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Small and Versatile – Formyl Anion and Dianion Equivalents

Andreas Kirschning,*[a] Christof Kujat,[a] Silke Luiken,[a] and Ernst Schaumann[b]

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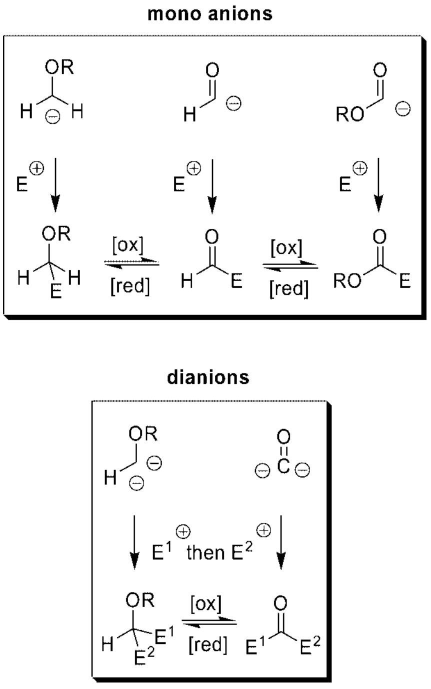
This account provides a short overview of the synthetically important class of formyl anions and the less studied formyl dianion equivalents. A brief literature survey, which particularly focusses on asymmetric homologation strategies, is complemented by a detailed description of lithiated (dimethoxymethyl)diphenylphosphane oxide, which is an ideal formyl anion equivalent in reactions with aldehydes. Under acidic conditions the intermediate ketene O,O-acetals afford homologated carboxylic esters whereas asymmetric dihydroxylation of ketene acetals leads to collapse of the intermediate diols furnishing the corresponding α-hydroxy carboxylic esters with high stereocontrol. Additionally, it is demonstrated that the silyl-substituted carbanion may be looked upon as a latent dianion that can react either with two electrophiles or with bis-electrophiles, the latter transformation yielding ring-closure coproducts. It is advantageous if the electrophiles are epoxides or epoxides carrying a remote leaving group. The carbanion will ring-open the epoxide and allow a C→O silyl shift, thus generating the new carbanion. This then reacts with the second electrophile, either inter- or intramolecularly. The versatility of these two formyl anion equivalents is demonstrated by selected examples from natural product synthesis.

1. Introduction

The nucleophilic formylation of carbon electrophiles (E) such as aldehydes, enones or oxiranes is a principal transformation in organic synthesis (Scheme 1). Formyl anion or dianion formation requires temporary reversal ("Umpolung") of the carbonyl reactivity.[1]

The synthetic importance of formal formyl anion equivalents becomes particularly evident when designing synthetic strategies towards complex natural products. Here, in the past the use of biosynthetic considerations has increasingly guided retrosynthetic planning as can be demonstrated for polyketide-based macrolide or macrolactam antibiotics.[2] Amphotericin B **1** represents an almost "ideal" polyketide except for the hydroxy group at C-8 which disrupts the perfect 1,3-relationship of the oxygen functionalities. Thus, by mimicking nature's concept of mastering synthetic chemistry, a series of aldol-type reactions or analogous transformations such as allylations of aldehydes may be considered in a retrosynthetic analysis. Geldanamycin **2**, which evolves from the same biosynthetic concept except that the aromatic mC_7N moiety serves as a starter unit, shows two irregularities consisting of additional oxygen functionalities (marked as methoxy groups).



Scheme 1. Formal transformations of formyl anion and dianion equivalents with electrophiles (to show the generality of the strategy the possible different oxidation states of the anions are depicted).

Synthetically, this irregular pattern of oxygen distribution can be addressed by α-oxygenated enolates [Equation (1)], by α-oxygenation of a carbonyl precursor [Equation (2)] or by formyl anion addition to aldehydes [Equation (3)], just to name the most important options

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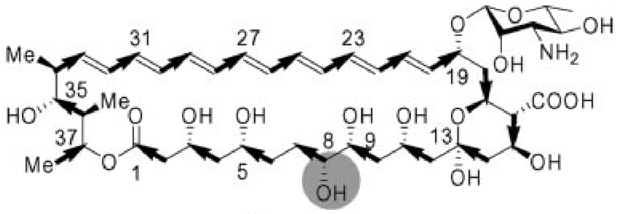
[a] Institut für Organische Chemie, Leibniz Universität Hannover, Schneiderberg 1b, 30167 Hannover, Germany
Fax: +49-511-726-3011
E-mail: andreas.kirschning@oci.uni-hannover.de
[b] Institut für Organische Chemie, Clausthal University of Technology,
Leibnizstraße 6, 38678 Clausthal-Zellerfeld, Germany



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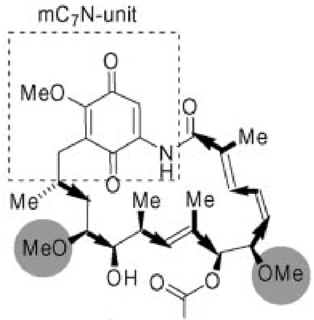

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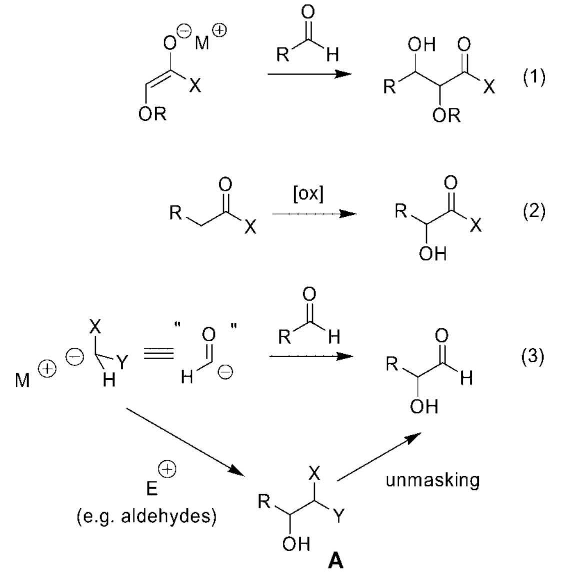
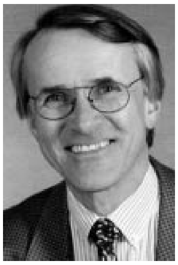


Scheme 2. Concepts for preparing α-oxygenated carbonyl groups.

Andreas Kirschning studied chemistry at the University of Hamburg and Southampton University (UK). In Hamburg, he joined the group of Prof. E. Schaumann and received his Ph. D. in 1989 working in the field of organosilicon chemistry. After a postdoctoral stay at the University of Washington (Seattle, USA) with Prof. H. G. Floss, supported by a Feodor-Lynen scholarship from the Alexander-von-Humboldt foundation, he started his independent research at the Clausthal University of Technology in 1991, where he finished his habilitation in 1996. In 1997 he held a position as guest professor at the Humboldt-University in Berlin and in 1998 and 2003, respectively, was a visiting professor at the universities of Wisconsin in Madison (USA) and Rennes (France). In 2000 he moved to the University of Hannover and became director of the Institute of Organic Chemistry. He is one of the editors of RÖMPP online, Natural Product Reports, and The Beilstein Journal of Organic Chemistry. His research interests cover the total synthesis and mutasynthesis of natural products, glycochemistry, and synthetic technology (solid-phase-assisted synthesis, microreactors).

