Amino Acids (1996) 11: 283–299

Amino
Acids

Synthesis of γ,δ-unsaturated amino acids via ester enolate Claisen rearrangement of chelated allylic esters

Review Article

U. Kazmaier

Organisch-Chemisches Institut der Universität, Heidelberg,
Federal Republic of Germany

Accepted March 20, 1996

Summary. Deprotonation of *N*-protected amino acid allylic esters with LDA at −78°C and subsequent addition of a metal salt presumably results in the formation of a chelated metal enolate which undergoes Claisen rearrangement upon warming up to room temperature, giving rise to unsaturated amino acid. Many different metal salts can be used for chelation, but in general the best results are obtained with zinc chloride. Due to the fixed enolate geometry, as a result of chelate formation, and a strong preference for the *chair like* transition state, the rearrangement proceeds with a high degree of diastereoselectivity. This methodology can be applied to acyclic as well as to cyclic substrates, and even to peptides, and allows for the synthesis of amino acids containing quaternary carbon centers.

Keywords: Amino acids – Chelate-enolate Claisen rearrangement – Chair like transition state – Unsaturated amino acids

Introduction

γ,δ-Unsaturated amino acids are of current interest, not only as naturally occurring non-proteinogenic amino acids like the isoleucine antagonist cyclopentenylglycine **1** (Edelson et al., 1958; Cramer et al., 1980) and the antibiotic furanomycine **2** (Katagiri et al., 1967), but also as important intermediates for the synthesis of complex amino acids as illustrated by the derivatives **3–5** (Bartlett et al., 1982a; Ohfune et al., 1985, 1986; Baumann and Duthaler, 1988; Broxterman et al., 1992).

Therefore, various approaches to the synthesis of this class of amino acids have been developed during the last few years. Besides the *N*-sulfonylimine ene reaction (Achmatowicz and Pietraszkiewicz, 1981; Tschaen and Weinreb,

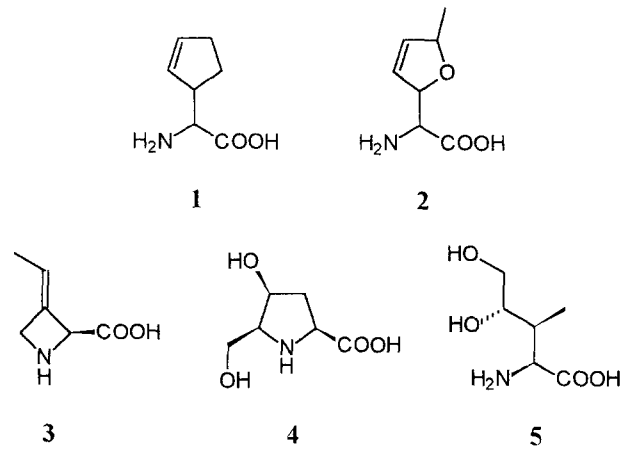
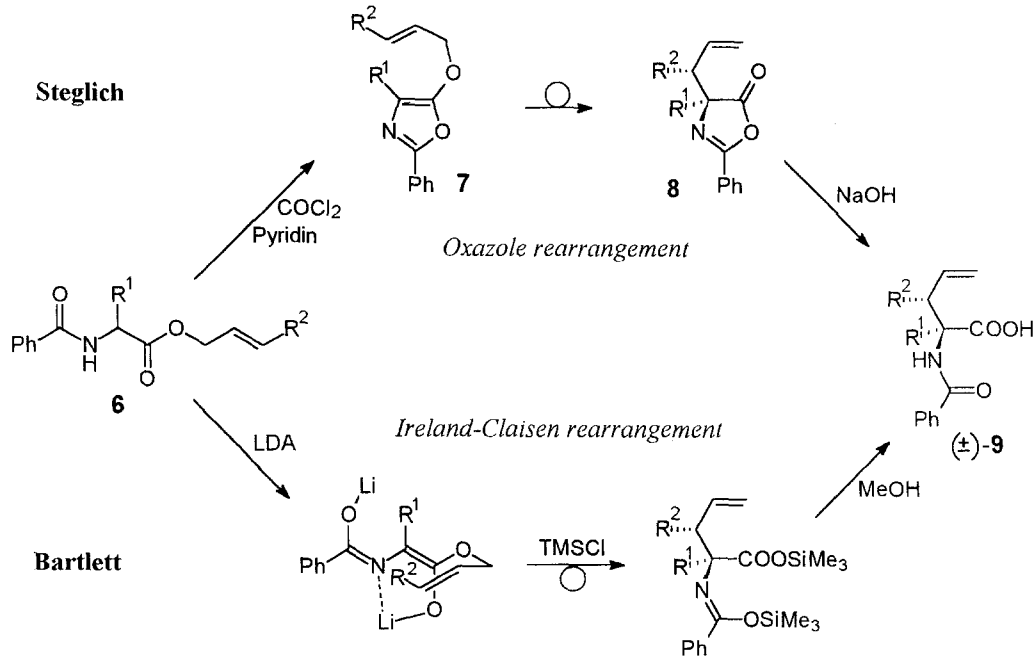


Fig. 1



Scheme 1

1982, 1984) and the nucleophilic allylation of glycine cation equivalents (Williams et al., 1988; Easton and Scharfbillig, 1990; Roos et al., 1992, 1993), the sigmatropic rearrangement processes are well suited for the introduction of unsaturated side chains (Williams, 1989) (Scheme 1).

The first synthesis of allylic amino acids by Claisen rearrangement was described in 1975 by Steglich et al. (Kübel et al., 1975; Engel et al., 1977). Treatment of *N*-Benzoyl amino acid allylic esters **6** with dehydrating agents such as phosgen results in the formation of allyloxazolinones **8** *via* Claisen rearrangement of the primarily formed oxazole intermediates **7**. The reaction is especially suitable for the synthesis of α-alkylated allylic amino

acids ($R^1 \neq H$) because, in this case, epimerization of the α-chiral center *via* enolization of the oxazolone **8** is not possible (Fischer et al., 1986; Burger et al., 1988; Castelhano et al., 1988; Colombo et al., 1991; Holladay and Nadzan, 1991).

As a result of the fixed olefin geometry in the oxazole ring and a strong preference of the *chair like* transition state these α-alkylated amino acids **9** are formed in a highly diastereoselective fashion. Unfortunately, this elegant methodology is limited to *N*-benzoyl amino acid esters (or related aromatic or heteroaromatic N-acyl derivatives), while other common protecting groups like carbamates (Z, BOC, FMOC, etc.) show no cyclization to the corresponding oxazole. For these derivatives another rearrangement process has to be applied.

