Scheme 12** <1997CC367, 1997J(P1)1617, 1997J(P1)2247>. Electrophilic thiazylation that occurred at the more nucleophilic C-3 position of the furan ring was favored as the mechanism. This reaction could also be performed using a premixed mixture of ethyl carbamate, thionyl chloride, and pyridine. Furans having electron-withdrawing groups directly at the 2-position are poor substrates <2001J(P1)1304, 1999S757>. 4-Chloro- and 3-chloromethylisothiazole side products were obtained with substituted 2-methylfurans <1997J(P1)2247>.



Scheme 12

Aminomethylation of furans that directly delivered primary furfurylamine products was realized using *N*-silyl-*N*,*O*-acetal **27** under Lewis acid-catalyzed conditions, as illustrated in Equation (19). However, furans are less nucleophilic toward **27** than pyrroles <2003JOC483>.

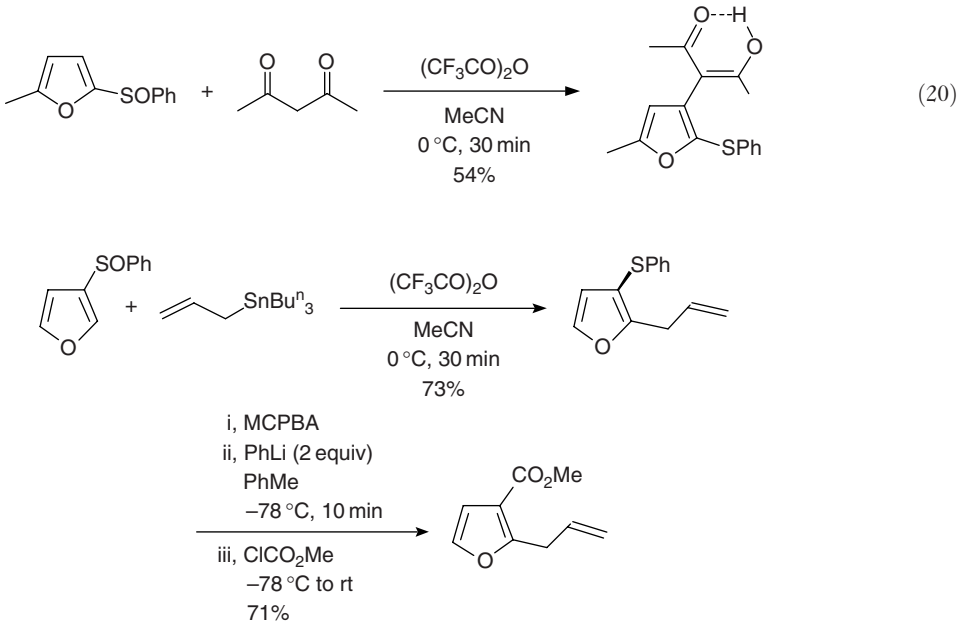


(19)

3.06.2.1.2 Reactions with nucleophiles

The addition of Grignard reagents to 2-nitrofuran provided *trans*-2,3-disubstituted 2,3-dihydrofurans as the predominant isomers <2003TL3167>. 2- and 3-(Phenylsulfinyl)furans underwent Pummerer-type reaction-initiated regioselective nucleophilic additions, as shown in Equation (20) and **Scheme 13**, respectively <2004OL3793>.

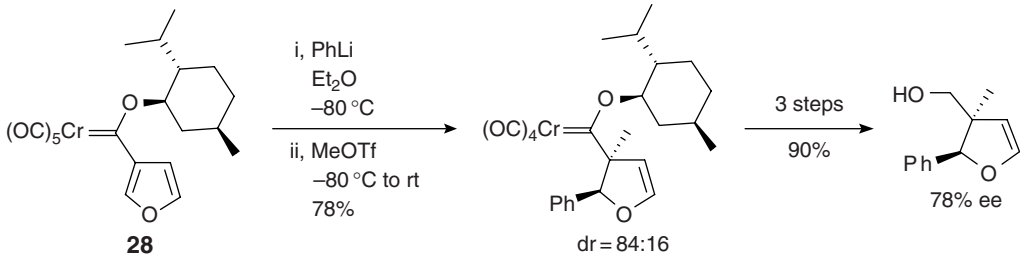
The sulfinyl group in the products enables further substitution of the furan ring, for example, via sulfoxide–lithium exchange (as illustrated in **Scheme 13**).



(20)

Scheme 13

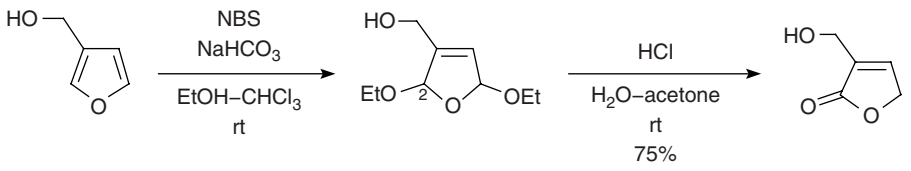
The chiral Fischer-type chromium carbene complex of furan **28**, shown in **Scheme 14**, participated in nucleophilic 1,4-addition with organolithium reagents followed by alkylation in a regioselective and diastereoselective manner, creating a quaternary C-3 stereocenter in the 2,3-trisubstituted 2,3-dihydrofuran products after oxidative decomplexation and reductive cleavage of the chiral auxiliary <2003CEJ5725>.



Scheme 14

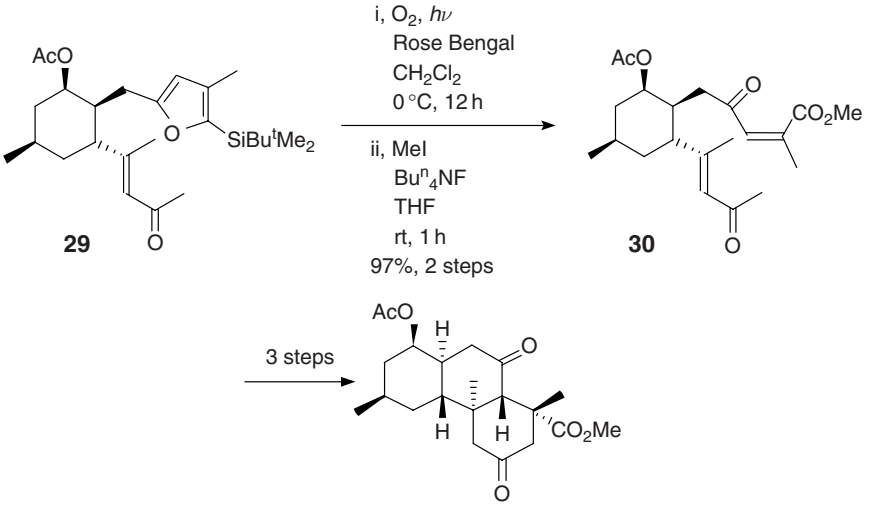
3.06.2.1.3 Reactions with oxidants

Useful new procedures for the oxidation of furans were reported. Mono-, di-, and trisubstituted furans were oxidized to (*Z*)-enediones by methyltrioxorhenium/urea hydrogen peroxide <1998TL5651>. $Mo(CO)_6$-catalyzed oxidation of 2,5-dialkyl furans by cumyl hydroperoxide provided (*E*)-enediones selectively. In the presence of Na_2CO_3, the corresponding (*Z*)-isomers were obtained <2003TL835>. Sodium chlorite in acidic aqueous medium was found to be an efficient oxidation system for the conversion of symmetrical 3,4-disubstituted furans to γ-hydroxybutenolides <2005JOC3318>, and 2-substituted and 2,5-disubstituted furans to α,β-unsaturated 1,4-dicarbonyl compounds <2005SL1468>. As shown in **Scheme 15**, a regioselective oxidation of 3-substituted furans (except 3-carboxylate) to α-substituted γ-butenolides was achieved by using *N*-bromosuccinimide (NBS), followed by elimination of the more acidic C-2 proton of the 2,5-diethoxy intermediate under acidic hydrolytic conditions <2005SL1575>.



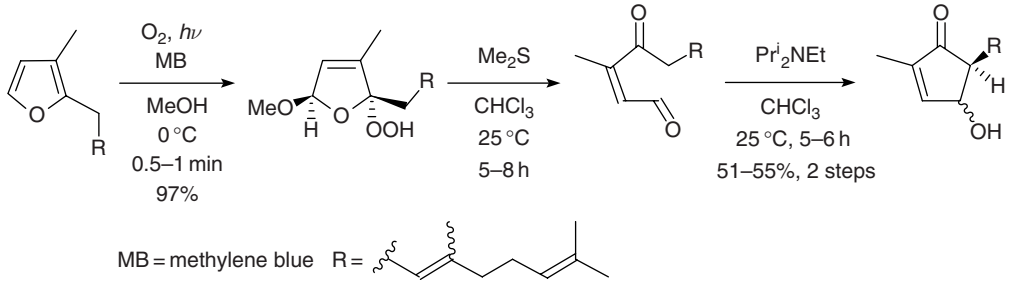
Scheme 15

The useful synthetic utilities of photosensitized oxidation of furans were demonstrated. A notable example was the oxidation of the trisubstituted furan **29** shown in **Scheme 16** to the (*Z*)-γ-keto-α,β-unsaturated ester intermediate **30**, a crucial step for the construction of the ABC ring system of the complex heptacyclic marine alkaloid norzoanthamine <2004SCI495>.



Scheme 16

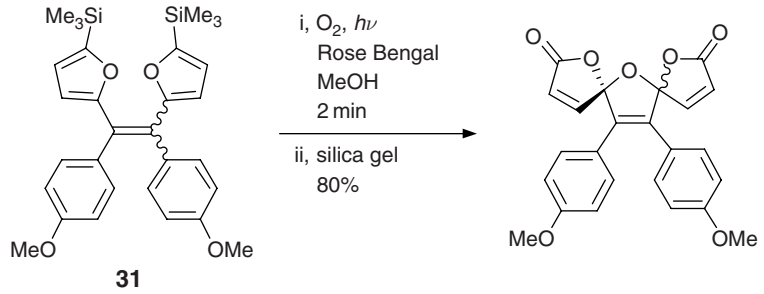
Another novel example as generalized in **Scheme 17** is the photooxidation of the furan moiety in the presence of two trisubstituted alkenes in the side chain during the total synthesis of litseaverticillols <2005CEJ5899, 2003AGE5465, 2004OL2039>.



Scheme 17

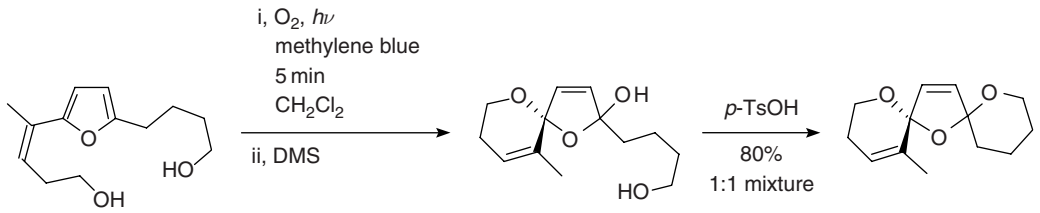
Photosensitized oxidation of a bis(2-trimethylsilylfuran) followed by spirocyclization of the intermediate bis(γ-hydroxybutenolide) was employed to construct the tricyclic bis(spiroketal) core of prunolides. As shown in

Equation (21), both the (*Z*)- and (*E*)-isomers of **31** provided the same 2:1 mixture of the *trans*- and *cis*-products <2005OL2357>.



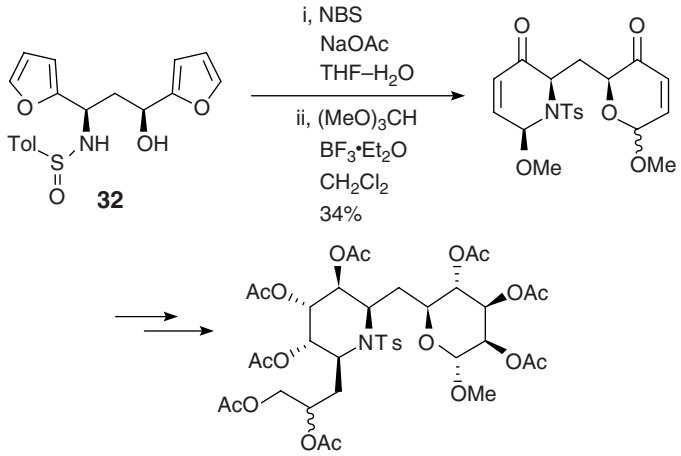
31 (21)

The oxidation of 2,5-disubstituted furans by NBS <2005OL27> and singlet oxygen <2006OL1945> was adopted for the synthesis of [5,5,5]- and [6,6,6]-bis(spiroketals). An interesting example is depicted in **Scheme 18**.



Scheme 18

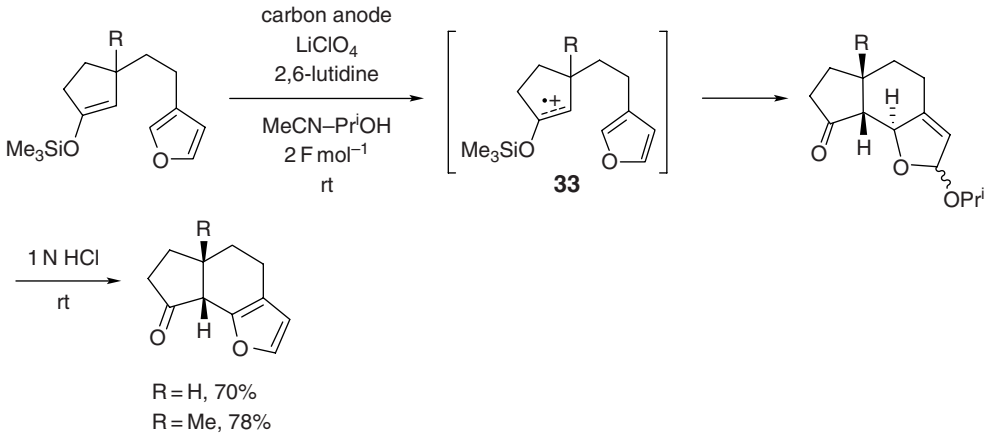
The aza-Achmatowicz oxidative ring expansion of furans and its synthetic application were reviewed <1998SL105>. An interesting example of performing the Achmatowicz oxidation of furfuryl alcohol and its aza variant simultaneously on the bisfuran-containing 1,3-amino alcohol **32** in the synthesis of aza-C-linked disaccharides is depicted in **Scheme 19** <2005CC1646>.



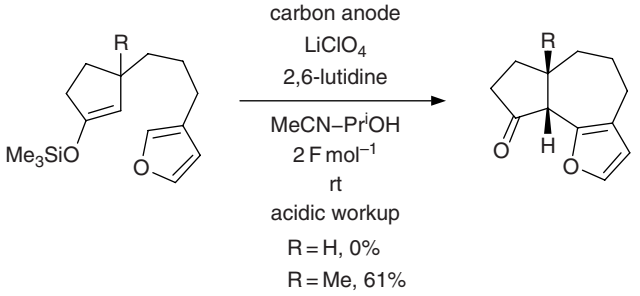
Scheme 19

Annulation of furans via electrochemical oxidation at the anode has become an important process for the synthesis of complex polycycles, and was covered in a review <2000T9527>. Furans tethered at the 3-position to electron-rich alkenes, enol ethers, or vinyl sulfides were converted to [6,5] and [7,5]-fused ring systems <1996JOC1578, 2002OL3763, 2004JOC3726, 2005JA8034>, as illustrated in **Scheme 20**. Analysis of crude reaction mixtures and side

products indicated that the furan moiety tethered to alkenes was oxidized to radical cation (initiator), while when tethered to methyl enol ether, it served as terminator to capture the enol ether radical cation <1996JOC1578>. Studies using cyclic voltammetry and probe molecules also suggested that in reaction involving furans tethered to silyl enol ether, the silyl enol ether was preferentially oxidized according to its lower oxidation potential to give a radical cation (e.g., **33**) <2004JOC3726>. In contrast to the six-membered ring formation (**Scheme 20**), annulations to form seven-membered rings were influenced by the *gem*-dialkyl effect, as evidenced by Equation (22) <2005JA8034>.

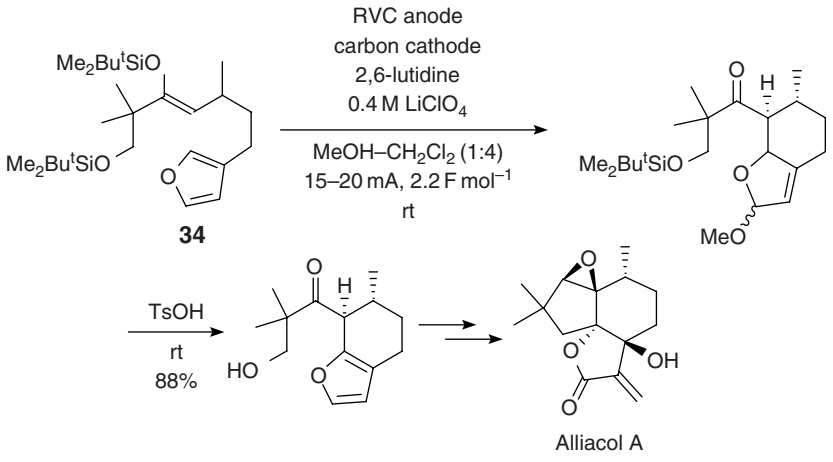


Scheme 20



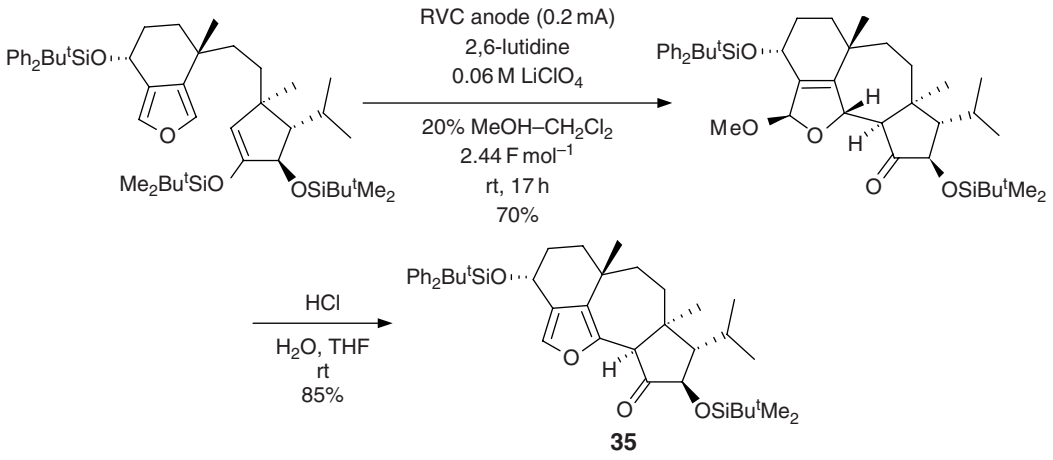
(22)

The anodic cyclization reaction of furans was applied as a key step to construct the [5-6-7]-fused tricyclic core of cyathins <1999OL1535>, and the [5-6-5]-fused tricyclic core of alliacol A using the acyclic silyl enol ether tethered furan **34** during its total synthesis (**Scheme 21**) <2004JA9106, 2003JA36>.



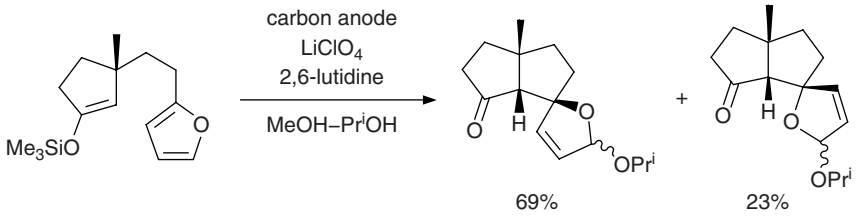
Scheme 21

Another example is the assembly of the complex [6-7-5]-fused tricyclic core **35** of guanacastepenes, obtained as a single diastereoisomer, as shown in **Scheme 22** <2005OL3425>. The efficiency of this reaction is consistent with the *gem*-dialkyl effect that is required for the seven-membered ring formation in this type of electron-transfer reaction.



Scheme 22

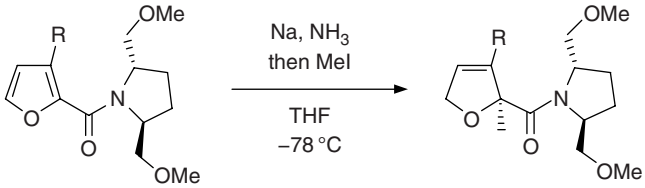
When furans were tethered at the 2-position to silyl enol ethers, an electrochemical spiroannulation occurred at the 2-position, as exemplified in Equation (23) <2006CC194>. This reaction pathway is a manifestation of the higher nucleophilicity of the furan C-2 position, resulting in the isolation of the kinetic products.



(23)

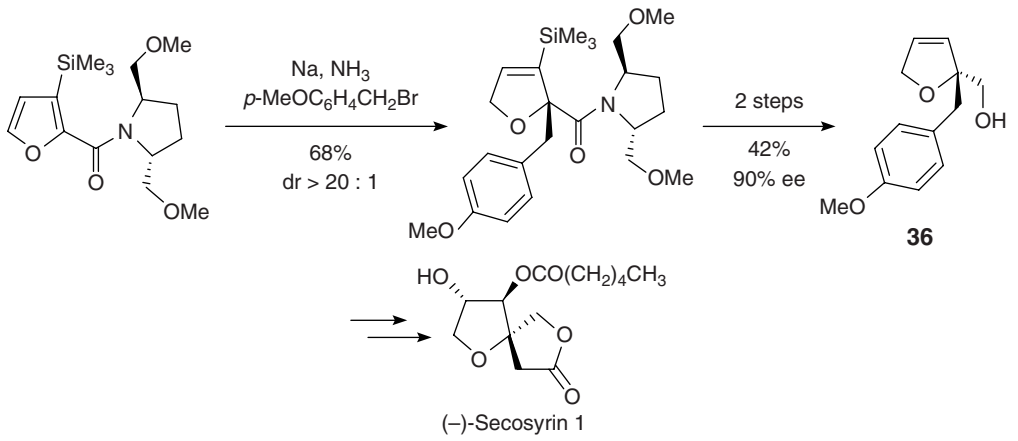
3.06.2.1.4 Reactions with reductants

The reduction of furans was reviewed in an article concerning the reduction of aromatic heterocycles <1996TA317>. Birch reduction of 2-silyl-3-furoic acids provided 2-silyl-2,3-dihydrofuran-3-carboxylic acids as mixtures of *cis*- and *trans*-isomers <1996TL9119>. Stereoselective reduction of chiral 2-furoic amides to form dihydrofuran derivatives was accomplished under Birch-type reductive alkylation conditions. Methyl <1998TL3071, 2000J(P1)3724> and trimethylsilyl <2001TL5841, 2002J(P1)1748> substituents at the 3-position of the furan moiety are essential for achieving high diastereoselectivity in the alkylation step as illustrated in Equation (24), presumably by controlling the enolate geometry. This methodology was applied as a key step in the synthesis of (+)-nemorensic acid <2000CC465, 2002J(P1)1369>, (–)-*cis*- and (–)-*trans*-crobarbatic acids <1999TA1315>, eight- and nine-membered cyclic ethers <2001OL861>, dihydropyranones <2002OL3059>, and 2,5-dihydrofuran **36** for a formal total synthesis of (−)-secosyrin 1, as illustrated in **Scheme 23** <2004OL465>.



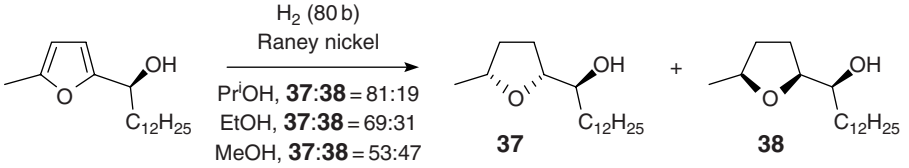
(24)

R = H (45%, dr = 41:59)
R = Me (98%, dr = 30:1)
R = $SiMe_3$ (94%, dr = 97:3)



Scheme 23

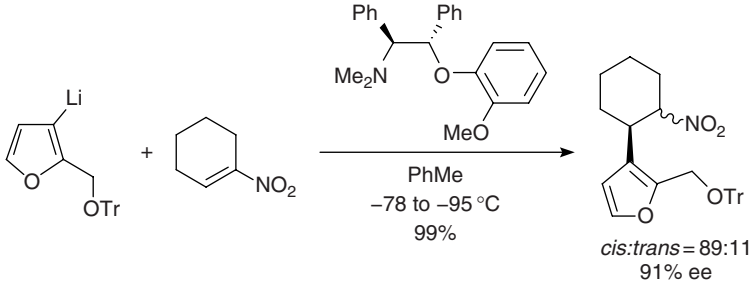
Hydrogenation of dimethyl 2-phenylfuran-3,4-dicarboxylates using Pd/C at 100 °C provided tetrahydrofuran (THF) products without undesired reduction of the phenyl ring. A 2:1 mixture of 2,3-*cis*-3,4-*cis*- and 2,3-*cis*-3,4-*trans*-diastereoisomers was obtained from 2-alkoxyphenyl substrates <2000S2069>. Hydrogenation of furfuryl alcohol derivatives to tetrahydrofuranylcarbinols using Raney nickel provided much higher *erythro*- (*anti*-)selectivity than using Pd/C or rhodium on alumina. Moreover, as illustrated in Equation (25), the *erythro*-selectivity in the formation of **37** and **38** was decreased by increasing the polarity of the alcohol solvent used, presumably by influencing the substrate conformation through the disruption of the intramolecular hydrogen bonding between the hydroxyl and the furan oxygen atom <1996S349>.



(25)

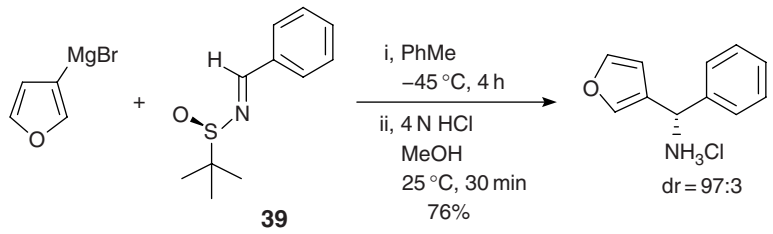
3.06.2.1.5 Reactions as nuclear anion equivalents

Applications of furanyl anion equivalents in stereoselective manner have been increased. An example of asymmetric conjugate addition of a furanyllithium to 1-nitrocyclohexene induced by a chiral amino alcohol derivative is shown in Equation (26). The 2-trityloxymethyl group was essential for obtaining the selectivity in the product, which was used as an entry to prepare arene-fused piperidine analogs <2004JA1954>.



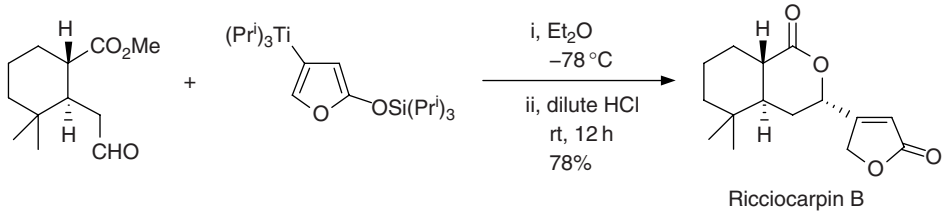
(26)

3-Furanylmagnesium bromide reacted with chiral *N*-[*p*-tolylsulfinyl]-bornane-10,2-sultam to provide 3-furanylsulfoxide with 99% ee <1997TL2825>, and with chiral *N*-*tert*-butanesulfinimines (e.g., **39**) to provide diarylmethylamines diastereoselectively <2002TA303>. The diastereoselectivity observed for the reaction indicated in Equation (27) is consistent with a six-membered magnesium chelate transition state. Di(2-furanyl)zinc added to a chiral glycal epoxide in the presence of trifluoracetic acid (TFA) to provide α-*C*-furanylglycoside selectively. Addition using 2-furanylzinc chloride also provided the product with similar efficiency <2003SL870>.



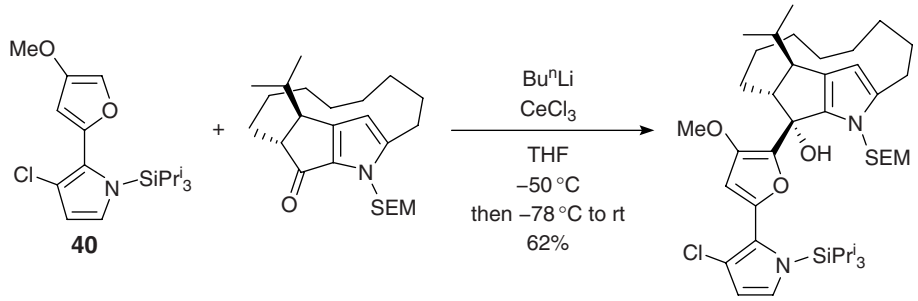
(27)

Furanyltitanium reagents were shown to add readily to aliphatic aldehydes in the absence of any promoter, providing more desirable yields and stereoselectivity than furanyllithium, magnesium, and zinc reagents. They were employed as key steps in the total syntheses of (+)-dysidiolide <1998JOC228> and (+)-ricciocarpins A and B <2004OL1749>, as depicted in **Scheme 24**.



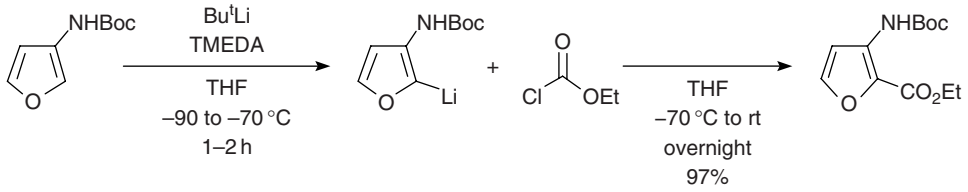
Scheme 24

The furanylcerium that was generated from lithiation/transmetallation of furan **40** as shown in Equation (28) was a highly nucleophilic species that added readily to the sterically hindered ketopyrrole to provide the penultimate intermediate during the total synthesis of roseophilin <1998JA2817>.



(28)

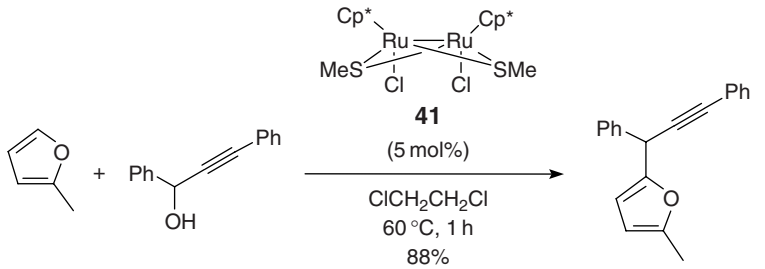
The lithiation of 3-(*N*-*tert*-butoxycarbonylamino)furan occurred regioselectively at the 2-position as a result of the apparent *ortho*-directing effect of the NHBoc group, providing 2-substituted-3-aminofurans after subsequent reactions with electrophiles, as represented in **Scheme 25** <2006SL789>. In contrast, the lithiation of 2-(*N*-*tert*-butoxycarbonylamino)furan took place exclusively at the 5-position instead of the 3-position <2003T5831>.



Scheme 25

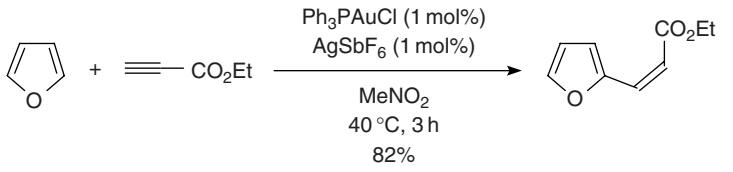
3.06.2.1.6 Reactions catalyzed by metals and metallic derivatives

The electrophilic propargylation at the C-2-position of furans with propargylic alcohols can be effected by using 5 mol% of the cationic methanethiolate diruthenium complex **41** as a catalyst (Equation 29). Substrates are limited to 1-phenyl-substituted secondary propargylic alcohols <2003AGE1495>.



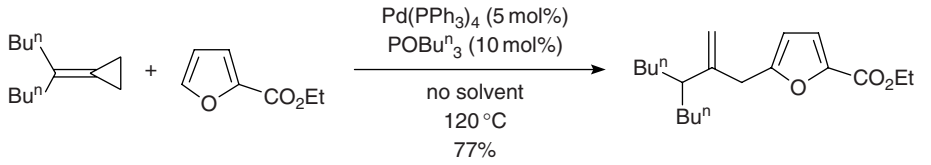
(29)

As shown in Equation (30), furan reacted with ethyl acetylenecarboxylate under gold-catalyzed conditions to form the hydroarylation product that contained a (*Z*)-alkene selectively <2003EJO3485>.



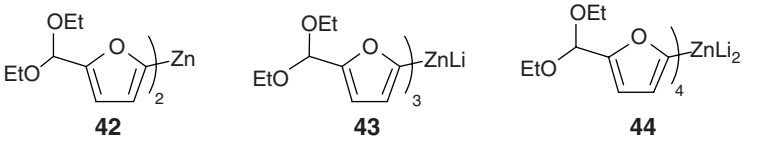
(30)

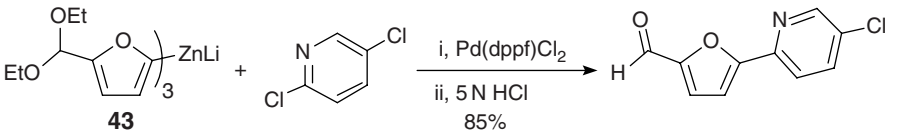
Palladium catalysts were able to catalyze the allylation of furans with alkylidenecyclopropanes, presumably via an allylpalladium intermediate, to furnish 2-allylated products, as illustrated in Equation (31) <2000JA2661>.



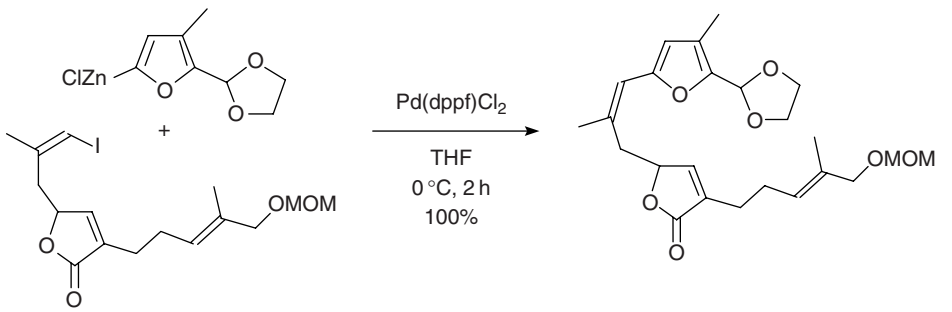
(31)

The diorganozinc **42** and the high-order zincates, **43** and **44**, of 2-furaldehyde diethyl acetal, as shown in Equation (32), participated in a Negishi-type cross-coupling reaction with 2-chloropyridines and bromobenzenes as effectively as the corresponding furanylzinc chloride. These reagents transfer all the organic groups during the reaction <2002OL375>. The synthetic utility of furanylzinc species is further illustrated by the elaborated coupling employed in the total synthesis of bipinnatin J, as shown in Equation (33) <2006OL543>.



