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O→C rearrangements: a powerful strategy for the synthesis of functionalised carbocycles

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1. Introduction

The aim of this report is to provide an overview of non-concerted[1] O→C rearrangements, exemplified by highlights of their use in the construction of biologically active molecules. All of the transformations discussed in this overview, either inter- or intramolecular, involve the rearrangement of molecules bearing latent electrophilic and nucleophilic moieties, the in situ molecular fragmentation of which results in the concomitant formation of a stabilised positive charge and an activated nucleophile. These species combine to generate the product by formation of a new carbon–carbon bond. Undoubtedly, the most prevalent oxygen-to-carbon rearrangements are those whereby the stabilisation of positive charge is mediated by an oxygen atom. Nonetheless, alternative modes of O→C transposition are known and will be described in the latter part of this report.

Keywords: Oxocarbenium ions; Rearrangements; Carbocycles; Stereoselective.
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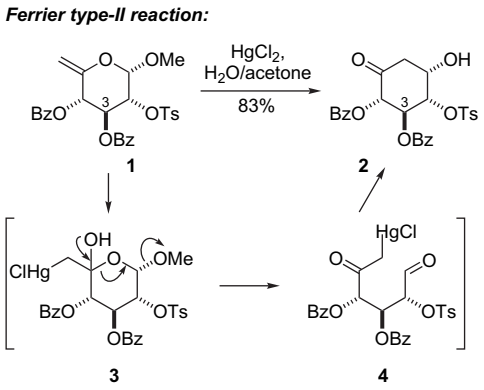
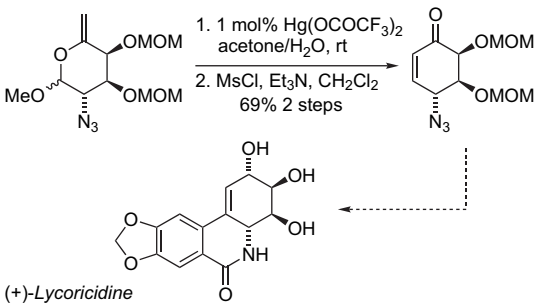
2. Oxocarbenium ion-mediated O→C rearrangements

Pioneering studies by Ferrier, in 1979, led to a convenient procedure for the conversion of carbohydrate-based exocyclic enol ethers into substituted cyclohexanones using mercury(II) salts, more commonly known as the Ferrier type-II reaction.[2] Ferrier demonstrated that treatment of hex-5-enopyranoside derivatives with mercury(II) chloride (1.0 equiv) in aqueous acetone afforded the corresponding cyclic ketones in good yield. The mechanism of the transformation is depicted in Scheme 1. Key to the success of the reaction is the regioselective hydroxymercuration to give unstable acetal **3** that decomposes to ketoaldehyde intermediate **4** via the loss of methanol. Mercuric-enolate **4** then takes part in an intramolecular aldol-cyclisation to generate cyclohexanone **2** in high yield, and as a single diastereomer in most cases. The stereochemistry of the newly formed hydroxyl moiety was found to be dependent on the stereochemistry of the C-3 substituent, whereby the two groups are generally trans-disposed. Additionally, it was found that mercury(II) acetate delivered the product ketones in higher yield than mercury(II) chloride.



Scheme 1.

The mild reaction conditions, coupled with the ready availability of the carbohydrate precursors, provide a synthetically significant transformation that leads to highly functionalised cyclohexanones. Subsequent to Ferrier's original findings, it has been shown that the reaction can be catalysed using substoichiometric amounts of the mercury Lewis acid, as well as by a number of other transition metals, e.g. Pd, Rh(I).[3,4] Application of the Ferrier type-II reaction in total synthesis was elegantly demonstrated by Ogawa and co-workers. This transformation was utilised to generate optically active subunit **6**, during the total synthesis of the antimitotic alkaloid, (+)-lycoricidine (Scheme 2).[5]

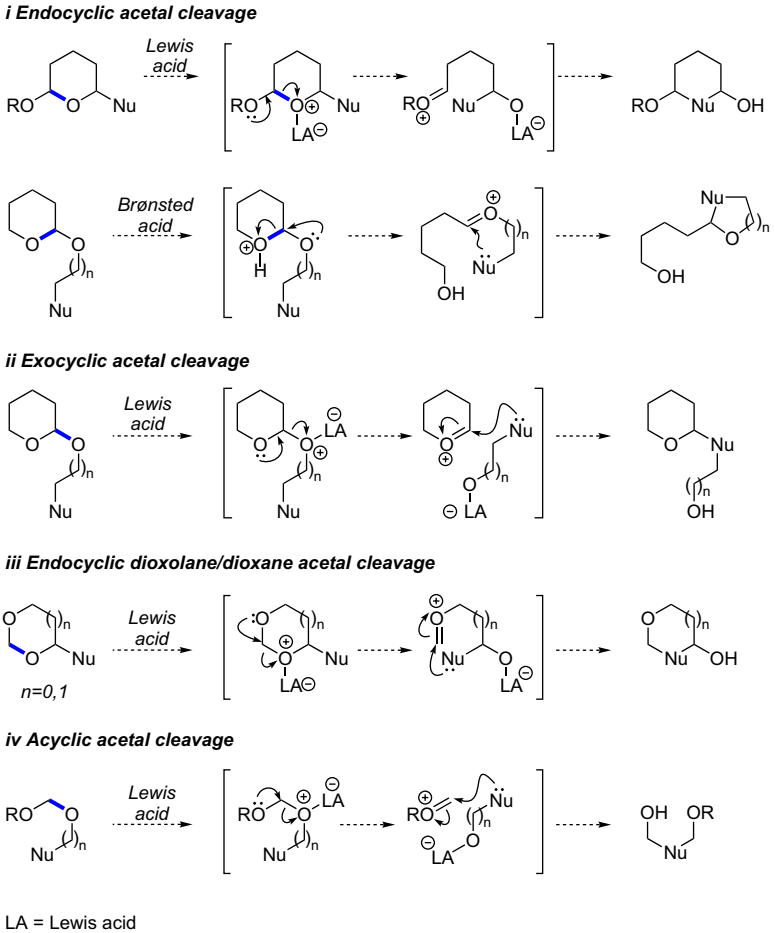


Scheme 2.

Subsequent to Ferrier's influential report, investigations into the scope of anomeric O→C rearrangements have proved to be a fruitful area of chemistry, the various strategies of which are summarised in Scheme 3. The rearrangements have been categorised according to the mode of acetal fragmentation.

