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Stereoselective syntheses using carbohydrates as chiral auxiliaries

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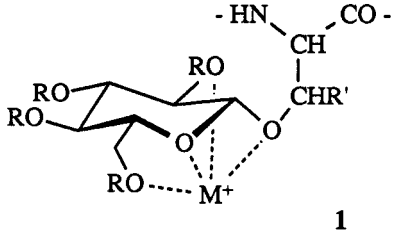
Abstract: Carbohydrates contain numerous functional groups and chiral centers in one molecular unit. Furthermore, they can exert marked complexing capabilities towards Lewis acids. Utilizing these properties, carbohydrates were applied for effective diastereodifferentiation in reactions on prochiral faces or groups of substrates. In this sense, Lewis acid-catalyzed Diels-Alder reactions of carbohydrate-linked dienophiles furnished the corresponding cycloadducts in high diastereoselectivity. The formation of a by-product during Diels-Alder reactions catalyzed with diethylaluminum chloride gave rise to the development of a new synthesis of β-branched carboxylic acids consisting of the 1,4 addition of dialkylaluminum chlorides to α,β-unsaturated N-acyl urethanes. The process combined with subsequent trapping reactions of the intermediates by electrophiles resulted in stereoselective syntheses of α-functionalized β-branched carboxylic acid derivatives. Glycosylamines proved to be particularly useful in stereoselective syntheses of α-amino acid derivatives, in asymmetric hetero Diels-Alder reactions and in Mannich reactions. In a new stereoselective reaction, Schiff bases of these glycosylamines with allylsilane gave chiral homoallylamines of high optical purity.

COMPLEXATION - A PRINCIPLE TO ACTIVATE AND ARRANGE CARBOHYDRATE FUNCTIONALITIES

Carbohydrate side chains of glycoproteins obviously play major roles in biological recognition processes and in the directed distribution of glycoproteins and glycolipids in multicellular organisms (1). In the course of our syntheses of glycopeptides (2) we came across the problem of base-catalyzed β-elimination of the carbohydrate portion from O-glycosylserine and -threonine derivatives (3). Since it is known from peptide chemistry that O-tert-butyl and O-benzyl ethers of serine and threonine are stable to bases, the easy base-catalyzed β-elimination of the carbohydrate from glycosylserine and -threonine is surprising. We ascribed the remarkable leaving group tendency of the carbohydrates in these compounds to their complexing abilities towards cations **1**. This activation of carbohydrates by complexation could be demonstrated in the development of a new peptide synthesis (4). Carbohydrate esters of amino acids, e.g. **2**, do not react with



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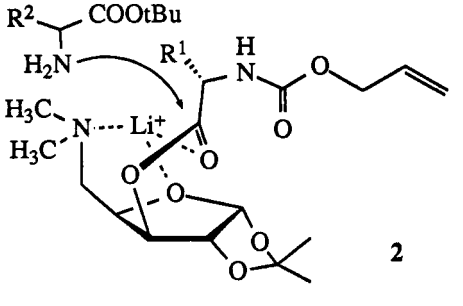


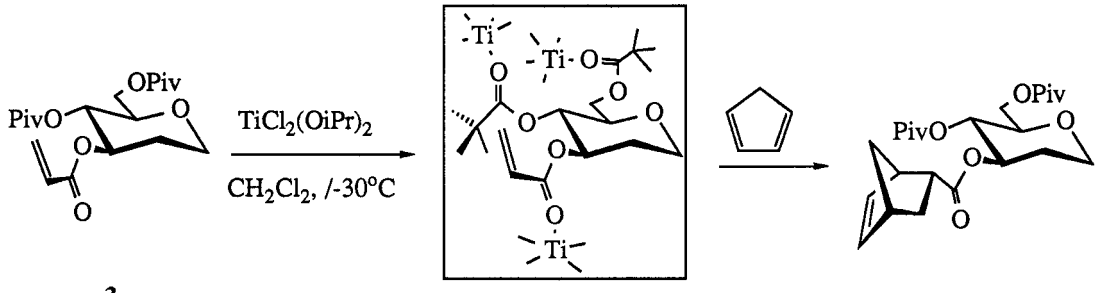
2

amino acid tert-butyl esters in dichloromethane. However, after addition of lithium bromide, these components smoothly formed the corresponding peptide.

