Part I
Carbohydrate Auxiliaries

General Remarks on the Use of Pseudo-Enantiomers of Carbohydrate Tools

The application of pseudo-enantiomers is of great importance when carbohydrate-derived chiral tools are used: While d-monosaccharides are easily available from the *chiral pool*, the corresponding l-enantiomers are mostly expensive and in some cases even unavailable. For the preparation of a pseudo-enantiomer of a given carbohydrate tool, a carbohydrate scaffold with opposite configuration at relevant stereocenters is chosen. These relevant stereocenters are usually those directly involved in the events determining the direction of the asymmetric induction, that is, the one(s) carrying the substrate (in the case of carbohydrate auxiliaries), coordinating metal centers (in the case of carbohydrate ligands), or shielding one face of a substrate. The remaining stereocenters, which are further from the reacting sites, are neglected and may have any configuration. Thus the synthesis of a pseudo-enantiomeric tool can start from other l-monosaccharides, which are more readily available, that is, l-rhamnose and l-fucose and even d-carbohydrates may be employed. By this approach the preparation of a real enantiomer from an expensive l-enantiomer of a d-carbohydrate can be avoided altogether. Attractive and powerful as this approach may be it is important to note that choosing suitable a pseudo-enantiomeric auxiliary offering high levels of stereoinduction is by no means trivial. Usually, several tentative pseudo-enantiomers can be envisioned for a given carbohydrate tool but which of them – if any – gives high levels of stereoinduction cannot, unfortunately, be predicted. Therefore, finding suitable pseudo-enantiomers remains a process of trial and error. With this in view, unsurprisingly, some highly efficient carbohydrate tools have remained without any suitable pseudo-enantiomer (e.g., the Duthaler–Hafner reagent, Chapter 7).

Carbohydrates – Tools for Stereoselective Synthesis, First Edition. Edited by Mike Martin Kwabena Boysen.

1
Reactions of Nucleophiles with Electrophiles Bound to Carbohydrate Auxiliaries

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1.1
Introduction

Carbohydrates are widespread chiral natural products found worldwide and they have been transformed into diverse, interesting chiral products in ex-chiral pool syntheses. However, carbohydrates were not used as chiral auxiliaries in stereoselective syntheses for a long time. About 30 years ago Vasella reported the earliest example of carbohydrate auxiliaries tools in organic synthesis [1]. During the following decades, carbohydrates slowly became recognized as versatile starting materials for chiral auxiliaries in stereoselective reactions, and today a multitude of structures has been developed and applied to various reactions [2].

1.2
Strecker Reactions

The three-component Strecker reaction as well as the hydrocyanation of imines (modified Strecker reaction) are fundamental carbon–carbon bond-forming processes [3], which are efficient methods for preparing α-amino acids (Scheme 1.1).

In 1987 Kunz and coworkers first reported pivaloyl protected D-galactosyl amine **3** as a very useful tool for asymmetric aminonitrile syntheses [4]. Galactosyl amine **3** can be obtained from penta-*O*-pivaloyl-β-D-galactopyranose **1** by reaction with trimethylsilyl azide/tin tetrachloride to give the galactosyl azide **2** followed by hydrogenation (Scheme 1.2) [4].

Condensation of **3** with aldehydes **4** yields galactosyl aldimines **5**, which undergo highly diastereoselective Strecker reactions with trimethylsilyl cyanide (TMSCN) in the presence of Lewis acids (Scheme 1.3). The observed diastereoselectivity is a result of the attack of the cyanide anion on the face of the (*E*)-imine opposite to the sterically demanding 2-*O*-pivaloyl group. Separation of the minor diastereoisomer and subsequent hydrolysis with hydrochloric acid affords the corresponding enantiomerically pure α-amino acid **7** (R = *p*-ClC_6H_4).

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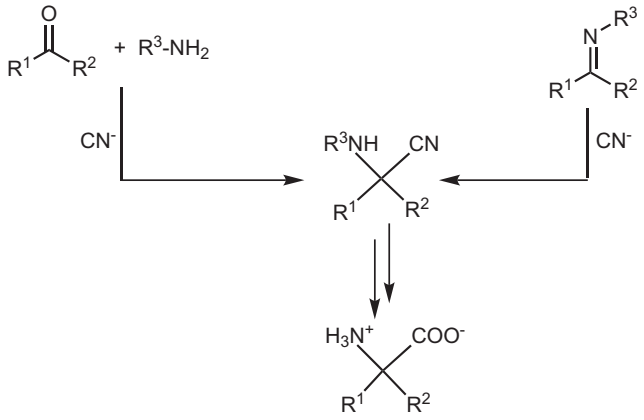
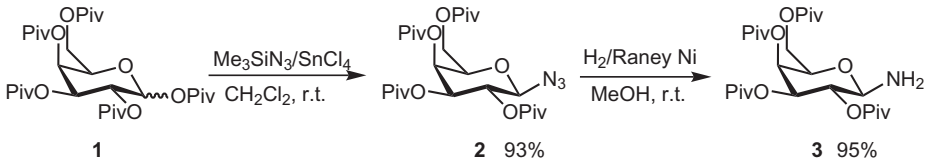


Scheme 1.1 Strecker-type reactions for the synthesis of α-amino acids.



1 **2** 93% **3** 95%

Scheme 1.2 Synthesis of D-galactosyl amine **3.**

The solvent has a strong impact on the direction of the stereoinduction. Stannic chloride in tetrahydrofuran or zinc chloride in isopropanol give α-aminonitriles with the *(R)* configuration with high diastereoselectivity [4a, b], while zinc chloride in chloroform reverses the direction of the asymmetric induction in favor of the *(S)* enantiomer [4c]. Therefore, this method is highly attractive for the preparation of α-amino acid derivatives as by simply changing the reaction conditions the aminonitrile product can be obtained in both configurations from the D-configured galactose auxiliary in a stereodivergent manner (Scheme 1.3).

Kunz ascribed the high selectivity of the Strecker reactions to steric and stereoelectronic effects arising from the carbohydrate auxiliary in combination with the Lewis acid. In the transition state (Figure 1.1) the activating Lewis acid catalyst $ZnCl_2$ is apparently coordinated by the imine nitrogen and the carbonyl oxygen of

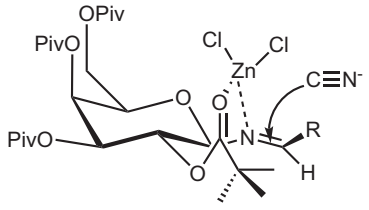
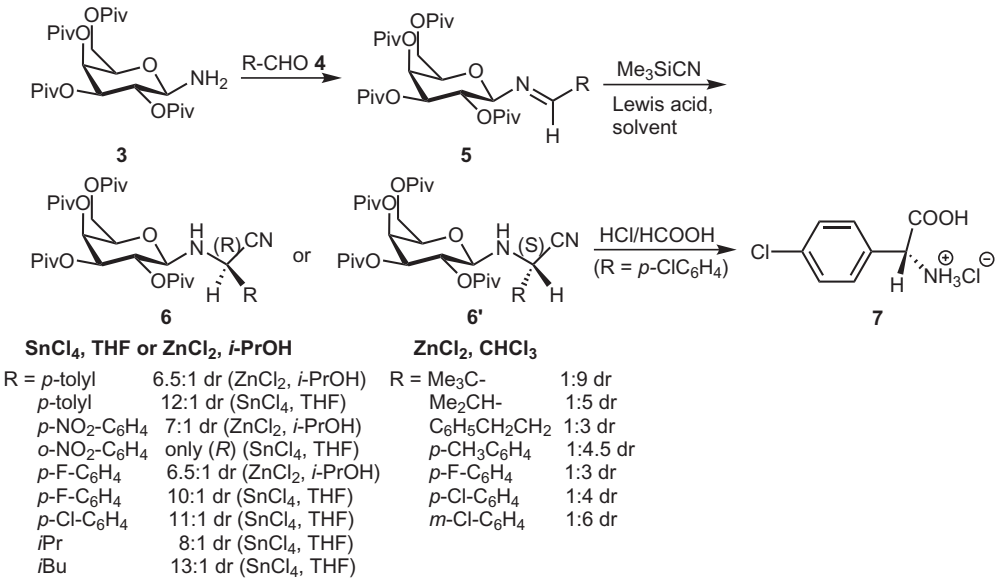


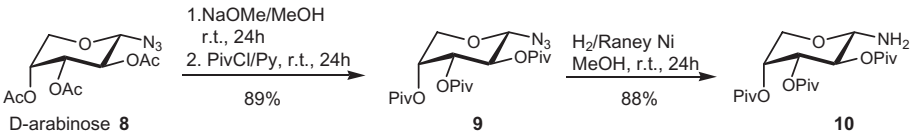
Figure 1.1 Proposed transition-state of Strecker reactions with the galactose auxiliary.



Scheme 1.3 Kunz's asymmetric Strecker reactions with a galactose-derived chiral auxiliary.

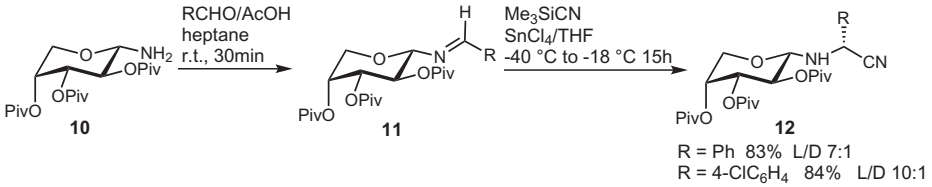
the 2-*O*-pivaloyl group. This complex is preferably attacked by the cyanide, which is liberated in the polar medium from TMSCN, from the sterically less hindered rear face, that is, the *Si* face of the imine [4a].

After the successful syntheses of D-amino acids via Lewis-acid-catalyzed Strecker reactions with galactosylamine **3** as the stereodifferentiating auxiliary, Kunz has developed the pivaloylated-arabinosylamine **10** as a new chiral auxiliary [5]. Apart from the missing hydroxy methyl group at C5, D-arabinose is a mirror image of D-galactose and therefore arabinosylamine can be regarded as a pseudo-enantiomer of D-galactosylamine **3.** To prepare pivaloylated-arabinosylamine **10,** the peracetylated arabinopyranose is transformed into arabinopyranosyl azide **8,** as has been described by Paulsen and coworkers [6]. After deacetylation and subsequent pivaloylation, **8** gives arabinopyranosyl azide **9,** which is subsequently reduced by hydrogenation with Raney nickel to furnish the auxiliary **10** (Scheme 1.4).