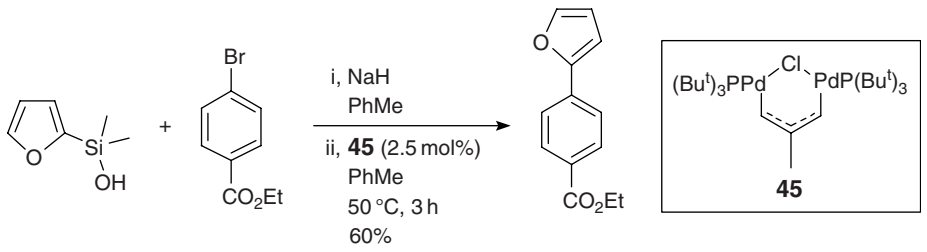


(32)



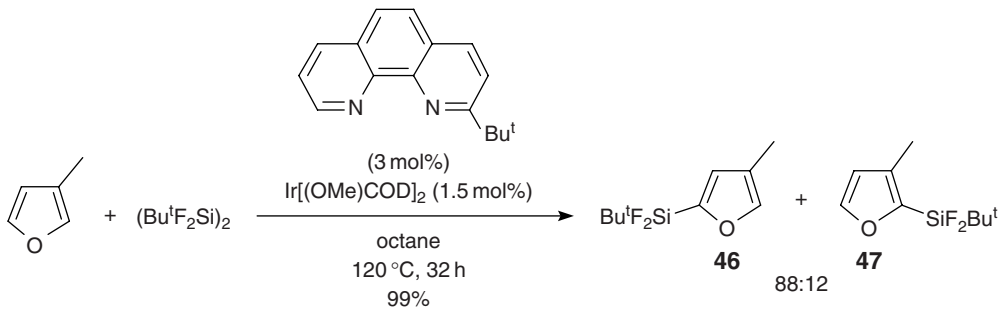
(33)

The cross-coupling of sodium 2-furanylsilanolate with aryl iodides and aryl bromides as catalyzed by palladium species **45** was developed, as illustrated in Equation (34). Coupling with aryl iodides could be performed at room temperature, using $Pd_2(dba)_3{\cdot}CHCl_3$ as the catalyst <2006OL793>.



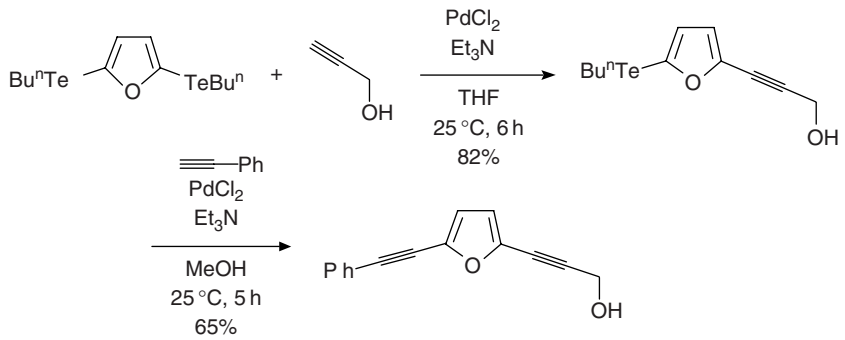
(34)

A method of forming 2-furanylsilane in a regioselective manner involved iridium catalyzed silylation using $(t\text{-}BuF_2Si)_2$ in the presence of 2-*tert*-butyl-1,10-phenanthroline as a ligand. As shown in Equation (35), 3-methylfuran provided the 5-silylated product **46** as the predominant regioisomer <2005CC5065>.



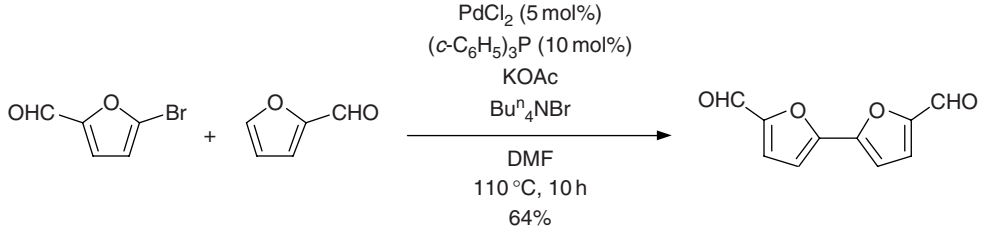
(35)

Unsymmetrical 2,5-disubstituted alkynylfurans could be prepared from 2,5-bis(butyltelluro)furan by sequential palladium-catalyzed cross-couplings. As represented in **Scheme 26**, the use of THF, a less effective solvent than MeOH for the symmetrical bis-coupling to alkynes, enabled the first monocoupling to occur <2003TL1387>.



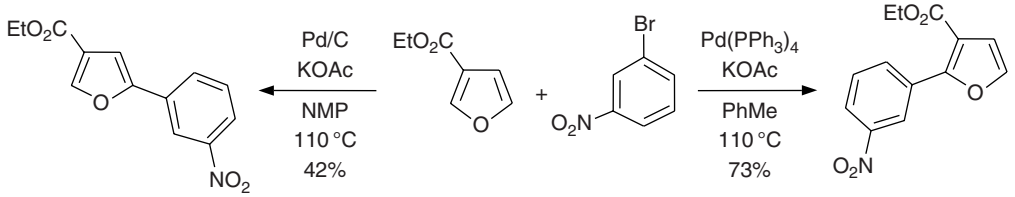
Scheme 26

A direct Heck-type coupling of 2-furaldehyde with various electron-rich and electron-deficient aryl iodides and bromides to provide 5-aryl-2-furaldehydes regioselectively was also developed <2001OL1677>. An interesting example is shown in Equation (36).



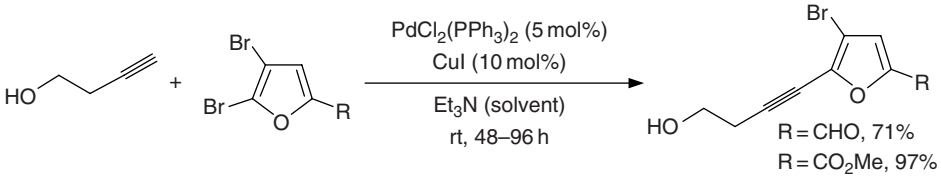
(36)

Regioselective palladium-catalyzed arylation of ethyl 3-furoate at either the 2- or the 5-position can be achieved by the judicious choice of solvent and palladium catalyst, as shown in **Scheme 27**. However, efficient arylation requires the use of aryl bromides substituted with electron-withdrawing groups (e.g., NO_2) <2003OL301>. This method was applied to the synthesis of furo[3,2-*c*]quinolinone from 1-bromo-2-nitrobenzene.



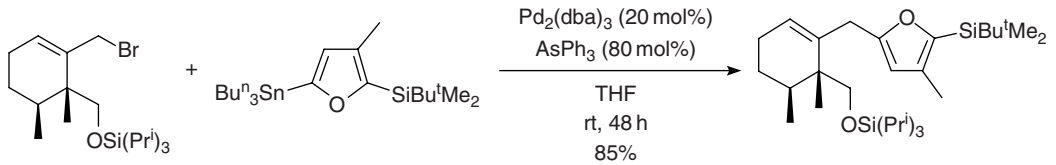
Scheme 27

As shown in Equation (37), 4,5-dibromo-2-furaldehyde and methyl 4,5-dibromo-2-furoate underwent regioselective cross-coupling reaction at the 5-position with alkynes under Sonogashira-type conditions, presumably due to the activation of the 5-position by the electron-withdrawing groups at the 2-position toward oxidative palladium insertion <1998TL1729, 1999EJO2045>.



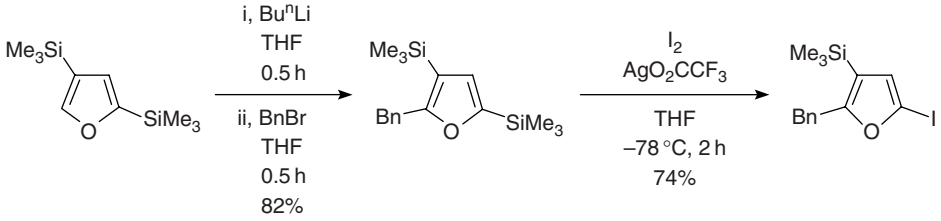
(37)

Palladium-catalyzed Stille cross-coupling of furanylstannanes to an allyl bromide was also regioselective. An example, as employed in the total synthesis of 6β-hydroxyeuryopsin, is depicted in Equation (38) <2004CC44>. This type of reaction could also be performed by using a catalytic amount of CuCl, rather than a palladium catalyst <1999SL1942>.



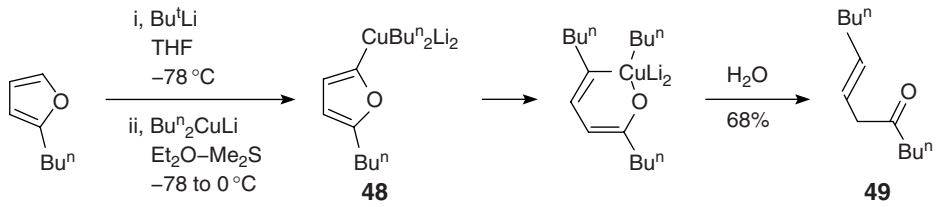
(38)

Analogous to 3,4-bis(trialkylsilyl)furans <1996PAC335, 1997LA459, 1998T1955, 1999CSR209>, the use of 2,4-bis(trialkylsilyl)furans, in which the silyl groups served as blocking groups and *ipso*-directing groups, for the regioselective synthesis of substituted furans was also developed. An application to the preparation of differentially functionalized furans as useful intermediates is shown in **Scheme 28** <1997T3497>.



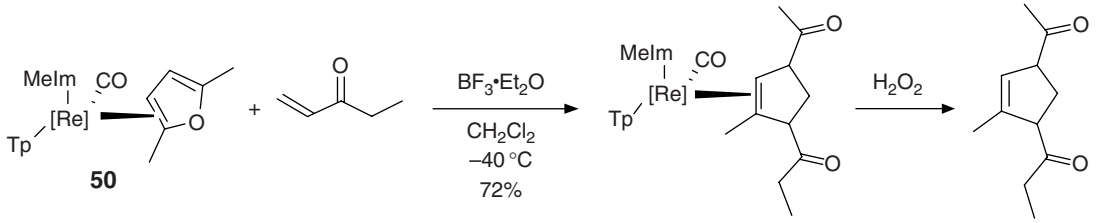
Scheme 28

2-Furanylcuprate **48** was discovered to undergo 1,2-metallate rearrangement, leading to ring opening to provide β,γ-unsaturated ketone **49**, as shown in **Scheme 29** <2003JOC4008>.



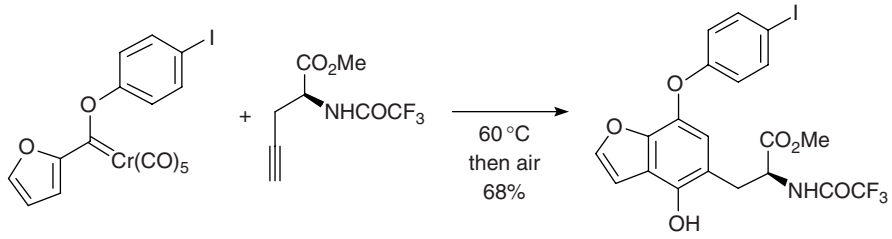
Scheme 29

Furan was demonstrated to function as a 1,3-propene dipole when it was dihapto-coordinated to a rhenium π-base, which enhanced the nucleophilicity of the uncoordinated C-3-position. As represented in **Scheme 30**, the 2,5-dimethylfuran complex **50** (Tp = hydridotris(pyrazolyl)borate; MeIm = 1-methylimidazole) reacted with Michael acceptors to form substituted cyclopentenes <2003JA14980, 2005OM2903>.



Scheme 30

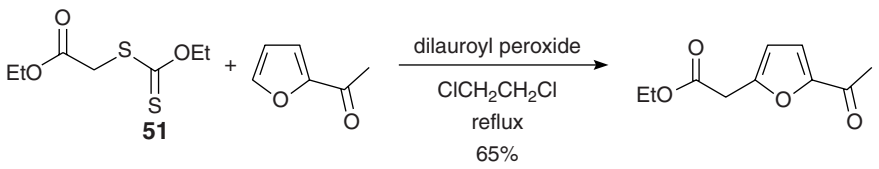
Fischer-type chromium carbene complexes of furans underwent Dötz benzannulation with alkynes to provide trisubstituted benzo[*b*]furan derivatives. An example used in the synthesis of isodityrosine is depicted in Equation (39) <2005JOC7422>. The efficiency of the reaction could be improved by ultrasound sonication <1999OL1721>.



(39)

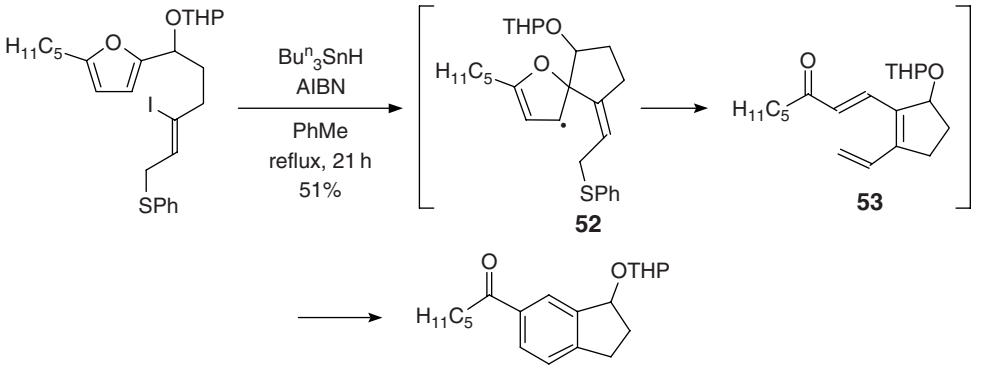
3.06.2.1.7 Reactions involving free radicals

Furans trapped aryl radicals, generated from the oxidation of arylboronic acids <2003JOC578> and from arylhydrazines <2002T8055> by $Mn(OAc)_3$, to give 2-arylfuran derivatives. A perfluoroalkyl radical, produced by using sodium dithionite, initiated dimerization of furan derivatives via addition to the furan 2-position <2002TL443>. The ethoxycarbonylmethyl radical, generated from xanthate **51** by dilauroyl peroxide, added to the 5-position of 2-acetylfuran, giving the addition product as shown in Equation (40) <2003CC2316>.



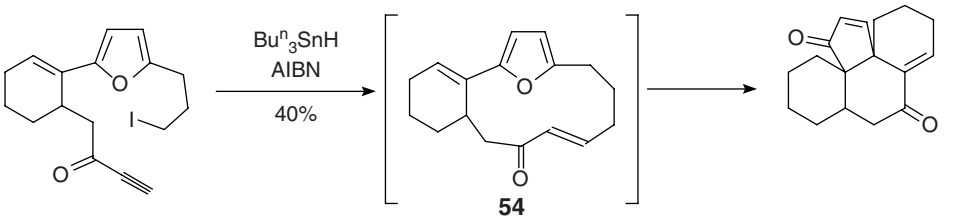
(40)

An intramolecular cascade reaction initiated by the addition of an alkenyl radical to a furan was used to synthesize an indene <1998SL1215>. As illustrated in **Scheme 31**, radical fragmentation in the spiro-dihydrofuran radical **52** provided the intermediate triene **53**, which underwent Cope-type rearrangement to form the product. A related reaction with 1-bromocyclohexene that led to unsaturated ketone product was also developed <2003EJO1729>.



Scheme 31

Similar methodology was employed to the synthesis of more complex polycyclic ring system, as shown in **Scheme 32** <1997TL9069>. The initial alkenyl radical **54**, formed by an intramolecular radical 13-*endo*-dig macrocyclization, initiated a radical cascade reaction by first reacting at the α-position of the furan ring.

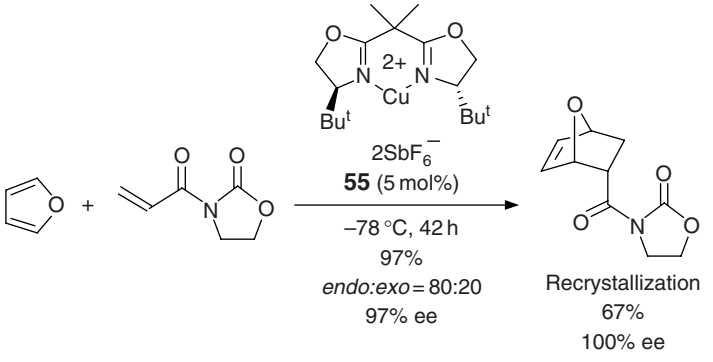


Scheme 32

3.06.2.1.8 Cycloaddition reactions

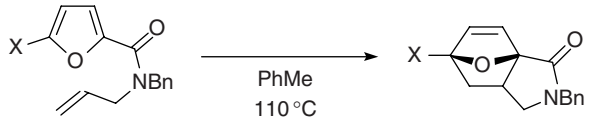
3.06.2.1.8(i) Diels–Alder reactions

The inter- and intramolecular Diels–Alder reactions of furans, and their applications to the synthesis of natural products as well as synthetic materials, were reviewed <1997T14179>. $HfCl_4$ promoted the *endo*-selective intermolecular Diels–Alder cycloadditions of furans with α,β-unsaturated esters <2002AGE4079>. The cycloaddition between furan and methacrylate was also achieved under these conditions, providing, however the *exo*-isomer as the major cycloadduct. A catalytic enantioselective Diels–Alder reaction between furan and acryloyl oxazolidinone to provide the *endo*-adduct in 97% ee was achieved by using the cationic bis(4-*tert*-butyloxazoline)copper(II) complex **55**, as shown in Equation (41) <1997TL57>.



(41)

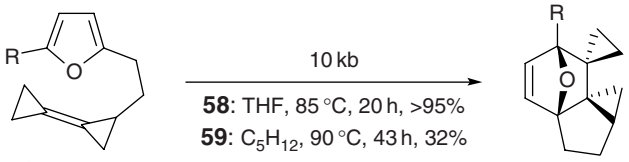
The presence of a halogen substituent at the 5-position of 2-furanyl amides markedly enhanced the rate of intramolecular Diels–Alder reaction. For example, 5-bromofuran **56** shown in Equation (42) provided the oxatricyclic adduct after heating for 90 min. In contrast, the 5-unsubstituted furan **57** required 1 week for the cycloaddition to be completed <2003OL3337>. The enhanced reaction rate and yield, as determined by CBS-QB3 calculations, were attributed to the decreased activation energy as well as a greater stabilization of the cycloadduct imparted by the halogen substitution. The computational results also suggested that substitution at the 2-position has a greater effect than that at the 3-position, and that a 2-methoxy group is as beneficial as a halogen <2006AGE1442>.



56: X = Br
57: X = H

(42)

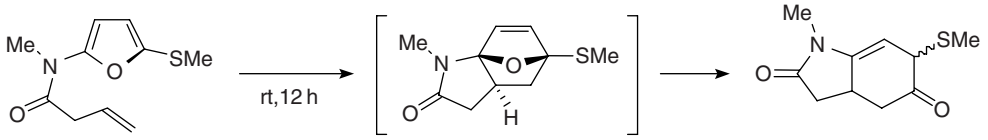
An intramolecular Diels–Alder reaction of a furan with a strained and sterically hindered bicyclopropylidene that proceeded under high pressure to provide the acid-labile cycloadduct is shown in Equation (43) <1996T12185>. An apparent increase in the reaction rate was observed with the 5-methoxyfuran **58** compared to the 5-unsubstituted analog **59**.



58: R = OMe
59: R = H

(43)

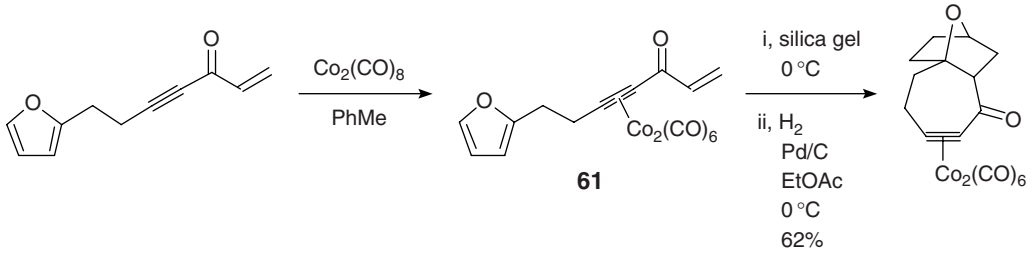
Structural elements can also be incorporated into the furan starting materials so that intramolecular cycloadditions proceed at or below ambient temperature even with an unactivated dienophile, such as the example illustrated in **Scheme 33** <2002OL473, 2002JOC3412>. Based on B3LYP/6-31G* calculations, the amidofuran substrate **60** was shown to be populated in a reactive conformation that was imparted by the amide carbonyl of the tether.



60

Scheme 33

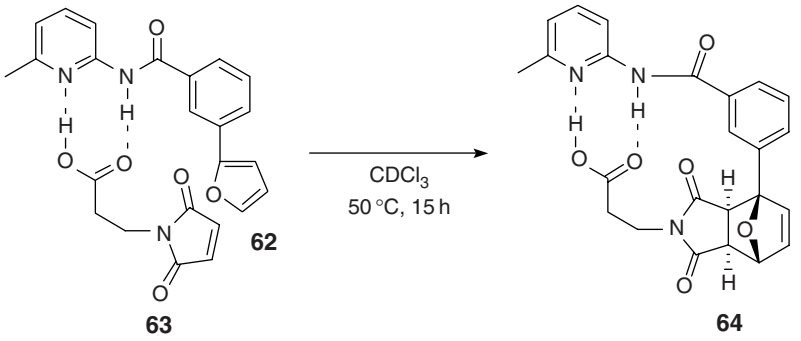
A complexation-induced intramolecular Diels–Alder cycloaddition of furan is depicted in **Scheme 34**. Upon exposure to silica gel, the alkyne–$Co_2(CO)_6$ complex **61** was transformed to the cycloadduct that contained a seven-membered ring <2000OL871>. This facile process was supposed to be arisen from the bending of the linear triple bond to a structure with a 140° angle between the two carbon substituents in the cobalt complex **61**.



61

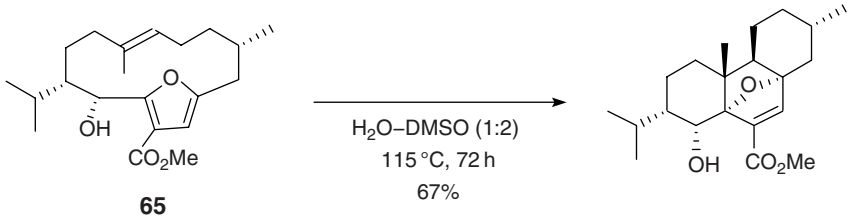
Scheme 34

Introduction of hydrogen-bonding recognition elements into furans and dienophiles could also facilitate disfavored Diels–Alder reactions. For example, the pair of hydrogen bonds formed between the phenylfuran **62** and maleimide **63** shown in Equation (44) enhanced the rate of the cycloaddition, as well as stabilized the ground state of the *exo*-product **64** <1999OL1087>.



62 **63** **64** (44)

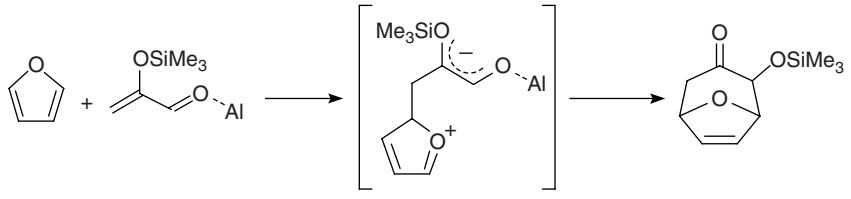
An interesting and rare example of inverse electron demand transannular Diels–Alder reaction of the furanophane **65** was employed for the synthesis of the chatancin core as depicted in Equation (45) <2003JOC6847>. The diastereoselectivity of this reaction was controlled by the macrocyclic conformation of **65** in the protic reaction medium.



65 (45)

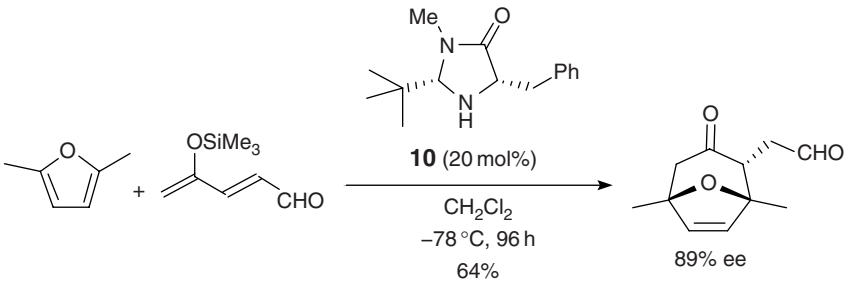
3.06.2.1.8(ii) Other cycloadditions

The inter- and intramolecular [4+3] cycloaddition between furans and oxyallyl cations to generate seven-membered rings were reviewed <B-1997MI351, 1997T6235, 2001ACR595>. Silyloxyacroleins <2000OL2703> and cyclopropanone hemiacetals <2001OL2891> were used as oxyallyl equivalents for the [4+3] cycloaddition with furans. A theoretical study at the B3LYP/6-31G* level of the $AlCl_3$-catalyzed intermolecular [4+3] cycloaddition between 2-(trimethylsilyloxy)acrolein and furan showed that the reaction was a three-step process that involved an initial nucleophilic Michael-type attack of furan at the β-conjugated position of acrolein, as illustrated in **Scheme 35** <2003OL4117>. Similar calculations of a $TiCl_4$-catalyzed intramolecular [4+3] cycloaddition between furan and allyl *p*-toluenesulfone-derived oxyallyl cation also suggested a stepwise mechanism <2001OL3663>.



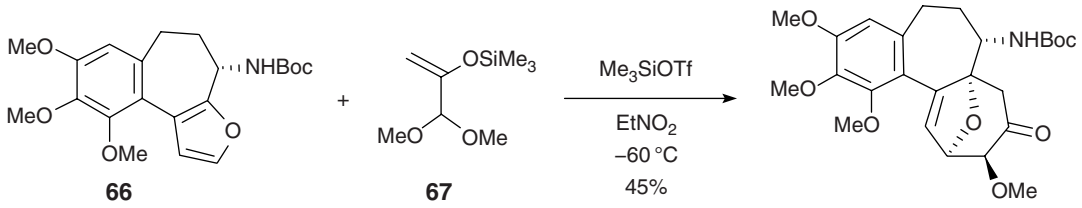
Scheme 35

The phenylalanine-derived chiral amine catalyst **10** was used to promote the asymmetric [4+3] cycloaddition between 2,5-dialkylfurans and trialkylsilyloxypentadienals to generate seven-membered carbocycles with *endo*-selectivity and 81–90% ee, as represented in Equation (46) <2003JA2058>. However, the absolute configurations of the cycloadducts have not been determined.



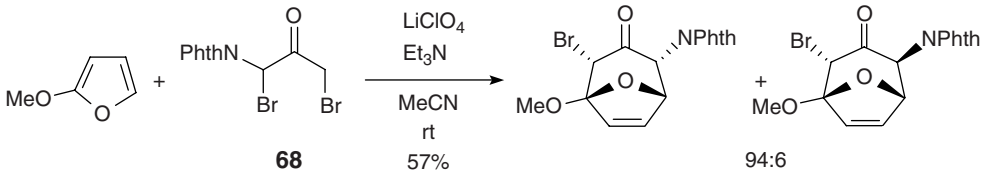
(46)

A [4+3] cycloaddition between 2,5-bis((*tert*-butyldimethylsilyloxy)methyl)furan and the oxyallyl cation generated from 1,1,3-trichloroacetone was a pivotal step for the construction of phorbol B ring during a formal total synthesis of (+)-phorbol <2001JA5590>. This type of furan–oxyallyl cation cycloaddition was used as a unifying strategy for the synthesis of tropoloisoquinoline alkaloids <2001JA3243>, and a key step in the total synthesis of colchicine, as shown in Equation (47) <1998JOC2804, 2000T10175>. Regioselective coupling of the complex furan **66** with the α-alkoxy-substituted oxyallyl cation generated from the silyl enol ether **67** provided the desired *endo*-adduct as a single diastereoisomer. Interestingly, the reaction of the *N*-acetyl analog of **66** gave the undesired regio- and diastereoselectivity.

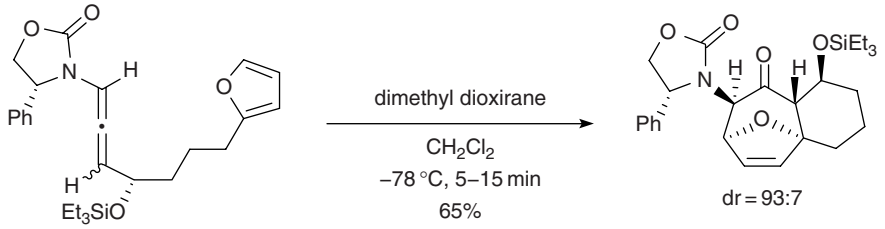


(47)

The intermolecular [4+3] cycloaddition between furan and the nitrogen-stabilized oxyallyl cation generated from *N*-(1,3-dibromoacetonyl)phthalimide **68** by $LiClO_4/Et_3N$, as represented in Equation (48), was predicted by frontier molecular orbital (FMO) calculations at the PM3 level to be a stepwise process <1996JOC1478>. The diastereoselective inter- and intramolecular [4+3] cycloadditions of a furan with a nitrogen-stabilized chiral oxyallyl cation, generated by epoxidation of a chiral oxazolidinone-substituted allenamide using dimethyl dioxirane, to form complex polycyclic structures were developed <2001JA7174, 2003JA12694>. This reaction was further extended to the use of a furan tethered to either the α- or γ-position of the allene, as demonstrated in Equation (49) <2004AGE615>. The catalytic enantioselective variant of this type of cycloaddition was also achieved by using a C_2-symmetric copper-(salen) complex, providing ee up to 99% <2005JA50>.

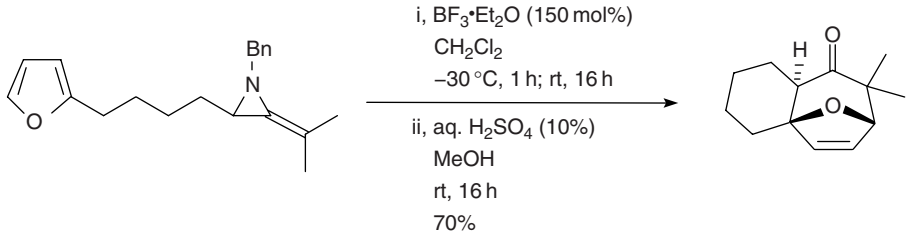


(48)



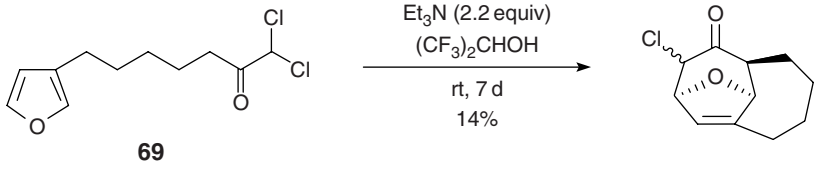
(49)

The [4+3] cycloaddition between furan and amino-stabilized allyl cations has not been as actively studied. An intramolecular cycloaddition between a furan and a 2-aminoallyl cation, generated from methyleneaziridine under Lewis acid-promoted conditions, is shown in Equation (50) <2004AGE6517>. An $AgBF_4$-promoted asymmetric intermolecular [4+3] cycloaddition of 2-aminoallyl cations, derived from chiral α-chloroimines, with furan to give cycloadducts of up to 60% ee was also reported <1997TL3353>.



(50)

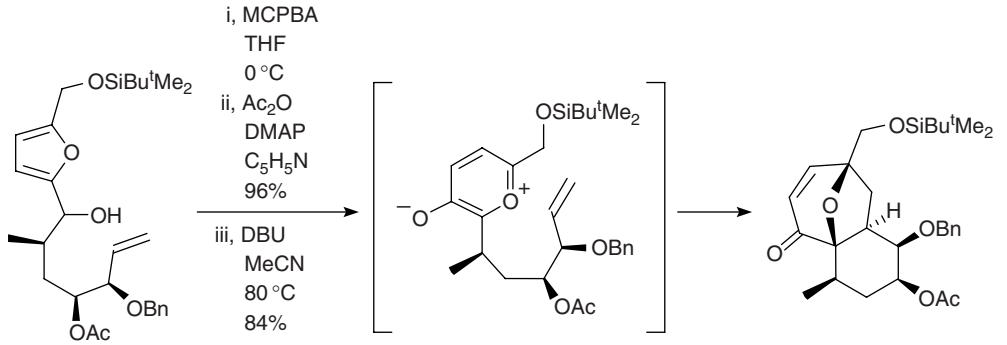
In contrast to the extensively developed type-I intramolecular [4+3] cycloadditions as illustrated above, type-II intramolecular [4+3] cycloadditions with cation moieties tethered to the 3-position of furans have not been shown to be versatile transformations. As shown in Equation (51), an attempt on the cycloaddition of furan **69** only resulted in a low yield of the fused tricycle product that resembled the BC ring of ingenol <2003JOC7899>.



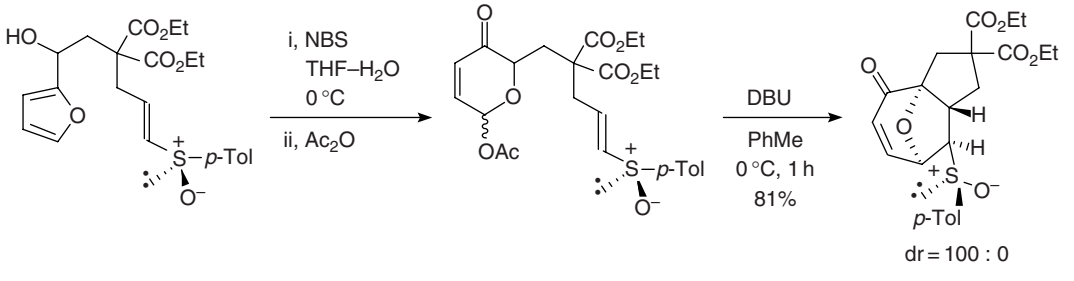
69

(51)

The intramolecular [5+2] cycloaddition of oxidopyrylium ions, obtained from the Achmatowicz oxidative ring expansion of furfuryl alcohols, with alkenes was employed as a key strategy for the construction of the [6,7]-fused BC ring system of the daphnane diterpene phorbol <1997JA7897> and resiniferatoxin (**Scheme 36**) <1997JA12976> during their total synthesis, as well as for the assembly of the cyathin diterpene skeleton <1999T3553>. A version of this type of cycloaddition using a chiral sulfinyl auxiliary on the alkene component is shown in **Scheme 37** <2002OL3683>.

