DOI: 10.1002/ejoc.200800604

Synthesis of Chiral Amines Using α-Amino Aldehydes

Ryan Hili,[a] Sivaraj Baktharaman,[a] and Andrei K. Yudin*[a]

Keywords: Amino aldehydes / Protecting groups / Chiral amines / Amino alcohols / Stereoselectivity

If one were to rank chemical reagents on the basis of their "synthetic content", loosely defined as the density of functional groups per arbitrary unit of molecular space, the α-amino aldehydes will find themselves close to the very top of that list. The presence of synthetically ubiquitous amine and aldehyde functionalities predisposes α-amino aldehydes towards highly convergent bond-forming operations. Such juxtaposition does not come without a price: incompatibility of these functional groups calls for protecting groups. We discuss challenges and recently identified opportunities in this field.

1. Introduction

Chiral amines are important structural components of natural products and therapeutic agents. The chemical structures of biologically active amines range from simple to extraordinarily complex. Recent years have witnessed increasing efforts in developing efficient and highly convergent strategies toward complex amines from simple starting materials. Of particular significance are chemical reagents that contain functional groups that allow for further elaboration in proximity to the amine. In this regard, the α-amino aldehydes are noteworthy, as their aldehyde groups can be transformed into a wide range of structural frameworks. Not surprisingly, α-amino aldehydes are among the most widely used intermediates in synthesis. Hundreds of papers dedicated to this subject corroborate this point. Several important industrial processes utilize α-amino aldehyde building blocks.[1] However, the inherent reactivity of amine and aldehyde functionalities is a significant challenge in the preparation and synthetic manipulation of α-amino aldehydes. Accordingly, a vast range of protocols for the synthesis and elaboration of suitably protected α-amino aldehydes have been developed. Ironically, nitrogen protection facilitates detrimental epimerization processes. In this review we

[a] Davenport Research Laboratories, Department of Chemistry, University of Toronto,
80 St. George Street, Toronto, Ontario, Canada, M5S 3H6
E-mail: ayudin@chem.utoronto.ca

Ryan Hili was born in Burlington, Canada in 1983. He received his B.Sc. in biological chemistry at the University of Toronto in 2005. He then joined the research group of Andrei K. Yudin where he is currently pursuing his doctorate degree on the synthesis and reactivity of unprotected aziridine aldehydes.

Sivaraj Baktharaman was born in 1978 in Vellore, Tami Nadu, India. He received a B. Sc. (Chemistry, The New College) and M. Sc (Organic Chemistry) from the University of Madras. He joined the research group of Professor Vinod K. Singh at the Indian Institute of Technology Kanpur, where he obtained his Ph.D. In November 2006 he joined in the research group of Professor Andrei K. Yudin at the University of Toronto as a postdoctoral fellow. Currently his research is focused on the development of new methodologies towards biologically active molecules.

Andrei K. Yudin joined the Department of Chemistry at the University of Toronto in 1998, after receiving a B.Sc. degree in chemistry from Moscow State University (1992), completing his doctoral studies with Professors Surya Prakash and George A. Olah at the University of Southern California (1996) and his postdoctoral studies with Professor K. Barry Sharpless at the Scripps Research Institute (1996–1998). He received early tenure in 2002 and became Full Professor in 2007. His main research interests are in the area of chemical synthesis.

discuss recent advances in α-amino aldehyde chemistry, including an overview of the most widely used preparative routes and their utility in stereoselective $C(sp^3)$–$C(sp^3)$ bond-forming reactions. An attempt has been made to focus on the most recent applications in synthesis, comment on protecting groups, and describe new solutions for the handling of unprotected amino aldehyde derivatives.

The history of α-amino aldehydes can be traced back to Fischer's discovery of glucosamine (Figure 1) in 1902,[2] in which unprotected amine and aldehyde functionalities are stabilized as a cyclic hemiacetal. Fischer later synthesized glycinal, which had to be characterized through degradation studies due to its inherent instability via self-condensation.[3]

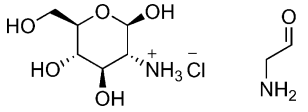


Figure 1. Glucosamine hydrogen chloride and glycinal.

In the case of α-amino aldehydes, there is no possibility for intramolecular stabilization. Owing to the presence of incompatible functional groups, this class of compounds is unstable. Although oxidation of simple α-amino alcohols by flame-induced ionization affords the corresponding amino acids via amino aldehydes,[4] this method has no preparative value. Accordingly, the bulk of synthetic efforts have been directed toward protected α-amino aldehydes, which can be categorized into *N*- and *C*-protected derivatives.

2. *N*-Protected α-Amino Aldehydes

N-Protected α-amino aldehydes are key building blocks for the synthesis of many biologically important amines. These molecules can be classified into *N*,*N*-disubstituted and *N*-monosubstituted amino aldehydes (Figure 2).

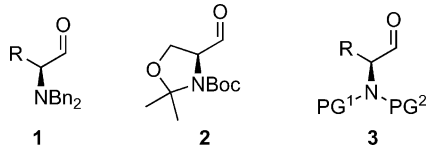
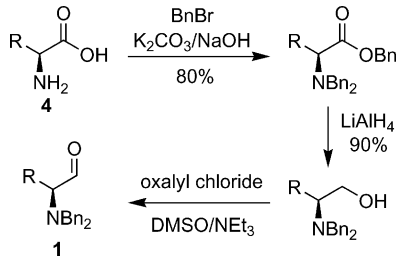


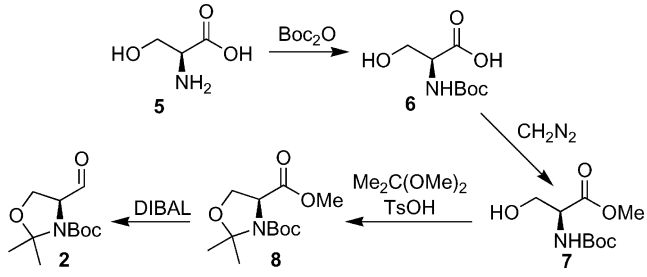
Figure 2. *N*-Protected α-amino aldehydes.

The molecules equipped with the *N*,*N*-dibenzyl group are important members of the disubstituted class of α-amino aldehydes.[5] The dibenzyl group protects the nitrogen center and also significantly influences the direction and degree of diastereoselectivity.[5,6] The *N*,*N*-dibenzyl α-amino aldehydes can be prepared from the α-amino acids **4** through sequential benzylation, reduction, and oxidation (Scheme 1).[5] A more atom-economical synthesis of the aldehydes **1** entails switching the order of the steps. Thus, the α-amino acids **4** can be reduced to the corresponding primary amino alcohols using conventional methods[7] followed by *N*-benzylation and oxidation. A 190-kg scale preparation of an advanced *N*,*N*-dibenzylamino aldehyde intermediate en route to an HIV protease inhibitor highlights the scaleability of this methodology.[7e]



Scheme 1. General synthesis of *N*,*N*-dibenzyl α-amino aldehydes.

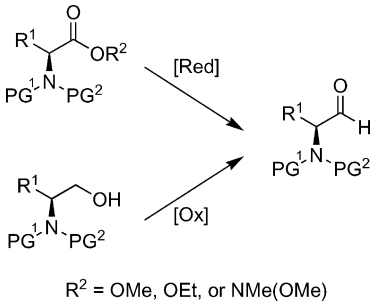
Another member of this class of reagents is the Garner aldehyde **2**, which has been extensively used as a chiral building block in organic synthesis.[8] More than 200 reports have appeared since its discovery. The original synthesis began with *N*-protection of L-serine **5** using di-*tert*-butyl dicarbonate to give the carbamate **6**,[9] which was subsequently converted into the methyl ester **7** upon treatment with diazomethane. Exposure of **7** to 2,2-bis(methoxy)propane in the presence of TsOH gave oxazolidine ester **8**, which was reduced using DIBAL in toluene to afford the title aldehyde **2** (Scheme 2). The original synthesis of the Garner aldehyde has been subjected to some modifications; for instance, the diazomethane step was replaced with MeI/K_2CO_3,[10] and DIBAL with $LiAlH_4$/Swern protocol.[11] In some instances the first two steps involving Boc protection and esterification have been reversed.[12] Later, a Weinreb amide was used in place of the methyl ester to allow direct reduction to the aldehyde using $LiAlH_4$.[13]



Scheme 2. Synthesis of the Garner aldehyde.

N-Monosubstituted α-amino aldehydes containing Boc, Cbz, Fmoc, Ac, or Ts group attached to the nitrogen centre are also widely known.[14] Among these protecting groups, the *N*-Boc substituent is frequently used, whereas the Ts group tends to be avoided due to harsh conditions required for its removal.[15] Reduction and oxidation are the key steps involved in the synthesis of protected α-amino aldehydes (Scheme 3). Particular care should be taken in order to avoid racemization during these processes.

