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Synthesis of Dihydrofurans Substituted in the 2-Position

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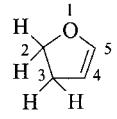
Keywords: Dihydrofurans / Heterocycles / Natural products / Synthesis / Heck reaction

Many natural products and biologically active compounds contain the dihydrofuran subunit. Molecules incorporating either 2-substituted, 2,2-disubstituted 2,3- or 2,5-dihydrofurans are widespread in the literature and represent key "molecular building blocks". The preparation of substituted dihydrofurans remains a current challenge in organic synthesis and this microreview details the various routes employed for their synthesis in the literature to the end of 2004.

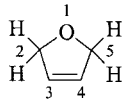
1. Introduction

Substituted dihydrofurans, numbered according to the position of the dihydro unit on the furan ring, occur frequently as subunits of many biologically important natural products such as clerodin (**3**).[1]



2,3-dihydrofuran

1

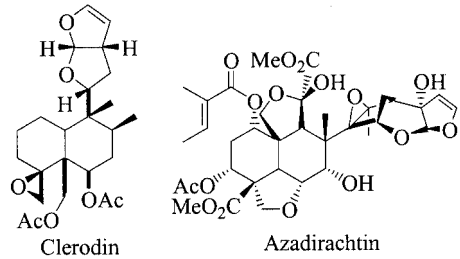


2,5-dihydrofuran

2

Other examples of 2,3-dihydrofuran subunits in nature are azadirachtin (**4**) and austocystin A (**5**).[2] Azadirachtin (**4**) is one of a number of insect antifeedants of the limonoid family isolated from the neem tree *Azadirachta indica*. This compound, which contains a hydroxy-2,3-dihydrofuran moiety, has potential use as a novel pest agent.[3] Austocystin A (**5**), was one of six novel metabolites extracted from maize meal cultures of *Aspergillus ustus*.[4]

The widespread occurrence of disubstituted 2,5-dihydrofuran units in a number of natural products has led to increased recent interest in versatile and stereoselective methods of preparing such compounds.[5–7] 2,5-Dihydrofurans represent pivotal structural elements of a wide variety of different biologically active molecules. For instance, 2,5-dihydrofurans can be found in mycotoxins, polyether antibiotics, spiroketals, and even amino acids.[8–12] Examples in nature include 2,5-dihydrofurans **6** and **7**, which are found in hops and similar spirans occur in the *Santalina* species.[13]

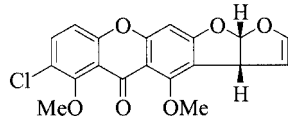


Clerodin

3

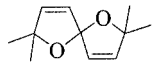
Azadirachtin

4

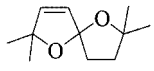


Austocystin A

5



6



7

This microreview details the various routes employed for the synthesis of 2-substituted dihydrofurans in the literature up until the end of 2004. We have divided this report into two sections based on the substitution pattern of the target compounds. The first section of the review deals with the synthesis of 2-substituted 2,3-dihydrofurans while the second section covers the synthesis of 2-substituted 2,5-dihydrofurans.

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

2. Synthesis of 2-Substituted 2,3-Dihydrofurans

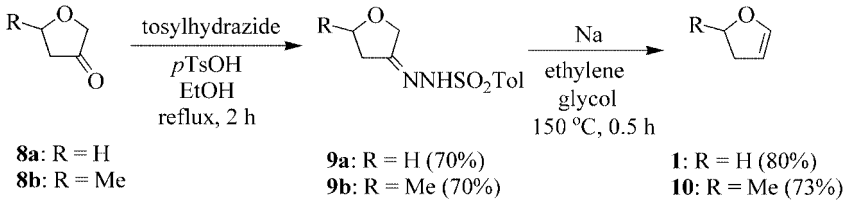
Substituted 2,3-dihydrofurans are potentially useful intermediates in the synthesis of a variety of substances, including γ-hydroxy aldehydes, γ-hydroxy ketones, γ-lactones, furans, cyclopropyl aldehydes and ketones, and hydroxyamino acids.[14–17] Polyfunctional 2,3-dihydrofurans are also of interest for the synthesis of natural compounds and potentially physiologically active compounds.[18]

In 1965, Gianturco reported the first direct synthetic route to 2,3-dihydrofurans using the Bamford–Stevens reaction, which, when applied to the *p*-(tolylsulfonyl)hydrazones **9a**, **9b** of the corresponding tetrahydrofuran-3-ones **8a**, **8b**, provided a convenient route to 2,3-dihydrofurans **1**, **10** (Scheme 1).[19]

Botteghi described the preparation of isomerically pure monoalkyl- and dialkyl-substituted 2,3-dihydrofurans by a rhodium-catalysed hydroformylation of allylic alcohols **11a**–**c** (Scheme 2).[20]

This hydroformylation of allylic alcohols **11a**–**c** was carried out using *trans*-bis(triphenylphosphane)carbonyl-(chloro)rhodium [$RhCl(CO)(PPh_3)_2$] as the catalyst in a triethylamine/benzene solution. The dehydration of the product lactols **12a**–**c** was achieved by distillation in the presence of a catalytic amount of ammonium nitrate and/or oxalic acid. The overall yields of the corresponding 2,3-dihydrofurans were in the 40–50% range with respect to the starting allylic alcohols.

For the synthesis of the optically active 2-methyl-2,3-dihydrofuran [(*R*)-**10**], 1-buten-3-ol (**11a**) was partially for-

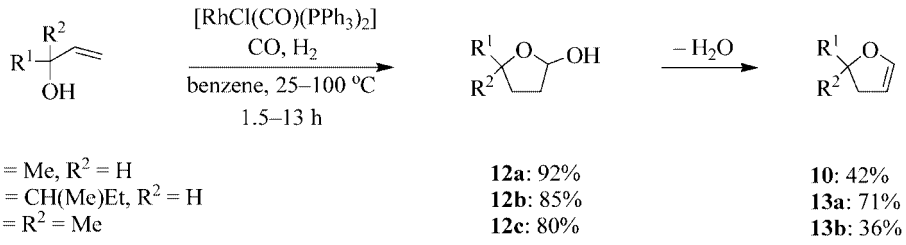


Scheme 1.

Tim Kilroy studied at University College Dublin receiving his Honours BSc. degree in Chemistry in 1999. Working in the group of Professor Pat Guiry he completed his PhD in 2003 where he researched the intermolecular asymmetric Heck reaction and associated ligands. He is currently employed in the pharmaceutical industry with Pfizer Pharmaceuticals in Cork.

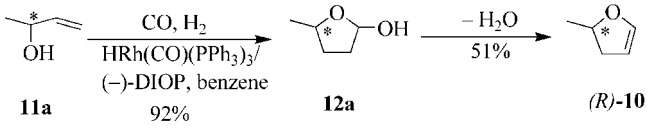
Tim O'Sullivan was born in County Kerry, Ireland. He studied at the University of Limerick receiving his Honours BSc. degree in Industrial Chemistry in 1997. He subsequently obtained a PhD under the guidance of Professor Lewis Mander at the Australian National University focussing on the total synthesis of diterpenoids. He returned to Ireland to work as a postdoctoral fellow with Dr Mary Meegan in the Department of Pharmaceutical Chemistry, Trinity College Dublin. He is currently employed as a senior postdoctoral fellow at the Centre for Synthesis and Chemical Biology, University College Dublin in the research group of Professor Pat Guiry and is involved in the synthesis of novel Lipoxin analogues.

Pat Guiry was born in County Tipperary, Ireland, and graduated with an Honours BSc. degree in Chemistry from University College Dublin in 1986. He stayed at University College Dublin for his PhD working under the supervision of Professor Dervilla Donnelly on the application of aryllead triacetates to the synthesis of natural products. During his PhD he also worked in Marseille in 1988 under the supervision of Dr Jean-Pierre Finet (Cu-catalysed N-arylation) and at Texas A&M in 1989 with Professor Sir Derek Barton (mechanistic studies of arylation/phenol arylation). He received his PhD degree in 1990 and moved to the group of Dr John Brown FRS at the Dyson Perrins Laboratory, Oxford University for postdoctoral studies in the area of asymmetric catalysis. During this three year stay he was appointed in 1991 as a Tutorial Fellow at Wadham College Oxford and in 1992 as College Lecturer / Director of Studies at St Hughs College Oxford. He returned to University College Dublin as a College Lecturer in 1993 where he started his independent research. His research interests are the design and preparation of chiral ligands and their application in a broad range of asymmetric catalytic transformations. He was a visiting researcher in the group of Professor Andreas Pfaltz at the Max Planck Institut für Kohlenforschung at Mülheim an der Ruhr (Germany) in 1996. He was the recipient of a President's Research Award in 1996 and a President's Teaching Award in 2000 from University College Dublin. He was the recipient of a President's Research Award in 1996 and a President's Teaching Award in 2000 from University College Dublin. He was promoted to Senior Lecturer in 2002 and to Professor in 2003. He was the Merck Frosst Visiting Professor at the University of Toronto in early 2004. He was appointed as the Chief Executive of the Conway Institute of Biomolecular and Biomedical Sciences at University College Dublin in 2004. A keen tennis player, he represented Ireland in 2005 in the Trabert Cup (ITF World Team Competition) in Perth where he was team captain.



Scheme 2.

mylated using $[HRh(CO)(PPh_3)_3]$/(–)-(DIOP) as the catalytic system (Scheme 3).



Scheme 3.

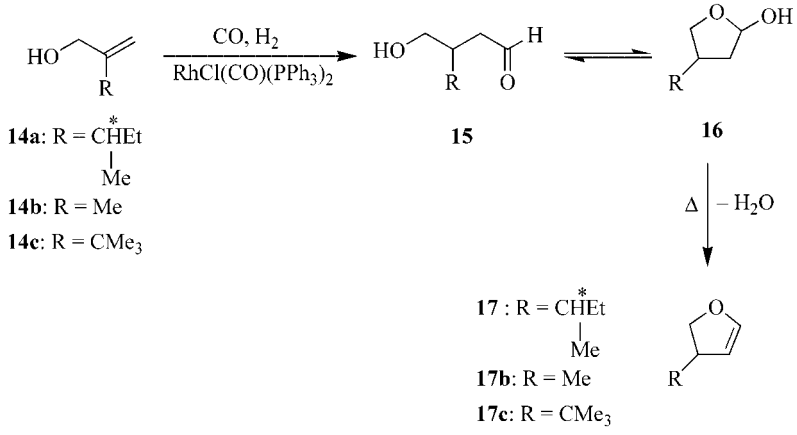
An earlier publication by the same author uses the same methodology to synthesise the optically active monoalkyl-substituted 2,3-dihydrofurans **17a**–**c**.[21]

In the case of **17a**, an asymmetric carbon is bonded directly to the heteroatom ring. These compounds are synthesised from the lactols **16**, which are produced by rhodium-catalysed hydroformylation of the 2-alkylallyl alcohols **14a**–**c** (Scheme 4).

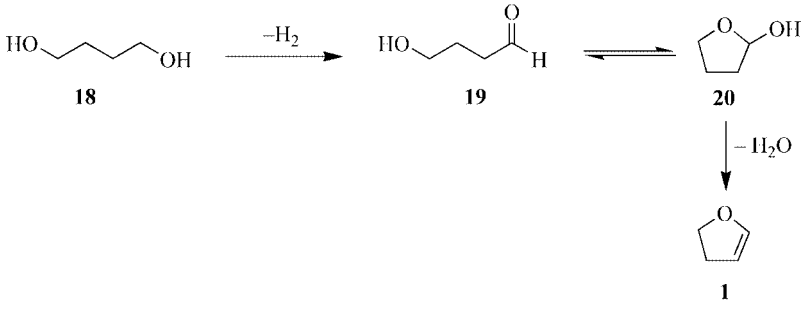
Using *trans*-bis(triphenylphosphane)carbonyl(chloro)-rhodium(I) as the catalyst, the hydroformylation of the 2-alkyl alcohol **14** forms the desired lactol **16** exclusively. Simple distillation promoted the dehydration of the lactol **16** to afford the 3-alkyl-2,3-dihydrofurans **17a**–**c** in yields ranging from 70–80%. In some cases a trace amount of ammonium nitrate was required to facilitate the dehydration.

