

Chiroselective synthesis: Catalysis and chiral pool hand in hand*

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Abstract: Nature provides us with a wonderful pool of enantiopure starting materials for synthesis: amino acids, sugars, and many (but not all!) terpenes can be isolated even in large quantities in an uncompromised 100 % ee. Vicinal amino alcohols constitute a versatile group of organic structures; they are, in principle, available in enantiopure form from the chiral pool compounds or through chiral catalysis; they are potent intermediates for the synthesis of natural products and medicinally/biologically active compounds, and they provide a highly desirable scaffold for the construction of ligands for metals as well as organocatalysts. These new techniques will open up valuable new possibilities for the invention of new technologies for chemical synthesis, the desired course of chemical discoveries for the future. A robust entry to enantiopure vicinal amino alcohols from inexpensive naturally occurring amino acids has therefore become a key challenge for our endeavors in the development of methodology.

Keywords: amino acids; asymmetric synthesis; natural products; organic chemistry; synthesis.

INTRODUCTION

Wöhler's synthesis of urea in 1828 was proof that man can construct molecules of living matter, and this individual event was the culmination point of developments that literally created a new science. The study of chemical substances had previously been concerned with observations of existing substances. Entering the age of chemical synthesis, man was now capable of creating the objects of his study, which is the landmark feature of chemistry as we have known it since the early 19th century. Man's capability to create—synthesize—new objects of study and exploitation distinguishes this science from other forms and descendants of natural philosophy, and gives this branch of science a certain feel of magic. And since a synthetic chemist is a relative of wizards, sorcerers, or druids, society has an implicit right to place expectations to the powers of these magicians to produce new compounds to heal diseases, promote longevity, abolish all shortages, repair the damages caused by human endeavors, and many more often selfish goals—and all this while simultaneously providing for increased entertainment and less effort.

The realization, mainly around the middle of the last century, that any conceivable molecule can be synthesized (given unlimited resources), placed a new impetus for the development of synthesis. As it became clear that resources are not limitless, one had to devise better ways of performing synthesis.

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In the period between the 1950s and 1970s (roughly), new reagents were created to effect more selective reactions, chromatographic and other separation methods found their way from the laboratories of specialists to the rooms of practicing synthetic chemists, and spectroscopic methods became available to quickly confirm the authenticity of the structures created. Simultaneously, theory (physical chemistry) was also developed, very much as an extension of “modern physics” of the earlier part of the century.

Systematization was also brought to chemical synthesis. Chemists had now taken a major step from the era of monumental syntheses of fearless efforts to the era of logic and beauty in synthesis. One can now weigh the pros and cons of alternative synthetic pathways and evaluate whether the value of the synthesis is worth the effort. In other words, one could now make arguments to validate the choice of the targets for synthesis.

The 1990s saw yet again a major shift in the scope of chemical synthesis. By now, society had decided that the valuable goal was to provide immortality to mankind, and therefore health (and environment) would be the best justification for expenses in science. Coupled with the power of synthesis (“anything can be made”) and the logics of reasoning in synthesis planning (“I can make anything”), the prevailing economic prosperity spurred the generation of massive efforts to “quickly produce large collections of compounds”—the combinatorial chemistry age. These were the spearheads especially in the pharmaceutical industry, but found followers in academic circles, too.

Modern organic synthesis is concerned with the rational construction of complex organic compounds from readily available starting materials. Such an endeavor requires several reaction steps and thus careful planning emphasizing all aspects of efficiency, related to both individual steps (tactical level) as well as to complete reaction sequences (strategy level). Of equal significance is the growing awareness regarding the necessity of using enantiopure chiral substances whenever they are expected to interact with a chiral environment.

NATURAL PRODUCT SYNTHESIS/TOTAL SYNTHESIS

Professor Gustav Komppa completed the first total synthesis of camphor in 1903, and thereby emphasized the value of synthesis in the study of complex natural products. At the inauguration of Helsinki University of Technology in 1908, he described the efforts of synthetic chemist: “In this kind of experimental research in the field of organic chemistry—the presentiment, that is ‘the chemical sensation’, has a very great importance. ... On the other hand, we have to admit that *this kind of work*, where, together with purely scientific and sharply logical contemplation, imagination has been given an important position, *yields inner satisfaction that best can be compared to what an artist feels about his work, when this work also bears great practical importance.*” Chemistry, as indeed all science, must be strongly curiosity driven, but at the same time it must be practical. Industrial applicability is required in the sense of robust and scalable syntheses instead of reactions capable of producing only minimal quantities of product. Usefulness and meaningfulness of synthesis are displayed by the generality of the reactions, diversity of the possible targets where the reactions can be applied, and atom, step, redox, and complexity economies. We can safely claim that the state of the art of organic synthesis is defined by the complexity of the targets that can be attacked and surmounted. Synthetic chemistry as the central science [1,2] plays a crucial role, be it from the standpoint of energy [3], health [4], or manufacturing [5].