Scheme 1.4 Synthetic pathway to arabinosylamine **10.**

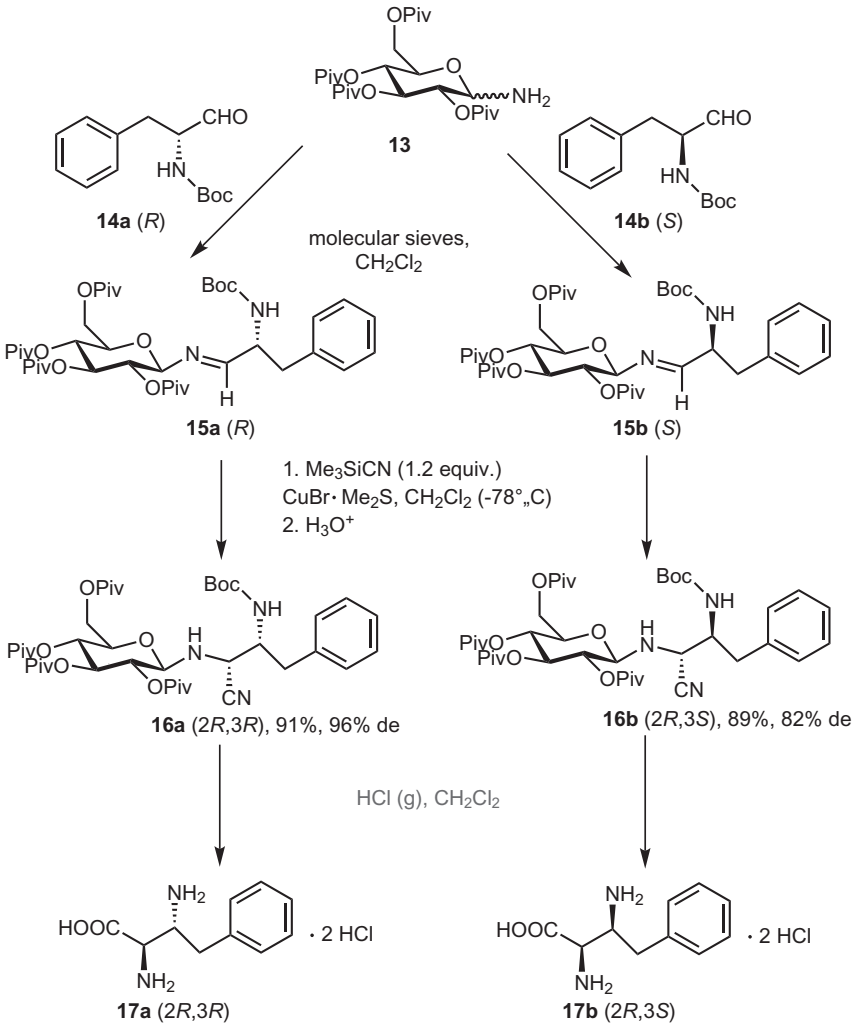
By using the arabinosylamine **10** in the Strecker reaction L-amino nitriles have been successfully obtained. To this end, **10** was condensed with aldehydes to give the *N*-arabinosylimines **11**, which with TMSCN/tin tetrachloride furnish the α-amino nitriles **12.** The diastereoselectivity was determined as 7–10 : 1 in favor of the L-diastereomer after hydrolysis and cleavage of the aminonitrile from the auxiliary Hydrolysis of pure **12** with hydrogen chloride/formic acid forms exclusively L-phenylglycine (Scheme 1.5) [5].



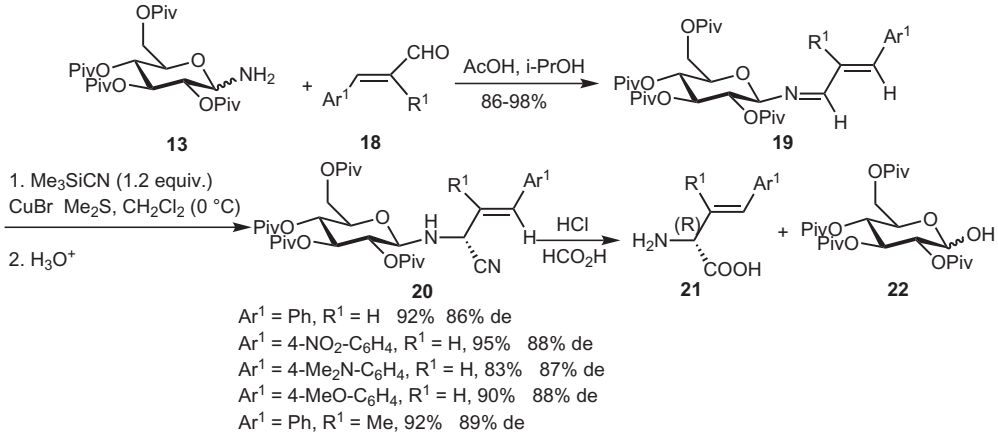
Scheme 1.5 Synthesis of α-L-amino nitriles **12** by Strecker reaction on a D-arabinose template.

The asymmetric Strecker synthesis using carbohydrate auxiliaries has also been studied in some detail by Zhang using a D-glucose-based chiral template [7]. In continuation of Kunz's studies a general protocol for the asymmetric synthesis of α,β-diamino acids involving enantiomerically pure α-amino aldehydes, *O*-pivaloylated glucopyranosylamine, and TMSCN was developed. The α-aminoaldehydes **14** reacted with glucopyranosylamine **13** in CH_2Cl_2 to give the corresponding imines **15a** and **15b** in high yields. The nucleophilic addition of TMSCN to aldimines **15a** and **15b** employed CuBr · Me2S as promoter to activate the C=N group and afforded α,β-diaminonitriles **16a** and **16b**, respectively. The absolute configuration of the new stereocenter formed in the Strecker reaction is predominantly controlled by the carbohydrate auxiliary, which overrules the stereoinduction by the stereocenter stemming from the amino aldehyde part. The diastereoselectivities were 96% and 82% de, respectively, indicating only a small matched/mismatched effect between carbohydrate auxiliary and the stereocenters from the amino-aldehyde substrates. The bis-hydrochlorides **17a** and **17b** were obtained by hydrolysis of the α,β-diaminonitriles in acidic medium (Scheme 1.6).

Zhang and coworkers also studied the copper(I)-promoted Strecker reaction of sugar-modified α,β-unsaturated imines [8]. Under acidic conditions, the imines **19** were prepared from glucosyl-amine **13** and a series of substituted cinnamic aldehydes **18.** The nucleophilic addition of TMSCN to aldimines **19** afforded the products **20** with the aid of CuBr · Me_2S (1 equiv.) as the Lewis acid. In all reactions, only 1,2- rather than 1,4-addition products were observed [9]. This indicates that the carbohydrate auxiliary plays a significant role in controlling the regio- and diastereoselective 1,2-addition of cyanide to the α,β-unsaturated aldimines. The *(R)*-configured 2-amino-4-phenylbut-3-enoic acids **21** can be obtained by hydrolysis of compounds **20** in acidic medium (Scheme 1.7).



Scheme 1.6 Asymmetric synthesis of α,β-diamino acids via Strecker reaction of aldimines **15.**



Scheme 1.7 Copper(I)-induced regio- and diastereoselective Strecker reaction.

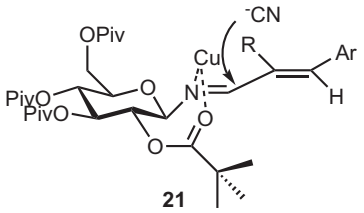
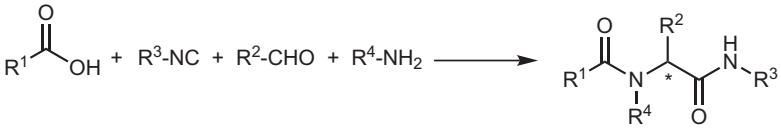


Figure 1.2 Proposed transition-state for Strecker reactions of α,β-unsaturated imines bound to a D-glucose-derived template.

Figure 1.2 shows the proposed transition state **23** leading to products **20.** It is very similar to the one invoked by Kunz for Strecker reactions of galactose-modified imines. The Lewis acid CuBr is coordinated to both the N-atom of the imine and one of the O-atoms of the 2-*O*-pivaloyl group. This would decrease the electron density at the C-atom of the C=N moiety and direct the attachment of cyanide.

1.3 Ugi Reactions

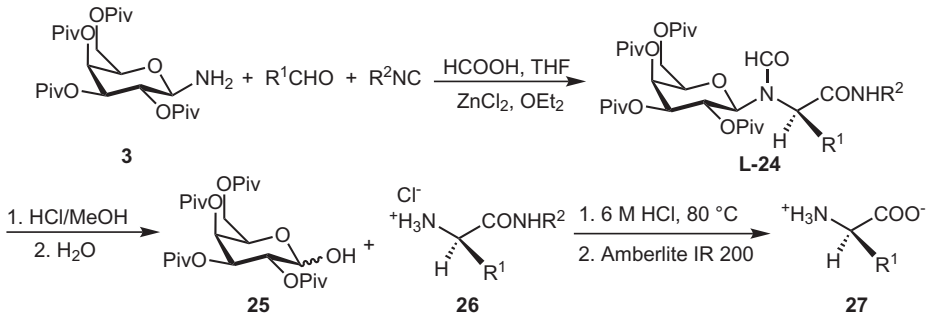
The terms Ugi four-component reaction (Ugi-4CR) or Ugi four-component condensation (U-4CC) usually refer to the reaction of an amine (usually a primary amine; less frequently ammonia or a secondary amine), a carbonyl compound (an aldehyde), an isocyanide, and a carboxylic acid [10]. In the course of the reaction two peptide bonds and one carbon–carbon bond are formed and a new chiral center is created (Scheme 1.8) [11].



Scheme 1.8 General outline of a four-component Ugi reaction.

A major difficulty in conducting Ugi reactions stereoselectively is that reaction conditions for the transformations vary considerably (e.g., solvent, temperature, and highly diverse starting materials) and consequently the reactions follow different mechanisms. In one successful example Kunz employed his galactosylamine auxiliary as chiral template in the Ugi reaction (Scheme 1.9) [12].

