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Diastereoselective synthesis of vicinal amino alcohols

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The vicinal amino alcohol is a common motif in natural products and pharmaceuticals. Amino acids constitute a natural, inexpensive, and enantiopure choice of starting material for the synthesis of such functionalities. However, the matters concerning diastereoselectivity are not obvious. This Perspective takes a look in the field of diastereoselective synthesis of vicinal amino alcohols starting from amino acids using various methods.

Introduction

Amino alcohols are a common structural motif found in a range of natural molecules (Fig. 1). In proteins, one encounters the hydroxy amino acids serine (**1**) and threonine (**2**). In lipid bilayers and participating in cellular signalling pathways one cannot avoid the diverse class of sphingoids, *e.g.* sphingosine (**3**). The hormones epinephrine (**4**) and norepinephrine (**5**) are amino alcohols as well. Many others can be encountered beyond the safety of the human body ranging from small hydroxylated alkaloids like the glycosidase inhibitor nojirimycin (**6**) and the antimalarial agent febrifugine (**7**) to depsipeptides like the anti-cancer agent hapalosin (**8**) to amino sugars like antibiotic neomycin (**9**). Due to the diverse biological activities the amino alcohol moiety has been incorporated into pharmaceuticals as well. Randolazine (**10**) is a compound used in antianginal preparations. Metoprolol (**11**) and nebivolol (**12**) are β_1 receptor blockers used for the treatment of a number of cardiovascular conditions. Zanamivir (**13**) is a neuraminidase inhibitor used in the treatment of influenza. Docetaxel (only the amino alcohol containing side chain is drawn) (**14**) is an antimitotic compound used to combat metastatic cancers.

Beyond the medicinal use, the synthetic community has taken interest in the amino alcohol moiety, primarily as ligands for organometallic chemistry and as chiral auxiliaries.¹ The general construction of amino alcohols has been recently reviewed.²

In the era of enantioselective transformations several creative and efficient methods have been developed for the asymmetric synthesis of amino alcohols from achiral or racemic starting materials. However, one should not forget the wonderful collection of enantiopure compounds provided by Nature, the chiral pool. In this Perspective we wish to remind readers that diastereoselective transformations are still useful as reflected partly through the work being conducted in our laboratory. The reader

will hopefully gain insight into how to control the stereochemistry of these fickle molecules.

Amino acids constitute a natural choice of starting material for the synthesis of amino alcohols. Natural L-amino acids are available in bulk quantities at very affordable prices. The corresponding D-enantiomers are more expensive, but generally also available in large quantities. A number of methods allow the preparation of unnatural amino acids using natural ones as templates. However, such methods are beyond the scope of this article.³

Our group has been actively involved in the synthesis of non-peptide natural products from amino acids, and consequently we have investigated the synthesis of (vicinal) amino alcohols over the course of years. The following sections sum up our results relating to this subject backed up by a wide variety of results from the literature.

Additions to α -aminoaldehydes

Conventions used in this text

Addition of organometallics and other nucleophiles to α -amino aldehydes constitutes a straightforward method for direct synthesis of vicinal amino alcohols. The selectivity observed in the addition is usually explained with the Felkin–Anh/Cram chelate models. We shall first briefly explain the model and how it is interpreted in this text.

The Newman projection of the generalized amino aldehyde along the carbonyl axis is shown on the top of the Fig. 2. The Felkin–Anh model would place the electronegative NPg-group perpendicular to the carbonyl axis due to favourable $n-\pi^*$ interaction from the nitrogen lone pairs. The nucleophile (Nu^-) then attacks the carbonyl along the least hindered Bürgi–Dunitz trajectory. The product obtained is the Felkin-product, which is referred interchangeably in the text as the *anti*-product. The formation of the *anti*-Felkin (or *syn*-product) is often explained by chelated model where the carbonyl and the nitrogen (or the nitrogen protecting group) are bound together, thus placing the

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Fig. 1 Structural diversity of vicinal amino alcohols.

Fig. 2 The Felkin–Anh model.

R group perpendicular to the carbonyl axis. Addition along the least hindered trajectory would indeed produce the *syn*-product.

Since the concepts of *syn* and *anti* are not unambiguous, the compounds in this text are always drawn as in the above figure: the R-group and the nucleophile are drawn into plane. Thus, the terms *syn* and *anti* always refer to the mutual arrangement of the amino and alcohol groups.

Sometimes the observed diastereoselectivities are given as diastereomeric excesses (% de) or as diastereoselectivity percentages (% ds). For ease of comparison, these units have been converted into diastereomeric ratios (dr). For transparency, the drs are always presented in parentheses along with the original value.

