

Part One
Synthesis and Chemistry of Modified Amino Acids

1

Synthesis and Chemistry of α,β -Didehydroamino Acids

Uli Kazmaier

1.1

Introduction

Although α,β -didehydroamino acids (DDAAs), where the term “didehydro-” is used to indicate the lack two hydrogen atoms, do not belong to the group of proteinogenic amino acids, they are commonly found in nature as building blocks of didehydro-peptides (DDPs), mainly as secondary metabolites of bacteria and fungi or other lower organisms. Most of these compounds show interesting biological activities, such as the β -lactam antibiotics of the cephalosporin group [1], the herbicidal tetrapeptide tentoxin [2], or the antitumor agent azinomycin A (carzinophilin) [3] (Figure 1.1).

From a chemical point of view, DDAAs are interesting candidates for the synthesis of complex amino acids (e.g., via additions to the double bond). Therefore, it is not surprising that the research on this important class of amino acids has been reviewed frequently (e.g., by Schmidt [4], Chamberlin [5], and König *et al.* [6]). This chapter gives an overview of the different protocols for the synthesis of DDAAs and their typical reaction behavior.

1.2

Synthesis of DDAAs

1.2.1

DDAAs via Eliminations

1.2.1.1 DDAAs via β -Elimination

1.2.1.1.1 **From β -Hydroxy Amino Acids** The elimination of water from the corresponding β -hydroxy amino acids is a straightforward approach towards DDAAs, especially if the required hydroxy acids are readily available such as serine and threonine. On elimination didehydroalanine (Δ Ala) and didehydroaminobutenoate

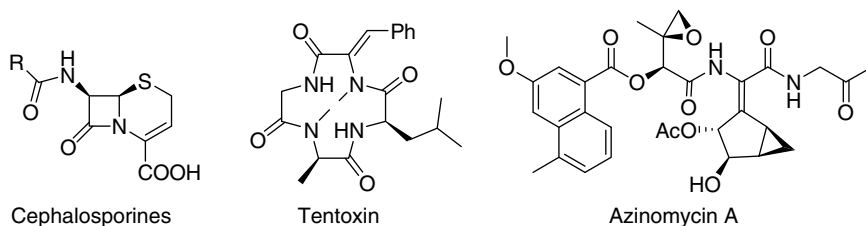


Figure 1.1 Naturally occurring DDPs.

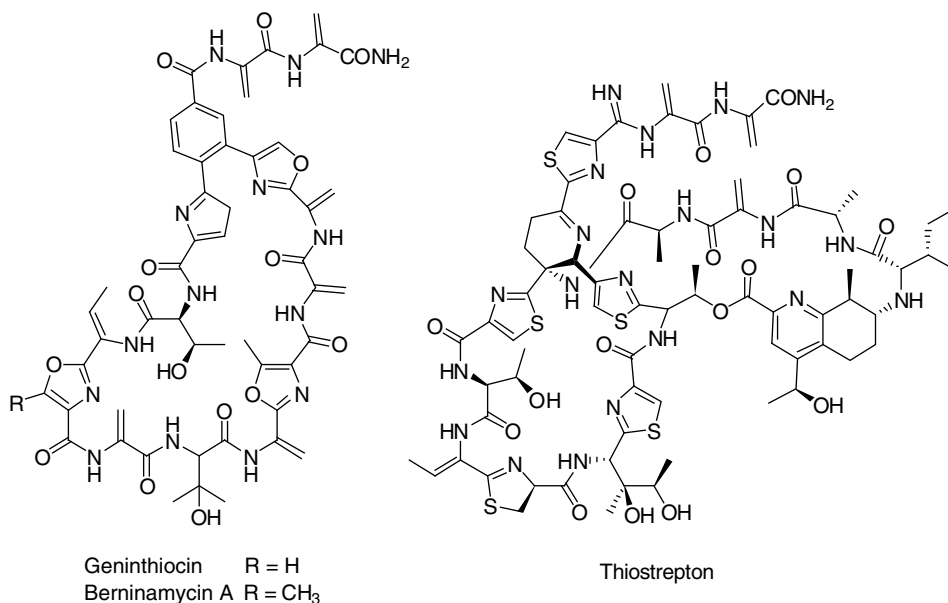
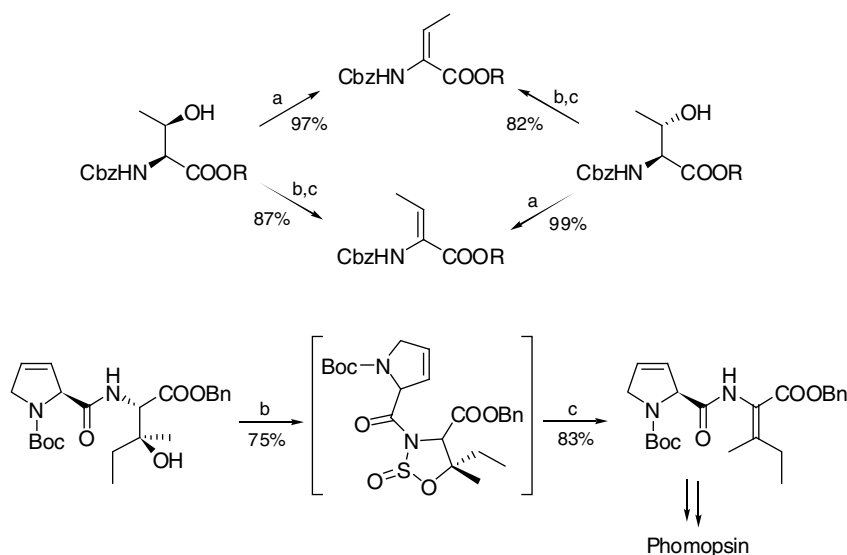


Figure 1.2 Naturally occurring didehydroalanine- and didehydroaminobutenoate-containing peptides.

(Δ Abu) are formed, two DDAAAs also found widely in nature, such as in geninthiocin [7], berninamycin A [8], or thiostrepton (Figure 1.2) [9].

A wide range of reagents can be used for the activation of the OH group and elimination occurs in the presence of a suitable base. Useful combinations are oxalyl chloride [10], (diethylamino)sulfur trifluoride [11], dichloroacetyl chloride [12], tosyl chloride [13], and pyridine or NEt_3 . PPh_3 /diethyl azodicarboxylate [14] and carbodiimides in the presence of CuCl [15] can be used as well, and in general the thermodynamically more stable (*Z*) isomer is formed preferentially [16]. With respect to an application of this approach towards the synthesis of natural products, a stereoselective protocol is required, providing either the (*E*)- or (*Z*)-DDAA. Sai *et al.* reported a high selectivity for the (*E*)- Δ Abu from threonine by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in the presence of CuCl_2 , while the (*Z*) isomer was obtained from *allo*-threonine (Scheme 1.1) [17]. Short reaction times



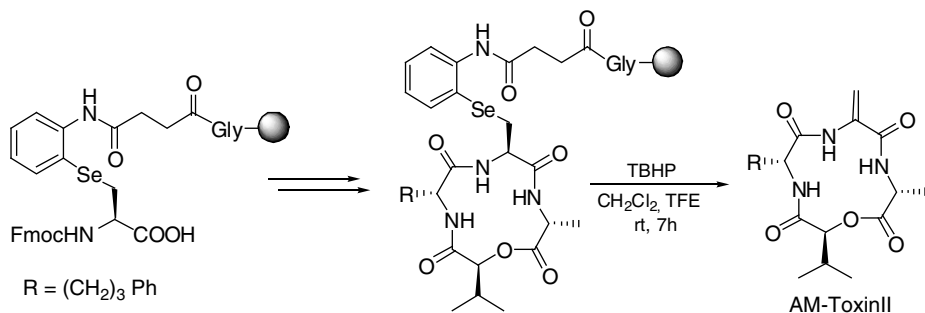
Scheme 1.1 Synthesis of DDAAAs via β -elimination of water:

- (a) 2 equiv. EDC, 0.1 equiv. CuCl_2 , toluene, 80°C , 0.5 h;
 (b) 20 equiv. NEt_3 , 10 equiv. SOCl_2 , CH_2Cl_2 , -78°C , 30 min,
 (c) 10 equiv. DBU, CH_2Cl_2 , 0°C , 30 min.

(0.5 h) are required for good (*E*) selectivity, because isomerization is observed under the reaction conditions. Therefore, longer reaction times strongly favor the thermodynamic (*Z*) product.

An alternative approach was reported by Wandless *et al.* [18]. They described a stereoselective elimination using SOCl_2 /1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This reaction proceeds via a cyclic sulfamidite that can be isolated and purified, undergoing elimination on treatment with DBU. This protocol provides the opposite isomer compared to the Sai *et al.* procedure. Wandless *et al.* used their method for the stereoselective synthesis of disubstituted DDAAAs in their synthesis of phomopsin and illustrated that this protocol is also suitable for the synthesis of DDPs.

1.2.1.1.2 From β -Thio- and Selenoamino Acids One of the best methods for the synthesis of didehydroalanine, and peptides containing this amino acid, starts from *S*-methylcysteine derivatives. *S*-Alkylation provides sulfonium salts that undergo elimination in a basic medium under relatively mild conditions [19]. Alternatively, the oxidation of thio- [20] and selenoamino acids [21] and subsequent thermolysis provides DDAAAs in high yield. This approach was used successfully in natural product synthesis [22]. Nahamura *et al.* reported on a solid-phase synthesis of cyclic DDP AM-Toxin II using a selenated alanine as an anchoring residue (Scheme 1.2). After peptide synthesis and cyclization the seleno group was oxidized with *tert*-butylhydroperoxide (TBHP) and subsequent cleavage from the resin providing the natural product [23].



Scheme 1.2 Synthesis of AM-Toxin II according to Nakamura *et al.*

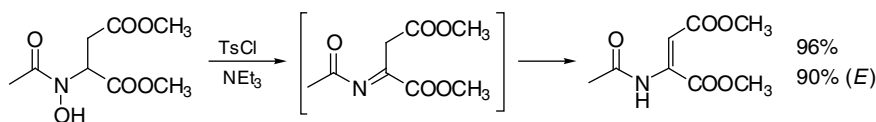
1.2.1.2 Elimination from *N*-Hydroxylated and -Chlorinated Amino Acids and Peptides

In 1944, Steiger reported on the elimination of H₂O from *N*-hydroxy amino acids in the presence of acetic anhydride/pyridine [24]. The *in situ* formed *O*-acetylated derivatives can be eliminated at room temperature in the presence of NEt₃ [25] or DBU [26]. The most convenient approach is the elimination using tosyl chloride/NEt₃, which gives the required DDAA in minutes with good (*E*) selectivity and nearly quantitative yields (Scheme 1.3) [27].

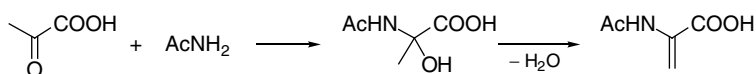
Similar good results are obtained in eliminations of *N*-chlorinated amino acid derivatives which can easily be obtained by oxidation of acylated amino acids with *t*BuOCl/NaOR [28] or NaOCl [29]. Primarily, an iminoester is formed, which undergoes isomerization to the enamide structure.

1.2.1.3 DDAA from α -Oxo Acids and Amides

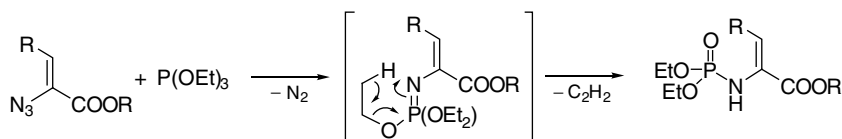
α -Oxo acids undergo addition of carboxamides on heating. α -Hydroxy- α -acylamino-carboxylic acids are formed primarily, which can undergo elimination of H₂O giving rise to DDAA (Scheme 1.4) [30]. Using amino acid amides, this protocol can also be applied for the synthesis of DDPs. Best results are obtained with Cbz- or trifluoroacetic acid-protected amino acid amides, while side-products are observed with Boc-protected derivatives [31]. *N*-Alkylated DDAA can be obtained in a similar manner by condensing primary amines with pyruvates, followed by acylation of the imine formed [32].



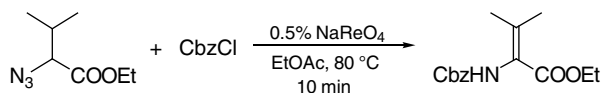
Scheme 1.3 Synthesis of DDAA from *N*-hydroxyamino acids.



Scheme 1.4 Synthesis of DDAA from α -oxo acids.



Scheme 1.5 Synthesis of DDAAs from azidoacrylates.



Scheme 1.6 Synthesis of DDAAs from azidoarboxylates.

1.2.1.4 DDAAs from Azides

α -Azidoacrylates are also suitable candidates for the synthesis of DDAAs. The azido group can be reduced electrolytically [33] or via Staudinger reaction [34]. In the latter case, with phosphines or phosphites the corresponding iminophosphoranes or phosphoric amides are obtained (Scheme 1.5).

Saturated α -azidocarboxylates can be converted into DDAAs on treatment with strong bases such as BuLi or lithium diisopropylamide. The *in situ* formed iminoester can be directly acylated to the corresponding *N*-acylated DDAA [35]. By far the best method for the conversion of α -azidocarboxylates to DDAAs is their reaction with acyl halides or chloroformates in the presence of Re_2S_7 or NaReO_4 (Scheme 1.6) [36]. With phosgene as the acylating reagent, the corresponding Leuch's anhydrides are formed [37].

