Pergamon

Tetrahedron 54 (1998) 1955–2020

TETRAHEDRON

Tetrahedron report number 441

Regioselective Syntheses of Substituted Furans

Xue Long Hou,*[b] Hui Yin Cheung,[a] Tung Yue Hon,[a] Po Lo Kwan,[a] Ting Hang Lo,[a] Sing Yip Tong,[a] and Henry N.C. Wong*[a,1]

a) Department of Chemistry, The Chinese University of Hong Kong,

Shatin, New Territories, Hong Kong.

and

b) Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences,

354 Feng Lin Road, Shanghai 200032, China.

Received 30 October 1997

Contents

* *E-mail : hncwong@cuhk.edu.hk* *FAX : +852 2603 5057*

PII: S0040-4020(97)10303-9

Introduction

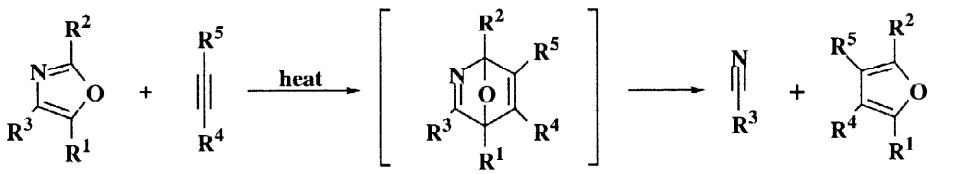
Furan, as one of the representative five-membered heterocycles, can be found in many naturally occurring compounds. Polysubstituted furans play an important role in organic chemistry not only due to their presence as key structural units in many natural products[2] and in important pharmaceuticals,[3] but they can also be employed in synthetic chemistry as building blocks and a lot of transformation reactions have been documented for them. For this reason the syntheses of polysubstituted furans continue to attract the interest of many synthetic chemists. Although a number of reviews on the synthesis of furans have appeared in the literature,[4-10] only very few of them deal with the regioselective methods for preparing furans. In this review, we will describe the regioselective preparation of furans according to their substitution patterns. Rather than attempting an exhaustive literature survey of all the relevant syntheses that have been recorded between 1980 and 1996, we have focused our attention on the more general procedures which should be useful for a pragmatic preparation of these intriguing molecules in a regioselective manner.

1. Syntheses of 3-Substituted Furans

1.1. From Tandem Diels—Alder Cycloaddition - Retro Diels—Alder Reaction

3-Substituted furans can be synthesized by employing the Diels—Alder cycloaddition - retro Diels—Alder reaction strategy (Scheme 1).[11,12] Using oxazole derivatives **1** and dienophiles as starting materials, bicyclic compounds could be produced. The intermediates concerned could not be isolated and could directly provide 3-substituted furans **2** under thermal conditions.

Scheme 1



1

a, $R^1 = R^2 = H$; $R^3 = Me$
b, $R^1 = R^2 = H$; $R^3 = Ph$

2

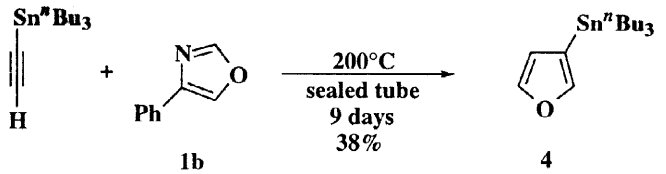
3

a, $R^1 = R^2 = R^4 = H$
R^5 = substituent

The advantages of this method lie in the functional group compatibility as well as the starting material accessibility. It allows the production of large quantities of 3-substituted furans in a single step with good to excellent yields. In addition, this method can also be employed to prepare polysubstituted furans (*vide infra*). If the availability of starting materials is not a problem, this procedure may be regarded as the simplest and the most efficient.

Utilizing this strategy, 3-tri-*n*-butylstannylfuran (**4**)[13] was obtained in 38% yield (Scheme 2). As we can see later compound **4** is a very versatile starting material for the preparation of other 3-substituted furans.

Scheme 2

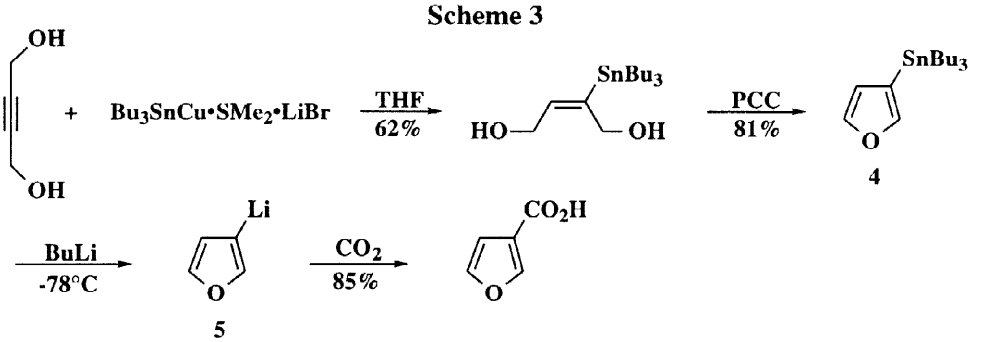


1.2. From Acyclic Precursors

Although the construction of furan rings from acyclic precursors is a workable process, there have been relatively few literature reports on applying this method to the synthesis of 3-substituted furans.

A simple, two-step reaction using 3-tri-*n*-butylstannylfuran (**4**) was reported.[13,14] Furan **4** could be easily converted to 3-lithiofuran (**5**). Noteworthy is that both **4** and **5** play important roles as building blocks for other 3-substituted furans (Scheme 3).[14]

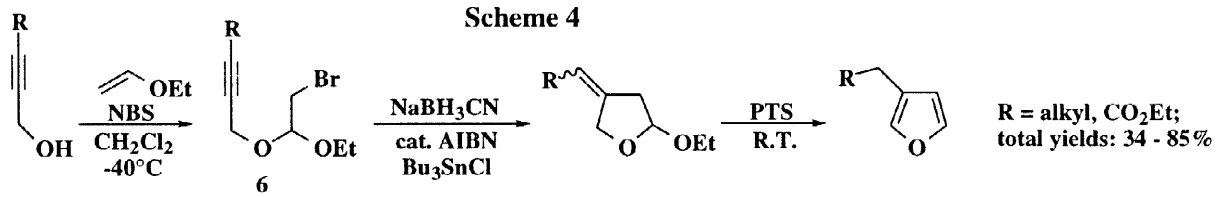
Scheme 3

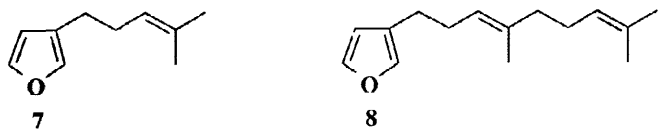


Fleming's method in which 3-tri-*n*-butylstannylfuran (**4**) was prepared was by utilizing the relatively inexpensive 2-butyne-1,4-diol as a starting material. The diol was found to react with Piers' stannyl-cuprate reagent to produce (*E*)-stannylbutenediol, oxidation of which with PCC furnished the desired **4** in satisfactory yield.[14]

Another example on ring closure to form 3-substituted furans was provided by employing a radical cyclization reaction (Scheme 4).[15] Thus, radical cyclization of the bromoacetal **6**, which was obtained by bromination of ethyl vinyl ether in the presence of alk-2-ynyl alcohol, was achieved by *in situ* generated tri-*n*-butylstannyl hydride in the presence of a catalytic amount of azobisisobutyronitrile to provide the 2-ethoxy-4-alkylidene tetrahydrofuran, which on acid catalyzed aromatization led to 3-substituted furans. Two natural terpenoids, perillene (**7**) and dendrolasin (**8**) were synthesized by using this methodology.

Scheme 4

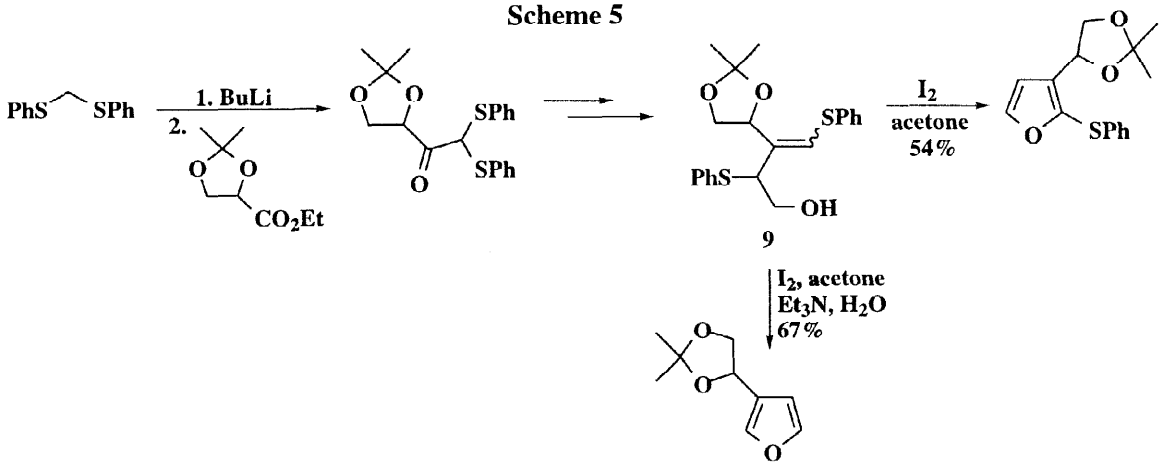




7 8

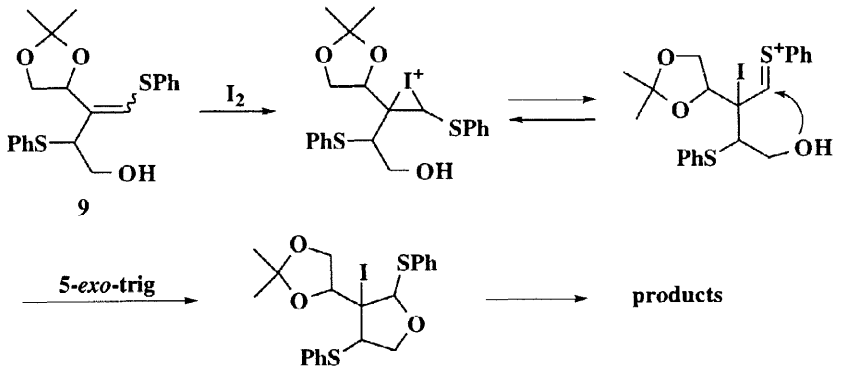
Recently, da Silva[16] described a five-step synthesis of 3-substituted furans by employing bis(phenylthio)methylenes and ethyl glycerate 2,3-acetonide as starting materials (Scheme 5).

Scheme 5



Although the cyclization of **9** is a disfavored pathway in accordance to Baldwin's rules (5-*endo*-trig),[17] this difficulty was overcome by the reaction route shown in which an intermediate formed from **9** could undergo a favored 5-*exo*-trig cyclization (Scheme 6).

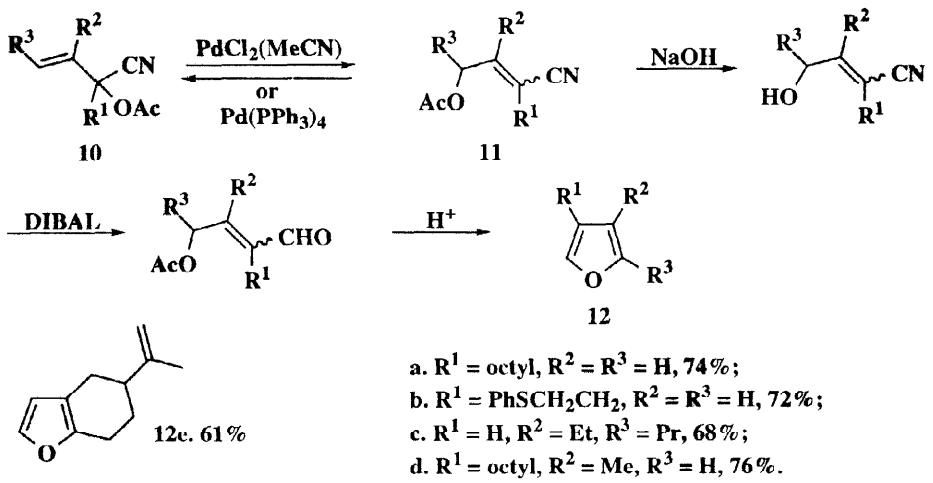
Scheme 6



It is noteworthy that 2,3-disubstituted furans could also be obtained through the reactions as depicted in Scheme 5 and 6 and the original configuration of the 3-substituents was preserved. This may be important for the synthesis of chiral molecules.

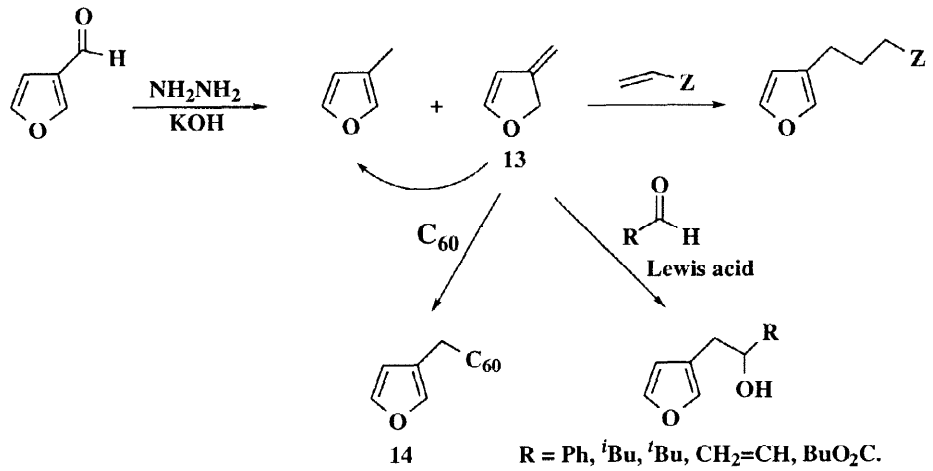
The rearrangement of α-cyanoallyl acetate **10**, catalyzed by $PdCl_2(MeCN)_2$ or $Ph(PPh_3)_4$ gave γ-cyanoallyl acetate **11**, which reacted with NaOH, DIBAL, and HCl sequentially to provide 3-substituted furans **12** with good total yields (Scheme 7).[18] This procedure was also used for the preparation of 2,3- and 3,4-disubstituted furans such as **12c**, **12d** and **12e**.

Scheme 7



3-Substituted furan can also be prepared from 3-methylene-2,3-dihydrofuran (**13**) and enophiles, such as CH_2=CHCOMe, CH_2=CHCN or RCHO by way of an ene reaction.[19] By employing this procedure, 1-(3-furylmethyl)-1,9-dihydrofullerene-60 (**14**) was synthesized from 3-methylene-2,3-dihydrofuran and C_{60} in 46% yield (Scheme 8).[20]

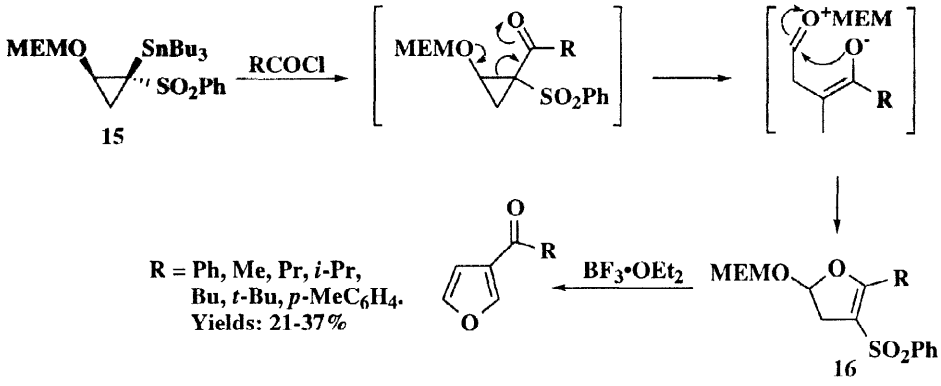
Scheme 8



When **13** reacted with (*R*)-glyceraldehyde acetonide in the presence of a catalytic amount of either Yb(fod)$_3$ or $AlMe_3$, high diastereoselectivity (> 98% de) was realized. Furthermore, a chiral alcohol was obtained in 81% ee when Ti(IV)-(*S*)-BINOL was used as a catalyst in the reaction of **13** with benzaldehyde.[19b]

Cyclopropane derivative **15** was applied successfully in the preparation of 3-acylfurans (Scheme 9).[21] Destannylative acylation of **15** provided dihydrofuran **16** in good yields, which was transformed into 3-acylfurans under the action of BF_3 in moderate yields. This method provides a general operation for the preparation of 3-acylfuran despite the fact that the total yields are usually low.

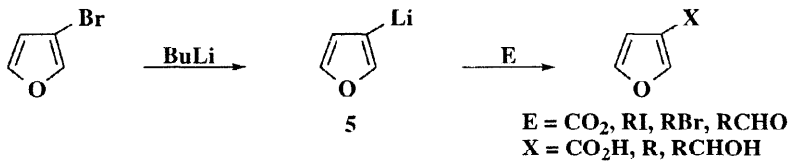
Scheme 9



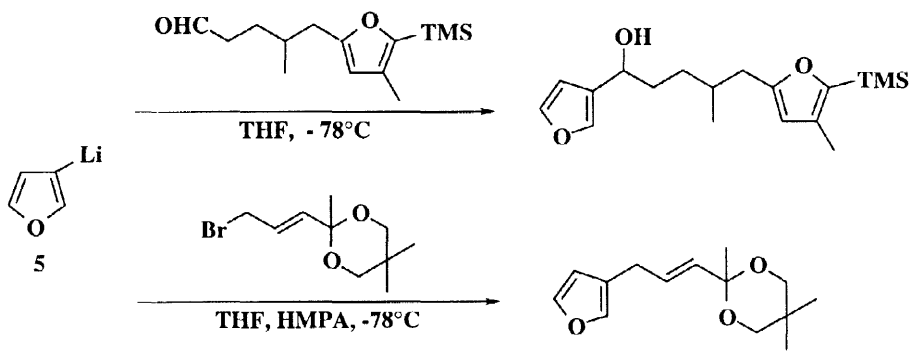
1.3. From Organometallics

Recently organometallic compounds have found a significant deployment in furan synthesis. For example, reaction of 3-bromofuran with *n*-butyllithium generated 3-lithiofuran (**5**),[22] which was converted to other 3-substituted furans upon quenching with various electrophiles (Scheme 10). The electrophiles were either halides or carbonyls (Scheme 11).[23]

Scheme 10



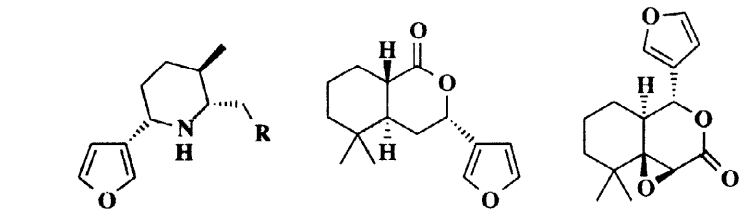
Scheme 11



Some natural products or their structurally related molecules containing 3-furyl moiety, such as (-)-anhydronupharamine (**17a**), (—)-nupharamine (**17b**),[24] ricciocarpin (**18**),[25] and a limonoid model **19**[26] were prepared from 3-lithiofuran (**5**).

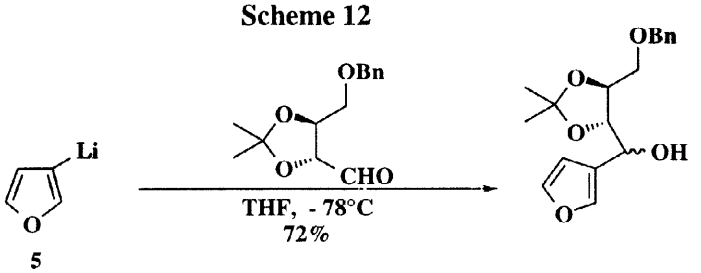
The main shortcoming of the use of 3-lithiofuran (**5**) as a precursor is that very low temperatures must be maintained throughout the reaction, because isomerization of **5** to 2-lithiofuran would take place at temperatures higher than -40°C. Furthermore, the chemoselectivity of **5** is also rather low, so that bifunctional electrophiles such as compounds with both aldehyde and ester functionalities would give rise to multiple nucleophilic attacks. For some less reactive reagents, like primary alkyl halides, good yields are obtained only in the presence of

HMPA. Despite this shortcoming, Paquette described the application of **5** to prepare a 3-substituted furan (Scheme 12),[27] which was employed to construction zaragozic acid/squalestatin backbone *via* photooxygenation procedure.



17a. R = $CH{=}CMe_2$;
17b. R = $CH_2C(OH)Me_2$ **18** **19**

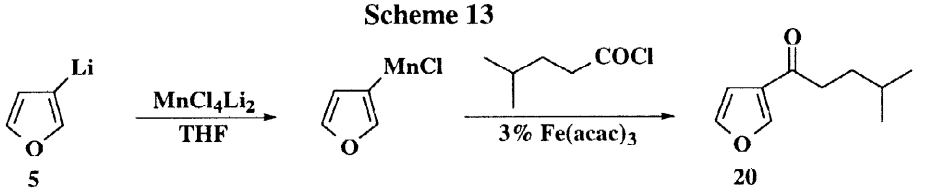
Scheme 12



5

A similar strategy was also utilized to the synthesis of perilla ketone (**20**) (Scheme 13).[28] In this approach, 3-lithiofuran (**5**) was allowed to react with one equivalent of $MnCl_2{\cdot}2LiCl$ complex to form an organomanganese compound. Subsequent acylation was performed by adding an equimolar amount of isohexanoyl chloride in the presence of a catalytic amount of iron (III) acetylacetone to furnish the desired **20**.

Scheme 13

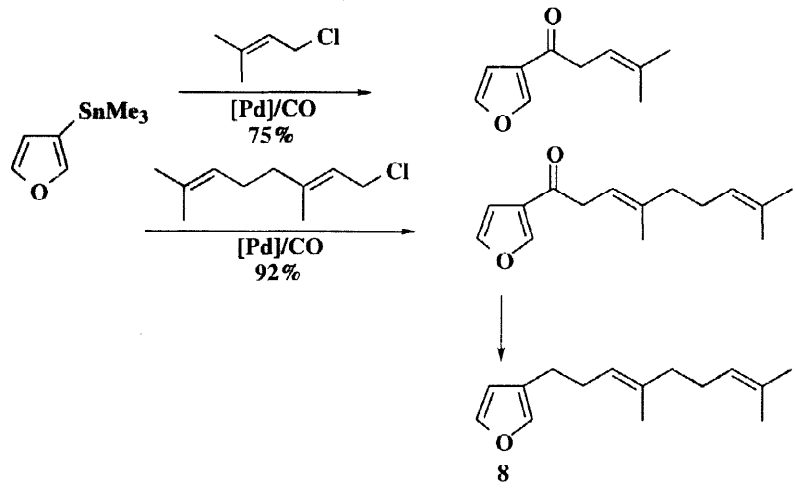


5 **20**

In addition to titanium and manganese derivatives, organocopper,[29] zinc[30] [see Section on 2,3,5-trisubstituted furans] and tin have all been utilized to the preparation of 3-substituted or polysubstituted furans. Organotin compounds are very versatile intermediates, which are able to react with a variety of electrophiles, including acid chlorides, allyl, vinyl or aryl halides, through palladium-catalyzed cross-coupling reactions to provide the corresponding products. They are able also to react with organohalides in the presence of CO under palladium-catalyzed carbonylation conditions to deliver carbonyl products. As expected for the palladium-catalyzed reactions, a number of functional groups are tolerated so that protection-deprotection procedures are not necessary.

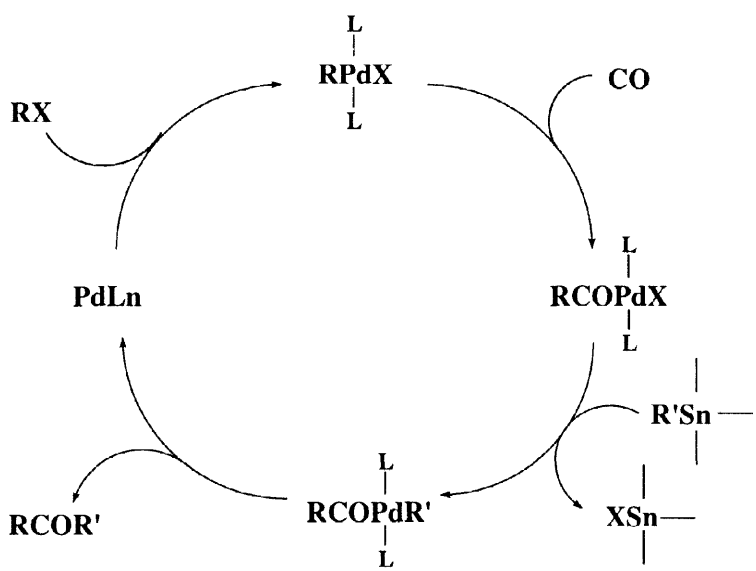
Stille studied the palladium-catalyzed direct cross-coupling of allyl halides with organotin reagents as well as the coupling of these reagent in the presence of carbon monoxide[31] and found that high regio- and stereoselectivities could be realized. 3-Substituted furans could also be obtained through this reaction as depicted in Scheme 14.

Scheme 14



A variety of palladium complexes, such as $PdCl_2(CH_3CN)_2/PPh_3$, $Pd(dba)_2/PPh_3$, $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$, can all catalyze the aforementioned reaction effectively. The actual catalyst is considered to be the palladium(0) species which is produced by *in situ* reduction of palladium (II). The reaction pathway includes oxidative addition of allyl halide to the palladium(0) catalyst to give an allylpalladium(II) halide. Transmetallation of the organotin reagent with allylpalladium(II) halide then yields the diorganopalladium complex, which gives the coupling product through reductive elimination (Scheme 15).

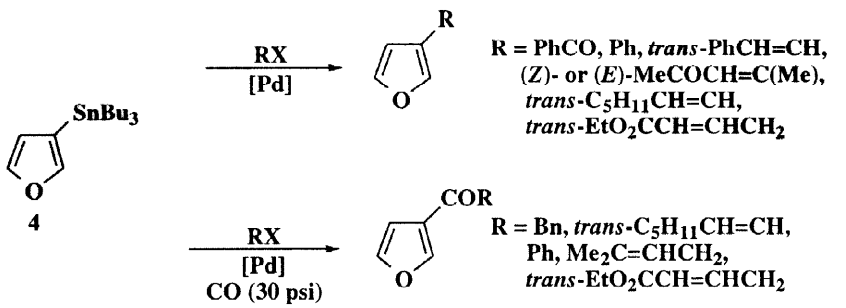
Scheme 15



Notwithstanding that the Stille cross-coupling reactions have been widely studied and exploited in organic synthesis, there have been only very few relevant applications in the literature concerning the preparation of 3-substituted furans. Making use of the Stille coupling reaction, Bailey[32] reported a short synthesis of perilla ketone (**20**) by employing 3-tri-*n*-butylstannylfuran (**4**). Degl'Innocenti[33] registered another Stille coupling example in which 3-iodopropenoylsilane reacted with **4** under palladium-catalyzed condition to furnish 3-(3'-furyl)propenoylsilane. As there are several functional groups in the substituent, it is likely that other 3-substituted furans could easily be obtained by functional group transformations. Balas and coworkers[34] also

carried out the Stille reaction to synthesize 3-furylamides or esters successfully through palladium catalyzed carbamoylation and alkoxycarbonylation of **4**. Yang and Wong[35] systematically studied the use of the Stille coupling reaction to realize 3-substituted and 3,4-disubstituted furans. They found that 3-(tri-*n*-butylstannyl)furan (**4**) and 3,4-bis(tri-*n*-butylstannyl)furan were excellent building blocks for the synthesis of substituted furans (*vide infra*). In their studies, a number of 3-substituted furans were obtained by using **4** as the staring material (Scheme 16).[35]

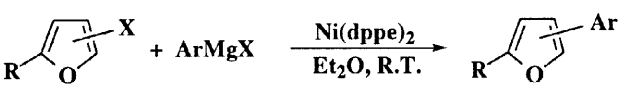
Scheme 16



The inherent advantage of the palladium-catalyzed coupling reaction of **4** is its mild reaction conditions, so that many functional groups can be tolerated, and it is also more chemoselective than 3-lithiofuran (**5**) (*vide supra*). In addition, the use of **4** eradicates the over-addition problem which hinders the use of other organometallic reagents such as cadmium, zinc, and magnesium. Aryl, vinyl, allyl halides, and acid chlorides can undergo palladium-catalyzed coupling reactions with **4** to produce the corresponding 3-substituted furans and halides and vinyl triflate can undergo carbonylation reactions with **4** to generate 3-furyl ketones.[35]

Coupling reaction can also be achieved under nickel-catalysis. Pridgen[36] carried out the cross-coupling reaction by using bromofurans and Grignard reagents as starting materials and Ni(dppe)Cl_2 as catalyst. This reaction provided the coupling products in excellent yields (Scheme 17). Takagi[37] reported the homo-coupling of 3-bromofuran to 3-(3'-furyl)furan by using Ni(COD)$_2$ as a catalyst.

Scheme 17

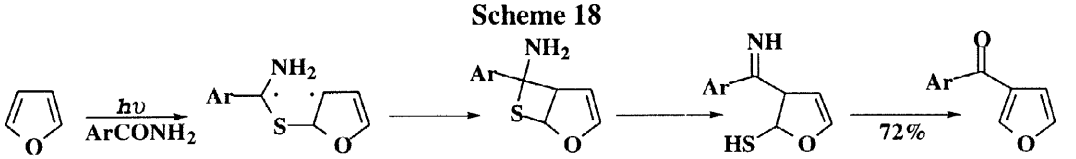


R = H, Bu; X = 2-, 3-Br; Ar = Ph, *o*-, *m*-, *or p*-MePh

1.4. From Miscellaneous Methods

Although the direct electrophilic attack on furan cannot provide 3-substituted furans, 3-acylfuran was obtained in a regioselective manner through a photo-induced reaction of arenecarbothioamide with an excess of furan as shown in Scheme 18.[38]

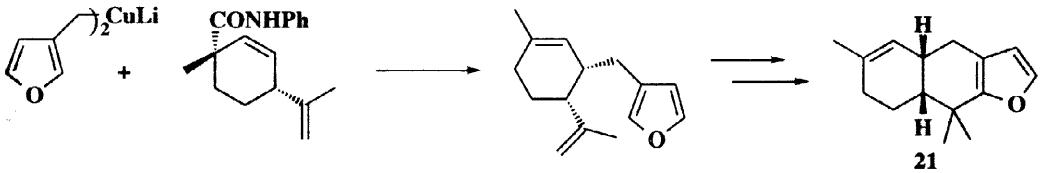
Scheme 18



Ar = Ph, 3- or 4-pyridyl, 2-furyl, 2-thienyl

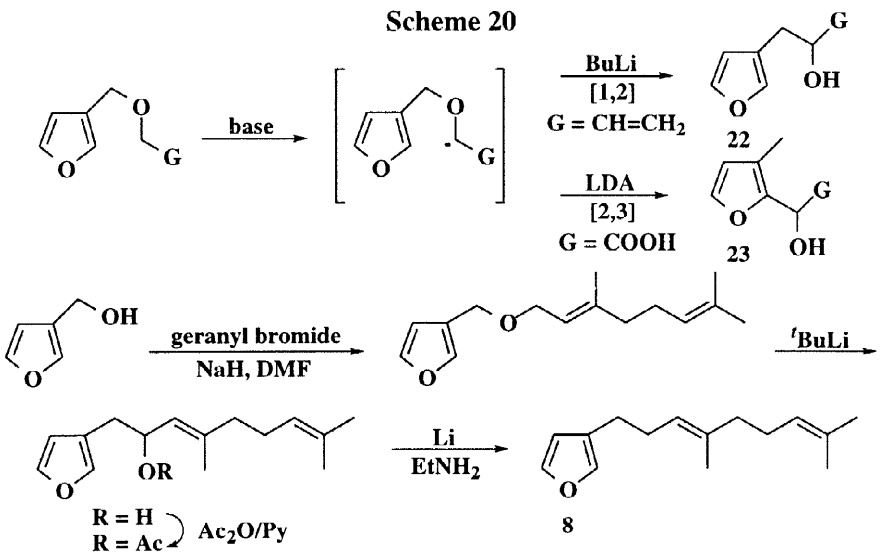
In addition to the aforementioned methods for the syntheses of 3-substituted furans, there are also some literature procedures in which 3-substituted furans can be obtained through the functional group transformations of substituents at the 3-position of a furan ring. Ho[39] reported the reaction of lithium di(3-furylmethyl)cuprate and *N*-phenylcarbamate to stereoselectively generate a 3-substituted furan, which can then serve as an intermediate for the synthesis of (—)-furodysin (**21**) (Scheme 19).