On the other hand, the complexation of cations or other Lewis acids which results in an organized arrangement of the functional groups of a carbohydrate seemed to be the key to an effective use of carbohydrate templates as stereodifferentiating tools in asymmetric synthesis. Until the mid eighties, when we begun to realize this concept, carbohydrates were regarded as too complex to be useful as the chiral auxiliaries in stereodifferentiations. They were mainly applied as the starting materials in ex-chiral-pool syntheses, and only a few isolated examples had been reported for carbohydrates as stereodifferentiating templates in asymmetric reductions (5) and cycloaddition reactions (6, 7).

DIASTEREOSELECTIVE DIELS-ALDER REACTIONS

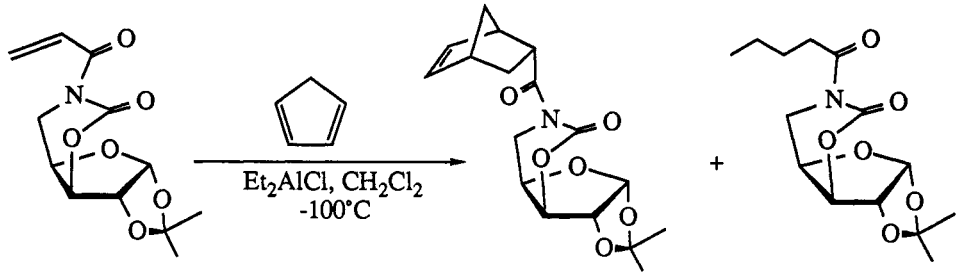
For Diels-Alder reactions the polyfunctionality of carbohydrates allows to link both, the dienophile and a Lewis-acid promoter to the chiral framework. Reactions of the 3-O-acryloyl-1,2-O-isopropyliden-α-D-glucofuranose catalyzed by an intramolecular titanate group resulted in the formation of the adduct with high stereoselectivity (8). Due to the reduced Lewis acid potency of the titanate, only reactive dienes, e. g. cyclopentadiene, underwent the reaction at low temperature. To overcome these limitations, the acrylate **3** containing the dihydroglucal framework was investigated. This compound allows a coordinative fixation of the Lewis acid promoter. Logically, the Lewis acid strength can be varied in Diels-Alder reactions of **3** with dienes of different reactivity. Reactive dienes require only moderate Lewis acid catalysis to give the corresponding adduct **4** in a high yield and high diastereoselectivity, whereas dienes of lower reactivity demand strong Lewis acid promoters to form the corresponding cycloadduct in good yield and excellent diastereoselection (9).



3 **5** **4**

The efficiency of the stereoselection in the cycloaddition reactions of the acrylate **3** obviously originates from the clear diastereofacial differentiation arising in the intermediary complex **5.** The 4-O-pivaloyl group enlarged by complexation perfectly shields the *Re*-face of the acrylate. The outlined concept also offers the possibility to stereoselectively synthesize the opposite enantiomers of the cycloadducts by simply employing the analogous 4-O-pivaloyl-dihydro-L-rhamnal as the chiral auxiliary (9).

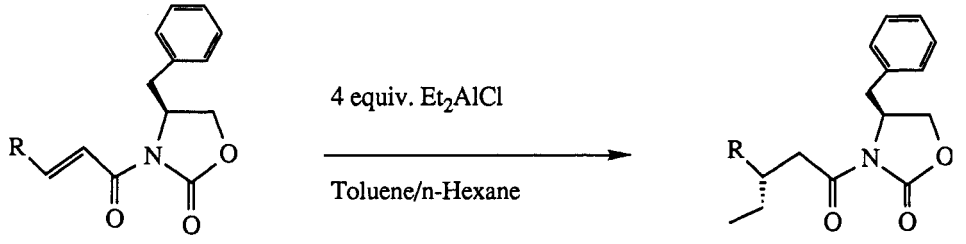
However, the efficiency of the carbohydrate-directed Diels-Alder reaction depends upon the type of the carbohydrate auxiliary. For example, the reaction of cyclopentadiene with the acryloyl oxazinone **6** derived from xylofuranose under catalysis with diethylaluminum chloride displayed only low diastereoselectivity in the formation of the cycloadduct **7.** During this reaction a by-product **8** was formed. Its structural analysis revealed that compound **8** was formed by a 1,4 addition of the diethylaluminum chloride to the dienophile. As this reaction was unknown at that time and, furthermore, constitutes a new access to β-branched carboxylic acid derivatives, we considered the formation of **8** the interesting outcome of the attempted cycloadditions on the N-acyl oxazinone **6** (10).