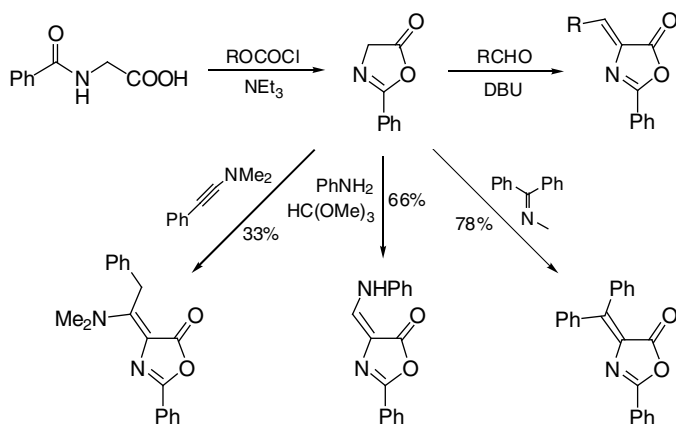
1.2.2

DDAAs via C=C Bond Formation

1.2.2.1 DDAAs via Azlactones [5(4H)-Oxazolones]

The Erlenmeyer azlactone synthesis [38] is a classical method for the synthesis of DDAAs, preferentially bearing aromatic or heteroaromatic substituents. Often this reaction is performed as a one-pot protocol by melting an aldehyde, acylglycine, acetic anhydride, and sodium acetate at about 140 °C [39]. For sensitive aldehydes a two-step procedure is more convenient, where the azlactone is prepared first and the subsequent aldol condensation is carried out in the presence of base under mild conditions [40]. The (*Z*) oxazolones are formed preferentially, but these can undergo isomerization to the corresponding (*E*) derivatives in the presence of phosphoric acid or HBr [39b]. Apart from aldehydes, a wide range of electrophiles can be reacted with the deprotonated azlactone (Scheme 1.7). While imines give the same products such as aldehydes and ketones [40, 41], amines in the presence of orthoesters give rise to β -aminoalkylidene oxazolidinones [42]. Similar structures are obtained in the reaction with ynamines [43].

Ring opening of the oxazolinone is possible with a wide range of nucleophiles. While hydrolysis gives the *N*-benzoylated DDAAs, with alcohols the corresponding esters are obtained [39b]. Ring cleavage with amino acid esters gives direct access to DDPs containing a *N*-terminal DDAA [44].

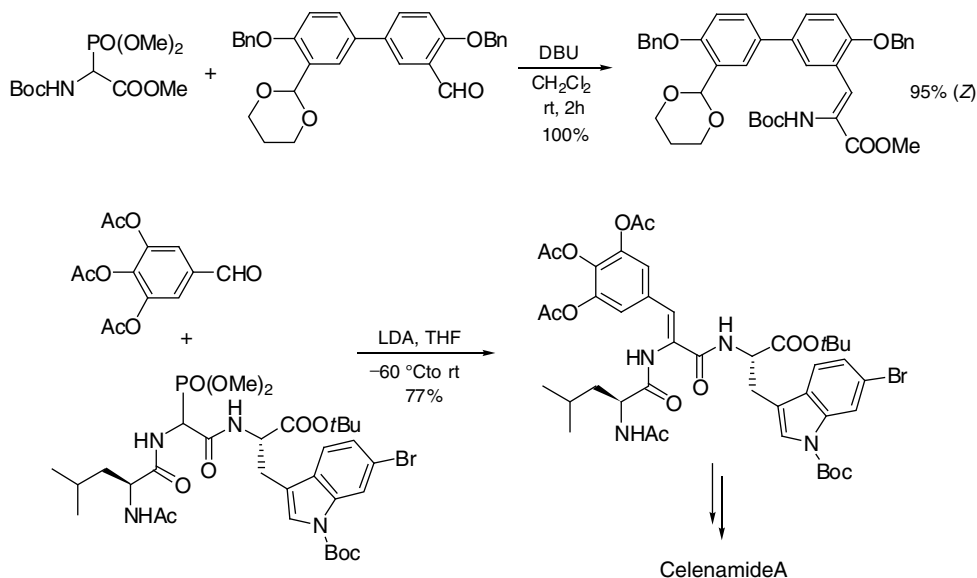


R = Ph, m-NO₂-Ph, PhCH=CH-

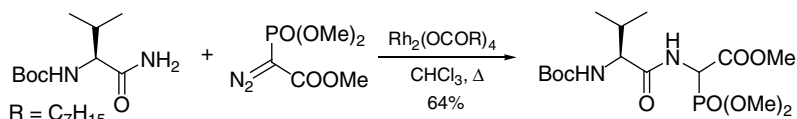
Scheme 1.7 Reactions of azlactones.

1.2.2.2 DDAAs via Horner–Emmons and Wittig Reactions

A quite popular approach towards DDAAs was developed by Schmidt *et al.* based on a phosphonate condensation of *N*-protected dimethoxyphosphoryl glycines [45]. The Cbz- and Boc-protected derivatives are commercially available or can be prepared in large scale from glyoxylic acid [45, 46]. Condensations of these phosphonates with aldehydes, also highly functionalized ones, proceed well in the presence of KO^tBu or DBU as a base, and the (*Z*)-DDAAs are formed preferentially (Scheme 1.8) [47]. Subsequent asymmetric catalytic hydrogenation (see Section 1.3.1.4) provides



Scheme 1.8 Synthesis of DDAAs and DDPs via Horner–Emmons reaction.



Scheme 1.9 Phosphono-peptides via NH insertion.

straightforward access to nonproteinogenic amino acids. Therefore, this approach has found many applications in amino acid [48] and natural product syntheses [49]. Incorporating dimethoxyphosphoryl glycine into peptides allows a direct synthesis of DDPs [47], as has been illustrated in the synthesis of celenamide A [47a, 50] and antrimycin D [51].

During their synthesis of stephanotic acid, Moody *et al.* [52] developed an independent approach towards phosphoryl glycine-containing peptides based on a rhodium-catalyzed NH insertion of the corresponding carbenes into amino acid amides (Scheme 1.9) [53].

By incorporating an alkoxyphosphoryl glycine into heterocycles such as hydantoins (1) this phosphonate condensation approach can be used for the synthesis of cyclic DDAA derivatives (Figure 1.3) [54]. Introduction of stereogenic centers into the heterocycle allows subsequent diastereoselective reactions of the DDAAs obtained. Williams *et al.* introduced the chiral phosphonate 2 as a precursor for “chiral” didehydroalanine, which was subjected to modifications on the double bond, such as cycloadditions [55]. Chai *et al.* described phosphonates 3 as a precursor for methylene piperazine-2,5-diones, which were used as templates for amino acid syntheses [56].

Comparable to these phosphonate condensations are the corresponding Wittig reactions using *N*-acyl- α -triphenylphosphonioglycinates. These Wittig reagents can be obtained either from the corresponding α -hydroxyglycinates via halogenation/ PPh_3 substitution [46] or from the corresponding 4-triphenylphosphoranylidene azlactones [57]. Elimination occurs on treatment with base, giving an equilibrated mixture of the *N*-acylimino acetates and the phosphonium ylides. Addition of nucleophiles results in the formation of substitution products [58], while on addition of electrophiles, such as aldehydes, the formation of DDAAs (as a *E/Z* mixture) is observed (Scheme 1.10) [59]. This approach found several applications in the synthesis of β -lactams [60].

Steglich *et al.*, who were the first to describe the synthesis of these Wittig reagents, observed a dimerization of halogenated glycinates on treatment with PPh_3 [46]. This can easily be explained by a reaction of the *N*-acylimino acetates and the phosphonium ylides formed *in situ*. This dimerization process can also be transferred to peptides giving rise to cross-linked DDPs (Scheme 1.11) [61].

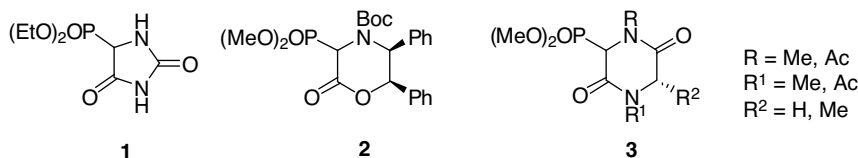
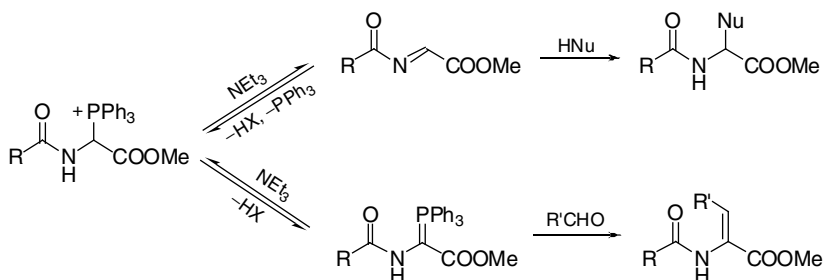
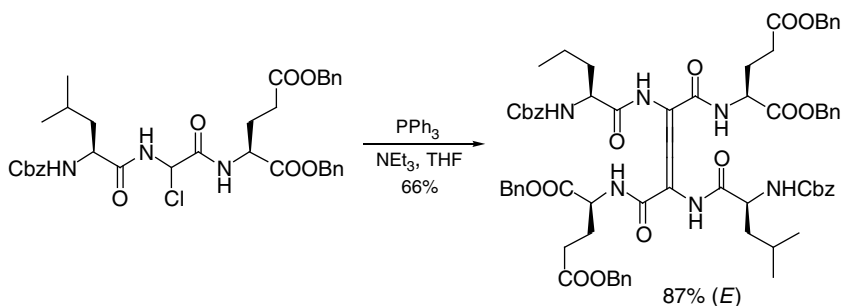


Figure 1.3 Heterocyclic phosphonates.



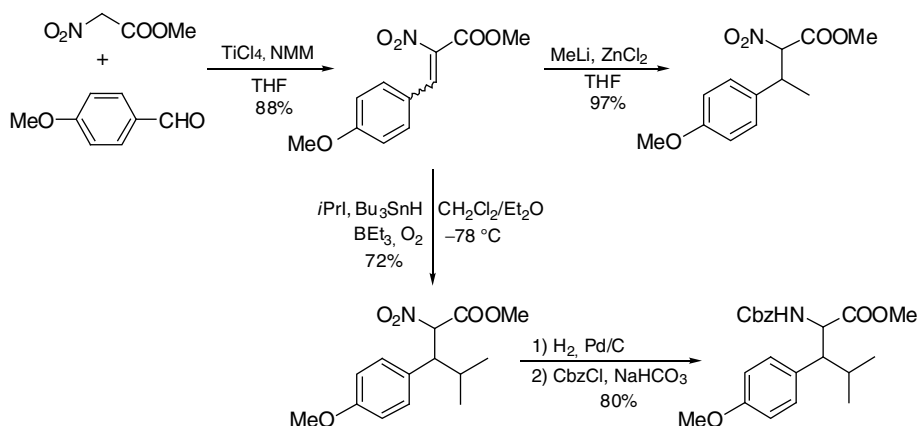
Scheme 1.10 Synthesis of DDAAs via Wittig reaction.



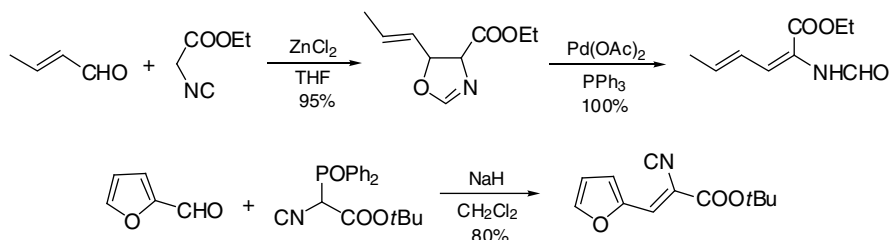
Scheme 1.11 Synthesis of cross-linked DDPs.

1.2.2.3 DDAAs via Enolates of Nitro- and Isocyano- and Iminoacetates

Nitroacetic esters can easily undergo Knoevenagel reactions with a wide range of aldehydes [62] or imines [63] giving rise to α,β -unsaturated α -nitro esters. β -Alkoxy- or β -amino-substituted derivatives are obtained from orthoformates [64] or dialkylformamide dialkylacetals [65]. Condensation in the presence of TiCl_4 /base is an especially mild protocol and gives high yields of an isomeric mixture (Scheme 1.12) [66]. The unsaturated nitro esters obtained are excellent Michael



Scheme 1.12 Synthesis of DDAAs from nitroacetates and subsequent reactions.



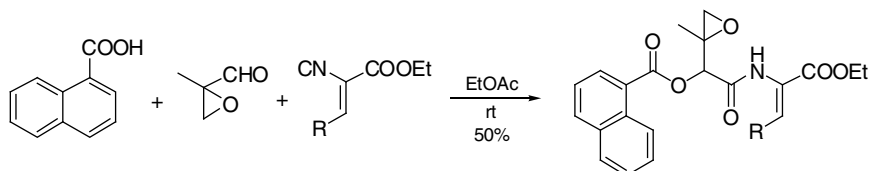
Scheme 1.13 Synthesis of DDAAs from isocyanoacetates.

acceptors. Nucleophilic or radical addition and subsequent reduction of the nitro group provides easy access to highly substituted amino acids [67b,67]. The nitro group of the unsaturated esters can be reduced easily without affecting the double bond using aluminum amalgam [68], zinc in glacial acetic acid [69], or by catalytic hydrogenation using Raney nickel [70] or Pt/C [71].

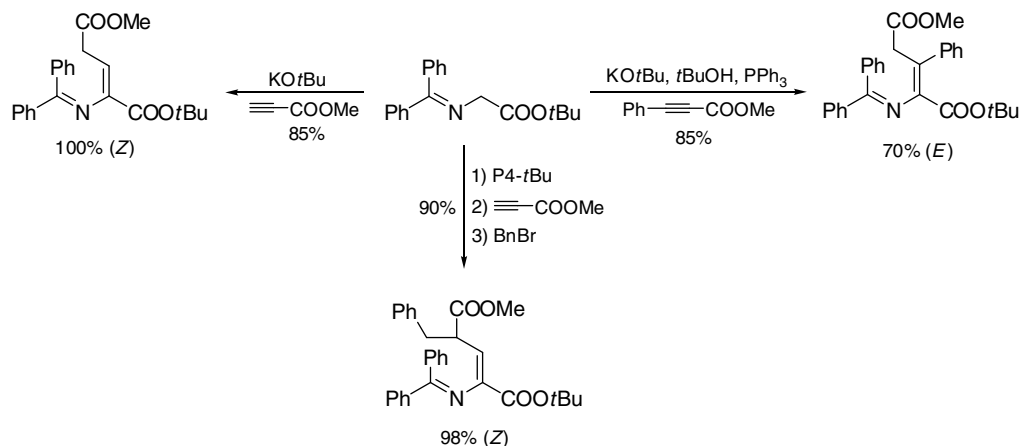
Schöllkopf *et al.* reported on similar condensation reactions using isocyanoacetates. Condensation with aldehydes [72] and ketones [73] in aprotic solvents gives rise to *N*-formylated DDAAs, probably via oxazoline intermediates [74]. The reaction conditions are relatively mild and allow the condensation of sensitive carbonyl compounds. Best results with α,β -unsaturated carbonyls are obtained in the presence of Lewis acids such as ZnCl_2 or CuCl (Scheme 1.13) [75]. The unsaturated oxazoline obtained can be cleaved to the *N*-formylated DDAA using $\text{Pd}(\text{OAc})_2/\text{PPh}_3$. According to comparable reactions described for the nitro acetates, orthoformates [76] and dimethylformamide acetals [77] give rise to the corresponding β -alkoxy or β -amino substituted DDAAs. α,β -Unsaturated isocyanoacetates can be obtained via phosphonate condensation [78].