In 1960, Dimroth and Pasedach reported the synthesis of a variety of 2,3-dihydrofurans from the dehydration of 1,4-diols using high temperature and pressure conditions.[22] If the 1,4-diol **18** loses a molecule of H_2, the aldehyde **19** formed equilibrates between itself and the hemiacetal form **20** as shown (Scheme 5). Loss of water from the hemiacetal leads to the 2,3-dihydrofuran compound **1**.

A number of 2,3-dihydrofuran compounds were synthesised in this manner using elevated temperatures (Table 1).

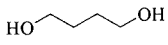
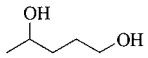
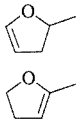
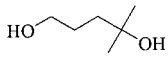
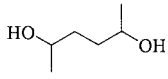
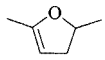


Scheme 4.

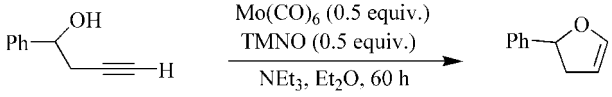


Scheme 5.

Table 1. Synthesis of 2,3-dihydrofurans from the dehydration of 1,4-diols.

Substrate	Reaction temp. [°C]	Product	Yield
	210–230		81%
	195–200		83%
			68%
	195–200		76%

McDonald reported the pentacarbonylmolybdenum/triethylamine-promoted single step cyclisation of 1-alkyn-4-ols as a further route to 2,3-dihydrofurans.[23] The reaction of hexacarbonylmolybdenum and trimethylamine *N*-oxide (TMNO) with **21** produced 2-phenyl-2,3-dihydrofuran (**22**) (Scheme 6).



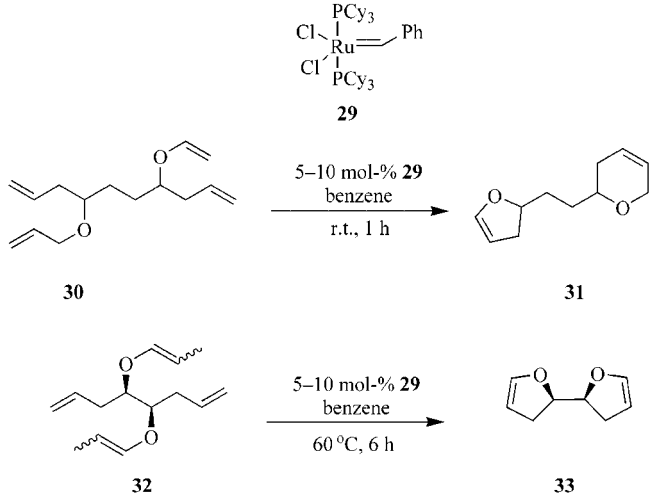
21 **22**

Scheme 6.

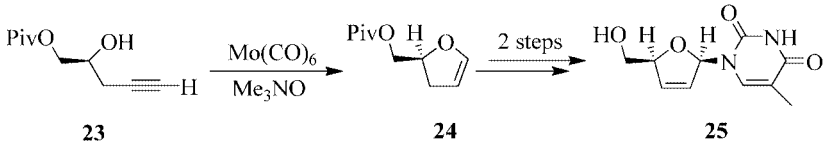
The use of the chiral 1-alkyn-4-ol **23** as a substrate using the above cycloisomerisation process is shown in the key step of a synthesis of the *anti*-AIDS nucleoside 2′,3′-didehydro-2′,3′-dideoxythymidine (**25**) (Scheme 7).

A further two routes to 2-phenyl-2,3-dihydrofuran (**22**) were reported by Doutheau and co-workers.[24] In the first route, 5-methyl-2-(phenylsulfonyl)dihydrofuran-3-one (**26**) was converted into the acetate **27**, which was subjected to the samarium iodide-mediated reductive elimination to give 2-phenyl-2,3-dihydrofuran (**22**) in 46% yield. In the second pathway, conversion of **26** to the thioester **28** was followed by radical-promoted elimination to give **22** in a higher yield of 52% (Scheme 8).

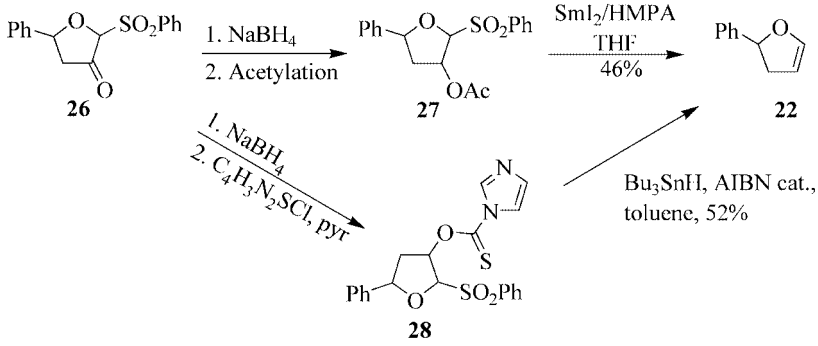
Ring-closing metathesis has emerged as a powerful tool for preparing cyclic structures in organic chemistry. This is mainly due to the highly reactive molybdenum alkylidene and the more stable ruthenium alkylidene catalysts developed by Schrock and Grubbs, respectively. Mioskowski, Heck and Baylon reported similar methods in the synthesis of unsaturated polycyclic ethers and two metathesis products isolated were the polycyclic ethers **31** and **33** (Scheme 9).[25]



Scheme 9.



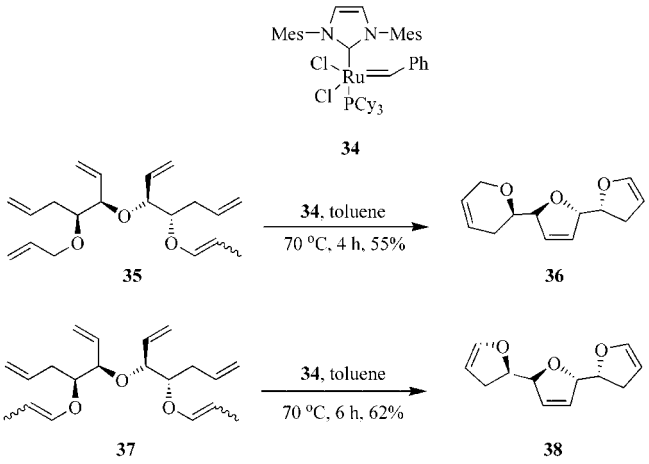
Scheme 7.



Scheme 8.

It is postulated that for the metathesis substrate **32**, which bears substituted olefins, the Ru catalyst **29** adds to the unsubstituted olefins to give a single product. Substitution of the olefin was found to decrease the rate of ring-closing metathesis, and hence a higher temperature and longer reaction time were required compared to the unsubstituted case.

Heck further reported the triple ring-closing metathesis reaction in the synthesis of adjacent cyclic ethers from acyclic hexaenes (Scheme 10).[26]



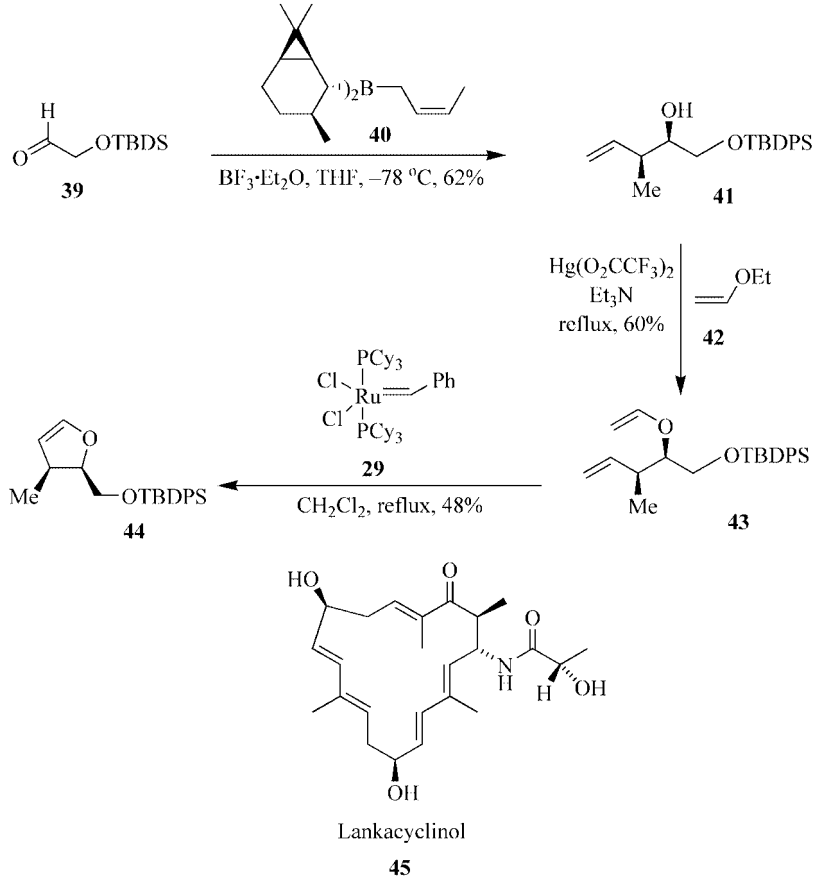
Scheme 10.

The Grubbs' catalyst led to incomplete cyclisations unlike the ruthenium-based imidazolinylidene complex **34**, which in both cases gave tris(cyclic) ethers as single products in good yields. It is worth noting that the products **36** and **38** each contain a 2,3-dihydrofuran and 2,5-dihydrofuran ring and that the product **38** possesses three adjacent five-membered ring ethers which are present in several natural type D acetogins.

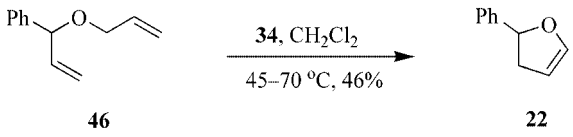
In the total synthesis of Lankacyclinol (**45**), one of a family of lankacidins, which are structurally unique antibiotics, Williams et al. utilise a *cis*-disubstituted 2,3-dihydrofuran in the construction of one of the key fragments (Scheme 11).[27] The synthesis of the dihydrofuran **44** involves the preparation of a vinyl ether followed by ring-closing metathesis.

Addition of the (*Z*)-crotyl-di-(2-isocaranyl)borane (**40**) to the aldehyde **39** gave the *syn*-homoallylic alcohol **41** as a single diastereomer. Transetherification to afford the vinyl ether **43** followed by ring-closing metathesis using the original ruthenium Grubbs' catalyst gave the required 2,3-dihydrofuran **44** as a single product in 48% yield.

Snapper et al. have reported the preparation of cyclic enols, including a 2-substituted 2,3-dihydrofuran, by means of a metathesis/isomerisation reaction of allyl ethers involving the ruthenium complex **34** pre-treated with hydrogen (Scheme 12).[28]



Scheme 11.

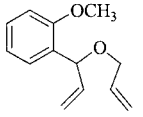
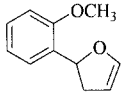
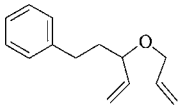
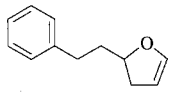
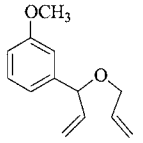
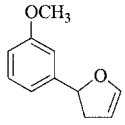


46 22

Scheme 12.

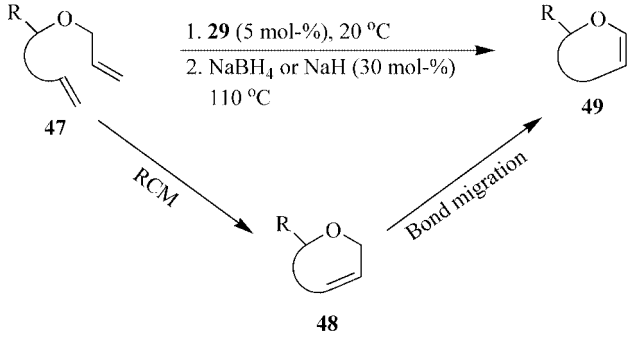
Schmidt has similarly described the direct conversion of allyl ethers to cyclic enol ethers by tandem metathesis/bond migration with Grubbs' catalyst **29** (Table 2).[29]

Table 2. Conversion of allyl ethers to cyclic ethers.

Substrate	Product[a]	Yield[b]
		79% (8.0:1)
		70% (4.8:1)
		64% (3.6:1)

[a] Reaction conditions: toluene, **29** (5 mol-%), 20 °C, then NaH (30 mol-%), 100 °C. [b] Ratio of regioisomers given in parentheses.