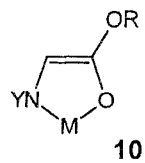
The Ireland-Claisen rearrangement (Ireland and Mueller, 1972) of different *N*-protected glycine allylic esters was intensively studied by Bartlett and Barstow (1982). This method is applicable to various protecting groups and can be applied to the synthesis of *normal* ($R^1 = H$) as well as to α-alkylated amino acids. However, the diastereoselectivity of the rearrangement strongly depends on various reaction parameters, like solvent or the base used, the *N*-protecting group, and the substitution pattern of the allylic ester moiety. As a result, this methodology is not *generally* suitable to the diastereoselective synthesis of these unsaturated α-amino acids.

The chelate-enolate Claisen rearrangement

Working in the field of amino acid synthesis, we are mainly interested in reactions of chelated amino acid ester enolates **10** (Fig. 2). These chelated enolates have several advantages in comparison to their non chelated analogues:

a) The chelated enolates are significantly more stable than the corresponding, probably non chelated, lithium enolates. In contrast to lithium enolates, the chelate enolates can be warmed up to room temperature without decomposition. Side reactions such as ketene formation *via* elimination can be suppressed in most cases. This allows the expansion of the field of enolate chemistry to reactions which can not be carried out with *normal*, non stabilized enolates.

b) Because of the fixation of the enolate geometry by chelation, many reactions of these enolates proceed with a high degree of diastereoselectivity. For example, aldol reactions of **10** with various aldehydes occur in a highly diastereoselective fashion in the presence of titanium or zinc salts, whereas



10

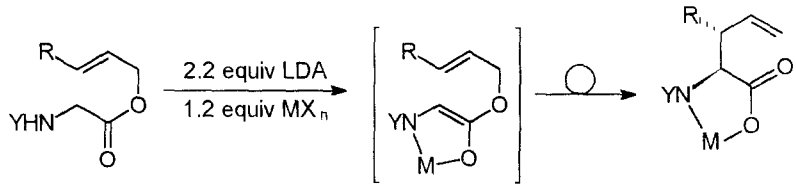
M: metal
Y: protecting group

Fig. 2

the corresponding lithium enolates show only modest selectivity (Kazmaier and Grandel, 1995).

c) Many manipulations on enolates such as **10** as possible. Besides variations of the protecting group X, an excessive *metal tuning* should allow the modification of the reactivity and selectivity of these enolates. Because, in most cases, the coordination sphere of the metal ion M is not saturated in the bidentate enolate complex, the additional coordination of external ligands on the chelated metal is possible. *Ligand tuning* with chiral ligands should probably allow enolate reactions to be carried out not only in a diastereoselective but also in an enantioselective way.

It is important to know if a chelate enolate is formed under certain reaction conditions, because many variations of the reaction parameters are possible. Therefore we were looking for a reaction that provides us with the desired information. A reaction, especially suitable for our purpose, is the ester enolate Claisen rearrangement, which is known to proceed preferentially via a *chair like* transition state. Therefore, the relative configuration of substituents in the rearrangement product strongly depends on the enolate geometry. If high diastereoselectivities are observed, one of the two possible enolates is significantly favored (Ziegler, 1988; Blechert, 1989; Wipf, 1991; Pereira and Srebnik, 1993; Frauenrath, 1995). E.g. the high *syn*-selectivity in the enolate Claisen rearrangement of chiral α-alkoxysubstituted allylic



11 **12** **(±)-13**

Scheme 2

Table 1. Rearrangement of *N*-protected glycine allylic esters **11**

Entry	Y	MX_n	R	Yield [%]	ds [%]
1	Z	$ZnCl_2$	CH_3	90	95
2	Z	$CoCl_2$	CH_3	78	93
3	Z	$MgCl_2$	CH_3	85	91
4	Z	$Al(OiPr)_3$	CH_3	75	90
5	Z	$Ti(OiPr)_4$	CH_3	50	90
6	Z	Me_3SiCl	CH_3	60	83
7	Z	$ZnCl_2$	H	88	–
8	Z	$ZnCl_2$	C_3H_7	76	95
9	BOC	$ZnCl_2$	CH_3	84	96
10	BOC	$ZnCl_2$	C_3H_7	78	96
11	TFA	$ZnCl_2$	C_3H_7	79	95

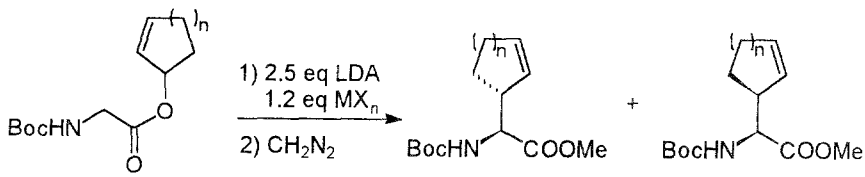
esters is explained by the rearrangement *via* a primarily formed chelated ester enolate (Bartlett et al., 1982b; Burke et al., 1983; Kallmerten et al., 1986).

Recently we described a new variation of the ester enolate Claisen rearrangement, one that is especially suitable for α-amino acid synthesis (Kazmaier, 1994a). Deprotonation of *N*-protected amino acid allylic esters (Scheme 2) like **11** with LDA at −78°C and subsequent addition of a metal salt (MX_n) presumably results in the formation of a chelated metal enolate **12** which undergoes Claisen rearrangement upon warming up to room temperature, giving rise to unsaturated amino acid **13**.

In contrast to the corresponding lithium enolates, which do not show this rearrangement because they decompose during warming up, the chelate-enolates are much more stable. Many different metal salts can be used for chelation (Table 1) and, in general, yields and diastereoselectivities are high. The best results are obtained with zinc chloride while the lower yield in the reaction with titaniumisopropoxyd (entry 5) results from a partially split of the allylic ester *via* titanium catalyzed transesterification. Otherwise, the metal enolates are clearly superior to silylketene acetals (entry 6), both in terms of their reactivity and selectivity. The driving force for the accelerated rearrangement of the chelate enolates is probably the transformation of the high-energy ester enolate **12** into a chelate bridged, stabilized carboxylate **13**. Due to the fixed enolate geometry, as a result of chelate formation, the rearrangement proceeds with a high degree of diastereoselectivity independent of the substitution pattern and the protecting groups Y used.

Because of the good results obtained with acyclic substrates, the chelate-enolate rearrangement was also applied to cycloalkenyl glycinates **14** (Scheme 3) (Kazmaier, 1994b). These substrates are of special interest, not only because of the biological activity of the resulting amino acids, but also because it is known, that cyclic allylic esters prefer to rearrange *via* the *boot like* transition state. The influence of the ring size as well as the metal salt used for chelation of the ester enolate was investigated. The results are listed in Table 2.

