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Synthetic Studies with Carbohydrate-Derived Chiral Auxiliaries

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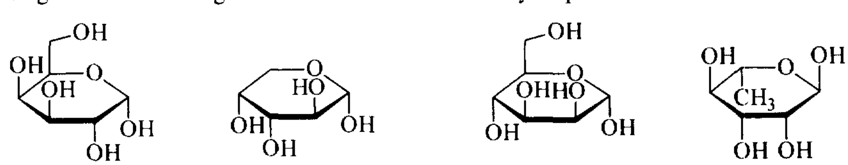
INTRODUCTION

The use of stoichiometric chiral auxiliaries is, for many chemists, the most flexible and predictable method by which stereocontrol can be imposed on chemical transformations, particularly in the formation of new carbon–carbon bonds. This remains the case, notwithstanding the tremendously exciting advances that have been made in asymmetric catalysis using transition metals[1a] or enzymes.[1b] Indeed, the study of chiral auxiliaries can also aid in the development of effective chiral ligands for catalytic systems. There is considerable current interest in auxiliary-based synthetic methods. A recent book[2] provides excellent general coverage of both auxiliary- and catalyst-based methods for asymmetric organic synthesis, while a review has discussed the current state of chiral auxiliaries derived from vicinal amino alcohols.[3] Carbohydrates are another readily available source of chiral non-racemic materials from which successful auxiliaries have been made. Surprisingly, despite the low cost and ready availability of many monosaccharides, carbohydrate chiral auxiliaries have sometimes been given rather short shrift.[2] Nevertheless, since major reviews of carbohydrate-derived auxiliaries appeared in 1993,[4] many reports of further developments in this field have appeared. An overview of the contributions of H. Kunz and his co-workers was published in 1995.[5] The present review updates and expands on the coverage provided by these earlier surveys.

We will focus on chemistry in which the carbohydrate was used as a chiral directing group, covalently bound to a major structural component in a chemical transformation, but intended to be removed at a later point in the synthesis. Our discussion will not address the enormous literature in which carbohydrate starting materials have been elaborated and incorporated into the structures of complex target molecules ("ex-chiral-pool" approaches). The reader interested in such sugar "building blocks" is referred to the very useful book by Bols.[6] This book also contains much that will interest chemists seeking new carbohydrate chiral auxiliary structures. We also omit carbohydrate-based ligands for chiral reagents and catalysts from our survey, although admittedly the distinction between chiral auxiliary and chiral reagent approaches to synthesis may occasionally be ambiguous.

Important Aspects of Monosaccharide Structure

In the past some chemists have wrongly concluded that, because monosaccharides exist in nature preponderantly in one enantiomeric form (usually the D-series), methods based on sugar auxiliaries cannot be used to stereoselectively synthesize both enantiomers of a desired product. Certainly the uncommon enantiomers of many common sugars are quite expensive, but both enantiomers of some monosaccharides (for example, arabinose) and monosaccharide derivatives (such as gulonic γ-lactone) are available at reasonable cost from commercial sources. Certain pairs of common sugars can serve as "pseudo-enantiomers" of one another as well, notably D-galactose and D-arabinose,[7] or D-mannose and L-rhamnose[8] (Figure 1). Methods developed using one of these sugars have often been efficiently implemented with the other to obtain the



α-D-galactopyranose α-D-arabinopyranose α-D-mannopyranose α-L-rhamnopyranose

Figure 1

opposite product stereochemistry. In addition, the chemist's own ingenuity can devise ways to reverse the selectivity imposed by a single chiral auxiliary, and several examples of this are noted in this review.

The structure of the typical pyranose or furanose offers several features that can be used to impose stereocontrol on the reactions of an attached group. The differing configurations of the monosaccharides provide various template geometries, and well-documented manipulations are available to produce further variations on these basic themes (e.g. Figure 2).[6,9] The hydroxyl groups around the sugar ring offer a diverse choice of environments in which a reacting group can be attached. They can serve as attachment points for bulky groups to block regions of space around the reactive centre. Appropriately positioned aromatic groups on the sugar auxiliary may also influence the stereochemical outcome of a reaction through π-stacking. The ring oxygen atoms can also coordinate metal ions, a trait that can be either a benefit or a drawback. In many instances, appropriate coordination between a reagent and the chiral template organizes the transition state for a reaction, and can dramatically enhance its selectivity. On the other hand, Kunz found that in certain cases, cation complexation can stabilize a developing negative charge on the sugar group, and thus promote elimination of the auxiliary from an attached enolate, as shown below in Scheme 1.[10]

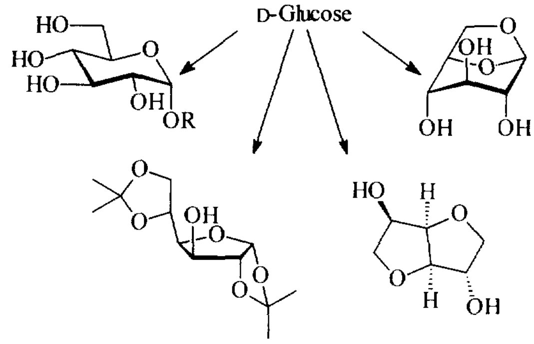
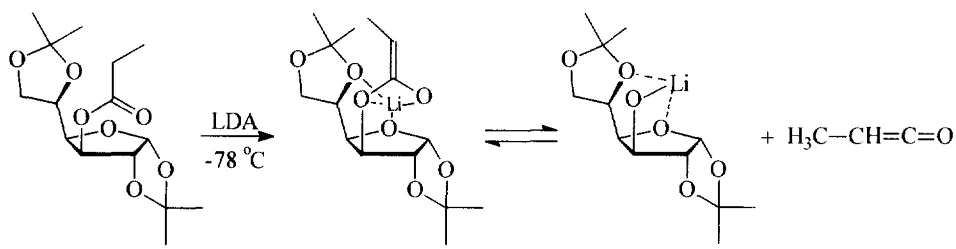
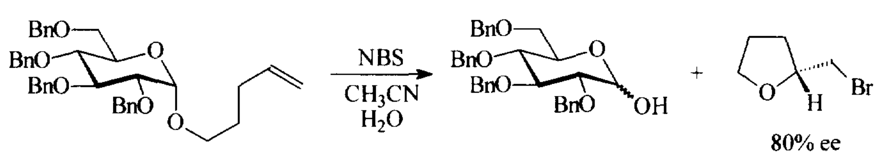


Figure 2



Scheme 1

The conformational behavior of a pyranose ring is a function of the interplay between the sterically imposed equatorial preferences of the ring substituents and the stereoelectronic influence of the anomeric effect,[11] but the dominant conformer is frequently unambiguous. While furanose conformations are more complex, the flexibility of the ring is restricted in the corresponding bicyclic acetal or ketal derivatives, and indeed most furanose auxiliaries are of this type. Simple derivatives of monosaccharides thus provide a fairly rigid template on which stereoselective reactions may take place. The *exo*-anomeric effect is an important determinant of the conformation of the aglycon in a glycoside. This stereoelectronic effect imposes a



1

Scheme 2

preference for a *gauche* relationship between the O-5–C-1 bond and the O-1–aglycon bond. Fraser-Reid's observation that NBS-promoted hydrolysis of *n*-pentenyl α-glucosides (e.g. **1**) was remarkably enantioselective[12] illustrates the potential importance of this effect in stereoselective processes, even involving flexible appendages on the sugar ring. The *exo*-anomeric effect has been invoked to explain the stereoselectivity observed in several of the studies that will be discussed in this review.

The monosaccharide ring offers an additional practical advantage for use in a chiral auxiliary. In protected sugar derivatives, the NMR signals of many of the ring protons are readily distinguished. The vicinal coupling constants and intra-ring nOes observable among these signals are sensitive to conformational changes in the auxiliary that may be induced by an attached moiety. With the conformation of the ring well established, its protons can usually be used as fixed points in nOe experiments, to assist in determining the stereochemical outcome of a synthetic transformation performed on a pendant group. The growing interest in carbohydrate structure driven by advances in glycobiology has also provided computational tools optimized for sugars,[13] that can aid the synthetic chemist in the conformational analysis of monosaccharide chiral auxiliary systems.

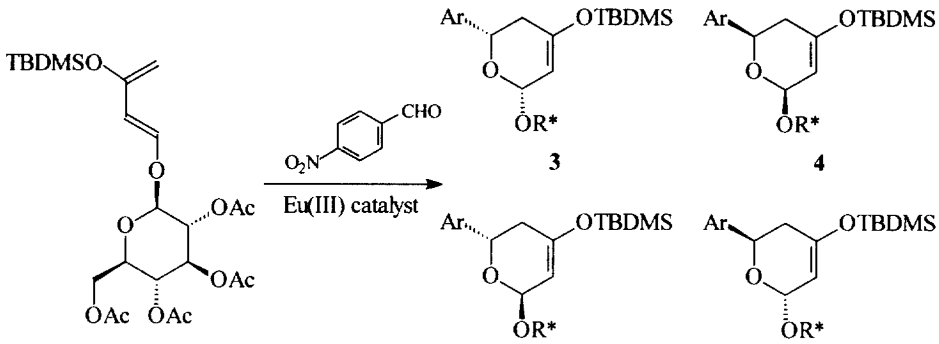
ASYMMETRIC CYCLOADDITION REACTIONS

Cycloadditions have been among the most popular and successful synthetic applications of carbohydrate auxiliaries. In fact, the use of sugar auxiliaries is one of the most effective ways of producing many types of stereochemically pure cycloadducts. The topic was the subject of an ACS Symposium volume[14] in which several of the authors whose work is reviewed here have described their earlier results.

[4+2] Cycloadditions

Sugar-Linked Dienes. The hydrophilic nature of unprotected monosaccharides makes carbohydrate auxiliaries attractive for synthetic reactions conducted in aqueous solvents. Apart from the environmental benefits of using water as a solvent, many reactions proceed much faster in water than in organic solvents.[15] Lubineau has studied the influence of a sugar auxiliary on the kinetics of Diels–Alder reactions of butadienyl glycosides in water.[16] Despite their kinetic advantages, the diastereoselectivity of these aqueous cycloadditions is not particularly high. This selectivity has been modestly enhanced by performing the reaction on a solid chiral matrix rather than in solution.[17] The reaction of β-D-glucopyranosyloxy-1,3-butadiene and methyl vinyl ketone in water gave only 20% diastereomeric excess (de), but when the materials were deposited on a solid sucrose matrix, the *endo* cycloadduct was obtained with 76% de.

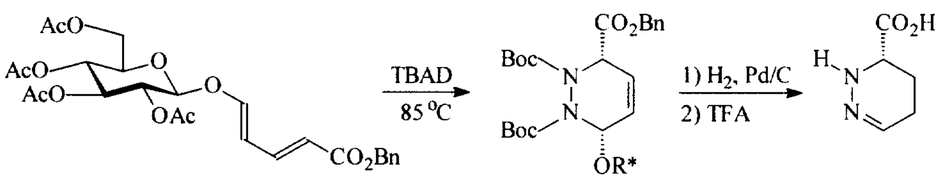
More conventional Diels–Alder reactions of butadienyl glucosides have been intensively examined by Stoodley and co-workers, resulting in a predictive model for the stereochemistry of these reactions, based on *exo*-anomeric considerations.[18] Recently, they have examined hetero-Diels–Alder reactions of sugar dienes. The glucosyl analogue **2** of Danishefsky's diene (Scheme 3) underwent a stereoselective [4+2] reaction with *p*-nitrobenzaldehyde in the presence of Eu(III) catalysts to give dihydropyrans **3–6**.[19] When chiral catalysts were used in a double stereodifferentiating approach[20] to this process, the reaction showed a matched/mismatched pairing: (+)-Eu(hfc)$_3$ afforded a 1.2:1 ratio of **3** and **4**, while (–)-Eu(hfc)$_3$ gave an 8:1:1 mixture of **3**, **4** and **5**, from which **3** was isolated in 39% yield. On the other hand, the achiral catalyst Eu(fod)$_3$ provided mostly compound **5** when the reaction was conducted in CH_2Cl_2. In this case, the product mixture was found to be both solvent- and time-dependent. Stoodley concluded that the cycloaddition gave a kinetically controlled 9:1 mixture of **3** and **4** in all solvents studied. Subsequent epimerization promoted by the Eu(III) catalyst led to varying amounts of the more-stable **5** and **6**, depending on the solvent used and the reaction time. The best result was obtained when the reaction was conducted in CCl_4, affording a 17.4:1:1.6:~0 mixture of **3–6**. These cycloadducts provide an entry point into the synthesis of novel (1→1)-disaccharides, and they can also be converted into chiral β-hydroxy acids.



2 3 4 5 6

Scheme 3

The butadienyl β-D-glucoside **7** was the key to an efficient route to the dehydropiperazic acid **9**, a constituent of the anti-tubercular antrimycin peptides.[21] Thermal cycloaddition of **7** with di-(*t*-butyl)azodicarboxylate gave **8** (76%) as a single diastereomer. Further processing released enantiomerically pure amino acid **9** in 58% overall yield from **7**; the glucose auxiliary was recovered for re-use with its protecting groups intact.



7 8 9

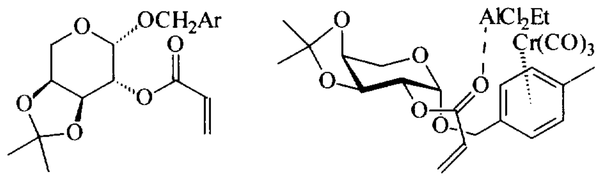
76% 76%

Scheme 4

The highly selective cycloaddition of an acyclic azodienophile to **7** was remarkable, because [4+2] additions of alkenes to **7** afforded only about 5.7:1 selectivity. Further study of this reaction[22] showed that a variety of cyclic azo compounds reacted with **7** to give only single cycloadducts, while their alkene analogues led to diastereomeric mixtures. In all cases, Stoodley's *exo*-anomeric model correctly predicted the major stereoisomer. He attributed the higher selectivity of the azodienophiles to the effect of the short C-N bond length. This would be expected to emphasize steric congestion in the transition state for the hetero-cycloaddition relative to the olefinic process, leading to greater diastereoselectivity.

Sugar-Linked Dienophiles. Metal coordination has played a key role in determining the facial selectivity of sugar-linked dienophiles. An η^6-chromium complex with the aromatic aglycon of 2-*O*-acryloyl-α-L-arabinoside **10** resulted in significant enhancements in the *si* face selectivities of its Diels–Alder reactions with a range of dienes, as compared with the uncomplexed dienophile.[23] For example, the $EtAlCl_2$-promoted reaction of **10** with isoprene afforded a 3.5:1 product mixture (60%), while the chromium complex gave 19:1

selectivity and 77% yield. The authors attributed this purely to increased rigidity from steric crowding in the activated complex **11**, since the NMR resonances of the vinylic hydrogens did not suggest that there was any electronic interaction between the complexed arene and the dienophile.

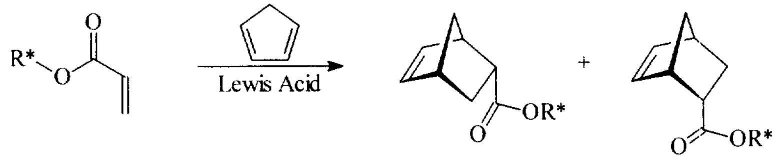


10 **11**

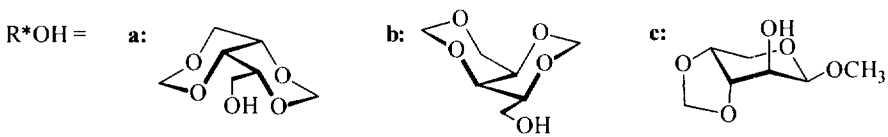
Figure 3

Bicyclic 1,3:2,4-di-*O*-methylene acetals of xylitol (**15**) and arabitol (**16**) are chiral *cis*-decalin-like systems having pendant hydroxymethyl groups to which reactive ligands can be attached (Figure 4). Both D- and L-arabitol are readily available. Xylitol is a *meso* compound, but its 1,3:2,4 diacetal **15** is chiral and is easily made from D-sorbitol. Acrylate esters derived from these acetals reacted highly stereoselectively with cyclopentadiene in the presence of $EtAlCl_2$.[24] For example, the D-arabitol-derived **12b** gave the (*R*)-adduct **13b** in 99% yield. The authors suggested that this high selectivity was due to an aluminum chelate involving one dioxane ring oxygen and the carbonyl. This would result in a conformation of **12b** in which the alkene's *re* face was relatively inaccessible to the dienophile. The importance of chelation was indicated by the fact that uncatalyzed cycloadditions were much less selective.

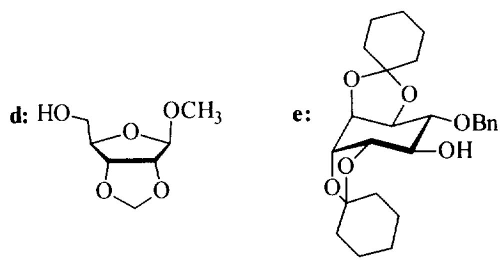
Methyl 3,4-*O*-methylene-β-D-arabinopyranoside (**17**) and methyl 2,3-*O*-methylene-β-D-ribofuranoside (**18**) can also act as chiral auxiliaries in Lewis acid-promoted Diels–Alder reactions (Figure 4).[25] In the



12a-e **13a-e** **14a-e**



15 **16** **17**



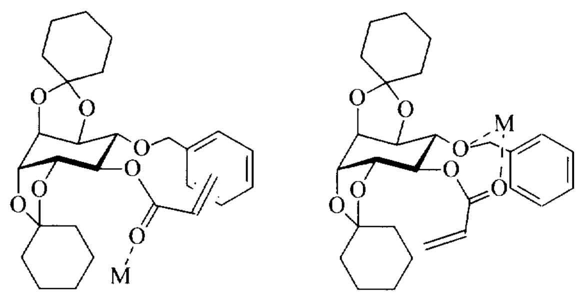
18 **19**

Figure 4

presence of $TiCl_4$ the acrylate **12c** gave the (*S*)-*endo* cycloadduct **14c** in 82% yield and >99% de, while the ribose-derived acrylate **12d** afforded **14d** in no more than 24% de. As with the xylitol and arabitol acetals, the selectivity of these reactions arose from chelation of the metal with the carbonyl group and an oxygen in the sugar auxiliary. The D-*arabino* system **12c** formed titanium chelates that exposed the *re* face of the dienophile to the diene. A bidentate chelate of **12c** with $EtAlCl_2$ is not possible, presumably due to the shorter Al-O bond length, and this catalyst gave poor selectivity. The D-*ribo* acrylate **12d** cannot form a bidentate titanium chelate due to geometric constraints, and its reaction with cyclopentadiene was thus also relatively unselective.