6 **7** 48% (R) : (S) = 72 : 28 **8** 10%

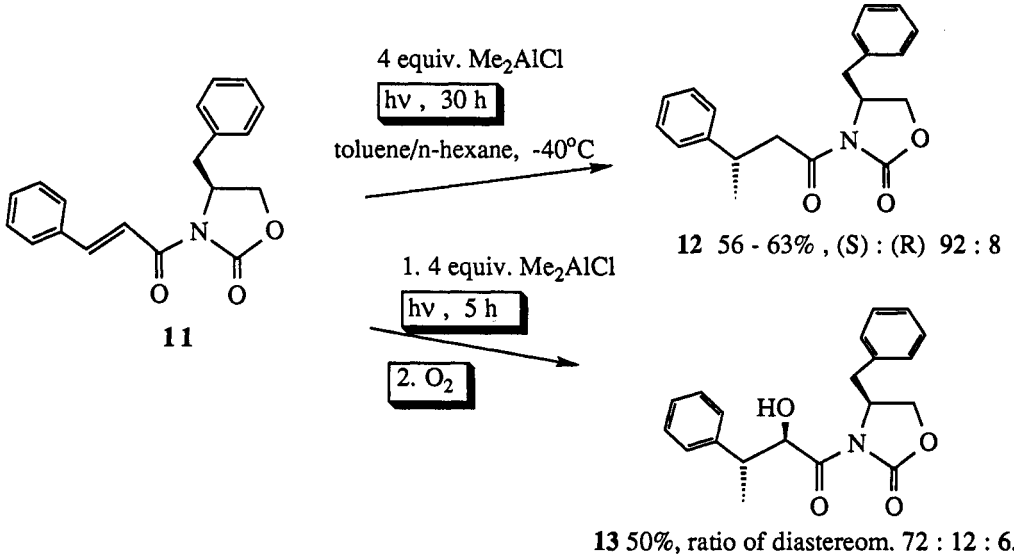
1,4 ADDITION OF DIALKYLALUMINUM CHLORIDES TO N-ACYL OXAZOLINONES

The 1,4 addition of diethylaluminum chloride to N-acyl urethanes can be performed as a preparative synthesis of β-branched carboxylic acid derivatives, when two or more equivalents of the organoaluminum chloride are applied (10). Under optimized conditions, the α,β-unsaturated oxazolidinones **9** containing the Evans auxiliary (11) reacted with four equivalents of diethylaluminum chloride in toluene/n-hexane to give the corresponding β-branched compounds **10** in good yield and a diastereoselectivity up to 10:1.



9 **10**

Whereas higher homologues of diethylaluminum chloride showed analogous 1,4-addition, the transfer of a methyl group from dimethylaluminum chloride to the acceptor, e. g. **11**, was achieved only by photochemical activation or in the presence of a radical initiator (12). As the formation of the β-methyl compound **12** can be completely inhibited by addition of a radical scavenger, it has to be concluded that the strong Lewis acid dimethylaluminum chloride in contrast to the higher homologues surprisingly reacts with the pronouncedly polar acceptor **12** not via a polar but via a homolytic pathway.