Scheme 19



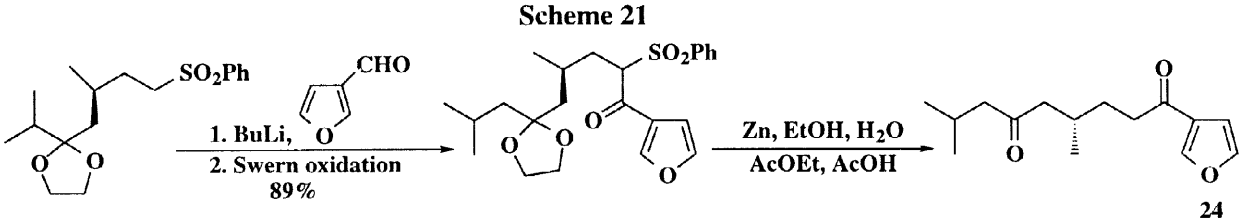
Tsubuki[40] showed that the Wittig rearrangement of 3-furylmethyl ether could be applied to the synthesis of dendrolasin (**8**). Thus, 3-furylmethyl ethers underwent rearrangement to give [1,2]- or [2,3]-sigmatropic shift products 3-substituted furans **22** and 2,3-disubstituted furans **23**, whose ratio depended upon the reaction condition and substituent G. When G was a vinyl group and the base used was *t*-butyllithium the ratio of [1,2]-rearrangement products and [2,3]-rearrangement products was >95 : <5. When G was COOH and the base was LDA only [2,3]-rearrangement product was produced. Dendrolasin (**8**) was accordingly synthesized (Scheme 20).

Scheme 20



Enders[41] achieved the synthesis of (—)-(*S*)-myoporone (**24**) by using 3-furylaldehyde as a reagent (Scheme 21).

Scheme 21



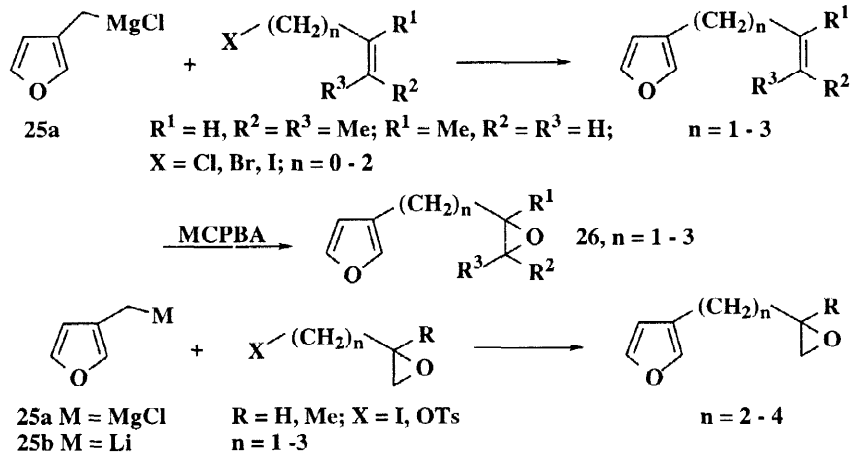
In a straightforward manner, Wiley[42] obtained 3-alkyl and 3-alkenyl substituted furans *via* the reaction of 3-furylmethanol tosylate and lithium dialkylcuprate (Scheme 22).

Scheme 22

R = Me, Bu, $Me_2C{=}CHCH_2$.

Tanis[43] used 3-furylmethyl-Grignard reagent **25a** as a starting material to prepare several 3-furyl epoxides **26**, which could undergo a cationic cyclization in the presence of Lewis acids to afford 2,3-disubstituted furans (Scheme 23).

Scheme 23



25a $R^1 = H, R^2 = R^3 = Me$; $R^1 = Me, R^2 = R^3 = H$; X = Cl, Br, I; n = 0 - 2

26, n = 1 - 3

R = H, Me; X = I, OTs; n = 1 -3

n = 1 - 3

n = 2 - 4

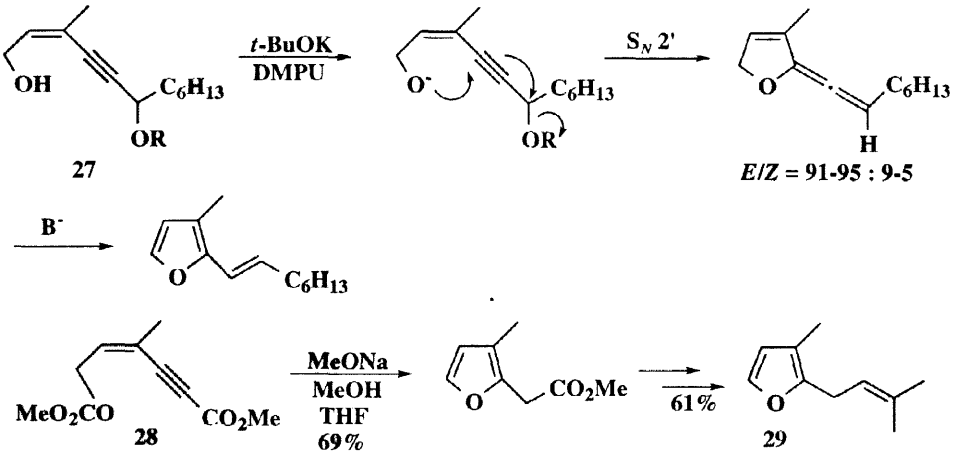
The coupling of Grignard reagent with a variety of 1-haloalkenes proceeded smoothly and in high yields in the presence of Li_2CuCl_4 or anhydrous $FeCl_3$ as catalyst. The lithium derivative of 3-methylfuran **25b** also underwent such coupling reactions in the presence of HMPA. It is noteworthy that the epoxide ring remains intact in this coupling reaction and no side-products, resulting from the anion rearrangement or epoxide opening, could be detected.[43]

2. Syntheses of 2,3-Disubstituted Furans

2.1. From Acyclic Precursors

Recently a novel methodology for the synthesis of 2,3-disubstituted furans by using 3-alkynyl allylic alcohols as ring cyclization precursors under basic conditions was described (Scheme 24).[44] In this manner, reaction of alkynyl allylic alcohol **27** (R = 2,6-dimethoxybenzoyl) with *t*-BuOK in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (dimethyl-1,3-propanediylurea, DMPU) produced alkoxide, which then underwent an S_N2' cyclization and subsequent isomerization to provide 2,3-disubstituted furan.

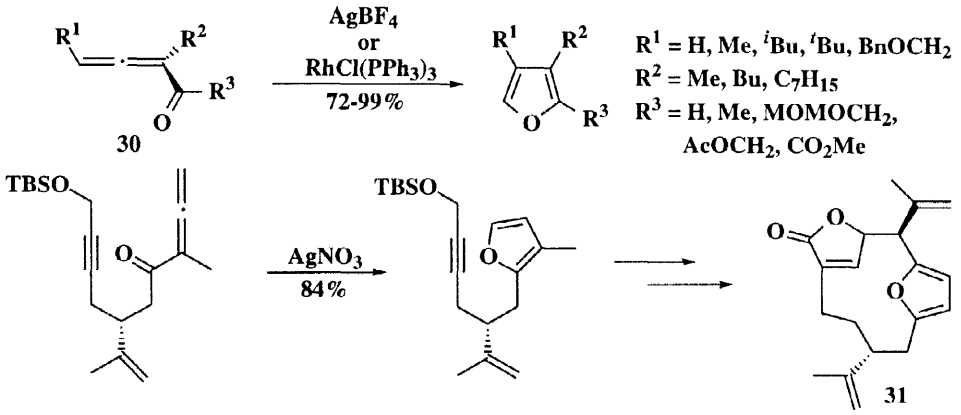
Scheme 24



This strategy appears to be ideally suited to for the preparation of acid-sensitive furans. DMPU can be replaced by 18-crown-6 in the reaction. Synthesis of rosefuran (**29**) may serve as a good example.[45] Because of its acid lability, the traditional acid-catalyzed cyclization of prenylated γ-keto aldehyde is obviously unsuitable for the synthesis of **29**. By using diester **28** as a starting material, a furan derivative was obtained in 69% yield. Further transformation of this furfurylacetate provided rosefuran (**29**) in 61% yield.

Another route to prepare 2,3-disubstituted furans involves Ag(I) or Rh (I) catalyzed cyclization of allenyl ketones and aldehydes **30** in MeCN (Scheme 25).[46] Further study of this reaction demonstrated that better results could be obtained using acetone-water-calcium carbonate.[47] Better results still were obtained if the reaction was carried out in acetone.[48] This procedure provides an approach to C-2 functionalized furans. Such compounds are of particular interest as intermediate prototypes for the synthesis of some naturally occurring molecules. To illustrate, kallolide B (**31**) was synthesized from a substituted furan intermediate by utilizing this cationic cyclization strategy (Scheme 25).[49] Needless to say this method can also be employed to prepare 2,4- and 2,3,4-substituted furans.

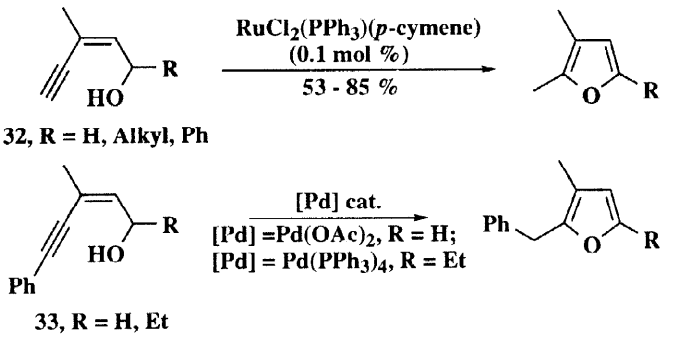
Scheme 25



γ-Ethynylallyl alcohol **32**, a similar starting material used by Marshall, undewent the ruthenium complex catalyzed transformation to form substituted furans. The reaction is carried out through an intramolecular addition of an alcohol functionality to a terminal triple bond. Noteworthy is that internal enynols **33**, which

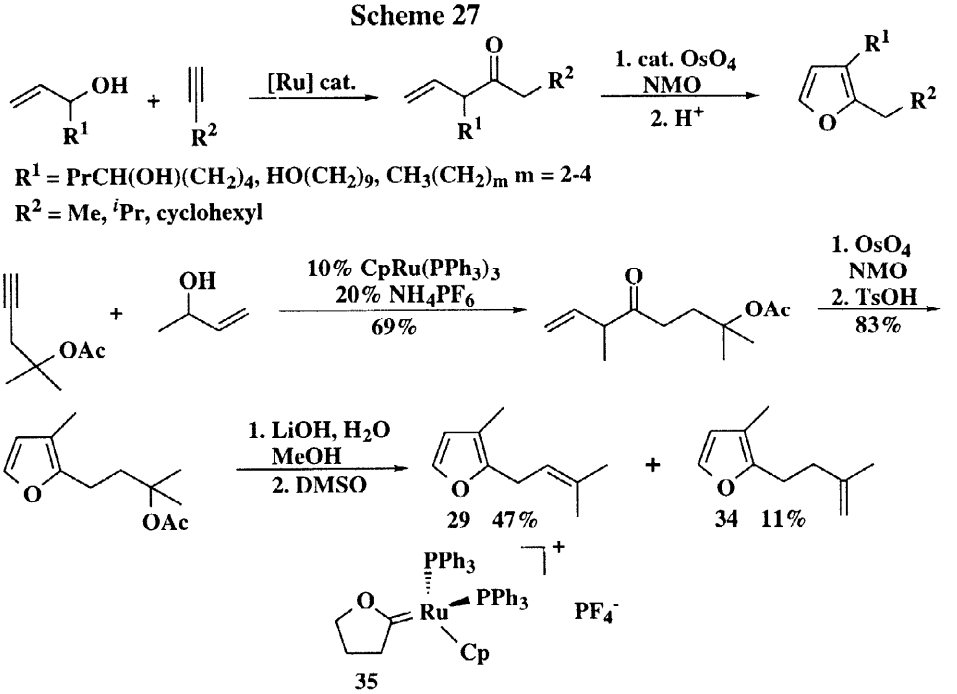
could not undergo the cyclization promoted by ruthenium complex, were transformed into furans by using palladium complexes as catalysts. In this way, the furans obtained can contain one extra C-2 substituent (Scheme 26).[50] This ruthenium-catalyzed cyclization reaction is a good method for the synthesis of 2-methylfurans with base-sensitive groups and complements Marshall's procedure, although it is only suitable for (Z)-enynols. Obviously, these Ru- and Pd-catalyzed reactions can also be employed for the synthesis of trisubstituted furans when R is alkyl, aryl or some other substituents.

Scheme 26



A two-step synthesis of 2,3-disubstituted furans from simple acetylenes and allyl alcohols was recently developed by Trost (Scheme 27).[51]

Scheme 27

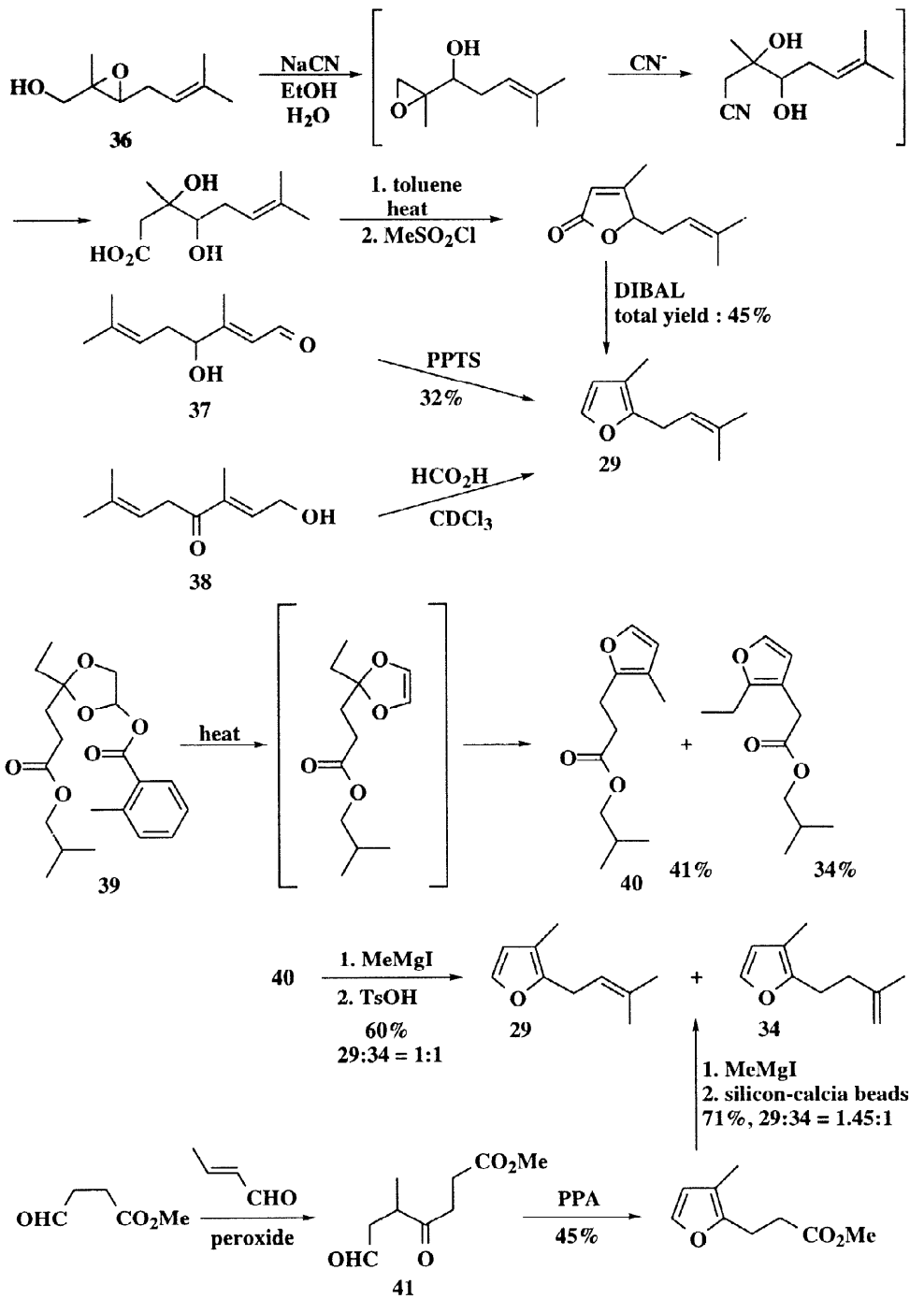


The advantage of this strategy is that the overall procedure consists of only two steps starting from terminal acetylenes and allyl alcohols, the first step being a simple addition. The second step involves only the loss of water with all reagents being used catalytically except for NMO. However, there are also some severe limitations, i.e. the R group of acetylenes cannot possess a hydroxy group because of the formation of a stable alkoxylidene complex **35**, and for the same reason, the amino group or other groups that may function likewise

should also be absent. Another restriction is that the osmium-catalyzed reaction will not allow the presence of other carbon-carbon unsaturation which is more nucleophilic than the β,γ-double bond of the substrates. The scope of this strategy can be illustrated by the straightforward synthesis of rosefuran (**29**).

Because of the structurally interesting and olfactive property of rosefuran (**29**), several reports describing the synthesis of this 2,3-disubstituted furan appeared in the last decade.[52] It is noteworthy that almost all these methods made use of 1,4-difunctional compounds as starting materials (Scheme 28).

Scheme 28

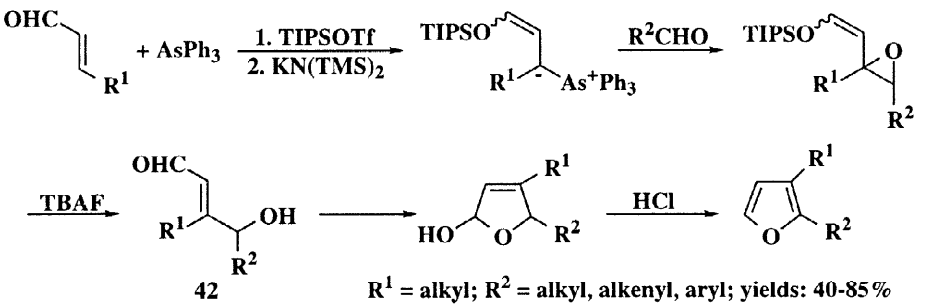


Takano[52a] chose hydroxymethyl substituted epoxide **36** as a starting material and employed the Payne

rearrangement as a pivotal step (Scheme 28). Furthermore, aldehyde **37** and ketone **38** also provided rosefuran (**29**) as a sole product with 32% and quantitative (by NMR analysis) yields respectively by using pyridinium *p*-toluenesulfonate (PPTS) and HCOOH as reagents.[52c] It must be noted that the preparation of **37** and **38** was not trivial.[52c] On the other hand, the protected γ-keto ester **39** was used in Meier's procedure as a ring cyclization precursor.[52b] Disappointingly, about equal amounts of isomers were produced in the cyclization and elimination stages. Although ester **41** also gave rise to an isomer in addition to rosefuran (**29**) after the Grignard reaction, the preparation of starting materials was in practice much simpler.[52d]

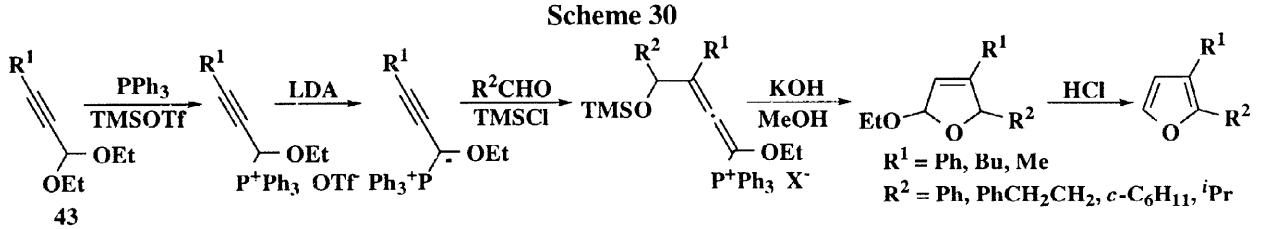
In addition to rosefuran (**29**), some other 2,3-disubstituted furans could also be prepared through cyclization of 1,4-difunctional substrates. For example, γ-hydroxy-α,β-unsaturated aldehydes **42** furnished 2,3-disubstituted furans under acidic conditions.[53] Aldehydes **42** were in turn produced from the following reactions: (1) treatment of enals and triphenylarsine with triisopropylsilyl triflate and base provided the ylides; (2) the ylides was quenched by aldehyde to afford epoxides; (3) reaction of epoxides and tetrabutylammonium fluoride gave aldehydes **42** (Scheme 29). It is worth noting that this furan synthesis route is a one-pot reaction with yields ranging from 51% to 85% and the R group of RCHO can either be alkyl or aryl.

Scheme 29



A similar procedure was also recorded when substituted acetylenic acetals were used as substrates.[54] The reaction of 1,1-dialkoxy-2-alkynes **43** with an equimolar amount of triphenylphosphine and TMSOTf yielded 1-ethoxy-2-alkynylphosphonium salts. Treatment of these salts with LDA generated the ylides, which reacted with aldehydes in the presence of TMSCl to produce allene derivatives. The removal of triphenylphosphine with methanolic KOH afforded cyclized products. Elimination of EtOH by using HCl eventually provided 2,3-disubstituted furans. Although the whole procedure involved four steps it was actually an one-pot reaction and suitable for both aromatic and aliphatic aldehydes (Scheme 30).[54]

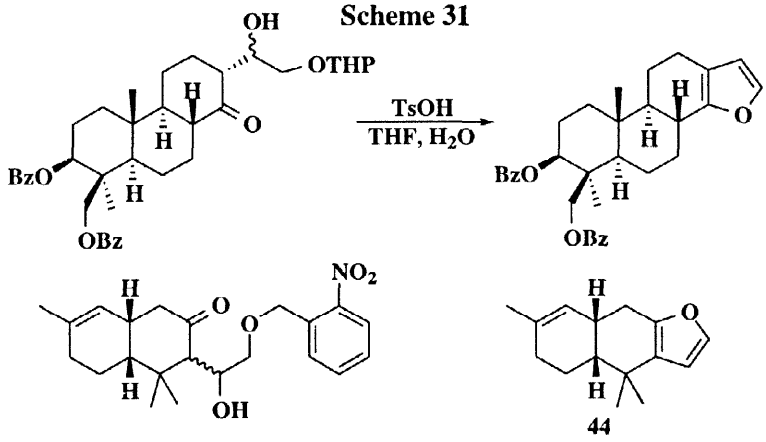
Scheme 30



Furan synthesis from 1,4-difunctional groups has also been employed to the preparation of natural products. Thus, the hydrolysis of 4-oxo-1-protected-1,2-dihydroxy compound with aqueous THF and *p*-TsOH gave furan derivative in good yield.[55] Similarly, (—)-furodysinin (**44**) was obtained from a similar starting material by photolyzed deprotection of the substituted benzyl group and acid catalyzed cyclization (Scheme

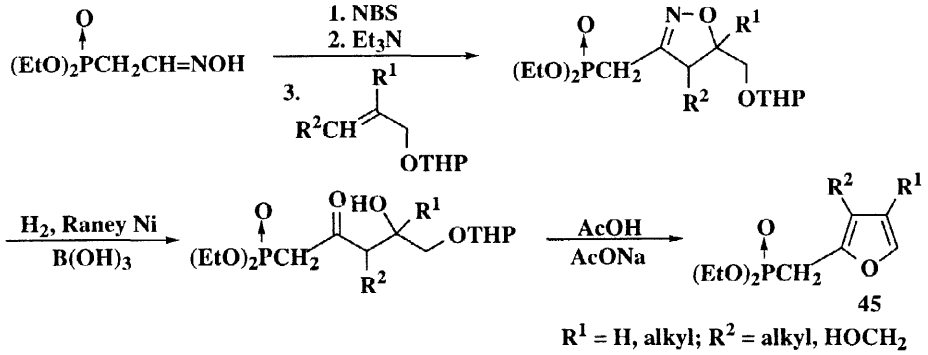
31).[56]

Scheme 31



Acid catalyzed cyclization of β,γ-dihydroxy ketones also led to substituted furans **45**. This avenue was first explored by starting from ketones obtained from a regioselective cycloaddition of a phosphorus-functionalized nitrile oxide to *O*-protected allyl alcohols and hydrogenation of products through reductive N-O bond fission (Scheme 32).[57] These phosphorus-containing furans **45** can be further transformed into 2-(1-phosphorylalkyl)furans, 2-(1-alkenyl)furans, and 2-acylfurans through an alkylation, olefination or oxidation of the phosphorus-stabilized carbanions derived from **45**. As can be seen from Scheme 32, this method can also be applied to the preparation of 2,4- and 2,3,4-substituted furans.

Scheme 32

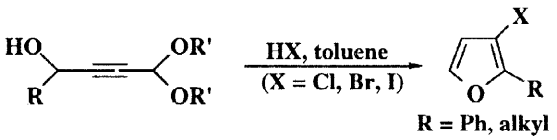


R^1 = H, alkyl; R^2 = alkyl, $HOCH_2$
R^1R^2 = -$(CH_2)_3$-

As shown previously, γ-acetoxy-α,β-unsaturated nitriles could be used to generate 2,3-disubstituted furans (Scheme 7).[18]

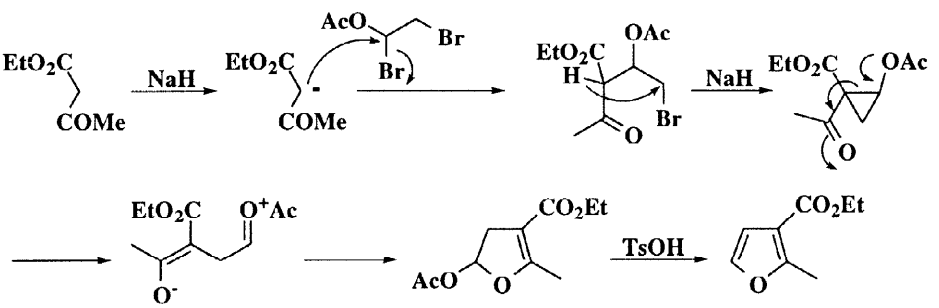
Acetylenic acetals were good precursors for the preparation of 3-halo-2-substituted furans.[58] As such, the acetals were normally allowed to react with HX in toluene under reflux to produce the desired furans with good to excellent yields (Scheme 33). Due to the fact that the halides can easily be metallated and substituted,[59] this method can be extended to other 2,3- and polysubstituted furans. Furthermore, acetylenic acetals can be replaced by acetylenic ketones.

Scheme 33



1,2-Dibromoethyl acetate could be used as a starting material for the Feist-Benary condensation to form substituted furans.[60] To exemplify, treatment of ethyl acetoacetate with bromoacetate and sodium hydride provided in 74% yield dihydrofuran, which reacted with *p*-TsOH to furnish a quantitative yield of disubstituted furan (Scheme 34). Although this procedure is befitting for 2-substituted-3-alkoxycarbonylfurans the scope of this method is somehow limited to the synthesis of 2,3-disubstituted furans because alkyl-substituted dibromoacetates appear to be rather unstable.

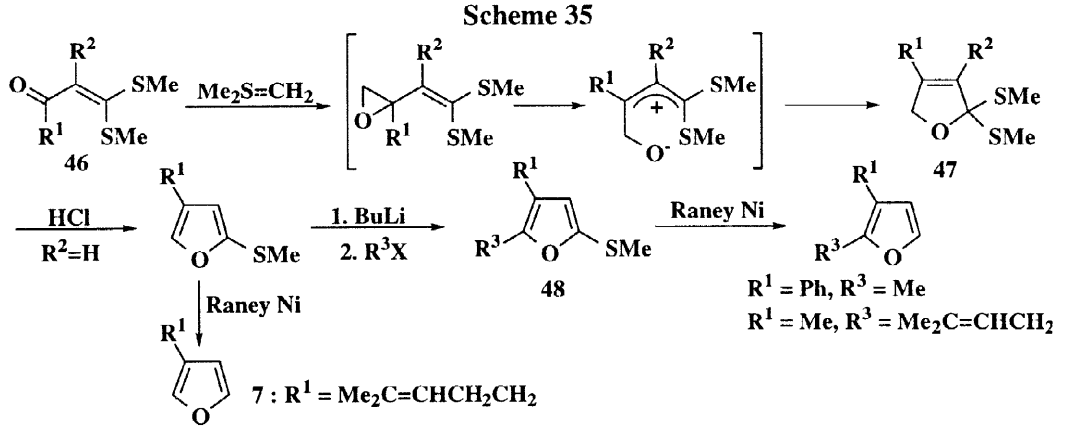
Scheme 34



Diphenylthiohomoallylic alcohol could also be cyclized to form 2,3-disubstituted and 3-substituted furans (Scheme 5).[16]

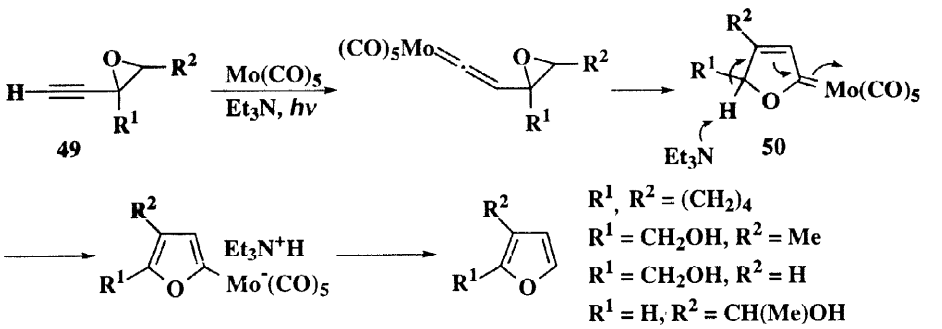
Ketene dithioacetals **46**, readily prepared through the reaction of ketones or aldehydes with carbon disulfide, reacted with dimethylsulfonium methylide to generate 2,2-bis(methylthio)-2,5-dihydrofurans **47**. Treatment of **47** with HCl followed by lithiation at the furan α–position and subsequent electrophile attack gave 2-methylthiofuran derivatives **48**. Raney nickel desulfurization of the SMe group of **48** yielded 2,3-disubstituted furans (Scheme 35).[61] Because R^1 and R^2 of dithioacetals **46** can be introduced by choosing appropriate starting materials and the coupling reaction of SMe group is performed with Grignard reagents, dihydrofurans **47** can also serve as synthons for a variety of substituted furans (*vide infra*).