Christof Kujat was born in Freiburg (Germany) in 1977. He studied chemistry at the Universities of Hannover and Stanford (USA), obtaining his diploma in chemistry in 2003. After an internship at Schering's Research Center Europe in Berlin he started his dissertation in the group of Prof. Kirschning working on the total synthesis of ripostatin A and B.

Silke Luiken was born in Hannover (Germany) in 1978. After having attended a three-year apprenticeship as laboratory assistant at SOLVAY GmbH in Hannover she studied chemistry at the Leibniz University Hannover. She received her diploma in chemistry in 2005 working in the field of polymer-supported cleavage of 1,3-dithianes. Currently she is in the second year of her Ph.D. in organic chemistry under the supervision of Prof. Andreas Kirschning. Her research work is focused on the synthesis of natural-product-based cyclopentanes through silicon-mediated cascade reactions.



Ernst Schaumann was educated at the University of Hamburg where he obtained his Ph. D. with Professor Wolfgang Walter in 1970. He did postdoctoral work with Prof. John E. Baldwin at the University of Oregon (1977). Schaumann did his habilitation at the University of Hamburg in 1976 and stayed there as associate professor from 1977 to 1990. Since then, he has a chair of organic chemistry at Clausthal University of Technology. From 2000 to 2004 he was Rector and President of this university. Schaumann was a visiting professor at the University of Wisconsin, Madison (1980), the University of California, Irvine (1986), and the Australian National University, Canberra (2004). He is a member of the editorial board of Science of Synthesis (formerly Houben-Weyl, Methods of Organic Chemistry) and is member of the Braunschweigische Wissenschaftliche Gesellschaft. His main research interests are the development of heteroatom (sulfur, silicon, phosphorus)-based synthetic methods, small-ring chemistry, and thiocarbonyl compounds.

(Scheme 2).[3] The third concept requires appropriate substitution of the nucleophilic carbanion with two or three heteroatoms which leads to masked formyl anion equivalents. In the presence of electrophiles, these carbanions can be used for the preparation of masked aldehydes, carboxylic acids or esters (structure A, Scheme 2) that subsequently have to be unmasked to yield the desired carbonyl compounds. The heteroatoms of choice are sulfur,[4] tin[5] and to a lesser extent silicon,[6] in some cases in combination with oxygen substituents.[7] Additionally, the carbanion can be stabilised by nitrogen[8] which is often part of a heterocycle.

2. Concepts for Formyl Anions and Dianions – A Short Literature Survey

2.1 Formyl Anion Equivalents

Specific examples of formyl anion equivalents are summarised in Figure 1 and Figure 2. Lithiated dithioacetals such as 1,3-dithiane **3** are still the most widely used formyl anion equivalents[1c,9] and are complemented by lithiated sulfoxide **4**,[10] lithiated or silylated thiazole **5**[11] and benzotriazole **6**.[12] Furthermore, these types of formyl anion equivalents can be made chiral as exemplified for lithiated *N*-Boc-thiazolidine **7**[13] [in the presence of (–)-sparteine], chiral metallated thiazolidine **8a** as well as silylthiazolidine **8b**[14] and lithiated thiomethyloxazolidinone **9**.[15]

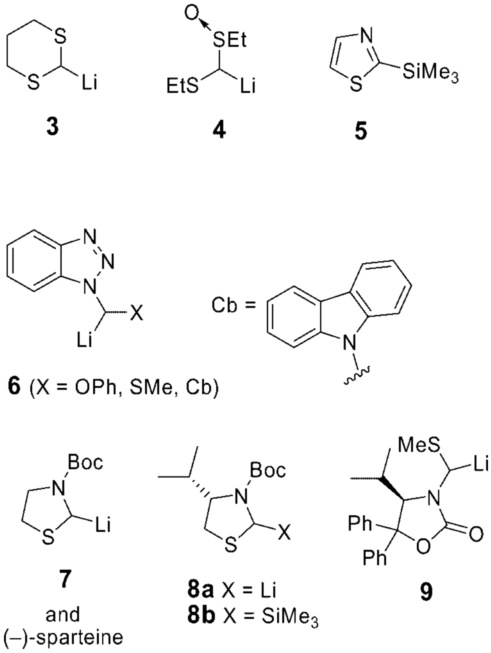


Figure 1. Formyl anion equivalents based on heterosubstituted C1 donors.

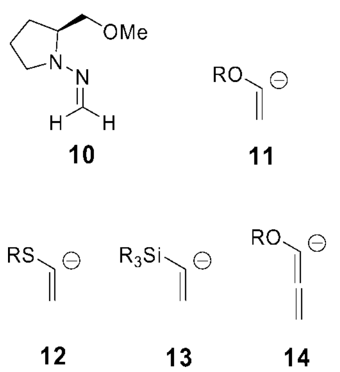
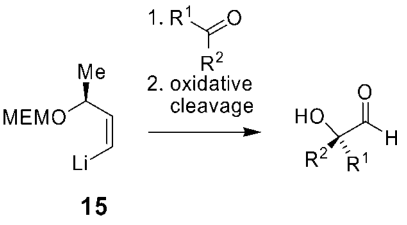


Figure 2. Formyl anion and hydroxycarbonyl anion equivalents based on heterosubstituted alkenes and allenes.

The issue of lithiation is conventionally solved by using existing powerful bases and additives while liberation of the carbonyl group from the primary adducts is still a major challenge for all these methods (soft electrophiles such as mercury salts, iodine reagents or in the case of heterocycles like **5**, multistep sequences).

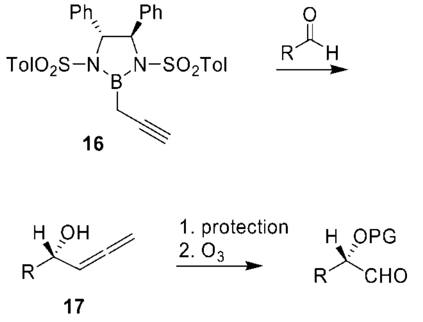
Therefore a second group of formyl and hydroxy carbonyl anion equivalents was developed based on α-lithiated alkoxy-,[16] thio-[17] and silyl-substituted[18] alkenes **11**–**13** as well as alkoxyallenes **14**[19] (Figure 2). Here, after reaction with aldehydes or ketones, oxidative cleavage (e.g., ozonolysis) of the alkene double bond liberates the carbonyl group thereby forming α-hydroxy carbonyl compounds. Compared with substrate-controlled asymmetric formylation reactions chiral formyl anion equivalents have the advantage of providing greater stereochemical flexibility because achiral aldehydes can be used and both stereochemical series in principle become accessible. Typical examples of this strategy are the use of C_2-symmetric *trans*-1,3-dithiane *S*,*S*-dioxides,[20] chiral O,S-acetals[21] and amino cyanides.[22] A neutral chiral formyl anion equivalent is formaldehyde SAMP hydrazone **10**.[23] It can be used as a nucleophile with a variety of electrophiles (e.g., aldehydes, nitroalkenes, α,β-unsaturated ketones and lactones). The aldehyde functionality is liberated after ozonolysis of the C=N double bond.[23]

A chiral version of a lithiated vinyl species was disclosed by Braun and co-workers (Scheme 3)[24] that utilises anion **15** (prepared from MEM-protected lactic acid). The MEM group was chosen because of its chelating properties which helped to achieve high stereoselectivities in reactions with aldehydes or ketones.



Scheme 3. Braun's concept of a chiral formyl anion equivalent based on vinyllithium.