When galactosylamine **3** was allowed to react with an aldehyde, an isocyanide, and a carboxylic acid (preferably formic acid) in the presence of zinc chloride in THF, *N*-galactosyl amino acid amide derivatives **24** were obtained in almost quantitative yield and high dr. The *N*-galactosyl amino acid amide derivatives **24** can be transformed into a series of valuable chiral products, for example, 1,2-diamines and β-amino alcohols. At –25 °C (for aliphatic imines –78 °C) D-configured amino acid derivatives **24** were formed with a diastereoselectivity of about 95 : 5

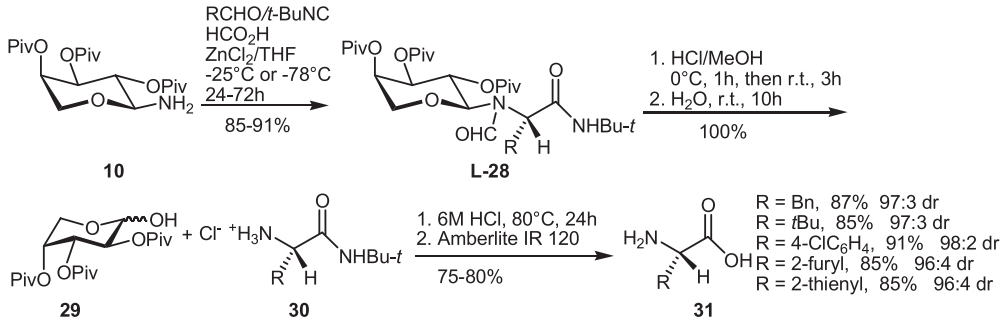


R' = *n*Pr, R'' = *t*Bu, 80% 94:6 dr
R' = *i*Pr, R'' = *t*Bu, 86% 95:5 dr
R' = *t*Bu, R'' = *t*Bu, 80% 96:4 dr
R' = Bn, R'' = *t*Bu, 80% 95:5 dr
R' = 2-furyl, R'' = *t*Bu, 90% 95:5 dr
R' = 2-thienyl, R'' = *t*Bu, 93% 96:4 dr
R' = Ph, R'' = *t*Bu, 81% 91:9 dr
R' = *p*-Cl-C_6H_4, R'' = *t*Bu, 92% 97:3 dr
R' = *p*-NO_2-C_6H_4 R'' = *t*Bu, 91% 94:6 dr
R' = styryl, R'' = *t*Bu, 75% 95:5 dr
R' = N≡C-$(CH_2)_3$, R'' = Ph, 81% 94:6 dr

Scheme 1.9 Asymmetric Ugi reaction using a galactose-derived chiral auxiliary.

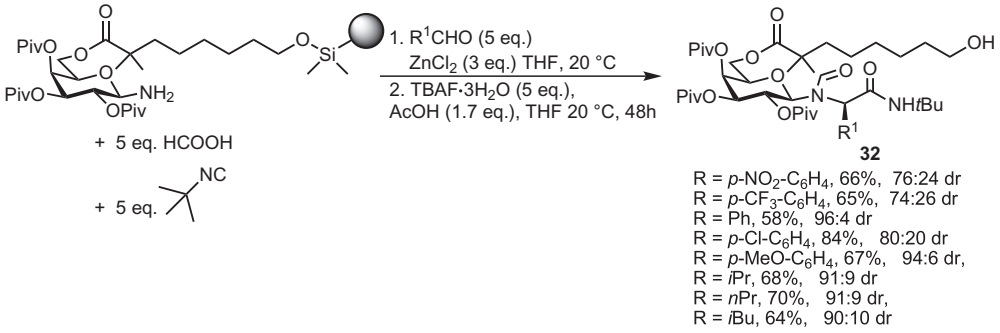
(Scheme 1.9). After acidolytic cleavage of the N-glycosidic bond the tetra-O-pivaloyl-galactose **25** is reisolated in quantitative yield. Hydrolysis of the amino acid amides **26** and subsequent deprotonation gives the free α-D-amino acids **27** [12].

The arabinosylamine **10** also was applied in Ugi reaction by Kunz and shows a slightly enhanced reactivity in comparison to the galactosylamine [5, 13]. At –25 °C, **10** reacts with aldehydes, *tert*-butyl isocyanide, and formic acid in the presence of zinc chloride in THF to form the *N*-formyl-*N*-arabinosyl amino acid amides **28** in almost quantitative yield. The diastereomeric ratio for the L-amino acid derivatives **28** ranges from 22 : 1 to 30 : 1. The free enantiomerically pure L-amino acids **31** can easily be released from the carbohydrate templates by a two-step acidic hydrolysis and the carbohydrate template can be recovered in quantitative yield (Scheme 1.10).



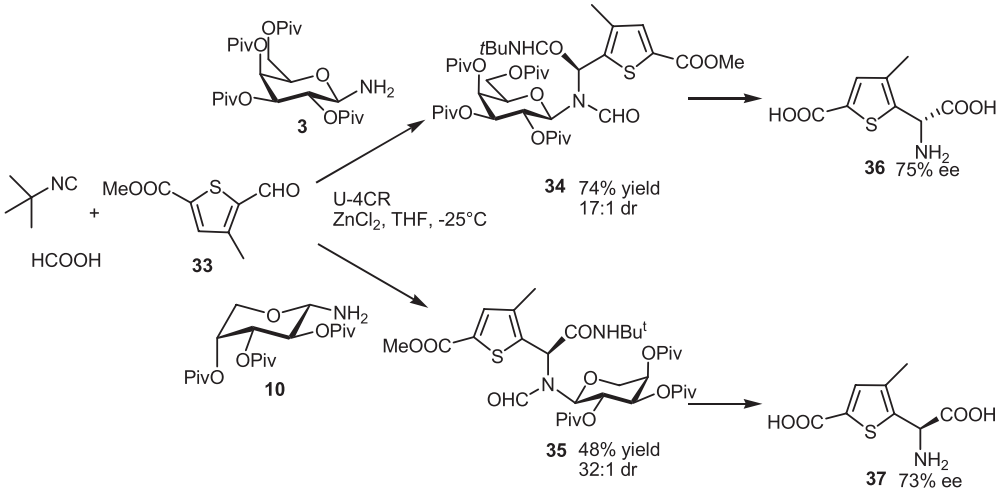
Scheme 1.10 Stereoselective synthesis of L-amino acid derivatives **31** using a D-arabinose-derived auxiliary.

Kunz and coworkers introduced their chiral carbohydrate based auxiliaries successfully onto a solid phase [14]. They synthesized 2,3,4-tri-*O*-pivaloylated-β-D-galactopyranosyl azide bearing a hydroxyl-functionalized spacer unit at the C6 position of the galactose and immobilized this on a solid phase by using a polymer-bound chlorosilane. The azide was reduced to the corresponding galactopyranosylamine, which served as a versatile chiral auxiliary in highly diastereoselective Ugi four-component condensation reactions at ambient temperature. Fluoride-induced cleavage from the polymeric support furnished N-glycosylated N-acylated α-amino acid amides **32** (Scheme 1.11).



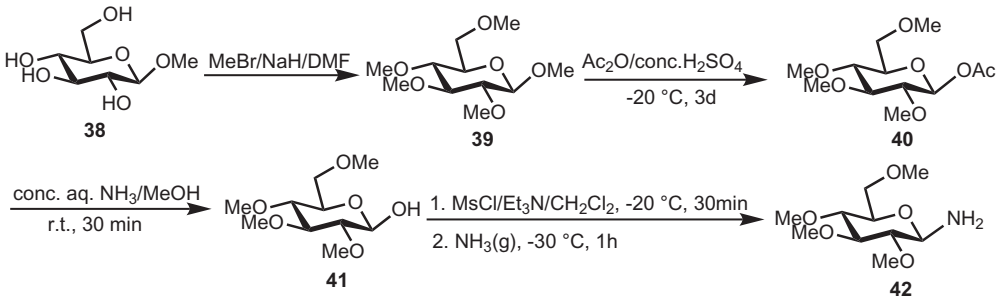
Scheme 1.11 Kunz's auxiliary made available on solid phase and its use in an Ugi reaction.

Pellicciari *et al*. have reported the stereoselective synthesis and preliminary biological evaluation of (+)- and (–)-3-methyl-5-carboxythien-2-ylglycine (3-MATIDA), **36** and **37.** They used chiral sugar based auxiliaries **3** and **10** to prepare the enantiomerically pure unnatural amino acids using a U-4CR [15]. The reaction of thiophenecarbaldehyde **33** with *tert*-butylisocyanide, formic acid, and D-galactosylamine **3** or D-arabinosylamine **10,** respectively, in the presence of zinc chloride in THF at –25 °C and subsequent cleavage afforded the *N*-formyl-*N*-galactosyl amino acid amide **34** in a 17 : 1 diastereomeric ratio and the *N*-formyl-*N*-arabinosyl amino acid amides **35** in a 32 : 1 diastereomeric ratio, respectively (Scheme 1.12).



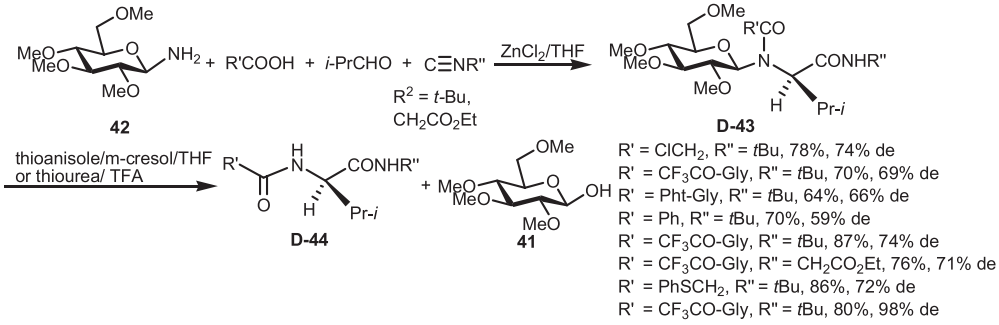
Scheme 1.12 Enantioselective preparation of carboxythiophene α-amino acids by Ugi reactions.

Ugi and coworkers have presented a highly improved sugar derived auxiliary, which was tested as amine compounds for peptide synthesis [16]. Glucopyranosides **39** were prepared from methyl α-D-glucopyranoside (**38**) by methylation. Subsequent acetolysis to give **40** followed by ammonolysis yielded **41**, which was transformed into the auxiliary tetra-*O*-methyl glucopyranosylamine **42** [17] by mesylation and subsequent treatment with gaseous ammonia in a one-pot reaction developed by Vasella (Scheme 1.13) [18].



Scheme 1.13 Synthetic pathway to tetra-*O*-methyl-glucopyranosylamine auxiliary **42.**

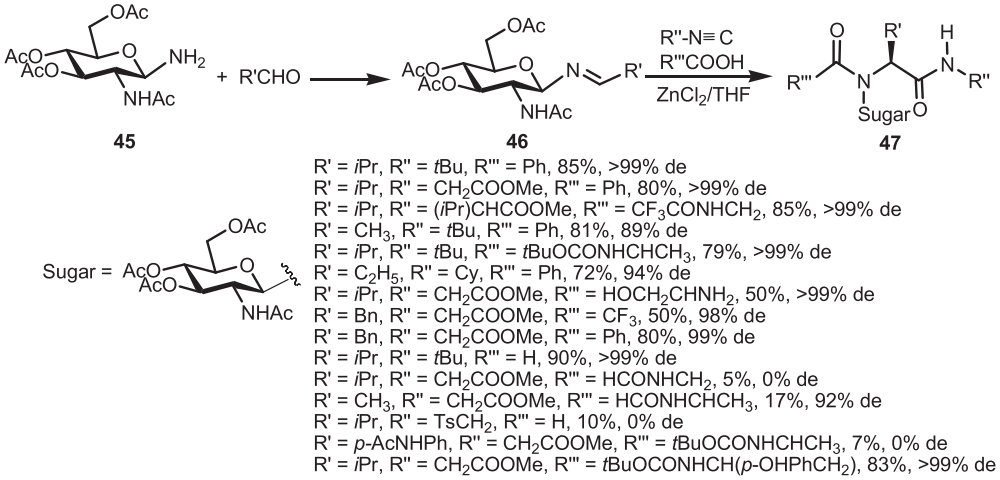
Glycosylamine **42** has been tested as chiral template in various types of Ugi reaction, and the results show that the major diastereomers of the products **43** have the D-configuration at the newly installed stereocenter [19]. Trifluoroacetic acid (TFA) in combination with a soft base can cleave the Ugi product **43** into peptide **44** and the carbohydrate auxiliary (Scheme 1.14).