Scheme 35



Epoxyalkynes **49** were converted to substituted furans in the presence of a catalytic amount of triethylamine and molybdenum pentacarbonyl under irradiation (Scheme 36).[62] The products can be 2-, 3-, and 2,3-substituted furans. It is believed that the reaction proceeded through a concerted rearrangement of epoxyvinylidenecarbenes to the cyclic α,β-alkenyloxacarbene intermediate **50**. Deprotonation of **50** and subsequent protonation of the molybdenum-furan bond then yielded furans.

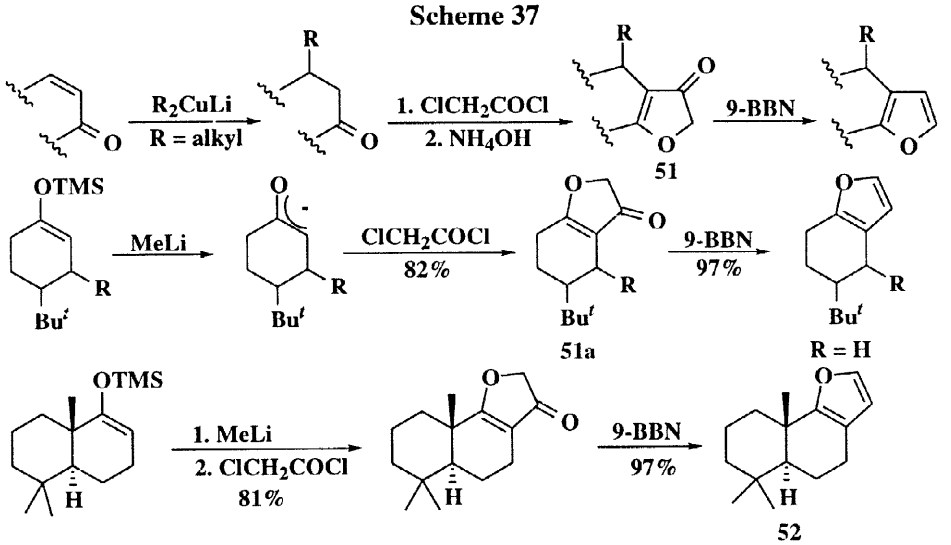
Scheme 36



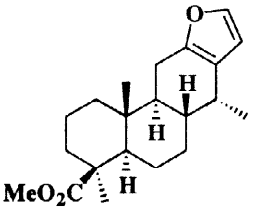
49 **50**

β-Oxodihydrofurans **51** were easily reduced to 2,3-disubstituted furans by using 9-BBN (Scheme 37).[63] Two general methods were chosen to prepare β-oxodihydrofurans. Conjugate addition of lithium dialkylcuprate to an α,β-unsaturated ketones and subsequent quenching with chloroacetyl chloride followed by base promoted an intramolecular ring closure, providing a convenient entry to **51**. By following this route, γ-substituted 2,3-disubstituted furans (R = alkyl) were made. Trimethylsilyl enol ether reacted with MeLi followed by trapping of enolate with chloroacetyl chloride afforded another approach to β-oxodihydrofuran. This procedure furnished γ-unsubstituted 2,3-disubstituted furans (R = H).[63] The occurrence of natural products having this structural unit is widespread. Using this procedure the natural molecule pallescensin A (**52**) was synthesized in high yields (Scheme 37).[64] Similarly, the natural products (+)-methyl vouacapenate (**53**) and racemic 7-*epi*-pinguisone (**54**) were also prepared using this strategy.[64]

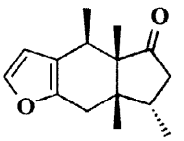
Scheme 37



51 **51a** **R = H** **52**



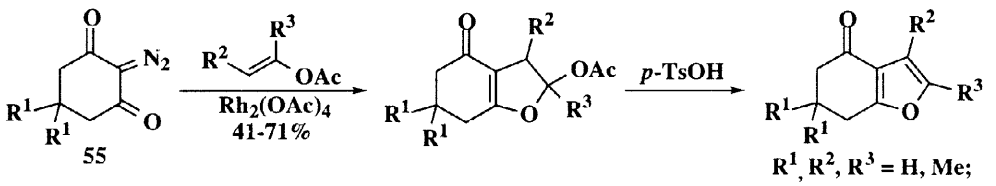
53



54

Furans fused with six-membered rings at C2-C3 could also be realized from diazocyclohexane-1,3-diones **55** which reacted with vinyl acetate in the presence of a rhodium catalyst to furnish dihydrofurans through 1,3-dipolar cycloaddition. Direct treatment of these dihydrofurans with a catalytic amount of *p*-TsOH gave desired substituted furans (Scheme 38).[65]

Scheme 38

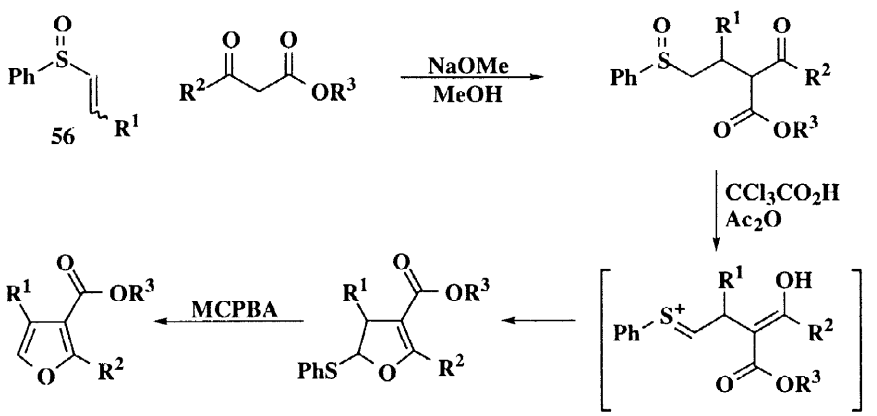


55

R^1, R^2, R^3 = H, Me;

Chan and Lee showed that alkenyl sulfoxides **56** were able to react with β-ketoesters through a Michael addition, which was followed by consecutive Pummerer rearrangement and oxidation-elimination to furnish 2,3-disubstituted furans (R^1 = H) in good overall yields 2,3,4-trisubstituted furans if R^1 is not H (Scheme 39).[66]

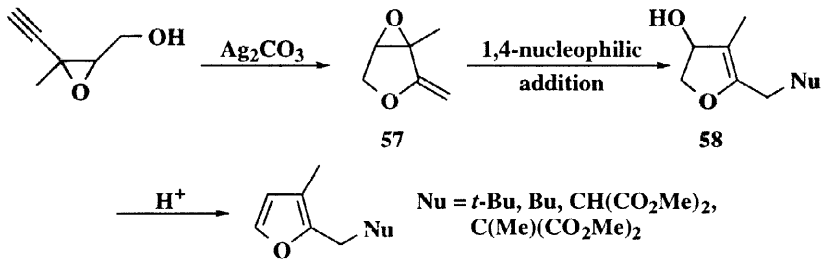
Scheme 39



R^1 = H, Me; R^2 = Me, Et, Ph, Bn; R^3 = Me, Et

3,4-Epoxy-2-methylene oxolane **57**, which was easily prepared form ethynyl epoxide through a silver assisted heterocyclization,[67a] can be conveniently converted to functionalized 3,4-dihydrofurans through nucleophilic 1,4-addition by using cyanocuprate or Pd(0)-catalyzed addition of malonate derivatives. Aromatization of these dihydrofurans under an acidic condition provided 2,3-disubstituted furans in high yields (Scheme 40).[67b] Although 1,4-addition of carbon nucleophiles to vinyl epoxides is known when soft nucleophiles such as organocopper reagents are used, the reaction of Bu_2CuLi with **57** did not lead to the expected 1,4-addition product. More nucleophilic cyanocuprates, however, gave addition products **58** in high yields.

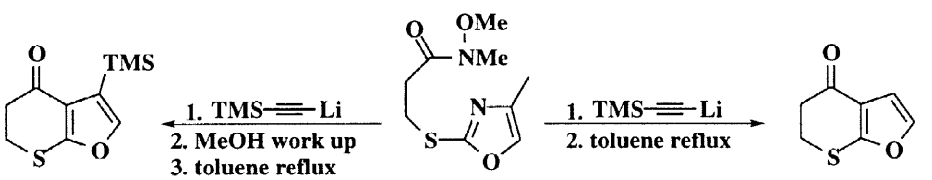
Scheme 40



Radical cyclization of bromoacetals can also provide 2,3-disubstituted furans when 3-substituted propargy alcohols were replaced by 1,3-disubstituted propargyl alcohols (Scheme 4).[15b]

Cycloaddition-retro cycloaddition of monosubstituted acetylenes with appropriately substituted oxazole **1** also gave 2,3-disubstituted furans (Scheme 1, R^4 = H; R^3 = Me; R^1 or R^2 = substituent, R^2 or R^1 = H).[11] In these cases the reaction products often delivered mixtures of 2,3- and 2,4-disubstituted furans because of poor regioselectivities of the key cycloaddition step. An intramolecular version of this reaction was applied to the synthesis of 2,3-disubstituted furans (Scheme 41).[68] This reaction provided an approach to 2,3-disubstituted furans with α-thio atom substituent. The fused ring size can be 5-, 6- or 7-membered rings. Another benefit of this reaction is that it also afforded 4-trimethylsilyl substituted furans which were transformed into some other 2,3,4-trisubstituted furans.

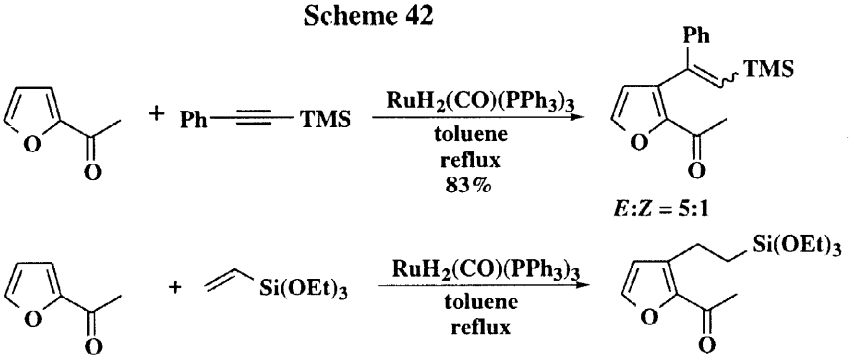
Scheme 41



2.2. From 2-Substituted Furans

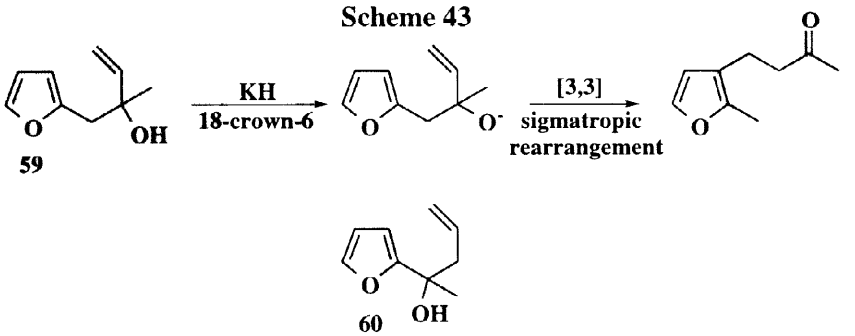
2-Furyl ketone was able to react with alkenes or internal acetylenes under the catalysis of $Ru(H)_2(CO)(PPh_3)_3$ through substitution of the multiple bonds at C-3 of the furyl ketone to produce 2,3-disubstituted furans with high regioselectivity (Scheme 42).[69] These findings represent a direct and catalytic addition of otherwise inactive C-H bonds in aromatics across carbon-carbon multiple bonds. Surprisingly, the addition of furan ketone to terminal acetylenes did not take place.

Scheme 42



In the presence of KH and 18-crown-6, (2'-furyl)-butenol **59** could undergo the anionic oxy-Cope rearrangement to furnish the corresponding product. In this reaction the use of crown ether was crucial, because in its absence the recovered alcohol was the major product. Under the same reaction condition the reaction failed for furan **60** (Scheme 43).[70]

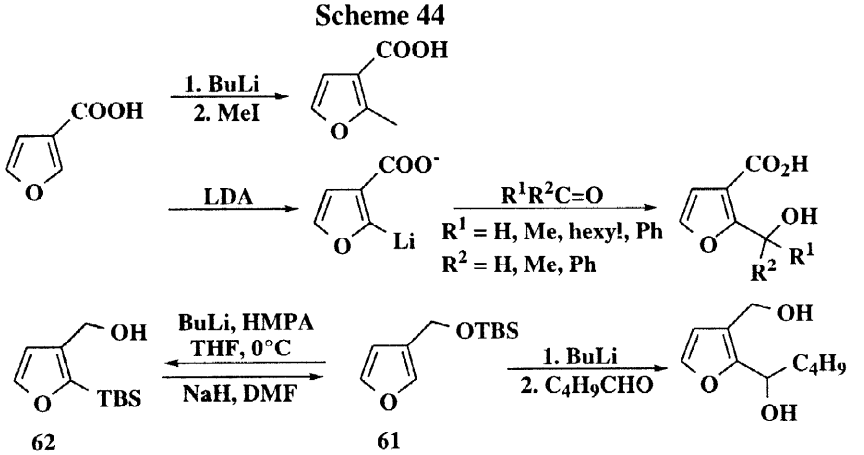
Scheme 43



2.3. From 3-Substituted Furans

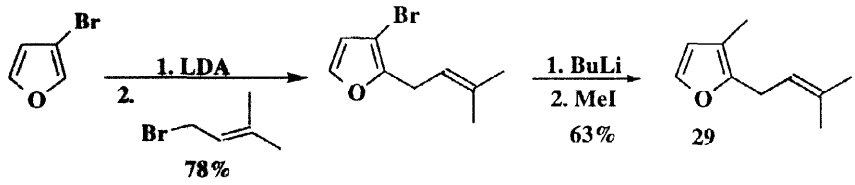
Lithiation of 3-substituted furan can be performed with high regio-control and quenching of the resulting 2-lithiofuran with an electrophile produced 2,3-disubstituted furans.[59] Lithiation of 3-furoic acid with LDA or BuLi produced a dianion, which reacted with aldehydes, ketones and MeI to afford the corresponding disubstituted furans.[71] 3-Furfuryl alcohol derivatives could also be lithiated at C-2.[72] It is interesting that the silyl group of 3-[(*t*-butyldimethylsilyl)oxymethyl]furan (**61**) could rearrange to C-2 through an 1,4-O—C-migration[73] and the reverse 1,4-C—O-rearrangement reaction occurred when 2-silyl-3-hydroxymethylfuran **62** was treated with NaH in DMF or THF (Scheme 44).[74]

Scheme 44



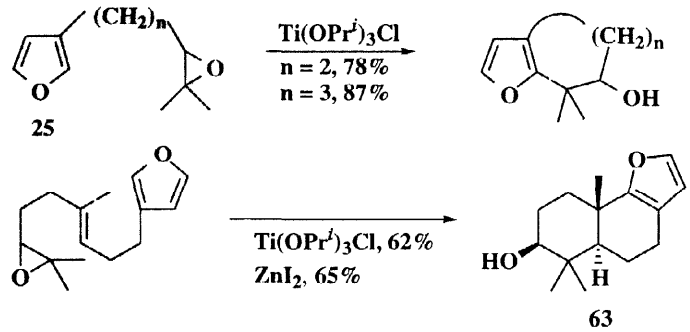
Using a combination of the aforementioned method with metal-bromine exchange rosefuran (**29**) was obtained from 3-bromofuran with good yield (Scheme 45).[59,75] Regioselective lithiation at C-2 with LDA and quenching of the anion with an isoprenylbromide provided 2-prenyl-3-bromofuran. Lithium-bromine exchange using BuLi and quenching with MeI led to rosefuran (**29**).

Scheme 45



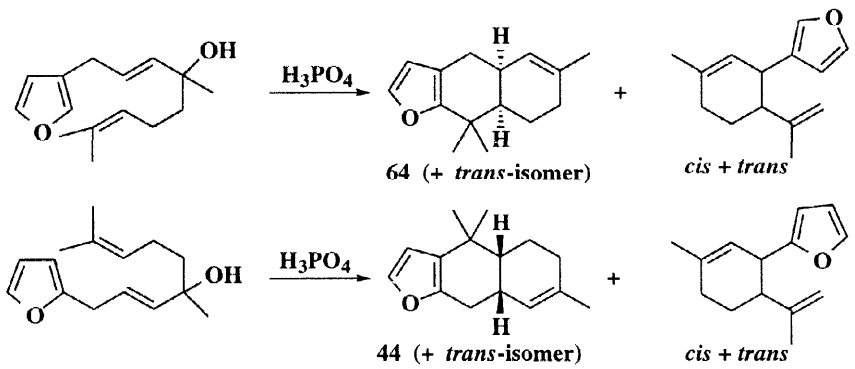
Epoxy furans (Scheme 23) were converted to bicyclofurans in high yields under cationic cyclization conditions using a Lewis acid. A naturally occurring molecule, namely 3β-hydroxypallescensin (**63**), could be synthesized by this protocol (Scheme 46).[76]

Scheme 46



Racemic forms of natural products, furodisinine (**64**) and furodisine (**44**) were produced from 2- or 3-substituted furans through a cationic cyclization process. The reaction was usually accompanied by some *trans*-fused isomers and limonene derivatives as side-products (Scheme 47).[77]

Scheme 47



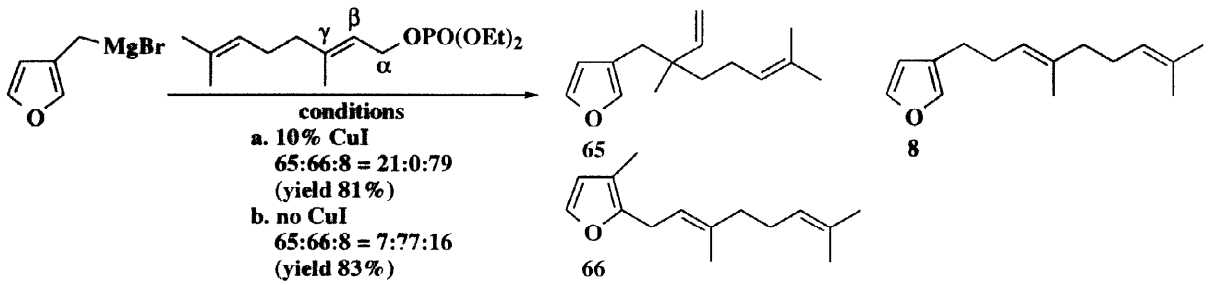
It is interesting to note that the (3-furfuryl)methyl Grignard reagent shown in Scheme 48 reacted with geranyl diethyl phosphate to produce 2,3-disubstituted furan **66** with about 25% of **65**, the product of γ-attack. However, in the presence of CuI the reaction gave rise to the α-attack furan **8** as the major product. When geranyl bromide, a softer electrophile than the phosphate, was employed the γ-regioselectivity decreased from 77% to 45% (Scheme 48).[78]

A direct bromination could be realized regioselectively by reaction of 3-methylfuran with NBS (Scheme 49).[79] The product 2-bromo-3-methylfuran could be converted to other furans through further transformations.

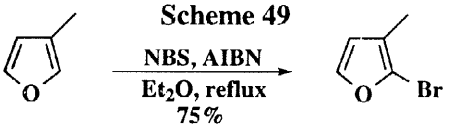
As has been discussed, 3-furfuryl ether could be rearranged to 2,3- and 3-substituted furans (Scheme

20).[40]

Scheme 48



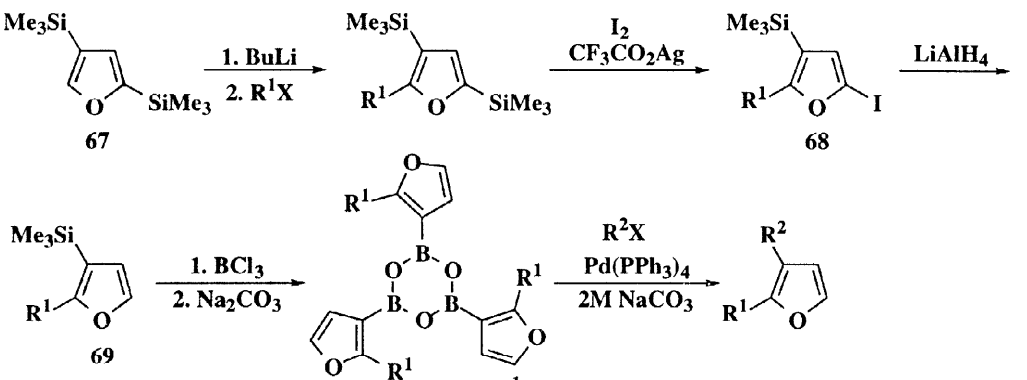
Scheme 49



2.4. From Other Substituted Furans

2,3-Disubstituted furans can be conveniently synthesized from 2,4-bis(trimethylsilyl)furan (**67**).[80] Regioselective lithiation/quenching could be achieved at C-5 position. Regiospecific *ipso*-iodination followed by $LiAlH_4$ reduction afforded 2-substituted-3-trimethylsilylfurans **69**. Conversion of **69** with BCl_3 and Suzuki coupling eventually provided 2,3-disubstituted furans (Scheme 50). The iodine atom of **68** can be converted to other substituents *via* other reactions, such as metal mediated coupling reaction and lithiation-electrophile substitution. Thus, 2,4-bis(trimethylsilyl)furan (**67**) can serve as a versatile building block for the preparation of substituted furans.

Scheme 50

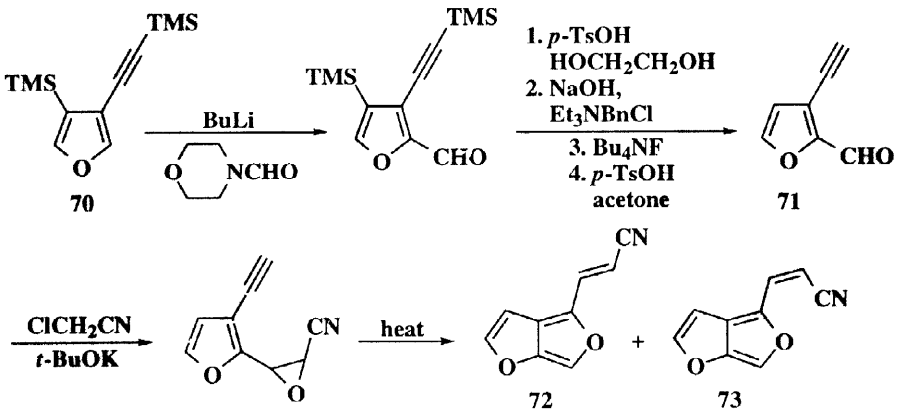


3,4-Disubstituted furan **70** could be transformed to 2,3-disubstituted furan **71**, which led to furo[3,4]furan **72** and **73**, interesting compounds containing diheteropentalene skeletons (Scheme 51).[81]

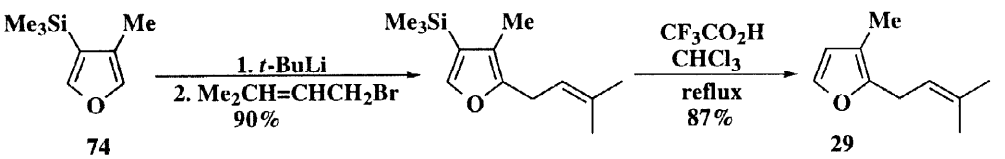
3,4-Disubstituted furan **74** can also be converted to 2,3-disubstituted furans and the preparation of rosefuran (**29**) shown in Scheme 52 is an appropriate example.[80] Deprotonation appeared to take place at the less hindered C-2 position when using *t*-BuLi as base. Electrophile attack and protodesilylation furnished

rosefuran (**29**) in an overall yield of 78% from **74**. This procedure provides an efficient preparation of **29** in high yield and good regioselectivity.

Scheme 51

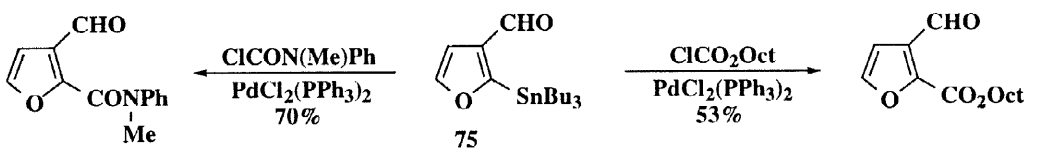


Scheme 52



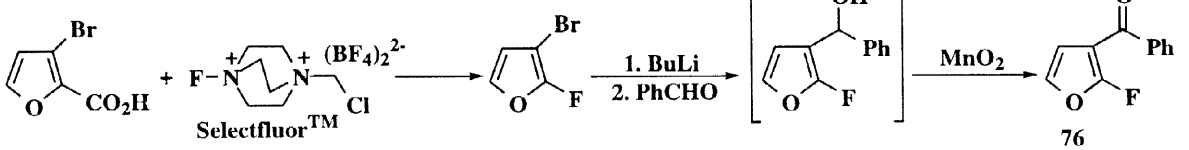
Similar to 3-trialkylstannylfuran, 2-tributylstannylfuran **75** also coupled with chloroformates and carbamoyl chlorides in the presence of palladium complex to produce the corresponding coupling compounds (Scheme 53).[82]

Scheme 53



Fluoro organic compounds are of importance in medicinal and agricultural chemistry because of their unique biological activities. In this area, Forrest recently reported the preparation of fluorofurans *via* fluorodecarboxylation (Scheme 54).[83] In this method, 3-bromo-2-furoic acid was treated with Selectfluor™ reagent to provide 3-bromo-2-fluorofuran. Lithium/bromine exchange and trapping of the fluorolithiofuran led to the expected but unstable fluorofuran. A direct oxidation finally produced 2-fluoro-3-benzoylfuran (**76**) in 11% overall yield.

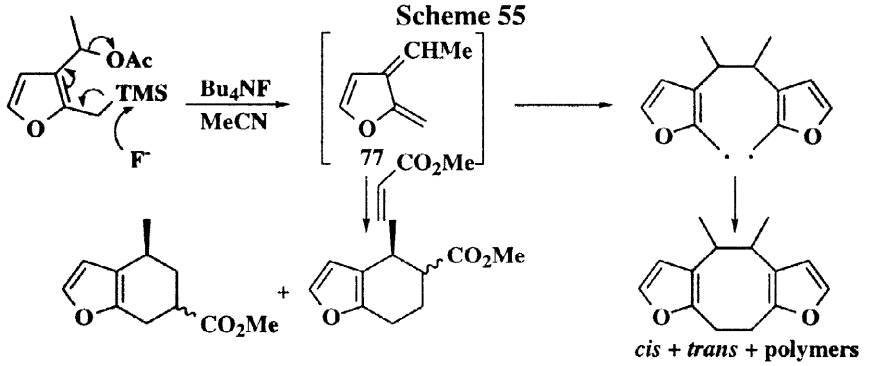
Scheme 54



Fluoride-promoted 1,4-conjugative elimination of furan as expected generated 2,3-dimethylene-2,3-

dihydrofuran **77**, the furan-based *o*-quinodimethane, which could undergo [4+4] addition through a radical mechanism to produce head-to-head dimer and by Diels—Alder reaction to give furanocyclohexane rings (Scheme 55).[84] In this manner, eight-membered ring compounds fused with furan rings can be obtained.

Scheme 55

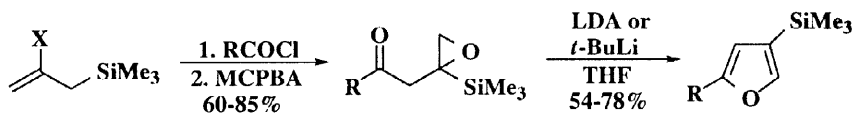


3. Synthesis of 2,4-Disubstituted furans

3.1 From Acyclic Precursors

The synthesis of 2-substituted-4-trimethylsilylfurans was achieved by treatment of the epoxycarbonyl derivatives **78** with LDA or *t*-BuLi.[85] The epoxycarbonyl compounds were obtained through the reaction of a variety of acid chlorides with either 2,3-bis(trimethylsilyl)propene or 2-trialkylstannyl-3-trimethylsilylpropene in the presence of a Lewis acid and was followed by epoxidation with MCPBA (Scheme 56).[85] This reaction could be used as a general method to prepare 2-substituted-4-trimethylsilylfurans. Combining with transmetallation of trimethylsilyl group at the furan ring, other 2,4-disubstituted furans can be produced.

