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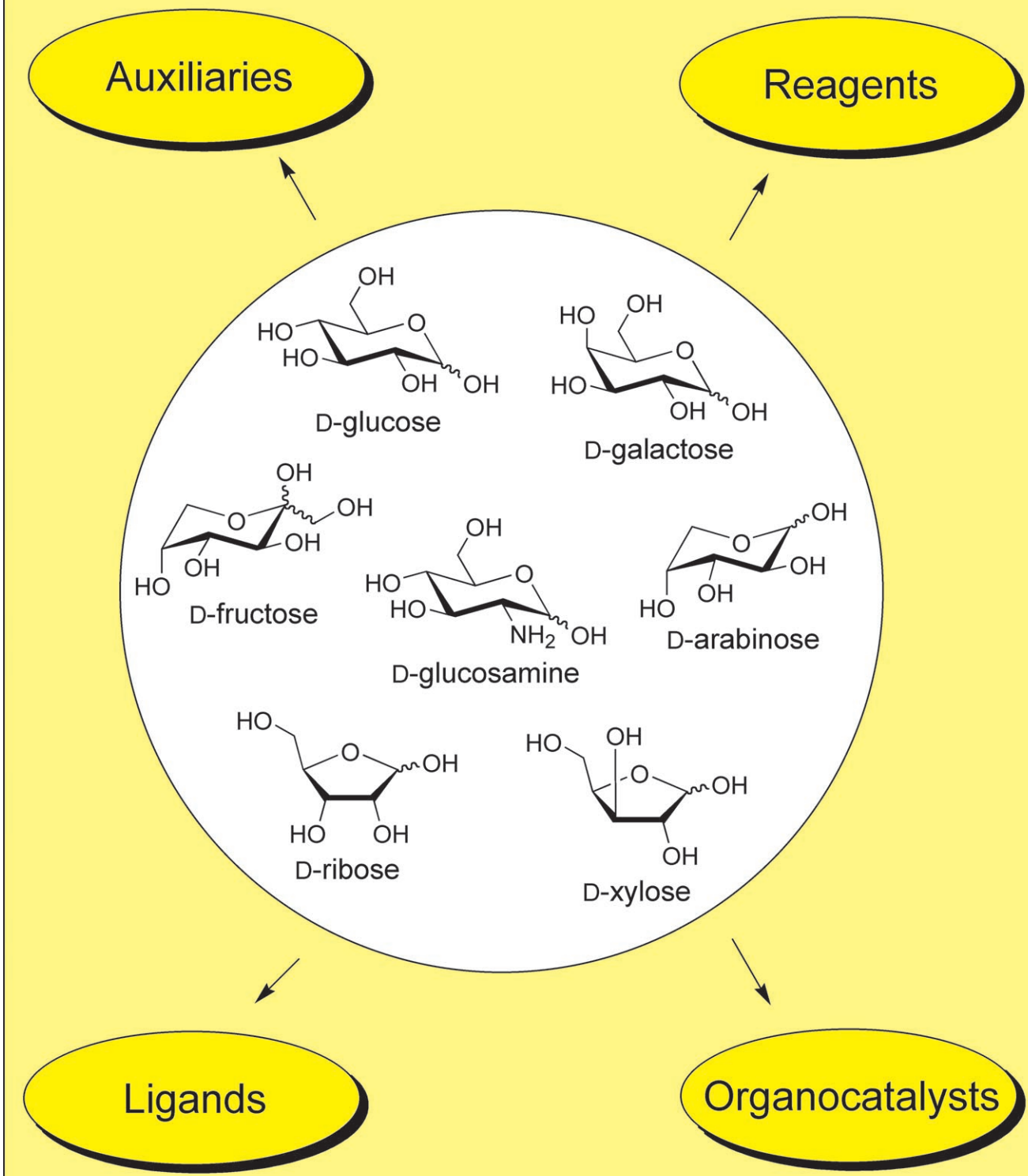
Carbohydrates as Tools in Organic Synthesis



Carbohydrates as Synthetic Tools in Organic Chemistry

Mike M. K. Boysen*[a]

Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday

Abstract: While amino acids, terpenes and alkaloids have found broad application as tools in stereoselective organic synthesis, carbohydrates have only lately been recognised as versatile starting materials for chiral auxiliaries, reagents, ligands and organocatalysts. The structural diversity of carbohydrates and the high density of functional groups offer a wide variety of opportunities for derivatization and tailoring of synthetic tools to a specific problem.

Keywords: carbohydrates · chiral auxiliary · chiral ligand · organocatalyst · stereoselective synthesis

Introduction

As the preparation of enantiomerically pure compounds is essential in natural product synthesis as well as in medicinal chemistry, intense effort has gone into the development of chiral auxiliaries, chiral reagents and chiral catalysts, which have in many cases been honed to a high level of efficiency. A lot of these synthetic tools are based on amino acids, terpenes and alkaloids, while carbohydrates, the most abundant compound class from the chiral pool have received considerably less attention. Carbohydrates, which are available in many different architectures have long been regarded as ill-suited as precursors, mainly because of their plentiful polar functional groups. However, the functional groups can be used to advantage: By modifying the functional groups reactive and coordinative sites can be introduced into the carbohydrate framework. Further, bulky groups blocking certain faces of a coordinated or bound substrate can be affixed to these groups. Exploiting this concept, some very valuable synthetic tools have been developed.

One problem with synthetic tools from the chiral pool is that generally only one enantiomer is easily accessible and, indeed, the L-enantiomers of most naturally occurring D-carbohydrates are either prohibitively expensive or unavailable. This problem can often be solved by the use of pseudo-enantiomers, which are only mirror images where the configuration of parts essential for stereodifferentiation are concerned. Therefore pseudo-enantiomers can also be prepared from the D-series.

This article aims to give an overview of prominent and recent examples for carbohydrate tools with pyranose or furanose substructure. Acyclic compounds and heterocyclic structures based on carbohydrates will not be discussed.

Carbohydrate Auxiliaries

Although it is 30 years since the earliest examples of such tools were reported,[1] broader investigations only started 20 years ago. Since then a multitude of structures has been developed and applied to various reactions.[2] One very versatile tool is pivalyl protected D-galactosyl amine **1** introduced by Kunz and co-workers.[3] Condensation with aldehydes yielded galactosyl aldimines **3** which underwent highly diastereoselective Strecker reactions with trimethylsilyl cyanide in the presence of Lewis acids[3] (Scheme 1). The solvent had a crucial influence on the stereoselectivity, $SnCl_4$ in THF and $ZnCl_2$ in isopropanol yielding α-aminonitriles **4**[3a,b] while Strecker products **5** with opposite configuration at the new stereocenter were obtained with $ZnCl_2$ in the less polar chloroform.[3c] Diastereomerically pure compounds were obtained by simple recrystallisation; then the auxiliary was cleaved with diluted acid and could be recovered. The products were further elaborated into α-amino acids.