The stability of carbohydrate methylene acetals such as **15**–**18** towards Lewis acids is noteworthy. Nouguier et al. have recently published an improved synthesis of this type of compound, suitable for large-scale work.[26] No doubt improved access to these robust carbohydrate derivatives will lead to many new uses for them as chiral auxiliaries in metal-promoted processes.

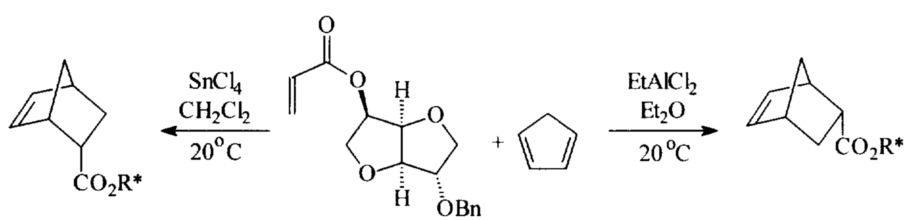
The diastereoselectivity of Lewis acid-catalyzed Diels–Alder reactions of *chiro*-inositol-derived acrylate **12e** (Figure 4) was reversed by appropriate choice of the solvent.[27] The major cyclopentadiene cycloadduct was (*S*)-*endo* **14e** (90%; *endo*:*exo* = 15.7:1, (*S*):(*R*) = >99:<1) when the reaction was carried out using $TiCl_4$ in ether at −78 °C. However, when the solvent was toluene, (*R*)-*endo* **13e** became the major product, and the best result was obtained with $SnCl_4$ at -78 °C (97%; *endo*:*exo* = 98:2, (*S*):(*R*) = 1:7.3). No solvent-induced reversal was observed when $AlCl_3$ was used. The authors argued that monodentate complex **20** (Figure 5) formed when Ti(IV) or Sn(IV) acids interacted with **12e** in coordinating solvents such as ether, but that the bidentate complex **21** was favored by these chelating Lewis acids in non-coordinating solvents like toluene. $AlCl_3$ formed complex **20** with the acrylate in all solvents.



20 **21**

Figure 5

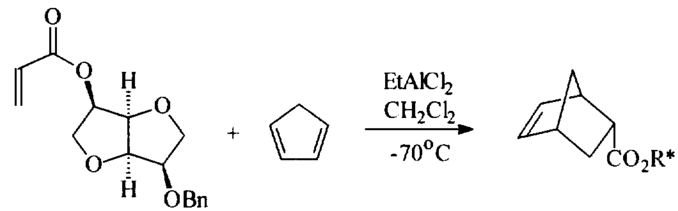
The nature of the Lewis acid catalyst employed in the Diels–Alder reactions of the isosorbide acrylate **23** with cyclopentadiene (Scheme 5) induced a striking reversal in the stereoselectivity of the cycloaddition.[28] In the presence of chelating acids such as $TiCl_4$ or $SnCl_4$, the (*S*)-*endo* product **22** was favored, while monodentate acids like $EtAlCl_2$ or $BF_3{\cdot}OEt_2$ afforded primarily the (*R*)-*endo* cycloadduct **24**. The authors of this study did not provide any detailed rationale to explain how the Lewis acids effected this reversal, although



22 77%; 24:1 **23** **24** 60%; 6.7:1

Scheme 5

one might suppose that arguments similar to those put forth to rationalize the chemistry of Figure 4 would be applicable here as well. The (*R*) selectivity obtained with **23** never exceeded 6.7:1, but when the isomannide acrylate **25** was treated with cyclopentadiene in the presence of $EtAlCl_2$ (Scheme 6), the (*R*)-*endo* adduct **26**



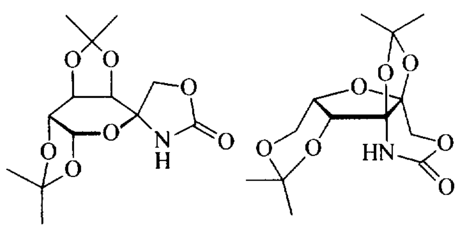
25 **26**

79%; 19:1

Scheme 6

was obtained in 79% yield, and with 19:1 selectivity. The authors suggested that this improvement in selectivity might be a consequence of a π-stacking interaction between the acrylate and the benzyl ether protecting group in **25**, since in this molecule, both groups are constrained to lie in close proximity on the *endo* face of the auxiliary.

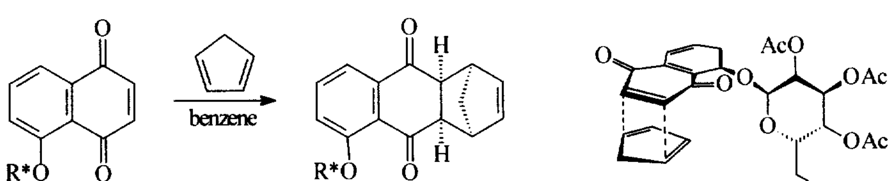
M.R. Banks et al. have developed the versatile carbohydrate oxazolidinone **27** and oxazinone **28** (from D-galactose and 2-keto-L-gulonic acid respectively) using an interesting nitrene insertion reaction. These auxiliaries have been employed in a variety of reactions.[29] The Et_2AlCl-catalyzed [4+2] reactions of their acryloyl and crotonyl imide derivatives with cyclopentadiene proceeded with excellent *endo*:*exo* selectivity, and better than 9:1 diastereoselectivity. The authors noted that **27** and **28** and their derivatives were highly crystalline, and also that their stereoisomeric products were very easily separated by chromatography. Removal of the cycloadduct from the auxiliary was achieved by the standard methods developed for other oxazolidinone chiral auxiliaries. Unfortunately, the spirooxazolidinone **27** was epimerized at the spiro centre by treatment of its imides with nucleophilic cleavage agents, preventing its efficient re-use.[29c]



27 **28**

Figure 6

Glucosyl juglone derivative **29** provided high yields of stereoisomerically pure cycloadducts (e.g. **30**; Scheme 7) from its Diels–Alder reactions with several dienes, despite the distance separating the chiral



29 **30** **31**

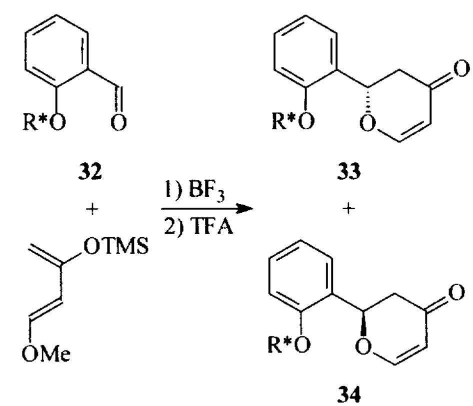
83%

R*OH = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose

Scheme 7

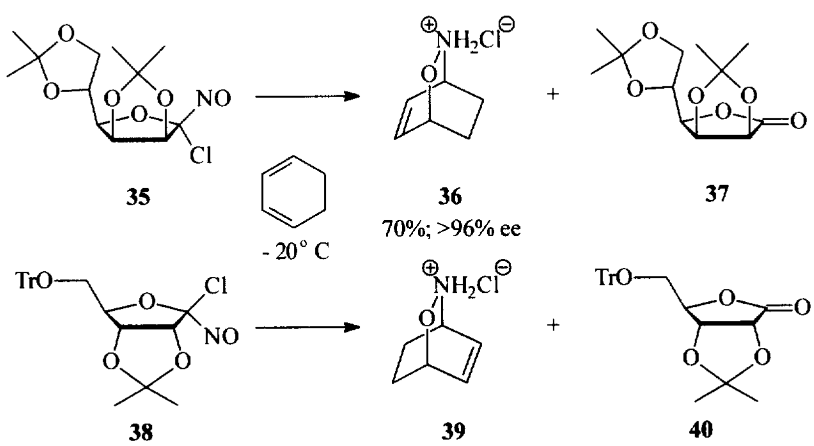
auxiliary in **29** from the reacting centres.[30] Acidic hydrolysis to remove the chiral auxiliary from **30** was complicated by concurrent oxidation of the aglycon to the anthraquinone, but presumably this might be suppressed by rigorous exclusion of oxygen from the reaction. Based on a crystal structure of **29**, the authors proposed an *endo* transition state similar to **31** to explain the preference for [4+2] addition to the *si,re* face of the alkene. They suggested that the orientation of the juglone moiety relative to the sugar was controlled by the *exo*-anomeric effect. In this conformation, a close steric contact between the quinone O-4 and the C-2 acetate group of the sugar ring apparently induced the quinone to adopt a boat-like conformation. In this geometry, approach to the *re,si* ("top") face of the C-2–C-3 alkene by a dienophile was impeded by the puckering of the ring.

Sugar-Linked Hetero-dienophiles. Hetero-dienophiles attached to sugar auxiliaries also undergo stereoselective cycloadditions. Danishefsky's diene added to benzaldehyde derivative **32** under $BF_3{\cdot}OEt_2$ catalysis, to give a 9:1 mixture of dihydropyranones **33** and **34** after an acidic work up.[31] The major product isomer **33** could be isolated in 70% yield by crystallization. The selectivity of the reaction depended on the catalyst used; in the presence of $Eu(fod)_3$ **34** was the major cycloadduct in a ratio of 3:1. Acyclic intermediates observed by the authors before acid work-up indicated that the BF_3-promoted reaction followed an aldol rather than a pericyclic pathway. On the other hand, the $Eu(fod)_3$ reaction gave cyclized intermediates typical of a pericyclic [4+2] cycloaddition. This mechanistic difference may explain the reported selectivity reversal. As in the juglone dienophile **29** studied by the same workers, the chiral auxiliary in **32** was remote from the reacting centres, and yet it induced very good diastereoselectivity in these cycloaddition reactions.



R*OH = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose

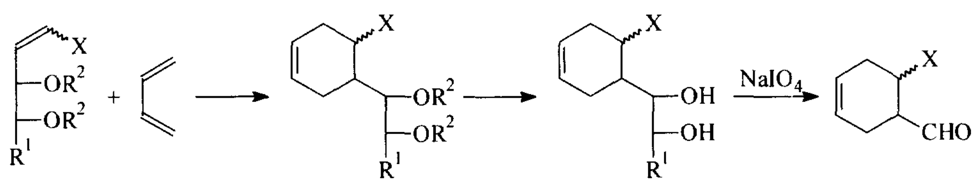
Scheme 8



Scheme 9

Chloronitrosofuranosides **35** and **38** (Scheme 9) reacted with cyclic or acyclic dienes in an extremely stereoselective fashion.[32] The cycloadditions all afforded essentially a single product, in from 63% to 96% yield. The chiral auxiliaries were spontaneously detached from the cycloadducts during the work up procedures, and were recovered as the aldonolactones **37** or **40**. D-*Manno* **35** and D-*ribo* **38** behaved as pseudo-enantiomers; their cycloadditions led to enantiomeric cycloadducts **36** and **39** respectively, with equally high selectivity. The authors also found that a racemic diene was kinetically resolved during cycloaddition with **35** or **38**, giving essentially complete selectivity when the diene was in excess. The dihydrooxazines made by this route were easily converted into aminocyclitols or into hydroxy- or amino-acids. More recently, Defoin et al. have prepared congeners of nojirimycin in excellent overall yields, beginning with the [4+2] cycloaddition of **35** to sorbaldehyde *O*-methyloxime.[33]

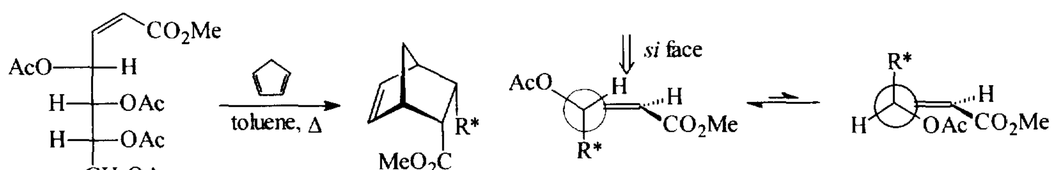
Acyclic Sugar Dienophiles. Aldoses react with Wittig reagents or with the nitromethyl anion to form acyclic alkenes.[9] In several cases, such alkene homologues of common hexoses and pentoses have been employed as dienophiles in Diels–Alder cycloadditions. While this type of reaction incorporates the sugar C-1 into the newly-formed ring, the remainder of the sugar chain can be (destructively) removed from the product



Scheme 10

by oxidative diol cleavage, making this at least formally a chiral auxiliary system. Studies of these acyclic sugar alkenes have highlighted some interesting facets of Diels–Alder stereocontrol.

Horton and Koh have studied the thermal Diels–Alder reaction of *Z* dienophile **41** with cyclopentadiene.[34] The alkene was obtained by a Horner–Emmons reaction of D-arabinose (the enantiomeric dienophile would be equally available from L-arabinose). The [4+2] cycloaddition of **41** was highly diastereoselective, giving cycloadduct **42** in a >19:<1 mixture with one other isomer. The major adduct **42** was isolated in 81%

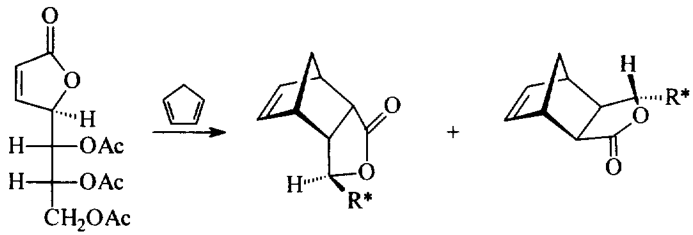


41 **42** **43** **44**

81%

Scheme 11

yield. The diene reacted with the *si* face of the dienophile, which Horton attributed to steric blocking of the dienophile's *re* face by the sugar chain in preferred conformer **43** (Scheme 11). The importance of the sugar chain was supported by the observation that butenolide **45** (Scheme 12) afforded only cycloadducts **46** and **47** (5.6:1), arising from *endo* and *exo* attack respectively, at the *re* face. Because **45** was constrained to adopt a conformation analogous to **44**, the steric bulk of the sugar chain blocked approach to the alkene's *si* face.



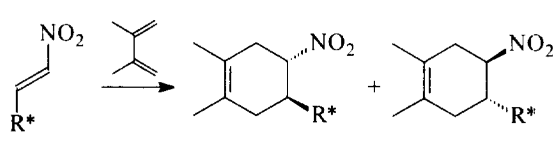
45 46 47

70% 11%

Scheme 12

In contrast to the high selectivity obtained from (*Z*) dienophile **41**, Horton and Koh found that sugar-derived (*E*) dienophiles were much less selective in their Diels–Alder reactions with cyclopentadiene.[35] This was especially true when the sugar hydroxyls were acetylated, due to the flexibility of the side chain. Dienophiles having D-*ribo* and D-*xylo* side chains (3*R* configuration) slightly favored reaction on their *re* faces, while D-*arabino* and D-*lyxo* compounds (3*S* configuration) favored their *si* faces. When the hydroxyls were protected as isopropylidene ketals, the dienophiles became more rigid and somewhat higher *re*:*si* selectivity was obtained. In all cases, the cycloadditions displayed a slight preference for *exo* addition. Horton suggested that these results could be understood in terms of conformations analogous to **43** and **44** (Scheme 11). In the (*E*) compounds, the $A^{(1,3)}$ strain that disfavored conformer **44** was absent. In consequence, the faces of the dienophile were less strongly distinguished.

(*E*)-nitroolefins **48a,b** made from D-galactose and D-mannose were likewise modestly selective in their Diels–Alder reactions.[36a] As in the reactions just discussed, facial selectivity was controlled by the configuration of the allylic position. However, in reactions of **48**, the relationship between the allylic configuration and the product stereochemistry was reversed: D-*galacto* olefin **48a** (3*R*) favored addition on its *si* face (**49a**:**50a** = 5.25:1), while D-*manno* olefin **48b** (3*S*) preferred its *re* face (**49b**:**50b** = 1:1.85). The same facial preferences were observed in reactions with unsymmetrical dienes. Nevertheless, while 1-acetoxybutadiene reacted with **48a** to give a single cycloadduct in 75% yield, the overall diastereoselectivities of [4+2] additions of **48** to unsymmetrical dienes were generally moderate.[36b]



48 49 50

a: R* = D-*galacto*-$(CHOAc)_4$-CH_2OAc
b: R* = D-*manno* -$(CHOAc)_4$-CH_2OAc

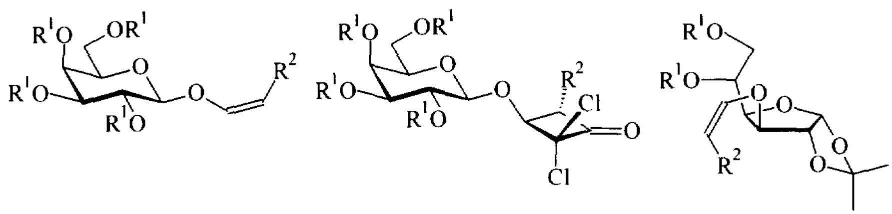
Scheme 13

These results can be rationalized in terms of conformations in which the 3-position acetoxy group blocks one face of the alkene. This rationale would imply that (*E*)-nitroolefins **48** preferred conformations quite different from those proposed for α,β-unsaturated esters by Horton, in which it was the sugar chain that hindered approach to the alkene (see **43** and **44**, Scheme 11). It is also noteworthy that Diels–Alder reactions of **48a,b** with cyclopentadiene were studied some years ago,[37] and while the selectivities of these processes were low, their *re*:*si* preferences fit the Horton model and not that proposed to explain the stereochemistry of 2,3-dimethylbutadiene addition (Scheme 13).[36a] It would appear that there is merit in Franck's observation that predictions of diastereofacial selectivity based only on the ground-state conformation of one partner in a cycloaddition will not always be completely satisfactory.[38]

[2+2] Cycloadditions

In general, carbohydrate chiral auxiliaries have been only modestly successful in controlling the facial selectivity of [2+2] cycloaddition reactions.[4a] This is an area where further development is definitely necessary.