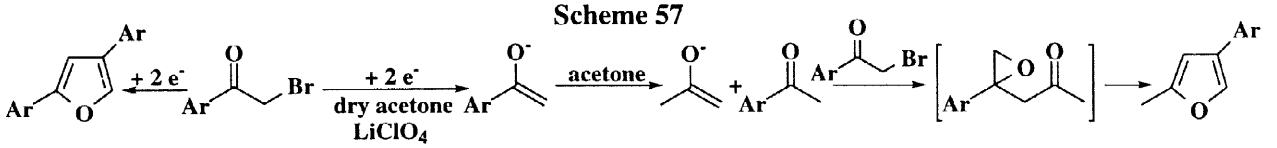
Scheme 56



X = $SnBu_3$, $SiMe_3$ — **78** — R = Ph, Me_2C=CH, *i*-Bu, *c*-C_6H_{11}, 2-furyl, (*E*)-PhCH=CH

Epoxycarbonyl intermediates can also be produced by an electrochemical method.[86] The epoxy carbonyl intermediates were then converted to 4-aryl-2-substituted furans (Scheme 57).[86] The advantage of this procedure is the easy availability of starting materials and good yields. However, the disadvantage lies in the fact that only half of phenacyl bromide can be consumed in the reaction. This electrochemical procedure was used earlier to prepare 2,4-diarylfurans using α-bromoacetylarenes.[87]

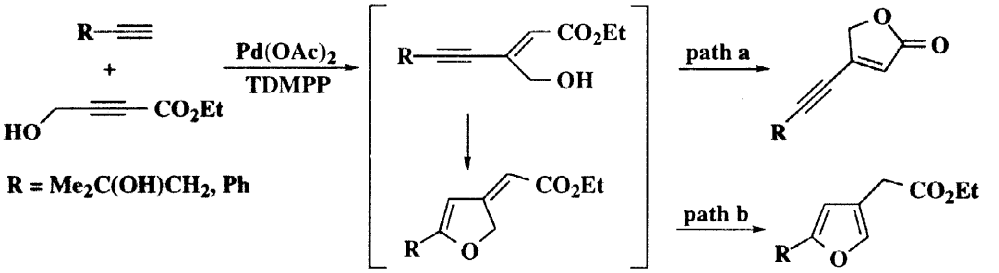
Scheme 57



The addition of terminal alkynes to γ-hydroxyalkynoates catalyzed by palladium is another entry to form

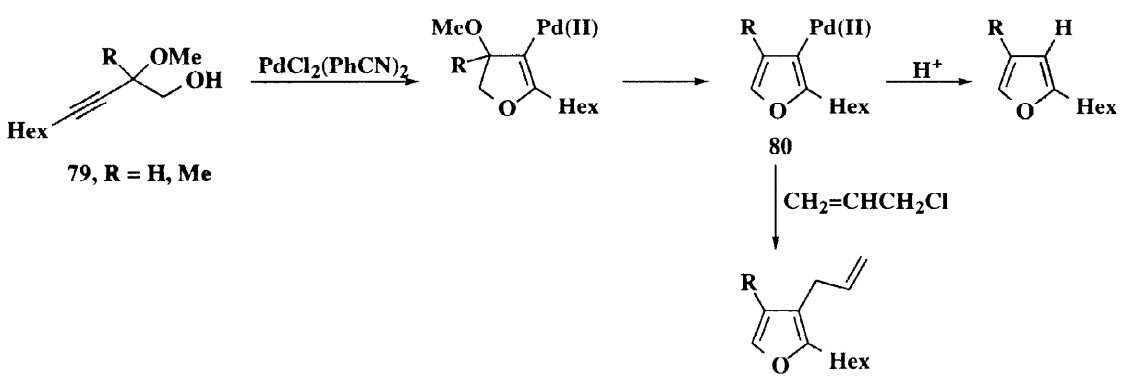
2,4-disubstituted furans (Scheme 58).[88] In this approach, the ratio effect of palladium salt to ligand, tris(2,6-dimethoxyphenyl)phosphine (TDMPP), was critical. When 2 mol% $Pd(OAc)_2$ and 2 mol% TDMPP were used, the reaction gave rise to butenolides with a small amount of furans. On the contrary, when the reaction is carried out by using 5 mol% $Pd(OAc)_2$ and 2 mol% TDMPP followed by 0.75-1.5 equiv. of DBU, 87% and 73% of 2,4-disubstituted furans were furnished in the case when R is $Me_2C(OH)CH_2$ and Ph, respectively. The role of DBU is to complete the tautomerization of isofurans.

Scheme 58



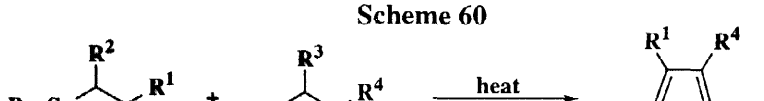
Palladium complex can also catalyze the conversion of substituted 3-alkyne-1,2-diols **79** to 2,4-disubstituted furans (Scheme 59).[89] This procedure affords various types of substituted furans *via* intramolecular addition of 3-alkyne-1,2-diols. The catalyst may be $PdCl_2(PhCN)_2$ or $PdCl_2(MeCN)_2$. Palladium chloride afforded a lower yield and when $Pd(PPh_3)_4$ was used, starting materials were recovered. Addition of a trace amount of water or dilute HCl can improve the yields. Allyl chloride may also be used to trap the 3-Pd-furan intermediates to provide 2,3-disubstituted or 2,3,4-trisubstituted furans. The addition of oxiranes can increase the yield of allylfuran because they could serve as proton scavenger.[89]

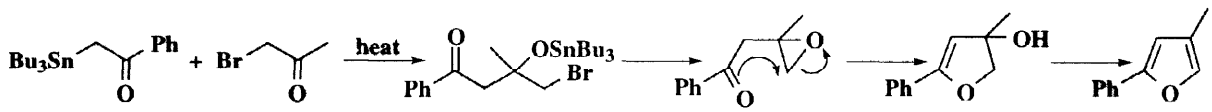
Scheme 59



2,4-Disubstituted furans can also be prepared by the reaction of tributyltin enolates **81** and α-haloketones (Scheme 60).[90] However, the furans were not derived from the normal cross-coupling product of the starting 1,4-diketones. The reaction might proceed through the addition of an enolate to the carbonyl of the α-bromoketone, followed by elimination of tributyltin bromide to provide the β,γ-epoxy ketone, which then cyclized. The reaction took place without catalysis or additional reagents. If there were more substituents at the tin enolate and/or haloketone, furans with substitution patterns other than 2,4- can be obtained.

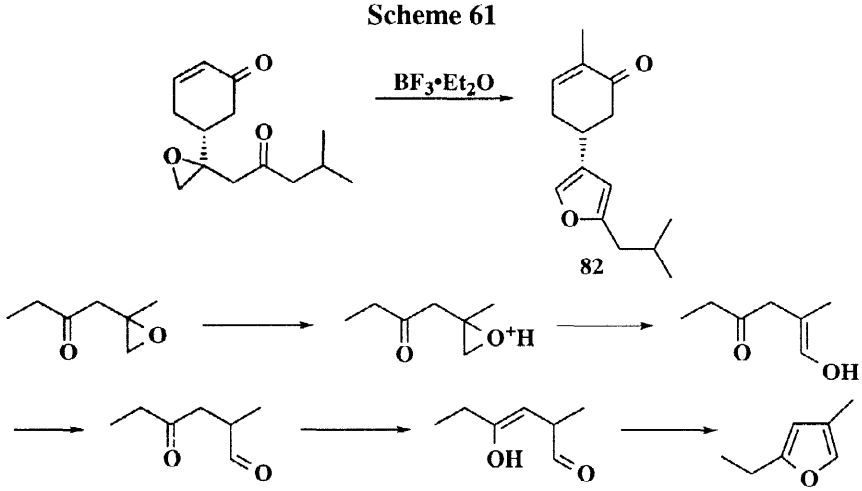
Scheme 60





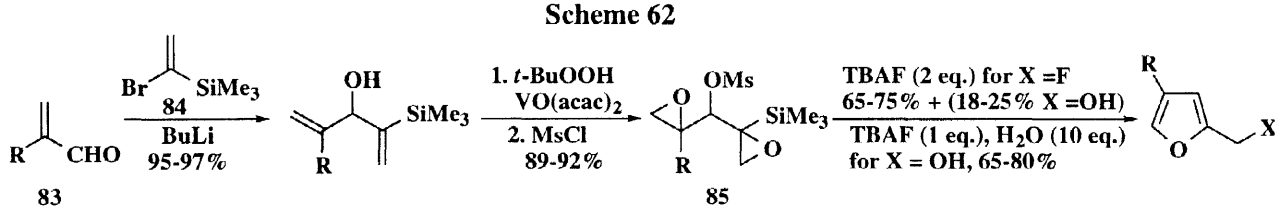
The β,γ-epoxy ketone route to 2,4-disubstituted furan was successfully put to use in the synthesis of natural products such as a monoterpenoid trisubstituted furan[91a] and (+)-bilobanone (**82**)[91b] by using epoxyketones as starting materials. It was believed that the protonation first took place at the epoxy ring, then 1,4-dicarbonyl compound was produced which could be separated and transformed to furan products (Scheme 61).[92] It is noteworthy that when BF_3•Et_2O was employed as catalyst, 1,4-dicarbonyl intermediate could not be detected.

Scheme 61



2-Hydroxymethyl- or 2-fluoromethyl-4-alkylfurans was produced from diepoxides **85** by using fluoride or water as a ring opening agent (Scheme 62).[93] Diepoxides **85** were available from the reaction of α-substituted acroleins **83** and 1-bromo-1-trimethylsilane **84** in high yields. Because **83** and **84** are easily accessible and a number of reagents can be used for the purpose of ring opening, this simple, multi-step synthesis of 2,4-disubstituted furans is a potentially reliable method.

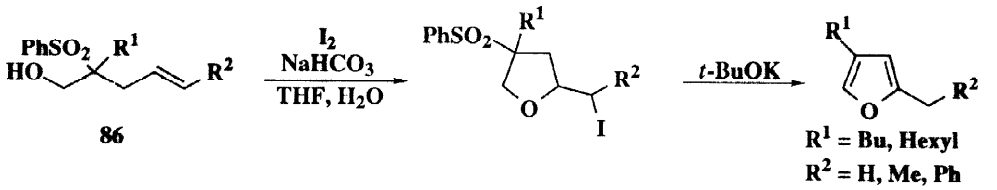
Scheme 62



β-Hydroxysulfones **86** can be transformed to 2,4-disubstituted furans in 75-89% yield by halocyclization followed by treatment of the intermediate with *t*-BuOK (Scheme 63).[94] It was found that the rate of cyclization

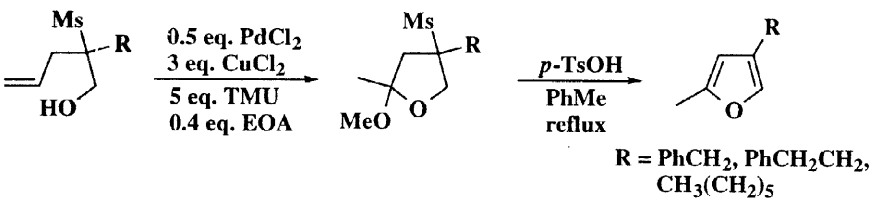
reaction depended upon the amount of iodine used and the reaction could be accelerated by using an excess of iodine. When 3.3 equiv. of iodine was used the tetrahydrofuran could be obtained quantitatively.

Scheme 63



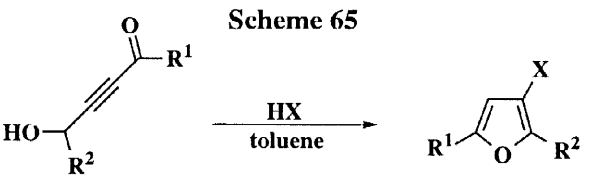
Under palladium-catalyzed condition similar substrates can also be transformed to 2,4-disubstituted furans through an intramolecular cyclization followed by acid-catalyzed aromatization (Scheme 64).[95] The reaction was carried out in the presence of $PdCl_2$ as catalyst and *N,N,N',N'*-tetramethylurea (TMU) as a HCl quencher together with ethyl orthoacetate (EOA). In this transformation the cycloacetalization first took place and the tetrahydrofuran intermediates can be separated.

Scheme 64



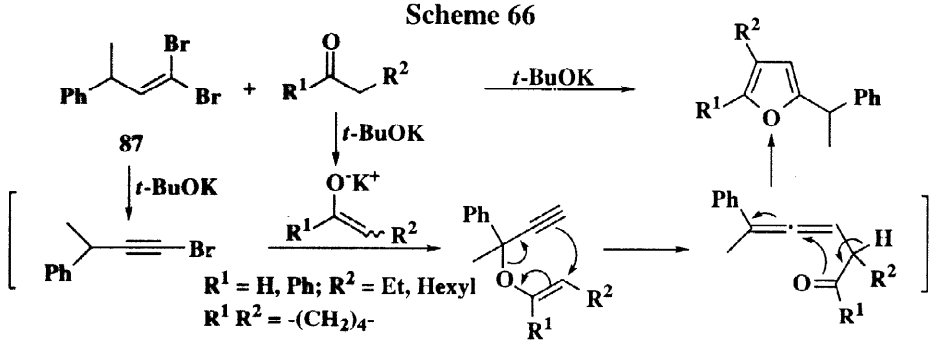
Similar to acetylenic esters **27** (Scheme 24), acetylenic ketones can also be converted to 4-halo-2-substituted furans in high yields (Scheme 65).[96]

Scheme 65



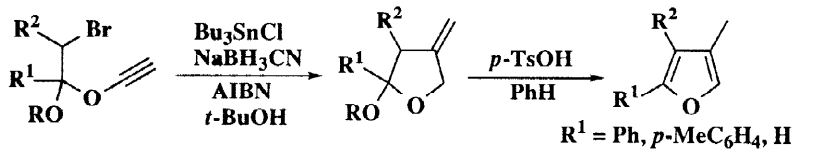
1,1-Dibromo-3-phenyl-1-butene (**87**) reacted with aldehydes in the presence of *t*-BuOK to provide 2,4-disubstituted furans *via* a convergent [2+3] annulation reaction in a single step with moderate yields. It is believed that the reaction proceeded through consecutive dehydrobromination, S_N2' substitution, and a tandem Claisen rearrangement—cyclization reaction (Scheme 66).[97] This reaction is also suitable for the preparation of 2,3,5-trisubstituted furans when the aldehydes are replaced by ketones.

Scheme 66



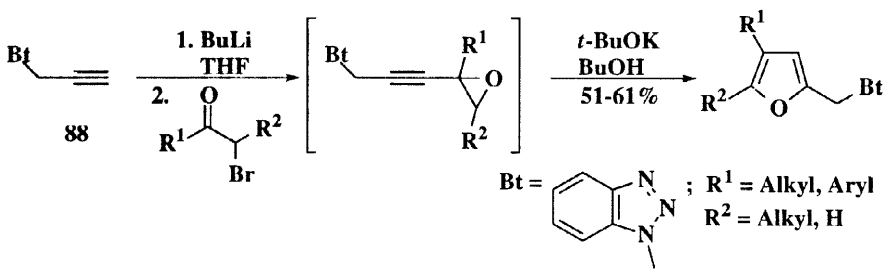
In previous Sections the radical cyclization of bromoacetals was discussed and it has been established that this reaction was suitable for the formation of 3-substituted and 2,3-disubstituted furans. In this Section and in the next Section, examples will be cited to demonstrate that this method is also appropriate for the preparation of 2,4-disubstituted furans (R^2 = H) and 2,3,4-trisubstituted furans ($R^2 \neq$ H) (Scheme 67).[98]

Scheme 67



i-Propargylbenzotriazole **88** was able to react with α-bromo ketones in the presence of a base to lead to 2,4-disubstituted furans (R^2 = H) and 2,3,5-trisubstituted furans ($R^2 \neq$ H) in good yields. This is an one-pot process and the mechanism was believed to involve an alkynyloxirane intermediate (Scheme 68).[99]

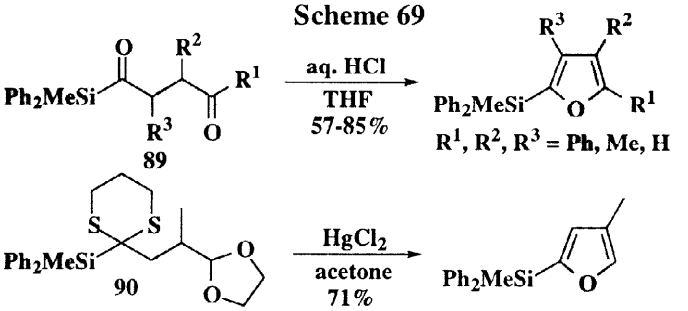
Scheme 68



It is known that acid-catalyzed cyclization of β,γ-dihydroxy ketones leads to 2,4-disubstituted furans.[100] Ag(I) or Rh(I) promoted cyclization of allenyl ketones and aldehydes is also a good procedure for the preparation of these compounds (Scheme 25).[46-48] Thus, 2,2-bis(methylthio)-2,5-dihydrofurans **47** (R^2 = H) can also be converted to 2,4-disubstituted furans when treated with HCl followed by nickel-catalyzed Grignard coupling reaction (Scheme 35).[61] As 1,4-dicarbonyl compounds were traditionally used in the synthesis of furans, acylsilane dicarbonyl derivatives **89** have also been employed to the preparation of 2,4-disubstituted furans under milder conditions and in good to excellent yields. Similarly, protected dithiane acetal **90** was also transformed into furan derivatives by an one-pot hydrolysis/cyclization sequence. Due to the fact that the reaction gave 2-silyl substituted furans regiospecifically this method serves to provide a route to another

substituted furans by either electrophilic substitution or metallation/addition strategies (Scheme 69).[101]

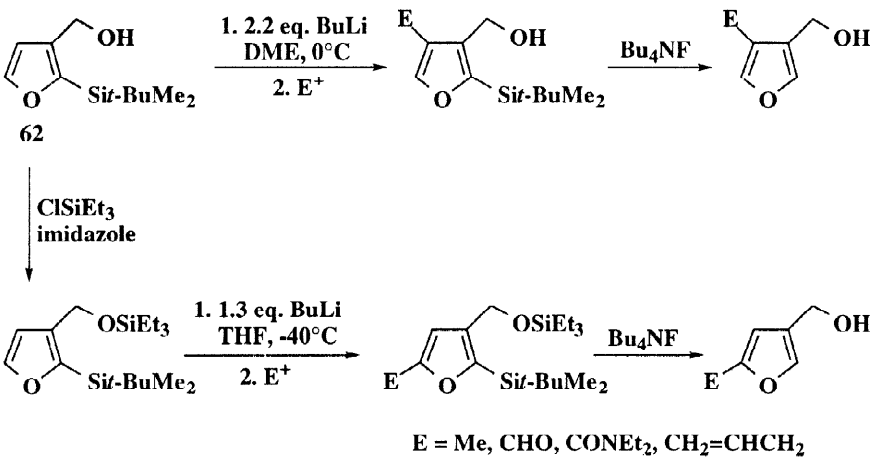
Scheme 69



3.2 From Other Furans

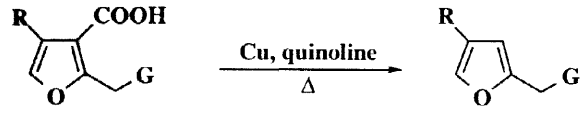
The preparation of 2,4-disubstituted furans by using other substituted furans as starting materials is difficult due to the propensity of the furan ring to react with electrophiles or to be lithiated predominantly at the C-2 and/or C-5 positions. Therefore the strategy of using blocking and/or directing group is necessary. In this connection, 2-*tert*-butyldimethylsilyl-3-hydroxymethylfuran (**62**) was regiospecifically lithiated at C-5 by treatment with 1.3 equiv. of BuLi in THF at -40°C after hydroxy group protection. Subsequent electrophile addition and desilylation provided 2,4-disubstituted furans in good yields (Scheme 70).[102] It is interesting to note that the direct lithiation of the free hydroxy compound somehow led to C-4 lithiated furan (*vide infra*). Lithiation can also be carried out at C-5 position for 2-bromo-3-methylfuran.[103]

Scheme 70



3-Carboxy-2,4-disubstituted furans **91** can be converted to 2,4-disubstituted furans through a decarboxylation reaction (Scheme 71).[104] One shortcoming of this method is that the starting materials are not easily available.

Scheme 71

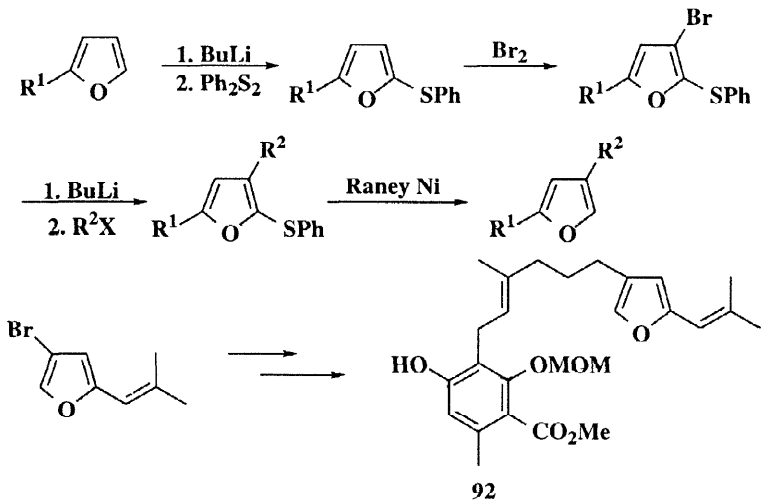


91 G = OBn, CO_2Et; R = Me, Bn

Regioselective bromination can be achieved at C4-position of 2-phenylthio-5-alkylfurans. Lithium-bromine exchange then was followed by an electrophilic attack and desulfurization to give 2,4-disubstituted furans (Scheme 72).[105] In this reaction the functions of phenylthio group are to block the C5-position during subsequent steps and to activate the 4-position for electrophilic attack.

From a 4-bromofuran derivative, bromine-lithium exchange strategy was also used in the synthesis of a natural product derivative, namely cristatic acid derivative **92** (Scheme 72).[106]

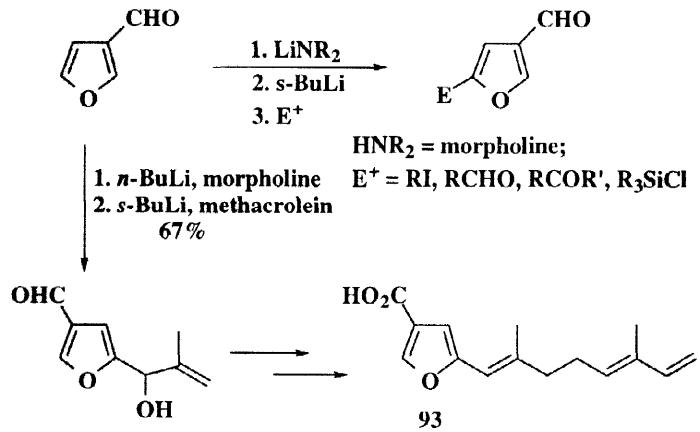
Scheme 72



92

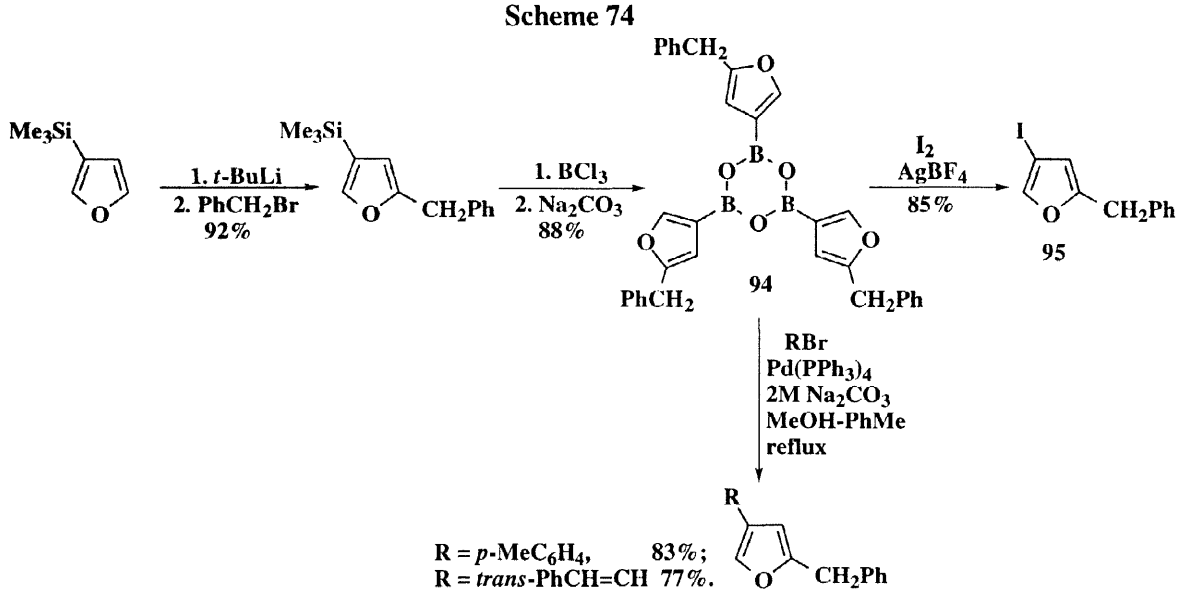
Although blocking and/or directing group deployment is very often applied to the synthesis of 2,4-disubstituted furans from other substituted furans, procedures for direct metallation to convert 3-substituted furans into 2,4-disubstituted furans are also available. Thus, *in situ* protection of 3-furaldehyde with lithium morpholide followed by metallation at C-5 regioselectively and subsequent trapping of the metallated furan with several electrophiles eventually afforded 2,4-disubstituted furans in 30-70% yields (Scheme 73).[107] To exemplify, the synthesis of the anti-inflammatory sesquiterpene (1'*E*, 5'*E*)-2-(2', 6'-dimethylocta-1', 5', 7'-trienyl)-4-furoic acid (**93**) was accomplished from 3-furaldehyde.[108]

Scheme 73



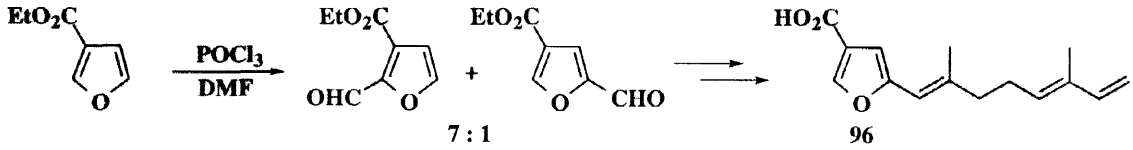
Regiospecific lithiation-electrophile trapping strategy is also successfully utilized to the preparation of 2,4-disubstituted furans from 3-trimethylsilylfuran, which, upon consecutive treatment with *t*-BuLi and benzyl bromide, gave 2-benzyl-4-trimethylsilylfuran as a sole product (Scheme 74).[80] 2-Benzyl-4-trimethylsilylfuran was converted to boroxine **94** from which several 2,4-disubstituted furans were obtained *via* Suzuki reactions. From **94**, the preparation of iodide **95** was also accomplished and 2,4-disubstituted furans could be produced by using palladium-mediated reactions. As can be seen, this procedure provides a convenient access to 2,4-disubstituted furans with diverse substituents.

Scheme 74



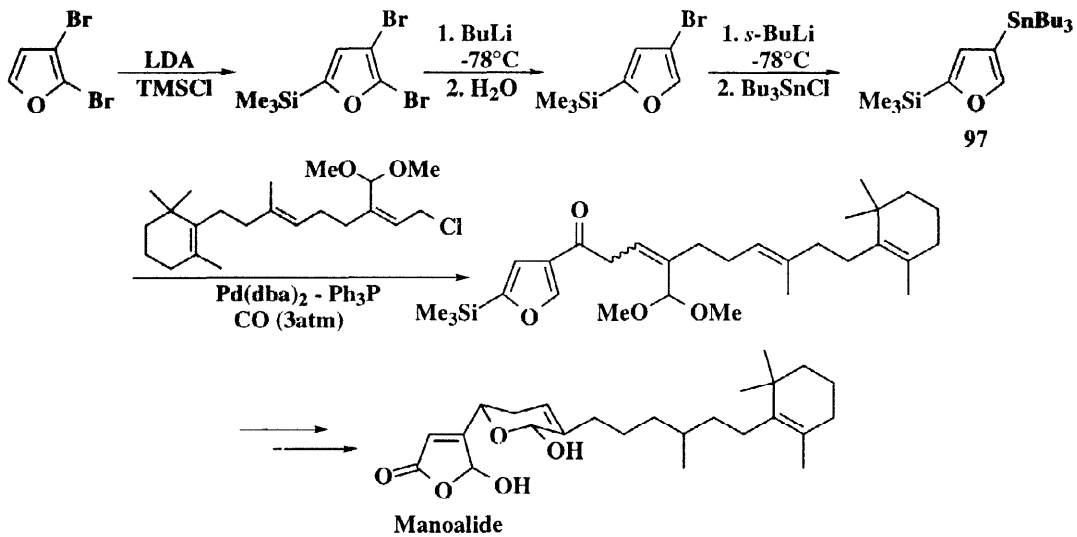
Direct Vilsmeier formylation has also been employed to prepare 2,4-disubstituted furan from 3-substituted furan. Again, this strategy was utilized for the synthesis of (1'*E*, 5'*E*)-2-(2', 6'-dimethylocta-1', 5', 7'-trienyl)-4-furoic acid (**96**) (Scheme 75).[109]

Scheme 75



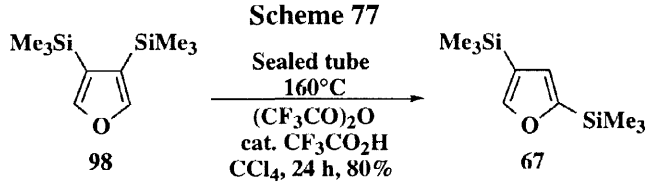
Although lithium-bromine exchange can be achieved when BuLi is used (Scheme 10), lithiation can also take place elsewhere on a bromofuran if a different base is used. The synthesis of 2-trimethylsilyl-4-tributylstannylfuran (**97**),[110] an useful intermediate for the synthesis of various natural products having butenolide or furan function, serves as an excellent example (Scheme 76).[111a] A titanium protocol has also been recommended for modifying the reactivity of 3-lithiofuran (**5**), in which the highly reactive lithium furan derivative was first converted to the moderately reactive titanium furan. A number of 2,4-disubstituted furans were obtained with high chemoselectivity and in acceptable yields when the titanium furan was allowed to react with electrophiles.[111b] It has been clearly shown that chemo- and regioselective lithiation at different positions of the furan ring could be realized through a careful selection of lithium bases.[111a]

Scheme 76



3,4-Bis(trimethylsilyl)furan (**98**) was recently converted to 2,4-bis(trimethylsilyl)furan (**67**) in high yield through an acid-promoted rearrangement (Scheme 77).[80] The driving force for the rearrangement of a trimethylsilyl group from C-3 to C-2 is due to the sterically unfavorable orientation of the two trimethylsilyl groups at C-3 and C-4. As we have seen previously, **67** was transformed efficiently into 2,3-disubstituted furans (Scheme 50).