The best results concerning yield as well as stereoselectivity are obtained with cyclohexenyl glycinate (n = 2). In this case all metal salts give the desired product with excellent yields. The same high degree of diastereoselectivity is obtained in the rearrangement of the homologous cycloheptenyl derivative (n = 3), whereas the selectivity decreases in the case of the smaller ester

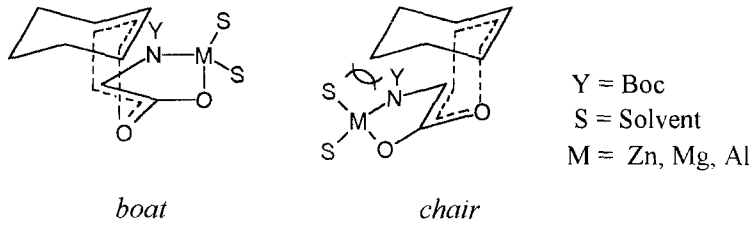


14 (±)-**15** (±)-**16**

Scheme 3

Table 2. Rearrangement of *N*-Boc protected cycloalkenyl glycinates **14**

MX_n n	$ZnCl_2$		$MgCl_2$		$Al(OiPr)_3$		$SnCl_2$	
	Yield [%]	Ratio 15:16	Yield [%]	Ratio 15:16	Yield [%]	Ratio 15:16	Yield [%]	Ratio 15:16
1	79	80:20	57	79:21	47	75:25	76	67:33
2	83	90:10	94	92:8	91	90:10	88	71:21
3	73	92:8	79	92:8	69	89:11	71	63:67
4	57	86:14	78	91:9	42	79:21	74	41:59



boat *chair*

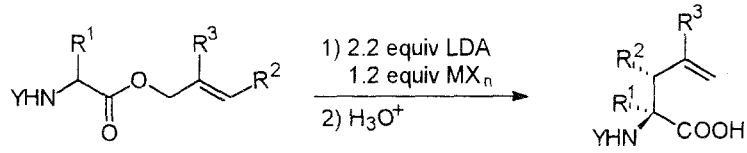
Fig. 3

(n = 1) and larger, probably more flexible cyclooctenyl ester (n = 4). The results with tin(II) chloride are in sharp contrast to the selectivities obtained in the presence of the other metal salts. Obviously, tin(II) chloride is not able to form chelated enolates under the usual reaction conditions. Although the diastereomer **15** was formed preferentially in good yields, the diastereomeric ratio varies and is even inverted in the case of the cyclooctenyl ester. Even though this phenomenon is surprising, it is also observed in the rearrangement of acyclic substrates.

The product formation as well as the high diastereoselectivity observed in the rearrangement of the six- and seven- membered allylic esters can be explained by rearrangement *via* a *boat-like* transition state which is discussed frequently for cyclic allylic substrates (Fig. 3). Steric interactions between the cycloalkenyl ring and the probably solvated chelating metal obviously disfavor the *chair-like* transition state.

Synthesis of quaternary amino acids

The good results obtained with acyclic as well as cyclic glycine allylic esters encouraged us to evaluate the chelate-enolate rearrangement to the synthesis of sterically high demanding amino acids containing quaternary carbon centers. Therefore, the rearrangement was also applied to esters of other amino acids **17** (Scheme 4, $R^1 \neq H$). The influence of the protecting group Y, the side chain R^1, the substitution pattern ($R^2 - R^3$) as well as the metal salt MX_n used for chelation of the ester enolate was investigated (Kazmaier and Maier, 1995, 1996). The results are listed in Table 3. As in the examples mentioned earlier, no dependence on the protecting group is observed for the rearrangement.



17 (±)-18

Scheme 4

Table 3. Rearrangement of various amino acid allylic esters **17**

Entry	Y	R^1	R^2	R^3	MX_n	Yield [%]	ds [%]
1	Z	H	H	CH_3	$ZnCl_2$	92	–
2	BOC	CH_3	H	CH_3	$ZnCl_2$	81	–
3	Z	C_2H_5	H	CH_3	$ZnCl_2$	87	–
4	Z	C_2H_5	H	CH_3	$MgCl_2$	80	–
5	Z	$CH(CH_3)_2$	H	CH_3	$ZnCl_2$	39	–
6	Z	CH_2Ph	H	CH_3	$ZnCl_2$	63	–
7	TFA	CH_2Ind^a	H	CH_3	$ZnCl_2$	34	–
8	TFA	CH_2Ind^a	H	CH_3	$MgCl_2$	79	–
9	Z	$(CH_2)_4NHBOC$	H	CH_3	$ZnCl_2$	69	–
10	BOC	$(CH_2)_2SCH_3$	H	CH_3	$ZnCl_2$	80	–
11	TFA	CH_3	CH_3	H	$ZnCl_2$	84	96
12	TFA	CH_3	Ph	H	$ZnCl_2$	65	94
13	TFA	CH_3	CH_3	H	$ZnCl_2$	84	92
14	TFA	CH_3	CH_3	H	$MgCl_2$	89	94
15	TFA	Ph	CH_3	H	$ZnCl_2$	94	95
16	Z	$(CH_2)_4NHBOC$	CH_3	H	$ZnCl_2$	74	94

[a] *Ind* 3-Indolyl.

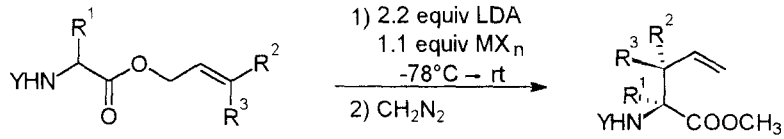
Overall, best results are obtained in the presence of zinc chloride as the chelating metal salt. Among all the other metal salts which can be employed, particularly magnesium chloride gives comparable yields in many cases (entries 13 and 14). For the tryptophan derivative the yield is even higher (entries 7 and 8). This example also shows that this methodology is not restricted to amino acids with aliphatic or aromatic side chains but can also be applied to derivatives of functionalized amino acids like tryptophan, lysine (entries 9 and 16), or methionine (entry 10). These examples have been chosen, because especially the tryptophan and lysine derivatives are critical substrates for α-alkylation reactions (Gander-Coquez and Seebach, 1988). The α-alkylated methionine derivative is also an interesting substrate, because it can be converted easily into other amino acids like ethyl glycine (Raney-Ni) (Schöllkopf and Konsky, 1983) or vinyl glycine (*via* an oxidation-elimination pathway) (Weber et al., 1986). The diastereoselectivities observed for the *E*-configurated allylic esters (entries 11–16) are comparable to the results obtained with the corresponding glycine derivatives (Table 1).