Ganz and Kunz reported routes to chiral cyclobutanes from vinyl D-galactopyranosides and D-glucofuranosides.[39] Dichloroketene made from dichloroacetyl chloride and Et_3N did not react with **51**, but the ketene made from Cl_3CCOCl with Zn/Cu couple reacted at room temperature to give a 4:1 mixture of diastereomeric cyclobutanones **52**. The authors suggested that metal salts present in the latter reaction activated the ketene

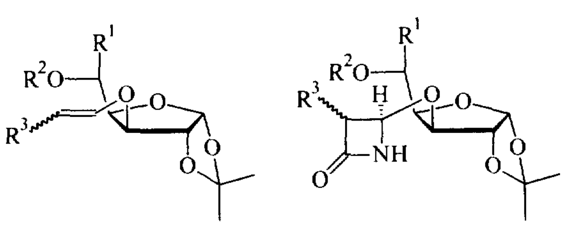


51 **52** **53**

Figure 7

towards attack by the weakly nucleophilic enol ether **51**, but unfortunately little stereodirecting effect arose from metal interactions with the chiral auxiliary. The facial selectivities of these reactions were consistent with reactive conformations similar to those proposed by Stoodley[18] for Diels–Alder reactions. Similar reactions of 3-*O*-alkenyl glucofuranoses **53** gave the corresponding cyclobutanone products in from 2:1 to 5:1 selectivity. In all cases, the cyclobutanones were too unstable to be purified, but stable cyclobutanols were isolated in fair yields after reduction of the ketone.

Enol ethers incorporating non-anomeric hydroxyls (e.g. **53**) are not conveniently used as chiral auxiliaries, since the sugar portion usually must be removed by destructive oxidation. Nevertheless it is instructive to examine the stereochemical effects of structural variations in the sugar moiety, documented by Kaluza et al. in [2+2] cycloadditions of chlorosulfonyl isocyanate to furanose enol ethers (Figure 8).[40a,b] Reactions of 5,6-*O*-isopropylidene D-glucofuranose **53** (Figure 7) were weakly selective and low yielding, as observed by Ganz and Kunz. In contrast, reaction with 5,6-di-*O*-tosyl **54** gave exclusively the 4′-(*R*) azetidin-



54
56a-e

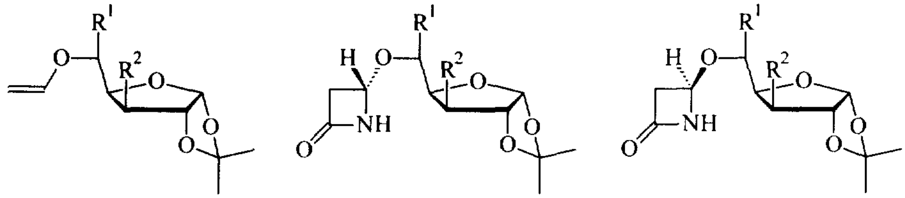
55
57a-e

		R^1	R^2	R^3
54	**55**	CH_2OTs	Ts	H
56a	**57a**	H	Ts	H
b	**b**	H	TIBS	H
c	**c**	H	$SiPh_3$	H
d	**d**	H	Tr	*cis*-CH_2CH_3
e	**e**	H	Tr	*trans*-CH_2CH_3

Figure 8

one **55**. In the D-*xylo* series (R^1 = H), blocking O-5 with tosyl (**56a**) or tri(isopropyl)benzenesulfonyl (TIBS; **56b**) groups resulted in low selectivity for the production of **57**, while the 5-*O*-triphenylsilylated auxiliary **56c** afforded exclusively the 4′-(*R*) azetidinone **57c**.[40a] Likewise, the 3-*O*-(1-butenyl)-5-*O*-trityl xylofuranoses **56d,e** reacted with chlorosulfonyl isocyanate to give exclusively the 4′-(*R*) products **57d** and **57e** respectively, in good yields.[40b]

Kaluza et al. also examined the [2+2] cycloaddition reactions of 5-*O*-vinyl furanoses **58**.[40c] They found that the nature of the groups at C-3 and C-5 dictated the degree and direction of the reaction's facial selectivity. The highest selectivity was obtained when the top face of the sugar at C-3 was relatively unhindered, and when the R^1 substituent was bulky. In these cases the 4′-(*S*) azetidinone **59** was obtained in greater than 92% de. On



58 **59** **60**

Figure 9

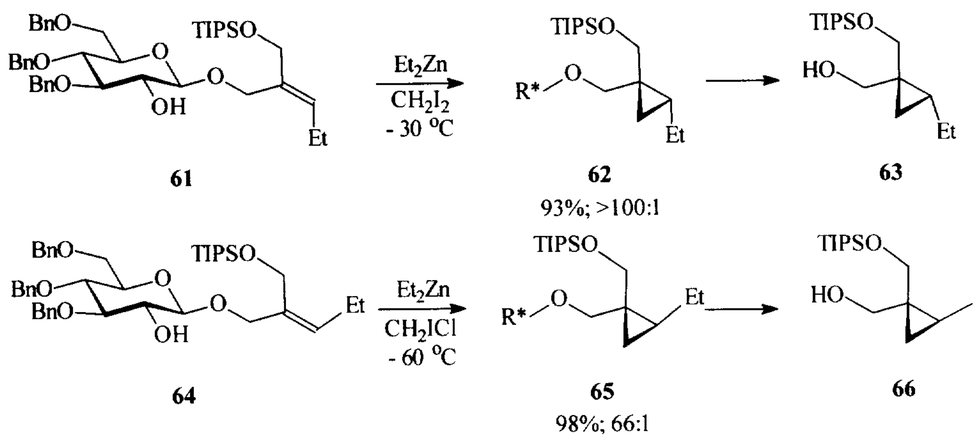
the other hand, if R^2 was a bulky group, and R^1 was small, the 4′-(*R*) product **60** predominated (40% de). These results illustrate some of the opportunities for tuning the selectivity of a reaction offered by sugar auxiliaries. It is clearly important to consider not only the stereochemistry of the sugar template itself, but also the subtler steric and electronic characteristics of the groups attached to its periphery.

Imine derivatives of D-glucosamine propane-1,3-dithioacetal were employed by Anaya et al. in Staudinger reactions leading to carbapenem antibiotics.[41] These reactions were not highly stereoselective, but some improvement (up to 3.5:1) was achieved by replacing the 3,4:5,6-di-*O*-isopropylidene protecting groups of the acyclic sugar auxiliary with *O*-triethylsilyl groups. The auxiliary was separated from the finished carbapenem by oxidative cleavage with periodate or triphenyl bismuth carbonate.

Cyclopropanations

Charette et al. showed some years ago that allylic glycosides of 3,4,6-tri-*O*-benzyl-β-D-glucopyranose undergo very diastereoselective Simmons–Smith cyclopropanations, usually with more than 50:1 selectivity.[42a] The selectivity arose from coordination of the zinc reagent with the unprotected 2-OH of the chiral auxiliary. They also described an interesting method for removing the chiral auxiliary from the hydroxymethyl cyclopropane product that regenerates 3,4,6-tri-*O*-benzyl-D-glucal, the starting point for the synthesis of the allylic glycosides.[42b] Charette has reviewed his studies on the Simmons–Smith reaction using carbohydrate chiral auxiliaries.[42c]

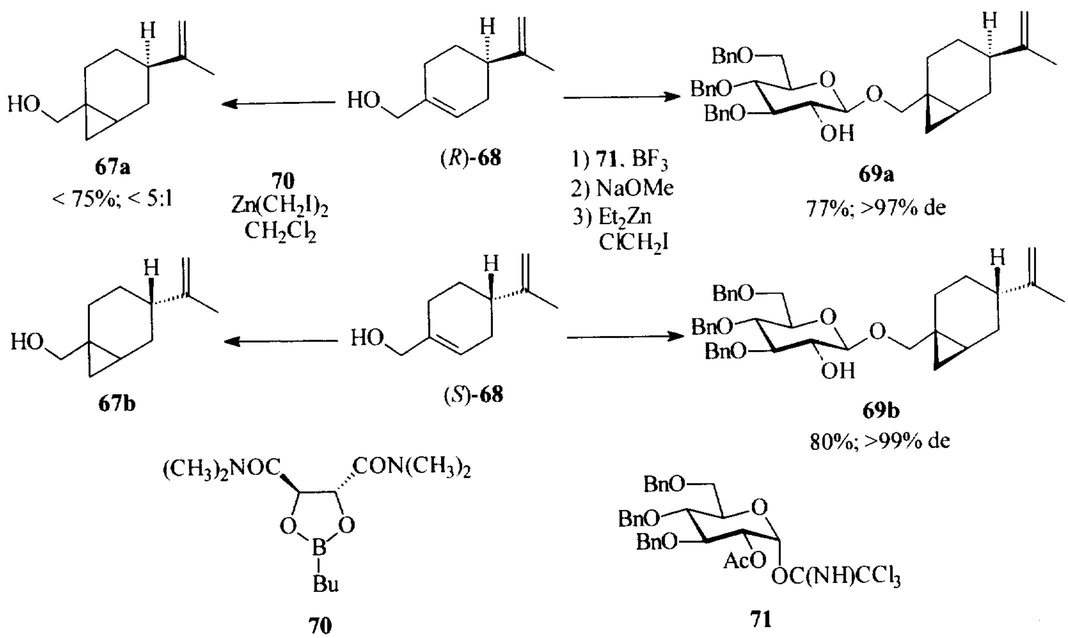
Charette and Côté have applied this method to the synthesis of all four isomers of coronamic acid, a cyclopropyl amino acid with important agrochemical applications.[43] The (*E*)-allylic glycoside **61** was smoothly converted to **62** in 93% yield and >100:1 selectivity under standard Simmons–Smith conditions (Scheme 14). The reaction of (*Z*) glycoside **64** was sluggish and less selective under these conditions, but when **64** was treated with Et_2Zn/CH_2ICl at −60 °C, **65** was obtained in 98% yield and with a 66:1 diastereomer ratio. The cyclopropanes were separated from the D-glucose auxiliary using Charette's method,[42b] and **63** was



Scheme 14

then converted in a few steps into either (−)-coronamic acid or (−)-*allo*-coronamic acid, while **66** gave the corresponding (+) enantiomers.

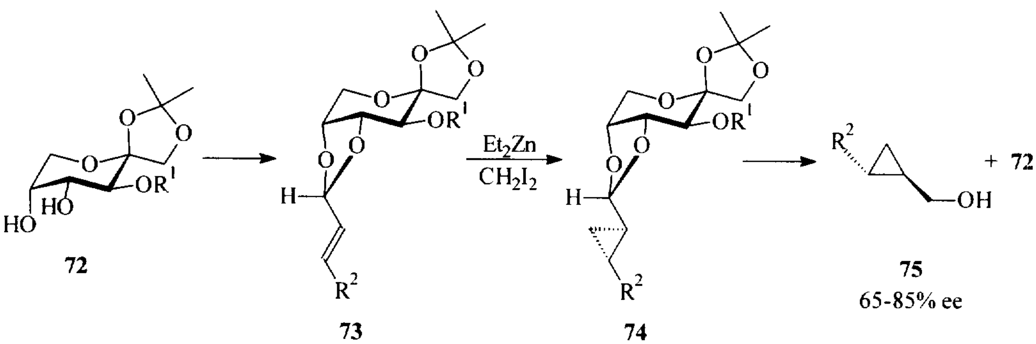
The power of the D-glucopyranose auxiliary in asymmetric Simmons–Smith reactions can be clearly seen in Scheme 15. The dioxaborolane ligand **70** is a versatile additive that can induce high levels of stereoselectivity in many cyclopropanation processes. Nevertheless, in some cases it does not provide a satisfactory result, as in the regioselective cyclopropanation of (*R*)- and (*S*)-perillyl alcohols **68**.[44] The cyclopropanes **67** were obtained in modest yields with less than 5:1 diastereoselectivity. On the other hand, Charette's chiral auxiliary approach transformed (*R*)-**68** into **69a** (>97% de), and afforded **69b** (>99% de) from (*S*)-**68**. It is



Scheme 15

particularly noteworthy that the glucose auxiliary overrode any effect exerted by the stereogenic centre in perillyl alcohol, giving the same cyclopropane stereochemistry in each instance. In contrast, the reactions using ligand **70** produced **67a** and **67b** with opposite configurations, although these were not identified.

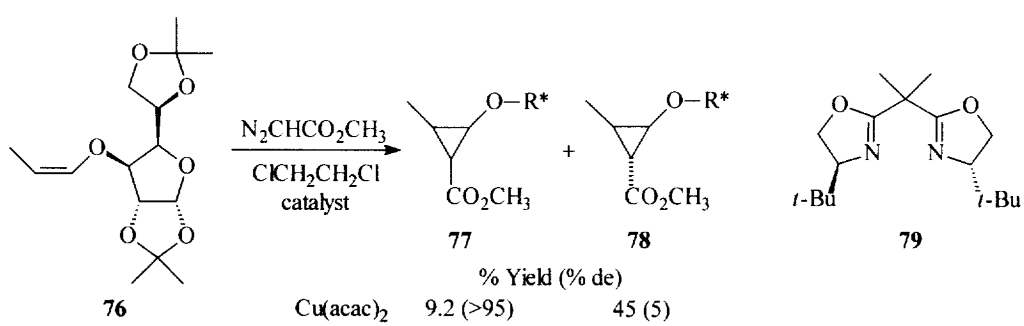
Another asymmetric Simmons–Smith reaction was described by Kang and co-workers.[45] The β-D-fructopyranoside **72** formed *endo* acetal derivatives **73** (along with the *exo* isomers) on treatment with α,β-unsaturated aldehydes. Cyclopropanation of **73** occurred predominantly on the "back" face of the alkene, giving **74**, when the R^1 group on O-3 was sufficiently bulky to hinder access to the "front" face. Mild acid hydrolysis of **74** followed by reduction provided the hydroxymethyl cyclopropanes **75**. The *endo* acetals afforded the best selectivity, typically giving (2*R*,3*R*)-**75** with 65–85% e.e. The *exo* acetals reacted much less selectively, but afforded the enantiomeric product. The levels of stereoselectivity were lower than typically obtained using Charette's approach, possibly because considerable conformational flexibility was still



Scheme 16

available to the R^1 group in **73**. Kang et al. noted that the D-psicopyranose analogue of **72** (epimeric at C-3) did not induce useful diastereoselectivity in similar cyclopropanation reactions.

Enol ethers linked to a diacetone-D-glucose auxiliary have been cyclopropanated by diazoacetates in the presence of copper or rhodium catalysts.[46] These reactions were modestly stereoselective, but the product distribution depended on the nature of the catalyst in a very intriguing fashion. In the presence of $Cu(acac)_2$ or $Rh_2(OAc)_4$, the reaction of **76** with methyl diazoacetate afforded approximately 1:4 mixtures of *cis* and *trans* cyclopropanes **77** and **78** (27-54%). Nevertheless, the minor *cis* product **77** was obtained with better than 95%



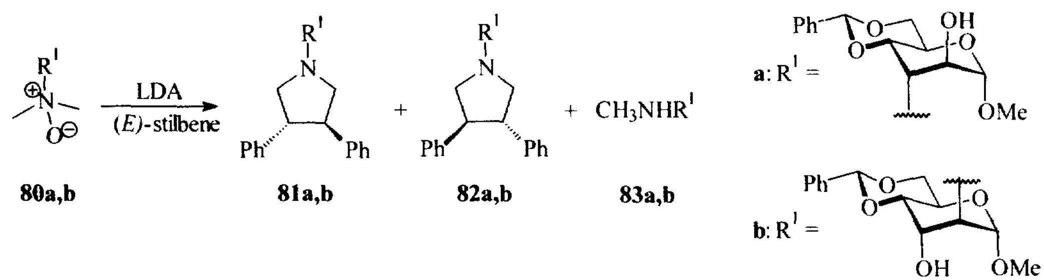
	77	**78**
	% Yield (% de)	
$Cu(acac)_2$	9.2 (>95)	45 (5)
$Rh_2(OAc)_4$	5.7 (>95)	21 (4)
79•CuOTf	-	74 (60)

Scheme 17

de, while the *trans* product **78** had only a 5% de. In contrast, if the reaction was catalyzed by Cu(OTf) in the presence of Evans' *bis*-oxazoline ligand **79**, the sole product was **78** (74%), having 60% de. Clearly the chiral catalyst **79**·Cu(OTf) was interacting strongly with the sugar auxiliary in this reaction. Comparison studies with model achiral enol ethers implied that the carbohydrate auxiliary was also exerting a considerable stereochemical bias, but its influence was much greater in the transition state leading to **77** than in that giving **78**. Unfortunately, the authors did not report the absolute configurations of the cyclopropanes, nor did they give a detailed mechanistic interpretation of these curious results.

Dipolar Cycloadditions

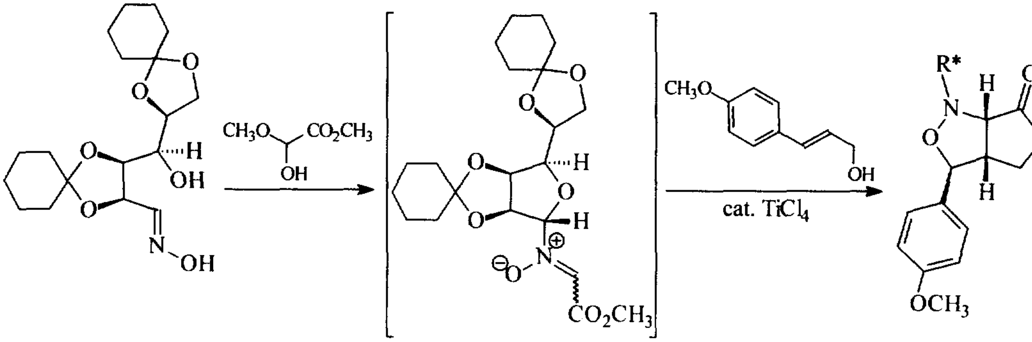
Cycloaddition of azomethine ylides to olefins provides a convenient access to pyrrolidines, which are useful synthetic intermediates. Many pyrrolidines are also versatile chiral auxiliaries or ligands in chiral catalysts. Roussi et al. reported that highly reactive ylides were produced on deprotonation of conformationally locked *N*-oxides **80a** and **80b**.[47] The *N*-oxides were obtained in two steps from the corresponding 2,3-anhydro-D-*manno*- and allopyranosides. Deprotonation of **80a** in the presence of (*E*)-stilbene gave the pyrrolidines **81a** and **82a** in 40% yield, while the reaction of **80b** afforded **81b** and **82b** in 60% yield. The pyrrolidines were accompanied by amines **83a,b** arising from decomposition of the unstabilized ylides. The cycloadducts were obtained with only 70% de, but the reaction of **80a** favored the (3'*R*,4'*R*) product **81a**, while



Scheme 18

80b gave the (3'*S*,4'*S*) diastereomer **82b** as the major product. The authors rationalized this reversal of selectivity in terms of transition states that placed the dipoles' negative ends as far as possible from oxygen groups in the sugar auxiliaries. The pyrrolidines were easily separated in good yield from the sugar auxiliaries by treatment with $CHCl_3$/aq. NaOH, followed by basic hydrolysis of the resulting *N*-formyl derivatives. The sugars were recovered as their 2,3-anhydro derivatives, ready for re-use, in nearly quantitative yields.