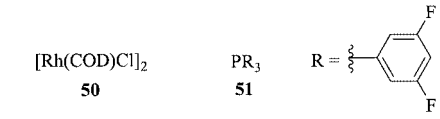
The ruthenium carbene complex was activated to catalyse the double-bond migration by addition of a hydride donor, such as $NaBH_4$ or NaH (Scheme 13). Ring-closing metathesis of the substrates proceeds smoothly with complete consumption of the diene **47** being observed after 1 hour at ambient temperature. Formation of the cyclic enol ethers **49** requires elevated temperatures and is usually complete within two to five hours.

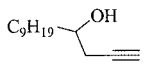
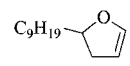
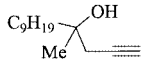
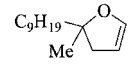
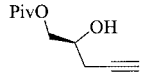
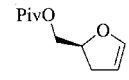
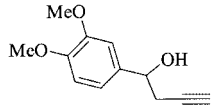
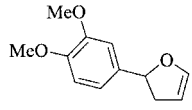


Scheme 13.

Trost and Rhee have developed a rhodium(I)-catalysed cycloisomerisation of homo- and bis-homopropargyllic alcohols incorporating various combinations of ligands and complexes to furnish a range of dihydrofurans and dihydropyrans (Table 3).[30]

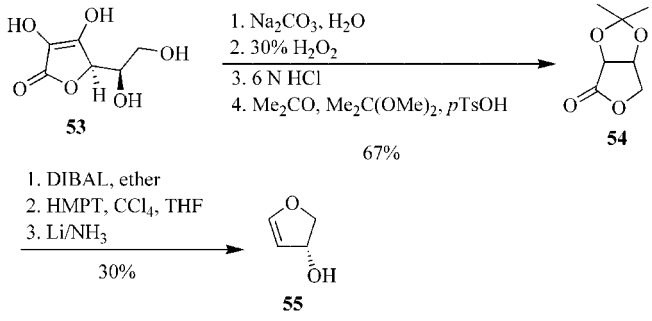
Table 3. Rhodium(I)-catalysed cycloisomerisation of homopropargylic alcohols.



Substrate	Product	Method[a]	Conv.	Yield[b]
		A	100%	69%
		B	85%	52%
		C	100%	68%
		A	90%	62%
		A	100%	71%
		C	100%	68%
		A	100%	74%
		B	>98%	67%

[a] Method A: catalyst **50** (2.5%), ligand **51** (55%). Method B: catalyst **50** (1.5%), ligand **51** (33%). Method C: catalyst **52** (5%), ligand **51** (30%). [b] Isolated yield.

Ireland described the preparation of a furanoid glycal system **55** from D-(–)-isoascorbic acid (**53**) (Scheme 14).[31]

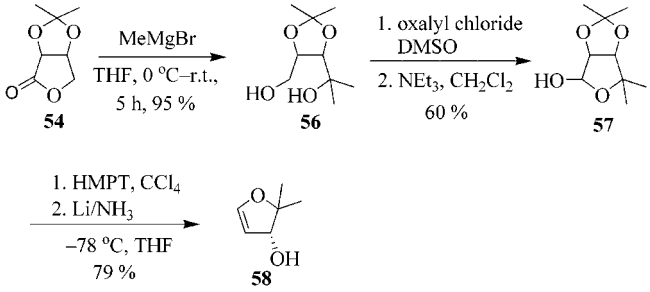


Scheme 14.

The erythronolactone **54** is readily prepared in four simple steps from isoascorbic acid (**53**) in 67% yield. The diol obtained after oxidative degradation was protected by forming the acetal using 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid in acetone. Following treatment of **54** with DIBAL, the resultant alcohol was reductively eliminated to give the 3-hydroxy-2,3-dihydrofuran (**55**) in 30% overall yield from **53**.

Pirrung and Lee prepared the related 2,2-dimethyl-3-hydroxy-2,3-dihydrofuran (**58**) using the same methodology as Ireland in the final steps of their total synthesis of Pseudosemiglabrin (Scheme 15).[32]

Grignard addition to the lactone **54** gave the diol **56** in 95% yield and a small amount of the mono-addition product hemiketal. The primary alcohol was selectively oxidised to the lactol **57** in 60% yield using Swern conditions. By employing the same methodology as Ireland, the 2,2-disubstituted dihydrofuran **58** was formed in 79% yield.



Scheme 15.

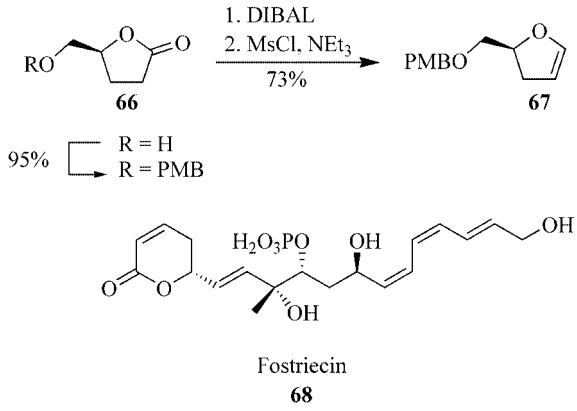
Paquette described the enantioselective synthesis of a 2,3-dihydrofuran as a building block in his synthesis of both natural (+)-dactyloxene-B and (+)-dactyloxene-C by actuation of an oxonium ion-initiated pinacol rearrangement (Scheme 16).[33]

Ozonolysis of the commercially available (*R*)-(–)-linalool (**59**) under the above conditions ensured regioselective attack of the more electron-rich double bond to give **60** as a 1:1 diastereomeric mixture. Conversion to the benzoate ester followed by pyrolysis led to **61** in a 47% yield, an key intermediate in the synthesis of (+)-dactyloxene-B (**62**).

The synthetic strategy of leaving-group formation and elimination to afford dihydrofurans was used to similar effect in a later study by the same author in the synthesis of *cis*- and *trans*-theaspirones (Scheme 17).[34]

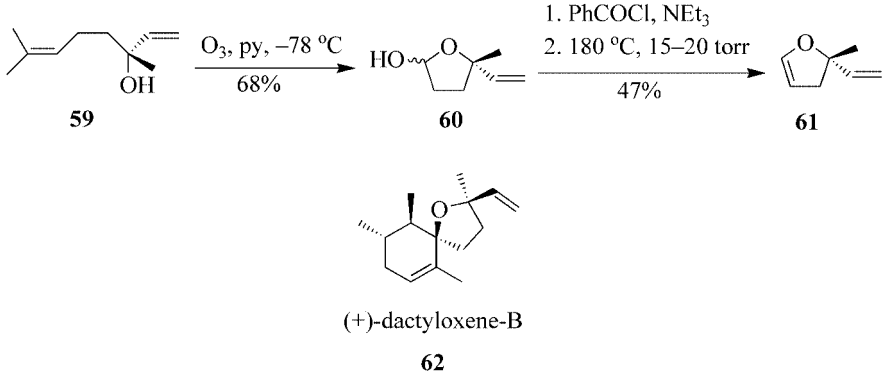
γ-Valerolactone (**63**) was reduced to the lactol with DIBAL and esterified with benzoyl chloride to give **64** in 94% yield. Pyrolysis at 180 °C under reduced pressure afforded 2-methyl-2,3-dihydrofuran (**10**) in 73% yield, which was further elaborated to eventually give *trans*-theaspirone (**65**).

Boger used the same methodology in the construction of the 2,3-dihydrofuran **67**, an important intermediate in the total synthesis of Fostriecin (Scheme 18).[35]

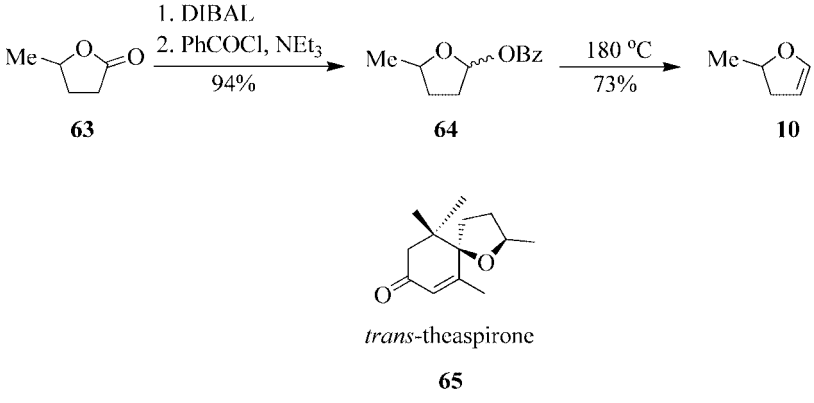


Scheme 18.

In this particular case, extensive dimerisation of the lactol was observed unless the mesylation was controlled at a dilution of between 0.02–0.03 M.



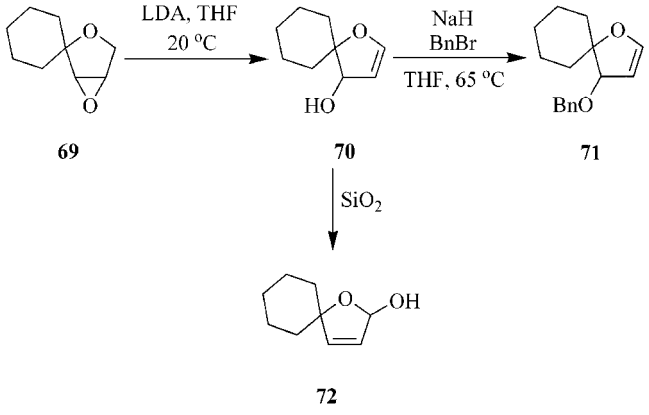
Scheme 16.



Scheme 17.

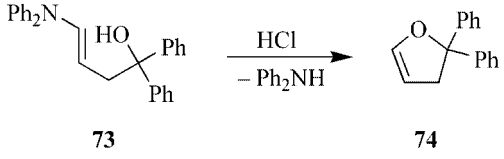
Schmidt, in his paper on the synthesis of 2,3-dihydropyrans and dihydrofurans, referred to the synthesis of a 2,3-dihydrofuran with a hydroxy group in the allylic position using the base-induced rearrangement of dihydrofuran oxides.[36] Previously, these compounds were normally prepared from carbohydrate-derived starting materials using elimination reactions or from nucleosides.[37,38] They are useful building blocks in the synthesis of polyether antibiotics or C-nucleosides.[39–41]

Starting from the dihydrofuran oxide **69**, base-induced rearrangement using LDA afforded the product **70**, which proved unstable on silica and underwent partial rearrangement to the hemiacetal 2,5-dihydrofuran **72** unless protected as the benzyl ether **71** (Scheme 19).



Scheme 19.

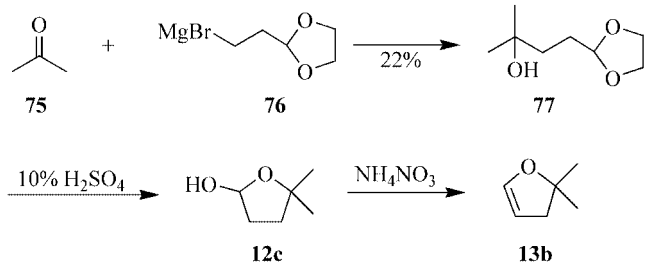
In his description of the lithiation and isomerisation of allylic amines as a general route to enamines and their carbonyl derivatives, Eisch referred to the cyclisation of an enamine to its corresponding oxygen heterocycle, accompanied by the elimination of diethylamine on treatment with dilute, aqueous hydrochloric acid.[42] 2,2-Diphenyl-2,3-dihydrofuran (**74**) was prepared in such a manner from 4-diphenylamino-1,1-diphenylbut-3-en-1-ol (**73**) (Scheme 20).



Scheme 20.

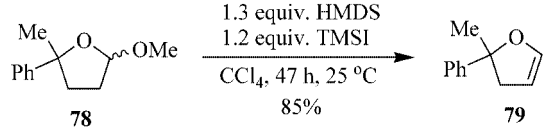
In a publication on the synthesis of naphtharazin and juglone derivatives, Tanoue et al. described the synthesis of 2,2-dimethyl-2,3-dihydrofuran (**13b**).[43] Grignard addition to acetone afforded the 1,3-dioxolane **77** in 22% yield (Scheme 21).