On amino aldehydes

The use of amino aldehydes does have one major drawback. The inherent instability of the amino aldehyde moiety can be an issue, as they are prone to racemization under basic conditions and even on prolonged storage. In our hands, the serinal derivative **16** (Garner's aldehyde, Scheme 1), introduced by Garner, has proven to be convenient to work with and configurationally stable even after years of storage.⁴

The methyl ester **15** is conveniently synthesized in 3 steps from serine. Serine is esterified with methanolic HCl and then Boc-protected. The acetonide functionality is introduced under Lewis acidic conditions to give **15** typically in 70–80% overall yield after vacuum distillation. The concomitant DIBAL-H reduction has been problematic due to the tedious workup

Scheme 1 Synthesis of Garner's aldehyde.

involving gelatinous aluminium salts. During a synthetic endeavour we required access to large amounts of **16** (>100 mmol). After extensive experimentation we discovered that the reduction is best achieved in dichloromethane, then quenched with a large excess of MeOH followed by two equivalents (relative to DIBAL-H) of tartaric acid. The resulting mixture can then be filtered, concentrated and distilled under high vacuum to give **16** reproducibly in 70–80% yield and >97% ee by GC. If one wants to avoid the use of DIBAL, **15** can be reduced to the alcohol with LiAlH_4 and reoxidized under standard Swern conditions.⁵

Since the construction of oxazolidine structures similar to **16** is not possible from other amino acids except threonine, a different strategy must be adopted. *N,N*-Dibenzyl α -amino aldehydes (**17**, Fig. 3) have been successfully used in diastereoselective synthesis and are reported to be reasonably stable.⁶ The *N,N*-dibenzylamino aldehydes **17** are generally synthesized by dibenzylation of the corresponding amino alcohol followed by Parikh–Doering or Swern oxidation. Under no circumstance should the aldehydes be purified by column chromatography. In some cases rearrangements occur and in most cases extensive, even total, racemization as per Whiting *et al.*'s report.⁷

The third class of amino aldehyde that appear in the literature with some frequency are the singly protected amino aldehydes. The protecting group must be chosen with care, as the high nucleophilicity of the amino moiety must be kept in check. Carbamate protected amino aldehydes like **18** are most frequently used ones, but they are by far the most sensitive ones, as they are reported to suffer from the erosion of enantiomeric excess during synthesis and purification.^{8,9} Use of bulky protecting groups like trityl (**20**) or 9-phenylfluorenyl (**19**) renders the amine essentially non-nucleophilic and can sometimes protect the substrate from racemization, even under harsh conditions.¹⁰ There are other protecting groups as well, and some are briefly touched on in this review.

Additions to monoprotected amino aldehydes

Addition of organometallic reagents to carbamate protected amino aldehydes generally exhibit low diastereoselectivity. Boc-group is preferable over Cbz as it is less vulnerable to organomagnesium or -lithium reagents.

Fig. 3 Common protective groups used with amino aldehydes.

Protected prolinals behave differently compared to other singly protected amino aldehydes, since they lack the acidic NH-proton. Also, the aldehyde is more configurationally stable than its counterparts. We found out that addition of the acetylide **22** to prolinal **21** proceeds with moderate diastereoselectivity and yield (Scheme 2). This product was then advanced to the castanospermine derivative **24**.¹¹ The stereochemical integrity was checked by oxidation the acetylenic function of **23** back to Boc-protected proline followed by derivatization with (*S*)-phenethylamine and HPLC-analysis.

Scheme 2 Synthesis of castanospermine derivative **24**.

Interestingly, addition of a Grignard reagent prepared from TMS-acetylene to the prolinal **21** proceeded with almost no selectivity (Scheme 3). The authors also reported that the addition of the corresponding lithium acetylide only advanced to about 20% conversion presumably due to competing enolization.¹²

Scheme 3 Ethynylation of prolinal.

Cella *et al.* reported that crotylation of *N*-Boc prolinal **21** with a crotyl trifluoroborate salt proceeds with high *anti*–*syn* preference in a biphasic system with TBAI (tetrabutylammonium iodide) as phase transfer catalyst (Scheme 4). Allylation of *N*-Boc valinal **28** and leucinal **29** with the same system using an allyl fluoroborate salt proceeds similarly with high *anti*-selectivity and yield.¹³

Scheme 4 Crotylation and allylation with trifluoroborate salts.

Koide and Shahi reported that silver acetylides (generated from the corresponding acetylene and silver nitrate) added to *N*-Boc leucinal **29** with *syn*-selectivity in the presence of stoichiometric zirconocene dichloride and catalytic silver triflate (Scheme 5). Without the added silver triflate the reactions were sluggish and low yielding.¹⁴

Scheme 5 Ethynylation with silver acetylide.

In some cases 9-phenylfluorenyl-protected amino aldehydes undergo highly *syn*-selective additions with alkynyl Grignard reagents, as noted by Park *et al.* (Scheme 6). Substrates with aromatic side (**32–34**) groups exhibit favourable π -interactions with the Pf-group, thus enhancing the chelation control. The interaction was clearly visible in the crystal structure of *N*-Pf-L-Phe-OMe. This also explains why substrates with aliphatic side groups (**35–38**) gave low selectivity.¹⁵

Scheme 6 π -Interaction aided chelation control.

