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Review

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Synthesis of *y*,*δ*-unsaturated amino acids by Claisen rearrangement - last 25 years

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In dedication to Professor Zbigniew Czarnocki on the occasion of his 66th anniversary

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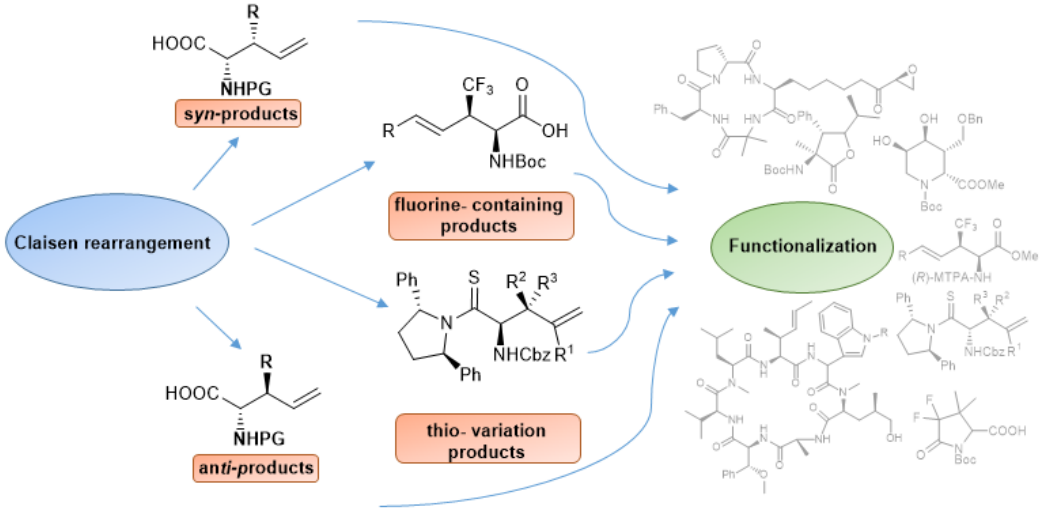
Abstract

This mini review summarizes achievements in the synthesis of *y*,*δ*-unsaturated amino acids via Claisen rearrangements. The multitude of products that can be obtained using the discussed protocol shows that it is one of the most important reactions in organic synthesis. Moreover, many Claisen rearrangement products are building blocks in the synthesis of more complex molecules with potential biological activity.



Keywords: *y*,*δ*-Unsaturated amino acids, Claisen rearrangement, fluorine-containing *y*,*δ*-unsaturated amino acids, diastereoselectivity, optically active compounds

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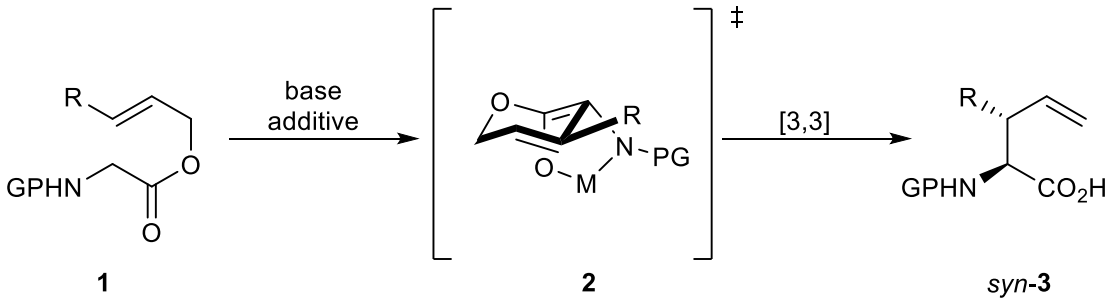
1. Introduction

Ludwig Claisen introduced the rearrangement in 1912,[1] and since then many aspects of this [3,3]-sigmatropic reaction have been investigated. The Claisen rearrangement is a pericyclic reaction involving a cyclic transition state, which delivers *γ,δ*-unsaturated carbonyl compounds with a high predictability of the stereochemical outcome.[2] Generally, the Claisen rearrangement tolerates various substituents, as well as functional groups. Steglich et al. described for the first time a synthesis of a protected allylic glycine using this protocol in 1975.[3,4] The preparation of unnatural amino acids, especially with *γ,δ*-unsaturation, has been of scientific interest for decades.[5] It is mainly related to their a variety of biological activities. On the other hand, the Claisen rearrangement is a convenient way to extend application of a very reactive double bond towards the chemoselective synthesis, e.g. natural products.[2,6] Moreover, *γ,δ*-unsaturated amino acids can be used as molecular probes in the synthesis of stapled peptides.[7]

2. Chelated Claisen Rearrangement

A chelated Claisen rearrangement reaction is a very useful method for synthesis of organic molecules with defined stereochemistry. Diastereoselectivity of this reaction depends on a geometry of an enolate which is stabilized by a chelate formation. Moreover, researchers noted that during the reaction, a chair-like transition state **2** is created. Therefore stereochemical outcome of the rearrangement is controlled mainly by the transition state, the *syn* configured rearranged products are formed in a stereoselective fashion (Scheme 1).[8,9]

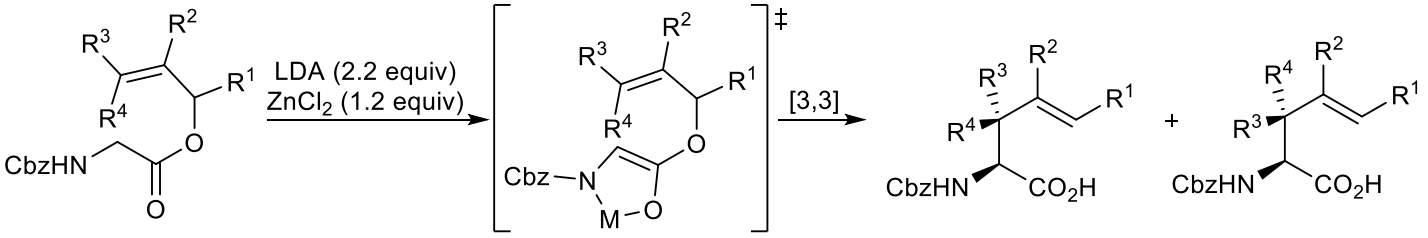


Scheme 1. The chelated Claisen rearrangement.

Kazmaier described this reaction based on the use of N-protected glycine crotyl esters **4** in a presence of LDA and metal chlorides. After base driven deprotonation of substrate **4**, addition of metal salts (such as:

$ZnCl_2$, $MgCl_2$, $CoCl_2$) was intended to convert the enolate ester into a chelate-bridged, stabilized carboxylate **5** (Table 1). This moiety undergoes rearrangement through a chair-like transition state when the reaction mixture is warmed to room temperature. The corresponding lithium enolates decompose completely without addition of metal chlorides and the rearrangement did not occur. The best results were achieved using $ZnCl_2$, and rearranged *syn* acids **6** were obtained with very good diastereoselectivity and yields. The reaction can also be carried out using substrates with different blocking groups, e.g., Cbz, Boc, TFA, as well as with aliphatic substituents attached to the double bond of the starting substrates **4** (Table 1).[10]

Table 1. $ZnCl_2$-catalyzed rearrangement of **4** and synthesis of **6**[10]

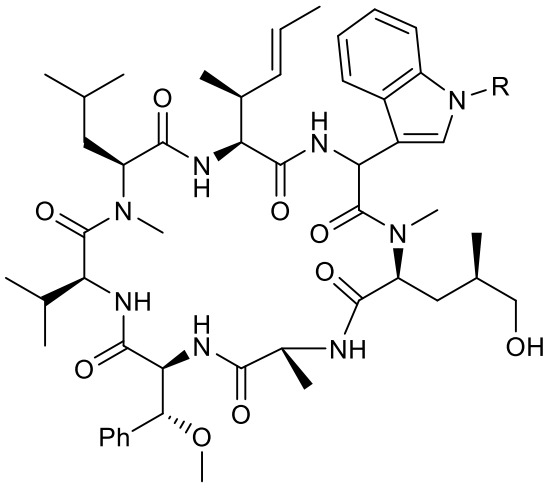


4 **5** *syn*-(rac)-**6** *anti*-(rac)-**6**

Entry	PG	R^1	R^2	R^3	R^4	*dr*	Yield (%)
1	Cbz	H	H	H	H	-	88
2	Cbz	H	Me	H	H	-	78
3	Cbz	H	H	Pr	H	95:5	76
4	Cbz	Me	H	Me	H	93:7	88
5	Cbz	Et	H	Me	H	95:5	98
6	Cbz	Et	H	H	Bu	95:5	73
7	Boc	Me	H	Me	H	96:4	84
8	Boc	H	H	Pr	H	96:4	78
9	TFA	H	H	Pr	H	95:5	79
10	TFA	Et	H	H	Bu	94:6	65
11	Cbz	H	H	H	$CH_2OTBDPS$	98.5:1.5	75