Amongst reductive methodologies, the most commonly used route is the reduction of carboxylic acid methyl or ethyl esters by diisobutylaluminium hydride (DIBAL). In many cases over-reduction to the respective alcohol has been observed.[16] In a few cases the reduction with DIBAL



Scheme 3. Reductive and oxidative pathways to α-amino aldehydes.

has led to erosion of enantiomeric purity to 86–90%.[11b–11d,12,17] The hydride reduction has been reported to be problematic with the substrates containing reducible functionalities, such as *N*-acylamino group.[18] DIBAL reduction of *N*-Boc amino acids, commonly used in peptide chemistry, affords the respective aldehydes with negligible racemization.[19] For instance, treatment of *N*-Boc amino acids with peptide coupling reagents in the presence of H_2-Pd/C afforded the corresponding aldehyde with no significant racemization and in good yield.[20]

Weinreb amides are very useful in the preparation of α-amino aldehydes due to the fact that over-reduction and racemization are not observed. The amide can be reduced to the aldehyde through the use of $LiAlH_4$,[21] LiAl(*t*BuO)$_3$H, or lithium tris[(3-ethyl-3-phenyl)oxy]aluminum hydride (LTEPA).[22] A wide range of *N*-protecting groups are stable under these conditions.[21,22] A kilogram-scale preparation of *N*-Boc protected α-amino aldehyde was reported by Schwindt et al. using sodium bis(2-methoxyethoxy)aluminium hydride.[23]

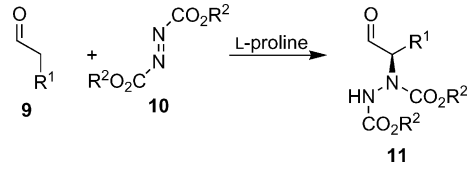
Oxidation of amino alcohols and amino diols is another common way to prepare α-amino aldehydes. The alcohol is generally obtained through the reduction of the corresponding α-amino acid or ester, which is followed by oxidation. The final step can be carried out using a wide range of methods, for example, Swern,[24] Dess–Martin,[25,26] or Parikh–Doering[27] oxidations. Marko's oxidation using molecular oxygen, azodicarboxylate as hydride acceptor, and a catalytic amount of a Cu^{II} complex is a more recent development.[28] Swern oxidation remains the most widely used method in the synthesis of α-amino aldehydes.[24] Racemization problems encountered during Swern oxidation can be solved by switching from Et_3N to Hünig's base.[11d] With this modification, the enantiomeric purity of the product aldehyde can exceed 97% *ee*. Giacomelli[29] showed an alternative approach to the classical Swern method by using 2,4,6-trichloro-1,3,5-triazine (TCT) instead of moisture sensitive oxalyl chloride. Under these conditions, α-amino aldehydes were isolated in moderate yields without significant racemization.

Leanna and co-workers[30] used oxoammonium-promoted oxidation of α-amino alcohols to α-amino aldehydes in the presence of a catalytic amount of 2,2,6,6-tetrametyl-1-piperidinyloxy free-radical (TEMPO). *N*-Mono and *N*,*N*-disubstituted amino aldehydes were obtained with good yields and high enantiomeric purities. The procedure was further improved by changing the oxidation agents.[31] This method is compatible with *N*-Boc, *N*-Cbz and *N*-Fmoc-protecting groups. The use of Dess–Martin oxidation procedure is best for *N*-Fmoc-protected amino alcohols[26] but not for *N*-Boc protected counterparts.[32]

Braun and co-workers described the synthesis of α-amino aldehydes from chiral dibromo olefins and sulfonylimines, where ozonolysis is the final step to obtain the above compound.[33] Duréault and co-workers described the synthesis of α-amino aldehydes starting from D-mannitol involving cleavage of the diol functionality though $NaIO_4$ oxidation to produce the corresponding *N*-protected α-amino aldehyde.[34]

2.1 Catalytic Enantioselective Synthesis of α-Amino Aldehydes

Catalytic enantioselective α-amination of enolizable aldehydes is a recent approach to the synthesis of α-amino aldehydes.[35] List[36] and Jørgensen[37] independently developed the enantioselective synthesis of α-amino aldehydes using L-proline-catalyzed α-amination of aldehydes (Scheme 4). This C–N bond-forming reaction affords high levels of enantioselectivity in the formation of the stereogenic α-carbon center.



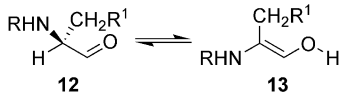
Scheme 4. Asymmetric α-amination of aldehydes.

For instance, aldehyde **9** reacts with diethyl azodicarboxylate (DEAD) **10** in the presence of L-proline as catalyst, to give the aminated product **11** in 93% yield and with 92% *ee*. The main drawback to this approach is that the products formed by the direct α-amination of aldehydes tend to be configurationally unstable.[37] In addition, cleavage of the N–N bond is a significant challenge.

2.2 Stability of *N*-Protected α-Amino Aldehydes

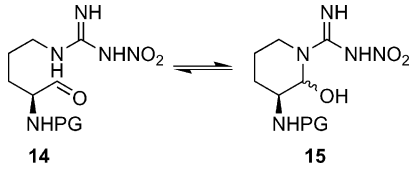
In general, *N*-protected α-amino aldehydes are colorless crystals or oils that are soluble in most organic solvents. They are relatively unstable, both chemically and configurationally, particularly in solution. In many cases configurational stability of α-amino aldehydes can only be maintained at low temperature.[38] Ito et al. documented the erosion of enantiomeric integrity of some *N*-protected α-amino aldehydes during chromatography on silica gel.[25] The stability of α-amino aldehydes on silica gel decreases in the following order: Cbz-S-Bzl-L-cysteinal >> Cbz-phenylalaninal > Cbz-leucinal >> Cbz-N^G-nitroagininal. The alde-

hydes with the R^1 group stabilizing their enol forms (e.g., Cbz-S-Bzl-L-cysteinal) are most easily racemized upon contact with silica gel (Scheme 5).



Scheme 5. Acid-promoted enolization of α-amino aldehydes.

The extended carbon chain of L-argininal derivative **14** forms a cyclic carbinolamine structure **15**, which prevents racemization. It is by this structure that the authors explain the configurational stability of (*Z*)-*N*-nitro-L-argininal (Scheme 6). In other cases, the enantiomeric integrity of α-amino aldehydes can be preserved by converting them into semicarbazones,[39] imidazolidines[40] or acetals,[41] which can be purified by chromatography.



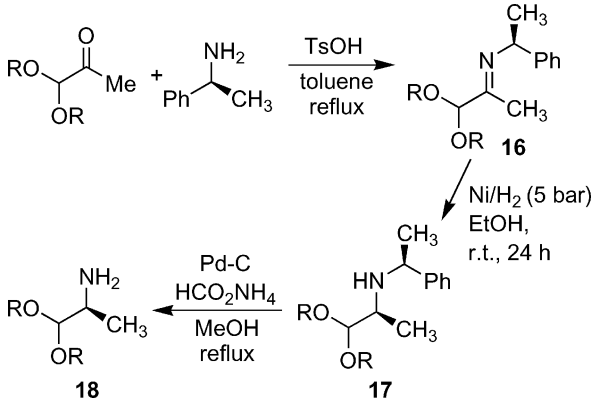
Scheme 6. (*Z*)-N^G-Nitro-L-argininal exists as a mixture of tautomers.

3. *C*-Protected α-Amino Aldehydes

C-Protected α-amino aldehydes in which the amino group is free and the aldehyde is protected have been much less explored.[42] The carbonyl group of α-amino aldehydes can be protected as an acetal or amino nitrile. *C*-Protected α-amino aldehydes have been used as precursors in the synthesis of complex natural products.[43]

3.1 Acetal-Protected α-Amino Aldehyde

Bringmann and Geisler synthesized *C*-protected α-amino aldehydes in three steps starting from (*R*)- or (*S*)-phenylethylamine.[42a] The reaction of ketones with phenylethylamine under standard conditions yielded *E*/*Z* mixtures of

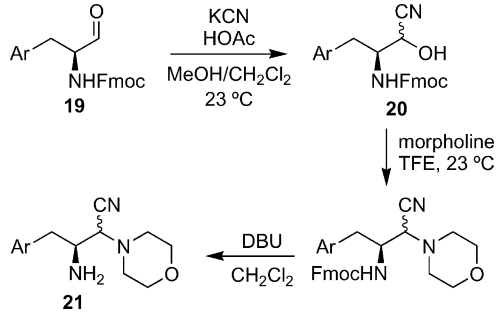


Scheme 7. Preparation of an acetal-protected α-amino aldehyde.

the imine **16**, which was not isolated in order to avoid hydrolytic decomposition (Scheme 7). Subsequent hydrogenation with Raney nickel yielded compound **17** with high diastereoselectivity following column chromatography. Hydrogenation of compound **17** gave the acetal-protected α-amino aldehyde **18**.

3.2 Amino Nitrile Functionality for *C*-Protection

Myers et al. have developed a novel series of *C*-protection strategies for α-amino aldehydes that are based upon the amino nitrile functionality.[43] Syntheses of such compounds were achieved from the corresponding *N*-protected α-amino aldehydes (Scheme 8). This series has the advantage over existing acetal-based protective groups due to more mild conditions involved in their preparation, which are essential to avoid racemization. For instance, treatment of *N*-Fmoc-protected aldehyde **19** with hydrogen cyanide afforded the cyanohydrin **20** in 88% yield and 96% *ee*. Reaction of compound **20** with morpholine, followed by cleavage of the Fmoc group, gave the morpholino-nitrile **21** in 86% yield. Similarly, the authors prepared *N*-Cbz and *N*-trifluoroacetyl derivatives of **21**, which were scaled up to gram quantities with up to 96% *ee*.



Scheme 8. Preparation of a *C*-protected α-amino aldehyde.