In our own work, thorough understanding of the chemical behavior of small, information-rich molecules, such as the derivative of L-serine in the center of Fig. 1, has prompted our studies in not only the total synthesis of complex natural products, but also in various fields of technological improvement. We have been attracted to develop chiral nanoparticles for possible applications in materials and nanosciences [6]. Our understanding of the behavior of these molecules has required deeper theoretical understanding in their use [7]. Obviously, development of synthetic technologies is a natural extension of such chemical studies, and this has enticed us into applications in organocatalysis [8], solid-phase

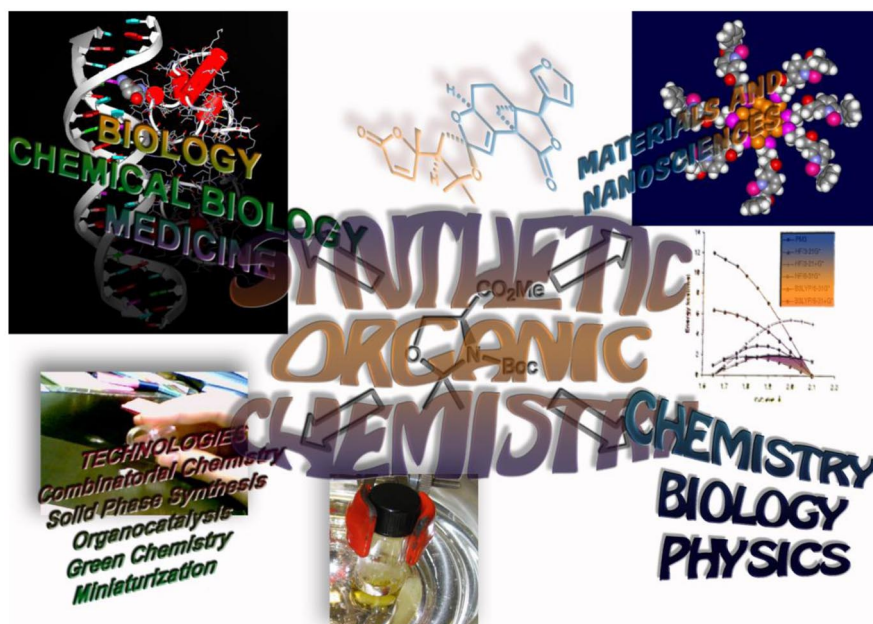


Fig. 1 Synthetic organic chemistry as the central science.

synthesis [9], and combinatorial chemistry [10]. The new potentials provided by the new chemistry have also lured us into journeying in bordering fields such as chemical biology [11,12].

Synthetic entry to chiral molecules is of paramount value. Catalytic processes seldom afford complete control of chirality transfer. Nature provides a wealth of important starting materials in 100 % enantiopurity. We should strive toward understanding the intricate mechanisms of asymmetric induction (chirality transfer) to the level where we can completely avoid loss of enantiopurity during our synthetic efforts. This often means that we must learn to utilize the small energetic differences leading to diastereomeric transition states.

VICINAL AMINO ALCOHOLS

Nature provides us with a wonderful pool of enantiopure starting materials for synthesis: amino acids, sugars, and many (but not all!) terpenes can be isolated even in large quantities in an uncompromised 100 % ee. Vicinal amino alcohols constitute a versatile group of organic structures; they are, in principle, available in enantiopure form from the chiral pool compounds or through chiral catalysis [13]; they are potent intermediates for the synthesis of natural products and medicinally/biologically active compounds, and they provide a highly desirable scaffold for the construction of ligands for metals as well as organocatalysts as such (Fig. 2). These new techniques will open up valuable new possibilities for the invention of new technologies for chemical synthesis, the desired course of chemical discoveries for the future. A robust entry to enantiopure vicinal amino alcohols from inexpensive naturally occurring amino acids has therefore become a key challenge for our endeavors in the development of methodology.