The Claisen rearrangement reaction is often used in the synthesis of intermediates of complex molecules. A similar protocol was used in the synthesis of a building block, in the preparation of Cyclomarins **7**, novel antimalarial and antitubercular agents (Figure 1).[11] In the total synthesis of Chlamydocin **8**, a cyclic peptide showing histone deacetylase (HDAc) inhibition, the chelated Claisen reaction was one of the key steps (Figure 1).[12]

The discussed procedure can also be applied to N-protected allylic esters of *α*,*β*-unsaturated amino acids **9** (Table 2). The rearrangement products contain both allylic, and vinyl moieties in their structure. In case of reaction of **9(3)**, apart from desired rearrangement product **10(3)**, a side product was observed resulting from a cleavage of the Cbz group. Compounds **10** can be used as substrates for their further modification in the synthesis of potentially biologically active compounds.[13]



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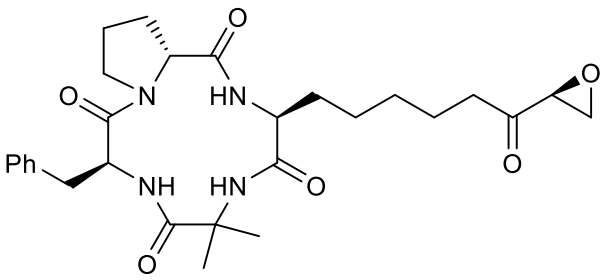

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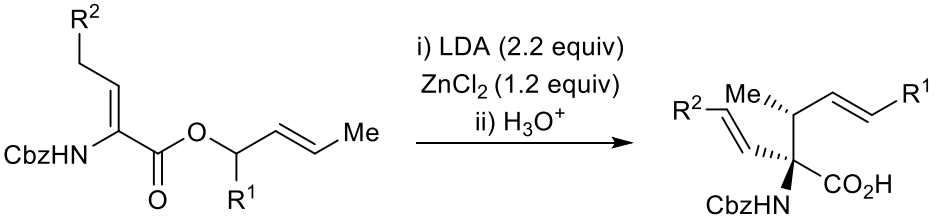
Figure 1. Chemical structures of Cyclomarins **7** and Chlamydocin **8**.

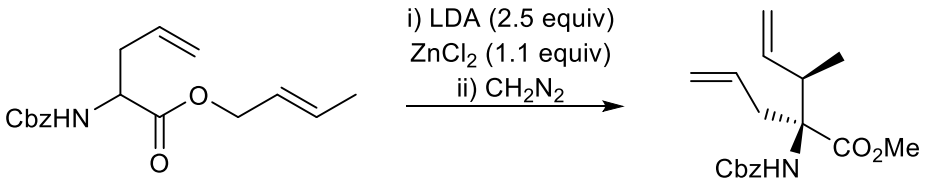
Table 2. Rearrangement of N-protected allylic esters of *α*,*β*-unsaturated amino acids **9** to give compounds **10**[13]



9 **10**

Entry	R^1	R^2	Yield (%)
1	Me	Me	61
2	H	Ph	53
3	Me	H	-

Moreover, formation of the diallylated amino acid **12** is also possible by chelated Claisen rearrangement (Scheme 2). During the reaction, two chiral centers are introduced diastereoselectively (*ds* = 93%).[14]



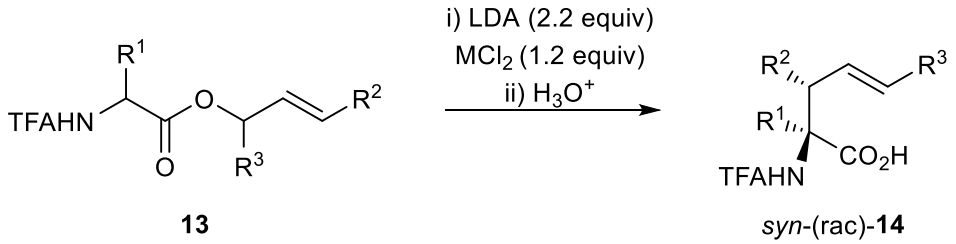
11 **12** (64%)

Scheme 2. Synthesis of the diallylated amino acid **12**.[14]

The chelated Claisen rearrangement can also take place in sterically crowded substrates **13**. Kazmaier postulate the formation of a chelated metal enolate as the key step in such synthesis (Table 3). TFA was used

as a nitrogen blocking group; the substituents of R were both aliphatic and aromatic groups. The best results were obtained by applying $ZnCl_2$ or $MgCl_2$ as enole chelating agents. As a result *γ*,*δ*-unsaturated amino acids **14** were synthesized with very good yields and diastereselectivity (Table 3).[15]

Table 3. Chelated Claisen rearrangement of **13** to give *γ*,*δ*-unsaturated amino acids **14**[15]

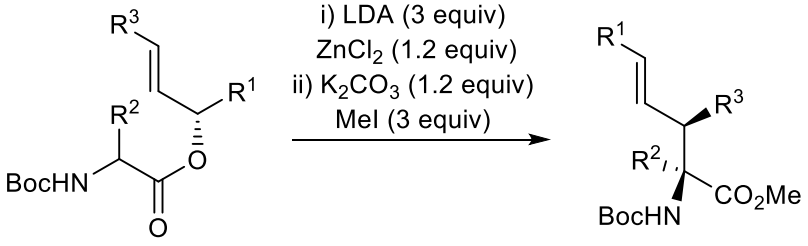


13 *syn*-(rac)-**14**

Entry	R^1	R^2	R^3	MCl_2	*de* (%)	Yield (%)
1	H	Me	H	$ZnCl_2$	88	86
2	H	Me	H	$MgCl_2$	82	81
3	Me	Me	H	$ZnCl_2$	96	84
4	Me	Me	H	$MgCl_2$	90	83
5	Me	Ph	H	$ZnCl_2$	94	65
6	Me	Ph	H	$MgCl_2$	90	54
7	Me	Me	Et	$ZnCl_2$	92	84
8	Me	Me	Et	$MgCl_2$	94	89

The stereoselective synthesis of optically active (2*S*,3*S*) *γ*,*δ*-unsaturated amino acid esters **16** is an example of a chelated Claisen rearrangement reaction (Table 4). Allylic amino acid esters **15** were obtained from chiral allylic alcohols and N-Boc protected glycine or alanine in a DCC coupling reaction. The *γ*,*δ*-unsaturated amino acid esters **16** have a high synthetic potential attributed to their structure. The authors highlighted the usefulness of these compounds in the synthesis of lactones **17** and **18** in ozonolysis/reduction or iodolactonization reactions (Figure 2).[16]

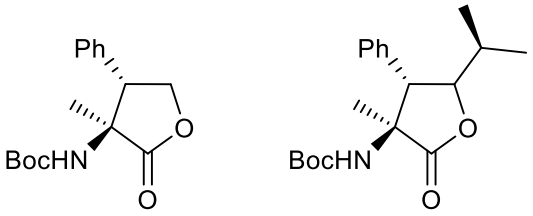
Table 4. Rearrangement reaction of **15** into amino acid esters **16**[16]