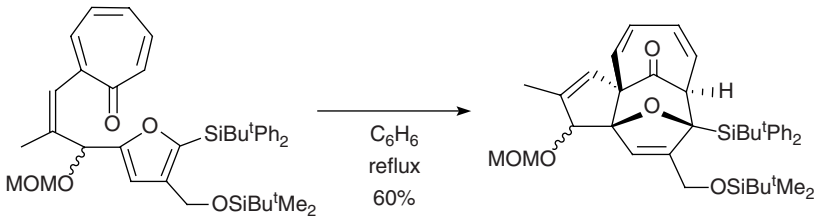


Scheme 36



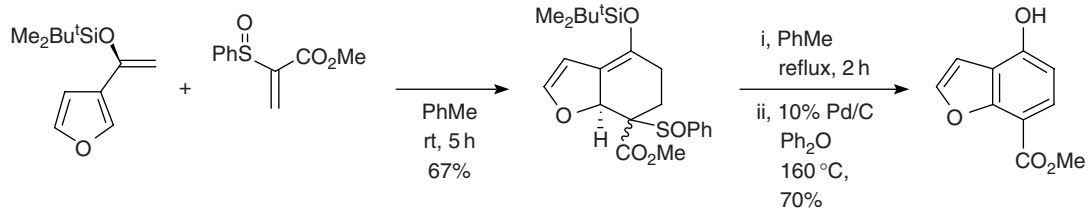
Scheme 37

As shown in Equation (52), the intramolecular [6+4] cycloaddition between a furan and a tropone was successfully achieved for the first time during the construction of the highly functionalized ABC ring of ingenol <2005SL2501>.



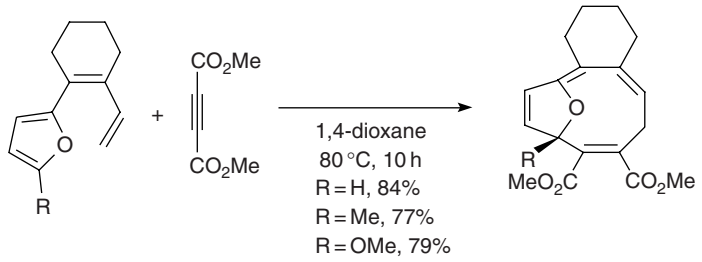
(52)

Methyl 2-methyl-5-vinyl-3-furoate participated in intermolecular extraannular [4+2] cycloadditions in which the 5-vinyl group and the furan 2,3-π bond acts as the 4π-component with dienophiles to form tetrahydrobenzo[*b*]furans. However, the reaction was very sluggish under either thermal or high-pressure conditions <2002EJO3589>. Extraannular [4+2] cycloadditions of 3-vinylfurans were also slow, except for reactions with phenylsulfinylated dienophiles, which occurred at room temperature with shorter reaction times. An application to the regioselective synthesis of substituted benzo[*b*]furan is illustrated in **Scheme 38** <1996JOC1487>. A 5-trialkylsilyl substituent could enhance tendency of 2- and 3- vinylfurans toward the extraannular [4+2] cycloadditions <1997H(45)1795>.



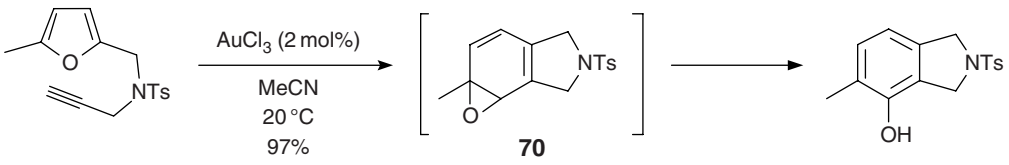
Scheme 38

In contrast, the [8+2] cycloaddition of 2-butadienylfurans, that participated as 8π-components, with dimethyl acetylenedicarboxylate (DMAD) was facile, giving oxygen-bridged 10-membered [8+2] cycloadducts, as illustrated in Equation (53) <2005OL1665>.



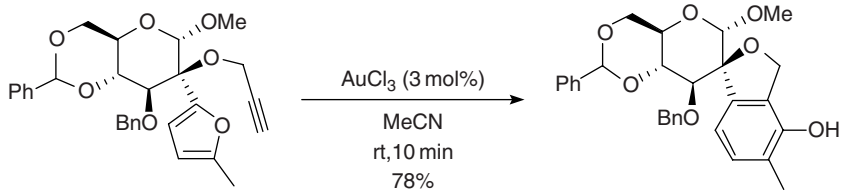
(53)

Gold(III) catalyzed the cycloisomerization of furans tethered via carbon, oxygen, and nitrogen linkages to a terminal alkyne to produce phenols, as depicted in **Scheme 39** <2000JA11553>. This reaction was also catalyzed by $PtCl_2$ <2001AGE4754>. Based on density functional theory (DFT) calculations and on the trapping of reaction intermediates, the mechanism was proposed to involve a cyclopropyl platinacarbene complex <2003JA5757> that led to



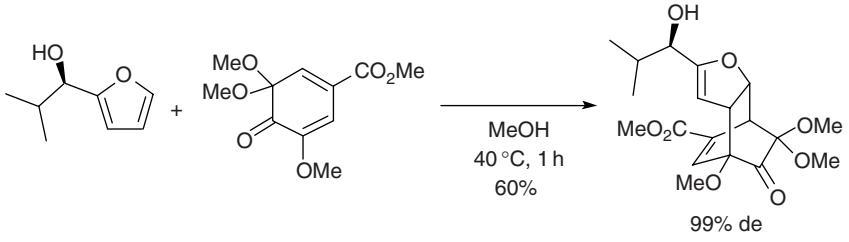
Scheme 39

an arene oxide intermediate (e.g., **70**), which was observed experimentally for the first time under the gold-catalyzed conditions <2005AGE2798>. New gold(III)–pyridine-2-carboxylate complexes that provided higher reaction conversions than $AuCl_3$ were developed <2004AGE6545>. This methodology was adapted to the synthesis of interesting spiroannulated dihydrobenzo[*c*]furans containing pentofuranosides, hexofuranosides, and hexopyranosides, as represented in Equation (54) <2006TL3307>.

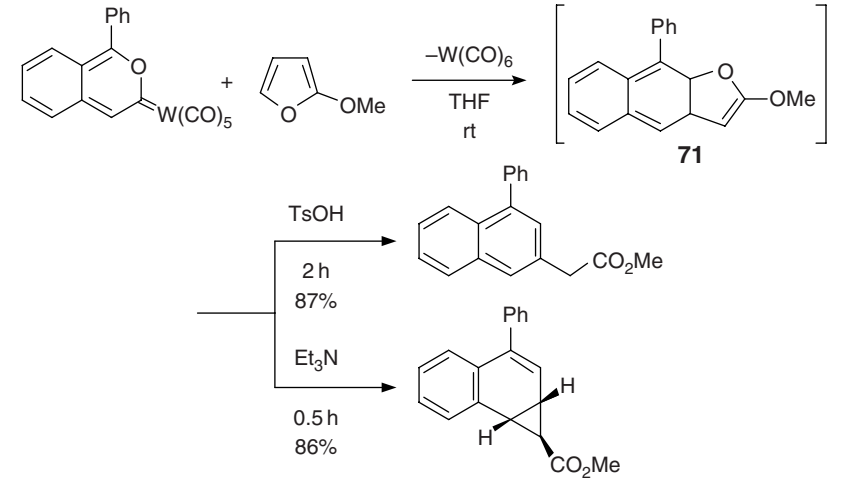


(54)

The furan 2,3-double bond was found to participate in regio- and stereoselective cyclization with masked *o*-benzoquinones <1998JA13254, 1999CC713>. An example of a diastereoselective cyclization involving (*R*)-furfuryl alcohol in which the α-hydroxyl group controlled the facial selectivity to produce the *ortho*,*endo*-adduct is shown in Equation (55) <2003OL1637>. DFT <2002JOC959> and experimental <2003JOC7193> studies suggested a stepwise mechanism with the nucleophilic attack of furan to the conjugated dienone as the rate-determining step for this reaction. The 4,5-double bond of 2-methoxyfuran underwent inverse electron demand cycloaddition with pentacarbonylbenzopyranylidenetungsten(0) complexes in THF at room temperature. As illustrated in **Scheme 40**, subsequent elimination of $W(CO)_6$ and rearrangement of the adduct provided intermediate **71**, which was converted to naphthalene and benzonorcaradiene derivatives in the presence of TsOH and triethylamine, respectively <2002CL124>.



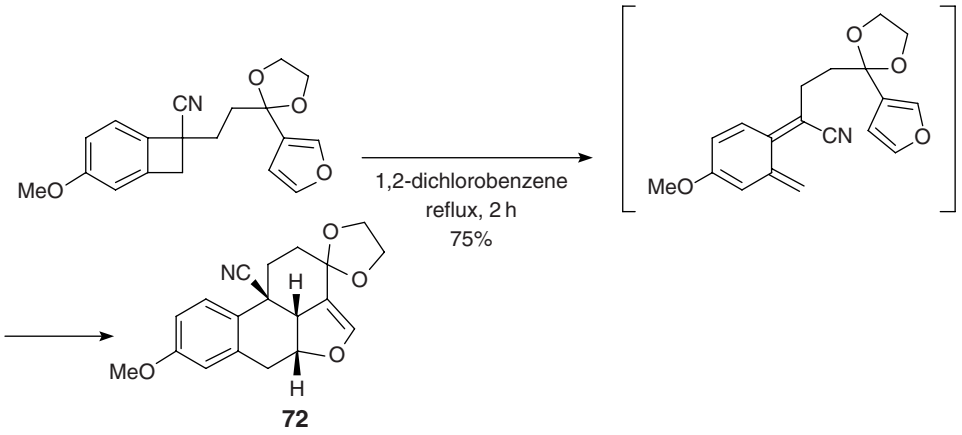
(55)



Scheme 40

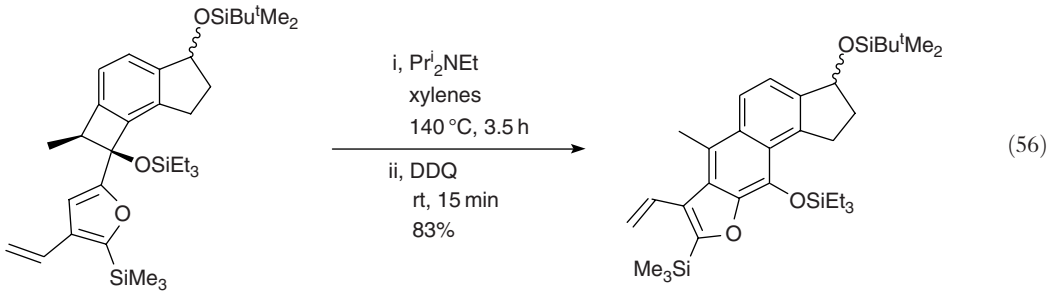
As depicted in **Scheme 41**, an intramolecular cycloaddition of the furan 2,3-double bond of a furan tethered to a cyano-substituted benzocyclobutene via an intermediate quinone dimethide was used for the synthesis of the tetracyclic core of halenaquinol and halenaquinone <2001SL1123, 2002T6097>. The reaction proceeded via an *endo*-transition state to produce the cycloadduct **72** exclusively. A related chemistry is shown in Equation (56), in

which the furan 2,3-double bond of the furanylbenzocyclobutene participated in an efficient 6π-disrotatory electrocyclization with the intermediate quinone dimethide to form the fused tetracyclic ring system of the furanosteroid, viridin <2004AGE1998>. Additional examples of furan-substituted bicyclo[3.2.0]heptenones that participated in oxy-Cope transannular rearrangement involving furan 2,3-double bond were reported <1996JOC7976>, demonstrating a feasible approach for the synthesis of poly [5,5]-fused ring systems.



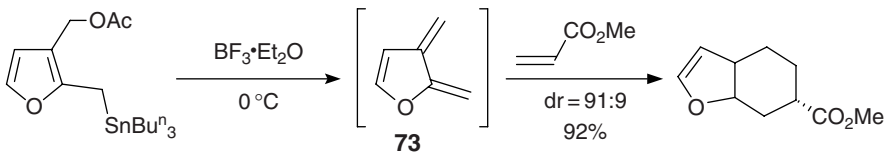
72

Scheme 41



(56)

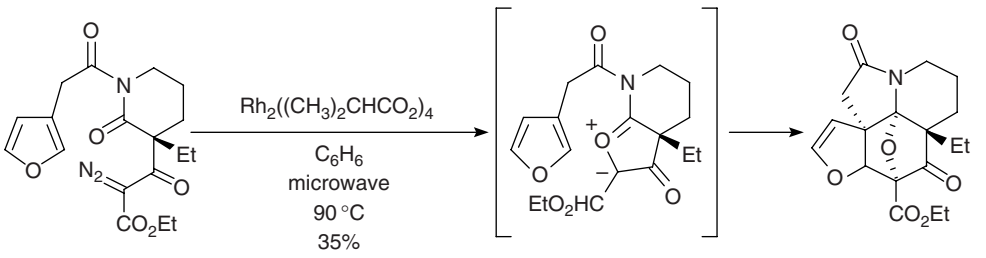
2,3-Dimethylene-2,3-dihydrofuran **73** was generated from 3-(acetoxymethyl)-2-(tributylstannylmethyl)furan by using $BF_3{\cdot}Et_2O$ and captured by dienophiles to form adducts in a regioselective manner <1996CC2251>. The reaction with methyl acrylate is illustrated in **Scheme 42**.



73

Scheme 42

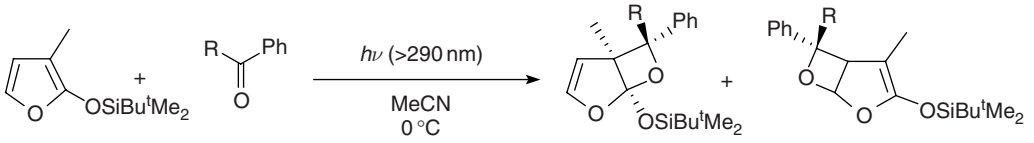
Intermolecular [3+2] 1,3-dipolar cycloaddition of a D-glyceraldehyde-derived nitrile oxide to the 4,5-double bond of 2-methylfuran gave a 60:40 diastereomeric ratio of the two furoisozaxoline isomers. This chemistry was employed in the synthesis of L-furanomycin <2005EJO3450>. As depicted in **Scheme 43**, an intramolecular cycloaddition of a furan with a carbonyl ylide dipole proceeded under rhodium-catalyzed microwave-promoted conditions to provide the cycloadduct in a modest yield <2004OL3241>.



Scheme 43

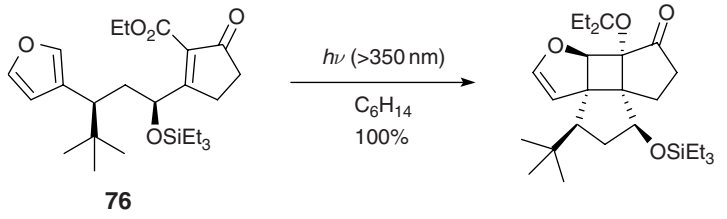
3.06.2.1.9 Photochemical reactions

The regio- and stereoselectivities of the Paternò–Büchi [2+2] photocycloaddition of furans with carbonyl compounds are determined by the conformational stability of the triplet diradical intermediates <2004JA2838>. As illustrated in a study with 2-silyloxyfurans shown in Equation (57) <2000JOC3426>, reaction with ketones provided higher substituted products regioselectively (e.g., **74**, R = Me), while those with aldehydes were nonselective. As usual, *exo*-oxetanes were produced predominantly in both examples. *exo*/*endo*-Selectivity was, however, influenced by the substituents of the carbonyl compounds. For example, the *exo*-selectivity was completely reversed by electronegative substituents (e.g., OMe and CO_2R), providing *endo*-isomers as the predominant products <1998JOC3847>.



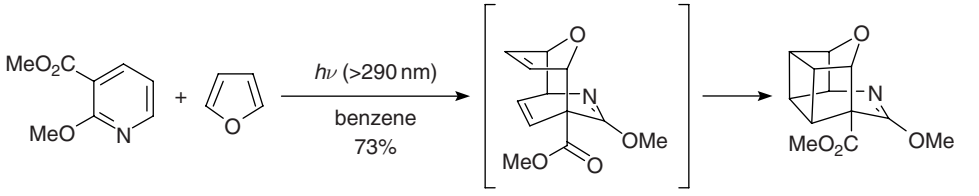
(57)

A remarkable example of [2+2] photocycloaddition of furans with alkenes, as shown in Equation (58), is the pivotal intramolecular cyclization employed in the total synthesis of ginkgolide B <2000JA8453>. The stereochemical outcome of this triplet transformation was predominately influenced by the relative 1,3-stereochemistry of the substrate **76**.



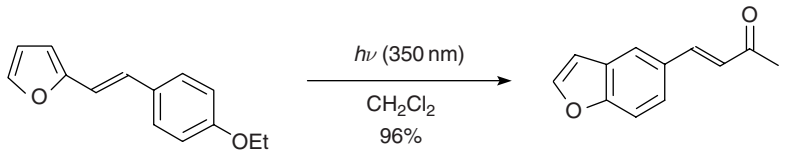
(58)

Furan underwent photocyclization reactions with 2-alkoxy-3-cyanopyridines <1999J(P1)171> and 2-alkoxynicotinic acid esters <2002TL6103>, forming cage-like adducts, as shown in **Scheme 44**, that presumably resulted from a singlet [4+4] cycloaddition followed by a triplet [2+2] cycloaddition. Reaction of 2-cyanofuran, however, provided the [4+4] product as the major isomer <2004TL4437>.



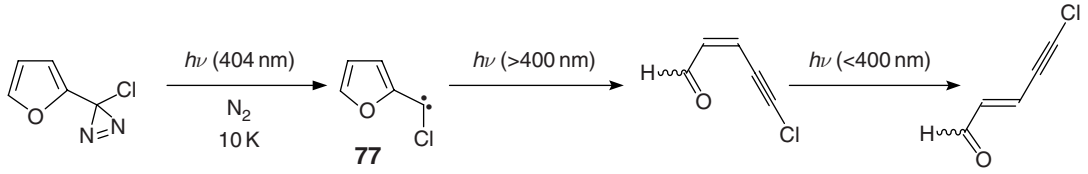
Scheme 44

Photocyclization of *N*-alkylfuran-2-carboxyanilides conducted in inclusion crystals with optically active tartaric acid-derived hosts led to the formation of tricyclic *trans*-dihydrofuran compounds with up to 99% ee <1996JOC6490, 1999JOC2096>. 2-(*p*-Alkoxystyryl)furans underwent photocyclization to give 5-(3-oxo-(*1E*)-butenyl)benzo[*b*]furans as the predominant isomers in undehydrated dichloromethane as shown in Equation (59). The intermediate alkyl enol ether could be obtained by performing the reaction in anhydrous benzene <1999OL1039>.

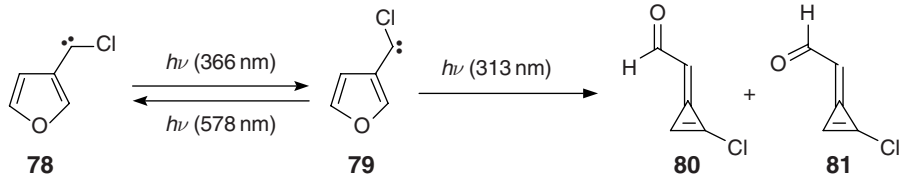


(59)

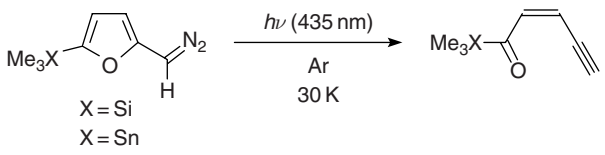
Unlike 2- and 3-furanylcarbenes <1997LA897>, 2- and 3-furanylchlorocarbenes could be characterized in a nitrogen matrix at low temperature. The *syn*-2-furanylchlorocarbene **77** was more photoreactive than its *anti*-isomer and rearranged to a mixture of conformers of 5-chloropent-2-en-4-yn-1-al (**Scheme 45**). It could also be trapped in solution by alkenes at room temperature <1998JA233>. The *syn*- and *anti*- isomers of 3-furanylchlorocarbene **78** and **79**, respectively, could be photochemically interconverted. Both isomers rearranged to an isomeric mixture of methylenecyclopropenes **80** and **81** upon irradiation (**Scheme 46**) <1999OL1091>. The effect on the ring-opening rearrangement by the substituent on the carbene moiety was further investigated by *ab initio* calculations, which were found to be consistent with experimental results <1999JOC9170>. Substituents with a lone pair of electrons increased the energy barrier due to greater stabilization on the carbene reactant than on the transition state, suggesting that carbenes with this kind of substituents could be isolated experimentally. The predicted tendency of rearrangement is in the order: $SiH_3 > H > CH{=}CH_2 > CH_3 > Br > Cl > F > NH_2 > OH$. Substituents on the furan ring also affected the outcome of the photo-rearrangement. For example, photolysis of 2-diazomethyl-5-trimethylsilylfuran and 2-diazomethyl-5-trimethylstannylfuran at >420 nm provided the (*Z*)-isomer of 1-(trimethylsilyl)pent-2-en-4-ynone and 1-(trimethylstannyl)pent-2-en-4-ynone, respectively (Equation 60). However, both were very stable and did not isomerize to the (*E*)-isomers on prolonged irradiation <2001EJO269>.



Scheme 45



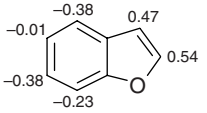
Scheme 46



(60)

3.06.2.2 Reactivity of Fully Conjugated Benzo[*b*]furans

According to the frontier orbital theory, the frontier electron populations of the parent benzo[*b*]furan **82** are represented as illustrated <B-1976MI58>. It should be noted that the more positive the numerical values, the more reactive is the corresponding carbon toward electrophiles.

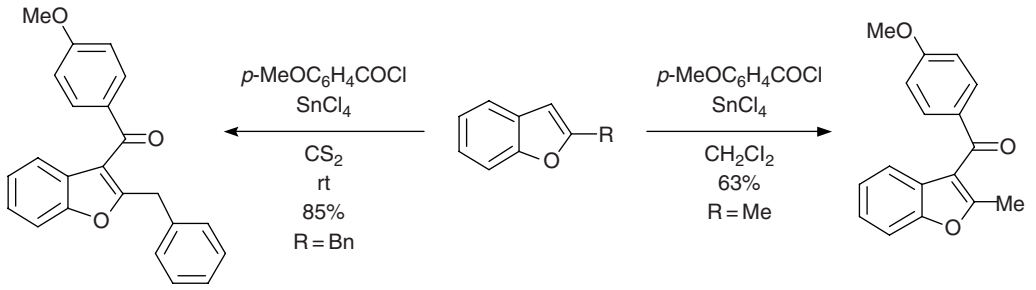


82

3.06.2.2.1 Reactions with electrophiles

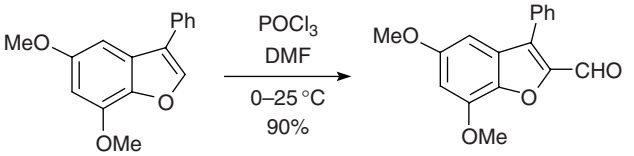
3.06.2.2.1(i) Acylation

Two types of 3-benzoylbenzo[*b*]furans were regioselectively prepared from their corresponding starting materials 2-methylbenzo[*b*]furan and 2-benzylbenzo[*b*]furan through a Friedel–Crafts reaction pathway, as shown in **Scheme 47** <2002JME623>.



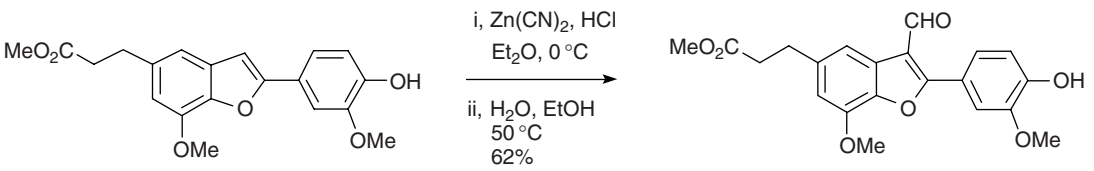
Scheme 47

Regioselective formylation was also achieved by treatment of a 3-phenylbenzo[*b*]furan with *N*,*N*-dimethylformamide and phosphoryl chloride (Vilsmeier reagent) at 0–25 °C to give 2-carbaldehyde derivative in 90% yield (Equation 61). In addition, a variety of interesting 2-acylbenzo[*b*]furan derivatives were described in the same article <2002T5125>.



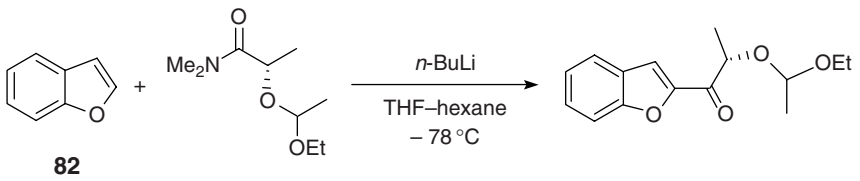
(61)

With 2-substituted benzo[*b*]furans, the regioselective electrophilic aromatic substitutions of formyl and nitro groups to C-3 of 5-alkyl-7-methoxy-2-phenylbenzo[*b*]furans were achieved (Equation 62). Further synthetic transformations of the resulting formyl group into methyl, hydroxymethyl, 1-hydroxyethyl, and cyano groups were also reported <1992JOC7248>.



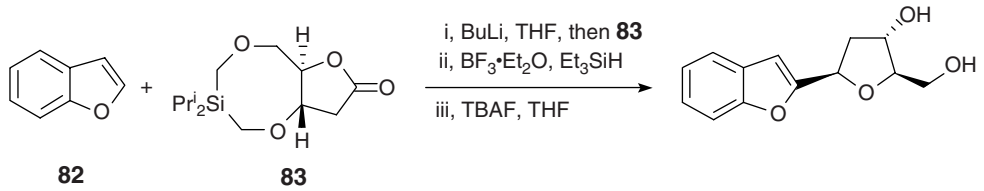
(62)

2-Lithiated benzo[*b*]furan was found to be a useful reagent in reactions with amides to give the corresponding 2-acylbenzo[*b*]furan product (Equation 63). The acylation yield was not reported <2002TL6937>.



82 (63)

A key synthetic step to an unnatural nucleotide bearing benzo[*b*]furan by the reaction of 2-lithiated benzo[*b*]furan with lactone **83** is illustrated in Equation (64) <2003JA6134>.

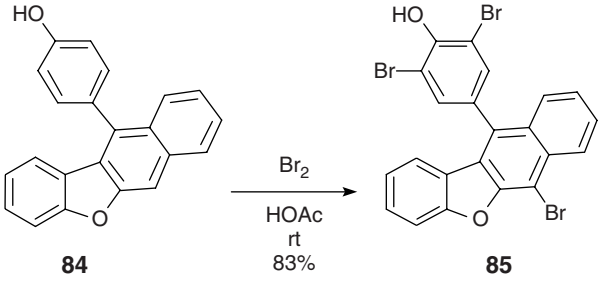


82 **83** (64)

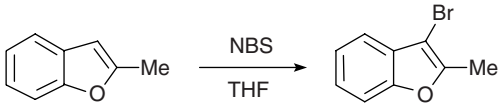
3.06.2.2.1(ii) Halogenation

Since halogen-substituted benzo[*b*]furans play an important role in the transition metal-catalyzed coupling of benzo[*b*]furans with other substrates, synthetic methods to regioselectively synthesize substituted benzo[*b*]furan halides have become very critical routes. Several syntheses of benzo[*b*]furan based aryl halides are described here.

When benzo[*b*]furan derived polycyclic phenol **84** was allowed to react with bromine, tribromide **85** was formed in high yield (Equation 65) <1999JME3199>. 3-Bromo-2-methyl-benzo[*b*]furan **87** could also be made by reaction of *N*-bromosuccinimide (NBS) with 2-methyl benzo[*b*]furan **86** at room temperature, as illustrated in Equation (66) <2005JOC10323>.

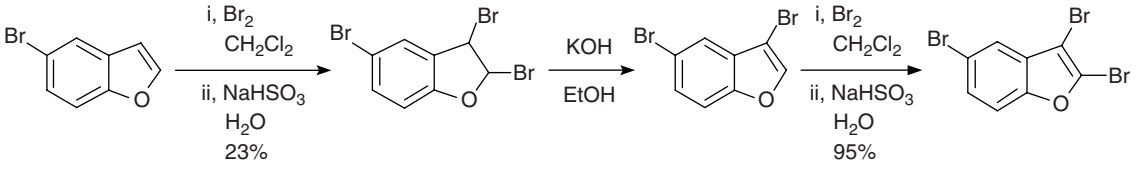


84 **85** (65)



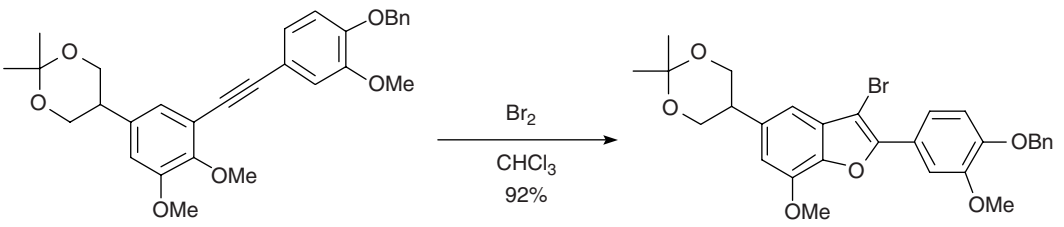
86 **87** (66)

Another interesting bromination strategy was developed to obtain 3,5-dibromobenzo[*b*]furan and 2,3,5-tribromobenzo[*b*]furan by sequential treatment of the corresponding benzo[*b*]furans with bromine followed by the base-mediated elimination of HBr (**Scheme 48**) <2003S925>.



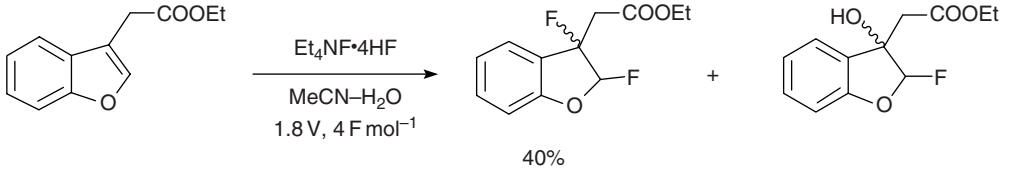
Scheme 48

In a total synthesis of XH14 reported recently, the key intermediate 3-bromobenzo[*b*]furan was made by bromine-promoted cyclization of an *o*-methoxy phenylacetylene, as depicted in Equation (67) <2002JOC6772>.



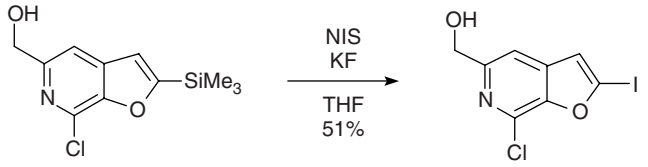
(67)

As depicted in Equation (68), anodic fluorination of ethyl 3-benzo[*b*]furanyl acetate was applied to the synthesis of a 2,3-difluoro-2,3-dihydrobenzo[*b*]furan derivative. A 2-fluoro-3-hydroxyl derivative was also obtained as a minor product <2003SL1631>.



(68)

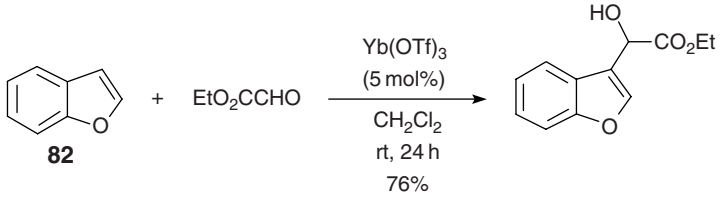
The C-2 trimethylsilyl-derived pyridino[*b*]furan was treated with the combined reagent NIS/KF to give 2-iodopyrido[*b*]furan, a key intermediate for the synthesis of sesquiterpenoid furanoeudesmanes (NIS = *N*-iodosuccinimide) (Equation 69) <2003T325>.



(69)

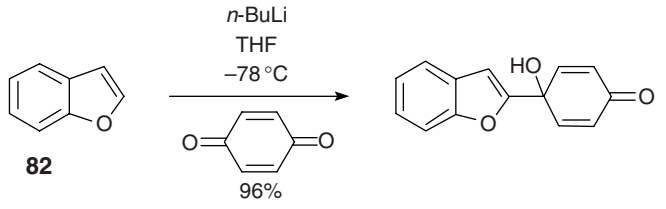
3.06.2.2.1(iii) Reactions with aldehydes and ketones

Due to the electronic richness of the C-3 of benzo[*b*]furan **82**, the Yb-catalyzed electrophilic substitution of benzo[*b*]furan **82** with glyoxalate led to a 3-α-hydroxybenzo[*b*]furan ester in a regioselective manner, as depicted in Equation (70) <2000JOC4732>.



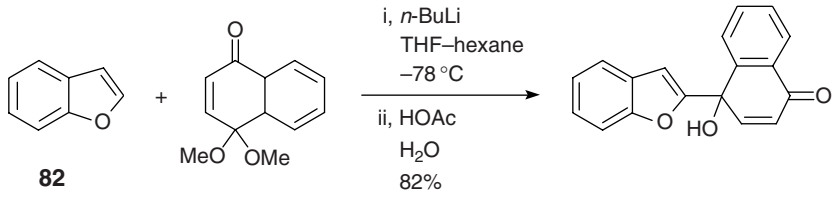
(70)

The C-2 proton of benzo[*b*]furan **82** underwent regioselective metallation by treatment with *n*-butyllithium to form 2-lithiated benzo[*b*]furan, which directly reacted with electrophiles, such as 1,4-cyclohexadienone to form 4-(benzo[*b*]furan-2-yl)-4-hydroxy-2,5-cyclohexadien-1-one in high yield, as shown in Equation (71) <2005TL7511>.



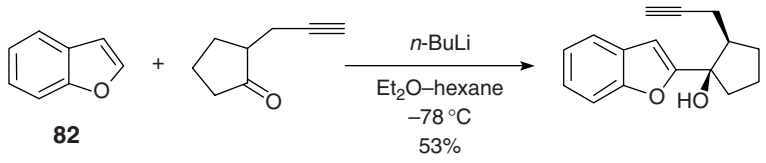
(71)

Another application of 2-lithiated benzo[*b*]furan to generate a structurally interesting benzo[*b*]furan derivative was realized by reaction of 2-lithiated benzo[*b*]furan with 4,4-dimethoxy-4*H*-naphthalen-1-one, followed by hydrolysis, as shown in Equation (72) <2003JME532>.



82 (72)

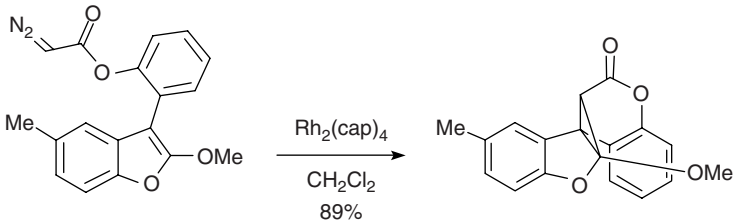
A benzo[*b*]furan derived acetylenic alcohol was also prepared by reaction of 2-lithiated benzo[*b*]furan with a cyclopentanone (Equation 73) <2004SL2579>.