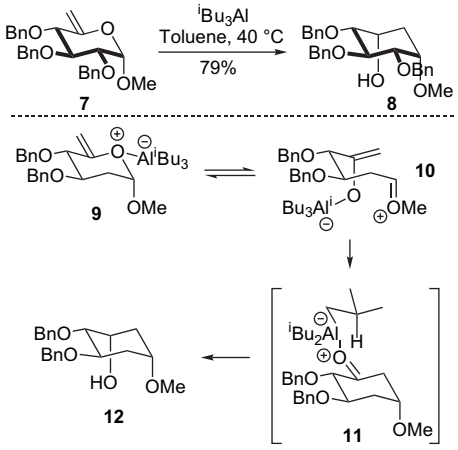
2.1. Endocyclic acetal cleavage rearrangements

The intramolecular reductive rearrangement of unsaturated glycosides, promoted by triisobutylaluminium (TIBAL), leads to highly substituted cyclohexane derivatives such as **8** (Scheme 4).[6] *endo* Activation of the glycosidic moiety causes rupture of the pyran to generate oxocarbenium-



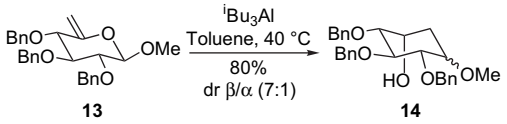
Scheme 3.

Al-enolate **10**, which cyclises to ketone **11** via a 6-(enolendo)-*exo-trig* ring closure.[7] Under the reaction conditions, ketone **11** rapidly undergoes diastereoselective reduction to the corresponding alcohol **12** (for the mechanism in Scheme 4, C-2 benzyl ether is omitted for clarity).



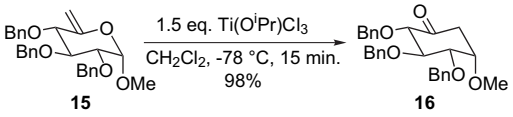
Scheme 4.

The rearrangement was found to be stereoretentive with respect to the aglycon moiety, as the converse β-anomer **13** yielded the major diastereomeric product **14** with the methoxy group equatorially disposed (Scheme 5). It was postulated that the observed stereochemical memory at the anomeric centre was due to the zwitterionic aluminium enolate intermediate proceeding via a tight ion pair (cf. Scheme 4).



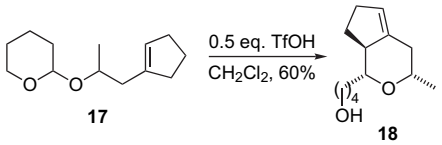
Scheme 5.

Alternatively, Sinaÿ also demonstrated that titanium-based Lewis acids could be used to enact a similar transformation. As outlined in Scheme 6, however, rearrangement of **15** was not followed by carbonyl reduction and ketone **16** was isolated in excellent yield.[8]



Scheme 6.

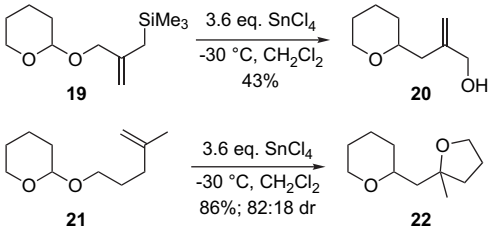
An example of *endo*-acetal cleavage was reported by Ley and co-workers, who found that Brønsted acids could be used to catalyse the ring opening and cyclisation of tetrahydropyran ring systems by anomerically linked homoallylic alcohols (Scheme 7).[9] Triflic acid proved to be the optimum catalyst, delivering the products resulting from a Prins-type cyclisation in good yield. Interestingly, the rearrangement of **17** proceeded with complete diastereocontrol.



Scheme 7.

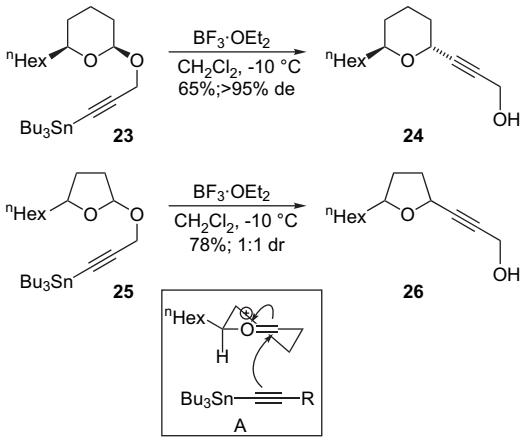
2.2. Exocyclic acetal cleavage rearrangements

O→C rearrangements in which the nucleophilic component is attached to the anomeric oxygen via a saturated carbon-chain linker has been extensively studied by Ley and co-workers.[10] For example, the interception of the tetrahydropyranyl oxocarbenium ions by the in situ generation of carbon-centred nucleophiles, formed by treatment of pyrans such as **19** and **21** with a Lewis acid, smoothly furnishes the corresponding substituted tetrahydropyran products **20** and **22**, respectively (Scheme 8).



Scheme 8.

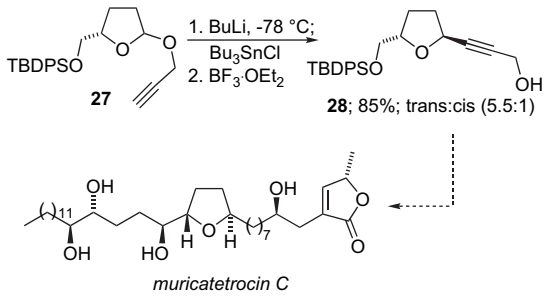
The influence of substitution at the 6-position leads to a diastereoselective transformation **23**→**24** (Scheme 9), whereby the product stereochemistry is rationalised by the half-chair transition state **A**. The alkyl substituent resides in a pseudo-equatorial position with pyramidalisation of the oxocarbenium ion occurring trans-diaxially on the *si*-face. By direct analogy, the same transformation in tetrahydrofuran systems, e.g. **25**→**26**, was found to be non-selective.



Scheme 9.

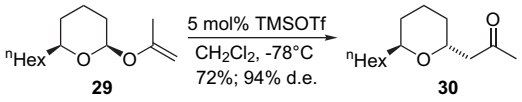
In studies directed towards the total synthesis of muricatetrocin C, glycidol-derived tetrahydrofuran **27** was subjected to a two-step rearrangement protocol that provided multigram quantities of the *trans*-alkynylated tetrahydrofuran **28**.[11] In contrast to the alkyl-substituted example in Scheme 9, the use of a bulky TBDPS ether to enforce greater geometric

constraints leads to an increase in the diastereoselection in the alkynylation (Scheme 10).