Scheme 1.14 Formation of α-acylamino acid derivatives **44** by diastereoselective Ugi reaction on carbohydrate template **42.**

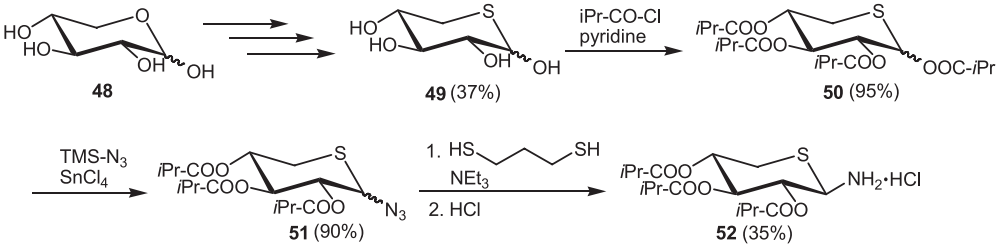
In 1995, Ugi examined the stereoselective syntheses of peptide derivatives with acetylated 1-amino-glucopyranose **45** as the chiral template [20]. The acetylated amino-glucopyranose **45** as auxiliary is prepared from readily available *N*-acetylglucosamine in three steps [21]. Condensation of an aldehyde with the amine **41** yielded glucosyl aldimines **46**, which reacted with isocyanide and acid in the

presence of zinc chloride to form the N-glucosyl peptide derivatives **47** in good yields (Scheme 1.15).



Scheme 1.15 Selection of Ugi reaction products obtained with amino-glucopyranose as auxiliary.

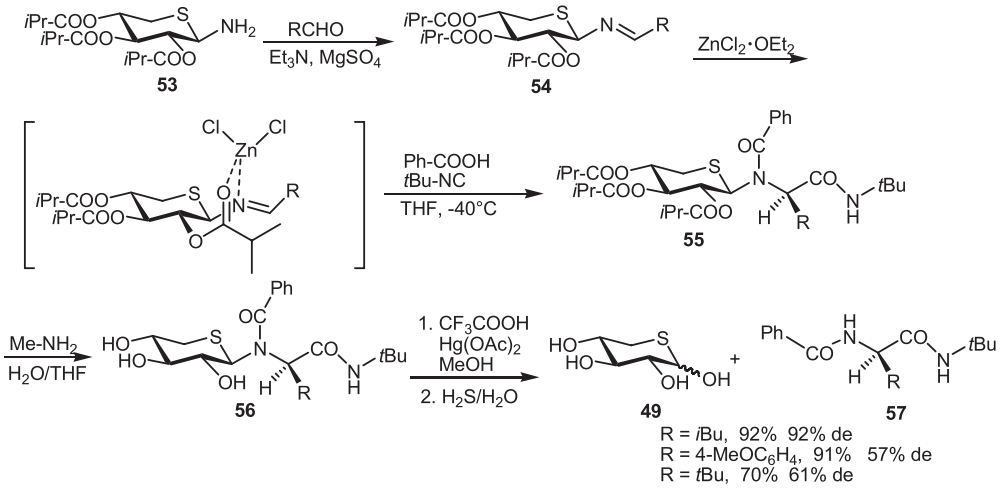
Ugi also reported a thiasugar as a chiral auxiliary for the stereoselective reaction four-component synthesis of amino acids [22]. According to Ingles and Whistler's method [23] 5-desoxy-5-thio-D-xylose **49** can be prepared in six steps from D-xylose **48.** This product can be peracylated to **50** by an excess of isobutanoyl chloride in pyridine. In the presence of tin tetrachloride, **50** can be converted into azide **51** by treatment with trimethylsilyl azide. The anomerically pure β-amine hydrochloride **52** is obtained from the α/β-azide mixture **51** by reduction with 1,3-propanedithiol. During workup, β-amine **53** can be precipitated from an etheric solution as the hydrochloride salt **52** (Scheme 1.16) [24].



Scheme 1.16 Synthesis of thiasugar auxiliary **52** from D-xylose.

The free amine **53** and isovaleraldehyde are subsequently converted into the imine **54,** which is reacted under Ugi reaction conditions with zinc chloride diethyl etherate, *tert*-butyl isocyanide, and benzoic acid. The product **55** is formed in 92% de (diastereomeric ratio 24 : 1) and a yield of 92%. The readily crystallizing

product **56** is obtained from **55** by removing its *O*-acyl groups by aminolysis with methyl amine. The *O*-deacylated chiral auxiliary **49** can be cleaved off under mild acidic conditions to afford the *N*-benzoyl-D-leucine-*tert*-butylamide **57** (R = *t*Bu) (Scheme 1.17) [25].



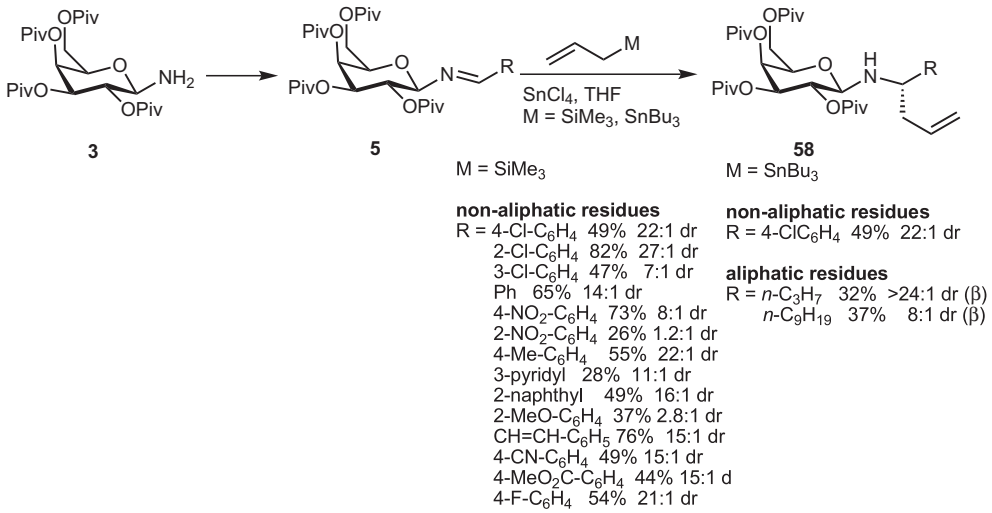
Scheme 1.17 Stereoselective U-4CR with thiasugar auxiliary **53.**

1.4 Allylations

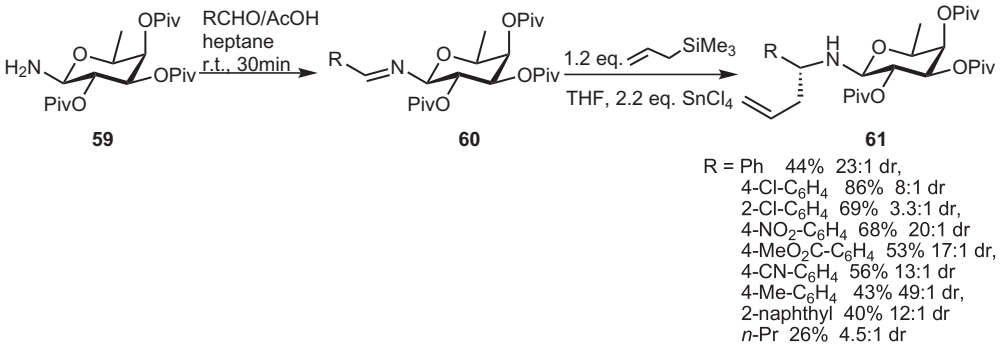
Homoallyl amines are useful precursors of a various compounds, especially β-amino acids and β-lactam antibiotics, which can be obtained by subsequent functionalization of the double bond. An attractive method for the synthesis of homoallyl amines is the organometallic allylation of chiral imines carrying a chiral template on the nitrogen, which can be successively removed [26].

Kunz reported that *(S)*-configured homoallylamines can be synthesized diastereoselectively by the Lewis acid induced addition of allylsilanes to Schiff bases of tetra-*O*-pivaloyl-galactosylamine **3** (Scheme 1.18) [27a, c] giving moderate to good diastereoselectivity for imines 5 with non-aliphatic residues. The nucleophilicity of the allylic organometallic compound can be improved by changing the metal from silicon to tin [27c]. Thus imine **5** with R = 4-Cl-C_6H_4 was converted into the corresponding homoallyl amines **58** by using allyltributylstannane instead of allyltrimethylsilane under identical conditions, resulting in an increased yield, but reduced asymmetric induction.

When the reaction is conducted with the *O*-pivaloyl-protected L-fucosylamine **59** instead of *N*-galactosylamine **3**, the *(R)*-configured homoallyl amines **61** can be isolated in high diastereoselectivities [27b, c]. The advantage of this reaction is that most *N*-fucosyl-homoallyl-amines **61** are crystalline and can be obtained as the pure *(R)* diastereomer or as a strongly enriched mixture simply by recrystallization (Scheme 1.19) [27b, c]. It should be noted that allyltributylstannane is used instead



Scheme 1.18 Asymmetric synthesis of *(S)*-configured homoallyl amines using galactosyl amine **3.**



Scheme 1.19 Asymmetric synthesis of *(R)*-configured homoallyl amines using fucosyl amine **58.**

of allyl trimethylsilane in the allylic addition of the corresponding β-L-fucosyl imines **60** (R = *n*Pr).

Schiff bases derived from glucosyl amines and aliphatic aldehydes do not react with allyltrimethylsilane under the same conditions. Even at low temperature (–78 °C), only anomerization and decomposition occurred. However, these imines could be converted into the corresponding homoallylamines using allyltributylstannane instead of the silane at –78 °C, and $SnCl_4$ (1.2 equiv) was used to activate the imine.

The homoallylamines **62** can be released from the carbohydrate template using aqueous HCl in methanol. Homoallylamine hydrochlorides **62** could easily be N-protected and were subsequently oxidized to yield the N-protected β-amino acid **64**, which was finally deprotected to the corresponding β-amino acid **65** (Scheme 1.20).