15 **16**

Table 4. Continued

Entry	R^1	R^2	R^3	*ds* (%)	*ee* (%)	Yield (%)
1	Me	H	Ph	>99	>99	84
2	Me	Me	Ph	>99	>99	87
3	Et	Me	Ph	>99	>99	88
4	Me	H	4-$MeOC_6H_4$	>99	97	69
5	Me	H	2-NAPH	>99	99	79
6	Me	H	4-Tol	98	>99	84
7	Me	Me	4-BrC_6H_4	>99	98	83
8	Et	Me	4-BrC_6H_4	97	>99	89

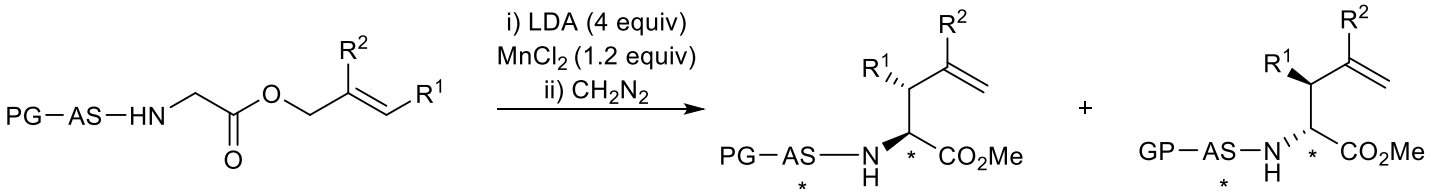


17 **18**

Figure 2. Chemical structures of lactones **17** and **18**.

Kazmaier also wanted to use such a protocol in a synthesis of functionalized peptides **20**. However, when $ZnCl_2$ was used for chelation, low yields were obtained (20%). As it turned out, the chelated Claisen rearrangement can also be successfully carried out in the presence of $MnCl_2$, obtaining products with yields up to 98% (Table 5).[17]

Table 5. $MnCl_2$-catalyzed rearrangement of **19** to give peptides **20**[17]

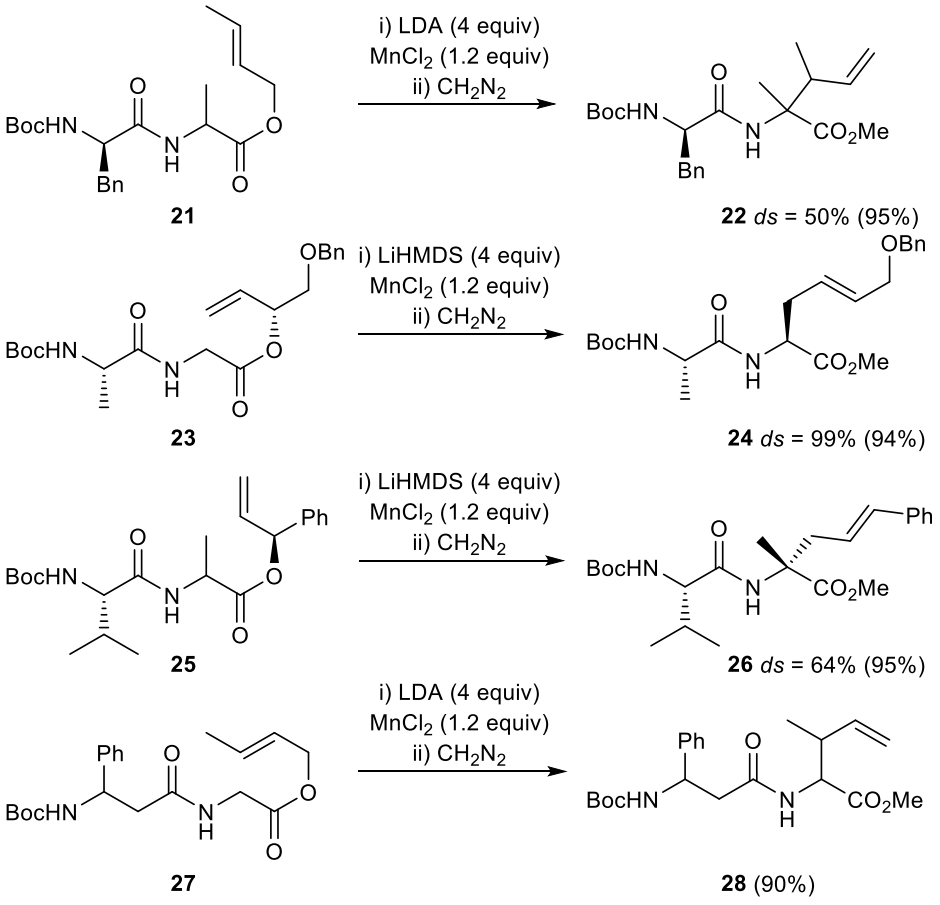


19 **(*S*,*S*)-20** **(*S*,*R*)-20**

Table 5. Continued

Entry	PG	AS	R^1	R^2	*SS*:*SR*	Yield (%)
1	Boc	Val	H	Me	51:49	88
2	Boc	Phe	H	Me	63:37	90
3	Cbz	Phe	H	Me	66:34	88
4	Cbz	Val	Me	H	61:39	92
5	Boc	Val	Me	H	37:63	93
6	Boc	Phe	Me	H	62:38	93
7	TFA	Phe	Me	H	47:53	98
8	Ts	Phe	Me	H	35:65	92
9	Ts	Ile	Me	H	35:65	83
10	Boc	Met	Me	H	33:67	88
11	Boc	Lys(Boc)	Me	H	42:58	78

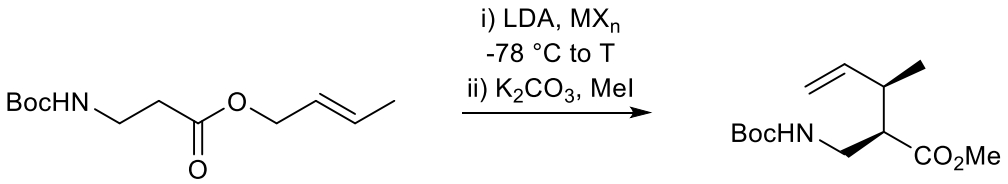
Optimized reaction conditions could be adapted for peptide synthesis. Both sterically crowded **21**, chiral **23**, **25**, as well as *β*-amino acid **27** derivatives, can be used as starting materials (Scheme 3). In each case, the rearrangement products were obtained with very good yields and diastereoselectivities. From the point of view of their potential application in medicine, the structures of the above compounds are interesting. What is more, they can be substrates for their further modification.



Scheme 3. $MnCl_2$-catalyzed rearrangement reactions.[17]

Examples of a chelated Claisen rearrangement of the crotyl ester of *N*-protected *β*-alanine **29** are also known in the literature (Table 6). Kim and coworkers carried out the reaction under standard Kazmaier-Claisen rearrangement conditions, obtaining **30** with a very good diastereoselectivity, which supported the formation of the corresponding chelated compound as an intermediate product. However, the yield of the reaction was not satisfactory. In all cases, the conversion of starting substrate **29** was incomplete, but the obtained ratio of *syn*:*anti* isomers **30** was up to 98:2. An increase of the yield of the reaction was possible by using the Ireland-Claisen rearrangement conditions, but in this case the diastereoselectivity of the process slightly decreased (Table 6, entry 3).[18] Kim and coworkers tried the chelated Claisen rearrangement to obtain one of the building blocks needed for synthesis of (-)-Cephalotaxine. As it turned out, under standard conditions (LiHMDS or LDA and Al(O*i*-Pr)$_3$ or $ZnCl_2$) the rearrangement reaction did not occur at all. On the other hand, application of the Ireland-Claisen rearrangement conditions afforded in the desired rearrangement product.[19]