Closely related is Corey and co-worker's approach (Scheme 4).[25] His group utilised a nucleophilic chiral propargyl borane **16** in an addition reaction to aldehydes. After protection and ozonolysis of the resulting 1,2-dienyl carbinols **17**, α-hydroxyaldehydes are generated with up to 99% *ee*. However, all these reagent-based strategies are often hampered by irreversible loss of the chiral auxiliary.



Scheme 4. Corey's formyl anion concept; PG = protecting group.

Several other hydroxycarbonyl anion equivalents are known of which the cyanide anion **18** is the oldest and simplest example (Figure 3).[26] Additionally, metallated tris(methylthio)orthoformate **19**[27] as well as acyl anion cuprate **20**, which can be generated by insertion of CO into copper(I) amides, have served as formyl anion equivalents.[28]

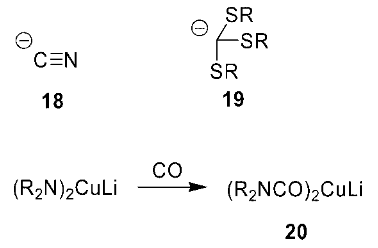
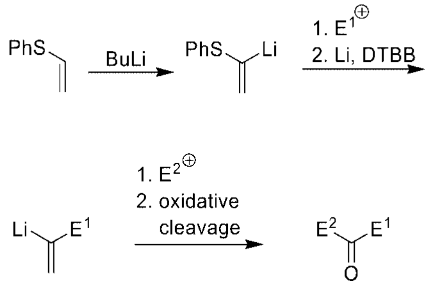


Figure 3. Selected hydroxycarbonyl anion equivalents.

2.2 Formyl Dianion Equivalents

In principle some of the formyl anion equivalents reported above can serve as formal dianion equivalents if the first anion formation can be repeated after being trapped by the first electrophile. This is definitely true for d^1-synthons **3**, **4**, **6** and **8–10** although this option has not been exploited in a broad sense. In this context, vinyl sulfides have also served as dianion equivalents, as depicted in Scheme 5.[29]

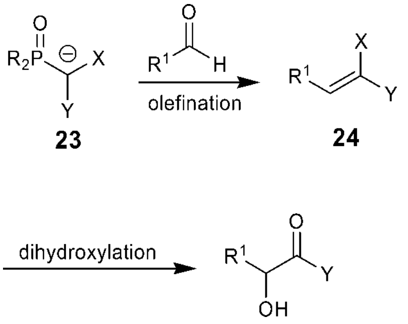


Scheme 5. Vinyl sulfides as dianionic d$_1$ synthons; DTTB = 4,4′-di-*tert*-butylbiphenyl.

In this short account we focus on our methodological studies in this field which are based on phosphorus-stabilised formyl anion equivalents and sulfur/silicon-stabilised C$_1$ anions in the case of dianion equivalents.

3. Asymmetric Formylation of Aldehydes Based on Phosphorus-Substituted C$_1$ Anions

Recently we disclosed a new acylation concept[30] that circumvents most of the drawbacks (stereocontrol, liberation of the carbonyl group) described for the classical approaches via intermediate **A** (Scheme 2). The fundamental difference lies in the fact that homologation and build up of the stereogenic centre at C-2 are separated in time by first creating the homologous alkene **24** which is subsequently oxidised (Scheme 6). This new strategy utilises a phosphane oxide stabilised formyl anion equivalent **23** which, in its reaction with aldehydes, affords a prochiral 1,1-diheterosubstituted alkene **24**. In this respect, the approach can be regarded as a hybrid concept based on two methods, as described in Equations (2) and (3) in Scheme 2.



Scheme 6. Formylation concept via 1,1-disubstituted alkenes.

In fact, several phosphorus-stabilised d^1-synthons are known which may have served as formyl anion equivalents. Phosphite ylides **25** were first introduced for the homologation of aldehydes in olefination reactions but their use is limited to reactive aldehydes.[31] Phosphonate-stabilised carbanions **26** can also serve as d^1-synthons for the formation of ketene S,S- or O,S-acetals.[32] However, they have not been utilised in a formylation strategy yet.[33] Thirdly, metallated phosphane oxides **27**[34] yield ketene O,O-acetals in reactions with aldehydes and this marks the starting point of our formylation strategy (Figure 4).[30]

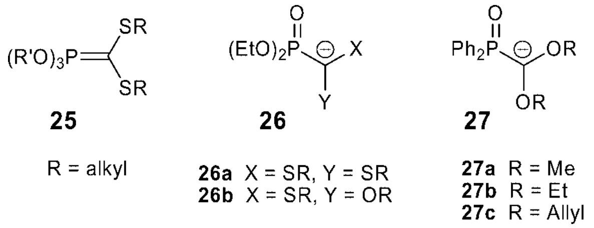
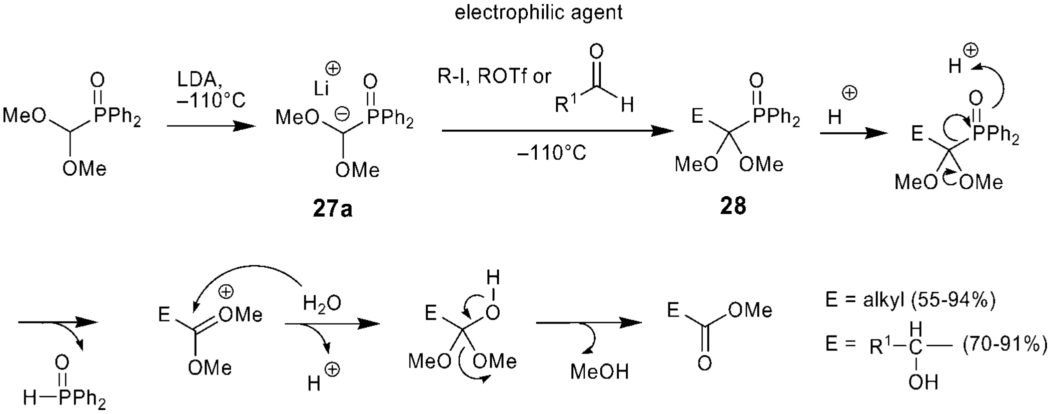


Figure 4. d^1-Synthons based on phosphorus-substituted C$_1$ anions.

Thus, deprotonation of (dimethoxymethyl)diphenylphosphane oxide with LDA at –110 °C yields carbanion **27a**, which reacts with different types of electrophiles (e.g., alde-

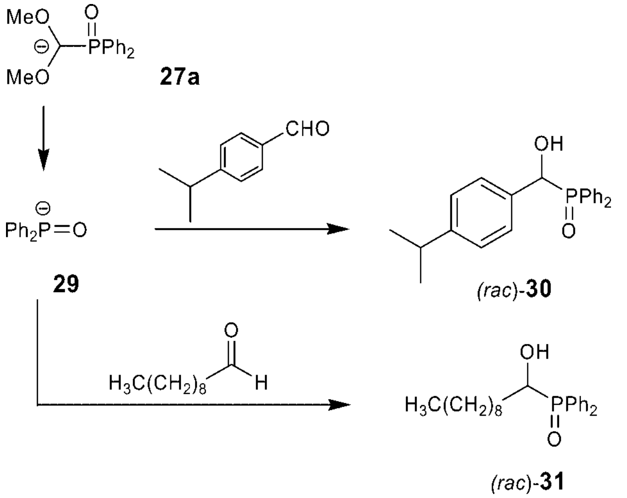


Scheme 7. Reaction of anion **27a** with electrophiles and the proton-induced fragmentation mechanism.

hydes, alkyl halides and activated carboxylic acids). For a formylation method to be useful it is important that the carbonyl group can be liberated easily and in high yield. So we were pleased to note that starting from alkyl halides or triflates as well as aldehydes, adducts **28** are quantitatively hydrolysed in wet dichloromethane under protic conditions. Detailed mechanistic studies allowed us to propose the mechanism summarised in Scheme 7.[35] Alkylation proceeds best with alkyl iodides and triflates, whereas only reactive bromides such as allyl and benzyl bromides give satisfactory results.

