Synthesis and Diastereoselective Reactions of *N*,*N*-Dibenzylamino Aldehydes and Related Compounds

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Contents

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I. Introduction

The idea of employing α-amino acids as chiral building blocks in synthetic organic chemistry is not new.[1] Most of the early examples pertain to the use of naturally occurring *L*-amino acids. However, today the chiral pool of amino acids includes *D*-enantiomers as well as structural variations which do not occur in nature.[2] This is due to several developments, including improved chromatographic methods for antipode separation, efficient enzymatic kinetic resolution, and industrially viable methods for asymmetric synthesis based on stoichiometric reagents and/or chiral transition metal catalysts.

Organic chemists have employed α-amino acids as chiral building blocks in one of two ways.[1,3] According to one strategy, a specific α-amino acid is incorporated in a target molecule such as a natural product or a biologically active synthetic compound. The elegant syntheses of cytochalasine B[4] and (+)-preussin[5] based on phenylalanine are prominent examples. In contrast, the second strategy entails a completely different intention. Accordingly, the goal is to transform a broad range of α-amino acids into different classes of compounds. A case in point is the widely used reduction of α-amino acids with formation of the corresponding primary amino alcohols, a process that can be performed without any undesired racemization.[6]

A much greater challenge is to transform the α-amino acids into the corresponding α-amino aldehydes and then to consider diastereoselective C−C bond forming processes such as Grignard-type reactions, aldol and HCN additions, epoxide-forming sulfur ylide reactions, and hetero Diels−Alder reactions.[3,7] Because α-amino aldehydes are not chemically stable, the amino function must be protected. Until 1987, this was generally accomplished by preparing *N*-*tert*-butoxycarbonyl (Boc), *N*-benzyloxycarbonyl (Cbz), or *N*-*iso*-propoxy carbonyl (Poc) amino aldehydes **2** from the corresponding α-amino acids **1**.[7] Although these α-amino aldehydes can be handled in cold ether without appreciable racemization, the

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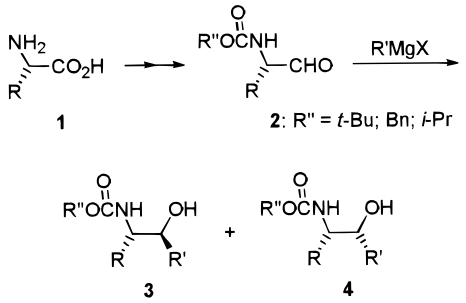
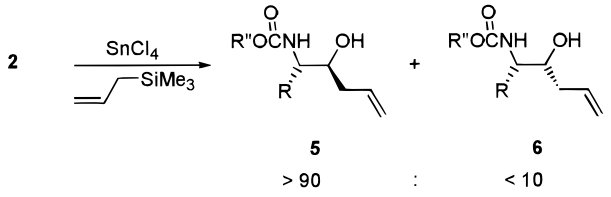
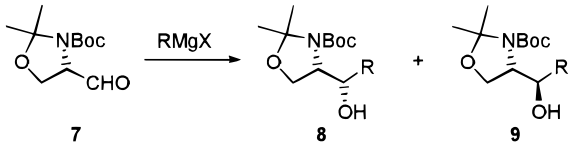
vast majority of reactions with Grignard reagents, lithium enolates, KCN/H^+, and sulfur ylides turned out to afford mixtures of chelation and nonchelation controlled adducts **3** and **4**, respectively, with unacceptable degrees of diastereoselectivity (1:1 to 3:1 diastereomer ratios).[7] Furthermore, in many of the early studies the question of partial racemization was not routinely addressed. In rare cases selectivity is higher, as in the Li^+-mediated reaction of aldehydes **2** with $Me_3SiCH_2CH{=}PPh_3$, which affords the chelation controlled vinyl adducts **3** (R′ = $CH_2{=}CH$) with > 95% diastereoselectivity after hydrolysis of the silyl ether initially formed.[8] Currently the most selective alkyl−metal reagents are cuprates or manganese compounds which add to aldehydes **2** with 80−95% chelation control,[9a] but generalization to include aryl and vinyl reagents has not been achieved. Occasionally, other protective groups have been used.[9b,c] For example, the bulky 9-phenyl-9-fluorenyl group results in greater configurational stability but not in enhanced stereoselectivity.[10]



It is useful to compare the chemistry of α-amino aldehydes with that of α-alkoxy aldehydes.[11] In the latter case, nonchelation control is possible only in special cases using bulky organotitanium reagents of low Lewis acidity such as $MeTi(Oi\text{-}Pr)_3$, whereas chelation control is routinely achieved by "tying up" the molecules via chelate formation with such bidentate Lewis acids as $TiCl_4$, $SnCl_4$, or $MgCl_2$ and reacting these intermediates with allylsilanes or enolsilanes, zinc reagents, or Me_3SiCN.[11] This concept was subsequently applied to the reaction of allylsilane with α-amino aldehydes **2** with formation of the chelation controlled products **5**.[12] Along similar lines, $TiCl_4$-mediated Mukaiyama aldol additions to aldehydes **2** (R′ = *i*-Pr) were shown to proceed with excellent degrees of chelation control.[13] Certain substituted allylsilanes react with Boc-protected α-amino aldehydes **2** in the presence of BF_3 to afford predominantly the nonchelation controlled adducts.[14]

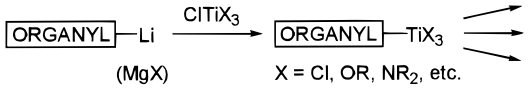


Another synthetically important development concerns the Garner aldehyde **7**, prepared in almost enantiomerically pure form (ee = 95%) in four steps from serine **1** (R = CH_2OH).[15] Addition of Grignard reagents, alkynyllithium compounds, or lithium enolates occurs with 84−98% nonchelation control (preferential formation of adducts **9**). Under more Lewis acidic conditions, diastereoselectivity can be reversed in some cases. Aldehyde **7** has been used successfully in a number of applications, as in the preparation of sphingoid bases. However, diastereoselectivity is not always satisfactory.[16]



Despite these synthetic advancements, a more general solution to the problem of diastereoselective reactions of α-amino aldehydes was needed, especially with respect to nonchelation control.[3] Theoretically, reagent control based on the use of chiral reagents or catalysts should solve all problems. Indeed, several cases have been described (section IID). However, this usually entails a higher degree of complexity and costs. Indeed, if a substrate already contains a stereogenic center, then any C−C bond forming process that occurs diastereoselectively due to the chiral information present constitutes a much more efficient strategy.[17] To maximize diastereoselectivity without recourse to chiral reagents, metal and ligand tuning are the two most important instruments at hand. One such possibility is the titanation of classical carbanions such as RLi, RMgX, Li-enolates, lithiated nitriles, sulfones, and heterocycles using $ClTiX_3$ (X = Cl, OR, NR_2, etc.).[11,18] Because the electronic and steric properties of the ligands X at titanium can be varied widely, such an approach offers many possibilities to optimize the stereoselectivity of a given C−C bond forming reaction (Scheme 1).

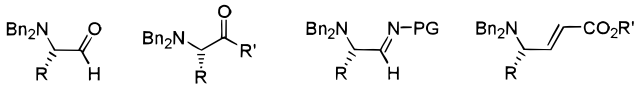
Scheme 1. Titanation as a Means to Control Carbanion Selectivity



A third and sometimes neglected instrument available to the practicing organic chemist is protective group tuning.[19,20] Accordingly, the nature of the protective group dictates the direction and degree of diastereoselectivity. If necessary, metal, ligand, and protective group tuning are combined properly to maximize diastereoselectivity. It is this strategy which forms the basis of the chemistry to be discussed here.

This review focuses on the synthesis and reactions of a new class of α-amino aldehydes, namely *N*,*N*-dibenzylamino aldehydes **10**.[21] These building blocks can be prepared from the corresponding α-amino acids **1** or from other chiral sources. It turns out that the presence of *two* protective benzyl groups is of crucial importance in influencing the direction and degree of diastereoselectivity.[3,20] The reactions of related *N*,*N*-dibenzylamino ketones **11**,[22] aldimines **12**,[23] and α,*β*-unsaturated esters **13**,[24] which are also

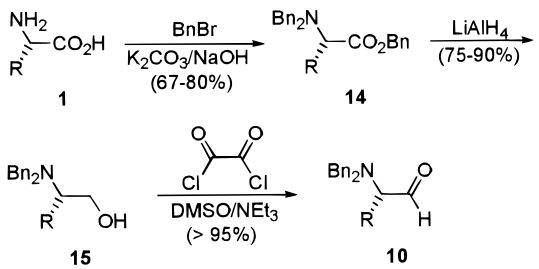
accessible in enantiomerically pure form from the corresponding α-amino acids **1**, are also reviewed. Attention is likewise paid to those examples in which the *N,N*-dibenzylamino carbonyl compounds are prepared from enantiomerically pure precursors which are *not* α-amino acids. The chemistry of racemic *N,N*-dialkylamino aldehydes and ketones prepared from various achiral or racemic building blocks has been reviewed elsewhere.[25]



II. N,N-Dibenzylamino Aldehydes

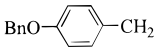
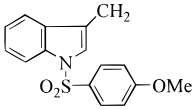
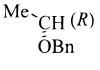
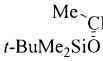
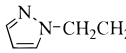
A. Synthesis

The original and still widely used synthesis of *N,N*-dibenzylamino aldehydes **10** starting from α-amino acids **1** involves three simple steps, namely, benzylation, reduction, and oxidation.[21,26,27] The final reaction is based on Swern oxidation of *N,N*-dibenzylamino alcohols **15** which occurs practically quantitatively with formation of aldehydes **10** in enantiomerically pure form. Alternative procedures such as the Parikh−Doering[26−29] or Dess−Martin[30] oxidations also work well. The Markó oxidation using molecular oxygen, azodicarboxylates as hydride acceptors, and catalytic amounts of a Cu complex constitutes the newest version.[31] It is easy to perform, utilizes the cheapest and environmentally safest oxidant, and also occurs without any racemization. Although aldehydes **10** can be isolated and handled at room temperature, it is best to use them in crude form as they are produced. Chromatographic purification is not necessary and, in fact, should be avoided because of partial racemization.[26] Upon storing the aldehydes for long periods of time (months), partial rearrangement to achiral α-amino ketones may occur,[32−34] a process that is accelerated by bases or acids.[32,33] Keeping these precautions in mind, handling the aldehydes is straightforward, even on an industrial scale.[29,35−38] If long-term storage and/or shipping is necessary, stabilization can be achieved by transformation into the sodium bisulfite addition product as described in a patent.[39]



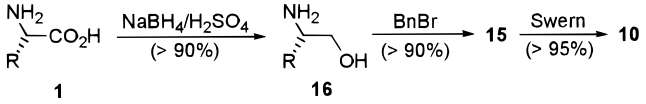
More recently, a significant improvement in the synthesis of aldehydes **10** was devised which entails switching the order of the three synthetic steps.[26,27,29,32,37] Thus, α-amino acids **1** are first reduced to the corresponding primary amino alcohols **16** using conventional methods based on $BH_3{\cdot}SMe_2$/$BF_3{\cdot}OEt_2$,[6a] $LiBH_4/Me_3SiCl$,[6b] $NaBH_4/Me_3SiCl$,[6b] $NaBH_4/H_2SO_4$,[6c] or $NaBH_4/BF_3$[6d] followed by N-benzylation and Swern (or other) oxidation. This strategy avoids the use of $LiAlH_4$ and circumvents the necessity to separate the alcohols **15** from benzyl alcohol which is formed in the reduction of esters **14**. Details of both versions have been checked and accepted by *Organic Synthesis*.[26] From a practical point of view, this version is the method of choice. Indeed, several industrial reports concerning the large-scale production of certain aldehydes **10** based on this approach have appeared.[29,35−38] For example, aldehyde **10b** (see Table 1), which is used in the synthesis of HIV-protease inhibitors such as palinavir,[36,37] can be prepared on a 573 mol (∼ 190 kg) scale, the optical purity being > 99.9%.[29] Table 1 shows a number of common *N,N*-dibenzylamino aldehydes **10** which have been synthesized by these methods. Although these aldehydes have been prepared and used by

Table 1. Common *N,N*-Dibenzylamino Aldehydes 10 Prepared from α-Amino Acids 1[a]

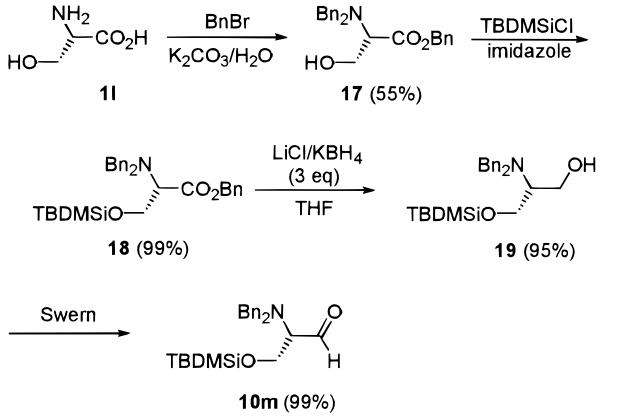
Entry	amino acid	aldehydes	R	ref(s)
1	Ala (**1a**)	**10a**	Me	21,26-28
2	Phe (**1b**)	**10b**	Bn	21,26-29
3	Val (**1c**)	**10c**	*i*-Pr	21,26-28
4	Leu (**1d**)	**10d**	*i*-Bu	21-28
5	*i*-Leu (**1e**)	**10e**	*s*-Bu (*S*)	27,40
6	*t*-Leu (**1f**)	**10f**	*t*-Bu	41
7	Hexahydro-Phe (**1g**)	**10g**		42
8	Orn (**1h**)	**10h**	$Bn_2N(CH_2)_3$	3,27
9	Lys (**1i**)	**10i**	$Bn_2N(CH_2)_4$	3,27
10	Tyr (**1j**)	**10j**		28
11	Tryp (**1k**)	**10k**		43
12	Ser (**1l**)	**10l**	$BnOCH_2$	40
13	Ser (**1l**)	**10m**	*t*-$BuMe_2SiOCH_2$	44-46
14	Threo (**1m**)	**10n**		46
15	Threo (**1m**)	**10o**		46
16	Allo (**1n**)	**10p**[b]		3,46
17	Glu (**1o**)	**10q**	*t*-$BuMe_2SiO(CH_2)_3$	47
18	Asp (**1p**)	**10r**	*t*-$BuMe_2SiOCH_2CH_2$	48
19	Asp (**1p**)	**10s**	$MesOCH_2CH_2$	49
20	Asp (**1p**)	**10t**		50
21	Meth (**1q**)	**10u**	$HOCH_2CH_2$	51
22	Ph-gly (**1r**)	**10v**	Ph	52

[a] In most cases, naturally occurring L-amino acids were used with formation of (*S*)-configurated aldehydes **10**. However, the chemistry is identical when using D-amino acids, and in some cases the corresponding (*R*)-configurated aldehydes **10** have in fact been prepared. [b] This aldehyde corresponds to allothreonine, but in fact was produced from threonine (see text).

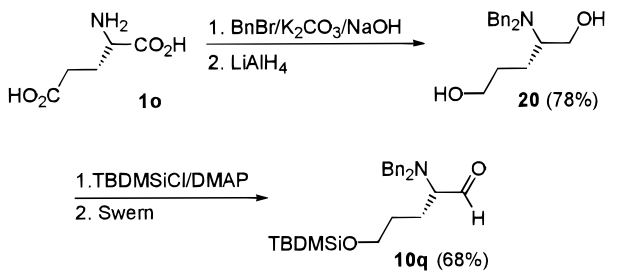
many groups (section II), Table 1 lists only those citations in which original or improved protocols were reported. In most cases, enantiomeric purity was checked and found to be > 98%, usually at the stage following an addition reaction (section IIB).



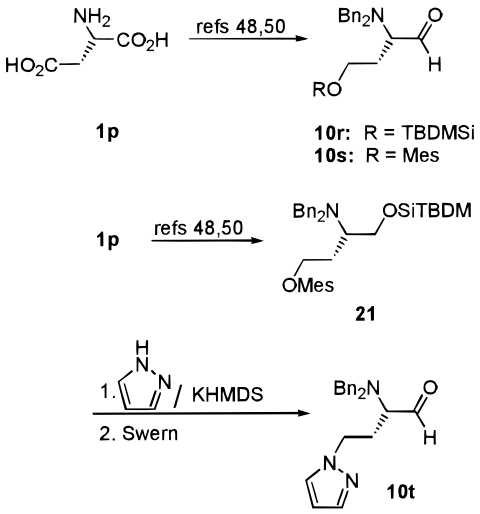
As Table 1 (entries 8, 9) indicates, the synthetic sequence involving ornithine and lysine affords aldehydes **10h**−**i** in which the primary amino groups in the side chain are also protected by two benzyl groups. This occurs at the benzylation stage in a one-pot process. In the case of other amino acids **1** having functional groups in the side chain, additional steps involving protection and/or functional group manipulation allow for synthetically interesting diversity, e.g., tryptophanal (**10k**). Another case is serinal **10m** which is accessible from serine **1l** as shown below. A variation of this sequence has been reported in which N,N-dibenzylation of serine methyl ester is performed under slightly different conditions ($BnBr/NaHCO_3$), leading to the methyl ester analogue of **17**.[45] Silylation, $LiBH_4$-induced reduction and Swern oxidation then afford **10m** in enantiomerically pure form.[45] Similarly, threonine (**1m**) has been used as the starting material for aldehydes **10n**−**o**.[46] Although in principle allo-threoninal **10p** should be accessible from allo-threonine **1n**, this particular amino acid has not been subjected to the usual synthetic sequence because of its high cost. Therefore, a simple synthesis of aldehyde **10p** was devised based on a stereoselective reaction of threoninal **10o**[46] (section IIB).



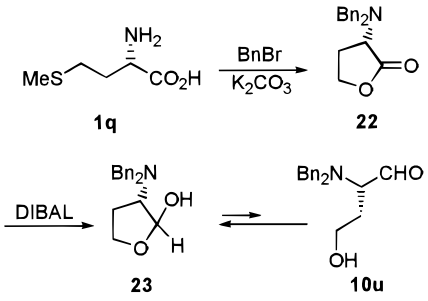
In the case of glutamic acid **1o** with the ultimate formation of aldehyde **10q**, the carboxy function in the side chain was reduced and the resulting primary hydroxy group selectively protected by silylation.[47]



Related is the conversion of aspartic acid **1p** into the *N*,*N*-dibenzylamino aldehydes **10r**,**s**.[48,50] Compound **21** is also accessible from aspartic acid.[48,50] It is a synthetically useful building block because various nucleophiles react at the mesylate function to produce new precursors of hitherto unknown *N*,*N*-dibenzylamino aldehydes. For example, a variety of heterocycles such as pyrazole can be introduced (cf **10t**).[50] Chain extension by the reaction with cuprates or KCN is also possible.[50]

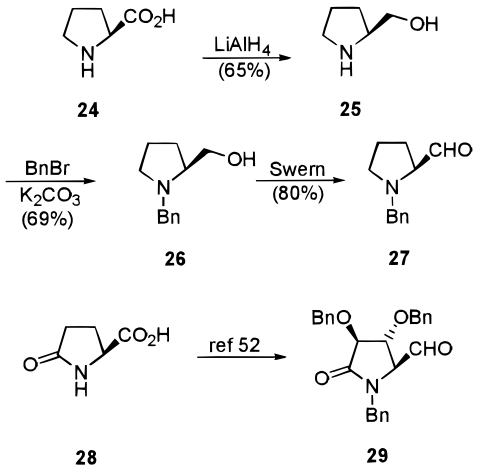


In some cases, the functionality in the side chain of the *N*,*N*-dibenzylamino aldehyde participates in yet other ways. For example, benzylation of methionine **1q** leads in a one-pot reaction to lactone **22**.[51] This interesting compound can be reduced to the lactol **23**, which is nothing but homoserinal **10u**. Although the equilibrium lies completely on the side of the lactol **23**, the compound undergoes diastereoselective Grignard-type reactions.[51] Of course, aldehyde **10u** is related to the O-protected forms **10r**,**s**, which were prepared from aspartic acid.[48−50]

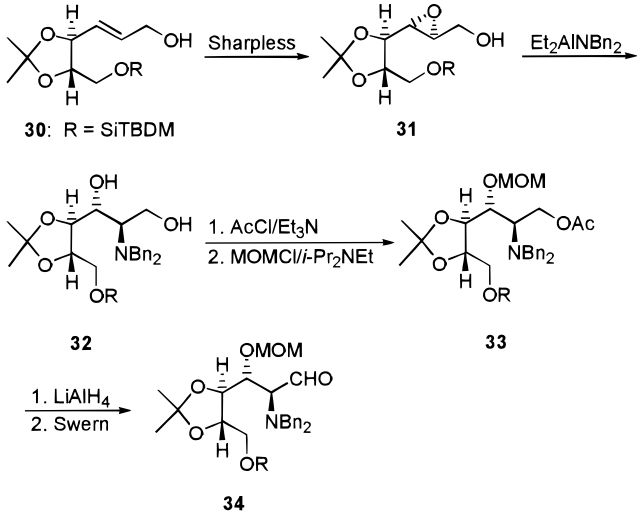


Amino acids containing a secondary amino function can be converted into the corresponding aldehydes having only one protective benzyl group at nitrogen. Examples are aldehydes **27**[32] and **29**[53a] prepared from proline **24** and pyroglutamic acid **28**, respectively. A structurally related aldehyde prepared from serine has also been described.[53b]

Because of the enormous synthetic potential of *N*,*N*-dibenzylamino aldehydes as chiral building blocks (section IIB), it appeared attractive to develop complementary methods of preparation which are based on

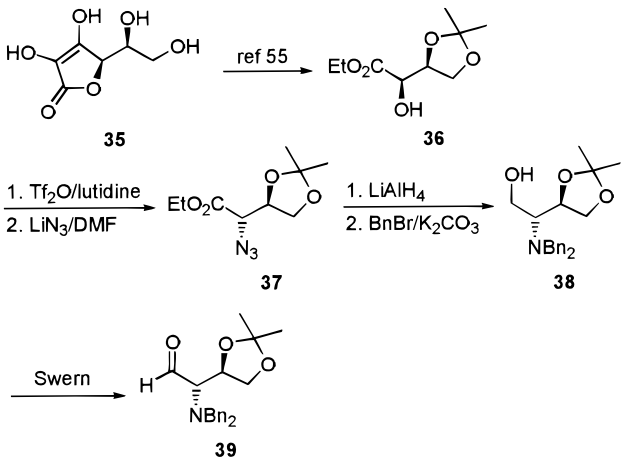


chiral starting materials other than α-amino acids. Indeed, several cases have been reported. The first one concerns the preparation of aldehyde **34** starting from compound **30** which in turn is accessible in enantiomerically pure form from diethyl *L*-tartrate.[54] This example is important not only because aldehyde **34** is a useful building block in the total synthesis of (+)-castanospermine and (+)-1-epicastananospermine (see section IIB); but it also suggests that a fairly wide variety of *N*,*N*-dibenzylamino aldehydes having additional functional groups should be accessible in both enantiomeric forms from allylic alcohols using the Sharpless epoxidation followed by regioselective ring opening and Swern or Markó oxidation.

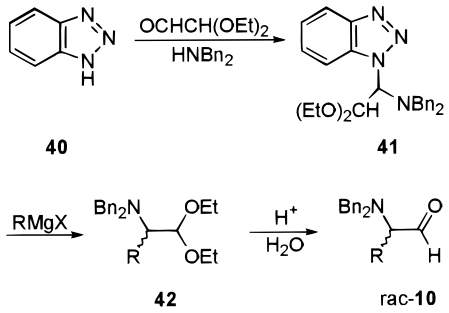


In another study, vitamin C (**35**) served as the starting material in the preparation of the *N*,*N*-dibenzylamino aldehyde **39**,[55] which was used as a chiral building block in the synthesis of side chain truncated analogues of *N*-acetylneuraminic acid (section IIB).

Finally, the Katritzky method for the synthesis of *racemic N*,*N*-dibenzylamino aldehydes **10** (and alternatively protected forms) based on the leaving group ability of benzotriazole **40** is worthy of note.[56] If an



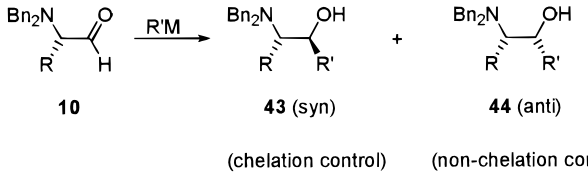
enantioselective version could be developed, many new perspectives would evolve.



B. Nonchelation Controlled Addition and Cycloaddition Reactions

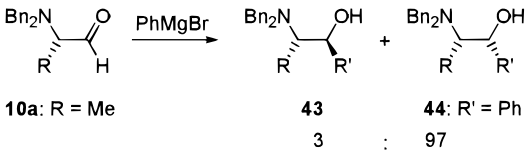
1. Achiral Reagents

In this section, the reactions of common achiral organometallic reagents with aldehydes **10** are summarized. Adducts **43** are the result of chelation control, whereas the diastereomers **44** constitute the nonchelation controlled products. In many studies they are designated as syn and anti adducts, respectively.



The first reaction of an *N*,*N*-dibenzylamino aldehyde to be studied was the Grignard addition of phenylmagnesium bromide to alaninal (**10a**).[21] Because similar reactions using α-alkoxy aldehydes such as α-benzyloxy propanal had been known to occur nonselectively with formation of 2:1 mixtures of chelation and nonchelation controlled adducts,[11] there was little reason to believe that aldehyde **10a** would display a high degree of diastereoselectivity. Nevertheless, it might be argued that a tertiary amino group is a better donor ligand for Mg(II) than an ether moiety and that compounds **10** should therefore show pronounced chelation control in Grignard-type reactions. These speculations turned out

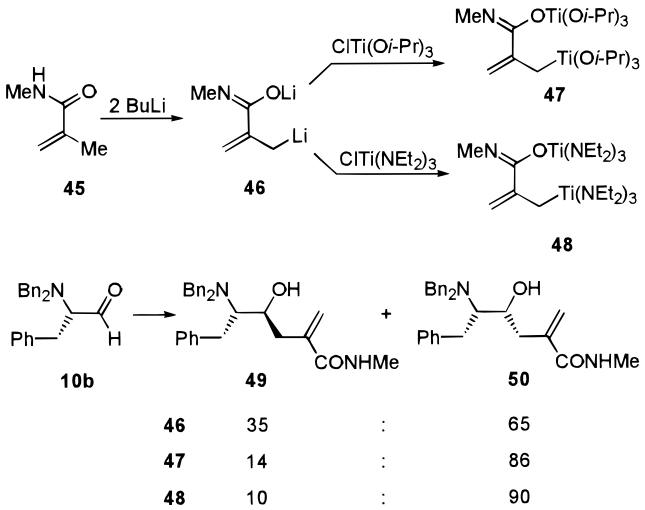
to be false. Experimentally, it was gratifying to observe essentially a single diastereomer in the reaction of aldehyde **10a** with PhMgBr. However, the product was not **43** (R = Me; R′ = Ph) having the syn configuration, but rather the nonchelation controlled adduct **44** (R = Me; R′ = Ph) with the anti configuration resulting from attack at the Re-face of the aldehyde[21] (Table 2, entry 7).