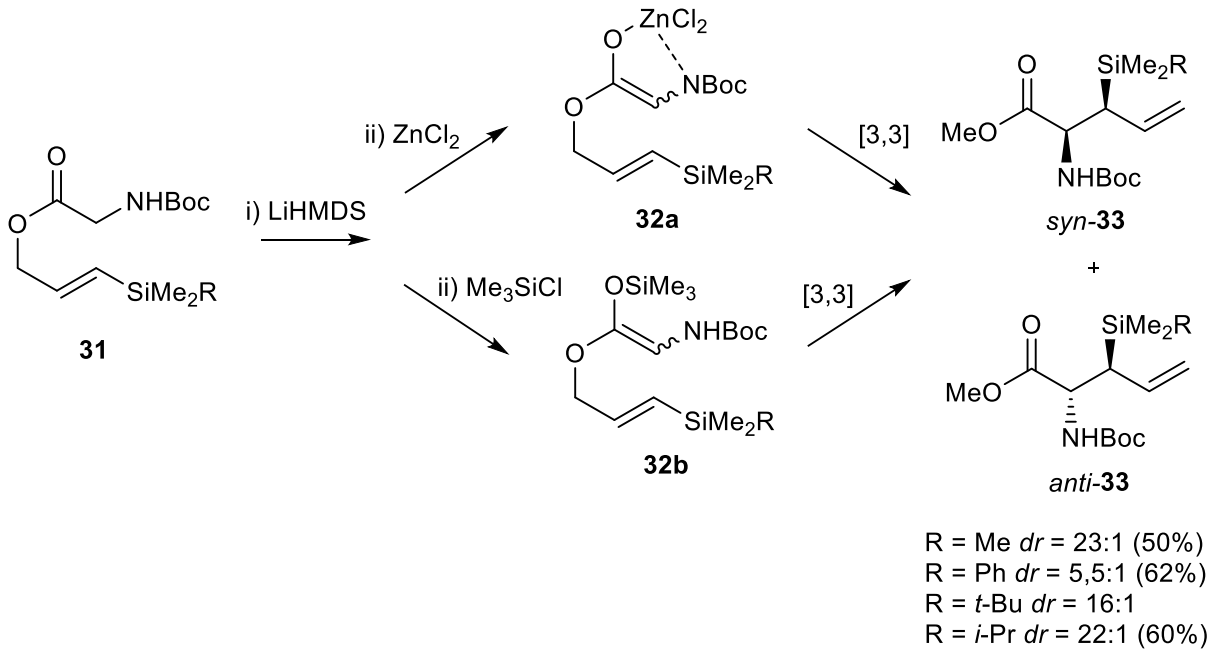
Table 6. Chelated Claisen rearrangement of *β*-amino acid derivative **29** to isomers **30**[18]



29 **30**

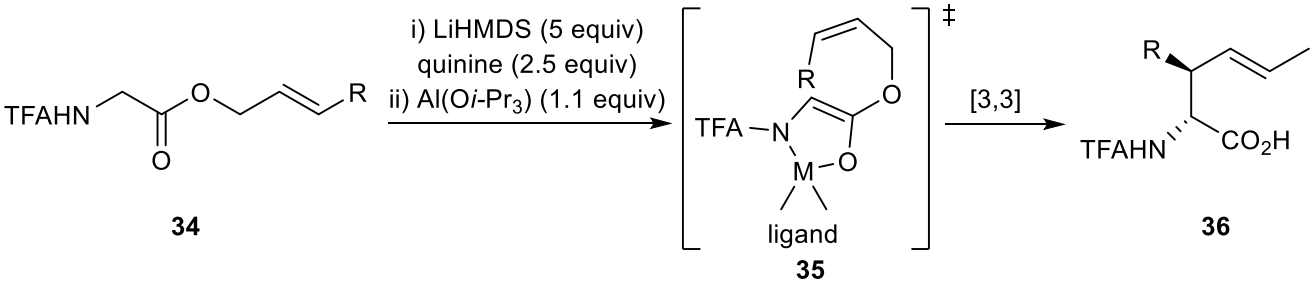
Entry	MX_n	T (°C)	*ds*	Yield (%)
1	$ZnCl_2$	rt	96:4	35
2	ClTi(O*i*-Pr)$_3$	rt	98:2	24
3	$ClSiMe_3$	60	86:14	86

The Zn-chelated enolate variant of the Claisen rearrangement was used by Mohamed and Brook in the synthesis of *α*-allylsilane functionalized amino acids (Scheme 4).[20] This method gave acceptable results, both in terms of the reaction yield (50%), and the diastereoselectivity (*syn/anti*, 23:1). However, a hydrolysis of the starting ester was observed in this approach. The use of Ireland-Claisen conditions gave satisfactory results. The order of the reagent addition was crucial: addition of the base to the ester increased the yield (82%) and diastereoselectivity (29:1). The studies also proved the influence of the silyl groups (R = Me, *i*-Pr, *t*-Bu, Ph) on the stereoselectivity of the reaction. The best results were obtained for esters with methyl and isopropyl substituents.

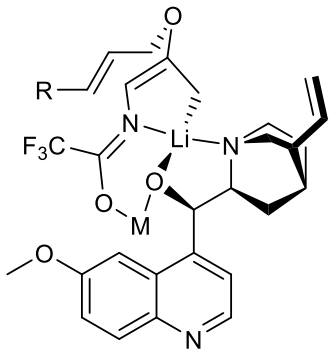


Scheme 4. Claisen rearrangement of silylallyl glycinate.[20]

The above-discussed chelated Claisen rearrangement may also run asymmetrically in the presence of chiral bidentate ligands (Scheme 5).[21] The best asymmetric induction was observed for cinchona alkaloids. Probably, quinine coordinates as a bidentate ligand to the aluminum chiral to stabilize the lithium enolate **35** (Figure 3).[22] The authors noted that the use of chiral amino alcohol, diol or diamine as a catalyst for this purpose did not give a significant asymmetric induction. The reactions proceeded under standard metal salt (Al(*i*OPr)$_3$ or Mg(OEt)$_2$)/base (LDA) conditions, additionally a chiral ligand was added to the reaction mixture.



Scheme 5. Chelated Claisen rearrangement in the presence of quinine.[21]



35

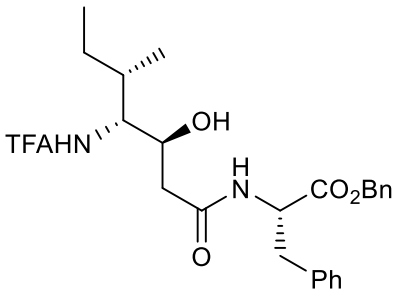
Figure 3. Structure of transition state **35**.[22]

In all cases, high diastereoselectivity was observed, much higher than without a presence of a chiral catalyst. Unnaturally configured (2*R*) *γ*,*δ*-unsaturated amino acids **36** (Table 7, entry 1-7) were obtained with high enantiomeric excesses (up to 90%). The corresponding 2*S* analogues **36** (Table 7, entry 8-9) were obtained when quinidine was employed. Kazmaier showed that the enantomeric purity was improved even up to 99.8% by crystallization of the crude product with S-(-)-phenylalanine or by enzyme-catalyzed resolution.[23,24] Moreover, those enantiomeric pure compounds were further used in the synthesis of blocked isostatin **37** or diastereomerically pure hydroxyornithine derivative **38** (

Figure 4 4).[23,25]

Table 7. Synthesis of *γ*,*δ*-unsaturated amino acids **36**[21]

Entry	R	chiral ligand	*ds* (%)	*ee* (%)	Yield (%)	Conf.
1	H	quinine	-	80	92	(2*R*)
2	Me	quinine	98	86	98	(2*R*,3*S*)
3	Et	quinine	98	88	88	(2*R*,3*S*)
4	*n*-Pr	quinine	98	80	87	(2*R*,3*S*)
5	*i*-Pr	quinine	98	88	72	(2*R*,3*S*)
6	*t*-Bu	quinine	98	90	66	(2*R*,3*R*)
7	Ph	quinine	98	79	97	(2*R*,3*R*)
8	Me	quinidine	98	86	96	(2*S*,3*R*)
9	Ph	quinidine	98	82	95	(2*S*,3*R*)



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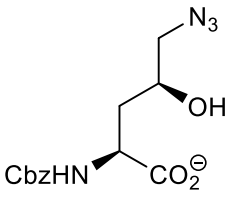

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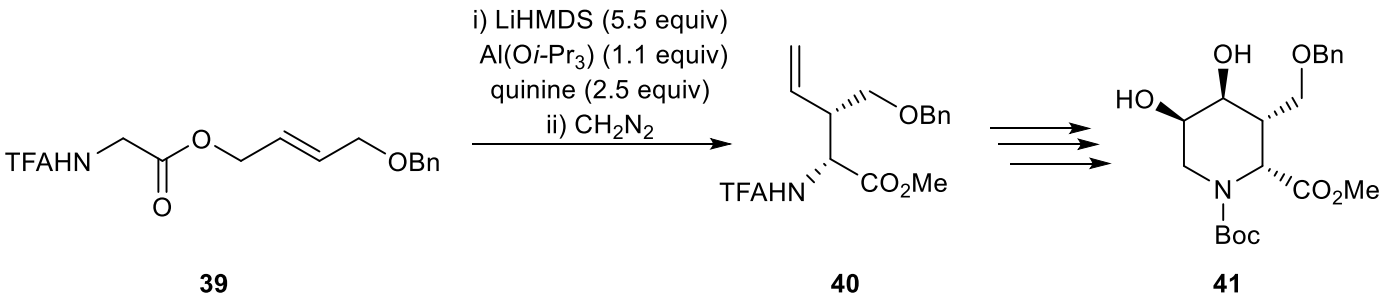
Figure 4. Chemical structures of isostatin **37** and hydroxyornithine **38**.