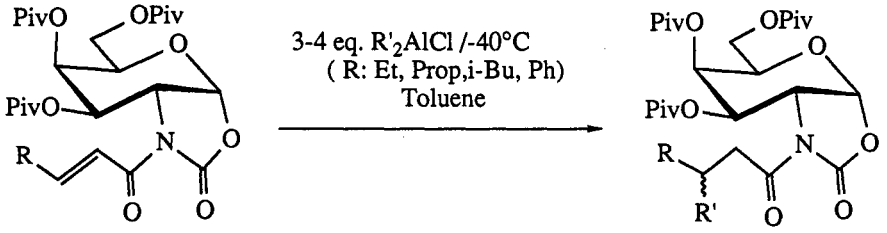


11

12 56 - 63% , (S) : (R) 92 : 8

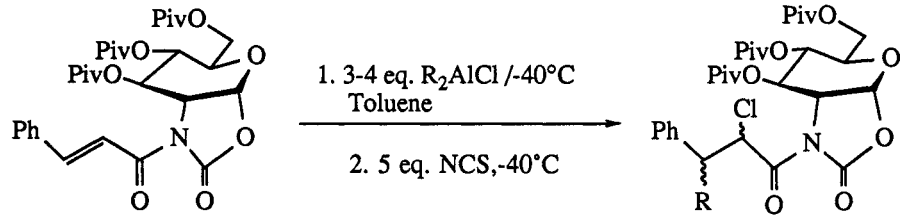
13 50%, ratio of diastereom. 72 : 12 : 6.5 : 4.5

When the photochemical methyl transfer from dimethylaluminum chloride is combined with a subsequent oxidation of the intermediate with oxygen, β-branched α-hydroxy carboxylic acid derivatives **13** are obtained (12). In this process two new chiral centers are formed. Among the four possible diastereomers one *anti* isomer was found in an useful stereoselectivity. However, the stereodifferentiation in the 1,4 addition exhibited by oxazolidinones derived from phenylalanine did not exceed a ratio of 12:1. As a consequence, we have introduced bicyclic oxazolidinones derived from 2-amino-2-deoxy galactose and glucose. We expected that a more effective *exo* versus *endo* differentiation during addition reactions to the enoate group should be achieved by means of these auxiliaries. The polar reactions of diethylaluminum chloride, dipropylaluminum chloride and diphenylaluminum chloride with the crotonoyl and cinnamoyl derivatives **14** of the oxazolidinone from galactosamine proceeded with excellent stereoselectivity to furnish the β-branched compounds **15** (13, 14).



14 **15** ratio of diastereom. up to > 99 : 1

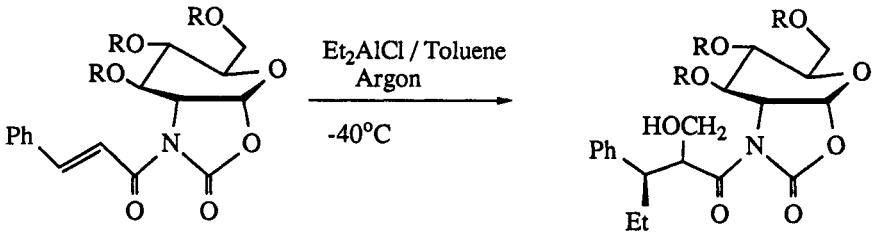
Depending upon the choice of the group R in the acceptor and R' in the organoaluminum reagent both series of enantiomers of β-branched carboxylic acid derivatives can be synthesized selectively. When the intermediary aluminum enolates of these polar reactions are trapped with N-chloro- or N-bromosuccinimide, β-branched α-halocarboxylic acid derivatives **17** were obtained with high induction and anti selectivity (15). In these cascade-type functionalizations of the enoate double bond, the glucosamine-derived oxazolidinone **16** revealed itself to be more efficient than the galactosamine analogue.



16

17 R = Et, 77%,
ratio of diastereom. 91.8 : 7.1 : 1.1

Not only the carbohydrate but also the protecting groups influence the stereoselection in these processes. The tandem process consisting of the initial 1,4 addition of diethylaluminum chloride and the subsequent reaction of the enolate with formaldehyde showed higher diastereoselectivity with the O-benzoyl protected oxazolidinone **18** in comparison to the O-pivaloyl analogue **16**. Also in these cases, out of the four possible diastereomers of the products **19** or **20**, respectively, one isomer was formed in a high selectivity (16).