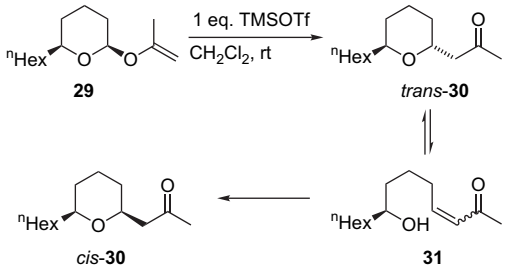
Scheme 10.

The employment of enol moieties in this class of rearrangement is illustrated in Scheme 11. Treatment of vinyl acetal *cis*-**29** with 5 mol % trimethylsilyl trifluoromethanesulfonate (TMSOTf) delivered *trans*-2,6-disubstituted tetrahydropyran **30** with high diastereoselection.[12]



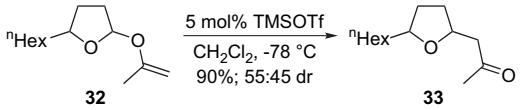
Scheme 11.

In the case when 1.0 equiv of Lewis acid was used at room temperature, the reaction was found to be highly selective for the cis-isomer. Control reactions revealed that the observed stereochemical reversal is the result of isomerisation of the initially formed kinetic trans-product to the thermodynamically favoured cis-diastereomer via the enone intermediate **31** (Scheme 12).



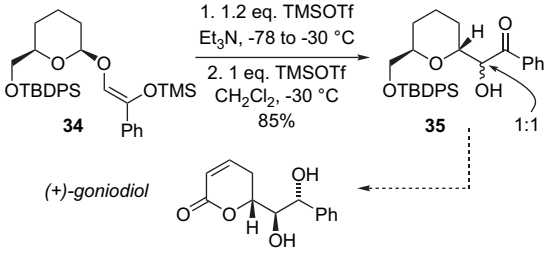
Scheme 12.

The diastereoselectivity observed in pyranyl systems does not extend to the TMSOTf-promoted rearrangement of tetrahydrofuranyl-based vinyl acetals. Transformation of **32** to disubstituted ether **33** with 5 mol % TMSOTf, whilst high yielding, afforded an almost 1:1 cis/trans mixture of diastereomers (Scheme 13).



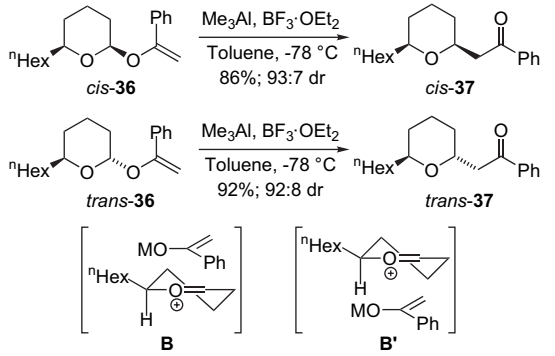
Scheme 13.

Ley has also studied the Lewis acid-promoted rearrangement of anomerically linked silyl enol ethers,[13] and used this to great effect in the rapid synthesis of the potent cytotoxin, (+)-goniodiol (Scheme 14).[14]



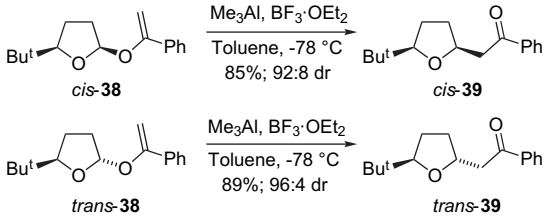
Scheme 14.

More recently, Rovis examined a similar transformation, whereupon it was found that the use of a mixed Lewis acid promoter system effected a stereoretentive rearrangement.[15] Treatment of either *cis*- or *trans*-**36** vinyl acetals with $Me_3Al/BF_3\cdot OEt_2$ affords the respective products with retention of stereochemistry (Scheme 15). A tenable rationale to explain the stereospecific recombination of the Lewis acid-bound vinyl acetal, further validated by crossover experiments, was the occurrence of a contact ion-pair mechanism in operation (**B** vs **B′**).



Scheme 15.

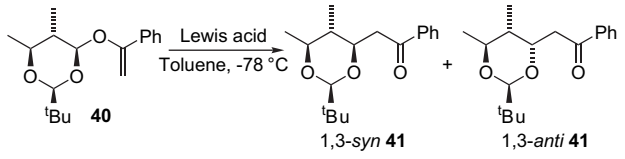
In an analogous fashion, the same stereochemical outcome was observed for tetrahydrofuranyl substrates *cis*/*trans*-**38** when the aluminium/boron Lewis acid protocol was employed (Scheme 16).



Scheme 16.

Rovis has utilised the retention of stereochemistry observed with $Me_3Al/BF_3\cdot OEt_2$ to construct 1,3-polyol fragments by the oxygen-to-carbon transposition of dioxanyl-derived vinyl acetals.[16] By a simple choice of Lewis acid, it is possible to generate both *syn*- and *anti*-3,5-dihydroxy ketone units such as **41** in a highly stereocontrolled fashion (Scheme 17). $BF_3\cdot OEt_2$ afforded the product consequent to

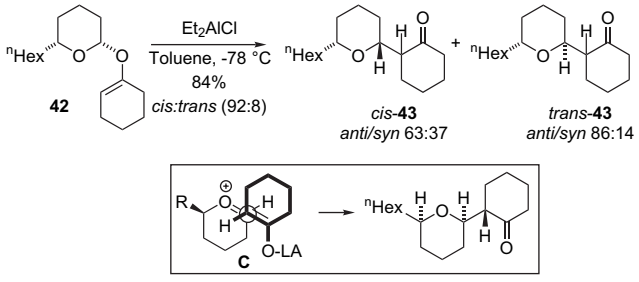
a solvent-equilibrated ion pair and trans-diaxial nucleophilic attack to the *si*-face of the oxocarbenium ion.



Lewis acid	1,3-*syn* **41**:1,3-*anti* **41**	Yield(%)
$BF_3{\cdot}OEt_2$	2:98	89
$AlMe_3$, $BF_3{\cdot}OEt_2$	96:4	81

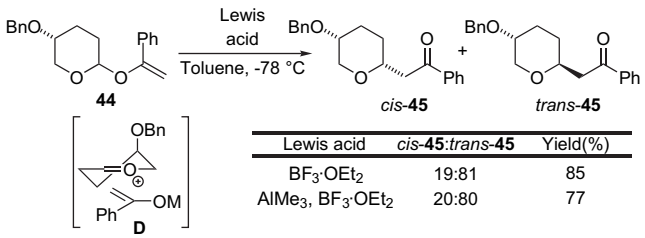
Scheme 17.