The isocyanides can not only be hydrolyzed to the corresponding *N*-formyl DDAAs [79], they can also be used in multicomponent couplings such as the Passerini [80] or Ugi [81] reactions. This allows direct incorporation of DDAAs into peptides. Armstrong *et al.* used such an approach during their synthesis of azinomycins (Scheme 1.14) [81a,b].

O'Donnell's imino glycinate are very useful nucleophiles and valuable precursors for the synthesis of complex amino acids [82]. Alvarez-Ibarra *et al.* reported on their applications in DDAA synthesis via nucleophilic addition to alkynoates (Scheme 1.15). Reaction with methyl propiolate gave rise to the (*Z*)-configured DDAA in a thermodynamically driven process. The *in situ* formed vinyl anion underwent 1,3-hydride shift and subsequent migration of the double bond to the



Scheme 1.14 DDPs via Passerini reaction.



Scheme 1.15 Addition of imino glycinates towards alkynoates.

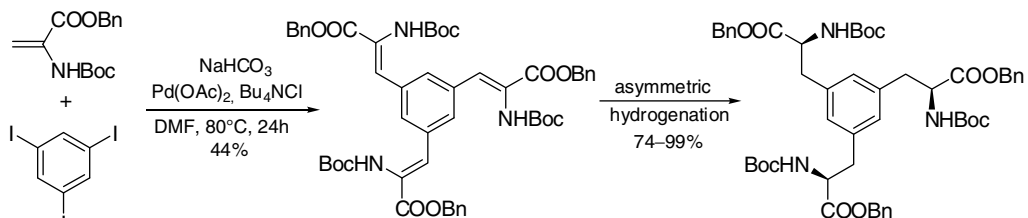
α,β -position [83]. On the other hand, β -substituted derivatives were best prepared by treatment of deprotonated imino glycinates with substituted alkynoates giving (*E/Z*) mixtures of products [84]. By using naked enolates, prepared in the presence of crown ethers or by using Schwesinger base [85], the enolate formed after isomerization could be trapped with electrophiles such as benzyl bromide [83].

1.2.3

DDAAs via C–C Bond Formation

1.2.3.1 DDAAs via Heck Reaction

The synthesis of a wide range of DDAAs from the most simple and easily available representative, didehydroalanine, is a straightforward and highly attractive approach [86]. Especially the reaction of aryl halides in combination with asymmetric catalytic hydrogenation of the DDA formed gives easy access to libraries of substituted phenylalanines [87]. Frejd *et al.* applied this approach for the synthesis of dendrimers, containing a C-3-symmetric phenylalanine derivative as the center unit (Scheme 1.16) [88]. Gibson *et al.* used an intramolecular Heck reaction as the cyclization step in their synthesis of didehydrophenylalanine cyclophanes [89].



Scheme 1.16 Trifold Heck reaction of didehydroalanine.

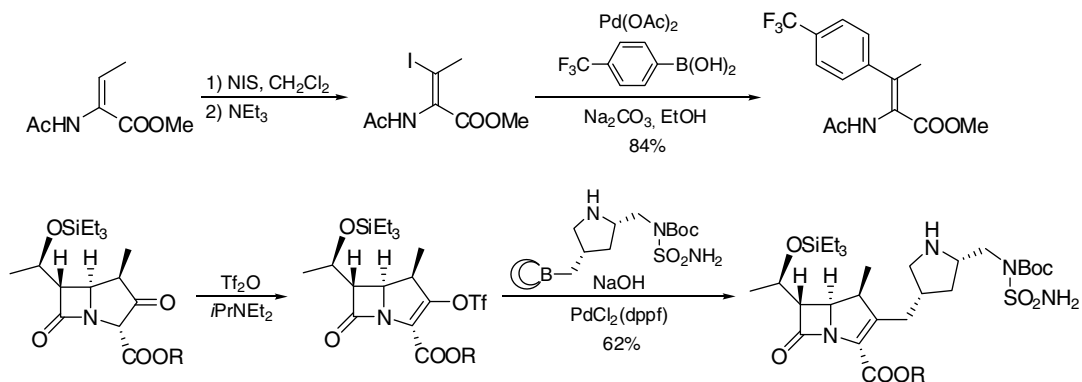
The Heck reaction can also be performed under solvent-free conditions in a ball mill [90] or on solid support [91].

1.2.3.2 DDAAs via Cross-Coupling Reactions

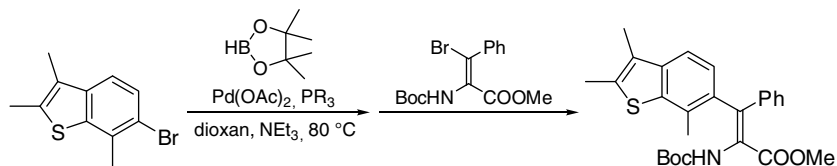
DDAAs containing a leaving group at the β -position can be subjected to a wide range of cross-coupling reactions such as Suzuki, Stille, or Sonogashira couplings, allowing the synthesis of highly functionalized and complex amino acids. β -Brominated or iodinated DDAAs, easily obtained by a halogenation/elimination approach (see Section 1.3.3) can be coupled with a wide range of boranes [92], borates [93], or boronic acids (Scheme 1.17) [94]. Cross-coupling occurs under retention of the olefin geometry. In general, the (*E*)- β -halogen DDAAs give higher yields of the substituted (*E*)-DDAAs, compared to the (*Z*) derivatives [95]. The corresponding triflates are easily obtained from the corresponding β -keto amino acids as nicely illustrated in the synthesis of functionalized carbapenems [96].

Queiroz *et al.* reported on an interesting one-pot reaction consisting of a palladium-catalyzed borylation of aryl halides and subsequent Suzuki coupling with β -brominated DDAAs (Scheme 1.18). The DDAAs obtained were subjected to a metal-assisted intramolecular cyclization giving indoles [97].

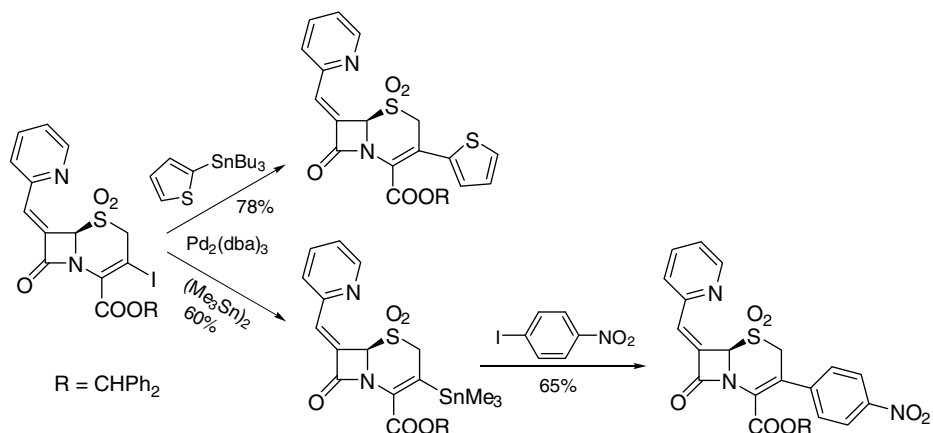
Stille couplings [98] have found several applications in the modification of β -lactams [99]. Iodinated bicyclic DDAAs were coupled with a wide range of nucleophiles such as vinyl and (het)aryl stannanes as well as stannyl acetate, thiolate, and acetylide (Scheme 1.19). The reaction with $(\text{Me}_3\text{Sn})_2$ allowed the synthesis of stannylated β -lactams that could be coupled with electrophiles [100].



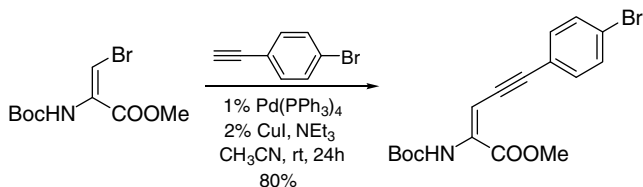
Scheme 1.17 Synthesis of DDAAs via Suzuki coupling.



Scheme 1.18 Domino borylation/Suzuki coupling.



Scheme 1.19 Synthesis of DDAA derivatives via Stille coupling.



Scheme 1.20 Synthesis of DDAA derivatives via Sonogashira coupling.

Sonogashira couplings of halogenated DDAA derivatives with terminal alkynes allows the synthesis of highly unsaturated amino acids [29]. Coupling with *p*-bromophenyl acetylene, for example, gives rise to a brominated DDAA, which can be further modified, for example, via Suzuki coupling (Scheme 1.20) [101].

1.3

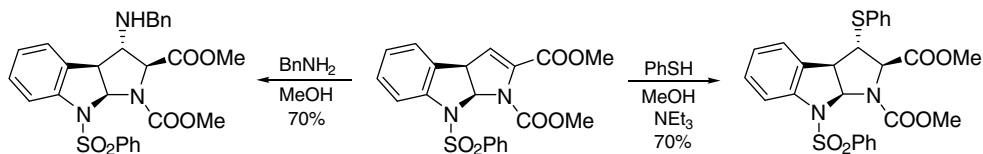
Reactions of DDAA

1.3.1

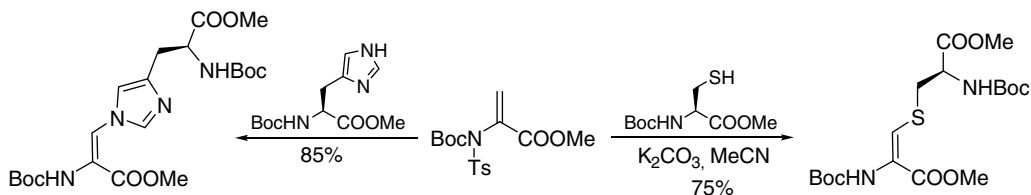
Additions to the C=C Bond

1.3.1.1 Nucleophilic Additions

In principle, suitably protected DDAA derivatives react in the same way as acrylic acid derivatives, undergoing 1,4-addition of a wide range of nucleophiles, such as amines [102], thiols [103], or electron-rich *N*-heterocycles (Scheme 1.21) [104]. For example, addition to didehydroproline derivatives proceeds stereoselectively, giving the 1,4-addition products as single stereoisomers [102]. It should be mentioned that under acidic conditions the addition of the nucleophile occurs preferentially to the α -position of the DDAA [105].



Scheme 1.21 Nucleophilic attack on didehydroprolines.



Scheme 1.22 DDAAs via nucleophilic addition/elimination.

Best results in the 1,4-addition are obtained with substrates containing two electron-withdrawing groups on the nitrogen, as illustrated in the addition of several heterocycles [106]. If one of these electron-withdrawing groups is a tosyl group, the substituted DDAAs are obtained via an addition/elimination mechanism (Scheme 1.22) [107].

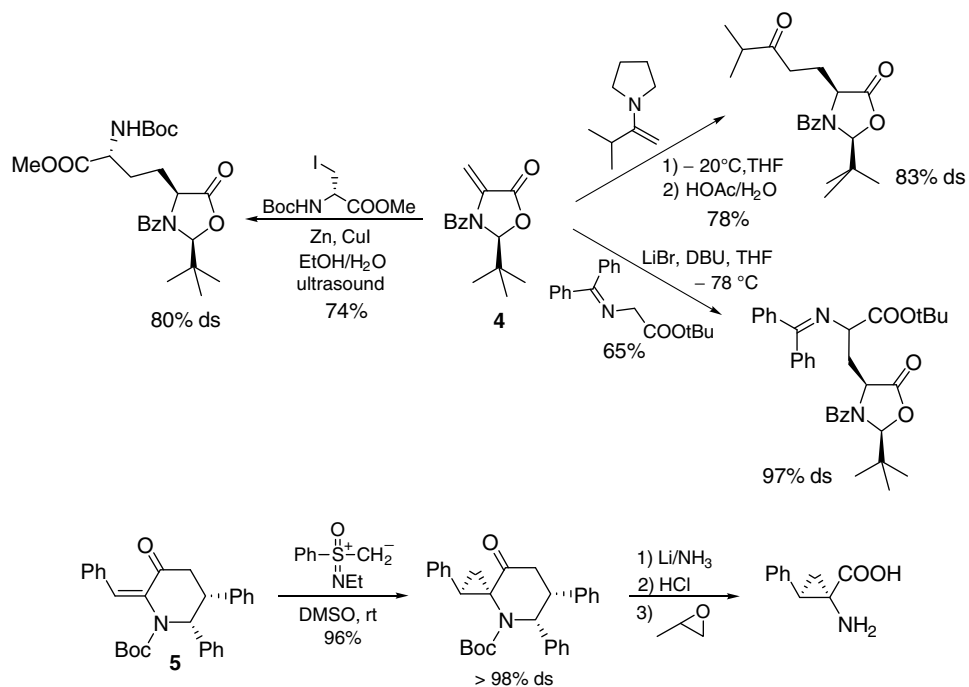
Additions of stabilized carbanions [108] and enols [109] or enamines [110] result in the elongation of the amino acid side-chain. The application of chiral modified DDAAs [111] allows the stereoselective synthesis of unnatural amino acid derivatives (Scheme 1.23) [112]. Furthermore, highly functionalized substituents can be introduced via cuprate addition [113] – a reaction that also gives good selectivities with cyclic chiral DDAAs such as **4** [114]. 1,4-Additions to acyclic chiral esters in general are less selective [115]. If the cuprate is generated *in situ* from a halide via halogen–zinc exchange (Luche conjugate addition) [116] the reaction can be carried out under aqueous conditions [117].

The addition of sulfur ylides to DDAAs is a straightforward approach to 1-aminocyclopropane carboxylic acids [118]. Williams *et al.* described the first asymmetric synthesis of a cyclopropane amino acid via addition of a sulfur ylide to a chiral modified DDAA **5** (Scheme 1.23). Excellent yields and diastereoselectivities were obtained, and the free amino acid was obtained via reduction under Birch conditions and subsequent cleavage of the Boc protecting group [55, 119].