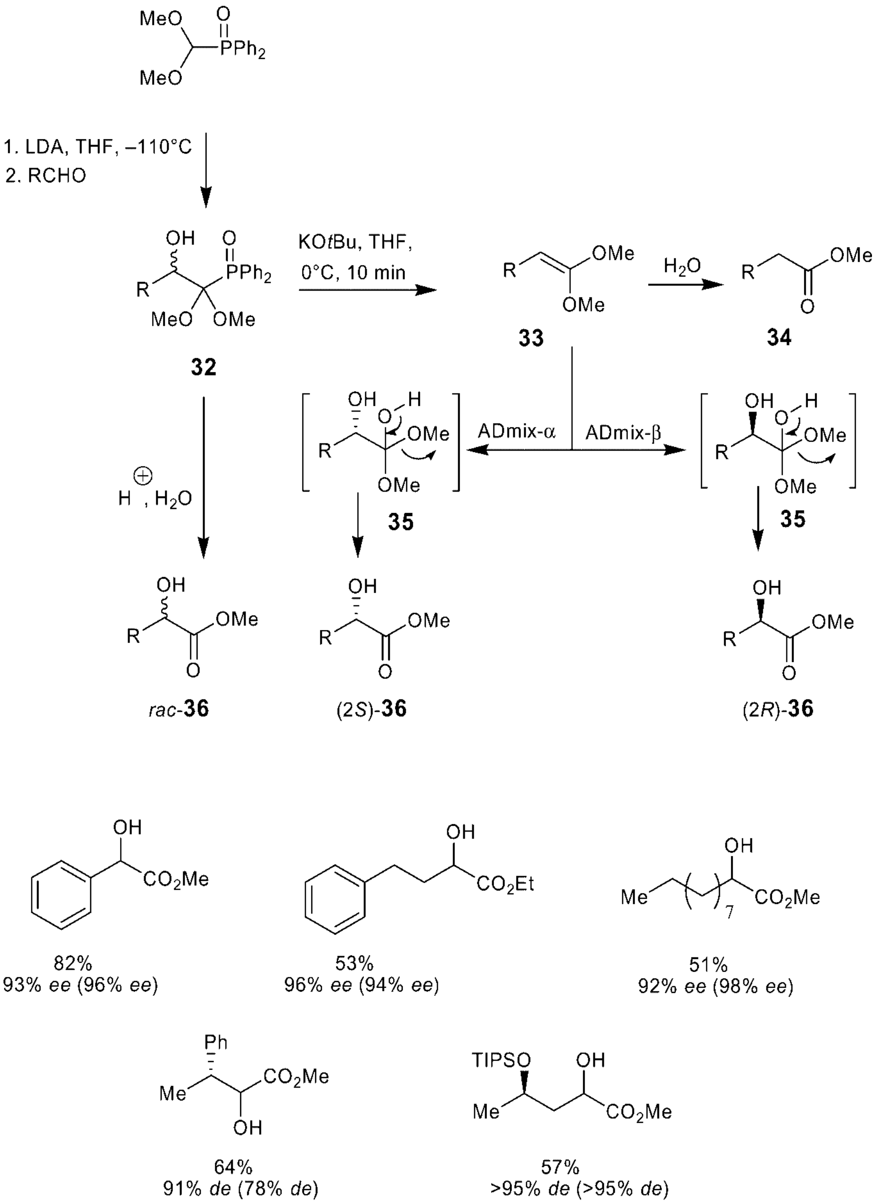
β-Ketophosphanes that are derived from the reaction with acyl chlorides cannot be hydrolysed under these conditions which can be explained by the proton-induced fragmentation mechanism.[35] The reaction of anion **27a** with aldehydes proceeds in better yields. Transmetallation by addition of metal salts such as $ZnBr_2$, $MgBr_2OEt_2$ or $Ti(O\textit{i}Pr)_4$ does not further improve the process, which can be ascribed to the inherent instability of anion **27a**. In fact, if the reaction time exceeds 2 h decomposition of the anion to the phosphane oxide anion **29** occurs. The same degradation product is formed when the temperature is raised above –90 °C as was proven by the isolation of adducts **30** and **31** (Scheme 8).

These results paved the way to the development of an asymmetric variant as the reaction of anion **27** with aldehydes is the first step of the Horner–Wittig olefination process (Scheme 9).[36] Formation of the corresponding ketene O,O-acetals **33** can either be achieved by direct elimination from the metallated primary coupling products at elevated temperatures or in a two-step procedure by employing KO*t*Bu-induced elimination of the intermediate isolated adducts **32**. The latter procedure commonly affords slightly improved yields. Ketene acetal **33** is directly hydrolysed by water to furnish ester **34**. However, in order to afford the α-hydroxylated formylation product derived from the starting aldehyde, the electron-rich olefinic double bond has to be dihydroxylated preferentially under the conditions developed by Sharpless et al.[37] The primary 1,2-diol **35** spontaneously undergoes fragmentation to yield α-hydroxy ester **36** with a controlled absolute configuration.



Scheme 8. Fragmentation of carbanion **27a** and subsequent nucleophilic addition of metallated phosphane oxide anion **29** to aldehydes.

In general, we encountered a better stereoselectivity with dimethoxymethylphosphane oxide **27a** than with diethoxymethylphosphane **27b** which can be ascribed to the smaller size of the methyl group relative to ethyl group. Anion **27** also has a basic character which explains the higher overall yields for non-enolisable aldehydes. The asymmetric Sharpless dihydroxylation (AD) of intermediate ketene O,O-acetals affords α-hydroxy esters in 70–93% yield with good-to-excellent enantiomeric excess. In some cases ketene O,O-acetals derived from aromatic aldehydes tend to be overoxidised to yield the corresponding α-keto esters as byproducts. Chiral aldehydes afford diastereomeric homologation products (*dr* = 3:1 to 8:1). Remarkably, the homologation of α-D-*galacto*-dialdopyranose **37** yields the corresponding heptoses. These naturally rare glycosidic moieties act as biosynthetic intermediates[38] or as components of enterobacterial lipopolysaccharides of Gram-negative bacteria.[39] Treating hexose-derived aldehyde **37** with carbanion **27a** furnished the phosphane adduct as a single isomer.