Cyclisation of the 1,3-dioxolane **77** with 10% sulfuric acid afforded the lactol **12c**, followed by dehydration with a catalytic amount of powdered ammonium nitrate to yield the dihydrofuran **13b** using the procedure of Botteghi.[20]



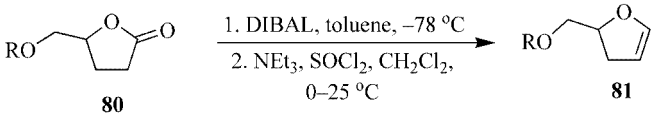
Scheme 21.

Miller and co-workers reported a facile preparation of methyl enol ethers from acetals using trimethylsilyl iodide.[44] Normally, vigorous conditions such as elevated temperatures or strong acid catalysis are needed to facilitate this reaction. The method described is both mild and selective for the preparation of these methyl vinyl ethers. In the synthesis of 2-methyl-2-phenyl-2,3-dihydrofuran (**79**), carbon tetrachloride was unexpectedly found to be the solvent of choice. It was noted that the use of solvents such as dichloromethane and chloroform were unsuitable as the product was unstable in such solutions. Even though a lower rate was observed in carbon tetrachloride, the highest yield of 85% was obtained (Scheme 22).



Scheme 22.

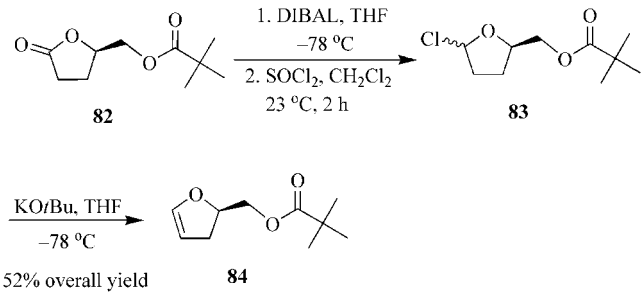
In their study of stereocontrolled glycosylations by additions of sulfur electrophiles to glycols, Liotta and coworkers used addition–elimination methodology for the preparation of a furanoid glycal **81** (Scheme 23).[45]



Scheme 23.

Mild reduction of the lactone **80** with DIBAL provided the lactol in quantitative yield, followed by dehydration with thionyl chloride and triethylamine to give the 2,3-dihydrofuran **81**.

Kim and Misco utilised addition reactions to a furanoid glycal in the synthesis of ddA and d4T antiviral nucleosides.[46] The glycal, a 2,3-dihydrofuran **84**, was synthesised in a similar fashion to the method reported by Liotta (Scheme 24).

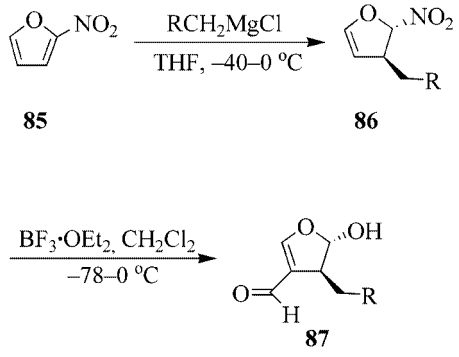


Scheme 24.

DIBAL reduction followed by chlorination of the lactol **82** with thionyl chloride, and finally elimination with potassium *tert*-butoxide gave the requisite furanoid glycal **84** in 52% overall yield.

In a report on transformations of 2-nitro-2,3-dihydrofurans to multi-functionalised dihydrofurans, Hwu et al. prepared a number of substituted 2,3-dihydrofurans.[47]

By treating 2-nitrofuran (**85**) with the appropriate Grignard reagent, the corresponding dihydrofurans **86** were obtained in 58–68% yields (Scheme 25; only one enantiomer is shown for clarity). These compounds were then converted into the novel 4-formyl-2-hydroxy-3-substituted 2,3-dihydrofurans **87** using boron trifluoride–diethyl ether. It should be noted that two mol of **86** are consumed in this reaction for every one mol of **87** produced. Substrate **86** serves as a dipole at the nitro group and as a dipolarophile at the olefinic part of the dihydrofuran ring, and thereby acts as the source for the newly introduced formyl group. The conversion of the readily available nitro compounds to the relatively unknown dihydrofurans bearing a C-4 formyl and C-2 hydroxy groups with various substituents provides easy access to these multi-substituted dihydrofurans.

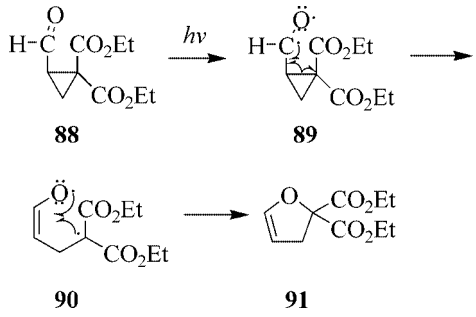


R = Ph, *o*-MeC_6H_4, *p*-BrC_6H_4, 1-naphthyl, *i*Pr, Bn

Scheme 25.

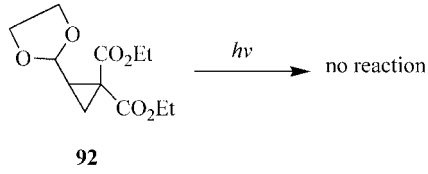
Engel and co-workers reported an unexpected product in their attempts to synthesise α-pyrones from α,β-unsaturated aldehydes.[48] Attempts to irradiate a cyclopropane derivative to form an aliphatic olefin led to the preparation of the unexpected dihydrofuran **91** (Scheme 26).

Irradiation of the cyclopropane derivative **88** in benzene solution using a Pyrex filter led to the dihydrofuran **91**. In the proposed mechanism (Scheme 26), the participation of



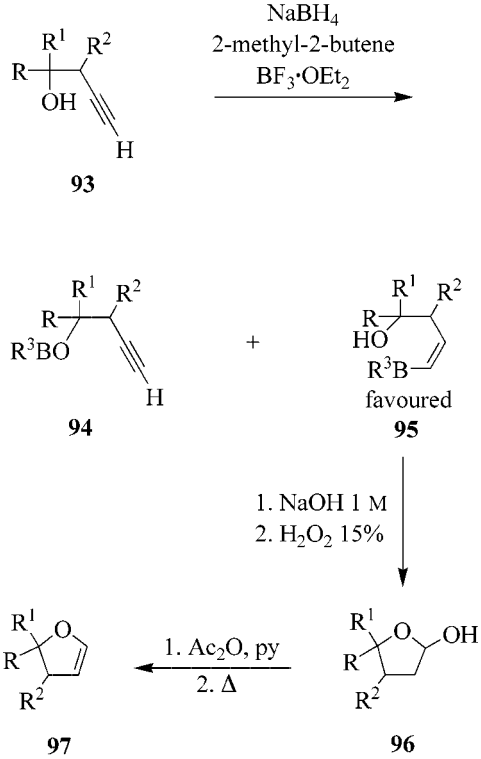
Scheme 26.

the aldehyde carbonyl group in the ring opening is confirmed by the fact that a similar compound, the ethylenedioxy derivative **92**, shows no photolytic ring opening (Scheme 27).



Scheme 27.

Touboul described a new method for the preparation of a range of 2,3-dihydrofurans using the hydroboration of acetylenic alcohols as the key step (Scheme 28).[49,50]



Scheme 28.

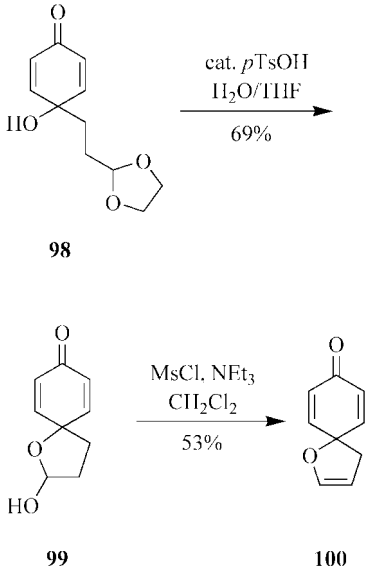
The first step of the synthesis involves the hydroboration of β-acetylenic alcohols **93**, using a mixture of sodium borohydride, 2-methyl-2-butene and boron trifluoride–di-

Table 4. Synthesis of dihydrofurans **97a**–**n** by hydroboration of acetylinic alcohols.

	R	R^1	R^2		R	R^1	R^2
97a	Ph	H	H	**97h**	*n*Hex	H	H
97b	Ph	Me	H	**97i**	Et_2CH	H	H
97c	Ph	*i*Pr	H	**97j**	Ph	H	Me
97d	Ph	Ph	H	**97k**	Ph	Me	Me
97e	Mes	H	H	**97o**	Mes	Me	Me
97f	Mes	Me	H	**97m**	Ph	*i*Pr	Me
97g	Cy	H	H	**97n**	Mes	H	Me

ethyl ether. Competition between substitution and addition, which led to two products, determined the rate of the reaction depending on which product is formed preferably. Oxidation of the favoured alkenylboranes **95** afforded the lactols **96**, which are then dehydrated to the corresponding 2,3-dihydrofurans **97** by pyrolysis. The overall sequence gave good yields with hindered alcohols and its stereochemistry can be controlled during the Grignard synthesis of the starting β-acetylenic alcohol (Table 4); yields were not quoted.

During a study of the cyclisation of *p*-quinols, Wong reported the preparation of the 2,2-disubstituted 2,3-dihydrofuran **100**, a spiro-enol ether (Scheme 29).[51]

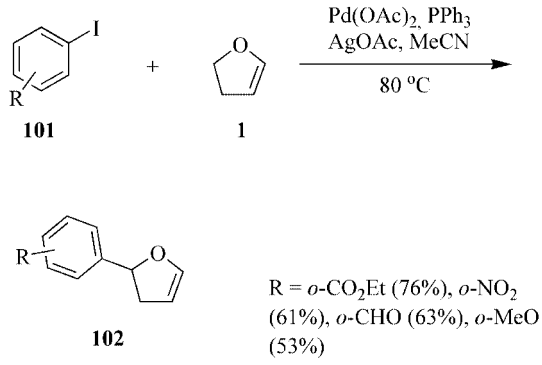


98 **99** **100**

Scheme 29.

The *p*-quinol **98** cyclised to the spirolactol **99** under mildly acidic condition in 69% yield. Treatment of **99** with methanesulfonyl chloride and triethylamine in dichloromethane afforded the spiro-enol ether **100** in 53% isolated yield.

The Heck reaction is the substitution of a vinylic hydrogen by an alkenyl or aryl group catalysed by Palladium(0) complexes.[52–55] This transformation affords another route to both 2-substituted 2,3-dihydrofurans and 2-substituted 2,5-dihydrofurans.[56] While examples of the synthesis of 2-substituted 2,5-dihydrofurans using the Heck reaction predominate in the literature (vide infra), there is also an increasing number of references to the preparation of 2-substituted 2,3-dihydrofurans in this fashion. For example, Larock and Gong have described conditions whereby they can selectively produce a range of aryl-substituted 2,3-dihydrofurans **102** from various aryl iodides **101** (Scheme 30).[57]

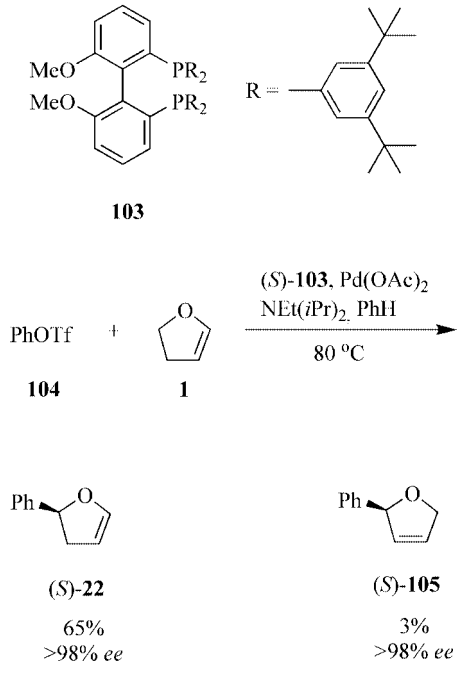


101 **1** **102**

R = *o*-CO_2Et (76%), *o*-NO_2 (61%), *o*-CHO (63%), *o*-MeO (53%)

Scheme 30.