The four component Ugi reaction[4] is an attractive alternative to the Strecker protocol as it yields α-amino acid derivatives directly. Kunz et al. achieved excellent *de* values for this reaction with various aldehydes and galactose deriv-

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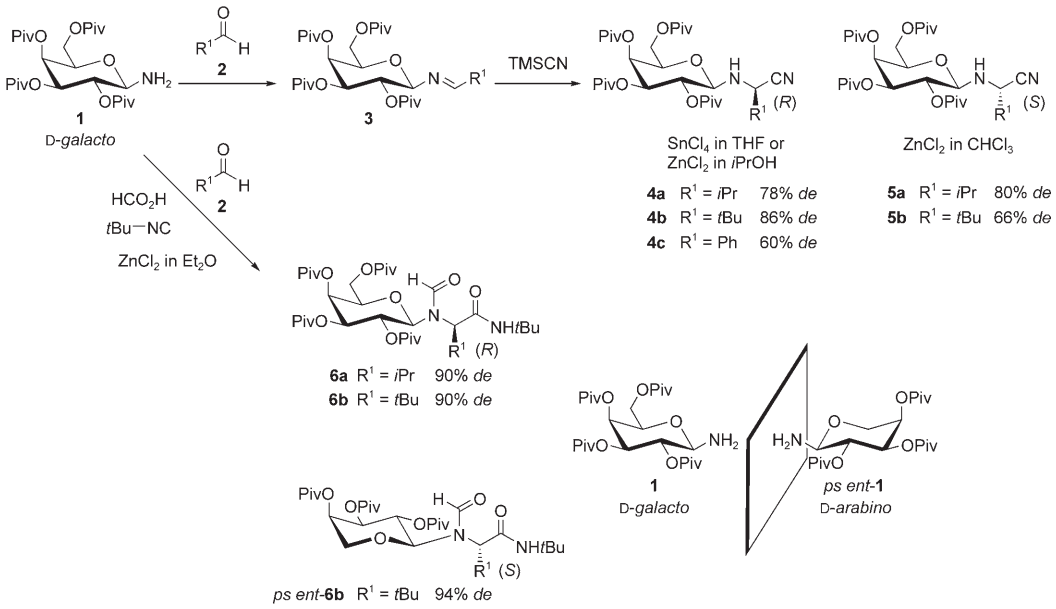


Scheme 1. Diastereoselective Strecker and Ugi reactions with a D-galactose auxiliary.

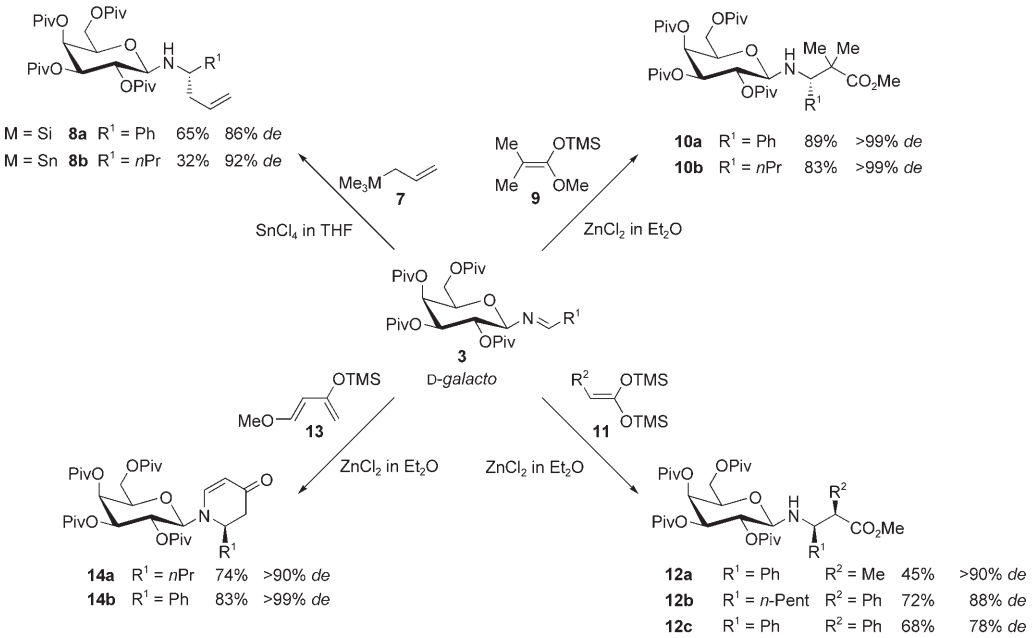
ative **1** as the amine component, obtaining **6** in the presence of zinc chloride[5a,b] (Scheme 1). As a reversal of stereoinduction was not possible by changing the solvent, pseudo-enantiomeric auxiliary *ps ent*-**1** was prepared from D-arabinose,[5c,d] which is the pseudo mirror image of D-galactose. Using *ps ent*-**1** the Ugi product *ps ent*-**6b** was obtained in excellent *de* with *S* configuration at the new stereocenter (Scheme 1). Later Ugi and co-workers extended the method to other carboxylic acids and isocyanides employing an auxiliary based on glucosamine.[6]

Various other carbon nucleophiles could be added diastereoselectively to galactosyl imines **3** (Scheme 2). Homoallyl amine **8a** was prepared from the corresponding imine and allyl trimethylsilane in the presence of $SnCl_4$ with good *de* values,[7a,b] the aliphatic **8b** imine could only be obtained using allyl trimethylstannane in similar *de* but in lower yield.[7b] The pseudo-enantiomeric approach by using arabinose was unsuccessful, however, the more expensive L-fucose satisfactorily reversed the stereoinduction.[7b,c] Mannich-type reactions were explored with ketene acetal **9**, which added to imines **3** in the presence of $ZnCl_2$.[8] Bis-*O*-TMS ketene acetals **11** with one α-substituent generated two new stereocenters.[8b] Both reactions proceeded with good to excellent *de*. Reactions of **3** with Danishefsky's diene[9] (**13**) proceed via a tandem Mannich reaction Michael addition sequence rather than a hetero Diels–Alder reaction and yielded 2-substituted dehydropiperidin-4-ones **14** in excellent *de*.[10]