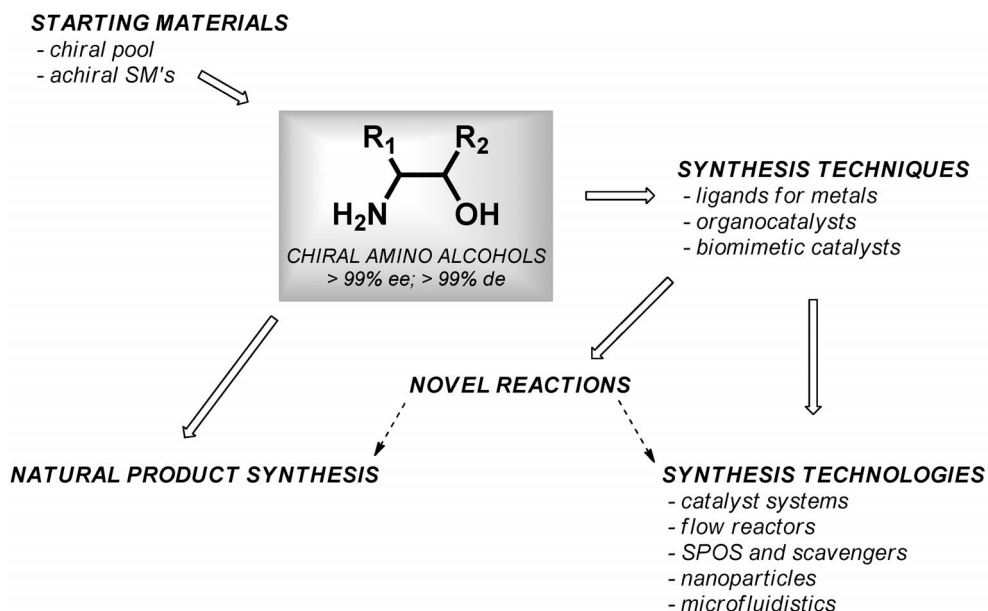
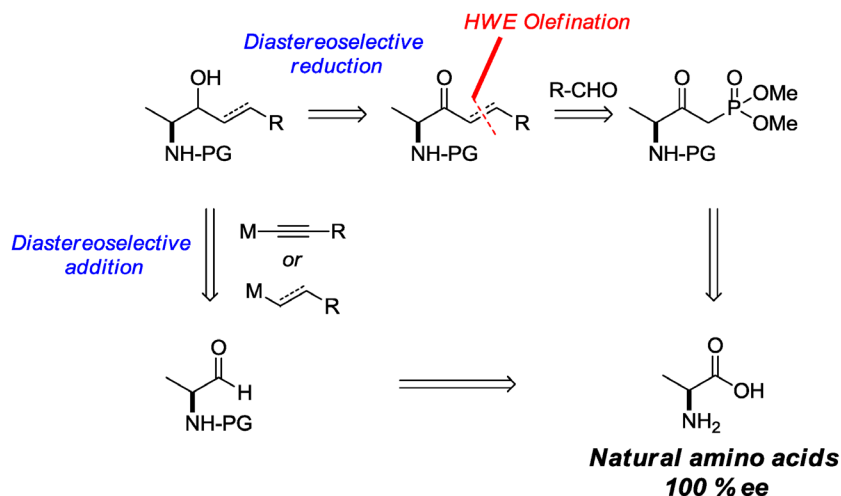


Fig. 2 Roles of amino alcohols for science and technology. (SM = starting material, SPOS = solid-phase organic synthesis.)