A tentative reaction mechanism was proposed by the authors. In the transition state the tin atom of the Lewis acid $SnCl_4$ has octahedral coordination, with sites occupied by chlorine atoms, the imine nitrogen and the carbonyl oxygen of the

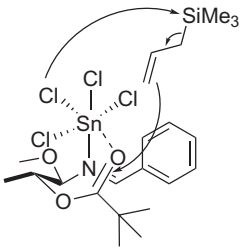
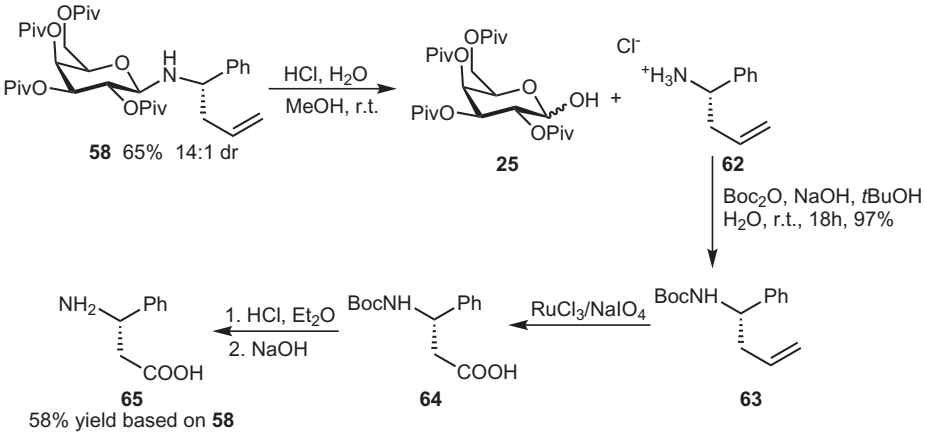


Figure 1.3 Transition state proposed by Kunz for the allylation reaction of glycosyl imines.



Scheme 1.20 Conversion of *N*-galactosyl-*N*-homoallylamines into β-amino acids.

(C2) pivaloyloxy group; one of the four chlorines is removed when allyltrimethylsilane is added. The S_N2'-type attack of the allylic compound occurs preferentially from the rear face of the imine, as the 2-O pivaloyl group effectively shields the front face. The mechanism indicates that the pivaloyl group in the aldimines **5** and **60** plays a significant role in controlling the diastereoselective addition of allyltrimethylsilane (Figure 1.3).

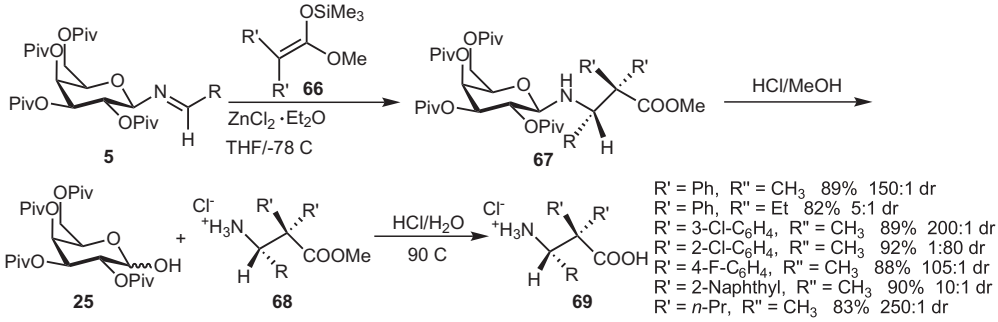
1.5 Mannich-Type Reactions

Mannich-type reactions are among the most important transformations in organic chemistry because they afford synthetically and biologically important β-amino carbonyl compounds [28]. Asymmetric Mannich-type reactions provide useful routes for the synthesis of optically active β-amino ketones or esters that are versatile chiral building blocks in the preparation of many nitrogen-containing biologically important compounds [29].

The first asymmetric Mannich reactions were diastereoselective and involved the addition of preformed enolates and enamines to performed imines using stoichiometric amount of chiral auxiliaries [30]. More recently, direct catalytic

asymmetric Mannich-type reactions have been reported [31]. The transformations are catalyzed by both organometallic complexes and metal-free organic catalysis. The different catalysts are highly stereoselective and complementary in their applicability and selectivity.

During investigations on Mannich-type reaction, *N*-galactosyl aldimines **5** were employed as the chiral template [32]. Like α-amino acids generated by the Strecker reaction, β-amino acid derivatives accessible via Mannich reactions are important building blocks for the construction of natural products [33]. The *N*-galactosyl-β-amino acid esters **67** were obtained by the treatment of silyl ketene acetals **62** with the Schiff bases **5** in the presence of zinc chloride at −78 to −30 °C within 24 h. The β-phenyl-β-alanine ester derivatives **68** can be removed from the carbohydrate template almost quantitatively with HCl in methanol (Scheme 1.21).

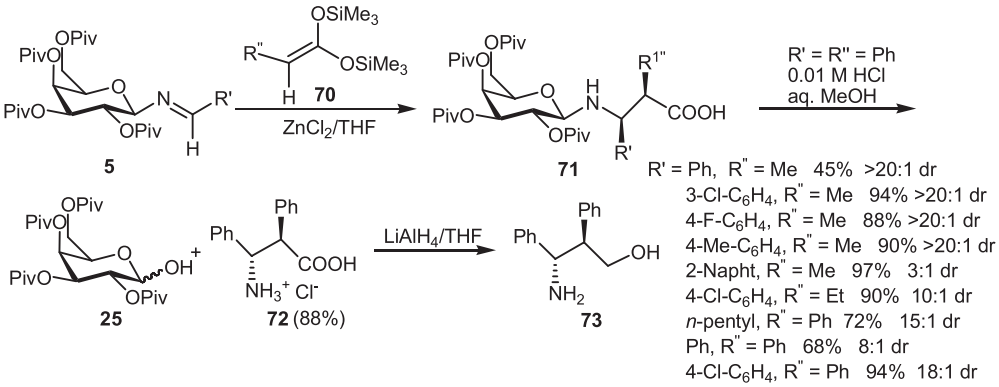


Scheme 1.21 Diastereoselective Mannich-type reaction of ketene acetals with imine **5** for the synthesis of β-alanine derivatives.

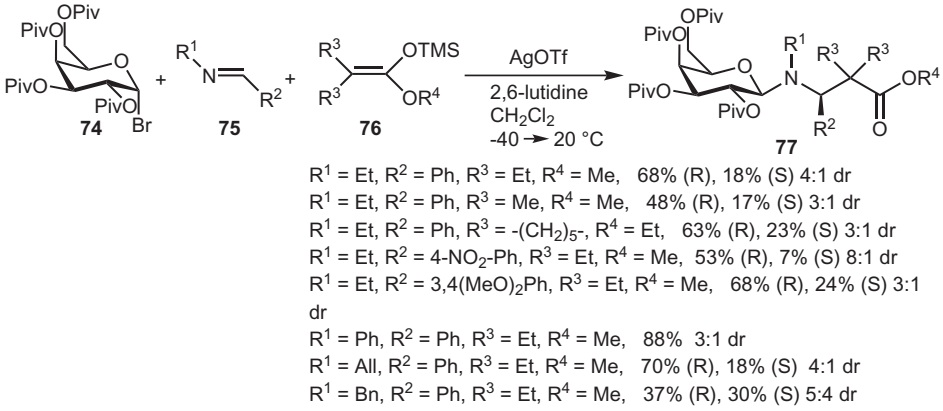
The diastereoselective Mannich reaction of *O*-pivaloylated *N*-galactosyl aldimines **5** containing two new stereocenters bis-silyl ketene acetals **70,** which was reported by Kunz, proved an efficient stereoselective access to chiral β-amino acid derivatives **71** [34]. The yields and diastereoselectivities of these Mannich reactions are high and only two of the four possible diastereomers are formed. In most cases one of them is obtained in large excess. The *N*-glycosidic bond of compound **71** was readily cleaved under mildly acidic conditions to give enantiomerically pure β-amino acids or their hydrochlorides **72** (Scheme 1.22). To assign the configuration of the β-amino acids **73,** 2,3-diphenyl-β-alanine **72** was released from **71** with 0.01M HCl in methanol. Subsequent reduction with lithium aluminum hydride yields 3-amino-2,3-diphenylpropanol **73.**

To extend the scope of asymmetric reactions using *N*-glycosyl imines to *N*-alkyl or *N*-aryl amino acid derivatives, *O*-pivaloylated galactosyl bromide **74** was employed in Mannich reactions of *N*-alkyl and *N*-aryl aldimines **75** with *O*-trimethylsilyl ketene acetals **76.** The reactions were carried out in a one-pot procedure to give the β-amino acid esters **77** in high yield and with moderate diastereoselectivity (Scheme 1.23) [35].

3,4-dihydroisoquinoline (**78**) reacted with silyl ketene acetal **79** after activation by *N*-galactosylation to give the β-amino acid ester **80** with high diastereoselectivity (Scheme 1.24) [35].

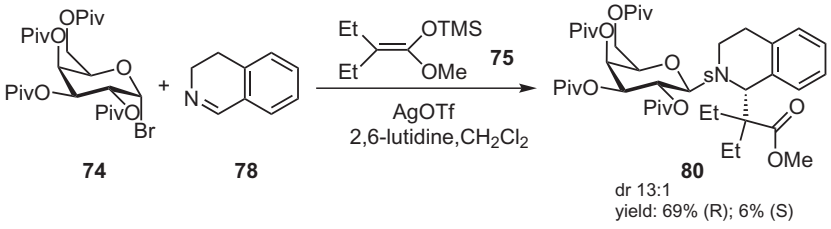


Scheme 1.22 Diastereoselective synthesis of β-amino acids **73.**

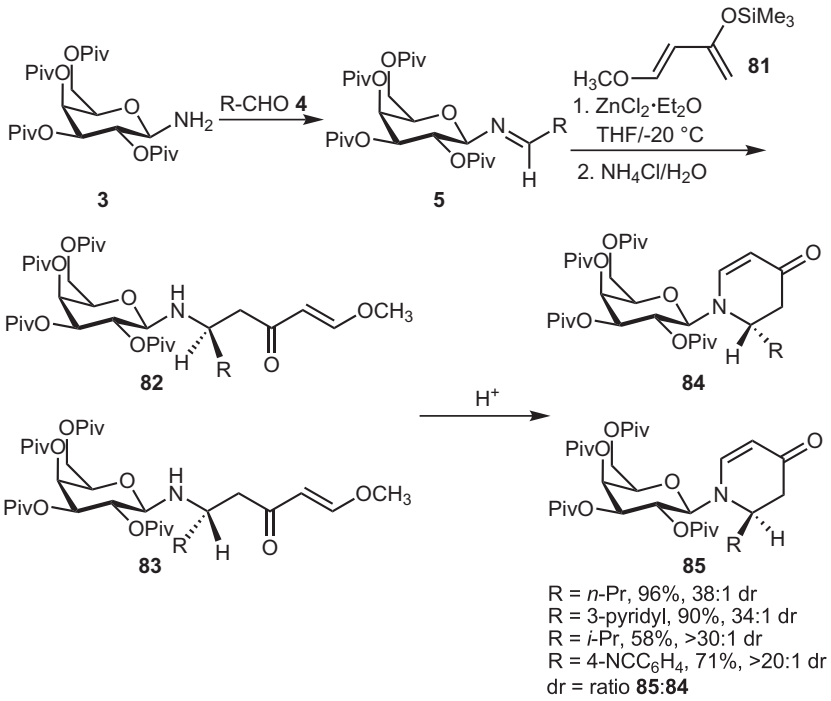


Scheme 1.23 Diastereoselective synthesis of β-amino acid esters via an *in situ* glycosylation method.