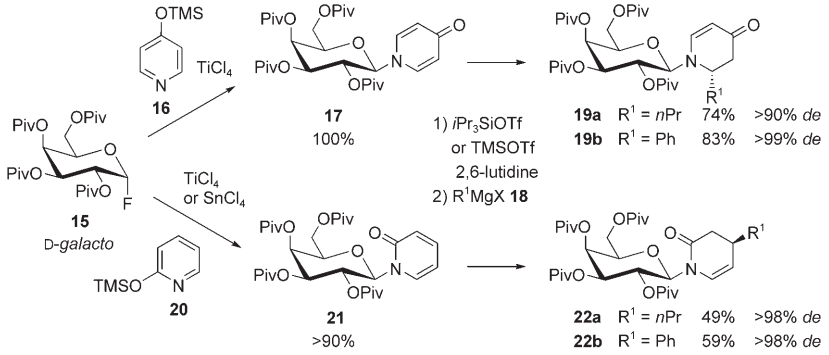
An alternative access to 2-substituted dehydropiperidin-4-ones is the desymmetrisation of 4-pyridone, with the aid of a galactose auxiliary (Scheme 3). 4-Trimethylsiloxypyridine (**16**) was treated with galactosyl fluoride **15** and the resulting *N*-galactosyl 4-pyridone (**17**) was submitted to Grignard reactions under Lewis acid activation.[11a,c] The 2-aryl or 2-alkyl substituted dehydropiperidin-4-ones **19** formed with opposite stereochemistry compared to those from the tandem Mannich–Michael reaction with Danishefsky's diene (cf. products **14**, Scheme 2). When 2-trimethylsilylpyridine (**20**) was used, the resulting pyridones **21** underwent 1,4-addition with Grignard reagents to yield 4-substituted dehydropiperidin-2-ones **22**.[11b,c] Again yields and *de* were excellent. These heterocycles were elaborated into alkaloid structures.

Tadano and co-workers extensively studied the selectivity of 1,4-additions of cuprates to crotonates fixed onto various carbohydrate scaffolds[12] (Scheme 4). In all cases the crotonate was assumed to be locked in an s-*trans* conformation due to complexation by metal salts from the reaction mixture. For the D-*gluco* auxiliaries **23** with a 4-*O*-crotonate, the size of the 3-*O*-substituent had large impact on the selectivity. The cuprate attacked preferentially from the rear face of the crotonate as the front was shielded by 3-*O*-substituent R^1. Thus, the efficiency of the stereoinduction increased with the bulk of this substituent, the opposite trend was observable for the C-6 substituents. With 3-*O*-crotylated D-*manno* auxiliaries **25** the size of the axial 2-*O*-substituent influenced the sense of stereoinduction. With 2,4-di-*O*-benzylated auxiliary **25a** the 4-*O*-benzyl group had the largest shielding effect, while the 2-*O*-pivalate residue in **25b** blocked the front face, leading to **26b** with the opposite configuration at the new stereocenter of **26**.

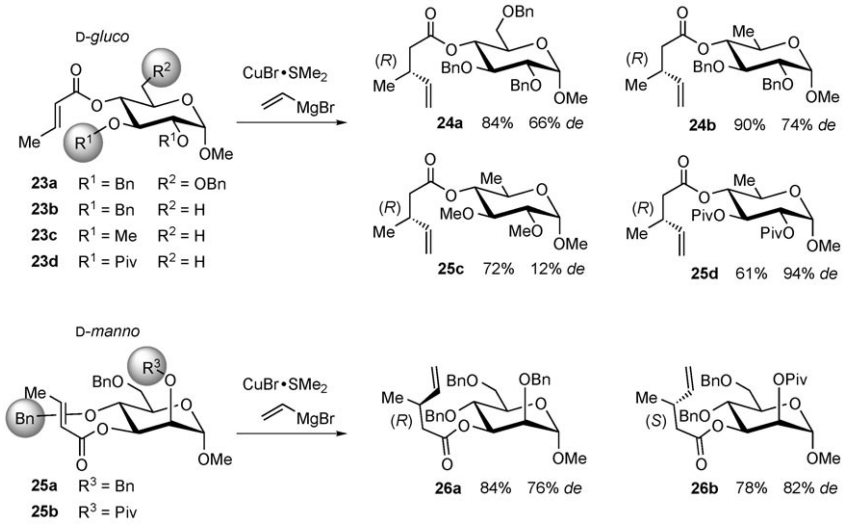
Similar studies of the same group conducted for α-alkylations of propionates[12c,13a] and Diels-Alder reactions of acrylates[12c,13b,c] identified derivatives of 6-deoxy glucose with bulky 2-*O* and 3-*O* substituents (Piv, TBS) as efficient auxiliaries. While in most cases the dienophile is attached to the carbohydrate auxiliary for practical reasons, the groups of Stoodley, Marazano and Lubineau reported examples of



Scheme 2. Diastereoselective reactions of galactosyl imines with various carbon nucleophiles.



Scheme 3. Stereoselective addition of Grignard reagents to piperidinone galactosides.

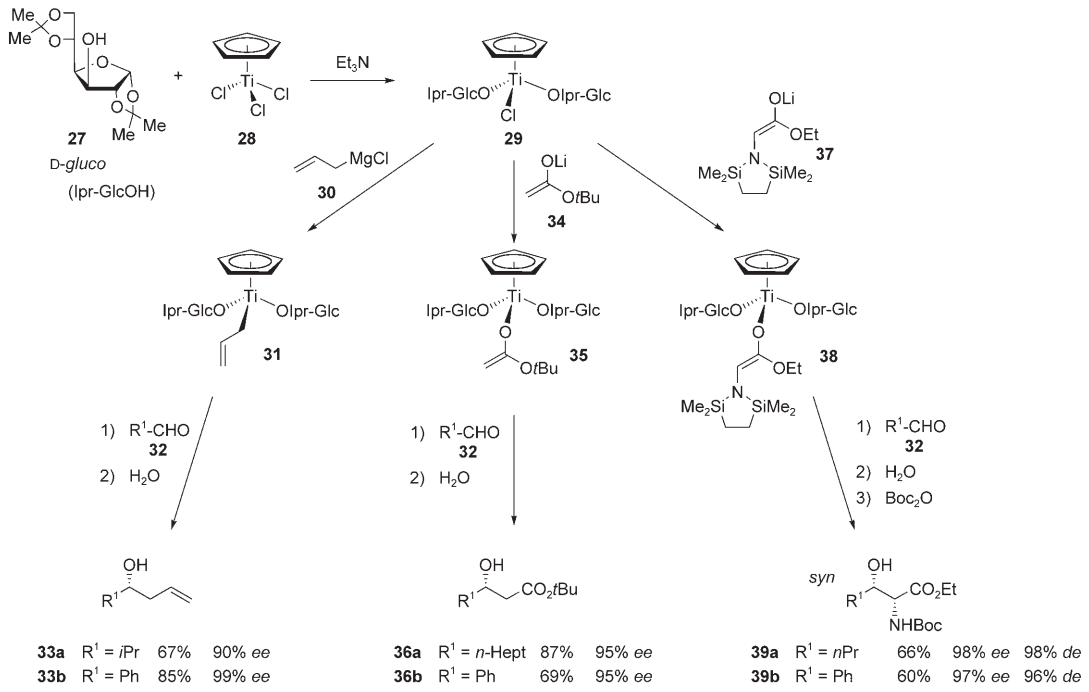


Scheme 4. Impact of different auxiliary architectures and of the size of blocking groups on the 1,4-addition of cuprates to crotonate esters.

reactions with carbohydrate-modified dienes,[14] achieving moderate to good diastereoselectivities. Stoodley and co-workers explored a glucose analogue of Danishefsky's diene while Marazano et al. used 1,2-dihydropyridine *N*-glycosides of xylose, arabinose and glucose, while Lubineau et al. prepared diene enol ethers of unprotected glucose for reaction in water.