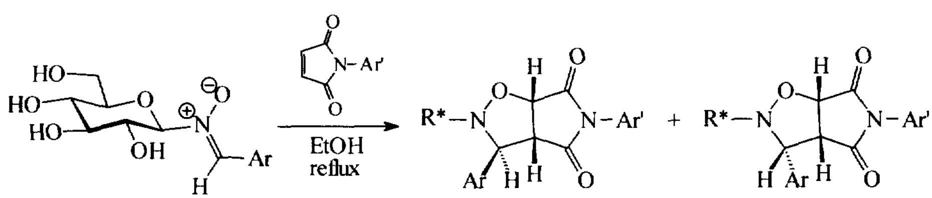
Pioneering studies of the dipolar cycloaddition reactions of carbohydrate-derived nitrones by Vasella and others have already been reviewed.[4a] Other workers have recently incorporated this chemistry into an ingenious synthesis of the aminoacyl sidechain of the antifungal agent nikkomycin Bz (Scheme 19).[48] The unstable *N*-mannofuranosyl glyoxylate nitrone **85** was generated by treating L-gulose oxime **84** with methyl glyoxylate hemiacetal in boiling toluene. Addition of (*E*)-*p*-methoxycinnamyl alcohol and a catalytic amount of $TiCl_4$ to the mixture led to transesterification and *in situ* 1,3-dipolar cycloaddition, forming exclusively the bicyclic lactone adduct **86**. Three further steps afforded a lactone equivalent to the nikkomycin sidechain. It must be noted, however, that other allylic alcohols tested underwent this tandem transesterification-cycloaddition process with considerably lower stereoselectivity.



84 85 86
75% overall

Scheme 19

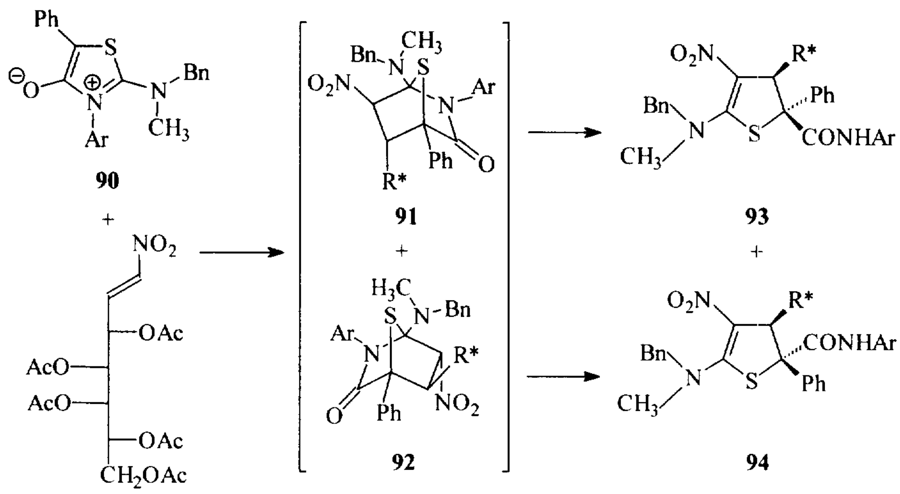
Fišera et al.[49] prepared chiral nitrones **87** directly from unprotected D-glucopyranosyl oxime. These nitrones underwent [3+2] cycloaddition with substituted *N*-arylmaleimides to give (in most cases) the *anti* isoxazolidines **88** as the major cycloadducts (**88**:**89** = 2.3:1 to 19:1). Only when the Ar′ group in the dipolarophile was 2,6-disubstituted did the reaction favor the *syn* product **89**, with better than 9:1 selectivity. The authors suggested that a hydrogen bond between the nitrone oxygen and OH-2 in **87** controlled the conformation of the dipole, and hence the stereoselectivity of these reactions.



87 88 89

Scheme 20

In a rather complex process, the D-*galacto* nitroalkene **48a** underwent 1,3-dipolar cycloadditions with 1,3-thiazolium-4-olates **90** (thioisomünchnones) in moderate yield.[50] Dihydrothiophenes (4*S*,5*R*)-**93** and (4*S*,5*S*)-**94** were isolated in up to a 1:6 ratio, after *in situ* rearrangement of the initial cycloadducts **91** and **92**. The cycloaddition was totally facially selective with respect to the alkene **48a**. This result contrasts with the relatively unselective Diels–Alder chemistry of **48a** shown in Scheme 13.[37] The diastereomeric mixture resulted from the low *endo/exo* preference of the cycloaddition. The overall process reflected a balance between the kinetic selectivity of the cycloaddition, the differing rates at which **91** and **92** rearrange, and slow dipolar cycloreversion of **92**. A D-mannose-derived nitroalkene analogous to **48a** afforded the enantiomeric products (4*R*,5*S*)-**93** and (4*R*,5*R*)-**94**, but in only a 1:2.9 ratio. The authors did not detach the carbohydrate auxiliaries from the dihydrothiophenes, but they could be (destructively) removed by hydrolysis and periodate oxidation.



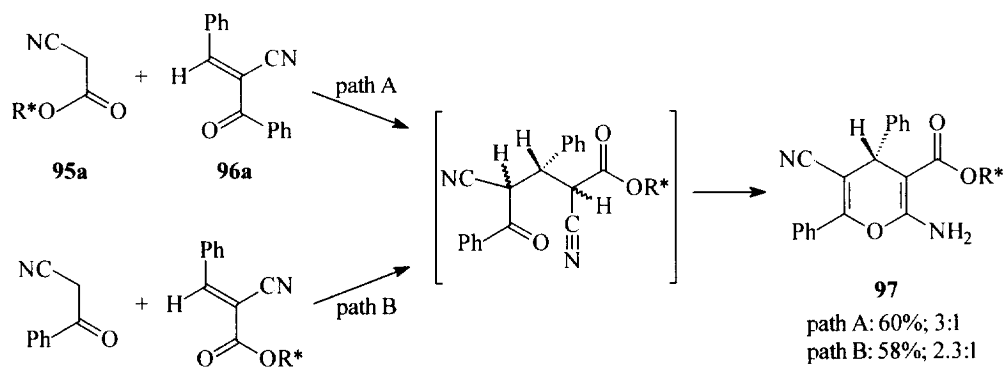
48a R* = D-*galacto* $(CHOAc)_4CH_2OAc$

Scheme 21

STEREOSELECTIVE ALKYLATIONS, ACYLATIONS, AND ALDOLS

1,4-Addition Reactions

Chiral 2-amino-4*H*-pyrans **97** were the products of a modestly diastereoselective variant of the classic Michael reaction.[51] The authors of this study linked terpene, lactate or diacetone D-glucose auxiliaries to either the nucleophile (**95a**) or the α,β-unsaturated acceptor (**96b**). While the best diastereoselectivity was obtained using a (–)-borneol auxiliary (*S*:*R* = 4:1 by path A), the glucofuranose system was nearly as successful, and gave similar selectivity when it was attached either to the nucleophile (path A, 3:1) or to the electrophile (path B, 2.3:1). Most of the non-carbohydrate auxiliaries afforded much lower selectivity by path B.



95b **96b** R*OH = 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose

Scheme 22

α,β-Unsaturated imide derivatives of carbohydrate-based oxazolidin-2-one auxiliaries afforded much greater diastereoselectivity in their 1,4-addition reactions with dialkylaluminium chlorides (Figure 10).[5,52]

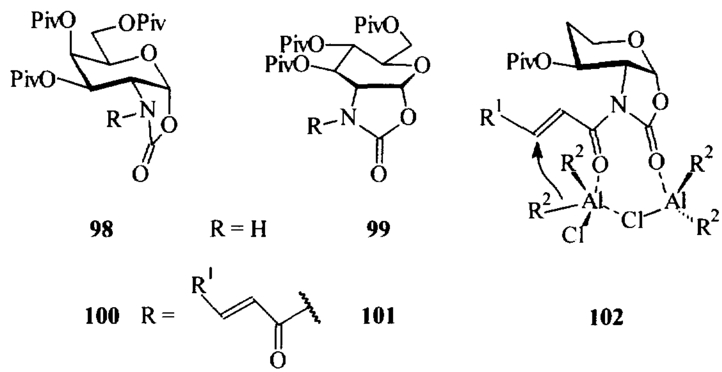
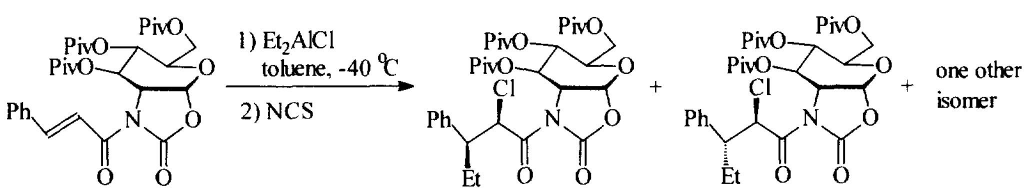


Figure 10

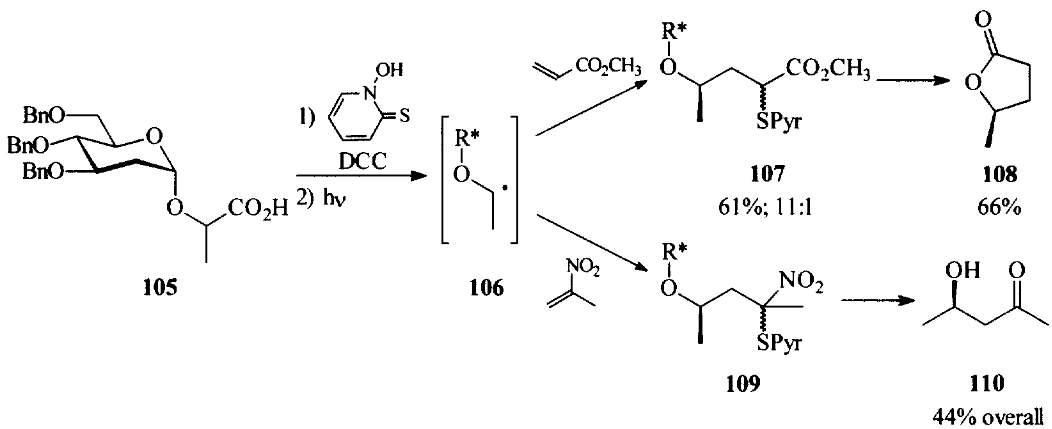
Bicyclic D-*galacto* oxazolidin-2-one **98** was prepared from D-galactal by a somewhat involved sequence,[52a] but the analogous D-*gluco* auxiliary **99** was made very simply and in high yield from 2-deoxy-2-amino-D-glucose.[52b] These were *N*-acylated with α,β-unsaturated acyl halides in the presence of MeMgBr, to form imides **100** and **101**. Conjugate addition of an alkyl group from $(R^2)_2AlCl$ to the galactosyl imides **100** occurred on the exposed *exo* face of the acceptor, presumably *via* aluminum complexes such as **102** (Figure 10), with better than 19:1 selectivity. The glucosyl imides **101** reacted with Et_2AlCl with somewhat lower selectivity (9:1) than did the galactosyl compounds. It is interesting that methyl group transfer from Me_2AlCl to **100** was unsuccessful unless the reaction was irradiated with UV light, which induced a radical reaction pathway.[52a]

The aluminum enolate intermediates arising from the addition of dialkylaluminium chlorides to **100** or **101** were also trapped with *N*-halosuccinimides (Scheme 23).[52b] The net result of this two step, one-pot process was the addition of RX across the double bond. The diastereoselectivity of the second (halogenation) step depended on which chiral auxiliary was used. With D-*galacto* systems (**100**), the halogenation selectivity was poor. The results suggested a "mismatched pair" relationship between the influence of the sugar auxiliary and that of the stereogenic centre formed in the first step by addition of the alkylaluminium. In contrast, the D-*gluco* systems (**101**) provided much higher overall selectivity in this "cascade" process, and the



Scheme 23

stereochemistry of the halogenation step was exclusively controlled by the sugar auxiliary. Thus, when **101a** was treated with diethylaluminum chloride, followed by *N*-chlorosuccinimide, adducts **103**, **104** and one other isomer (83.5:6.45:1) were obtained in 64% yield. Changing the sugar protecting groups in **101** from pivalate esters to benzoates improved the selectivity of the cascade, but also slowed the reactions considerably. Although typically three of the four possible diastereomeric adducts were formed in these reactions, the major adducts could be purified from the product mixtures by chromatography or crystallization, in acceptable yields.



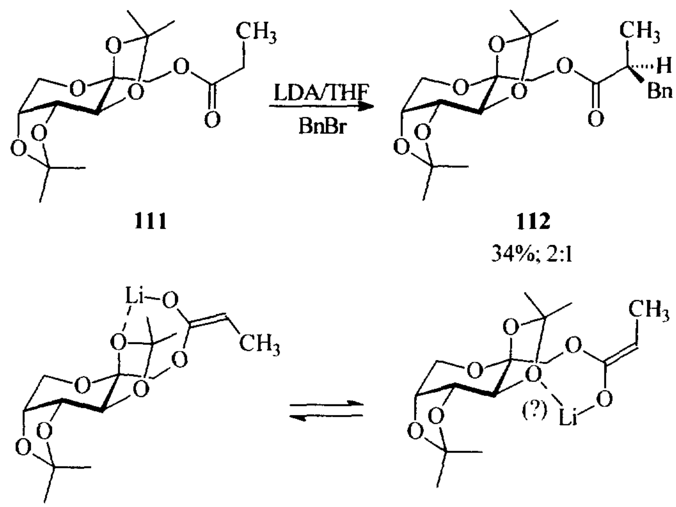
Scheme 24

While most of the diastereoselective 1,4-addition reactions using monosaccharide chiral auxiliaries that have been studied were ionic processes, some very selective *radical* additions have been accomplished. Garner and Cox generated chiral radical **106** by Barton decarboxylation of *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)lactic acid (**105**).[53a] Radical **106** was trapped by methyl acrylate, giving **107** in 61% yield and 11:1 diastereoselectivity. Addition occurred predominantly from the *si* face of **106**. The authors reported that calculations implied that the barrier to *re* attack on **106** was a consequence of the sugar auxiliary impeding torsional motions in the transition state, and not steric approach control in the normal sense. They therefore proposed that the selectivity of the reaction was primarily *entropic* in origin. After reductive removal of the 2-thiopyridyl group from **107**, acidic solvolysis released the γ-butyrolactone **108**. Garner et al. have also trapped radical **106** with 2-nitropropene, to give aldol-like products **110** (with up to 8:1 selectivity) after Nef reaction of **109** and removal of the auxiliary.[53b] The levels of selectivity provided by this radical approach were modest in comparison with those obtainable by standard aldol methods, but the stereochemical influence of the sugar was nonetheless quite significant.

Alkylation of Carbohydrate-Linked Enolates

The asymmetric alkylation of ester and amide enolates is one of the most popular applications of chiral auxiliaries in general.[54] In the past few years, there have been several investigations into the use of monosaccharide auxiliaries in these processes. Highly selective enolate alkylations require that the (*E*)- or (*Z*)-enolate[55] be cleanly generated, and the stereotopic faces of this enolate must be strongly differentiated. When the enolate is attached as an exocyclic appendage to a sugar auxiliary, restricting its motion has sometimes been a major challenge. The coordinating ability of sugars can be very useful in this regard, although in some cases strong interactions between the auxiliary and the enolate counter-ion have promoted elimination of the ester moiety as a ketene derivative (see Scheme 1).[10]

Given the importance of metal coordination to obtaining selectivity in sugar-linked enolate reactions, it is somewhat surprising that many researchers in this field have not explored the full range of metals and metalloids available for enolate generation. Certainly the advent of boron, titanium and tin enolates enhanced the value of the Evans-type oxazolidinone auxiliaries made from amino acids,[56] yet most studies of alkylation or aldol reactions on carbohydrate-derived auxiliaries have used only lithium or sodium enolates. Thus, although some of the studies reviewed here obtained only moderate levels of diastereoselectivity, considerable potential for optimization remains to be explored.

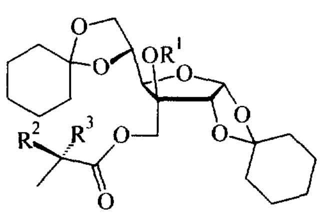


111 112 34%; 2:1

113 114

Scheme 25

2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose is inexpensive and very readily prepared. Its primary hydroxyl group may be easily acylated for use as a chiral auxiliary in enolate chemistry. However, a recent study by Costa et al. illustrated the difficulties that may be encountered in controlling enolate appendages on the periphery of this type of sugar auxiliary.[57a] The ester **111** was deprotonated by LDA in THF to give a 3.35:1 mixture of the (*E*) and (*Z*) lithium enolates, that were then alkylated with benzyl bromide. The product (*S*)-**112** was obtained in modest yield (34%), while the diastereoselectivity was only 2:1. This was consistent with alkylation of the (*E*) enolate from the less hindered face of the complex **113**, but the lower overall selectivity compared with the (*E*):(*Z*) ratio suggested that **113** was likely exchanging with another form such as **114** (perhaps involving coordination of lithium by O-3). Performing the reaction in THF/HMPA reversed the enolate selectivity to (*Z*):(*E*) = 6.1:1 as one would expect.[54] Even so, **112** was obtained as a 1:1 mixture, consistent with HMPA disrupting lithium coordination. Costa et al. have also recently reported the use of this fructose auxiliary, as well as diacetone glucose, diacetone allose, and three terpene-derived auxiliaries, in the preparation of β-piperonyl-γ-butyrolactone, an intermediate in the synthesis of chiral lignans.[57b]



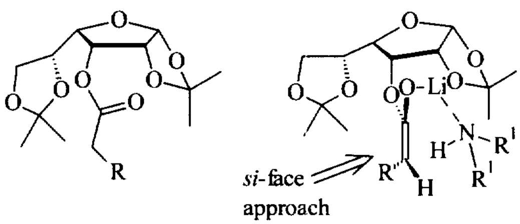
115a: R^1 = H; R^2, R^3 = H
b: R^1 = TMS; R^2,R^3 = H
116a: R^1 = H; R^2 = H; R^3 = Bn
b: R^1 = TMS; R^2 = Bn; R^3 = H

Figure 11

A 3-hydroxymethyl furanose auxiliary made from dicyclohexylidene-D-glucofuranose provided a more controlled environment for enolization and alkylation of its esters **115a,b** (Figure 11).[58] The hydroxyl group at C-3 in **115a** was a key coordination site for the enolate counter-ion. Treating the lithium enolate of **115a** with benzyl bromide and an excess of LiCl, led to highly selective formation of (*R*)-**116a** (60%; (*R*):(*S*) = 24:1). In the presence of HMPA the same reaction was almost totally unselective.