Scheme 77

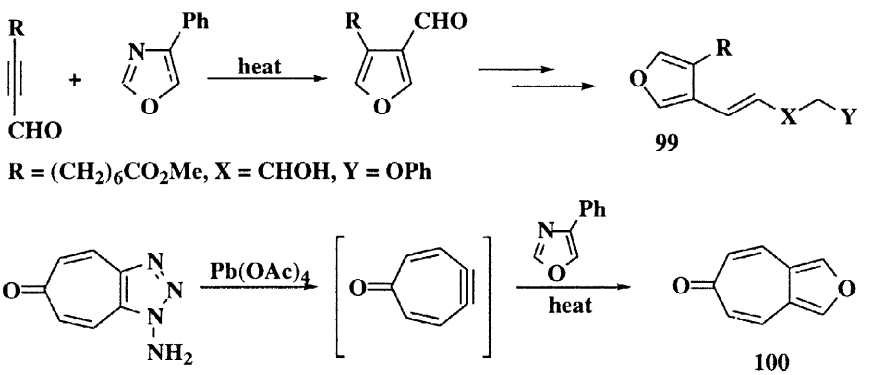


4. Synthesis of 3,4-Disubstituted Furans

4.1 From Tandem Diels—Alder Cycloaddition - Retro Diels—Alder Reaction and Related Reactions

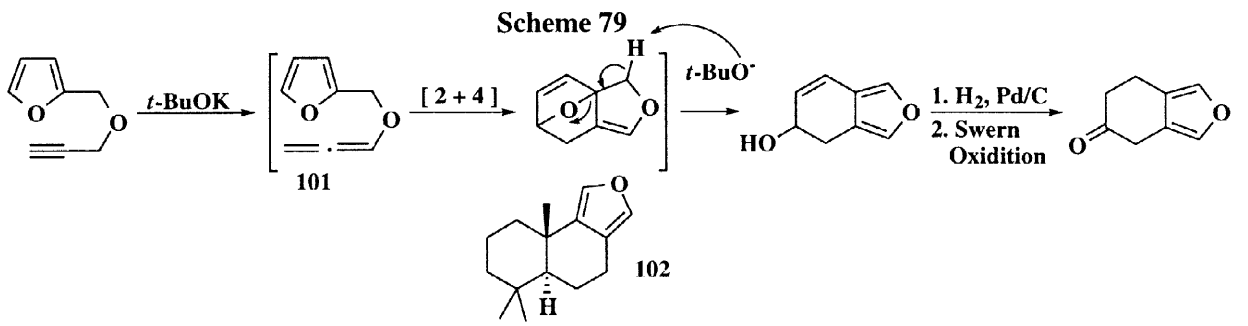
One of the most important procedures for the preparation of 3,4-disubstituted furans is the tandem Diels—Alder cycloaddition - retro Diels—Alder reaction. In Scheme 1 it was demonstrated that when R^1 and R^2 of the oxazoles are H, and R^4 and R^5 are carbon substituents the reaction will lead to 3,4-disubstituted furans.[11] In these transformations, R^4 and R^5 may be aryl, CH_2OR, and ester. Moreover, R^4 and R^5 may or may not be identical.[11,112] Some interesting products, such as furan prostanoids **99** and furo[3,4-*d*]tropone **100**, can be synthesized by using this strategy (Scheme 78).[113] Phenyl oxazole was used in these examples, because its high boiling point renders it possible to perform the cycloaddition as well as the subsequent cycloreversion at atmospheric pressure. This is an advantage over syntheses involving 4-methyloxazole or other substituted oxazoles which require elevated pressure for the decomposition of the cycloadduct.

Scheme 78



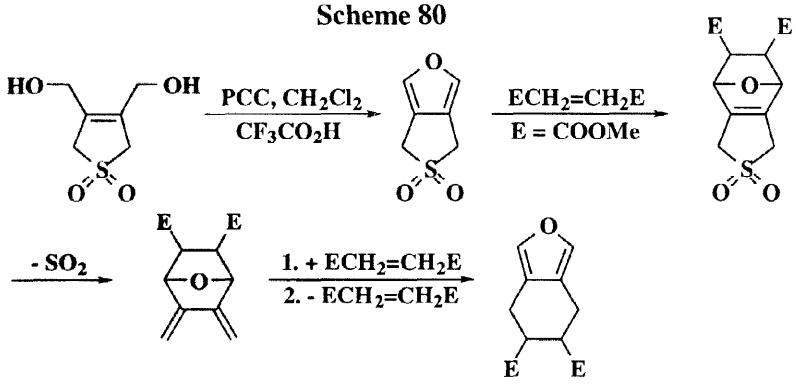
3,4-Disubstituted furan can also be prepared from 2-substituted furan through the so-called "furan ring transfer reaction" by utilizing allene as a dienophile and furan as a diene. The reaction proceeded *via* an intramolecular Diels—Alder reaction of allenyl furfuryl ether **101** produced *in situ* from propargyl furfuryl ether under the action of *t*-BuOK. The allene unit is a versatile dienophile in the intramolecular Diels—Alder reaction due to the absence of unfavorable nonbonded interactions in the transition state. Oxa ring cleavage of the adduct finally afforded the desired furan product. Because the furan compound is acid sensitive it was immediately hydrogenated and oxidized to a ketone derivative. This "furan ring transfer reaction" strategy was successfully used for the synthesis of the marine natural product, euryfuran (**102**) (Scheme 79).[114]

Scheme 79



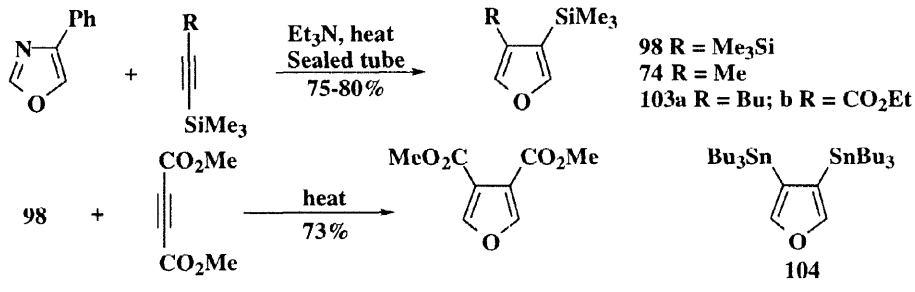
In addition to the aforementioned compounds, furan-annulated sulpholene is also reactive towards dienophiles. The resultant adducts underwent a retro-cycloaddition to afford new 3,4-disubstituted furans (Scheme 80).[115]

Scheme 80



As mentioned previously 3-tri-*n*-butylstannylfuran (**4**) can be synthesized by employing this strategy (Scheme 2).[13,116] In addition to tin derivatives of furan **104**, 3,4-bis(trimethylsilyl)furan (**98**) and 4-substituted-3-(trimethylsilyl)furan **74** and **103** were also obtained through a similar procedure. 3,4-Bis(trimethylsilyl)furan (**98**), with σ–donating trimethylsilyl groups at the β-position, is a better diene than other furans with σ-accepting substituents. As a result, other 3,4-disubstituted furans were produced through a tandem Diels—Alder Cycloaddition - retro Diels—Alder Reaction (Scheme 81).[117] A number of other 3,4-disubstituted furans were obtained conveniently from these versatile intermediates, namely tin derivative of furan **104** and silyl substituted furan **74**, **98** and **103** (*vide infra*).

Scheme 81



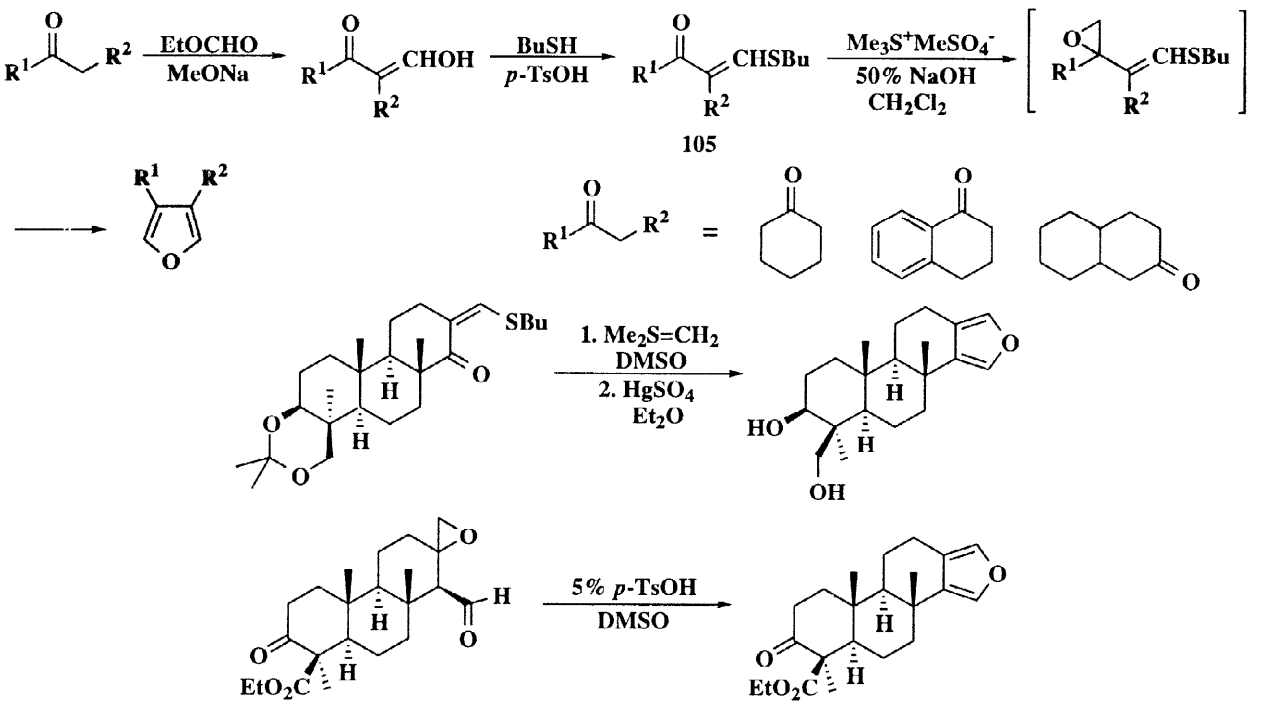
4.2 From Acyclic Precursors

Very few methods are available for the preparation of furans with substituents only at C-3 and C-4 positions because most electrophilic substitutions and lithiation of furans occur at the 2,5-positions, and many acyclic precursors, e.g. 1,4-dicarbonyl compounds which are widely used as starting materials, are more easily prepared with substituents at positions destined to become the furan C-2 and C-5 substituents.

S-Butyl-α-thiomethylene ketone **105** reacted with trimethylsulfonium methylsulfate under phase-transfer condition to produce 3,4-disubstituted furans (Scheme 82).[118] As a modified version of Garst-Spencer procedure,[119] this method uses trimethylsulfonium methylsulfate under phase-transfer condition instead of nonstabilized sulfur ylide prepared from trimethylsulfonium fluoroborate and BuLi at -78°C, thus avoiding the

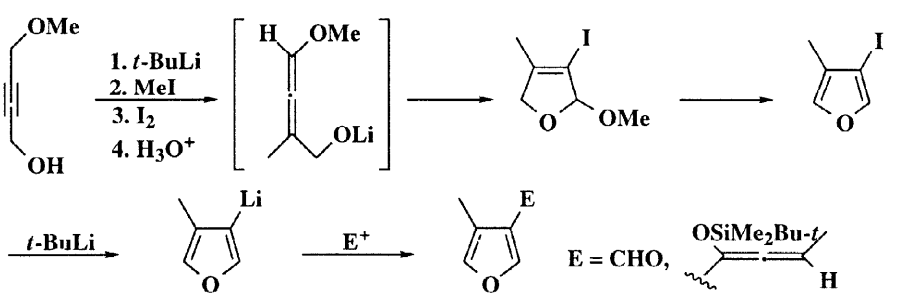
use of anhydrous solvents, strong organic bases and low temperature condition. Some furanoditerpenes were realized by utilizing a similar route.[120] *S*-Alkyl-α-thiomethylene epoxide is believed to be an intermediate in this reaction. If the *S*-alkyl-α-thiomethylene group was seen as a carbonyl equivalent, β,γ-epoxy carbonyl compounds could be employed as the starting material for the realization of 3,4-disubstituted furans. Indeed, β,γ-epoxy aldehydes were adopted as an intermediate in the synthesis of furanoditerpenes.[120b]

Scheme 82



3-Methyl-4-substituted furans could be obtained from 2-butyne-1,4-diol.[121] The procedure included methylation of the dianion, iodo-cyclization and aromatization, followed by metal-iodine exchange and electrophilic substitution (Scheme 83).[121] Intermediate compounds, the allene derivative (as its silyl ether) and iododihydrofuran, can be isolated. Also the intermediate iodofuran and lithium furan could provide access to a wide variety of other furans by derivatization of iodine and lithium.

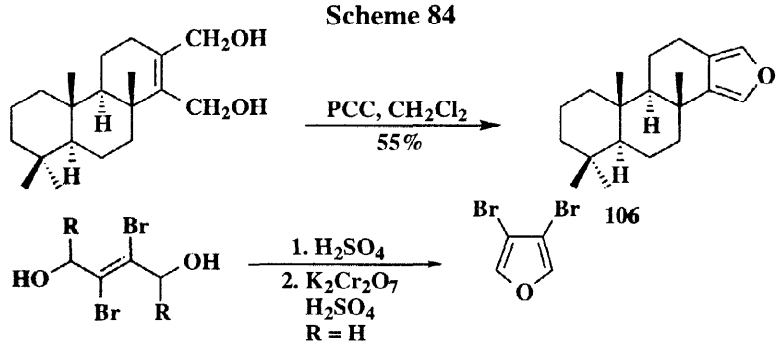
Scheme 83



3,4-Disubstituted furans can also be prepared by the oxidation of (*Z*)-but-2-ene-1,4-diols by using PCC and this method was used in the synthesis of natural product, spongia-13(16),14-diene (**106**) (Scheme 84).[122] In addition to the *Z*-form, the *E*-form of but-2-ene-1,4-diols can also be converted to 3,4-disubstituted furan.[123]

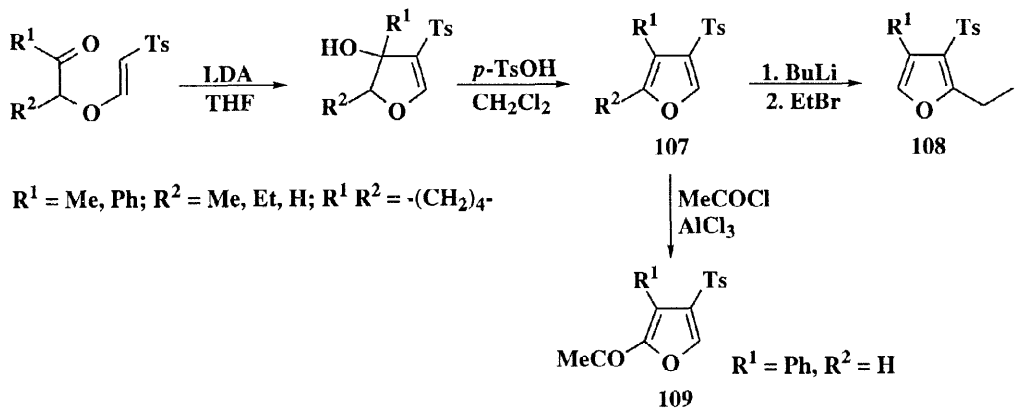
The 3,4-dibromofuran obtained is a versatile starting material for the preparation of 3-, 2,3-, 3,4-, and 2,3,4-substituted furans (cf. Scheme 87). It is interesting that the reaction fails to afford a furan derivative when R is methyl.

Scheme 84



Reaction of β-ethenyloxyketone with strong base, was known to afford dihydrofurans, which were then converted to furan under the action of *p*-TsOH (Scheme 85).[124] The tosyl group showed different directing effects, in the conversion of **107** to **108** through metallation and alkylation and in the Friedel-Crafts acylation of **107** to give **109** through exclusive 2-substitution. In these reactions, the phenyl group is not crucial, such that its replacement by an alkyl group resulted in identical selectivity. Reductive cleavage of sulfur-carbon bond of **107** could be carried out by using Na-Hg/KH_2PO_4 to give 3-phenyl furan. This reaction can also be applied to the preparation of 2,3,4-trisubstituted furans when R^1 and R^2 are not H.

Scheme 85

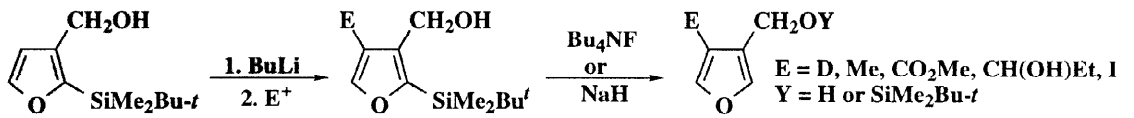


2,2-Bis(methylthio)-2,5-dihydrofurans **47** are versatile precursors and can be used in the synthesis of 3-, 2,3, and 2,4-substituted furans. They have also been applied to the preparation of 3,4-disubstituted furans. Thus, treatment of **47** with MeI in acetone-water or a catalytic amount of HCl followed by hydrogenation in the presence of Raney Ni furnished the desired 3,4-disubstituted furans (cf. Scheme 35).[61] From Scheme 7 it can be seen that when R^3 is H, the unsaturated nitriles can be used to the synthesis of 3,4-disubstituted furans as well.

4.3 From Other Furans

Generally the lithiation of 2,3-disubstituted furans will take place at C-5 position due to the increased acidity of the α-proton over β-proton on furan rings (*vide infra*). However, if there is a sterically hindered group at C-2, such as *t*-butyldimethylsilyl and *ortho*-directing group, such as hydroxymethyl, at C-3 position of the furan ring, the lithiation takes place at C-4 position (Scheme 86). The oxygen of the hydroxymethyl group coordinates with lithium at C-4, thereby stabilizing the lithio-intermediate. Electrophilic attack followed by desilylation or silyl group migration from carbon to oxygen (see Scheme 44) provided 3,4-disubstituted furans.[125] Besides the hydroxymethyl group, a carboxyl group can also function as a *ortho*-directing group[126]

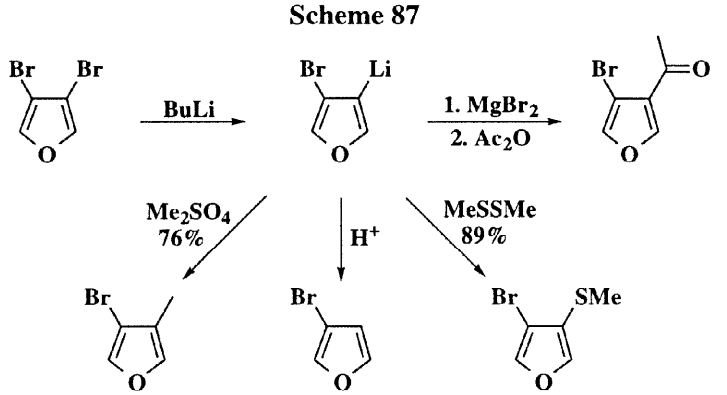
Scheme 86



62

Lithium-halogen exchange of one bromine of 3,4-dibromofuran was accomplished with BuLi. Although the trapping of 3-bromo-4-lithiumfuran with bromoacetate failed, acylation can nevertheless be carried out if the furyllithium is treated with magnesium bromide followed by acetic anhydride. In addition, 3-bromo-4-lithiumfuran can be trapped by dimethyl disulfide, dimethyl sulfate and hydrochloric acid to furnish the corresponding methylthio-, methyl- and 3-bromofuran (Scheme 87).[125b,127] The ability of 3-methylthio and 3-phenylthio substituents in directing the metallation at position α relative to the substituent allowed the regiospecific alkylation of 3-methylthio- and 3-phenylthio-4-bromofuran. Evidently, metal-bromine exchange and acid trapping followed by *ortho*-metallation and electrophile trapping of 3-bromo-4-methylthiofuran led to 2-substituted-3-methylthiofurans. These reactions have made 3,4-dibromofuran a prominent starting material for synthesis of polysubstituted furans bearing a S-function at C-3 position.[127]

Scheme 87

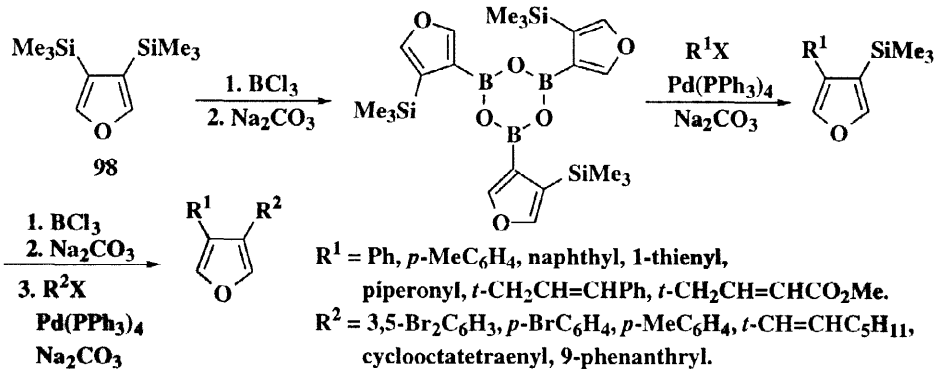


Due to the convenient access of furan tin derivative **104** and silyl substituted furan **98** and **86** through Diels—Alder reaction and retro Diels—Alder reaction (Scheme 2 and 69), *ipso*--substitution of these tin- or silyl- groups might serve as flexible procedures for the synthesis of a variety of 3,4-disubstituted furans.

3,4-Bis(trimethylsilyl)furan (**98**) underwent *ipso*-substitution with BCl_3 regiospecifically although the direct substitution of **98** with aryl or alkenyl groups by Pd-catalyzed coupling was unfruitful. Treatment of the resulting dichloroborane with dilute HCl or Na_2CO_3 afforded the air-stable tris[(4-trimethylsilyl)furan-3-

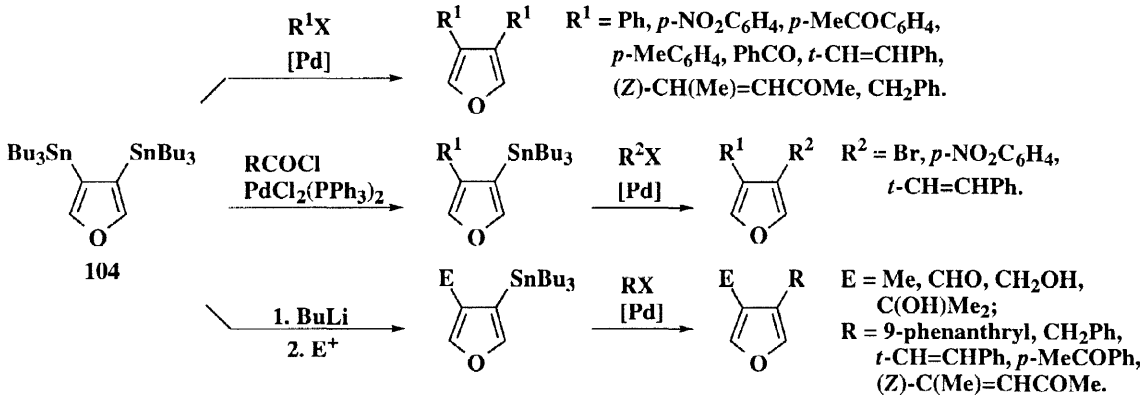
yl]boroxine, which reacted smoothly with aryl, benzyl- or allyl-type halides according to the Suzuki-type cross coupling to provide 3-substituted-4-(trimethylsilyl)furans. Further conversion under similar procedures led eventually to 3,4-disubstituted furans (Scheme 88).[117b,128]

Scheme 88



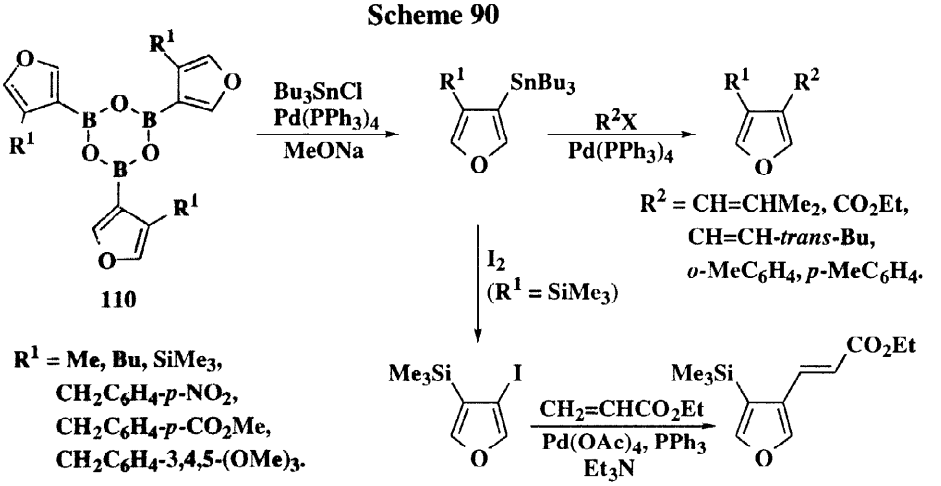
3,4-Bis(tri-*n*-butylstannyl)furan (**104**), similar to 3-tri-*n*-butylstannylfuran (**4**), could undergo Stille coupling to generate symmetrically and unsymmetrically 3,4-disubstituted furans (Scheme 77).[35,116] Unsymmetrically 3,4-disubstituted furans can also be obtained from 3,4-bis(tri-*n*-butylstannyl)furan (**104**) after its reaction with BuLi and an electrophile, followed by a Stille reaction (Scheme 89).[35,116]

Scheme 89



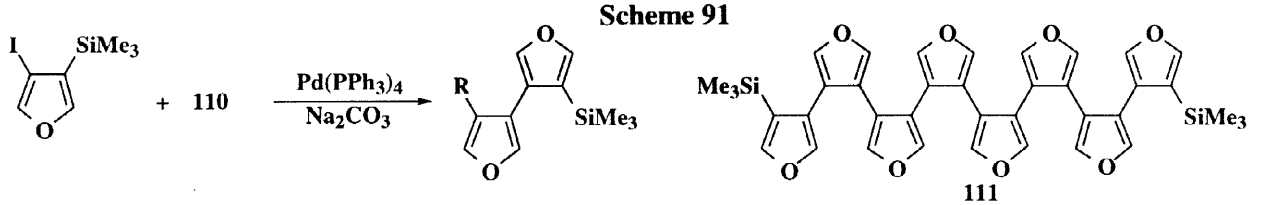
Boroxines **110** are able to react not only with aryl, benzyl- or allyl-type halides but also with tri-*n*-butylstannyl chloride. The resulting organotin compounds were converted through the Suzuki-type reaction to the corresponding coupling products or were converted to an iodide, which, through Heck reaction, provided also the desired 3,4-disubstituted furans (Scheme 90).[117c]

Scheme 90



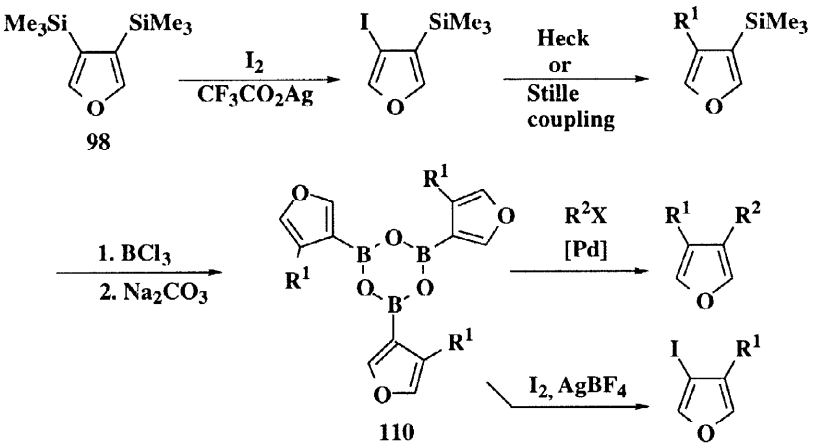
From boroxines **110**, furan-3,4-diyl oligomers such as octamer **111** can be obtained (Scheme 91).[117c] These oligomeric furans may serve as prototypical models for the study of novel furan-3,4-diyl polymers[129] and non-linear optical materials.[130]

Scheme 91



In addition to the reaction with BCl_3, **98** was also reacted with iodine in the presence of silver trifluoroacetate to provide 3-iodo-4-(trimethylsilyl)furan. The iodine atom and trimethylsilyl group can be converted to a number of different substituents. Thus, this approach provided another entry to unsymmetrically 3,4-disubstituted furans from **98** (Scheme 92).[131]

Scheme 92



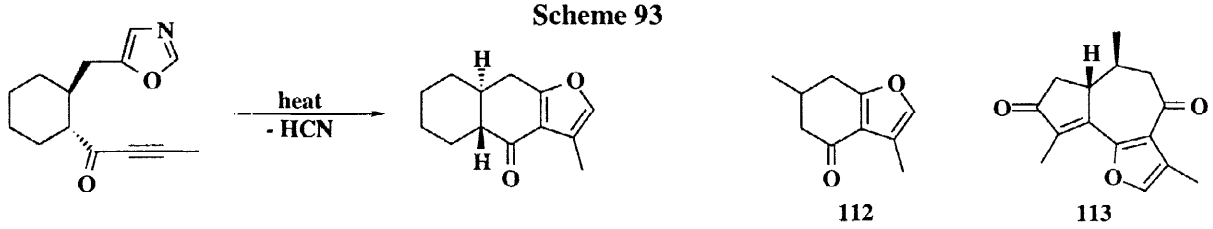
5. Synthesis of 2,3,4-Trisubstituted Furans

5.1 From Tandem Diels—Alder Cycloaddition - Retro Diels—Alder Reaction and Related Reactions

In previous Sections the application of the title reaction sequence to the synthesis of substituted furans has been discussed. In this Section more examples will be given to show the versatility of this strategy, especially the uses in the realization of polycyclic molecular architectures.

As can be seen in Scheme 93, when the oxazole is connected to an acetylenic dienophile the reaction will undergo an intramolecular pathway. One advantage of this approach is its high regioselectivity because of the geometrical constraints concerning intramolecular Diels—Alder reaction. This synthetic method is suitable for furanoterpenes containing both β-methyl substituent on the furan ring and an oxygen functionality at a position adjacent to the furan ring junction. Naturally occurring furanoterpene evodone (**112**),[132] and furanoditerpenes gnididione (**113**)[133] were synthesized in this manner.

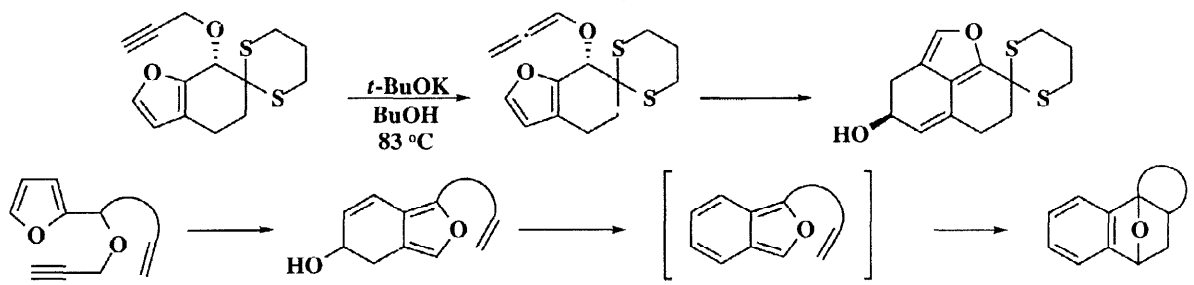
Scheme 93



112 **113**

The "furan ring transfer" reaction has also found its applications in the synthesis of 2,3,4-trisubstituted furans (Scheme 88) (cf. Scheme 79).[114,134] As can be seen, the chirality of the α-carbon of the starting material can be transferred to another part of the product.[135] In addition, the "furan ring transfer" reaction product proved to be a useful precursor to functionalized isobenzofurans, which may undergo intramolecular Diels—Alder reaction to afford other useful products.