Carbohydrate Reagents

A successful example of a carbohydrate reagent is titanium complex **29** which was prepared by Duthaler and co-workers from half-sandwich titanium compound **28** and diisopropylidene glucose (Ipr-GlcOH) **27**[15] (Scheme 5). When treated with an allyl Grignard, **31** was formed, which transferred the allyl residue to aldehydes with good to excellent *ee*.[15,16a,e] Reagent **29** has proved especially valuable in aldol reactions. Titanium enolate **35** formed from acetate enolate **34** was be used



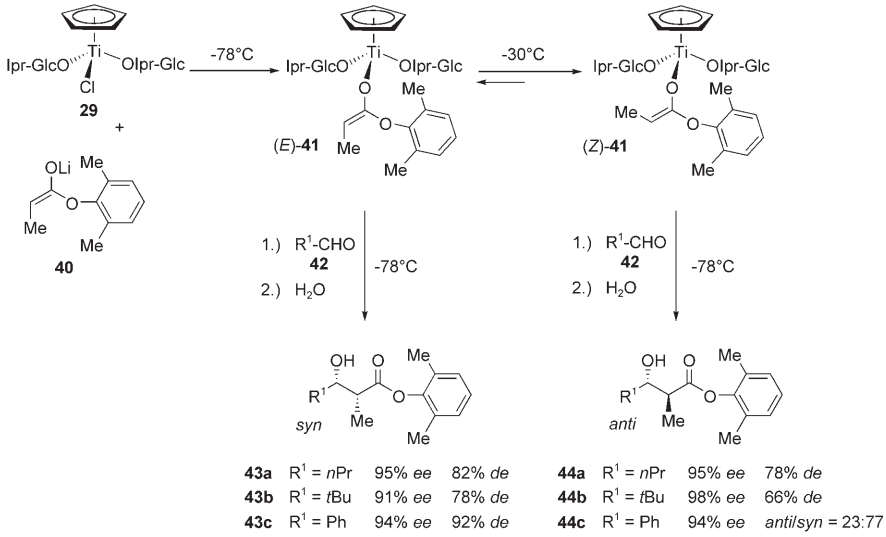
Scheme 5. Titanium reagents modified with diisoproylidene glucose for addition of carbon nucleophiles to aldehydes.

for highly enantioselective aldol additions.[15,16b] The corresponding glycine ester enolate **38** yielded *syn*-configured β-hydroxy-α-amino acids **39** in excellent *ee* and *de*.[15,16c]

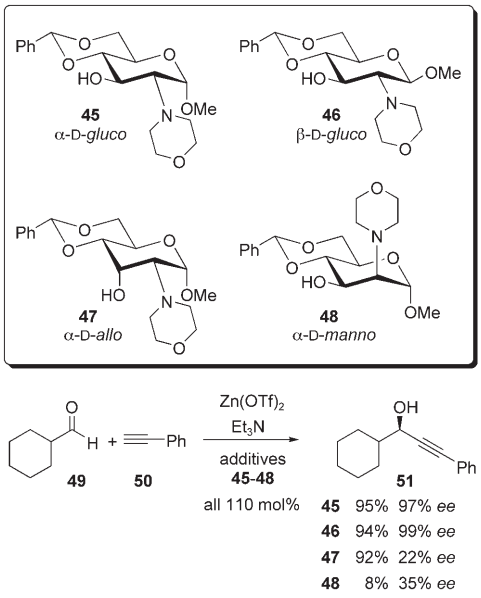
Aldol reactions of propionyl enolates derived from **29** were explored as well[15,16d] (Scheme 6). Titanium enolate (*E*)-**41** formed from the lithium enolate **40** at −78 °C yielded *syn*-aldol addition products **43** in high *ee* and good *de*. The (*E*)-enolate was easily isomerised to (*Z*)-**41** by simple stirring and warming to −30 °C for a few hours. (*Z*)-**41** formed *anti* aldol addition products of aliphatic aldehydes in excellent *ee* and moderate to good *de*. However, no *anti* selectivity was observed with benzaldehyde.

Attempts to prepare pseudo-enantiomeric titanium reagents by attaching other carbohydrate derivatives were unsuccessful, leading to severely decreased selectivities.[15,16e] In some cases a tartrate derived titanate could be used for stereoinduction reversal.[15]

Recently Davis et al. investigated the asymmetric alkynylation of aldehydes with zinc triflate,[17] using series of carbohydrate-derived amino alcohols as chiral additives[18a] (Scheme 7). These had been employed earlier for addition of diethyl zinc to aldehydes.[18b] The *gluco* configured additives **45** and **46** gave excellent yield and *ee*, while *allo*-configured **47** and *manno*-configured **48** led to poor results. Pyranose **47** still catalyzed the reaction but with low selectivity, while **48** proved to be completely inefficient. Several other alkynes as well as aliphatic and aromatic aldehydes gave good selectivities. These results are among the best achieved for this transformation.[18a]



Scheme 6. Stereoselective aldol reactions with titanium propionyl enolates.



Scheme 7. Enantioselective alkynylation of aldehydes with carbohydrate amino alcohols as additives.

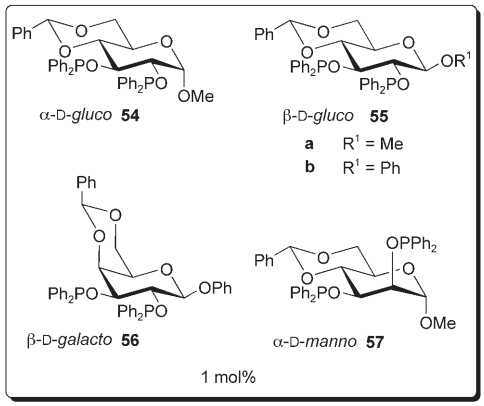
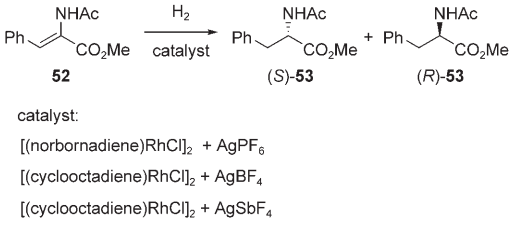


Figure 1. Early examples for carbohydrate ligands and their application in asymmetric hydrogenation.