82 (73)

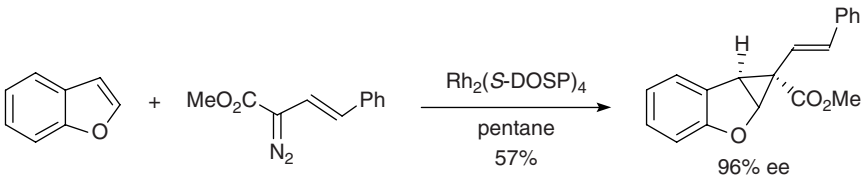
3.06.2.2.1(iv) Reactions with diazonium salts and diazo compounds

Benzo[*b*]furan-based diazobutenoates were used as a substrate to make a cyclopropane in 89% yield via a rhodium-catalyzed intramolecular process, as can be seen in Equation (74). Cyclopropane **88** was the key intermediate for the total synthesis of diazonamide A <2000OL3521>.



88 (74)

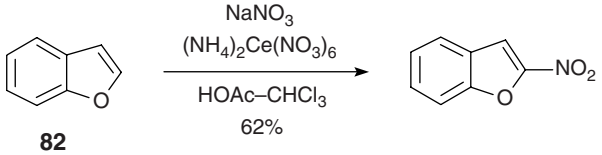
The rhodium-catalyzed intermolecular cyclopropanation of diazobutenoates with benzo[*b*]furan **82** resulted in the formation of a benzo[*b*]furan-derived cyclopropane in a diastereo- and enantioselective manner, as depicted in Equation (75) <1998JOC6586>.



82 (75)

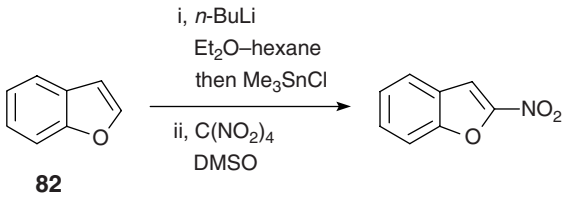
3.06.2.2.1(v) Reactions with other electrophiles

Direct nitration of benzo[*b*]furan **82** is another important reaction to provide benzo[*b*]furan derivatives. Because of its electronic richness, benzo[*b*]furan **82** can undergo regioselective nitration to give 2-nitrobenzo[*b*]furan in 62% yield by using sodium nitrate and ceric ammonium nitrate under ultrasonic conditions (Equation 76) <1996OM499>.



82 (76)

As illustrated in Equation (77), the regioselective nitration of 2-(trimethylstannyl)benzo[*b*]furan was also applied to the synthesis of 2-nitrobenzo[*b*]furan. The reaction proceeded by an initial treatment of benzo[*b*]furan **82** with *n*-BuLi/Me_3SnCl, and was then followed by reaction with tetranitromethane (TNM) or dinitrogen tetroxide <2003EJO1711>.

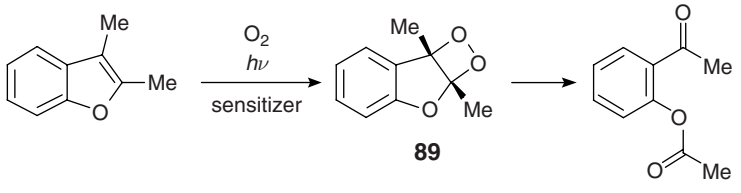


(77)

3.06.2.2.2 Reactions with oxidants

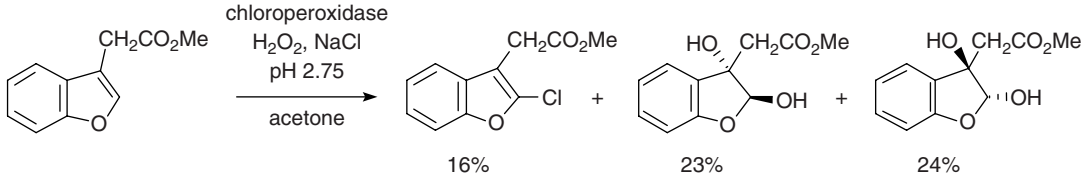
In contrast to furan, because of its large resonance energy, the benzene ring of benzo[*b*]furan **82** is dominant to such an extent that [4+2] cycloadditions of the furan ring are not possible. On the other hand, photochemical [2+2] cycloaddition occurs readily on the C-2/C-3 double bond.

For example, photooxygenation of 2,3-dimethylbenzo[b]furan at −78 °C produced dioxetane **89**, which isomerized at room temperature to give 2-acetoxyacetophenone (as shown in **Scheme 49**) <1995ACR289>.



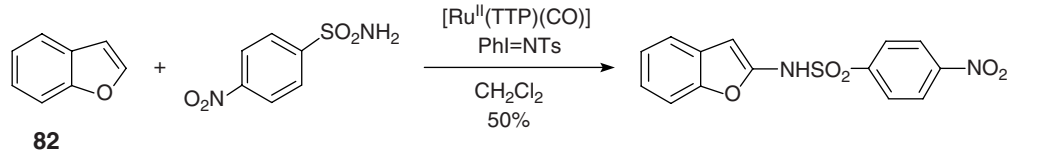
Scheme 49

3-Alkylbenzo[*b*]furans were oxidized by chloroperoxidase from *Caldariomyces fumago* to their *trans*-2,3-diols as major products, and these were all fully characterized because of their stability (Equation 78) <2001T8581>.



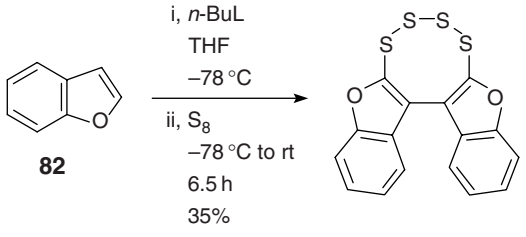
(78)

The ruthenium(II) porphyrin-catalyzed amidation of benzo[*b*]furan **82** was reported for the first time to make 2-*N*-nosylamide in 50% yield under mild conditions, as can be seen in Equation (79) <2004OL2405>.



(79)

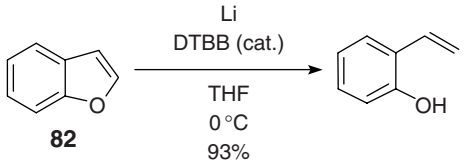
The structurally interesting bis(benzo[4,5]-furo)[2,3-*e*:3′,2′-*g*][1,2,3,4]tetrathiocine was obtained by an oxidative coupling reaction of 2-lithiated benzo[*b*]furan with elemental sulfur (Equation 80) <2002JOC6220>.



(80)

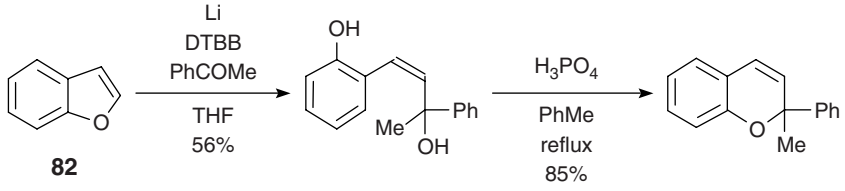
3.06.2.2.3 Reactions with reductants

At 0 °C, the reduction of benzo[*b*]furan **82** with lithium in the presence of a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 5 mol%) in THF was observed to give 2-vinylphenol in high yield, as illustrated in Equation (81) <2002T4907>.



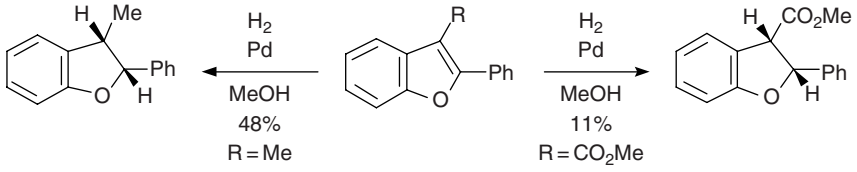
(81)

Another regioselectively reductive ring-opening of benzo[*b*]furan **82** was also utilized to afford the active vinyllithium species in the presence of a catalytic amount of DTBB (5 mol%) in THF at 0 °C, and the formed vinyllithium was able to further react with electrophiles (such as *t*-BuCHO, PhCHO, $Ph(CH_2)_2CHO$, Me_2CO, *n*-PrCOMe, PhCOMe, $(CH_2)_4CO$) at –78 °C to give their corresponding (*Z*)-products. Further reaction of the diols led to substituted 2*H*-chromenes under acid-catalyzed cyclization, as depicted in **Scheme 50** <2001EJO2809>.



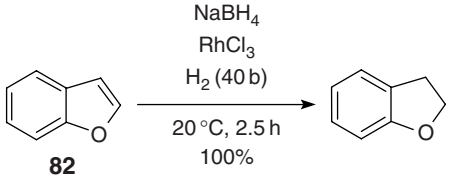
Scheme 50

3-Substituted-2-phenylbenzo[*b*]furans were able to undergo a palladium-catalyzed hydrogenation reaction to give their corresponding 2,3-dihydrobenzo[*b*]furans, but the yields are quite low (**Scheme 51**) <2002T4261>.



Scheme 51

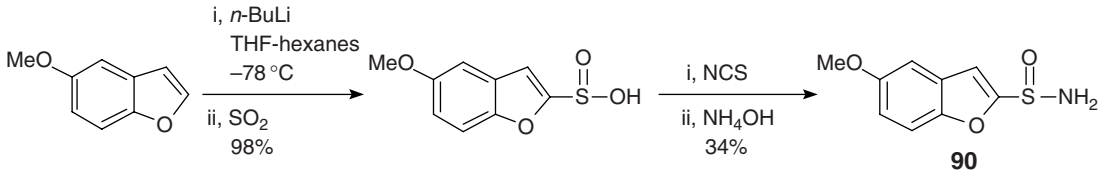
The surfactant-stabilized aqueous colloidal rhodium(0) was used to hydrogenate unsubstituted nitrogen-, oxygen-, or sulfur-derived heterocycles (such as benzo[*b*]furan **82**) in quantitative yield, as can be seen in Equation (82) <2004ICA3099>.



(82)

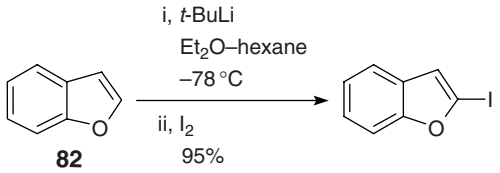
3.06.2.2.4 Reactions as nuclear anion equivalents

2-Metallated benzo[*b*]furans play a very important role as nucleophiles in the quest for structurally diverse 2-substituted benzo[*b*]furans. For example, benzo[*b*]furan-2-sulfonamide **90** was synthesized by sequential reactions of a benzo[*b*]furan with *n*-BuLi/SO_2, *N*-chlorosuccinimide (NCS), and NH_4OH (**Scheme 52**) <1990JME749>.



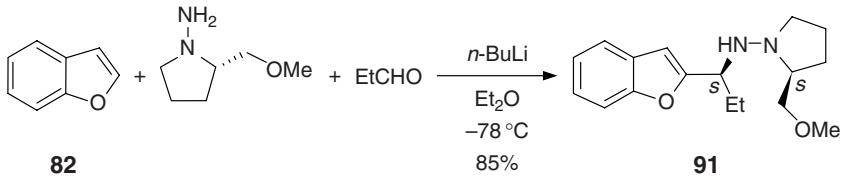
Scheme 52

As shown in Equation (83), 2-iodobenzo[*b*]furan was also prepared by reaction of benzo[*b*]furan **82** with *tert*-butyllithium in ether at –78 °C, followed by reaction with iodine <2002JOC7048>.



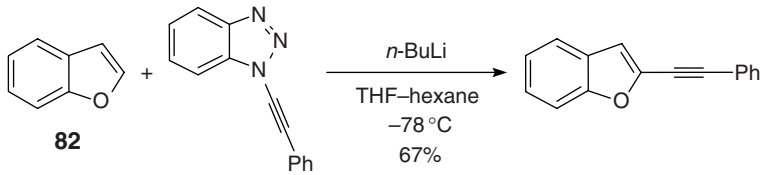
(83)

An efficient approach for asymmetric syntheses of benzo[*b*]furan-1-alkylamines was developed by reaction of 2-lithiated benzo[*b*]furan with aldehyde–SAMP-derived hydrazones (SAMP = (*S*)-(−)-1-amino-2-methoxymethyl-pyrollidine; Equation 84). In this way, an efficient synthesis of hydrazine **91** was achieved <2004TA747>.



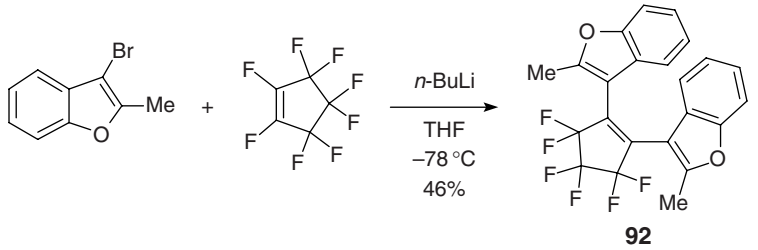
(84)

A phenylacetylene-substituted benzo[*b*]furan was prepared by reaction of 2-lithiated benzo[*b*]furan with 1-(phenylethynyl)-1*H*-1,2,3-benzotriazole (Equation 85) <2002JOC7526>.



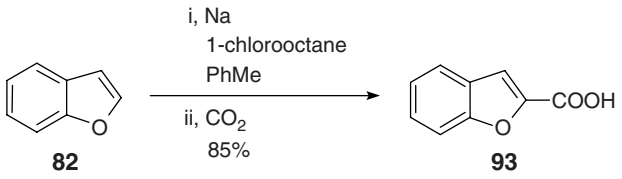
(85)

The synthesis of a novel compound 1,2-bis(2-methylbenzo[*b*]furan-3-yl)-perfluorocyclopentene **92** was realized by reaction of octafluorocyclopentene with 3-lithiated 2-methylbenzo[*b*]furan, which was generated by the treatment of 2-methyl-3-bromobenzo[*b*]furan with *n*-BuLi at −78 °C in THF, as can be seen in Equation (86) <2005JOC10323>.



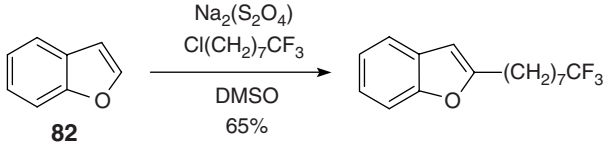
(86)

An initial formation of a sodium salt of benzo[*b*]furan **82** with sodium sand in the presence of 1-chlorooctane gave the 2-sodium salt of benzo[*b*]furan, which with CO_2 gave the carboxylic acid **93** (Equation 87) <2002AGE340>.



(87)

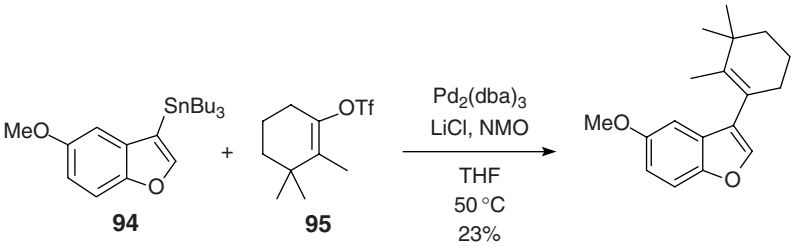
As can be seen in Equation (88), the 2-sodium salt of benzo[*b*]furan could also be formed by treatment of benzo[*b*]furan **82** with sodium dithionite in the presence of fluoroalkyl chlorides in dimethyl sulfoxide (DMSO), leading to the corresponding fluoroalkylated products in moderate yields <2001JFC107>.



(88)

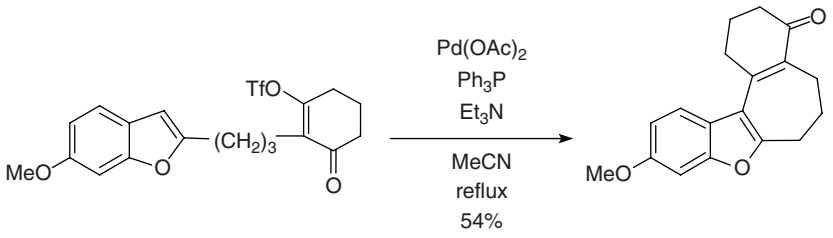
3.06.2.2.5 Reactions catalyzed by metals and metallic derivatives

In the total synthesis of naturally occurring frondosin B, the palladium-catalyzed coupling reaction of C-3 stannylated benzo[*b*]furan **94** with the vinyl triflate **95** was employed as a key step to build up the framework of the final target, as depicted in Equation (89) <2001JA1878>.



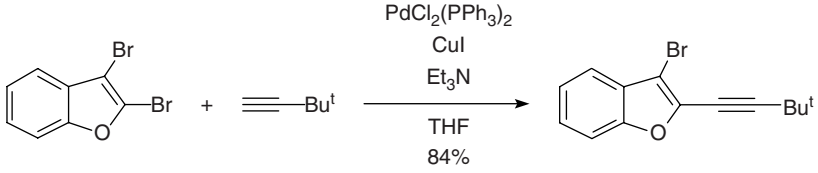
(89)

A palladium-catalyzed cyclization was applied to establish the skeleton of the benzo[*b*]furan derived tetracyclic ring in frondosin B (Equation 90) <2004T9675>.



(90)

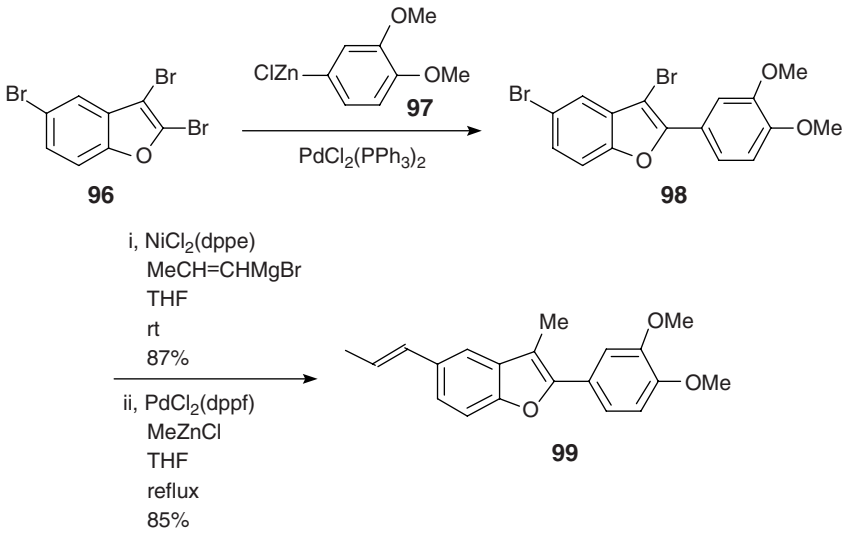
The regioselective coupling reaction of 2,3-dibromobenzo[*b*]furan with several terminal acetylenes was achieved using a palladium-catalyzed Sonogashira reaction, as exemplified in Equation (91) <2003S925>.



(91)

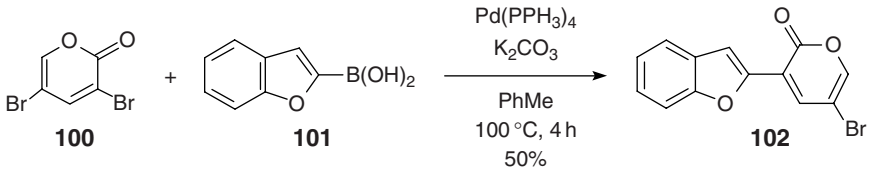
Other regioselective C–C bond formation reactions were also reported by using palladium-catalyzed coupling of 2,3,5-tribromobenzo[*b*]furan **96** as a substrate. Thus, the palladium-catalyzed coupling between tribromide **96** and arylzinc **97** gave a dibromide **98**, which underwent sequential Kumada coupling with a Grignard reagent and a

Negishi coupling with methyl zinc chloride to regioselectively afford a trisubstituted benzo[*b*]furan **99**, as illustrated in **Scheme 53** <2002TL9125>.



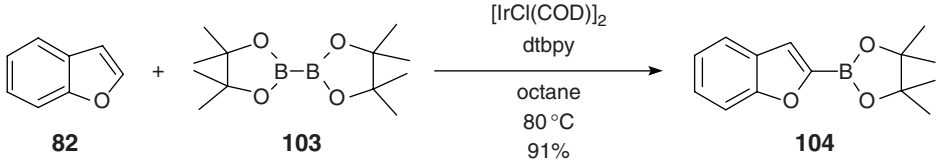
Scheme 53

The palladium-catalyzed Suzuki–Miyaura reaction of 3,5-dibromo-2-pyrone **100** with benzo[*b*]furan-2-boronic acid **101** was applied to the synthesis of 3-(benzo[*b*]furan-2-yl)-5-bromo-pyrone **102** in 50% yield (Equation 92) <2004SL2197>.



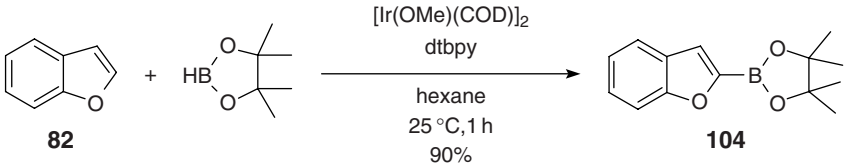
(92)

The C–H coupling of benzo[*b*]furan **82** with bis(pinacolato)diboron **103** was carried out in octane with $[IrCl(COD)]_2$-(4,4′-di-*tert*-butyl-2,2′-bipyridine) as a catalyst (3 mol%), leading to the formation of the 2-borylated product **104**, as can be seen in Equation (93) <2002TL5649>.



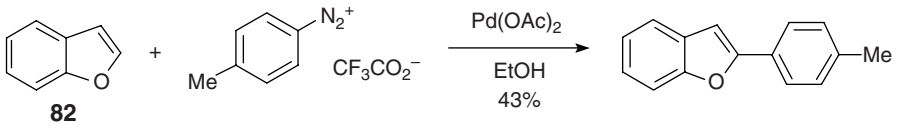
(93)

A highly regioselective borylation of arenes and heteroarenes (such as benzo[*b*]furan **82**) was achieved by the iridium-catalyzed C–H activation reaction, as shown in Equation (94) <2003CC2924>.



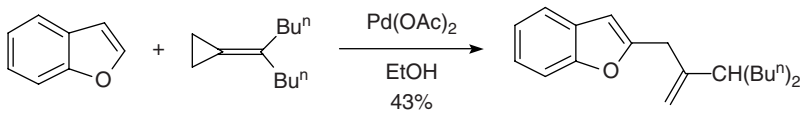
(94)

An additional method to prepare 2-aryl benzo[*b*]furan was realized by the palladium-catalyzed C–H activation of benzo[*b*]furan with aryldiazonium trifluoroacetate (Equation 95) <1999EJO1357>.



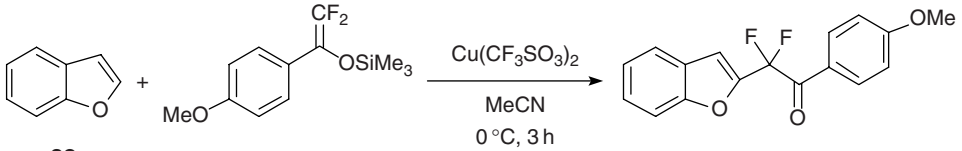
82 (95)

The palladium-catalyzed hydrofuranylation of alkylidenecyclopropane **105** with unfunctionalized benzo[*b*]furan was utilized in the synthesis of a 2-allylbenzo[*b*]furan derivative **106**, as illustrated in Equation (96) <2000JA2661>.



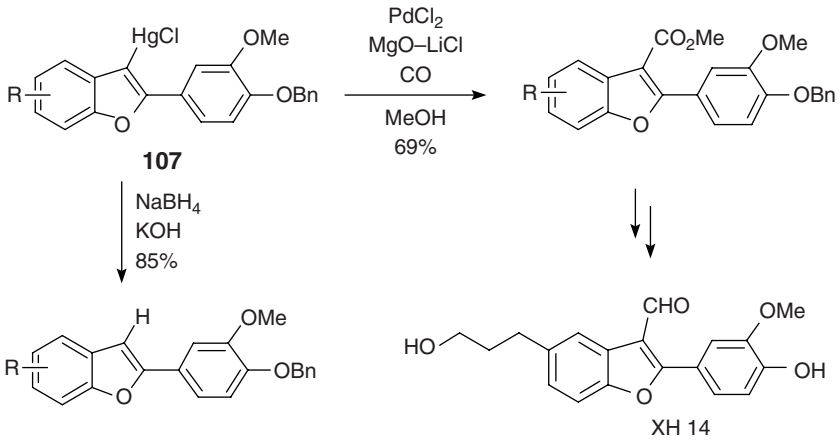
82 **105** **106** (96)

As depicted in Equation (97), oxidative cross-coupling of α-aryl-β,β-difluoroenol silyl ether with unfunctionalized benzo[*b*]furan **82** in the presence of $Cu(OTf)_2$ in wet acetonitrile proceeded smoothly to give benzo[*b*]furan difluoromethyl aryl ketone in 50% yield <2004OL2733>.



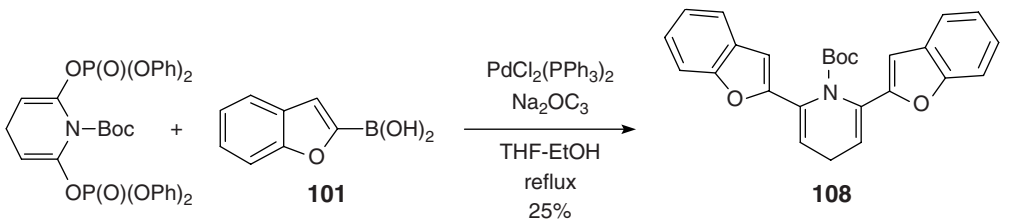
82 (97)

3-Chloromercurio-benzo[*b*]furans **107** were key intermediates for the syntheses of natural product XH14 and its analogs. The synthesis proceeded by the palladium-catalyzed carbonylation reaction as a pivotal step. The 3-chloromercurio-benzo[*b*]furan **107** was also reduced to form its hydride derivative by $NaBH_4$ reduction, as illustrated in **Scheme 54** <2002JOC6772>.



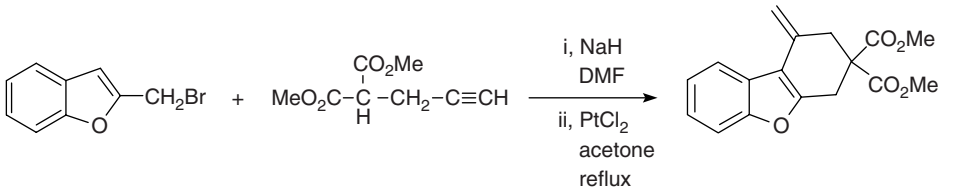
Scheme 54

A C_2-symmetric benzo[*b*]furan-containing heterocycle **108** was constructed by the palladium-catalyzed coupling reaction between the lactam-derived vinyl phosphates and benzo[*b*]furan-2-boronic acid **101** (Equation 98) <2005TL3703>.



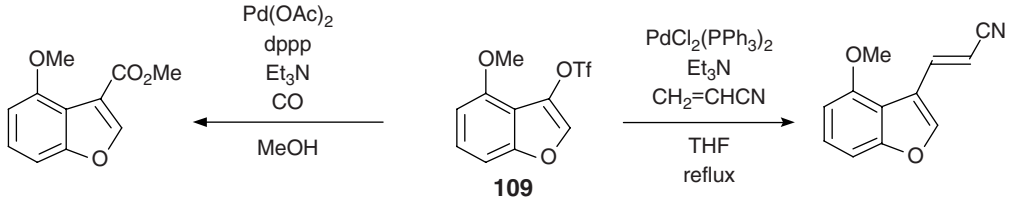
(98)

As can be seen in Equation (99), a platinum-catalyzed intramolecular cyclization was also utilized in the formation of benzo[*b*]furan-based tricycles. A platinum carbene was proposed as an intermediate in this reaction <2003JA5757>.



(99)

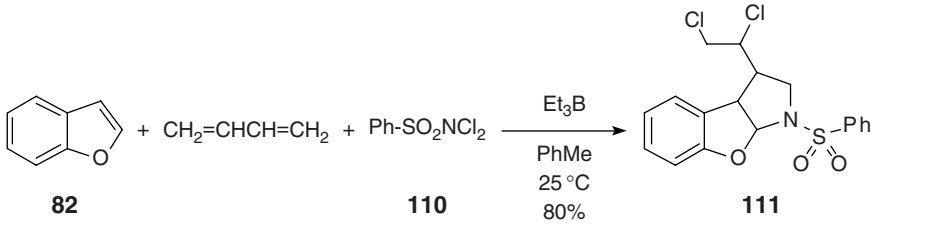
Triflates of 3-benzo[*b*]furans were prepared, and evaluated in the palladium-catalyzed Stille, Heck, Suzuki, and Sonogashira coupling reactions. As can be seen in **Scheme 55**, results demonstrated that benzo[*b*]furan-3-triflate **109** was a good coupling partner in the metal-catalyzed reactions, and good to excellent results were obtained <2002SL501>.



Scheme 55

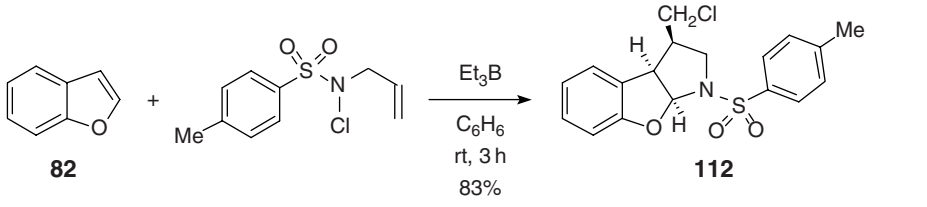
3.06.2.2.6 Reaction involving free radicals

A regioselective addition of *N*,*N*-dichlorobenzenesulfonamide (dichloramine-B) **110** to benzo[*b*]furan **82** was achieved to make a pyrrolidine-derived tricyclic compound **111** at room temperature in good yield. Triethylborane was selected as a radical initiator in this reaction (Equation 100) <2003JOC3248>.



(100)

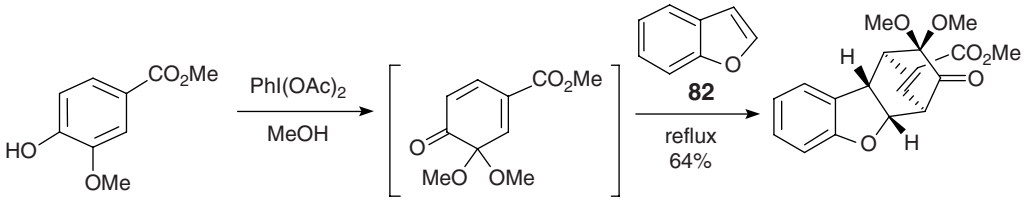
Under similar conditions, a radical-initiated [3+2] cycloaddition of N-centered radical with benzo[*b*]furan **82** was examined. A benzo[*b*]furan-derived pyrrolidine **112** was obtained in good yield with again Et_3B as a radical initiator (as depicted in Equation 101) <2001OL2709>.



(101)

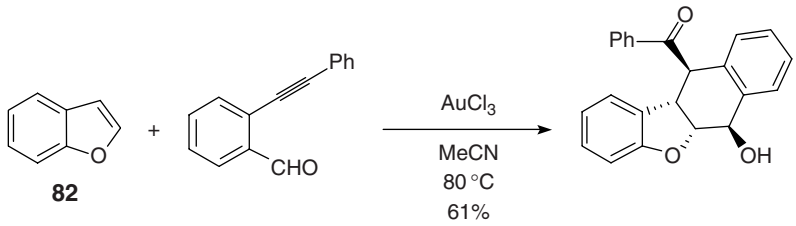
3.06.2.2.7 Cycloaddition reactions

Benzo[*b*]furan **82** is a very important building block in materials science and drug discovery. Because it is electronically rich at C-2 and C-3, many important synthetic transformations occur at these two positions. For example, *o*-benzoquinones oxidatively generated from the corresponding substituted 2-methoxyphenols reacted with benzo[*b*]furan **82** to form polycyclic molecules, as depicted in **Scheme 56** <1999JA13254>.



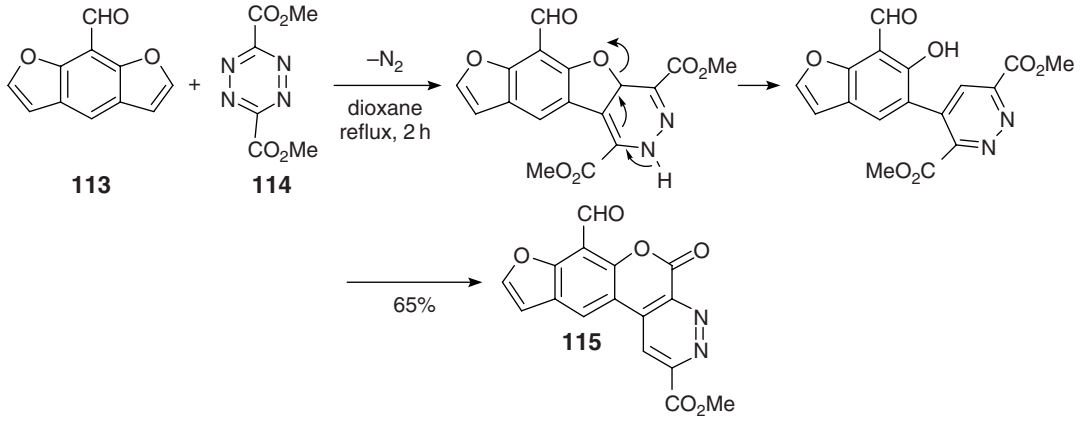
Scheme 56

A domino process for the construction of a tetracyclic ring was achieved by the gold-catalyzed formation of an isobenzopyrylium derived from a phenylacetylene-based benzaldehyde. This was followed by reaction with electron-rich benzo[*b*]furan as a dienophile in a Diels–Alder reaction with inverse electron demand (Equation 102) <2003AGE4399>.



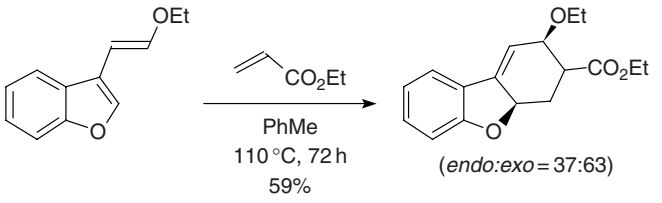
(102)

The reaction of benzodifuran **113** with 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine **114** proved to be an efficient way to make pyridazino–psoralen-based aromatic polycycles such as **115** through a reaction sequence illustrated in **Scheme 57** <2005T4805>.



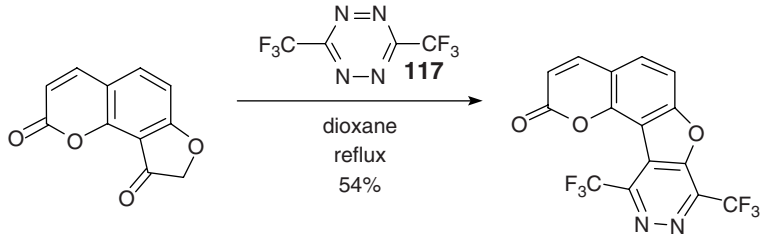
Scheme 57

3-Vinylbenzo[*b*]furans, 3-vinylfuropyridines, and 3-vinylindoles were employed as conjugated dienes in the Diels–Alder reaction with ethyl acrylate, affording tricyclic adducts in fair to good yields, as shown in Equation (103) <2002OL2791>.