Amino acids containing quaternary β-carbon centers are, in addition to α-alkylated amino acids, an especially interesting class of non-proteinogenic

amino acids. The most common representative, *tert.*-leucine, occurs as a building block in various complex natural products. Recently, *tert.*-leucine was used as a precursor for the synthesis of chiral auxiliaries and ligands applied to asymmetric synthesis. While various methods are known for the synthesis of α-alkylated amino acids, there are fewer procedures available for the formation of amino acids containing quaternary β-centers (Martin, 1980; Fuji, 1993). Besides Michael- and cycloadditions, the sigmatropic rearrangement processes are suitable for this purpose (Takano et al., 1984; Ito et al., 1988).

Because of the promising results obtained with *E*-configurated allylic esters, the chelate-enolate rearrangement was also applied to the rearrangement of highly substituted allylic esters such as **19** (Scheme 5), giving rise to amino acids containing quaternary β-carbon centers. Starting from amino acids other than glycine ($R^1 \neq H$) allows for the generation of two vicinal quaternary centers in one step (Kazmaier, 1995).

As in the other systems investigated, various metal salts can be used for chelation (Table 4, entries 1–4) as well, but in general, best results are obtained with zinc chloride and methylaluminium dichloride. Therefore, zinc chloride is applied for this purpose in standard reactions because it is less expensive and easier to handle.



19 (±)-**20**

Scheme 5

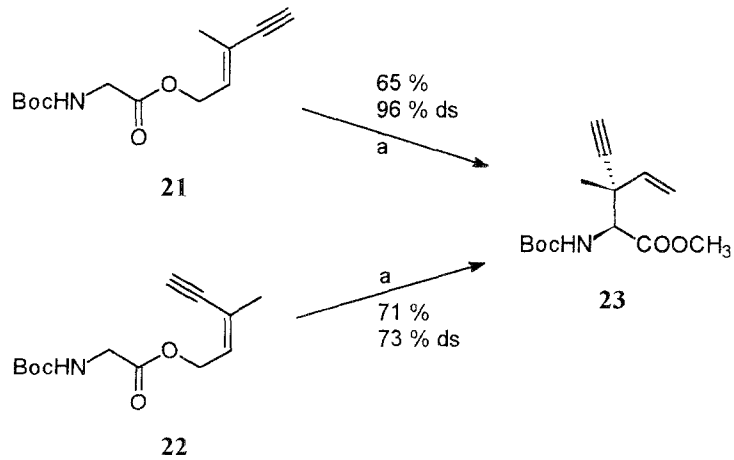
Table 4. Ester enolate Claisen rearrangement of amino acid allylic esters **19**

Entry	Y	R^1	R^2	R^3	MX_n	Yield [%]
1	Z	H	CH_3	CH_3	$ZnCl_2$	81%
2	Z	H	CH_3	CH_3	$AlMeCl_2$	78%
3	Z	H	CH_3	CH_3	$MgCl_2$	75%
4	Z	H	CH_3	CH_3	$Al(OiPr)_3$	36%
5	BOC	H	$-(CH_2)_4-$		$ZnCl_2$	64%
6	BOC	H	$-(CH_2)_4-$		$AlMeCl_2$	62%
7	BOC	H	$-(CH_2)_5-$		$ZnCl_2$	45%
8	BOC	H	$-(CH_2)_5-$		$AlMeCl_2$	69%
9	BOC	CH_3	CH_3	CH_3	$ZnCl_2$	68%
10	Z	Bn	CH_3	CH_3	$ZnCl_2$	69%
11	BOC	Bn	CH_3	CH_3	$ZnCl_2$	64%
12	TFA	Bn	CH_3	CH_3	$ZnCl_2$	67%
13	Tos	Bn	CH_3	CH_3	$ZnCl_2$	75%
14	TFA	Ph	CH_3	CH_3	$ZnCl_2$	69%

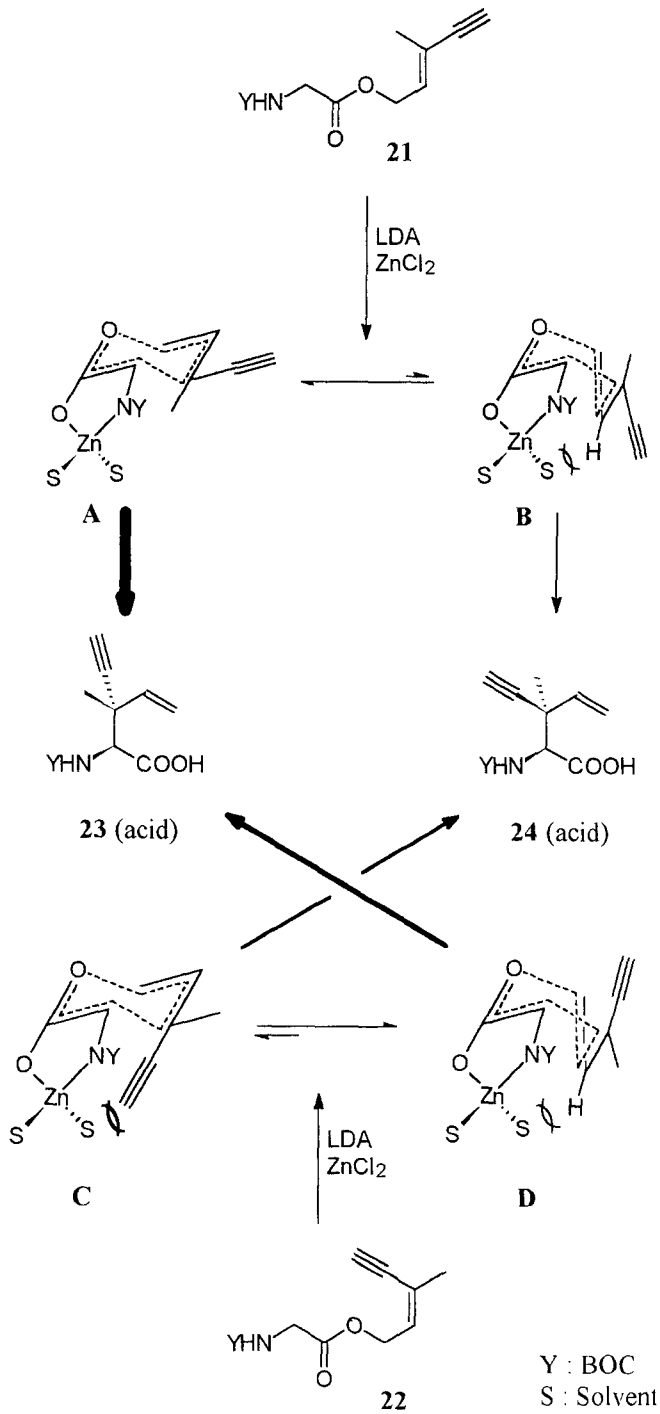
The rearrangement can be applied to acyclic as well as to cyclic substrates (entries 5–8). This methodology is not limited to glycine esters illustrated by the rearrangement of various amino acid allylic esters (entries 9–15). Aliphatic as well as aromatic sidechains are suitable and even the extremely sterically demanding α-alkylated amino acids are obtained in good yields. The influence of the protecting group Y is investigated for the phenylalanine derivatives (entries 11–14). No significant dependence on the protecting group is observed for the rearrangement. This makes the method of general value for the synthesis of various *N*-protected amino acids.