Carbohydrate Ligands

The first carbohydrate ligands[19] were reported independently by the groups of Cullen, Thompson, Selke and Descotes, describing diphosphophosphinite ligands prepared from D-glucose for the rhodium catalyzed hydrogenation of (*Z*)-α-acetamidocinnamic acid (**52**) to L-phenylalanine (*S*)-**53** (Scheme 8). In an early study on the impact of the carbohydrate structure on stereoselectivity, Selke's group examined D-*galacto*-, D-*manno*-, and α- and β-D-*gluco*-configured diphosphinite ligands in this reaction[20] (Figure 1). While the yields were good to excellent for all ligands studied, the stereochemical outcome strongly depended on the ligand structure. The β-*gluco* ligands **55a** and **55b** with all-equatorial substituents gave the best results, **55b** yielding (*S*)-**53** in excellent *ee*. The α-*gluco* ligand **54** was less efficient while *galacto* ligand **56** and *manno* ligand **57** gave low or no *ee*, respectively. As this study shows the relative orientation of the two coordinative sites (2,3-*trans* for **54**–**56** and 2,3-*cis* for **57**) has the biggest impact on the stereoinduction, but configurational changes at more remote stereocenters also have a surprisingly strong influence on the stereochemical outcome.



Scheme 8. Catalytic asymmetric hydrogenation of α-acetamidocinnamic acid.

Since the first reports a large number of carbohydrate ligands has appeared in the literature, many of them featuring at least one phosphorus-based donor site. Phosphinites, phosphites and phosphoroamidites are the most abundant types, as they can be easily prepared from hydroxy or amino functions with chlorophoshines or phosphorochloridites. As this topic has already been covered by several reviews,[21] this section mainly introduces recent examples.

The pseudo-enantiomeric approach also works for carbohydrate ligands. RajanBabu and co-workers, who found that electron-donating substituents on the aromatic residues of the phosphinites had a beneficial effect on the selectivity in the hydrogenation of **52**, prepared 3,4-phosphinite ligand *ps ent*-**58** from D-glucosamine. Regarding the relative orientation of the P-donor sites, 3,4-phosphinite *ps ent*-**58** is the mirror image of 2,3-D-*gluco* ligand **58**.[22] Hydrogenation of **52** with this ligand yielded (*R*)-**53** in high *ee* (Figure 2). The yields for the hydrogenation products were excellent in both cases. Phosphinites with electron-withdrawing residues on the phosphinite aryl groups gave low *ee* values in hydrogenation reactions but were successful in hydrocyanation of vinylarenes[23a,b] and dienes.[23c]

Palladium-catalyzed asymmetric allylic substitutions[24] are often used as benchmark reactions for new ligands. Scheme 9 shows the allylation of malonate or benzyl amine with sterically demanding acetate **59** and malonate allylation with cyclic **61** and acetates **63** and **64**. Sterically demanding **59**, giving rise to a symmetrical allyl species coordinated to palladium, is an easy substrate. The cyclic substrates **61** and acyclic **63** and **64** are more challenging, the former due to their low steric demand and the latter because of the formation of achiral linear side product **66** along with the desired branched product **65**.

Very recently Diéguez and Pàmies introduced highly modular 3-phosphite-5-phosphoroamidite ligands for these

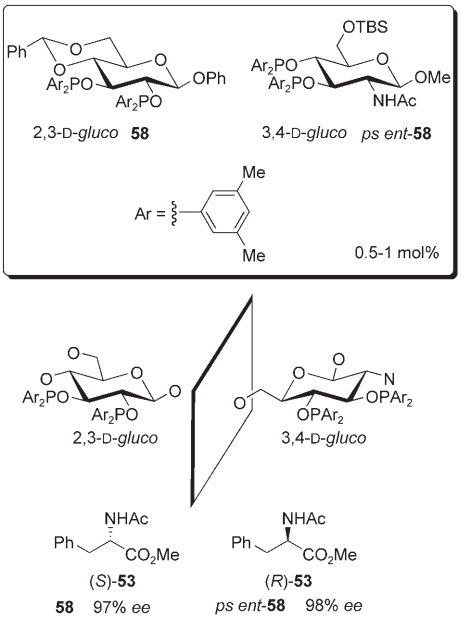
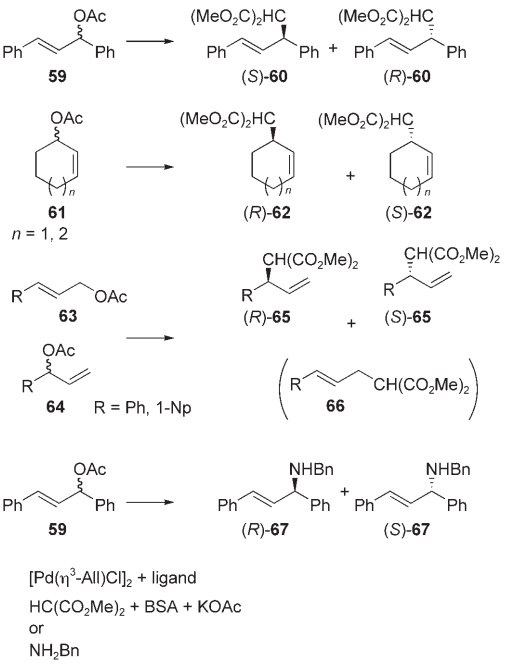


Figure 2. Glucose-based diphosphinite ligand and its glucosamine pseudo enantiomer.



Scheme 9. Asymmetric allylic substitution reactions.

reactions[25] (Figure 3). The P-donor sites of D-*xylo* ligands **68** and D-*ribo* ligands **69** carry either an (*R*)- or (*S*)-BINOL as an additional chiral element or biphenyls with bulky substituents. (*S*)-BINOL-substituted *xylo* ligand **68b** was well suited for symmetrical substrate **59**, while unsymmetrical substrate **64** gave excellent *ee* with *ribo* ligand **69a** with (*R*)-BINOL residues. The cyclic substrates **61** gave good to excellent *ee* values with *ribo* ligand **69c**. The results achieved

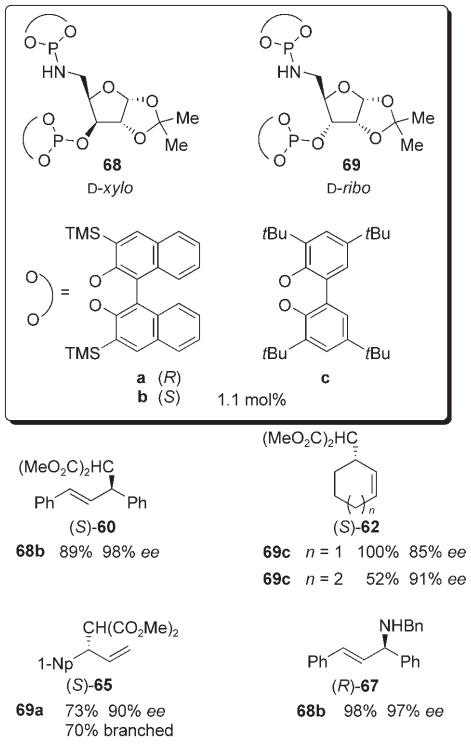


Figure 3. Mixed phosphoroamidite-phosphite ligands for palladium-catalyzed allylations.