In connection with a total synthesis programme directed towards polyether natural products of the marine toxin family, Rovis surveyed the formation of C–C bonds between contiguous fused oxacycles, via the O→C rearrangement of cyclic vinyl acetals.[17] The use of Et_2AlCl proved to mediate the transformation with the retention of stereochemistry at the anomeric centre with higher selectivity than that observed when $Me_3Al/BF_3{\cdot}OEt_2$ was employed (cf. 55:45 cis/trans). Conversely, the use of boron trifluoride diethyl etherate affords the trans-isomer in high diastereoselection (>99:1). In all three Lewis acid-mediated reactions, however, the *anti*-diastereomer is favoured, presumably via transition state **C**, depicted in Scheme 18.



Scheme 18.

Woerpel has investigated the involvement of a contact ion-pair mechanism operating in the oxygen-to-carbon transposition of alkoxy-substituted six-membered ring vinyl acetals (Scheme 19).[18] Studies revealed that the stereoelectronic effects of the C-4 alkoxy substituent controlled the diastereoselectivity of the rearrangement, and that the reaction proceeds through solvent-equilibrated oxocarbenium ion intermediates **D**. Application of the Rovis mixed Lewis acid protocol did not result in stereoretention in the ketone products.

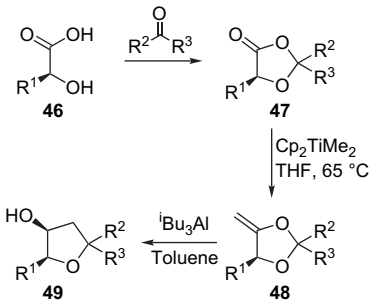


Lewis acid	*cis*-**45**:*trans*-**45**	Yield(%)
$BF_3{\cdot}OEt_2$	19:81	85
$AlMe_3$, $BF_3{\cdot}OEt_2$	20:80	77

Scheme 19.

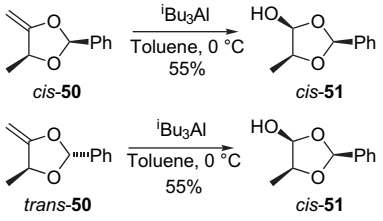
2.3. Endocyclic dioxolane and dioxane cleavage rearrangements

One of the most significant oxygen-to-carbon transformations that has been utilised in the total syntheses of numerous complex biologically active natural products is the Petasis variation of the Ferrier type-II reaction.[19] The transformation sequence involves the conversion of α- or β-hydroxy acids **46** into vinyl acetals **48** via a titanium-mediated methylenation. Reaction of substrates such as **48** with *i*-Bu_3Al leads to the rapid formation of tetrahydrofurans **49** at 0 °C. When $R^1 \neq H$ and $R^2 \neq R^3$, the process can be used to generate tetrahydrofurans with a high degree of stereocontrol (Scheme 20). Notably, the configuration of the acetal carbon established during acetalisation is retained during the rearrangement. In the context of Baldwin's rules for the classification of ring closures,[7,20] the 5-(enolendo)-*endo-trig* cyclisation for tetrahydrofuran formation is formally disfavoured.

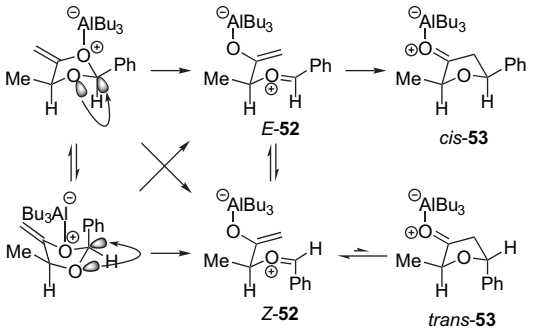


Scheme 20.

Interestingly, in the rearrangement of stereochemically pure *cis*- and *trans*-**50** under identical conditions, both afforded the same tetrahydrofuran *cis*-**51** (Scheme 21). The observed stereochemical preference was attributed to the model in Scheme 22.



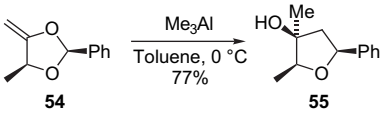
Scheme 21.



Scheme 22.

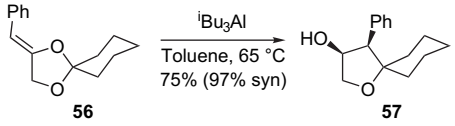
Initial coordination of the aluminium with the enolic oxygen atom leads to ring opening assisted by the antiperiplanar lone pair of the other acetal oxygen atom. Equilibration of *Z*-**52** and *E*-**52** was expected to favour the *E*-isomer in order to minimise $A^{1,3}$-strain. In addition, cyclisation of *E*-**52** to *cis*-**53** may be much faster, compared to cyclisation of *Z*-**52** to *trans*-**53**. Alternatively, overall equilibration takes place prior to the irreversible stereoselective reduction.

The use of stronger Lewis acids such as $BF_3 \cdot OEt_2$, $SnCl_4$, $LiClO_4$, $EtAlCl_2$, Et_2AlCl, TMSOTf and $TiCl_4$ did not mediate the dioxolane rearrangement. The use of trialkylaluminiums proved most efficient; Me_3Al was found to effect the 1,3-transformation in good yield, but gave the methyl addition product (e.g., **54**→**55**, Scheme 23). The same reactivity was observed for Et_3Al, which afforded the ethyl addition product.



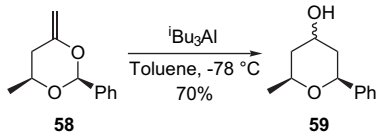
Scheme 23.

An interesting application of this methodology is the employment of spiroacetals to generate the corresponding spiro-ethers (Scheme 24). For example, **56** was smoothly transformed into **57** in good yield as essentially a single *syn*-isomer.



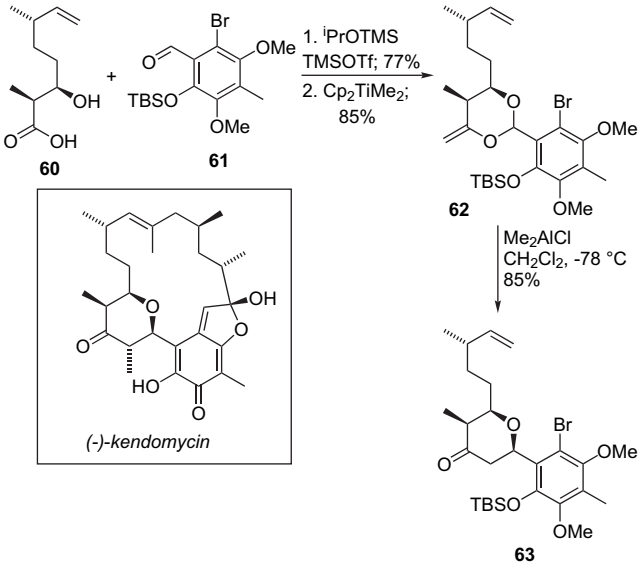
Scheme 24.