In 1989, Kunz reported the stereoselective tandem Mannich–Michael reactions for the synthesis of piperidine alkaloids again using galactosylamine **3** as an effective chiral auxiliary [36]. A subsequent publication described how the *N*-galactosyl aldimines **5** react with silyl dienol ether **81** in the presence of zinc chloride in tetrahydrofuran at –20 °C to give the Mannich bases **82/83** with high diastereoselectivities. The Michael addition then occurs to give the dehydropiperidones **84/85** in high yields upon hydrolysis with 1M HCl (Scheme 1.25) [37].

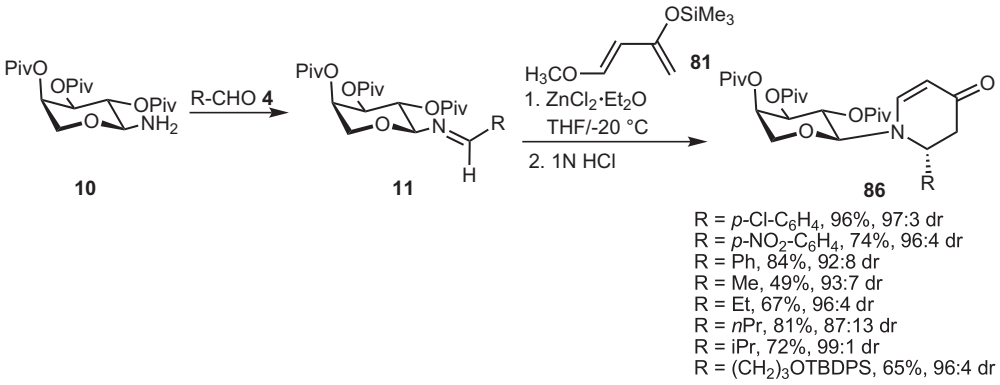


Scheme 1.24 Diastereoselective synthesis of β-amino acid ester **80** from dihydroquinoline **78.**



Scheme 1.25 Diastereoselective synthesis of *N*-galactosyldehydropiperidones **84** and **85.**

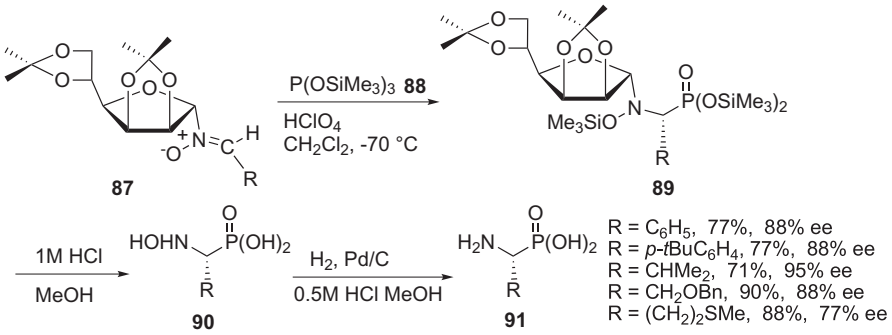
In 2004, Kunz reported the application of arabinosylamine **10** as a suitable *pseudo* enantiomeric auxiliary to the galactosylamine **3** [38a]. *N*-Arabinosylimines **11** react with silyl dienol ether **81** in a domino Mannich–Michael reaction sequence to give 2-substituted 5,6-dehydropiperidinones **86.** The 2-substituted dehydropiperidinones are formed with opposite stereochemistry compared to those from the tandem Mannich–Michael reaction with D-galactosylamine as auxiliary (Scheme 1.26).



Scheme 1.26 Diastereoselective synthesis of 2-substituted *N*-arabinosyl dehydropiperidinones **86.**

1.6
Addition of Phosphites

Vasella and coworkers first reported the stereoselective synthesis of α-aminophosphonic acids by means of carbohydrate auxiliaries [39, 40]. In the first experiments *N*-mannofuranosylnitrones **87** (R = *i*Pr, CH_2OBn, Me) were reacted with lithium dialkyl phosphites, affording the corresponding α-aminophosphonic acids with up to 90% de [39]. In a second approach, which was amenable to a wider range of *N*-mannosylnitrones **87**, tris(trimethylsilyl)phosphite (**88**) was employed under acid catalysis with $HClO_4$, giving *(R)*-*N*-hydroxyphenylphosphaglycines **90** in high yield and with an optical purity of 88% after acidic work-up. Hydrogenolysis of **90** gives *(R)*-phenylphosphaglycines **91**, with optical purities of up to 88% (Scheme 1.27) [40].

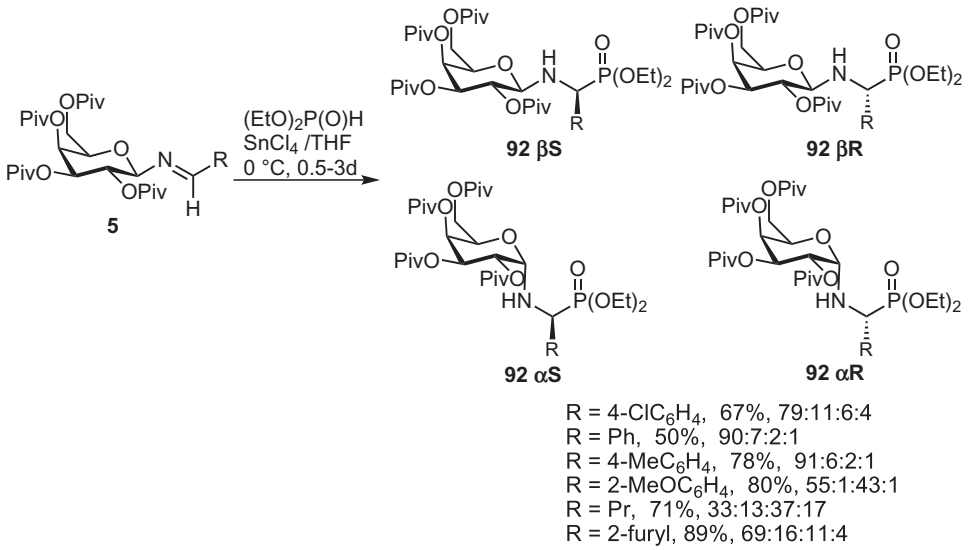


Scheme 1.27 Synthesis of *(R)*-phenylphosphaglycine **91** using a mannose-derived carbohydrate auxiliary.

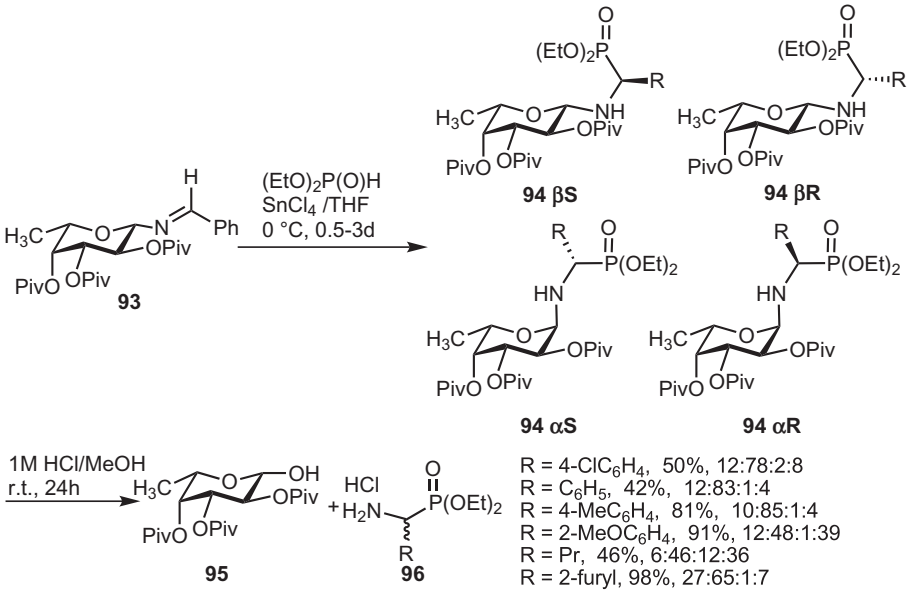
In 1992 Kunz and coworkers reported the stereoselective synthesis of α-aminophosphonic acid derivatives from *O*-pivaloylated galactosylamine as chiral auxiliary [41]. The galactosyl amine **3** was reacted with various aldehydes to give *N*-galactosyl aldimines **5**, which were reacted with diethyl phosphite to furnish the four diastereomeric *N*-galactosylphenyl phosphonoglycine esters **92** in high yield by catalysis with tin(IV) chloride in THF (Scheme 1.28). The new stereocenter in esters **92** was preferentially obtained in *(S)*-configuration, and the anomeric configuration was predominantly β, except for the cases with R = 2-$MeOC_6H_4$ and R = Pr, where substantial amounts of the α-anomers were found.

The *(R)*-configured aminophosphonic acids can be obtained by employing the L-fucose-derived Schiff base **93** as a *pseudo* enantiomeric auxiliary [41]. The diastereomeric mixture of the addition products **94** was treated with 1M hydrogen chloride in methanol at room temperature, giving the carbohydrate template and the α-aminobenzylphosphonate hydrochloride **96** in quantitative yield (Scheme 1.29).

Miao has also reported the diastereospecific formation of α-aminophosphonic acids derivatives in high yield via a Mannich-type reaction [42]. The reaction was

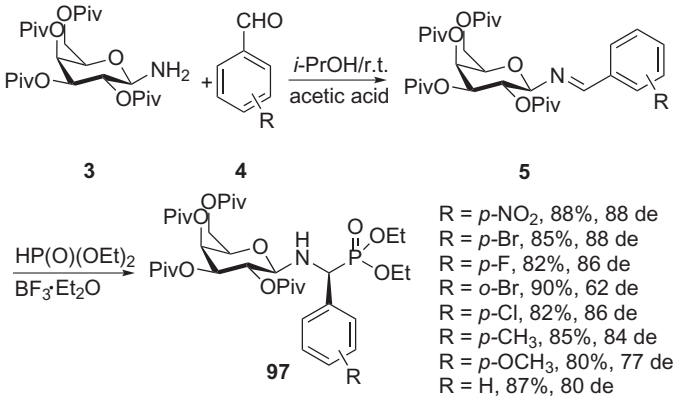


Scheme 1.28 Synthesis arylphosphonoglycine esters using carbohydrate auxiliary **3.**



Scheme 1.29 Diastereoselective synthesis of *(R)*-aminophosphonates using L-fucose auxiliary.

performed by using *O*-pivaloylated galactosylamine **3** as a chiral template and boron trifluoride diethyl etherate as a catalyst in THF. Imines **5** [4b] of aromatic aldehydes and diethyl phosphite were converted into *N*-galactosyl α-aminoalkylphosphonates **97** with diastereomeric ratios higher than 19:1 (Scheme 1.30).