for unsymmetrical and cyclic substrates are among the best reported to date,[25] with D-*ribo*-configured 3,5-diphosporoamidites the results could even be improved for cyclic substrates.[25b]

Examples for structurally very simple, C_2-symmetrical S,S-donor ligands were described by Khiar et al. who prepared bis(thioglucoside) **70** from ethanedithiol,[26] and its pseudo-enantiomer *ps ent*-**70** derived from D-arabinose[26b,c] (Figure 4). Upon coordination to a metal, the sulphur of these ligands becomes stereogenic, therefore, even an enantiomerically pure ligand can give rise to mixtures of diastereomeric complexes. If all of these are catalytically active, low selectivity can ensue as for each diastereomeric complex the preferred transition state may have a different geometry.[27] Surprisingly, even though ligand **70** appears conformationally very flexible at first glance, only one complex was detected in solid state as well as in solution.[28] The same group also described 2-phosphinite-thioglycoside ligand **71** based on D-galactose and its pseudo-enantiomer *ps ent*-**71** derived from D-arabinose.[29] Both ligand types gave good to excellent results in allylic substitution reactions with substrate **59**.

Carbohydrate oxazoline ligands derived from D-glucosamine have not been described before 1998, although *N*-acyl derivatives of this amino sugar easily form bicyclic oxazolines. Kunz and co-workers prepared phosphine oxazoline (phox) ligand **72**,[30] and Uemura and Ohe introduced a diphenyl phosphinite group in the 3-positions of oxazolines varying the size of the oxazoline substituent, generating

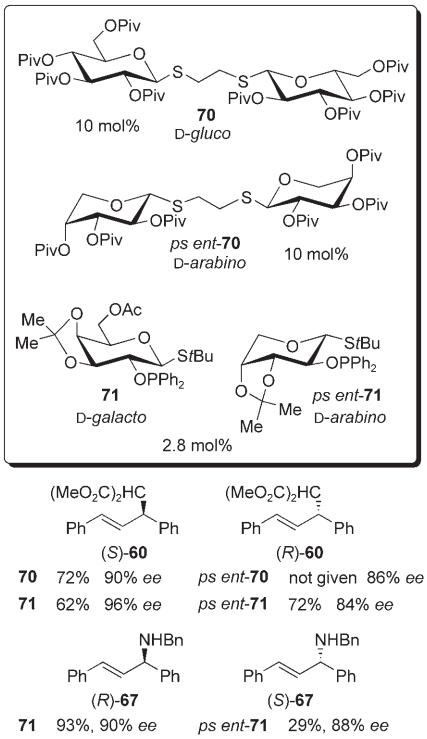


Figure 4. Thio-donor ligands for allylic substitution reactions.

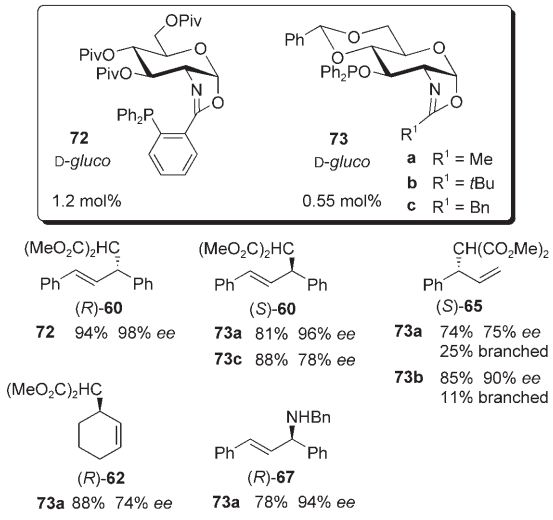
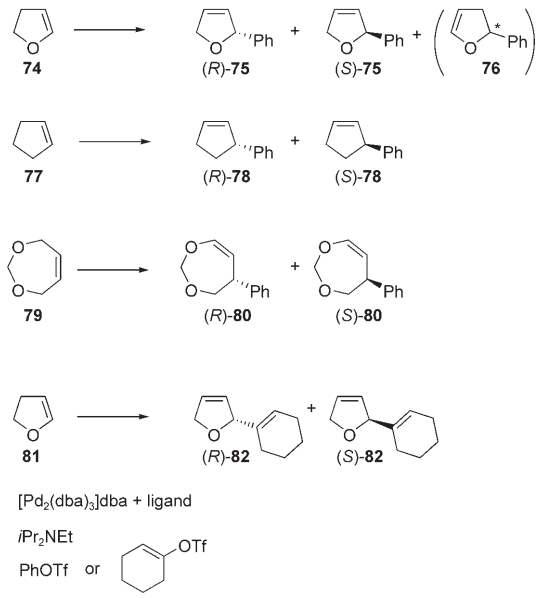


Figure 5. Carbohydrate phox and phosphinite-oxazoline ligands for allylic substitution.

73a–c[31] (Figure 5). All ligands were tested in asymmetric allylic substitutions. Ligands **72** and **73a** gave products **60** in excellent *ee* but with opposite configuration. Compounds **73** were also tried on the more challenging substrates **61** and **63**. For ligands **73** small substituents R^1 on the oxazoline were found to have a beneficial effect on the *ee* of (*R*)-**62**, the opposite trend was observed for the branched substitution product (*S*)-**65**, where the selectivity increased with increasing steric demand of R^1 on the oxazoline. Yet the overall result for (*S*)-**65** was unsatisfactory as undesired product **66** was formed predominantly.

The stereoselective intermolecular Heck reaction[32] of 2,3-dihydrofuran (**74**) with phenyltriflate, first described by Hayashi,[33] is also nowadays a popular test reaction for new ligands. Using phox-type ligands 2-phenyl-2,3-dihydrofuranes (**75**) are predominantly obtained, while 2-phenyl-2,5-dihydrofuranes (**76**) are formed as by-products.[34] These reactions and similar transformations with cyclopentene (**77**) and cyclic acetal **79** are depicted in Scheme 10.



Scheme 10. Asymmetric intermolecular Heck reactions.

The reaction of dihydrofuran **74** with phenyltriflate in the presence of ligand **73c** reported by Uemura and Ohe yielded (*R*)-**75** as the sole product in excellent *ee*[31d] (Figure 6). Diéguez and Pàmies prepared structurally related ligands **83a–d**, attaching phosphites carrying biphenyl residues with bulky substituents to position 3 of different oxazolines. These highly modular ligands were extensively studied in allylic substitutions[35a,c] as well as in asymmetric Heck reactions.[35b,c] It was found that for the Heck reaction of **74** enantioselectivity as well as the ratio of main product **75** to by-product **76** depended both on the size of the oxazoline substituent and the steric demand and the number of substituents on the biphenyl moiety. The best result for furan product (*R*)-**75** was obtained for **33b**, for all the other Heck substrates **83a** gave the best results. This ligand was also successful for most substrates in allylic substitution reactions. The exception was the unsymmetrical substrate **64** leading to product (*S*)-**65**.