Furthermore, not only the symmetrically substituted allylic esters ($R^1 = R^2$), but also the unsymmetrically substituted esters ($R^1 \neq R^2$) are of special interest. The rearrangement of the *E*-configurated esters results in the formation of the *syn*-configurated amino acids in a highly diastereoselective fashion. The observed diastereoselectivity ($\geq$95% ds) results from a preferential rearrangement *via* a *chair like* transition state and agrees with the selectivities observed for other *E*-configurated allylic esters. On the other hand, the rearrangement of the *Z*-configurated esters gives rise to the opposite diastereomer, although with a significantly lower degree of selectivity. The lower diastereoselectivity may result from interactions of the *cis*-oriented side chain and the chelated enolate. These interactions should destabilize the *chair like* transitions state with the consequence that the *boat like* transition state should become more favored.

To prove this possibility, the acetylenic substrates **21** and **22** were also subjected to rearrangement (Scheme 6). Because of the acidic acetylenic proton, 3.5 equiv LDA are used for the rearrangement of these substrates. While the *E*-configurated ester **21** give the expected product **23** in a highly diastereoselective fashion, the oppositely configurated *Z*-ester **22** unexpectedly yield the same product – although less selectively. The formation of the same product from these complementary precursors can be explained by a change of the transition state geometry (Scheme 7).



Scheme 6



Scheme 7

The *E*-configurated ester **21** rearranges preferentially *via* the expected *chair like* transition state **A**. In the case of the *Z*-configurated ester **22**, strong steric interactions could arise in the corresponding transition state **C** between the triple bond and the presumably solvated chelated metal. The system can

switch to the *boat like* transition state **D** to avoid these possible interactions, accepting the less dramatic interaction of the axial hydrogen and the chelate. Consequently the *syn* product **23** is produced preferentially.

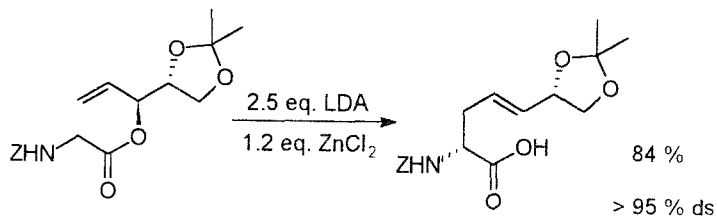
Introduction of bulky substituents (aryl or trialkylsilyl groups) on the acetylenic moiety has no further influence on the reaction. Yield and diastereoselectivity were comparable to the results obtained with ester **21**.

Asymmetric Claisen rearrangements

As illustrated, it is possible to carry out the ester enolate Claisen rearrangement in a highly diastereoselective fashion *via* control of the enolate geometry. Although from a synthetic point of view, the generation of racemic products is not fully satisfying. For an application to amino acid synthesis, it is important not only to control the *relative*, but also the *absolute* configuration of the stereogenic centers. The Claisen rearrangement is also very suitable for this purpose as well, because of the high preference for the *chair like* transition state (Ziegler, 1988; Blechert, 1989; Wipf, 1991; Pereira and Srebnik, 1993; Frauenrath, 1995). Due to the concerted, suprafacial nature of the Claisen rearrangement the degree of 1,3-chirality transmission (from C-4 to C-6 of the 1,5 dienic system) is often >90% to nearly quantitative. If esters of chiral allylic alcohols are used, chirality transfer occurs not only from the ester moiety (C-4) to C-6 but also to the α-position (C-1) of the carboxylic acid subunit (1,4-chirality transfer). The degree of this chirality transfer not only depends on the transition state structure (*chair vs. boat*) but also on the enolate geometry (*E*-enolate *vs. Z*-enolate) of the intermediary formed ester enolate. Therefore, the influences (solvent etc.) on the chirality transfer are rather complex. However, the same factors which control the 1,4-chirality transmission of the chiral esters should also affect the relative orientation of the newly formed chiral centers at the α and the β position of the rearrangement product (*syn/anti* selectivity).

The diastereoselectivities observed in our investigated version of the ester enolate Claisen rearrangement are generally very high (≅95% ds). For that reason we applied this methodology also to amino acid esters of chiral allylic alcohols such as **25** (Scheme 8).

As expected, the rearrangement occurs with a high degree of chirality transfer giving rise to optically active amino acids like **26**. The rearrangement

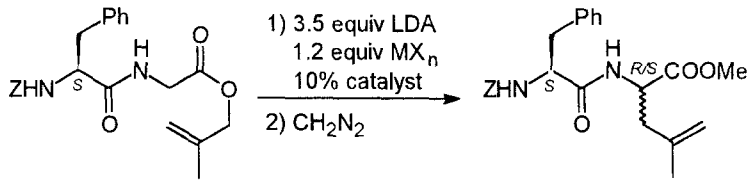


25 **26**

Scheme 8

can be applied to various substituted allylic, esters, which allows the synthesis of highly functionalized amino acids. On the other hand, these derivatives can be used as precursors for the synthesis of polyhydroxylated pyrrolizidine and indolizidine alkaloids.

Besides this more or less *classical* approach to chirality transfer we are also interested in other possibilities of chiral induction. In addition to using chiral alcohols and transferring chirality from the carboxyl-terminus to the α-position of the amino acid, the chiral information can also be placed in the amino-terminus of the amino acid. Although chiral protecting groups are not very common, the introduction of the amino acid allylic ester moiety into a peptide chain is an interesting approach. Carrying out the rearrangement with peptide esters would allow the introduction of allylic side chains onto an already existing peptide chain. This concept of peptide modification was developed by Seebach in 1983 (Seebach, 1988), allowing an extremely economical modification of sarcosine subunits of linear (Seebach et al., 1991) as well as cyclic peptides (Miller et al., 1993). In application of this technique, the immunosuppressive cyclic undecapeptide cyclosporin was alkylated in a highly regio- as well as stereoselective fashion (Seebach et al., 1993). Another interesting approach using this concept of side chain introduction was described by Reetz with the stereoselective addition of cuprates to vinylic pseudopeptides (Reetz et al., 1992). However, the control of the *stereochemistry* in the alkylation step is not trivial. Therefore, we focused mainly on the question, whether it would be possible to transfer the chiral information *via* some peptide metal enolate complexes from the peptide chain to the new chiral center formed during the rearrangement process.