18 R = Bz
16 R = Piv

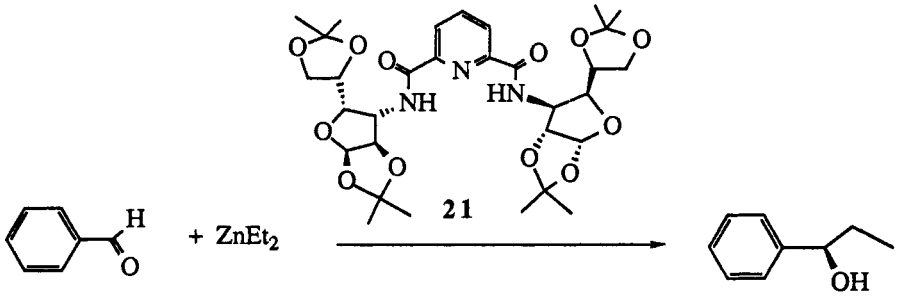
19 R = Bz, 62%, ratio of diastereom. 13 : 1.5 : 1
20 R = Piv, 44%, ratio of diastereom. 10 : 3.3 : 1

It should be mentioned that the treatment of the N-acryloyl oxazolidinone of type **18** with 1 or 2 equivalents of diethylaluminum chloride resulted in a stereoselective oligomersisation of the acrylate (16).

CARBOHYDRATES AS ENANTIOSELECTIVE CATALYSTS

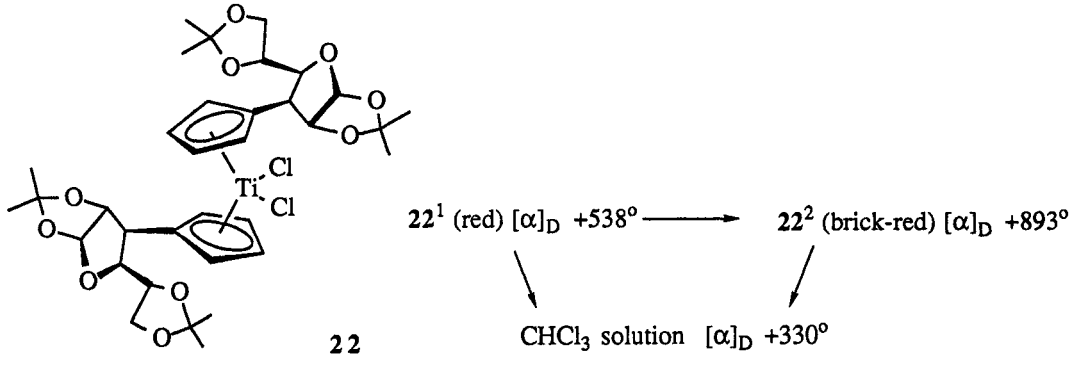
Preliminary investigations showed that carbohydrate derivatives could be promising enantioselective catalysts. The addition of diethylzinc to benzaldehyde (17, 18) catalyzed by the carbohydrate-substituted pyridine-2,6-dicarboxylic acid diamide **21** gave 1-phenyl propanol with high chemoselectivity and an enantiomeric ratio of 93:7 in favour of the (S)-enantiomer (19).

In context with the construction of carbohydrate catalysts, we have synthesized the titanocene **22** carrying two 1,2-5,6-di-O-isopropylidene-3-deoxy-α-D-glucofuranose substituents (18). Compound **22** surprisingly exists in two crystalline configurations differing in their optical rotation. It is assumed that the two forms of **22** are atropisomeric diastereomers which are isolated in enriched form due to a retarded rotation of the cyclopentadienyl ligands relative to each other.



70 - 90% (S) : (R) up to 93 : 7

The first experimental investigations with these compounds showed that the bis-trifluoromethanesulfonate corresponding to **22** efficiently catalyzes C-C-bond forming reactions, for example aldol reactions and the formation of cyanohydrines. However, the enantioselectivity attained is not sufficient so far (19).