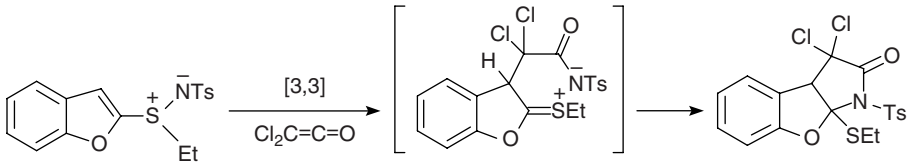
(103)

The enol form of dihydrofuro[2,3-*h*]coumarin-9-one **116** was also employed as a dienophile in the Diels–Alder reaction with 3,6-bis(trifluoromethyl)1,2,4,5-tetrazine **117** to afford the desired tetracyclic product **118** in 54% yield (Equation 104) <2002S43>.



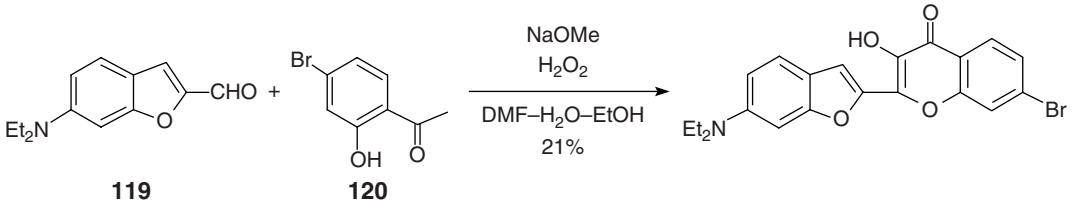
(104)

As can be seen in **Scheme 58**, a new synthesis of γ-lactams was also achieved by reaction of benzo[*b*]furan-derived vinyl sulfilimines with dichloroketene, a reaction which proceeded through a [3,3] sigmatropic rearrangement <2005OL839>.



Scheme 58

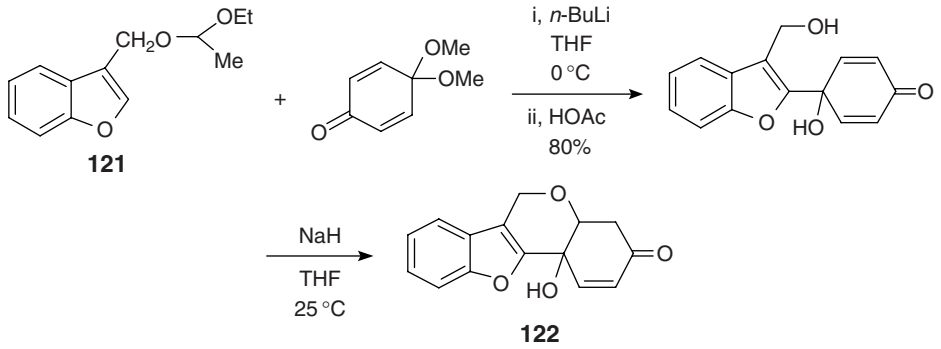
As illustrated in Equation (105), 6-(diethylamino)benzo[*b*]furan-2-carbaldehyde **119** reacted with 4′-bromo-2′-hydroxyacetophenone **120** in dry dimethyl formamide (DMF) in the presence of an excess of sodium methoxide to afford a heterodimer of benzo[*b*]furan and flavone <2004TL8391>.



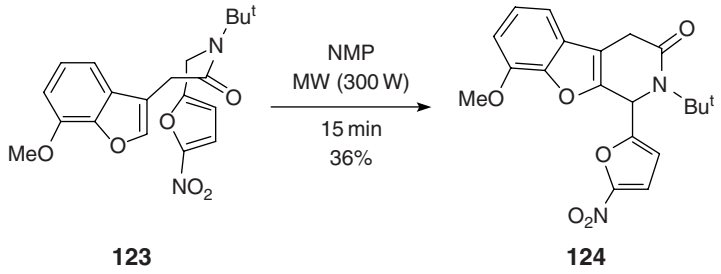
(105)

A regioselective lithiation was achieved by treatment of 3-substituted benzo[*b*]furan **121** with *n*-BuLi at 0 °C in THF, and the 2-lithiated benzo[*b*]furan so generated was allowed to couple with quinone monoketal followed by a regioselective cyclization to give kushecarpin A's analog **122** (**Scheme 59**) <2005TL7511>.

Under microwave conditions, 5-nitro-substituted furfuryl amide **123** underwent an unusual isomerization–cyclization reaction pathway to give 1,4-dihydro-2*H*-benzo[4,5]-furo[2,3-c]pyridine-3-one **124** (Equation 106) <2003OL3337>.

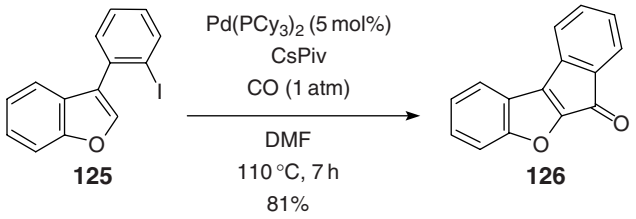


Scheme 59



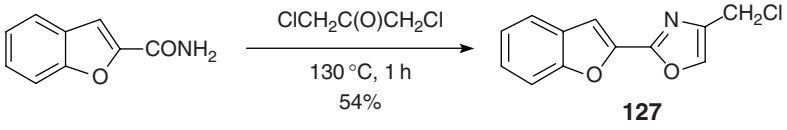
(106)

The palladium-catalyzed carbonylative annulation of 3-(2-iodophenyl)-benzo[*b*]furan **125** provided benzo[*b*]-indeno[1,2-*d*]furan-6-one **126** in 81% yield, as can be seen in Equation (107) <2002JOC5616>.



(107)

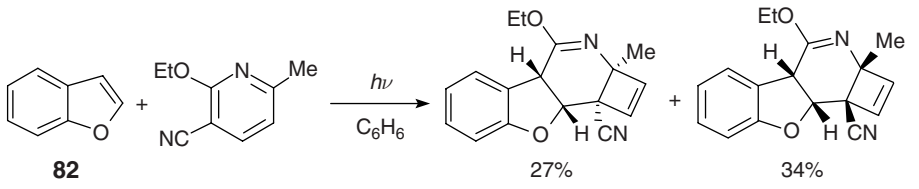
2-Benzo[*b*]furyl-4-chloromethyl-1,3-oxazole **127**, an important intermediate for the synthesis of potent and highly selective D3 receptor ligands, was realized by a direct condensation of benzo[*b*]furan-2-carbamide and 1,3-dichloropropan-2-one (Equation 108) <2003JME3822>.



(108)

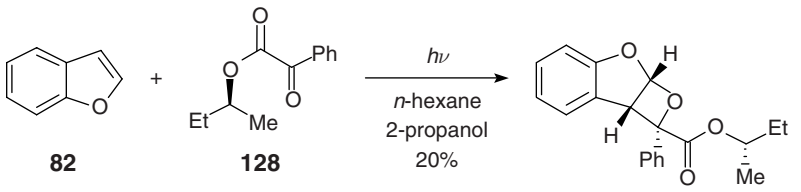
3.06.2.2.8 Photochemical reactions

As shown in Equation (109), irradiation of a benzene solution containing 3-cyano-2-ethoxypyridine (0.02 M) and benzo[*b*]furan **82** (0.5 M) resulted in the formation of two tetracyclic stereoisomeric adducts <2000CC1201>.



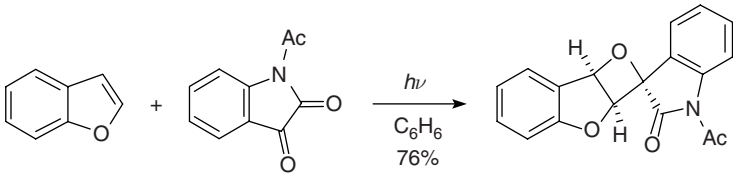
82 (109)

The diastereoselective Paternò–Büchi reaction of benzoin **128** with benzo[*b*]furan **82** was utilized to stereoselectively construct a [6-5-4] tricyclic heterocycle **129** (Equation 110). The observed diastereoselective excess was also explained <2004TL3877>.



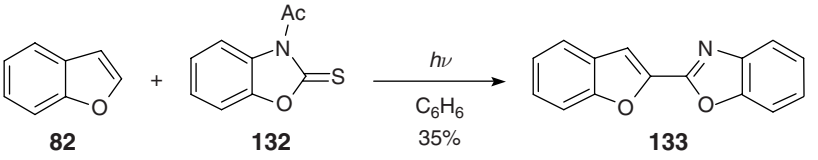
82 **128** **129** 58% de (110)

The photoinduced Paternò–Büchi reaction of 1-acetylisatin **130** with benzo[*b*]furan **82** was employed to make a structurally interesting spiro-type molecule **131** in good yield, as depicted in Equation (111) <2002J(P1)345>.



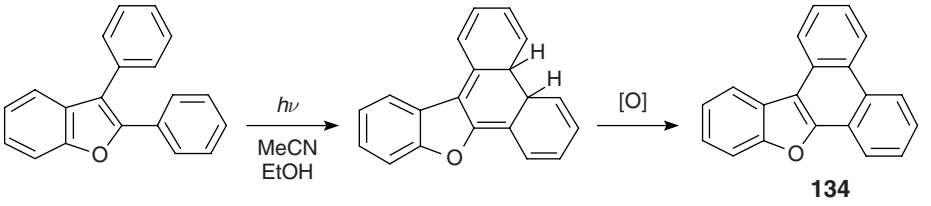
82 **130** **131** (111)

As shown in Equation (112), the photolytic reaction of benzoxazole-2-thione **132** with unsubstituted benzo[*b*]furan **82** was utilized to make 2-benzofuryl-benzoxazole **133**, but the yield is relatively low <2003HCA3255>.



82 **132** **133** (112)

A novel tandem photolysis was observed for the synthetic conversion of 2,3-diphenylbenzo[*b*]furan to benzo[*b*]-phenanthro[9,10-*d*]furan **134**. This process might involve sequential photochemical cyclization and aerial oxidation (**Scheme 60**) <2003TL3151>.



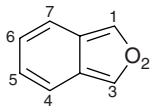
134

Scheme 60

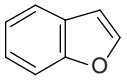
3.06.2.3 Reactivity of Fully Conjugated Benzo[*c*]furans

A review article summarizing various aspects of the chemistry of benzo[*c*]furans (isobenzofurans) bridging the gap between these theoretically interesting but usually fugitive molecules and natural products was published <B-1998MI1>. Another review deals with the recent advances in the chemistry of these molecules <1999AHC1>. The main reactions of benzo[*c*]furans are cycloaddition reactions, which are summarized in Section 3.06.2.3.1.

AM1 <1998JMT165>, FMO <1997T13285>, and DFT <2000J(P2)1767, 2004JMM87> computational studies concerning Diels–Alder reactions of benzo[*c*]furans, as well as their addition reactions with azulene-1,5-quinones and azulene-1,7-quinones <1999J(P1)2129>, have all been reported. The Bird's aromaticity indexes (BAIs) of benzofurans have been reevaluated by Schleyer making use of Becke3LYP/6-311+G** geometries, and the results obtained show that the aromaticity of benzo[*c*]furan **135** is greater than that of benzo[*b*]furan **82** <1996AGE2638>. Moreover, Schleyer also discovered that the computed ^{1}H NMR chemical shifts (GIAO-HF/6-31+G*//Becke3LYP/6-311+G**) of **135** corresponded closely to those for furan and benzene, suggesting that **135** retains significant aromaticity.

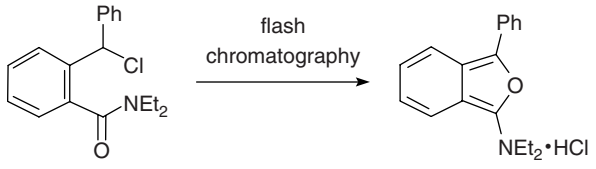


135



82

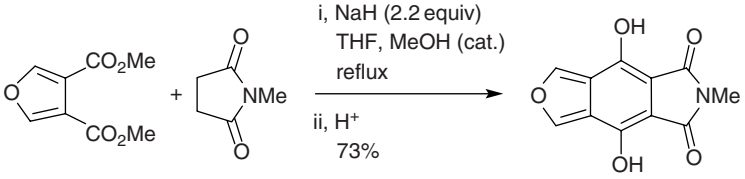
Although many research articles state that **135** and its derivatives are rather reactive and as a result are difficult to be isolated at room temperature unless electron-withdrawing or bulky groups are substituted at the C-1 or C-3 position, there are reports concerning the isolation of stable derivatives of **135**. For example, as shown in Equation (113), attempts to purify **136** by flash chromatography led to the formation of 1-(diethylamino)-3-phenylbenzo[*c*]-furan hydrochloride **137** in a yield as high as 81% <1997JME2936>.



(113)

136 **137**

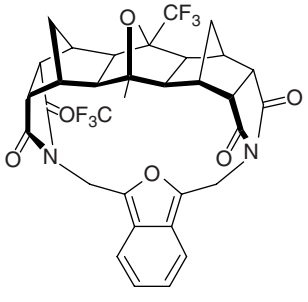
Other intriguing observations were the identification of relatively stable 1-*t*-butyldimethylsilyl-4-methylbenzo[*c*]furan <1996JA10766>, and the preparation of the stable benzo[*c*]furan derivative **138** starting from dimethyl 3,4-furandicarboxylate and *N*-methyl succinimide via a base-promoted condensation reaction, as can be seen in Equation (114) <1996S1180>.



(114)

138

A novel crystalline benzo[*c*]furan **139** was also reported by Warrener, in which the 1,3-positions are linked with an alicyclophane <2001CC1550>.

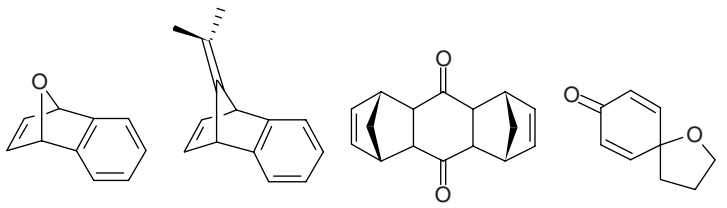


139

In addition to being a very reactive Diels–Alder diene, 1,3,4,5,6,7-hexaphenylbenzo[*c*]furan was reported to be highly fluorescent in toluene solution, as well as in its solid state. This benzo[*c*]furan may therefore be used as electron transport material in an organic light-emitting diode <2002SM247>.

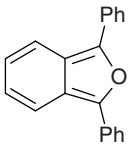
3.06.2.3.1 Cycloaddition reactions

Although being itself rather elusive, freshly generated **135** has been used time and again in trapping reactions. For example, its Diels–Alder cycloaddition with dienophiles such as quinone <1999AJC1123> and DMAD <2002SL1868, 2002OL3355> led to the formation of cycloaddition adducts. Benzo[*c*]furan **135** was also used to trap dienophiles **140** <2000J(P1)195>, **141** <2001SC1167>, **142** <2003CEJ2068>, and **143** <2003OL2639>.



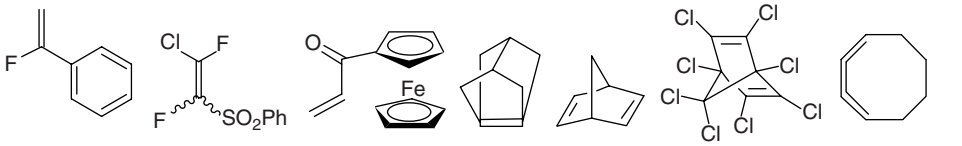
140 **141** **142** **143**

Several reviews summarized the use of benzo[*c*]furan derivatives in trapping reactions <1996BCJ1149, 1997SL145, 1998CC1417>. The most popular benzo[*c*]furan derivative used in trapping reactions must be the 1,3-diphenyl derivative **144**, which is commercially available and is a crystalline compound.

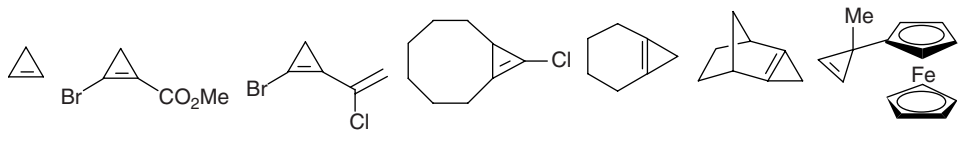


144

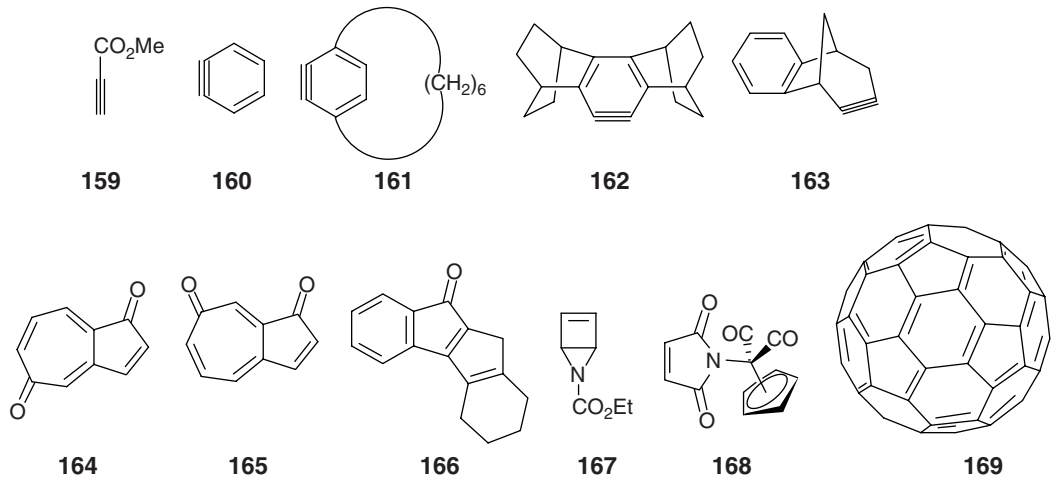
There is a plethora of reactive and/or unstable dienophiles **145** <1996TL7251, 2001J(P1)1929>, **146** <1998TL6529>, **147** <1996JOC3392, 1998T9175>, **148** <1996TL8605>, **149** <1997SL44>, **150** <1996J(P2)1233>, **151** <1996TL4907>, **152** <1996JOC6462>, **153** <1996T3409>, **154** <1996T10955>, **155** <1996JCCS297>, **156** <1996JOC764>, **157** <1997JOC3355>, **158** <1998JOM1>, **159** <2004JOC7220>, **160** <2000TL6611>, **161** <1997BCJ1935>, **162** <1997TL4125>, **163** <2001JOC3806>, **164**, **165** <1996H(43)527, 1998BCJ711>, **166** <1997JOC1642>, **167** <1996CC1519>, **168** <1997JOM41>, and **169** <1998JCD755> that were successfully trapped by **144**.



145 **146** **147** **148** **149** **150** **151**



152 **153** **154** **155** **156** **157** **158**

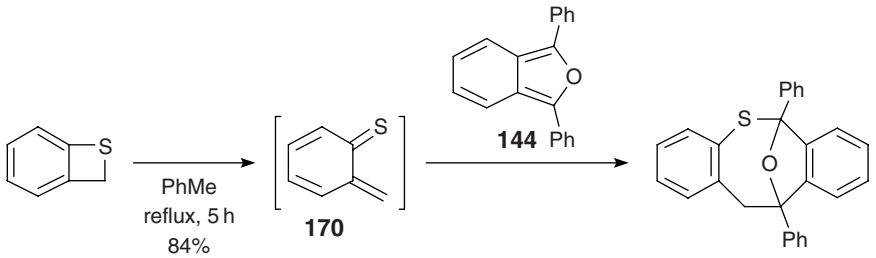


159 **160** **161** **162** **163**

164 **165** **166** **167** **168** **169**

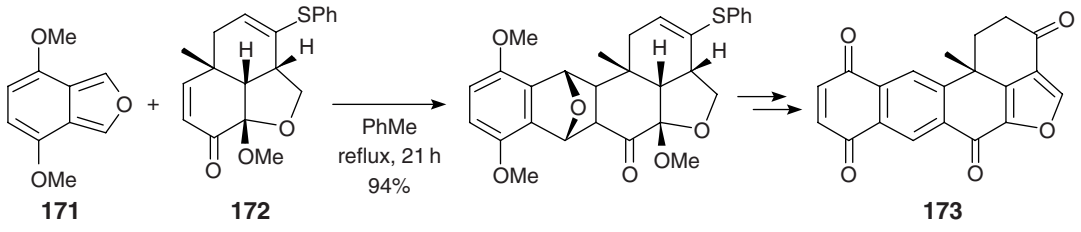
Diels–Alder cycloaddition of **144** and its derivatives with singlet oxygen, leading eventually to the formation of 1,2-dibenzoylbenzenes, has been employed to determine the presence of singlet oxygen <1996NJC571, 1996JPH49, 1997JPPA273, 1997JA5286, 1997OM4386>.

An [8π+8π] cycloaddition was observed for **144** and *o*-thiobenzoquinonemethide **170**, as shown in **Scheme 61** <1996JHC1727>.



Scheme 61

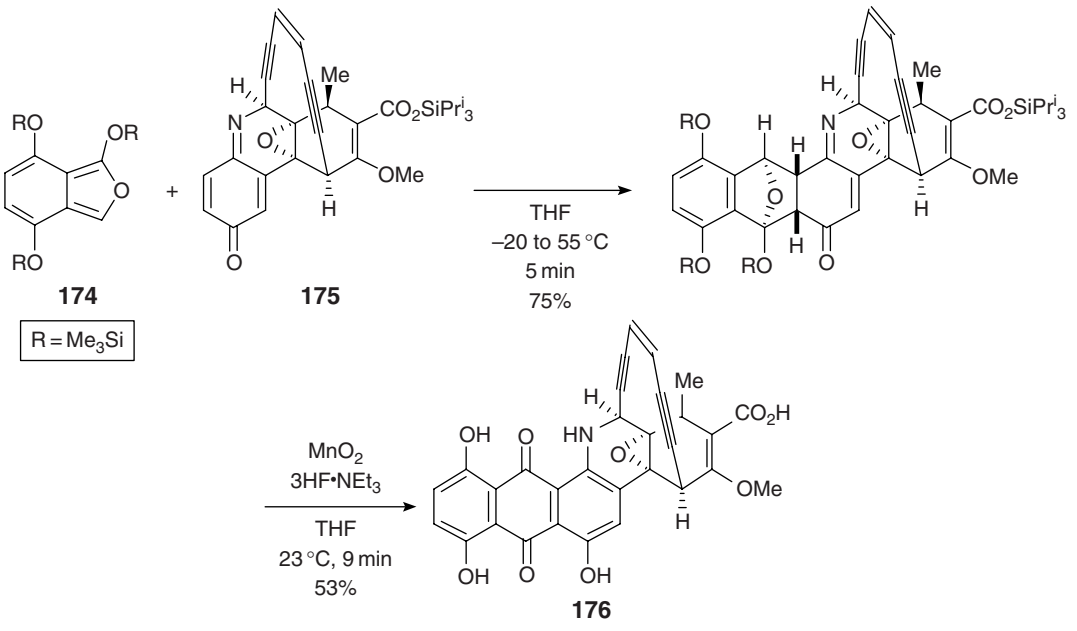
Substituted benzo[*c*]furans played a very important role in the quest for natural as well as non-natural molecules. The schemes depicted here are examples showing the use of substituted benzo[*c*]furans in the synthesis of complex molecules. A short synthesis of (±)-halenaquinone **173** was reported <2001JOC3639>, in which the pivotal step was the Diels–Alder cycloaddition of 4,7-dimethoxybenzo[*c*]furan **171** to **172**, as illustrated in **Scheme 62**. In a similar manner, the total synthesis of (±)-xestoquinone, (±)-9-methoxyxestoquinone, (±)-10-methoxyxestoquinone <2001T309>, and the naphtho[2,3-*h*]quinoline portion of dynemicin A <1997JA5591> was also achieved.



171 **172** **173**

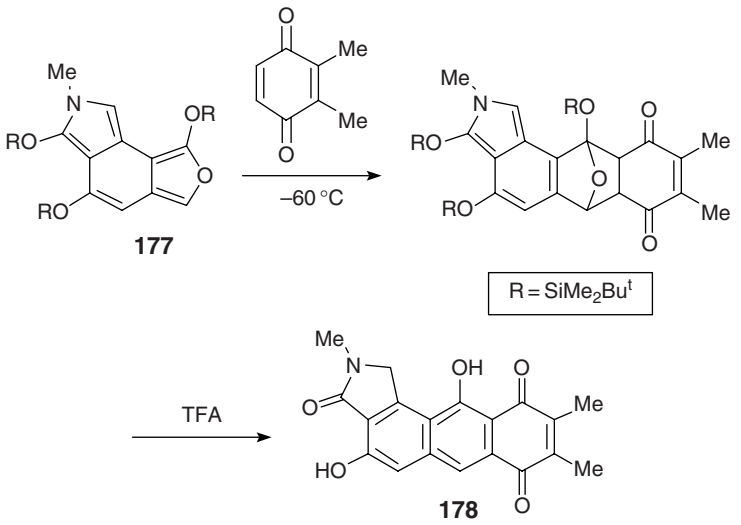
Scheme 62

Diels–Alder cycloaddition between 1,4,7-tris(trimethylsilyloxy)benzo[*c*]furan **174** and the dienophile **175** was also the key step in the total synthesis of (+)-dynemicin A **176** reported by Myers <1997JA6072>, as can be seen in **Scheme 63**.



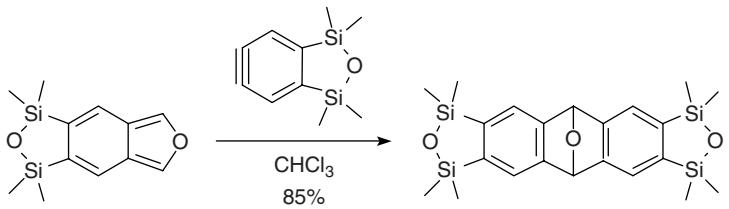
Scheme 63

Kelly reported a short synthesis of the CDEF fragment of lactonamycin **178** in eight steps. As can be seen in **Scheme 64**, the Diels–Alder reaction between the tricyclic **177** and 2,3-dimethylbenzoquinone was used for construction of the tetracyclic skeleton <2002OL1527>.

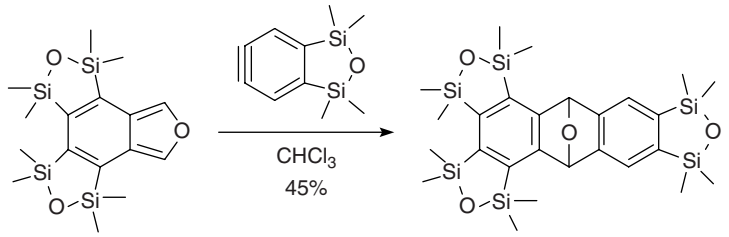


Scheme 64

Two novel mono- and bisoxadisilole-fused benzo[*c*]furans were prepared and isolated. They were shown to undergo facile Diels–Alder cycloaddition reactions with dienophiles such as the oxadisilole-fused benzyne, as illustrated in Equations (115) and (116), to form acene precursors <2006JOC3512>.

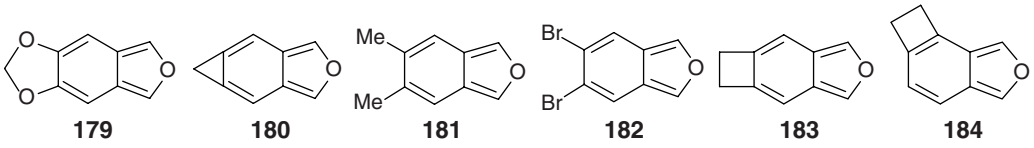


(115)

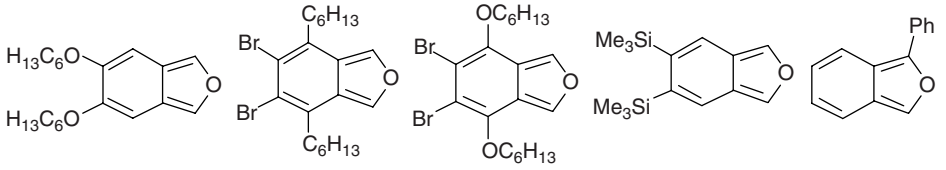


(116)

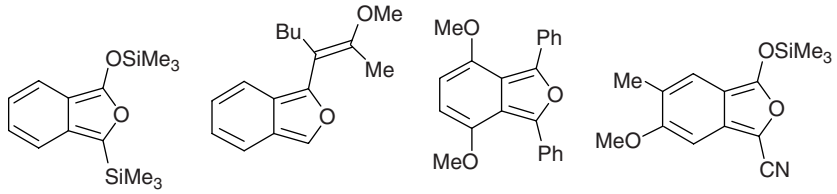
Many benzo[*c*]furan derivatives have been prepared and their intermolecular Diels–Alder cycloaddition reactions led to many intriguing structures. These benzo[*c*]furans are: **179** <1996JA9426, 1996TA1577>, **180–184** <1996AJC1263, 1997T3975>, **185–187** <1997LA663>, **188** <2000TL5957, 2002T9413>, **189** <2000OL923, 2001JOC3797>, **190** <2000IJB738>, **191** <2000OL1267>, **192** <1996TL6089>, **193** <1996TL6797>, **194** <1996TL5963>, **195** <1996JOC3706>, **196** <1996JOC6166>, **197**, **198** <1996JOC3706>, **199–201** <1997JOC2786, 1997S1353>, **202** <1997SL47>, **203** <2004OM4121>, **204** <1996JA741, 1997AGE1531>, **205** <1998EJO99>, **206** <1996S77>, **207** <2001TL789>, and **208** <1996TL8845, 2003JOC8373, 2003JA2974>.



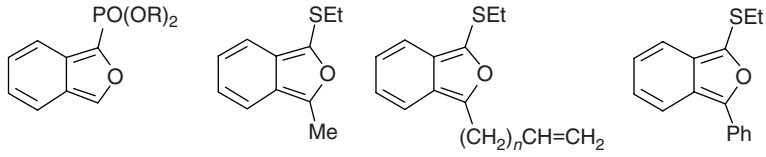
179 **180** **181** **182** **183** **184**



185 **186** **187** **188** **189**



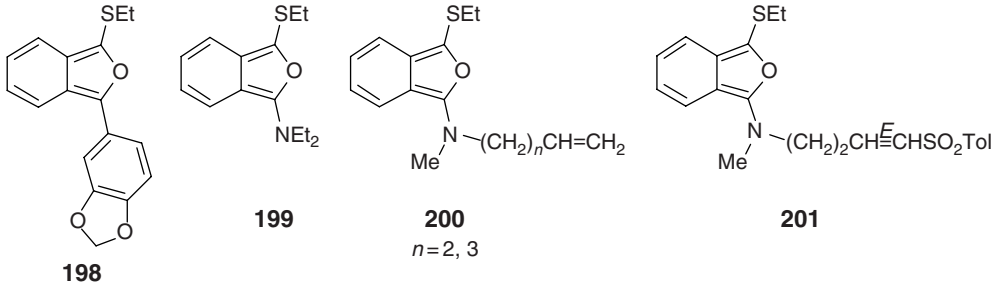
190 **191** **192** **193**

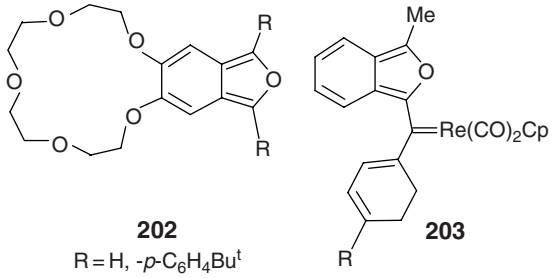


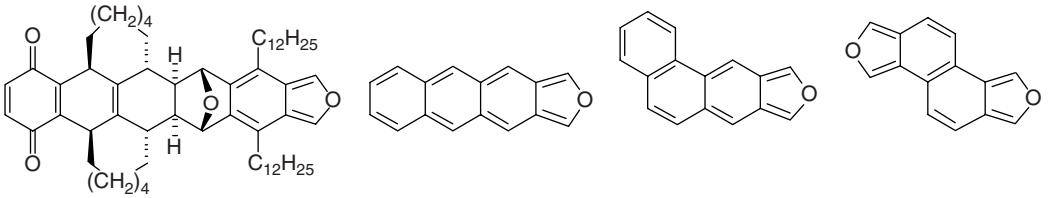
194 **195** **196** **197**

R = Me, Et, *n*-Pr, *i*-Pr

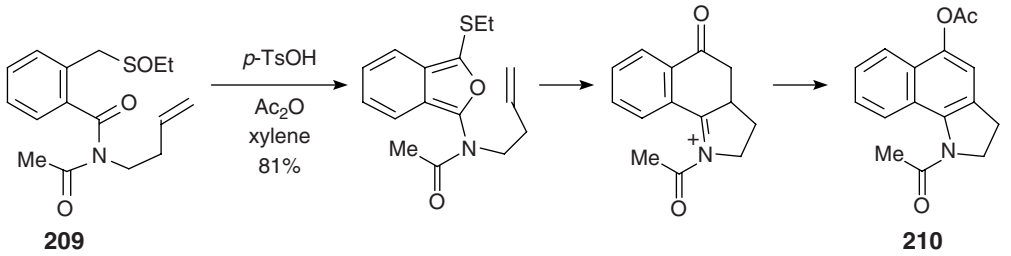
n = 3, 4





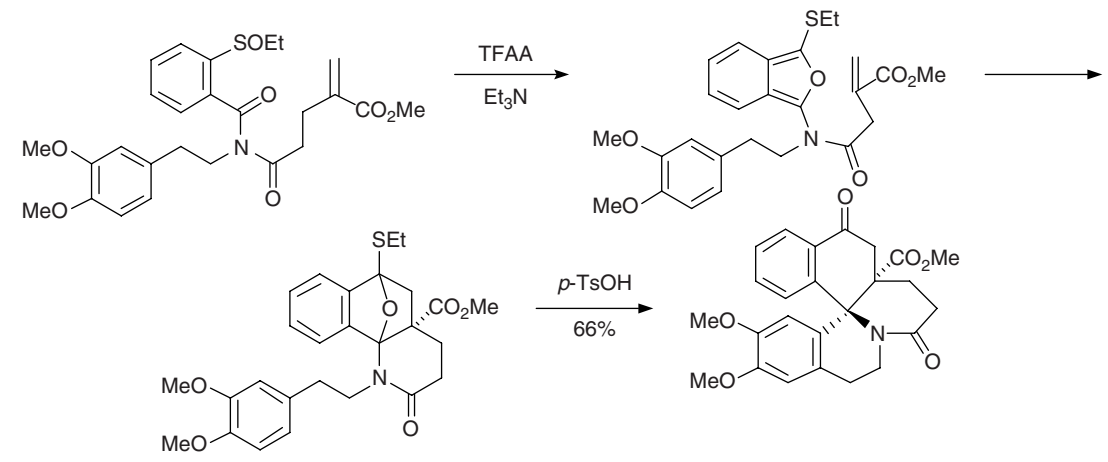


Intramolecular Diels–Alder reactions involving *in situ* generation of benzo[*c*]furan species have also been a viable method in the construction of polycyclic molecules. As can be seen in **Scheme 65**, a nitrogen-containing heterocycle **210** was obtained via a sequence of Pummerer reaction and Diels–Alder cycloaddition, starting from the enesulfoxide **209**, presumably via a benzo[*c*]furan intermediate <1997JOC2786>. A new entry into the erythrinane skeleton was achieved by employing a similar strategy, as illustrated in **Scheme 66** <1996JOC4888, 1998JOC1144>.