Meanwhile, the additions of sulfur ylides to a range of other chiral DDAA derivatives, such as the pivane derivative **6** [120], the oxazinone **7** [121], the diketopiperazine **8** [122], or the oxazolone **9** [123], were described (Figure 1.4).

1.3.1.2 Radical Additions

DDAAs are good acceptors for radicals, generated for example, from alkyl or acyl halides using the Bu₃SnH/AIBN protocol [124]. This approach has found many applications, especially in cyclization reactions [125] (e.g., for the synthesis of pyroglutamates starting from α -halo amides [126]). In principle, the primarily



Scheme 1.23 Additions of C-nucleophiles towards chirally modified DDAA derivatives.

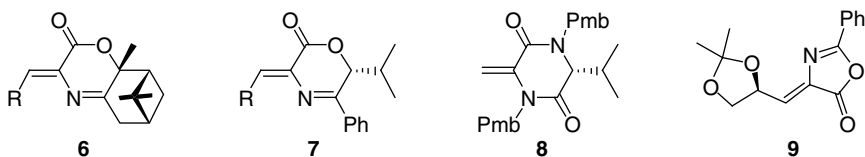
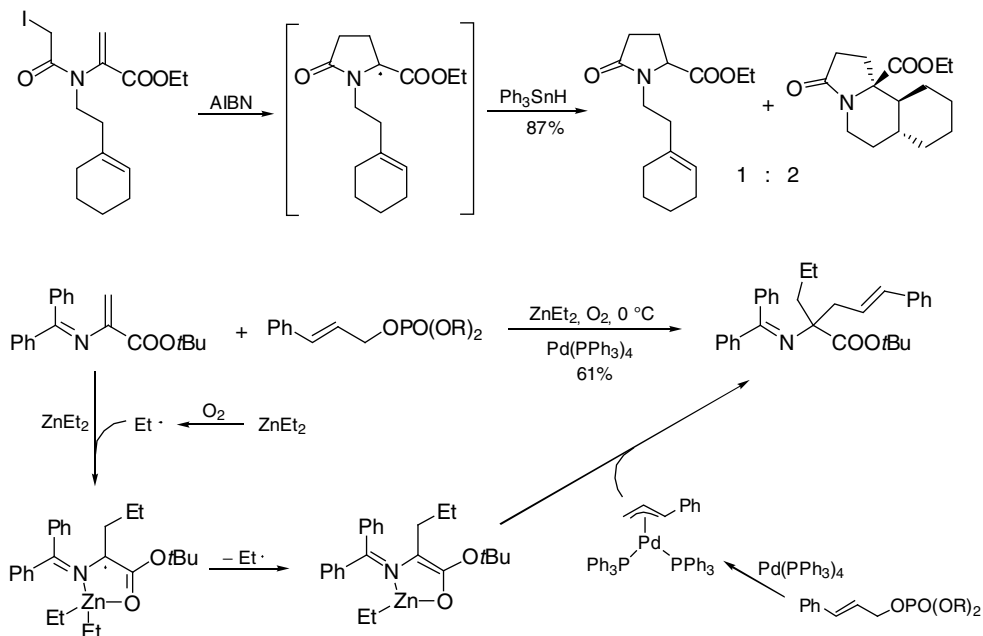


Figure 1.4 Chirally modified DDAA derivatives used in cyclopropanation reactions.

formed cyclic radical can be trapped with another radical acceptor [127] or can undergo a domino cyclization if a suitable double bond is present in the molecule (Scheme 1.24). Depending on the substitution pattern and the tin hydride used, mixtures of mono- and bicyclic products are obtained as single regio- and diastereomers, as a result of a 5-*endo*-6-*endo* cyclization [128]. Alternatively, the radicals can also be generated from epoxides using TiCl₃ – an approach which was used for the synthesis of glycosylated amino acids [129].

An interesting combination of radical addition and palladium-catalyzed allylic alkylation was reported by Takemoto *et al.* [130]. The initially formed chelated radical is converted into a chelated enolate, which then undergoes subsequent allylic alkylation (Scheme 1.24).

Vederas *et al.* reported on the generation of radicals from protected glutamates via the corresponding diacyloxyiodobenzene [131]. Additions to didehydroalanine derivatives gave rise to DDAA derivatives, which were converted into diaminopimelic acids via



Scheme 1.24 Radical additions to DDAAs.

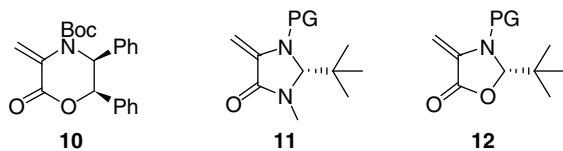


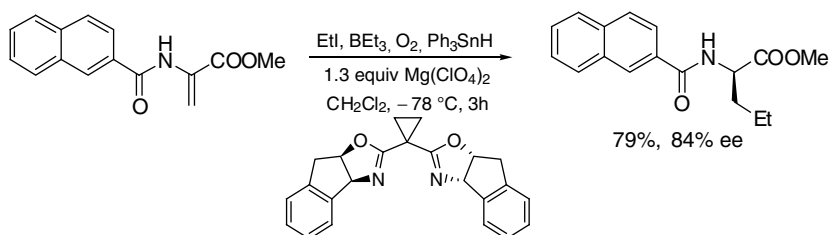
Figure 1.5 Chirally modified DDAAs used in radical additions.

catalytic hydrogenation. The reaction was also carried out with commonly used chiral didehydroalanine analogs, such as oxazinone **10** [132], imidazolidinone **11** [133], and oxazolidinone **12** (Figure 1.5) [134]. In the last case the expected dimerization products were also obtained. The chirally modified DDAAs allow the diastereoselective generation of amino acids. In principle, chiral auxiliaries can be used as well, such as chiral esters [135].

Sibi *et al.* reported another elegant protocol for enantioselective radical additions using a selective hydrogen atom transfer from tin hydride in the presence of a Lewis acid and a chiral ligand. The results strongly depend on the reaction conditions, especially the Lewis acid used, but under optimized conditions enantiomeric excesses up to 85% are possible (Scheme 1.25) [136].

1.3.1.3 Cycloadditions

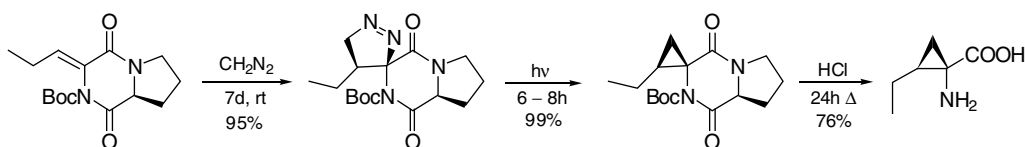
Cycloadditions of DDAAs give rise to quaternary amino acids. This area of reactions was covered by an excellent review by Cativiela and Diaz-de-Villegas [137]. Therefore, only the general principle and new developments will be discussed herein.



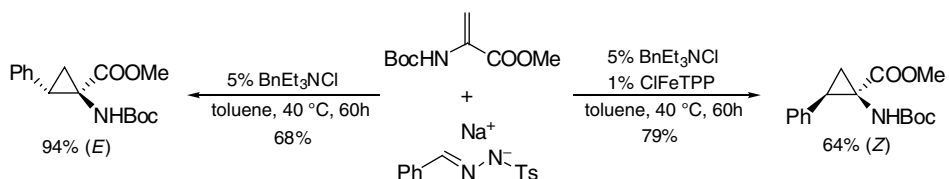
Scheme 1.25 Asymmetric radical addition towards DDAAs.

1.3.1.3.1 [3 + 2] Cycloadditions The addition of diazo compounds towards DDAAs is an interesting approach for the synthesis of aminocyclopropane carboxylic acids (see also *S*-ylide addition, in Section 1.3.1.1). The reaction occurs via a 1,3-dipolar cycloaddition providing a pyrazoline. Extrusion of N_2 , either thermally or on photolysis, gives rise to cyclopropane derivatives [120b,138]. Various chiral modified DDAAs have been used to control the stereoselective outcome of the reaction [139]. Excellent results were obtained with proline-containing diketopiperazines, which gave the corresponding pyrazolines almost as single diastereomers (>95% d.s.). Photolysis produced the spirocyclopropanes, which could be cleaved under acidic conditions to the free amino acids (Scheme 1.26). Best results were obtained with the *N*-Boc-protected diketopiperazines [140].

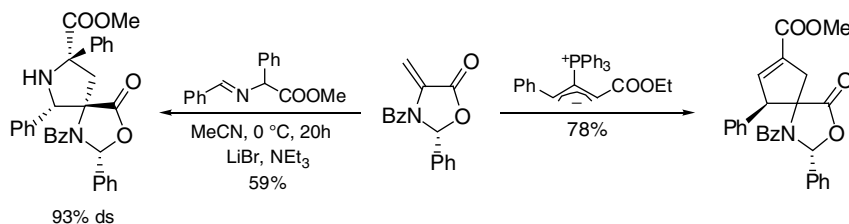
Due to the toxicity and lability of the diazo compounds, recent studies primarily focused on practical aspects and the handling of the diazo compounds. Aggarwal and Cox described asymmetric cyclopropanations with diazo compounds that were released *in situ* from tosylhydrazones. Interestingly, the (*E*)-configured product was formed preferentially by simple warming of the components to 40 °C. The (*Z*) isomer was the major one in the presence of an iron porphyrin (ClFeTPP) catalyst, although in this case the selectivity was moderate (Scheme 1.27) [141].



Scheme 1.26 [3 + 2] Cycloaddition of diazomethane.



Scheme 1.27 Cyclopropanation with *in situ* generated diazo compounds.



Scheme 1.28 [3 + 2] Cycloadditions of azomethine and phosphor ylides.

The 1,3-dipolar cycloaddition of azomethine ylides, easily obtained from *N*-alkylidene amino acid esters, to electron-deficient alkenes is a straightforward approach for the synthesis of functionalized prolines. Pyne *et al.* investigated the cycloaddition of chiral oxazolidinones (Scheme 1.28). The azomethine ylides were generated *in situ* in the presence of the DDAA-derivative by treating their tetrahydrofuran (THF) or MeCN solution with base (DBU or NEt_3). In nearly all cases investigated the reactions were completely regioselective with a high preference for the *exo* diastereomer. The auxiliary could be removed easily by saponification [142].

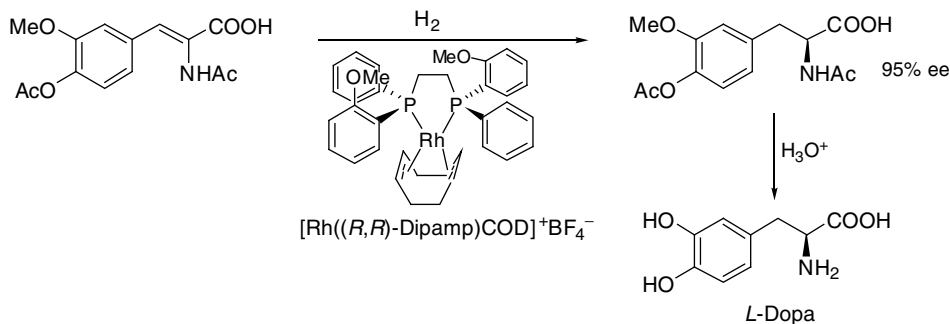
Similar results were also obtained with nitrones [143] and nitrile oxides [144]. Cyclopentenyl glutamates were obtained by a [3 + 2] cycloaddition of phosphor ylides [145], obtained by nucleophilic attack of phosphines on allenic or alkynoic acid esters [146].

1.3.1.3.2 [4 + 2] Cycloadditions The Diels–Alder reaction is probably the most efficient method for the stereoselective synthesis of six-membered rings. This protocol has found widespread application in amino acid synthesis [137] and nearly all chiral modified DDAA's described so far have been used in this reaction [147]. Several functionalized cyclohexane α -amino acids have been synthesized as conformationally constrained amino acid analogs [148].

The reactions can be carried out thermally or in the presence of Lewis acids, while the rate of the Diels–Alder reaction as well as the *exo/endo* selectivity strongly depends on the Lewis acid used. Moderate selectivities were obtained with chiral modified aluminum and titanium complexes [149].

1.3.1.4 Catalytic Hydrogenations

The asymmetric catalytic hydrogenation of DDAA's is an important and straightforward approach to optically active amino acids. In principle, two major protocols are applied to introduce chirality: either hydrogenation under substrate control using chiral (modified) DDAA's or DDP's, or the application of chiral catalysts. DDAA's are standard substrates for the evolution of new chiral metal/ligand complexes. This chapter cannot go into detail, but the newest developments are covered in a series of recent reviews [150]. The development of the homogeneous asymmetric hydrogenation started with the discovery of Wilkinson's catalyst [151]. In the late 1960s, Horner [152] and Knowles [153] reported on the first asymmetric hydrogenations, albeit with moderate enantioselectivity. A breakthrough was the introduction of



Scheme 1.29 DOPA synthesis via asymmetric catalytic hydrogenation.

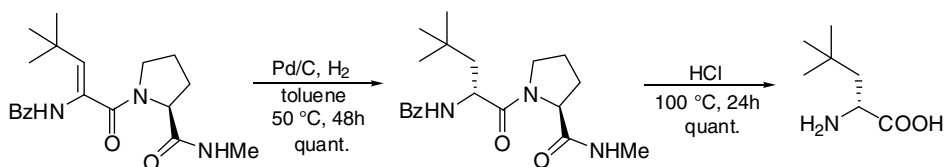
a bidentate chelating ligand 1,2-bis[(*o*-anisyl)-(phenyl)phosphino]ethane (DI-PAMP) [154], a highly efficient ligand for rhodium-catalyzed hydrogenations. The process found application at Monsanto for the industrial production of 3,4-dihydroxyphenylalanine (DOPA) (Scheme 1.29) [155] – a development that won Knowles the Nobel Prize in 2001 [156]. This chiral catalyst system was applied by Schmidt *et al.* [49, 157] and others [158] to the synthesis of a wide range of unusual amino acids and peptides.

This was the starting point for the development of new ligands and hundreds of them are now in use or under investigation [150]. One of the advantages of the homogeneous hydrogenation is the possibility to use the catalyst not only for the catalytic hydrogenation, but also for other transition metal-catalyzed processes. For example, Robinson *et al.* reported on the synthesis of cyclic amino acids via a combination of a rhodium-catalyzed hydrogenation/hydroformylation and subsequent ring closure [159].