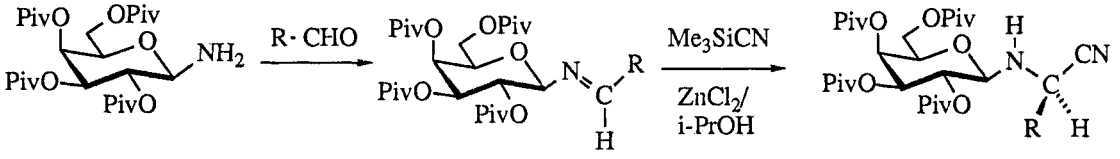


22

GLYCOSYLAMINES AS CHIRAL AUXILIARIES IN STEREOSELECTIVE SYNTHESIS

Glycosylamines can be considered asymmetric synthons of ammonia in stereoselective syntheses of nitrogen containing compounds, because of the possibility to achieve the acidolytic cleavage of the N-glycosidic bond present in the formed products.

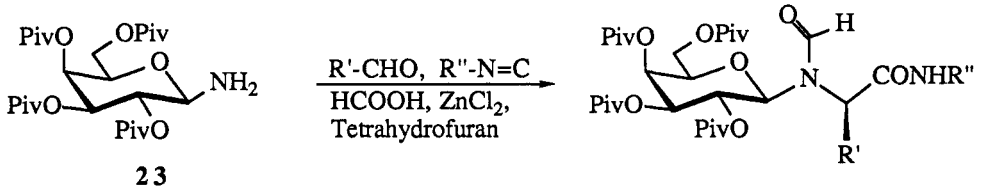
The reaction of O-pivaloyl protected galactosylamine **23** with aldehydes yielded Schiff bases **24** which on treatment with trimethylsilyl cyanide and zinc chloride in isopropanol gave the amino nitriles **25** in almost quantitative yield and a diastereoselectivity of 7 to 15:1 in favour of the D-amino nitrile diastereomers. By simple recrystallization from n-heptane the pure D-isomers were obtained in yields of 75 to 90% (20, 21).



23 **24** **25** (D) : (L) 7 to 15 : 1

A remarkable feature of the Strecker reactions with galactosyl imines that we have studied is that the direction of asymmetric inductions can be reversed by a change of the solvent. In chloroform under otherwise analogous conditions the L-amino nitriles are formed in excess (22). Furthermore, for the latter process we observed an interesting increase of asymmetric induction at elevated temperature from (L) : (D) = 1,5 : 1 at -30°C to 5 : 1 at +20°C (23).

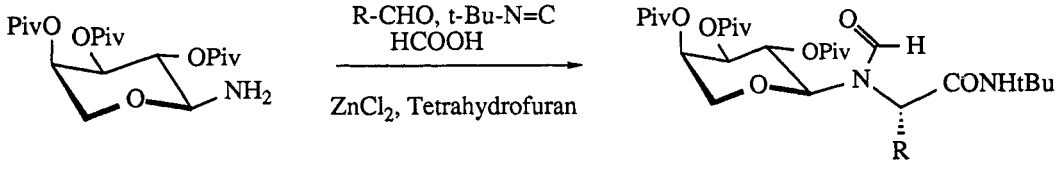
A highly stereoselective Ugi synthesis of amino acid derivatives **26** was found when the galactosylamine **23** was reacted with an aldehyde, an isocyanide and a carboxylic acid in the presence of zinc chloride in tetrahydrofuran (24). The crude amino acid amide derivatives **26** displayed diastereomeric ratios of 15 to 30:1.



23 **26**, >95%, (D) : (L) 93 :7 to 97 : 3

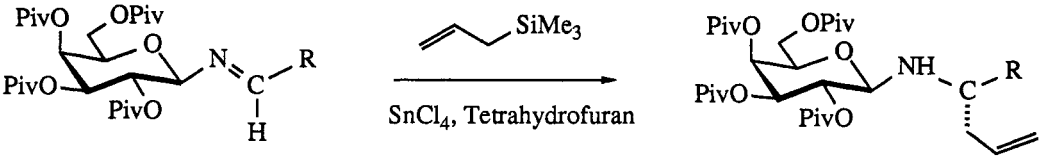
After recrystallization or flash-chromatography the diastereomerically pure amino acid amides **26** were isolated in yields of 75 to 95% (24, 25). They can be transformed to enantiomerically pure α-amino acids (22), β-amino alcohols or, via 1,2 diamines, to chiral imidazolidinones (26).