27 28

Scheme 9

Table 5. Rearrangement of dipeptide **27** in the presence of various metal salts (MX_n) and catalysts

Entry	MX_n	Catalyst	Diastereomeric ratio (S,S):(S,R)	Yield [%]
1	$ZnCl_2$	–	62:38	28
2	$ZnCl_2$	$PdCl_2(COD)$	65:35	20
3	$ZnCl_2$	$Pd(PPh_3)_4$	50:50	75
4	$SnCl_2$	$Pd(PPh_3)_4$	70:30	36
5	$CoCl_2$	$Pd(PPh_3)_4$	35:65	35
6	$AlCl_3$	$Pd(PPh_3)_4$	40:60	50

As a first example we investigated the rearrangement of allylic ester **27** (Scheme 9 and Table 5) in the presence of zinc chloride (entry 1) (Kazmaier, 1994c). Subsequent esterification of the rearranged product with diazomethane results in the formation of unsaturated dipeptide **28** in only moderate yields. The (*S,S*)-diastereomer is formed preferentially.

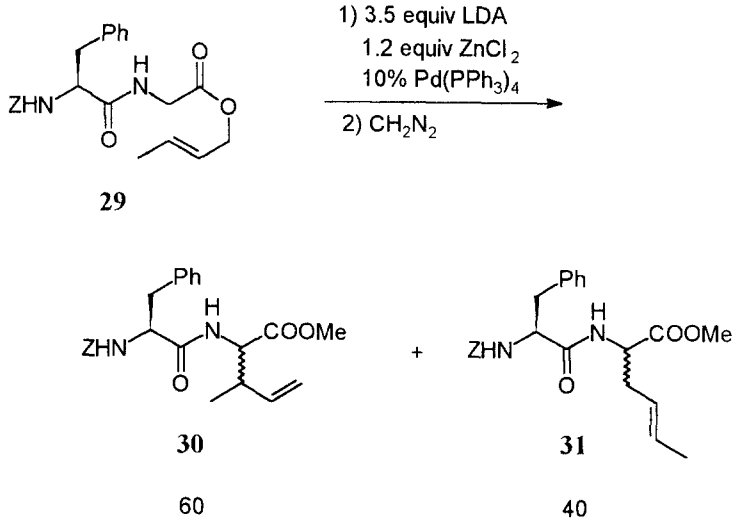
Since the tremendous work done by Overman and others on rearrangement catalysis (Overman et al., 1976, 1978, 1982, 1984, 1990; Lutz, 1984; Schenck and Bosnich, 1986) many applications, especially of Pd(II)-catalyzed rearrangements, have been described in the literature. In our case addition of 10 mol % Pd(II) results in a decreased yield without affecting the stereoselectivity (entry 2). The formation of a less reactive palladium enolate, which does not rearrange, becomes probable, because Pd(II) is known to form stable complexes with peptides (Sigel and Martin, 1982). In contrast, Pd(0) (10 mol %) catalyzes the reaction in the expected manner (entry 3). Various metal salts (MX_n) were employed (entries 4–6), to verify the influence of the chelated metal on the diastereoselectivity of the rearrangement. Although the yields are generally lower in comparison to zinc chloride, better selectivities are obtained. Addition of tin chloride (entry 4) also leads to the preferential formation of the (*S,S*)-diastereomer, while cobalt chloride (entry 5) and aluminum chloride (entry 6) generate the opposite (*S,R*)-diastereomer, probably because of a different complex geometry. This methodology is suitable for various *N*-protecting groups. So far the best results are obtained with *N*-Tosyl protected peptides. Rearrangement in the presence of zinc chloride or tin chloride provides the corresponding allylated dipeptides in very good yields (Kazmaier 1994c).

In order to distinguish between the two possible mechanisms, [3,3]-sigmatropic rearrangement or intermolecular allylic alkylation *via* a π-allylpalladium complex, the reaction of the crotyl ester **29** (Scheme 10) was investigated.

The rearrangement products **30** and **31** are formed in comparable amounts. This fact as well as the nearly complete lack of diastereoselectivity in the newly generated amino acid of **30** (*syn:anti* 2:1), is a clear indication for a π-allylpalladium intermediate. Similar observations have been made by Kellogg for the Pd(0)-catalyzed rearrangement of imines of amino acid allylic esters (Van der Werf and Kellog, 1988). The minor product **31** is formed with clean *trans* double bond geometry. No cis product was detected by NMR.

A second experiment with a mixture of two different allylic esters was carried out to confirm the intermolecular pathway *via* a dissociated π-allylic complex. All four possible diastereomeric peptides are formed in this cross reaction in comparable ratios. These results make an intermolecular process probable.

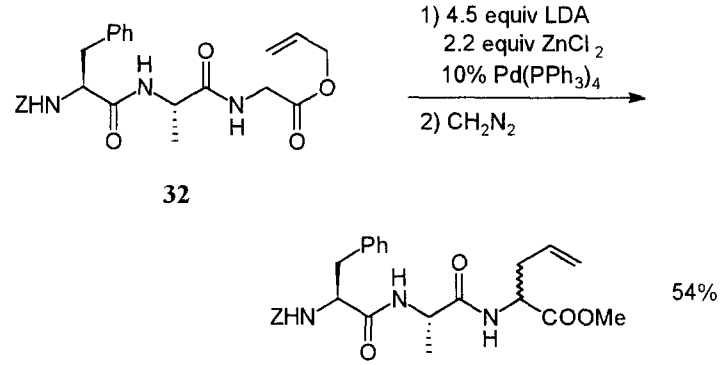
Dipeptide **28** was also used to check if racemization of chiral peptides occurs during the reaction. Catalytic hydrogenation yields phenylalanyl-leucine methylester which was analyzed by chiral GC (Chirasil-L-Val) after trifluoroacetylation. *No racemization was observed!* As described by Seebach et al., the chiral centers of peptides are protected by deprotonation of the



29

30 60 + 31 40

Scheme 10



32

33

Scheme 11

amide bonds. This also seems to be the case with our chelate complexes, even at room temperature.