Moreover, a variety of other organometallic reagents such as MeLi, MeTi(O*i*-Pr)$_3$, MeCeCl$_2$, and MeMnX likewise react to form the nonchelation controlled product **44** (R = R′ = Me) with high levels of diastereoselectivity[21] (Table 2, entries 1−6). Even the cuprate Me$_2$CuLi, which is known to undergo chelation controlled additions to α-amino aldehydes **2**[9a] and chiral *β*-alkoxy aldehydes,[57] affords product **44** (R = R′ = Me) preferentially. In practice it usually suffices to employ the conventional reagents RLi or RMgX.[21,27] In further experiments it was demonstrated that nonchelation control is quite general for a wide variety of different *N*,*N*-dibenzylamino aldehydes and various organometallic reagents and metal-free reaction partners. Table 2 shows typical examples; additional examples are reported in the cited literature.

In those cases in which the organolithium or magnesium reagent is exceptionally reactive and therefore somewhat less diastereoselective, control of carbanion selectivity can be achieved by transmetalation using titanating agents according to Scheme 1 (Table 2, entries 12, 39, 58, 64, 67, 93, 109). For example, CH$_2$=CHCH$_2$MgCl is highly reactive and reacts with aldehyde **10b** to deliver the nonchelation controlled adduct with only 72% diasteroselectivity, whereas prior treatment of the reagent with ClTi(NEt$_2$)$_3$ boosts selectivity to 93%.[21,27] Allylindium reagents in water also show relatively low degrees of nonchelation control (ds = 66−86%) (Table 2, entries 21, 40), unless La(OTf)$_3$ is used as a promoter (Table 2, entry 69). In contrast, similar reactions in water using zinc usually occur with high levels of nonchelation control (e.g., Table 2, entries 22, 24, 41, 59, 66, 72, 112). In the case of CH$_2$=C(CO$_2$Me)CH$_2$-Br/Zn, the products can be cyclized to α-methylene lactones, which react stereoselectively with cuprates.[67b] The metal-free Baylis−Hillman reaction of aldehydes **10** constitutes another case of mediocre diastereoselectivity[72] (Table 2, entry 33).

An informative example illustrating the power of metal, ligand, and protective group tuning pertains to the lithium reagent **46** which reacts unselectively with **10b** to afford a mixture of adducts **49**/**50**.[3,27] Titanation[18] with ClTi(O*i*-Pr)$_3$ or ClTi(NEt$_2$)$_3$ generates reagents **47** and **48**, which results in diastereoselectivities of 86% and 90%, respectively.[3,27,32] In contrast, the Ti reagent **47** adds to the analogous Boc-protected amino aldehyde **2** (R = Bn; R″ = *t*-Bu) with only 60% diastereoselectivity.[81] Thus, it is the proper combination of reagent and protective group tuning that ensures maximum diastereoselectivity. Adducts of the type **50** (or **49**) can be lactonized and hydrogenated stereoselectively, resulting in compounds which can be viewed as products of homoaldol reactions.[32] Other forms of metalated homoenolates also react diastereoselectively with aldehydes **10** (Table 2, entries 14, 25, 32, 55, 65, 66, 72, 79, 112). The products of such reactions are of interest in a variety of areas, including peptidomimetics.



In view of the high number of reactions performed, not every single product was checked for enantiomeric purity. However, in the early work a fair number of reactions involving a wide variety of different reagents ranging from such basic compounds as RLi and Li enolates to such Lewis acidic reagents as TiCl$_4$/Me$_2$Zn and TiCl$_4$/enolsilanes (section IIC) were in fact scrutinized for possible racemization.[21,32] In all cases, > 98% enantiomeric purity was observed. This means that in the synthesis and reactions, configurational integrity is maintained. Nevertheless, it is wise to check this routinely, because the nature of the aldehyde and the type of reagent may differ considerably from case to case. Should partial racemization occur, the optimization of the reaction conditions may help. An instructive example concerns the nonchelation controlled addition of sulfur ylides CH$_2$=SMe$_2$, prepared in situ from Me$_3$S$^+$I$^-$ and NaH, to aldehydes **10** with preferential formation of epoxides **52**.[19] In this study, not all of the products were checked for optical purity. Indeed, later investigations using **10b** revealed that a considerable amount of racemization had occurred.[27,28] The reason for this untypical behavior remains unclear. However, the problem of obtaining epoxides **52** diastereoselectively in enantiomerically pure form was solved by optimizing the reaction. Upon working under salt-free conditions at −20 °C to room temperature (48 h), epoxides **51b**/**52b** (R = Bn) were obtained in a ratio of 30:70, the enantiomeric purity being > 99%.[27] The reason for the somewhat lower

Table 2. Typical Nonchelation Controlled Reactions of *N,N*-Dibenzylamino Aldehydes Using Achiral Reagents

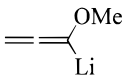
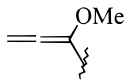
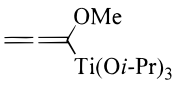
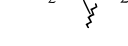
entry	aldehyde	reagent	R' in **43**/**44**	yield (%)	**43** : **44**	ref(s)
1	**10a**	MeMgI	Me	87	5 : 95	21,27
2	**10a**	MeLi	Me	91	9 : 91	21,27
3	**10a**	$MeTi(Oi\text{-}Pr)_3$	Me	78	3 : 97	21,27
4	**10a**	Me_2CuLi	Me	80	25 : 75	21,27
5	**10a**	$MeCeCl_2$	Me	70	10 : 90	21,27
6	**10a**	MeMnX (X = Cl, Br, I)	Me	>85	5 : 95	27,58
7	**10a**	PhMgBr	Ph	85	3 : 97	21,27
8	**10a**	EtMgBr	Et	85	5 : 95	21,27
9	**10a**	*i*-PrMgBr	*i*-Pr	75	<3 : >97	21,27
10	**10a**	*t*-BuMgBr	*t*-Bu	72	5 : 95	21,27
11	**10a**	*t*-BuLi	*t*-Bu	88	<3 : >97	21,27
12	**10a**	$CH_2{=}CHCH_2Ti(NEt_2)_3$	$CH_2{=}CHCH_2$	74	4 : 96	21,27
13	**10a**			94[a]	5 : 95	59
14	**10a**		$MeOC{\equiv}CCH_2$	53[b]	6 : 94	60
15	**10a**			>80	9 : 91	61
16	**10a**			49	13 : 87	27,62
17	**10a**	$ClCH_2Li$	$ClCH_2$	72[c]	5 : 95	63
18	**10a**	$ICH_2Cl/Et_2Zn/$ 	—[d]	85	16 : 84	64
19	**10a**	CH_2I_2/Sm	ICH_2	72[e]	10 : 90	65
20	**10a**	$Me_2C(CN)Li$	$Me_2C(CN)$	85	4 : 96	66
21	**10a**	$CH_2{=}CHCH_2Br/In/H_2O$	$CH_2{=}CHCH_2$	50	23 : 77	41
22	**10a**	$CH_2{=}CHCH_2Br/Zn/H_2O$	$CH_2{=}CHCH_2$	95	14 : 86	67
23	**10a**	$PhSCH_2Li$	$PhSCH_2$	85	6 : 94	40
24	**10a**	$Me_2C{=}CHCH_2Br/Zn/H_2O$	$Me_2C{=}CHCH_2$	90	4 : 96	67
25	**10a**	$CH_2{=}C(CO_2Et)CH_2Br/CrCl_2$	$CH_2{=}C(CO_2Et)CH_2$	?	10 : 90	68
26	**10a**	$MeNO_2/TBAF \bullet x\ H_2O$	O_2NCH_2	88	20 : 80	69
27	**10a**	$Me_3S^+I^-/NaH$	—[d]	73	13 : 87	19
28	**10a**	$Me_2S{=}CH_2$ (salt-free)	—[d]	80	30 : 70	27
29	**10a**	$MeAs^+Ph_3/KN(SiMe_3)_2$	$Ph_3P^+AsCH_2$	78[f]	<5 : >95	19
30	**10a**	$Me_3SiCN/ZnBr_2$	CN	74	5 : 95	70
31	**10a**	$Me_3SiCN/LiClO_4$	CN	75	22 : 78	71
32	**10a**	$Cl_2(Oi\text{-}Pr)TiCH_2CH_2CO_2Me$	—[g]	45	7 : 93	43
33	**10a**	$CH_2{=}CHCO_2Me/DABCO$		71[h]	28 : 72	72

Table 2. (Continued)

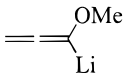
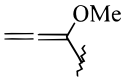
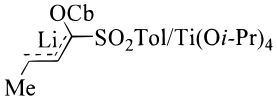
entry	aldehyde	reagent	R' in **43**/**44**	yield (%)	**43** : **44**	ref(s)
34	**10b**	MeMgI	Me	85	8 : 92	21,27
35	**10b**	MeMnBr	Me	91	<1 : >99	27,58
36	**10b**	PhMgBr	Ph	84	3 : 97	21,27
37	**10b**	PhC≡CLi	PhC≡C	72	<4 : >96	21,27
38	**10b**	CH_2=$CHCH_2MgCl$	CH_2=$CHCH_2$	82	28 : 72	21,27
39	**10b**	CH_2=$CHCH_2Ti(NEt_2)_3$	CH_2=$CHCH_2$	81	7 : 93	21,27
40	**10b**	CH_2=$CHCH_2Br/In/H_2O$	CH_2=$CHCH_2$	70	14 : 86	41
41	**10b**	CH_2=$CHCH_2Br/Zn/H_2O$	CH_2=$CHCH_2$	90	10 : 90	67
42	**10b**	*t*-$BuMe_2SiOP(OEt)_2/TiCl_4$	$(EtO)_2P(O)$	86	<2 : >98	73
43	**10b**	$MeNO_2$/TBAF • x H_2O	O_2NCH_2	63	9 : 91	69
44	**10b**	Me_3SiCN/BF_3 • OEt_2	CN	74	5 : 95	70
45	**10b**	$Me_3SiCN/ZnBr_2$	CN	79	5 : 95	70
46	**10b**	$Me_3SiCN/SnCl_4$	CN	67	13 : 87	70
47	**10b**	$Me_3SiCN/LiClO_4$	CN	74	10 : 90	71
48	**10b**	$Me_3SiCN/Yb(CN)_3$	CN	91	28 : 72	74
49	**10b**			94[a]	5 : 95	59
50	**10b**	$ClCH_2Li$	$ClCH_2$	70-96[c]	11 : 89 16 : 84	28,29,35, 37,63
51	**10b**	$Ph_2P(O)CH_2Li$	$Ph_2P(O)CH_2$	50	20 : 80	75
52	**10b**	$BrCH_2Li$	$BrCH_2$	81	10 : 90	63
53	**10b**	$Me_2CHCH_2N(NO)CH_2Li$	$Me_2CHCH_2N(NO)CH_2$	83	20 : 80	76
54	**10b**	CH_2I_2/Sm	ICH_2	70[e]	10 : 90	65
55	**10b**	$Cl_2(O$*i*-$Pr)TiCH_2CH_2CO_2Et$	—[g]	60-95	<8 : >92	43,77
56	**10c**	MeMgI	Me	87	5 : 95	21,27
57	**10c**	PhMgBr	Ph	69	9 : 91	21,27
58	**10c**	CH_2=$CHCH_2Ti(NEt_2)_3$	CH_2=$CHCH_2$	83	4 : 96	21,27
59	**10c**	CH_2=$CHCH_2Br/Zn/H_2O$	CH_2=$CHCH_2$	84	11 : 89	67
60	**10c**	$Me_3SiCN/ZnBr_2$	CN	81	5 : 95	70
61	**10d**	MeMgI	Me	85	10 : 90	21,27
62	**10d**	$MeTi(O$*i*-$Pr)_3$	Me	80	6 : 94	21,27
63	**10d**	PhMgBr	Ph	84	3 : 97	21,27
64	**10d**	CH_2=$CHCH_2Ti(NEt_2)_3$	CH_2=$CHCH_2$	81	3 : 97	21,27
65	**10d**	$Cl_2(O$*i*-$Pr)_2TiCH_2CH_2CO_2Me$	—[g]	65	9 : 91	43
66	**10d**	CH_2=$C(CO_2Me)CH_2Br/La(OTf)_3/Zn/H_2O$	CH_2=$C(CO_2Me)CH_2$	88	9 : 91	78
67	**10d**		MeCH=CHC(O)	83[i]	<1 : >99	79

Table 2. (Continued)

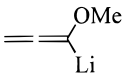
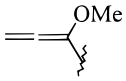
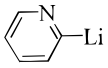
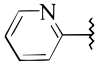
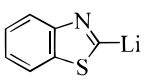
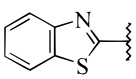
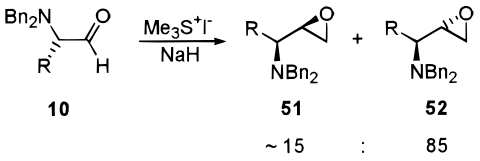
entry	aldehyde	reagent	R' in **43**/**44**	yield (%)	**43** : **44**	ref(s)
68	**10d**	ICH_2Li	ICH_2	80	10 : 90	63
69	**10d**	$CH_2=C(CH_3)CH_2Br/La(OTf)_3/In/H_2O$	$CH_2=C(Me)CH_2$	88	10 : 90	78
70	**10d**	CH_2I_2/Sm	ICH_2	65[e]	10 : 90	65
71	**10e**			93	<1 : >99	27,62
72	**10e**	$CH_2=C(CO_2Me)CH_2Br/Zn/H_2O$	$CH_2=C(CO_2Me)CH_2$	87	<5 : >95	67
73	**10f**	$CH_2=CHCH_2Br/In/H_2O$	$CH_2=CHCH_2$	48	34 : 66	41
74	**10f**	$Me_3SiCN/LiClO_4$	CN	76	<4 : >96	71
75	**10g**	$Me_2CHCH_2CH_2MgBr$	$Me_2CHCH_2CH_2$	>65	?	42
76	**10h**	MeMgI	Me	62	6 : 94	4,27
77	**10h**	*n*-BnMgCl	*n*-Bu	91	5 : 95	27,80
78	**10i**	MeMgI	Me	76	4 : 96	4,27
79	**10k**	$Cl_2(Oi\text{-}Pr)TiCH_2CH_2CO_2Me$	—[g]	28	<10 : >90	43
80	**10l**	EtMgBr	Et	71	<5 : >95	27,46
81	**10l**	$n\text{-}C_{15}H_{31}MgBr$	$n\text{-}C_{15}H_{31}$	79	<5 : >95	27,46
82	**10l**	*t*-BuLi	*t*-Bu	54	12 : 88	27,46
83	**10l**	PhMgBr	Ph	78	7 : 93	4,27
84	**10m**	MeMgBr	Me	85	<5 : >95	45
85	**10m**	*i*-PrMgCl	*i*-Pr	>88	<5 : >95	45
86	**10m**	*n*-PrMgBr	*n*-Pr	74	3 : 97	27,46
87	**10m**	*n*-BuLi	*n*-Bu	30	<5 : >95	45
88	**10m**	$n\text{-BuLi/CeCl}_3$	*n*-Bu	75	<5 : >95	45
89	**10m**	$n\text{-}C_{13}H_{27}MgBr$	$n\text{-}C_{13}H_{27}$	77	6 : 94	4,27
90	**10m**	PhMgBr	Ph	81	3 : 97	27,46
91	**10m**	$CH_2=CHMgBr$	$CH_2=CH$	65	10 : 90	27,46
92	**10m**	$c\text{-}C_3H_5Li$	$c\text{-}C_3H_5$	84	10 : 90	27,46
93	**10m**	$CH_2=CHCH_2Ti(NEt)_3$	$CH_2=CHCH_2$	83	16 : 84	27,46
94	**10m**			90[a]	14 : 86	59
95	**10m**			53	9 : 91	27,62
96	**10m**			67	9 : 91	27,62
97	**10m**			61	14 : 86	27,62
98	**10n**	MeLi	Me	82	48 : 52	27,46
99	**10n**	MeMgI	Me	87	15 : 85	27,46
100	**10n**	Me_2CuLi	Me	82	<5 : >95	27,46
101	**10o**	MeLi	Me	81	65 : 35	27,46
102	**10o**	MeMgI	Me	67	57 : 43	27,46

Table 2. (Continued)

entry	aldehyde	reagent	R' in **43**/**44**	yield (%)	**43** : **44**	ref(s)
103	**10o**	Me_2CuLi	Me	70	9 : 91	27,46
104	**10p**	MeLi	Me	68	26 : 74	27,46
105	**10p**	MeMgI	Me	88	14 : 86	27,46
106	**10p**	$MeTi(Oi\text{-}Pr)_3$	Me	73	7 : 93	27,46
107	**10p**	Me_2CuLi	Me	67	12 : 88	27,46
108	**10u**	MeMgI	Me	72	5 : 95	51
109	**10u**	$MeTi(Oi\text{-}Pr)_3$	Me	71	<2 : >98	51
110	**10u**	PhMgBr	Ph	74	8 : 92	51
111	**27**	MeLi	Me	70	33 : 67	32
112	**39**	$CH_2{=}C(CO_2Et)CH_2Br/Zn/H_2O$	$CH_2{=}C(CO_2Et)CH_2$	87	<1 : >99	55

[a] Product is the result of α-attack on the reagent which is then an acyl anion equivalent (see text). [b] Product is the result of γ-attack on the reagent which is then a homoenolate equivalent. [c] Quenching the reaction at low temperatures results in the production of chlorohydrins, which can be treated with MeLi to form the epoxides **52**. Quenching at higher temperatures also leads to epoxide formation.[63] [d] Products are β-hydroxy arsonium salts which can be converted into epoxides **52** using NaH. [g] Products are lactones resulting from homoaldol addition followed by lactonization. [h] Products are adducts resulting from Baylis–Hillman reaction. [i] Products are the result of formal acyl anion addition.

diastereofacial selectivity under salt-free conditions is not completely clear (section IIB2).

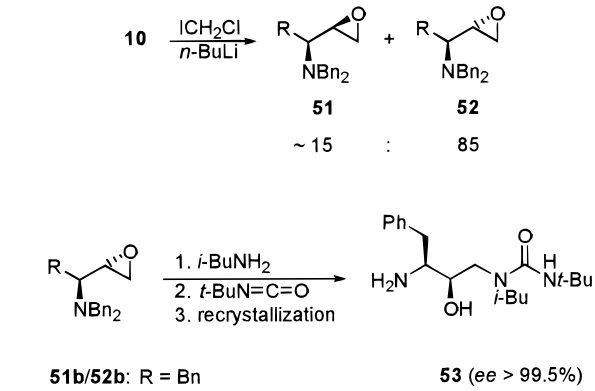


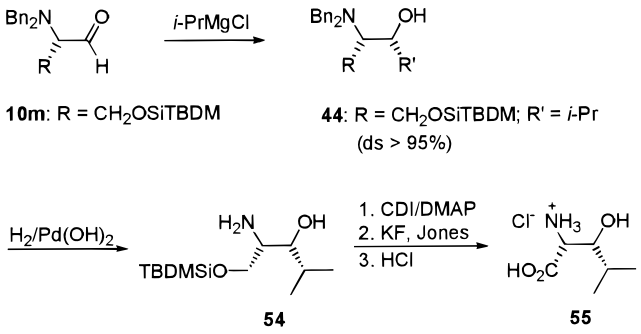
10 **51** **52**

~ 15 : 85

A different way to obtain the same epoxides with considerably higher degrees of diastereoselectivity is based on the reaction of the reagent $PhSCH_2Li$ (Table 2, entry 23) followed by treatment with Meerwein reagent.[40] A third approach was described independently by several groups.[28,29,35,37,63] Accordingly, lithium carbenoids XCH_2Li (X = Cl, Br, I) were reacted with aldehydes **10**, nucleophilic addition occurring at low temperatures with the expected nonchelation control followed by in situ intramolecular S_N2 reaction of the intermediate β-haloalkoxides at higher temperatures. In an impressive industrial process, the reaction was performed on a multikilogram scale without any appreciable racemization.[29,36,37] The adduct derived from *L*-phenylalanine served as an intermediate in the synthesis of an HIV protease inhibitor. Thus, compounds of the type **53** were readily obtained from the mixture **51b**/**52b**, separation of the diastereomers being possible by simple recrystallization at that stage. Incorporation into peptides completed the synthesis of HIV protease inhibitors. Another route to epoxides **52** is based on the combination of reagents ICH_2Cl/Et_2Zn in the presence of thio-tetrahydrofuran (Table 2, entry 18).

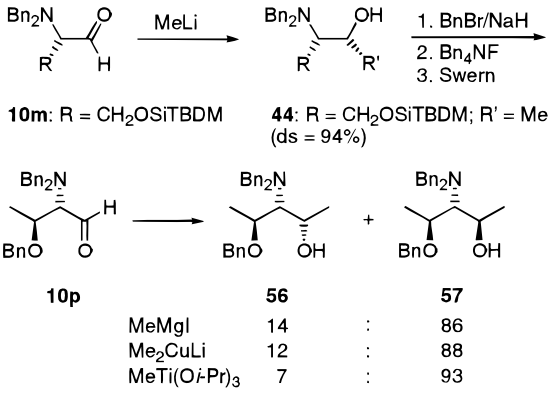
Many other applications of nonchelation controlled addition reactions of aldehydes **10** with simple organometallic reagents have been described. For example, the reaction of serinal **10m** with *i*-PrMgCl affords adduct **44** (R = *t*-$BuMe_2SiOCH_2$; R′ = *i*-Pr), which was readily transformed into (2*S*,3*S*)-β-hydroxyleucine **55**, a compound that is not easily prepared by other means.[45]



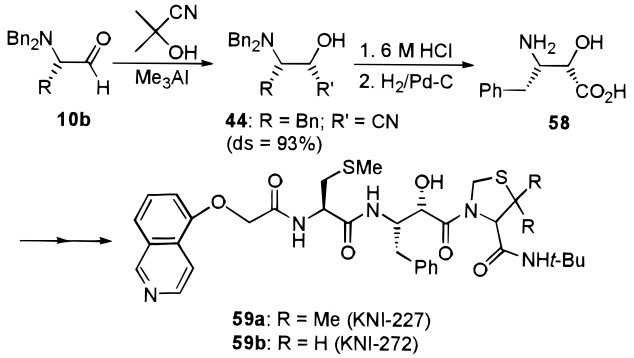


In another application of the same aldehyde **10m**, the adduct **44** (R = *t*-$BuMe_2SiOCH_2$; R′ = Me) was O-benzylated, desilylated, and oxidized to afford enantio- and diastereomerically pure allo-threonine

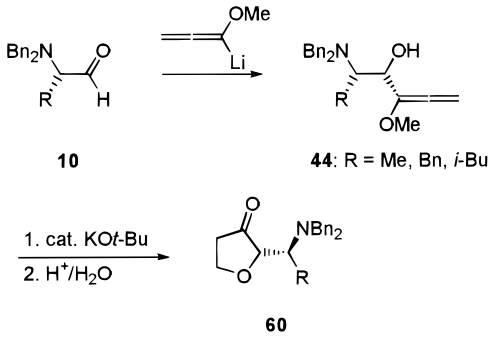
10p,[3,27,46] a compound that theoretically can also be prepared from expensive allo-threonine. The aldehyde **10p** reacts with various methylmetal reagents to form adduct **57** preferentially. This is the diastereomer expected on the basis of the general behavior of *N*,*N*-dibenzylamino aldehydes, but in the case of Me_2CuLi may actually involve 1,3-chelation with the alkoxy moiety,[27] as is known in cuprate reactions of α-methyl-β-benzyloxy aldehydes.[11,57]



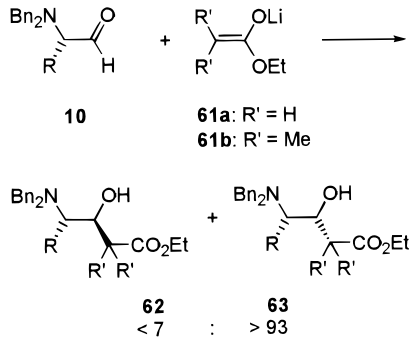
Cyanohydrins derived from *N*,*N*-dibenzylamino aldehydes **10** are synthetically useful intermediates due to the versatility of the cyano group.[70] The original procedure for their preparation was based on trimethylsilylcyanide Me_3SiCN, a reagent readily accessible from Me_3SiCl and KCN/KI.[82] In the presence of stoichiometric amounts of $ZnBr_2$ (catalytic amounts were not tested), diastereoselectivity of cyanohydrin formation in favor of nonchelation controlled adducts **44** (R′ = CN) amounts to 95% (Table 2, entries 30, 45, 60). Other Lewis acids or $Yb(CN)_3$ itself can also be used but are often not as selective (Table 2, entries 31, 44, 46−48, 74). It is possible to replace Me_3SiCN by acetone cyanohydrin (which has been claimed to be more industrially benign), provided that Me_3Al or $EtAlCl_2$ are used as Lewis acids.[83] Diastereoselectivities of 90−93% are common, as in the synthesis of cyanohydrin **44** (R = Bn; R′ = CN), which was converted into (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid (**58**), a key component of the HIV protease inhibitors KNI-227 and KNI-272 (**59a**,**b**).[83]



In another interesting application, 1-lithio-1-methoxy-allene was added to aldehydes **10** with 80−99% nonchelation control and excellent regioselectivity in favor of α-attack.[59] Thus, the reagent serves as an acyl anion equivalent. The adducts are precursors of synthetically versatile 3(2*H*)-dihydrofuranones **60** which can be regarded as protected analogues of muscarone.[59] Nucleophiles such as MeMgBr or $NaBH_4$ react stereoselectively at the carbonyl function of compounds **60**.[59] In situ titanation[18] of the lithium reagent with $ClTi(Oi\text{-}Pr)_3$ generates the titanium analogue which shows the opposite regioselectivity in reactions with aldehydes **10**, i.e., nonchelation controlled adducts (methoxypropargyl alcohols) resulting from γ-attack are formed (Table 2, entry 14). These kinds of products can be considered to be homoaldol adducts and, in fact, have been used as such.[60]

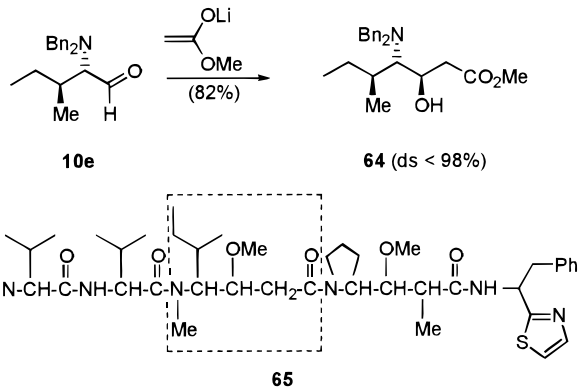


The nonchelation controlled aldol reaction of aldehydes **10** also extends their synthetic utility considerably.[21,27] Even the reactive lithium enolate **61a** derived from ethyl acetate results in the preferential formation of aldols **63**, which means that modulation of reactivity and selectivity via titanation or other transmetalation is not necessary.