Application of the O-pivaloyl α-D-arabinosylamine **27** as the chiral template in the Ugi reaction results in the preferred formation of the corresponding L-amino acid derivatives **28** in high yield and high diastereoselectivity (25, 27). Again, by recrystallization or flash chromatography pure L-diastereomers **28** were isolated in excellent yields.



27 **28**, >95% (L) : (D) 96 : 4 to 98 : 2

In contrast to simple Schiff bases, N-galactosyl imines **24** reacted with allyltrimethylsilane under promotion by tin tetrachloride in tetrahydrofuran to furnish chiral homoallylamines **29** (28). Although this conversion required temperatures of 0°C or even room temperature, the accomplished diastereoselectivity was high in most cases.

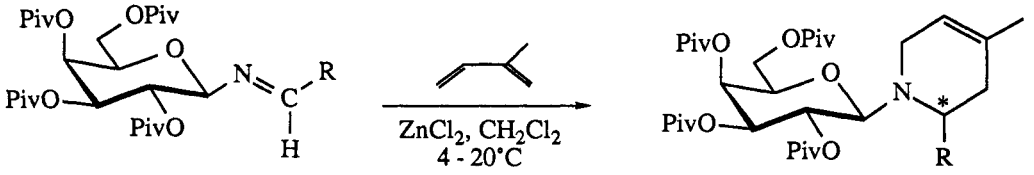


24

29, ratio of diastereom. 7 to 27 : 1

The homoallylamines **29** are valuable synthons. For example, they can be transformed to chiral β-amino acids. Application of L-fucosyl imines instead of the galactosyl derivatives resulted in the stereoselective synthesis of homoallylamines with opposite configuration (29, 30).

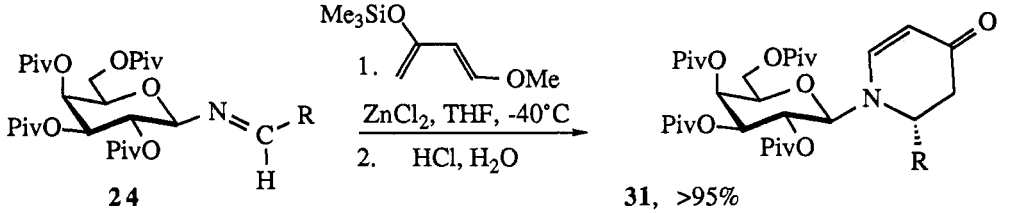
N-Glycosyl imines, for instance **24**, were also applied as dienophiles in hetero Diels-Alder reactions. With isoprene the corresponding cycloadducts **30** were formed with complete regioselectivity and a diastereoselection up to 10:1 (31).



24

30, ratio of diastereom. 5 to 10 : 1

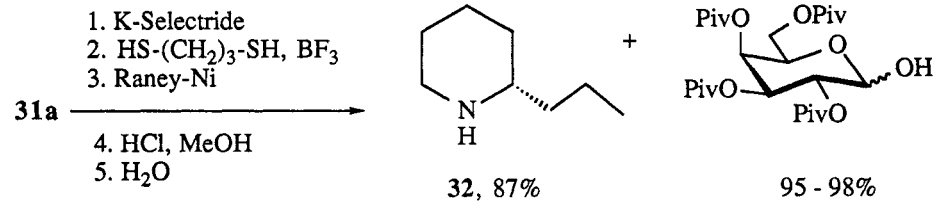
For reactions of glycosyl imines **25** with silyl dienol ethers, as for example the Danishefsky diene (32), a tandem Mannich and Michael reaction sequence occurred resulting in a highly stereoselective formation of the cyclic enaminones **31** (33).