Krische *et al.* described a highly *syn*-selective rhodium catalyzed addition of vinyl ketones **40a–b** to Boc-protected amino aldehydes (Scheme 7). The authors invoked a chelated cyclic transition state to explain the high selectivity. In the presence of a hydrogen bond donor (*t*-amyl alcohol) the selectivity was eroded; a result which supports the chelate model. The reaction conditions were also shown to be non-epimerizing: *N*-Boc phenylalaninal **42** of 88% ee was reacted with methyl vinyl ketone and was cleanly transformed into product **43b** with 88% ee.⁹

Somfai *et al.* reported a highly diastereoselective [3 + 2] annulation of tosyl protected amino aldehydes and 1,3-bis(silyl)-propene (Scheme 8). Pyrrolidines **50** were obtained as single diastereomers in moderate yields. The high selectivity was attributed to strongly chelation controlled initial *syn*-addition. The products are amenable to Tamao–Fleming oxidation, which was demonstrated on substrate **50d** to give the polyhydroxylated pyrrolidine **51** (50% yield over 2 steps).¹⁶

Additions to *N,N*-dibenzylamino and other doubly *N*-protected aldehydes

Additions of magnesium and lithium reagents to *N,N*-dibenzyl-amino aldehydes generally proceed with high Felkin selectivity.

Scheme 7 Rhodium catalyzed *syn*-selective addition of vinyl ketones.

Scheme 8 Diastereoselective [3 + 2] annulation.

The bulky dibenzylamine group efficiently directs the addition of organometallics and prevents chelation control. Perez-Encabo *et al.* described the addition of homoallylmagnesium bromide to several *N,N*-dibenzylamino aldehydes (Scheme 9).¹⁷

Scheme 9 Addition of homoallylmagnesium bromide to dibenzyl-protected aldehydes.

High Felkin–Anh selectivity is achieved with alanine and serine derived aldehydes **52** and **53** and good selectivity for *D*-phenylglycine derived one (**ent-54**). Similarly, the addition of Büchi's reagent (**56**) to serinal **53** proceeds in excellent yield and diastereoselectivity (Scheme 10).¹⁸

Scheme 10 Addition of Büchi's reagent to serinal **53**.

Nicholas and Molinski required access to both diastereomers of amino alcohols **59** and **61** during the synthesis of a dimeric sphingolipid oceanapiside (Scheme 11).¹⁹ Addition of propylmagnesium bromide to aldehydes **52** and **58** provided the *anti*-diastereomers in good selectivity. Remarkably, they found out that the Sakurai-allylation can be used to access the *syn*-diastereomers **60** and **62** in good diastereomer ratio. This represents one of the few cases where the Felkin–Anh selectivity has been overridden.

Scheme 11 Reversal of stereoselectivity *via* Sakurai-reaction.

Hanessian and Devasthale have used the TBAF (tetrabutylammonium fluoride) catalyzed Henry-reaction between several *N,N*-dibenzylamino aldehydes and nitro compounds (**65a–c**) to build stereodiads and triads **66** with high selectivity (Scheme 12). The aldehydes were shown not to epimerize under the reaction conditions and the product distribution was kinetically controlled. The observed *anti,anti*-configuration of the products follows the Felkin–Anh model.²⁰

Scheme 12 TBAF catalyzed Henry reaction.

Hanessian *et al.*'s group has also studied aldol reactions between several *N,N*-dibenzylamino aldehydes and γ -butyrolactone (Scheme 13).²¹ Treatment of *N,N*-dibenzylamino aldehydes with the lithium enolate of γ -butyrolactone generated the *anti-anti* adducts **68** as the major product with various amounts of the three other diastereomers. Mukaiyama-aldol with the TMS-enol ether of γ -butyrolactone in the presence of different Lewis acids significantly altered the product ratios. Treatment of aldehyde **67** with the silyl enol ether in the presence of ZnBr₂ gave the *anti-syn* adduct **69** in high selectivity, whereas YbFOD gave the all-*syn* diastereomer **70**.

Scheme 13 Aldol and Mukaiyama-aldol additions to *N,N*-dibenzylamino aldehydes.

Samarium diiodide initiated Barbier reactions between bromo (nitro)methane and *N,N*-dibenzylamino aldehydes also follow Felkin–Anh control, as demonstrated by Concellón *et al.* (Scheme 14). Interestingly, the selectivity decreased as the R-group's steric demand was increased. The stereochemical integrity was retained throughout the reaction and the products were isolated in good yields.²²

Scheme 14 Samarium mediated Barbier reaction.

Treatment of **53** with lithium iodomethane, generated from diiodomethane and methyl lithium, directly furnished the *anti*-epoxide **72** in high yield and practically as a single diastereomer (Scheme 15). No racemization was detected in the addition.²³

Mukaiyama aldol reaction between *N*-Bn-*N*-Ts protected valinal **73** and *t*-butylmethylketone derived enol ether in the presence of a Lewis acid produced the *anti*-adduct **74** in high yield

Scheme 15 Direct conversion of dibenzyl-protected amino aldehyde to amino epoxide.

Scheme 16 Mukaiyama aldol addition to *N*-Bn, *N*-Ts protected valinal.

and as a single diastereomer (Scheme 16), thus demonstrating that the tosyl group seems to have directing power similar to a benzyl group.²⁴

Additions to Garner's aldehyde

The stereochemical outcome of nucleophilic additions to Garner's aldehyde can be controlled by selecting the appropriate conditions. Felkin-products are usually predominant (Fig. 4, A). *Anti*-Felkin products dominate when the reaction is run in the presence of a chelating agent (Fig. 4, B). This result can be rationalized by imagining the chelating agent binding the two carbonyl groups together. The chelating effect is often pronounced in diethyl ether compared to THF where chelates are better solvated.