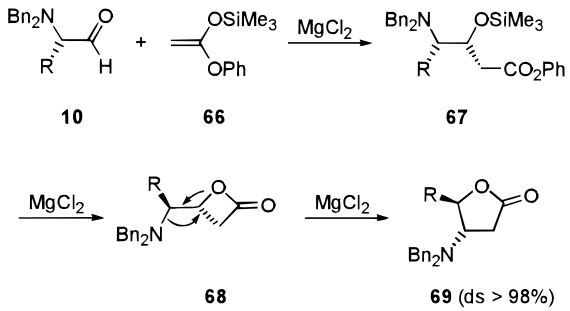
An application is the aldol reaction of isoleucinal **10e** which affords adduct **64** exclusively.[27,40] This compound has the correct absolute and relative configuration to qualify as a building block in the synthesis of dolastatin-10 (**65**), a marine natural product with unusually high antineoplastic activity.[84] The reaction of the Li enolate with the traditional Cbz-protected aldehyde **2** derived from isoleucine occurs unselectively with formation of a 3:2 mixture of diastereomers (33% yield).[84] Because similar components are found in many other natural products (e.g., didemnin A and B),[85] it is likely that the importance of aldol reactions of *N*,*N*-dibenzylamino aldehydes **10** will increase in the future. Indeed, in the synthesis of a peptidomimetic analogue of the binding domain of rapamycin, the Li enolate derived from a functionalized methyl ketone was added to (*R*)-**10a** (prepared from unnatural D-alanine) with

exclusive formation of the corresponding nonchelation controlled aldol adduct.[86]

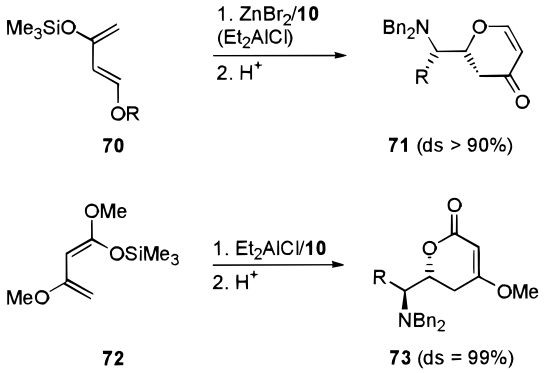


Early attempts to perform $TiCl_4$-mediated Mukaiyama aldol additions of $CH_2{=}C(OMe)OSiMe_3$ resulted mainly in the formation of the aldol condensation products,[3,21] compounds that can be prepared more easily by Horner−Wittig reactions[24] (section V). However, $Me_2C{=}C(OMe)OSiMe_3/TiCl_4$ reacted with aldehydes **10a**, **c**, **d** to provide the aldol adducts with a surprising 95−97% nonchelation control.[27,32] In an attempt to perform $MgCl_2$-catalyzed Mukaiyama-type aldol additions of *O*-phenyl-*O*-silylketene ketal **66** to aldehydes **10**, the unexpected formation of β-amino-γ-lactones **69** in diastereo- and enantiomerically pure form was observed.[51] This unusual transformation is the result of three consecutive $MgCl_2$ catalyzed reactions in one pot: nonchelation controlled aldol addition with formation of adducts **67**, β-lactone formation (**68**), and stereospecific dyotropic rearrangement with double inversion of configuration. β-Amino-γ-lactones are of interest in the synthesis of unusual amino acids and amino sugars (e.g., ristosamine). In the case of aldehyde **10e** derived from isoleucine, a lactone having three contiguous stereocenters with perfect control of relative and absolute configuration is formed.[51] Upon using $ZnBr_2$ or $SnCl_2$ the reaction can be stopped at the stage of the aldol adducts **67** (ds = 95%, 74%, and 64% yield, respectively).[27] In a related two-step sequence, the Li enolates of thioesters derived from isobutyric acid were added to **10a**, resulting in the β-lactone analogues of **68**, which were then subjected to $MgBr_2$-mediated dyotropic rearrangement.[87] Later studies devoted to a variety of other Mukaiyama aldol reactions of aldehydes **10** showed that *O*-alkyl-*O*-silylketene ketals in the presence of stoichiometric amounts of $EtAlCl_2$ provide the normal adducts of the type **63** with excellent nonchelation control (ds = 94−99%).[88] Similar results can be obtained by using *catalytic* amounts of $LiClO_4$ in CH_2Cl_2 (which is much more convenient than traditional 0.5 M solutions of $LiClO_4$ in ether), resulting in >98% nonchelation control.[89]

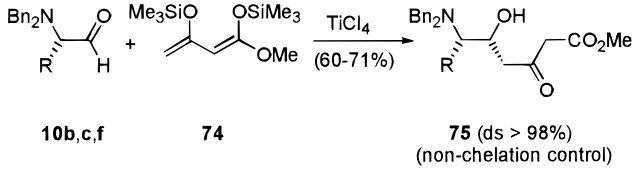
The Lewis acid mediated reaction of siloxy-butadiene derivatives **70** or **72** with aldehydes **10** provides hetero Diels−Alder adducts with excellent nonchelation control (cf. **71** and **73**).[3,27,90,91] Either Et_2AlCl or $ZnBr_2$ are very effective. Mechanistically, either a two-step aldol/Michael addition sequence or a genuine [2 + 4]-cycloaddition is possible, the latter being



more likely. The reactions can also be carried out in 0.5 M solutions of $LiClO_4$ in ether[92] or under high pressure (5 kbar) in the absence of Lewis acids.[93]

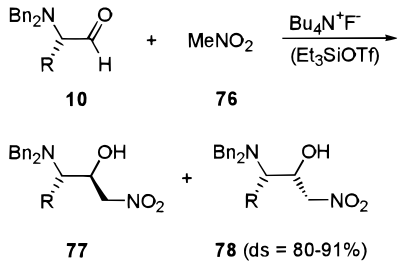


$TiCl_4$ was not tested in these reactions. However, reagent **74** which is related to **72** was shown to undergo a Mukaiyama-type aldol addition to aldehydes **10b**, **c**, and **f** with complete nonchelation control and without any appreciable racemization.[94a] No product resulting from a hetero Diels−Alder reaction mode was observed. The adducts **75** are valuable intermediates in a concise synthesis of functionalized 1,3-diols simply by performing $Bu_3B/NaBH_4$ mediated reduction of the ketone function of compounds **75** (ds > 96%).

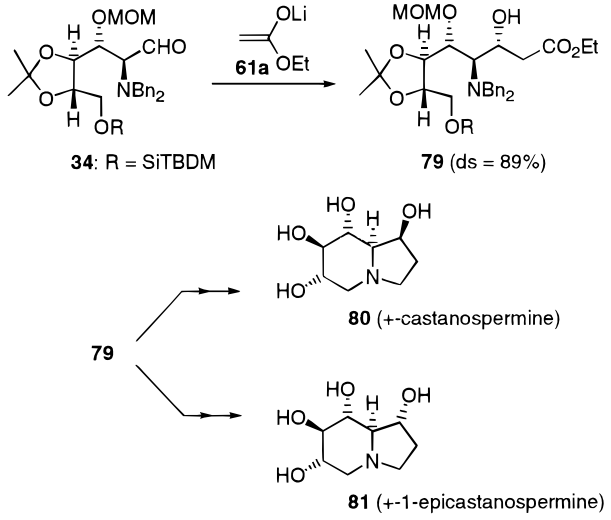


The nitro-aldol or Henry reaction has also been applied successfully to *N*,*N*-dibenzylamino aldehydes **10**.[69] Using $Bu_4N^+F^-{\cdot}xH_2O$ as the catalyst in the presence or absence of Et_3SiOTf, adducts **78** were obtained in good yield, the degree of nonchelation control depending upon the particular reaction conditions. This method has been extended to nitroethane and homologues,[69] reactions in which simple diastereoselectivity is also relevant (section IIB3). Since the nitro group is a versatile function, many synthetic avenues for further transformations can be envisioned.[69,95]

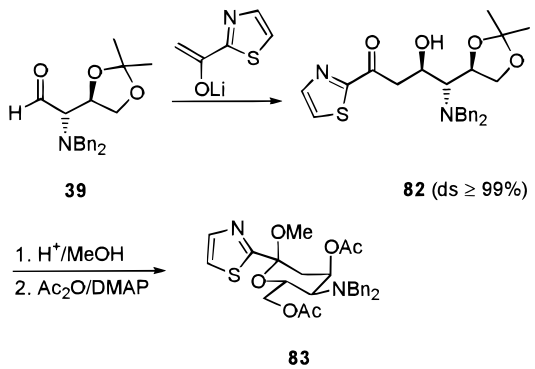
N,*N*-Dibenzylamino aldehydes derived from chiral precursors other than α-amino acids (section IIA) have also been used in nonchelation controlled C−C bond formation. The first example to be reported concerns the addition of enolate **61a** to aldehyde **34**.[54]



The major diastereomer **79** was then used as an intermediate in a noncarbohydrate-based synthesis of (+)-castanospermine (**80**) and (+)-1-epicastanospermine (**81**).[54] Compound **80** is a nitrogen-containing analogue of glucopyranoside and has been shown to exhibit high anticancer, antiviral, and antiretroviral activities, besides being a potent inhibitor of various α- and *β*-glucosidases including glucosidases I of glycoprotein processing.[96]

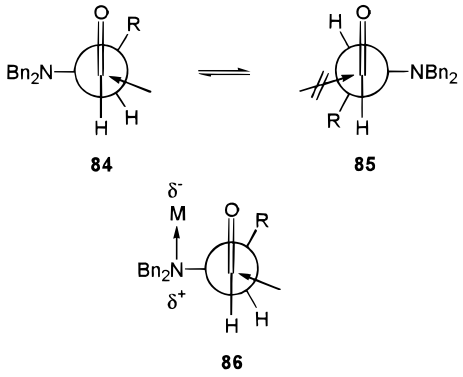


A more recent example in which an *N*,*N*-dibenzylamino aldehyde derived from a non-amino acid route was successfully used in a nonchelation controlled process concerns the aldol reaction of **39** with the Li enolate derived from 2-acetylthiazole, resulting in the exclusive formation of adduct **82**.[55] The product was treated with 20% methanolic HCl and then peracetylated to afford the *N*,*N*-dibenzyl protected amine **83**, which embodies the sialic acid core. This type of approach was modified to include the synthesis of epimeric derivatives based on the diastereomer of aldehyde **39** and a related *N*,*N*-dibenzyl amino ketone.[55]



2. Models for Nonchelation Control

It is abundantly clear that many different types of achiral reagents undergo nonchelation controlled reactions with *N*,*N*-dibenzylamino aldehydes, the degree of diastereoselectivity usually being remarkably high. In view of the fact that nonchelation control in reactions of the analogous α-benzyloxy aldehydes is difficult to achieve because of the participation of various conformers having similar reactivity,[11] the present results are surprising. What is the reason for this unusual intrinsic property? Formally, the experimental results concerning preferential attack at the *re* face of the aldehydes are in line with the Felkin−Anh model, which was originally developed to explain the stereochemical outcome of reactions of chiral α-chloro and α-alkoxy carbonyl compounds.[97,98] Accordingly, the most reactive conformer of such compounds is the one in which the C−Cl or C−O *σ*-bond is aligned with the *π*-system of the carbonyl moiety in such a way that π^*-σ^*_{C-Cl} or π^*-σ^*_{C-O} conjugation is maximized, causing the highest degree of LUMO lowering. Such conformers have the highest reactivity, attack of the nucleophilic reagent then occurring anti to the chloro or alkoxy moiety in a Bürgi−Dunitz trajectory. Two electronically similar conformers are relevant, one of which reacts faster because of steric reasons. Upon applying this traditional model to *N*,*N*-dibenzylamino aldehydes **10**, conformers **84** and **85** need to be considered.[3,27] Obviously, steric interaction between the incoming reagent and the R-group at the stereogenic center is lowest in the case of **84**, which would be in accord with nonchelation control.



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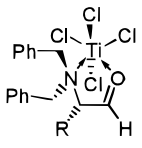
The problem with this interpretation is the fact that ab initio quantum mechanical calculations do not indicate pronounced LUMO lowering induced by the amino group, because the σ^*_{C-N} orbital is relatively high lying, in contrast to σ^*_{C-Cl} or σ^*_{C-O}.[3,20b,99] It was then speculated that in organometallic reactions of aldehydes **10** the metal may coordinate to the amino function without undergoing chelation to the carbonyl group as in **86**. This could have a dramatic influence on the electronic nature of the amino group. Consequently, using BH_3 as a Lewis acid and H_2NCH_2CHO as a model aldehyde, various conformers of the corresponding amine complex were calculated. The result was considerable LUMO lowering associated with the carbonyl function, caused by drastic lowering of the σ^*_{C-N} orbital.[3,20b,99] Thus,

this modified version of the Felkin−Anh model appears reasonable. This may actually be the reason why certain metal-free reactions show relatively low degrees of nonchelation control (Table 2). But why does the reaction not follow a chelation mode? (See section IIC for exceptions.) Indeed, even the strongly Lewis acidic $TiCl_4$, which is normally capable of bidentate like ligation with formation of octahedral complexes, often results in extremely high levels of nonchelation control in reactions of aldehydes **10**!

Steric inhibition of chelation has been proposed to account for these seemingly strange results.[3,27] Indeed, whereas chiral α-benzyloxy aldehydes and ketones react with $TiCl_4$ or $SnCl_4$ to form discrete structurally well-defined five-membered chelates as characterized by ^1H- and ^{13}C NMR spectroscopy and X-ray crystallography,[11,100] *N*,*N*-dibenzylamino aldehydes **10** fail to do so. Instead, they react with $SnCl_4$ or $TiCl_4$ to form at least three different species in solution, even at low temperatures as shown by ^{13}C NMR spectroscopy.[70] Moreover, in the case of **10b**/$SnCl_4$, a ^{119}Sn−NMR study showed the existence of three species as judged by the appearance of three signals at −591, −604, and −629 ppm at −80 °C.[101] Unfortunately, the complexes could not be separated or identified unambiguously. The reason the hypothetical chelate **87** is not the only species (it may be one of them), has to do with steric factors. There appears to be too much steric crowding in the chelate. Thus, depending upon the nature of the nucleophile (which also needs to find room near the carbonyl group in the transition state), either chelate **87** or acyclic adducts such as **88** (or 2:1 complexes) participate in the reaction. In the case of RMgX, RLi, RTi(O*i*-Pr)$_3$, Li enolates and other reagents in the absence of additional Lewis acids, steric inhibition of chelation is also operating, which means that alternative species such as those defined by the Felkin−Anh model can effectively compete for the nucleophile.



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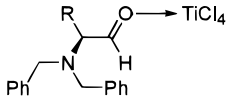

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An alternative explanation is based on ground-state arguments.[3,20,27] Force-field calculations of alaninal **10a** predict that the conformer shown in Figure 1a, which is slightly different from the Felkin−Anh geometry **84**, represents the energetically most stable form.[3,27] Small conformational changes involving the benzyl groups result in minor energy differences. It is clear that the backside (i.e., *si* side) is sterically shielded. Thus, assuming that the ground-state conformation correlates with the geometry in the transition state, attack from the front side (i.e., *re* side) should dominate. Such a process would be in line with the observed stereochemical outcome. Upon rotating the formyl moiety by about 180 °C, the opposite π-face is exposed, but this results in a conformer which is about 2 kcal/mol higher in energy.[3,27] This means that such a conformer is hardly

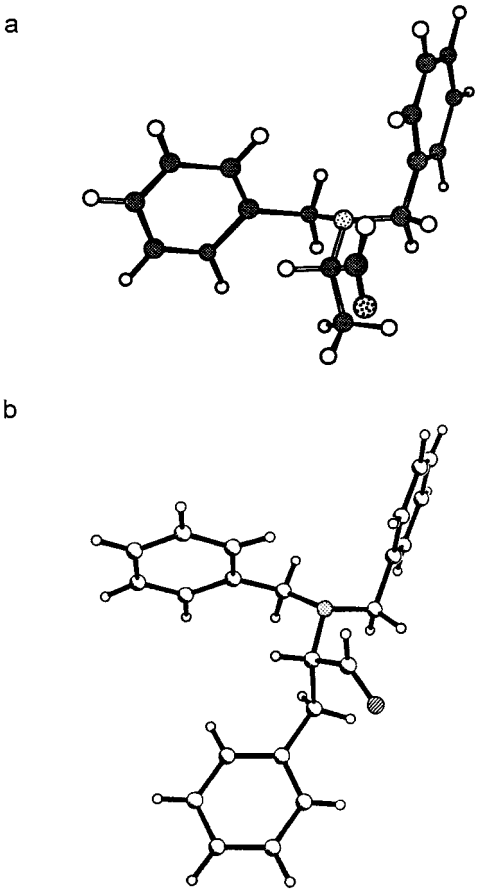


Figure 1. (a) Energetically most stable conformer of aldehyde **10a** as derived from force-field calculations. (b) Structure of aldehyde **10b** as determined by X-ray crystallography.[3]

populated, nor is there any reason to expect it to be more reactive. It was not possible to obtain crystals of aldehyde **10a** suitable for an X-ray structural analysis. However, the structure of phenylalaninal **10b** in the solid state (Figure 1b) confirms the validity of the force-field calculations.[3,27]

To gain some more theoretical insight, the rotational profile of the *N*,*N*-dimethyl analogue **89a** of aldehyde **10a** was calculated using ab initio methods at the MP2/6-31G*//3-21G level.[102] The three-dimensional potential energy surface of this molecule shows the existence of six major minima (Figure 2), the most stable one (**89a′**) being very similar to that of the benzyl analogue (Figure 1a) in that the α-methyl group is essentially eclipsed with the carbonyl oxygen atom. This corresponds to a favorable dipole/dipole interaction, which is the reason why simple aldehydes such as propanal in the gas phase also have the carbonyl function and the α and *β* C-atoms essentially in one plane.[103] Any theoretical treatment is difficult because solvent effects may influence the conformational preference.[104] Despite this difficulty, it becomes clear that the backside of the carbonyl function in the *N*,*N*-dimethylamino aldehyde **89** is not as sterically shielded as in the case of the *N*,*N*-dibenzyl analogue **10a**. Indeed, ab initio calculations of transition states do not predict pronounced nonchelation control in the case of reactions involving *N*,*N*-dimethylpropanal **89a**.[105] Finally, the smaller *N*-methyl groups should not inhibit chelation as

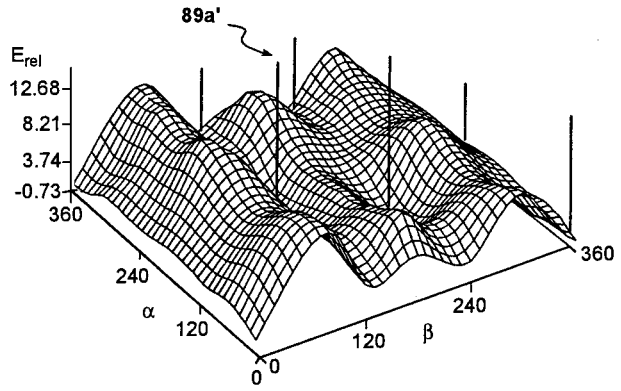
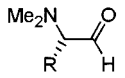
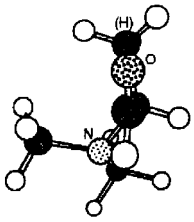


Figure 2. MP2/6-31G*//3-21G energy surface of **89a**;[102] energy values are given in kcal mol^{-1}. The most stable conformer is **89a′**.

much as the *N*-benzyl groups, i.e., it is conceivable that chelation begins to compete in this case.

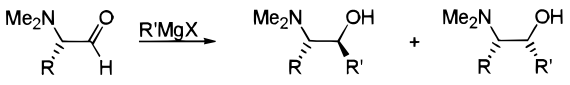


89a: R = Me
89b: R = Bn



89a'

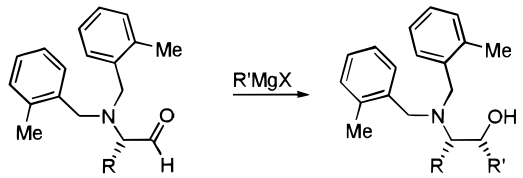
Indeed, Grignard reactions of *N*,*N*-dimethylamino aldehydes **89a**,**b** are essentially stereorandom, leading to diastereomeric mixtures **90**/**91**.[3] In fact, ab initio calculations of the transition state of LiH addition as a model process do not predict high stereoselectivity.[105] Because of the structural complexity of the *N*,*N*-dibenzylamino aldehydes **10**, ab initio calculations were not attempted. Experimentally, it was also found that α-amino aldehydes protected in the form of 2-isoindolinyl derivatives, which are sterically less encumbered than the *N*,*N*-dibenzyl analogues, react with MeLi, MeMgI, and $MeCeCl_2$ fairly unselectively, whereas Me_2CuLi provide the chelation controlled adducts.[3,27] This again demonstrates the crucial effect of the size of the two protective groups at nitrogen. Moreover, the *N*,*N*-dimethylamino aldehydes **89** react with Me_2CuLi[27] or allylindium reagents[41] with almost complete chelation control. Of course, the products of such reactions cannot easily be deprotected at the nitrogen function, which limits the value of such reactions.



89a: R = Me
89b: R = Bn

90a: R = Me; R′ = Ph **91** (50:50)
90b: R = Bn; R′ = Me (35:65)
90c: R = Bn; R′ = Ph (48:52)

In summary, although more refined calculations regarding transition-state modeling still need to be carried out for the *N*,*N*-dibenzylamino aldehydes **10**, ground-state arguments can be invoked to explain the stereochemical results. This means that the ground-state geometry correlates with the geometry of the transition state, a postulate that is not necessarily a violation of the Curtin−Hammett principle. Such a simple model explains why α-amino aldehydes having only *one* protective group react more or less stereorandomly, even if it is bulky as the 9-phenyl-9-fluorenyl moiety.[10] The model also predicts that any increase in steric bulk of the protective group should result in a further increase in diastereoselectivity.[3,27] Indeed, *N*,*N*-di(*o*-methyl)benzylamino aldehydes **92** react with R′MgX to form the nonchelation controlled adducts **93** exclusively (ds ≥ 99%).[3,19,27] Increased diastereoselectivity is also observed in the reactions of sulfur ylides with these sterically more hindered aldehydes (ds ∼ 90%).[19] Older experimental data concerning reactions of racemic *N*,*N*-dialkylamino aldehydes having large alkyl groups on nitrogen are in line with the present model.[25,106]

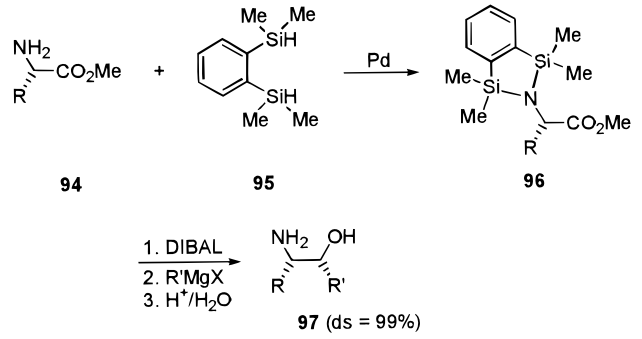


92 **93** (ds ³ 99%)

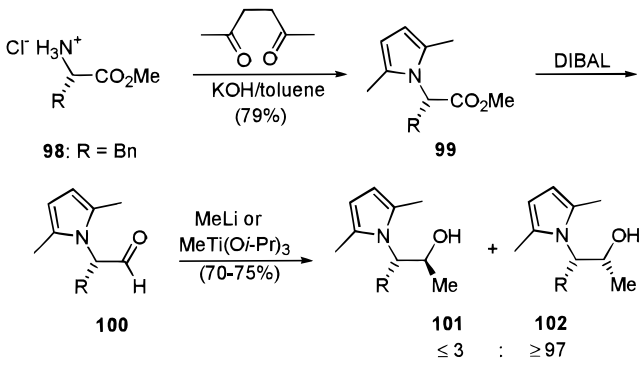
All of the present experimental and theoretical data point to the necessity of having *two* protective groups, the steric properties of which determine the degree of diastereoselectivity.[3,20,27,105] For example, the *N*,*N*-diallyl analogue of **10b** reacts with MeLi to form the nonchelation controlled adduct preferentially (ds = 88%).[32] Moreover, other N,N-disubstituted α-amino aldehydes such as *N*-benzyl-*N*-*t*-butoxycarbonyl, *N*-benzyl-*N*-benzyloxy carbonyl, or *N*-benzyl-*N*-tosyl derivatives also undergo nonchelation controlled reactions,[7,33,107] although such substrates require additional steps regarding protection and deprotection, and diastereoselectivity may be slightly lower in certain cases. For example, the *N*-benzyl-*N*-tosyl analogue of **10b** reacts with MeLi in a nonchelation controlled mode (ds = 90%).[33a] The presence of two protective groups is also the reason the Garner aldehyde **7** reacts so selectively.[15] If the desired final product contains a secondary amino function with one *N*-methyl group, a reasonable strategy is to prepare and react the corresponding *N*-benzyl-*N*-methyl or *N*-benzhydryl-*N*-methyl protected aldehyde, and then to deprotect. Deprotection is best effected by the Yoshida method based on the Pearlman catalyst [$Pd(OH)_2$].[108]

Nonetheless, the development of new protective groups remains a worthwhile endeavor, one example being the benzostabase (BSB) protective group.[109] It can be introduced smoothly into amino acid esters **94** using Pd catalysis. A one-pot reaction of the protected esters **96** entails DIBAL reduction followed by in situ reaction of the intermediate aldehyde (or complex thereof) with RMgX or RLi and subsequent deprotective acidic workup. The chemically and enantiomerically pure products **97** can be isolated in 40−60% yield, which is quite respectable given that three steps are involved.[109]

The above steric model based on ground state conformational properties is also in line with the

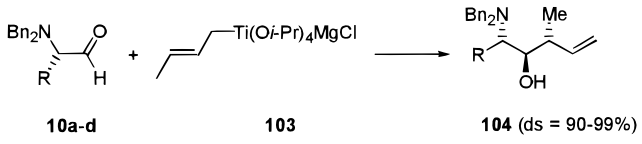


results obtained from the reactions of phenylalaninal **100** in which the amino group is protected as a 2,5-dimethylpyrrole moiety.[46] Reagents MeLi and MeTi(O*i*-Pr)$_3$ afford practically only the nonchelation controlled adduct **102**. This product is an unusual heterocycle, but attempts to deprotect the amino function were not successful so far.[46]

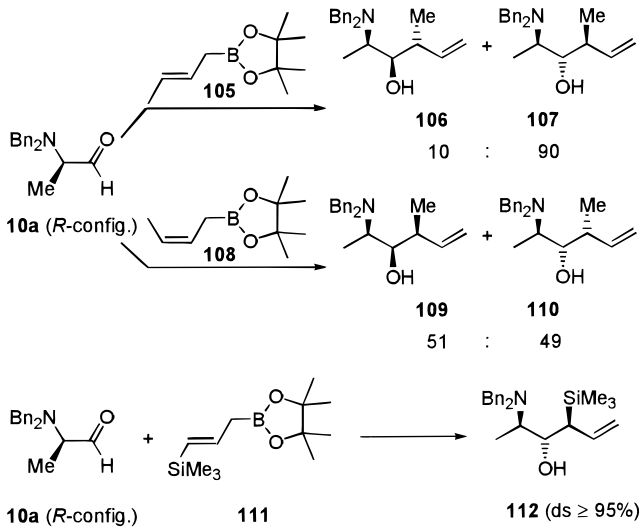


3. Prochiral Reagents

In reactions of prochiral reagents such as crotylmetal compounds,[110] an additional stereochemical element is relevant, namely simple diastereoselectivity, resulting in four possible diastereomeric adducts. Upon reacting **10a** with crotylmagnesium chloride (which is a mixture of *E*- and *Z*-isomers and the regioisomer), a totally unselective reaction was observed.[111] However, prior in situ titanation[18] with Ti(O*i*-Pr)$_4$ (which generates reagent **103** selectively)[112] results in essentially only one diastereomer **104**.[3,27,40] This implies the usual nonchelation control as well as a high level of simple diastereoselectivity (anti selectivity) expected for *E*-configurated crotyltitanium reagents.