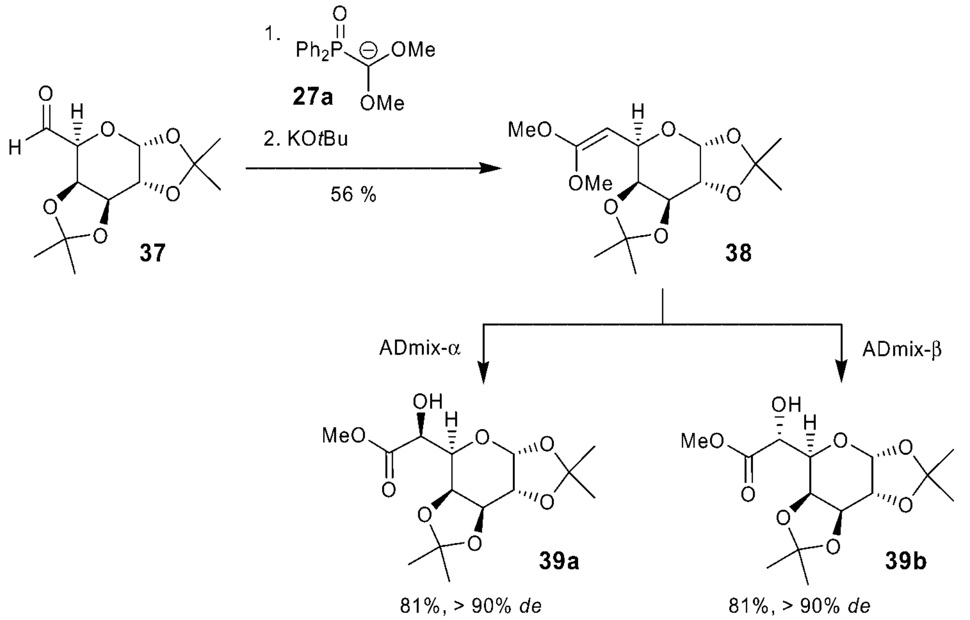
Scheme 9. Formylation procedures for aldehydes with selected formylation examples with ADmix-α and ADmix-β in brackets.

Termination of the sequence via ketene acetal **38** afforded methyl esters **39a** and **39b** in 81% yield with remarkably high diastereofacial selectivity (*de* > 90%) for both series (Scheme 10).

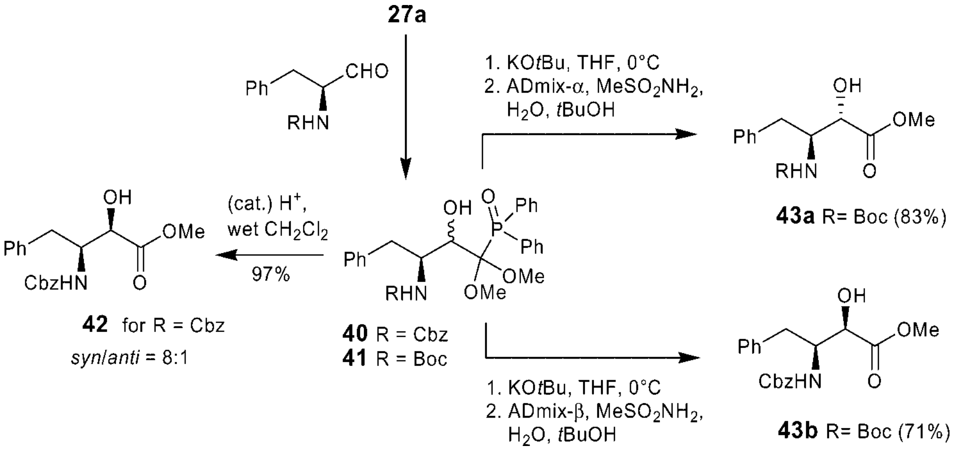
Finally, homologation can be carried out with α-chiral amino aldehydes to yield α-hydroxy-β-amino esters.[40] These β-amino esters, for example, esters **42** and **43**, are important precursors for peptide synthesis with β-amino acids as well as for the synthesis of natural products such as paclitaxel.[41] Importantly, both possible diastereoisomers **43a** and **43b** can be prepared with high selectivity using the appropriate AD mixture (Scheme 11).

Related ketene acetals such as ketene S,S-acetals **45** (prepared from phosphonate anion **44**) are not transformed under Sharpless conditions, whereas ketene O,S-acetals **47** (prepared from silyl-substituted carbanion **46** by means of a Peterson olefination process)[42] afford α-hydroxy esters in low yields (7–37%) and moderate *ee* values (62–80%) under AD conditions irrespective of the alkene configuration (Scheme 12).

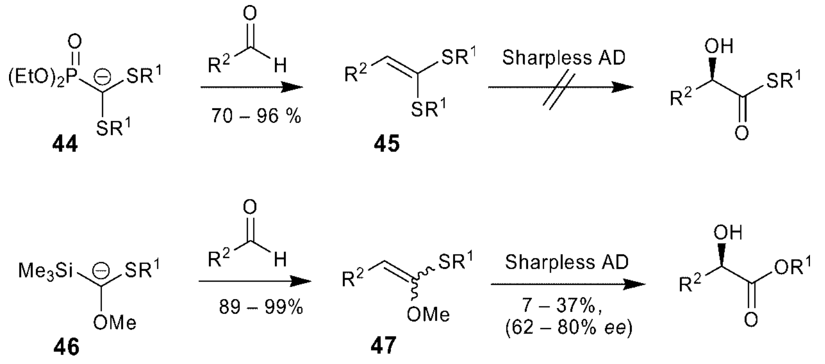
The formylating strategy with phosphane oxide stabilised carbanion **27a** was also applied in a more complex context, namely as part of our synthetic studies of the northern hemisphere **51** of the macrocyclic diterpene tonantzitlolone **52** (Scheme 13).[43] Thus, **27a** was treated with Roche-ester-derived aldehyde **48** which yielded addition product **49** (*syn*/*anti* = 3:1) upon hydrolysis. This mixture of alcohols was subjected to typical elimination conditions and furnished the corresponding labile ketene O,O-acetal which was transformed into α-hydroxy ester **50** after subjection to the Sharpless asymmetric dihydroxylation conditions using AD-mix-α.



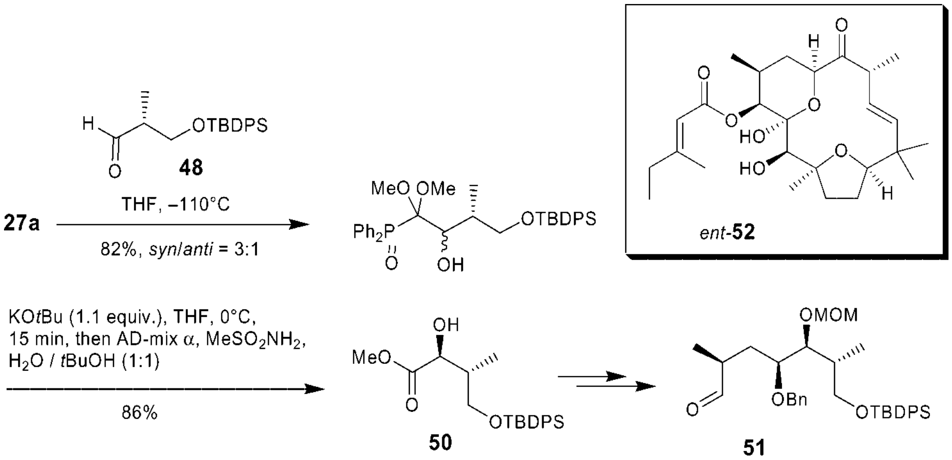
Scheme 10. Homologation of α-D-*galacto*-dialdopyranose **37**.