Scheme 1.30 Synthesis of *N*-galactosyl α-aminoalkylphosphonates **97.**

The diastereomerically pure compounds **97** were obtained by simple recrystallization from *n*-hexane and diethyl ether. To determine the absolute configuration of the main isomer of the diethyl phosphite addition to *N*-galactosyl aldimines **5**, a single-crystal X-ray diffraction study of **97** (R = *p*-Cl) was performed. The molecular structure of **97** (R = *p*-Cl), shown in Figure 1.4, proves that the absolute configuration of the main product is *(S)* [42].

Figure 1.5 shows a possible mechanism for the reaction. The preferred formation of the *(S)*-configured diastereomers of **97** can be rationalized by an attack of diethyl phosphite from the *Si* side of *N*-galactosylaldimines **5.** Initially, the Lewis acid boron trifluoride is coordinated to the imine nitrogen of **5.** The *Re*-face of the imine is shielded by the 2-*O*-pivaloyl group, leaving the *Si*-face exposed. Upon attack of the diethyl phosphite in the transition state, one fluoride may be removed from the Lewis acid and the vacant coordination site may then be filled by the carbonyl oxygen of the 2-*O*-pivaloyl group.

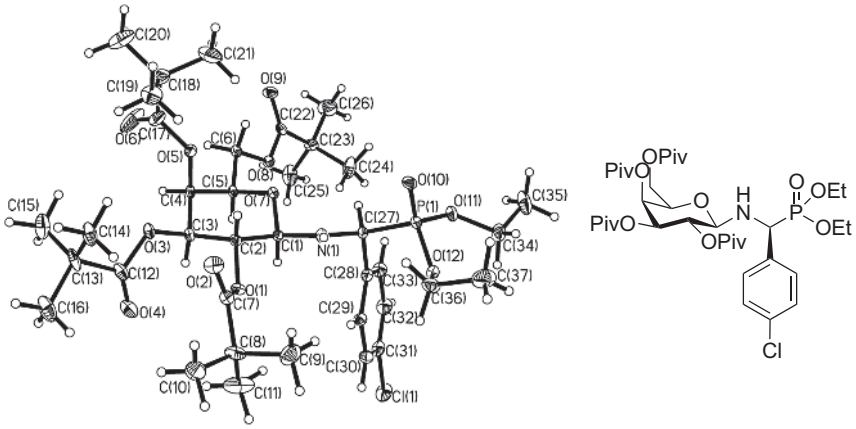


Figure 1.4 ORTEP presentation of the crystal structure of **97** (R = *p*-Cl).

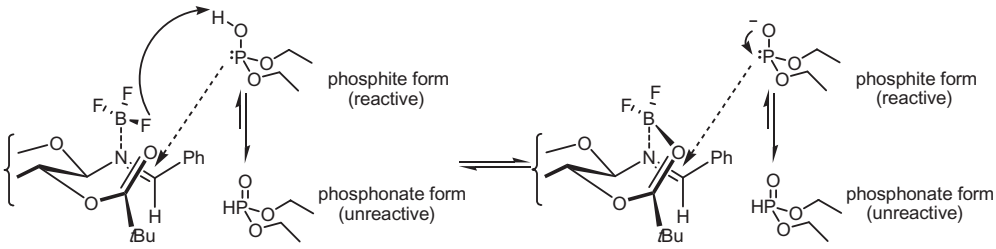
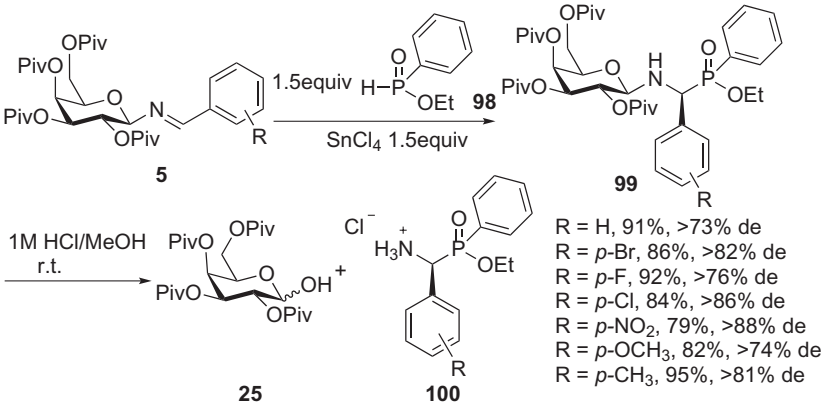


Figure 1.5 Plausible reaction mechanism of the addition of phosphites to galactosyl imines **5.**

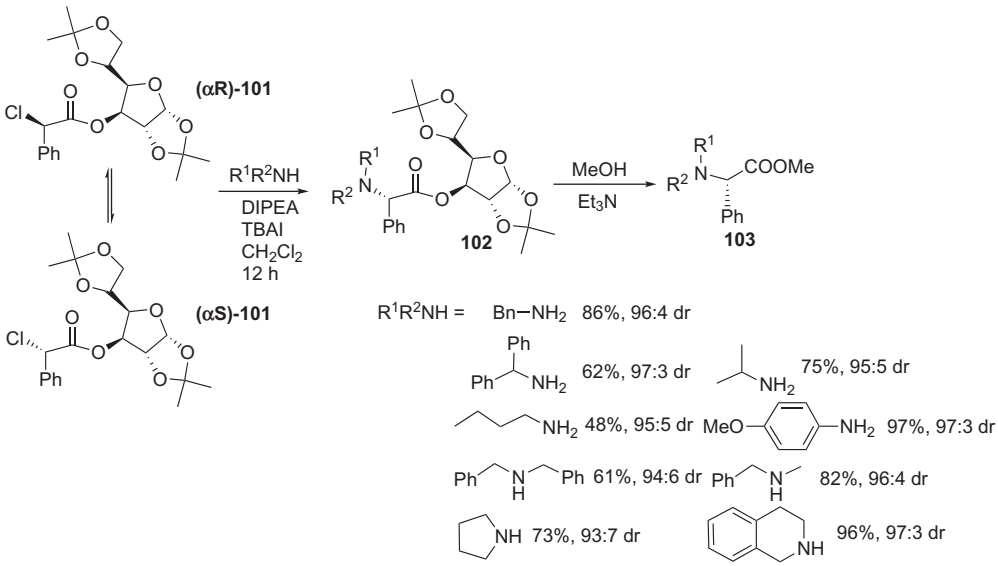
In 2009, Miao reported the stereoselective synthesis of α-amino(phenyl)methyl (phenyl)phosphinic acids with D-galactosylamine as chiral auxiliary [43]. Aldimines **5** of aromatic aldehydes and ethyl phenylphosphinate **98** were converted into *N*-galactosylarylphosphonoglycine esters **99** with diastereomeric ratios higher than 20 : 1. α-Amino(phenyl)methyl-(phenyl)phosphinic acids **100** can be obtained by treatment with 1M hydrogen chloride in methanol (Scheme 1.31).



Scheme 1.31 Synthesis of *N*-galactosyl arylphosphonoglycine esters **99.**

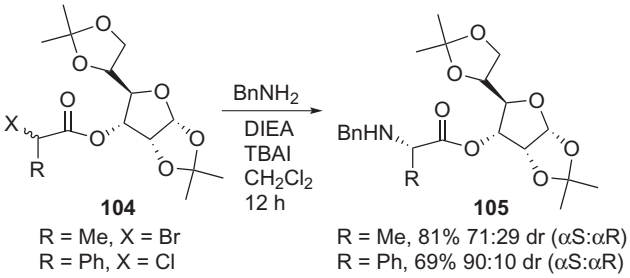
1.7
Dynamic Kinetic Resolution of α-Chloro Carboxylic Esters

Another interesting application of carbohydrate-derived auxiliaries is the dynamic kinetic resolution of racemic α-halogenated carboxylic esters [44]. Park reported a D-glucose-derived auxiliary in the dynamic resolution of α-halo esters in an asymmetric nucleophilic substitution [45, 46]. α-Chloro-α-phenyl ester **(α*RS*)-101** was obtained as a diastereomeric mixture by the reaction of diacetone-D-glucose and racemic α-chloro-α-phenylacetyl chloride in the presence of Et_3N. Treatment of **(αRS)-101** with various amines, and diisopropylethylamine (DIPEA) in the presence of tetrabutylammonium iodide (TBAI), gave the amino acid derivatives **102** in high yields and high diastereomeric ratios. After treatment of esters **102** in methanol with Et_3N at room temperature, the chiral auxiliary was successfully removed (Scheme 1.32).



Scheme 1.32 Dynamic kinetic resolution of α-chloro ester **101** in nucleophilic substitution.

Park also employed D-allofuranose as auxiliary for the dynamic kinetic resolution of α-chloro esters in nucleophilic substitutions [46]. Using the same reaction conditions previously for D-glucose derivative **101** and benzylamine as the nucleophile, dynamic resolution of α-chloro acetate **104** took place with high stereoselectivity, affording **105** in moderate isolated yield with 90 : 10 dr (α*S*:α*R*) (Scheme 1.33).



Scheme 1.33 Dynamic kinetic resolution of α-chloro ester **104** in nucleophilic substitution.

Based on the results, a plausible mechanism for the nucleophilic substitutions of D-glucose derivatives and D-allose derivatives has been suggested (Figure 1.6) [46]. The authors proposed two transition states in which the α-R group and the C=O bond in the ester substituent adopt an *s-cis* conformation, while the ester carbonyl group is in an eclipsed position relative to the hydrogen atom at C3 of the furanose. The nucleophilic attack of an amine nucleophile may then be aided by hydrogen bond formation with one oxygen atom from the 5,6-*O* and 1,2-*O*

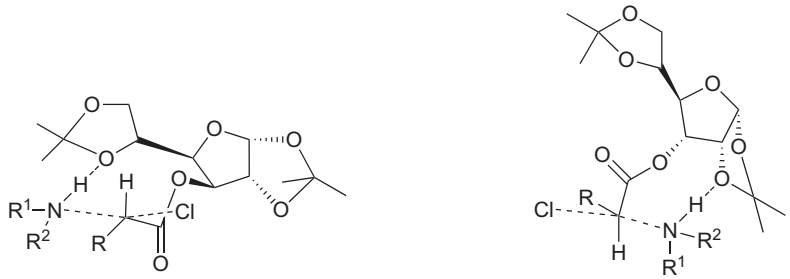


Figure 1.6 Proposed transition state structures for dynamic kinetic resolution of α-halo esters of glucose- and allose-derived carbohydrate auxiliaries.

dioxolanes of the chiral auxiliaries in **(α*R*)-101** and **(α*S*)-101**, respectively. These tentative transition states explain the *(S)*-configurations of the products observed for both the D-glucose and D-allose derived auxiliary.