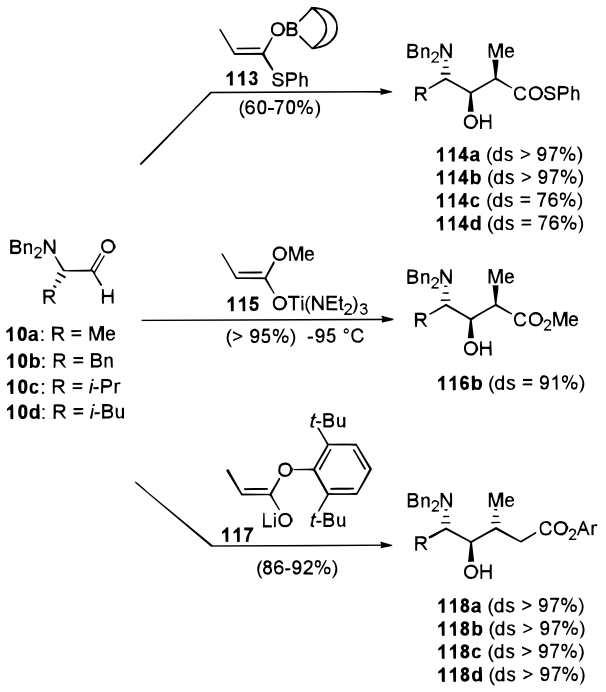


From a methodological viewpoint, the possibility of reversing the sense of simple diastereoselectivity (syn selectivity) on an optional basis would be desirable. This might be possible by using *Z*-configurated crotyltitanium reagents. However, since such reagents are not available due to rapid $Z \rightarrow E$ isomerization,[18] there was no way to test this. In contrast, *Z*- and *E*-crotylboron compounds such as boronates **105** and **108** are readily prepared and constitute one of the most stereoselective classes of organometallic reagents known.[110] Achiral aldehydes are known to react with **105** to provide the anti configurated adducts with ≥ 95% stereoselectivity, whereas the *Z*-analogue **108** affords ≥ 95% of the syn adducts. In the case of chiral aldehydes such as 2-phenylpropanal, the rule regarding simple diastereoselectivity is maintained, but diastereofacial selectivity depends on the sense of prochirality of the reagents.[113a] Cram selectivity was observed with **105** and anti Cram selectivity with **108**. Convincing models have been proposed to account for these trends. Upon reacting aldehyde (*R*)-**10a** (prepared from *D*-alanine) with reagent **105**, a 10:90 mixture of **106**/**107** was obtained,[113a] which is similar to the reaction of (*S*)-**10a** with the titanium reagent **103** (note that this is the enantiomeric series).[3,27,40] However, the *Z*-boronate **108** afforded a 1:1 mixture of **109**/**110**. This means complete simple diastereoselectivity but essentially no diastereofacial selectivity (formally chelation or nonchelation control). It was not possible to explain this result on the basis of transition-state modeling using force-field calculations.[113a] In the reaction of a highly substituted allylic titanium reagent with aldehyde **10d**, stereorandom behavior was also observed.[113b] In contrast, the prochiral *E*-boronate **111** afforded a single adduct **112** which means complete nonchelation control as well as > 99% simple diastereoselectivity (anti selectivity).[113a]

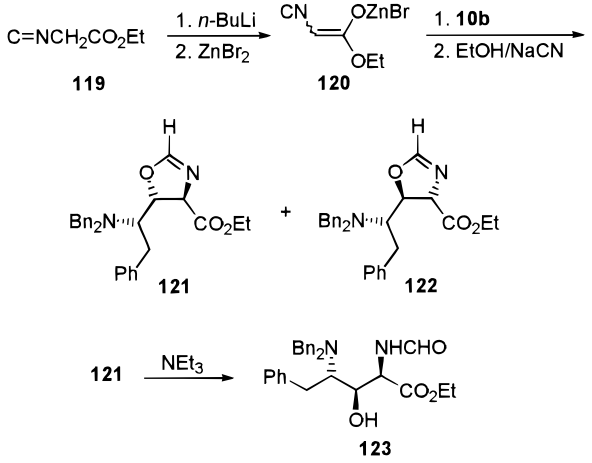


Although a whole arsenal of syn and anti selective enolates derived from propionic acid are known,[114] only a few have been tested in reactions with *N*,*N*-dibenzylamino aldehydes **10**. The syn-selective Masamune reagent **113** reacts with exclusive formation of the nonchelation controlled adducts **114a**,**b**.[3,20,27] In the case of bulky aldehydes **10c**,**d**, a second diastereomer is formed in appreciable amounts, the structure of which has not been elucidated. Related is the reaction of aldehyde **10b** with the Ti enolate **115**, readily prepared by treating the Li enolate of propionic acid ester with ClTi(NEt$_2$)$_3$. At −95 °C diastereoselectivity in favor of the aldol adduct **116** amounts to 91%.[20,27] Other aldehydes **10** were not tested. In contrast, the anti selective Heathcock enolate **117** affords only one of the four possible

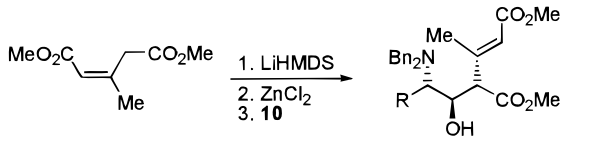
diastereomers **118** in excellent yield for a variety of aldehydes **10a-d**.[3,20,27]



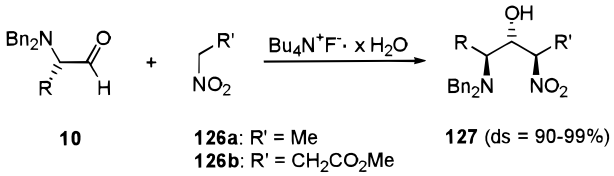
The zinc enolate **120** (but not the Li precursor) prepared from isocyanoacetic acid ester (**119**) adds to aldehyde **10b** with 90% nonchelation control, but simple diastereoselectivity is poor.[115] However, if the crude product is subjected to cis/trans equilibration under weakly basic conditions (NaCN/EtOH), only the two trans configurated adducts **121**/**122** are obtained in a ratio of 90:10. Recrystallization from ethanol resulted in an 81% yield of pure **121**, which was subjected to Et_3N-promoted stereospecific ring-opening hydrolysis with exclusive formation of compound **123**, the structure of which was proven by X-ray crystallography. Other members of these novel α,γ-diamino-β-hydroxy amino acids were prepared by a modified protocol.[115]



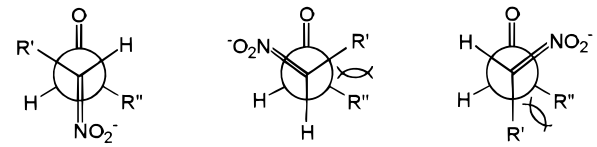
In another study, the Zn-enolate derived from dimethyl-3-methylglutaconate (**124**) was reacted with aldehydes **10**, providing mainly one of four possible diastereomeric adducts.[116] Although the structure was not rigorously proven, the configuration shown for compounds **125** was suggested on the grounds of plausibility. Such compounds serve as precursor in the preparation of functionalized lactones.



The $Bu_4N^+F^-\cdot xH_2O$-catalyzed nitroaldol addition of $MeNO_2$ to aldehydes **10** (section IIB1) also works well in the case of various homologues $R'CH_2NO_2$.[69] Because the intermediate nitronate anions are prochiral, four diastereomeric products are possible. Depending upon the conditions used, excellent selectivities in favor of nonchelation control and anti configuration with respect to simple diastereoselectivity were achieved (cf. **127**). Diastereoselectivity usually ranges between 90% and 99%. The enantiomeric (*R*)-aldehydes **10** were also subjected to these reactions.[69]



Mechanistically, these synthetically important results are in line with an antiperiplanar approach of the nitronate at the *re* face of the aldehyde **10** in accord with the Felkin−Anh model (or with an attack on the ground-state conformer as delineated in section IIB2). With respect to simple diastereoselectivity, transition-states **128**, **129**, and **130**, all being consistent with the observed anti selectivity, were considered. Transition-state **128** was favored because it avoids energetically unfavorable gauche (R′ and R″) and dipolar interactions.[69] Indeed, ab initio calculations (up to MP4SDQ/6−31 + G*//MP2(FU)/6−31 + G* + ΔZPVE) on several model nitroaldol reactions support this postulate.[117]

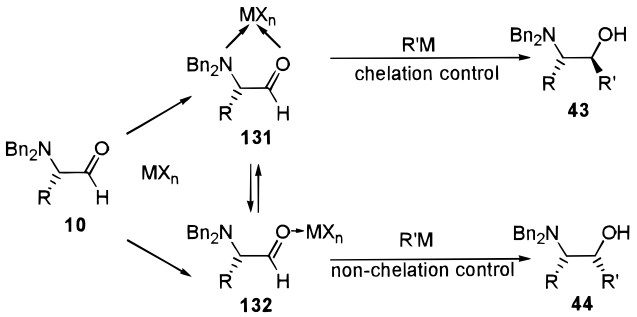


Whatever the precise mechanism may be, the method allows for stereoselective access to acyclic compounds bearing differentiated nitrogen-containing functionality as well as diverse end groups. The products are precursors of the corresponding 1,3-diamino-2-alcohols which are substructures of a number of medicinally important compounds. In another application, the nitroaldol reaction of *N,N*-dibenzylamino aldehydes **10** was carried out in order

to prepare C_2 symmetric 1,5-diamino alcohols for use as components in HIV protease inhibitors (section III).[95]

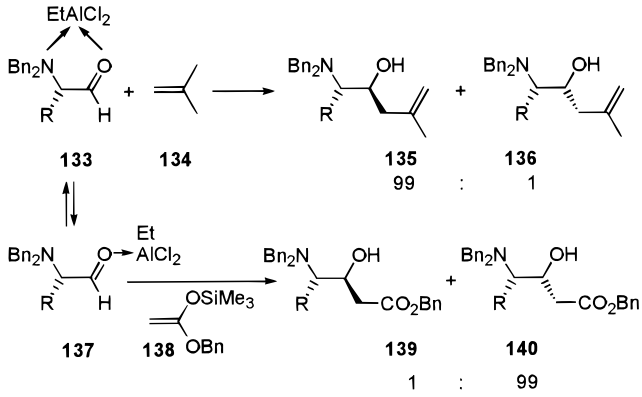
C. Chelation Controlled Reactions

Chelation control in C−C bond forming reactions of chiral α-alkoxy aldehydes is readily achieved by treating the substrate with a Lewis acid capable of bis ligation (e.g., $TiCl_4$, $SnCl_4$, MgX_2) and reacting the intermediate chelates with such C-nucleophiles as R_2-Zn, allylsilanes, enolsilanes, or Me_3SiCN in non-ethereal solvents.[11] In sharp contrast to this well-known chemistry, chelation control in the case of *N*,*N*-dibenzylamino aldehydes **10** is more difficult to achieve.[3,27] The reason for this has to do with steric factors arising from the two *N*-benzyl groups (section IIB2). Nevertheless, it is useful to focus on those reactions of *N*,*N*-dibenzylamino aldehydes **10** that do in fact occur with chelation control and to pose the question as to why this is possible. In most of the successful cases, a Lewis acid MX_n was employed in the hope of generating intermediates of the type **131**. These are expected to react with the proper reagents selectively at the *si* face of the aldehyde moiety. However, it must be remembered that such Lewis acids can also form normal aldehyde adducts of the type **132** or 2:1 complexes which would react with nonchelation control (see previous discussion of **10**/$TiCl_4$ adducts (section IIB2).



Upon attempting to perform a $TiCl_4$-promoted allylsilane addition to aldehyde **10b** at −78 °C, no reaction occurred, and at higher temperatures a complex mixture of products was observed.[32] In contrast, $SnCl_4$ led to acceptable conversions at −78 °C with good to excellent degrees of chelation control[21,27,32] (Table 3, entries 2, 6, 10, 13, 23). However, in some cases diastereoselectivity is poor (Table 3, entry 21). Moreover, in going to slightly bulkier allylic silanes substituted at the 2-position, chelation control is mediocre.[33] The highly Lewis acidic methyl reagent $MeTiCl_3$ also leads to chelation control,[21,27] although diastereoselectivity decreases drastically as the bulkiness of the R-group at the stereogenic center increases (Table 3, entries 1, 5, 20, 22, 27). The reagent combination comprising $TiCl_4$/Me_2Zn also leads to chelation control (Table 3, entries 25, 26). These trends support the previous observation that Lewis acidic reagents may form several different types of complexes with aldehydes **10**, the direction and extent of diastereoselectivity being difficult to predict. Indeed, as previously mentioned (section IIB1), Me_2C=C(OMe)$OSiMe_3$ reacts with **10a**/$TiCl_4$ under 95−97% nonchelation control, indicating that nonchelated $TiCl_4$ adducts **88** of the aldehydes react in a kinetically controlled process according to the Curtin−Hammett principle.[27,32] Other cases have also been reported, e.g., the $TiCl_4$-mediated nonchelation controlled aldol reaction of aldehydes **10** with Brassard-type of siloxy butadienes **74** leading to adducts **75**[94] (section IIB). Although chelated aldehydes such as bidentate complexes **131** and related species are believed to be more reactive than monocomplexed analogues (e.g., monodentate complexes **132**) in other reactions,[11,88,118] it is clear that this cannot be generalized.

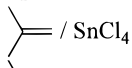
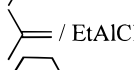
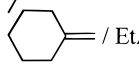
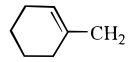
In summary, the stereochemical outcome of a reaction in a particular system comprising **10**/$TiCl_4$ depends on the nature of the reagent that is added in the second stage of the one-pot process. This interesting phenomenon is not restricted to $TiCl_4$ as the Lewis acid. An example concerns $EtAlCl_2$-promoted ene reactions of aldehydes **10** (which occur with 99% chelation control)[88] and Mukaiyama-type aldol additions mediated by the same Lewis acid (which occur with 99% nonchelation control[88] as already mentioned in section IIB1). Thus, products **135** and **140** have opposite relative configurations. Again, the Curtin−Hammett principle as applied to competing chelated and nonchelated complexes **133** and **137**, respectively, can be invoked in these synthetically important reactions.



The special case of aldehyde **29** derived from (*S*)-pyroglutamic acid deserves mention. The $TiCl_4$-mediated reaction of CH_2=$CHCH_2SiMe_3$ proceeds here in good yield with complete chelation control.[53a] The adduct was then transformed into the alkaloid (+)-1,8-diepiswainsonine. Similar reactions involving related aldehydes such as **27**[32] need to be studied in order to make generalizations.[53a,b]

The major problem in Lewis acid mediated reactions of aldehydes **10** concerns the limited ability to predict the stereochemical outcome of a given reaction. However, based on trial and error, trends and therefore guidelines are emerging (Table 2 versus Table 3). Another example that also entails a reaction of significant synthetic importance is cyanohydrin formation. Whereas $ZnBr_2$ or BF_3 leads to 95% nonchelation control (Table 2, entries 30, 44, 45, 60), $TiCl_4$ and $MgBr_2$ (but not $SnCl_4$!) induce the opposite sense of diastereoselectivity (ds = 78−84% as summarized in Table 3 (entries 3, 11, 12, 14, 24).

Table 3. Typical Chelation Controlled Reactions of *N,N*-Dibenzylamino Aldehydes 10[a]

entry	aldehyde	reagent	R' in **43**/**44**	yield (%)	**43** : **44**	ref(s)
1	**10a**	$MeTiCl_3$	Me	82	94 : 6	21,27
2	**10a**	CH_2=$CHCH_2SiMe_3/SnCl_4$	CH_2=$CHCH_2$	85	84 : 16	21,27
3	**10a**	$Me_3SiCN/TiCl_4$	CN	61	82 : 18	27,70
4	**10a**	Et_2Zn	Et	95	88 : 12	52
5	**10b**	$MeTiCl_3$	Me	63	78 : 22	21,27
6	**10b**	CH_2=$CHCH_2SiMe_3/SnCl_4$	CH_2=$CHCH_2$	79	78 : 13	21,27
7	**10b**	$HP(O)(OEt)_2/TiCl_4$	$(EtO)_2P(O)$	46	93 : 7	73
8	**10b**	Et_2Zn	Et	70	90 : 10	52
9	**10c**	$MeTiCl_3$	Me	65	65 : 35	21,27
10	**10c**	CH_2=$CHCH_2SiMe_3/SnCl_4$	CH_2=$CHCH_2$	79	95 : 5	21,27
11	**10c**	$Me_3SiCN/TiCl_4$	CN	63	84 : 16	21,27
12	**10c**	$Me_3SiCN/MgBr_2$	CN	75	82 : 18	21,27
13	**10d**	CH_2=$CHCH_2SiMe_3/SnCl_4$	CH_2=$CHCH_2$	78	90 : 10	21,27
14	**10d**	$Me_3SiCN/TiCl_4$	CN	63	88 : 12	27,70
15	**10d**	$Me_3SiCN/Eu(fod)_3$	CN	84	95 : 5	119
16	**10d**	Et_2Zn	Et	62	92 : 8	52
17	**10d**		CH_2=$C(Me)CH_2$	59[b]	73 : 27	88
18	**10d**		CH_2=$C(Me)CH_2$	71[b]	>99 : <1	88
19	**10d**			48[b]	>99 : <1	88
20	**10l**	$MeTiCl_3$	Me	50	82 : 18	27,46
21	**10l**	CH_2=$CHCH_2SiMe_3/SnCl_4$	CH_2=$CHCH_2$	49	59 : 41	27,46
22	**10m**	$MeTiCl_3$	Me	23	77 : 23	27,46
23	**10m**	CH_2=$CHCH_2SiMe_3/SnCl_4$	CH_2=$CHCH_2$	51	97 : 3	27,46
24	**10m**	$Me_3SiCN/MgBr_2$	CN	53	64 : 36	27,46
25	**10o**	$Me_2Zn/TiCl_4$	Me	30	83 : 17	27,46
26	**10p**	$Me_2Zn/TiCl_4$	Me	60	93 : 7	27,46
27	**10p**	$MeTiCl_3$	Me	29	95 : 5	27,46
28	**10p**	Me_2TiCl_2	Me	71	74 : 26	27,46
29	**10v**	Et_2Zn	Et	65	>99 : <1	52

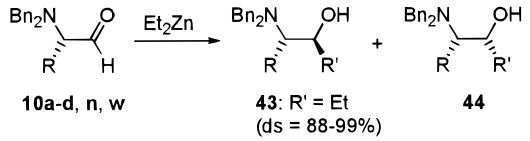
[a] Further examples can be found in the references cited. [b] An ene reaction is involved.

Chelation controlled cyanohydrin formation is also possible using only 5 mol % of $Eu(fod)_3$[119] (Table 3, entry 15). Thus, this is the most efficient way to obtain chelation-controlled cyanohydrins from *N,N*-dibenzylamino aldehydes, although generalization of the method needs to be documented. In this system, a lanthanide-induced shift (LIS)-NMR analysis of **10d**/$Eu(fod)_3$ was carried out, indicating significant chelation.[119] Nevertheless, this observation in itself has only limited value, because it is conceivable that other types of nucleophiles will result in poor asymmetric induction or even in reversal of diastereofacial selectivity. Indeed, $Eu(hfc)_3$-catalyzed hetero Diels–Alder reactions of aldehydes **10** with siloxy-butadienes afford > 90% of the nonchelation controlled cycloadducts[91] (section IIB1)!

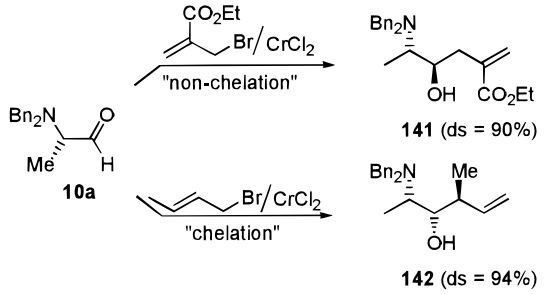
Sometimes the nucleophilic reagent may actually react with the Lewis acid used to chelate the aldehyde **10**, in which case an excess of the Lewis acid is advisable. An example concerns the $TiCl_4$-promoted hydrophosphorylation of aldehyde **10b** using diethyl phosphite $HP(O)(OEt)_2$[73] (Table 3, entry 7). A 3-fold excess of $TiCl_4$ is necessary in order to obtain a high degree of chelation control. This is yet another case

in which the nature of the nucleophile determines the sense and degree of diastereoselectivity (the use of t-$BuMe_2SiOP(OEt)_2$ in the presence of $TiCl_4$ results in 98% nonchelation control;[73] see Table 2, entry 42; section IIB1).

In a completely different approach, diethylzinc (Et_2Zn) was reacted with aldehydes **10** at 0 °C to afford the chelation controlled adducts **43** preferentially, diastereoselectivity amounting to 88−99%.[52] This result is unprecedented since all previously used organometallics such as RLi, RMgX, RMnX, $RCeCl_2$, and R_2CuLi afford the opposite diastereomers **44** selectively.[3,21,27] The reason for this intriguing difference has not been pinpointed. However, it was noted that the addition of Et_2Zn to the *N*,*N*-dibenzylamino aldehydes **10** proceeds at an unusually high rate. Normal aldehydes do not react with dialkylzinc reagents unless promoters such as $TiCl_4$[120] or catalysts such as β-amino alcohols[121] are present. Thus, ligand acceleration promoted by the *N*,*N*-dibenzylamino group appears to be operating,[52] perhaps in an autocatalytic fashion.[122] It would be interesting to see whether the use of chiral amino alcohols as catalysts has any effect on the stereochemical outcome of the reaction.



As mentioned in section IIB3, it is well-known that the sense and degree of Cram/anti Cram selectivity in reactions of prochiral allylmetal reagents with chiral aldehydes such as 2-phenylpropanal depend on the configuration of the reagent (*Z* versus *E*).[113a] Under nonchelating conditions, reactions of *N*,*N*-dibenzylamino aldehydes **10** can be considered to constitute Cram/anti Cram problems, although assigning the relative size of the substituents (R^S, R^M, R^L) may not be straightforward. Nevertheless, it has been shown experimentally that diastereofacial selectivity in reactions of *E*-crotylboronates **105** with aldehydes **10** is very high in favor of nonchelation control (in a formal sense), whereas the *Z*-analogues **108** do not result in any significant degree of 1,2-asymmetric induction (formally chelation:nonchelation = 51:49)[113a] (section IIB3). Thus, the intrinsic tendency of aldehydes **10** to produce the nonchelation controlled adducts **44** (or specifically **110**) is counteracted by an unknown effect arising from the interaction with the *Z*-configurated crotylboronate. Whatever the effect might be, it is not strong enough to reverse diastereoselectivity completely in favor of the formal chelation controlled adduct **109**. A case in which such a phenomenon appears to be operating concerns the Hiyama−Nozaki allylation/crotylation of aldehyde **10a**. Whereas simple γ-unsubstituted allylic bromides react with **10a** and similar *N*,*N*-diprotected aldehydes in the presence of $CrCl_2$ with > 90% nonchelation control (section IIB1) as in the formation of **141**, the prochiral crotylbromide results in complete reversal of 1,2-asymmetric induction (formally chelation control) as well as excellent simple diastereoselectivity (anti selectivity) with formation of adduct **142**.[68] Although the reasons for this interesting switch are not completely understood, a transition state leading to the chelation controlled product without involving chelation of the amino group was proposed.[68] Experimental results of this kind are not only of synthetic significance, they are also likely to stimulate theoreticians into probing theoretical models and methods.

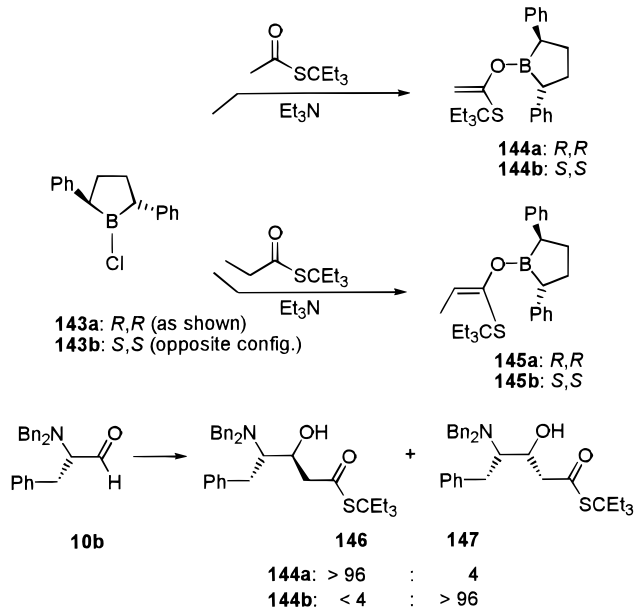


D. Reactions with Chiral Reagents or Catalysts

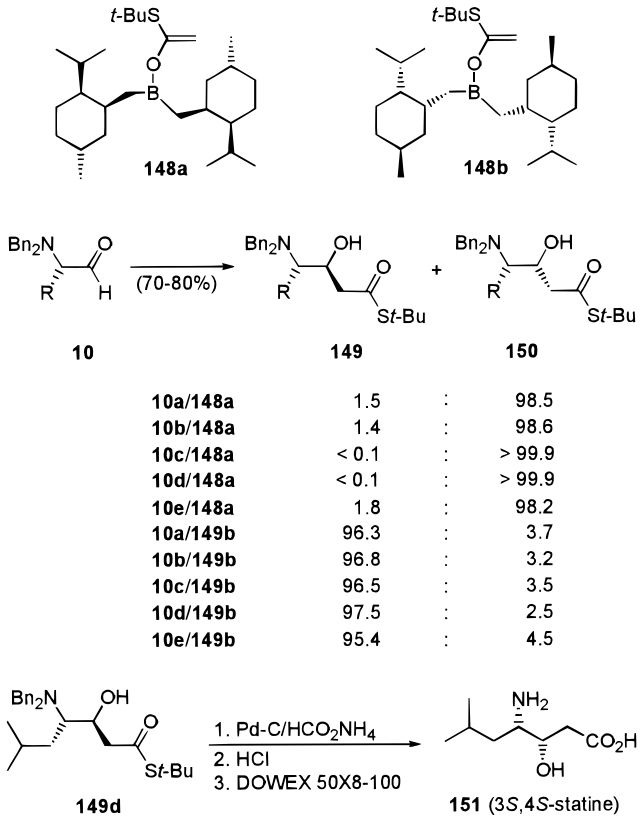
Very different types of chiral reagents have been reacted with *N*,*N*-dibenzylamino aldehydes **10**. The reasons for doing so differ considerably. The most obvious motivation is reagent control, i.e., the prospect of determining the topicity of attack at the carbonyl function on an optional basis irrespective of the influence of the stereogenic center already present in the aldehyde. The first system to be studied with this goal was based on the C_2-symmetric 2,5-diphenylborolane **143** which can be used to borolate thioacetic or thiopropionic acid esters with formation of reagents **144** and **145**, respectively, either with the (*R*,*R*)- or (*S*,*S*)-configuration.[123]

The (*R*,*R*)-reagent **144a** undergoes aldol additions to *N*,*N*-dibenzylamino aldehydes such as **10b** with preferential formation of adduct **146** which formally corresponds to chelation control (ds = 93−97%).[123] In contrast, the enantiomeric reagent **144b** affords the opposite diastereomers with similar selectivity, corresponding to formal nonchelation control. Upon subjecting the enantiomeric (*R*)-configurated aldehydes **10** to the reagents, the expected opposite behavior was observed. Relevant is the unexpected finding that achiral boron enolates such as $CH_2{=}C(SCEt_3)OBEt_2$ react with **10** to produce 1:1 mixtures of diastereomers.[123] This rare case of stereorandom behavior is difficult to explain. Of course, from a practical viewpoint nonchelation control is most easily achieved by using achiral enolates such as $CH_2{=}C(S$*t*$\text{-Bu})OLi$ or $CH_2{=}C(OEt)OLi$ (section IIB1). Reagent control is also possible in reactions involving the prochiral reagents **145**. For example, the (*S*,*S*)-reagent **145b** reacts with (*S*)-**10** and (*R*)-**10** to produce in each case essentially one of four possible diastereomers.[123]

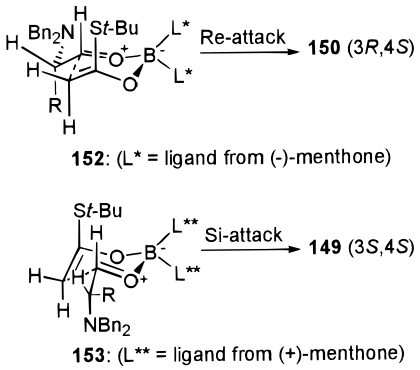
A similar strategy based on more easily accessible boron reagents **148a** and **148b** derived from (−)- and (+)-menthone, respectively, has a more practical character.[124] The former reagent adds to the *re* face of achiral aldehydes, the latter to the *si* side. High facial selectivity is maintained in the case of the chiral aldehydes **10**. Thus, this is a simple way to



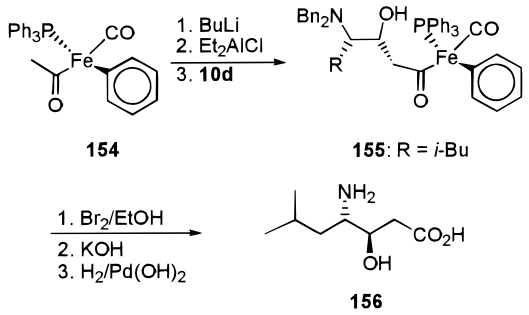
obtain products **149** or **150** on an optional basis. Adduct **149d** has the (3*S*,4*S*)-configuration and was readily converted into (3*S*,4*S*)-statine (**151**),[124] a naturally occurring γ-amino acid found in the hexapeptide pepstatin (a strong inhibitor of such aspartic proteinases as pepsin, cathepsin and renin).