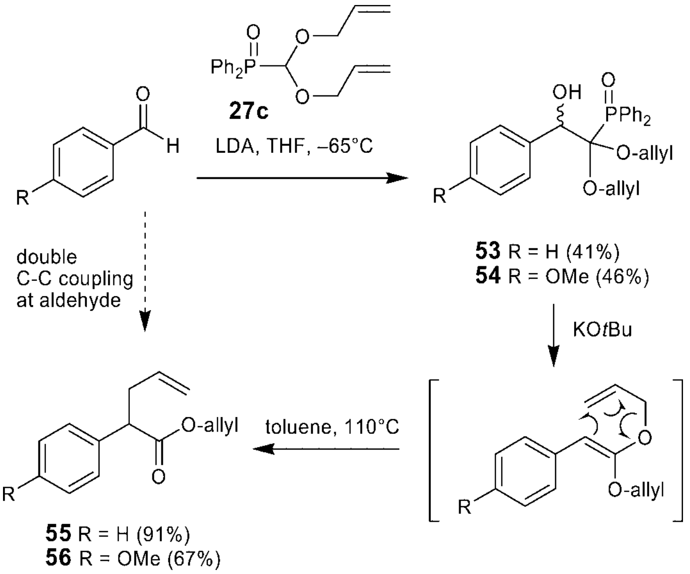
Scheme 11. Formylation of protected α-amino aldehydes.



Scheme 12. Sharpless AD of S,S- and O,S-ketene acetals.



Scheme 13. Synthetic studies toward tonantzitlolone **52**.

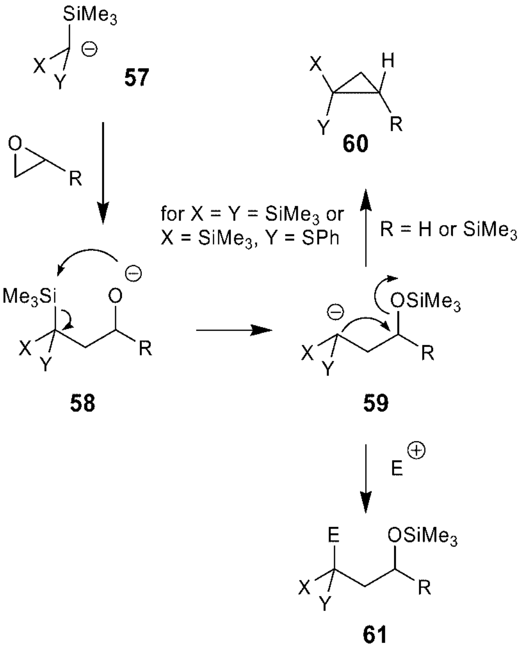


Scheme 14. Horner–Wittig reaction with phosphane oxide **27c** and subsequent Claisen rearrangement.

Finally, ketene O,O-acetals can serve as substrates in Claisen rearrangements. For this purpose phosphane oxide **27c** containing two allyl substituents was subjected to the Horner–Wittig reaction conditions (Scheme 14). It turned out that phosphane oxide **27c** is less reactive so that coupling with aldehydes proceeded only at –65 °C. Owing to the fragmentation process described in Scheme 8, adducts **53** and **54**, respectively, were formed in only moderate yields. After KO*t*Bu-induced elimination, heating of the intermediate ketene O,O-acetals to 110 °C in toluene directly induced the Claisen rearrangement. In this cascade sequence, which involves elimination followed by [3,3] sigmatropic rearrangement, a new C–C bond at C-2 is formed and the carboxylic acid is liberated as the allyl ester. The Claisen products **55** and **56**, respectively, are obtained as racemic mixtures in good yields.[44]

4. Dianion Equivalents Based on Silyl-Substituted Dithioacetals

In the course of synthetic studies dedicated to the homo-Peterson olefination of oxiranes by silicon-stabilised carbanions, Fleming and our group found that anion-stabilising groups X and Y strongly influence the course of this reaction (Scheme 15). The key step in this process is clearly the 1,4 C→O silicon shift which can be looked upon as a homo-Brook rearrangement leading to carbanion formation.[45] If X and Y are silyl substituents (X = Y = $SiMe_3$)[46] or mixed silyl and thio substituents (X = $SiMe_3$, Y = SR),[47] the resulting anion **59** is reactive enough to initiate nucleophilic displacement of the poorly nucleofugic siloxy group leading to homo-Peterson products, namely cyclopropanes **60**. The use of silyloxiranes also favours this cyclisation reaction.[47,48] The driving force for silyl migration is clearly the stronger Si–O bond compared with the corresponding Si–C bond (bond dissociation energies: $Me_3Si–OMe$ 530 kJ/mol, $Me_3Si–CH_3$ 360 kJ/mol).[49] On the other hand, based on the electronegativities and pK_a values, an alkoxide such as **58** should be favoured over a carbanion such as **59**.[45a,45c,50]

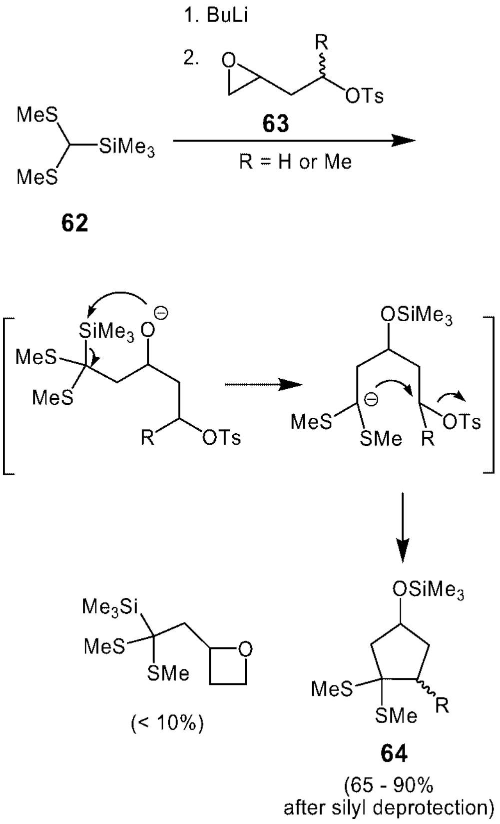


Scheme 15. The formyl dianion concept of Schaumann and Kirschning.

The reluctance of the carbanion **59** to undergo nucleophilic attack on the siloxy group can be exploited by trapping the intermediate carbanion by a second electrophile (E^+) to yield **61**. From a preparative standpoint, the Brook migration has to be quantitative which we found can be encouraged by the addition of 12-crown-4 ether to solvate the lithium used as the cation;[51] HMPA or DMPU[52] have also been suggested as additives.[53]

Considering the overall reaction towards **61**, carbanion **57** reacts as a 1,1-dianion (see Scheme 1) with the second negative charge formed by silyl migration. This concept was first proven for a [4+1] cyclisation approach towards cyclopentanes by employing epoxides that have a suitably positioned nucleofugic group as in epoxy tosylate **63** (Scheme 15).[51] The formal dianion precursor **62** sequentially forms two C–C bonds to yield cyclopentanes (Scheme 16).