The above procedure was highly effective with a range of α-(*N*-Fmoc)amino aldehydes. When *N*-Fmoc phenylglycinal was later investigated as a substrate, racemic products were obtained. The procedure was modified by conducting the cleavage of *N*-Fmoc in dimethylformamide (DMF), followed by exposure to trifluoroethanol and additional morpholine to give the corresponding morpholino-nitrile with only slight racemization.[43b]

3.3 Stability of *C*-Protected α-Amino Aldehydes

Myers and co-workers extensively studied the amino nitrile as *C*-protecting group.[43a] They prepared several derivatives of compound **21** with less than 2% epimerization in each case. Among the amino nitrile derivatives, those formed from cyclic secondary amines were found to be the most stable. The order of stability is shown in Figure 3. The main drawback of the synthesis of *C*-protected α-amino aldehydes is that it requires several steps.

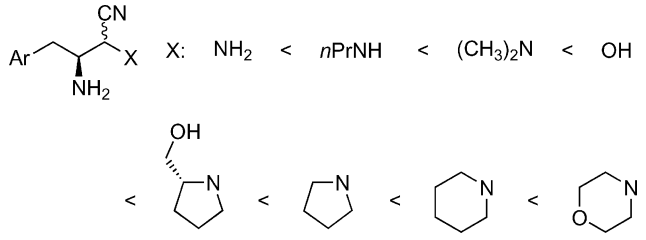
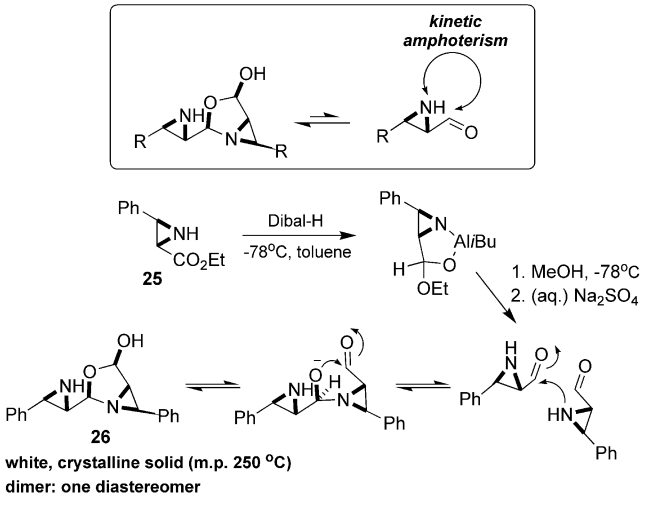


Figure 3. Stablity of the amino nitrile function in *C*-protected amino aldehydes.

4. Amphoteric α-Amino Aldehydes

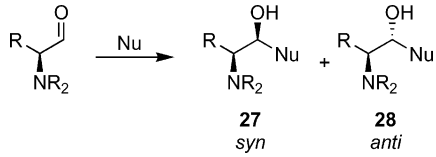
Until recently, it was thought that an unprotected secondary amine could not coexist with an aldehyde in the same molecule due to thermodynamically favourable condensation resulting in an iminium/enamine system. In a recent breakthrough, the goal of creating such presumably "suicidal" molecules has been achieved by Yudin and coworkers using an unprotected aziridine as the secondary amine.[44] The thermodynamic driving force to undergo condensation has been offset by a high barrier imposed on this process by the aziridine ring strain (Scheme 9). The unprotected aziridine aldehydes can be readily prepared by the reduction of aziridine esters. In the course of preparation, these molecules undergo diastereoselective homodimerization. The so-called *kinetic amphoterism* has been coined in order to describe the co-existence of an unprotected aziridine and aldehyde groups in such molecules. As aziridine rings are widely considered as stepping-stones to complex amines, these unprotected derivatives hold tremendous potential for protecting group-free operations.



Scheme 9. Unprotected α-amino aldehydes.

5. Nucleophilic Additions to α-Amino Aldehydes

The addition of nucleophiles to chiral α-amino aldehydes can result in two diastereomeric products, namely, *syn*-**27** and *anti*-**28** β-amino alcohols (Scheme 10). There have been considerable efforts in achieving highly stereoselective additions to α-amino aldehydes in order to access both diastereoisomers, which are equally important structural motifs in biologically active molecules, as well as key building blocks in chemical synthesis.[5c]



Scheme 10. Nucleophilic addition to α-amino aldehydes.

5.1 General Models for Nucleophilic Attack at α-Amino Aldehydes

The stereochemical outcome of nucleophilic addition to α-amino aldehydes is based upon the substituents on the nitrogen atom. In the case of *N*,*N*-disubstituted α-amino aldehydes, there are two possible governing models for explaining selectivity (Figure 4). As a general rule, when the substituents on nitrogen are small, *chelation-control* can occur if there is a chelating metal present, which would lead to a *syn*-amino alcohol. However, with larger substituents on nitrogen, a *Felkin–Anh* model controls the facial attack, irrespective of a chelating metal being present or absent from the reaction medium. This model results in an *anti*-amino alcohol. Despite this being a general rule, there are exceptions, and more importantly, substituents of medium steric bulk may result in poor selectivities due to the lack of delineation between the governing models.

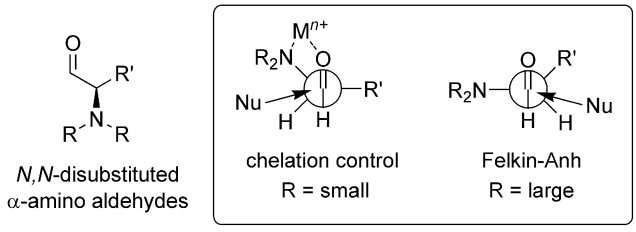


Figure 4. Models for nucleophilic addition to *N*,*N*-disubstituted α-amino aldehydes.

The situation becomes more complex with monosubstituted α-amino aldehydes (Figure 5). Chelation-control predominates when chelating metals are in solution; however, different binding modes can occur, which may affect the level of stereocontrol. When non-chelating Lewis acids such as $BF_3{\cdot}OEt_2$ are present, Felkin–Anh selectivity can arise, albeit intramolecular hydrogen bonding between the amine and aldehyde is possible, in which case erosion or even reversal of stereoselectivity may be observed due to *anti*-Felkin–Anh attack.

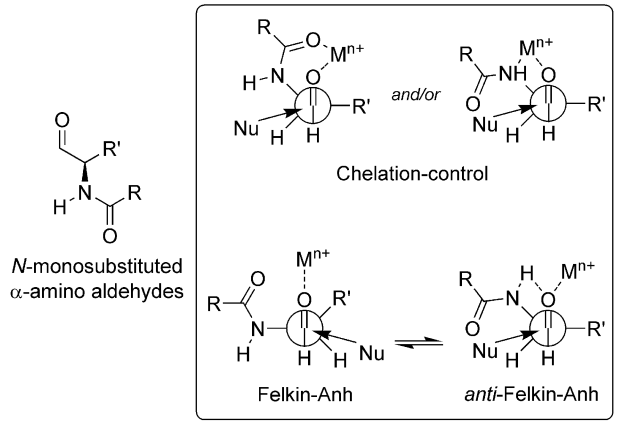
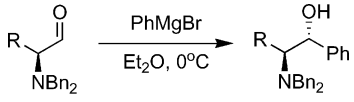


Figure 5. Models for nucleophilic addition to *N*-monosubstituted α-amino aldehydes.

5.2 Additions of Carbon Nucleophiles to α-Amino Aldehydes in the Absence of Chelation Control

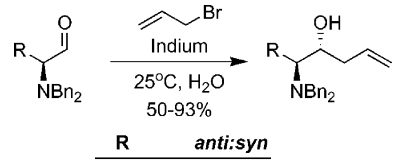
There have been several reports dealing with the addition of carbon-based nucleophiles to *N*,*N*-dibenzylamino aldehydes.[5] In an extensive investigation by Reetz and coworkers,[45] it was found that Grignard and organolithium reagents add to *N*,*N*-dibenzylamino aldehydes to yield *anti*-amino alcohols with high diastereoselectivities and without any observable racemization (Scheme 11).



R	Yield	*anti:syn*
Me	85%	97:3
Bn	84%	97:3
*i*Bu	84%	97:3
*i*Pr	69%	91:9

Scheme 11. Addition of Grignard reagents to *N*,*N*-disubstituted α-amino aldehydes.

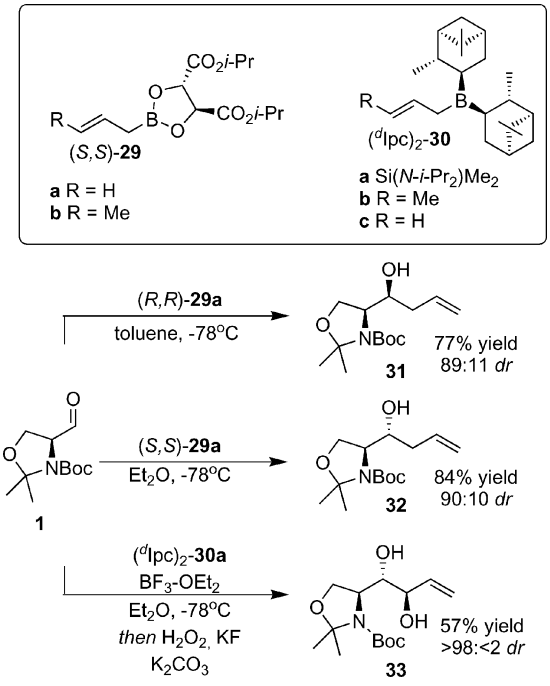
The authors attributed the observed stereochemical outcome to the prevention of a five-membered ring chelate due to the steric hindrance of the benzyl groups on nitrogen. Thus, the Felkin–Anh model is governing the addition. It should be noted that only moderate decreases in selectivity with increasing steric bulk of the α-carbon substituent are observed in organometallic additions to *N*,*N*-dibenzylamino aldehydes. However, in their study on the diastereoselectivity for the allylindium addition to α-amino aldehydes,[46] Paquette et al. have shown that when the steric bulk of the α-carbon substituent was greatly increased, significant erosion of stereoselectivity was observed (Scheme 12). This was attributed to the gradual loss of Felkin–Anh selectivity as the size of the α-carbon substituent became comparable with the dibenzylated nitrogen.