Mechanistically, transition-state **152** was proposed in the reaction of reagent **148a** leading to products **150** having the (3*R*,4*S*) configuration,[124] corresponding to formal nonchelation control. In contrast, transition-state **153** was postulated to explain the reaction of the enantiomeric reagent **148b** with formation of products **149** having the (3*S*,4*S*) configuration, corresponding to formal chelation control.



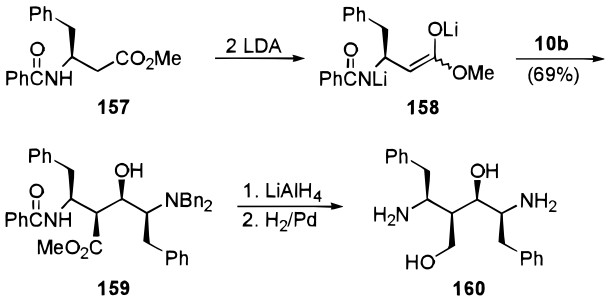
In another report, the (*R*)- and (*S*)-configurated Davies auxiliary **154** was used successfully in reagent controlled aldol additions to aldehydes **10**.[30] This methodology was applied to the synthesis of (3*R*,4*S*)-**156**, a diastereomer of naturally occurring statine **151**. Accordingly, the matched pair reaction of the Al enolate derived from (*S*)-**154** with aldehyde **10d** provided the (*S*,*R*,*S*)-configurated adduct **155** as a single diastereomer. Following decomplexation, ester hydrolysis, and deprotection, compound **156** was obtained in 68% yield. It is also accessible by reacting the achiral Li enolate derived from ethyl acetate with aldehyde **10d**.[3,21,27]



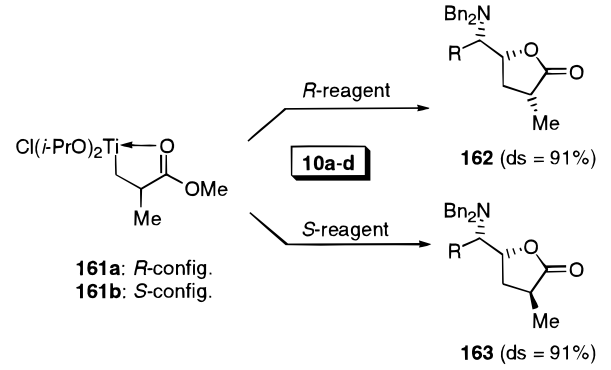
Although many *catalytic* enantioselective C−C bond forming reactions of achiral aldehydes are known, only the Ti-catalyzed Et_2Zn addition has been applied to *N*,*N*-dibenzylamino aldehydes **10**.[125] However, it is known that chiral rare earth Li−BINOL complexes catalyze the nitroaldol addition of $MeNO_2$ to Boc-, Cbz-, and Phth-protected α-amino aldehydes,[107f] a reaction that has not been applied to aldehydes **10**.

Along a different line, several reactions of aldehydes **10** with enolates or homoenolates bearing stereogenic centers in the carbon skeleton of the reagent have been reported. For example, the Li enolate **158** prepared by dilithiation of the chiral *N*-benzoyl methyl ester **157** adds to aldehyde **10b** with complete nonchelation control.[126] Because none of the other three possible diastereomers are formed, the generation of the stereocenter bearing the ester function is also completely selective. It is currently unclear whether the stereochemical outcome is actually influenced by the absolute configuration at the stereogenic center of the enolate **158**, since the enantiomeric reagent was not tested. However, it was reported that upon going from the *N*-benzoyl to the

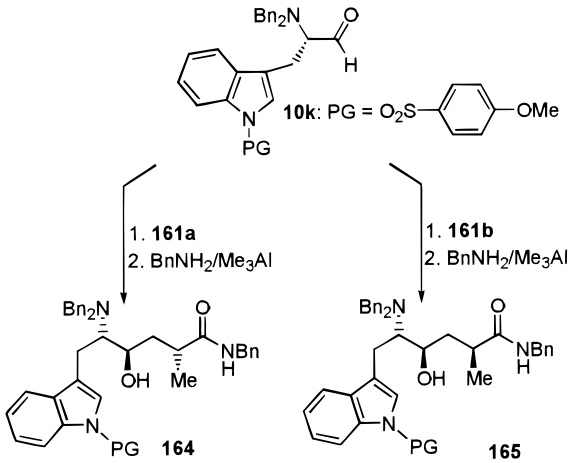
N-Boc protective group in the reagent, selectivity is reduced drastically.[126] The single diastereomer **159** was readily converted into the 1,4-diamino alcohol **160**, a novel dihydroxy 1,4-diamine which is of potential use as a building block in the synthesis of HIV protease inhibitors.[126]



Chiral homoenolates of the type **161a**,**b** undergo C−C bond formation with aldehydes **10**, a process which is followed by spontaneous lactonization with formation of compounds **162** and **163**, respectively.[43] Nonchelation control amounts to > 90% and is independent of the absolute configuration of the homoenolates **161a**/**161b**. Treatment of the lactones with primary amines in the presence of Me_3Al results in the formation of the corresponding acyclic amides which are of interest in peptidomimetic chemistry.

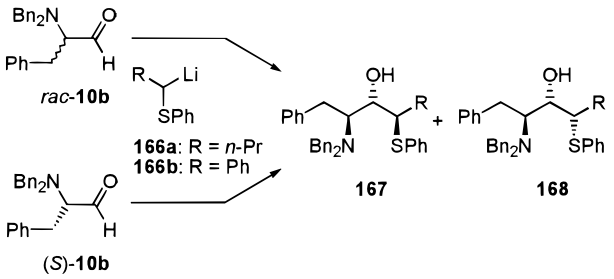


This interesting methodology was applied to the diastereoselective synthesis of 2-amino alcohols **164** and **165** which are useful derivatives in the preparation of inhibitors of the endothelin converting enzyme.[43]



A completely different practical and theoretical question arises when considering the reaction of chiral aldehydes **10** with secondary chiral organolithium reagents R^1R^2CHLi. Such reagents are more or less configurationally labile, unless stabilizing substituents such as alkoxy groups are attached directly to the stereogenic center bearing the lithium, e.g., R(R′O)CHLi.[127] Although the latter have not been reacted with aldehydes **10**, one might expect nonchelation control in the formation of the new stereogenic center as well as preservation of stereochemical integrity of the enantiomerically pure organolithium reagents. However, if the reagent is configurationally labile, the state of affairs is quite different. It is of considerable interest to gain information concerning the configurational stability or lability of this type of chiral reagents. In addition to classical methods (e.g., lithiation of enantiomerically pure precursors), a fundamentally different approach has been developed, namely, the Hoffmann test which is composed of two separate experiments:[128] (1) A racemic organolithium reagent is reacted with a racemic electrophile, and the ratio of diastereomeric products is determined; (2) The experiment is repeated with the same racemic reagent but with an enantiomerically pure electrophile. The decision as to the configurational stability of the reagent on the time scale of its reaction is based on the comparison of the two ratios of diastereomers. If they are identical, the reagent is configurationally labile.

Although various chiral substrates may serve as the electrophile in the Hoffmann test,[128,129] the *N*,*N*-dibenzylamino aldehyde **10b** has been used most often.[75,130,131] This has to do with the pronounced intrinsic diastereoselectivity and configurational stability of this aldehyde. A prominent example pertains to the investigation of the configurational stability of sulfur-substituted organolithium reagents **166a**,**b**.[130] The reactions with aldehyde *rac*-**10b** and (*S*)-**10b** resulted in diastereomeric products **167** and **168**, the ratios of which varied according to the nature of the R-group in the reagents **166**. Because the intrinsic diastereoselectivity of aldehyde **10b** is so pronounced (complete nonchelation control), only two diastereomers were formed. It is the ^{1,3}syn:^{1,3}anti ratio which is of interest in the Hoffmann test. Without going into details here, the conclusions based on the experimental data are as follows: reagent **166a** is configurationally stable on the time scale of the reaction, whereas the phenyl analogue **166b** undergoes relatively rapid enantiomerization (Table 4).[130]

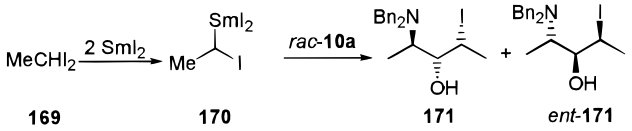


Many other types of chiral secondary organolithium reagents have been subjected to the Hoff-

Table 4. Hoffmann Test Involving Chiral Reagents 166a-b and Aldehyde 10b[130]

reagent	aldehyde	**167** : **168**	conclusion
166a	*rac*-**10b**	70 : 30	config stable
166a	(*S*)-**10b**	52 : 48	
166b	*rac*-**10b**	39 : 61	config unstable
166b	(*S*)-**10b**	40 : 60	

mann test based on the use of aldehyde **10b**, including 2-methylbenzyllithium, α-phenylselenoalkyllithium compounds, carbenoids as well as lithiated phosphine oxides and sulfones.[75,130,131] In some of the cases, stereoselectivity is so high that the products can be used in synthetically meaningful ways. Theoretically, it is possible that a single diastereomer is formed, provided that enantiomerization of the chiral reagent is fast and one enantiomeric form reacts more rapidly than the other in a stereoselective process. This seems to hold in the SmI_2-promoted reaction of the prochiral di-iodide **169** with aldehyde **10a**, a process in which the chiral Sm reagent **170** is involved as an intermediate.[132] In this case the racemic aldehyde was used, resulting in a single diastereomer **171** as a racemate. Unfortunately, the analogous reaction with optically active aldehyde **10a** was not tested.



169 **170** **171** *ent*-**171**

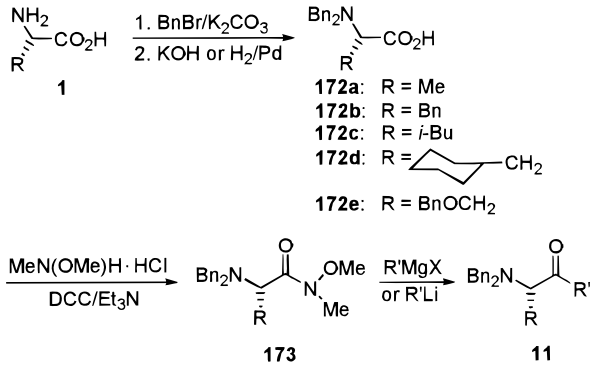
III. N,N-Dibenzylamino Ketones

A. Synthesis

If the intrinsic property of *N*,*N*-dibenzylamino aldehydes **10** to undergo nonchelation controlled nucleophilic additions also operates in reactions of the analogous ketones **11**, then hydride reduction reactions should be expected to proceed with preferential formation of compounds **43**. Formally, these are the products that arise from chelation controlled C−C bond forming reactions of aldehydes **10**. Because the latter are not as general as one would like, nonchelation controlled hydride reduction of ketones **11** constitutes an important complementary strategy.[3,133,134] Moreover, ketones **11** can be transformed in other ways as well, reduction in the final step then being an option.

One way to prepare ketones **11** is to oxidize the aldehyde addition products **43**/**44**.[27,42,46,67a,75b,95,135,136] Such a sequence has been used to convert the *N*,*N*-dibenzyl protected serinal **10m** into allo-threoninal **10p**[27,46] (section IIB1). It is also a way to invert the configuration at the alcohol function of amino alcohols **44**, since the ketones can be reduced stereoselectively to the diastereomers **43** (see section IIIB). Such a sequence appears to be the only successful method for achieving inversion of configuration at the alcohol function because Mitsunobu reactions of alcohols **44** and S_N2 reactions of the corresponding triflates result in either retention of configuration or rearrangement, both processes being due to the neighboring group effect of the *N*,*N*-dibenzylamino group.[32,66]

In most cases it is more elegant to prepare the ketones directly from activated amino acid derivatives which in turn are accessible from the *N*,*N*-dibenzylamino acids **172**.[22,133,134] Accordingly, the latter are first prepared by tribenzylation of amino acids **1** with $BnBr/K_2CO_3$ in water followed by the addition of KOH, 1,4-dioxane and methanol to the reaction mixture containing the intermediate esters **14**. A reflux period of 6−28 h is then necessary for ester hydrolysis, depending upon the particular substrate.[22,33b,134] More traditional conditions fail to effect hydrolysis.[137] Perhaps the easiest way to obtain the acids **172** is not by hydrolysis, but by chemoselective debenzylation of the intermediate tribenzyl compounds **14** at the ester moiety using H_2/Pd, but this needs to be tested. Alternatively, the *N*,*N*-dibenzylamino methyl esters can be hydrolyzed with LiI/NaCN.[137] The acids **172** are then converted into Weinreb-type amides **173**.[22,134] This has been carried out for **173a**, **b**, **d**, and **e** in yields of 53−72%. The formation of amide **173b** was optimized (92% yield) by choosing 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide as the activator in the presence of Hünigs base in DMF instead of the usual DCC/Et_3N.[138] The amides were then reacted with Grignard or organolithium reagents at −30 to −40 °C.[22,134,138] Under these conditions, there is no erosion of configurational integrity of the ketones (at −10 to 0 °C, 5−10% racemization may occur).[22,134]



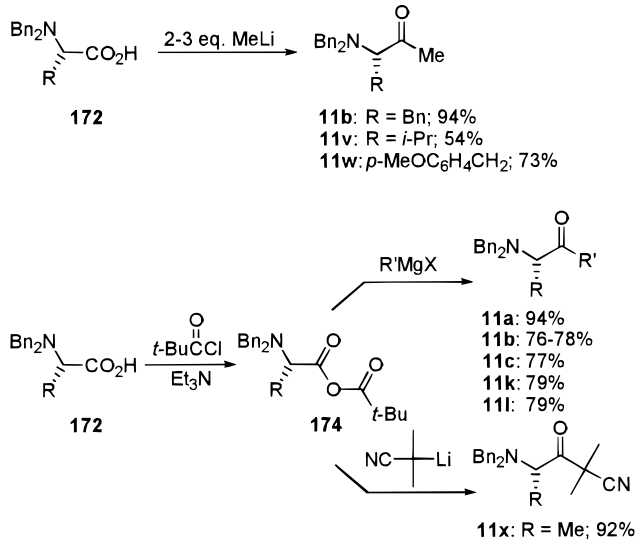
1

172a: R = Me
172b: R = Bn
172c: R = *i*-Bu
172d: R =
172e: R = $BnOCH_2$

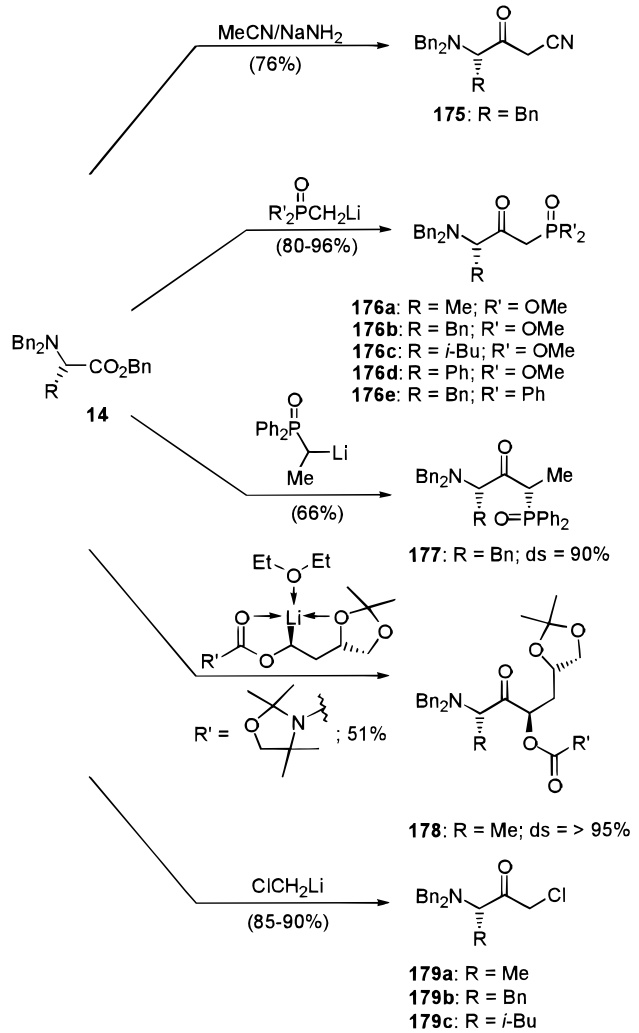
173 **11**

Some of the compounds were also prepared by application of the Gilman−Jorgenson ketone synthesis (**11b**, **v**, **w**)[22,134,139,140] or the Mukaiyama one-pot ketone preparation based on the use of anhydrides **174** (**11a**, **b**, **c**, **k**, **l**, **x**).[22,134,139]

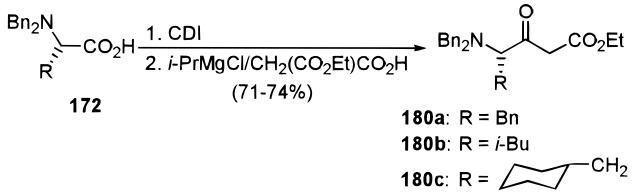
Although no attempts were made to treat the benzylesters **14** themselves with simple alkyllithium or Grignard reagents, several cases are known in which functionalized organolithium reagents do in fact undergo smooth acylation with formation of the desired ketones without displaying undesired double addition, e.g., **175**,[141] **176a**,[142] **176b**,[142,143] **176c**,**d**,[142] **176e**,[75,144] **177**,[75,144] **178**,[145] and **179**.[63] Diastereoselectivity in the case of ketone **177**[75,144] is due to thermodynamic control based on epimerization of the stereogenic center bearing the phosphine−oxide moiety, whereas diastereomerically pure ketone **178** results from kinetic control.[145] In the case of the chloromethyl ketones produced by carbenoid reactions, compound **179a** was prepared from the benzyl ester **14**, while analogues **179b**,**c** were synthesized



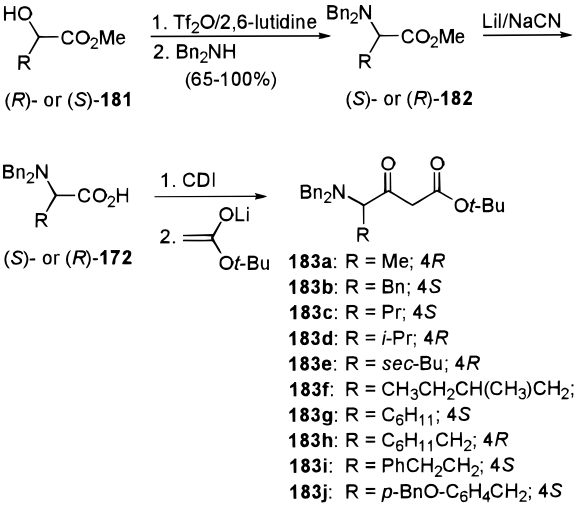
similarly using the corresponding ethyl esters.[63] The latter are accessible by N-benzylation of amino acid ethyl esters using BnBr/EtN(*i*-Pr)$_2$.[63]



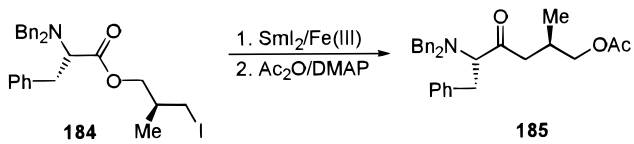
β-Keto esters of the type **180** are accessible by reaction of the benzyl esters **14** with the enolate CH_2=C(OEt)OLi, albeit in low yields (∼ 40%).[133] More efficiently, the *N*,*N*-dibenzylamino acids **172** can be activated via imidazolide formation using carbonyldiimidazole (CDI) and reacted in situ with the magnesium enolate of malonic acid monoethyl ester, which affords enantiomerically pure *β*-keto esters **180** following decarboxylative acidic workup.[133]



In a synthetically versatile variation of this strategy, *N*,*N*-dibenzylamino acids **172**, prepared either from the corresponding α-amino acids **1** or from chiral α-hydroxy acids **181**, were again activated by CDI, but this time reacted with lithio *tert*-butyl acetate to afford excellent yields of products **183**.[137] The ketones turned out to be optically pure (ee > 97%), the only exceptions being **183a** (ee = 70%) and **183j** (ee = 94%). Because many different α-hydroxy esters are known, this approach is very powerful. Indeed, esters **182** are also potential candidates for the synthesis of *N*,*N*-dibenzylamino aldehydes **10**, especially in those cases in which the classical route via α-amino acids **1** is not feasible.



In other novel work with a different goal, the SmI_2-mediated intramolecular nucleophilic acyl substitution (INAS) reaction was successfully applied to the ester **184**, affording the *N*,*N*-dibenzylamino ketone **185** with perfect preservation of stereochemical integrity.[146] The intermediate Sm reagent adds intramolecularly to the ester function which is then acylated. This methodology opens the way to a diverse set of new chiral α-*N*,*N*-dibenzylamino ketones containing additional functional groups and/or stereogenic centers in the side chain.



B. Reactions

1. Hydride Reductions and Grignard-Type Additions

N,N-Dibenzylamino ketones are useful chiral building blocks in a variety of different reactions, hydride reduction being an important option. Indeed, many but not all of these ketones have been subjected to reduction. The initial expectation that *N,N*-dibenzylamino ketones such as **11** react with hydride reagents of the kind $NaBH_4$ to produce the nonchelation controlled products **43** having the syn configuration was completely fulfilled.[22,134] High levels of 1,2-asymmetric induction are characteristic of this reaction, even if such simple reducing agents as $NaBH_4$ in methanol or ethanol are employed (Table 6). Generally the products are enantiomerically pure, which means that synthesis and reduction entail no significant racemization (ee > 98%). $LiAH_4$ can also be used and is sometimes the method of choice,[22,63,134] but in certain cases partial racemization may occur.[22] The diastereo- and enantiomerically pure amino alcohols are useful intermediates. For example, treatment of the syn configurated chlorohydrins (Table 6, entries 25−27) with MeLi as a deprotonating agent results in the formation of syn configurated aminoalkyl epoxides **51**. Thus, the sequence is stereochemically complementary to the reaction of carbenoids XCH_2Li with aldehydes **10** which provide the diastereomers **52** (section IIB1).

Table 5. Synthesis of Ketones 11 from Weinreb Amides 173

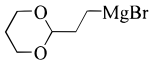
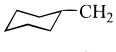
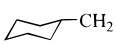
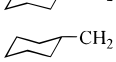
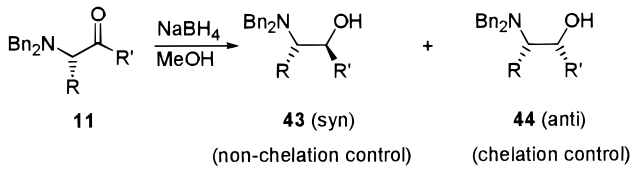
entry	R in **173**	R'M	ketone	yield (%)	ref(s)
1	Me	MeLi	**11a**	85	134
2	Bn	MeLi	**11b**	94	22,134
3	Bn	MeMgI	**11b**	92	22,134
4	Bn	EtLi	**11c**	89	22,134
5	Bn	*n*-BuLi	**11d**	72	22,134
6	Bn	PhLi	**11e**	89	22,134
7	Bn		**11f**	74	22,134
8	Bn	n-$C_{11}H_{23}MgBr$	**11g**	52	22,134
9	Bn		**11h**	>90	138
10	Bn	CH_2=$CHMgBr$	**11i**	71	134
11	Bn	Ph≡CLi	**11j**	83	134
12	*i*-Bu	MeLi	**11k**	96	22,134
13	*i*-Bu	EtLi	**11l**	89	22,134
14	*i*-Bu	*n*-BuLi	**11m**	57	22,134
15	*i*-Bu	PhLi	**11n**	87	22,134
16	*i*-Bu		**11o**	75	22,134
17		MeLi	**11p**	83	22,134
18		EtLi	**11q**	66	22,134
19		*n*-BuLi	**11r**	67	22,134
20		PhLi	**11s**	96	22,134
21			**11t**	78	22,134
22	$BnOCH_2$	MeLi	**11u**	78	46

Table 6. $NaBH_4$ Induced Nonchelation Controlled Reduction of *N-N*-Dibenzylamino Ketones with Preferential Formation of Syn Configurated Amino Alcohols

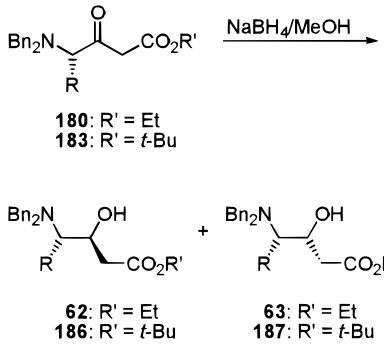
entry	ketone	yield (%)	syn : anti	ref(s)
1	**11b**	88	94 : 6	22,134
2	**11c**	93	95 : 5	22,134
3	**11d**	94	95 : 5	22,134
4	**11e**	86	95 : 5	22,134
5	**11f**	90	95 : 5	22,134
6	**11g**	87	95 : 5	22,134
7	**11h**	95	97 : 3	138
8	**11i**	78	86 : 14	134
9	**11j**	82	82 : 18	134
10	**11k**	90	90 : 10	22,134
11	**11l**	92	92 : 8	22,134
12	**11m**	98	94 : 6	22,134
13	**11n**	95	95 : 5	22,134
14	**11o**	84	95 : 5	22,134
15	**11p**	81	94 : 6	22,134
16	**11q**	93	92 : 8	22,134
17	**11r**	90	91 : 9	22,134
18	**11s**	86	95 : 5	22,134
19	**11t**	92	95 : 5	22,134
20	**11u**	91	97 : 3	46,134
21	**11w**	85	>95 : <5	140
22	**11x**	84	96 : 4	66
23	**176e**	>95	90 : 10	75,144
24	**177**	>95	90 : 10	75,144
25	**179a**	76	88 : 12	63
26	**179b**	70	95 : 5	63
27	**179c**	75	95 : 5	63
28	**180a**	86	94 : 6	133
29	**180b**	84	90 : 10	133
30	**180c**	84	93 : 7	133
31	**183b**	90	96 : 4	137
32	**183d**	91	98 : 2	137
33	**183e**	87	94 : 6	137
34	**183f**	90	>98 : <2	137
35	**183g**	89	99 : 1	137
36	**183h**	91	>96 : <4	137
37	**183i**	92	>96 : <4	137



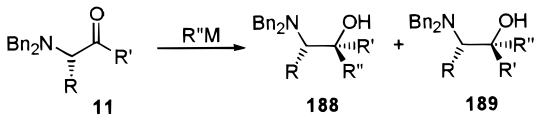
11 **43** (syn) (non-chelation control) **44** (anti) (chelation control)

Many different *N,N*-dibenzylamino keto esters **180**[133] and **183**[137] have been subjected to $NaBH_4$ reduction with diastereoselective formation of alcohols **62** and **186**, respectively (Table 6, entries 28−37). This is an attractive alternative to chelation controlled aldol addition to α-amino aldehydes (section IIC). For example, a simple synthesis of statine based on the reduction of **179** (R = *i*-Bu) has been reported.[133] It is also possible to carry out a wide variety of carbonyl-preserving reactions of the ketones and then to follow up with nonchelation controlled reduction (section IIIB2).