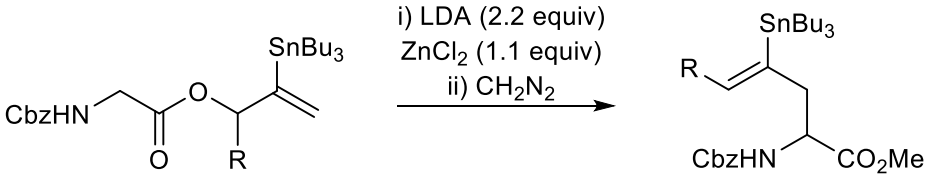
An Asymmetric chelate-Claisen rearrangement was adapted to *δ*-benzyloxycrotyl ester **39**. The rearrangement occurred with very good efficiency and diastereoselectivity, but with moderate enantioselectivity. Nevertheless, the product of this transformation was crucial in the synthesis of the pipecolinic acid derivative **41** (Scheme 6).[25]



39 **40** **41**

Scheme 6. Synthesis of pipecolinic acid **41**.[20]

Unsaturated amino acids can also be obtained via the chelated Claisen rearrangement of *α*-stannylated esters **42** (Scheme 7). The substrates for this reaction can be obtained in a few steps from propargylic acetate or carbonate. The rearrangement itself takes place under the same conditions as its non-stannylated version. The first step is deprotonation with a base in the presence of $ZnCl_2$ at -78 °C. When the reaction mixture is warmed to room temperature, a rearrangement occurs. Next, the resulting amino acids were immediately converted into their methyl esters **43** by treatment with diazomethane. The products undergo partial decomposition during purification on a chromatography column, therefore, they should be used promptly for subsequent reactions.[26]

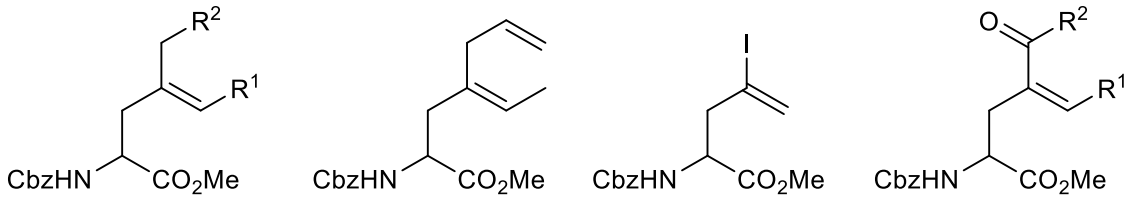


42

43a R = H (70%)
43b R = Me (46%)

Scheme 7. Synthesis of methyl esters **43**.

The derivatives containing a vinylstannane side chain can be used in the synthesis of highly functionalized, unsaturated amino acids, using the Still reaction. For example, derivatives **44a-d**, and **45**, were obtained by a cross-coupling of stannanes with benzylbromide, bromobenzyl bromide, allylbromide, in the presence of $[allylPdCl]_2$ as a catalyst and Ph_3As as a ligand. Vinyl iodide **46** was obtained by reacting **43a** with iodine. This compound may be subjected to subsequent cross-coupling reactions. On the other hand, the synthesis of **47a-b** was possible when benzoyl or acetyl chloride and palladium catalyst were used (Figure 5). Due to the presence of the *α*,*β*-unsaturated carbonyl group, these compounds can be applied as substrates for further modifications, e.g. in the Michael reaction.[26,27]



44a R^1 = H, R^2 =Ph (81%)
44b R^2 = Me, R^2 = Ph (59%*)
44c R^1 = H, R^2 = 2-BrC_6H_4 (58%)
44d R^2 = Me, R^2 = 2-BrC_6H_4 (37%*)

45 (57%)

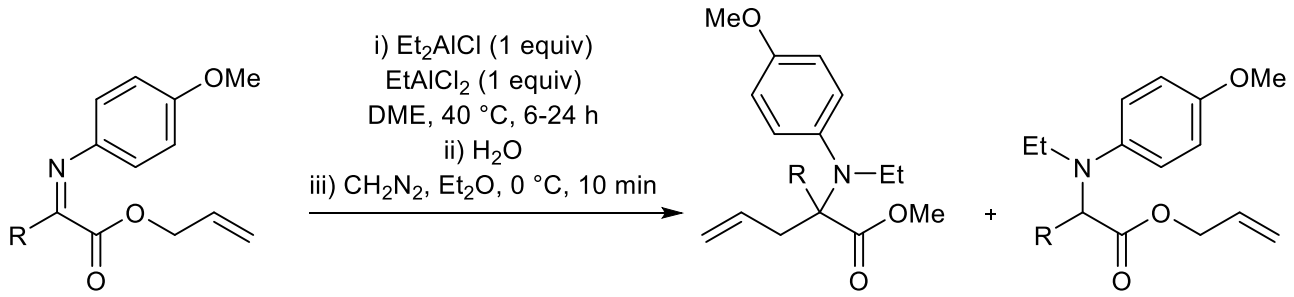
46 (95%)

47a R^1 = H, R^2 = Ph (88%)
47b R^1 = Me, R^2 = Ph (52%*)

***Overall yields for two steps (Claisen rearrangement and cross coupling).

Figure 5. Chemical structures of **44-47**.

Mizota et al. proposed a one-pot synthesis of *γ,δ*-unsaturated quaternary *α*-alkylamino acids utilizing a Claisen rearrangement of the aluminium enolate obtained from umpolung reaction (Scheme 8).[28] First, imino ester **48** reacted with diethylaluminium chloride and ethylaluminium dichloride in DME then the reaction mixture was treated with diazomethane in Et_2O at 0 °C for 10 min.



48 **49** **50**

Scheme 8. The umpolung reaction followed by a Claisen rearrangement.[28]

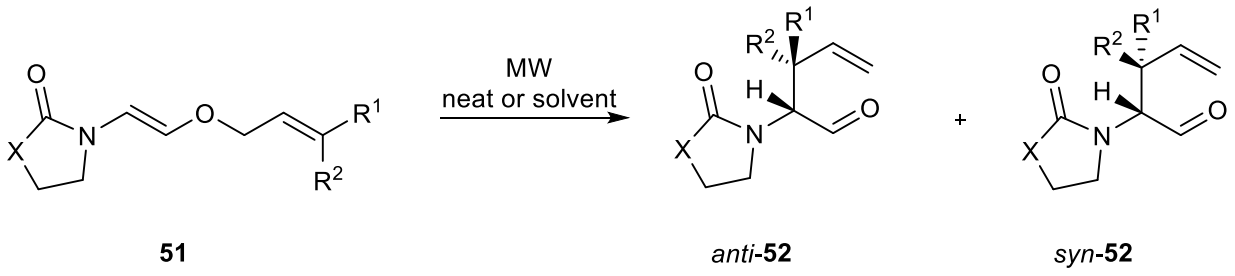
The yields of the desired compounds varied depending on the R substituent, as summarized in the Table 8. The best results were obtained for molecules with an aromatic substituent, except for the 4-methoxyphenyl derivative (Table 8, entry 6). Besides, the *tert*-butyl derivative gave no rearranged product (Table 8, entry 9). Furthermore, sterically hindered alkylating reagents did not give the desired results. Reaction with diisobutyl aluminium chloride led to only 14% yield of the rearranged product.[28]

Table 8. Examination of the scope of substrates.[28]

Entry	R substituent	Yield of compound **49** (%)
1	Ph	60
2[a,b]	3-FC_6H_4	76
3[a]	4-FC_6H_4	65
4[c]	4-ClC_6H_4	58
5	3-$MeOC_6H_4$	79
6[a,d]	4-$MeOC_6H_4$	0
7[e,f]	2-Thienyl	30
8[a]	*c*-Hex	40
9	*t*-Bu	0

[a] Et_2AlCl (2 equiv) was used.
[b] *N*-Ethyl-4-methoxybenzenamine **50** was obtained in a 23% yield.
[c] At rt.
[d] *N*-Ethyl-4-methoxybenzenamine **50** was obtained in a 95% yield.
[e] At 0 °C.
[f] *N*-Ethyl-4-methoxybenzenamine **50** was obtained in a 70% yield.