Besides the quest for quantitative silyl migration, the domino process strongly relies on the chemoselective attack of deprotonated **62** on the epoxide unit in **63** rather than on the carbon carrying the leaving group.[54] As a side-reaction oxetanes are formed if silyl migration is too slow. They are formed upon direct nucleophilic attack of the intermediate alkoxide anion on the carbon bearing the leaving group. However, this side-reaction is conveniently suppressed with secondary tosylates. Alternatively, other electrophiles such as a second epoxide group or bromide may also serve as leaving groups (vide supra),[55] whereas chloride as leaving group may reduce the efficiency of the ring closure.[56]

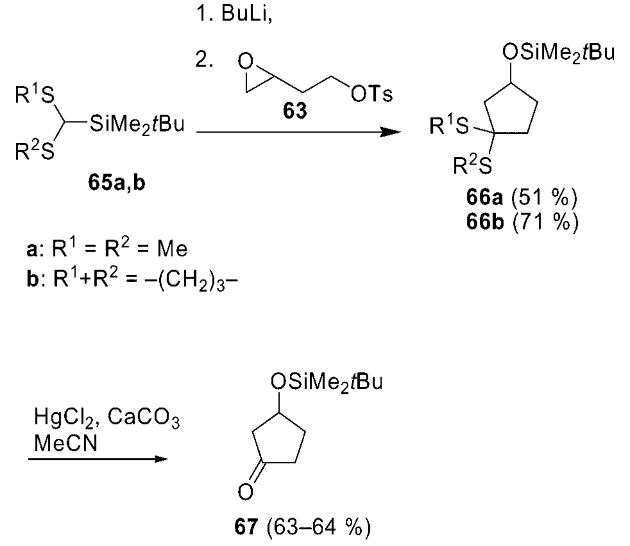


Scheme 16. Formation of a cyclopentane from a silyl-substituted carbanion and an epoxyhomoallyl tosylate.

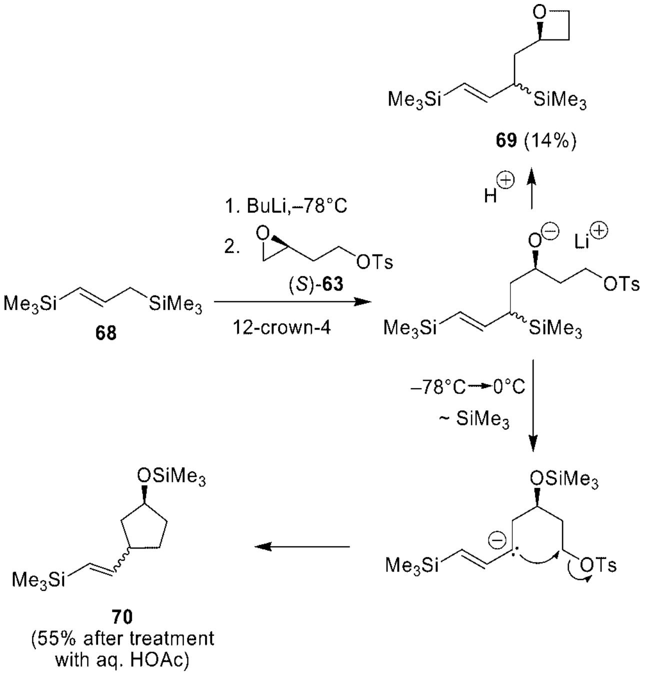
Other possible dianion precursors are the corresponding dithiane, bis(trialkylsilyl)methanes[57] as well as bis(trialkylsilyl)phenylthiomethane. Also α-silylacetonitrile is a suitable d^1-precursor for this [4+1] cyclisation reaction.[58] Detailed studies have allowed the relative migratory ability of the silyl group to be evaluated. It turned out that electronic activation by one phenyl group on the silicon atom favours the rearrangement, whereas the steric hindrance of two phenyl groups reduces the migratory ability. The common trimethylsilyl group exhibits intermediate electronic activation and steric hindrance ($PhMe_2Si > SiMe_3 > SiPh_2Me$).[59]

TBDMS as a migrating silyl group has the advantage that it may serve as a protecting group for the alcohol function when it is planned that the dithioacetal should be cleaved (Scheme 17).

When expanding the scope of this domino process from stabilised carbanions to allylic anion precursors such as **68** the reaction mechanism gets more complex (Scheme 18). Reaction of lithiated **68** with epoxy toluenesulfonate (*S*)-**63** generates the oxirane ring-opened product **70** as a 1:1 diastereomeric mixture in 55% yield after acidic work-up.[51a] Oxetane **69** is also formed because of the reluctance of silyl migration in this case.

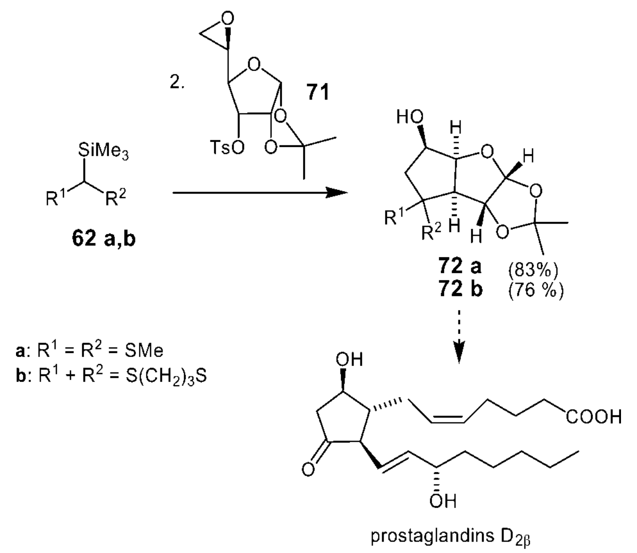


Scheme 17. Formation and modification of TBDMS cyclopentyl ethers.[51b]



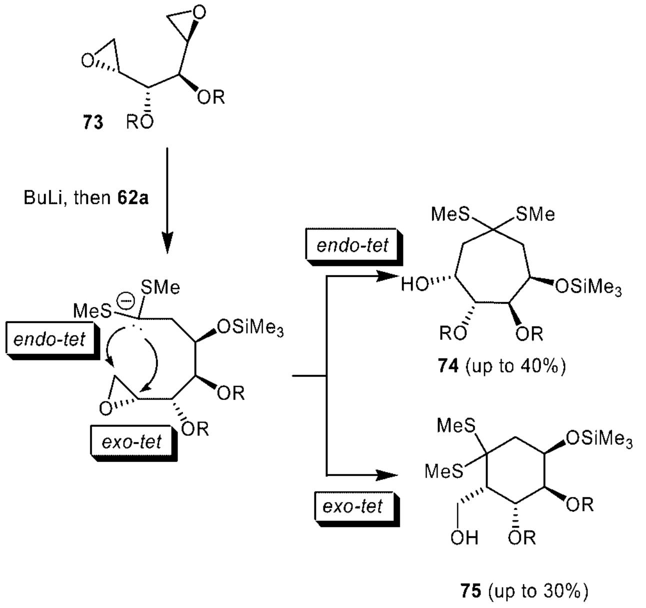
Scheme 18. Cyclopentane ring closure with bis-silylated propene **68**.

An important feature of this domino strategy is the clean transfer of chirality into the cyclopentane unit when using optically active epoxy homoallyl derivatives.[51b] Thus, when an epoxy homoallyl tosylate unit is incorporated into carbohydrate **71**, which is readily obtained from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose, the remarkable domino process leads to a cyclopentane that is annulated to the carbohydrate-derived furanose.[60] Note that the clean S_Ni reaction step is remarkable because nucleophilic substitution reactions on carbohydrate-based furans or pyrans are in general difficult to achieve not only due to the ring strain in the S_N2-type transition state but also because of the abundance of several non-bonded electron pairs that impede the carbanion's approach to the electrophilic centre.[61] Product **72** is a promising precursor of prostaglandin $D_{2\beta}$ with the correct configuration at C-9 and C-12 (referring to the prostaglandin nomenclature). An olefination reaction at the anomeric centre should install the ω side-chain, whereas the α chain can be introduced by an S_N2 reaction. In essence, this synthetic approach introduces in a single domino process all the stereochemical information required for prostaglandin synthesis (Scheme 19).