In contrast, using the silylated derivative **115b**, the (*R*)-selectivity of the alkylation reaction was only 2.5:1. However, in the presence of HMPA, the reaction became highly selective, affording the (*S*)-benzylated product **116b** (95%; (*R*):(*S*) = 1:21). The authors explained these results in terms of a (*Z*)-enolate of **115a** (R^1 = H). They proposed that it would adopt a conformation that put its enolate oxygen *syn* to O-3 when R^1 = H, to permit chelation of its lithium counter-ion. An uncomplexed form, with the enolate oxygen turned away from O-3, would then be preferred in the case of **115b** (R^1 = TMS) where chelation was hindered. This conformer became more even more important in the presence of HMPA, which would further disrupt chelation of the counter-ion.

While chelation was critical in the reactions of **115**, a very interesting study by Mulzer et al.[59] suggested that it may not always control the selectivity of enolate alkylation reactions on furanose auxiliaries. They prepared 3-*O*-acyl derivatives of 1,2:5,6-di-*O*-isopropylidene-D-gulofuranose (**117**; Figure 12), anticipating that their enolates would be very strongly chelated by the "basket" of oxygens on the bottom face of the sugar. One might predict, based on Kunz's earlier observations,[10] that such enolates would readily eliminate the acyl moiety as a ketene, but this did not occur. Enolization by LDA or LTMP was essentially completely (*E*)-selective for all the esters, and methylation occurred on the *si* face of the enolate with from 4:1 to 10:1 selectivity. Additives that could interfere with complexation (TMEDA, HMPT) or that might enhance complex formation ($MgBr_2$, $ZnCl_2$) did not affect the selectivity.

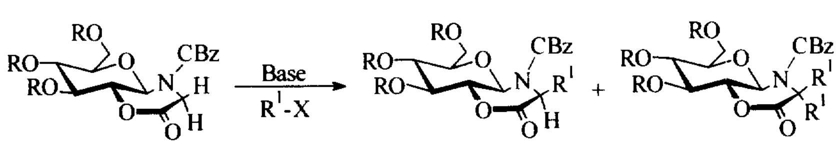


117 **118**

Figure 12

This observation led Mulzer et al. to propose an uncomplexed enolate conformation. According to their interpretation, the preference for alkylation on the (apparently more-hindered) *si* face was due to a "post-enolization" complex **118** in which the protonated base blocked the *re* face. This idea was supported by the fact that LHMDS effected complete enolization of **117**, but the methylated products were obtained in only about 45% yield, along with corresponding amounts of recovered starting material. They proposed that this resulted from internal proton return from the base to the enolate in complex **118** (R^1 = TMS), because the electrophile's approach to the enolate β-carbon atom was excessively hindered in this case.

Internal proton return may also be relevant to results obtained with the D-glucose-derived oxazinones **119**.[60] This "chiral glycine" system was designed to provide a rigid stereochemical environment for an enolate, without requiring complexation of the counter-ion. Deprotonation of **119a** or **119b** with LHMDS in THF readily formed the corresponding enolates. These were unreactive in THF alone, but adding HMPA promoted reaction with active alkyl halides or TBDMSCl. Alkylation with CH_3I, allyl bromide, or benzyl bromide gave monoalkylated products **120** with very high diastereoselectivity (>49:1) but the total conversions were only about 50%, and starting material was always recovered. On the other hand, when the non-ionic phosphazene P-4 base was used, HMPA was unnecessary and alkylated products could be recovered in *ca.* 70% yields. This behavior was consistent with Mulzer's observations in experiments employing LHMDS.[59]



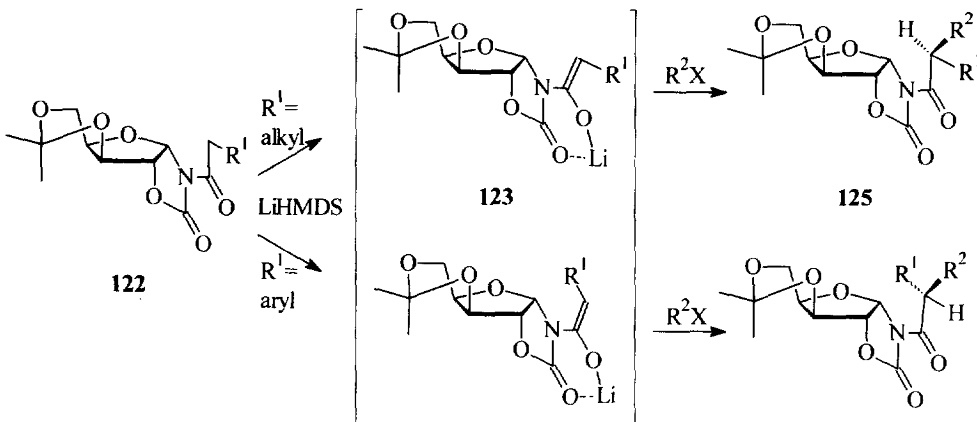
119a: R = Piv
b: R = Bn

120 **121**

Scheme 26

While methylation of **119** gave only the monoalkylated products **120**, reactions with the other electrophiles gave significant amounts of **121** as well. The stereoselectivity of monoalkylation of **119** was not a consequence of coordination, but probably arose from the interplay of stereoelectronic and conformational factors in the enolate. The amino acid products were easily separated from the glucose template by hydrogenolysis of the CBz group, followed by treatment with hydrochloric acid.[61]

Köll and Lützen developed a simple oxazolidinone auxiliary that can be made in two easy steps from D-xylose,[62a] and have explored its use in a range of alkylations, acylations, and halogenations of the imides **122**.[62b,c] In keeping with the behavior of other oxazolidinone imides, alkylation of lithium enolates of **122** required active alkyl halides. The yields of these reactions were generally moderate, and the diastereoselectivities were typically in the range of 5–10:1, although with bulkier R^1 groups higher selectivities were observed. In an intriguing reversal, aliphatic and aryl R^1 groups in **122** afforded products apparently arising from different enolate structures. The authors proposed that their aliphatic imides formed lithium-chelated

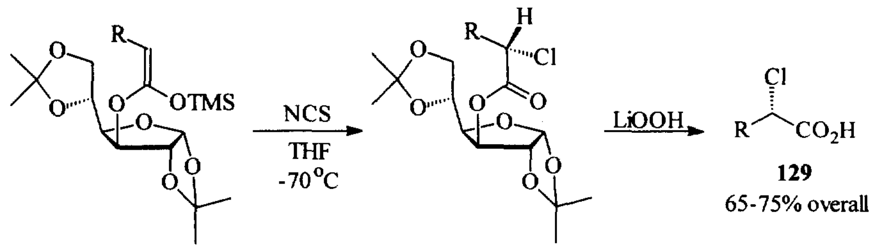


Scheme 27

(*Z*)-enolates **123**, that were alkylated on their exposed *si* faces to yield adducts **125**. The aryl-substituted imides appeared to form (*E*) enolates **124** predominantly, so that in these cases the products (**126**) arose from reaction at the *re* face. They postulated that this (*E*)/(*Z*) reversal might be due to some undetermined stereoelectronic interaction between the sugar ring oxygen and the aromatic ring of the imide.[62b]

The imides **122** could also be acylated *via* their lithium enolates,[62c] with diastereoselectivities in the range of 5–15:1. Boron enolates of these imides were halogenated by *N*-halosuccinimides with 3–5:1 selectivity. Again, the aliphatic imides gave products that were consistent with approach of the electrophile to the *si* face of a chelated (*Z*)-enolate similar to **123**, while the aryl imides showed the opposite preference.

Somewhat more selective α-halogenation of aliphatic silyl ketene acetals was achieved by Duhamel and co-workers using a diacetone D-glucose template.[63] When **127** was treated with *N*-chlorosuccinimide, (*S*)-2-chloroester products **128** were obtained with between 9:1 and 49:1 diastereoselectivity. Bromination by NBS was less selective. The authors noted that both the (*Z*) and (*E*) ketene acetals gave the same (*S*) halide in all cases. The haloacid products **129** were separated from the sugar auxiliary by treatment with cold lithium hydroperoxide, without racemizing the new stereogenic centre. The two steps typically gave the haloacid in about 70% overall yield, and the auxiliary was also recovered in good yield at the end of the sequence.

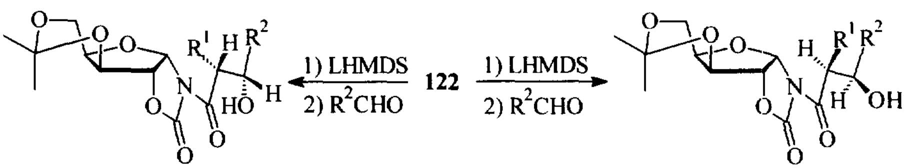


127 128 129

Scheme 28

Aldol Condensations

Köll has also used his D-xylofuranosyl oxazolidinone in aldol condensations.[64] Deprotonation of imides **122** with LHMDS and quenching with simple aliphatic aldehydes gave *syn* (2′*R*,3′*S*) aldols **130** *via* (*Z*) lithium enolates (**123**, R^1 = aliphatic). The diastereomeric *syn* (2′*S*,3′*R*) aldols **131** were obtained *via* (*E*) enolates (**124**) when R^1 was an aryl group. The major products were obtained with 5–15:1 selectivity with respect to

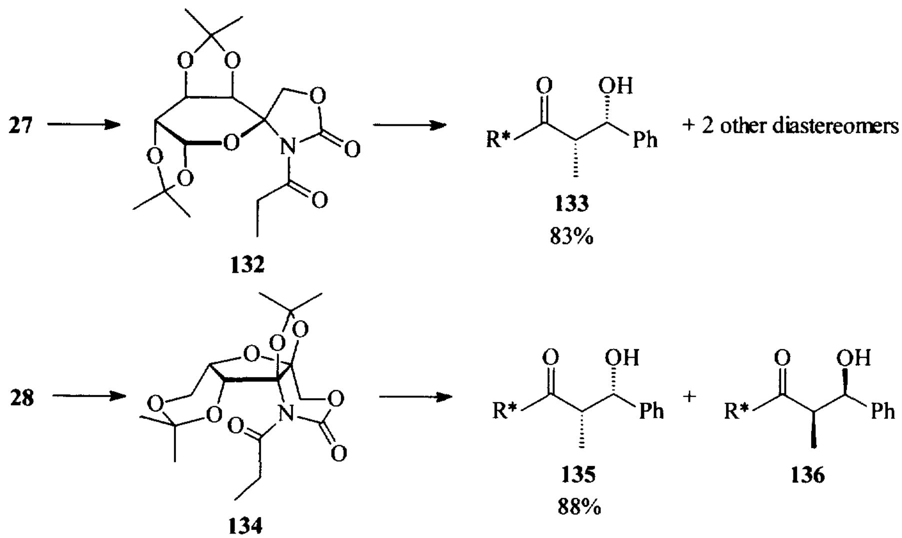


130 (R^1 = aliphatic) **131** (R^1 = aryl)

Scheme 29

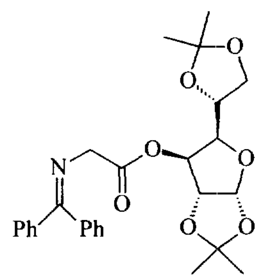
the other three possible aldols. Condensations with aldehydes that contained aryl groups gave poor selectivity, and the major diastereomer produced varied depending on the aldehyde that was used. Köll explained these results in terms of the conventional chair transition states, but suggested that when aryl groups were present, boat or twist transition states became competitive or even predominant. While this method gave direct access to the "non-Evans" *syn* aldol diastereomers,[54] the yields of the major products were quite low in all the cases presented. This might reflect internal proton return, as postulated by Mulzer.[59] It is also possible that better yields and selectivities could be obtained using metals other than lithium as the enolate counter-ions.

The spirooxazolidinone **27**[29b] and the oxazinone **28**[29c] were already discussed as auxiliaries for Diels–Alder chemistry (Figure 6). Banks et al. have shown that they can also be used in aldol condensations (Scheme 30). For example, when the lithium enolate of propionyl imide **132** was treated with benzaldehyde, a mixture of three diastereomeric aldol products resulted in an 17.8:1.2:1 ratio, from which the (2′*S*,3′*S*) *syn* product **133** was obtained in 83% yield. A similar process employing **134** was more selective, giving only *syn* adducts **135** and **136**, with (2′*S*,3′*S*)-**135** predominating (10:1). The major aldol **135** was obtained in 88% yield from this reaction. Banks et al. noted that **132** and **134** afforded higher selectivity than they were able to obtain from amino acid or terpene-derived auxiliaries under the same conditions, although under other reaction conditions Evans-type oxazolidinones have delivered much higher selectivities. Because of the limited scope of these studies, the general utility of **27** and **28** in aldol chemistry is not yet fully clear.



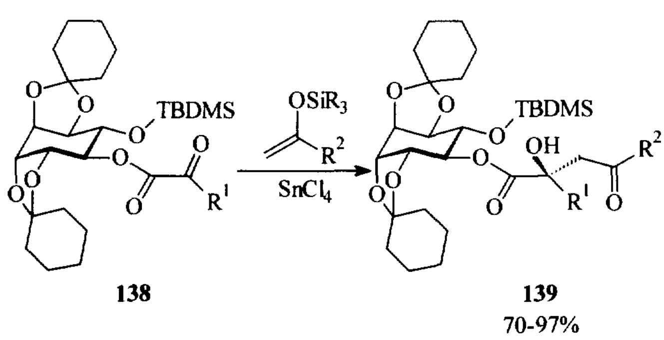
Scheme 30

Schiff base derivatives of glycine are very readily enolized, and they have been employed very successfully in the asymmetric synthesis of α-amino acids under mildly basic phase transfer conditions.[65] However, under similar conditions, the diacetone-D-glucose iminoglycinate ester **137** was recently reported to undergo aldol condensations with tetradecanal with very poor diastereoselectivity.[66] These disappointing results are perhaps not too surprising given the role of chelation in many of the examples of alkylation and aldol reactions of sugar-derived enolates in the literature. The conditions used to effect the reactions of **137** (K_2CO_3, *i*PrOH, catalyst) do not seem to favor the formation of a stereochemically constrained enolate complex involving the sugar. However, it is unexpected that the titanium enolate of **137**, prepared using $ClTi(OiPr)_3$ in CH_2Cl_2, was reported in the same paper to give very low selectivity and extremely poor chemical yield in an analogous aldol condensation under conventional conditions. It is difficult to assess the full significance of these results, however, since the authors provided few details of their experiments.



137

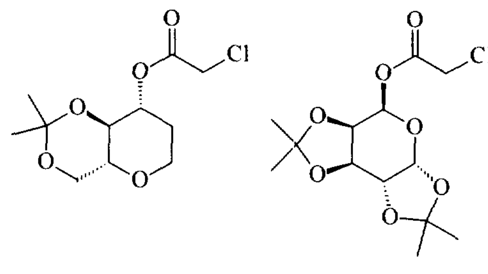
Figure 13



Scheme 31

A carbohydrate auxiliary can also be linked to the electrophilic component of an aldol condensation. Very highly selective Mukaiyama aldol reactions have been achieved using cyclitol pyruvate or phenylglyoxylate esters **138** (Scheme 31, R^1 = CH_3 or phenyl).[67] This approach provided an efficient enantioselective synthesis of chiral *tertiary* aldols, which are often difficult to prepare. Essentially a single diastereomer (**139**) was obtained in 70–97% yield from reactions of **138** with several silyl enol ethers or silyl ketene acetals in the presence of $SnCl_4$. The cyclitol auxiliary was easily removed from the aldol by simple base-promoted hydrolysis of **139**.

The Darzens reaction is a variation on the aldol process that affords α,β-epoxyester products. In an attempt to apply carbohydrate auxiliaries to this reaction,[68] Nangia et al. found that the D-glucal-derived chloroester **140** gave a 1.86:1 mixture of epoxides (80%) when reacted with *p*-anisaldehyde in the presence of NaH. In contrast, **141** (from D-galactose) afforded the glycidic ester product as essentially a single diastereomer. They postulated that the increased selectivity was due to improved coordination of the sodium counter-ion by the galactosyl auxiliary, which fixed the geometry of the enolate with respect to the auxiliary in **141**. Unfortunately, this tighter coordination also promoted elimination of the enolate, resulting in a very low yield (25%). The authors did not report the absolute configuration of the epoxide obtained from **141**.