Very recently our group introduced C_2-symmetrical bis-(oxazoline) (box) ligand **84** derived from D-glucosamine (Scheme 11). The ligand was tried in copper-catalyzed cyclopropanations of styrene derivatives with diazoacetates.[36] Good selectivities were achieved with ethyl diazoester **86a**,

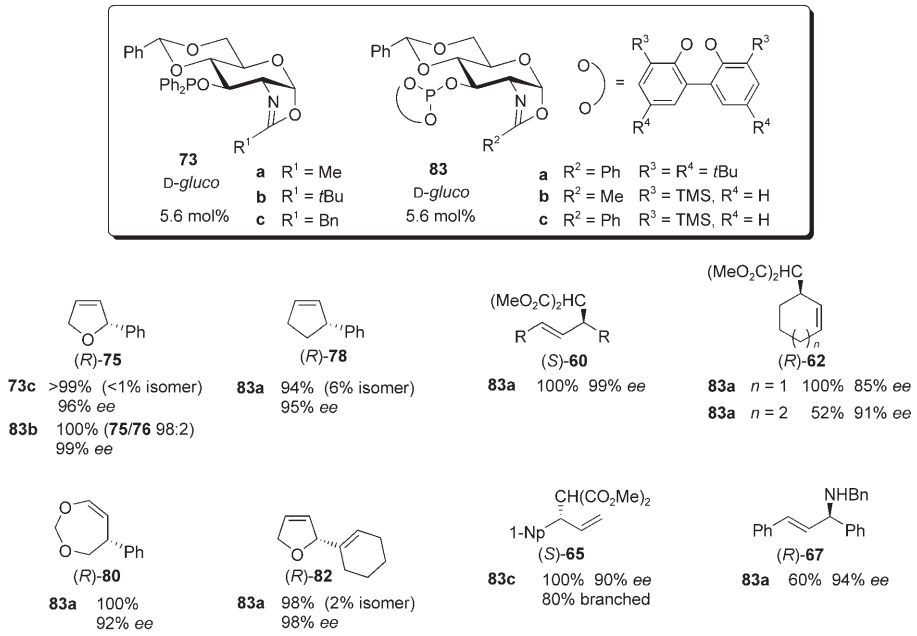
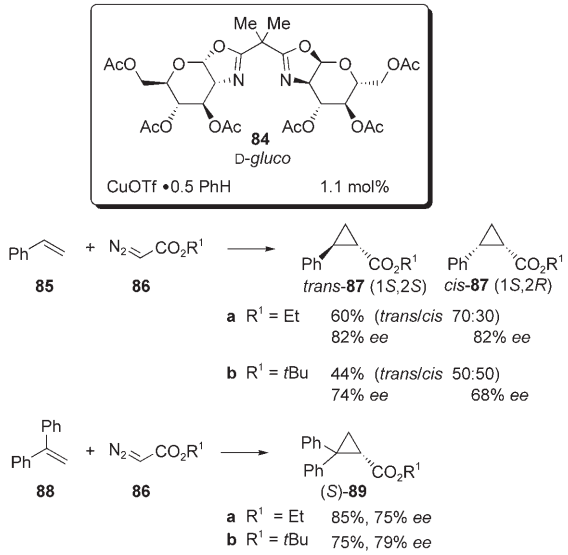


Figure 6. Phosphinite–oxazoline ligands for asymmetric Heck reactions.

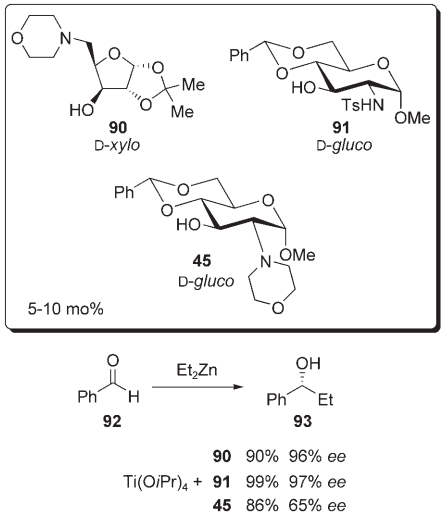
Carbohydrate Organocatalysts

The most prominent example for this kind of tool is the D-fructose-based ketone **94** used for the Shi epoxidation[39] (Scheme 13). A dioxirane is formed in situ from **94** and Oxone which epoxidized 1,2-*trans* di- and trisubstituted alkenes in good to excellent *ee*.[40] The substrate scope includes hydroxyalkenes,[41a] enynes,[41c] enol esters[41d] and dienes.[41b] The enantiomer of ketone **94** was prepared from readily available L-sorbose avoiding the use of the expensive L-fructose.[40c,42] Ketone **94** gave poor results for terminal and 1,2-*cis*-configured alkenes but by replacing the spiro ketal with a spiro oxazolidinone, efficient catalysts could be developed for these substrates. Ketones **101** gave good results for 1,2-*cis* alkenes with aromatic or unsaturated side chains[43a,c] as well as styrenes,[43b,c] complementing the substrate scope of catalyst **94** (Scheme 13). Extensive studies by Shi et al.[44] led to excellent results for *cis* dienes[45] and enynes.[46]

The most favorable transition states (TS) for both ketone types are presented in Scheme 13. In case of **94** steric interactions between the alkene residues and the spiro ketal are minimised, for **101** the olefin substituents point away from the pyranose but unsaturated residues (R^{π}) are proximal to the spiro oxazolidinone due to attractive interactions.



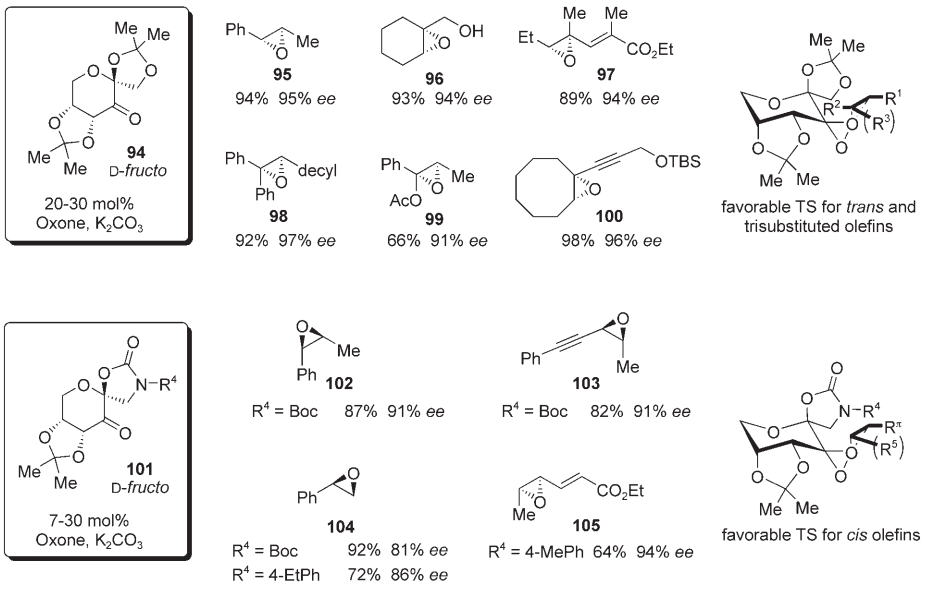
Scheme 11. Bis(oxazoline) ligand for asymmetric cyclopropanation.