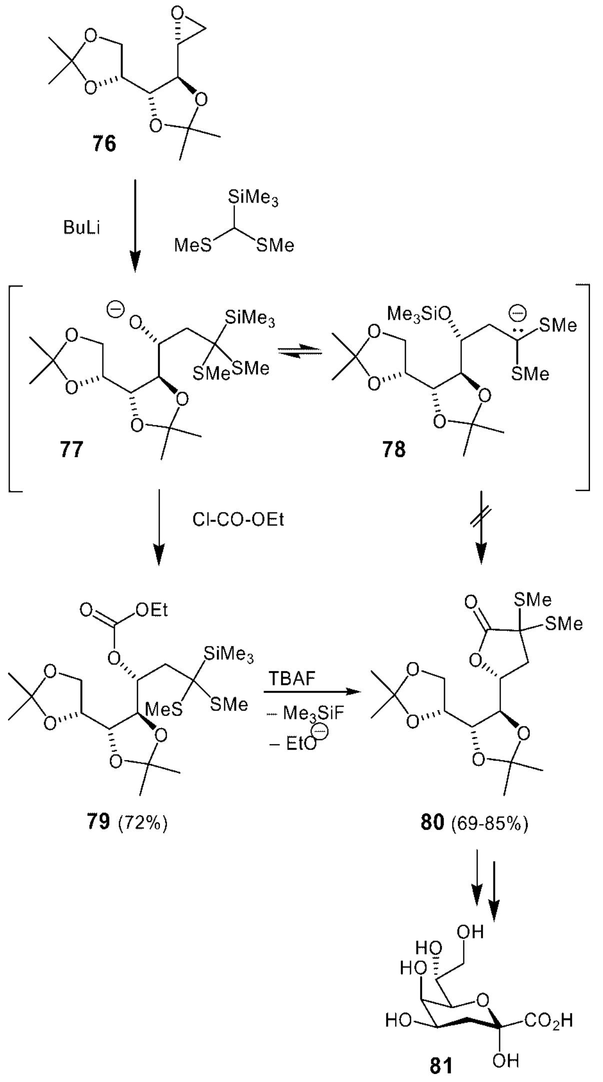
Scheme 19. A new synthetic strategy towards prostaglandins $D_{2\beta}$.

Carbohydrate-based C_2-symmetrical bis-epoxide **73** is a versatile bis-electrophile that yields cycloheptane **74** or cyclohexane **75**, respectively, when treated with dianion equivalent **62a** (Scheme 20). In the final ring closure competition



Scheme 20. Domino reaction towards cycloheptane **74** and cyclohexane **75**.

between a 7-*endo*-*tet* and a 6-*exo*-*tet* process is observed[62] which in part is governed by the choice of protecting group R and by the reaction temperature.[63]



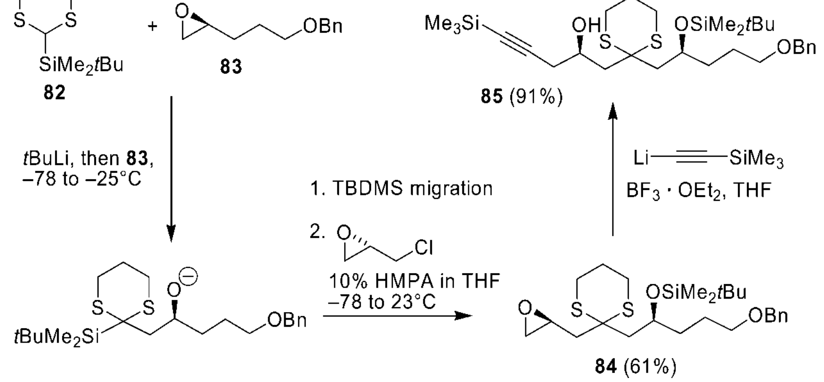
Scheme 21. Total synthesis of KDO **81**.

This domino reaction may also be carried out in an intermolecular fashion by using two different electrophiles. We tested this idea in the synthesis of 3-deoxy-D-*manno*-octulosonic acid (KDO) **81** in which D-mannitol-derived oxirane **76** and ethyl chlorocarbonate serve as electrophiles (Scheme 21).[64] Quenching of the reaction showed that a 1:1 equilibrium between epoxide ring-opened product **77** and the Brook-rearranged product **78** exists. However, the latter carbanion is not removed from the equilibrium by the second electrophile; alkoxide **77** gives only carbonate **79**. Protected KDO lactone **80** can be formed by fluorine-induced desilylation of **79** even though **80** cannot be produced directly from carbanion **78**.

Adopting our strategy and the Tietze modification, which is based on double alkylation using two epoxides,[65] Smith III and co-workers developed creative applications for these kind of dianion equivalents in natural product synthesis, particularly in constructing the polyketide chains found in mycoticin A and B subtargets,[66] in spongistatin precursors[67–70] as well as (–)-indolizidine 223AB.[71,72] Epoxides and a different second electrophile (epoxide, aziridine, alkyl bromide, aldehyde) served as electrophiles in these domino reactions, occasionally termed “linchpin coupling”.[73,74] Recently, Maier and co-workers adopted this approach to a four-component coupling with dianion equivalent **82**, as depicted in Scheme 22. Reaction with epoxide **83** followed by HMPA-supported silyl migration and alkylation with optically active (*S*)-epichlorohydrin provided epoxide **84** which could be used to add lithiated silylacetylene as the fourth component. This domino reaction provided **85**[75] which served as an advanced intermediate in the synthesis of the benzolactone apicularen A.[76]

5. Conclusions

Formyl anion and hydroxy carbonyl anion equivalents are important d^1-synthons in organic synthesis with applications in natural product chemistry. In transformations with aldehydes, α-hydroxy aldehydes or esters, respectively, are formed. For asymmetric strategies it is very advan-



Scheme 22. Maier’s four-component coupling based on TBDMS migration.

tageous to separate C–C bond formation from the creation of the stereogenic centre in time so that achiral aldehydes can be employed (reagent control). Excellent flexibility provides protocols that first generate appropriately functionalised alkenes in the homologation step that then can be converted into the target α-hydroxy aldehydes or esters. This strategy is exemplified for lithiated (dimethoxymethyl)diphenylphosphane oxide as a d^1-synthon. When carbon-bound silyl groups are present the formyl anion equivalent can become a dianion equivalent because a second carbanion can be liberated by silyl migration. Our contributions have paved the way for such domino processes to be regarded in a more general context, which, when two independent electrophiles are employed, are occasionally termed "linchpin coupling" reactions. This most recent example of silyl migration reaction is referred to as "anion relay chemistry".[77] It can certainly be stated that this field is far from being exhausted. In particular, catalytic reactions with acyl anion equivalents have recently seen a dramatic increase in interest. They undoubtedly will soon provide asymmetric processes for formyl anion and hydroxy carbonyl anion equivalents and thus will dramatically improve this synthetic transformation.[78]

Acknowledgments

This account is based on the work of many highly motivated and hard-working collaborators whose names can be found in the references. Support of our work by the Deutsche Forschungsgemeinschaft (DFG) (SCHA 231/9 and 231/11) and by the Fonds der Chemischen Industrie is gratefully acknowledged.

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