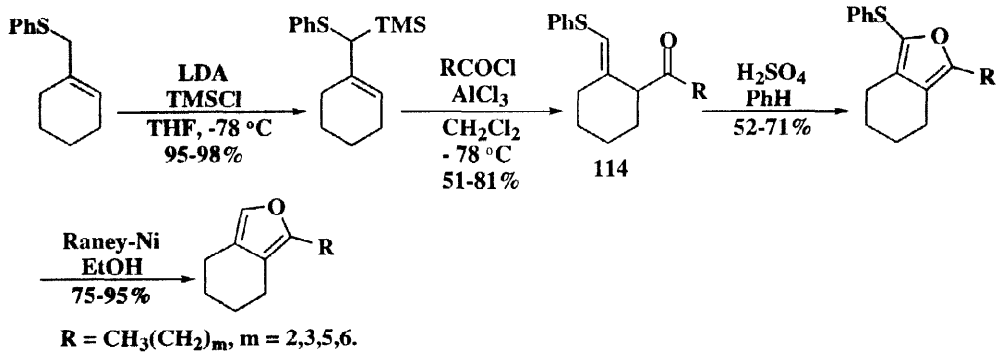
Scheme 94



5.2 From Acyclic Precursors

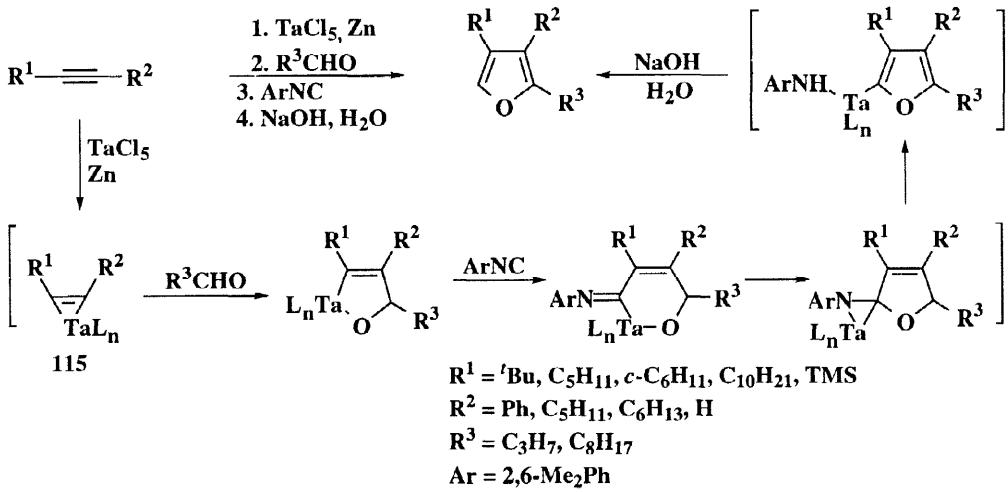
Suitably substituted ω-phenylthio-β,γ-unsaturated ketones **114** have been converted to 2,3,4-trisubstituted furans when treated with concentrated H_2SO_4. The starting materials in turn can be synthesized from allyl sulfides. Aluminum chloride catalyzed acylation of the resulting α-silylallylic sulfides with acid chlorides gave γ-acylated vinylsulfides with complete regioselectivity (Scheme 95).[136]

Scheme 95



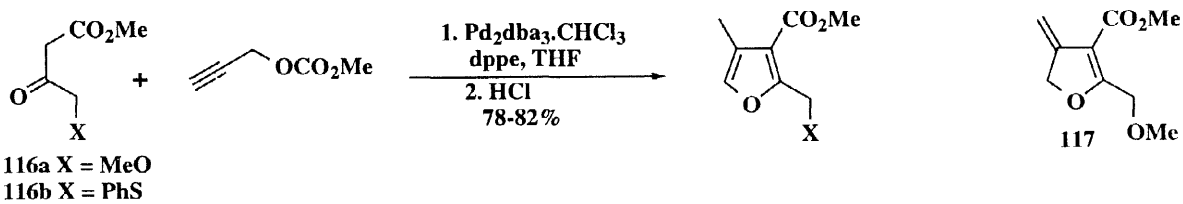
The reaction between acetylenes, aldehydes, and isocyanide was found to provide 2,3,4-trisubstituted furans regioselectively by means of low-valent tantalum. This is an one-pot procedure and might go through an oxatantalacyclopentene intermediate **115** and the mechanism is shown below (Scheme 96).[137]

Scheme 96



Palladium catalyzed reaction of 4-methoxyacetate **116a** and 2-propynyl carbonate generated 2,3,4-trisubstituted furan in good yield. In this transformation the most effective catalyst was the one produced *in situ* from tris(dibenzylideneacetone)dipalladium(0)-chloroform ($Pd_2dpb_3 \cdot CHCl_3$) and 1,2-bis(diphenylphosphino)ethane (dppe) in dry THF. Also 4-phenylthioacetate **116b** furnished the furan product under the same conditions (Scheme 97). Dihydrofuran **117** has been isolated as an intermediate in the cyclization of 4-methoxyacetate **116a**.[138]

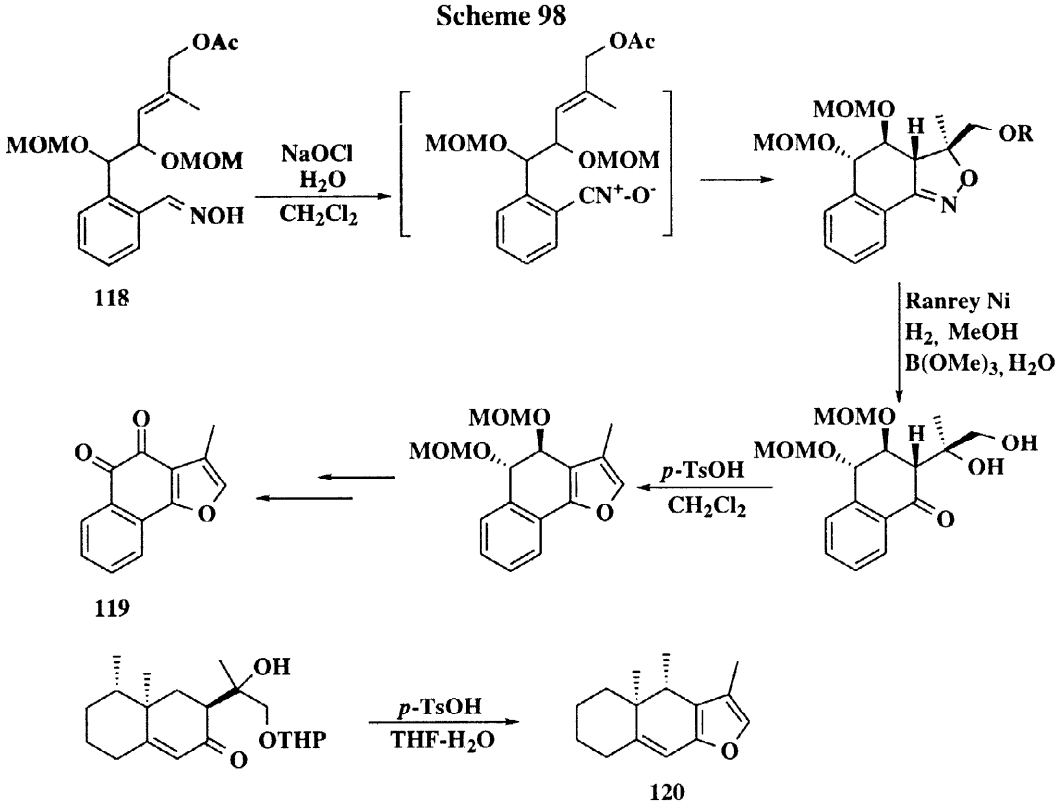
Scheme 97



β,γ-Dihydroxyketones **118** also served as a key precursor for furan ring synthesis. This starting material was produced from an intramolecular [3+2] dipolar cycloaddition of a nitrile oxide with subsequent reductive

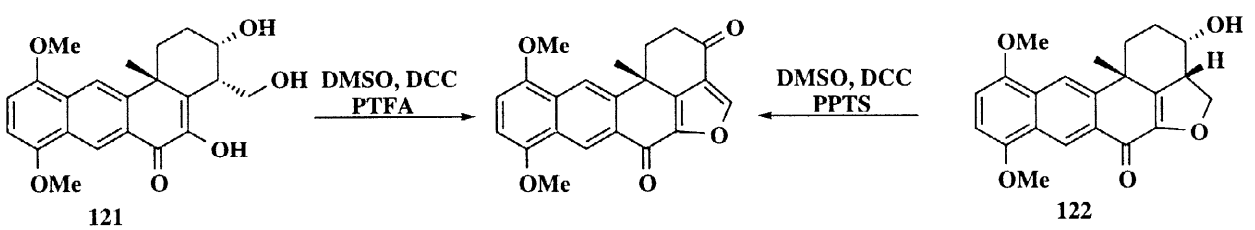
hydrolysis as discussed before (cf. Scheme 32).[57] This method was used in the synthesis of the BCD ring system **119**, a common structural unit of tanshinones which are active components isolated from the Chinese folk medicine Danshen (Scheme 98).[139] β,γ-Dihydroxyketone was also used in the construction of several eremophilane sesquiterpenes, such as 9,10-dehydrofuranoeremophilane (**120**).[140] It is believed that the β,γ-dihydroxyketones serve as latent 1,4-dicarbonyls for furan ring construction.

Scheme 98



A furan was produced by the oxidation of alcohol **121** or dihydrofuran **122** with DMSO/DCC in the presence of PPTS or PTFA and this reaction was employed in natural product synthesis (Scheme 99).[141] Again, this furan ring assemblage was a result of the cyclization of a 1,4-dicarbonyl.

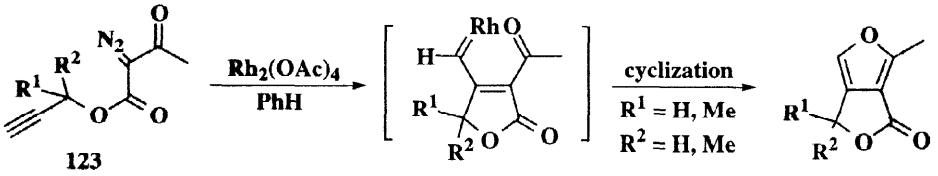
Scheme 99



2-Alkynyl 2-diazo-3-oxobutanoates **123** were transformed into substituted furans under the catalysis of rhodium(II) acetate. The reaction may proceed through carbene addition to an acetylenic π-bond followed by cyclization (Scheme 100).[142] The convenience with which Rh(II)-catalyzed cyclization reaction of 2-alkynyl 2-diazo-3-oxobutanoates occurs makes this route particularly attractive for the preparation of a wide variety of furo[3,4-*c*]furans. The substituents that flank the diazomethylene group play an important role during the

reaction. The rate of cyclization is faster when R^1 and R^2 of **123** are H. 2,3,4-Trisubstituted furans were also produced in this way from the reaction of diazocyclohexane-1,3-diones and vinyl acetate in the presence of a rhodium catalyst with subsequent elimination (cf. Scheme 38).[65]

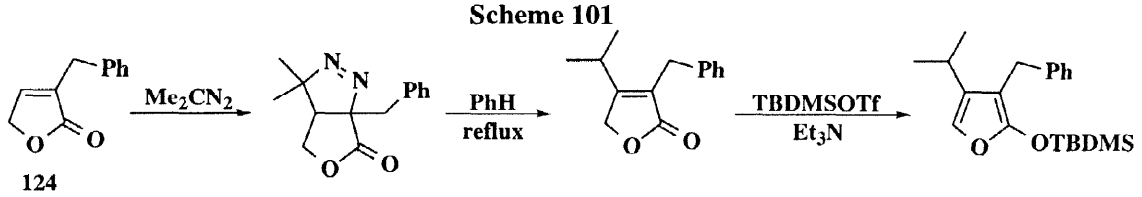
Scheme 100



123

A 2,3,4-trisubstituted furan was obtained from 2-benzyl-2-butenolide **124**. The substituent at C-4 of the furan ring was introduced through the reaction of butenolide with 2-diazopropane regioselectively and thermolysis of the resulting pyrazolinolactone. Aromatization was then realized by treatment of the product with *t*-butyldimethylsilyl triflate and Et_3N (Scheme 101).[143]

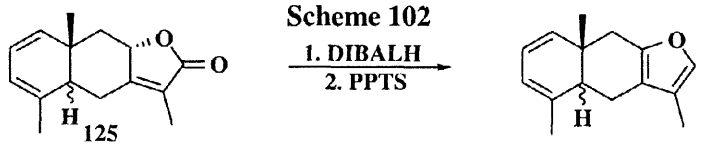
Scheme 101



124

In a similar manner, 2-butenolide **125** was transformed into another 2,3,4-trisubstituted furan through a reduction-dehydration procedure. The method was commonly used in the synthesis of furanoeudesmanes in which the construction of the C ring (furan ring) was always the last step in the synthesis (Scheme 102).[144]

Scheme 102



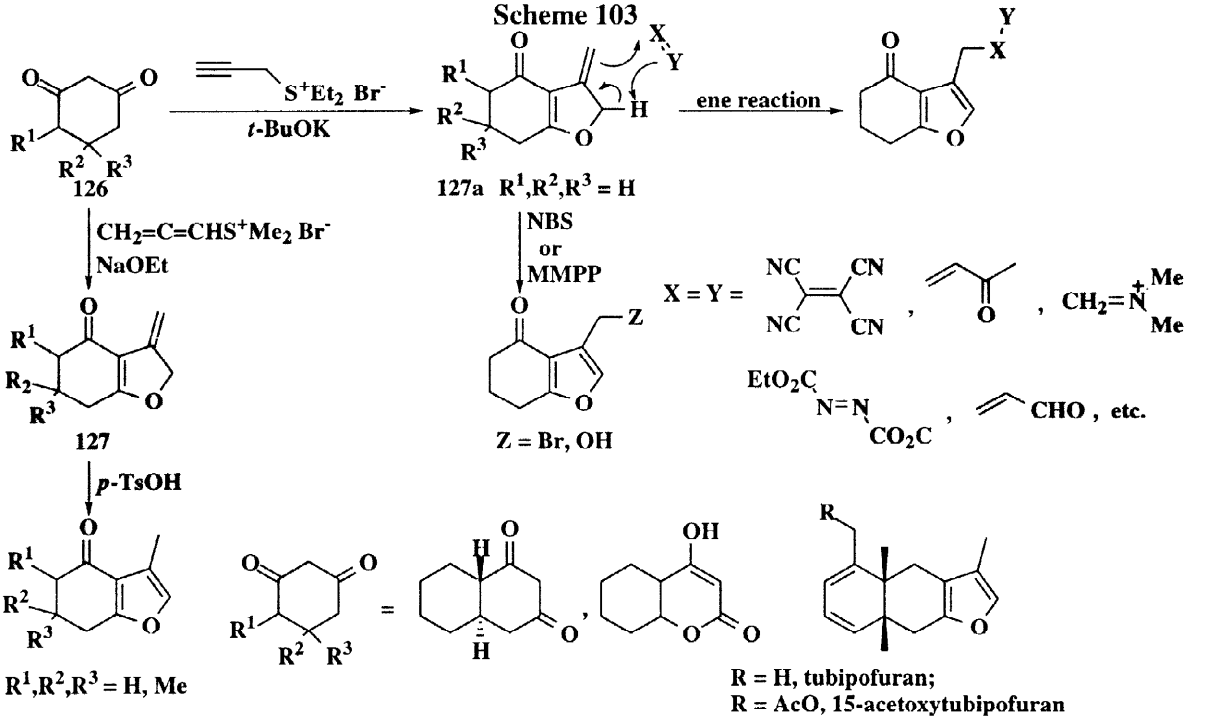
125

cis* or *trans

cis* or *trans

From Scheme 85 it can be seen that β-ethenyloxyketones can be converted to 2,3,4-trisubstituted furans.[124] The use of radical cyclization in the preparation of 2,3,4-trisubstituted furans was shown in Scheme 67.[98] Reaction of alkenyl sulfoxides and β-ketoesters provided 2,3,4-trisubstituted furans with good yields (cf. Scheme 39).[66]

Scheme 103



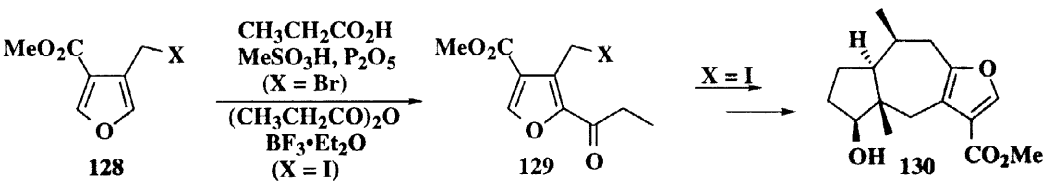
The ene reaction has been utilized successfully in the synthesis of 3-substituted furans and may be effectively applied to the synthesis of 2,3,4-trisubstituted furans.[145] In these cases, the starting materials, annulated 3-methylene-2,3-dihydrofurans, were prepared from the reaction of cyclic 1,3-diketones and propynyl or allenic sulfonium salts. The annulated 3-methylene-2,3-dihydrofurans are extremely acid sensitive as well as somewhat heat sensitive, and easily isomerize to bicyclic 3-methylfurans. Only in the case of cyclohexane 1,3-dione was a product, **127a**, isolated and it required storage in a refrigerator. It is noteworthy that the ene reaction of annulated 3-methylene-2,3-dihydrofurans **127** with highly active enophiles, such as Eschenmoser's salt, diethyl azocarboxylate, and tetracyanoethylene, proceeded at room temperature, but other enophiles, such as methyl vinyl ketone, acrolein, and dimethyl fumarate, needed more severe conditions (110°C). This is also in contrast with 3-methylene-2,3-dihydrofuran (**13**) (cf. Scheme 8) and is probably due to the stability of **127** which reduces the driving force for the rapid ene reaction leading to the more stable aromatic furan system. The enophiles are a variety of double bond compounds with electron withdrawing groups. In addition to the enophiles, NBS and monoperoxyphthalic acid magnesium salt (MMPP) also reacted with the methylene dihydrofuran to produce fused 3-substituted methyl furans (Scheme 103). This procedure provided annulated furans with various 3-substituents. Some naturally derived furanoterpenoids possessing fused 3-methylfuran structures as a common structural unit such as tubipofuran and 15-acetoxytubipofuran were synthesized by employing this methodology.[145c]

5.3 From Other Furans

Regioselective acylation of the furan ring can be realized in good yields when 3,4-disubstituted furans were used as starting materials (Scheme 104). High yields were obtained for small scale reactions when X was iodine but only about 50% yields were achieved for a 10 g reaction scale by using propanoic anhydride and BF_3-Et_2O

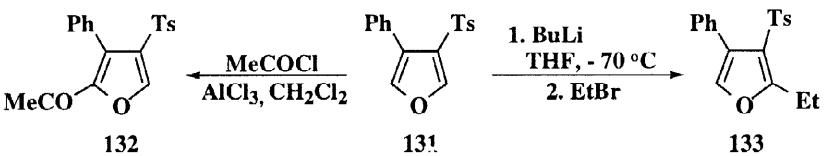
as the reagents. When X was bromine and the reagents were propanoic acid, methanesulfonic acid and phosphorus pentoxide the reaction gave the product in 74% yield for a 22 g scale (Scheme 104).[146] The ester group in **128** was not only used as a directing group during acylation reaction but it also plays an important role in stabilizing the furan ring during the elaboration of **129** to the perhydroazulene **130**.

Scheme 104



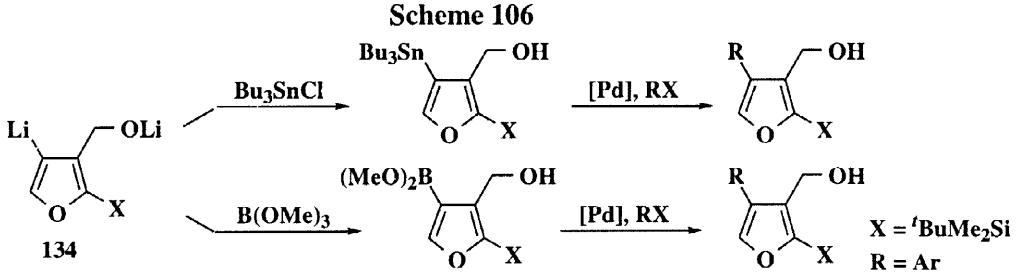
Acylation can also be performed at the C-5 position of a furan ring when 3-tosyl-4-substituted furans **131** are allowed to react with acetyl chloride and $AlCl_3$. It is interesting to note that electrophilic substitution exclusively gives 2-substituted furan **132** while lithiation usually gives furan **133** (Scheme 105).[124]

Scheme 105



It has been demonstrated in Section 4.3 that lithiation took place at the C-4 position of 2-(dimethyl-*t*-butylsilyl)-3-hydroxymethylfuran (cf. Scheme 86).[125] This can be considered as one of the methods for the preparation of 2,3,4-trisubstituted furans if the lithiated furans were allowed to react with electrophiles. In fact metal-substituted furans **134** were also prepared and transformed to 2,3,4-trisubstituted furan through Suzuki coupling[147] and Stille coupling (Scheme 106).[148]

Scheme 106



In Scheme 52 it was shown that regioselective lithiation-electrophile trapping of **74** was realized when *t*-BuLi was used as base. Substitution of trimethylsilyl group by iodine atom was accomplished when $I_2/AgBF_4$ was used as reagent system although the yield was low.[80] Thus, **74** and related compounds, such as **103a**, can also be used as the starting material for the preparation of 2,3,4-trisubstituted furans.

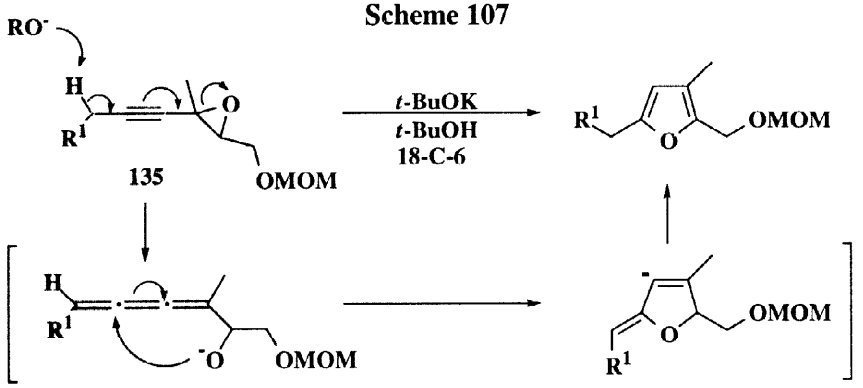
6. Synthesis of 2,3,5-Trisubstituted Furans

6.1 From Acyclic Precursors

The conversion of alkynyloxiranes **135** to 2,3,5-trisubstituted furans was realized by treatment with *t*-

BuOK in a mixture of *t*-BuOH and 18-crown-6. The reaction pathway likely involves base initiated 1,4-elimination of alkynyloxirane to cumulenyl alkoxide followed by cyclization to a vinylic anion, which then transforms to furan products (Scheme 107).[149]

Scheme 107

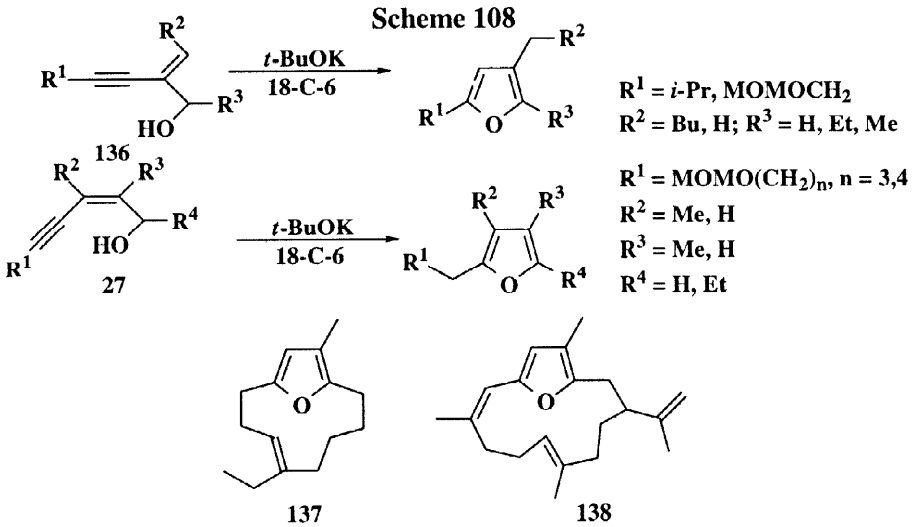


R^1 = BnO, $HOCH_2$, $HO(CH_2)_3$, C_5H_{11}, C_3H_7

In Section 2.3, the conversion of γ-alkynyl allylic alcohol **27a** to 2,3-disubstituted furan has been described.[44] This reaction is also suitable for the synthesis of 2,3,5-substituted furans (cf. Scheme 24). In addition to γ-alkynyl allylic alcohols **23**, β-alkynyl allylic alcohols **114** can also undergo an analogous transformation (Scheme 108).[150]

Cyclization of β–allenyl, β–alkynyl, γ–alkynyl allylic alcohols through favorable 5-*exo-dig* or 5-*endo-dig* processes proceeds readily at or below room temperature and provides a reasonably general procedure for the preparation of 2,3-, 2,4-, and 2,3,5-substituted furans in high yields. The *Z*-configuration is necessary for γ–alkynyl allylic alcohols and it requires the presence of an acidic proton at the α-position of the R^3 substituent in the corresponding *E*-isomers to effect the *E* to *Z* isomerization prior to cyclization. Using these methodologies, pseudopterane and furanocembrane ring systems **137** and **138**, having relative strained ring systems, were prepared.[151]

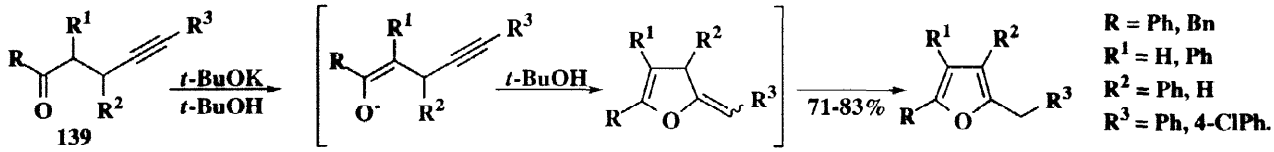
Scheme 108



A similar reaction took place when 4-pentynones **139** were treated with *t*-BuOK. The reaction probably involves the cyclization of alkynone enolates and isomerization (Scheme 109).[152] However, reactive allenes

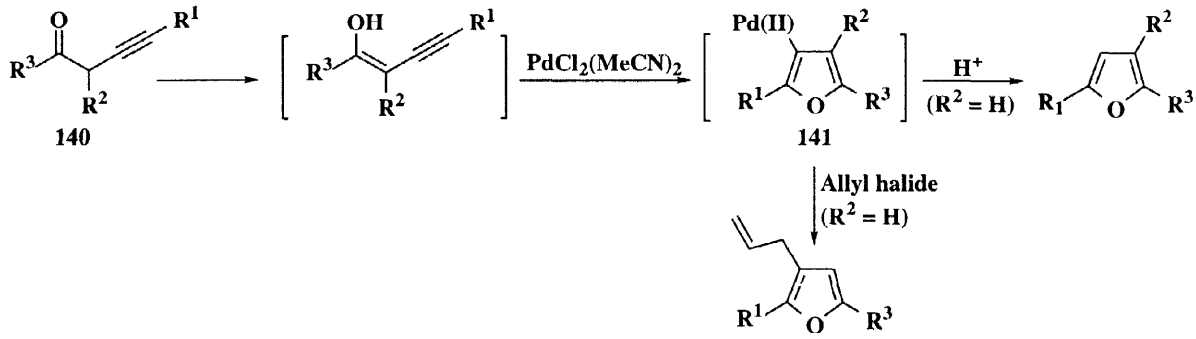
may also be the intermediate as can be seen in the case of 3-alkynyl allylic alcohols (cf. Scheme 24).[44] Interestingly, conjugated dienones were the products when these alkynones were allowed to react with NaOMe in MeOH.

Scheme 109



Trisubstituted furans can also be provided by β,γ-acetylenic ketones **140** as shown in Scheme 110. The reaction was carried out by a Pd(II)-catalyzed cyclization through oxypalladation. The furan products were derived from intermediates **141** by protodepalladation or carbodepalladation with allyl halides (Scheme 110).[153]

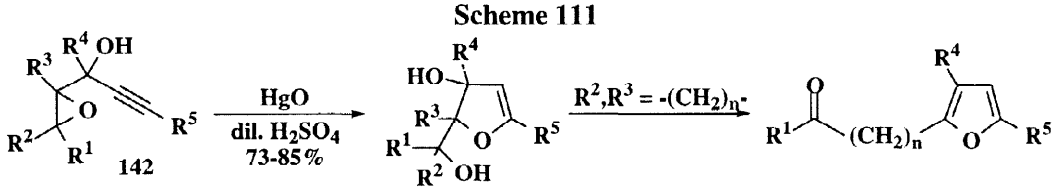
Scheme 110



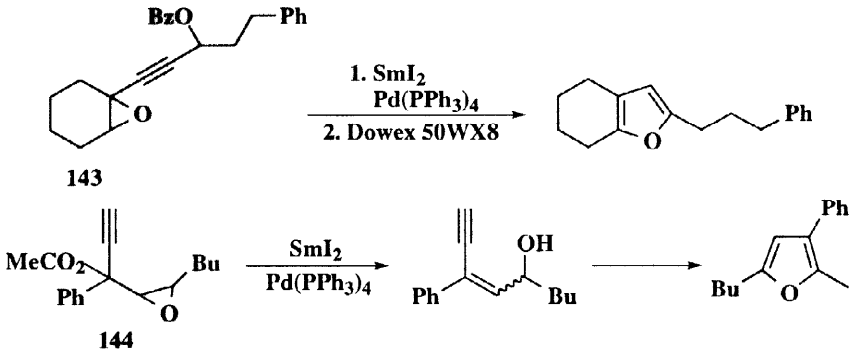
γ-Alkynyl allylic alcohols undergo both base-catalyzed isomerization as well as Ru- or Pd-catalyzed transformation to form substituted furans (cf. Scheme 26).[50]

Epoxypropargyl esters **142** were converted to trisubstituted furans under the action of HgO and dilute H_2SO_4,[154] and a similar reaction made use of SmI_2-$Pd(PPh_3)_4$ (Scheme 111).[155] SmI_2-Pd(0) Promoted reductive elimination of epoxy-alkynyl esters **144** also provided an efficient synthesis for γ–alkynyl allylic alcohols from simple and readily available starting materials. Like Marshall's procedures,[150] the usefulness of this methodology is restricted to those cases where it can be used in combination with a successful *E*- to *Z*-enynol isomerization or where geometrical constraints impede the formation of *E*-products.