24

31, >95%

31a. R = n-Pr, (S) : (R) = 97.5 : 2.5
31b. R = 4-Cl-Ph, (S) : (R) = 98 : 2

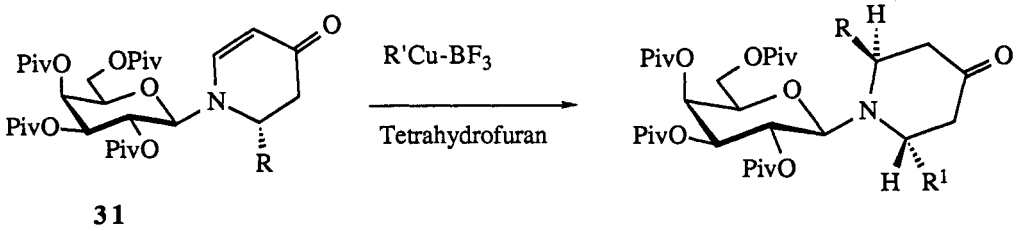


32, 87%

95 - 98%

For example, the 2-propyl derivative **31a** was obtained in a diastereomeric ratio of 97.5 : 2.5 in the crude reaction mixture. It was isolated in diastereomerically pure form in a yield of 81% and then converted to enantiomerically pure (S)-coniin **32** in high yield.

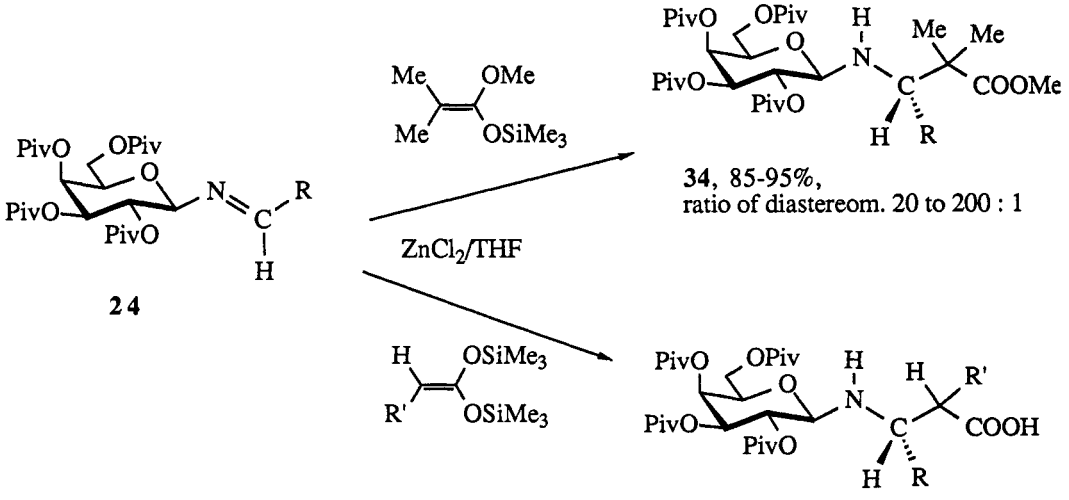
In addition, the enaminones **31** are useful synthons which can be reacted with organocuprate-borontrifluoride complexes (34) to give 2,6-di-substituted piperidin-4-ones **33** with excellent diastereoselectivity (35).This reaction sequence opens up the possibility for the stereoselective synthesis of a series of alkaloids, for example epi-pumiliotoxin.



31

33, R = 4-Cl-Ph, R' = i-Pr: 77%, d.r. 25 : 1

The Mannich-type reaction of silyl ketene acetals with glycosyl imines, as for example **24**, affords an efficient and highly stereoselective access to chiral β-amino acid derivatives **34** (36). The reaction of the prochiral ketene acetal with **24** under catalysis by zinc chloride furnished the amino acid derivative **35** containing two new chiral centers with an excellent stereoselectivity (37).



24

34, 85-95%,
ratio of diastereom. 20 to 200 : 1

35, R = 4-Me-Ph, R' = Me: 88%
ratio of diastereom. >20 : 1

The examples outlined here may illustrate, that carbohydrates are in fact efficient stereodifferentiating tools in the synthesis of a great variety of interesting chiral compounds (15). This holds true, in particular, if complexation of the carbohydrate functionalities induces a favourable positioning of the shielding groups relative to the reacting substrate structure linked to the carbohydrate. As the chiral compounds produced can often be released from the carbohydrate template by a mild cleavage of the glycosidic bond and the carbohydrate auxiliary can be recovered after the reaction, the use of carbohydrates in stereodifferentiating processes is considered a promising concept in asymmetric synthesis.

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