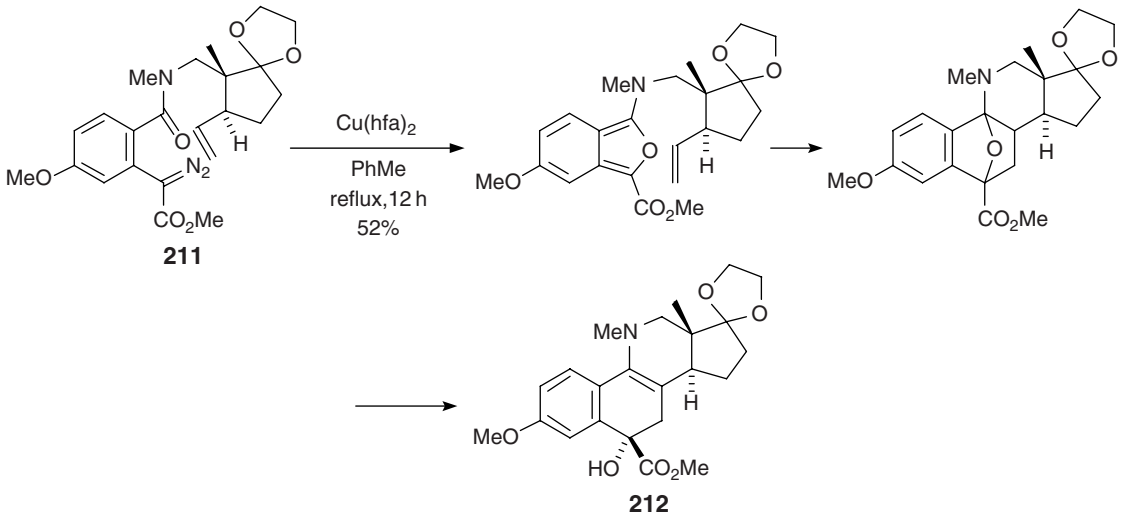


Scheme 65

The Hamaguchi–Ibata methodology was employed in the conversion of dizaoketone **211** to benzo[*h*]quinoline **212** <1999J(P1)59>, as depicted in **Scheme 67**, again via a benzo[*c*]furan. Benzo[*c*]phenanthridines can be obtained in a similar way <1998TL9785>.

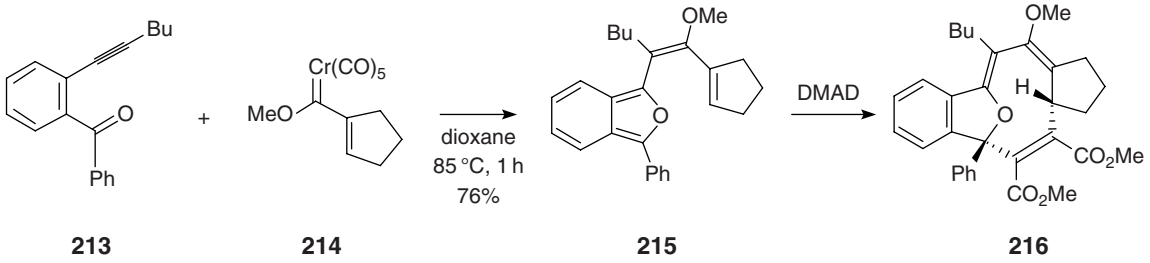


Scheme 66



Scheme 67

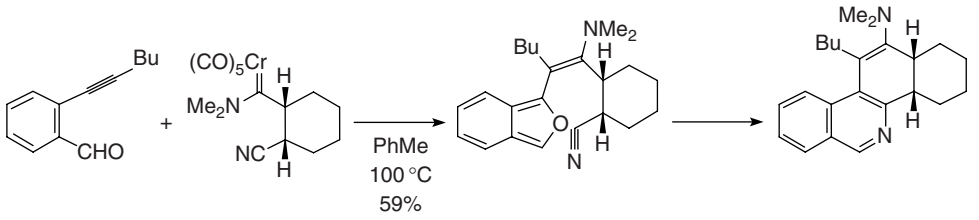
A more structurally intriguing furanophane **216** was obtained by Herndon, who utilized an [8+2] cycloaddition of dienylbenzo[*c*]furan **215** and DMAD (**Scheme 68**). The dienylbenzo[*c*]furan, in turn, was generated from a reaction between alkynylbenzophenone **213** and an alkenyl chromium carbene **214** <2003JA12720>.



213 **214** **215** **216**

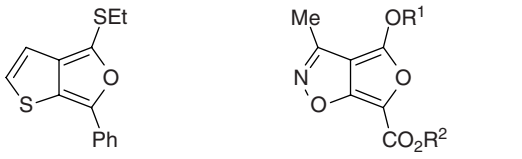
Scheme 68

A similar one-pot synthesis as can be seen in **Scheme 69** led to the formation of isoquinolines after spontaneous deoxygenation <2003OL4261>.



Scheme 69

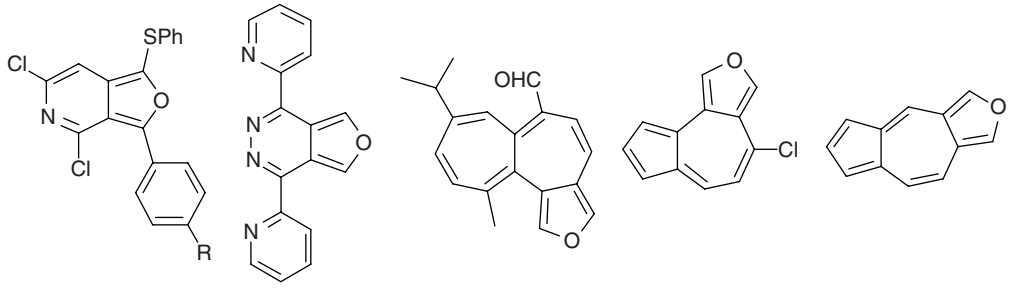
The syntheses of several nonbenzenoid and heterocyclic benzo[*c*]furans were reported in 1996–2005. These heterocycles undergo similar cycloaddition reactions as their benzenoid analogs. These molecules are: **217** <1996JOC6166>, **218** <1996H(43)1165>, **219** <1998H(48)853, 1998JOC7680>, **220** <1999TL397>, **221** <2003JOC6919>, **222** <2003AJC811>, **223** <1997HCA2520, 2005HCA1250>, **224** and **225** <2003OBC2383>.



217 **218** **219** **220**

R^1 = Me, Ph, -$(CH_2)_3C{\equiv}CH$, -$(CH_2)_3C{\equiv}CCO_2Me$
R^2 = Me, -$CH_2C{\equiv}CH$

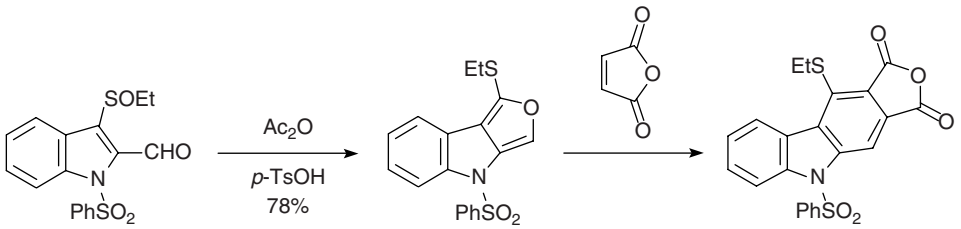
$R^1 = R^2 = R^3 = H$
R^1 = H; $R^2 = R^3$ = Me
R^1 = H; $R^2 = NPr^i_2$; R^3 = H
$R^1 = R^2$ = H; $R^3 = NEt_2$
R^1 = H; $R^2 = CO_2Me$; $R^3 = NEt_2$
R^1 = Cl; $R^2 = CO_2Me$; $R^3 = NEt_2$



221 **222** **223** **224** **225**

R = H
R = Me
R = OMe

An appropriate example to show the reactivity of a nonbenzenoid benzo[*c*]furan is the realization of a fused carbazole **228** from maleic anhydride and benzo[*c*]furan **227**, which was generated from sulfoxide **226** through a Pummerer reaction as shown in **Scheme 70** <1996JOC6166>.

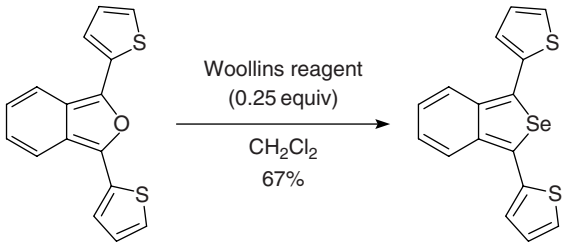


226 **227** **228**

Scheme 70

3.06.2.3.2 Miscellaneous reactions

1,3-Dithienylbenzo[*c*]furan **229** was converted to benzo[*c*]selenophene **230** on interaction with Woollins reagent at room temperature, as can be seen in Equation (117) <2005TL7201>.



229 **230**

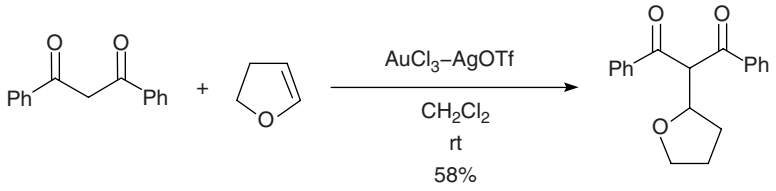
(117)

3.06.3 Rereactivity of Nonconjugated Rings

3.06.3.1 Reactivity of Dihydrofurans and Tetrahydrofurans

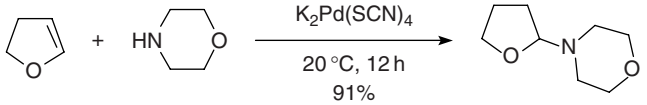
3.06.3.1.1 Reactions of 2,3-dihydrofurans and 2,5-dihydrofurans

As depicted in Equation (118), the regioselective addition of an active methylene compound to 2,3-dihydrofuran was promoted by catalytic amounts of $AuCl_3$–AgOTf, providing a 2-substituted THF as the product <2005OL673>.



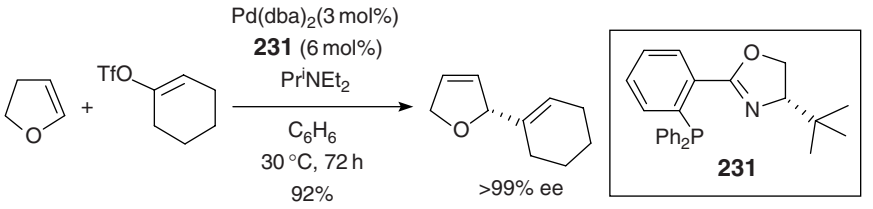
(118)

Palladium-catalyzed regioselective hydroamination of 2,3-dihydrofuran under ligand-free and neutral conditions was found to be general with secondary alkyl amines, as exemplified in Equation (119) <2001T5445>.

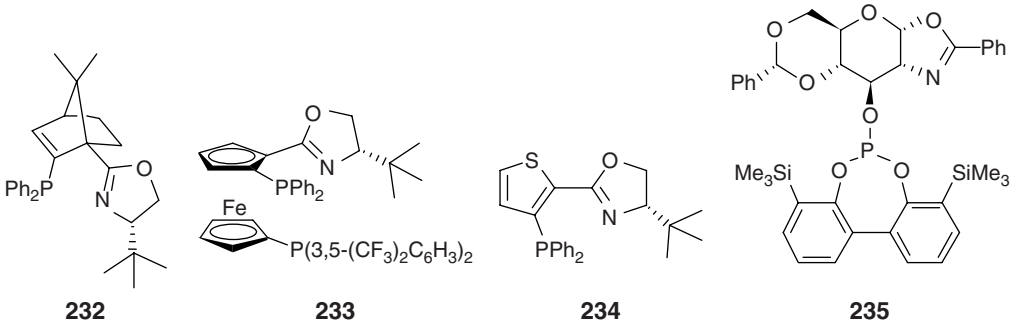


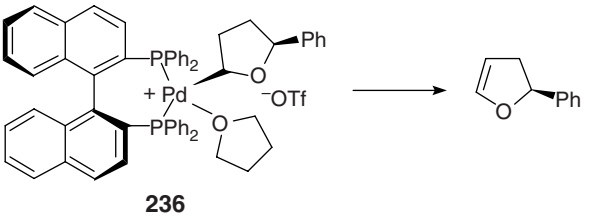
(119)

Palladium-catalyzed enantioselective Heck reaction of 2,3-dihydrofuran to provide 2-substituted-2,5-dihydrofurans was achieved by using the chiral phosphinooxazoline ligand **231**, as shown in Equation (120) <1996AGE200>. Analogous chiral phosphinooxazoline ligands **232** <2001OL161>, **233** <2003CEJ3073>, **234** <2004SL106>, as well as phosphite-oxazoline **235** <2005OL5597> were also effective for this reaction. This Heck coupling, in contrast to that using 2,2-bis(diphenyl-phosphanyl)-1,1-binaphthyl (BINAP) to obtain 2-substituted-2,3-dihydrofuran isomers, was reviewed <1997S1338, 2004S1879>. As indicated in Equation (121), a transient intermediate **236** that was probably formed by a double dyotropic rearrangement of the initial Pd arylation adduct for the BINAP–palladium-catalyzed reaction was characterized spectroscopically at low temperature <2001HCA3043, 1997AGE984>.



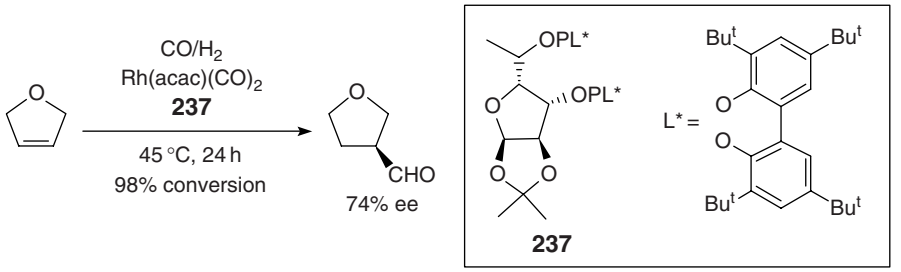
(120)





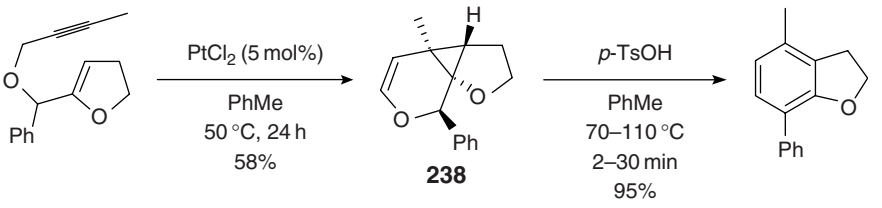
(121)

As represented in Equation (122), a rhodium-catalyzed hydroformylation of 2,3- and 2,5-dihydrofuran using furanoside-derived chiral diphosphite ligands, for example, **237**, provided 3-formyltetrahydrofuran as the major product with ee up to 75% <2005CC1221>.



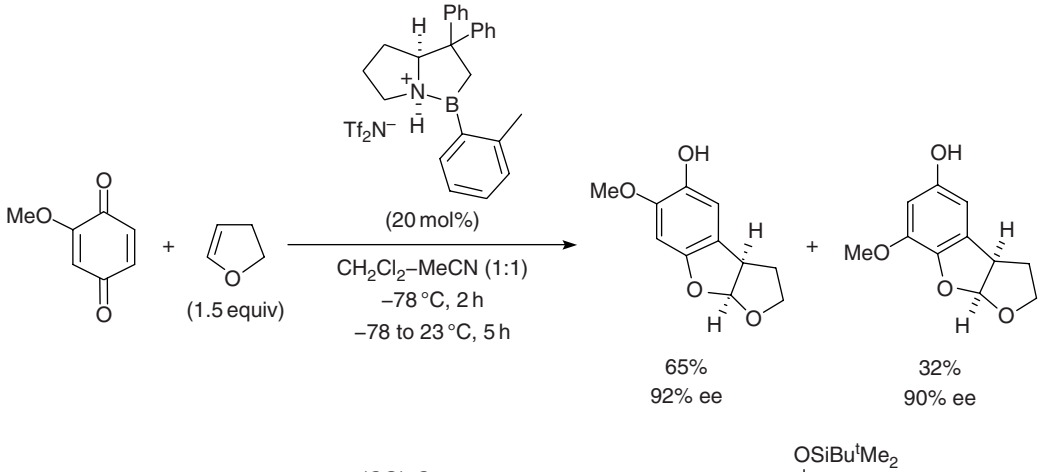
(122)

Platinum-catalyzed cyclization of a 2,3-dihydrofuran to the tethered alkyne provided the fused tricyclic compound **238**, as shown in **Scheme 71**. Acid-promoted benzannulation of **238** then produced the dihydrobenzofuran, presumably via a retro-hetero-Diels–Alder opening of the dihydropyran ring <2004OL3191>.

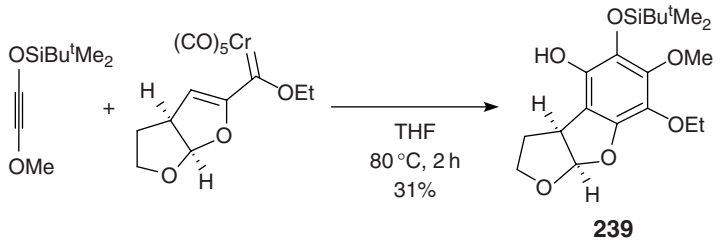


Scheme 71

Enantioselective [3+2] cycloaddition between 2,3-dihydrofuran and 1,4-benzoquinones was performed using the oxazaborolidinium catalyst. As shown in Equation (123), reaction of unsymmetrical 1,4-benzoquinones gave a mixture of two regioisomers. This methodology was applied to a concise total synthesis of aflatoxin B_2 <2005JA11958>. A Dötz benzannulation involving a dihydrofuran containing chromium carbene complex and an alkyne was also employed to form the aflatoxin B_2 skeleton regioselectively <2006TL2299>. As depicted in Equation (124), annulated product **239** was the only regioisomer obtained.



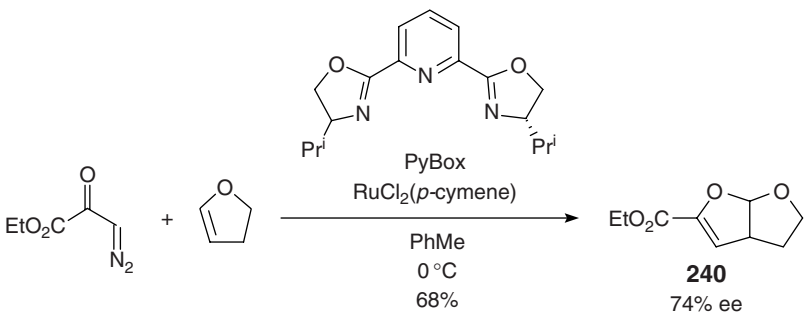
(123)



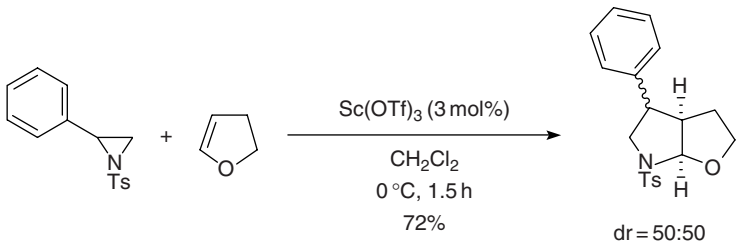
239

(124)

An example of enantioselective 1,3-dipolar cycloaddition of ethyl diazopyruvate to 2,3-dihydrofuran, catalyzed by a chiral ruthenium-PyBox complex, to provide a tetrahydrofurofuran was reported (Equation 125). However, the adduct **240** was only obtained in 74% ee, and its absolute configuration not determined <2004SL2573, 2005HCA1010>. As shown in Equation (126), 2,3-dihydrofuran also participated in 1,3-dipolar cycloaddition with dipoles derived from aziridines under $Sc(OTf)_3$-catalyzed conditions, forming *cis*-fused furopyrrolidines <2001TL9089>.

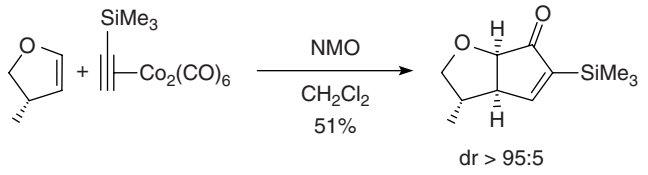


(125)



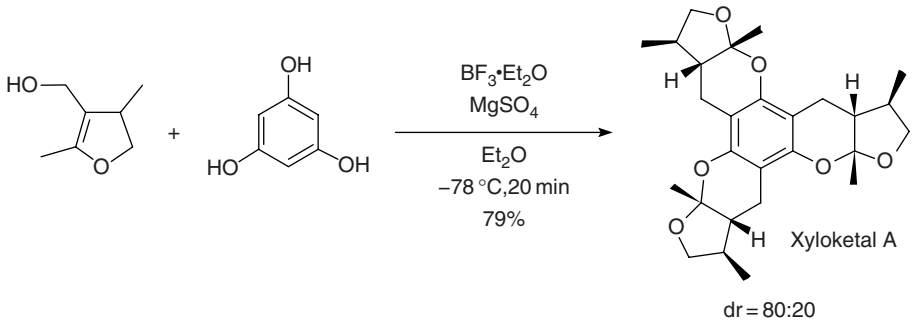
(126)

2,3-Dihydrofuran participated in Pauson–Khand reaction with alkyne–dicobalt complexes, giving furocyclopentenones regioselectively <2001JOM104>. An example of employing this reaction as a starting point for a total synthesis of terpestacin is shown in Equation (127) <2003JA11514>.



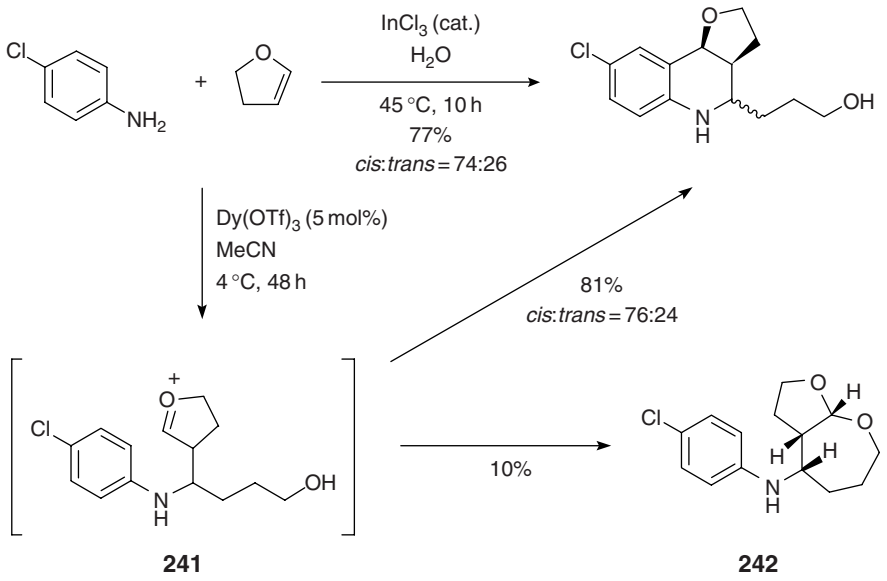
(127)

An interesting example of triple electrophilic aromatic substitution between a dihydrofuran derivative and phloroglucinol was exploited for the total synthesis of the C_3-symmetric xyloketal A, as shown in Equation (128) <2006OL1427>.



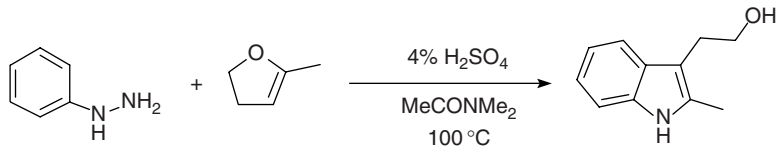
(128)

Two equivalents of 2,3-dihydrofuran, that served as two different reaction components, were coupled to anilines to form *cis*-fused furotetrahydroquinolines by using catalytic amounts of $Dy(OTf)_3$ <2001TL7935> and $InCl_3$ in water <2002JOC3969>, as illustrated in **Scheme 72**. Similar reactions making use of $Sc(OTf)_3$ in 1-butyl-3-methylimidazolium hexafluorophosphate were also reported <2002S2537>. The isolation of a furo[2,3-*b*]oxepin side product **242** <2001TL7935>, which was the major product obtained in the $InCl_3$-catalyzed coupling between 2,3-dihydrofuran and 2-methylindoles <2003TL2221>, suggested a stepwise pathway involving an oxonium intermediate **241** for the second reaction. $InCl_3$ in water catalyzed the hydration of dihydrofuran to the corresponding lactol, which was the first reactive species in the reactions described above and also in an indium-promoted allylation with various allylic bromides to provide allylated 1,4-diols <2004SL829>.



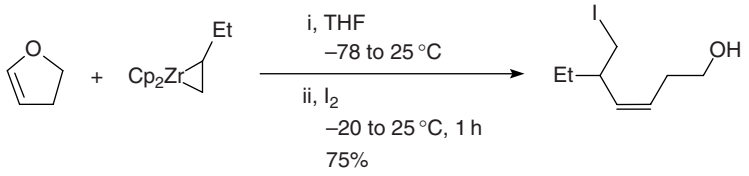
Scheme 72

Dihydrofuran was used as a ketone equivalent in a Fischer-type indole synthesis with an aryl hydrazine under strongly acidic conditions to give a tryptophol. As shown in Equation (129), 5-methyl-2,3-dihydrofuran gave rise to 2-methyltryptophol regioselectively <2004OL79>.



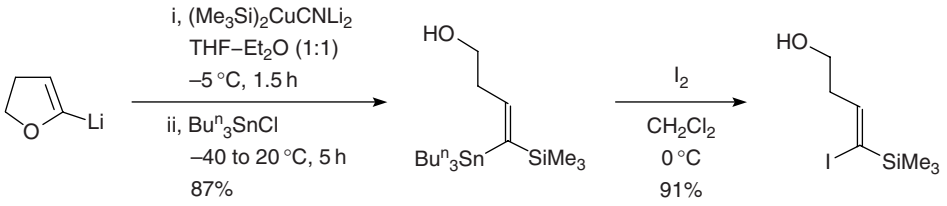
(129)

Coupling of 2,3-dihydrofuran with alkene–zirconocene <2004AGE3932> or aryne–zirconocene <2005SL2513> complexes and subsequent addition of an electrophile provided *cis*-disubstituted homoallylic alcohols, as illustrated in Equation (130). An insertion/β-elimination pathway that involved the formation of an oxazirconacyclooctene intermediate was proposed for the reaction mechanism.

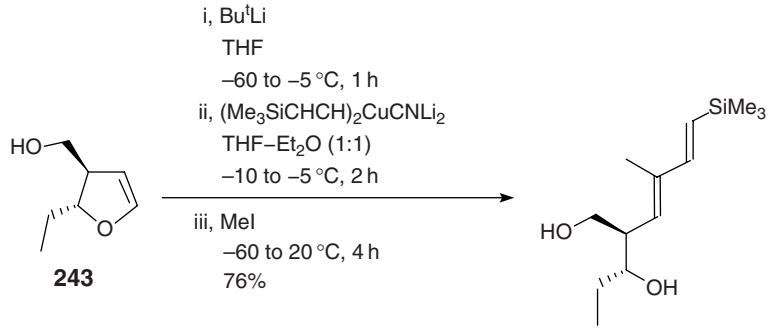


(130)

The dyotropic rearrangement of lithiodihydrofuran-derived dihydrofuranyl cuprate followed by electrophilic addition was further extended to the stereoselective preparation of differentially functionalized 1,1-disubstituted alkenes, as illustrated in **Scheme 73** <2003SL955, 2003S2530>. This method was applied to the elaborated dihydrofuran **243** for the synthesis of the C-10–C-15 segment of tylosin II <1996SL1125, 1996T6613>, as depicted in Equation (131), as well as to the synthesis of the C(12)–C(15) segment of apoptolidin <2005T401>.

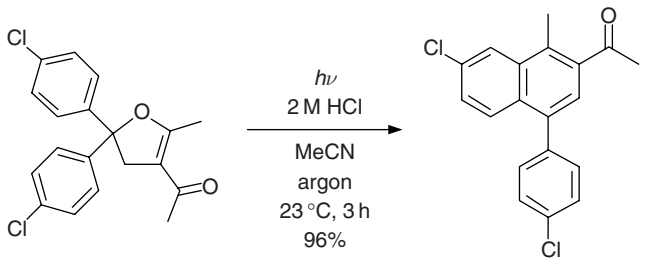


Scheme 73



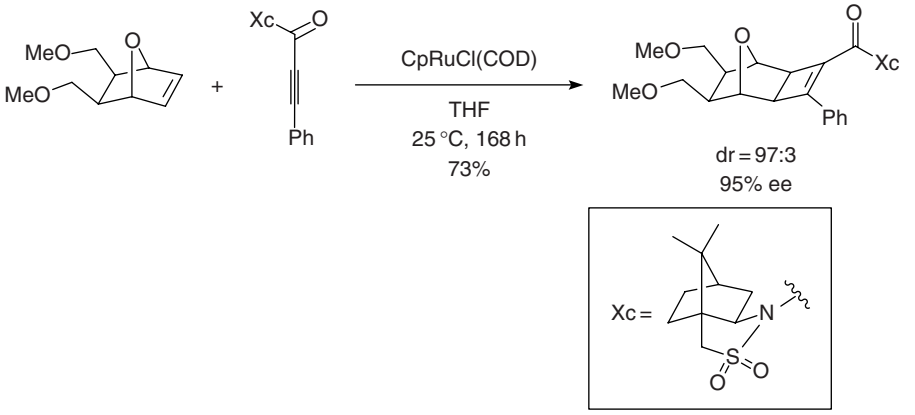
(131)

As shown in Equation (132), dihydrofurans having a 3-acetyl group underwent benzannulation via photoinduced cleavage of the dihydrofuran ring to give naphthalene products <2001TL3351>. Helicene-type compounds and benzo[*kl*]xanthenes were also produced by this method <2005TL7303>.



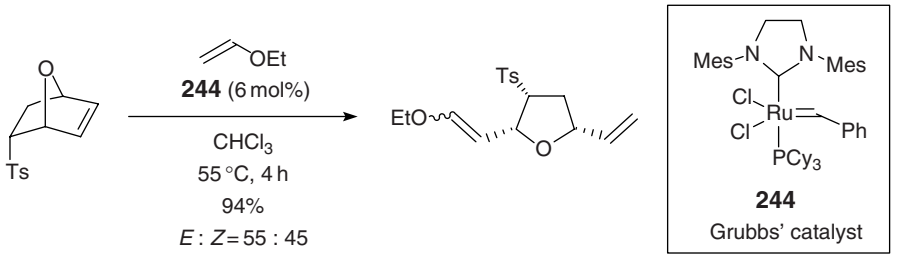
(132)

The diastereoselective and enantioselective [2+2] cycloaddition of a 7-oxanorbornene with a chiral alkynyl acyl sultam was effected by using a ruthenium catalyst to provide the *exo*-cycloadduct as shown in Equation (133) <2004AGE610>.

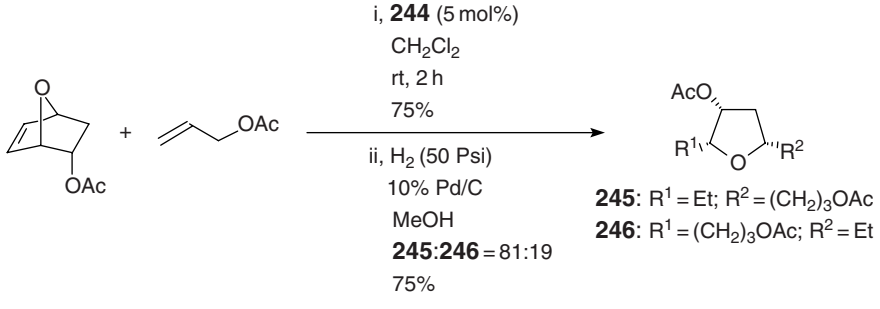


(133)

As demonstrated in Equation (134), a tandem ring opening/cross metathesis of *endo*-2-tosyl-7-oxanorbornene with vinyl ether or vinyl acetate as catalyzed by Grubbs' second generation catalyst **244** afforded a 2,5-disubstituted THF as a single regioisomer. The same regioselectivity was obtained from the reaction of the 2-*exo*-isomer. 2-Carboxylate and benzoxymethyl groups could also exert a similar directing effect on this reaction as the tosyl group <2004OL1625, 2005OL131>. However, opposite regioselectivity (viz. the formation of **245** and **246**) was observed with an acetate substituent (Equation 135) <1999JOC9739, 2000TL9777>. These reactions were reviewed <2003EJO611>.

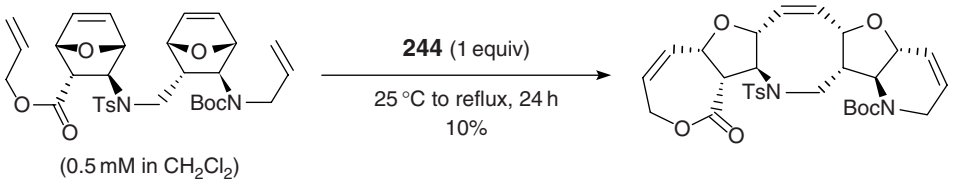


(134)



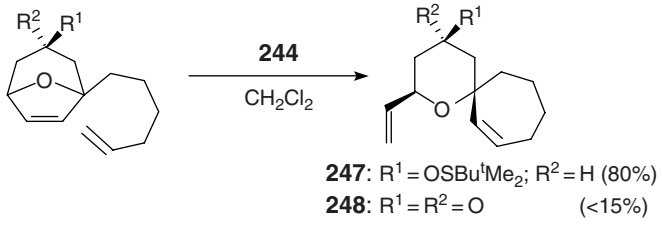
(135)

The tandem ring-opening/ring-closing metathesis of 7-oxanorbornene derivatives as catalyzed by Grubbs' catalyst **244** was applied to synthesize a key bicyclic cyclopentenone intermediate in a total synthesis of *trans*-kumausyne <2005OL3493>, bicyclic seven- and eight-membered sulfonamides <2006TL189>, a seven-membered ring in a spirotricyclic β-lactam <2005HCA1387>, and the 9-oxabicyclo[4.2.1]nona-2,4-diene of mycoepoxydiene <2004JOC8789>. Equation (136) depicts an interesting example of this type of reaction in which the formation of new six-, seven-, and eight-membered rings in the polycyclic product was achieved in a single step, although a stoichiometric amount of the catalyst was used <2004OL3821>.