Pregosin et al. developed the use of MeO-BIPHEP **103** in the palladium-catalysed enantioselective Heck reaction with dihydrofurans (Scheme 31).[58] High regioselectivity and excellent enantioselectivity was observed.



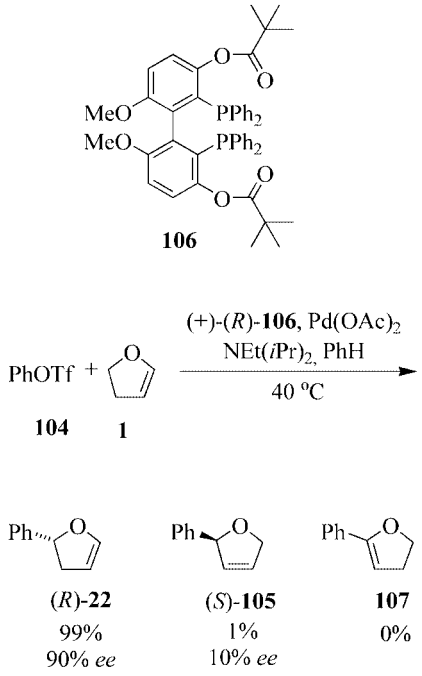
103 **104** **1**

(*S*)-**22** 65% >98% *ee*

(*S*)-**105** 3% >98% *ee*

Scheme 31.

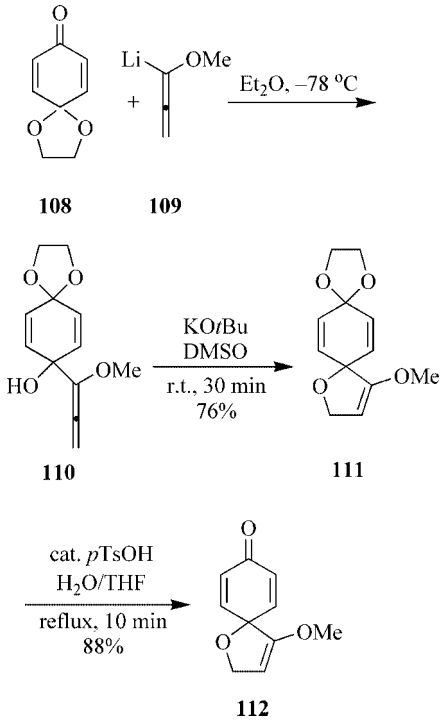
Keay has recently designed a modified version of MeO-BIPHEP **106**, which displays higher yields albeit with lower *ee*s (Scheme 32).[59]



Scheme 32.

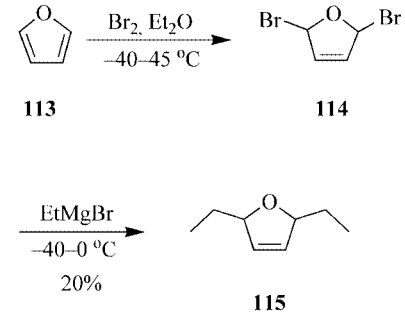
3. Synthesis of 2-Substituted 2,5-Dihydrofurans

Wong et al. described the synthesis of a 2,5-dihydrofuran spiro-enol ether by an organometallic-mediated approach.[51] The *p*-benzoquinone ethylene monoketal **108** reacted with the lithiated methoxyallene derivative **109** to give the 1,2-addition product **110** (Scheme 33). The crude product was then converted into the corresponding tricyclic enol ether **111** by treatment with potassium *tert*-butoxide. Selective hydrolysis furnished the spiro-enol ether **112** in 88% yield.



Scheme 33.

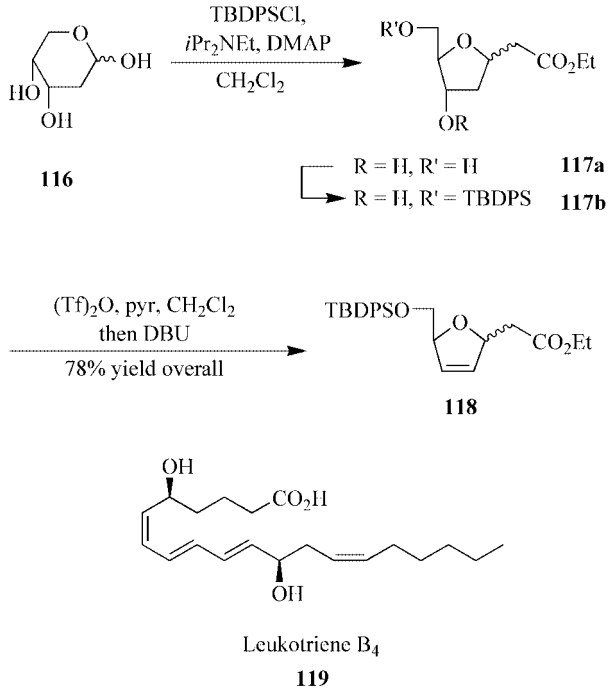
Masamune and co-workers reported the synthesis of 2,5-diethyl-2,5-dihydrofuran **(115)** (Scheme 34).[60]



Scheme 34.

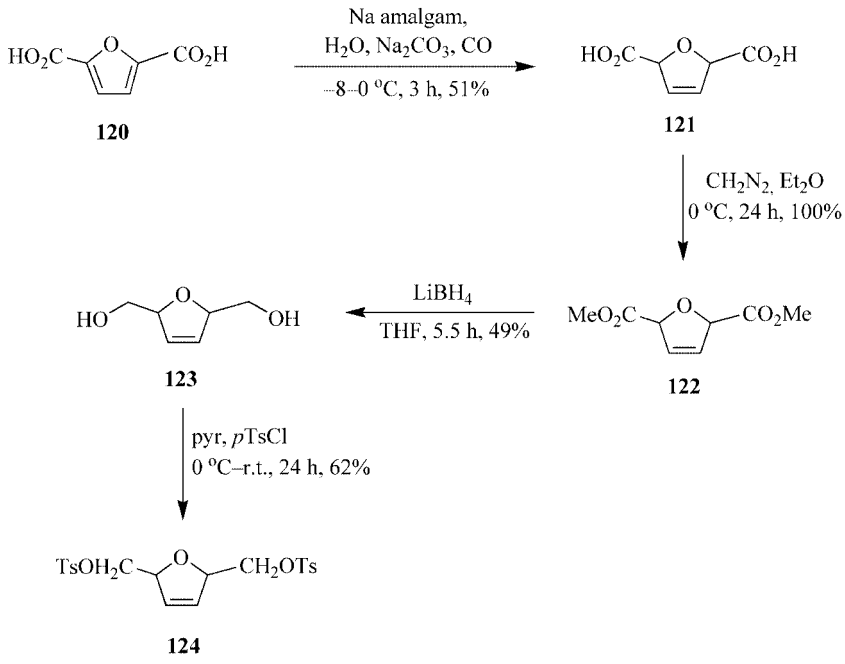
When furan (**113**) was treated with bromine, 2,5-dibromo-2,5-dihydrofuran (**114**) was formed. Addition of ethylmagnesium bromide to **114** furnished 2,5-diethyl-2,5-dihydrofuran (**115**) in 20% yield.

In 1986, Guindon and Delorme reported the total synthesis of leukotriene B_4 **(119)** analogues, which have important roles in allergic, inflammatory and immunological reactions.[61] The synthetic strategy incorporated the 2,5-dihydrofuran compound **118** as a key intermediate (Scheme 35). To that end, 2-deoxy-D-ribose (**116**) was converted to C-nucleoside **117b** using previously established chemistry. Formation of the secondary triflate ester followed by treatment with DBU afforded the target molecule **118** in 78% overall yield.



Scheme 35.

C-Nucleosides are nucleosides in which the sugar glycosidic position is connected to the pendant heterocyclic base



Scheme 36.

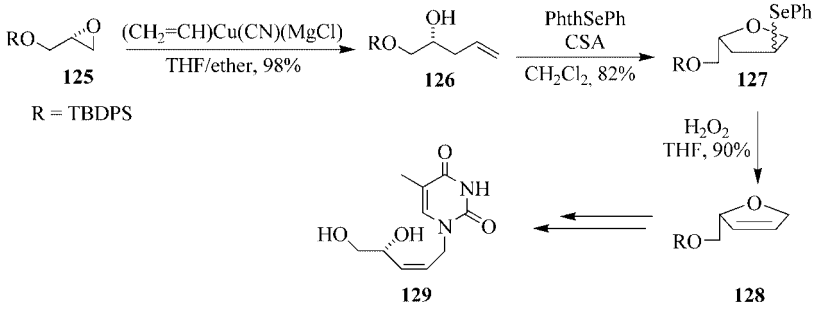
by way of a carbon atom instead of a nitrogen atom. Gensler, in his attempted synthesis of a triazole homo-C-nucleoside, described the preparation of a number of substituted 2,5-dihydrofuran compounds in his synthetic sequence (Scheme 36).[62]

Partial reduction of furandicarboxylic acid (**120**) with sodium amalgam gave 2,5-dihydrofuran-2,5-dicarboxylic acid (**121**). Treatment of the diacid with diazomethane led to the dimethyl ester **122**. This was then further reduced with lithium borohydride to give the glycol **123**, which was tosylated to the disulfonate **124** in 62% yield.

Castillón and co-workers, in their synthesis of D4T-based acyclonucleosides, utilised dihydrofuran the **128** as a key intermediate (Scheme 37).[63] Starting from a known compound **125**, the epoxide was opened with vinylcuprate to afford the alkenediol **126**. Reaction of **126** with phenylselenylphthalimide in the presence of camphorsulfonic acid-initiated cyclisation to the selenotetrahydrofuran **127**, which was oxidised with hydrogen peroxide to the dihydrofuran **128**, a precursor to target compound **129**.

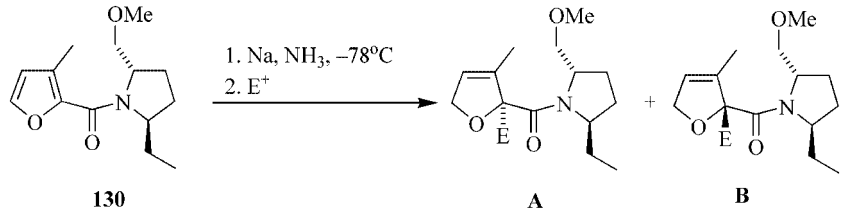
Donohoe et al. have shown that Birch reduction of the furans **130** using C_2 symmetrical amines as chiral auxiliaries proceeds with very high levels of stereochemical control (Table 5).[64] Initial work demonstrated that an alkyl group was required at the C-3 position in order to obtain good diastereoselectivity. A wide range of electrophiles was tolerated and although the ratio of diastereomers for entry 5 was lower, the two compounds were separable by column chromatography. The chiral auxiliary was readily removed with aqueous acid to furnish the dihydrofuran.

Donohoe further refined this approach by the incorporation of a temporary trimethylsilyl (TMS) group into the C-3 position.[65] Thus, high levels of stereochemical control could be maintained, and both the TMS group and the chiral auxiliary could be easily removed with aqueous acid after the Birch reduction. This work was recently applied to the formal synthesis of (–)-secosyrin 1 (**135**), a natural product isolated from *pseudomonas syringae* pv. *tomato*.[66] The key intermediate **132** could be synthesised by reacting furoic acid derivative **131** with BuLi and trimethylsilyl chloride (Scheme 38). Birch reduction of **132** followed by addition of a benzylic bromide electrophile afforded the dihydrofuran **133**. Subsequent cleavage of the TMS group and of the chiral auxiliary gave the carboxylic acid which was reduced

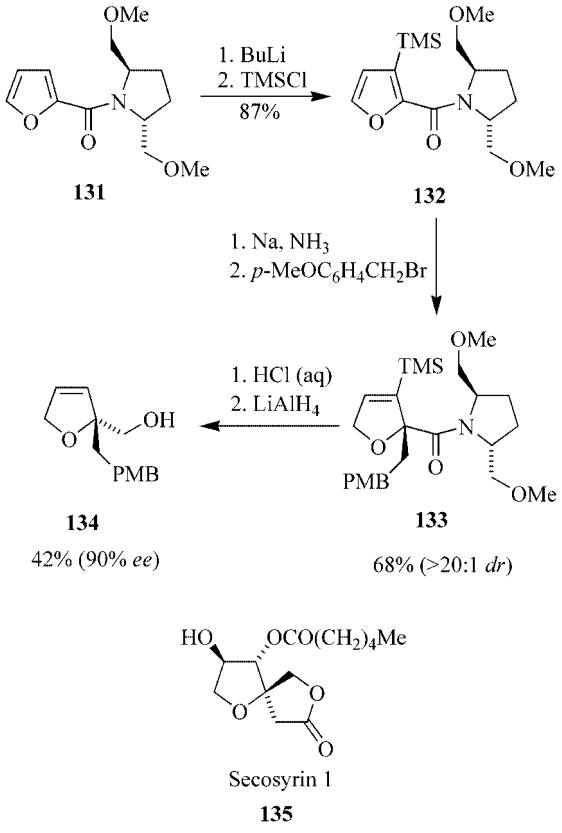


Scheme 37.