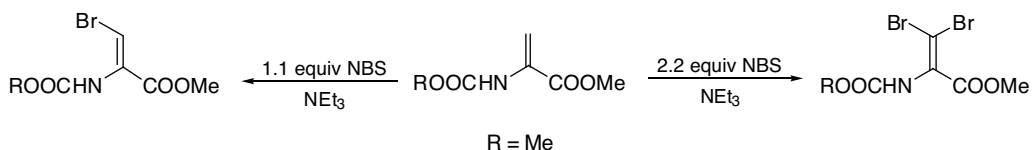
The major disadvantage of homogeneous catalysis is the problem of pollution of the product by the soluble catalysts. Therefore, attempts have been made to use chirally modified heterogeneous catalysts for asymmetric hydrogenations, but the selectivities are significantly worse compared to the homogeneous version [160]. The immobilization of homogeneous chiral catalysts on solid supports could solve some of the problems, such as difficult separation and recycling of the expensive chiral catalyst [152a]. However, the immobilized ligands or catalysts often display a lower selectivity and reactivity as compared to the corresponding homogeneous systems. Fan *et al.* applied a MeO-polyethylene glycol-supported ligand in the rhodium-catalyzed hydrogenation of α -acetamidocinnamic acid [161]. Enantiomeric excesses up to 96% were obtained and the polymer catalyst was recycled at least 3 times without loss of enantioselectivity. In contrast, the insoluble polymer-supported catalyst lost its selectivity in the second cycle [162].

Achiral (heterogeneous) catalysts can be used for asymmetric hydrogenations of chirally modified DDAAs. Best results are obtained with cyclic derivatives such as **6** [163], **8** [116a] (Figure 1.3), **10** [164], and **11** [165] (Figure 1.4).

In principle, the chiral information of a peptide chain can also be used to control the stereochemical outcome of a hydrogenation of an incorporated DDAA. In



Scheme 1.30 Substrate controlled hydrogenation of DDPs.



Scheme 1.31 Bromination of DDAAs.

general, the chiral induction is moderate, but can be increased by addition of metal salts [166]. Alternatively, chiral ligands can be applied in homogeneous hydrogenations of DDPs [167]. Schmidt *et al.* reported on highly diastereoselective heterogeneous hydrogenations of DDPs containing a C-terminal (*S*)-proline amide (Scheme 1.30) [168]. The (*R*)-configured amino acid could be obtained after hydrolysis of the dipeptide in quantitative yield.

1.3.2

Halogenations of DDAAs

β -Halogenated DDAAs are interesting building blocks and starting materials for cross-coupling reactions, which allow the synthesis of more complex DDAAs (see Section 1.2.3.2). The most commonly used β -brominated DDAAs are easily obtained using bromine [169] or *N*-bromosuccinimide (NBS) and a base such as NEt_3 . In general, the (*Z*) isomer is obtained preferentially [29,94a,170]. Substituted DDAAs often give mixtures of isomers [171]. Application of more than 2 equiv. of NBS gives rise to β,β -dibrominated DDAAs (Scheme 1.31).

In an analogous manner the corresponding chlorinated and iodinated amino acids can be obtained by using either chlorine [172] or *N*-iodosuccinimide [95b], while the fluorinated DDAAs requires a more complicated protocol [173].

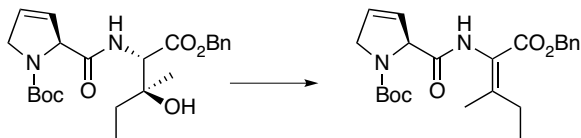
1.4

Conclusions

DDAAs are not only interesting building blocks for the synthesis of natural products and drug-like molecules, but also important intermediates for the (stereoselective) synthesis of all kinds of α -amino acids. A wide range of protocols have been developed for their synthesis and especially, modern cross-coupling reactions have enlarged their synthetic potential dramatically.

1.5 Experimental Procedures

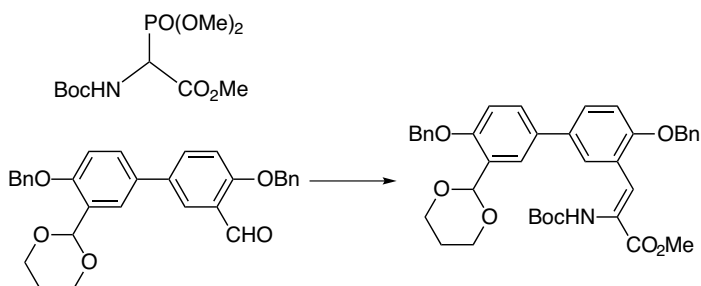
1.5.1 General Procedure for the Two-Step Synthesis of Dehydroisoleucine Derivatives [18]



Synthesis of sulfamidite from β -hydroxyisoleucine derivatives The β -hydroxyisoleucine derivative was dissolved in distilled CH_2Cl_2 (to give a concentration of 10 mM) in an oven-dried flask under an argon atmosphere and the solution was cooled to -78°C . Distilled triethylamine (20 equiv.) was added via syringe and allowed to stir 5 min. Distilled thionyl chloride (10 equiv.) was added dropwise. The reaction was allowed to stir at -78°C for 30 min before quenching with methanol (10 equiv.) at -78°C . This solution was poured into a separatory funnel, and partitioned between water and CH_2Cl_2 . The organic layer was dried with MgSO_4 , concentrated, and the product was purified using silica gel chromatography.

Elimination of sulfamidite to yield α,β -dehydroisoleucine derivative The purified sulfamidite (or mixture of diastereomers) was dissolved in distilled CH_2Cl_2 (to give a 100 mM solution) in an oven-dried flask under an argon atmosphere and the solution was cooled to 0°C . DBU (10 equiv.) was added and the solution was stirred 30 min. This solution was poured into a separatory funnel, and partitioned between CH_2Cl_2 and saturated aqueous NaHCO_3 . The organic layer was dried over MgSO_4 , concentrated, and the product was purified using silica gel chromatography.

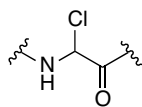
1.5.2 General Procedure for the Synthesis of α,β -Didehydroamino Acid Esters by the Phosphorylglycine Ester Method using DBU [45]



To a solution of methyl 2-acylamino-2-(dimethoxyphosphoryl)acetate (364 mg, 1.1 mmol) in the CH_2Cl_2 (2 ml) was added DBU (160 mg, 1.05 mmol). After 10 min, the respective carbonyl compound (1 mmol) was added. After 2 h the solution was diluted with EtOAc (20 ml), washed with 1 N H_2SO_4 (5 ml), dried (MgSO_4), and concentrated under vacuum. The residue was filtered through silica gel (hexane/EtOAc, 1: 1) to remove excess phosphorylglycine ester. The (*E/Z*) ratio of the product can be determined by high-performance liquid chromatography and ^1H -nuclear magnetic resonance (NMR) spectroscopy.

1.5.3

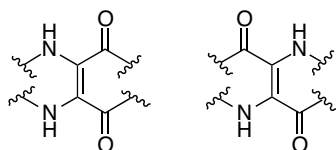
General Procedure for the Synthesis of α -Chloroglycine Derivatives: [61]



To a solution of the α -(ethylthio)glycyl peptide (1.0 mmol) in CH_2Cl_2 (30 ml) was added a 1 M solution of SO_2Cl_2 (1.1 ml, 1.1 mmol) in CH_2Cl_2 at 0°C . After 30 min stirring, the solvent and all volatile byproducts were evaporated (cool trap), and the resulting residue was dried under high vacuum. The resulting α -chloropeptides were used for the next step without further purification.

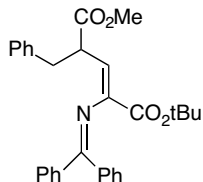
1.5.4

General Procedure for the Synthesis of Homomeric Dimers [61]

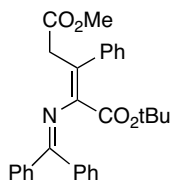


To a solution of the α -chloroglycyl peptide (1.0 mmol) and PPh_3 (0.2 mmol) in THF (50 ml) was added NEt_3 (0.15 ml, 1.1 mmol) in THF (30 ml) dropwise during 5 h. After continued stirring overnight, petroleum ether (200 ml) was added and the mixture filtered through Celite. Evaporation of the filtrate *in vacuo* yielded an oily residue which was purified by column chromatography on silica gel (petroleum ether/EtOAc).

1.5.5

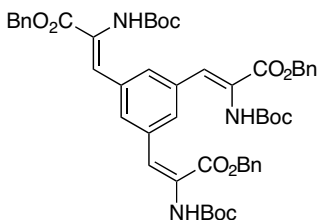
General Procedure for the Synthesis of (Z)- γ -Alkyl- α,β -Didehydroglutamates from Imino Glycinates [83]**Reactions with P4-*t*Bu base**

To a solution of the imino glycinates (0.48 mmol) in THF (2.0 ml) at -78°C was added dropwise with vigorous stirring a 1.0 M solution of P4-*t*Bu base in hexane (0.48 ml, 0.48 mmol) prediluted in THF (1.0 ml) followed by a solution of the corresponding propiolate (0.48 mmol) in THF (0.5 ml). The mixture was stirred for 5 min, and the electrophile RX (5.0 mmol) was added. The temperature was slowly raised to 25°C and stirring was maintained for 18 h. Et_2O was added, and the precipitate was filtered *in vacuo* and washed with Et_2O (3×2 ml). Evaporation of the solid afforded an oil which was purified by column chromatography with a hexane/ Et_2O mixture (80: 20). The didehydroglutamates (colorless oils) were obtained as a mixture of epimers.

Reactions with 18-crown-6

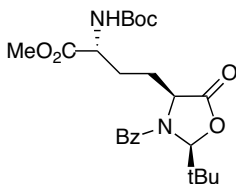
To a solution of KO*t*Bu (0.6 mmol) in THF (1.0 ml) at -78°C was added a solution of the imino glycinates (0.48 mmol) in THF (1.0 ml) and the mixture was stirred for 30 min. A solution of the propiolate (0.6 mmol) in THF (0.5 ml) was added and the mixture was stirred for 10 min. A solution of 18-crown-6 (0.6 mmol) in THF (0.5 ml) was added and the mixture was stirred for 10 min. The corresponding electrophile RX (2.4 mmol) was added, the temperature was slowly raised to 25°C , and stirring was continued for 18 h. Water (0.5 ml) was added, the organic layer was decanted, and the aqueous one was extracted with Et_2O (3×10 ml). The combined organic extracts were dried over MgSO_4 . Evaporation of the solvent afforded an oil that was purified by column chromatography with a hexane/ Et_2O mixture (80: 20). The didehydroglutamates (colorless oils) were obtained as a mixture of epimers.

1.5.6

Palladium-Catalyzed Trifold Heck Coupling [88a]

1,3,5-Triiodobenzene (0.46 g, 1.0 mmol), *N*-protected didehydroalanine (1.0 g, 3.6 mmol), NaHCO_3 (0.63 g, 7.5 mmol), Bu_4NCl (0.83 g, 3.0 mmol), and $\text{Pd}(\text{OAc})_2$ (22 mg, 0.10 mmol) were mixed in DMF (5 ml) in a screwcap vial. A few crystals of hydroquinone were added to prevent polymerization of the acrylate and the mixture was freed from O_2 by N_2 bubbling for 5 min. The vial was sealed and heated at 80°C for 24 h. The dark reaction mixture was allowed to cool and was diluted with EtOAc (50 ml). The resulting mixture was washed with water (2×50 ml) and brine (2×50 ml), and was then dried over Na_2SO_4 . Evaporation of the solvent followed by flash chromatography using heptane/EtOAc (2: 1) as eluent gave the crude DDAA as a yellow semisolid (0.75 g), $R_f = 0.21$. Recrystallization twice from EtOAc/heptane yielded a pale yellow solid (0.40 g, 44%), melting point $123\text{--}131^\circ\text{C}$, which contained about 20% (by $^1\text{H-NMR}$) of an impurity of the same R_f . This material was used directly in the hydrogenation step.

1.5.7

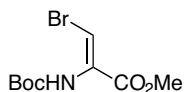
General Experimental Procedure for Conjugate Addition of Alkyl iodides to Chiral α,β -Unsaturated Amino Acid Derivatives: [117c]

CuI (2 mmol) and zinc (6 mmol) were added to a solution of the chiral Michael acceptor **4** (1 mmol) and alkyl iodide (2–6 mmol) in aqueous EtOH (5 ml, 70%) under ultrasonic irradiation. After a few minutes, more aqueous EtOH (5 ml, 70%) was added and sonication was continued for 45 ± 90 min. In the cases where the α,β -unsaturated system was not completely consumed (thin-layer chromatography test), more CuI (1 mmol) and zinc (3 mmol) were added, and the sonication was continued for 3 h. The mixture was diluted with Et_2O (25 ml), sonicated a further

10 min, and filtered through a short pad of Celite. The solids were washed with Et₂O (3 × 30 ml). The organic phase was washed with brine (30 ml), dried (Na₂SO₄), filtered, and concentrated under reduced pressure (20–30 mmHg). The residue was purified by flash chromatography to afford, after concentration, the desired 1,4-addition product.

1.5.8

Bromination of *N*-*tert*-Butyloxycarbonyldidehydroamino Acids: [171]



Boc- Δ Ala-OMe (1.01 g, 5 mmol) was dissolved in dichloromethane (0.1 ml) and 1.2 equiv. of NBS was added with vigorous stirring. After reacting for 16 h, triethylamine (1.5 equiv.) was added and stirring was continued for an 1 h. The solvent was then evaporated at reduced pressure, and the residue was partitioned between dichloromethane (100 ml) and KHSO₄ solution (1 M, 50 ml). The organic phase was washed with KHSO₄ (1 M), NaHCO₃ (1 M), and brine (3 × 30 ml). After drying over MgSO₄ the extract was evaporated at reduced pressure to afford the (*E*)-configured brominated didehydroalanine (1.15 g, 82%) as a colorless oil.