Petasis extended the Al-mediated [1,3]-shift of vinyl acetals to dioxane systems to construct tetrahydropyrans (Scheme 25).[21] In contrast to the tetrahydrofuran systems, transformation of the six-membered ring vinyl acetals such as **58** into tetrahydropyran **59** occurs at −78 °C in high yield. The enhanced reactivity of tetrahydropyran systems is presumed to be the result of a more favourable 6-(enolendo)-*endo-trig* cyclisation, which is stereoelectronically favoured.[7] Additionally, the numerous methods available for the construction of enantiopure β-hydroxy carboxylic acids (e.g., aldol reaction) allow a convergent stereoselective approach to enantiopure tetrahydropyrans.



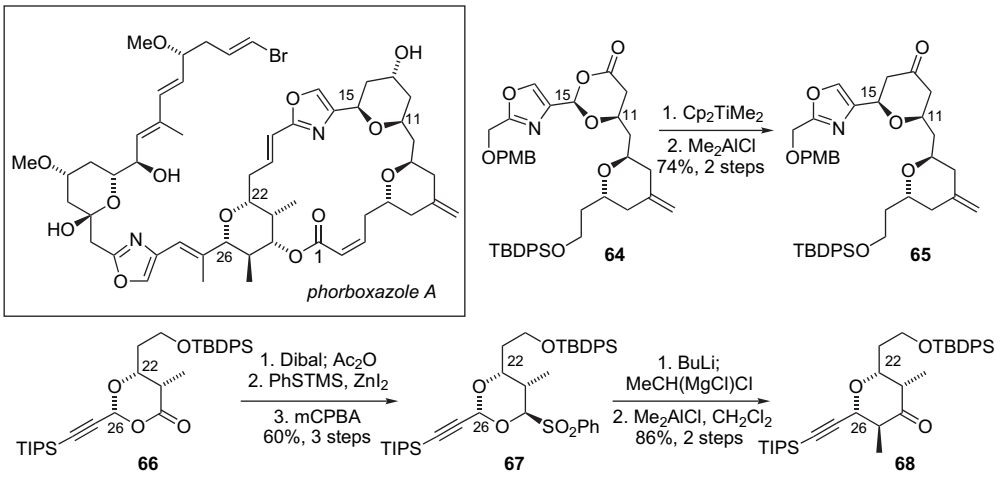
Scheme 25.

2.3.1. Petasis–Ferrier reaction in total synthesis. Smith and co-workers have elegantly employed the Petasis–Ferrier reaction, delineated above, in the synthesis of numerous complex natural products.[22] The two examples illustrated in Schemes 26 and 27 are related to the total synthesis of (−)-kendomycin and phorboxazole A, respectively, which demonstrates the powerful linchpin strategy by which the Petasis–Ferrier union/rearrangement can be used to construct complex molecules. The key tetrahydropyranone motif **63** in (−)-kendomycin was efficiently assembled via condensation of β-hydroxy acid **60**, formed by a diastereoselective Evans aldol condensation[23] with aldehyde **61**, followed by the Petasis–Ferrier sequence (Scheme 26). Notably, Me_2AlCl was found to be the most effective Lewis acid to promote the oxygen-to-carbon transposition, which halts at the ketone. Subsequent functionalisation of the aryl bromide and a ring-closing metathesis strategy provided the target molecule, (−)-kendomycin.



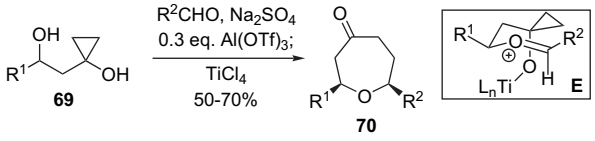
Scheme 26.

The Petasis–Ferrier sequence developed in the Smith laboratories provided a cornerstone strategy in the total synthesis of the potent antiproliferative agent, (+)-phorboxazole A. Employment of the Petasis–Ferrier rearrangement served as a linchpin tactic in the construction of two of the substituted tetrahydropyrans, as displayed in Scheme 27. The convergent approach permitted rapid assembly of the key fragments, which required minimal endgame operations to generate the target compound. Synthesis of the C11–C15 *cis*-tetrahydropyran proceeded smoothly to give **65** as a single diastereomer in high yield. The more complex penta-substituted tetrahydropyran **68** proved more difficult to address. Thus, a type-II Julia olefination protocol had to be used to synthesise the intermediate enol ether, albeit with no *E*/*Z*-diastereoselection. Fortunately, when treated with Me_2AlCl, both *E*- and *Z*-enol ethers were found to converge to the desired diastereomer of tetrahydropyran **68**. The stereochemical outcome was rationalised by analysing the possible transition states for C–C bond formation in the *E*- and *Z*-geometrical isomers. It was proposed that the *Z*-enol ether cyclised to the product via a chair transition state, whereas ring closure of the *E*-enol ether is favoured via a boat transition structure; a chair transition state for the *E*-enol ether is disfavoured, due to non-bonded steric interactions engendered by the axial C23 methyl group.



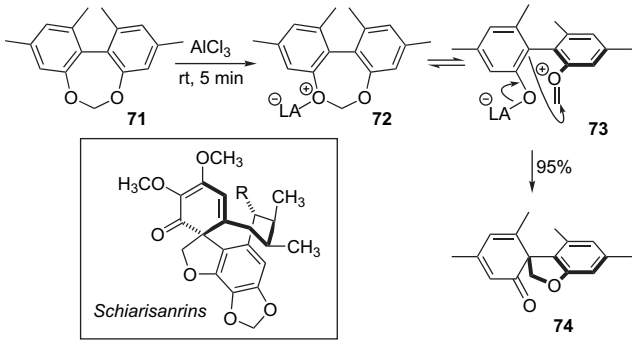
Scheme 27.