Table 5. Birch reduction of furans using C_2-symmetrical amines as chiral auxiliaries.



Entry	E^+	E	Ratio A/B	Yield
1	MeI	Me	30:1	88%
2	EtI	Et	>30:1	74%
3	*t*BuI	*t*Bu	>30:1	68%
4	CH_2CHCH_2Br	CH_2CHCH_2	>30:1	62%
5	NH_4Cl	H	10:1	65%



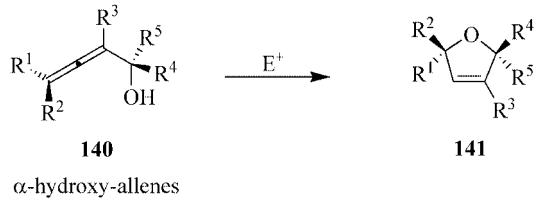
Scheme 38.

with $LiAlH_4$ to produce the primary alcohol **134**, a precursor to the target compound **135**.

Martin and co-workers reported the synthesis of the 2,2-disubstituted 2,5-dihydrofuran lactol **139** in their stereoselective synthesis of 2,2,6,6-tetrasubstituted tetrahydropyrans (Scheme 39).[67]

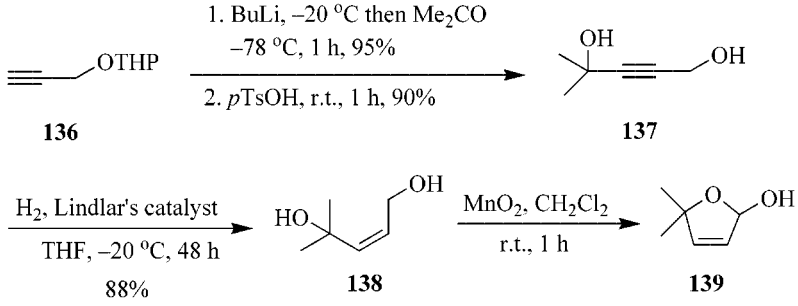
Addition of the anion of the tetrahydropyranyl derivative of propargylic alcohol **136** to acetone followed by deprotection produced diol **137**. Hydrogenation at low temperature afforded the olefin **138**, which was oxidised to the lactol, 5,5-dimethyl-2,5-dihydro-furan-2-ol **139**, using manganese dioxide.

Krause et al. recently described a novel procedure for the preparation of the 2,5-dihydrofurans **141** using the electrophilic cyclisation of the α-hydroxyallenes **140** (Scheme 40).[68,69]



Scheme 40.

The required α-hydroxyallenes were available by either oxidation of enolates of 3,4-dienoates formed in situ or by an S_N2'-substitution reaction of propargylic epoxides with organocuprates. All the α-hydroxyallenes **140** tested in their

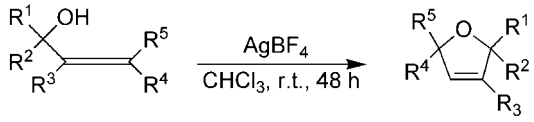


Scheme 39.

Table 6. Cyclisation of the hydroxyallenes **140a**–**i** to the 2,5-dihydrofurans **141a**–**i**.

Substrate	R^1	R^2	R^3	R^4	R^5	Electrophile	Product	Yield
140a	*t*Bu	Me	H	CO_2Et	H	HCl	**141a**	90%
140a	*t*Bu	Me	H	CO_2Et	H	Amberlyst15	**141a**	100%
140a	*t*Bu	Me	H	CO_2Et	H	$AuCl_3$	**141a**	74%
140b	*t*Bu	Me	H	CO_2Et	Me	HCl	**141b**	92%
140c	*t*Bu	*n*Bu	H	CO_2Et	H	HCl	**141c**	80%
140c	*t*Bu	*n*Bu	H	CO_2Et	H	$AuCl_3$	**141c**	100%
140d	*t*Bu	*n*Hex	H	CO_2Et	H	HCl	**141d**	90%
140e	*t*Bu	H	Me	CH_2OTBS	H	$AuCl_3$	**141e**	95%
140f	*t*Bu	Me	Me	CH_2OMe	H	$AuCl_3$	**141f**	90%
140g	H	*n*Hex	Me	CH_2OTBS	H	$AuCl_3$	**141g**	65%
140h	H	Me	Me	CH_2OTBS	H	$AuCl_3$	**141h**	77%
140i	H	H	Me	CH_2OTBS	H	$AuCl_3$	**141i**	86%

Table 7. Synthesis of substituted-2,5-dihydrofurans by silver(I)-catalysed cyclisation of α-hydroxyallenes **142a**–**b**.



142 **143**

Substrate	R^1	R^2	R^3	R^4	R^5	Reaction time [h]	Yield
142a	H	H	H	Me	*t*Bu	48	63%
142b	H	H	Me	H	Pr	48	55%
142c	H	*i*Pr	H	Me	Me	48	61%
142d	H	*i*Pr	H	H	H	72	25%
142e	Me	*n*Pr	H	H	H	96	35%
142f	$-(CH_2)_5-$	–	H	H	H	96	20%

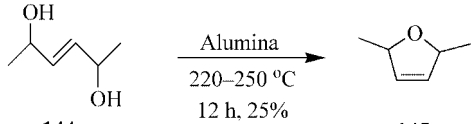
study were smoothly converted into the corresponding 2,5-dihydrofurans **141** with complete axis to central chirality control (Table 6).

Whereas compounds **140a**–**d** were easily converted using acidic media, the silylated derivatives **140e**–**i** required milder reactions and were efficiently cyclised using 5–10 mol-% gold(III) chloride as the catalyst. This process provided a wide range of tri- and tetra-substituted 2,5-dihydrofurans **141** in good yields and is a flexible route to these compounds compared to previous approaches.

Olsson and Claesson reported a related synthesis of substituted 2,5-dihydrofurans **143** by silver(I)-catalysed cyclisation of the α-hydroxyallenes **142** (Table 7).[70] The δ-monoalkyl- or δ,δ-dialkyl-substituted α-hydroxyallenes **142a**–**f** were treated with a catalytic amount of silver tetrafluoroborate in chloroform. In the cases of **142a**–**c**, complete cyclisation was observed, affording the 2,5-dihydrofurans **143** within 48 h at room temperature. The δ-unsubstituted allenes **142d**–**f**, however, only gave low yields under the same conditions.

Inoue et al., in their report on a convenient one-step preparation of oxacyclanes by dehydration of diols over alumina, found that in one case the dehydration of a diol led to a 2,5-dihydrofuran.[71]

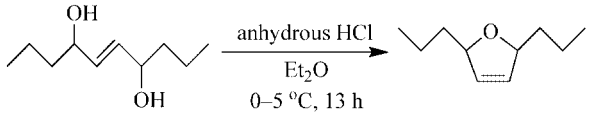
3-Hexene-2,5-diol (**144**) was simply mixed with alumina and heated to 220–250 °C (Scheme 41). This conversion, however, only proceeded in a moderate 25% yield after distillation of the product, 2,5-dimethyl-2,5-dihydrofuran (**145**).



144 **145**

Scheme 41.

In their attempts to dehydrate an olefin-1,4-diol **146** to form an aliphatic triene, Werner and Reynolds reported the formation of 2,5-dipropyl-2,5-dihydrofuran (**147**) (Scheme 42).[72]



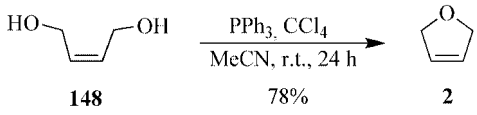
146 **147**

Scheme 42.

Their initial aim was to form the dichloride followed by elimination to the triene. Most of the diol **146**, however, was converted into the monochloro compound, which de-

composed during the initial distillation to yield the dihydrofuran derivative **147**.

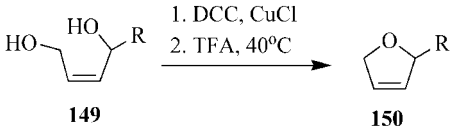
Although the dehydration of (*Z*)-1,4-dihydroxyalk-2-enes to give 2,5-dihydrofurans is a simple and attractive route to these compounds, the conditions employed are often quite harsh, leading to unwanted side products such as α,β-unsaturated carbonyls.[73] While milder reagents have been developed, many of these also have significant drawbacks. Examples include diaryldialkoxysulfurane[74] (expensive), diethyltriphenylphosphorane[75] (explosive starting material) and butyltrichlorotin[76] (toxic). With this in mind, Evans and Barry have investigated the triphenylphosphane/tetrachloromethane-promoted chlorination and cyclodehydration of simple diols (Scheme 43).[77,78]



Scheme 43.

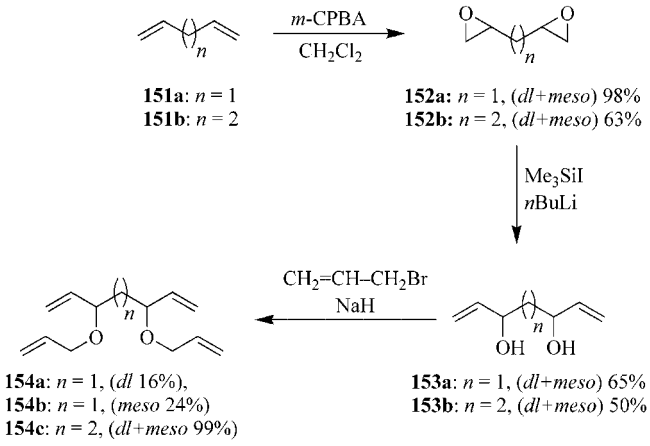
More recently, Grayson and Duffy have developed the use of dicyclohexylcarbodiimide (DCC) and copper(I) chloride for the synthesis of a range of 2-substituted 2,5-dihydrofurans from the corresponding diols.[79] Thus, a number of dihydrofurans **150** were synthesised via an intermediate isourea formed by the reaction of the diols **149** with DCC in the presence of a catalytic amount of CuCl and subsequently treated with trifluroacetic acid to affect cyclisation (Table 8).

Table 8. Synthesis of 2,5-dihydrofurans from diols using dicyclohexylcarbodiimide and copper(I) chloride.



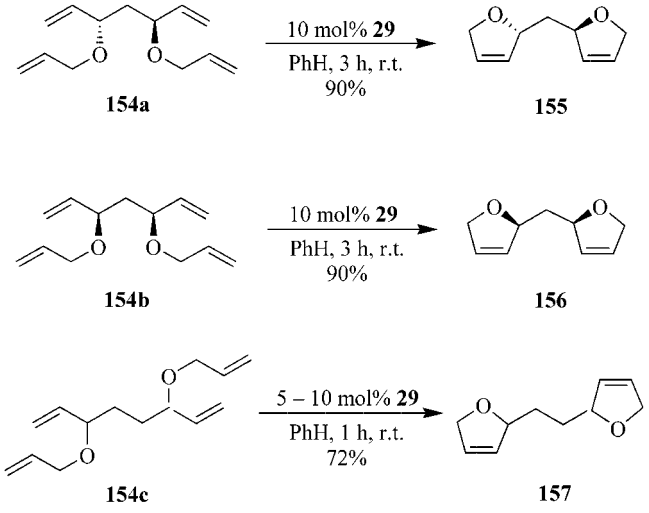
Entry	R	Yield
1	*n*-hexyl	90%
2	*n*-nonyl	89%
3	Bn	64%
4	Ph	79%
5	*o*-$MeOC_6H_4$	86%

As in the synthesis of 2,3-dihydrofurans using ring-closing metathesis discussed earlier, a number of 2,5-dihydrofurans have also been synthesised using this methodology. Baylon, Heck and Mioskowski reported their preliminary findings in the ring-closing metathesis reaction to from polycyclic ethers in 1999.[25] In their efforts toward the synthesis of natural and non-natural acetogenins and polyether antibiotics, they developed an efficient application of catalytic intramolecular olefin metathesis of acyclic tetraenes which allows for the generation of a variety of polyunsaturated oxygen heterocycles. Using Grubbs' catalyst in a double ring-closing metathesis reaction of acyclic tetraenes, two rings and two carbon–carbon bonds are formed in a single step yielding polycyclic unsaturated ethers. The acyclic tetraenes were synthesised from the commercially available dienes **151a**–**b** (Scheme 44). Once converted to the epoxides **152a**–**b** using *m*-chloroperoxybenzoic acid, addition of an excess of dimethylsulfonium methylide furnished the allylic alcohols **153a**–**b**. These were then converted into the allyl ethers **154a**–**c** using 3-bromopropene and sodium hydride (Scheme 44).