(136)

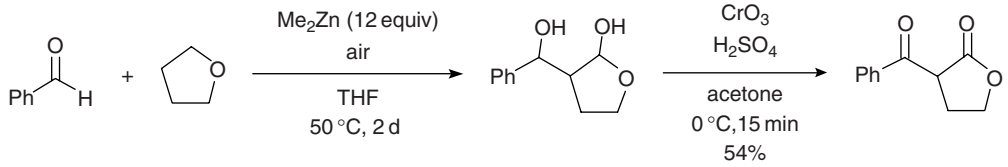
The synthetic applications of 8-oxabicyclo[3.2.1]oct-6-en-3-ones as polyoxygenated building blocks were reviewed <2004AGE1934>. The reactivity of 8-oxabicyclo[3.2.1]octane toward the inter- and intramolecular ring-opening/ring-closing metathesis could be modulated by substitution on the ring <2001OL4275, 2002AGE4560>. For example, the intramolecular formation of a spiro-seven-membered ring, as shown in Equation (137), was more effective in the substrate **247** that has an *endo*-hydroxyl group than in substrate **248** which has a keto group.



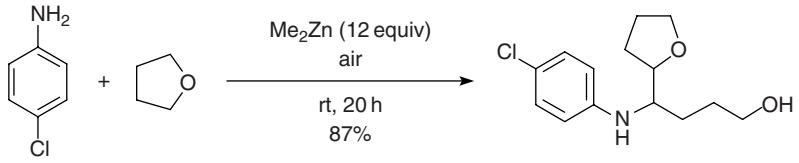
(137)

3.06.3.1.2 Reactions of tetrahydrofurans

It was found that the THF α-radical was readily generated from THF by dimethylzinc and air. The THF α-radical added to aldimines at room temperature to form *threo* THF-substituted benzylamine derivatives as major isomers <2002OL3509>. It was less reactive toward aldehydes, although reaction with aldehydes was made possible at 50 °C to give α-hydroxylated β-substituted THFs, which were isolated as the keto-lactones in modest yields after Jones oxidation (**Scheme 74**). The initially generated THF α-radical probably reacted with molecular oxygen to generate an α-peroxygenated THF β-radical as the key intermediate <2004TL795>. Generation of a THF oxonium ion by the oxidation of the initially formed THF α-radical was proposed to account for the 4-tetrahydrofuranyl-4-aminobutanols obtained in the reaction of two THF molecules with anilines at room temperature under the dimethylzinc/air conditions, as indicated in Equation (138) <2005T379>.

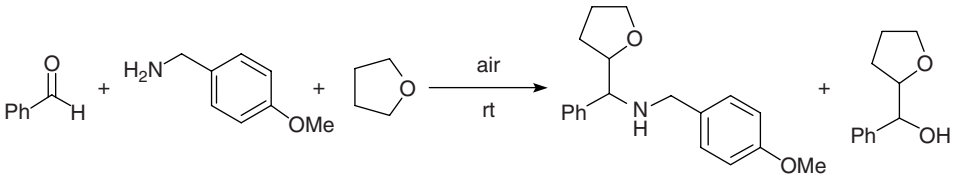


Scheme 74



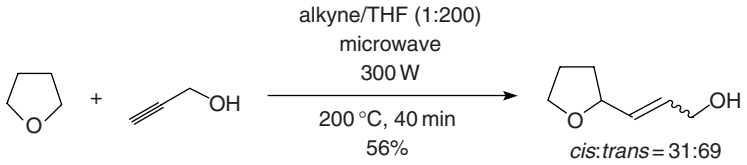
(138)

Triethylborane together with air <1999CC1745> or *tert*-butylhydroperoxide <2003JOC625> also generated the THF α-radical from THF at room temperature, and promoted its addition to aldehydes to provide the *threo*-adducts as the major isomers. This method was applied to the synthesis of the cytotoxin muricatacin <2003JOC7548>. As demonstrated in Equation (139), chemoselective addition of THF α-radical to an aldimine or an aldehyde could therefore be achieved in a three-component reaction system, depending on the radical initiator used <2003OL1797>.



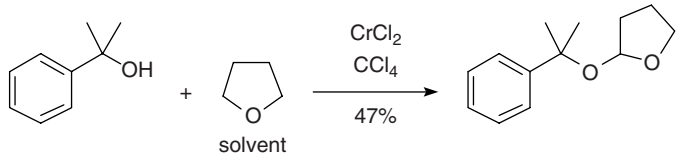
(139)

Addition of the THF α-radical, generated by using triethylborane or benzoyl peroxide, to styrylsulfimides produced 2-styryltetrahydrofurans <1996TL909>. As exemplified in Equation (140), THF was coupled to a variety of aryl- and alkyl-substituted terminal alkynes under microwave irradiation to provide a mixture of *cis*- and *trans*-2-vinyltetrahydrofurans <2004TL7581>. It was proposed that the THF α-radical was the reactive species that was generated by oxygen under the microwave conditions.



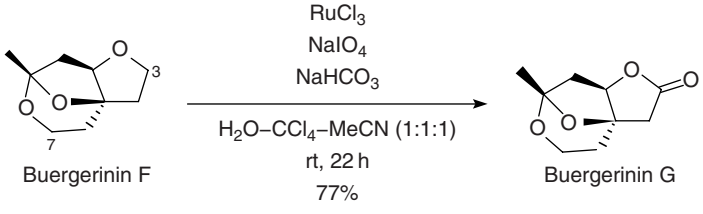
(140)

Tetrahydrofuranyl ethers, which served as hydroxyl protecting groups, were prepared from the reaction between THF and alcohols via the THF α-radical by using $CrCl_2/CCl_4$ <2000OL485>, or $BrCCl_3$/2,4,6-collidine <2000TL6249>, or 1-*tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one/CCl_4 <2004TL3557>. THF ethers can also be formed by the reaction of alcohols with THF using (diacetoxyiodo)benzene under microwave irradiation <2004SL2291>. The sole example of a reaction with a hindered tertiary alcohol <2000OL485> under these newly developed conditions is shown in Equation (141).

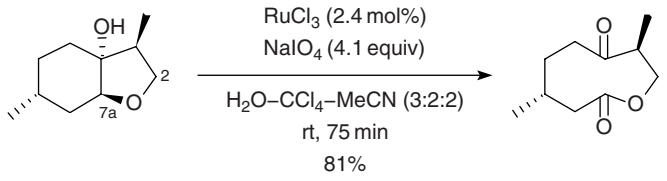


(141)

The hydroxylation at the C-2 position of THF to form lactol by iodosylbenzene in the presence of an Mn(III)–salen complex was reported <1997SL836>. Selective oxidation of the C-3 methylene carbon of the tetrahydrofuran moiety over the C-7 methylene carbon of the bicyclic ketal of buergerinin F to form its lactone analog, buergerinin G, was performed by using ruthenium tetroxide (Equation 142) <2003JOC4117>. An unusual oxidation of hexahydrobenzofuran-3a-ol using a catalytic amount of *in situ*-generated RuO_4 provided nine-membered keto-lactones as shown in Equation (143). The usual regioselectivity in RuO_4-promoted oxidation of ethers was reversed in this example, with the tertiary C-7a proton oxidized selectively over the secondary C-2 proton <2003OL1337>.

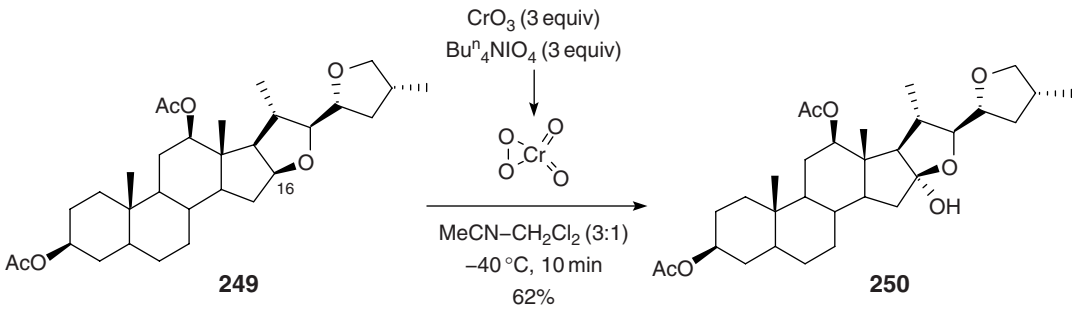


(142)



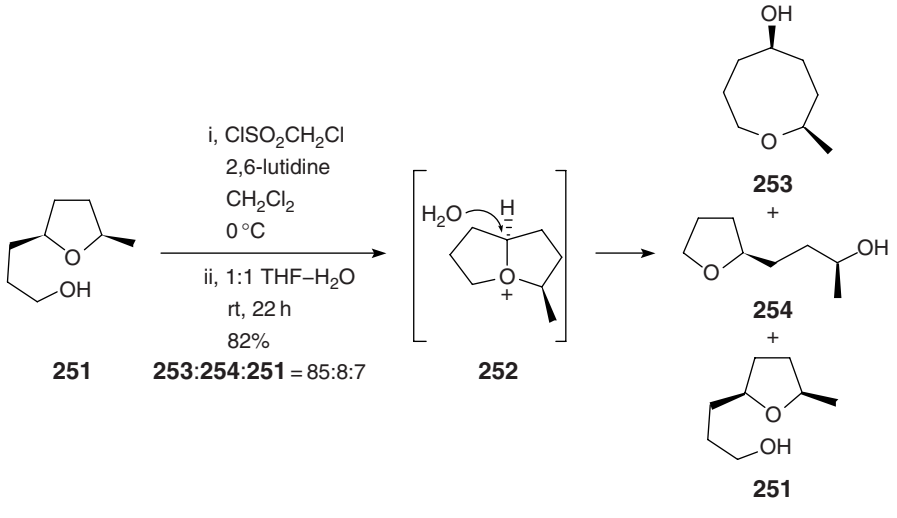
(143)

Similar regioselective hydroxylation of the C-16 tertiary α-carbon of the tetrahydrofuran moiety in cephalostatin-related steroids could also be achieved with retention of configuration by *in situ*-generated dioxoperoxy CrO_4 (from a mixture of CrO_3 and *n*-Bu_4NIO_4). Notably, alkenes and iodides were unaffected under these conditions <2004OL1437>. A remarkable example, as shown in Equation (144), is the preferential oxidation by this Cr(VI) oxidant at C-16 of the bis-THF containing substrate **249** to provide **250** as the major product.

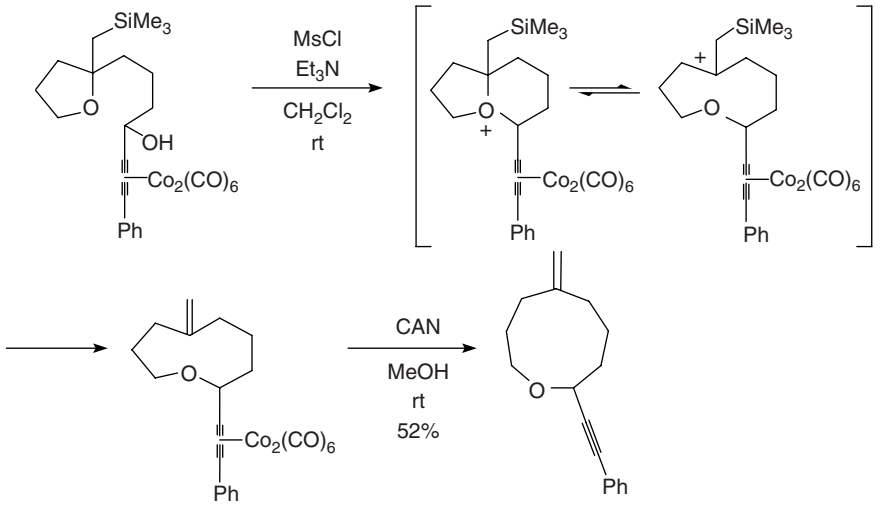


(144)

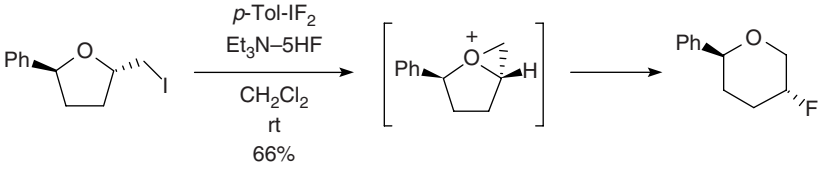
Bicyclo[3.n.0]oxonium ions derived from THFs could produce either ring expansion, ring-switched, or non-rearranged products in the presence of protic nucleophiles <1996J(P1)413>. Tetrahydrofurfuryl monochlorates underwent a $Zn(OAc)_2$-induced regio- and stereoselective 1,2-rearrangement/ring expansion via bicyclo[3.1.0]oxonium ions to provide tetrahydropyrans <1999TL2145>. Extension of this methodology to a novel stereoselective and stereospecific 1,4-rearrangement/ring expansion of **251** via bicyclo[3.3.0]oxonium ions **252** to form oxocanes **253** and **254** is depicted in **Scheme 75** <2002OL675>. Related methodology in which the THF oxygen atom trapped a dicobalthexacarbonyl-stabilized cation to generate the bicyclo[3.3.0]oxonium and bicyclo[3.4.0]oxonium ions for the formation of oxocane and oxonane (**Scheme 76**) respectively was also developed <2000T2203>. Ring expansion of 2-(iodomethyl)tetrahydrofurans by *p*-iodotoluene difluoride/Et_3N–HF to give 3-fluorotetrahydropyrans also involved bicyclo[3.1.0]oxonium intermediates (**Scheme 77**) <2003TL4117>.



Scheme 75

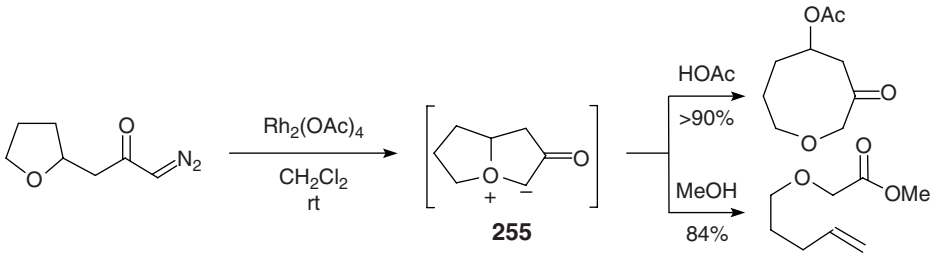


Scheme 76



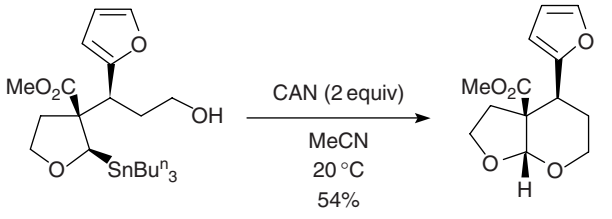
Scheme 77

As shown in **Scheme 78**, the transient bicyclo[3.3.0]oxonium ylide **255** that was generated from a THF-substituted diazoketone was first protonated by acetic acid to the corresponding bicyclo[3.3.0]oxonium ion, which then provided the ring expansion product <1996CC1077>. In the presence of the weakly acidic MeOH, the ylide underwent a concerted [3+2] cycloreversion to a ketene intermediate to form the ring cleavage product <2004JOC1331>.



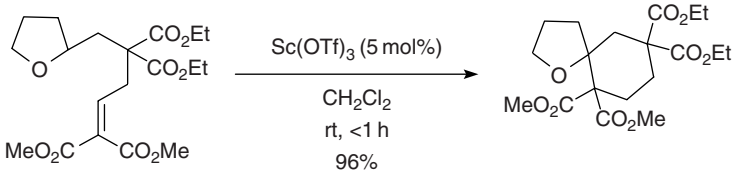
Scheme 78

Transient oxonium ions could be generated from 2-tetrahydrofuranylsilanes <1996TL9119> and 2-tetrahydrofuranylstannanes <2006TL3607> by oxidation with cerium ammonium nitrate. Intramolecular capture of the cations by the hydroxyl group provided furo[2,3-*b*]pyrans, as depicted in Equation (145).

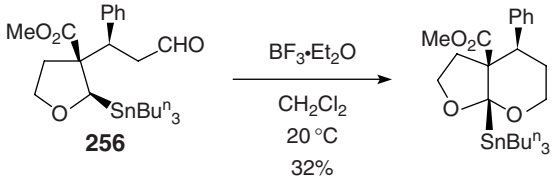


(145)

As illustrated in Equation (146), the C-2 hydrogen of 2-substituted THFs was found to undergo 1,5-hydride migration to pendant electron-deficient alkenes <2005JA12180> and aldehydes <2005OL5429> under Lewis acid-promoted conditions, providing spiro-carbocycles and spiro-ketals, respectively, after subsequent cyclization. Such a transformation occurred with 2-tetrahydrofuranylstannane **256** and in the absence of the Thorpe–Ingold effect, as shown in Equation (147) <2006TL3607>.

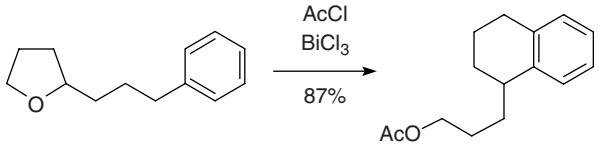


(146)



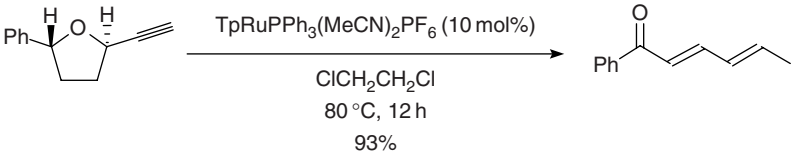
(147)

Regioselective acylative cleavage of 2-methyltetrahydrofuran to 4-halopentanoates could be achieved by using bismuth(III) halides as catalyst <2005T4447>. This methodology was applied to the synthesis of a tetralin, as shown in Equation (148).



(148)

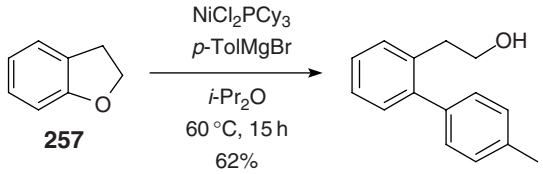
As illustrated in Equation (149), 2-alkyne-substituted THFs could be ring-opened via intramolecular transfer hydrogenation using $TpRuPPh_3(MeCN)_2PF_6$ (Tp = tris(1-pyrazolyl)borate) as a catalyst to provide dienyl ketones <2004JOC4692>.



(149)

3.06.3.2 Reactivity of Dihydrobenzo[*b*]furans

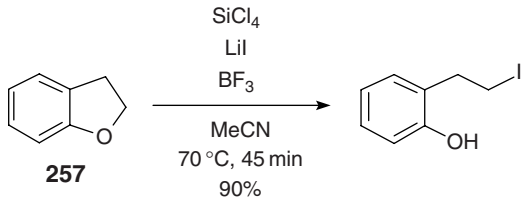
The chemistry of 2,3-dihydrobenzo[*b*]furan **257** discussed herein is focused on the furan part, rather than on the phenyl part, where its chemistry is similar to that of benzenoid molecules. For the chemistry based on the furan part, the frequent reports are related to the C–O bond cleavage. For example, by using an electron-rich ligand-based PCy_3/$Ni(acac)_2$ as a catalyst, 2,3-dihydrobenzo[*b*]furan **257** was employed to couple aryl group to afford biaryl compounds, as can be seen in Equation (150) <2004AGE2428>.



(150)

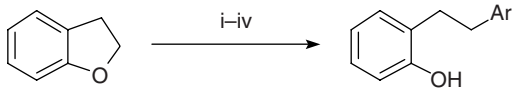
As shown in Equation (151), in the presence of a catalytic amount of BF_3, 2,3-dihydrobenzo[*b*]furan **257** was converted to its corresponding phenol iodide by treatment with $SiCl_4$/LiI <2004TL3729>. *o*-2-Bromoethylphenol

was also obtained by reaction of 2,3-dihydrobenzo[*b*]furan **257** using the high nucleophilicity of bromide ion in an ionic liquid, 1-*n*-butyl-3-methyl-imidazolium bromide ([bmim][Br], although the yield is low at 40% <2004JOC3340>.



257 (151)

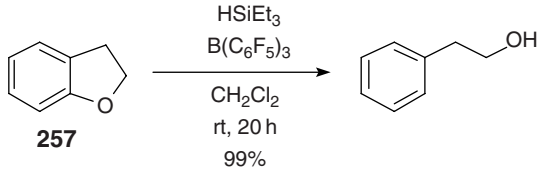
The DTBB-catalyzed lithiation of 2,3-dihydrobenzo[*b*]furan **257** in THF at 20 °C led to a suspension, which, after filtration of the excess of lithium, gave a solution of the corresponding functionalized organolithium compound. This intermediate was treated with zinc bromide (1:1 molar ratio), and then the generated organozinc reagent was successfully coupled with aryl bromide by the palladium-catalyzed Negishi reaction to yield the expected coupling product (Equation 152) <2002EJO1989, 2001TL5721>. The reaction of the organolithium compound derived from 2,3-dihydrobenzo[*b*]furan **257** with a variety of electrophiles was also reported <2002T4907, 1998TL7759>.



257

i, Li, DTBB, THF, 20 °C; ii, $ZnBr_2$, THF, 20 °C; iii, ArBr, $Pd(PPh_3)_4$, THF, 70 °C; iv, HCl–H_2O (152)

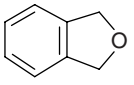
2,3-Dihydrobenzo[*b*]furan was reported to be reductively cleaved by treatment with hydrosilanes in the presence of catalytic amounts of $B(C_6F_5)_3$ in high yield, as depicted in Equation (153) <2000JOC6179>.



257 (153)

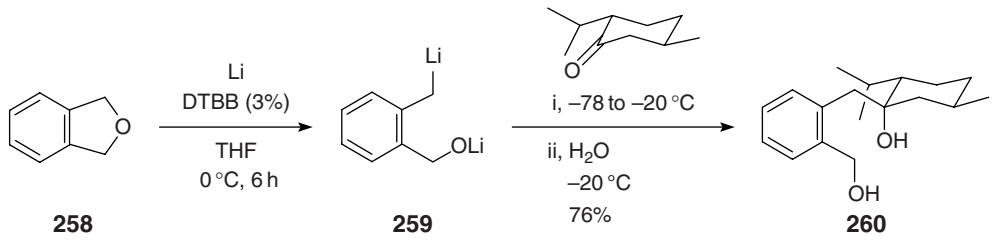
3.06.3.3 Reactivity of Dihydrobenzo[*c*]furans

The thermal reactions of dihydrobenzo[*c*]furan **258** were studied behind reflected shock waves in a single pulse shock tube over the temperature range 1050–1300 K to lead to products from a unimolecular cleavage of **258** <2001PCA3148>. Intriguingly, carbon monoxide and toluene were among the products of the highest concentration, while benzo[*c*]furan, benzene, ethylbenzene, styrene, ethylene, methane, and acetylene were the other products. Trace amounts of allene and propyne were also detected.



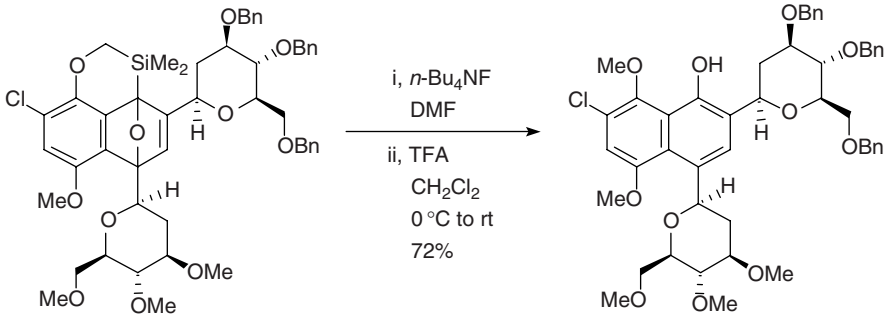
258

As depicted in **Scheme 79**, reductive ring opening of **258** using a small excess of Li and a substoichiometric amount of DTBB led to the organolithium species **259**, which was quenched by the electrophile (–)-menthone to give diol **260** in 76% yield <2004S1115>. In a similar manner, lithiation reactions catalyzed by linear and cross-linked arene-based polymers generated the same organolithium species **259** that reacted with electrophiles such as 3-pentanone, cyclohexanone, *tert*-pentanal, benzaldehyde, and acetophenone to give diols of diversified structures <2004RJOC795>.

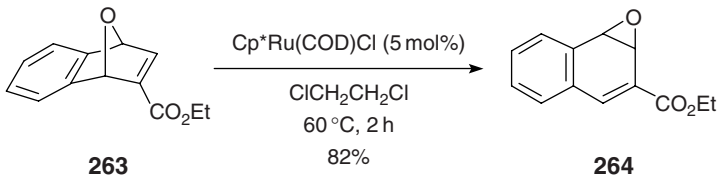


Scheme 79

Exhaustive cleavage of the carbon–silicon bond followed by treatment with an acid converted the complex benzo[*c*]furan **261** to phenol **262**, as illustrated in Equation (154) <2003JA12994>. Villeneuve and Tam were able to interrupt this phenol formation by choosing $Cp^*Ru(COD)Cl$ as the catalyst. Thus, the reaction of 1,4-epoxy-1,4-dihydronaphthalene **263** with a ruthenium catalyst in 1,2-dichloroethane at 60 °C afforded the 1,2-naphthalene oxide **264** (Equation 155) <2006JA3514>.

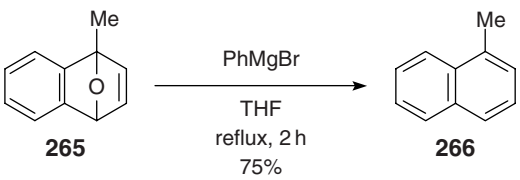


(154)



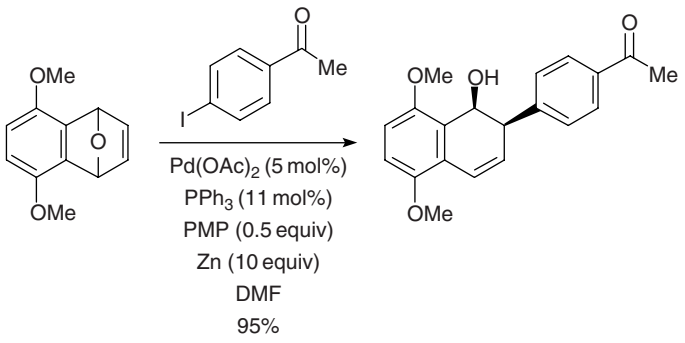
(155)

Another way in which 1,4-epoxy-1,4-dihydronaphthalenes can react is via the deoxygenation reaction to form naphthalenes. For example, as shown in Equation (156), when **265** was allowed to react with 10 equiv of a commercially available Grignard reagent in refluxing THF, naphthalene **266** was obtained <1997TL4761>.

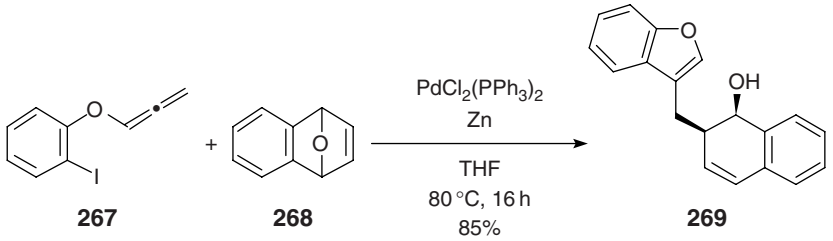


(156)

Ring opening of 1,4-epoxy-1,4-dihydronaphthalenes in general follows an *exo*-S_N2' or S_N2'-like mechanism, leading to *cis*-alcohols. A review summarizing these conversions appeared in 1996 <1996S669>. An example depicting this transformation is shown in Equation (157) <2004OL3581>. Cheng also made use of nickel-catalyzed reactions to open 1,4-epoxy-1,4-dihydronaphthalenes by alkynyl <2002OL1679> and alkenyl groups <2004JOC8407>. Butyllithium was also used to open 1,4,5,8-diepoxy-1,4,5,8-tetrahydroanthracenes to give similar ring-opening products <1998H(47)977>. Most interestingly, an efficient ring closure of 2-iodophenoxyallene **267** catalyzed by palladium(0), followed by ring opening of 1,4-epoxy-1,4-dihydronaphthalene **268**, led to the formation of 2-benzofuran-3-ylmethyl-1,2-dihydro-1-naphthalenol **269** in very good yield (Equation 158) <2006OL621>.



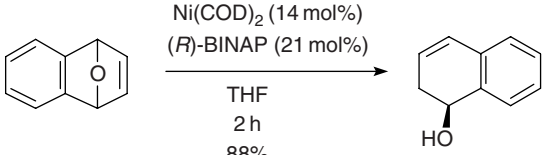
(157)



267 **268** **269**

(158)

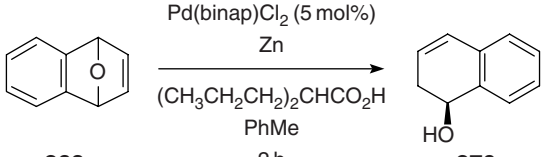
Enantioselective ring opening of 1,4-epoxy-1,4-dihydronaphthalene remains a very active research area because the use of chiral catalysts to control the absolute stereochemistry of products could lead to optically active building blocks that can be employed in the quest for complex bioactive molecules. Lautens reported in 1997 that the oxygen bridge of **268** can be reductively opened, utilizing $Ni(COD)_2$ as a catalyst and (*R*)-BINAP as a ligand to give alcohol **270** in good chemical and optical yields as depicted in Equation (159) <1997JOC5246, 1998T1107>.



268 **270**
98% ee

(159)

Nickel- or palladium-catalyzed asymmetric reductive ring opening of **268** and its derivatives with organic acids and zinc powder under mild conditions also led to the formation of alcohols such as **270**, as shown in Equation (160) <2003OL1621>.

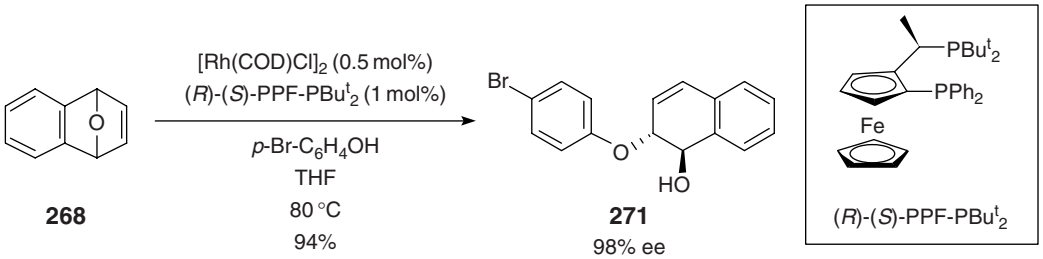


268 **270**
90% ee

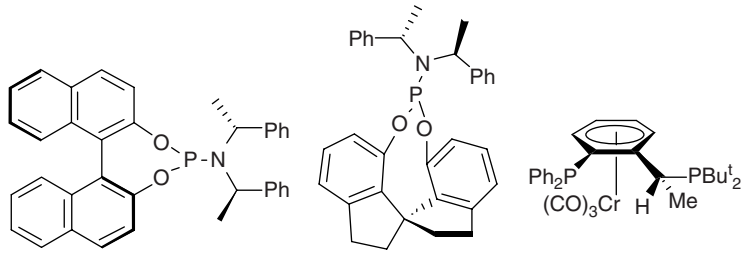
(160)

It is also known that the formation of *trans*-alcohols through a rhodium-catalyzed ring opening of 1,4-epoxy-1,4-dihydronaphthalenes by amines can be achieved <2003CCL697>. This transformation is believed to involve the formation of a new carbon–nitrogen bond via an intermolecular highly regioselective allylic displacement of the bridgehead oxygen with a piperazine derivative. Another example for the formation of the *trans*-1,2-diol derivative **271** was reported by Lautens and co-workers <2000OL1677, 2001T5067, 2001JOM259, 2002JOC8043, 2004PNAS5455>, who treated **268** with a rhodium catalyst in the presence of phenols or carboxylates as nucleophiles, and (*R*)-(*S*)-PPF-PBu^t_2 and other chiral ferrocenes as ligands. Good yields and high enantioselectivities were obtained, as can be seen in the example shown in Equation (161). Copper-catalyzed enantioselective ring opening of

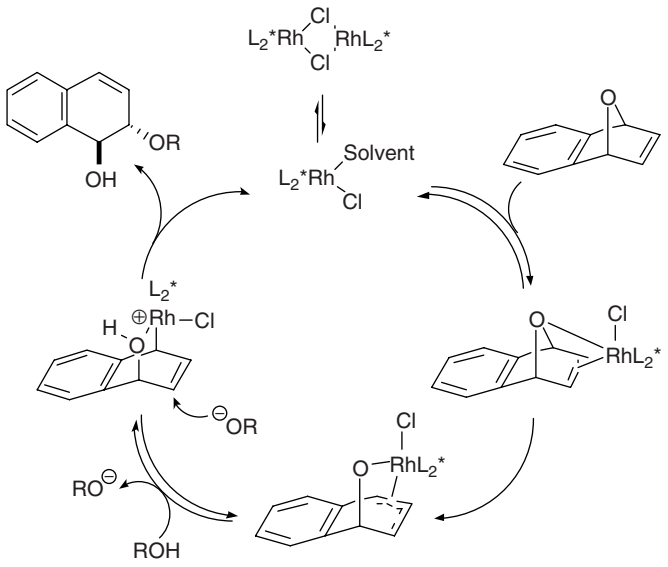
268 and its derivatives by dialkylzinc or Grignard reagents to form *trans*-alcohols was also reported by Feringa <2002OL2703> and Zhou <2005JOC3734>, making use of phosphoramidite catalysts **272** and **273**, respectively. Salzer <2005JOM1166> also reported the optimized synthesis of a *trans*-alcohol in 59% yield and 97.5% ee using a rhodium-catalyzed reaction in the presence of the 'Daniphos'-ligand **274**. The formation of *trans*-alcohols can be explained by a rhodium-catalyzed mechanism, as outlined in **Scheme 80** <2004PNAS5455>.



268 **271** 98% ee (161)

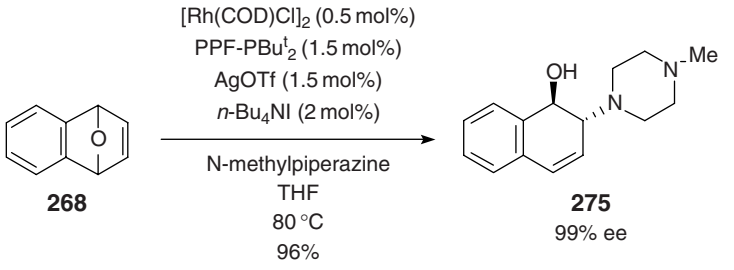


272 **273** **274**



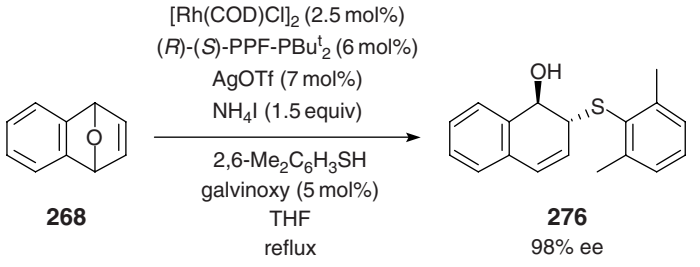
Scheme 80

Rhodium-catalyzed nucleophilic ring opening of 1,4-epoxy-dihydronaphthalenes to form amino-alcohols was reported by Lautens <2002JOC8043>. An enantioselective rhodium-catalyzed version of this approach was recorded <2003JA14884> in which **268** was converted to an amino-alcohol **275**, as illustrated in Equation (162). Biaryl and binaphthyl monodentate and bidentate catalysts have also been shown by Pregosin to provide similar results <2004OM2295>.