R	*anti:syn*
Bn	6.1:1
*i*Pr	3.5:1
*i*Bu	1.9:1

Scheme 12. Allylindium addition to *N*,*N*-dibenzyl α-amino aldehydes.

A greater degree of diastereoselection for the allylation of α-amino aldehydes has been realized using homochiral allylboranates. Roush and Hunt applied the asymmetric allylboration of the Garner aldehyde **1** towards the total synthesis of calicheamicin γ_1^I, a potent antitumor antibiotic.[47] The favoured diastereoisomer (66:34) of this allylation reaction is the *anti*-amino alcohol **32**, which was determined using an achiral allylboronate. This is due to the facial selectivity being governed by Felkin–Anh control. When homochiral allylboronates were used, such as Roush's reagent **29**, the stereochemical outcome of the reaction was controlled by the reagent (Scheme 13). In case of (*S*,*S*)-**29a**, *anti*-amino alcohol **32** was obtained with 90:10 diastereoselectivity, which matched the expected Felkin–Anh product. When the (*R*,*R*)-**29a** was used, an 89:11 diastereomeric ratio in favour of the *syn*-amino alcohol **31** was documented (*anti*-Felkin–Anh product). The proposed transition states are exhibited in Figure 6.



Scheme 13. Asymmetric allylboration of the Garner aldehyde.

Brown allylation has also been implemented in the asymmetric allylation of α-amino aldehydes. In connection with their efforts toward the synthesis of the potent marine protein phosphatase inhibitor calyculin A, Barrett and Male-

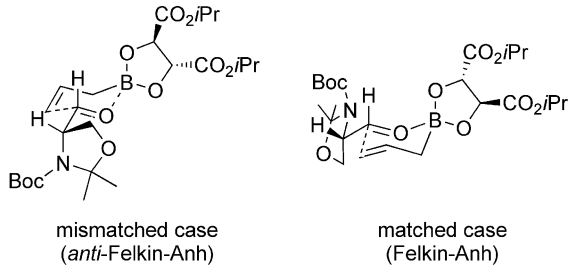
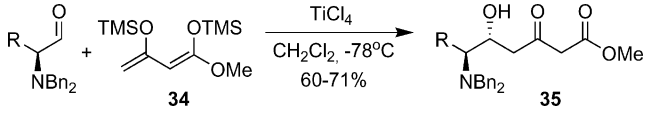


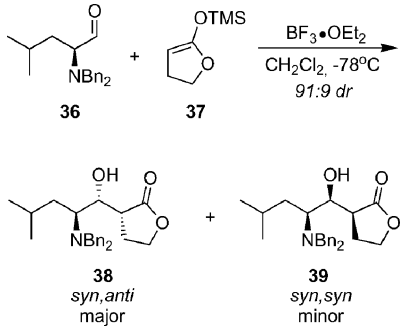
Figure 6. Transition-state models for Roush allylation of the Garner aldehyde.

cha[48] subjected the Garner aldehyde to Brown allylation using (^{d}Ipc)$_2$-**30a**, followed by Tamao oxidation[49] to furnish the amino diol **33** in 57% yield as a single diastereoisomer (Scheme 13). The reaction proceeds as a matched case to afford the Felkin–Anh product with excellent diastereoselectivity.

The Mukaiyama-type aldol addition to *N*,*N*-dibenzylamino aldehydes was developed in order to access key structural precursors to HMG-CoA-reductase-inhibitors.[50] The additions of **34** resulted in *anti*-amino alcohol aldol adducts **35** as single diastereoisomers without any appreciable deterioration of enantiomeric purity (Scheme 14). Notably, the size of the α-carbon substituent had no observable effect on the diastereoselectivity of the reaction. Hanessian et al. also studied the Mukaiyama aldol reaction with α-amino aldehydes in their investigation into the effectiveness of constrained oxacyclic hydroxyethylene isosteres of aspartic protease inhibitors.[51] Using $BF_3{\cdot}OEt_2$ as a Lewis acid, a *syn*,*anti*-selective Mukaiyama aldol addition of **37** to *N*,*N*-dibenzylleucinal (**36**) was achieved in high diastereomeric ratio (Scheme 15).



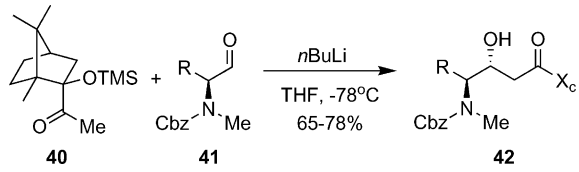
Scheme 14. $TiCl_4$-promoted Mukaiyama aldol addition to *N*,*N*-dibenzyl α-amino aldehydes.



Scheme 15. $BF_3{\cdot}OEt_2$-promoted Mukaiyama aldol addition to *N*,*N*-dibenzyl α-amino aldehydes.

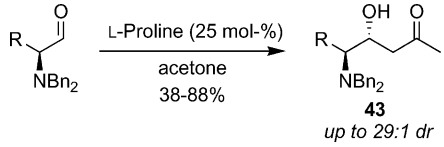
The same authors also examined lithium enolate additions, which afforded good selectivity for the *anti*,*anti*-aldol product. The mode of selectivity for this reaction is assumed to arise from a Zimmerman–Traxler transition state, which is governed by Felkin–Anh control. It was essential to have disubstituted nitrogen under these reaction conditions. When monosubstituted α-amino aldehydes were subjected to the same conditions, the diastereoselectivity was lost due to competing intramolecular hydrogen bonding between the amine and aldehyde, which favours the formation of *syn*-amino alcohols.

In their concise total synthesis of Hapalosin,[52] a naturally occurring depsipeptide shown to be active in reversing multidrug resistance, Palomo et al. have employed their chiral acetate reagent **40**[53] in aldol additions to the α-amino aldehydes **41** with remarkable diastereoselectivity (Scheme 16). In all cases, only the *anti*-amino alcohol **42** was observed from which the chiral auxiliary was easily removed using cerium ammonium nitrate. An interesting observation was that even with the monosubstituted amino aldehyde, *N*-Boc leucinal, only the *anti*-diastereoisomer was observed, which implies that Felkin–Anh control successfully dominated intramolecular hydrogen bonding under these reaction conditions.



Scheme 16. Chiral acetate addition to α-amino aldehydes.

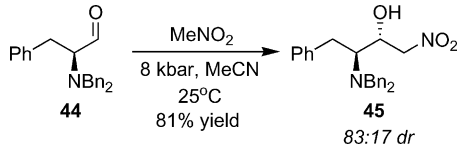
The proline-catalyzed diastereoselective aldol addition to α-amino aldehydes has been studied by Pan and co-workers (Scheme 17).[54] They found that *N*,*N*-dibenzylamino aldehydes gave the best yields and selectivities of the *anti* adduct **43**, while *N*-Boc amino aldehydes were found to give the poorest diastereoselectivity. When using D-proline, *syn*-amino alcohols were isolated in a low 67:33 diastereomeric ratio. Clearly, L-proline and (*S*)-*N*,*N*-dibenzylamino aldehydes constitute a matched pair for diastereoselective induction. The authors also employed cyclopentanone and hydroxyacetone as reaction partners with *N*,*N*-dibenzylamino aldehydes, all of which supplied the corresponding aldol adducts in moderate to excellent yield and diastereoselectivity.



Scheme 17. Proline-catalyzed aldol addition to *N*,*N*-dibenzyl α-amino aldehydes.

By taking advantage of the basic character of amino aldehydes, a substrate-catalyzed diastereoselective Henry reaction was achieved under high pressure by using the starting α-amino aldehyde as the base in the reaction (Scheme 18).[55] *anti*-Amino alcohols **45** were obtained in good yields and diastereomeric ratios; however, up to 10% racemization of the starting amino aldehyde was observed under these reaction conditions. The highest selectivity was

obtained using 2-nitropropane, from which a greater than 99:1 diastereomeric ratio in favour of the *anti*-product was isolated in 68% yield. The authors found that the solvent greatly affects the yield and selectivity for the reaction, with MeCN giving the best results. The proposed mechanism involves initial deprotonation of nitroalkane by amino aldehyde followed by nucleophilic attack via a Felkin–Anh model at the formyl carbon of the *N*,*N*-dibenzylamino aldehyde. Similar *anti*-selectivity was observed in the sodium iodide catalyzed nitro-aldol reaction involving *N*,*N*-dibenzylalaninal.[56] Using bromonitromethane, the corresponding *anti,anti*-aldol product was obtained as a 85:15 ratio in 98% enantiomeric excess.