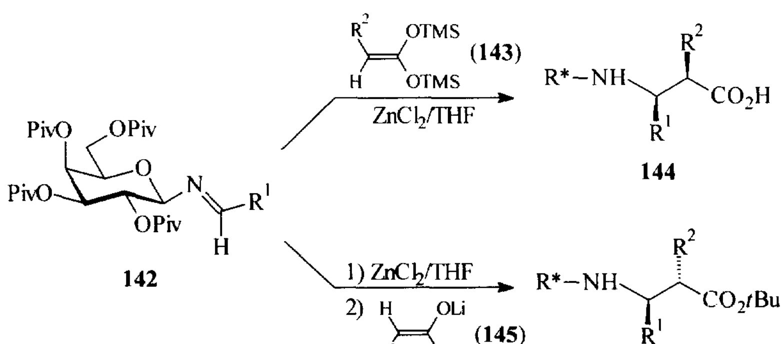


140 **141**

Figure 14

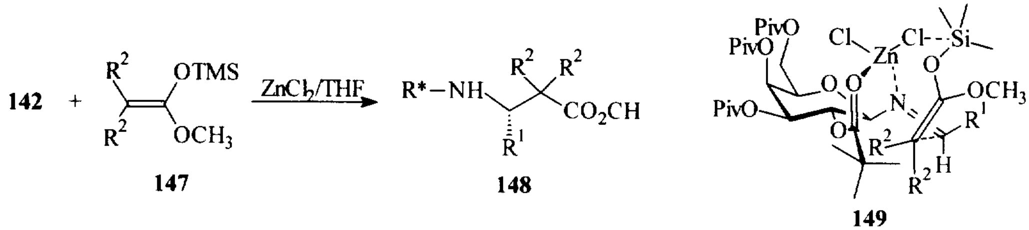
Other Additions to C=X Bonds

Nucleophilic addition reactions of *N*-galactosylaldimines have been extensively explored by Kunz et al., and their earlier results in this area were summarized in previous reviews.[4a,5] A recent publication from this group describes an improved approach to α-alkyl-β-amino acids.[69] Bis(*O*-trimethylsilyl)ketene acetals **143** reacted with D-galactopyranosylimine **142** in the presence of $ZnCl_2$ to give β-amino acid adducts. The *erythro* products **144** were obtained in most cases with better than 10:1 selectivity, and several of the reported reactions gave essentially a single product. The *threo* diastereomers were not detected in any of the reactions



Scheme 32

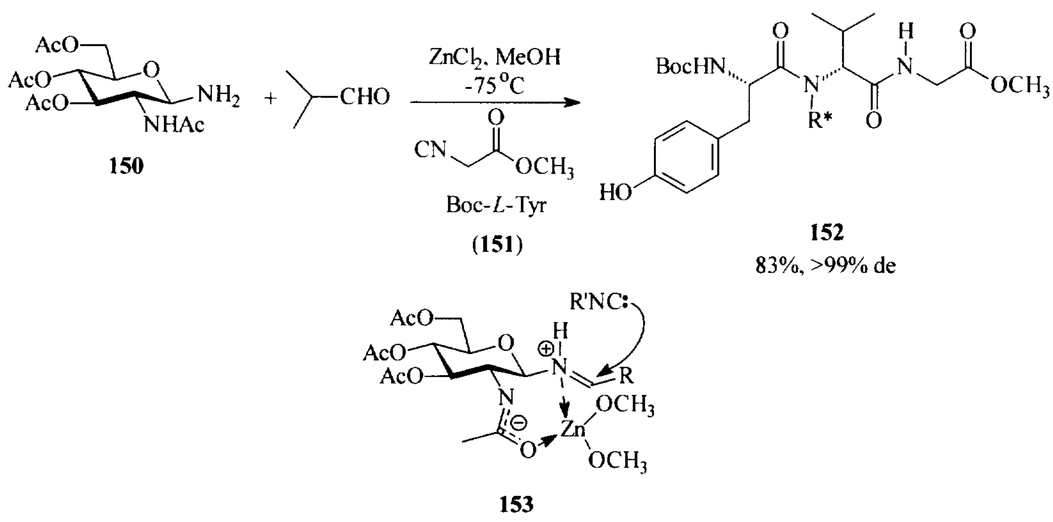
studied. On the other hand, *threo* products **146** were obtained from the reaction of **142** with lithium ester (*E*)-enolate **145** in the presence of $ZnCl_2$, although with only modest (3:1) selectivity. The sugar auxiliary was easily separated from the *N*-glycosyl amino acid products **144** and **146** by mild acid hydrolysis.



Scheme 33

If the reactions shown in Scheme 32 are compared with earlier results reported by Kunz and Schanzenbach,[70] (Scheme 33) an intriguing aspect of the chemistry of galactosylimine **142** becomes apparent. When disubstituted silyl ketene acetals **147** reacted with **142** in the presence of $ZnCl_2$, β-aminoester products **148**, possessing amino group configurations *opposite* to that in **144**, were obtained. The formation of **148** required attack at the more-hindered *re* face of the $ZnCl_2$-activated imine. Kunz has explained this outcome by proposing reactive complex **149** (Scheme 33).[4a] A "closed" structure of this type, while consistent with the formation of **148**, is not believed to be involved in most reactions of silyl enol ethers or ketene acetals with electrophiles.[71] Reaction on the less-hindered *si* face of $ZnCl_2$-activated **142** (as in Scheme 32) may reflect the involvement of an "open" transition structure, although it is unclear why **147** and **143** should behave differently towards **142** under apparently similar reaction conditions.

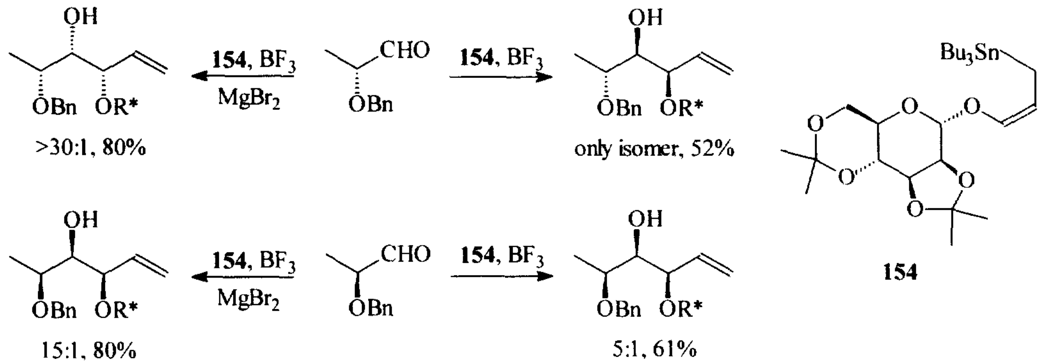
The four-component Ugi condensation of an amine, an aldehyde, an isocyanide, and a carboxylic acid is a very efficient route to α-amino acids. Some years ago, Kunz demonstrated that 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine induced excellent levels of stereoselectivity (10:1–32:1) in the presence of a zinc catalyst.[4a] Ugi recently reported that 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucosylamine (**150**) was a superior auxiliary-linked amine for the direct preparation of peptide products (e.g. **152**) when protected amino acids (e.g. **151**) were employed as the acid components.[72] Using **150**, diastereomerically pure (*R*) products were obtained in most cases. Ugi attributed the enhanced selectivity obtained using **150** to the involvement of a



Scheme 34

zwitterionic complex such as **153** between the *N*-acetyl group, the zinc catalyst, and the imine. This complex constrained the isocyanide nucleophile to approach the "back" face of the imine function, leading to nearly exclusive formation of (*R*) products.

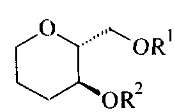
Roush and co-workers have used the (3-tributylstannylprop-1-enyl) α-D-mannopyranoside **154** in asymmetric allylations of representative chiral aldehydes.[73] These reactions represent a reversal of the usual regioselectivity of additions to enol ethers, forming the new C–C bond adjacent to the oxygen. The stereogenic centre of the aldehyde was an important element in these reactions, since achiral aldehydes afforded very poor



Scheme 35

selectivity. A "matched/mismatched pair" relationship between the sugar auxiliary and the aldehyde component was clearly implicated, particularly in the case of α-alkoxy aldehydes. Adding $MgBr_2$ to reactions of **154** with α-alkoxy aldehydes revealed an especially surprising result. This additive not only enhanced the selectivity of the process, but also *reversed* its stereochemical preference. Like the Diels–Alder reactions studied by Stoodley, these allylations seem to have been controlled by an *exo*-anomeric conformation in which the mannose C-1–O-5 bond was nearly perpendicular to the enol ether aglycon. The steric influence of this bond induced the electrophile to approach the *si* face of the allyltin nucleophile. The authors suggested that $MgBr_2$ influenced the conformation of the α-alkoxy aldehyde, rather than interacting directly with the sugar auxiliary in **154**.

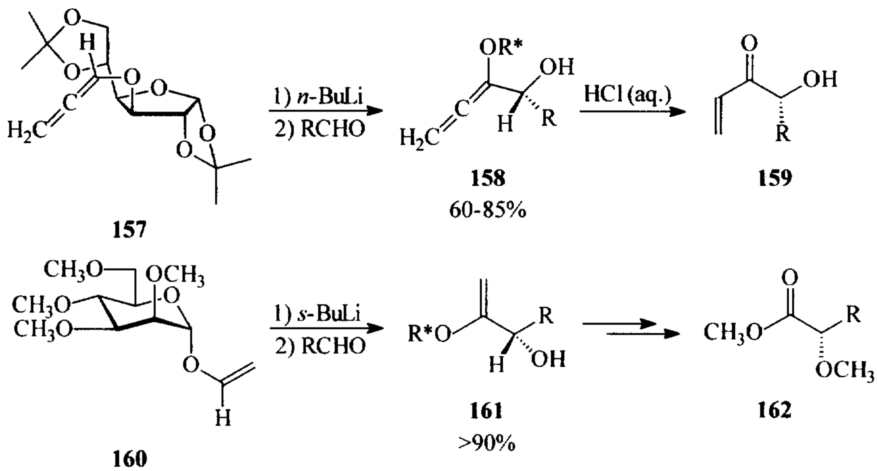
In a similar series of experiments, Yamamoto employed allylstannanes linked to a D-glucal-derived auxiliary at the primary hydroxyl or at a secondary non-anomeric position.[74] Allylstannane **155**, in which the connection to the auxiliary involved a secondary hydroxyl group, afforded *syn* diols in 63–94% de and up to 82% yield. Yamamoto found that **156**, in which the allylstannane was connected to the primary hydroxyl, did not give good stereoselectivity in reactions with aldehydes. The Sakurai reaction of allylsilanes with aldehydes is similar to these allylstannane additions. A recent study of the use of allylsilyl ethers of D-arabinose in this reaction also obtained only low selectivity.[75] This may simply reflect the distance between the reacting atoms and the stereogenic centres of the auxiliary, in contrast to the more selective stannane additions described above.



155: R^1 = TBDPS
R^2 = (*Z*)-CH=CHCH_2SnBu_3
156: R^1 = (*Z*)-CH=CHCH_2SnBu_3
R^2 = TBDPS

Figure 15

Enantiomerically enriched, chiral α-hydroxy vinyl ketones **159** have been made by the reaction of chiral alkoxyallene anions with aldehydes.[76] Three monosaccharide derivatives, as well as several amino alcohols and terpenes, were examined as chiral auxiliaries for this process. The best diastereoselectivity (12.3:1) was obtained in the reaction of D-glucofuranosyl allene **157** with benzaldehyde, but other aldehydes afforded much lower selectivity in reactions with **157**. Vinyl ketone **159** was released from the auxiliary by acidic hydrolysis of enol ether **158**, with no loss of stereochemical integrity. In a similar but unrelated study,[8] vinyl 2,3,4,6-tetra-

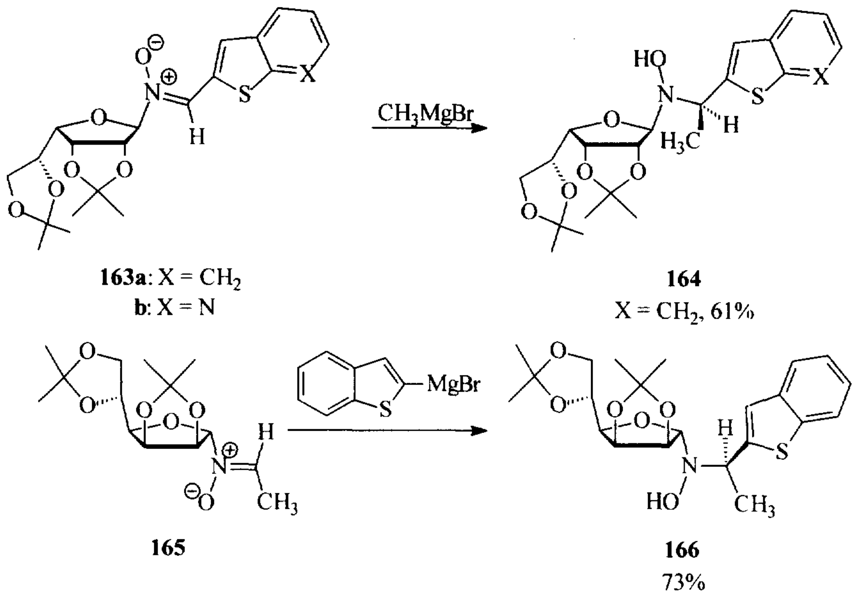


Scheme 36

O-methyl-α-D-mannopyranoside (**160**) was deprotonated with *s*-BuLi, and reacted with various aldehydes to give allylic alcohols **161**. The best selectivity was obtained with benzaldehyde (13.3:1), while aliphatic aldehydes were less satisfactory. The allylic alcohols **161** could be converted in a few steps to chiral α-alkoxyesters **162**, with minimal loss of stereochemical integrity. Analogous chemistry of vinyl α-L-rhamnopyranosides, which are pseudo-enantiomers of **160**, gave the opposite absolute configuration at the newly formed stereogenic centre with equal levels of selectivity. No detailed rationales to explain the stereoselectivities of these reactions were offered by the authors of either study.

Nitrones were previously discussed in the context of dipolar cycloadditions (see Scheme 20), but they can also act as electrophiles. Sugar-linked nitrones have been stereoselectively alkylated by various organometallic nucleophiles. Dondoni and co-workers have done much recent work in this area, but they have focused on *C*-linked sugar nitrones as "chiral pool" building blocks rather than as reusable auxiliaries.[77] Nevertheless, chemists interested in employing an auxiliary-linked nitrone as an electrophile in a synthesis will find much useful background information in Dondoni's work.

Unlike *C*-linked sugar nitrones, which do not include a readily cleavable linkage, *N*-glycosyl nitrones are well suited to use in the chiral auxiliary mode. Two separate industrial groups have used D- or L-gulofuranosyl- and D-mannofuranosylnitrones in the stereoselective synthesis of the 5-lipoxygenase inhibitors Zileuton and RS-27871.[78] Both *gulo*[78a] and *manno*[78b] auxiliaries induced completely diastereoselective additions of MeMgBr to nitrones containing a bulky heteroaryl group (e.g. **163a**). On the other hand, the less-hindered nitrone **165** reacted with the corresponding heteroaryl nucleophile with only moderate selectivity (9.2:1).[78b] The stereochemistry of the major adducts **164** and **166** was consistent with Vasella's earlier



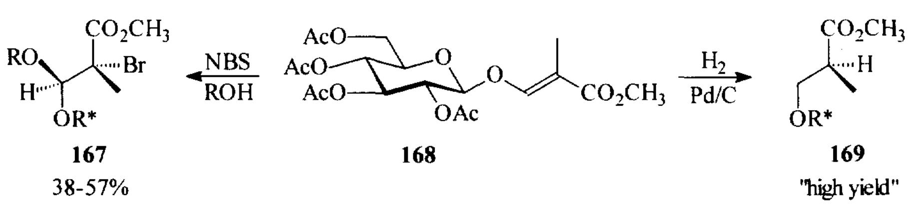
Scheme 37

proposal that nucleophiles prefer *anti* approach to an *O-endo* conformation of a glycosyl nitrone.[79] The *gulo* system **163a** is probably the better auxiliary of the two for this reaction, since both D- and L-gulose are readily available, and also since the *manno* nitrone afforded a significant amount of a bis-addition product in addition to the desired monoadduct. In the preparation of the pyrido analogue RS-27871, MeMgBr added to nitrone **163b** with poor selectivity (1.86:1 (*R*):(*S*)) unless trimethylaluminum was present. Under these conditions, the major adduct was the *enantiomer* of **164**, isolated in 63% yield with 82% de[78a] The authors did not offer an explanation for this dramatic selectivity reversal, but the metal-bound nitrone may favor an *O-exo* conformation rather than the *O-endo* form usually adopted by glycosyl nitrones.

In a recent patent application, workers at SmithKline Beecham Corp. have described the preparation of chiral, heterocyclic *N*-hydroxylamines and *N*-hydroxyureas by stereoselective additions of various nucleophiles to D- or L-mannofuranosyl nitrones analogous to **165**.[80]

STEREOSELECTIVE OXIDATIONS AND REDUCTIONS

Alkenes are a rich source of other functionality, so it is not surprising that monosaccharide auxiliaries have been applied to their asymmetric re-functionalization. Vinyl glycosides are obvious substrates for such reactions, and Stoodley has explored both oxidation and reduction of these alkenes.[81] Based on his obser-

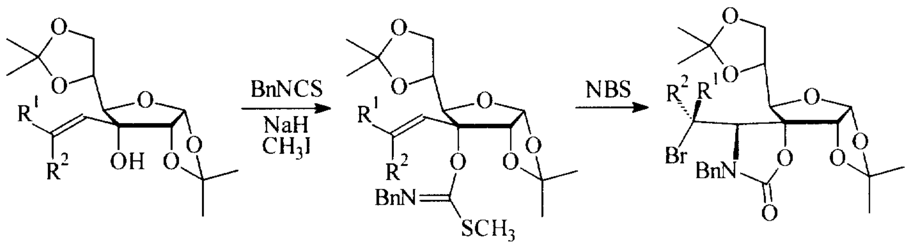


Scheme 38

vations of the cycloaddition chemistry of vinyl glucosides, Stoodley predicted that bromoalkoxylation of **168** would proceed by initial addition of Br^+ to the *re* face of the alkene, with subsequent *anti* addition of an alcohol to give **167**. This expectation was borne out experimentally, although the overall selectivity obtained was only about 6:1. The major adducts were obtained in 38–57% yield and in a stereochemically pure state by simple crystallizations. This process only worked with primary alcohols, but since the alcohol group in **167** was lost when solvolysis of the sugar auxiliary released the latent carbonyl in the aglycon, this may not be a serious limitation. The loss of stereochemistry at this carbon also means that the *anti* addition of the alcohol is of less significance than is the *re* facial preference of the initial halogenation. The vicinal trifunctional array in **167** is potentially of considerable use in synthesis, nonetheless.