Grignard-type additions to ketones **11** also occur with excellent degrees of nonchelation control with preferential formation of tertiary alcohols **189**[33b,147] (Table 7). The only exception appears to be phenyllithium which results in diastereoselectivities of only 72−85%. In the case of Grignard reagents having



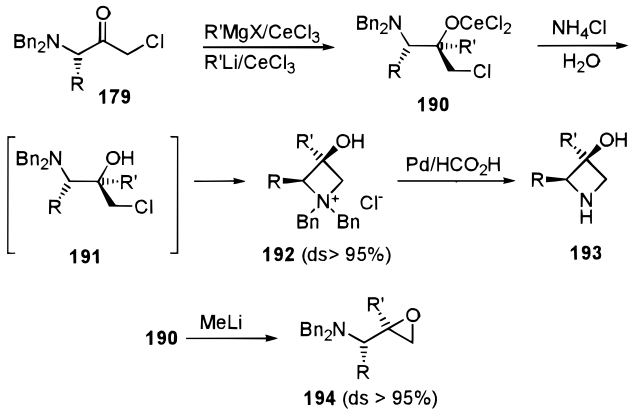
β-hydrogens, a serious side reaction is caused by β-hydride reduction (which occurs with complete nonchelation control), a problem that can be circumvented by using alkyllithium reagents. The products are optically pure (ee > 98%). All four possible stereoisomers of compounds of the type **188**/**189** can be prepared on the basis of this strategy. Thus, the diastereomeric products **188** are accessible by switching the order of the reaction sequence (first introducing R″ then reacting with R′M), while the mirror images can be prepared by using (*R*)-configurated α-amino acids as the starting materials. The structural element of tertiary β-amino alcohols occurs in a number of alkaloids and in certain pharmaceuticals.[148]



Another area of potential application concerns the nonchelation controlled addition of organocerium reagents to the chiral 1-aminoalkyl chloromethyl ketones **179**.[149] The products **191** are formed with > 95% diastereoselectivity and undergo spontaneous intramolecular N-alkylation with the formation of azetidinium salts **192**. Deprotection with Pd/HCO_2H affords the corresponding neutral 3-azetidinols **193** in excellent yield.[149] Alternatively, treatment of the primary adducts **190** with MeLi prior to workup makes α-amino epoxides of the type **194** accessible which in turn are useful building blocks in further transformations.

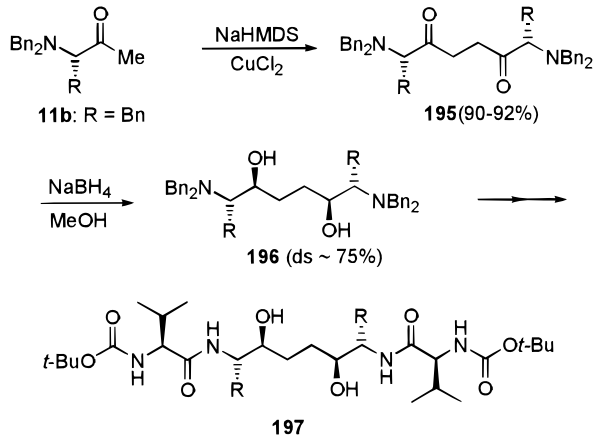
Table 7. Nonchelation Controlled Grignard-Type Reactions of *N*,*N*-Dibenzylamino Ketones 11[33b,147]

entry	ketone	R″M	conversion (yield %)	**188** : **189**
1	**11b**	*n*-BuLi	75 (46)	5 : 95
2	**11b**	*n*-$BuCeCl_2$	100 (72)	<5 : >95
3	**11b**	PhLi	80 (51)	15 : 85
4	**11d**	MeLi	100 (84)	5 : 95
5	**11d**	$MeCeCl_2$	100 (77)	<5 : >95
6	**11d**	Ch_2=$CHMgBr$	100 (73)	8 : 92
7	**11d**	CH_2=$CHCH_2MgBr$	100 (86)	<5 : >95
8	**11d**	PhLi	100 (76)	28 : 72
9	**11e**	MeLi	100 (81)	<5 : >95
10	**11e**	*n*-BuLi	90 (69)	<5 : >95
11	**11e**	CH_2=$CHCH_2MgBr$	100 (89)	<5 : >95
12	**11k**	PhLi	90 (65)	14 : 86
13	**11m**	MeLi	100 (87)	5 : 95
14	**11n**	MeLi	100 (89)	5 : 95
15	**11n**	*n*-BuLi	100 (84)	<5 : >95



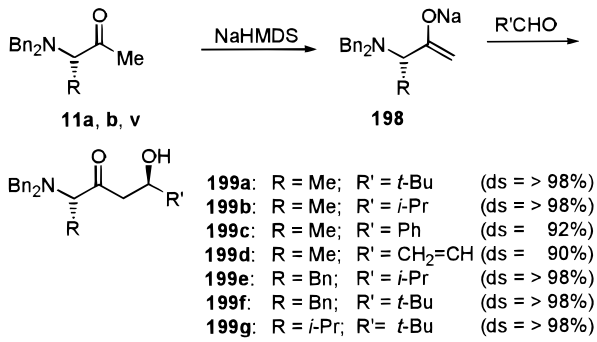
2. Transformations with Initial Preservation of the Ketone Function

Several fundamentally different strategies for the transformation of *N*,*N*-dibenzylamino ketones of the type **11** with preservation of the carbonyl function have been developed recently. In one approach, the methyl ketone **11b** was deprotonated and the intermediate enolate oxidatively dimerized with formation of the 1,4-diketone **195**.[135] Upon subjecting the latter to the usual $NaBH_4$ reduction, the (*S*,*S*)-configurated diol **196** was obtained with 75% diastereoselectivity. More bulky reducing agents such as L-Selectride are likely to be more selective (see below). Following deprotection and peptide coupling, the C_2 symmetric diol **197** was obtained, which is of interest as an HIV protease inhibitor.[135] In another study, methyl ketones **11a**,**b** were also deprotonated regioselectively, but in this case the corresponding Na enolates were alkylated with $BrCH_2CO_2t$-Bu to afford keto esters which were then subjected to the usual $NaBH_4$ reduction (ds > 99%).[150a] The products are valuable because further transformations such as lactone formation followed by stereoselective α-alkylation are possible.

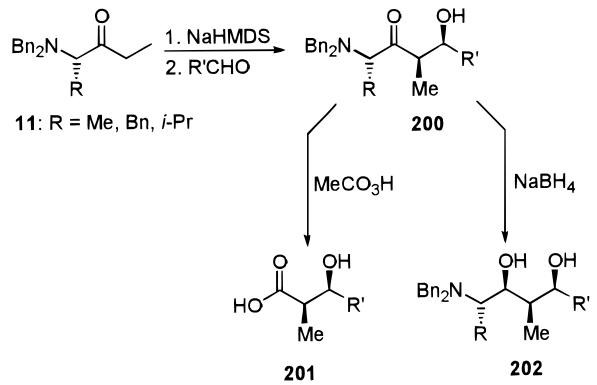


Enolates derived from these methyl ketones also proved to be highly diastereoselective in aldol reactions. For example, ketones **11a**, **b**, **v** were treated with LDA,[33b,139] LiHMDS,[150b] NaHMDS,[150b] or KHMDS[150b] with formation of the corresponding enolates. In reactions with aldehydes, the sodium enolates **198** turned out to be most selective, the aldol adducts **199** being formed in yields of 72−94% and

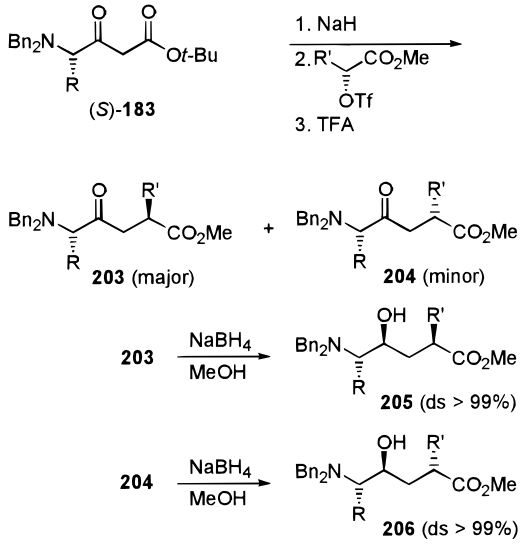
diastereoselectivities of 92−99%.[150b] Although intramolecular metal complexation may be involved in the case of the less selective Li enolates, an "open" transition state was proposed for the reactions of the Na enolates. The products **199** are useful in a number of ways, including oxidative cleavage of the aminoalkyl moiety with formation of enantiomerically enriched aldols R′CH(OH)CH_2CO_2Me.[150] In the case of **11b**/LDA, the aldol addition to acetaldehyde provided a 70:30 mixture of diastereomers, whereas the reaction with benzaldehyde led to the aldol condensation product even at −78 °C in a slow reaction.[33b] Thus, it appears that the outcome of the reactions of such Li enolates depends on the details of the experimental protocols.[33b,139,150]



In the case of the analogous aldol reaction of the α-(*N*,*N*-dibenzylamino) ethyl ketones **11** (R = Me, Bn, *i*-Pr), essentially one of four possible diastereomers **200** was formed.[136] In this process, the aldehydes R′CHO can be varied considerably. This means that the previously observed diastereofacial selectivity is maintained and that simple diastereoselectivity is also complete in favor of syn stereochemistry. Again, oxidative cleavage is possible, in this case affording the propionic acid aldol products **201** in enantio- and diastereomerically pure form.[136] In view of the commercial availability of NaHMDS, this methodology is a cost-effective alternative to the usual procedures based on boron or titanium enolates derived from other chiral precursors. Compounds **200** can also be subjected to $NaBH_4$ reduction with formation of the expected nonchelation controlled adducts **202** having four contiguous stereogenic centers with perfect control of absolute and relative configuration.[136] Interesting synthons which have been prepared but not applied in organic synthesis are enolsilanes derived from ketones **11**.[33b,136]



In an important application of *N*,*N*-dibenzylamino β-keto esters **183**, the Na enolates derived thereof were reacted with (*R*)-2-triflyloxy esters to form the corresponding tricarbonyl compounds which were immediately treated with TFA.[151] The overall process involves S_N2 alkylation and decarboxylation with formation of γ-keto esters **203**/**204**. Although the sequence might be expected to be stereospecific with inversion of configuration, the ratios of products **203**/**204** turned out to range between 85:15 and 97:3, indicating a small amount of stereochemical erosion. The enantiomeric purity of the major adduct **203** was checked and found to be complete (ee > 95%). Use of the (*S*)-configurated 2-triflyloxy esters produces products **204** preferentially, which demonstrates convergence. Both diastereomers react with $NaBH_4$ under complete nonchelation control to afford alcohols **205** and **206**, respectively, which are useful hydroxyethylene dipeptide isosteres.[151]



In another application, ketone **176b** was converted into keto ester **207** which was subjected to Cu-catalyzed conjugate addition reactions.[143] Although the yields of adducts **208** are modest (37−65%), 1,4-asymmetric induction turned out to be remarkably high. The X-ray crystal structure of compound **207** shown in Figure 3 indicates that one of the two

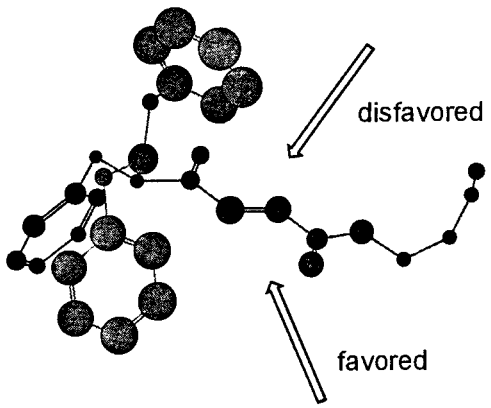
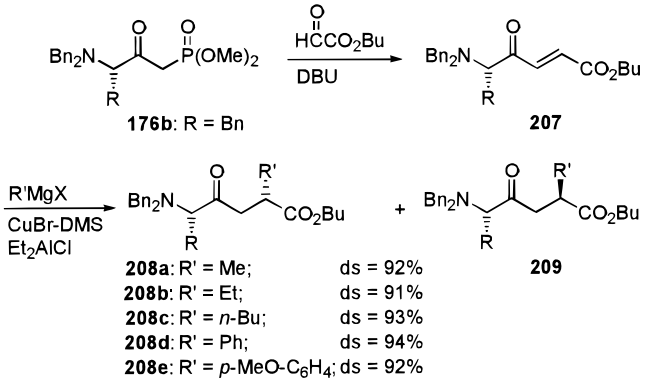
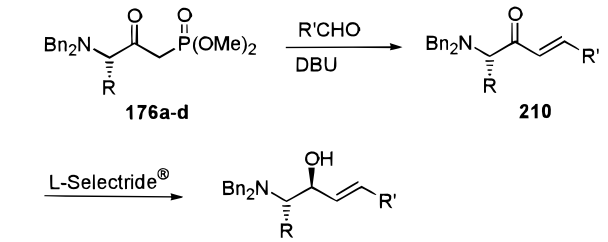


Figure 3. Structure of compound **207** as determined by X-ray crystallography.[143]

benzyl groups of the *N*,*N*-dibenzylamino moiety shields the top face of the enone in a conformer which may also predominate in solution. Therefore, attack of the organocopper reagent would be expected to occur on the face opposite to the *N*,*N*-dibenzylamino group and at the electronically more reactive position.[143] Indeed, this is what was observed.

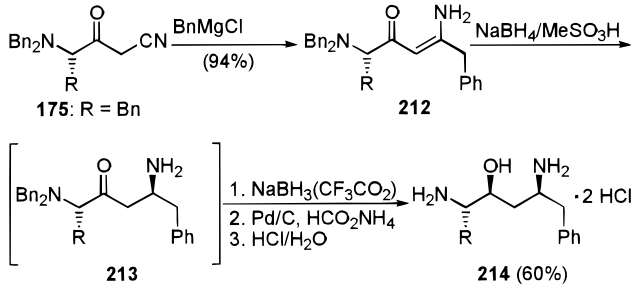


In other work, enones **210** were prepared by Horner−Wittig reactions and then reduced with such reagents as $NaBH_4$, $NaCNBH_3$, $NaBH_4/ZrCl_4$, $NaBH_4/SnCl_4$, $NaBH_4/ZnCl_2$, $NaBH_4/TiCl_4$, or L-Selectride.[142] Although $NaBH_4$ resulted in > 90% diastereoselectivity in favor of the expected nonchelation controlled products **211**, L-Selectride turned out to be the reagent of choice in all cases (ds ≥ 99%). These results suggest that this bulky achiral reagent ought to be tested in reactions of ketones **11** as well.

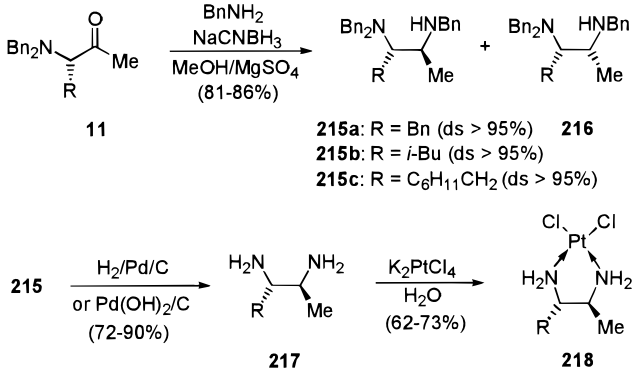


211a: R = Me; R' = Ph
211b: R = Me; R' = *p*-CF_3-C_6H_4
211c: R = Me; R' = *m*-NO_2-C_6H_4
211d: R = Bn; R' = *p*-CHO-C_6H_4
211e: R = Bn; R' = *p*-MeO-C_6H_4
211f: R = Bn; R' = α-naphthyl
211g: R = Bn; R' = Ph
211h: R = R' = Ph
211i: R = *i*-Bu; R' = Ph

Cyano ketones of the type **175** are versatile compounds of considerable synthetic potential.[141] One application concerns the Grignard addition of benzylmagnesium chloride, affording the enaminone **212** as a crystalline compound in 94% yield and an ee of > 99.5%. Although enaminones are usually quite resistant to reduction, a special and highly stereoselective experimental protocol was devised. Accordingly, a THF/*i*-PrOH solution of enaminone **212** was added to a mixture of $NaBH_4$ (2.5 equiv) and $MeSO_3H$ (6.3 equiv) in THF at 5 °C, resulting in the intermediate ketone **213** with a diastereoselectivity of 95%.[141] This remarkable result was explained by intramolecular H-bonding in the enaminone **212**. The fact that hydride delivery occurs selectively from the bottom side is reminiscent of cuprate attack on the related enone **207**, which occurs with the same sense of diastereoselectivity.[143] Whatever the explanation may be, compound **213** cannot be isolated because of NH_3 elimination. Further reduction by $NaBH_4$ is not observed because the immediate product is actually bound as a boron enolate. However, addition of $NaBH_3(CF_3CO_2)$ causes sequential protonation and nonchelation controlled reduction in a one-pot procedure, deprotection and workup delivering compound **214** in 60% overall yield (ds = 93%; ee > 99%).[141] Variation of the reaction components should make a diverse set of analogues accessible. Thus, the sequence constitutes an efficient, flexible, and economical synthetic protocol which is likely to be of industrial interest.

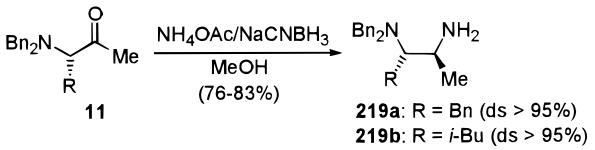


The synthetic value of *N*,*N*-dibenzylamino ketones is also illustrated by reductive amination with preferential formation of diamines **215**.[33b,147] Ketimines are likely intermediates which are reduced with high levels of nonchelation control. Unfortunately, the yields are acceptable only in the case of methyl ketones. Homologues appear to be so sterically hindered that essentially no reaction occurs. Compounds **215** were deprotected and converted into Pt complexes **218** which are of potential interest as *cis*-platinum analogues in cancer therapy.[147] The optical purity of the diamines was checked in one case (**217c**) by double acylation using the Mosher-chloride and analysis of the corresponding bis amide, demonstrating an ee value of > 93%.



Some of the ketones were also subjected to reductive amination using ammonia instead of benzylamine.[33b,147] Again, only the methyl ketones reacted. Regiospecifically protected diamines **219** were iso-

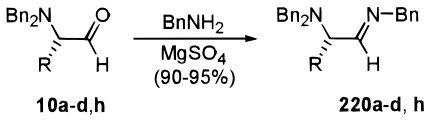
lated as the sole products. More work is necessary in this interesting area.



IV. Synthesis and Reactions of N,N-Dibenzylamino Aldimines

In principle, vicinal diamines are not only accessible by reductive amination of α-amino ketones as shown above, but also by C−C bond formation of α-amino aldimines. If the reactions of *N*,*N*-dibenzylamino aldehydes **10** described in section II could be extended to include the analogous aldimines, then a wide variety of different vicinal diamines would be accessible in a diastereoselective manner. Because vicinal diamines occur as components in certain natural products, pharmaceuticals, and ligands for asymmetric metal catalysis,[152] such an approach is of considerable synthetic value. However, it must be remembered that most aldimines are much less electrophilic than aldehydes, which means that reactivity with respect to such nucleophilic processes as Grignard-type additions is usually lower. Another potential difficulty is the possibility of partial racemization in the synthesis of α-*N*,*N*-dibenzylamino aldimines. Finally, because the donor properties of aldimines with respect to Lewis acids or organometallic reagents are different from those of the analogous aldehydes, the theoretical and practical question of chelation versus nonchelation control must be considered anew. Ideally, both diastereomers in a given reaction should be accessible on an optional basis.

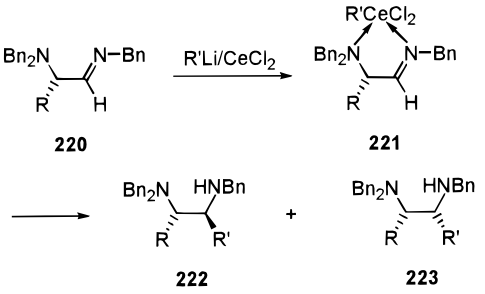
Many, but not all of these problems have been solved by combining metal and protective group tuning.[3] *N*,*N*-Dibenzylamino aldimines of the type **220** were first prepared by a simple condensation reaction in which aldehydes **10** were stirred with benzylamine in CH_2Cl_2 in the presence of $MgSO_4$ at 0 °C (90−95% yield).[23] No significant racemization occurs under these conditions.



Initial attempts to perform Grignard-like additions using R′MgX in various solvents, R′Li in THF, or R'_2CuLi/BF_3 failed. In contrast, the reaction of alkyllithium reagents in ether proved to be successful.[23] Cerium reagents R′Li/$CeCl_3$ constitute an alternative (Table 8). The yields in the case of the parent compound MeLi are poor but can be raised to acceptable values by employing three parts of MeLi per one part of $CeCl_3$, which presumably generates the very reactive and nonbasic Me_3Ce. The surprising aspect of all of these reactions is the fact that the chelation controlled products **222** are formed preferentially.[23] This selectivity pattern contrasts with the previously described reactions of R′Li and R′Li/$CeCl_3$ with the corresponding *N*,*N*-dibenzylamino aldehydes **10** (section IIB1). Thus, α-amino aldimines **220** appear to be better chelators for these reagents than the aldehydes **10**, which means that intermediate chelates of the type **221** are likely. In addition to differences in metal−oxygen and metal−nitrogen bond energies and bond lengths, the initial Lewis acid/Lewis base coordination involving an organometallic reagent or Lewis acid and an aldehyde RCHO occurs anti to the R-group,[153] whereas in the case of aldimines RCH═NR′ (which are *E*-configurated) coordination is necessarily syn to the R-group, which is a prerequisite for chelation.[153d]

Table 8. Chelation Controlled Grignard-Type Reactions of Aldimines 220[23]

entry	R	reagent	yield (%)	**222** : **223**
1	Me	*n*-BuLi	54	86 : 14
2	Me	*n*-BuLi/$CeCl_3$	71	88 : 12
3	Bn	MeLi	40	>95 : <5
4	Bn	MeLi/$CeCl_3$	28	>95 : <5
5	Bn	3 MeLi/$CeCl_3$	78	>95 : <5
6	Bn	3 MeLi/$LaCl_3$	63	>95 : <5
7	Bn	3 MeLi/$YbCl_3$	40	>95 : <5
8	Bn	*n*-BuLi	80	93 : 7
9	Bn	*n*-BuLi/$CeCl_3$	84	93 : 7
10	*i*-Pr	*n*-BuLi	85	93 : 7
11	*i*-Pr	*n*-BuLi/$CeCl_3$	80	89 : 11
12	*i*-Bu	*n*-BuLi	77	82 : 18
13	*i*-Bu	*n*-BuLi/$CeCl_3$	86	82 : 18
14	*i*-Bu	3 MeLi/$LaCl_3$	83	83 : 13
15	*i*-Bu	*n*-BuLi	76	87 : 13

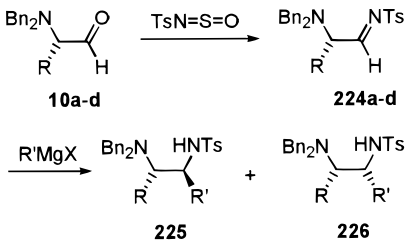


To reverse the sense of diastereoselectivity, it is necessary to weaken the donor strength of at least one of the nitrogen moieties in the aldimines to the point where effective chelation no longer occurs. This was accomplished by protective group tuning. Accordingly, the benzyl group at the aldimine nitrogen was replaced by the electron-withdrawing tosyl group.[23] The required aldimines **224** were prepared by the Weinreb procedure[154] and subjected to in situ Grignard reactions.[23] Because the *N*-tosyl group renders the aldimines **224** much more electrophilic and therefore more reactive than the *N*-benzyl analogues **220**, they were expected to show reactivity and selectivity patterns similar to the aldehydes **10**. Indeed, an excess of R′MgX gave rise to acceptable yields of the nonchelation controlled adducts **226**[23]

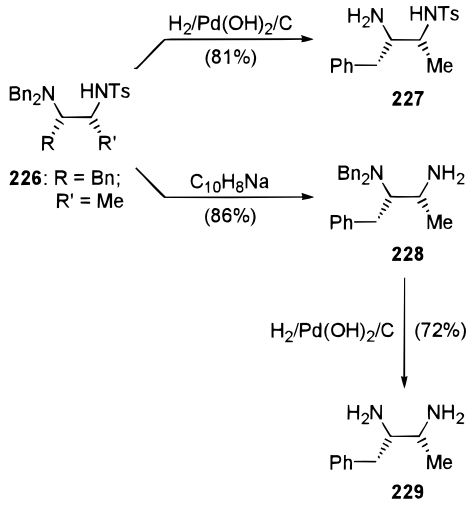
Table 9. Nonchelation Controlled Reactions of Aldimines 224[23]

entry	R	reagent	yield (%)	**225** : **226**
1	Me	MeMgBr	90	11 : 89
2	Me	EtMgBr	89	<5 : >95
3	Me	*n*-BuMgCl	76	15 : 85
4	Me	PhMgCl	89	8 : 92
5	Me	CH_2=CHMgBr	85	6 : 94
6	Me	CH_2=$CHCH_2$MgCl	71	6 : 94
7	Bn	MeMgBr	95	7 : 93
8	Bn	EtMgBr	72	9 : 91
9	Bn	*n*-BuMgCl	71	10 : 90
10	Bu	PhMgBr	82	6 : 94
11	Bu	CH_2=CHMgBr	79	6 : 94
12	Bu	CH_2=$CHCH_2$MgCl	86	<5 : >95
13	*i*-Pr	MeMgBr	91	7 : 93
14	*i*-Pr	EtMgBr	86	6 : 94
15	*i*-Pr	*n*-BuMgCl	61	6 : 94
16	*i*-Pr	PhMgCl	88	<5 : >95
17	*i*-Pr	CH_2=CHMgBr	69	8 : 92
18	*i*-Pr	CH_2=$CHCH_2$MgCl	57	8 : 92
19	*i*-Bu	MeMgBr	72	<5 : >95
20	*i*-Bu	EtMgBr	76	8 : 92
21	*i*-Bu	*n*-BuMgCl	80	10 : 90
22	*i*-Bu	PhMgCl	70	6 : 94
23	*i*-Bu	CH_2=CHMgBr	75	<5 : >95
24	*t*-$BuMe_2SiOCH_2$	MeMgBr	74	6 : 94

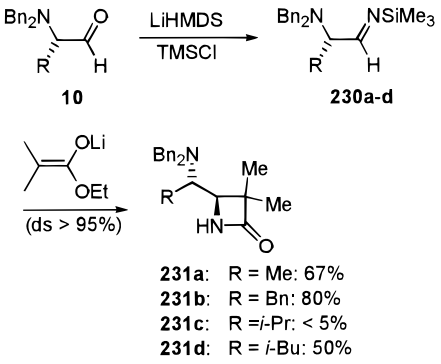
(Table 9). Thus, aldehydes **10** and aldimines **224** do in fact react analogously.