This model appears to be quite general, although some interesting reagent dependent behaviour has been reported concerning Grignard reagents (Scheme 17). Williams *et al.* reported that the addition of phenylmagnesium bromide to **16** proceeds *via* the expected non-chelated pathway, but isopropylmagnesium bromide addition follows the chelated pathway.²⁵

Jurczak *et al.* have shown that lithiated *t*-butyldimethylsilyl propargyl ether can be added to **16** in either chelated or non-chelated mode furnishing *anti*-Felkin (*syn*) or Felkin (*anti*) products, correspondingly (Scheme 18).²⁶ High selectivity for *anti*-addition can be achieved using HMPA (hexamethylphosphoramide) to break the lithium aggregates and chelates. Conversely, *syn*-selective additions are predominant when a bidentate chelating agent is used, albeit at reduced yields.

We have used these results as a basis for several total syntheses. The introduction of a propargyl alcohol into a molecule brings in three carbon atoms, all of which can be readily further functionalized. This renders the propargyl alcohol a very useful three carbon synthon for various purposes.

During the total synthesis of *altro*-deoxynojirimycin (**79**) we noted that *anti*-**76** can be synthesized simply by performing the coupling in THF without additives (Scheme 19). This reaction readily scaled up to 100 mmol thus providing ample supply of *anti*-**76** with a very useful diastereoselectivity (>15:1). The *anti*-**76** was advanced the allylic chloride **77** which was then dihydroxylated under modified Upjohn conditions to furnish the

Fig. 4 Newman projections of Felkin-Anh (A) and chelated (B) transition states.

Scheme 17 Conflicting stereochemical outcome of Grignard additions to Garner's aldehyde.

Scheme 18 Stereocontrol in addition of a lithium acetylide to Garner's aldehyde.

Scheme 19 Total synthesis of (-)-*altro*-deoxynojirimycin.

triol **78** in 6:1 dr for the Kishi product. Three more operations led to the target structure **79**.²⁷

We had a hypothesis, that a *Z*-vinyl lithium species would offer higher selectivity on the basis that it is sterically more demanding than the bullet-like acetylene. Unfortunately, it was found to behave in similar fashion to lithium acetylenes, as noted during the synthesis of jaspine B (**81**) and its diastereomers (Scheme 20). The urea derivative DMPU (1,3-dimethyl-tetrahydropyrimidin-2(1*H*)-one) turned out to be a useful

Scheme 20 Total synthesis of jaspine B (pachastrissamine).

alternative to the toxic HMPA furnishing the *anti*-**80** in 17 : 1 diastereomeric ratio and 57% yield. Use of Lewis acids reversed the selectivity, however the use of tin(IV)chloride only gave 1 : 1.7 selectivity in contrast to Jurczak's results. In this case the monodentate $\text{BF}_3\cdot\text{OEt}_2$ gave the highest selectivity (1 : 6) for the *syn*-**80** with mediocre yield. The products were then advanced to jaspine B and 3 of its diastereomers.^{28,29}

We were not happy with the performance of lithium acetylides or vinyl lithium species under *anti*-addition conditions. In search of a complementary method we turned to zinc nucleophiles which had been reported to add to α -chiral aldehydes in high *anti*-Felkin selectivity.³⁰ Using the Wipf procedure the nucleophile was generated by hydrozirconation of the acetylene, followed by transmetalation into the vinyl zinc species.³¹ This was found to add to **16** with virtually complete diastereocontrol (Scheme 21) for the desired *syn*-product. Furthermore, we proved that the conditions are non-epimerizing thus providing facile access to enantiopure **84**.³²

The diastereoselective addition of different titanium reagents, prepared from unsaturated hydrocarbons and $\text{Ti}(\text{O-}i\text{Pr})_4\text{-}2i\text{PrMgCl}$ complex, to Garner's aldehyde was investigated by Sato *et al.* (Scheme 22). Titanium-alkyne complexes added to **16** in very high diastereoselectivity and good yield to give the allyl alcohols **85**. Allyltitanium complexes delivered the homo-allyl alcohols **86** and **88** in good diastereoselectivities. Unfortunately, the crotyltitanium complex added in low selectivity and with almost no control over the methyl group. Propargylations and the single allenylation proceeded with good to high selectivity and in good yields.³³

Additions to amino ketones

Direct addition of organometallic reagents to amino ketones

Reetz and Schmitz have studied the addition of simple organometallics to *N,N*-dibenzyl protected amino ketones, along with their other work concerning dibenzyl protected amino acid derivatives. As can be seen from Scheme 23, the additions generally proceed with excellent *syn*-selectivity. The authors

state, that simple primary Grignard reagents tend to reduce the ketone (thus lower yields for **97c** and **97f**), a reaction that presumably proceeds *via* β -hydride elimination. However, cerium reagents (generated by addition of lithium reagents to CeCl_3) or lithium reagents show no tendency for such side reactions.³⁴

Concellón *et al.* reported a highly diastereoselective addition of lithium ester enolates into α -chloromethylketones (Scheme 24). Upon concentration, the initial chlorohydrin products underwent further reactions. In cases where R_3 is other than hydrogen, epoxide formation takes place to give complex epoxyesters **101**. Acetate enolates could also be reacted in this

Scheme 22 Additions of titanium reagents to Garner's aldehyde.