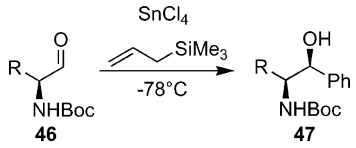


Scheme 18. Henry reaction with *N*,*N*-dibenzyl α-amino aldehydes.

5.3 Chelation- and *anti*-Felkin–Anh Control in Carbon Nucleophile Additions to α-Amino Aldehydes

C–C bond forming reactions with α-amino aldehydes where the attack of the carbon nucleophile is governed by chelation-control or an *anti*-Felkin–Anh model have resulted in poorer stereoselectivities. This has been largely accredited to the protecting groups on nitrogen interfering with chelate formation. However, the governance of selectivity is not clearly delineated, and predicting the stereochemical outcome is rather difficult. Notwithstanding, some general trends in predicting selectivity will be discussed along with some recent advances that have overcome problems encountered when chelation control is desired.

Extensive investigation into the stereoselective addition of carbon-based nucleophiles to monosubstituted α-amino aldehydes has taken place. These substrates tend to undergo additions through chelation-control by virtue of there being less steric hindrance preventing chelate formation. In their research toward the synthesis of dipeptide isosteres, Prasad and Rich[57] have demonstrated that high diastereocontrol for the tin-mediated allylation of *N*-Boc α-amino aldehydes **46** can be achieved to produce the corresponding *syn*-amino alcohols **47** in good yields (Scheme 19). They also observed

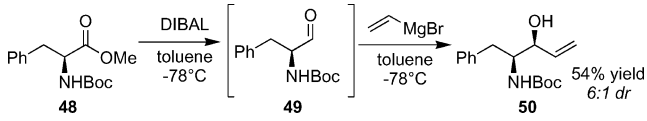


R	Yield	*anti:syn*
Bn	65%	83:17
*n*Bu	80%	91:9
*i*Bu	68%	>95:5

Scheme 19. Tin-mediated allylation of *N*-Boc α-amino aldehydes.

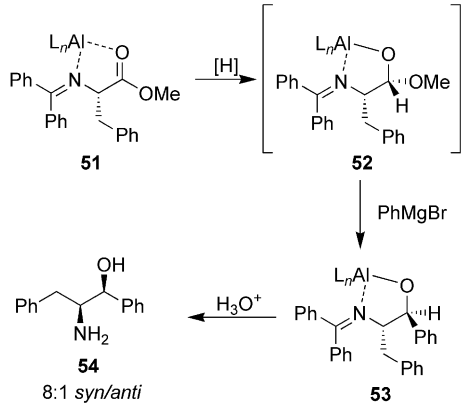
that the diastereoselectivity increased with increasing steric bulk of the α-carbon substituent.

Grignard additions to monosubstituted α-amino aldehydes also proceed with chelation-control. In developing a concise industrial synthesis toward key building blocks of HIV protease inhibitors, Green et al. of Abbott Laboratories[58] reported the diastereoselective vinyl Grignard addition to *N*-Boc-phenylalaninal (**49**) to yield a 6:1 diastereomeric mixture in favour of the *syn* amino alcohol **50** in 54% yield (Scheme 20).



Scheme 20. Vinyl Grignard addition to in situ generated α-amino aldehydes.

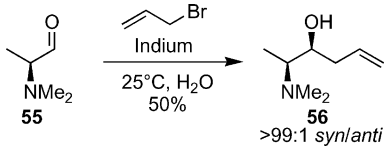
The amino aldehyde **49** was generated in situ from the reduction of amino ester **48**, which was found to be crucial to the diastereoselectivity of the reaction, because the vinyl Grignard addition to purified *N*-Boc-phenylalaninal was previously found to be unselective.[59] This suggests that aluminum is integral to the selectivity of the reaction. Indeed, this has been suggested by Polt et al. while investigating chelation-controlled addition to α-amino aldehydes as a generalized approach to the synthesis of sphingosines.[60] The authors have demonstrated that diastereoselectivies greater than 20:1 in favour of the *syn*-amino alcohol **54** can be achieved by reducing α-imino esters **51** with iBu$_2$AlH-iBu$_3$Al followed by addition of an organolithium or Grignard reagent (Scheme 21). The initial hydride delivery is suggested to occur via chelation-control, while the attack of the carbon nucleophile is speculated to occur through an S_N2-type inversion mechanism of the resulting aluminoxy acetal **52**. The mechanism was supported by the observation that increasing the steric bulk of the initial ester led to a marked increase in stereoselectivity of the reaction sequence.



Scheme 21. Grignard addition to in situ generated aluminoxy acetal.

The allylindium addition to *N*,*N*-disubstituted α-amino aldehydes where the nitrogen substituents are small have been shown to proceed through chelation-control.[46] Excel-

lent selectivity for *syn*-amino alcohol **56** was observed in the case of *N*,*N*-dimethylalaninal (**55**) (Scheme 22), which was attributed to the cyclic transition state shown in Figure 7 (a). Although there was not an extensive investigation into the effect of the size of the α-carbon substituent, when *N*,*N*-dimethylphenylalaninal was subjected to the same conditions, only a 1.8:1 *syn*/*anti* ratio was produced suggesting that there is a small window in which chelation-control effectively operates. An interesting finding was that the diastereoselectivity of the reaction was highest at neutral pH. At lower pH, it was proposed that an intermolecular addition to protonated **55** was occurring (Figure 7, b), which is presumably less selective. A significant drawback to this approach is the fact that *N*-demethylation of the resulting products is particularly difficult. In contrast to the indium-mediated allylation of *N*,*N*-disubstituted α-amino aldehydes, Boc- or Cbz-protected α-amino aldehydes undergo various metal-mediated additions with increasing *syn* selectivity as the steric bulk of the α-carbon side chain is increased.[61] This is expected as increasing the bulk of the side chain should better direct the facial preference for nucleophilic attack at the aldehyde carbon.



Scheme 22. Allylindium addition to *N*,*N*-dimethylalaninal.

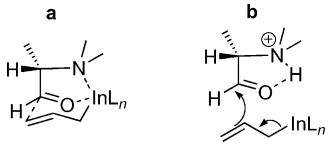
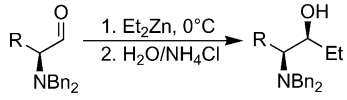


Figure 7. Proposed transition states for allylindium addition to α-amino aldehyde derivatives.

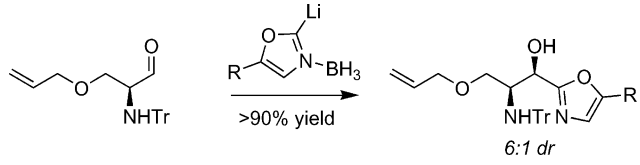
Although the *N*,*N*-dibenzyl α-amino aldehydes are generally used when Felkin–Anh selectivity is desired, conditions have been developed where chelation-control occurs, yielding *syn*-amino alcohols with high selectivities. Andrés et al. have established a highly selective addition of diethylzinc to α-amino aldehydes **57** to afford *syn*-amino alcohols **58** (Scheme 23).[62] The diastereoselectivity of the reaction mirrored the steric bulk of the α-carbon substituent. The reaction was conducted in the absence of an additive donor, which has been shown to increase the reactivity of diethylzinc additions.[63] This takes advantage of the donor property of the dibenzylamino group to both enhance the reactivity of diethylzinc and to ensure chelate formation. The steric bulk of the α-carbon substituent does not necessarily increase the diastereoselectivity of the reaction as was demonstrated by the chelation-controlled addition of methyl group by the highly Lewis acidic $MeTiCl_3$.[45] In the case of *N*,*N*-dibenzylalaninal, a 94:6 ratio in favour of the *syn* amino alcohol was isolated in 82% yield. However, as the substituent of α-carbon increased in size, yields were dramatically reduced; such is the case with *N*,*N*-dibenzylvalinal where the corresponding amino alcohol was produced in 65% yield as a 65:35 *syn*/*anti* mixture of diastereoisomers.



R	Yield	*syn*:*anti*
Me	95%	88:12
Bn	70%	90:10
*i*Bu	62%	92:8
*i*Pr	64%	>99:1

Scheme 23. Diethylzinc addition to *N*,*N*-dibenzyl α-amino aldehydes.

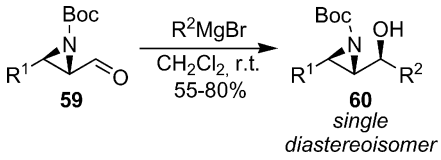
N-Trityl α-amino aldehydes are a synthetically useful class of compounds due to their high configurational stability[64] and the mildly acidic deprotection protocol required for trityl group removal. For these very reasons, *N*-trityl α-amino aldehydes have been used as chiral building blocks in total synthesis and medicinal chemistry.[65] Despite the bulky nature of the trityl group, chelation-controlled addition has been shown to occur with good selectivity. An interesting application of *N*-trityl α-amino aldehydes was provided by Vedejs et al. in their synthesis of a class aziridinomitosenes, which are DNA alkylating agents (Scheme 24).[66]



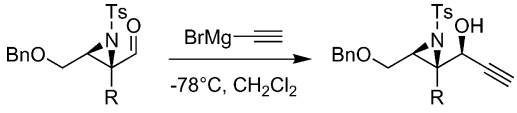
Scheme 24. Organolithium addition to *N*-trityl α-amino aldehyde.