To show that our methodology is not limited to dipeptides but can also be applied to larger peptides, the allylic ester **32** was also subjected to rearrangement (Scheme 11). The expected product **33** was formed as a nearly 1:1 diastereomeric mixture in reasonable yields.

Acknowledgement

I thank Prof. Dr. G. Helmchen as well as the Bayer AG for their generous support of this work. Financial support by the Deutsche Forschungsgemeinschaft as well as Fonds der Chemischen Industrie is gratefully acknowledged.

References

Achmatowicz O Jr, Petraszikewicz M (1981) Ene reaction of the active imino group. A novel synthesis of α-amino acids. J Chem Soc Perkin Trans 1: 2680–2683

Bartlett PA (1980) Stereocontroll in the synthesis of acyclic systems: application to natural product synthesis. Tetrahedron 36: 3–72

Bartlett PA, Barstow JF (1982) Ester-enolate Claisen rearrangement of α-amino acid derivatives. J Org Chem 47: 3933–3941

Bartlett PA, Tanzella DJ, Barstow JF (1982a) Stereoselective synthesis of the dihydroxyisoleucine constituent of the amanita mushroom toxins. Tetrahedron Lett 23: 619–622

Bartlett PA, Tanzella DJ, Barstow JF (1982b) Ester-enolate Claisen rearrangement of lactic acid derivatives. J Org Chem 47: 3941–3945

Baumann H, Duthaler RO (1988) Synthesis of ethyl (2RS,3SR)-1-tosyl-3-vinylazetidine-2-carboxylate and (2RS,E)-3-ethylidene-1-tosylazetidine-2-carboxylate. Helv Chim Acta 71: 1025–1034

Blechert S (1989) The hetero-Cope rearrangement in organic synthesis. Synthesis: 71–82

Broxterman QB, Kaptein B, Kamphuis J, Schoemaker HE (1992) Synthesis of optically active sulfur-containing trifunctional amino acids by radical addition to unsaturated amino acids. J Org Chem 57: 6286–6294

Burger K, Geith K, Gaa K (1988) Ein einfacher Zugang zu 2-substituierten 3,3,3-Trifluoralanin-Derivaten. Angew Chem 100: 860–861; Angew Chem Int Ed Engl 27: 848–849

Burke SD, Fobare WF, Pacofsky GJ (1983) Chelation control of enolate geometry. Acyclic diastereoselection via the enolate Claisen rearrangement. J Org Chem 48: 5221–5228

Castelhano AL, Horne S, Taylor GJ, Billedeau R, Krantz A (1988) Synthesis of α-amino acids with γ,δ-unsaturated side chains. Tetrahedron 44: 5451–5466

Colombo L, Casiraghi G, Pittalis A, Rassu G (1991) Stereoselective synthesis of C-glycosyl α-amino acids. J Org Chem 56: 3897–3900

Cramer U, Rehfeldt AG, Spener F (1980) Isolation and biosynthesis of cyclopentenylglycine, a novel nonproteinogenic amino acid in flacourtiaceae. Biochemistry 19: 3074–3080

Easton CJ, Scharfbillig IM (1990) Homolytic allyl transfer reactions of 1- and 3-alkyl-substituted allyltributylstannanes. J Org Chem 55: 384–386

Edelson J, Fissekis JD, Skinner CG, Shive W (1958) 3-Cyclohexene-1-glycine, an isoleucine antagonist. J Am Chem Soc 80: 2698–2700

Engel N, Kübel B, Steglich W (1977) C-C-Verknüpfung von Carbonsäuren mit Allylalkoholen unter Verwendung von 2-Phenylglycin als Vehikel. Angew Chem 89: 408–410; Angew Chem Int Ed Engl 16: 394–396

Fischer J, Kilpert C, Klein U, Steglich W (1986) Stereochemistry of [3.3]-sigmatropic rearrangements in the oxazole series. Tetrahedron 42: 2063–2074

Frauenrath H (1995) Formation of C-C-bonds by [3.3]-sigmatropic rearrangements. In: Helmchen G, Hoffmann RW, Mutzer J, Schaumann E (eds) Houben-Weyl E, vol 21. Thieme, Stuttgart New York, pp 3301–3729

Fuji K (1993) Asymmetric creation of quaternary carbon centers. Chem Rev 93: 2037–2066

Gander-Coquoz M, Seebach D (1988) Herstellung enantiomerenreiner, α-alkylierter Lysin-, Ornithin- und Trypthophan-Derivate. Helv Chim Acta 71: 224–236

Holladay MW, Nadzan AM (1991) Synthesis of α-benzyl γ-lactam, α-benzyl δ-lactam, and α-benzylproline derivatives as conformationally restricted analogues of phenylalaninamide. J Org Chem 56: 3900–3905

Ito Y, Higuchi N, Murakami M (1988) Claisen rearrangement of allylic α-isocyanoesters-regioselective allylation of α-isocyanoesters at the α-carbon. Tetrahedron Lett 29: 5151-5154

Kallmerten J, Gould TJ (1986) Auxiliary-directed diastereoselectivity in the Claisen rearrangement of glycolate esters. J Org Chem 51: 1152–1155

Katagiri K, Tori K, Kimura Y, Yoshida T, Nagasaki T, Minato H (1967) Isolation and structure elucidation of the new antibiotic furanomycine. J Med Chem 10: 1149–1156

Kazmaier U (1994a) Synthese ungesättigter Aminosäuren durch [3,3]-sigmatrope Umlagerung chelatverbrückter Glycinesterenolate. Angew Chem 106: 1046–1047; Angew Chem Int Ed Engl 33: 998–999

Kazmaier U (1994b) Stereoselective synthesis of 2-(2′-cycloalkenyl) glycinates via [3,3] sigmatropic rearrangement of chelated ester-enolates. Tetrahedron 50: 12895–12902

Kazmaier U (1994c) Introduction of allylic side chains onto peptides by Pd(0)-catalyzed ester enolate Claisen rearrangement. J Org Chem 59: 6667–6670

Kazmaier U (1995) Diastereoselective synthesis of amino acids containing β-quaternary carbon centers via ester-enolate Claisen rearrangement. Synlett: 1138–1140

Kazmaier U, Grandel R (1995) Synthesis of sterically demanding α-amino-β-hydroxy acids via anti-selective aldol reactions. Synlett: 945–946

Kazmaier U, Maier S (1995) Stereoselective synthesis of α-alkylated γ,δ-unsaturated amino acids via Claisen rearrangement of chelated enolates. J Chem Soc, Chem Comm: 1991–1992

Kazmaier U, Maier S (1996) Synthesis of sterically high demanding α-alkylated amino acids via Claisen rearrangement of chelated enolates. Tetrahedron 52: 941–954