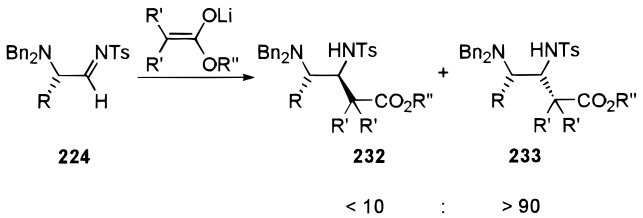
Because the products **226** have two differently protected amino groups, it is possible to perform regiospecific protective group manipulation (cf. **227**–**229**).[23]



Aldol-type reactions of achiral aldimines with Li enolates are well-known methods for the preparation of β-lactams,[155] one attractive possibility being based on the use of *N*-silyl aldimines.[156] Such aldimines are accessible by reacting the corresponding aldehydes with $(Me_3Si)_2NLi$ (LiHMDS).[156] A meaningful application of this method to the more complicated case of *N*,*N*-dibenzylamino aldimines requires the racemization-free synthesis and stereoselective aldol reaction of compounds **230**. Indeed, the reaction of the Li enolate prepared from isobutyric acid ester afforded single diastereomers **231**, the stereochemistry of which was identified unambiguously by X-ray crystallography.[3,157] The compounds are enantiomerically pure. As expected, they are the products of nonchelation control. The method has two limitations: (1) In the case of the bulky substrate **230c** derived from valine, no reaction occurs; (2) No products could be obtained using the parent Li enolate derived from ethyl or *tert*-butyl acetate. However, propionic acid ester enolates do in fact react smoothly.[157]



The more reactive *N*-tosyl-protected aldimines **224** undergo addition reactions with a variety of Li enolates to afford the nonchelation controlled aldol adducts **233** without concomitant lactam-forming cyclization.[3] The relative configuration was proven by X-ray analysis of a derivative of **233c**; control experiments showed complete enantiomeric purity (ee > 99%). However, initial attempts to deprotect by Na/NH_3- or Na/naphthalene-induced detosylation failed in these cases.[157] Other protective groups at the aldimine function need to be tested, e.g., hydrolytically labile R_2P=O groups.

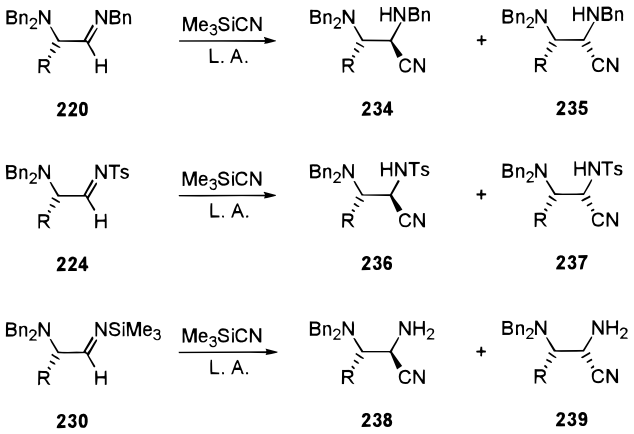


Lewis acid mediated Strecker-type reactions of *N*,*N*-dibenzylamino aldimines **220**, **224**, and **230** with Me_3SiCN afford the corresponding α,β-diamino nitriles with good degrees of nonchelation control[158] (Table 10). In the case of aldimines **230**, the silyl protective group is cleaved during workup with formation of nitriles **239**. The products are enantiomerically pure. In all cases, kinetic control pertains, as shown by control experiments.[158] Interestingly, such different Lewis acids as $TiCl_4$, BF_3, and ZnX_2 all induce the same sense of diastereoselectivity in favor of nonchelation control. So far it has not been

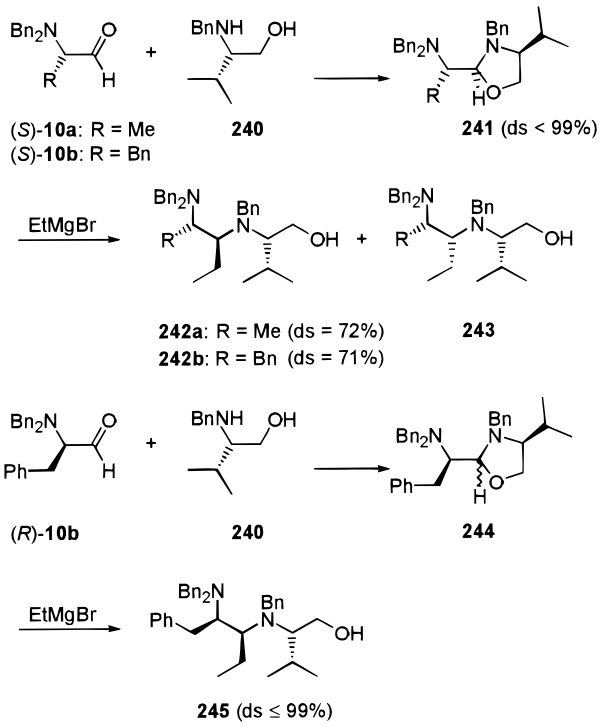
Table 10. Strecker-Type Reactions of Aldimines 220, 224, and 230[158]

entry	aldimine	reagent	yield (%)	chelation : non chelation **234** : **235** **236** : **237** or **238** : **239**
1	**220a**	$TiCl_4$	83	17 : 83
2	**220a**	$TiCl_4$	83	11 : 89
3	**220a**	$TiCl_4$	81	<5 : >95
4	**220a**	$SnCl_4$	75	19 : 81
5	**220a**	$SnCl_4$	75	8 : 92
6	**220a**	$SnCl_4$	78	11 : 89
7	**220a**	$BF_3{\cdot}OEt_2$	72	50 : 50
8	**220a**	$BF_3{\cdot}OEt_2$	76	6 : 94
9	**220a**	$ZnCl_2{\cdot}OEt_2$	81	13 : 87
10	**220a**	ZnI_2	84	24 : 76
11	**220a**	$ZnCl_2$	80	11 : 89
12	**220a**	Me_2AlCl	90	27 : 73
13	**220b**	$BF_3{\cdot}OEt_2$	22	<5 : >95
14	**224a**	$BF_3{\cdot}OEt_2$	49	10 : 90
15	**224b**	$BF_3{\cdot}OEt_2$	83	4 : 96
16	**224b**	$TiCl_4$	46	≤5 : ≥95
17	**224b**	Et_2AlCl	54	6 : 94
18	**224b**	Me_2AlCl	53	≤5 : ≥95
19	**224b**	$SnCl_4$	46	≤5 : ≥95
20	**224b**	$SnCl_4$	38	≤5 : ≥95
21	**224b**	$MgBr_2$	28	11 : 89
22	**224b**	$MgBr_2$	62	17 : 83
23	**224b**	$ZnBr_2$	61	17 : 83
24	**224b**	no L.A.	58	7 : 93
25	**224c**	$BF_3{\cdot}OEt_2$	53	≤5 : ≥95
26	**224d**	$BF_3{\cdot}OEt_2$	59	8 : 92
27	**230a**	Et_2AlCl	72	7 : 93
28	**230a**	Et_2AlCl	68	29 : 71
29	**230b**	Et_2AlCl	83	6 : 94
30	**230c**	Et_2AlCl	64	9 : 91
31	**230c**	Et_2AlCl	48	23 : 77

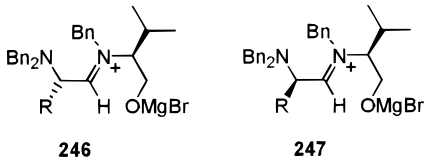
possible to reverse this trend in order to obtain the opposite diastereomers **234**, **236**, and **238**. It would be interesting to test $Eu(fod)_3$ which is known to effect chelation controlled reactions of Me_3SiCN to the *N,N*-dibenzylamino aldehydes **10**[119] (section IIC).



In the synthesis of stereochemically defined Ψ[CH-(alkyl)NH] pseudopeptides, a somewhat different approach to the preparation of dibenzyl-protected vicinal diamines was put into industrial practice.[159] Accordingly, (*S*)-configurated aldehydes **10** were converted into the oxazolidines **241** as single diastereomers by condensation with α-amino alcohols of known absolute configuration, e.g., *N*-benzyl valinol **240**. Grignard addition of EtMgBr, a well-known reaction in the case of other chiral oxazolidines,[160] resulted in ∼ 72:28 ratios of readily separable diamino alcohols **242**/**243** in > 80% yield.[159] Upon carrying out the same two-step reaction with (*R*)-**10b**, the corresponding oxazolidine **244** evolved as a 91:9 mixture of inseparable diastereomers, which was reacted with EtMgBr to form a single diamino alcohol **245**.

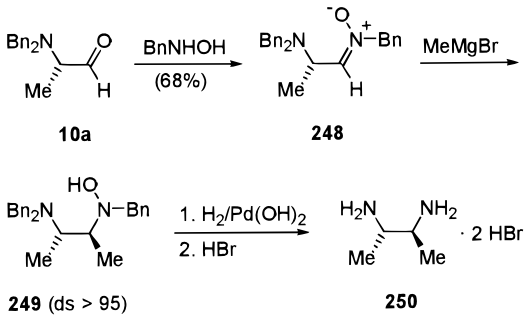


It is difficult to explain these remarkable results. However, intermediate iminium salts are likely, e.g., **246** and **247** or conformers thereof.[159] The *N,N*-dibenzylamino groups may well exert an effect similar to the one discussed in the case of the aldehydes **10** or aldimines **220**, **224**, and **230**. Formally, this would indeed lead to the preferential formation of adducts **242** and **245**. However, the additional stereogenic center in the intermediates **246**, **247** may also influence the reaction.



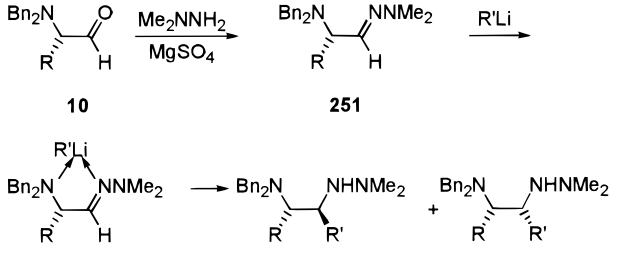
N,N-Dibenzylamino aldehydes **10** also serve as precursors for α-amino nitrones of the type **248**.[161] Reaction with MeMgBr proceeds with > 95% chelation control in favor of adducts **249**, albeit in low yield (25%). Reduction with $H_2/Pd(OH)_2$ affords (*S,S*)-2,3-diaminobutane (**250**) in enantiomerically pure form. A model derived from quantum mechanical calculations shows that a conformer is preferred in which the *re* side of the nitrone π-system is shielded by the benzyl groups.[161] However, coordination in the form

of a six-membered Mg-chelate would also explain the results.



10a **248** **249** (ds > 95) **250**

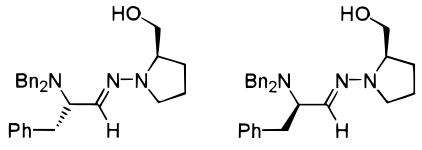
N,*N*-Dibenzylamino hydrazones **251** are readily prepared by condensation of aldehydes **10** with Me_2NNH_2.[162] The reaction with alkyllithium reagents results in preferential formation of the chelation controlled adducts **253** which can be deprotected with $H_2/Pd(OH)_2$ to afford novel β-amino hydrazines in enantiomerically pure form (ee > 98%).[162] Thus, aldimines **220** and hydrazones **251** react analogously, i.e., chelates **221** and **252**, respectively, are involved as reactive intermediates.



10 **251** **252** **253** **254**

253a: R = R' = Me (41%); ds = 92%
253b: R = Me; R' = *n*-Bu (71%); ds = 91%
253c: R =Bn; R' = Me (79%); ds = 94%
253d: R = Bn; R' = *n*-Bu (85%); ds = 91%
253e: R = *i*-Pr; R' = *n*-Bu (87%); ds = 86%

Finally, hydrazones **255** and **256** derived from the Enders auxiliary and (*S*)- and (*R*)-phenylalanine, respectively, are accessible without any signs of epimerization[130b] but have not yet been employed in synthetic reactions, in contrast to the methoxy analog.[94b]

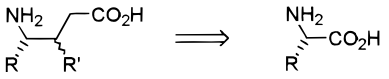


255 **256**

V. Synthesis and Reactions of γ-N,N-Dibenzylamino α,β-Unsaturated Carbonyl Compounds

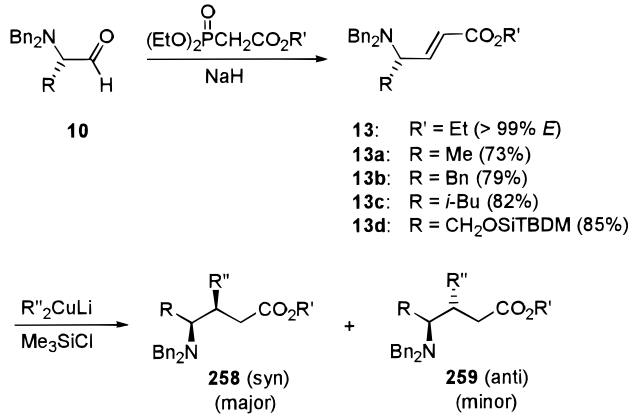
The development of stereoselective methods for the transformation of natural or unnatural α-amino acids **1** into γ-amino acids **257** is of considerable interest because of their potential biological activity, e.g., as GABA analogues.

This is one of the reasons why a great deal of effort has been invested in the synthesis and conjugate



257 **1**

addition reactions of vinylogous amino acid derivatives **13**.[3,24,163] Optimization of the Horner–Wittig reaction of aldehydes **10** affords the unsaturated esters **13** in good yields without any racemization.[24] Although Gilman reagents R'_2CuLi do not add to these compounds,[163] smooth reactions were observed in the presence of Me_3SiCl as an additive.[24] In almost all cases, excellent diastereoselectivity in favor of the syn adducts **258** was achieved (Table 11), even when the tin reagent *n*-Bu_3SnLi in the absence of copper salts was used (entry 8).

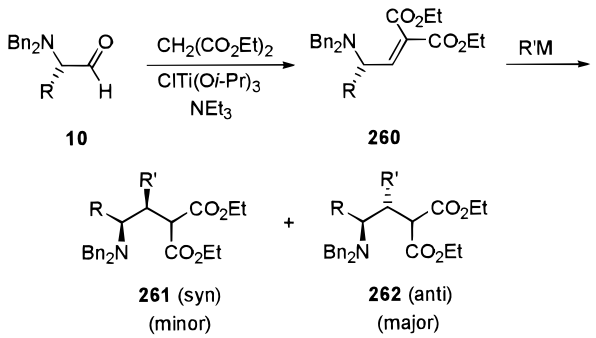


10

13: R' = Et (> 99% *E*)
13a: R = Me (73%)
13b: R = Bn (79%)
13c: R = *i*-Bu (82%)
13d: R = $CH_2OSiTBDM$ (85%)

258 (syn) (major) **259** (anti) (minor)

In the hope of reversing the sense of diastereofacial selectivity, reactions of the diesters **260** were envisaged,[24] because in this case 1,3-allylic strain[164] as a control element might be expected to operate. Whereas traditional Knoevenagel conditions failed to afford reasonable yields of optically active compounds **260**, application of a previously described version based on $ClTi(O\textit{i}\text{-}Pr)_3/Et_3N$[165] solved this synthetic problem. Compounds **260** turned out to be so reactive that even Grignard reagents in the absence of Cu salts undergo smooth addition. Moreover, diastereoselectivity is extremely high for a variety of reagents, the preferred adducts **262** having the anti configuration[24] (Table 11).



10 **260** **261** (syn) (minor) **262** (anti) (major)

Thus, conjugate addition reactions of the monoesters and diesters **13** and **260**, respectively, constitute stereochemically complementary methods. Indeed, hydrolysis/decarboxylation of the anti configurated diesters **262** affords the anti configurated monoesters **259**.[163] The explanation for the stereo-

Table 11. Conjugate Addition Reactions of Ethyl Esters 13 and Diesters 260[24]

entry	substrate	reagent	yield (%)	syn : anti **258** : **259** (or **261** : **262**)
1	**13a**	Me_2CuLi/Me_3SiCl	80	94 : 6
2	**13a**	$n\text{-}Bu_2CuLi/Me_3SiCl$	82	>95 : <5
3	**13a**	Ph_2CuLi/Me_3SiCl	80	95 : 5
4	**13b**	Me_2CuLi/Me_3SiCl	84	92 : 8
5	**13b**	$n\text{-}Bu_2CuLi/Me_3SiCl$	80	>95 : <5
6	**13b**	$(CH_2{=}CH)_2CuLi/Me_3SiCl$	46	94 : 6
7	**13b**	Ph_2CuLi/Me_3SiCl	78	95 : 5
8	**13c**	$n\text{-}Bu_3SnLi$	74	92 : 8
9	**13c**	Me_2CuLi/Me_3SiCl	87	93 : 7
10	**13c**	$n\text{-}Bu_2CuLi/Me_3SiCl$	81	>95 : <5
11	**13c**	$(CH_2{=}CH)_2CuLi/Me_3SiCl$	41	94 : 6
12	**13c**	Ph_2CuLi/Me_3SiCl	80	>95 : <5
13	**13c**	$Me_2CuLi/BF_3{\cdot}OEt_2$	71	>95 : <5
14	**13c**	$n\text{-}Bu_2CuLi/BF_3{\cdot}OEt_2$	70	93 : 7
15	**13d**	Me_2CuLi/Me_3SiCl	71	73 : 27
16	**260a**	$n\text{-}Bu_3SnLi$	71	5 : 95
17	**260a**	Me_2CuLi	68	21 : 79
18	**260b**	Me_2CuLi	77	<5 : >95
19	**260b**	$n\text{-}Bu_2CuLi$	81	<5 : >95
20	**260b**	Ph_2CuLi	82	<5 : >95
21	**260b**	MeMgBr	76	10 : 90
22	**260b**	EtMgBr	71	6 : 94
23	**260b**	$n\text{-}Bu_3SnLi$	79	<5 : >95

chemical outcome of the reactions involving the diesters **260** is traditional. On the basis of 1,3-allylic strain, reaction of conformer A (Figure 4a) would be expected to be favored relative to attack on conformer B. Indeed, force-field calculations of the *N,N*-dimethyl analogue predict the existence of two energy minima corresponding to A′ and B′, differing in energy by 3.0 kcal/mol[3] (Figure 4b). Thus, ground-state effects are expected to dictate the approximate geometry of the transition state as well.

In contrast, the stereochemical behavior of the monoesters **13** is more difficult to explain, and only one of several possibilities is discussed here.[24] Experimentally, the observed anti selectivity is not only pronounced, it is also general for other Michael additions (see below) and even 1,3-dipolar cycloaddition reactions involving nitrile oxides.[166] Force-field calculations of the *N,N*-dimethyl analogue of **13a** do not show a pronounced preference for any particular conformation (at most 0.33 kcal/mol difference)[3,167]

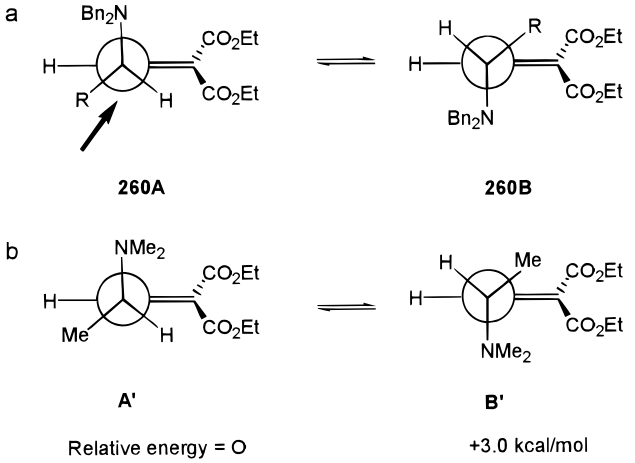


Figure 4. (a) Preferred direction of attack on conformer **260A**. (b) Calculated[3] relative energies of conformers A′ and B′ of the *N,N*-dimethyl analogue of **260**.

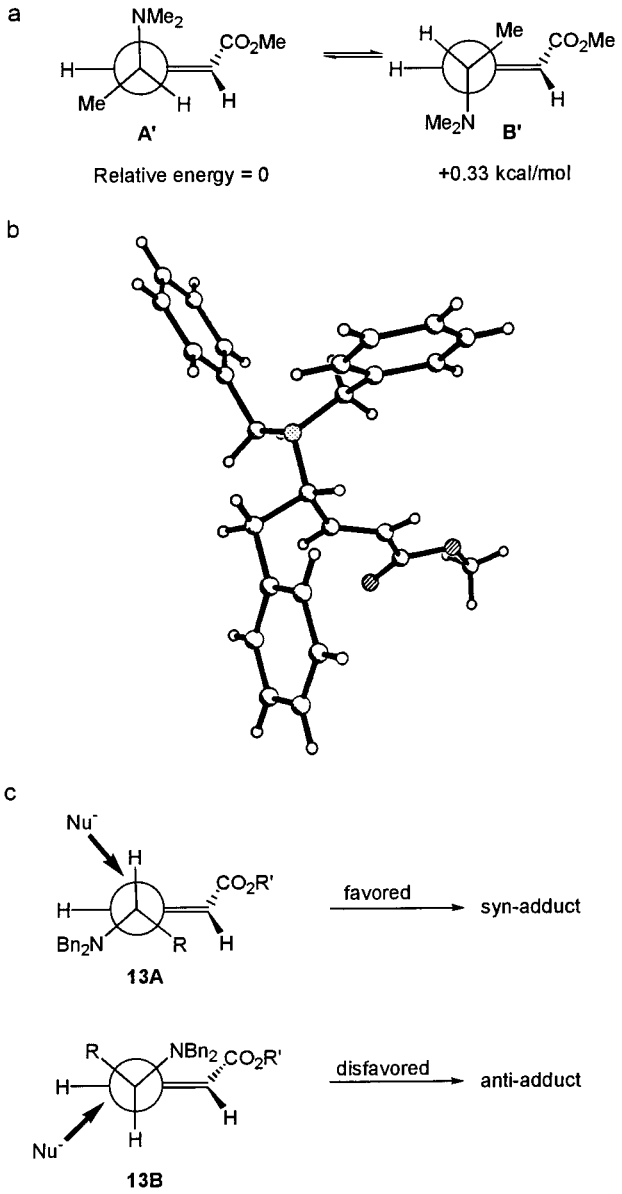
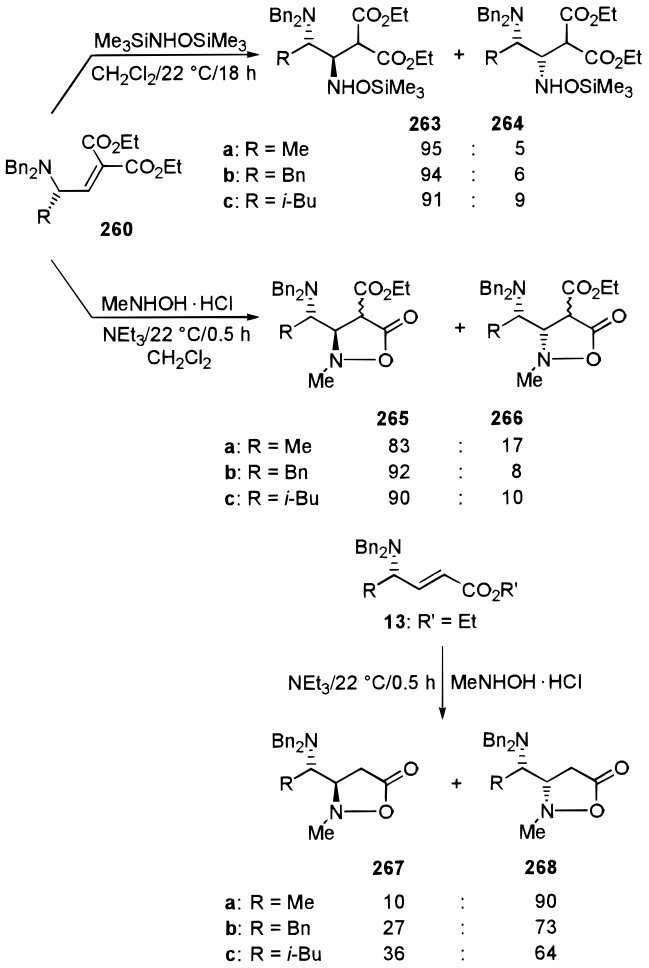


Figure 5. (a) Calculated relative energies of conformers A′ and B′ of the *N,N*-dimethyl analogue of **13a**.[167] (b) Structure of compound **13b** (R′ = Me) as determined by X-ray crystallography.[166] (c) Favored and disfavored modes of attack on conformers **13A** and **13B**, respectively.

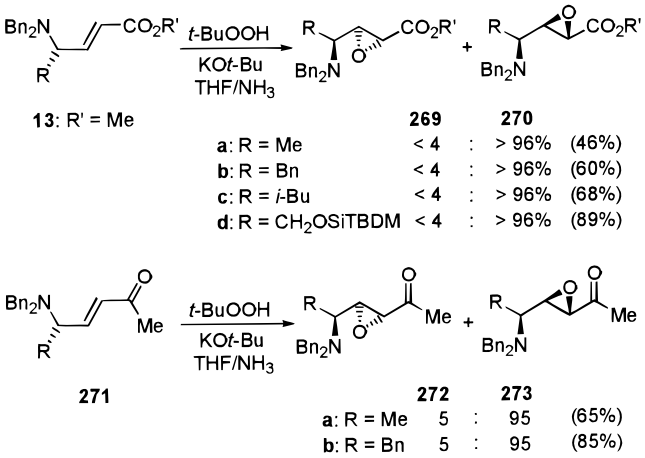
(Figure 5a). Furthermore, the X-ray crystal structure of **13b** (R′ = Me) (Figure 5b) shows the hydrogen at the stereogenic center to be in the inside position (corresponding to the calculated form of the most stable conformer of the *N,N*-dimethyl analog), but in solution the compound should be flexible.[166] If this is so, then the σ-bond between the sp^2-hybridized vinylic C-atom and the sp^3-hybridized C-atom of the stereogenic center might be expected to rotate in such a manner as to minimize steric interaction with the incoming reagent in the transition state. Such interactions are minimal if the smallest of the three substituents at the stereogenic center, namely hydrogen, points toward the incoming reagent. There are then two possibilities, namely A and B (Figure 5c). The former conformer with the large *N,N*-dibenzyl group in an outside position is preferred. This rather crude model needs to be checked by ab initio calculations of the actual transition states.