Vinyl glucoside **168** was also hydrogenated over Pd/C catalyst with the same stereochemical preference, giving the hydrocarbon **169** as a 5.7:1 mixture of diastereomers. These reactions were clearly not as selective as were the cycloadditions using the same D-glucose auxiliary. One might speculate that this reduced selectivity could be due to unfavorable interactions at the surface of the heterogeneous hydrogenation catalyst, but very similar selectivities were observed by other workers using soluble $ClRh(PPh_3)_3$ to reduce vinyl D-mannosides and L-rhamnosides.[8,82]

Halonium-ion-promoted intramolecular addition to a sugar-linked alkene provided a highly stereoselective route to deuterium-labeled L-serine, and other amino acids.[83] The 3-C-vinyl-allofuranoside **170** was readily obtained from diacetone-D-glucose, with deuterium in either the R^1 or R^2 positions. Its thiocarbamate derivative **171** cyclized on treatment with NBS, forming the oxazolidinone **172** (61–80%, 15:1). The authors

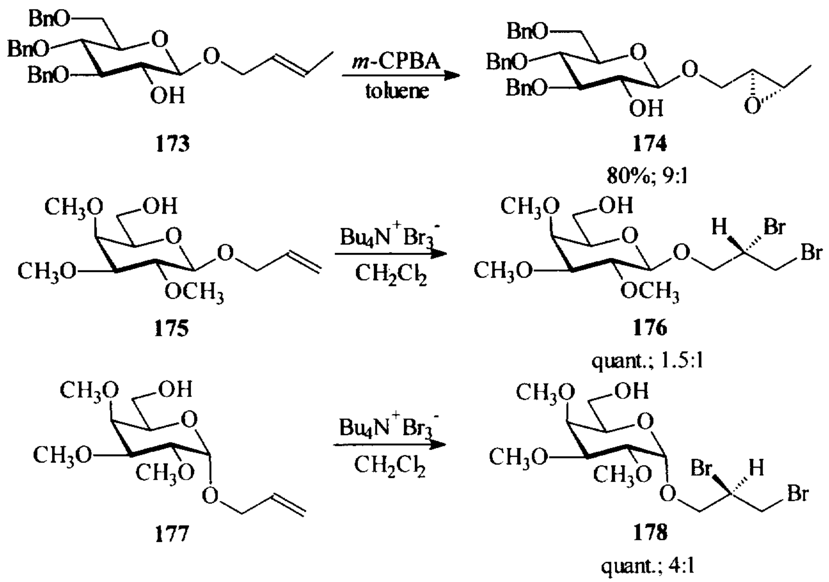


170 **171** **172**

Scheme 39

argued that the two isopropylidene groups on opposite faces of **171** acted in concert to constrain the positions of both components of the cyclization, leading to high selectivity. In order to transform **172** into a range of useful materials, they showed that its bromide could be displaced by acetate, thioacetate, malonate or cyanide nucleophiles. Amino acid products were finally obtained by the destructive oxidation of the furanose ring, after the removal of all protecting groups. This chemistry is closely related to other work by Kakinuma et al. on the Overman and Wittig rearrangements, discussed below (Scheme 47 and Figure 17).

Allyl glycosides were cyclopropanated in an extremely diastereoselective fashion,[42a] but their epoxidation,[84] dihydroxylation,[85] and dibromination[86] reactions (Scheme 40) have proven to be less satisfactory. As was the case with cyclopropanation, a free hydroxyl group in the vicinity of the alkene was important in obtaining good selectivity. Charette has found that **173** could be epoxidized by *m*-CPBA to form **174** with up to 9:1 selectivity when its C-2 hydroxyl was free, but that no selectivity was obtained when it was blocked as a

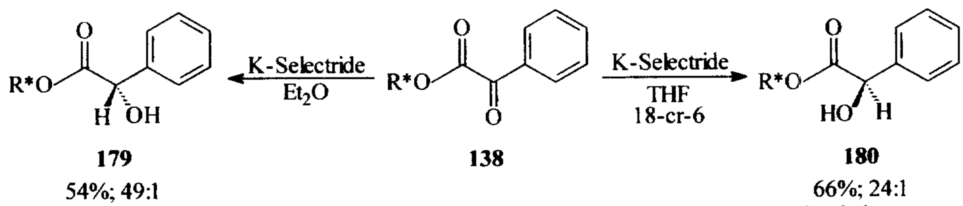


Scheme 40

silyl ether.[84] Given the success of the Simmons–Smith reaction of **173**, it was remarkable that metal-based epoxidizing reagents were unsuccessful in this case.

Bellucci et al. observed that brominations of various allyl glucosides and galactosides by $Bu_4N^+Br_3^-$ were unselective unless either the C-2 or C-6 hydroxyl group was free.[86] The bromination selectivity was only modest, but it is noteworthy that the reaction afforded different stereoselectivity depending on which hydroxyl was free. The selectivity was also reversed when the anomeric configuration was changed. Thus, the reaction of β anomer **175** afforded a 1.5:1 mixture favoring the (*S*) dibromide **176**, while the α anomer **177** gave the (*R*) dibromide **178** as the major component of a 4:1 mixture, under the same conditions. Charette has observed a similar reversal, dependent on the anomeric configuration, in cyclopropanation reactions.[42a,c]

Carbohydrate auxiliaries have also been applied to the stereoselective reduction of ketones. Akiyama found that either mandelate stereoisomer **179** or **180** could be obtained from the reduction of *chiro*-inositol phenylglyoxylate ester **138** (see also Scheme 31) by simply altering the reaction conditions.[87] Thus, it was not necessary to use enantiomeric auxiliaries to access enantiomeric products. K-Selectride® selectively attacked the *re* face of **138** in Et_2O solution (54%; **179**:**180** = 49:1), but reduction in THF in the presence of 18-crown-6 led to reduction at the *si* face (66%; **179**:**180** = 1:24). Akiyama proposed that the auxiliary provided a rigid

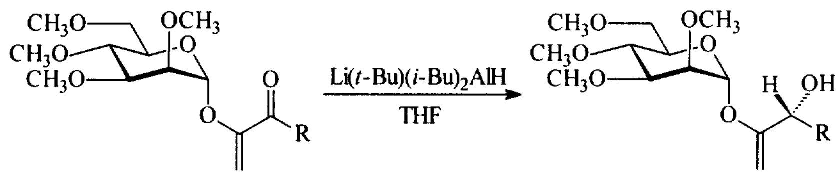


R*OH = 1L-3-*O*-(*t*-Butyldimethylsilyl)-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol

Scheme 41

chiral environment, and that the switch in selectivity resulted from two conformers of the ketoester. The *syn* arrangement of the carbonyls (presenting the ketone's *re* face to the approach of the reagent) was presumably favored by K^+ ion chelation, while the *anti* conformer predominated when the cation was sequestered by 18-crown-6.

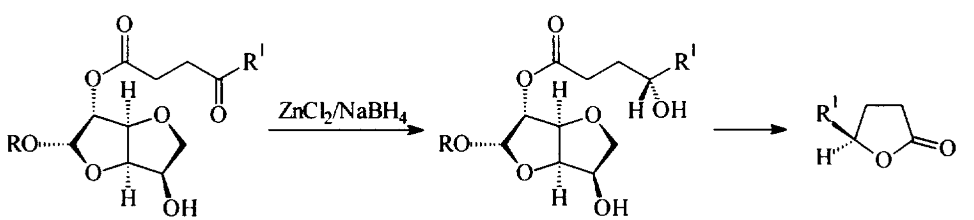
Glycosidic enones are essentially masked α-diketones or α-ketoesters. Selective 1,2-reduction of α-D-mannosyl enones **181** (Scheme 42) with a very bulky hydride reagent gave (*R*) allylic alcohols **182** as the major components of 9–19:1 mixtures of diastereomers.[8] Higher stereoselectivity was obtained when the enone contained bulkier R groups. The pseudo-enantiomeric α-L-rhamnosyl enones afforded the (*S*) alcohols with similar levels of selectivity. Considering the similarity between **181** and the dienes **2** (Scheme 3) studied by Stoodley,[18,19] these results can perhaps be understood in terms of conformations similar to those proposed for Diels–Alder reactions. This analysis would suggest that the orientation of the enone relative to the sugar auxiliary in **181** may be controlled by the *exo*-anomeric effect. It would be expected to adopt an *s-cis* conformation to minimize $A^{(1,3)}$ strain due to the steric bulk of the R group.



181 **182**
78-89%; 9-19:1

Scheme 42

A remarkable level of remote stereoinduction was obtained in reduction of the γ-ketoesters **183**, incorporating a bicyclic anhydro-D-glucose auxiliary.[88] $Zn(BH_4)_2$ reduced the ketone group with up to 28:1 diastereoselectivity. The resulting hydroxyesters **184** were hydrolyzed, and isolated as lactones **185** with 72–93% ee.



183, R = CH_3, Bn
R^1 = CH_3, C_6H_5

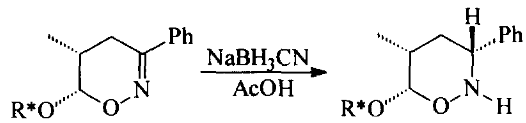
184
>90%; 6-28:1

185
80-82%; 72-93% ee

Scheme 43

On the other hand, analogous δ-ketoesters were reduced with no more than 3.5:1 selectivity. The authors proposed that chelation of the reagent was essential to obtain selectivity, since $NaBH_4$ was essentially unselective towards either type of ketone. Sodium ions would not interact as strongly with **183** as would Zn^{2+} ions.

A somewhat lower degree of remote induction was obtained in the $NaBH_3CN$ reduction of the diacetone-D-glucose-substituted 4*H*-1,2-oxazine **186**.[89] In this reaction the auxiliary did not appear to interact directly with the reagent, but simply blocked the α face of the oxazine. It is not clear that the anomeric effect of the oxazine would be sufficient to maintain the bulky glucofuranosyl group in the axial orientation required to effectively block the reagent's approach to this face of the C=N bond. The modest facial selectivity obtained in the formation of **187** (3.75:1) is thus not surprising. Comparable results were obtained when a terpenoid auxiliary was employed in place of diacetone glucose.



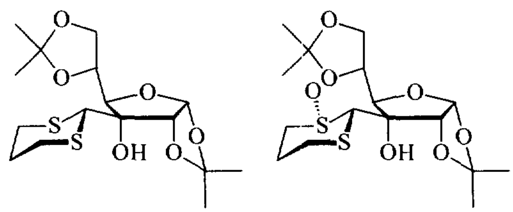
186 **187**

65%; 3.75:1

R*OH = 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose

Scheme 44

Highly enantiomerically enriched 1,3-dithiane-1-oxide may serve as a chiral acyl anion synthon. The (*R*) enantiomer of this sulfoxide was obtained by asymmetric oxidation of the 3-*C*-(1,3-dithian-2-yl)-allofuranoside **188**, easily prepared in two steps from diacetone-D-glucose *via* the 3-ulose derivative.[90] Oxidation of **188** by *m*-CPBA was unsatisfactory, giving only a modest yield and a 3.8:1 ratio of monosulfoxide diastereomers. In contrast, Ti(O-*i*-Pr)$_4$/(−)-diethyl tartrate/*t*-BuOOH afforded the (*R*)-*trans* sulfoxide **189** (91%, 13.3:1). With the use of this chiral oxidant system, a pronounced matched/mismatched pairing effect was observed. When the (−)-diethyl tartrate was replaced with its (+) enantiomer, **189** was produced as the main component of a 4:1 mixture with other sulfoxide diastereomers, along with 21% of a disulfoxide. Nevertheless, the authors noted that the sugar auxiliary exerted a greater stereochemical influence than did the tartrate, as (*R*)-**189** still predominated. (*R*)-Dithiane-1-oxide was efficiently liberated from **189** by basic hydrolysis, allowing the auxiliary to be recovered as the 3-ulose.



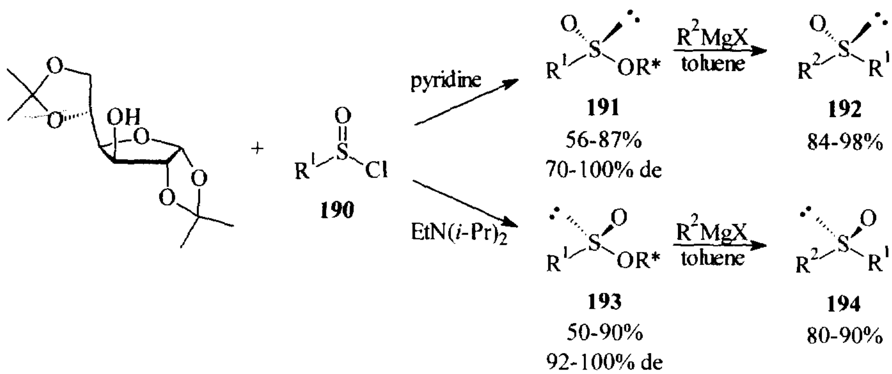
188 **189**

Figure 16

MISCELLANEOUS APPLICATIONS OF CARBOHYDRATE AUXILIARIES

Selective Displacement Reactions at Sulfur and Phosphorus

Sulfoxides can also be prepared by displacement of the alkoxide moiety from a sulfinate ester. While this reaction has been known for many years, in 1991 Llera et al. described the use of the ubiquitous diacetone-D-glucose as a chiral auxiliary for this process.[91] This method has since been developed further.[92] The key stereoselective step in this process was the formation of a sulfinate ester of diacetone glucose. Llera et al. found that the stereochemistry of the sulfinate depended on the base present during the reaction of **190** with the sugar. When pyridine was used, (*R*) sulfinates **191** were obtained in 70%–100% de, while Hünig's base promoted formation of (*S*) sulfinates **193** as single diastereomers in most cases. Grignard reagents displaced the auxiliary from **191** or **193** with complete inversion of configuration at sulfur[92b] so that enantiomerically pure sulfoxides **192** or **194** were readily obtainable from the appropriate sulfinate ester. Recently, the displacement of diacetone glucose 3-sulfinates by enolates (rather than alkyl or aryl Grignard reagents) has been explored as a route to β-ketosulfoxides.[93] While ketone potassium enolates reacted with **191** or **193** with very low enantioselectivity to give the corresponding sulfoxides, *N*,*N*-dimethylhydrazone lithium salts afforded

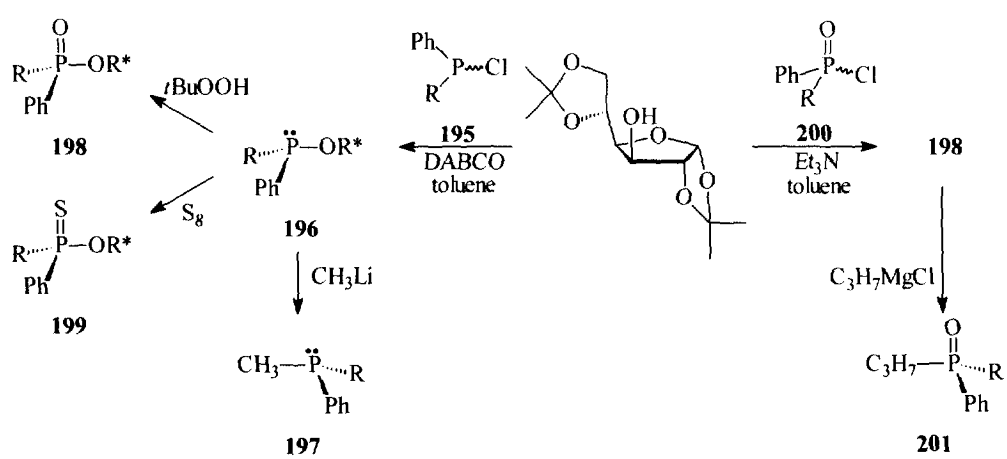


Scheme 45

complete inversion of configuration at sulfur. This approach was employed in the first asymmetric synthesis of both enantiomers of the immunosuppressant drug Oxisuran.

Similar chemistry using diacetone-D-glucose for the diastereoselective preparation of phosphines, phosphine oxides, and phosphinates has also been independently investigated by Kolodiazhnyi[94] and Khiar, Fernández et al..[95] The same base-dependent reversal of selectivity described above for the reactions of sulfinyl chlorides was observed by both groups in the reactions of asymmetric chlorophosphines with the sugar. Thus, chlorophosphines **195** reacted with the C-3 hydroxyl of diacetone glucose in the presence of DABCO or Et_3N, to give nearly exclusively the (*S*) phosphinites **196**. The selectivity of the process was reversed by the use of pyridine, although the diastereomeric excesses of the (*R*) products were only moderate. The phosphinites **196** were directly converted to chiral phosphines **197** (with inversion of configuration at phosphorus) on treatment with alkyl lithium reagents, or they could be oxidized to the corresponding phosphinates (**198**) or thiophosphinates (**199**) with complete retention of configuration. Several non-carbohydrate chiral auxiliaries were also studied, but much lower levels of diastereoselectivity were obtained.[94b]

Stereochemically defined phosphinates could also be obtained in a single step by the reaction of phosphinyl chlorides **200** with diacetone glucose (Scheme 46). The stereochemical influence of the base was noted

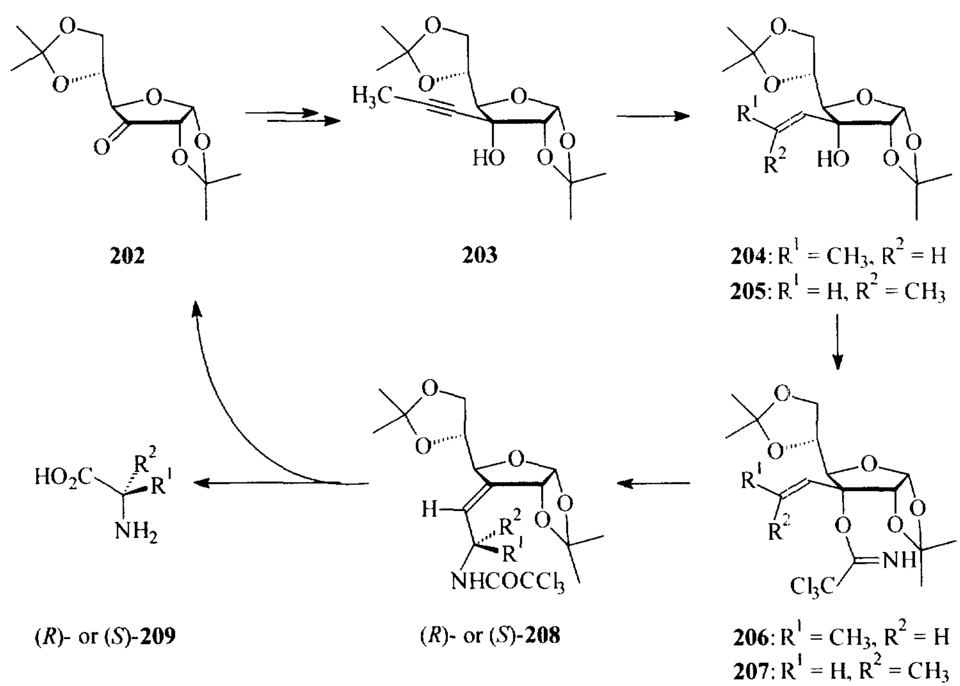


Scheme 46

in this process, with the same effect as was seen in the reactions of sulfinyl chlorides.[95] It was remarkable that, although the starting phosphinyl chlorides were racemic, the yields of diastereomerically pure phosphinates **198** produced by this route exceeded 50%, even when the reagents were used in a 1:1 ratio.[94b] Kolodiazhnyi proposed that this resulted from the thermodynamically controlled equilibration of an intermediate pentacoordinate phosphorus species involving the chiral auxiliary. Thus, both enantiomers of **200** could be transformed to a single diastereomer of **198**. The phosphinates were converted by Grignard reactions to enantiomerically pure phosphine oxides **201**, useful as chiral ligands for metal-based catalysts.[95] These Grignard reactions displaced the chiral auxiliary with complete inversion of configuration at phosphorus.