Scheme 21 Total synthesis of (-)-galacto-deoxynojirimycin.

Scheme 23 Addition of organometallic reagents to dibenzyl-protected amino ketones.

Scheme 24 Synthesis of complex epoxyesters from chloromethylketones.

Scheme 25 Synthesis of azetidinium salts from chloromethylketones.

way if water and NaH were added without isolating the intermediate chlorohydrin.

Without the addition of water and NaH, a ring closure took place to produce azetidinium salts **102** (Scheme 25). These could be further transformed into *N*-benzyl azetidines by hydrolysis. The products were reported to be enantiomerically pure.³⁵

Via reduction of amino ketones

The diastereoselective reduction of amino ketones has been studied by several groups, including ours. The section will be divided into two parts; the first one dealing with unsaturated amino ketones and the second part dealing with α,β -unsaturated amino ketones.

Fig. 5 Felkin-Anh model in the reduction of amino ketones.

It should be noted that the connotation of Felkin and *anti*-Felkin are reversed compared to the additions into aldehydes (Fig. 5). Chelated mode will produce the *anti*-product, whereas the *syn*-product arises through Felkin control.

Reduction of saturated amino ketones. Hoffman and co-workers have studied the reduction of the Cbz-protected simple amino ketone **103** (Scheme 26). Reasonably selective *anti*-reduction could be achieved using almost any borohydride (K, Na, Li and tetramethylammonium cations were tested). *Syn*-selective reductions were best achieved with the bulky lithium aluminum *tert*-butoxide in ethanol. Interestingly all selectivity was lost when the reduction was performed in THF. It seems that ethanol as a hydrogen bond donor is able to break all chelation in the molecule.³⁶

Scheme 26 Diastereoselective reduction of Cbz-protected phenyl alanine derivative.

During the total synthesis of amaminol A, we needed to reduce the amino ketone **105** in *syn*-selective manner (Scheme 27). The best selectivity we were able to obtain was 3:1 with LiAl(O-*t*-Bu)₃H in THF. If the *anti*-reduction is desired, then L-selectride is the reagent of choice. The chiral (*S*)-alpine hydride gave almost the same selectivity as

Scheme 27 Diastereoselective reduction of an advanced intermediate en route to amaminol A.

Scheme 28 Reduction of β -carbonyl amino ketones.

Scheme 29 Scalable synthesis of amino epoxides.

LiAl(O-*t*Bu)₃H but with lower yield. DIBAL-H (with or without ZnCl₂) gave roughly 1 : 1 mixture.³⁷

Reduction of the serine derived β -ketoester **107** with sodium borohydride at cold temperature provided the *anti*-product in mediocre selectivity (Scheme 28).³⁸ Joullie *et al.* have reported that good selectivities can be obtained by switching to potassium borohydride instead: valine and allo-isoleucine derivatives **109** and **111** could be reduced with very good selectivity.^{39,40}

Chemists at Bristol-Myers-Squibb reported a scalable synthesis of α -chloromethylketones from Boc-protected amino acid esters by Kowalski homologation, and their telescoped conversion into amino epoxides (Scheme 29). Treatment of a solution of the ester **113** and chloriodomethane with LDA gives the α -chloromethylketone **114** in 50–86% yield after crystallization. The chloroketone can be converted into amino epoxide **115** without isolation by treating the crude extract of the previous reaction with ethanolic sodium borohydride followed by KOH. The procedure was demonstrated with several other amino esters (alanine, tyrosine, proline and valine). The reductions typically proceeded in 4 : 1 dr but were easily purified by crystallization to full chemical and optical purity.⁴¹

Scheme 30 *Anti*-reduction of a bromomethylketone.

Similar to α -chloromethylketones, α -bromomethylketones can be reduced in a highly diastereoselective manner (Scheme 30) simply with sodium borohydride. Several reducing agents and conditions were screened and it should be noted that no conditions were able to provide the *syn*-product in better than 1 : 2 ratio. Switching from ethanol to THF has a dramatic effect on diastereoselectivity.⁴²

Reduction of *N,N*-dibenzyl protected chloromethylketone **118** with LAH at very low temperature proceeds with exceptional stereocontrol for the *syn*-isomer (Scheme 31). The halohydrin **119** was obtained practically as a single diastereomer with no detectable racemization.⁴³

Scheme 31 *Syn*-selective reduction of a dibenzyl-protected chloromethylketone.

In our hands, the *N*-Bn,Boc protected alanine derived α -chloroketone produced a single diastereomer upon reduction with sodium borohydride at low temperature (Scheme 32). Even though a carbamate was present in the molecule, no *anti*-product arising from chelation controlled reduction was detected.⁴⁴

Scheme 32 *Syn*-selective reduction of a *N*-Bn,*N*-Boc-protected chloromethylketone.

Similarly, the *N*-bisprotected tyrosine derivative **123** was obtained as a single *syn*-diastereomer and in excellent yield after treatment with L-Selectride (Scheme 33). Even a simple methyl group was enough to give full Felkin–Anh selectivity in this case.⁴⁵

Scheme 33 *Syn*-selective reduction of a Boc-protected methylamino ketone.