Scheme 44.

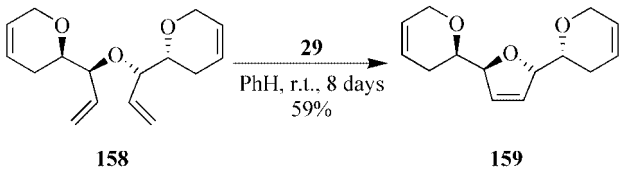
Mechanistically two products were possible from the cyclisation of the substrates **154a**–**c** via either a C-membered cyclisation (one RCM reaction) or an O-membered cyclisation (two RCM reactions). The results from the RCM reactions show that, even though cyclic alkenes were formed in small amounts, bicyclic compounds were isolated as the major products (Scheme 45).



Scheme 45.

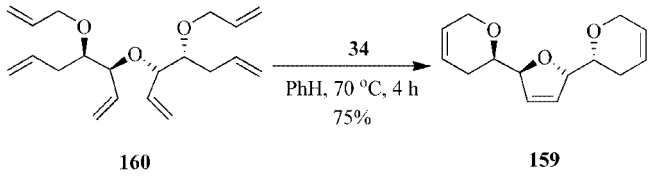
Heck later reported further findings involving triple ring-closing metathesis on acyclic hexaenes.[26] The acyclic hexaenes were submitted to typical metathesis reaction conditions. The results are the first examples involving a triple ring-closing metathesis reaction. When the bicyclic compound **158** was isolated from a previous RCM reaction and resubmitted to RCM conditions with successive additions

of Grubbs' catalyst **29** (30 mol-%), compound **197** was obtained in 59% yield after 8 days (Scheme 46).



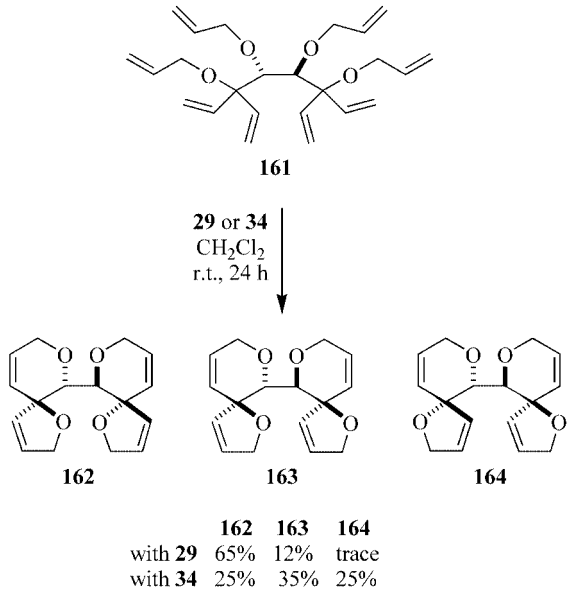
Scheme 46.

Because of higher thermal stability and higher reactivity displayed by the second-generation Grubbs' catalyst **34**, the RCM reaction was performed on substrate **160** using the imidazol-2-ylidene-modified ruthenium catalyst. This afforded the tri-adjacent cyclic ether **159** directly in 75% yield (Scheme 47).



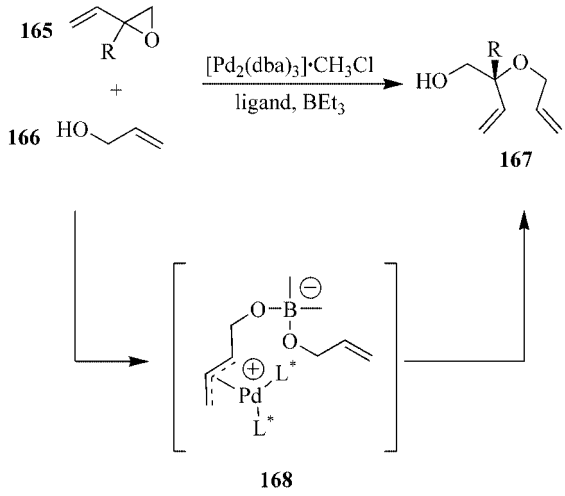
Scheme 47.

Wallace has recently described the first example of a quadruple RCM reaction.[80] Treatment of the octaene **161** with Grubbs' catalyst **29** led to two products on TLC after 24 hours, which were later separated by column chromatography in 74% yield (Scheme 48). The reaction proceeded in both a regioselective and stereoselective manner giving predominantly the C_2-symmetric compound **162**, along with a small amount of **163** and a trace amount of **164**. Use of the more reactive catalyst **34** afforded the bis-spirocyclic compounds in high yield but with little stereoselectivity.



Scheme 48.

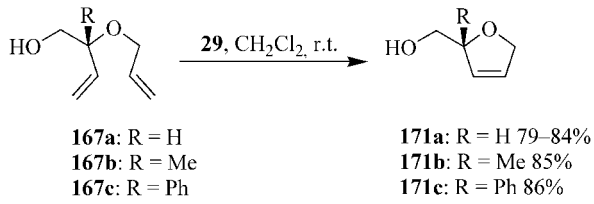
Trost has developed a novel strategy for the synthesis of nucleosides which involves dynamic kinetic asymmetric transformations (DYKAT) of racemic epoxides with alcohol nucleophiles using palladium-catalysed asymmetric allylic alkylation (PAA), followed by ruthenium-catalysed metathesis.[81] The Pd-DYKAT of racemic epoxides involves treatment of a 1:1 mixture of the vinyl epoxide **165** and the alcohol **166** with a chiral catalyst in the presence of triethylborane as a co-catalyst (Scheme 49). The role of the boron co-catalyst is twofold: 1) To enhance the ability of alcohols to serve as good nucleophiles through formation of "ate" complexes, and 2) to temporarily tether the nucleophile to the epoxide oxygen to help deliver it to the proximal carbon as per **168**.



Scheme 49.

The simple vinyl epoxide reacted cleanly to give the diene in 80% yield and 90% *ee* (Table 9, Entry 1). For isoprene mono-epoxide, no DMAP was required and both yields and *ee*s were higher (86% and 87%, respectively; Entry 2). However, the phenyl-substituted epoxide reacted quite sluggishly, requiring a much larger amount of DMAP and resulting in a yield of 33% and *ee* of 87% (Entry 3).

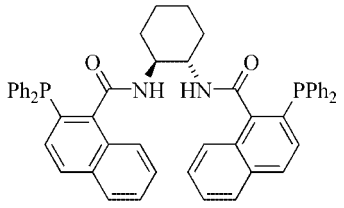
Subsequent ring-closing metathesis to form the five-membered rings proceeded well with Grubbs' catalyst **29** to produce the 2,5-dihydrofurans of high enantiopurity and without loss of the stereochemical integrity of their acyclic precursors (Scheme 50).



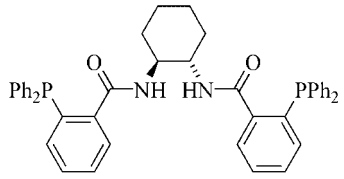
Scheme 50.

Schmidt and Wildemann described the preparation of a number of 2,2-disubstituted 2,5-dihydrofurans in their report on the synthesis of dihydrofuran oxides.[36] The diallyl

Table 9. Dynamic kinetic asymmetric transformations of racemic epoxides with alcohol nucleophiles using palladium-catalysed asymmetric allylic alkylation.



169

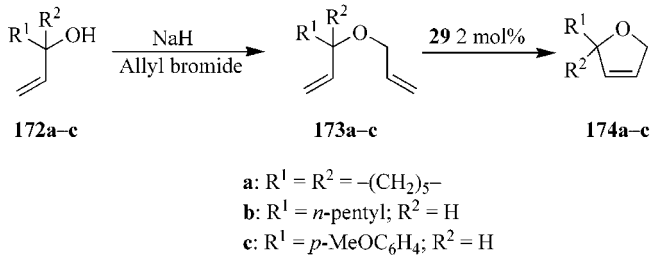


170

Entry	R	Method[a]	Product	Yield	*ee*
1	H	A	**167a**	80%	90%
2	Me	B	**167b**	86%	94%
3	Ph	C	**167c**	33%	87%

[a] Method A: 0.5 mol-% $[Pd_2(dba)_3]\cdot CHCl_3$, 1.5 mol-% **169**, 0.5 mol-% triethylborane, 5 mol-% DMAP in DCM at room temp.; Method B: 1 mol-% $[Pd_2(dba)_3]\cdot CHCl_3$, 3 mol-% **170**, 1 mol-% triethylborane in DCM at room temp.; Method C: 1 mol-% $[Pd_2(dba)_3]\cdot CHCl_3$, 3 mol-% **170**, 20 mol-% DMAP in dioxane at room temp.

ethers **173a**–**c**, obtained by allylation of the alcohols **172a**–**c**, underwent ring-closing metathesis in the presence of Grubbs' catalyst to form the 2,2-disubstituted 2,5-dihydrofurans **174a**–**c** (Scheme 51).

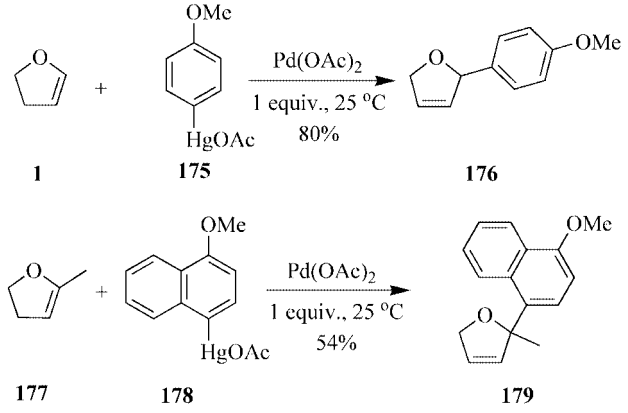


172a–c **173a–c** **174a–c**

a: $R^1 = R^2 = -(CH_2)_5-$
b: $R^1 = n$-pentyl; $R^2 = H$
c: $R^1 = p$-$MeOC_6H_4$; $R^2 = H$

Scheme 51.

Daves and Hallberg, in their review of 1,2-additions to heteroatom-substituted olefins by organometallic reagents, describe a number of reactions of enol ethers in the formation of a range of substituted 2,5-dihydrofurans.[82] For example, cyclic enol ethers [2,3-dihydrofuran (**1**) and the 5-methoxy-2,3-dihydrofuran (**175**)] readily undergo regiospecific palladium-mediated arylation with palladium reagents (Scheme 52).



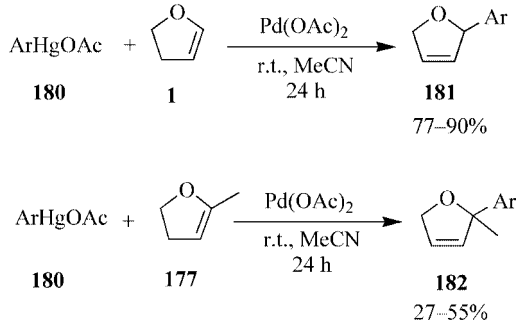
1 **175** **176**

177 **178** **179**

Scheme 52.

Lee and Daves also described the palladium-mediated reaction of these enol ethers with organomercuric acetate.[83]

In every instance, there is a regiospecific formation of a carbon–carbon bond between the aryl carbon bearing mercury and the enol ether olefinic carbon bonded to oxygen (Scheme 53). The strongly polarised nature of the enol ether olefinic bond is the influencing factor in each case, which is exemplified in the cases of 5-methyl-2,3-dihydrofuran (**177**) where the new bond is formed exclusively at the highly hindered tertiary carbon adjacent to the enol ether oxygen.