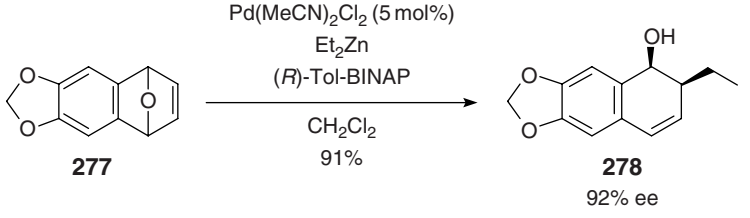
(162)

Sulfur nucleophiles are also able to afford 2-sulfanyl-1,2-dihydronaphthalen-1-ols such as **276** via rhodium catalyzed asymmetric ring-opening reactions, as shown in Equation (163) <2004JOC2194>.

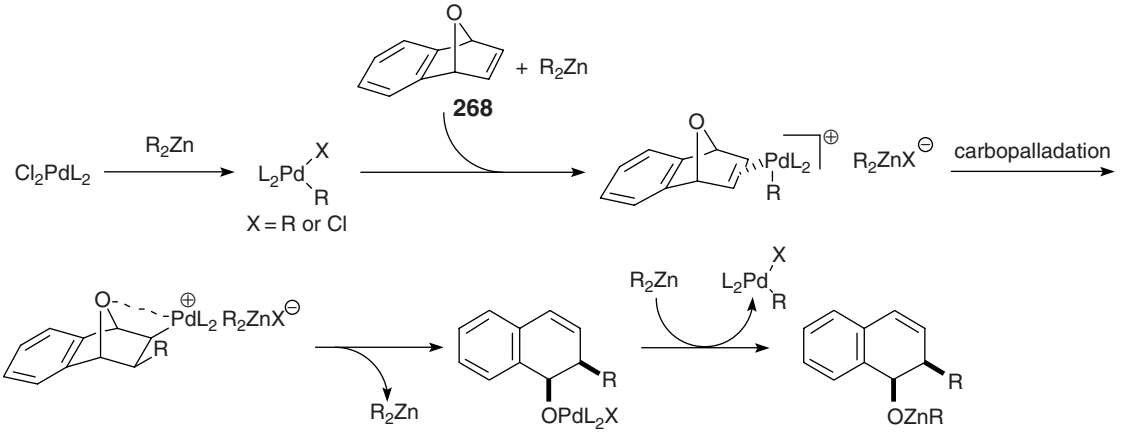


(163)

Palladium-catalyzed enantioselective alkylative ring opening of **277** and analogous molecules, on the other hand, was reported to lead to *cis*-alcohols such as **278** in good yields and high enantioselectivities. An example is shown in Equation (164) <2000JA1804, 2004JA1437>. Mechanistic studies <2001JA6834> and effects of halide ligands and protic additives <2001JA7170> have all been studied. The mechanism of the palladium-catalyzed ring opening of 1,4-epoxy-1,4-dihydronaphthalene **268** with dialkylzinc to form *cis*-alcohols was proposed to go through a carbopalladation pathway, as depicted in **Scheme 81** <2001JA6834>.

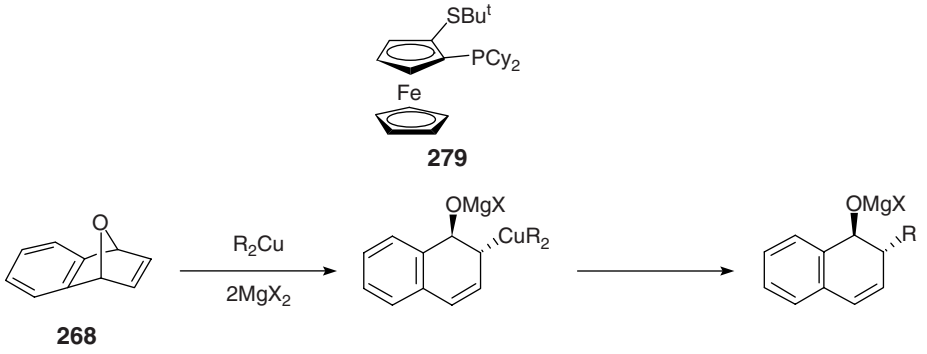


(164)



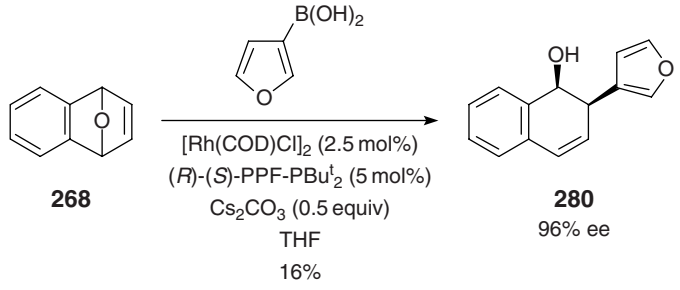
Scheme 81

Carretero and co-workers reported a similar palladium-catalyzed approach with the use of a ferrocene ligand **279** but the products are of opposite absolute structures <2002CC2512>. The same group also reported that in the presence of a Grignard reagent, the copper-catalyzed ring opening reaction of **268** and its derivatives afforded *trans*-alcohols as major products. **Scheme 82** shows a plausible mechanism. As can be seen, the results are consistent with a copper-catalyzed *endo* S_N2' attack of the organocuprate generated from a copper salt and a Grignard reagent, providing a *trans*-alcohol after a reductive elimination of the organocopper species and subsequent hydrolysis <2006S1205>.



Scheme 82

Lautens reported various limitations in rhodium-catalyzed *cis*-alcohol formation. As can be seen in Equation (165), the yield of **280** is only 16%, albeit with 96% ee <2003OL3695>. On the other hand, an identical reaction utilizing $Pd(dppp)Cl_2$ as a catalyst gave **280** in 82% yield but only with 71% ee (dppp = 1,3-bis(diphenylphosphino)propane) <2003OL3695>.

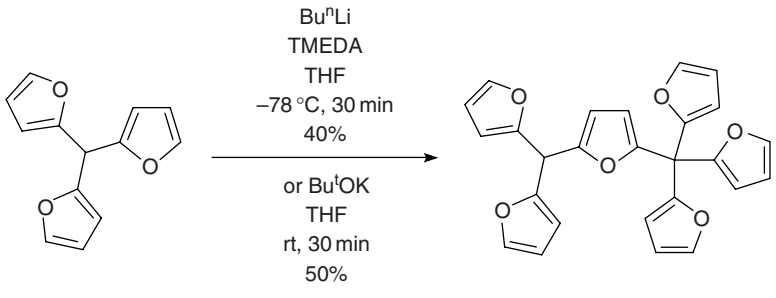


(165)

3.06.4 Reactivity of Substituents Attached to Ring Carbons

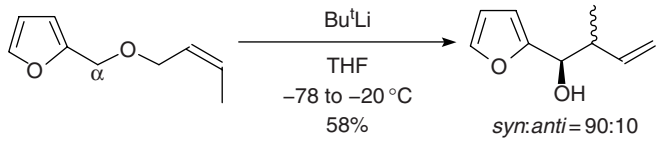
3.06.4.1 Alkyl and Substituted Alkyl Substituents

Treatment of tri-2-furylmethane with *n*-BuLi resulted in the unanticipated formation of 1,1-bisfuryl-1-[5-(tri-2-furylmethyl)]furylmethane, as shown in Equation (166). Presumably, a tri-2-furylmethane anion was generated in preference to a 2-furyl anion. The same product could also be obtained using Bu^tOK as the base <2004OL3513>.

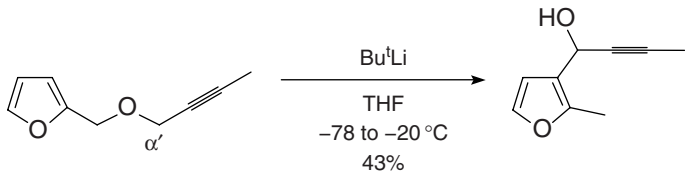


(166)

Deprotonation of allyl furfuryl ethers by *t*-BuLi occurred at the α-position, as shown in Equation (167), whereas deprotonation of the corresponding propargyl furfuryl ethers occurred at the α'-position (Equation 168). The resultant anions then underwent a [2,3]-Wittig rearrangement preferentially over a [1,2]-Wittig rearrangement, giving homoallylic alcohols and a propargyl alcohol, respectively <1999CC2263>.

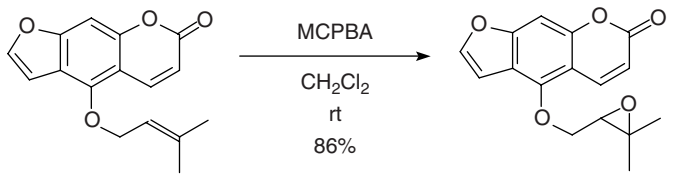


(167)



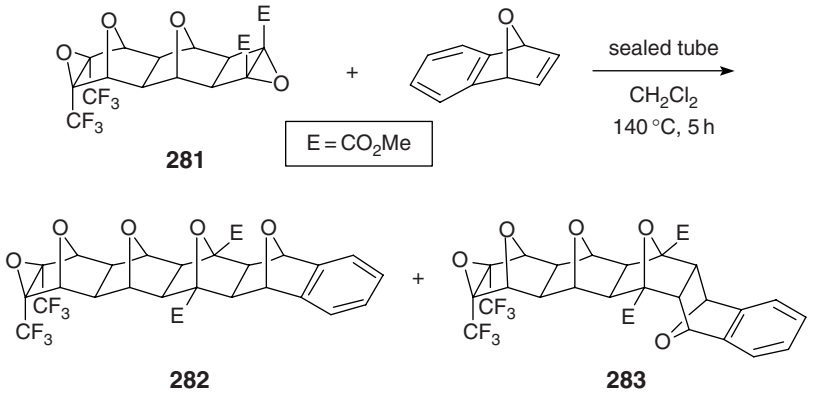
(168)

The double bond of the side chain in the benzo[*b*]furan as shown in Equation (169) was oxidized to an epoxide employing *m*-chloroperbenzoic acid (MCPBA), while the other double bonds in the molecule remained intact <2006OBC1604>.



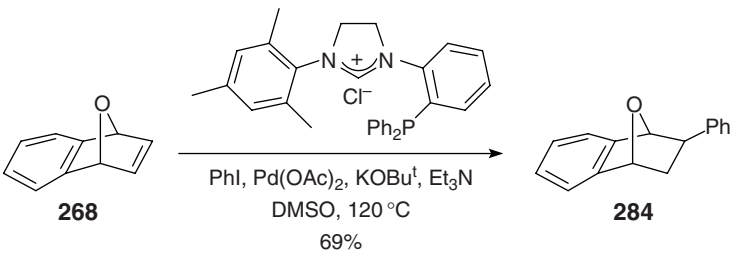
(169)

As can be seen in Equation (170), the dienophilic reactivity of the double bond in 1,4-epoxy-1,4-dihydronaphthalenes can further be illustrated by its reaction with bisepoxide **281**, leading to the formation of the structurally intriguing **282** and **283** in 34% and 44% yield, respectively <2001T571>.



(170)

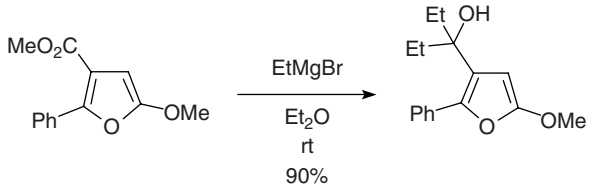
A new phosphine-functionalized N-heterocyclic carbene ligand as shown in Equation (171) for palladium-catalyzed hydroarylation reaction on **268** led to the formation of an aryl substituted compound **284** <2006SL1193>.



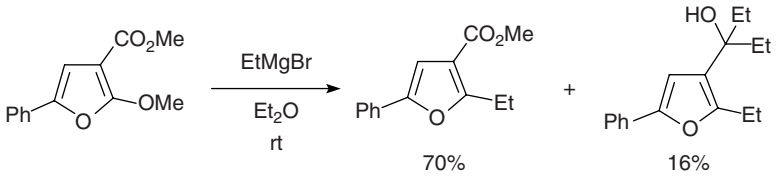
(171)

3.06.4.2 Carboxylic Acids and Their Reactions

The ester moiety of methyl 2-methoxy-4-furoates underwent the usual addition reaction with Grignard reagents to provide tertiary alcohols, as exemplified in Equation (172). However, displacement of the 2-methoxy group of the corresponding 3-furoate isomers occurred under the same reaction conditions, presumably via a six-membered organomagnesium chelate, to give 2-substituted-3-furoates as the major products (Equation 173) <2003TL5781>.

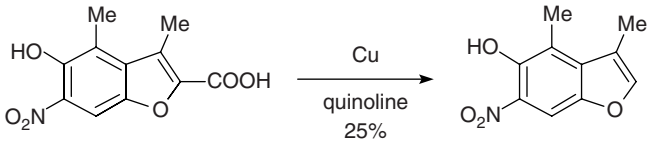


(172)



(173)

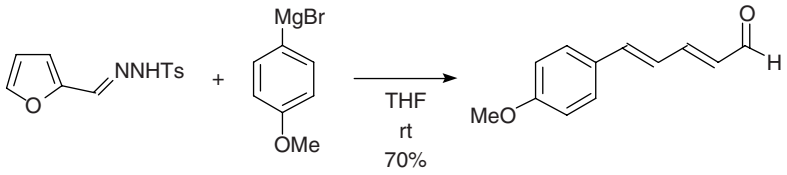
Copper-mediated decarboxylation was observed to convert benzo[*b*]furan-2-carboxylic acid into its corresponding benzo[*b*]furan, albeit in low yield (Equation 174) <2002EJO1937>.



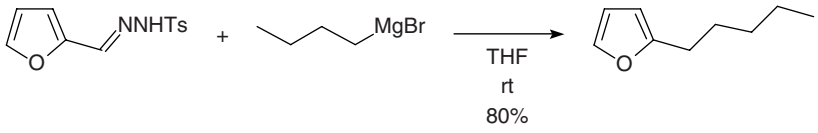
(174)

3.06.4.3 Acyl Substituents and Their Reactions

Furfural-derived 2-furylhydrazone underwent alkylated ring opening with phenyl Grignard reagents to produce dienal products, as shown in Equation (175). However, only reductive alkylation occurred with alkyl Grignard reagents (Equation 176) <2000TL2667>. Different elimination pathways of dinitrogen in the reaction intermediates, that is, [3,3]-sigmatropic rearrangement versus radical fragmentation, were probably responsible for the different products obtained.

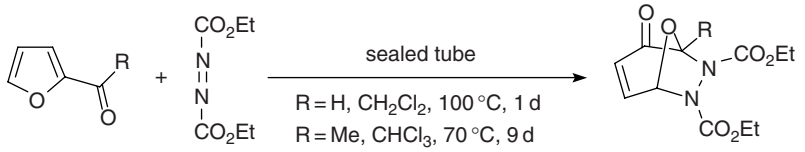


(175)



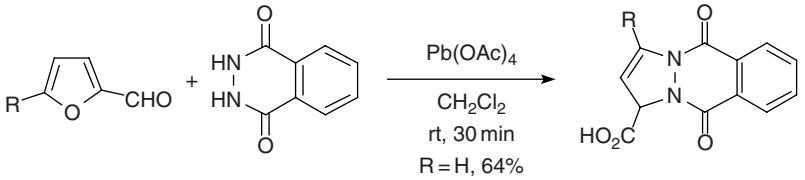
(176)

2-Formyl and 2-acetylfuran underwent an unusual reaction with ethyl azodicarboxylate to form adducts **285** and **286**, respectively, as depicted in Equation (177) <1997T9313, 1999J(P1)73>. Computational studies of the reaction suggested an initial Diels–Alder reaction between the furan and azodicarboxylate, followed by rearrangement of the cycloadducts. A similar transformation was observed for the reaction between furfurals and 1,4-phthalazinedione in the presence of $Pb(OAc)_4$, as shown in Equation (178) <2002OL773>.



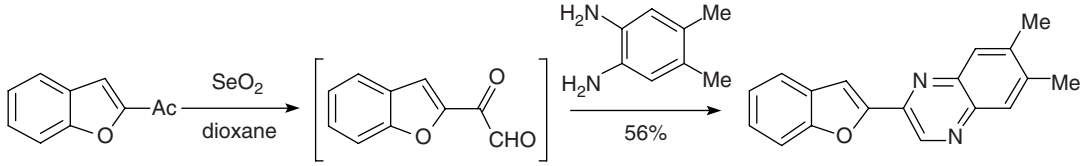
285 (40%)
286 (35%)

(177)



(178)

Biologically interesting benzo[*b*]furyl quinoxalines were prepared by sequential oxidation and condensation (**Scheme 83**) <2004T6063>.

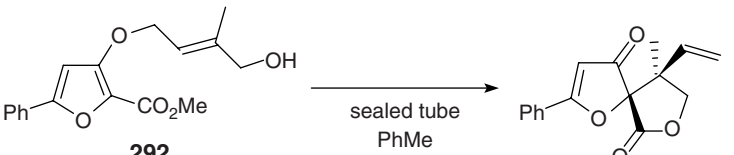


Scheme 83

Chou and co-workers discovered that flash vacuum pyrolysis (FVP) at 550 °C and ca. 10^{-2} Torr converted 7-oxa-1-naphthonorbornenyl)methyl benzoate **287** to isonaphthofuran **288**, which led to a mixture of **289**, **290**, and **291** in 48%, 9%, and 28% yield, respectively, as illustrated in **Scheme 84** <1998TL7381>. The same treatment of (1-benzo[*c*]furanyl)methyl benzoate led to a similar result <1997T17115>.

3.06.4.4 Heteroatom-Linked Substituents and Their Reactions

As shown in Equation (179), a tandem Claisen rearrangement–lactonization involving the C-3 side chain of furan **292** was employed for a concise synthesis of hyperolactone C <2003JNP1039>. Although the product yield was low, the reaction created two contiguous quaternary carbon centers in one step.

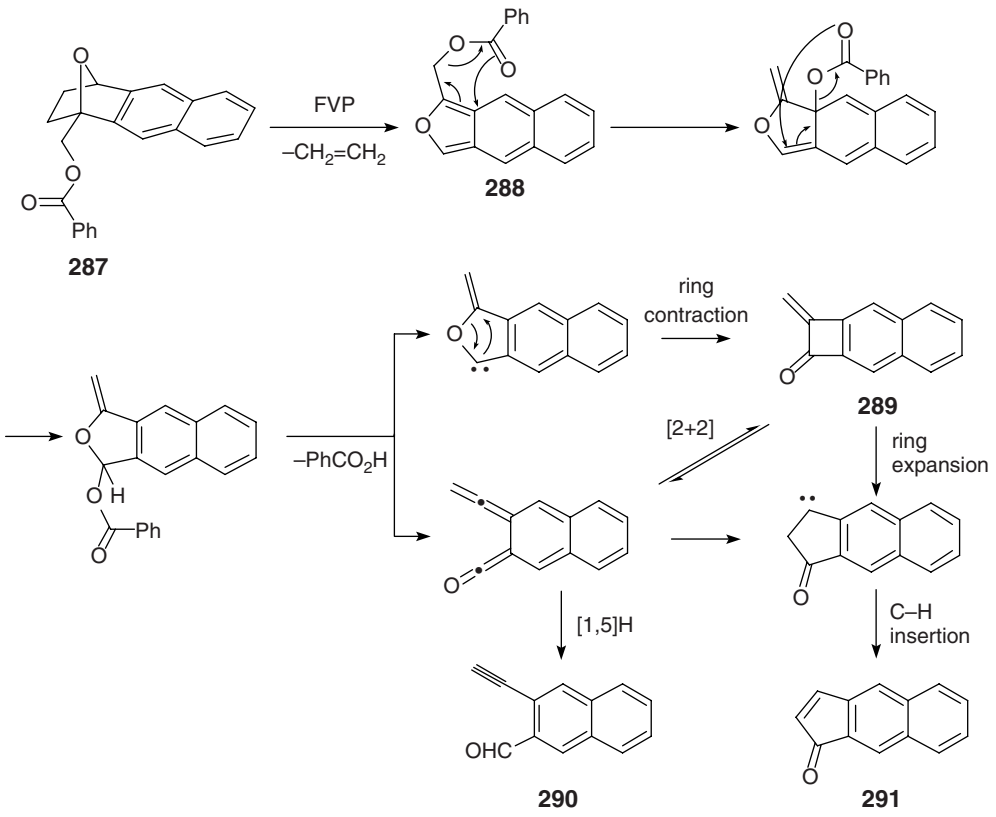


292

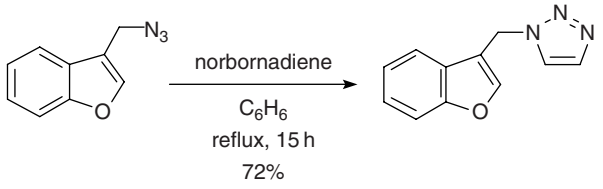
Hyperolactone C

(179)

Benzo[*b*]furan-based azide was also reported to undergo a 1,3-dipolar cycloaddition with norbornadiene as dipolarophile to give a triazole after extrusion of cyclopentadiene (Equation 180) <2001T7729>.

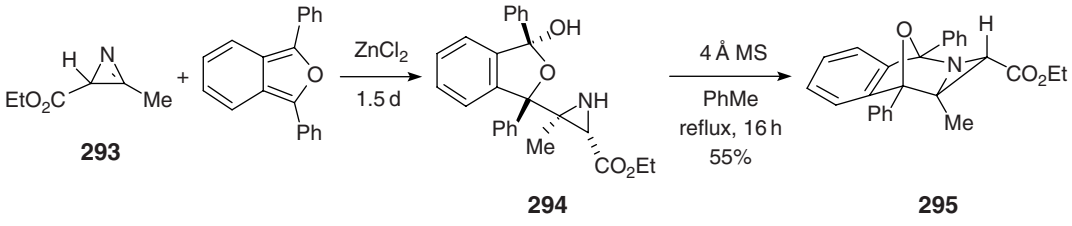


Scheme 84



(180)

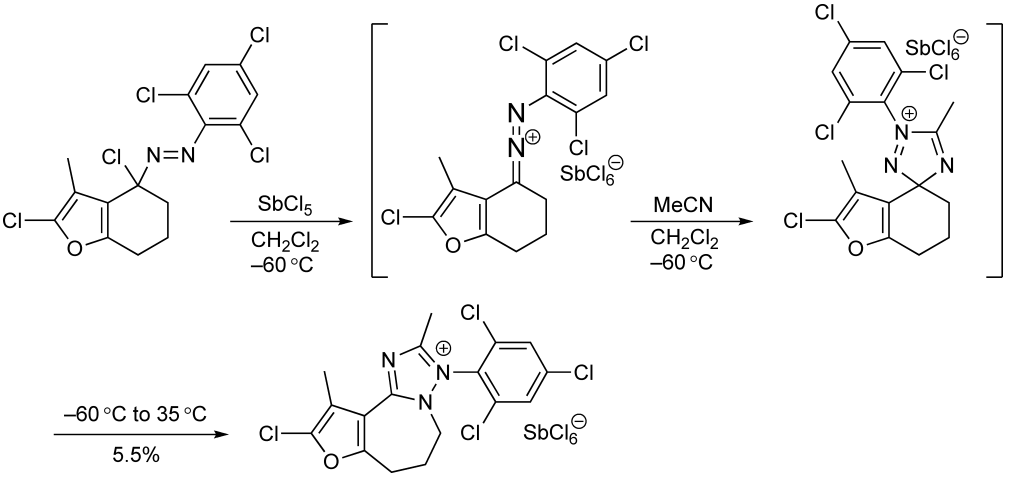
Cycloaddition of the less-electrophilic azirine **293** and 1,3-diphenylbenzo[*c*]furan was carried out in the presence of $ZnCl_2$, as shown in **Scheme 85**, which led to the formation of an adduct **294**. Thermolysis of **294** in toluene was shown to give another adduct **295** <2005H(65)1329>.



Scheme 85

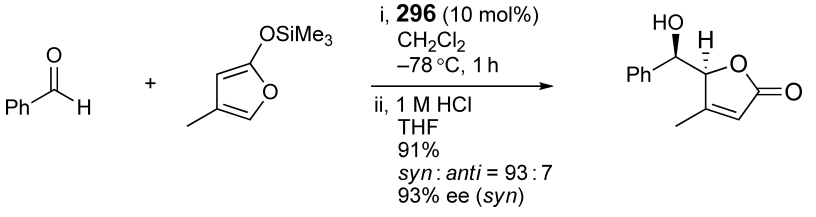
3.06.5 Further Developments

Reactions of furans, dihydrofurans, tetrahydrofurans and benzo[*c*]furans have been reviewed <2007PHC187>. Derivatives of new furan skeletons were synthesized from bicyclic azo compounds and nitriles in the presence of $SbCl_5$ or $AlCl_3$. An example of which is shown in **Scheme 86** <2007S33>.

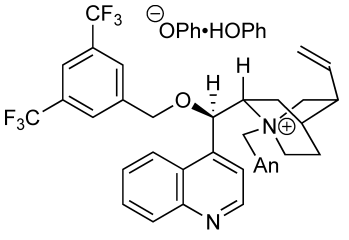


Scheme 86

Cinchonidine-derived quaternary ammonium phenoxides (e.g., **296**) have been shown to catalyze vinylogous aldol-type reaction between benzaldehyde and 4-methyl-2-(trimethylsilyloxy)furan, leading to the formation of a 5-substituted butenolide in good yield and good ee% as can be seen in Equation (181) <2007CL8>.



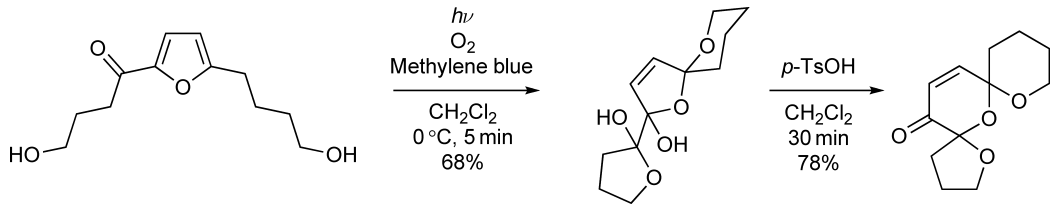
(181)



296

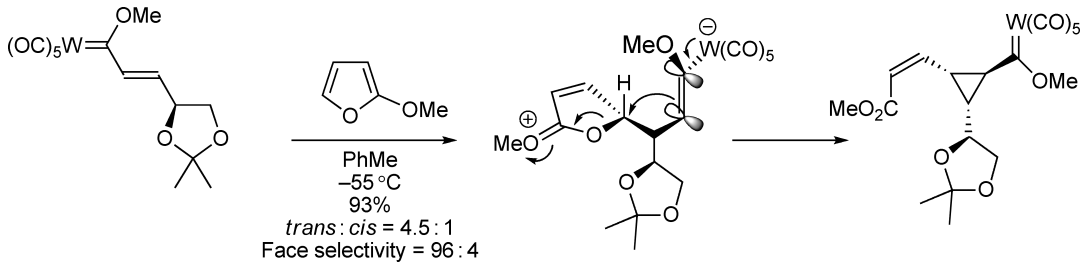
An = 9-Anthracenyl

Singlet oxygen reaction with a furan provided a spiroketal that reacted further under acidic condition to give eventually a bis-spiroketal as shown in **Scheme 87** <2007OBC772>.



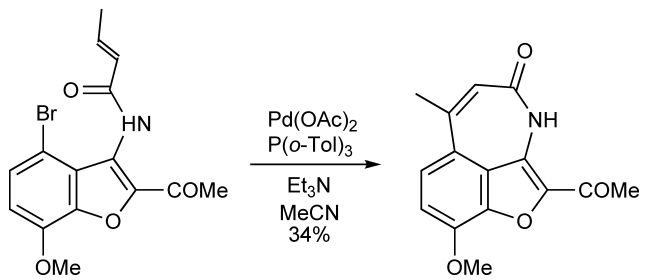
Scheme 87

An enantiopure Fischer carbene complexes was able to react with 2-methoxyfuran in an intriguing manner that led to the formation of trisubstituted cyclopropane molecules in excellent diastereoselectivities. The relevant mechanism for the formation of a cyclopropane is depicted in **Scheme 88** <2007CEJ1326>.



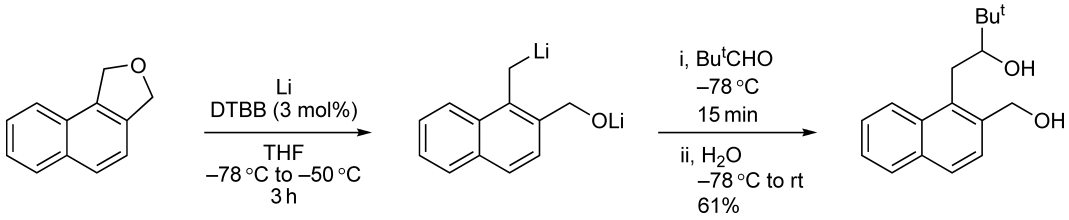
Scheme 88

As illustrated in Equation (182), a seven-membered lactam was formed by utilizing a ring closure reaction under Heck coupling conditions <2007OBC655>.



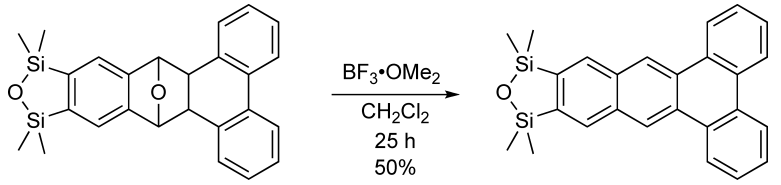
(182)

The lithiation of the phthalan shown in **Scheme 89** with an excess of lithium in the presence of a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) afforded a dianionic species, which on treatment with *tert*-pentanal provided a diol <2007TL3379>.



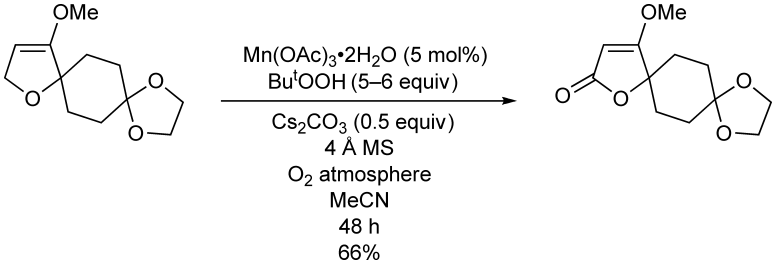
Scheme 89

Upon reaction of the benzobisoxadisilole shown in Equation (183) with 1.5 equivalents of $BF_3{\cdot}OMe_2$ for 25 hours at room temperature, 50% yield of the dehydration product was obtained together with the recovery of 31% unreacted starting material <2007TL2421>.



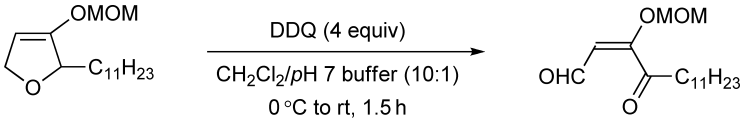
(183)

Reissig showed that when a variety of 3-alkoxy-2,5-dihydrofurans were subjected to manganese(III)-catalyzed allylic oxidation, β-alkoxylbutenolides were obtained as can be seen in Equation (184). The total synthesis of (±)-annularin H was achieved employing this procedure as a pivotal step <2007SL1294>.



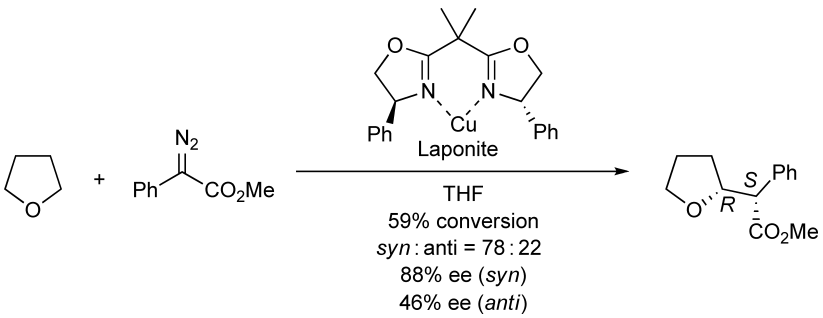
(184)

Reissig also oxidatively cleaved the aforementioned 3-alkoxy-2,5-dihydrofurans to lead to the formation of α,β-unsaturated γ-ketoaldehydes, as can be seen in Equation (185) <2007AGE1634>.



(185)

Immobilized box-Cu complexes were shown to efficiently catalyze the insertion of carbenes into the C–H bond of tetrahydrofuran with enantioselectivity of up to 88%ee. The use of immobilized catalysts allows their recovery and reuse. As can be seen in Equation (186), the major *syn*-isomer was shown to be of $2R,\alpha S$ absolute configuration by comparing its sign of optical rotation with that of an authentic sample <2007OL731>.



(186)

References

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Biographical Sketch

Henry N. C. Wong was born in Hong Kong, and he studied at the Chinese University of Hong Kong, where he obtained a B.Sc. in 1973. He obtained his Ph.D. from University College London in 1976 under the mentorship of Professor Franz Sondheimer. After spending 1976–78 at Harvard University under the direction of Professor Robert B. Woodward, he returned to University College London as a Ramsay Memorial Fellow. Subsequently, he did research at Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences in 1980–82, and finally returned to The Chinese University of Hong Kong in 1983, where he is now professor of chemistry and head of New Asia College. His scientific interests include syntheses and studies of non-natural molecules and natural products.

Kap-Sun Yeung was born in Fujian, China, and he studied at the Chinese University of Hong Kong, where he conducted undergraduate research with Professor Henry N. C. Wong and received his B.Sc. in 1990. He then spent a year as a research assistant with Professor Chi-Ming Che at the University of Hong Kong. In 1991, he was awarded a Croucher Scholarship to study at the University of Cambridge, where he was involved in the total synthesis of swinholide A and scytophycin C under the guidance of Professor Ian Paterson. After obtaining his Ph.D. in 1994, he carried out postdoctoral research in Professor Chi-Huey Wong's group at the Scripps Research Institute, California. In 1996, he joined the Bristol-Myers Squibb drug discovery chemistry group in Connecticut. His research interests include all aspects of synthetic organic chemistry, pharmaceutically important heterocycles, and drug design.

Zhen Yang was born in Liaoning, China, and got his B.Sc. in 1978 and M.Sc. in 1986 at the Shenyang College of Pharmacy. He spent three years as a graduate student at the Chinese University of Hong Kong, where he conducted his research under the guidance of Professor Henry N. C. Wong and received his Ph.D. in 1992. He carried out postdoctoral research with Professor K. C. Nicolaou at the Scripps Research Institute from 1992 to 1995, and was an assistant in Professor Nicolaou's domain from 1995 to 1998, where he was involved in the total syntheses of taxol, epothilone A, and brevetoxin A. He then moved to the Institute of Chemistry and Cell Biology, Harvard University, in 1998 as an institute fellow to conduct his independent research in the field of chemical genetics. In 1998, he joined the College of Chemistry and Molecular Engineering, Peking University, as a Changjiang Professor, and founded VivoQuest Inc. His research interests include total synthesis of natural product, organometallic chemistry, chemical biology, and drug discovery.