A Claisen rearrangement is used in organic synthesis not only to obtain directly *γ,δ*-unsaturated amino acids but also to get their precursors[29,30] that can be successfully transformed into non-natural amino acids. An excellent example of this type of application of the Claisen rearrangement reaction is the synthesis of *α*-aminoaldehydes. Ricard et al. presented their approach using a Cu-catalyzed vinylation reaction followed by a Claisen rearrangement.[31] The *β*-allyloxyenamides **51** were synthesized by Cu-catalyzed coupling reaction between *β*-iodoenamides and allylic alcohols under mild conditions. Conventional heating of the compounds gave good yields of the rearrangement products, but the authors were not satisfied with the diastereoselectivity. Therefore, they tested the reaction conducting it with the use of microwave, both domestic and laboratory (Scheme 9).

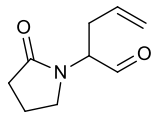
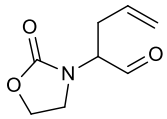
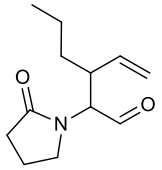
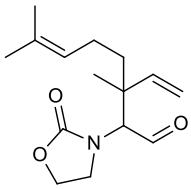


51 *anti*-**52** *syn*-**52**

Scheme 9. Synthesis of *γ,δ*-unsaturated *α*-aminoaldehydes being amino acids precursors by a Claisen rearrangement of *β*-allyloxyenamides.[31]

Application of a domestic microwave produced satisfactory yields and acceptable selectivities. Encouraged by these achievements, the authors also used microwave heating. The reactions were quantitative and led to a very good *dr* (Table 9). The presence of a solvent in the case of domestic microwave heating reduced the time of the process, while its type influenced the selectivity.

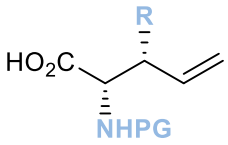
Table 9. The results of the reaction using domestic and laboratory microwave heating[31]

Entry	Substrate **51**	X R^1, R^2	Product **52**	Yield (%) (*anti/syn* ratio)[a] Reaction time (min)				
				Domestic MW [b]				Lab MW [c]
				Neat	DMF	H_2O	Ethylene glycol	Neat
1	**51a**	CH_2 H, H		96 (-) 1	-	-	-	>99 (-) 5
2	**51b**	O H, H		92 (-) 1	-	-	-	>99 (-) 5
3	**51c**	CH_2 $CH_2CH_2CH_3$, H		94 (4:1) 5	90 (1.5:1) 2	82 (6.1:1) 2	89 (9:1) 2	>99 (6.1:1) 10
4	**51d**	O $(CH_2)_2CH=C(CH_3)_2$, CH_3		90 (1:6.1) 7	88 (1:1.9) 4	94 (1:6.1) 4	91 (1:9) 3	>99 (1:6.1) 15

[a] Based on the 200 MHz ^{1}H NMR spectra of the crude reaction mixture.
[b] 30s pulses of heat at maximum intensity (700 W).
[c] Continuous heating at maximum intensity (400 W).

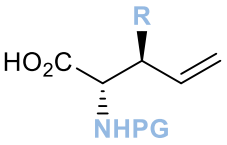
3. Related Versions of Claisen Rearrangement for *γ,δ*-Unsaturated Amino Acids

For two reasons the *β*-substituted *γ,δ*-unsaturated amino acids **53** and **54** (Figure 6) attract the interest of scientists: Firstly, the functionalization at the *β*-carbon atom can give an access to desired pharmacophores; and secondly, the terminal double bond with its orthogonal reactivity allows further chemical modifications during peptides and peptidomimetics synthesis.[32,33] The Kazmaier-Claisen rearrangement has become a very useful tool to the synthesis of these nonproteinogenic amino acids but this approach did not work for *anti*-*β*-substituted compounds.



53

Kazmaier-Claisen rearrangement *syn*-product



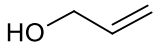
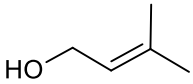
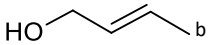
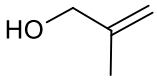
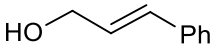
54

Eschenmoser-Claisen rearrangement *anti*-product

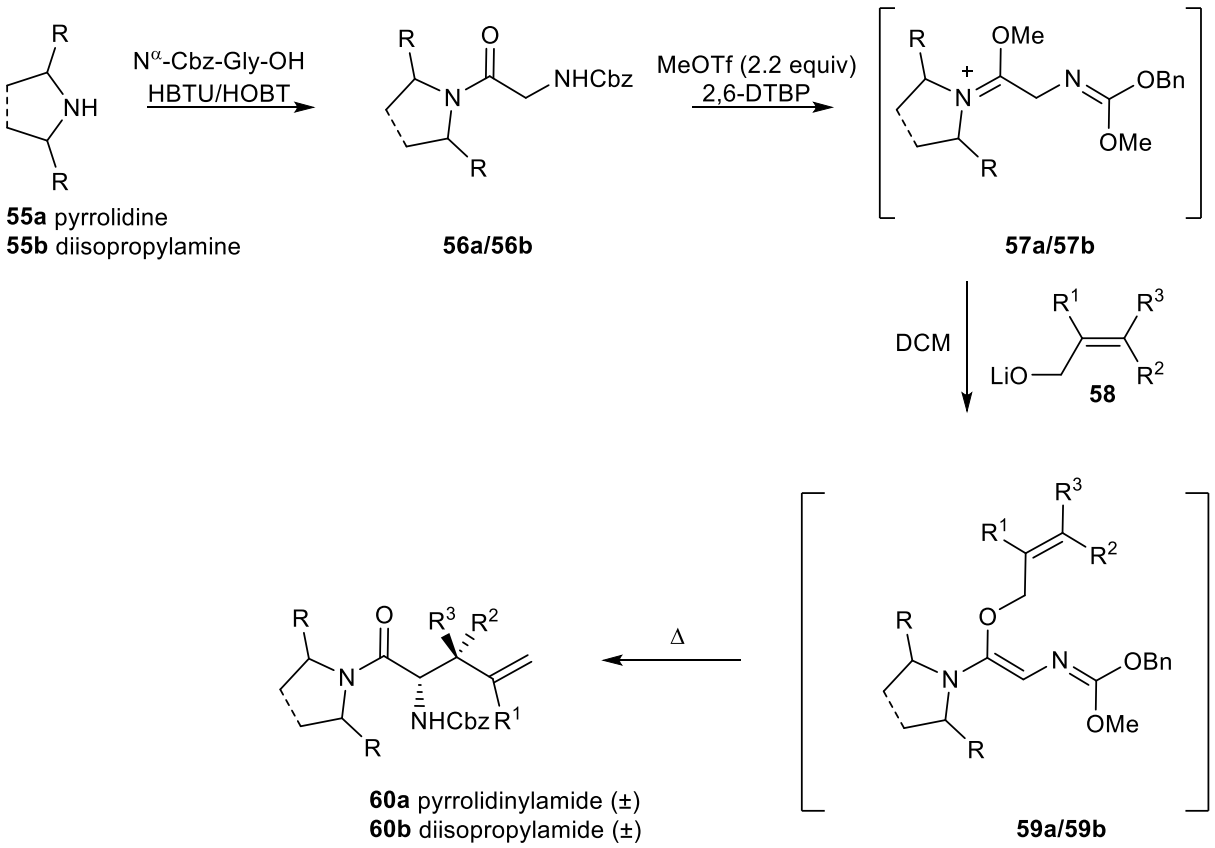
Figure 6. *Syn* and *anti-β*-functionalized *γ,δ*-unsaturated amino acids.