Qualitatively, however, it is useful whenever arguments based on the traditional application of 1,3-allylic strain fail. The Vedejs model[168] for explaining the stereochemical course of OsO_4-catalyzed dihydroxylation of chiral allylic alcohols and the Barrett stealth effect[168b] are related.

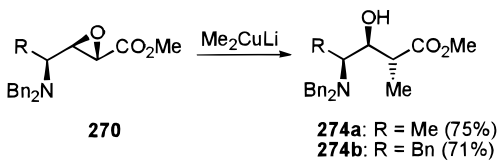
Michael addition of simple amines such as $BnNH_2$ to α,β-unsaturated esters **13** and **260** is hampered by preferred attack at the ester function with undesired formation of unreactive α,β-unsaturated amides.[163] However, hydroxylamines add smoothly without the need of a catalyst.[167] Even the sterically hindered compound $Me_3SiNHOSiMe_3$ reacts with diesters **260** (but not with monoesters **13**) to form the anti configurated hydroxylamines **263** preferentially. Upon using MeNHOH as the nitrogen nucleophile, stereoselective Michael addition is followed by spontaneous cyclization with formation of novel isoxazolidinones **265**.[167] Practically only one of four possible diastereomers is formed. The stereochemistry at the C-atom bearing the ester function is uniform, but unambiguous configurational assigment was not possible. However, in both reactions, the direction of nucleophilic attack is the same as in the cuprate reactions. Monoesters **13** also react, reversal of diastereoselectivity being the rule (cf. **268**).[167] However, the degree of diastereofacial selectivity is lower than in the case of the cuprate addition to the same substrates.



Under well-defined reaction conditions, epoxide-forming Michael additions of *t*-BuOOH to the α,β-unsaturated esters **13** and ketones **271** (prepared by Wittig reactions) are possible.[169] Essentially single diastereomers **270** and **273** result, the sense of diastereoselectivity being the same as in the case of cuprate and hydroxylamine additions. Mechanistically, highly stereoselective Michael additions followed by intramolecular S_N2 reactions by the intermediate enolate on the peroxide function are in line with the results.[169]

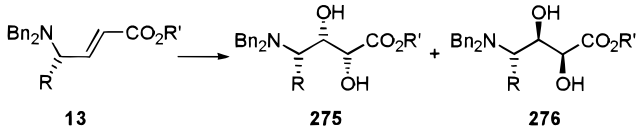


The synthetic value of epoxides **270** becomes apparent in regioselective ring-opening reactions with carbon or heteroatom nucleophiles such as cuprates or amines. They occur with complete inversion of configuration at the C-atom α to the carbonyl function. For example, cuprates react with esters **270** to provide compounds **274** as the sole products.[169] Such compounds have the structural elements of aldols. However, so far the diastereomers **274** are not accessible via stereoselective aldol additions to the *N*,*N*-dibenzylamino aldehydes **10**, since such reactions occur under nonchelation control with the formation of adducts having the opposite relative configuration in the amino alcohol portion of the compounds (section IIB3). Thus, of the four possible diastereomers of compounds of the type **274**, three are now readily accessible. The reaction of other nucleophiles such as amines with epoxides **270** also opens new synthetic perspectives.

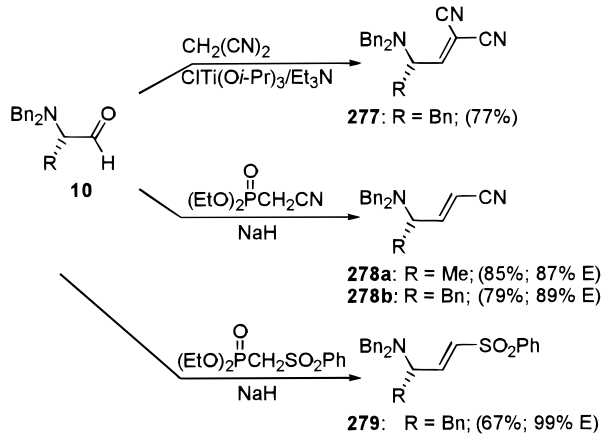


In another type of oxidation reaction, esters **13** were subjected to the Sharpless OsO_4-catalyzed asymmetric dihydroxylation using the AD-mix-α and AD-mix-β.[170] It turned out that the former represents the mismatched case and the latter the matched case. Thus, AD-mix-α favors diols **275** (ds = 72−92%), whereas AD-mix-β leads to diols **276** preferentially (ds = 86−95%). Interestingly, the situation is reversed upon dihydroxylating the *N*-Boc protected analogues. Thus, protective group tuning is capable

of turning the mismatched into the matched case, which is of practical and theoretical interest. It needs to be pointed out that the reactions of esters **13** are unusually slow (4−11 days).

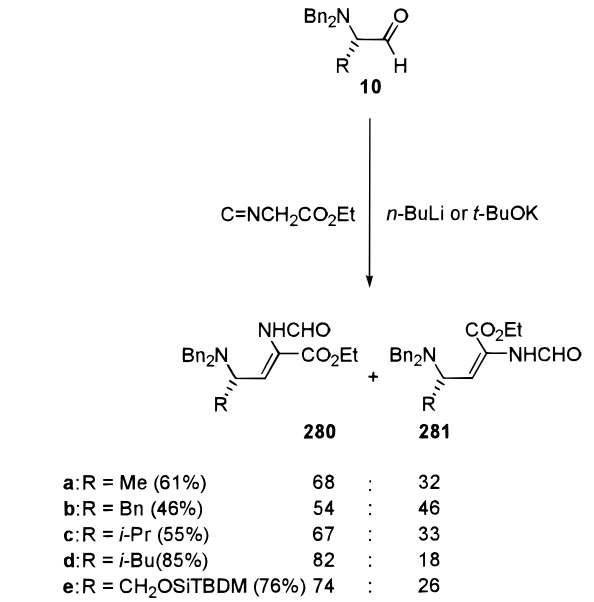


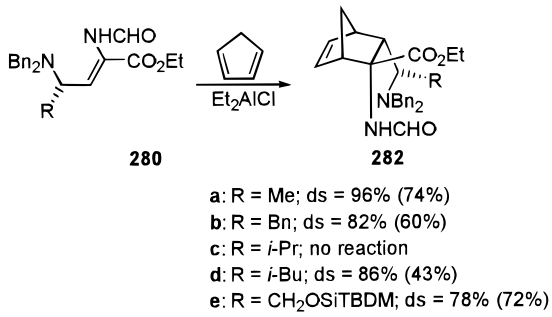
Other Horner−Wittig or Knoevenagel reactions of aldehydes **10** with formation of compounds of the type **277**−**279** have also been carried out.[163] Whereas cuprates do not readily react with these compounds, the previously mentioned enones **271** behave much like the esters **13**, provided ether serves as the solvent. In THF, exclusive 1,2-addition of R_2CuLi occurs at the ketone site with stereorandom formation of tertiary alcohols.[163] Other types of reactions of **277**−**279** remain to be explored. In an elegant study concerning the synthesis of enantiomerically pure pyrrolidines, 1,3-dipolar cycloaddition reactions of enones **271** with azomethine ylides were shown to proceed with > 95% diastereoselectivity.[171] In other work, the kinetic resolution of racemic aldehyde **10a** using a chiral lithiodimethylphosphonoacetate based on (−)-8-phenylmenthol was carried out, resulting in the Horner−Wittig product with 80% diastereoselectivity.[172]



Along a different line, aldehydes **10** were converted into γ-*N*,*N*-dibenzylamino α,β-didehydro amino acid esters **280**/**281** using the Schöllkopf isonitrile method.[44] The compounds were formed in enantiomerically pure form and could be separated by chromatography or fractional crystallization. The crystal structure of **280a** shows a conformation expected on the basis of 1,3-allylic strain[44] (Figure 6).

In view of the conformation revealed by the X-ray structural analysis, it was expected that Diels−Alder reactions should occur preferentially from the less shielded top face (C3−*si*, C4−*re* corresponding to the numbering shown in Figure 6). However, upon reacting compound **280a** with cyclopentadiene in the presence of Et_2AlCl, a single cycloadduct **282a** was formed, corresponding to a completely diastereoselective attack from the seemingly more shielded bottom side (C3−*re*, C4−*si*)![44] The other esters behave similarly, although with lower degrees of diastereofacial selectivity. 1,3-Dipolar cycloaddition using CH_2N_2 also proved to be diastereoselective (ds = 74−99%),[44] the preferred direction of attack being the same as in the case of the Diels−Alder reactions.





Clearly, the conformer shown in Figure 6 cannot be involved in the transition state of cycloaddition, although classical arguments based on 1,3-allylic strain[164] would predict this to be the case. A qualitative model similar to the one discussed for reactions of esters **13** was proposed.[44] Accordingly, in the transition state steric and torsional interactions

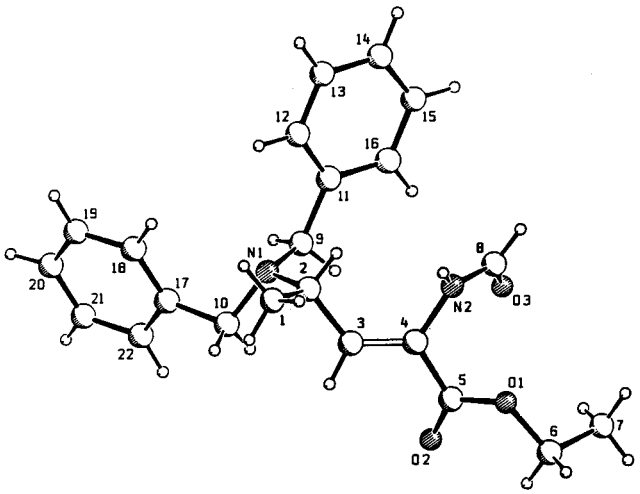


Figure 6. Crystal structure of α,β-unsaturated ester **280a**.[44]

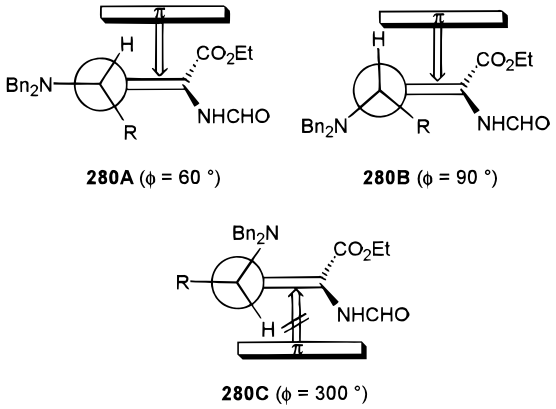
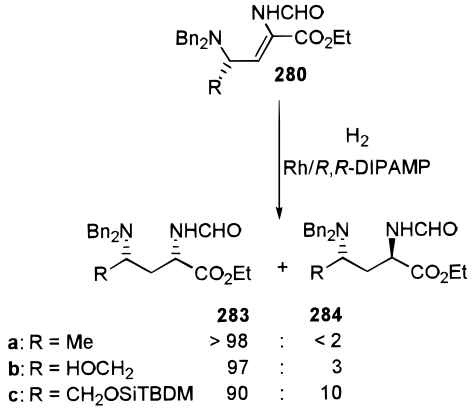


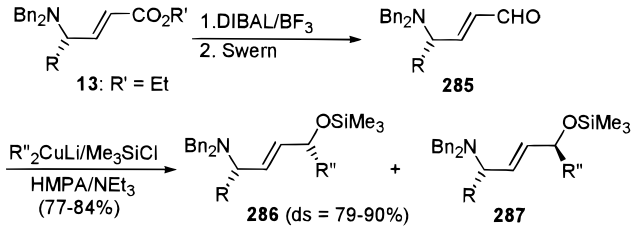
Figure 7. Favored modes of cycloaddition of conformers **280A** and **280B** and disfavored direction of attack on conformer **280C**.

within a compound **280** as well as steric repulsion between the two reactants need to be considered. A compromise can be anticipated if the allylic H-atom points more or less toward the incoming "flat" π-system achieved by rotation of the C2−C3 bond, as in A or B (Figure 7). This places the bulky amino group in the "outside" and the smaller R-group in the "inside" position. On this basis it becomes clear why diastereoselectivity decreases as R increases in size. Rotation of the C2−C3 bond in the other direction starts to place the bulky amino group in the "inside" position (cf. Figure 7C), giving rise to appreciable 1,3-allylic strain (steep rotational profile between ϕ = 270° and ϕ = 360°) as shown by force-field calculations.[44,99]

Compounds of the type **280** and **281** were also subjected to Rh-catalyzed hydrogenation with formation of α,γ-diamino acid esters, the direction and degree of asymmetric induction depending upon the nature of the protective groups and on the type of achiral phosphine utilized in the catalyst (ds = 52−90%).[173] The use of chiral phosphine ligands such as DIPAMP allows for higher levels of stereoselectivity as in the formation of 1,3-diamines **283a**−**c**.[173]



The question of the so-called vinylogous Cram/anti Cram selectivity crops up occasionally in the literature,[174] but systems capable of appreciable diastereoselectivity are rare.[175] The first successful efforts directed toward achieving such remote asymmetric induction were based on α,β-unsaturated aldehydes **285**, which can be considered to be the vinylogs of aldehydes **10**.[176] It was of interest to see if the *N*,*N*-dibenzylamino group is capable of exerting a steric or electronic effect across the π-system. However, such reagents as RLi, RMgX, or even the bulky titanium compound MeTi(O*i*-Pr)$_3$ led to 1:1 mixtures of the two possible diastereomeric allylic alcohols. In striking contrast, the reaction of cuprates R_2CuLi in the presence of Me_3SiCl, HMPA, and triethylamine (method A) resulted in significant levels of 1,4-asymmetric induction with preferential formation of adducts **286**. This also means pronounced regioselectivity in favor of 1,2-addition. Similar results were obtained by adding Me_3SiCl/HMPA/Et_3N to a mixture of the cuprate and the enal **285** at low temperatures (Method B).[176]

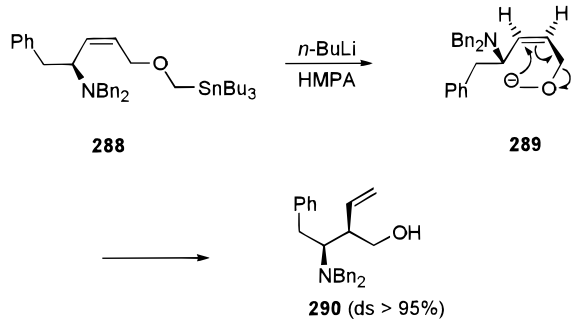


Because the 1,2-selective reagents RLi, RMgX, and RTi(O*i*-Pr)$_3$, which are known to react via transition states in which the metal is coordinated to the aldehyde function, show no diastereoselectivity whatsoever, the 1,2-addition reactions of the cuprates are not likely to proceed by a similar mechanism. This means that a different phenomenon must be involved. Indeed, the reactions are believed to be initiated by diastereoselective d,π*-complexation, which can be considered to be a type of 1,2-asymmetric induction leading to short-lived intermediates. This is followed by a "stereoselective walk" to the terminus of the extended π-system, ending with C−C bond formation at the aldehyde moiety.[176] The reason the d,π*-intermediates do not continue along the expected 1,4-pathway probably has to do with steric factors. The *Z*-analogues of aldehydes **285** react stereoselectively with alkyllithium reagents, a process which occurs by a different mechanism.[176]

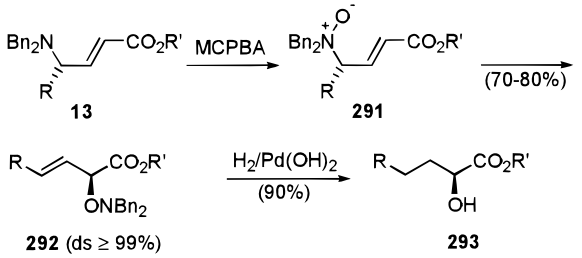
VI. Other Transformations of N,N-Dibenzylamino Compounds

The role of *N*,*N*-dibenzylamino groups in other types of reactions and classes of compounds has been studied in a few cases,[94b] and more can be expected. For example, Wittig−Still rearrangements involving tin compounds of the type **288** proceed with high diastereoselectivity.[177] Transition-state **289** has been postulated to account for these novel observations.

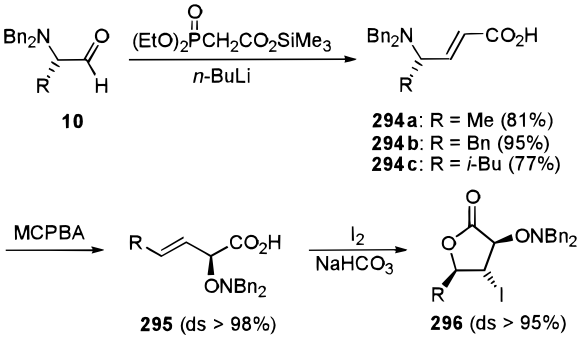
In another type of [2,3]-sigmatropic rearrangement, esters **13** were converted into hydroxylamines **292** with complete control of diastereoselectivity.[178] This type of self-immolative asymmetric synthesis involves rearrangement of the intermediate amine oxides **291**



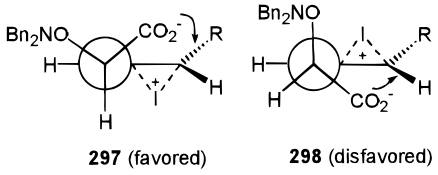
and can be utilized to prepare, inter alia, chiral hydroxy esters **293**.



The corresponding acids **295** were prepared analogously, diastereoselectivity again being > 99%. Iodolactonization provides the highly functionalized lactones **296** in a completely diastereoselective manner.[179]

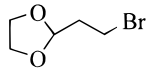


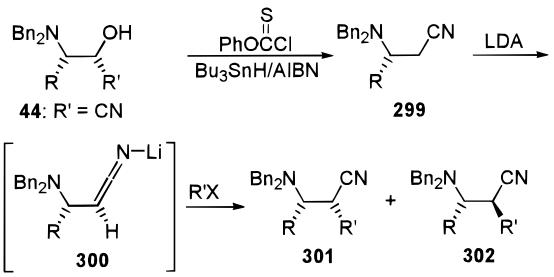
The results are best explained by trans addition of I^+ and RCO_2^- in a diastereofacially selective process (cf. **297**) in which the C−O σ-bond of the electronegative substituent has the outside position.[179] In the alternative transition-state **298**, this substituent occupies a position in which maximum π-σ^* interaction withdraws electron density from the olefinic π-system, making it less conducive to electrophilic attack.[168d]



Whereas all of the reactions of *N,N*-dibenzylamino aldehydes and aldimines involve *electrophilic* reaction centers next to a chiral *N,N*-dibenzylamino alkyl residue, the question arose whether *nucleophilic* centers would also react stereoselectively.[180] To this end the cyanohydrins **44** (R′ = CN) were first reduced to the nitriles **299**, which were then alkylated under basic conditions.[180] Table 12 shows that in most cases acceptable levels of 1,2-asymmetric induction in the preferential formation of nitriles **301** are possible. Intramolecular complexation of lithium by the *N,N*-dibenzylamino group appears not to be involved. The nitriles **301** are readily reduced by $LiAlH_4$ with production of 1,3-diamines having two stereogenic centers.[180]

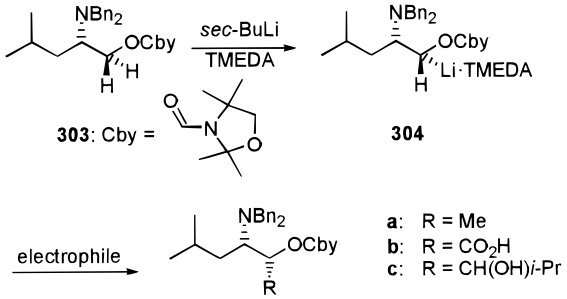
Table 12. Diastereoselective Alkylation of β-Amino Nitriles 296[180]

entry	R	R′-X	yield (%)	**301** : **302**
1	Me	MeI	53	60 : 40
2	Me	BnBr	45	80 : 20
3	Me	*i*-BuBr	39	75 : 25
4	Bn	MeI	77	71 : 29
5	Bn	BnBr	56	91 : 9
6	Bn		62	86 : 14
7	*i*-Pr	MeI	54	94 : 6
8	*i*-Pr	BnBr	46	>95 : <5
9	*i*-Pr	*i*-PrBr	40	87 : 13
10	*i*-Pr	*i*-BuBr	42	93 : 7



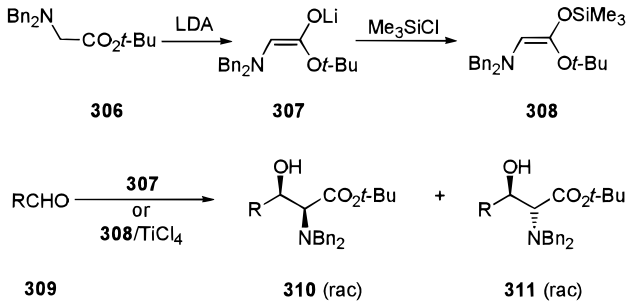
In a completely different type of chemistry, the carbamate **303** derived from leucinol was subjected to diastereoselective lithiation by *s*-butyllithium in the presence of TMEDA, resulting in selective reaction of only one of the diastereotopic protons.[181] The configurationally stable organolithium reagent **304** was then treated with electrophiles such as MeI, CO_2, and *i*-PrCHO, resulting in products **305** as single diastereomers. In the case of product **305a** formed by MeI alkylation, hydrolytic removal of the Cby-group afforded an alcohol which turned out to be identical to the product of the reaction of aldehyde **10d** with MeMgX (cf section IIB). Thus, the *N,N*-dibenzylamino group has a marked effect on stereoselectivity, just as in nucleophilic additions to *N,N*-dibenzylamino aldehydes **10**. Of course, the reasons must be different and are not yet fully understood. This elegant methodology is general, e.g., diastereoselectivity in the case of *N*-benzylprolinol is also complete.[181] In the case of achiral *N,N*-dibenzylamino ethanol, the corresponding carbamate can be deprotonated enantioselectively by the Hoppe method based on *s*-butyllithium/(−)-sparteine.[181] Stereose-

lective intramolecular carbolithiation of *N*,*N*-dibenzylamino-substituted alkynes has also been reported.[47]

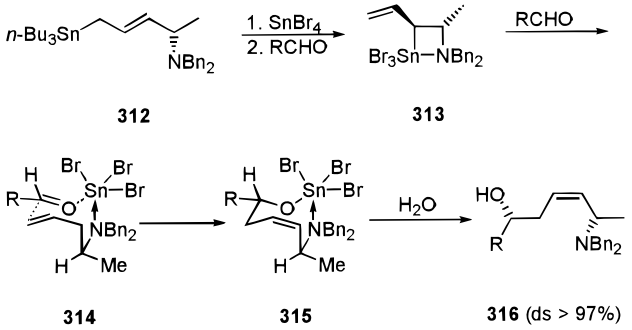


305 (ds > 95%)

The aldol addition of the lithium enolate **307** and the enolsilane **308** derived from the *N*,*N*-dibenzylaminoacetate **306** with aldehydes **309** has been described in detail.[182] Whereas **307** reacts anti selectively with preferential formation of aldols **311** (ds up to 83%), the $TiCl_4$-mediated addition of **308** yields predominantly the syn adducts **310** (ds up to 97%). In both cases, the degree of diastereoselectivity is highly dependent upon the nature of the aldehyde.[182] Acylation of **307** followed by $NaBH_4$-mediated reduction has also been described.[182]



Finally, an intriguing case of 1,5-asymmetric induction was reported in the $SnBr_4$-promoted reaction of the chiral 4-*N*,*N*-dibenzylaminoallylstannane **312** (prepared from the esters **13**) with aldehydes.[183] Essentially, single diastereomers **316** were obtained in enantiomerically pure form. Transmetalation of **312** and reaction of the intermediate allyltin bromide **313** with the aldehydes via a six-membered cyclic transition state **314** was postulated.[183]



VII. Conclusions

The chemistry summarized in this review shows that *N*,*N*-dibenzylamino aldehydes, prepared in enantiomerically pure form from α-amino acids or from other precursors, are extremely useful chiral building blocks in a wide variety of diastereoselective C−C bond forming reactions. These include Grignard-type reactions of RMgX, RLi, R_2CuLi, or $RTi(Oi\text{-}Pr)_3$, aldol additions of Li-enolates or enolboranes, homoaldol additions, ZnX_2-catalyzed Me_3SiCN additions, epoxide-forming carbenoid and sulfur ylide reactions, and hetero Diels−Alder cycloadditions, all of them proceeding with high levels of nonchelation control. The success of these reactions is based on protective group tuning. The phenomenon behind the unusual stereochemical behavior has not been unambiguously identified but is clearly based on the presence of two benzyl groups or sterically similar entities at the amino function. Although the results are formally in line with the Felkin−Anh model, ground-state conformational properties appear to correlate with the geometry in the transition state in which the *N*,*N*-dibenzylamino groups play a pivotal role. Reversal of diastereoselectivity is possible using reagents of high Lewis acidity, although chelation control is not as general. The directing effect of the *N*,*N*-dibenzylamino moiety at the stereogenic centers of other classes of compounds such as α-amino ketones, α-amino aldimines, and γ-amino α,β-unsaturated compounds also provides a means to control diastereoselectivity in many different reaction types.

In a number of cases, the preparation and C−C bond forming reactions of *N*,*N*-dibenzylamino aldehydes have reached an industrial scale (> 500 mol/run). The enantiomerically pure products are diverse forms of β-amino alcohols, aminoalkyl epoxides, unusual α-, β-, and γ-amino acids or nitriles, 1,2- and 1,3-diamines, α,β-diamino nitriles, amino lactones as well as novel amino-substituted heterocycles. Such classes of chiral compounds are of considerable interest in pharmaceutical chemistry, plant protection and/or natural products syntheses. The original patents[184] covering the preparation and use of *N*,*N*-dibenzylamino aldehydes **181a** and ketones **181b** were abandoned at a relatively early date; further industrial innovations followed.[28,29,35−37,39,185] Future developments in the area of *N*,*N*-dibenzylamino compounds at an academic as well as industrial level are likely, as shown by recent publications.[186]

VIII. Abbreviations

AIBN	2,2′-azobis(2-methylpropionitrile)
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BSB	benzostabase(2,3-dihydro-1*H*−2,1,3-benzazadisilole)
Bu	butyl
Cb	diisopropylcarbamoyl
Cbz	benzyloxycarbonyl
CDI	carbonyldiimidazole
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminum hydride
DIPAMP	1,2-bis(*o*-anisylphenylphosphino)ethane
DMAP	4-(dimethylamino)pyridine
Et	ethyl
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate

GABA	γ-amino butyric acid
hfc	3-(heptafluoropropylhydroxymethylene)-(+)-camphorate
HMPA	hexamethylphosphoramide
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
L-Selectride	lithium tri-*sec*-butylborohydride
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Mes	mesyl
MOM	methoxymethyl
NaHMDS	sodium bis(trimethylsilyl)amide
PG	protective group
Ph	phenyl
Poc	*iso*-propoxycarbonyl
Pr	propyl
TBDMSi	*tert*-butyldimethylsilyl
Tf	triflic (CF_3SO_2)
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
Tol	tolyl

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