Extension of the Petasis–Ferrier methodology, by replacement of the β-hydroxy acid moiety with a cyclopropyl diol unit, leads to a convergent approach to oxepanes via cyclopropanol fragmentation. The one-pot sequence developed in the Minbiole laboratories[24] comprises the $Al(OTf)_3$-catalysed condensation of alkyl-substituted cyclopropyl diols **69** with aryl and alkyl aldehydes, followed by the addition of titanium(IV) tetrachloride, which furnishes the rearranged heterocycle **70** (Scheme 28). Only the *cis*-oxepanes were observed under these conditions, consistent with a chair transition state **E**, wherein both R groups occupy equatorial positions.



Scheme 28.

In connection with studies towards the synthesis of schiarisanrins A–D, depicted in Scheme 29, the Coleman group developed a route to spiro cyclohexandiones via the O→C rearrangement of dibenzodioxepins such as **71**.[25] Acetal fragmentation of **71** occurs upon treatment with aluminium trichloride to engender formation of oxocarbenium ion **73** and, thus, collapse of the Al-phenolate results in concomitant

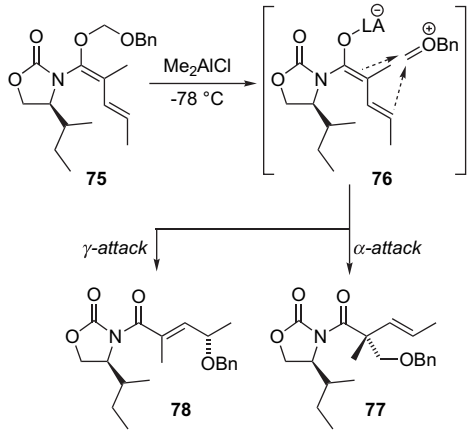


Scheme 29.

dearomatisation and spirocycle formation. The consequence is an overall intramolecular ring contraction, resulting in C-alkylation.

2.4. Acyclic acetal cleavage rearrangements

To date, the only reported example of an acyclic oxygen-to-carbon rearrangement is illustrated in Scheme 30.[26] Benzyloxymethyl chloride-derived vinylketene-*N*,*O*-acetals undergo a Lewis acid-promoted vinylogous Ferrier-type reaction to afford the corresponding 1,3- or 1,5-rearrangement *C*-alkylated products. The use of chiral imide **75** was found to afford the 1,3- and 1,5-products with high diastereoselection. The reaction was found to be strongly affected by the choice of solvent. Conducting the reaction in toluene affords the 1,3-product **77** as the major isomer, whereas moving to a more polar solvent such as CH_2Cl_2 causes a greater separation of the ion pair in the intermediate **76**, which leads to an increase in the isolation of the 1,5-*C*-alkylated product **78**.



Solvent	Eq. $MeAlCl_2$	**77** (%; dr)	**78** (%; dr)
toluene	5	57; 42:1	24; 20:1
CH_2Cl_2	4	39; 23:1	52; 20:1

Scheme 30.

The stereochemical outcome observed for the rearrangement in Scheme 30 is opposite to that observed when the same

substrate is generated under basic conditions, i.e., via enolate alkylation, and therefore is complementary. A possible transition structure depicted in Figure 1, was proposed by Kobayashi to explain the diastereofacial addition of the oxocarbenium ion to the prostereogenic α- or γ-carbon of the vinylketene-*N*,*O*-acetal. Coordination of two molecules of the Lewis acid to the dienolate anion and oxazolidinone, causes the oxazolidinone moiety to adopt an orientation almost perpendicular to the dienolate. Alkylation then ensues from the face opposite the *sec*-butyl group. The converse rotational isomer appears to suffer from non-bonded interactions between the *sec*-butyl and aluminium groups.

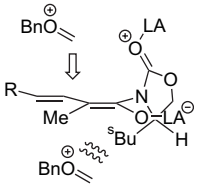
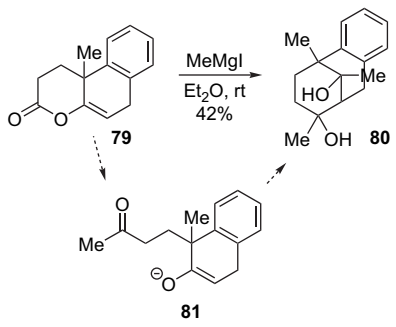


Figure 1.

3. Non-oxocarbenium ion-mediated O→C rearrangements

The addition of organometallic reagents to enol lactones provides an alternative means by which O→C rearrangement can take place via an in situ aldol addition process. An early exemplification of this concept was described by Fujimoto and co-workers, whereby the addition of Grignard reagents to enol lactone **79** provided **80** after interception of the ketone intermediate with excess MeMgI (Scheme 31).[27]

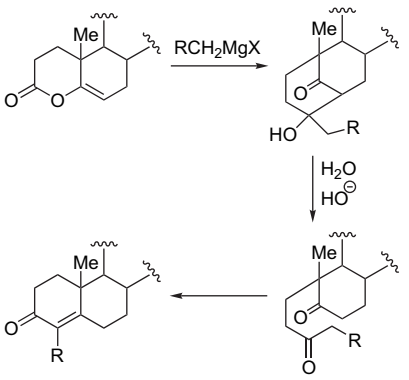


Scheme 31.

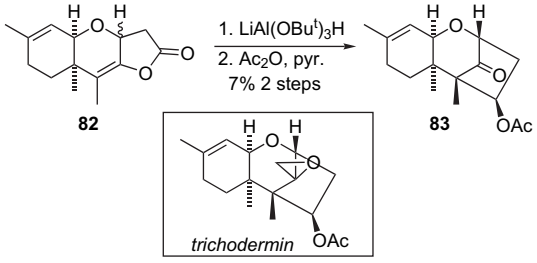
This transformation can lead further to α,β-unsaturated ketones via a retro-aldolisation–aldol condensation sequence and has become known as the Fujimoto–Belleau reaction (Scheme 32). This process became a popular and powerful method of steroid synthesis.[28]

An elegant application of the enol lactone O→C rearrangement in complex molecule synthesis was demonstrated by Colvin and Raphael in their approach to trichodermin (Scheme 33).[29] Tricycle **82** underwent rearrangement upon hydride reduction to provide a late-stage intermediate **83**, albeit in poor yield, over two steps.

Rodrigo and co-workers demonstrated the use of phthalides in the oxygen-to-carbon transposition in their synthesis of spirobenzylisoquinolines.[30] Specifically, treatment of

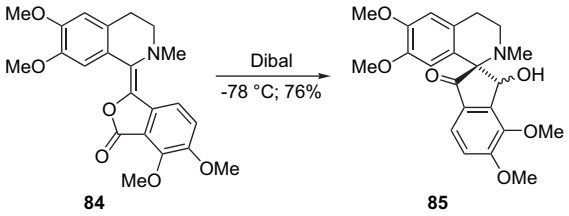


Scheme 32.