Kübel B, Höfle G, Steglich W (1975) Hetero-Cope Umlagerungen bei der Cyclisierung von N-Acylaminosäureallylestern und Propargylestern zu Oxazolin-5-onen. Angew Chem 87: 64–6; Angew Chem Int Ed Engl 14: 58–59

Kurokawa N, Ohfune Y (1986) Total synthesis of Echinocandins. 1. Stereocontrolled synthesis of the constitutent amino acids. J Am Chem Soc 108: 6041–6043

Lutz RP (1984) Catalysis of the Cope and Claisen rearrangement. Chem Rev 84: 205–247

Martin SF (1980) Methodology for the construction of quaternary carbon centers. Tetrahedron 36: 419–460

Miller SA, Griffiths SL, Seebach D (1993) C-Alkylation of sarcosine residues in cyclic tetrapeptides via lithium enolates. Helv Chim Acta 76: 563

Ohfune Y, Kurokawa N (1985) Efficient synthesis of naturally occurring 3,4-dihydroxyprolines: Electrophile mediated lactonization of 2-amino-3-hydroxy-4-pentenoic acid derivatives. Tetrahedron Lett 26: 5307–5308

Overman LE (1984) Quecksilber(II)- und Palladium(II)-katalysierte [3.3]-sigmatrope Umlagerungen. Angew Chem 96: 565–573; Angew Chem Int Ed Engl 23: 579–587

Overman LE, Campbell CB (1976) Mercury(II)-catalyzed [3.3]-sigmatropic rearrangements of allylic N,N-dimethylcarbamats. A mild method for allylic equilibrations and contrathermodynamic allylic isomer enrichments. J Org Chem 41: 3338–3340

Overman LE, Campbell CB, Knoll FM (1978) Mild procedures for interconverting allylic oxygen functionality. Cyclization-induced [3.3]-sigmatropic rearrangement of allylic carbamates. J Am Chem Soc 100: 4822–4834

Overman LE, Jacobsen EJ (1982) Chair topology for the palladium dichloride catalyzed cope rearrangement of acyclic 1,5-dienes. J Am Chem Soc 104: 7225–7231

Overman LE, Renaldo AF (1990) Mechanism of the palladium dichloride catalyzed Cope rearrangement of acyclic dienes. A substituent effect study. J Am Chem Soc 112: 3945–3949

Pereira S, Srebnik M (1993) The Ireland-Claisen rearrangement. Aldrichimica Acta 26: 17–29

Reetz MT, Kanand J, Griebenow N, Harms K (1992) Stereoselektive nukleophile Additionsreaktionen an reaktive Pseudopeptide. Angew Chem 104: 1638–1641; Angew Chem Int Ed Engl 31: 1626–1629

Roos EC, Mooiweer HH, Hiemstra H, Speckamp WN, Kaptein B, Boesten WHJ, Kamphuis J (1992) Synthesis of racemic α-amino carboxamides via Lewis acid-mediated reactions of α-methoxyglycinamide derivatives with allylsilanes: Enzymatic resolution of optically active amino acids. J Org Chem 57: 6769–6778

Roos EC, Lopez MC, Brook MA, Hiemstra H, Speckamp WN, Kaptein B, Kamphuis J, Schoemaker HE (1993) Synthesis of α-substituted α-amino acids via cationic intermediates. J Org Chem 58: 3259–3268

Schenck TG, Bosnich B (1985) Homogeneous catalysis. Transition-metal-catalyzed Claisen rearrangement. J Am Chem Soc 107: 2058–2066

Schöllkopf U, Konsky R (1983) Asymmetric syntheses via heterocyclic intermediates; XX. Enantioselective synthesis of (R)-(−)-isovaline. Synthesis: 675–676

Seebach D (1988) Struktur und Reaktivität von Lithiumenolaten, vom Pinakolon zur selektiven C-Alkylierung von Peptiden- Schwierigkeiten und Möglichkeiten durch komplexe Strukturen. Angew Chem 100: 1685–1715; Angew Chem Int Ed Engl 27: 1624–1654

Seebach D (1992) How we stumbled into peptide chemistry. Aldrichimica Acta 25: 59–66

Seebach D, Bossler H, Gründler H, Shoda S, Wenger R (1991) C-Alkylation of peptides through polylithiated and LiCl-solvated derivatives containing sarcosine lithium enolate units. Helv Chim Acta 74: 197–224

Seebach D, Beck AK, Bossler HG, Gerber C, Ko SY, Murtiashaw CW, Naef R, Shoda S, Thaler A (1993) Modification of Cyclosporin A: Generation of an enolate at the sarcosine residue and reactions with electrophiles. Helv Chim Acta 76: 1564–1590

Sigel H, Martin B (1982) Coordinating properties of the amide bond. Stability and structure of metal ion complexes of peptides and related ligands. Chem Rev 82: 385–426

Takano S, Akiyama M, Ogasawara K (1984) A new α-amino acid synthesis via an acetamidate rearrangement. J Chem Soc, Chem Commun: 770–771

Tschaen DM, Weinreb SM (1982) Stereochemistry of the glyoxylate N-sulfonylimine ene reaction. Tetrahedron Lett 23: 3015–3018

Tschaen DM, Turos E, Weinreb SM (1984) Stereochemical studies of thermal intermolecular and intermolecular N-sulfonylimine ene reaction. J Org Chem 49: 5058–5064

Van der Werf A, Kellogg RM (1988) Synthesis of α-amino acids by means of a palladium catalyzed intermolecular rearrangement. Tetrahedron Lett 29: 4981–4984

Weber T, Aeschimann R, Maetzke T, Seebach D (1986) Methionin als Vorläufer zur enantioselektiven Synthese α-verzweigter Vinylglycine und anderer Aminosäuren. Helv Chim Acta 69: 1365–1377

Williams RM (1989) Synthesis of optically active α- amino acids, vol 7. Organic chemistry series. In: Baldwin JE, Magnus PD (eds) Pergamon Press, Oxford

Williams RM, Sinclair PJ, Zhai D, Chen D (1988) Practical asymmetric syntheses of α-amino acids through carbon-carbon bond construction of electrophilic glycine templates. J Am Chem Soc 110: 1547–1557

Wipf P (1991) Claisen rearrangements. Comprehensive organic synthesis, vol 5. In: Trost BM, Fleming I (eds) Pergamon Press, New York, pp 827–873

Ziegler FE (1988) The thermal, aliphatic Claisen rearrangement. Chem Rev 88: 1423–1452

Author's address: Dr. U. Kazmaier, Organisch-Chemisches Institut der Universität, Im Neuenheimer Feld 270, D-69120 Heidelberg, Federal Republic of Germany.

Received February 3, 1996