Aziridine aldehydes, being configurationally stable by virtue of the increase in ring strain involved in the epimerization process, undergo chelation-controlled addition of alkyl-metal reagents with excellent selectivities and without epimerization. In the case of *trans*-*N*-Boc-protected aziridine aldehydes **59**, Grignard addition produced only the *syn*-diastereoisomer **60** (Scheme 25).[67] The cyclic magnesium chelate can be envisioned to form between the nitrogen lone pair and carbonyl oxygen; however, the Boc group may also be participating in coordination to magnesium. Grignard additions to *cis*-Boc-protected aziridine aldehydes were found to be unselective, which was attributed to poorer chelation of the *cis*-isomer.[67a] The stereoselective alkyl addition to *cis*-aziridine aldehydes is possible by using dialkylzinc reagents, where in several cases only chelation-controlled additions were observed.[67b] The addition of alkynylmagnesium reagents to *N*-tosylated aziridine aldehydes has also been shown to be highly diastereoselective for the *syn*-amino alcohol products (Scheme 26).[67c] The presence of chelation-control is still under question becaus substitu-

tion at the α-carbon unexpectedly increases the diastereoselectivity, while the addition of chelating agents produced no change in the selectivity.



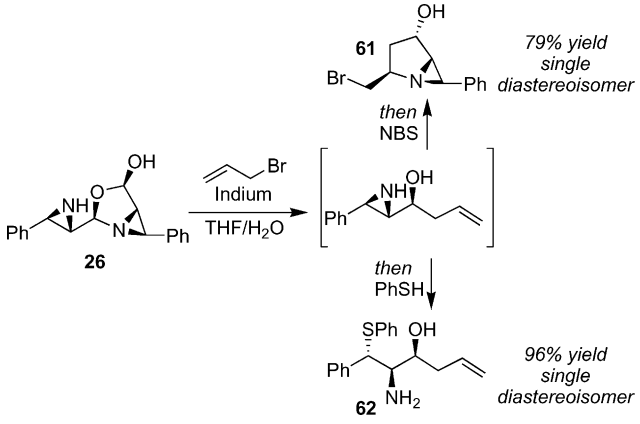
Scheme 25. Diastereoselective Grignard addition to aziridine aldehydes.



R	Yield	*syn:anti*
H	71%	2:1
Me	96%	>97:3

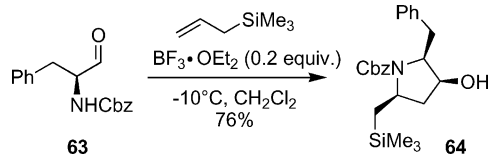
Scheme 26. Grignard addition to α-aziridine aldehydes.

In light of the recently discovered stability of unprotected α-aziridine aldehydes, the opportunity for stereoselective additions without recourse to protecting groups has been made possible. For instance, the indium-mediated allylation of the amino aldehyde dimer **26** occurs with complete stereocontrol to afford the *syn* amino alcohol (Scheme 27).[68] Since the aziridine is not protected, oxidative cycloamination[69] can be achieved in a one-pot protocol to yield **61** as a single diastereoisomer in 79% overall yield. Alternatively, a highly convergent synthesis of the unprotected thio amino alcohol stereo-triad **62** was performed in a one-pot allylation/nucleophilic ring-opening reaction, which quickly assembled **62** as a single diastereoisomer in 96% yield.



Scheme 27. Allylation of unprotected aziridine aldehydes.

The stereoselective $BF_3{\cdot}OEt_2$-catalyzed [3+2] annulation of monosubstituted α-amino aldehydes **63** with allyltrimethylsilane has been described by Kiyooka and co-workers (Scheme 28).[70] The resulting pyrrolidine products **64** are isolated as single diastereoisomers possessing a *cis*-2,3,5-trisubstitution pattern.



Scheme 28. Stereoselective $BF_3{\cdot}OEt_2$-catalyzed [3+2] annulation of *N*-Cbz-phenylalaninal with allyltrimethylsilane.

The initial stereoselective allylation step is explained through a synclinal transition state as shown in Figure 8 (a), which is followed by a highly stereoselective cyclization involving the nucleophilic attack by nitrogen at the carbon centre of the pentavalent intermediate (Figure 8, b). The authors note that with $TiCl_4$, no pyrrolidine was isolated, rather, only the *syn* amino alcohol was obtained.

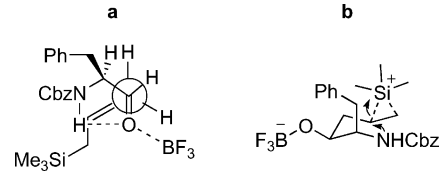
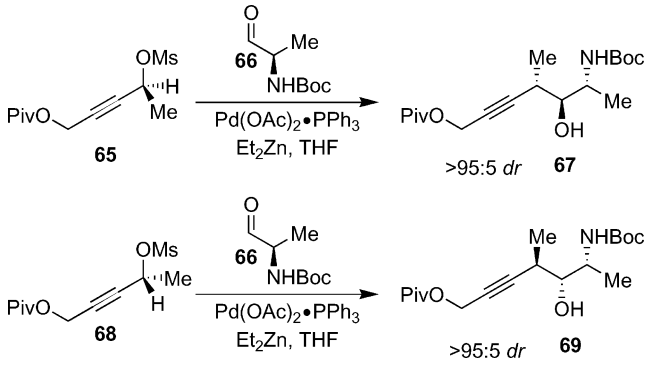


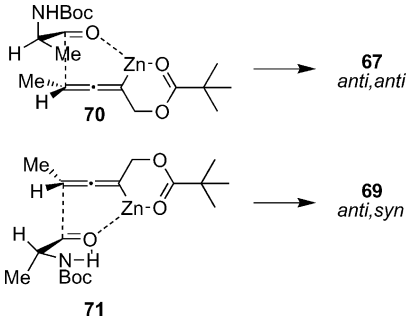
Figure 8. Proposed transition states towards **64**.

Convergent carbon–carbon bond-forming reactions with α-amino aldehydes that create more than two contiguous stereocentres are attractive strategies in chemical synthesis. In their development of new synthetic route towards Superstolide A, Marshall and Mulhearn[71] have demonstrated that the stereochemical outcome of allenylzinc addition to α-amino aldehydes **66** is determined by the configuration of the allenylzinc precursor through reagent control (Scheme 29).



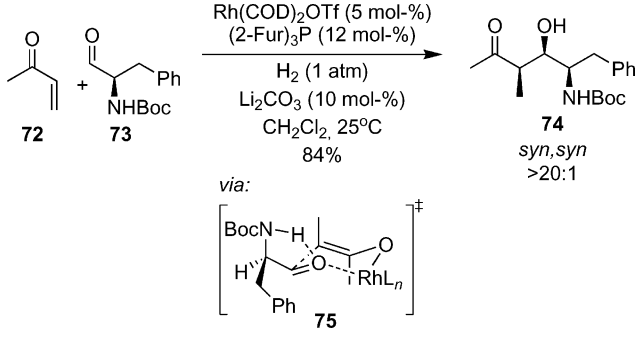
Scheme 29. Allenylzinc addition to *N*-Boc-alaninal.

Following the initial palladozincation, it is postulated that *anti*,*anti* diastereoisomer **67** arises from Felkin–Anh addition of the (*P*)-allenylzincate to the α-amino aldehyde via a zinc chelated transition state **70** (Scheme 30). On the contrary, (*M*)-allenylzincate undergoes *anti*-Felkin–Anh addition to α-amino aldehydes to produce *anti,syn* diastereoisomer **69** via a proposed intramolecular hydrogen-bonded zinc-chelated transition state **71**.



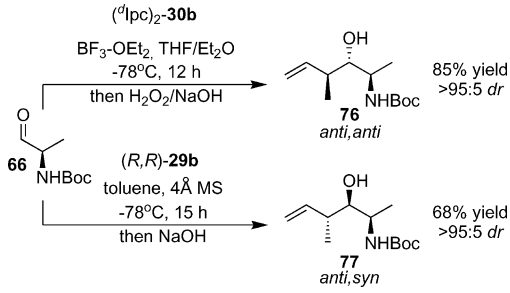
Scheme 30. Proposed transition state for allenylzinc addition to *N*-Boc-alaninal.

Another attractive strategy towards selective formation of stereotriads is through the rhodium-catalyzed reductive aldol addition to α-amino aldehydes.[72] The vinyl ketones **72** undergo highly stereoselective couplings with α-amino aldehydes to provide the *anti*-Felkin–Anh products such as *syn*,*syn*-**74** in good to excellent yields (Scheme 31). The selectivity of the reaction is postulated to arise from an intramolecular hydrogen-bond-assisted rhodium-chelated cyclic transition state **75**. The role of hydrogen bonding appears to be significant both in terms of reactivity and selectivity. When the hydrogen-bonding capability is deleted by using an *N*-Boc, *N*-Me disubstituted α-amino aldehyde, the yield is drastically decreased, and more interestingly, the diastereoselectivity is inverted to produce the *syn*-aldol (the Felkin–Anh product), as the major diastereoisomer.



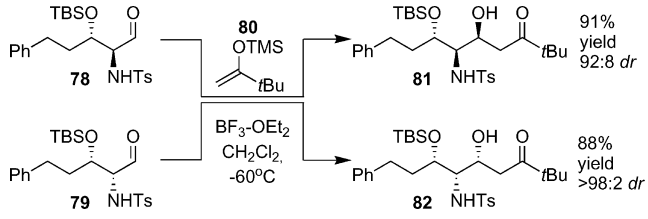
Scheme 31. Rhodium-catalyzed reductive aldol addition to *N*-Boc-phenylalaninal.