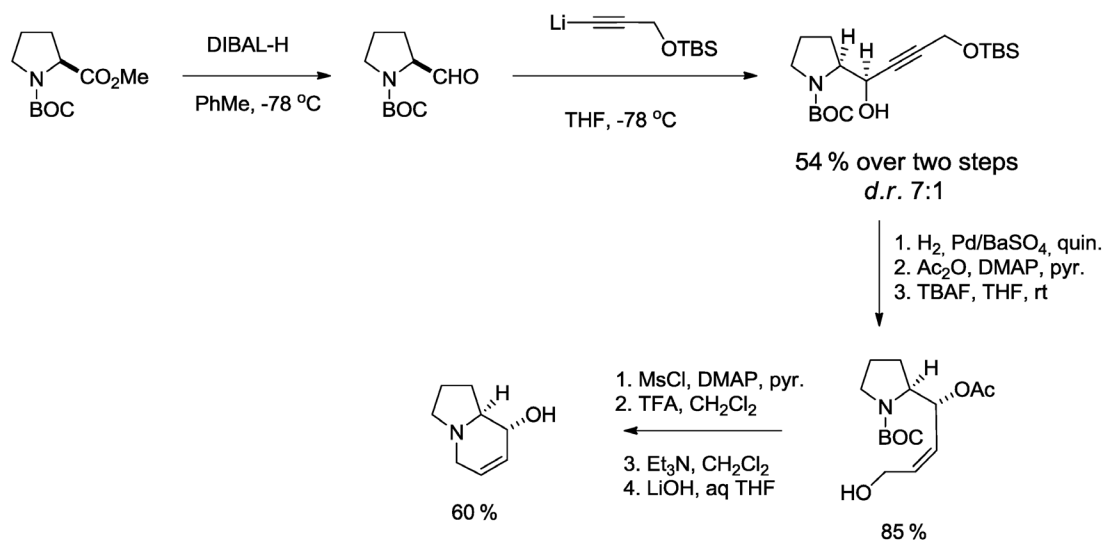
For the past two decades, we have been involved in the development of syntheses of natural products from naturally occurring amino acids, and in the course of these studies we have every now and then had the opportunity to investigate the synthesis of vicinal amino alcohol for various purposes. We have employed mainly two alternative strategies (Scheme 1). The more traditional one is based on the diastereoselective alkylation of amino aldehydes, whereas the alternative strategy is based on our original discovery that γ -chiral β -keto phosphonates can be converted to the corresponding enones via a Horner–Wadsworth–Emmons (HWE) olefination without epimerization [14]. Reductive operations on the alkene and/or diastereoselective reduction of the carbonyl functionality was considered as the suitable route to the amino alcohols.



Scheme 1 Routes to amino alcohols—original concepts.

AMINO ALDEHYDE ROUTE

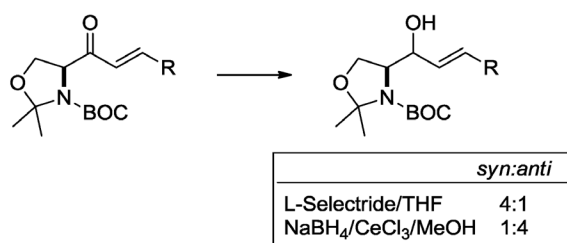
Our first results along these lines were obtained in connection with a synthesis of an intermediate toward polyhydroxylated indolizidines (Scheme 2) [15]. This route was based on the addition of a lithio acetylide onto an α -chiral aldehyde. The reaction follows the polar Felkin–Anh model, favoring the *anti* diastereomer with a 7:1 ratio.



Scheme 2 First diastereoselective route to indolizidines.

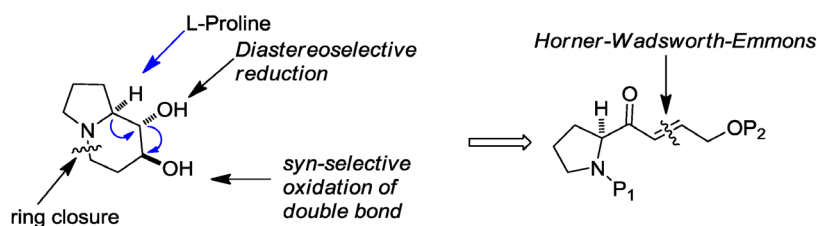
γ -CHIRAL β -KETO PHOSPHONATE ROUTE

In connection with syntheses of sphingosines and their derivatives, we examined a number of hydride reduction protocols for the reduction of the enones to allylic alcohols (Scheme 3) [16,17]. For serine-derived enones, reproducible, albeit modest diastereoselectivities could be obtained.



Scheme 3 Diastereoselective reduction of enones.

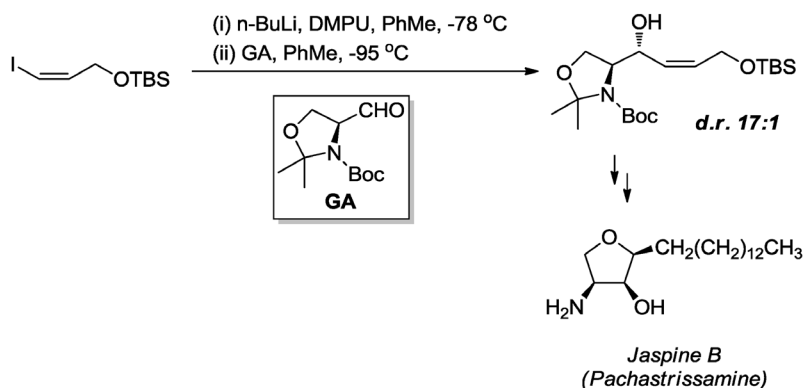
Although optimal protocols were found for sphingosine itself, the methods were highly sensitive to the nature of the substrate used in the reduction. Thus, in our later syntheses of deoxycastanospermine derivatives (Scheme 4) [18,19], the observed diastereoselectivity in the reduction was lower.