Rearrangements

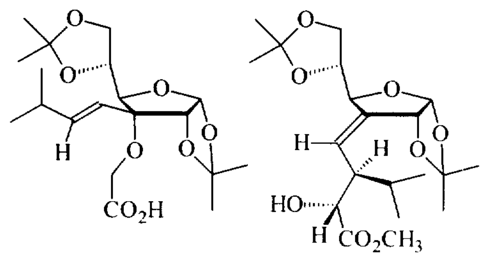
The Overman rearrangement of allylic trichloroacetimidates based on a D-glucofuranose chiral auxiliary selectively afforded either enantiomer of various α-amino acids.[96] As a demonstration of the technique, (*R*)-alanine was prepared with 94:6 selectivity by thermal [3,3] rearrangement of the (*E*)-allylic imidate **206**, while the (*Z*)-allylic imidate **207** led to (*S*)-alanine essentially as a single diastereomer. Both imidates were obtained from stereoselective reductions of the common precursor **203**, *via* olefins **204** and **205**. The oxidative release of the amino acids **209** using RuO_4 also regenerated the 3-ulose form of the chiral auxiliary (**202**) for re-use.



Scheme 47

Semi-empirical calculations on the transition states for these reactions suggested that the stereoselectivity arose from the co-operative action of the 1,2-*O*-isopropylidene ring and the C-4 side-chain in **206** or **207**, which restricted the possible conformations adopted by the imidate and the olefin during the rearrangement.[96b]

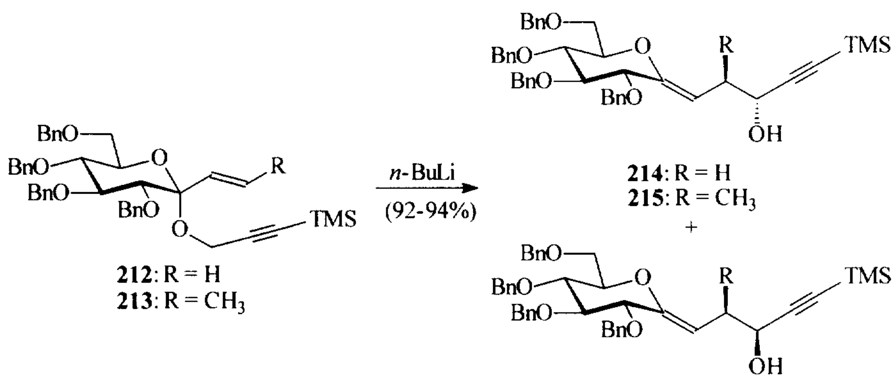
In a similar approach, Kakinuma et al. have also made various 3-alkylmalic acid derivatives using the [2,3]-Wittig rearrangement.[97] Thus, the *threo* rearrangement product **211** (Figure 17) was obtained in 78% yield and 19:1 selectivity when acid **210** was treated with an excess of LDA, followed by esterification. Separation of the malic acid product from **211** followed analogous chemistry to that described above. This rearrangement affords the same products as would a *threo*-selective aldol reaction of a glyoxylate ester, but it is operationally simpler.



210 **211**

Figure 17

A D-glucopyranose-derived auxiliary has also induced high levels of diastereoselectivity in [2,3]-Wittig rearrangements.[98] The necessary propargylic α-glycosides **212** and **213** were obtained from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose in three very efficient steps. When **212** was treated with *n*-BuLi, rearrangement afforded exclusively the propargylic alcohol **214** in 92% yield. The more substituted olefin **213** gave a 9:1 mixture of diastereomers **216** and **215** (94%), where the configuration of the major alcohol **216** was reversed with respect to that of **214**. The authors proposed that the rearrangements proceeded *via* transition states in which the olefins adopted *gauche* orientations relative to the endocyclic oxygen of the auxiliary. This type of geometry conforms to expectations based on the operation of the *exo*-anomeric effect. The change in selectivity at the alcohol centre was then explained in terms of different orientations of the silylacetylene chains in the transition states arising from **212** and **213**. These differences arose because of unfavorable steric interactions when the vinylic substituent was bulkier than hydrogen. Presumably, the auxiliary could be separated by ozonolysis of **214**–**216**, after the desired reactions of the alkyne groups were complete, although the authors did not comment on this.

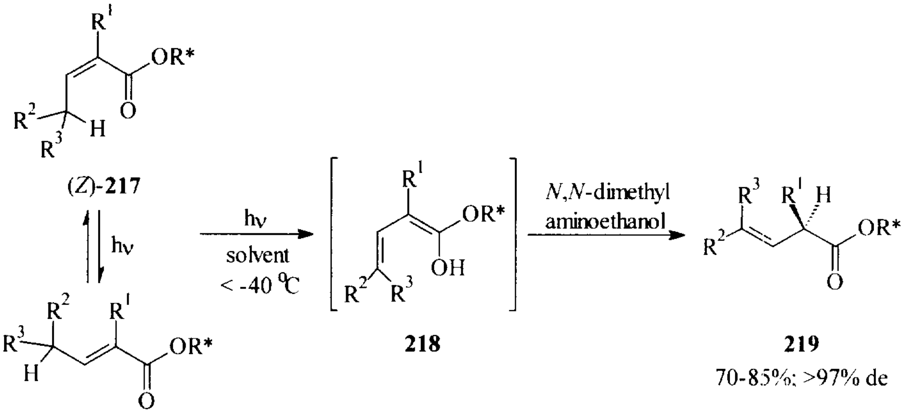


Scheme 48

While the rearrangements discussed above proceeded with high diastereoselectivity, the Claisen rearrangement of glucosyl allyl vinyl ethers has not yet become a synthetically useful process.[99] The unprotected D-glucose auxiliary allowed the reaction to proceed in an aqueous solution. In this solvent, the rearrangement was very fast, but the diastereomeric ratio of the products was only 1.5:1. Similarly, low selectivity was obtained using a protected D-glucose auxiliary in toluene solution, although the reaction was much slower. The noteworthy feature of these rearrangements was that changing the anomeric configuration of the substrates reversed the absolute configuration of the products. This result was rationalized by the authors using the *exo*-anomeric arguments proposed by Stoodley.[18]

Photochemical Transformations

α-Alkyl-α,β-unsaturated esters **217** may be photoenolized by 254 nm irradiation. Protonation of the resulting enols (**218**) results in deconjugation, producing a new stereogenic centre adjacent to the ester group in **219**. Piva and Pete showed that diacetone-D-glucose was an extremely effective chiral auxiliary for this process.[100] The reaction was essentially completely diastereoselective (>97% de, favoring the (*R*) configuration in **219**) when it was performed in hydrocarbon solvents at low temperatures, in the presence of dimethylaminoethanol as the proton source. Moreover, the structure of **217** seemed to have little effect on the stereo-

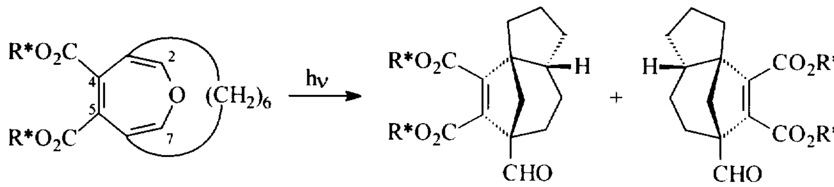


R*OH = 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose

Scheme 49

selectivity of the overall process, the only requirement being a suitable hydrogen atom for the photochemical [1,5]-sigmatropic enolization step. Photodeconjugation using the diacetone glucose auxiliary has been applied to the synthesis of the perfume components (*R*)-2-methyl-1-decanol and -undecanol,[101a] and also to the preparation of the terpene (*R*)-lavandulol.[101b] This reaction is an attractive alternative to the common enolate routes to α-alkylated esters, as it potentially avoids the use of strongly basic reagents under inert atmosphere conditions. Nevertheless, the necessary α,β-unsaturated ester precursors (**217**) are not always trivial to obtain.[101b]

Diacetone-D-glucose also induced excellent diastereoselectivity in the fascinating photochemical transformation of the crystalline oxepine diester **220** into the methanohydroazulene **221**.[102] When an ethereal *solution* of **220** was irradiated, the ensuing rearrangement produced a mixture of **221** and **222**, in a 1.25:1 ratio. In contrast, irradiation of an aqueous *suspension* of **220** afforded a 23:1 mixture of **221** and **222**, from which pure **221** was isolated in 54% yield. The carbohydrate fragments were crucial to this highly selective *solid state* process, since they imparted crystallinity as well as asymmetry to diester **220**. X-ray and infrared data for **220** suggested that the C-4 and C-5 ester carbonyls were twisted out of conjugation with the oxepine π-system to different extents, as a result of the bulky sugar groups. The authors proposed that because the ester group at C-5 was better conjugated, the initial disrotatory photocyclization step occurred preferentially between C-2 and



220 **221** **222**

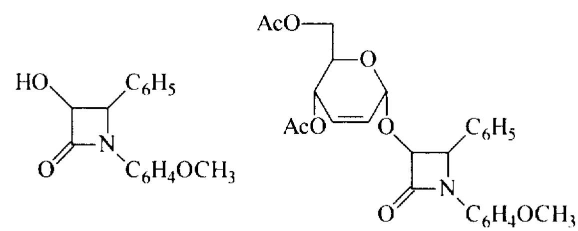
R*OH = 1,2:5,6-di-*O*-isopropylidene D- or L-glucofuranose

Scheme 50

C-5, leading (eventually) to **221**. The alternative cyclization, beginning with bond formation between C-4 and C-7, gave the diastereomeric product **222**. Naturally, the opposite stereochemical outcome was observed when diacetone-L-glucose auxiliaries were used. The authors reported that the sugars were efficiently separated from the methanohydroazulene ring system and could be recovered in 95% yield.

Resolution of Racemic Mixtures

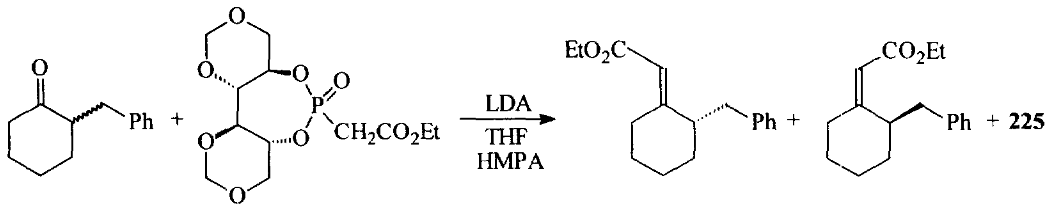
Despite the intrinsic elegance of highly selective asymmetric synthesis, the fact that both enantiomers are frequently desired for biological assays has sustained interest in resolution methods. There have been a few recent reports of carbohydrate auxiliaries employed in classical enantiomer resolutions. For example, Köll's D-xylofuranosyl oxazolidinone was originally described as a highly efficient auxiliary for the chromatographic separation of carboxylic and sulfonic acid enantiomers,[62a] before it was employed in the stereoselective reactions already discussed (see Scheme 27). Likewise, Bose et al. showed that *cis*-α-hydroxy-β-lactams (±)-**223** may be chromatographically resolved *via* their diastereomeric α-glycoside derivatives **224**, which were obtained by an iodine-catalyzed Ferrier reaction with tri-*O*-acetyl-D-glucal.[103] The β-lactam was separated from the sugar after the chromatography, by simple acid hydrolysis of **224**. This process suffers, however, from the fact that the auxiliary is not readily reusable.



(+/-)-**223** **224**

Figure 18

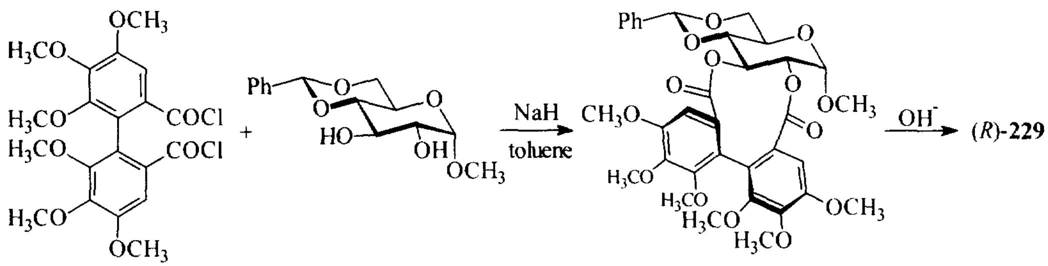
A somewhat unusual kinetic resolution by Wittig olefination of racemic α-alkyl cyclohexanones provided simple access to some chiral alkenes.[104] When the racemic cyclohexanone **225** was treated with the chiral phosphonate **226** (from D-mannitol) and an excess of LDA, the (*E*)-alkene (*S*)-**227** was obtained in 42% yield and 89% e.e., along with a small amount of the (*Z*)-alkene (*R*)-**228**. The starting ketone **225** was recovered in 39% yield, in a nearly racemic state. This indicated that under the conditions of the resolution, **225** was being epimerized, and thus in principle this resolution could be carried to 100% conversion. The scope of this process with respect to the racemic ketone substrates was not fully explored, but most of the α-alkyl group variations described by the authors significantly reduced the efficiency of the resolution.



(+/-)-225 226 (*S*)-227 42%; 89% ee (*R*)-228

Scheme 51

Itoh and co-workers have used D-glucopyranoside **230** to kinetically resolve axially chiral biaryl diacids.[105] The (*R*)-biaryl ester **231** could be obtained in good chemical yield and > 1500:1 diastereoselectivity, from acylation of **230** by the racemic acid chloride **229**. The choice of solvent and base was critical to the selectivity of this acylation; (*R*)-**231** was the major ester when the reaction was conducted using NaH in toluene, whereas (*S*)-**231** predominated (4.4:1) when the acylation occurred in THF with triethylamine as base. Unfortunately, both the diastereoselectivity and the chemical yield of the (*S*)-selective process were disappointing. Overall, however, this method should tolerate considerable variation in the structure of the biaryl units, as demonstrated by the resolution of binaphthyldicarboxylic acid *via* esterification with **230**. In a related area,



(+/-)-229 230 (*R*)-231 37%; >1500:1

Scheme 52

Feldman demonstrated completely (*S*)-selective oxidative coupling of galloyl groups attached to the O-4 and O-6 positions of glucopyranose, in the course of his synthetic investigations into the ellagitannin plant metabolites.[106] This work did not employ the sugar as a chiral auxiliary, since D-glucopyranose is the core of the ellagitannin structure, but it indicates a potential application for sugar auxiliaries in asymmetric aryl couplings.

SUMMARY

The many researchers whose efforts are summarized here and in earlier reviews have clearly demonstrated that monosaccharides are effective auxiliaries for many types of synthetically useful reactions. Monosaccharide auxiliaries have been particularly successful in cycloadditions, while reactions of sugar-linked enolates have given more variable results. Further enolate studies, exploiting a wider range of metal counterions, are necessary to fully determine the extent to which sugar-based auxiliaries can compete with other approaches. Sugars have been notably successful at inducing asymmetry in photochemical transformations, and very promising results have been obtained for free-radical reactions as well.

It is also evident that most research into carbohydrate auxiliaries is still at the "synthetic method development" stage. There have been comparatively few studies in which a carbohydrate auxiliary was employed in the total synthesis of a target molecule, in marked contrast to the widespread use of carbohydrates as chirons in total synthesis. This may simply reflect the fact that carbohydrate chemistry has only recently emerged into the mainstream of organic synthetic methodology. We can anticipate that as more organic chemists become familiar (and comfortable) with carbohydrates, they will find additional interesting ways to apply them in complex multi-step syntheses.

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Biographical Sketch

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Philip Hultin obtained his undergraduate education at Dartmouth College (Hanover, NH, USA) in 1983, specializing in organic chemistry. He then attended the University of Toronto, where he was granted the M.Sc. degree in 1985 and the Ph.D. in 1988. His thesis research, under the guidance of Dr. J. Bryan Jones, dealt with the applications of hydrolytic enzymes in asymmetric synthesis. After a year at the University of Wisconsin at Madison, he returned to Canada in 1989 to do additional postdoctoral studies in carbohydrate chemistry with Dr. Walter Szarek at Queen's University (Kingston, ON). He remained at Queen's, working on the synthesis of nucleoside analogues and sugar sulfate derivatives, until joining the Chemistry Department at the University of Manitoba as an Assistant Professor in 1993. His research interests include polymer-supported chiral auxiliaries based on monosaccharides or amino acids, and the preparation and study of semi-synthetic vaccines using oligosaccharide antigens from melanoma.

Marion Earle received the Honors B.Sc. degree from the University of Western Ontario in 1989. She spent two summers at the University of Victoria (Victoria, BC) as an NSERC Undergraduate Summer Scholarship student, where she worked on the synthesis of kojic acid with Dr. Gerry Poulton and carried out studies in organic photochemistry with Dr. Peter Wan. After graduation, Marion worked as a laboratory technician for 5 years, before beginning graduate studies at the University of Manitoba in 1994.

Manjula Sudharshan attended the University of Jaffna in Sri Lanka, obtaining the B.Sc.(Honors) in chemistry in 1992. After working as a demonstrator at the University of Jaffna and at the Open University of Sri Lanka in Colombo, she came to Manitoba in 1995 where she is a graduate student with Dr. Hultin.