Yakelis and Roush have recently provided an important insight into the crotylboration reactions on α-amino aldehydes.[73] The choice of crotylboration reagent and nitrogen protecting groups were found to be extremely important in achieving the desired stereochemical outcome of the reaction. For *N*,*N*-disubstituted α-amino aldehydes, as aforementioned, allylboration reactions occur via Felkin–Anh control. However, complications arise when working with monosubstituted α-amino aldehydes by virtue of their ability to participate in intramolecular hydrogen bonding. This was exemplified through the crotylation of *N*-Boc-alaninal using two different crotylboron reagents (Scheme 32). In the case of Brown's reagent (^{d}Ipc)$_2$-**30b**, Felkin–Anh addition to yield **76** was observed with high yield and excellent diastereoselectivity; however, Roush's reagent (*R*,*R*)-**29b** resulted in the formation of the *anti*-Felkin–Anh amino alcohol **77**. The authors[73] suggested that the *anti*-Felkin–Anh product arose from the intramolecular hydrogen bonding between the amine and aldehyde, which forced *re* face addition in order to avoid *syn*-pentane interaction between the methyl groups, which would have occurred for a *si* face attack. However, the more Lewis acidic Brown's reagent prevents the intramolecular hydrogen-bonding between the amine and aldehyde, thus establishing Felkin–Anh control. It should be noted that the formation of *syn*-amino alcohols is possible when using Brown's reagent, for instance, Nicolaou and co-workers used (^{l}Ipc)$_2$-**30b** as an allylation reagent for D-*N*-Boc,*O*-TPS-serinal in their total synthesis of Balanol.[74]



Scheme 32. Chiral allylboronate addition to *N*-Boc-alaninal.

α-Amino-β-silyloxy aldehydes are valuable precursors to amino diols, which have demonstrated various biological properties.[75] Restorp and Somfai[76] have investigated the Mukaiyama aldol addition of **80** to both *syn*- and *anti*-α-amino-β-silyloxy aldehydes (Scheme 33). When the amine group is monosubstituted, the additions occur with high yield and diastereoselectivity via intramolecular hydrogen-bonding (*anti*-Felkin–Anh), irrespective of the *syn* or *anti* relationship in the starting aldehyde, albeit the *syn*-α-amino-β-silyloxy aldehyde **79** produced slightly lower selectivity. When the amino group was disubstituted, the stereochemistry was reversed to afford only the Felkin–Anh product from *syn*-α-amino-β-silyloxy aldehydes, but is essentially lost when using *anti* α-amino-β-silyloxy aldehydes.



Scheme 33. Mukaiyama aldol addition to α-amino-β-silyloxy aldehyde.

6. Conclusions

α-Amino aldehydes have a proven track record as important chiral building blocks in chemical synthesis. Their utility as precursors to many biologically active compounds has been amply documented in recent years. Of particular

significance are carbon–carbon bond forming events that lead to the generation of useful 1,2-amino alcohol motifs with defined stereochemistry. The stereochemical outcome of nucleophilic additions to α-amino aldehydes can be controlled by the use of appropriate protecting groups appended to the nitrogen centre. Unfortunately, detrimental epimerization processes are also facilitated by these substituents. Recent findings using amphoteric amino aldehydes suggest that these unwanted events can be avoided without adversely affecting the stereoselectivity of nucleophilic additions.

Acknowledgments

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canadian Institutes of Health Research (CIHR) for financial support of this work.

[1] J. Izawa, T. Onishi, *Chem. Rev.* **2006**, *106*, 2811–2827.
[2] E. Fischer, H. Leuchs, *Ber. Dtsch. Chem. Ges.* **1902**, *36*, 24.
[3] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 956; E. Fischer, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 1019.
[4] S. Nomoto, M. Takasaki, N. Sakata, K. Harada, *Tetrahedron Lett.* **1983**, *24*, 3357–3360.
[5] For reviews see: a) M. T. Reetz, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531–1546; b) M. T. Reetz, *Chem. Rev.* **1999**, *99*, 1121–1162; c) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576.
[6] a) M. T. Reetz, *Pure Appl. Chem.* **1992**, *64*, 351–359; b) M. T. Reetz, in *Stereocontrolled Organic Synthesis* (Ed.: B. M. Trost), Blackwell, Oxford, **1994**, pp. 67–95.
[7] a) J. R. Gage, D. A. Evans, *Org. Synth.* **1990**, *68*, 77–82; b) A. Giannis, K. Sandhoff, *Angew. Chem.* **1989**, *101*, 220–222; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 218–219; c) A. Abiko, S. Masamune, *Tetrahedron Lett.* **1992**, *33*, 5517–5518; d) A. I. Meyers, T. R. Elworthy, *J. Org. Chem.* **1992**, *57*, 4732–4740; e) C. Li, J. S. Ng, J. R. Behling, C. H. Yen, A. L. Campbell, K. S. Fuzail, E. E. Yonan, D. V. Mehrotra, *Org. Proc. Res. Dev.* **1997**, *1*, 45.
[8] For reviews, see: X. Liang, J. Andersch, M. Bols, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2136–2157.
[9] a) P. Garner, *Tetrahedron Lett.* **1984**, *25*, 5855–5858; b) P. Garner, J. M. Park, *J. Org. Chem.* **1987**, *52*, 2361–2364.
[10] P. Garner, J. M. Park, *Org. Synth.* **1991**, *70*, 18–28.
[11] a) M. Yanagida, K. Hashimoto, M. Ishida, H. Shinozaki, H. Shirahama, *Tetrahedron Lett.* **1989**, *30*, 3799–3802; b) W. R. Roush, J. A. Hunt, *J. Org. Chem.* **1995**, *60*, 798–806; c) A. Dondoni, D. Perrone, P. Merino, *J. Org. Chem.* **1995**, *60*, 8074–8080; d) A. Dondoni, D. Perrone, *Synthesis* **1997**, 527–529; e) M. Hashimoto, K. Hashimoto, H. Shirahama, *Tetrahedron* **1996**, *52*, 1931–1942.
[12] a) A. McKillop, R. J. K. Taylor, R. J. Watson, N. Lewis, *Synthesis* **1994**, 31–33; b) L. Williams, Z. Zhang, F. Shao, P. J. Carroll, M. M. Joullié, *Tetrahedron* **1996**, *52*, 11673–11694.
[13] a) G. Bold, T. Allmendinger, P. Herold, L. Moesch, H.-P. Schär, R. O. Duthaler, *Helv. Chim. Acta* **1992**, *75*, 865–882; b) A. D. Campbell, T. M. Raynham, R. J. K. Taylor, *Synthesis* **1998**, 1707–1709.
[14] For reviews see: a) J. Jurczak, A. Golebiowski, *Chem. Rev.* **1989**, *89*, 149–164; b) D. Gryko, J. Chalko, J. Jurczak, *Chirality* **2003**, *15*, 514–541.
[15] K. J. M. Beresford, N. J. Chruch, D. W. Young, *Org. Biomol. Chem.* **2006**, *4*, 2888–2897.
[16] a) A. Ito, R. Takahashi, Y. Baba, *Chem. Pharm. Bull.* **1975**, *23*, 3081–3087; b) D. H. Rich, E. T. Sun, A. S. Boparai, *J. Org. Chem.* **1978**, *43*, 3624–3626.
[17] J. A. Marshall, B. M. Seletsky, P. S. Coan, *J. Org. Chem.* **1994**, *59*, 5139–5140.
[18] P. Zlatoisdsky, *Helv. Chim. Acta* **1994**, *77*, 150–154.
[19] P. Zlatoidsky, *Helv. Chim. Acta* **1994**, *77*, 575–578.
[20] M. Falorni, G. Giacomelli, A. Porcheddu, M. Taddei, *J. Org. Chem.* **1999**, *64*, 8962–8964.
[21] J. J. Wen, C. M. Crews, *Tetrahedron: Asymmetry* **1998**, 1855–1858.
[22] M. Paris, C. Pothion, A. Heitz, J. Martinez, J.-A. Fehrentz, *Tetrahedron Lett.* **1998**, *39*, 1341–1344.
[23] M. A. Schwindt, D. T. Belmont, M. Carlson, L. C. Franklin, V. S. Hendrickson, G. L. Karrick, R. W. Poe, D. M. Sobieray, J. Van DeVusse, *J. Org. Chem.* **1996**, *61*, 9564–9568.
[24] A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480–2482.
[25] J. W. B. Cooke, S. G. Davies, A. Naylor, *Tetrahedron* **1993**, *49*, 7955–7966.
[26] A. G. Myers, B. Zhong, M. Movassaghi, D. W. Kung, B. A. Lanman, S. Kwon, *Tetrahedron Lett.* **2000**, *41*, 1359–1362.
[27] a) J. S. Ng, C. A. Przybyla, C. Liu, J. C. Yen, F. W. Muellner, C. L. Weyker, *Tetrahedron* **1995**, *51*, 6397–6410; b) P. L. Beaulieu, P. Lavallèe, A. Abraham, P. C. Anderson, C. Boucher, Y. Bousquet, J.-S. Duceppe, J. Gillard, V. Gorys, C. Grand-Maître, L. Grenier, Y. Guindon, I. Guse, L. Plamondon, F. Soucy, S. Valois, D. Wernic, C. Yoakim, *J. Org. Chem.* **1997**, *62*, 3440–3448.
[28] I. E. Marko, M. Tsukazaki, P. R. Giles, S. M. Brown, C. Urch, *Angew. Chem.* **1997**, *109*, 2297–2299; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2208–2210.
[29] L. De Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.* **2001**, *66*, 7907–7909.
[30] M. R. Leanna, T. J. Swoin, H. E. Morton, *Tetrahedron Lett.* **1992**, *33*, 5029–5032.
[31] a) J. Jurczak, D. Gryko, E. Kobrzycka, H. Gruza, P. Prokopowicz, *Tetrahedron* **1998**, *54*, 6051–6064; b) L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 3041–3043.
[32] M. Soucek, J. Urban, *Collect. Czech. Chem. Commun.* **1995**, *60*, 693–696.
[33] M. Braun, K. Opendenbush, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 578–580.
[34] A. Durèault, I. Tranchepain, J.-C. Depezay, *J. Org. Chem.* **1989**, *54*, 5324–5330.
[35] For review see: a) C. Greck, B. Drouillat, C. Thomassigny, *Eur. J. Org. Chem.* **2004**, 1377–1385; b) T. Baumann, H. Vogt, S. Bräse, *Eur. J. Org. Chem.* **2007**, 266–282; c) R. O. Duthaler, *Angew. Chem. Int. Ed.* **2003**, *42*, 975–978; d) H. Iwamura, S. P. Mathew, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 11770–11771; e) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001–2011; f) S. Mukherjee, J. W. Yang, S. Hoffman, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
[36] B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657.
[37] a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868–1871; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793; b) N. Kumaraguruban, K. Juhl, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255.
[38] K. E. Rittle, C. F. Homnick, G. S. Ponticello, B. E. Evans, *J. Org. Chem.* **1982**, *47*, 3016–3018.
[39] a) B. Shimizu, A. Saito, A. Ito, K. Tokawa, K. Maeda, H. Umezawa, *J. Antibiot.* **1972**, *25*, 515–523; b) R. M. McConnel, J. L. York, D. Frizzel, C. Ezell, *J. Med. Chem.* **1993**, *36*, 1084–1089.
[40] W. Ried, P. Pfaender, *Justus Liebigs Ann. Chem.* **1961**, *640*, 111–126.
[41] T. Masaki, T. Tanaka, S. Tsunasawa, F. Sakiyama, M. Soejima, *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1604–1607.
[42] a) G. Bringmann, J.-P. Geisler, *Synthesis* **1989**, 608–610; b) M. Thiam, F. Chastrette, *Tetrahedron Lett.* **1990**, *31*, 1429–1432; c) D. Enders, R. Funk, M. Klatt, G. Raabe, E. R. Hovestreydt, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 418–421; d) S. E. Den-