References

- 1 Newton, G.G.F. and Abraham, E.P. (1956) *The Biochemical Journal*, **62**, 651–658.
- 2 Templeton, G.E. (1972) *Microbial Toxins*, **8**, 169–192.
- 3 Hata, T., Koga, F., Sano, Y., Kanamori, K., Matsumae, A., Sugawara, R., Hoshi, T., Shima, T., Ito, S. and Tomizawa, S. (1954) *Journal of Antibiotics*, **7**, 107–112.
- 4 Schmidt, U., Lieberknecht, A. and Wild, J. (1988) *Synthesis*, 159–172.
- 5 Humphrey, J.M. and Chamberlin, A.R. (1997) *Chemical Reviews*, **97**, 2243–2266.
- 6 Bonauer, C., Walenzyk, T. and König, B. (2006) *Synthesis*, 1–20.
- 7 Yun, B.-S., Hidaka, T., Furihata, K. and Seto, H. (1994) *Journal of Antibiotics*, **47**, 969–975.
- 8 Lau, R.C.M. and Rinehart, K.L. (1994) *Journal of Antibiotics*, **47**, 1466–1472.
- 9 Chen, G., Wang, G.-Y.-S., Li, X., Waters, B. and Davies, J. (2000) *Journal of Antibiotics*, **53**, 1145–1153.
- 10 Ranganathan, D., Shah, K. and Vaish, N. (1992) *Journal of the Chemical Society, Chemical Communications*, 1145–1147.
- 11 Somekh, L. and Shanzer, A. (1983) *The Journal of Organic Chemistry*, **48**, 907–908.
- 12 Goodall, K. and Parsons, A.F. (1995) *Tetrahedron Letters*, **36**, 3259–3260.
- 13 Photaki, I. (1963) *Journal of the American Chemical Society*, **85**, 1123–1126.
- 14 (a) Wojciechowska, H., Pawlowicz, R., Andruszkiewicz, R. and Grzybowska, J. (1978) *Tetrahedron Letters*, **19**, 4063–4064; (b) Cherney, R.J. and Wang, L. (1996) *The Journal of Organic Chemistry*, **61**, 2544–2546.
- 15 Miller, M.J. (1980) *The Journal of Organic Chemistry*, **45**, 3131–3132.
- 16 (a) Nugent, W.A. and Feaster, J.E. (1998) *Synthetic Communications*, **28**, 1617–1623; (b) Yokokawa, F. and Shioiri, T.

- (2002) *Tetrahedron Letters*, **43**, 8679–8682.
- 17 Sai, H., Ogiku, T. and Ohmizu, H. (2003) *Synthesis*, 201–204.
- 18 Stohlmeyer, M.M., Tanaka, H. and Wandless, T.J. (1999) *Journal of the American Chemical Society*, **121**, 6100–6101.
- 19 (a) Sokolovsky, M., Sadeh, T. and Patchornik, A. (1964) *Journal of the American Chemical Society*, **86**, 1212–1217; (b) Rich, D.H. and Tam, J.P. (1975) *Tetrahedron Letters*, **16**, 211–212; (c) Rich, D.H. and Tam, J.P. (1977) *The Journal of Organic Chemistry*, **42**, 3815–3820; (d) Miao, Z. and Tam, J.P. (2000) *Organic Letters*, **2**, 3711–3713.
- 20 (a) Brown, R.F.C. and Meehan, G.V. (1968) *Australian Journal of Chemistry*, **21**, 1581–1589; (b) Wolfe, S., Bowers, R.J., Hasan, S.K. and Kazmaier, P.M. (1981) *Canadian Journal of Chemistry*, **59**, 406–421.
- 21 (a) Walter, R. and Roy, J. (1971) *The Journal of Organic Chemistry*, **36**, 2561–2563; (b) Reich, H.J., Jasperse, C.P. and Renga, J.M. (1986) *The Journal of Organic Chemistry*, **51**, 2981–2988; (c) Zhu, Y., Gieselman, M.D., Zhou, H., Averin, O. and van der Donk, W.A. (2003) *Organic and Biomolecular Chemistry*, **1**, 3304–3315; (d) Back, T.G. and Moussa, Z. (2003) *Journal of the American Chemical Society*, **125**, 13455–13460.
- 22 Nicolaou, K.C., Safina, B.S., Zak, M., Lee, S.H., Nevalainen, M., Bella, M., Estrada, A.A., Funke, C., Zecri, F.J. and Bulat, S. (2005) *Journal of the American Chemical Society*, **127**, 11159–11175.
- 23 Horikawa, E., Kodaka, M., Nakahara, Y., Okuno, H. and Nakamura, K. (2001) *Tetrahedron Letters*, **42**, 8337–8339.
- 24 Steiger, R.E. (1944) *The Journal of Biological Chemistry*, **153**, 691–692.
- 25 Shin, C., Nanjo, K., Ando, E. and Yoshimura, J. (1974) *Bulletin of the Chemical Society of Japan*, **47**, 3109–3113.
- 26 Herscheid, J.D.M., Scholten, H.P.H., Tijhuis, M.W. and Ottenheijm, H.C.J. (1981) *Recueil des Travaux Chimiques des Pays-Bas*, **100**, 73–78.
- 27 Kolasa, T. (1983) *Synthesis*, 539.
- 28 (a) Poisel, H. and Schmidt, U. (1975) *Chemische Berichte*, **108**, 2547–2553; (b) Kolar, A.J. and Olsen, R.K. (1977) *Synthesis*, 457–459; (c) Shimohiagashi, Y. and Stammer, C.H. (1983) *Journal of the Chemical Society, Perkin Transactions 1*, 803–808; (d) Zhu, Y.-F., Yamazaki, T., Tsang, J.W., Lok, S. and Goodman, M. (1992) *The Journal of Organic Chemistry*, **57**, 1074–1081.
- 29 Miossec, B., Danion-Bougot, R. and Danion, D. (1994) *Synthesis*, 1171–1174.
- 30 (a) Bergmann, M. and Grafe, K. (1930) *Hoppe-Seyler's Zeitschrift für Physiologische Chemie*, **187**, 183–186; (b) Yonezawa, Y., Shin, C., Ono, Y. and Yoshimura, J. (1980) *Bulletin of the Chemical Society of Japan*, **53**, 2905–2909; (c) Labia, R. and Morin, C. (1986) *The Journal of Organic Chemistry*, **51**, 249–251.
- 31 Makowski, M., Rzeszotarska, B., Kubica, Z. and Pietrzynski, G. (1985) *Liebigs Annalen der Chemie*, 893–900.
- 32 Davies, D.T., Goodall, K., Kapur, N., O'Brien, M. and Parsons, A.F. (1997) *Synthetic Communications*, **27**, 3815–3822.
- 33 (a) Knittel, D. (1984) *Monatshefte für Chemie*, **115**, 1335–1343; (b) Knittel, D. (1985) *Monatshefte für Chemie*, **116**, 1133–1140.
- 34 (a) Yonezawa, Y., Shin, C., Kiyohara, M. and Yoshimura, J. (1979) *Tetrahedron Letters*, **20**, 3851–3854; (b) Fresneda, P.M., Molina, P., Delgado, S. and Bleda, J.A. (2000) *Tetrahedron Letters*, **41**, 4777–4780.
- 35 Manis, P.A. and Rathke, M.W. (1980) *The Journal of Organic Chemistry*, **45**, 4952–4954.
- 36 (a) Effenberger, F., Kühlwein, J. and Drauz, K. (1993) *Liebigs Annalen der Chemie*, 1295–1301; (b) Effenberger, F. and Beisswenger, T. (1984) *Chemische Berichte*, **117**, 1497–1512.

- 37 Effenberger, F., Niesert, C.-P., Kühlwein, J. and Ziegler, T. (1988) *Synthesis*, 218–219.
- 38 Erlenmeyer, E. (1900) *Ber*, 33, 2036–2041.
- 39 (a) Gaset, A. and Gorrichon, J.P. (1982) *Synthetic Communications*, 12, 71–79; (b) Catiuela, C., Diaz de Villegas, M.D., Mayoral, J.A. and Melendez, E. (1983) *Synthesis*, 899–902.
- 40 Tripathy, P.K. and Mukerjee, A.K. (1985) *Synthesis*, 285–288.
- 41 (a) Mukerjee, A.K. and Kumar, P. (1982) *Canadian Journal of Chemistry*, 60, 317–322; (b) Ivanova, G.G. (1992) *Tetrahedron*, 48, 177–186.
- 42 Wolfbeis, O.S. (1981) *Monatshefte für Chemie*, 112, 369–383.
- 43 Steglich, W., Höfle, G., König, W. and Weygand, F. (1968) *Chemische Berichte*, 101, 308–322.
- 44 Nitz, T.J., Lindsey, J. and Stammer, C.H. (1982) *The Journal of Organic Chemistry*, 47, 4029–4032.
- 45 Schmidt, U., Lieberknecht, A. and Wild, J. (1984) *Synthesis*, 53–60.
- 46 Kober, R. and Steglich, W. (1983) *Liebigs Annalen der Chemie*, 599–609.
- 47 (a) Schmidt, U. and Wild, J. (1984) *Angewandte Chemie (International Edition in English)*, 23, 991–993; (b) Horenstein, B.A. and Nakanishi, K. (1989) *Journal of the American Chemical Society*, 111, 6242–6246; (c) Kim, D., Li, Y., Horenstein, B.A. and Nakanishi, K. (1990) *Tetrahedron Letters*, 31, 7119–7122; (d) Apitz, G. and Steglich, W. (1991) *Tetrahedron Letters*, 32, 3163–3166; (e) Schmidt, U., Griesser, H., Leitenberger, V., Lieberknecht, A., Mangold, R., Meyer, R. and Riedl, B. (1992) *Synthesis*, 487–490.
- 48 (a) Ritzen, A., Basu, B., Wallberg, A. and Frejd, T. (1988) *Tetrahedron – Asymmetry*, 9, 3491–3496; (b) Schmidt, U., Lieberknecht, A., Kazmaier, U., Griesser, H., Jung, G. and Metzger, J. (1991) *Synthesis*, 49–55; (c) Coleman, R.S. and Carpenter, A.J. (1992) *The Journal of Organic Chemistry*, 57, 5813–5815; (d) Coleman, R.S. and Carpenter, A.J. (1993) *The Journal of Organic Chemistry*, 58, 4452–4461; (e) Schmidt, U., Braun, C. and Sutoris, H. (1996) *Synthesis*, 223–229; (f) Jorgensen, K.B. and Gautun, O.R. (1999) *Tetrahedron*, 55, 10527–10536; (g) Adamczyk, M., Akireddy, S.R. and Reddy, R.E. (2001) *Organic Letters*, 3, 3157–3159; (h) Wang, W., Xiong, C., Yang, J. and Hruby, V.J. (2002) *Synthesis*, 94–98; (i) Krause, N., Hoffmann-Röder, A. and Canisius, J. (2002) *Synthesis*, 1759–1774.
- 49 (a) Schmidt, U., Weller, D., Holder, A. and Lieberknecht, A. (1988) *Tetrahedron Letters*, 29, 3227–3230; (b) Schmidt, U., Stäbler, F. and Lieberknecht, A. (1992) *Synthesis*, 482–486; (c) Schmidt, U., Leitenberger, V., Griesser, G., Schmidt, J. and Meyer, R. (1992) *Synthesis*, 1248–1254; (d) Schmidt, U., Kleefeldt, A. and Mangold, R. (1992) *Journal of the Chemical Society, Chemical Communications*, 1687–1689; (e) Zhang, J., Xiong, C., Wang, W., Ying, J. and Hruby, V.J. (2002) *Organic Letters*, 4, 4029–4032; (f) Yamada, K., Kurokawa, T., Tokuyama, H. and Fukuyama, T. (2003) *Journal of the American Chemical Society*, 125, 6630–6631; (g) Okano, K., Tokuyama, H. and Fukuyama, T. (2006) *Journal of the American Chemical Society*, 128, 7136–7137.
- 50 Schmidt, U. and Wild, J. (1985) *Liebigs Annalen der Chemie*, 1882–1894.
- 51 Schmidt, U. and Riedl, B. (1992) *Journal of the Chemical Society, Chemical Communications*, 1186–1187.
- 52 Bentley, D.J., Slawin, A.M.Z. and Moody, C.J. (2006) *Organic Letters*, 8, 1975–1978.
- 53 (a) Buck, R.T., Clarke, P.A., Coe, D.M., Drysdale, M.J., Ferris, L., Haigh, D., Moody, C.J., Pearson, N.D. and Swann, E. (2000) *Chemistry – A European Journal*, 6, 2160–2167; (b) Bentley, D.J. and Moody, C.J. (2004) *Organic and Biomolecular Chemistry*, 2, 3545–3547.
- 54 (a) Molina, P., Tarraga, A., Curiel, D. and De Arellano, C.R. (1997) *Tetrahedron*, 53, 15895–15902; (b) Renard, A., Kotera, M.,