Izawa *et al.* reported a very useful method for preparing α -chloromethylketones (Scheme 34). They noticed that the diphenylmethine and even the benzylidene groups act as efficient, yet transient, protecting groups for the chloromethylation reaction. Treatment of the solution of bromochloromethane and **124** or **125** in THF with *n*-BuLi followed by acidic workup furnished the amine hydrochlorides in good yields and at uncompromised enantiomeric purity. Concomitant reduction with sodium borohydride proceeded only with mediocre selectivity, but intriguingly gave the *syn*-diastereomer as the major product, although strong chelation control might be expected.⁴⁶

Scheme 34 Preparation of chloromethyl *syn*-amino alcohol hydrochlorides.

During their synthesis of sphingosine derivatives Hoffman and Tao have studied the diastereoselective reduction of trityl-protected amino ketones (Scheme 35). They found out that efficient *syn*-selective reduction can be achieved with sodium borohydride. The conditions for synthesizing **128** and the following reduction were also shown to be non-epimerizing. The serine derivative **130** gave access to the *syn*-isomer **131**. In comparison, the oxazolidine derivative **132** produced the corresponding *anti*-diastereomer **133** with outstanding selectivity.⁴⁷

Scheme 35 Reduction of trityl-protected amino ketones with borohydride.

A very interesting case was the reduction of the trityl-protected α -ketoesters **134–136** with borohydrides (Scheme 36). Low selectivities and yields were obtained. Even more surprisingly the reduction was *anti*-selective. This is in stark contrast to the results presented in the previous scheme. The authors propose that the amino acid side chain (R-group) and the trityl amine are not sufficiently sterically differentiated. In light of previous data, this cannot be the only reason. Most likely the ester carbonyl is involved in a manner that reinforces the chelation controlled transition state.

If the unprotected amine salts **138–140** are reduced, excellent chelation control is achieved with much improved yields. This is

Scheme 36 Reduction of amino α -ketoesters.

Scheme 37 The MPV-reduction of amino ketones.

in contrast to the reduction of the α -chloromethylketone **126** (Scheme 34).⁴⁸

Meerwein-Ponndorf-Verley (MPV) reduction of alanine derived aryl ketones **142–144** proceeds with excellent diastereoselectivity in the presence of catalytic aluminium isopropoxide in toluene (Scheme 37). The authors propose a rigid six membered chair-like transition state to explain the selectivity. In the case of **143** and **144** the products completely retained their stereochemical integrity throughout the reaction. The authors

Scheme 38 Reduction of amino ketones bearing chiral center at β -position.

also showed that phenylalanine derived chloroketones can be reduced under the same conditions, and that the choice of the nitrogen protecting group significantly affects the selectivity.⁴⁹

According to Hoffman and Tao, reduction of β -chiral substrates with sodium borohydride proceeds with complete *syn*-selectivity regardless of the stereochemistry at the β -position (Scheme 38).⁵⁰ Similarly, Benedetti *et al.* noticed that the *N,N*-dibenzyl β -ketonitrile **156** produced a single diastereomer upon treatment with sodium borohydride. The corresponding Boc-protected compounds (**158** and **160**) showed the opposite stereochemical outcome with high dependence on the stereochemistry at the β -position.⁵¹

Reduction of α,β -unsaturated ketones. Enones are generally synthesized from amino acid derived β -ketophosphonates *via* Horner–Wadsworth–Emmons reaction with the desired aldehyde. General approach to β -ketophosphonates involves the addition of lithiated dimethylmethyl phosphonate (DMMP) to the corresponding amino ester. The conditions are non-epimerizing. However, the phosphonates themselves are not indefinitely configurationally stable. In our experience, prolonged storage or heating (for example during recrystallizations) leads to some degree of epimerization. Thus, some care must be exercised when dealing with such compounds.

We explored this strategy during the total syntheses of sphingosine and castanospermine derivatives.

The synthesis of sphingosine started with treatment of Garner's ester (**162**) with lithiated DMMP to deliver the β -ketophosphonate **163** in 65–90% yield (Scheme 39). The Horner–Wadsworth–Emmons (HWE) reaction was best achieved with potassium carbonate in acetonitrile. This protocol delivered the

Scheme 39 Total synthesis of sphingosine.

enone **164** in uncompromised enantiomeric purity and good yield (81%). After extensive screening good conditions were found for the diastereoselective 1,2-reduction of the enone. DIBAL-H in toluene produced the desired *anti*-amino alcohol in 92% yield as the sole diastereomer. On the other hand *L*-selectride produced exclusively the *syn*-product, albeit at lower yield. However, these selectivities are by no means general. If the electronic properties of the enone functionality are changed the selectivities are considerably lower.^{52,53}

Hoffman *et al.* have also studied the reduction of enones related to sphingosines (Scheme 40). They found out that efficient *syn*-reduction can be achieved with trityl-protected serine derivative **166** using simple sodium borohydride. The addition of cerium chloride was necessary to prevent conjugate reduction.⁴⁷ They also reported the reduction of **164** with sodium borohydride in high selectivity, which is in contrast to model studies by us (Scheme 41).

Scheme 40 Reduction of sphingosine related amino ketones.

Scheme 41 Model studies on reduction of sphingosine related amino ketones.