A new synthetic strategy for the construction of the *anti-β*-functionalized *γ,δ*-unsaturated amino acids has been proposed by the Hruby research group. The Meerwein Eschenmoser-Claisen rearrangement constituted a crucial tool for the synthesis of desired compounds (Scheme 10).[34] The secondary amines pyrrolidine **55a** and *N,N*-diisopropylamine **55b** were used to obtain glycine amide derivatives **56a**/**56b**. The commercially available allyl alcohols presented in Table 10 were applied for the rearrangement. During the optimization, it was important to carry out the reaction with a minimum of 2.2 equivalents of the alcohol to get good yields. 2,6-Di-*tert*-butylpyridine was essential for the triflic acid scavenging. The reactions afforded desired products with good to excellent diastereoselectivities (Table 10).[34]

Table 10. Investigation of the Eschenmoser-Claisen reaction conditions[34]

Entry	Allyl alcohols	Alcohol equiv.	T (°C)	Time (h)	*anti*/*syn*	Yield[a] (%)
1		4	-35 → RT	3.5	N/A	**60a-1** (75)
2		2.2	-35 → 35	4	N/A	**60a-2** (44)
3		2.2	-35 → RT	2	9.6:1	**60a-3** (61)
		2.2		4	8.0:1	**60b-3** (56)
4		4	-35 → RT	6	N/A	**60a-4** (72)
5		4	-35 → RT	4	16.8:1	**60a-5** (74)
		2.2		17	20:1	**60b-5** (77)

[a] Isolated yields. Compounds **a** are from pyrrolidinylamide, and compounds **b** are from diisopropylamide.
[b] Crotyl alcohol is a *trans/cis* mixture (95:5) from Sigma-Aldrich.



Scheme 10. The Meerwein Eschenmoser-Claisen rearrangement leading to *anti*-*β*-functionalized *γ,δ*-unsaturated amino acids.[34]

This satisfying diastereoselectivity might be explained by (*Z*)-*N,O*-ketene acetal formation (Figure 7). In contrast to the intermediate of the Kazmaier-Claisen rearrangement with the enolate oxygen standing *cis* to the glycyl nitrogen, here the Eschenmoser-Claisen intermediate can accept two configurations presented in Figure 7. The thermodynamically more stable (*Z*)-intermediate **61a** dominated likely the (*E*)-*N,O*-ketene acetal **61b**.

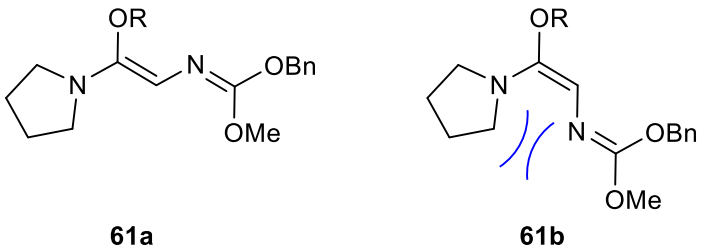
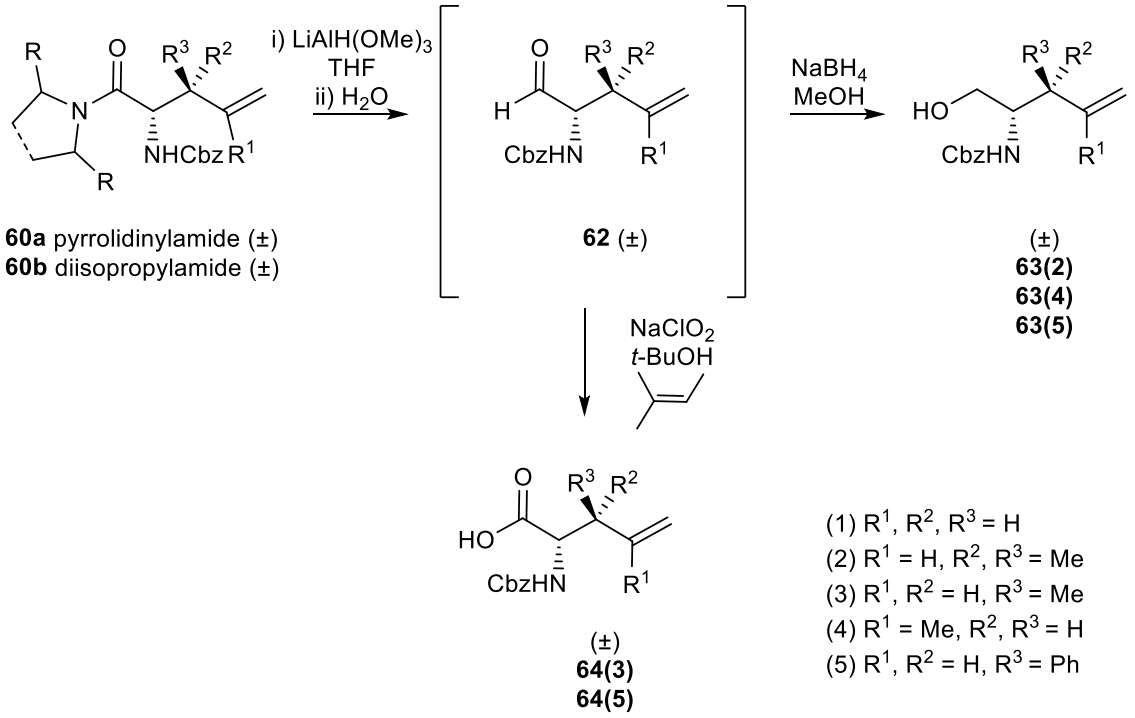


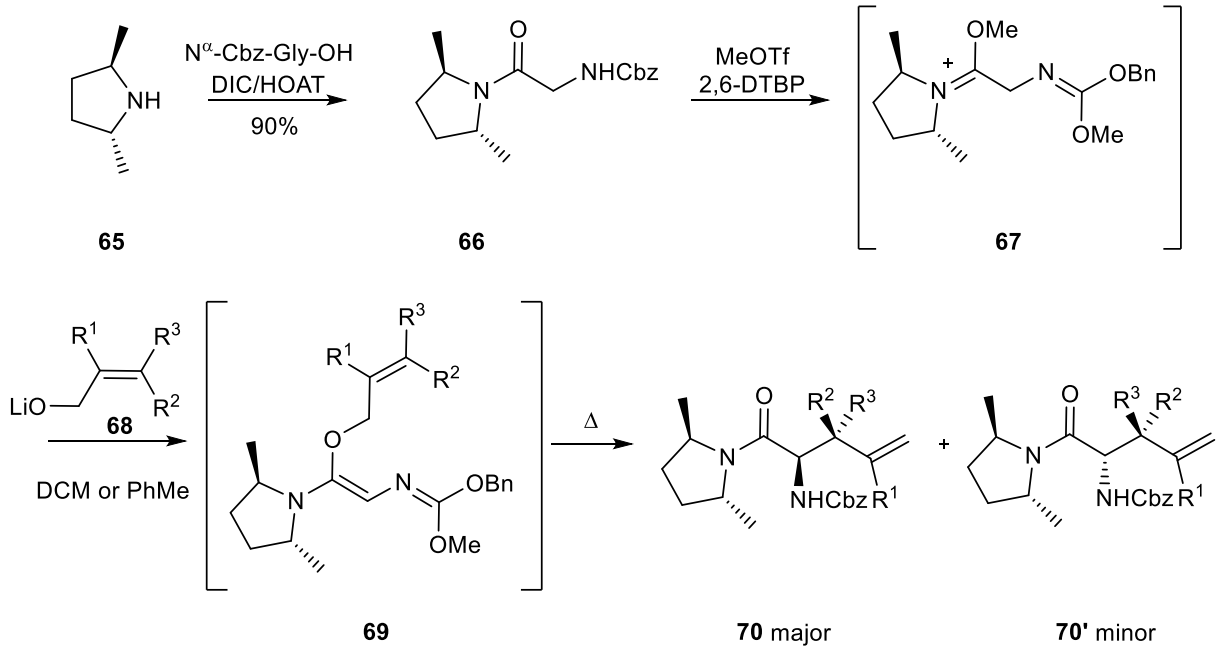
Figure 7. (*Z*)- and (*E*)-*N,O*-ketene acetal reaction intermediates.[34]