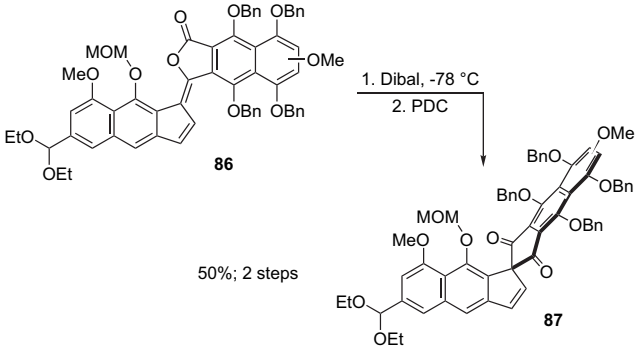
Scheme 33.

a readily available isoquinoline derivative **84** with Dibal resulted in the formation of the key spirocyclic product **85** as a 1:1 mixture of diastereoisomers at the carbinol stereocentre (Scheme 34).



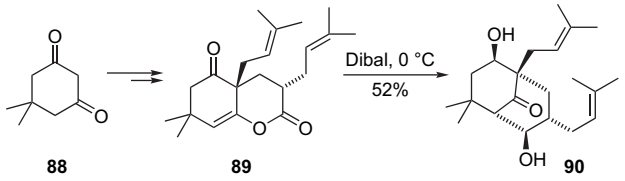
Scheme 34.

Moreover, Kelly and co-workers successfully employed this tactic in an elegant formation of the central spirodione motif of the potent anticancer compound, fredericamycin A. Dibal reduction and rearrangement of **86** provided diketone **87** after PDC oxidation (Scheme 35).[31]



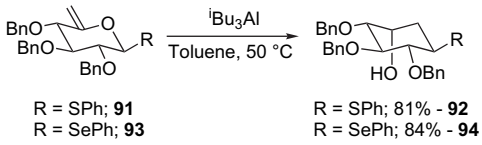
Scheme 35.

Very recently, the bicyclo[3.3.1]nonan-9-one core of the phloroglucins has been accessed from dimedone **88** in only a few steps by this enol lactol–aldol approach (Scheme 36).[32]



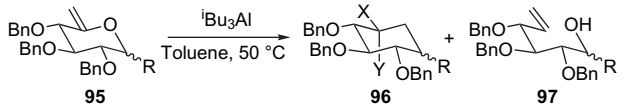
Scheme 36.

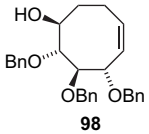
There have been relatively few reports concerning the replacement of the oxygen by other heteroatom functional groups, as the carbenium ion-stabilising moiety, in oxygen-to-carbon rearrangements. Studies by Sinaÿ demonstrated the feasibility of various alternative carbocationic stabilising groups for the transformation of unsaturated glycosides into the corresponding carbacycles,[33] a transformation previously discussed in Scheme 4. A salient factor is that the electron-donating functionality must be sufficiently Lewis basic to engender endocyclic ring fragmentation. The reaction of thio- and selenophenyl glycosides **91** and **93** with 5.0 equiv of *i*-Bu_3Al smoothly delivered the resultant carbocycles **92** and **94** in good yield and as single diastereomers. Notably, the stereochemical information of the aglycon is retained in the product (Scheme 37).



Scheme 37.

Analysis of the donor ability of various C-glycosides is summarised in Scheme 38. Attenuation in carbenium ion-stabilising ability results in a competing hydroalumination–elimination degradation pathway, which is dominant for alkyl substituents. Increasing the electron-donating aptitude of the substituent, however, e.g. trimethoxyphenyl (entry 5) and furyl (entry 6), exclusively affords the carbocyclised product **96**. Once again, the stereochemistry at the cationic centre is retained. Interestingly, in the case of the vinyl-substituted analogue **95** (R=–CH=CH_2), *i*-Bu_3Al catalyses a Claisen rearrangement to generate cyclooctene **98** in 98% yield.



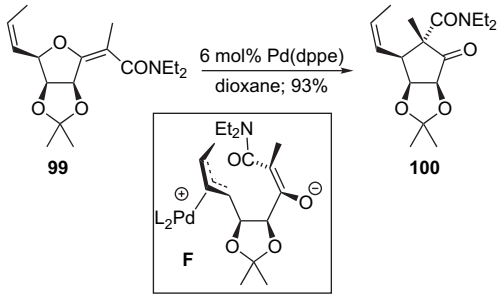


Entry	R	**96** (%; OH X:Y)	**97**
1	β-^{n}Bu	0	82
2	β-vinyl	98%; **98**	
3	β-Ph	35; 100:0	35
4	β-4-MeOPh	85; 80:20	10
5	β-2,4,6-$(MeO)_3$Ph	95; 60:40	0
6	α-2-furyl	83; 100:0	0

Scheme 38.

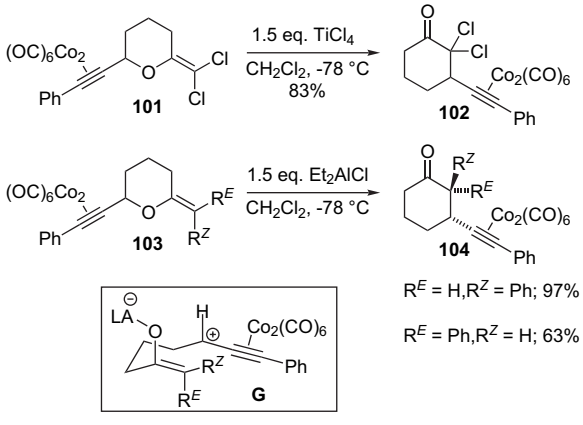
4. Metal-mediated O→C rearrangements

A small number of transition metal-mediated oxygen-to-carbon rearrangements have been reported. Trost demonstrated that palladium(0) catalyses the 1,3-alkyl shift of alkylidenetetrahydrofurans to functionalised cyclopentanones (Scheme 39).[34] The reaction proceeds under mild conditions and in a stereoselective manner. The proposed mechanism involves oxidative addition to the allyl ether **99** to form zwitterionic intermediate **F**, which collapses by C-alkylation to form the product **100**. The stereochemistry of the cyclopentanone indicates that the C–O bond is broken and replaced by the new C–C bond with complete retention of configuration. Additionally, the formation of a single stereoisomer at the quaternary centre implied that the stereochemistry of the alkylidene is maintained throughout the rearrangement. Classification of the ring-forming cyclisation is tantamount to a 5-(enolendo)-*exo-trig* process, which is disfavoured on stereoelectronic grounds.[7]



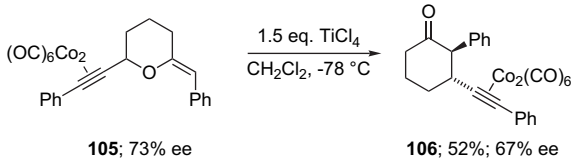
Scheme 39.