Mediocre selectivities were obtained with sodium borohydride or Luche conditions with each of the three model enones (**168–170**). No conjugate reduction was detected as compared to Hoffman's results. This highlights the substrate sensitivity of this particular transformation.⁵³

Recently Datta *et al.* reported a highly *anti*-selective chelation controlled reduction of two serine derived ketones **172** and **174** (Scheme 42) with zinc borohydride. Very good control was demonstrated for both α,β - and γ,δ -unsaturated ketones.⁵⁴

Scheme 42 Zinc borohydride mediated reduction.

We used an L-aspartic acid derived β -ketophosphonate **176** for the synthesis of a homosphingosine derivative (Scheme 43). The large phenylfluorenyl group (Pf) was used to prevent epimerization at the α -stereocenter.⁵⁵ Despite the crowded nature of the substrate the phosphonate underwent HWE reaction under the previously reported conditions in decent yield. Gratifyingly DIBAL-H reduction produced exclusively the desired *anti*-product which had undergone a reductive ring cleavage.

Scheme 43 Total synthesis of homosphingosine **179**.

During the synthesis of deoxycastanospermine (Scheme 44) we examined the reduction of an enone which contained a heteroatom at the allylic position (**181**). Unfortunately, in this case only mediocre selectivities were achieved, in accordance with previous results. The desired *syn*-selective reduction was best achieved under Luche conditions to give a 2.4 : 1 mixture of diastereomers, which were separable on MPLC. The *syn*-**182** was

Scheme 44 Total synthesis of deoxycastanospermine **183**.

then dihydroxylated under Upjohn-conditions and advanced to the desired product **183**.⁵⁶

Chung and Kang have reported that reduction of *N,N*-dibenzyl protected amino enones proceeds with high selectivity *via* non-chelation control (Scheme 45). In fact, they were unable to force chelation control by using strong Lewis acids. They also reduced amino enones derived from other than phenyl glycine and stated that the stereoselectivity was high, although no definite data was reported.⁵⁷

Scheme 45 Highly *syn*-selective reduction of dibenzyl-protected amino ketone.

Reduction of the serine derived *N,N*-dibenzyl enone **186** proceeded with complete diastereocontrol with LiAlH_4 to give the *syn*-product in nearly quantitative yield (Scheme 46). In fact, to access the *anti*-diastereomer, the authors had to use the Boc-protected derivative **188**. Now the reduction under Luche conditions provided the desired *anti*-isomer in excellent yield, albeit at much reduced selectivity.⁵⁸

Scheme 46 Protective group dependent reduction of amino enones.

Luthman *et al.* described the diastereoselective reduction of phenylalanine derived enone ester **190** (Scheme 47).⁵⁹ Chelation controlled reduction proved to be poorly selective except with the bulky $\text{LiAlH}(\text{O}-t\text{Bu})_3$. Notably, the native tendency for *anti*-reduction can be overridden only by using chiral reducing agents.

Scheme 47 Diastereoselective reduction of ester enone **190**.

Scheme 48 Stereoselective reduction of PF-protected substrates.

Recently, we attempted to diastereoselectively reduce PF-protected amino ketones **192** and **194** with various reducing agents (Scheme 48). For the conjugated system L-selectride gave exceptionally good results. However, when the reduction was attempted for the homo-enone **194** under the previous best conditions no selectivity was observed.⁶⁰

Reduction of ynones

Reduction of the cysteine derived ynone **196** was most efficiently achieved with LiAl(O-*t*-Bu)₃H in decent *anti*-selectivity (Scheme 49). The authors reported that DIBAL-H, Red-Al and the bulky diisobutylaluminum 2,6-di-*t*-butyl-4-methyl phenoxide gave inferior selectivity and that NaBH₄ produced a 1 : 1 mixture.⁶¹

Scheme 49 *Anti*-selective reduction of an ynone.

Treatment of the *O*-unprotected serine derivative **198** with sodium borohydride delivered **199** in 5 : 1 *anti*-selectivity (Scheme 50). The selectivity presumably arises from chelation of the reducing agent with the free hydroxyl group, since the *O*-silyl protected derivative **200** gives practically no selectivity.⁶²

Scheme 50 *O*-participation in borohydride reduction.

Good selectivity in reduction of the oxazolidinone **202** was achieved with the bulky diisobutylaluminum 2,6-di-*t*-butyl-4-methyl phenoxide (Scheme 51). Reductions with L-selectride and NaBH₄ gave 5 : 3 and 1 : 2 mixtures, respectively.^{63,64}

Scheme 51 *Anti*-selective reduction of a cyclic carbamate.

Oxidation of allyl amines

Epoxidation

Oxidation of amino acid derived allyl alcohols with *m*CPBA were studied by Ohfuné and Sakai during their synthesis of galantin I (Scheme 52). High selectivity was obtained for substrates with *Z*-configuration (**204**, **210**). The presence of the allylic alcohol was absolutely necessary as the reaction became slow (20% conversion after 3 days) and the selectivity was eroded (3 : 1 dr) if the alcohol was protected with a silyl group.⁶⁵

Scheme 52 Epoxidation *E*- and *Z*-allyl alcohol featuring cyclic and acyclic protection strategies.