Scheme 111

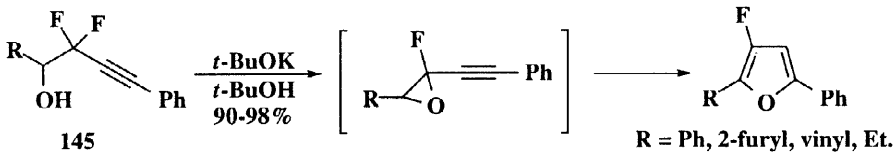


R^1 = Me, H; R^2,R^3 = -$(CH_2)_n$-, n = 3-5; R^4 = Me, C_6H_{13}, $PhCHCH_2CH{=}CH_2$;
R^5 = Pr, Bu, C_5H_{11}, $THPOCH_2$, Ph



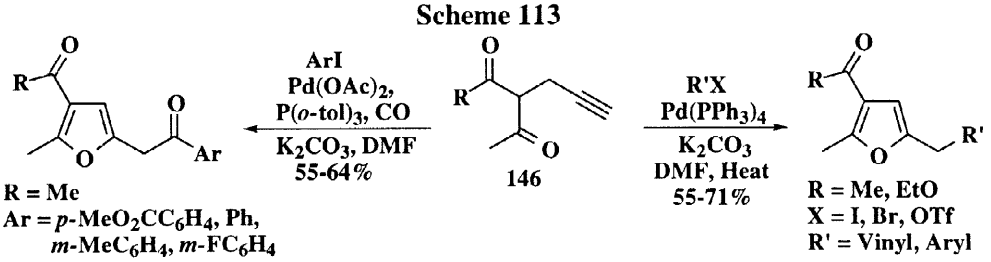
Under basic condition, β,β-difluoro-β-acetylenic alcohols **145** gave fluorine-containing furans. The intermediate is believed to be an epoxyacetylene (Scheme 112).[156]

Scheme 112



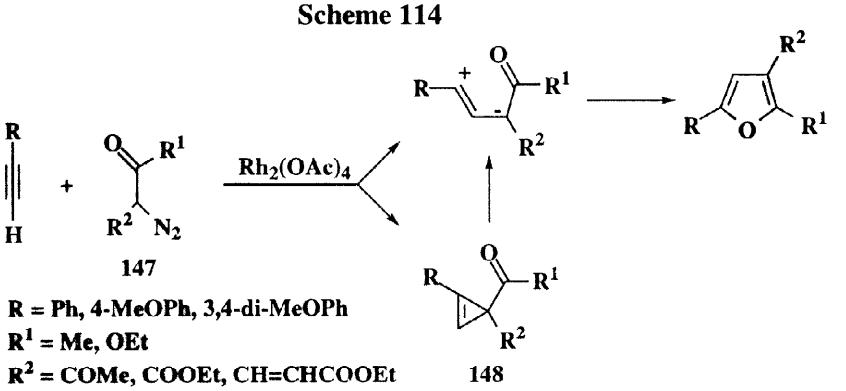
2-Propargyl-1,3-dicarbonyl compounds **146** are able to react with aryl or vinyl triflates or halides with Pd(0) catalysis to furnish 2,3,5-trisubstituted furans. When the reaction was carried out under a CO atmosphere, it provided different products. In this case, the use of weakly coordinating ligands gave more satisfactory results (Scheme 113).[157]

Scheme 113



Rhodium complexes have also found application in the synthesis of 2,3,5-trisubstituted furans. It is well known that rhodium(II) acetate can catalyze the decomposition of diazocarbonyls **147** to form carbenoids. Thus, Rh-stabilized carbenoids reacted with acetylenes to afford substituted furans although the reaction may also produces cyclopropenes (Scheme 114).[158]

Scheme 114

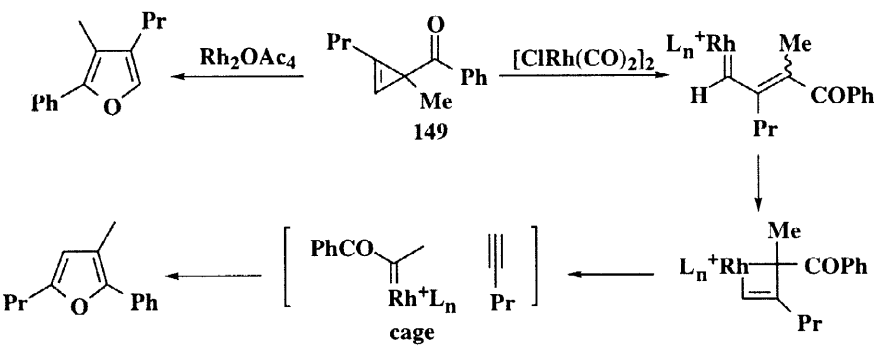


R = Ph, 4-MeOPh, 3,4-di-MeOPh
R^1 = Me, OEt
R^2 = COMe, COOEt, CH=CHCOOEt

In an attempt to avoid cyclopropene formation, diazo compounds with two electron withdrawing groups were used. The presence of electron donating groups on the acetylene prevented the generation of furans.

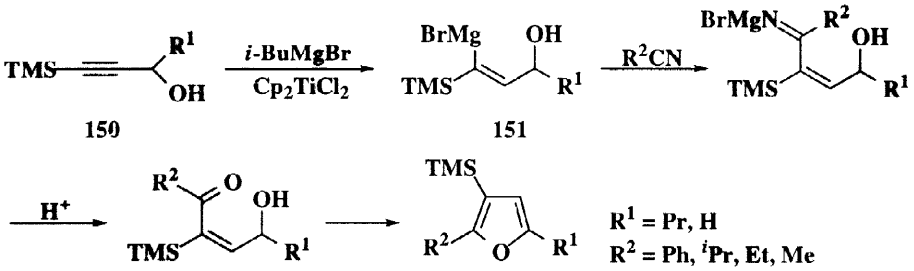
Similarly, a literature report also disclosed that Rh-catalyzed ring opening reaction of cyclopropene was regioselectively controlled by the oxidation state of the metal. Thus, 1,2,2-trisubstituted cyclopropenes **149** were converted to 2,3,4- and 2,3,5- trisubstituted furans in the ratio of 26:1 in the presence of a Rh(II) complex while a Rh(I) catalyst led exclusively to 2,3,5-trisubstituted furans. The mechanism might involve an electrophilic attack followed by ring opening and electrocyclization, yielding a metallocyclobutene. Retrocycloaddition and recombination then give rise to furan products. The ring cleavage step is highly regiospecific and the product composition markedly depends on the metal oxidation state (Scheme 115).[159] These results differ from that of Davies and Romines (cf. Scheme 114).[158] In the latter example, $Rh_2(OAc)_4$ catalyzed rearrangement of cyclopropene derivatives **126** afforded 2,3,5-trisubstituted furans.

Scheme 115



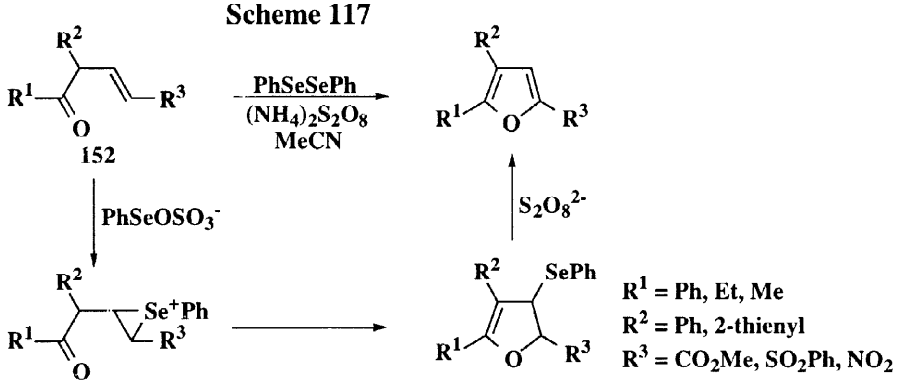
Hydromagnesiation of γ-trimethylsilylpropargyl alcohols **150** followed by treatment of the intermediate **151** with nitriles furnished furan derivatives. The addition of the Grignard reagent to the acetylenic group was catalyzed by Cp_2TiCl_2. The vinyl magnesium bromide then reacted with nitriles to produce ketimines which were hydrolyzed and dehydrated to furan products under acidic conditions (Scheme 116).[160] Acyl halides or acid anhydrides were also used instead of RCN to afford the corresponding furans although the yields were lower than those reactions with nitriles. In this reaction, the trimethylsilyl group can serve as a directing group.

Scheme 116



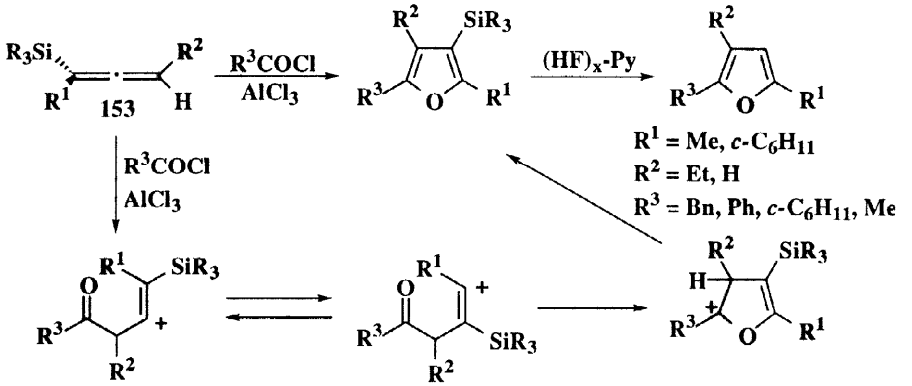
β,γ-Unsaturated ketones containing an electron withdrawing group at the α-position were able to react with diselenide and ammonium persulfate to produce substituted furans in moderate to good yields. The reaction was initiated by an attack of the strongly electrophilic phenylselenenyl sulfate, which was formed *in situ* by reaction of diphenyl diselenide and ammonium persulfate, to give the selenodihydrofuran. Oxidation of selenodihydrofuran eventually afforded the furan products (Scheme 117).[161] This one-pot conversion of unsaturated ketones into substituted furans by using phenylselenyl sulfate provided an attractive and convenient method for furan preparation, despite the fact that the preparation of β,γ-unsaturated ketones is not trivial.

Scheme 117



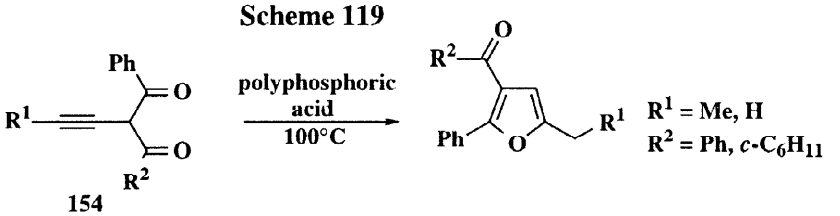
Furan frameworks were also formed by reaction of allenylsilanes **153** and acid chlorides in the presence of aluminum chloride. The process can be considered as a [2 + 3] annulation of allene and $^{+}C=O$. Desilylation of tetrasubstituted furans provided the desired products (Scheme 118).[162] The reaction was regiocontrolled and *t*-butyldimethylsilyl or triisopropylsilyl group was superior to trimethylsilyl group presumably due to the ability of the larger trialkylsilyl groups to suppress the undesirable desilylaton reaction. In addition, the trialkylsilyl substituents in the products have the capacity to facilitate electrophilic substitution reaction at C-3 position of the furan ring. On the other hand, if desired, the silyl group can be easily removed by acid treatment.

Scheme 118



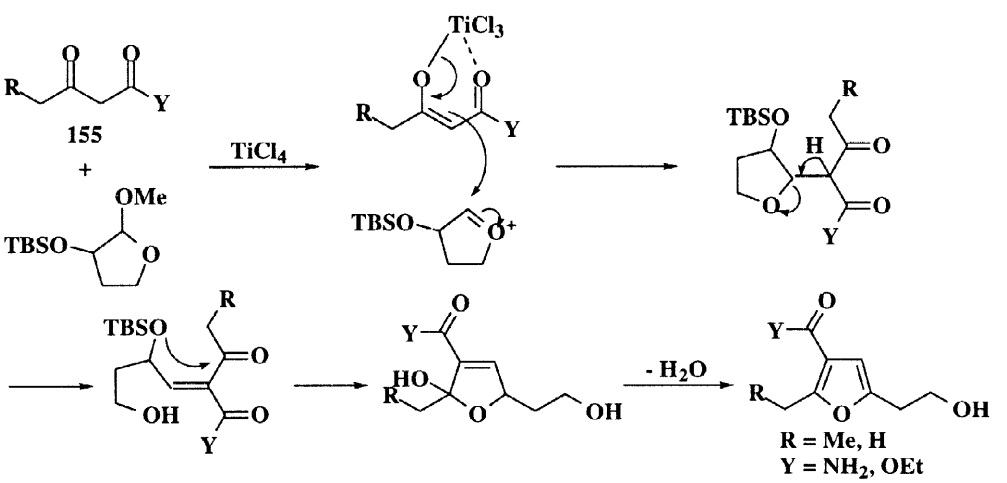
Intramolecular cyclization of propargyl substituted 1,3-diketones **154** led to the formation of 2,3,5-trisubstituted furans. The reaction was carried out in PPA (Scheme 119).[163]

Scheme 119



Coupling of β-keto esters or amides **155** with cyclic acetals promoted by $TiCl_4$ led to the formation of furan products. The reaction is presumed to proceed through the attack of titanium enolates at the reactive oxonium, generated also by the action of $TiCl_4$, and followed by cyclization to give the dihydrofuran. Dehydration then delivered 2,3,5-trisubstituted furans (Scheme 120).[164]

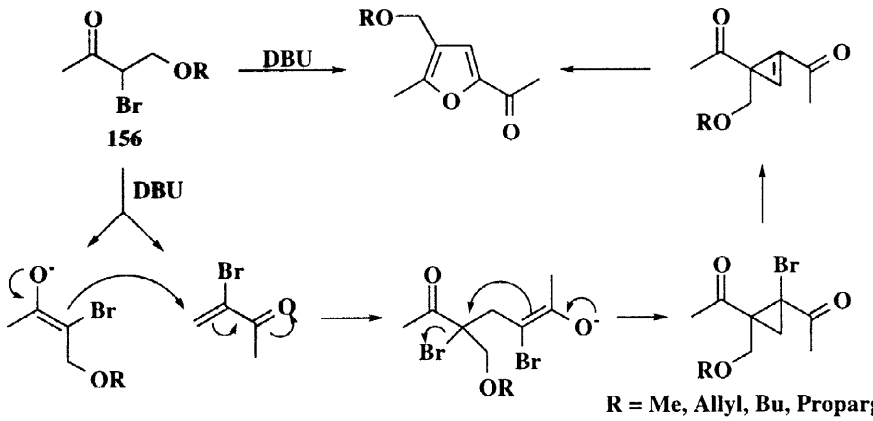
Scheme 120



Reaction of two molecules of α-bromo-β-alkoxyketones **156** in the presence of DBU afforded 2,3,5-trisubstituted furans. The elimination of ROH from the α-bromo-β-alkoxyketone produces α-bromo vinyl methyl ketone, which then reacted with another molecule of α-bromo-β-alkoxyketone in a Michael-type addition to give a new adduct. γ-Elimination and dehydrobromination provided diacyl cyclopropene.

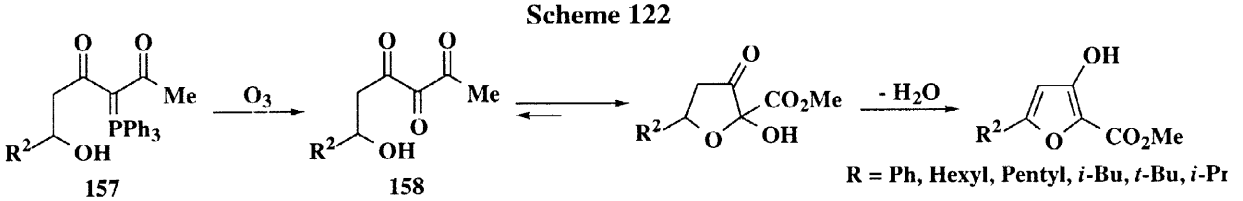
Rearrangement of this cyclopropene led to furan products (Scheme 121).[165] The reaction is very efficient and thus constitutes a new simple entry to the synthesis of relatively elaborate substituted furans which are valuable synthetic units of widespread occurrence in Nature.

Scheme 121



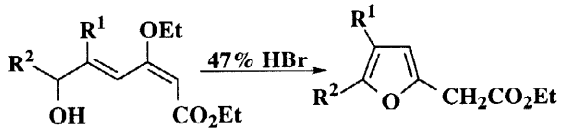
The formation of furan rings from 1,4-difunctional groups is one of the most popular methods in furan synthesis. Some procedures for preparing 2,3,5-trisubstituted furans are based on this strategy. The highly electrophilic nature of the central carbonyl in vicinal tricarbonyls **158** has been used in the synthesis of furan rings (Scheme 122).[166] In this example, the central carbonyl group of the starting materials acts as an acceptor for intramolecular addition of the alcohol group. Acid-catalyzed dehydration of the resulting dihydrofuranones produced furan derivatives.

Scheme 122

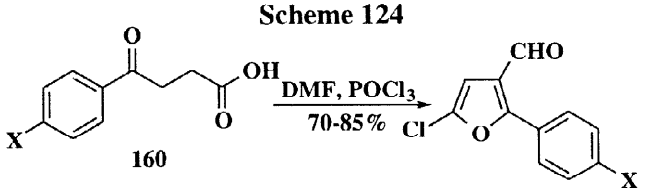


Conversion of 6-hydroxy-3-oxo-4-hexenoates **159** under acidic condition to furan derivatives is shown in Scheme 123.[167] The conversion of γ-oxo-carboxylic acids **160** to furans *via* a Vilsmeier reaction (Scheme 124) is another example making use of a similar strategy.[168]

Scheme 123



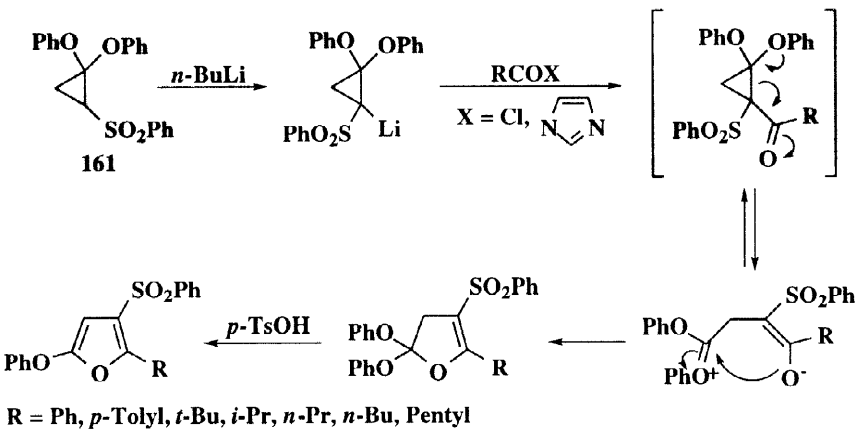
Scheme 124



Cyclopropanes **161** with donor and acceptor functionalities have been utilized as three-carbon building blocks for the preparation of furan rings. Thus, reaction of 1,1-diphenoxy-2-(phenylsulfonyl)cyclopropane with BuLi followed by the trapping of the carbanion with acylating agents provided dihydrofurans, which were

easily converted to 2,3,5-trisubstituted furans under the action of *p*-TsOH. For enolizable acyl agents the reaction also gave the undesired enolate of acyl cyclopropanes since the lithium derivative of cyclopropanes could serve as a base. To avoid this side reaction acyl imidazoles were used instead (Scheme 125).[169]

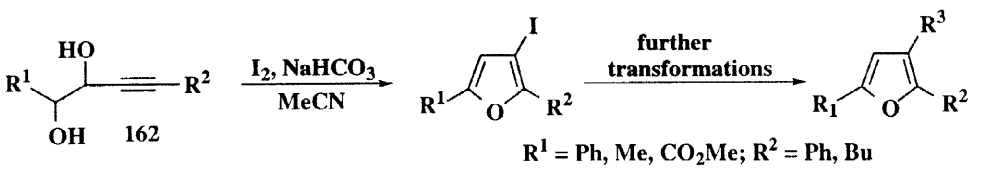
Scheme 125



R = Ph, *p*-Tolyl, *t*-Bu, *i*-Pr, *n*-Pr, *n*-Bu, Pentyl

Alk-3-yne-1,2-diols **162** reacted with iodine in MeCN to afford 3-iodofurans in good yields. It is presumed that the reaction involved a 5-*endo-dig* cyclization[17] to 3-hydroxy-4-iodo-2,3-dihydrofurans which rapidly underwent dehydration to give the corresponding iodofurans although all efforts to observe the intermediate were unsuccessful. It is interesting that the attempts to cyclize a 3,4-dihydroxyalk-1-yne also failed and the cyclization of *syn*-isomers was more rapid (about 2 h) than the *anti*-isomers (about 12 h). It is worth noting that these iodofurans were converted further to other 2,3,5-trisubstituted furans by using metal catalyzed coupling reactions or halogen-metal exchange (Scheme 126).[170]

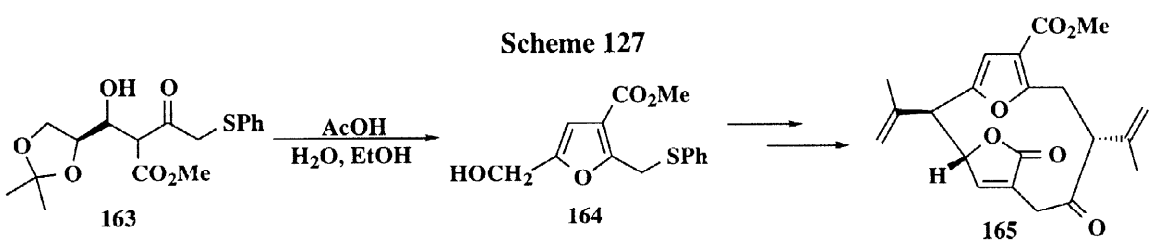
Scheme 126



R^1 = Ph, Me, CO_2Me; R^2 = Ph, Bu

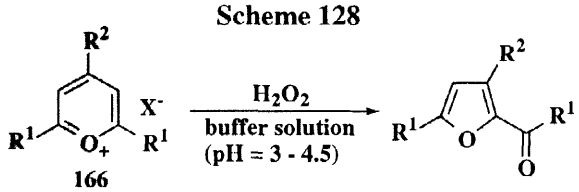
2,3,5-Trisubstituted furan **164**, which served as an intermediate in the total synthesis of a furanocembranolide, namely gorgiacerone (**165**), was also obtained from a 1,4-difunctional starting material **163** (Scheme 127).[171]

Scheme 127



Hydrogen peroxide oxidation of 2,4,6-trialkylsubstituted pyrylium salts furnished 2-acyl-3,5-dialkylfurans in moderate yields. When the reaction was carried out in buffer solutions (*p*H = 3-4.5) the yields were improved to 75% (Scheme 128).[172]

Scheme 128



R^1 = Me *i*-Pr; R^2 = Ph, Et, Me
X = ClO_4, BF_4

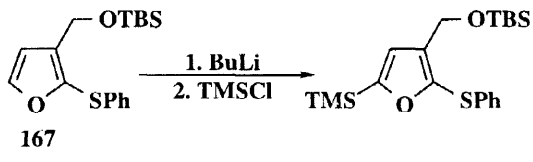
Ag(I) or Rh(I) promoted cyclization of allenyl ketones and aldehydes is a convenient method for the preparation of 2,3,5-trisubstituted furans (cf. Scheme 25).[46-49] In view of the mild reaction conditions these methods will be well suited to form sensitive furans and bisfuranomethanes.

The conversion of ketene dithioacetals to substituted furans under suitable conditions has been described (cf. Scheme 35).[61] In addition, 2,3,5-trisubstituted furans were also obtained through the reaction of diazocyclohexane-1,3-diones with vinyl acetate in the presence of a rhodium catalyst through a 1,3-dipolar cycloaddition and subsequent elimination of HOAc by using a catalytic amount of *p*-TsOH (cf. Scheme 38),[65] from substituted 3-alkyne-1,2-diols under palladium catalysis (cf. Scheme 59),[89] from acetylenic ketones (cf. Scheme 65),[96] from the reaction of 1,1-dibromo-3-phenyl-1-butene and ketones in the presence of *t*-BuOK (cf. Scheme 66),[97] and from propargylbenzotriazole and α-bromo ketones (cf. Scheme 68).[99] Trisubstituted furans were also produced from bromoacetals by a radical cyclization when 1,3-disubstituted propargyl alcohols and 2-methoxypropene were used as starting materials (cf. Scheme 4).[15,173]

6.2 From Other Furans

Lithiation-electrophile trapping strategy was also widely applied to the synthesis of 2,3,5-trisubstituted furans. These furyllithium species were obtained by various means, such as direct metallation of furans at the α-position using BuLi or LDA and metal-halogen exchange methodology, which allowed for the preparation of β-thio-furans. Blocking groups were occasionally used to lead the lithium to special position. In this aspect, trialkylsilyl groups are particularly useful not only because they play a role as a directing group but also because they are easily removed. Normally the lithiation of 2,3-disubstituted furans occurs at C-5 position. Thus, 2,3,5-trisubstituted furans can be obtained from these lithiated furan through an electrophilic attack (Scheme 129).[174]

Scheme 129

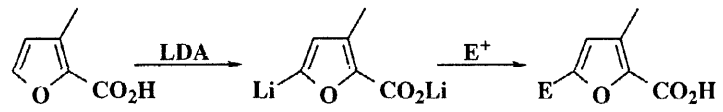


LNMP = lithium *N*-methylpiperazide

A similar reaction was also carried out for 3-methylfuran-2-carboxylic acid (**169**) (Scheme 130).[175] Furan dianion reacted very efficiently with aldehydes and ketones but not as satisfactorily with alkyl halides and

epoxides except with MeI and EtI. In spite of these shortcomings, this is an effective procedure for 2,3,5-trisubstituted furans preparation. Lithiation at the C-5 position of 2,3-disubstituted furans was also successfully established for 2-*t*-butyldimethylsilyl-3-(triethylsiloxymethyl)furan (cf. Scheme 70)[102] and 2-bromo-3-methylfuran.[103]

Scheme 130

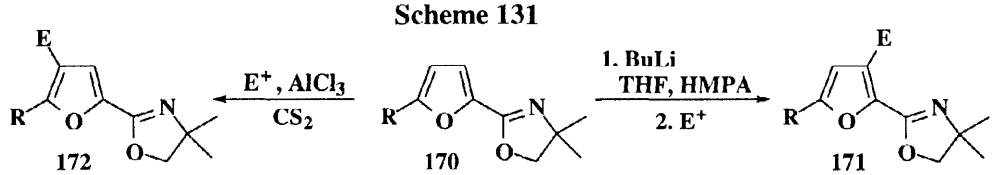


169

E = Me, Et, $R^1R^2C(OH)$,
R^1 = Ph, Me; R^2 = Me, H
R^1R^2 = -$(CH_2)_5$-

Lithiation-electrophilic trapping strategy has also been employed in the synthesis of 2,3,5-trisubstituted furans from 2,5-disubstituted furans. Regioselective lithiation at C-3 position can be carried out for (5-substituted-2-furyl)-4,5-dihydroxazoles **170** simply by using BuLi in THF-HMPA. Treatment of the lithiated furan with electrophiles provided 2,3,5-trisubstituted furans **171** in excellent yields (Scheme 131).[176] Interestingly, direct electrophilic aromatic substitution of **170** is preferred at C-4 position in spite of the strong electron-withdrawing effect of the oxazoline moiety and its tendency for *N*-quaternization. (3,5-Disubstituted-2-furyl)-4,5-dihydroxazoles were also obtained from 2-furyl-4,5-dihydroxazoles by dilithiation at 3,5-positions with subsequent electrophilic trapping.[177]

Scheme 131

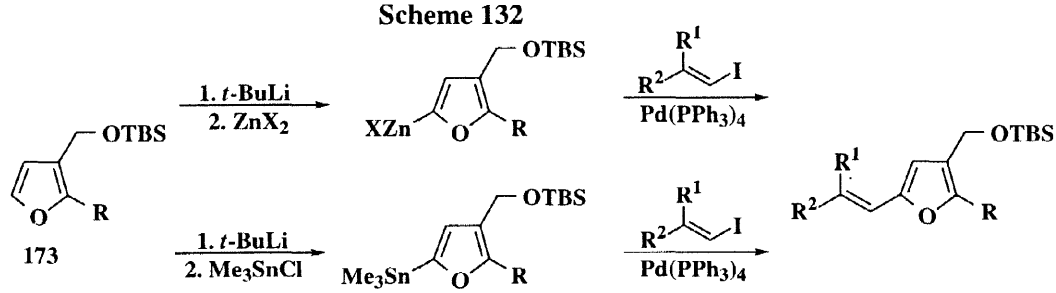


172 170 171

R = Me, Et, *i*-Bu, TMS
E = PhCH(OH), CHO, CO_2H, Me, CH_2=$CHCH_2$, $PhCH_2$

Another strategy of preparing 2,3,5-trisubstituted furans from 2,3-disubstituted furans is through transmetallation of 5-lithio-2,3-disubstituted furans followed by Pd-catalyzed coupling reaction (Scheme 132).[178]

Scheme 132

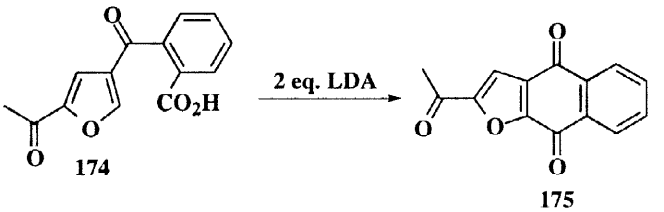


173

R = Me, ICH_2CH_2, $HOCH_2CH_2$,$HOCH_2CH(HO)CH_2$; R^1 = Me
R^2 = Bu, $TBSOCH_2CH(OCOCH_2COMe)CH_2$, $TBSOCH_2CH(OAc)CH_2$

2-Acylnaphtho[2,3-*b*]furan-4,9-dione **175**, isolated from *Tabebuia Cassinoides* (Lam.) DC (*Bignoniaceae*), was synthesized from 2-(2-acetyl-4-furanoyl)benzoic acid **174** (Scheme 133).[179]

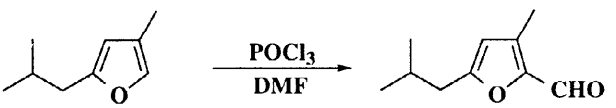
Scheme 133



174 175

5-Isobutyl-3-methyl-2-furancarbaldehyde (**177**), a monoterpene isolated from the essential oil of *Tagetes glandulifera* Schrank, was synthesized from a 2,4-disubstituted furan **176** by the use of Vilsmeier formylation (Scheme 134) (cf. Scheme 61).[91a]

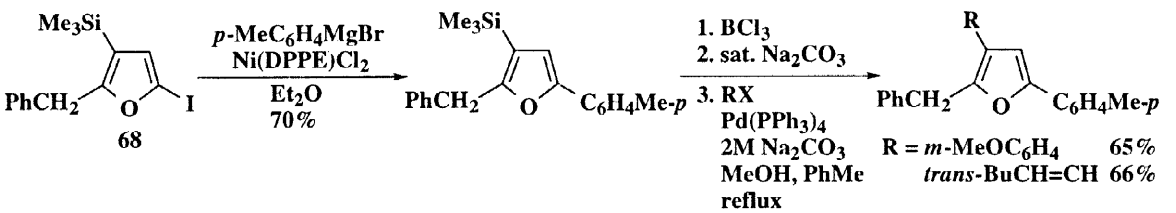
Scheme 134



176 177

Furan derivative **68** (cf. Scheme 50) has also been converted to 2,3,5-trisubstituted furans through the protocol of Ni-catalyzed coupling, boroxine formation and Suzuki reaction (Scheme 135).[80]

Scheme 135



68

Furthermore, 2,3,5-trisubstituted furans have been prepared from 2-phenylthio-5-alkylfurans through regioselective bromination followed by lithium-halogen exchange as well as electrophilic attack (cf. Scheme 72).[105] Lithium-halogen exchange with subsequent conversion of Li to Ti was followed by electrophilic attack to provide 2,3,5-trisubstituted furans. High regioselectivity was realized in this way when bifunctional electrophiles were used (cf. Scheme 12).[27]

Concluding Remarks

In this report, We have reviewed the regioselective syntheses of polysubstituted furans in accord to their substitution patterns. As mentioned in the Introduction, no encyclopaedic coverage is intended, the syntheses of furans are only discussed in this report mainly in conformity with the authors' interests. After the completion of this manuscript, many new examples have appeared in the literature for the preparation of 3-substituted,[180-185] 2,4-disubstituted,[186] 3,4-disubstituted,[187] 2,3,4-trisubstituted,[188-190] and 2,3,5-trisubstituted furans.[191-195] The untiring activities in the preparation of polysubstituted furans nonetheless manifest their significance. Notwithstanding the established procedures, there is still an urgent need to realize polysubstituted furans in a more regioselective style as well as in larger scales, which can be looked upon as a synthetic challenge to greater exertions.