mark, O. Nicaise, *Synlett* **1993**, 359–361; e) K. R. Muralidharan, M. K. Mokhallalati, L. N. Pridgen, *Tetrahedron Lett.* **1994**, *35*, 7489–7492; f) A. Alexakis, N. Lensen, J.-P. Tranchier, P. Mangeney, J. Feneau-Dupont, J. P. Declercq, *Synthesis* **1995**, 1038–1050.
[43] a) A. G. Myers, D. W. Kung, B. Zhong, M. Movassaghi, S. Kwon, *J. Am. Chem. Soc.* **1999**, *121*, 8401–8402; b) A. G. Myers, B. Zhong, D. W. Kung, M. Movassaghi, B. A. Lanman, S. Kwon, *Org. Lett.* **2000**, *2*, 3337–3340; c) S. Kwon, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 16796–16797.
[44] a) R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772–14773; b) X. Li, A. K. Yudin, *J. Am. Chem. Soc.* **2007**, *129*, 14152–14153; c) A. K. Yudin, R. Hili, *Chem. Eur. J.* **2007**, *13*, 6538–6542.
[45] M. T. Reetz, M. W. Drewes, A. Schmitz, *Angew. Chem. Int. Ed. Engl.* **1987**, *99*, 1186–1188.
[46] L. A. Paquette, T. M. Mitzel, M. B. Isaac, C. F. Crasto, W. W. Schomer, *J. Org. Chem.* **1997**, *62*, 4293–4301.
[47] W. R. Roush, J. A. Hunt, *J. Org. Chem.* **1995**, *60*, 798–806.
[48] A. G. M. Barrett, J. W. Malecha, *J. Org. Chem.* **1991**, *56*, 5243–5245.
[49] K. Tamao, T. Nakajima, R. Sumiya, H. Arai, N. Higuchi, Y. Ito, *J. Am. Chem. Soc.* **1986**, *108*, 6090.
[50] D. Enders, F. Burkamp, J. Runsink, *Chem. Commun.* **1996**, 609–610.
[51] S. Hanessian, Y. Hou, M. Bayrakdarian, M. Tintelnot-Blomley, *J. Org. Chem.* **2005**, *70*, 6735–6745.
[52] C. Palomo, M. Oiarbide, J. M. García, A. González, R. Pazos, J. M. Odriozola, P. Bañuelos, M. Tello, A. Linden, *J. Org. Chem.* **2004**, *69*, 4126–4134.
[53] C. Palomo, A. González, J. M. García, C. Landa, M. Oiarbide, S. Rodríguez, A. Linden, *Angew. Chem. Int. Ed.* **1998**, *37*, 180–192.
[54] Q. Pan, B. Zou, Y. Wang, D. Ma, *Org. Lett.* **2004**, *6*, 1009–1012.
[55] Y. Misumi, K. Matsumoto, *Angew. Chem. Int. Ed.* **2002**, *41*, 1031–1033.
[56] J. M. Concellón, H. Rodríguez-Solla, C. Concellón, S. García-Granda, M. R. Díaz, *Org. Lett.* **2006**, *8*, 5979–5982.
[57] J. V. N. V. Prasad, D. H. Rich, *Tetrahedron Lett.* **1990**, *31*, 1803–1806.
[58] B. E. Green, X. Chen, D. W. Norbeck, D. J. Kempf, *Synlett* **1995**, 613.
[59] G. J. Hanson, T. Lindberg, *J. Org. Chem.* **1985**, *50*, 5399.
[60] R. Polt, M. A. Peterson, L. Deyoung, *J. Org. Chem.* **1992**, *57*, 5469–5480.
[61] a) S. Steurer, J. Podlech, *Eur. J. Org. Chem.* **1999**, 1551–1560; b) L. C. Dias, E. Ferreira, *Tetrahedron Lett.* **2001**, *42*, 7159–7162.
[62] J. M. Andrés, R. Barrio, M. A. Martínez, R. Pedrosa, A. Pérez-Encabo, *J. Org. Chem.* **1996**, *61*, 4210–4213.
[63] R. Noyori, M. Kitamura, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49.
[64] C. Gros, C. Boulègue, N. G. Niel, P. Jouin, *Tetrahedron* **2002**, *58*, 2673–2680.
[65] a) J. F. Dellaria Jr., R. G. Maki, H. H. Stein, J. Cohen, D. Whittern, K. Marsh, D. J. Hoffman, J. J. Plattner, T. J. Perun, *J. Med. Chem.* **1990**, *33*, 534–542; b) U. Schmidt, J. Schmidt, *J. Chem. Soc., Chem. Commun.* **1992**, 529–530.
[66] E. Vedejs, B. N. Naidu, A. Klapars, D. L. Warner, V. S. Li, Y. Na, H. Kohn, *J. Am. Chem. Soc.* **2003**, *125*, 15796–15806.
[67] a) G. Righi, S. Pietrantonio, C. Bonini, *Tetrahedron* **2001**, *57*, 10039–10046; b) J. M. Andrés, N. de Elena, R. Pedrosa, A. Pérez-Encabo, *Tetrehedron* **1999**, *55*, 14137–14144; c) J. M. Schomaker, A. R. Geiser, R. Huang, B. Borhan, *J. Am. Chem. Soc.* **2007**, *129*, 3794–3795.
[68] R. Hili, A. K. Yudin, *Angew. Chem. Int. Ed.* **2008**, *120*, 4256–4259.
[69] a) M. Sasaki, A. K. Yudin, *J. Am. Chem. Soc.* **2003**, *125*, 14242–14243; b) G. Chen, M. Sasaki, X. Li, A. K. Yudin, *J. Org. Chem.* **2006**, *71*, 6067–6073.
[70] S.-I. Kiyooka, Y. Shiomi, H. Kira, Y. Kaneko, S. Tanimori, *J. Org. Chem.* **1994**, *59*, 1958–1960.
[71] J. A. Marshall, J. J. Mulhearn, *Org. Lett.* **2005**, *7*, 1593–1596.
[72] C.-K. Jung, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 17051–17056.
[73] N. A. Yakelis, W. R. Roush, *J. Org. Chem.* **2003**, *68*, 3838–3843.
[74] K. C. Nicolaou, M. E. Bunnage, K. Koide, *J. Am. Chem. Soc.* **1994**, *116*, 8402–8403.
[75] a) K. Burgess, I. Henderson, *Tetrahedron* **1992**, *48*, 4045–4066; b) J. P. Michael, *Nat. Prod. Rep.* **2001**, *18*, 520–542.
[76] P. Restorp, P. Somfai, *Org. Lett.* **2005**, *7*, 893–895.

Received: June 20, 2008
Published Online: September 10, 2008