References

1 Vasella, A. (1977) *Helv. Chim. Acta*, **60**, 1273.

2 (a) Cintas, P. (1991) *Tetrahedron*, **47**, 6079; (b) Reissig, H.U. (1992) *Angew. Chem. Int. Ed. Engl.*, **31**, 288; (c) Kunz, H. and Rück, K. (1993) *Angew. Chem. Int. Ed. Engl.*, **32**, 336; (d) Hale, K.J. (1993) *Second Supplement to the Second Edition of Rodd's Chemistry of Carbon Compounds*, vol. 1E/F/G (ed. M. Sainsbury), Elsevier, Amsterdam, Chapter 23b, p. 273; (e) Kunz, H. (1995) *Pure Appl. Chem.*, **67**, 1627; (f) Hultin, P.G., Earle, M.A., and Sudharshan, M. (1997) *Tetrahedron*, **53**, 14823; (g) Knauer, S., Kranke, B., Krause, L., and Kunz, H. (2004) *Curr. Org. Chem.*, **8**, 1739; (h) Boysen, M.M.K. (2007) *Chem. Eur. J.*, **13**, 8648; (i) Lehnert, T., Özüduru, G., Grugel, H., Albrecht, F., Telligmann, S.M., and Boysen, M.M.K. (2011) *Synthesis*, 2685.

3 (a) Enders, D. and Shilvock, J.P. (2000) *Chem. Soc. Rev.*, **29**, 359; (b) Merino, P., Marqués-López, E., Tejero, T., and Herrera, R.P. (2009) *Tetrahedron*, **65**, 1219.

4 (a) Kunz, H. and Sager, W. (1987) *Angew. Chem. Int. Ed. Engl.*, **26**, 557; (b) Kunz, H., Sager, W., Schanzenbach, D., and Decker, M. (1991) *Liebigs Ann. Chem.*, 649; (c) Kunz, H., Sager, W., Pfrengle, W., and Schanzenbach, D. (1988) *Tetrahedron Lett.*, **29**, 4397.

5 Kunz, H., Pfrengle, W., Rück, K., and Sager, W. (1991) *Synthesis*, 1039.

6 Paulsen, H., Györgydeak, Z., and Friedmann, M. (1974) *Chem. Ber.*, **107**, 1568.

7 Wang, D., Zhang, P.F., and Yu, B. (2007) *Helv. Chim. Acta*, **90**, 938.

8 Zhou, G.B., Zheng, W.X., Wang, D., Zhang, P.F., and Pan, Y.J. (2006) *Helv. Chim. Acta*, **89**, 520.

9 Porter, J.R., Wirschun, W.G., Kuntz, K.W., Snapper, M.L., and Hoveyda, A.H. (2000) *J. Am. Chem. Soc.*, **122**, 2657.

10 Ugi, I., Offermann, K., Herlinger, H., and Marquarding, D. (1967) *Justus Liebigs Ann. Chem.*, 7091.

11 (a) Dömling, A. (2006) *Chem. Rev.*, **106**, 17; (b) Dömling, A. and Ugi, I. (2000) *Angew. Chem. Int. Ed.*, **39**, 3168.

12 (a) Kunz, H. and Pfrengle, W. (1988) *J. Am. Chem. Soc.*, **110**, 651; (b) Kunz, H. and Pfrengle, W. (1988) *Tetrahedron*, **44**, 5487.

13 Kunz, H., Pfrengle, W., and Sager, W. (1989) *Tetrahedron Lett.*, **30**, 4109.

14 Zech, G. and Kunz, H. (2004) *Chem. Eur. J.*, **10**, 4136.

15 Costantino, G., Marinozzi, M., Camaioni, E., Natalini, B., Sarichelou, I., Micheli, F., Cavanni, P., Faedo, S., Noe, C., Moroni, F., and Pellicciari, R. (2004) *Farmaco*, **59**, 93.

16 Ugi, I., Marquarding, D., and Urban, R. (1982) *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, vol. 6 (ed. B. Eeinstein), Marcel Dekker, New York, p. 245.

17 Preobrazhenskaya, M.N. and Suvorov, N.N. (1965) *Zh. Obshch. Khim.*, **85**, 888.

18 Aebischer, B.M., Hanssen, H.W., Vasella, A.T., and Schweizer, W.B. (1982) *J. Chem. Soc. Perkin Trans. 1*, 2139.

19 Goebel, M. and Ugi, I. (1991) *Synthesis*, 1095.

20 Lehnhoff, S., Goebel, M., Karl, R.M., Klösel, R., and Ugi, I. (1995) *Angew. Chem. Int. Ed. Engl.*, **34**, 1104.

21 (a) Micheel, F. and Klemer, A. (1961) *Adv. Carbohydr. Chem.*, **16**, 95; (b) Pfleiderer, W. and Bühler, E. (1966) *Chem. Ber.*, **99**, 3022.

22 Ross, G.F., Herdtweck, E., and Ugi, I. (2002) *Tetrahedron*, **58**, 6127.

23 Ingles, D.L. and Whistler, R.L. (1962) *J. Org. Chem.*, **27**, 3896.

24 (a) Birkofer, L. and Ritter, A. (1965) *Angew. Chem. Int. Ed. Engl.*, **4**, 417; (b) Paulsen, H., Gyorgydeak, Z., and Friedmann, M. (1974) *Chem. Ber.*, **107**, 1568; (c) Strumpel, M.K., Buschmann, J., Szilagyi, L., and Gyorgydeak, Z. (1999) *Carbohydr. Res.*, **318**, 91.

25 Ross, G.F. and Ugi, I. (2001) *Can. J. Chem.*, **79**, 1934.

26 (a) Yamamoto, Y., Nishii, S., Maruyama, K., Komatsu, T., and Ito, W. (1986) *J. Am. Chem. Soc.*, **108**, 7778; (b) Yamamoto, Y., Komatsu, T., and Maruyama, K. (1984) *J. Am. Chem. Soc.*, **106**, 5031; (c) Yamamoto, Y., Komatsu, T., and Maruyama, K. (1985) *J. Chem. Soc., Chem. Commun.*, 814.

27 (a) Laschat, S. and Kunz, H. (1990) *Synlett*, 51; (b) Laschat, S. and Kunz, H. (1990) *Synlett*, 629; (c) Laschat, S. and Kunz, H. (1991) *J. Org. Chem.*, **56**, 5883.

28 (a) Risch, N., Arend, M., and Westermann, B. (1998) *Angew. Chem., Int. Ed. Engl.*, **37**, 1044 and references therein; (b) Tramontini, M. and Angiolini, L. (1994) *Mannich Bases, Chemistry and Uses*, CRC Press, Boca Raton, FL, and references therein; (c) Volkmann, R.A. (1991) *Comprehensive Organic Synthesis*, vol. 1 (eds B.M. Trost and I. Fleming), Pergamon, Oxford, UK, p. 355 and references therein.

29 Vilaivan, T., Bhanthumnavin, W., and Sritana-Anant, Y. (2005) *Curr. Org. Chem.*, **9**, 1315.

30 (a) Seebach, D. and Hoffmann, M. (1998) *Eur. J. Org. Chem.*, 1337; (b) Aoyagi, Y., Jain, R.P., and Williams, R.M. (2001) *J. Am. Chem. Soc.*, **123**, 3472 and references therein; (c) Evans, D.A., Urpi, F., Somers, T.C., Clark, J.S., and Bilodeau, M.T. (1990) *J. Am. Chem. Soc.*, **112**, 8215; (d) Kober, R., Papadopoulos, K., Miltz, W., Enders, D., Steglich, W., Reuter, H., and Puff, H. (1985) *Tetrahedron*, **42**, 1693; (e) Palomo, C., Oiarbide, M., Landa, A., Gonzales-Rego, M.C., Garcia, J.M., Gonzales, A., Odriozola, J.M., Martin-Pastor, M., and Linden, A. (2002) *J. Am. Chem. Soc.*, **124**, 8637 and references therein.

31 (a) Córdova, A. (2004) *Acc. Chem. Res.*, **37**, 102; (b) Loh, T.P. and Chen, S.L. (2002) *Org. Lett.*, **4**, 3647.

32 Kunz, H. and Schanzenbach, D. (1989) *Angew. Chem. Int. Ed. Engl.*, **28**, 1068.

33 (a) Braun, M., Sacha, H., Galle, D., and El-Alali, A. (1995) *Tetrahedron Lett.*, **36**, 4213; (b) Ojima, I., Habus, I., Zhao, M., Georg, G.I., and Jayasinghe, L.R. (1991) *J. Org. Chem.*, **56**, 1681.

34 Kunz, H., Burgard, A., and Schanzenbach, D. (1997) *Angew. Chem. Int. Ed. Engl.*, **36**, 386.

35 Allef, P. and Kunz, H. (2000) *Tetrahedron: Asymmetry*, **11**, 375.

36 Kunz, H. and Pfrengle, W. (1989) *Angew. Chem. Int. Ed. Engl.*, **28**, 1067.

37 Weymann, M., Pfrengle, W., Schanzenbach, D., and Kunz, H. (1997) *Synthesis*, 1151.

38 (a) Kranke, B., Hebranlt, D., Schulz-Kukula, M., and Kunz, H. (2004) *Synlett*, 671; (b) Kranke, B., and Kunz, H. (2006) *Can. J. Chem.*, **84**, 625.

39 Huber, R., Knierzinger, A., Obrecht, J.-P., and Vasella, A. (1985) *Helv. Chim. Acta*, **68**, 1730.
40 Huber, R. and Vasella, A. (1987) *Helv. Chim. Acta*, **70**, 1461.
41 Laschat, S. and Kunz, H. (1992) *Synthesis*, 90.
42 Wang, Y.D., Wang, F., Wang, Y.Y., Miao, Z.W., and Chen, R.Y. (2008) *Adv. Synth. Catal.*, **350**, 2339.
43 Wang, Y.D., Wang, Y.Y., Yu, J., Miao, Z.W., and Chen, R.Y. (2009) *Chem. Eur. J.*, **15**, 9290.
44 For examples using other auxiliaries see: (a) Valenrod, Y., Myung, J., Ben, R.N. (2004) *Tetrahedron Lett.*, **45**, 2545; (b) Nam, J., Lee, S.-K., and Park, Y.S. (2003) *Tetrahedron*, **59**, 2397; (c) Nam, J., Lee, S.-K., Kim, K.Y., and Park, Y.S. (2002) *Tetrahedron Lett.*, **43**, 8253; (d) Lee, S.-K., Nam, J., and Park, Y.S. (2002) *Synlett*, 790; (e) Ben, R.N. and Durst, T. (1999) *J. Org. Chem.*, **64**, 7700.
45 Kim, H.J., Shin, E.K., Chang, J.Y., Kim, Y., and Park, Y.S. (2005) *Tetrahedron Lett.*, **46**, 4115.
46 Kim, H.J., Kim, Y., Choi, E.T., Lee, M.H., No, E.S., and Park, Y.S. (2006) *Tetrahedron*, **62**, 6303.