Acknowledgement. Financial support from a Research Grants Council Earmarked Grant (CUHK 296/94P) is gratefully acknowledged.

References and Notes.

1. To whom correspondence should be addressed.
2. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
3. Nakanishi, K. *Natural Products Chemistry* Kodansha, Ltd.: Tokyo, 1974.
4. Lukevits, É.; Pudova, O. A. *Chemistry of Heterocyclic Compounds* **1995**, *31*, 377.
5. Lukevits, É.; Pudova, O. A. *Chemistry of Heterocyclic Compounds* **1995**, *31*, 412.
6. Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Bird, C.W.; Cheeseman, G. W. H., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 657-712.
7. Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.
8. Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167.
9. Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *31*, 237.
10. Sargent, M. V.; Dean, F. M. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, pp 599-656.
11. König, H.; Graf, F.; Weberndörfer, V. *Liebigs Ann. Chem.* **1981**, 668.
12. Liotta, D.; Saindane, M.; Ott, W. *Tetrahedron Lett.* **1983**, *24*, 2473.
13. Yu, P.; Yang, Y.; Zhang, Z. Y.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **1997**, *62*, 6359.
14. Fleming, I.; Taddei, M. *Synthesis* **1985**, 898.
15. (a) Srikrishna, A.; Sunderbabu, G. *Chem. Lett.* **1988**, 371; (b) Srikrishna, A.; Sunderbabu, G. *Tetrahedron Lett.* **1987**, *28*, 6393.
16. da Silva, G. V. J.; Pelisson, M. M. M.; Constantino, M. G. *Tetrahedron Lett.* **1994**, *35*, 7327.
17. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
18. Mandai, T.; Hashio, S.; Goto, J.; Kawada, M. *Tetrahedron Lett.* **1981**, *22*, 2187.
19. (a) Miles, W. H.; Berreth, C. L.; Smiley, P. M. *Tetrahedron Lett.* **1993**, *34*, 5221. (b) Miles, W. H.; Berreth, C. L.; Anderton, C. A. *Tetrahedron Lett.* **1996**, *37*, 7893.
20. Miles, W. H.; Smiley, P. M. *J. Org. Chem.* **1996**, *61*, 2559.
21. Pohmakotr, M.; Takampon, A. *Tetrahedron Lett.* **1996**, *37*, 4585.
22. Fukuyama, Y.; Kawashima, Y.; Miwa, T.; Tokoroyama, T. *Synthesis* **1974**, 443.
23. Bock, I.; Bornowski, H.; Rault, A.; Theis, H. *Tetrahedron* **1990**, *46*, 1199.
24. Honda, T.; Ishikawa, F.; Yamane, S. *J. Chem. Soc., Chem. Commun.* **1994**, 499.
25. (a) Ihara, M.; Suzuki, S.; Taniguchi,N.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1993**, 755. (b) Eicher,T.; Massonne, K.; Hermann, M. *Synthesis* **1991**, 1173.
26. (a) Renoud-Grappin, M.; Vanucci, C.; Lhommet, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 995. (b) Renoud-Grappin, M.; Vanucci, C.; Lhommet, G. *J. Org. Chem.* **1994**, *59*, 3902.
27. Maezaki, N.; Gijsen, H. J. M.; Sun, L.-Q.; Paquette, L. A. *J. Org. Chem.* **1996**, *61*, 6685..
28. Cahiez, G.; Chavant, P.-Y.; Metais, E. *Tetrahedron Lett.* **1992**, *33*, 5245.
29. Kojima, Y.; Wakita, S.; Kato, N. *Tetrahedron Lett.* **1979**, 4577.
30. Ennis, D. S.; Gilchrist, T. L. *Tetrahedron* **1990**, *46*, 2623.
31. Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833 and references cited

therein.

32. Bailey, T. R. *Synthesis* **1991**, 242.
33. Degl'Innocenti, A.; Capperucci, A.; Bartoletti, L.; Mordini, A.; Reginato, G. *Tetrahedron Lett.* **1994**, *35*, 2081.
34. Balas, L.; Jousseaume, B.; Shin, H.; Verhac, J.-B.; Wallian, F. *Organometallics* **1991**, *10*, 3 66.
35. Yang, Y.; Wong, H. N. C. *Tetrahedron* **1994**, *50*, 9583.
36. Pridgen, L. N.; Jones, S. S. *J. Org. Chem.* **1982**, *47*, 1590.
37. Takagi, K.; Hayama, N.; Sasaki, K. *Bull. Chem. Soc. Jpn.* **1984**, 1887.
38. Oda, K.; Machida, M. *Tetrahedron Lett.* **1989**, *30*, 4421.
39. Ho, T.-L.; Lee, K.-Y. *Tetrahedron Lett.* **1995**, *36*, 947.
40. Tsubuki, M.; Okita, H.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1995**, 2135.
41. Enders, D.; Jandeleit, B. *Synthesis* **1994**, 1327.
42. Wiley, R. A.; Choo, H.-Y.; McClellan, D. *J. Org. Chem.* **1983**, *48*, 1106.
43. (a) Tanis, S. P. *Tetrahedron Lett.* **1983**, *23*, 3115. (b) Tanis, S. P.; Merrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572.
44. Marshall, J. A.; Bennett, C. E. *J. Org. Chem.* **1994**, *59*, 6110.
45. Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3602.
46. Marshall,J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450.
47. Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 960.
48. Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169.
49. Marshall, J. A.; Wallace, E. M. *J. Org. Chem*, **1995**, *60*, 796.
50. (a) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1994**, 493. (b) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089. (c) Kücükbay, H.; Cetinkaya, B.; Guesmi, S.; Dixneuf, P. H. *Organometallics* **1996**, *15*, 2423.
51. Trost, B. M.; Flygare, J. A. *J. Org. Chem.* **1994**, *59*, 1078.
52. (a) Takano, S.; Morimoto, M.; Satoh, S.; Ogasawara, K. *Chem. Lett.* **1984**, 1261. (b) Meier, L.; Scharf, H.-D. *Liebigs Ann. Chem.* **1986**, 731. (c) Tsukasa, H.; Iriye, R. *Agri. Biol. Chem.* **1989**, *53*, 3091. (d) Uno, T.; Ohwa, I.; Konishi, A. *Agri. Biol. Chem.* **1990**, *54*, 1841.
53. Kim, S.; Kim, Y. G. *Tetrahedron Lett.* **1991**, *32*, 2913.
54. Kim, S.; Kim, Y. G. *Synlett* **1991**, 869.
55. Zoretic, P. A.; Shen, Z.; Wang, M. *Tetrahedron Lett.* **1995**, *36*, 2925.
56. Ho, T.-L.; Chein, R.-J. *J. Chem. Soc., Chem.Commun.* **1996**, 1147
57. Tsuge, O.; Kanemasa, S.; Suga, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2133.
58. Obrecht, D. *Helv. Chim. Acta* **1989**, *72*, 447.
59. Ly, N. D.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 2085.
60. Cambie, R. C.; Moratti, S. C.; Rutledge, P. S.; Woodgate, P. D. *Synth. Commun.* **1990**, *20*, 1923.
61. (a) Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Chem. Soc., Chem. Commun.* **1982**, 1055. (b) Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Org. Chem.* **1984**, *49*, 3819.
62. McDonald, F. E.; Schultz, C. C. *J. Am. Chem. Soc.* **1994**, *116*, 9363.
63. Gariboldi, P.; Jommi, G.; Sisti, M. *J. Org. Chem.* **1982**, *47*, 1961.
64. (a) Bernasconi, S.; Ferrari, M.; Garibold, P.; Jommi, G.; Sisti, M. *J. Chem. Soc., Perkin Trans. 1*

1981, 1994. (b) **Bernasconi, S.**; Gariboldi, P.; Jommi, G.; Sisti, M.; Tavecchia, P. *J. Org. Chem.* **1981**, *46*, 3719.

65. **Pirrung, M. C.**; **Lee, Y. R.** *Tetrahedron Lett.* **1994**, *35*, 6231.
66. **Chan, W. H.**; **Lee, A. W. M.**; **Chan**, E. T. T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 945.
67. (a) **Pale, P.**; **Chuche, J.** *Tetrahedron Lett.* **1987**, *28*, 6447. (b) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1996**, *37*, 2781.
68. Selnick, H. G.; Brookes, L. M. *Tetrahedron Lett.* **1989**, *30*, 6607.
69. (a) **Murai, S.**; **Kakiuchi, F.**; **Sekine, S.**; Tanaka,Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681.
70. **Martin, D.**; **Wurster, J. A.**; **Boylan**, M. J.; Borzilleri, R. M.; Engel, G. T.; Walsh, E. J. *Tetrahedron Lett.* **1993**, *34*, 8395.
71. (a) Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1125. (b) Perry, P. J.; Pavlidis, V. H.; Hadfield, J. A.; Coutts, I. G. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1085. (c) Yu, S.; Keay, B. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2600.
72. Honda, T.; Kobayashi, Y.; Tsubuki, M. *Tetrahedron* **1993**, *49*, 1211.
73. Bures, E. J.; Keay, B. A. *Tetrahedron Lett.* **1987**, *28*, 5965.
74. Spinazze, P. G.; Keay, B. A. *Tetrahedron Lett.* **1989**, *30*, 1765.
75. Weyerstahl, P.; Schenk, A.; Marschall, H. *Liebigs Ann. Chem.* **1995**, 1849.
76. Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572.
77. Moiseenkov, A. M.; Lozanova, A. V.; Surkova, A. A.; Veselovsky, V. V. *Mendeleev Commun.* **1996**, 89.
78. (a) Araki, S.; Butsugan, Y. *Chem. Lett.* **1982**, 177. (b) Araki, S.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1446.
79. Bock, I.; Bornowski, H.; Ranft, A.; Theis, H. *Tetrahedron* **1990**, *46*, 1199.
80. Wong, M. K.; Leung, C. Y.; Wong, H. N. C. *Tetrahedron* **1997**, *53*, 3497.
81. Eberbach, W.; Fritz, H.; Laber, N. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 568.
82. Jousseaume, B.; Kwon, H.; Verlhac, J.-B.; Denat, F.; Dubac, J. *Synlett* **1993**, 117.
83. Forrest, A. K.; O'Hanlon, P. J. *Tetrahedron Lett.* **1995**, *36*, 2117.
84. Leung, M.-k.; Trahanovsky, W. S. *J. Am. Chem. Soc.* **1995**, *117*, 841 and references cited therein.
85. Kang, K.-T.; U, J. S.; Hwang, S. S.; Jyung, K. K. *Synth. Commun.* **1994**, *24*, 2915.
86. Barba, F.; de la Fuente, J. F. *Tetrahedron Lett.* **1992**, *33*, 3911.
87. Barba, F.; Velasco, M. D.; Guirado, A. *Synthesis* **1981**, 625.
88. Trost, B. M.; McIntosh, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 7255.
89. Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655.
90. Kosugi, M.; Takano, I.; Hoshino, I.; Migita, T. *J. Chem. Soc., Chem. Commun.* **1983**, 989.
91. (a) Maurer, B.; Hauser, A. *Tetrahedron Lett.* **1984**, *25*, 1061. (b) Hegde, S. G.; Wolinsky, J. *J. Org. Chem.* **1982**, *47*, 3148.
92. Cormier, R. A.; Francis, M. D. *Synth. Commun.* **1981**, *11*, 365.
93. Kabat, M. M. *Tetrahedron Lett.* **1996**, *37*, 7437.
94. Jung, J. H.; Lee, J. W.; Oh, D. Y. *Tetrahedron Lett.* **1995**, *36*, 923.
95. Igarashi, S.; Haruta, Y.; Ozawa, M.; Nishide, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1989**, 737.

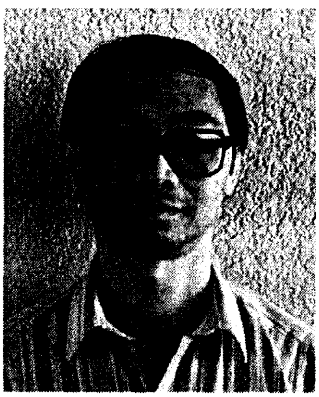
96. Obrecht, D. *Helv. Chim. Acta* **1989**, *72*, 447.
97. Frey, H. *Synlett* **1993**, 905.
98. Srikrishna, A.; Pullaiah, K. C. *Tetrahedron Lett.* **1987**, *28*, 5203.
99. Katritzky, A.; Li, J. *J. Org. Chem.* **1995**, *60*, 638.
100. Tsuge, O.; Kanemasa, S.; Suga, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2133.
101. (a) Siedem, C. S.; Molander, G. A. *J. Org. Chem.* **1996**, *61*, 1140. (b) Nakayama, K.; Harigaya, Y.; Okomoto, H.; Tanaka, A. *J. Heterocycl. Chem.* **1991**, *28*, 853. (c) Nakayama, K.; Tanaka, A. *Chem. Expr.* **1991**, *6*, 699. (d) Gill, M. *Tetrahedron* **1984**, *40*, 621.
102. Nieman, J. A.; Keay, B. A. *Tetrahedron Lett.* **1994**, *35*, 5335.
103. Bock, I.; Bornowski, H.; Ranft, A.; Theis, H. *Tetrahedron* **1990**, *46*, 1199.
104. (a) Brown, D. S.; Paquette, L. A. *J. Org. Chem.* **1992**, *57*, 4512. (b) Carling, R. W. *Synlett* **1993**, 40.
105. Nolan, S. M.; Cohen, T. *J. Org. Chem.* **1981**, *46*, 2473.
106. Chiarello, J.; Joullie, M. M. *Tetrahedron* **1988**, *44*, 41.
107. Lee, G. C. M.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Org. Chem.* **1992**, *57*, 3126.
108. William, D. H.; Faulkner, D. J. *Tetrahedron* **1996**, *52*, 4245.
109. (a) Sallins, D. M.; Bobik, T. A.; Wolfe, R. S.; Rinehart, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 6646. (b) Williams, D. H.; Faulkner, D. J. *Tetrahedron* **1996**, *52*, 4245.
110. Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.
111. (a) Katsumura, S; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1988**, *29*, 1173. (b) Haarmann, H.; Eberbach, W. *Tetrahedron Lett.* **1991**, *32*, 903.
112. Stetinova, J.; Lesko, J.; Dandarova, M.; Kada, R.; Koren, R. *Collect Czech. Chem. Commun.* **1994**, *59*, 2721.
113. (a) Ansell, M. F.; Caton, M. P. L.; North, P. C. *Tetrahedron Lett.* **1981**, *22*, 1727. (b) Nakazawa, T.; Ishihara, M.; Jinguji, M.; Miyatake, R.; Sugihara, Y.; Murata, I. *Tetrahedron Lett.* **1994**, *45*, 8421.
114. (a) Yamaguchi, Y.; Yamada, H.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1987**, *52*, 2040. (b) Yamaguchi, Y.; Tatsuta, N.; Soejima, S.; Hayakawa, K.; Kanematsu, K. *Heterocycles* **1990**, *30*, 223. (c) Kanematsu, K.; Soejima, S. *Heterocycles* **1991**, *32*, 1483. (d) Baba, Y.; Sakamoto, T.; Kanematsu, K. *Tetrahedron Lett.* **1994**, *35*, 5677. (e) Wu, H.-J.; Lin, S.-H.; Lin, C.-C. *Heterocycles* **1994**, *38*, 1507 and references cited therein.
115. Suzuki, T.; Kubomura, K.; Fuchii, H.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1990**, 1687.
116. (a) Yang, Y.; Wong, H. N. C. *J. Chem. Soc., Chem. Commun.* **1992**, 656. (b) Yang, Y.; Wong, H. N. C. *J. Chem. Soc., Chem. Commun.* **1992**, 1723.
117. (a) Ho, M. S.; Wong, H. N. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1238. (b) Song, Z. Z.; Ho, M. S.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 3917. (c) Song, Z. Z.; Wong, H. N. C. *J. Chin. Chem. Soc.* **1995**, *42*, 673.
118. Price, M. E.; Shore, N. E. *J. Org. Chem.* **1989**, *54*, 2777.
119. Garst, M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250.
120. (a) Zoretic, P. A.; Shen, Z.; Wang, M. *Tetrahedron Lett.* **1995**, *36*, 2925. (b) Zoretic, P. A.; Wang, M.; Zhang, Y.; Shen, Z. *J. Org. Chem.* **1996**, *61*, 1806.
121. Reich, H. J.; Olson, R. E. *J. Org. Chem.* **1987**, *52*, 2315.

122. Nakano, T.; Hernandez, M. I.; Gomez, M.; Medina, J. D. *J. Chem. Res. (S)* **1989**, 54.
123. (a) Gorzynski, M.; Rewicki, D. *Liebigs Ann. Chem.* **1986**, 625. (b) Alvarez-Ibarra, C.; Quiroga, M. L.; Toledano, E. *Tetrahedron* **1996**, *52*, 4065.
124. McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *Tetrahedron Lett.* **1987**, *28*, 4123.
125. (a) Bures, E. J.; Keay, B. A. *Tetrahedron Lett.* **1988**, *29*, 1247. (b) Danso-Danquah, R. E.; Scott, A. I. *Tetrahedron* **1993**, *49*, 8195. (c) Nieman, J. A.; Keay, B. A. *Tetrahedron Lett.* **1994**, *35*, 5335.
126. Yu, S.; Keay, B. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2600.
127. Alvarez-Ibarra, C.; Quiroga, M. L.; Toledano, E. *Tetrahedron* **1996**, *52*, 4065.
128. (a) Song, Z. Z.; Zhou, Z. Y.; Mak, T. C. W.; Wong, H. N. C. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 432. (b) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33. (c) Ye, X. S.; Yu, P.; Wong, H. N. C. *Liebigs Ann. Chem.* **1997**, 459.
129. (a) Scherf, U.; Müllen, K. *Synthesis,* **1992**, 23. (b) Qian, R.-Y. *Makromol. Chem. Makromol. Symp.* **1990**, *33*, 327 and references cited therein.
130. (a) Kaino, T.; Tomaru, S. *Adv. Mater.* **1993**, *5*, 172. (b) Buckley, A. *Adv. Mater.* **1992**, *4*, 153. (c) Eaton, D. F.; Meredith, G. R.; Miller, J. *Adv. Mater.* **1992**, *4*, 45.
131. Song, Z. Z.; Wong, H. N. C. *Liebigs Ann. Chem.* **1994**, 29.
132. Jacobi, P. A.; Walker, D. G.; Odeh, M. A. *J. Org. Chem.* **1981**, *46*, 2065.
133. Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041.
134. (a) Yamaguchi, Y.; Hayakawa, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1987**, 515. (b) Kanematsu, K.; Nishizaki, A.; Sato, Y.; Shiro, M. *Tetrahedron Lett.* **1992**, *33*, 4967.
135. Yamaguchi, Y.; Tatsuta, N.; Hayakawa, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1989**, 470.
136. Hiroi, K.; Sato, H. *Synthesis* **1987**, 811.
137. (a) Takai, K.; Tezuka, M.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 5310. (b) Kataoka, Y.; Tezuka, M.; Takai, K.; Utimoto, K. *Tetrahedron* **1992**, *48*, 3495.
138. Greeves, N.; Torode, J. S. *Synthesis,* **1993**, 1109.
139. Shishido, K.; Takata, T.; Omodani, T.; Shibuya, M. *Chem. Lett.* **1993**, 557.
140. Hagiwara, H.; Uda, H.; Kodama, T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 963.
141. (a) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1994**, *59*, 6606. (b) Harada, N.; Sugioka, T.; Ando, Y.; Uda, H.; Kuriki, T. *J. Am. Chem. Soc.* **1988**, *110*, 8483.
142. Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21.
143. Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897.
144. Blay, G.; Cardona, L.; Garcia, B.; Pedro, J. R.; Sanchez, J. J. *J. Org. Chem.* **1996**, *61*, 3815.
145. (a) Aso, M.; Ojida, A.; Yang, G.; Cha, O.-J.; Osawa, E.; Kanematsu, K. *J. Org. Chem.* **1993**, *58*, 3960. (b) Ojida, A.; Abe, A.; Kanematsu, K. *Heterocycles* **1994**, *38*, 2585. (c) Ojida, A.; Tanoue, F.; Kanematsu, K. *J. Org. Chem.* **1994**, *59*, 5970.
146. (a) Schultz, A. G.; Motyka, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 5800. (b) Schultz, A. G.; Motyka, L. A.; Plummer, M. *J. Am. Chem. Soc.* **1986**, *108*, 1056.
147. (a) Cristofoli, W. A.; Keay, B. A. *Tetrahedron Lett.* **1991**, *32*, 5881. (b) Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501.

148. **Keay, B. A.; Bontront, J. J.** *Can. J. Chem.* **1991**, *69*, 1326.
149. (a) **Marshall, J. A.; DuBay, W. J.** *J. Org. Chem.* **1991**, *56*, 1685. (b) Marshall, J. A.; **DuBay, W. J.** *J. Am. Chem. Soc.* **1992**, *114*, 1450.
150. **Marshall, J. A.; DuBay, W. J.** *J. Org. Chem.* **1993**, *58*, 3435.
151. **Marshall, J. A.; DuBay, W. J.** *J. Org. Chem.* **1994**, *59*, 1703.
152. (a) **Arcadi, A.; Marinelli, F.; Pini, E.; Rossi, E.** *Tetrahedron Lett.* **1996**, *37*, 3387. (b) Vieser, R.; Eberbach, W. *Tetrahedron Lett.* **1995**, *36*, 4405.
153. **Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H.** *J. Org. Chem.* **1991**, *56*, 5816.
154. **Marson, C. M.; Harper, S.; Wrigglesworth, R.** *J. Chem. Soc., Chem. Commun.* **1994**, 1879.
155. **Aurrecoechea, J. M.; Solay-Ispizua, M.** *Heterocycles* **1994**, 37, 223.
156. **Sham, H. L.; Betebenner, D. A.** *J. Chem. Soc., Chem. Commun.* **1991**, 1134.
157. (a) **Arcadi, A; Cacchi, S.; Larock, R. C.; Marinelli, F.** *Tetrahedron Lett.* **1993**, *34*, 2813. (b) Arcadi, A.; **Rossi, E.** *Tetrahedron Lett.* **1996**, *37*, 6811.
158. **Davies, H. M. L.; Romines, K. R.** *Tetrahedron* **1988**, *44*, 3343.
159. **Padwa, A.; Kassir, J. M.; Xu, S. L.** *J. Org. Chem.* **1991**, *56*, 6971.
160. (a) Sato, F.; Katsuno, H. *Tetrahedron Lett.* **1983**, *24*, 1809. (b) Tani, K.; Sato, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1993**, *34*, 4975.
161. Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *Synlett* **1994**, 373.
162. Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.
163. Barluenga, J.; Tomas, M.; Suarez-Sobrino, A. *Synlett* **1990**, 673.
164. Williams, R. M.; Esslinger, C. S. *Tetrahedron Lett.* **1991**, *32*, 3635.
165. Dulcere, J.-P.; Faure, R.; Rodriguez, J. *Synlett* **1992**, 737.
166. Wasserman, H. H.; Lee, G. M. *Tetrahedron Lett.* **1994**, *35*, 9783.
167. Kawano, T.; Ogawa, T.; Isiam, S. M.; Ueda, I. *Tetrahedron Lett.* **1995**, *36*, 7685.
168. Venugopal, M.; Balasundaram, B.; Perumal, P. T. *Synth. Commun.* **1993**, *23*, 2593.
169. Pohmakotr, M.; Takampon, A.; Ratchataphusit, J. *Tetrahedron* **1996**, *52*, 7149.
170. Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 1007.
171. (a) Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910. (b) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926.
172. Balaban, T. S.; Hiegemann, M. *Tetrahedron* **1992**, *48*, 9827.
173. Srikrishna, A.; Sundarababu, G. *Tetrahedron* **1990**, *46*, 7901.
174. (a) Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835. (b) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104.
175. Knight, D.W.; Nott, A.P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1125.
176. (a) Dominguez, C.; Csaky, A. G.; Plumet, J. *Tetrahedron* **1992**, *48*, 149. (b) Lenoir, J.-Y.; Ribereau, P.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2943.
177. Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, *26*, 5335.
178. Paterson, I.; Gardner, M. *Tetrahedron* **1989**, *45*, 5283.
179. Koyanagi, J.; Yamamoto, K.; Nakayama, K.; Tanaka, A. *J. Heterocyclic Chem.* **1995**, *32*, 1289.
180. Money, T.; Richardson, S. R.; Wong, M. K. C. *J. Chem. Soc., Chem. Commun.* **1996**, 667.

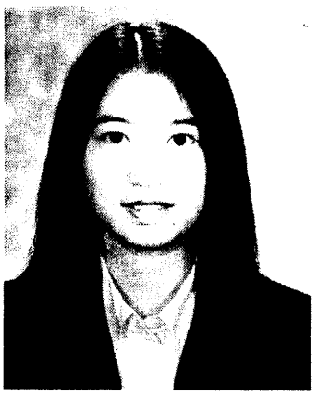
181. Potvin, S.; Canonne, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2821.
182. Trost, B. M.; McIntosh, M. C. *Tetrahedron Lett.* **1997**, *38*, 3207.
183. Mori, H.; Kubo, H.; Hara, H.; Katsumura, S. *Tetrahedron Lett.* **1997**, *38*, 5311.
184. Uenishi, J.; Kawahama, R.; Tanio, A.; Wakabayashi, S.; Yonemitsu, O. *Tetrahedron* **1997**, *53*, 2439.
185. Kanazawa, A.; Delair, P.; Pourashraf, M.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1911.
186. Díaz-Cortés, R.; Silva, A. L.; Maldonado, L. A. *Tetrahedron Lett.* **1997**, *38*, 2207.
187. Shimizu, S.; Nakamura, S.-i.; Nakada, M.; Shibasaki, M. *Tetrahedron* **1996**, *52*, 13363.
188. Sato, S.; Nakada, M.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 6141.
189. Yoshimatsu, M.; Hasegawa, J. *Tetrahedron Lett.* **1996**, *37*, 7381.
190. Lee, Y. R.; Kim, N. S.; Kim, B. S. *Tetrahedron Lett.* **1997**, *38*, 5671.
191. Shiu, L.-H.; Shu, H.-K.; Cheng, D.-H.; Wang, S.-L.; Liu, R.-S. *J. Chem. Soc., Chem. Commun.* **1996**, 1041.
192. Lee, C.-W.; Oh, D. Y. *Heterocycles* **1996**, *43*, 1171.
193. Perry, P. J.; Pavlidis, V. H.; Naik, M. *Appl. Organomet. Chem.* **1996**, *10*, 389.
194. Arcadi, A.; Rossi, E. *Tetrahedron Lett.* **1996**, *37*, 6811.
195. Sammond, D. M.; Sammakia, T. *Tetrahedron Lett.* **1996**, *37*, 6065.

Biographical sketch



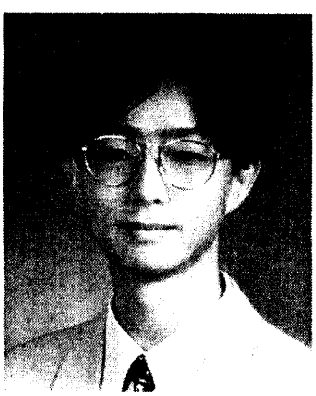
Henry N. C. Wong

Xue Long Hou

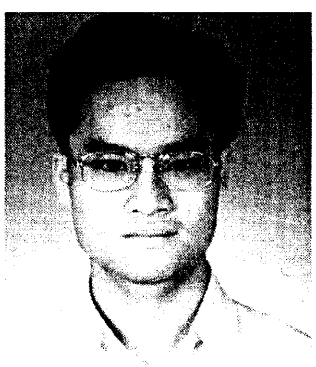


Hui Yin Cheung

Tung Yue Hon



Po Lo Kwan



Ting Hang Lo

Sing Yip Tong

Henry N.C. Wong, graduated from the Chinese University of Hong Kong in 1973 and obtained his Ph.D. degree in 1976 from University College London under the supervision of the late Professor Franz Sondheimer. After spending two years in the laboratories of the late Professor Robert B. Woodward as a postdoctoral fellow, he began his independent research career at University College London as Ramsay Memorial Fellow (1978-1979) and at Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences as Associate Research Fellow (1980-1982). He joined the Chinese University of Hong Kong in 1983 and is now Professor of Chemistry. His research interest involves syntheses of both non-natural and natural molecules.

Xue Long Hou, graduated from Shanghai First Medical College in 1978. After working as Teaching Assistant for two years in the same institution, he joined Henry Wong's research team at Shanghai Institute of Organic Chemistry and obtained his Ph.D. degree in 1986 under the joint supervision of Henry Wong and Professor Wei-Yuan Huang. He then spent two years as Alexander von Humboldt Fellow at Universität zu Köln, Germany, under the direction of Professor Emanuel Vogel. He is now Research Fellow (Professor) at Shanghai Institute of Organic Chemistry. His research interest concerns the synthesis of theoretically interesting molecules, as well as organometallics directed towards organic synthesis.

Hui Yin Cheung, obtained her B.Sc. degree from the Chinese University of Hong Kong in 1995, and is a Graduate Mistress (Chemistry) at Bishop Hall Jubilee School.

Tung Yue Hon, obtained her B.Sc. degree from the Chinese University of Hong Kong in 1995, and is teaching Mandarin at the Chinese Language Centre of the Chinese University of Hong Kong.

Po Lo Kwan, obtained his B.Sc. degree from the Chinese University of Hong Kong in 1995, and is a Programmer at Sanyo Extended Data System Ltd.

Ting Hang Lo, obtained his B.Sc. degree from the Chinese University of Hong Kong in 1995, is a Marketing Executive at Nu Life International Ltd.

Sing Yip Tong, obtained his B.Sc. degree from the Chinese University of Hong Kong in 1997.