Scheme 4 Retrosynthesis for deoxycastanospermine derivatives.

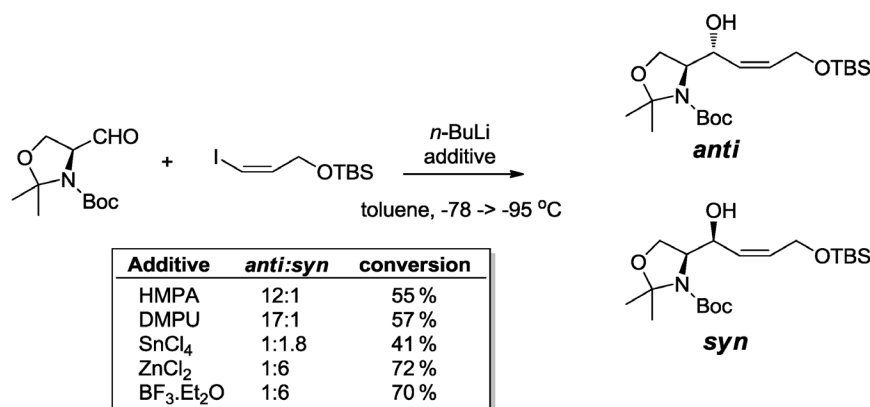
THE AMINO ALDEHYDE ROUTE REVISITED

In returning to the addition reactions onto the aldehydes, where we had obtained a 7:1 *anti:syn* ratio with a prolinal derivative, we reasoned that combining the effect of the dimethyl group on the five-membered ring, as in the previous case, should lead to improved selectivity. We further felt that increasing the steric bulk of the nucleophile to a vinyl lithium species should further increase the steric bias. This approach was successfully adopted in our synthesis of the C18 anhydrosphingosine jaspine B (pachastrissamine) (Scheme 5) [20,21]. Thus, addition of the *Z*-vinyl lithium nucleophile to Garner's aldehyde (GA) provided a 17:1 excess of the desired *anti* product in 55 % yield. This was then converted to the natural product in a few efficient steps, including a Pd-mediated ring closure of the tetrahydrofuran and a cross-metathesis.



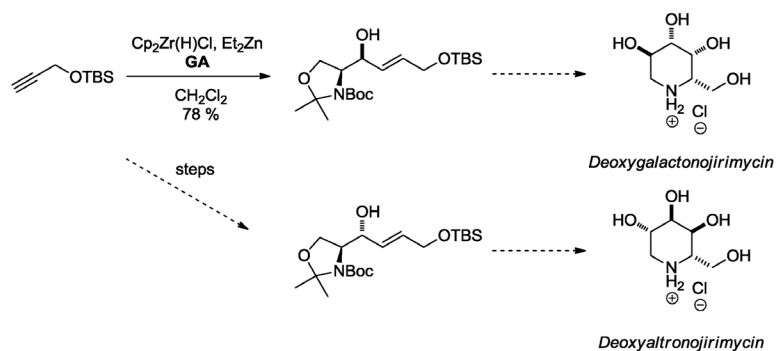
Scheme 5 Synthesis of jaspine B.

Having achieved the highest *anti* selectivity so far, we became interested in finding out whether the diastereoselectivity can be inverted. Toward this end, we examined the effects of various additives in the addition reaction (Scheme 6). It turned out that addition of Lewis bases enhances the *anti* selectivity, whereas addition of Lewis bases inverts the selectivity and gives acceptable levels of the *syn* product.