Scheme 12. Reactions with carbohydrate derived amino alcohols.

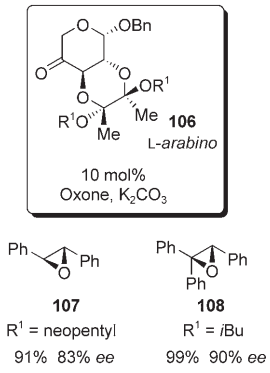
while the bulky *tert*-butyl diazoester **86b** decreased the *trans* selectivity along with the yields.

Amino alcohols based on carbohydrates have been used as ligands in the addition of diethyl zinc to aldehydes (Scheme 12). Cho et al. used D-*xylo* configured **90**,[37] Bauer and co-workers employed D-glucosamine-based **91** in the presence of a titanium Lewis acid.[38] Both ligands **90** and **91** led to high *ee* for the addition product of benzaldehyde. Davis et al. employed the pyranoses presented in Scheme 7, the best ligand, α-*gluco* configured **45** giving only moderate results.[18b]



Scheme 13. Epoxidation of alkenes with D-fructose-based ketone catalysts.

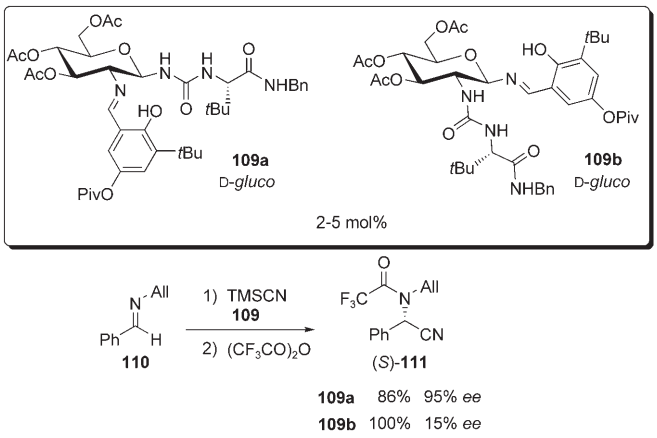
Chiral ketones **94** and **101** are among the best organocatalysts for asymmetric epoxidation and **94** has also been successfully used for the oxidation of disulfides to chiral thiosulfinates.[47] Other carbohydrate and non-carbohydrate systems provide less generality.[39,48] Another example are carbohydrate ketones derived from arabinose which were reported by Shing and co-workers.[49] Arabinose offers the rare advantage of being available in both enantiomeric forms at low cost. Good to excellent results were achieved for aromatic *trans* and trisubstituted olefins with ketone **106** (Scheme 14), aliphatic substrates gave lower selectivity.[49]



Scheme 14. Epoxidation with L-arabinose derived ketones.

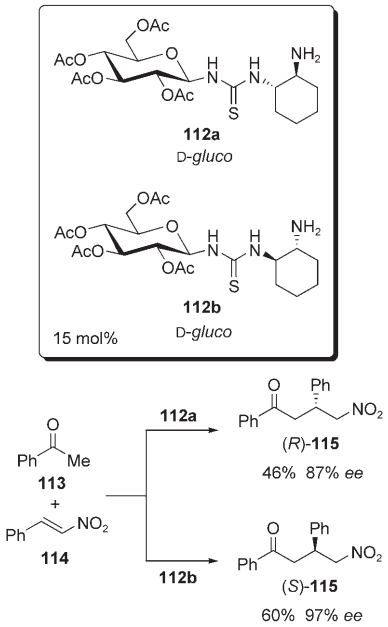
Very recently the first examples of carbohydrate urea and thiourea organocatalysts have appeared in the literature. Bifunctional urea Schiff base organocatalysts[50] were reported by Kunz et al.[51] (Scheme 15). In β-configured **109a** derived from D-glucosamine, the urea moiety was linked to the anomeric centre and the Schiff base to the 2-amino function, the pyranose thus supplanting a 1,2-*trans*-diaminocyclohexane unit. In the Strecker reaction of aldimine **110** with trimethylsilyl cyanide, catalyst **109a** yielded (*S*)-**111** in excellent *ee*. For other aromatic aldimines, save for the *p*-nitro compound, selectivities ranged from moderate to good, aliphatic substrates gave only low selectivities. Structural variants of **109a** were also tested. Catalyst **109b** in which positions of the Schiff base and the urea moiety were exchanged, gave only very low *ee* (Scheme 15). Changing the protective group pattern, that is, by introducing a 4,6-*O*-benzylidene acetal, was also detrimental for stereodifferentiation. This shows that even the protective group patterns of hydroxy groups remote from the catalytically active "site" can have severe impact on selectivity. Urea **109a** was also tried in enantioselective Mannich reactions giving rather low selectivity.

Ma and co-workers reported β-configured thioureas based on enantiomerically pure 1,2-*trans*-diaminocyclohexanes and D-glucose[52] as bifunctional thiourea amine catalysts[53]



Scheme 15. Urea organocatalysts derived from D-glucosamine.

(Scheme 16). Using both enantiomers of the diamine the diastereomeric thioureas **112a** and **112b** were prepared. Both were tested in the conjugate addition of acetophenone (**113**) to β-*trans*-nitrostyrene (**114**). Catalysts **112a** and **112b** exhibited opposite sense of stereoinduction, **112a** producing adduct (*R*)-**115** in good *ee* but poor yield, while **112b** gave (*S*)-**115** in excellent *ee* and significantly increased yield. In the case of **112b** carbohydrate and chiral diamine appear to be matched, while the other enantiomer of the diamine leads to mismatched **112a**. With catalyst **112b** good to excellent selectivities were achieved for other aromatic and aliphatic nitroalkenes, but yields dropped considerably for the latter. Substituted acetophenones also gave excellent results. As structural variants, thioureas from the disaccharides maltose and lactose were prepared but these exhibited much lower levels of selectivity.



Scheme 16. Glucose-based thiourea organocatalysts.

Conclusion

The examples presented in the previous sections clearly show the versatility and efficiency of carbohydrate tools in stereoselective synthesis. The selectivities achieved with the carbohydrate derivatives are comparable to those obtained with the more traditional derivatives from the chiral pool and thus make them interesting alternatives. With the rapid expansion of this field over the past two decades, starting with chiral auxiliaries, inducing the formation of only one new stereocenter to very sophisticated chiral ligands for asymmetric catalysis, novel cheap and structurally diverse carbohydrate-based tools can be expected to find more useful applications in the future.

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