- Brochier, M.-C. and Lhomme, J. (2000) *European Journal of Organic Chemistry*, 1831–1840.
- 55 (a) Williams, R.M. and Fegley, G.J. (1991) *Journal of the American Chemical Society*, **113**, 8796–8806; (b) Williams, R.M. (1992) *Aldrichimica Acta*, **25**, 11–23; (c) Williams, R.M. and Fegley, G.J. (1992) *Tetrahedron Letters*, **33**, 6755–6758; (d) Williams, R.M., Fegley, G.J., Gallegos, R., Schaefer, F. and Pruess, D.L. (1996) *Tetrahedron*, **52**, 1149–1164.
- 56 (a) Chai, C.L.L. and King, A.R. (1995) *Tetrahedron Letters*, **36**, 4295–4298; (b) Chai, C.L.L. and King, A.R. (1997) *Journal of Chemical Research-S*, 382.
- 57 Mazurkiewicz, R., Grymel, M. and Kuźnik, A. (2004) *Monatshefte für Chemie*, **135**, 799–806.
- 58 Mazurkiewicz, R. and Grymel, M. (1999) *Monatshefte für Chemie*, **130**, 597–604.
- 59 Mazurkiewicz, R., Kuźnik, A., Grymel, M. and Kuźnik, N. (2004) *Monatshefte für Chemie*, **135**, 807–815.
- 60 (a) Ernest, I. (1980) *Helvetica Chimica Acta*, **63**, 201–213; (b) Bateson, J.H., Robins, A.M. and Southgate, R. (1991) *Journal of the Chemical Society, Perkin Transactions 1*, 2399–2405; (c) Coulton, S. and Francois, I. (1991) *Journal of the Chemical Society, Perkin Transactions 1*, 2699–2705; (d) Dunlap, N.K., Dezube, M., Keith, D.D. and Weigele, M. (1992) *Tetrahedron Letters*, **33**, 6103–6106.
- 61 Schumann, S., Zeitler, K., Jäger, M., Polborn, K. and Steglich, W. (2000) *Tetrahedron*, **56**, 4187–4195.
- 62 Umezawa, S. and Zen, S. (1963) *Bulletin of the Chemical Society of Japan*, **36**, 1143–1145.
- 63 Dornow, A. and Menzel, H. (1954) *Liebigs Annalen der Chemie*, 40–44.
- 64 Wolfbeis, O. (1977) *Chemische Berichte*, **110**, 2480–2493.
- 65 Severin, T. and Böhme, H.-J. (1968) *Chemische Berichte*, **101**, 2925–2930.
- 66 (a) Lehnert, W. (1972) *Tetrahedron*, **28**, 663–666; (b) Fornicola, R.S., Oblinger, E. and Montgomery, J. (1998) *The Journal of Organic Chemistry*, **63**, 3528–3529.
- 67 (a) Versleijen, J.P.G., van Leusen, A.M. and Feringa, B.L. (1999) *Tetrahedron Letters*, **40**, 5803–5806; (b) Srikanth, G.S.C. and Castle, S.L. (2004) *Organic Letters*, **6**, 449–452; (c) He, L., Srikanth, G.S.C. and Castle, S.L. (2005) *The Journal of Organic Chemistry*, **70**, 8140–8147.
- 68 (a) Süs, O. (1948) *Liebigs Annalen der Chemie*, 92–101; (b) Shin, C.C., Masaki, M. and Ohta, M. (1967) *The Journal of Organic Chemistry*, **32**, 1860–1863.
- 69 Süs, O. (1948) *Liebigs Annalen der Chemie*, 31–46.
- 70 Süs, O., Schafer, W. and Grundkotter, M. (1951) *Liebigs Annalen der Chemie*, 201–225.
- 71 (a) Horwell, D.C., Nichols, P.D., Ratcliffe, G.S. and Roberts, E. (1994) *The Journal of Organic Chemistry*, **59**, 4418–4423; (b) Hammadi, A., Menez, A. and Genet, R. (1996) *Tetrahedron Letters*, **37**, 3309–3312.
- 72 Schöllkopf, U. and Meyer, R. (1981) *Liebigs Annalen der Chemie*, 1469–1475.
- 73 (a) Wüst, H.H., Bardenhagen, J. and Schöllkopf, U. (1985) *Liebigs Annalen der Chemie*, 1825–1837; (b) Stanfield, C.F. and Hruby, V.J. (1988) *Synthetic Communications*, **18**, 531–543; (c) Enders, D., Chen, Z.-X. and Raabe, G. (2005) *Synthesis*, 306–310.
- 74 Schöllkopf, U., Gerhart, F., Schröder, R. and Hoppe, D. (1972) *Liebigs Annalen der Chemie*, 116–129.
- 75 Ito, Y., Matsuura, T. and Saegusa, T. (1985) *Tetrahedron Letters*, **26**, 5781–5784.
- 76 Kantlehner, W., Wagner, F. and Bredereck, H. (1980) *Liebigs Annalen der Chemie*, 344–357.
- 77 Schöllkopf, U., Porsch, P.H. and Lau, H.H. (1979) *Liebigs Annalen der Chemie*, 1444–1446.
- 78 Rachon, J. and Schöllkopf, U. (1981) *Liebigs Annalen der Chemie*, 99–102.
- 79 Nunami, K., Hiramatsu, K., Hayashi, K. and Matsumoto, K. (1988) *Tetrahedron*, **44**, 5467–5478.

- 80 (a) Moran, E.J. and Armstrong, R.W. (1991) *Tetrahedron Letters*, **32**, 3807–3810; (b) Kim, S.W., Bauer, S.M. and Armstrong, R.W. (1998) *Tetrahedron Letters*, **39**, 7031–7034; (c) Bienayme, H. (1998) *Tetrahedron Letters*, **39**, 4255–4258.
- 81 Kolb, J., Beck, B. and Domling, A. (2002) *Tetrahedron Letters*, **43**, 6897–6901.
- 82 Reviews: (a) O'Donnell, M.J. (2001) *Aldrichimica Acta*, **34**, 3–15; (b) Soloshonok, V.A. (2002) *Current Organic Chemistry*, **6**, 341–364.
- 83 (a) Alvarez-Ibarra, C., Csáky, A.G., Ortega, E.M., De la Morena, M.J. and Quiroga, M.L. (1997) *Tetrahedron Letters*, **38**, 4501–4502; (b) Alvarez-Ibarra, C., Csáky, A.G., Martin, M.E. and Quiroga, M.L. (1999) *Tetrahedron*, **55**, 7319–7330.
- 84 Alvarez-Ibarra, C., Csáky, A.G. and de la Oliva, C.G. (2002) *The Journal of Organic Chemistry*, **67**, 2789–2797.
- 85 Schwesinger, R. and Schlemper, H. (1987) *Angewandte Chemie (International Edition in English)*, **26**, 1167–1169.
- 86 (a) Cutolo, M., Fiandanese, V., Naso, F. and Sciacovelli, O. (1983) *Tetrahedron Letters*, **24**, 4603–4606; (b) Carlström, A.S. and Frejd, T. (1989) *Synthesis*, 414–418; (c) Bozell, J.J., Vogt, C.E. and Gozum, J. (1991) *The Journal of Organic Chemistry*, **56**, 2584–2587; (d) Fairlamb, I.J.S., Kapdi, A.R., Lee, A.F., McGlacken, G.P., Weissburger, F., de Vries, A.H.M. and Schmieder-van de Vondervoort, L. (2006) *Chemistry – A European Journal*, **12**, 8750–8761.
- 87 (a) Gallou-Dagommer, I., Gastaud, P. and Rajanbabu, T.V. (2001) *Organic Letters*, **3**, 2053–2056; (b) Li, T., Tsuda, Y., Minoura, K., In, Y., Ishida, T., Lazarus, L.H. and Okada, Y. (2006) *Chemical & Pharmaceutical Bulletin*, **54**, 873–877.
- 88 (a) Ritzén, A., Basu, B., Wallberg, A. and Frejd, T. (1998) *Tetrahedron – Asymmetry*, **9**, 3491–3496; (b) Ritzén, A. and Frejd, T. (1999) *Journal of the Chemical Society, Chemical Communications*, 207–208; (c) Ritzén, A. and Frejd, T. (2000) *European Journal of Organic Chemistry*, 3771–3782.
- 89 Gibson, S.E., Jones, J.O., Kalindjian, S.B., Knight, J.D., Steed, J.W. and Tozer, M.J. (2002) *Chemical Communications*, 1938–1939.
- 90 Tullberg, E., Schacher, F., Peters, D. and Frejd, T. (2006) *Synthesis*, 1183–1189.
- 91 Yamazaki, K., Nakamura, Y. and Kondo, Y. (2003) *The Journal of Organic Chemistry*, **68**, 6011–6019.
- 92 (a) Collier, P.N., Patel, I. and Taylor, R.J.K. (2001) *Tetrahedron Letters*, **42**, 5953–5954; (b) Collier, P.N., Campbell, A.D., Patel, I., Raynham, T.M. and Taylor, R.J.K. (2002) *The Journal of Organic Chemistry*, **67**, 1802–1815.
- 93 Navarre, L., Darses, S. and Genet, J.-P. (2004) *European Journal of Organic Chemistry*, 69–73.
- 94 (a) Burk, M.-J., Allen, J.G., Kiesman, W.F. and Stoffan, K.M. (1997) *Tetrahedron Letters*, **38**, 1309–1312; (b) Hoerner, R.S., Askin, D., Volante, R.P. and Reider, P.J. (1998) *Tetrahedron Letters*, **39**, 3455–3458; (c) Burk, M.J., Allen, J.G. and Kiesman, W.F. (1998) *Journal of the American Chemical Society*, **120**, 657–663; (d) Zhang, J., Xiong, C., Wang, W., Ying, J. and Hruby, V.J. (2002) *Organic Letters*, **4**, 4029–4032; (e) Chapman, C.J. and Frost, C.G. (2003) *Advanced Synthesis and Catalysis*, **345**, 353–355.
- 95 Roff, G.J., Lloyd, R.C. and Turner, N.J. (2004) *Journal of the American Chemical Society*, **126**, 4098–4099.
- 96 Narukawa, Y., Nishi, K. and Onoue, H. (1997) *Tetrahedron*, **53**, 539–556.
- 97 Abreu, A.S., Ferreira, P.M.T., Queiroz, M.-J.R.P., Ferreira, I.C.F.R., Calhella, R.C. and Estevinho, L.M. (2005) *European Journal of Organic Chemistry*, 2951–2957.
- 98 Stille, J.K. (1986) *Angewandte Chemie (International Edition in English)*, **25**, 508–523.
- 99 Cook, G.K., Hornback, W.J., Jordan, C.L., McDonald, J.H. III and Munroe, J.E.

- (1989) *The Journal of Organic Chemistry*, **54**, 5828–5830.
- 100** (a) Buynak, J.D., Vogeti, L. and Chen, H. (2001) *Organic Letters*, **3**, 2953–2956; (b) Buynak, J.D., Vogeti, L., Doppalapudi, V.R., Solomon, G.M. and Chen, H. (2002) *Bioorganic & Medicinal Chemistry Letters*, **12**, 1663–1666.
- 101** Abreu, A.S., Ferreira, P.M.T., Queiroz, M.-J.R.P., Gatto, E. and Venanzi, M. (2004) *European Journal of Organic Chemistry*, 3985–3991.
- 102** Bruncko, M. and Crich, D. (1994) *The Journal of Organic Chemistry*, **59**, 4239–4249.
- 103** Probert, J.M., Rennex, D. and Bradley, M. (1996) *Tetrahedron Letters*, **37**, 1101–1104.
- 104** Yokoyama, Y., Hikawa, H., Mitsuhashi, M., Uyama, A., Hiroki, Y. and Murakami, Y. (2004) *European Journal of Organic Chemistry*, 1244–1253.
- 105** (a) Jin, S. and Liebscher, J. (1999) *Synlett*, 459–461; (b) Jin, S., Wessig, P. and Liebscher, J. (2000) *European Journal of Organic Chemistry*, 1993–1999; (c) de la Hoz, A., Diaz-Ortiz, A., Gomez, M.V., Mayoral, J.A., Moreno, A., Sanchez-Migallon, A.M. and Vazquez, E. (2001) *Tetrahedron*, **57**, 5421–5428.
- 106** Ferreira, P.M.T., Maia, H.L.S., Monteiro, L.S., Sacramento, J. and Sebastião, J. (2000) *Journal of the Chemical Society, Perkin Transactions 1*, 3317–3324.
- 107** (a) Ferreira, P.M.T., Maia, H.L.S. and Monteiro, L.S. (2003) *European Journal of Organic Chemistry*, 2635–2644; (b) Abreu, A.S., Silva, N.O., Ferreira, P.M.T., Queiroz, M.-J.R.P. (2003) *European Journal of Organic Chemistry*, 1537–1544.
- 108** (a) Ezquerra, J., Escribano, A., Rubio, A., Remuinan, M.J. and Vaquero, J.J. (1996) *Tetrahedron – Asymmetry*, **7**, 2613–2626; (b) Dugave, C., Cluzeau, J., Menez, A., Gaudry, M. and Marquet, A. (1998) *Tetrahedron Letters*, **39**, 5775–5778; (c) Crossley, M.J., Fung, Y.M., Potter, J.J. and Stamford, A.W. (1998) *Journal of the Chemical Society, Perkin Transactions 1*, 1113–1122; (d) Ballini, R., Balsamini, C., Diamantini, G. and Savoretti, N. (2005) *Synthesis*, 1055–1057.
- 109** Guevel, A.-C. and Hart, D.J. (1996) *The Journal of Organic Chemistry*, **61**, 473–479.
- 110** Pyne, S.G., Javidan, A., Skelton, B.W. and White, A.H. (1995) *Tetrahedron*, **51**, 5157–5168.
- 111** Zimmermann, J. and Seebach, D. (1987) *Helvetica Chimica Acta*, **70**, 1104–1114.
- 112** Javidan, A., Schafer, K. and Pyne, S.G. (1997) *Synlett*, 100–102.
- 113** Cardellicchio, C., Fiandanese, V., Marchese, G., Naso, F. and Ronzini, L. (1985) *Tetrahedron Letters*, **26**, 4387–4390.
- 114** (a) Seebach, D., Bürger, H.M. and Schickli, C.P. (1991) *Liebigs Annalen der Chemie*, 669–684; (b) Toyooka, N., Tanaka, K., Momose, T., Daly, J.W. and Garraffo, H.M. (1997) *Tetrahedron*, **53**, 9553–9574; (c) Bull, S.D., Davies, S.G. and O’Shea, M.D. (1998) *Journal of the Chemical Society, Perkin Transactions 1*, 3657–3658; (d) Toyooka, N., Okumura, M. and Nemoto, H. (2002) *The Journal of Organic Chemistry*, **67**, 6078–6081.
- 115** Cardillo, G., Gentilucci, L., Tolomelli, A. and Tomasini, C. (1999) *Tetrahedron*, **55**, 6231–6242.
- 116** (a) Petrier, C., Dupuy, C. and Luche, J.L. (1986) *Tetrahedron Letters*, **27**, 3149–3152; (b) Luche, J.L. and Allavena, C. (1988) *Tetrahedron Letters*, **29**, 5369–5372.
- 117** (a) Sestelo, J.P., de Una, O., Mourino, A. and Sarandeses, L.A. (2002) *Synlett*, 719–722; (b) Huang, T., Keh, C.C.K., Li, C.-J. (2002) *Chemical Communications*, 2440–2441; (c) Suarez, R.M., Sestelo, J.P. and Sarandeses, L.A. (2003) *Chemistry – A European Journal*, **9**, 4179–4187.
- 118** (a) Ahmad, S., Phillips, R.S. and Stammer, C.H. (1992) *Journal of Medicinal Chemistry*, **35**, 1410–1417; (b) Cativiela, C., Diaz-de-Villegas, M.D. and Jimenez, A.I. (1994) *Tetrahedron*, **50**, 9157–9166; (c) Matsumura, Y., Inoue, M., Nakamura, Y., Talib, I.L., Maki, T. and Onomura, O. (2000) *Tetrahedron Letters*, **41**, 4619–4622.