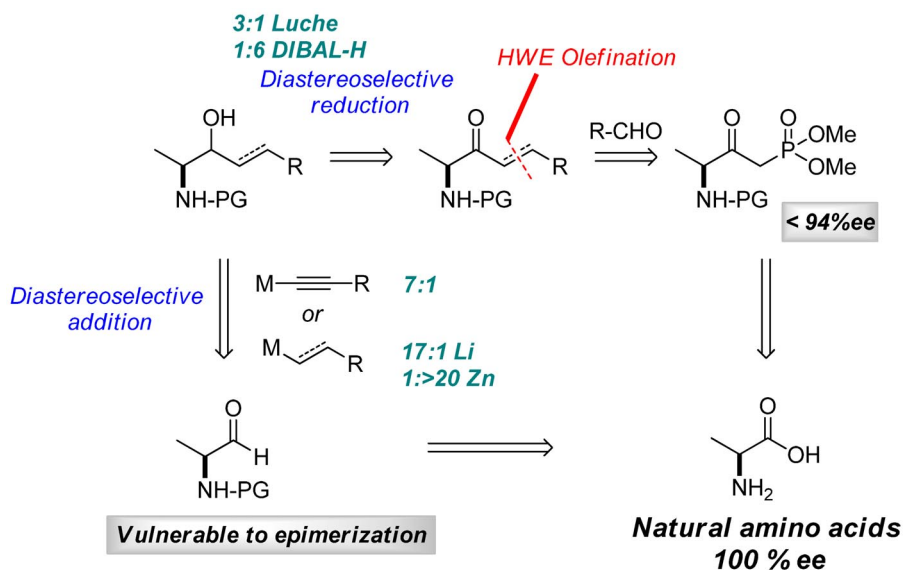
Scheme 6 Diastereoselective additions.

An improved procedure for the generation of the vinyl zinc species was sought, and the hydrozirconation–transmetallation sequence pioneered by Peter Wipf turned out to give excellent results [22]. Thus, treatment of TBS-protected propargyl alcohol with Schwartz’s reagent followed by transmetallation with diethyl zinc gave the *E* vinyl zinc species, which added onto the GA with practically complete diastereoselectivity. This high selectivity was utilized in the synthesis of deoxygalactonojirimycin [23], which was achieved in only eight steps from GA (Scheme 7). The diastereomeric vicinal amino alcohol could also be obtained using either the standard alkynyl lithium chemistry followed by reduction or by relying on the solvent dependency of the addition of the vinyl zinc species [24]. The *anti* amino alcohol was efficiently converted to deoxyaltronojirimycin [25].



Scheme 7 Diastereoselective additions toward nojirimycin derivatives.

So far (Scheme 8), we started our endeavors for the diastereoselective synthesis of vicinal amino alcohols by the addition of alkynyl lithium compounds onto the amino aldehyde. This gave a reasonable (7:1) *anti* selectivity. However, the organolithium compounds are known to be sufficiently basic to make the amino aldehyde derivatives prone to epimerization. Also, access to *syn* amino alcohols was initially elusive. A satisfactory solution for the selectivity reversal issue was initially found through the use of the enone chemistry, where *in best situations*, the *anti* and *syn* diastereomers could be obtained with excellent selectivities. However, the methodology is not robust enough and selectivities are highly dependent on the exact nature of the substrate. A further drawback in the use the HWE-olefination/reduction chemistry arises from the fact that the β -keto phosphonate itself is not con-



Scheme 8 Routes to amino alcohols—eventual outcomes.

figurationally stable. The phosphonate can be routinely made in very high enantiopurities, but prolonged storage or even heating (for recrystallization) can lead to lowering of the enantiopurity [26], so much that an upper limit of <94 % ee for the phosphonate can be reproducibly and routinely achieved in large-scale work.

Having realized this disappointing feature, we turned back to the amino aldehyde chemistry, and reasoned that the solution for the epimerization problem could reside by solving the nucleophile/base dichotomy of the alkyl metal species. Organozinc compounds are considerably less basic than the corresponding organoalkali compounds, and their employment in the addition reactions has allowed us to synthesize a number of vicinal amino alcohol natural compounds with excellent enantiopurity.

CONCLUSIONS AND OUTLOOK

During the course of the past two decades, we have had the chance to collect data on the detailed behavior of amino aldehydes and γ -chiral β -keto phosphonates for the selective production of chiral vicinal amino aldehydes. We have been able to solve most of the problems related to diastereoselectivity, and in certain cases excellent selectivity can be obtained. However, the synthetic methodology is still far from perfect; no one general approach can be inferred for all similar substrates. We have recently embarked on a more detailed investigation of the effect of the nitrogen protecting group to protect the stereogenic center against epimerization, and we have reason to believe that a sterically bulky 9-phenyl-9-fluorenyl group can give a more general solution to this problem [27–31]. However, these investigations are only in their infancy, and detailed reports of their success will be the topic of future disclosures.

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