Luthman *et al.* investigated the epoxidation of the phenyl-alanine derived allylic amines **212–215** during the synthesis of dipeptide isosteres (Scheme 53). While the observed selectivity can generally be explained by both the carbamate and the ester carbonyls coordinating to the approaching peracid, the large differences in the diastereoselectivities merit some explanation. The authors explained the observed selectivity with a simple but effective model (Fig. 6).

The favoured conformation (left hand side) minimizes the allylic strain while keeping both the ester and the carbamate on the same face, thus making double coordination possible. The conformation on the right hand side of the figure would deliver

Scheme 53 Epoxidation studies towards dipeptide isosteres.

Fig. 6 Analysis of conformations leading to observed products.

the minor diastereomer. The model nicely explains the low diastereoselectivity observed with substrate **213**.⁶⁶

Dihydroxylation

The dihydroxylation of an electron poor acyclic allylic amine proceeds with very low diastereoselectivity for the *Z*-configured allyl amine **217** (Scheme 54).⁶⁷ It should be noted that the major diastereomer corresponds to an *anti*-Kishi dihydroxylation (osmium approaches *syn* to the existing amino group). Interestingly, the dihydroxylation of a similar, but *E*-configured

Scheme 54 Dihydroxylation of electron deficient allyl amines.

allylamine **219** proceeds with excellent diastereocontrol, also in *syn*-manner relative to the amine.⁶⁸

We also examined the effect of allylic strain on the diastereoselectivity observed in dihydroxylation (Scheme 55) of electron poor double bonds.⁶⁹ This was prompted by at the time unexpectedly high selectivity noted in the dihydroxylation of **221**. When compared the reaction Shiori reported (Scheme 54) for the acyclic case (**217**), the difference is stark. We found out that dihydroxylation of the *Z*-configured allyl amine **223** proceeds with complete stereocontrol, whereas the *E*-configured **225** exhibits significantly lower selectivity. This was rationalized by considering allylic strain. Compound **225** exhibits lower rotational barrier around the double bond than **223**, thus allowing for attack from both faces of the double bond.⁷⁰

Scheme 55 Our studies regarding the effect of *E*- and *Z*-double bonds on the selectivity.

The directing effect of diaryl ketimine protecting groups was evaluated by Kim and co-workers (Scheme 56). Dihydroxylation of a range of *E*-configured allylic amines provided the corresponding *anti*-adducts with moderate to good selectivity. This is an interesting switch of selectivity when compared to the *N*-Boc protected **219**. Especially, the 3,3'-difluorobenzophenone ketimine protected amines **233–236** gave very useful selectivities. Dihydroxylation of the corresponding benzophenone ketimine protected *Z*-allyl amines proceeded with very good selectivity, a huge improvement from **217** (Scheme 54).⁷¹

Strong solvent effect was observed in the dihydroxylation of *Z*-configured serine derived allylic amines (Scheme 57). The often used THF–H₂O combination gave significantly lower selectivity than dichloromethane. Also, the *O*-protecting group was found to significantly influence the selectivity, with the acetyl protection giving practically a single isomer. The improvement in selectivity was explained by the two transition states **A** and **B** which lead to the *syn*- and *anti*-products, correspondingly. The transition state **B** is more favourable when a small protecting group is used on the oxygen, thus alleviating the large A^{1,2} strain between NBoc₂ and the vinylic hydrogen.⁷²

Dihydroxylation of a threonine derived cyclic substrate **249** proceeded uneventfully with complete diastereocontrol (Scheme 58). This is often the case with cyclic substrates.⁷³

Scheme 56 Dihydroxylation of ketimine protected substrates.

Scheme 57 Solvent effects in dihydroxylations.

Scheme 58 Dihydroxylation of a cyclic substrate.

Conclusions

The selectivity of nucleophilic additions to amino aldehydes is governed by many factors in which the nature of the protecting group(s) on the nitrogen plays a major role, along with the type of the approaching nucleophile. Felkin selectivity is often hard to override, and only in special cases can the *syn*-products be accessed. However, if *anti*-addition is desired, addition to an

amino aldehyde (especially *N,N*-dibenzyl amino aldehyde) can be a very powerful method, as the additions are typically facile and high yielding.

Amino ketones can usually be designed to be reduced to either diastereomer by judicious choice of protecting groups and the reducing agent. Simple carbamate protected amino ketones show great substrate dependence and the overall selectivity is difficult to predict beforehand. The *N,N*-dibenzyl protected, and other bis-protected, amino ketones show good selectivity for the *syn*-product. Thus complementary selectivity can be obtained using this method compared to the aldehyde additions.

Epoxidation of allyl amines can be highly selective, however careful substrate planning must be used. The presence of coordinating groups like esters, carbamates and alcohols in the molecule renders the reaction more facile and often more selective. Allylic strain plays an important part in determining the outcome, thus more rigid *Z*-conformers tend to give higher selectivity. Presumably allylic strain also affects dihydroxylations in an analogous manner.

With proper planning both *syn*- and *anti*-vicinal amino alcohols can be accessed from readily available amino acid derivatives with a wide variety of strategies in an entirely diastereoselective manner. Much work is still needed for real understanding of all the parameters governing the facial selectivities of reductions and additions.

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