An alternative metal-mediated strategy, stoichiometric in the transition metal, is via the use of a dicobalt hexacarbonyl–alkyne cluster to stabilise the carbocationic charge. The Nicholas carbocation approach has been employed in our laboratories to mediate the rearrangement of enol ether complexes such as **101** and **103** to access β-alkynyl ketones **102** and **104**, respectively (Scheme 40).[35] The transformation proceeds efficiently in high yield at low temperature. Additionally, the reaction can be promoted with Al-Lewis acids to provide the corresponding products with excellent control of stereochemistry.[36] The reaction appears to proceed via a chair-like transition state **G**.



Scheme 40.

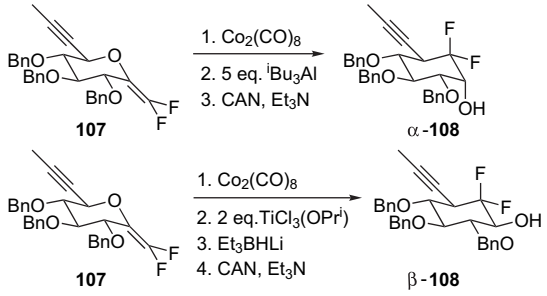
Further studies have confirmed that stereochemical control at the stereogenic centre can be maintained during the rearrangement process. Specifically, enantiomerically enriched complex **105** underwent rearrangement to afford **106** with minimal racemisation (Scheme 41).[35c]



105; 73% ee **106**; 52%; 67% ee

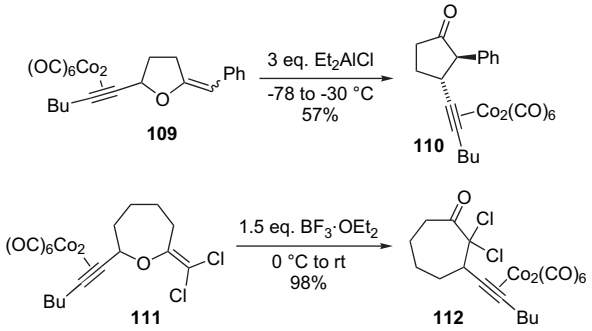
Scheme 41.

Sinaÿ and co-workers documented their progress in the synthesis of hydrolytically stable glycoside mimics by replacement of the endocyclic oxygen atom by another hydrogen bond acceptor group.[37] Accordingly, the cobalt-mediated rearrangement concept was utilised to synthesise *gem*-difluorocarba-D-glucose (Scheme 42). The diastereoselective rearrangement of **107** with either *i*-Bu_3Al or $TiCl_3(Oi\text{-}Pr)$ afforded the highly oxygenated cyclohexanone in good yield and as a single isomer. Subsequent stereoselective reduction afforded the desired α- and β-carbasugar analogues **108**. This example nicely demonstrates the employment of a diastereoselective rearrangement and its application to the generation of enantiomerically pure intermediates and serves to highlight the structural complexity of systems to which the Co-mediated rearrangement can be applied.



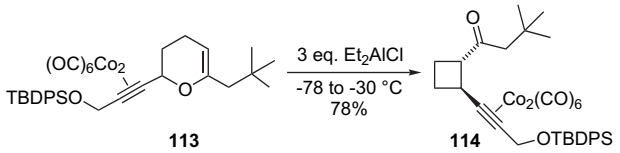
Scheme 42.

The Co-mediated rearrangement has also been shown to be effective for five- and seven-membered ring formation.[35a,36] Notably, once again, the former process (leading to **110**) appears to involve a disfavoured 5-(enolendo)-*exo-trig* cyclisation (Scheme 43).[7]



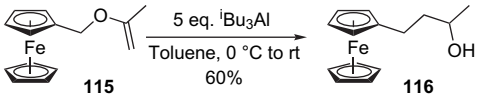
Scheme 43.

A related Co-mediated endocyclic cleavage that results in ring contraction has been developed recently in our labs.[38] Dihydropyran complexes such as **113** undergo rearrangement to provide the corresponding *trans*-1,2-disubstituted cyclobutane **114** in high yield and with excellent stereocontrol (Scheme 44).



Scheme 44.

The use of a cation-stabilising metal complex moiety has also been exploited in organoiron chemistry.[39] Ferrocenyl groups act as effective electron-donor substituents, as illustrated in Scheme 45. Ferrocene-derived enol ether **115** undergoes an O→C rearrangement when treated with *i*-Bu_3Al to provide alcohol **116** after in situ reduction.



Scheme 45.

5. Conclusions and outlook

The use of oxygen-to-carbon rearrangement strategies to generate new carbon–carbon bonds by the exploitation of latent nucleophile/electrophile motifs has enjoyed rich success for a number of decades. Whilst oxocarbenium ion intermediates represent the most heavily utilised forms of this approach, many alternatives can be envisaged. Accordingly, we anticipate that this area will continue to blossom and provide synthetic chemists with new and powerful tactics for the construction of complex organic molecules.

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Biographical sketch

Simon Meek received his MChem. from the University of Sheffield in 2003. As part of his undergraduate education, he completed a year of study at UCSB, USA, where he worked as an undergraduate researcher with Prof. Tom Pettus on the addition of chiral ligands to hypervalent iodide reagents for asymmetric dearomatisations of phenols. While attending UCSB, Simon was awarded the prestigious Robert H. DeWolfe summer undergraduate research award for 2002. He completed his Ph.D. degree under the supervision of Dr. Joe Harrity at the University of Sheffield (2003–2006) where he developed a series of Co-mediated O→C rearrangement processes. Simon is currently carrying out postdoctoral studies in Boston College, USA with Prof. Amir Hoveyda.

Joe Harrity is Reader in Organic Chemistry at the University of Sheffield. He received his B.Sc. degree from the University of Strathclyde in 1991 where he remained to undertake his Ph.D. studies (1991–1994) under the guidance of Prof. W. J. Kerr. He carried out postdoctoral studies in Boston College, USA (1994–1997) with Prof. Amir Hoveyda before returning to take up a lectureship in 1997 at the University of Sheffield. His recent research interests have focused on developing new strategies towards carbon–carbon bond forming processes for which he was awarded the Pfizer Discovery Academic Award in 2004 and the AstraZeneca Award in 2006.