- 119 Williams, R.M. and Fegley, G.J. (1993) *The Journal of Organic Chemistry*, **58**, 6933–6935.
- 120 Calmes, M., Daunis, J. and Escale, F. (1996) *Tetrahedron – Asymmetry*, **7**, 395–396.
- 121 Chinchilla, R., Falvello, L.R., Galindo, N. and Najera, C. (1998) *Tetrahedron – Asymmetry*, **9**, 2223–2227.
- 122 Bunuel, E., Bull, S.D., Davies, S.G., Garner, A.C., Savory, E.D., Smith, A.D., Vickers, R.J. and Watkin, D.J. (2003) *Organic and Biomolecular Chemistry*, **1**, 2531–2542.
- 123 Catiuela, C., Diaz-de-Villegas, M.D. and Jimenez, A.I. (1995) *Tetrahedron*, **51**, 3025–3032.
- 124 Yim, A.M., Vidal, Y., Viallefont, P. and Martinez, J. (1999) *Tetrahedron Letters*, **40**, 4535–4538.
- 125 (a) Gibson, S.E., Guillo, N. and Tozer, M.J. (1997) *Chemical Communications*, 637–638; (b) Horneman, A.M. and Lundt, I. (1998) *The Journal of Organic Chemistry*, **63**, 1919–1928.
- 126 (a) Goodall, K. and Parsons, A.F. (1996) *Tetrahedron*, **52**, 6739–6758; (b) Tamura, O., Matsukida, H., Toyao, A., Takeda, Y. and Ishibashi, H. (2002) *The Journal of Organic Chemistry*, **67**, 5537–5545.
- 127 Baker, S.R., Parsons, A.F. and Wilson, M. (1998) *Tetrahedron Letters*, **39**, 2815–2818.
- 128 (a) Baker, S.R., Parsons, A.F., Pons, J.-F. and Wilson, M. (1998) *Tetrahedron Letters*, **39**, 7197–7200; (b) Baker, S.R., Burton, K.I., Parsons, A.F., Pons, J.-F. and Wilson, M. (1999) *Journal of the Chemical Society, Perkin Transactions 1*, 427–436.
- 129 Parrish, J.D. and Little, R.D. (2002) *Organic Letters*, **4**, 1439–1442.
- 130 Miyabe, H., Asada, R., Yoshida, K. and Takemoto, Y. (2004) *Synlett*, 540–542.
- 131 Sutherland, A. and Vederas, J.C. (2002) *Chemical Communications*, 224–225.
- 132 (a) Axon, J.R. and Beckwith, A.L.J. (1995) *Journal of the Chemical Society, Chemical Communications*, 549–550; (b) Pyne, S.G. and Schafer, K. (1998) *Tetrahedron*, **54**, 5709–5720; (c) Jones, R.C.F., Berthelot, D.J.C. and Iley, J.N. (2001) *Tetrahedron*, **57**, 6539–6555.
- 133 Beckwith, A.L.J. and Chai, C.L.L. (1990) *Journal of the Chemical Society, Chemical Communications*, 1087–1088.
- 134 Kabat, M.M. (2001) *Tetrahedron Letters*, **42**, 7521–7524.
- 135 Yim, A.-M., Vidal, Y., Viallefont, P. and Martinez, J. (2002) *Tetrahedron – Asymmetry*, **13**, 503–510.
- 136 Sibi, M.P., Asano, Y. and Sausker, J.B. (2001) *Angewandte Chemie International Edition*, **40**, 1293–1296.
- 137 Catiuela, C. and Diaz-de-Villegas, M.D. (2000) *Tetrahedron – Asymmetry*, **11**, 645–732.
- 138 (a) Zhu, Y.F., Yamazaki, T., Tsang, J.W., Lok, S. and Goodman, M. (1992) *The Journal of Organic Chemistry*, **57**, 1074–1081; (b) Adams, L.A., Charmant, J.P.H., Cox, R.J., Walter, M. and Whittingham, W.G. (2004) *Organic and Biomolecular Chemistry*, **2**, 542–553.
- 139 (a) Alami, A., Calmes, M., Daunis, J., Escale, F., Jacquier, R., Roumestant, M.L. and Viallefont, P. (1991) *Tetrahedron – Asymmetry*, **2**, 175–178; (b) Catiuela, C., Diaz-de-Villegas, M.D., Garcia, J.I. and Jimenez, A.I. (1997) *Tetrahedron*, **53**, 4479–4486; (c) Rife, J. and Ortuño, R.M. (1999) *Tetrahedron – Asymmetry*, **10**, 4245–4260.
- 140 Alcaraz, C., Fernandez, M.D., de Frutos, M.P., Marco, J.L., Bernabe, M., Foces-Foces, C. and Cano, F.H. (1994) *Tetrahedron*, **50**, 12443–12456.
- 141 (a) Aggarwal, V.K., Alonso, E., Fang, G.Y., Ferrara, M., Hynd, G. and Porcelloni, M. (2001) *Angewandte Chemie International Edition*, **40**, 1433–1436; (b) Adams, L.A., Aggarwal, V.K., Bonnert, R.V., Bressel, B., Cox, R.J., Shepherd, J., de Vicente, J., Walter, M., Whittingham, W.G. and Winn, C.L. (2003) *The Journal of Organic Chemistry*, **68**, 9433–9440.
- 142 (a) Pyne, S.G., Safaei-G., J. and Koller, F. (1995) *Tetrahedron Letters*, **36**, 2511–2514;

- (b) Pyne, S.G., Safaei-G., J., Schafer, A.K., Javidan, A., Skelton, B.W. and White, A.H. (1998) *Australian Journal of Chemistry*, **51**, 137–158.
- 143** Pyne, S.G., Safaei-G., J., Skelton, B.W. and White, A.H. (1995) *Australian Journal of Chemistry*, **48**, 1511–1533.
- 144** Chai, C.L.L., Edwards, A.J., Wilkes, B.A. and Woodgate, R.C.J. (2003) *Tetrahedron*, **59**, 8731–8739.
- 145** (a) Pyne, S.G., Schafer, K., Skelton, B.W. and White, A.H. (1997) *Chemical Communications*, 2267–2268; (b) Ung, A.T., Schafer, K., Lindsay, K.B., Pyne, S.G., Amornraksa, K., Wouters, R., van der Linden, I., Biesmans, I., Lesage, A.S.J., Skelton, B.W. and White, A.H. (2002) *The Journal of Organic Chemistry*, **67**, 227–233; (c) Pham, T.Q., Pyne, S.G., Skelton, B.W. and White, A.H. (2005) *The Journal of Organic Chemistry*, **70**, 6369–6377.
- 146** (a) Trost, B.M. and Kazmaier, U. (1992) *Journal of the American Chemical Society*, **114**, 7933–7935; (b) Methot, J.L. and Roush, W.R. (2004) *Advanced Synthesis and Catalysis*, **346**, 1035–1050.
- 147** (a) Cativiela, C., Lopez, P. and Mayoral, J.A. (1991) *Tetrahedron – Asymmetry*, **2**, 449–456; (b) Pyne, S.G., Dikic, B., Gordon, P.A., Skelton, B.W. and White, A.H. (1991) *Journal of the Chemical Society, Chemical Communications*, 1505–1506; (c) Bunuel, E., Cativiela, C. and Diaz-de-Villegas, M.D. (1995) *Tetrahedron*, **51**, 8923–8934; (d) Chinchilla, R., Falvello, L.R., Galindo, N. and Najera, C. (1999) *Tetrahedron – Asymmetry*, **10**, 821–825; (e) Chai, C.L.L., Johnson, R.C. and Koh, J. (2002) *Tetrahedron*, **58**, 975–982.
- 148** Avenoza, A., Cativiela, C., Busto, J.H., Fernandez-Recio, M.A., Peregrina, J.M. and Rodriguez, F. (2001) *Tetrahedron*, **57**, 545–548.
- 149** Cativiela, C., Lopez, P. and Mayoral, J.A. (1991) *Tetrahedron – Asymmetry*, **2**, 1295–1304.
- 150** (a) Fan, Q.-H., Li, Y.-M. and Chan, A.S.C. (2002) *Chemical Reviews*, **102**, 3385–3465; (b) Noyori, R. (2002) *Angewandte Chemie International Edition*, **41**, 2008–2022; (c) Chelucci, G., Orru, G. and Pinna, G.A. (2003) *Tetrahedron*, **59**, 9471–9515; (d) Genet, J.-P. (2003) *Accounts of Chemical Research*, **36**, 908–918; (e) Tang, W. and Zhang, X. (2003) *Chemical Reviews*, **103**, 3029–3069; (f) Jäkel, C. and Paciello, R. (2006) *Chemical Reviews*, **106**, 2912–2942.
- 151** Osborn, J.A., Jardine, F.H., Young, J.F. and Wilkinson, G. (1966) *Journal of the Chemical Society, A: Inorganic, Physical, Theoretical*, 1711–1732.
- 152** Horner, L., Siegel, H. and Büthe, H. (1968) *Angewandte Chemie (International Edition in English)*, **7**, 942–943.
- 153** Knowles, W.S. and Sabacky, M.J. (1968) *Chemical Communications*, 1445–1446.
- 154** (a) Vineyard, B.D., Knowles, W.S., Sabacky, M.J., Bachman, G.L. and Weinkauff, D.J. (1977) *Journal of the American Chemical Society*, **99**, 5946–5952; (b) Knowles, W.S. (1983) *Accounts of Chemical Research*, **16**, 106–112.
- 155** Knowles, W.S. (1986) *Journal of Chemical Education*, **63**, 222–225.
- 156** Knowles, W.S. (2002) *Angewandte Chemie International Edition*, **41**, 1998–2007.
- 157** (a) Schmidt, U., Lieberknecht, A., Griesser, H. and Bartkowiak, F. (1984) *Angewandte Chemie (International Edition in English)*, **23**, 318–320; (b) Schmidt, U., Leitenberger, V., Meyer, R. and Griesser, H. (1992) *Journal of the Chemical Society, Chemical Communications*, 951–953.
- 158** (a) Poulin, J.C. and Kagan, H.B. (1982) *Journal of the Chemical Society, Chemical Communications*, 1261–1262; (b) Carlström, A.S. and Frejd, T. (1991) *Journal of the Chemical Society, Chemical Communications*, 1216–1217; (c) Nagel, U. and Krink, T. (1993) *Angewandte Chemie (International Edition in English)*, **32**, 1052–1054; (d) Ghosh, A.K. and Wang, Y. (1999) *Journal of the Chemical Society, Perkin Transactions 1*, 3597–3601.
- 159** (a) Teoh, E., Campi, E.M., Jackson, W.R. and Robinson, A.J. (2002) *Chemical*

- Communications, 978–979; (b) Teoh, E., Campi, E.M., Jackson, W.R. and Robinson, A.J. (2003) *New Journal of Chemistry*, **27**, 387–394.
- 160** (a) Borszeky, K., Mallat, T. and Baiker, A. (1997) *Tetrahedron – Asymmetry*, **8**, 3745–3753; (b) Blaser, H.U., Hönig, H., Studer, M., Wedemeyer-Exl, C. (1999) *Journal of Molecular Catalysis A – Chemical*, **139**, 253–257; (c) Sugimura, T., Watanabe, J., Okuyama, T. and Nitta, Y. (2005) *Tetrahedron – Asymmetry*, **16**, 1573–1575; (d) Szöllösi, G., Szabo, E. and Bartok, M. (2007) *Advanced Synthesis and Catalysis*, **349**, 405–410.
- 161** (a) Fan, Q.-H., Deng, G.-J., Lin, C.-C. and Chan, A.S.C. (2001) *Tetrahedron – Asymmetry*, **12**, 1241–1247; (b) Hu, X.-P., Huang, J.-D., Zeng, Q.-H. and Zheng, Z. (2006) *Chemical Communications*, 293–295.
- 162** Nagel, U. and Leipold, J. (1996) *Chemische Berichte*, **129**, 815–821.
- 163** (a) Cativiela, C., Diaz-de-Villegas, M.D. and Galvez, J.A. (1992) *Tetrahedron – Asymmetry*, **3**, 567–572; (b) Horti, A., Redmond, D.E. Jr and Soufer, R. (1995) *Journal of Labelled Compounds & Radiopharmaceuticals*, **36**, 409–423; (c) Kassem, T., Wehbe, J., Rolland-Fulcrand, V., Rolland, M., Roumestant, M.L. and Martinez, J. (2001) *Tetrahedron – Asymmetry*, **12**, 2657–2661.
- 164** Vigneron, J.P., Kagan, H. and Horeau, A. (1968) *Tetrahedron Letters*, **9**, 5681–5683.
- 165** (a) Poisel, H. and Schmidt, U. (1973) *Chemische Berichte*, **106**, 3408–3420; (b) Herscheid, J.D.M., Nivard, R.J.F., Tijhuis, M.W. and Ottenheijm, H.C.J. (1980) *The Journal of Organic Chemistry*, **45**, 1880–1885; (c) Davies, S.G., Rodriguez-Solla, H., Tamayo, J.A., Cowley, A.R., Concellon, C., Garner, A.C., Parkes, A.L. and Smith, A.D. (2005) *Organic and Biomolecular Chemistry*, **3**, 1435–1447.
- 166** Lisichkina, I.N., Ushakova, O.M., Alekseeva, M.O., Peregodov, A.S. and Belikov, V.M. (1999) *Russian Chemical Bulletin*, **48**, 1682–1684.
- 167** (a) Onuma, K., Ito, T. and Nakamura, A. (1980) *Chemistry Letters*, 481–482; (b) Yamagishi, T., Yatagai, M., Hatakeyama, H. and Hida, M. (1984) *Bulletin of the Chemical Society of Japan*, **57**, 1897–1901; (c) El-Baba, S., Nuzillard, J.M., Poulin, J.C. and Kagan, H.B. (1986) *Tetrahedron*, **42**, 3851–3861.
- 168** Schmidt, U., Kumpf, S. and Neumann, K. (1994) *Journal of the Chemical Society, Chemical Communications*, 1915–1916.
- 169** Nakatsuka, S., Tanino, H. and Kishi, Y. (1975) *Journal of the American Chemical Society*, **97**, 5008–5010.
- 170** Danion-Bougot, R., Danion, D. and Francis, G. (1990) *Tetrahedron Letters*, **31**, 3739–3742.
- 171** Silva, N.O., Abreu, A.S., Ferreira, P.M.T., Monteiro, L.S. and Queiroz, M.-J.R.P. (2002) *European Journal of Organic Chemistry*, 2524–2528.
- 172** Richards, K.D., Kolar, A.J., Srinivasan, A., Stephenson, R.W. and Olsen, R.K. (1976) *The Journal of Organic Chemistry*, **41**, 3674–3677.
- 173** (a) Zhou, H. and van der Donk, W.A. (2001) *Organic Letters*, **3**, 593–596; (b) Zhou, H. and van der Donk, W.A. (2002) *Organic Letters*, **4**, 1335–1338.