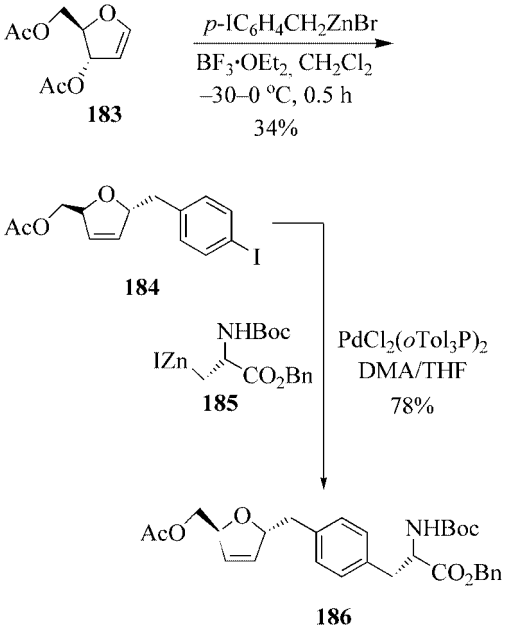
180 **1** **181**

180 **177** **182**

Scheme 53.

In their report on the synthesis of C-glycosyl tyrosines, Gallagher and co-workers described the preparation of a protected C-glycosyl tyrosine which has a 2,5-dihydrofuran moiety inherent in its core structure.[84] The Lewis acid-mediated reaction of crude di-*O*-acetyl-D-arabinal (**183**) with a zinc reagent derived from 4-iodobenzyl bromide gave the C-glycoside **184** as a single steroisomer in 34% yield (Scheme 54). Pd-mediated cross coupling of the two fragments **186** and **185** provided the protected C-glycosyl tyrosine **186** in 78% yield.

We have already seen how the Heck reaction can be exploited in the synthesis of 2,3-dihydrofurans. This is also the case for 2,5-dihydrofurans. For example, Glorious has reported the reaction of the 2-chloroacetamides **187** with 2,3-dihydrofuran (**1**) under Heck conditions (Table 10).[85]



Scheme 54.

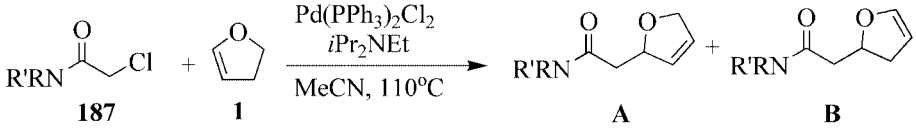
Carretero et al. have shown how sulfoxides can be utilised as stereochemical controllers in intermolecular Heck reactions.[86] The arylsulfinyl-2,3-dihydrofuran **188** was readily prepared in two steps by sulfenylation of 2,3-dihydrofuran with the aryl methyl sulfoxide under Pummerer reaction conditions and further oxidation of the thioether with *m*CPBA. The reaction of **188** with both electron-poor and electron-rich iodoarenes proceeded in moderate to good yields, with isomer **B** being the major product in most cases (Table 11). The only exception to this trend was the behaviour of the *ortho*-substituted iodoarene, which afforded an equimolar mixture of **A** and **B** isomers (Entry 6). The chiral auxiliary could be removed by oxidation of the sulfoxide to the corresponding sulfone, followed by palladium-catalysed reductive desulfurisation in the presence of a bulky Grignard reagent.

Hayashi investigated the cyclic olefin 2,3-dihydrofuran (**1**) in asymmetric intermolecular arylation reactions.[87] Palladium complexes of (*R*)-BINAP (**189**) induced asymmetry and a mixture of regioisomers (*S*)-**105** and (*R*)-**22** was obtained, with isomer (*R*)-**22** being formed in 96% *ee* and in 46% yield and favoured over (*S*)-**105** in a 71:29 ratio (Scheme 55). The choice of base was very important with the highly basic and sterically demanding 1,8-bis(dimethylamino)naphthalene (proton sponge) (**190**) providing the best results.

Larhed has recently shown how the use of microwave heating for these reactions can significantly reduce reaction times.[88]

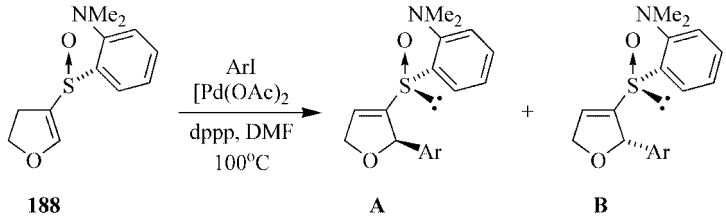
In an important extension to this work, Pfaltz has described the application of the amino alcohol-derived (di-

Table 10. Reaction of 2-chloroacetamides with 2,3-dihydrofuran under Heck conditions.

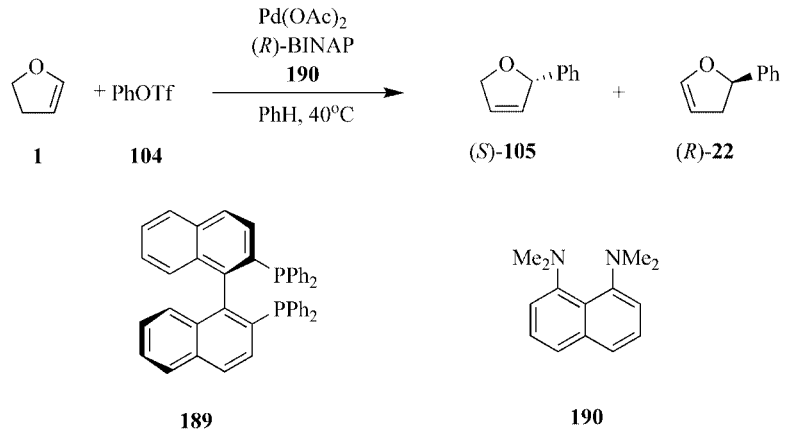


Entry	R	R′	Yield	Ratio A:B
1	Et	Et	65%	63:35
2	H	H	–	–
3	*t*Bu	H	67%	42:58
4	Hex	H	75%	51:49

Table 11. Incorporation of sulfoxides as stereochemical controllers in the intermolecular Heck reaction of dihydrofurans.

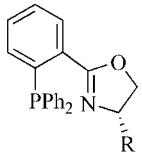


Entry	Ar	A:B ratio	Yield
1	Ph	6:94	80%
2	*p*-(MeO)C_6H_4	14:86	55%
3	*p*-(NO_2)C_6H_4	6:94	64%
4	*p*-(CO_2)C_6H_4	7:93	45%
5	3-Me-4-MeO–C_6H_3	15:85	86%
6	2,4-(MeO)$_2C_6H_3$	50:50	47%



Scheme 55.

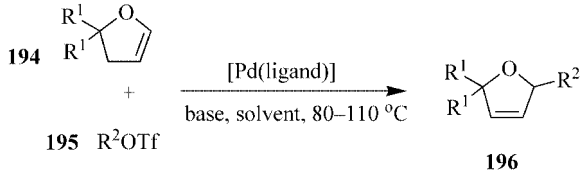
phenylphosphanyl)oxazoline ligands **191** to the arylation and alkenylation of 2,3-dihydrofuran (**1**), with complexes of the *tert*-butyl-substituted ligand **191b** affording both the best enantioselectivities and catalyst activity.[89,90]



191a: R = *i*Pr
191b: R = *t*Bu

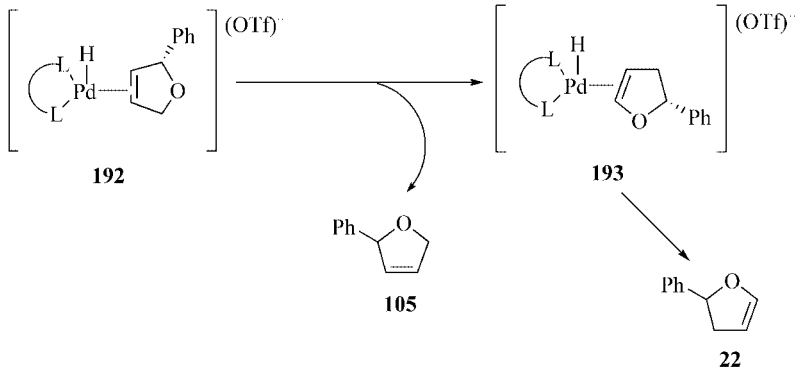
The use of 2,3-dihydrofuran in the asymmetric Heck reaction can lead to different products in various ratios depending on the ligand and the conditions employed. As stated for the cases of BINAP (**189**) and the (diphenylphosphanyl)oxazoline ligands **191a** and **191b**, the product ratio of the reaction depends on whether the intermediate formed after migratory insertion and initial β-elimination will dissociate or undergo a reverse β-elimination, β-elimination, dissociation pathway (Scheme 56).

Mechanistically it is clear that the isomer **22** can only be formed when there is a H substituent at C-2. A dihydrofuran disubstituted at this position would be a substrate which would provide a true comparative test for a range of palladium complexes. This is not the case for substrate **1**, as the final isomer ratio and enantioselectivities are complicated by kinetic resolution processes. Therefore, our research group prepared the 2,2-dialkyl-2,3-dihydrofurans **194** as test substrates for the intermolecular Heck reaction.[56,91] These disubstituted substrates should allow for a direct comparison of various ligands in this reaction because they form just a single regioisomeric Heck product (Scheme 57).

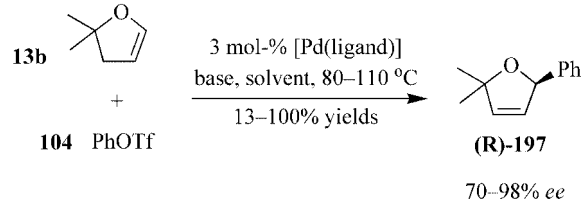


Scheme 57.

2,2-Dimethyl-2,3-dihydrofuran (**13b**) was tested as a new substrate for the asymmetric intermolecular Heck reaction.[92] Our initial application of this substrate was in the asymmetric phenylation with a variety of ligands, which proceeded in high yield and enantioselectivities of up to 98% of product (*R*)-**197** (Scheme 58).

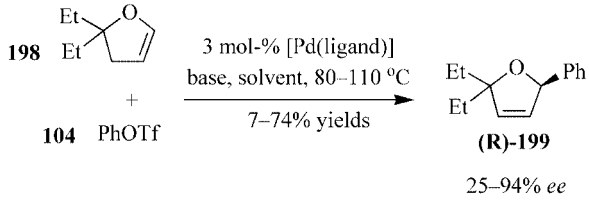


Scheme 56.



Scheme 58.

The 2,2-diethyl-2,3-dihydrofuran (**198**) was also prepared and applied in the intermolecular Heck reaction.[93] The increased bulk at the 2-position affected both the chemical yields and the *ee*s of the asymmetric Heck reactions carried out with this substrate (Scheme 59). In general, lower yields and *ee*s were observed compared to the 2,2-dimethyl-2,3-dihydrofuran substrate (Scheme 58).

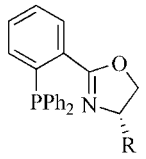


Scheme 59.

For further examples of the synthesis of chiral ligands and their application to the asymmetric Heck reaction of dihydrofurans, readers are directed to the relevant literature articles.[94–99]

The triphenylphosphane-induced ring contraction of the 1,2-dioxines **200** has been used by Taylor to produce the substituted 2,5-dihydrofurans **201** (Table 12).[100] When variously substituted 3,6-dihydro-1,2-dioxines were treated with 1.5 equivalents of triphenylphosphane at 60 °C in chloroform, the corresponding dihydrofurans were obtained in moderate yields.

Table 12. Synthesis of 2,5-dihydrofurans by triphenylphosphane-induced ring contraction of 1,2-dioxines.



191a: R = *i*Pr
191b: R = *t*Bu

Entry	R^1	R^2	Yield
1	cyclohexyl	H	63%
2	H	adamantyl	60%
3	H	cyclohexyl	35%

Conclusions

Many natural products and biologically active compounds contain the dihydrofuran subunit. Molecules incorporating either 2-substituted, 2,2-disubstituted 2,3- or 2,5-dihydrofurans are widespread in the literature and represent key "molecular building-blocks". In this microreview we have outlined some the varied approaches adopted in reaching this important family of synthetic targets and highlighted our own research in this field.

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