This method can also be used to synthesize other structural components of bioactive products, e.g. amino alcohols. Treating (±)-**60** with $LiAlH(OMe)_3$ afforded amino aldehydes **62** that underwent epimerization during workup. Acidic, as well as basic conditions caused the racemization of amino aldehydes. Additionally, the *γ*-double bond and the *β*-substitution prompted the significant lability of the proton adjacent to the carbonyl. Reduction of these aldehydes led to several amino alcohols. By contrast, the employment of Lindgren oxidation conditions yielded the carboxylic acids (Scheme 11).



Scheme 11. A reduction-hydrolysis with lithium trimethoxyaluminium hydride and sodium borohydride.

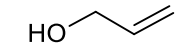
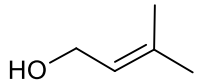
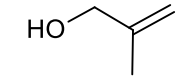
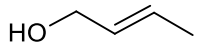
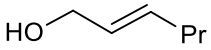
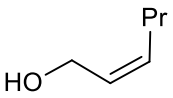
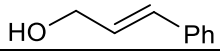
Optically active anti-*β*-functionalized *γ,δ*-unsaturated amino acids are other building blocks that have attracted great interest because of their biological potential and the use for the synthesis of peptidomimetics. This type of amino acids were obtained in another study by the same group.[35] The synthesis of these optically active compounds was accomplished by the asymmetric Eschenmoser-Claisen rearrangement, as the key step using a C_2-symmetric chiral auxiliary (2*R*,5*R*)-dimethylpyrrolidine **65** (Scheme 12).



Scheme 12. An asymmetric Eschenmoser-Claisen rearrangement.[35]

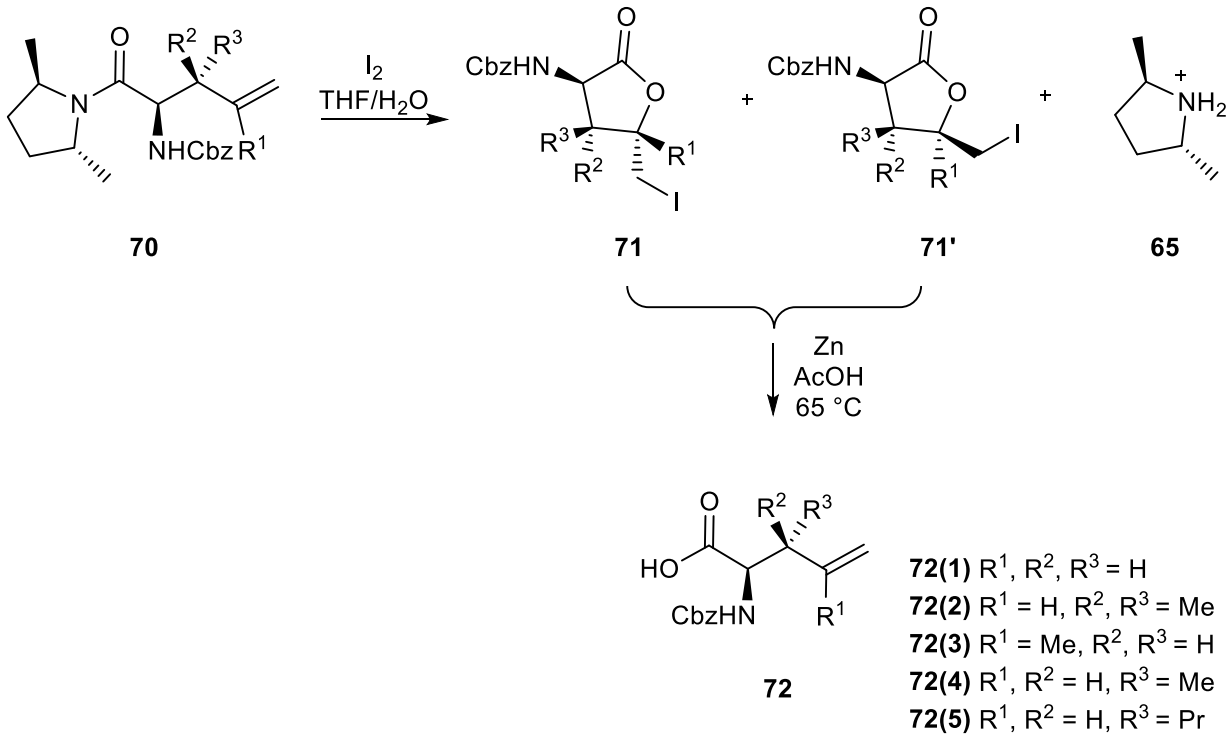
A series of the same primary allylic alcohols were used in this asymmetric approach (Table 11).[35] As previously mentioned,[34] the excellent diastereoselectivity was attributed to the (*Z*)-*N,O*-ketene acetal formation and pseudo chair-like conformation of the rearrangement intermediate. As shown in the studies, the stereochemistry of the double bond had an effect on the diastereoselectivity. *Trans* alcohols had two substituents R^1 and R^3 away from the C_2-symmetric chiral auxiliary in the transition state and their size had no influence on a stereoselectivity (Table 11, entries 4,5 & 7). The *cis* configured substituents of the allylic alcohols destabilized the chair-like transition state and decreased *de* (Table 11, entries 2 & 6).[35]

Table 11. Results of the asymmetric Eschenmoser-Claisen rearrangement[35]

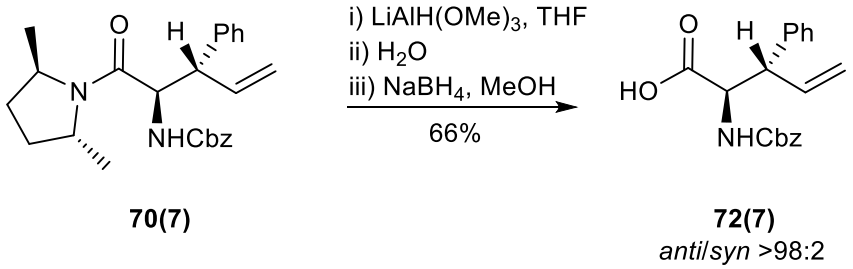
Entry	Allyl alcohols	*anti*/*syn*	*de* (%) **70:70'**	Yield[a] (%)
1		N/A	88 [b]	75
2		N/A	49 [c]	81
3		N/A	91 [b]	82
4		>98:2 [b]	87 [b]	85
5		>96:4 [b]	86 [b]	83
6		>87:13 [b]	54 [b]	65
7		>98:2 [b]	93 [c]	70

[a] Isolated yield of total isomers.
[b] Determined by chiral HPLC.
[c] Determined by ^{1}H NMR.

To remove the chiral auxiliary a two-step approach was applied (Scheme 13). The iodolactones formed in the first step were then subjected to zinc reduction giving the appropriate amino acids. The chiral auxiliary **65** has been recovered. This pathway gave good results except for derivative **70(7)** (from allyl alcohol 7; R^1, R^2 = H, R^3 = Ph, Table 11), where formation of the *syn* isomer was also observed (Scheme 14). This was probably due to the electron-withdrawing nature of the phenyl group, which disfavored the formation of iodolactone, or it was unstable under the reaction conditions. Thus, compound **72(7)** was obtained by a reduction/oxidation of **70(7)**. The method presented by Hruby et al. allowed access to many new *anti*-*β*-functionalized *γ,δ*-unsaturated amino acids with satisfactory diastereoselectivity.[35]

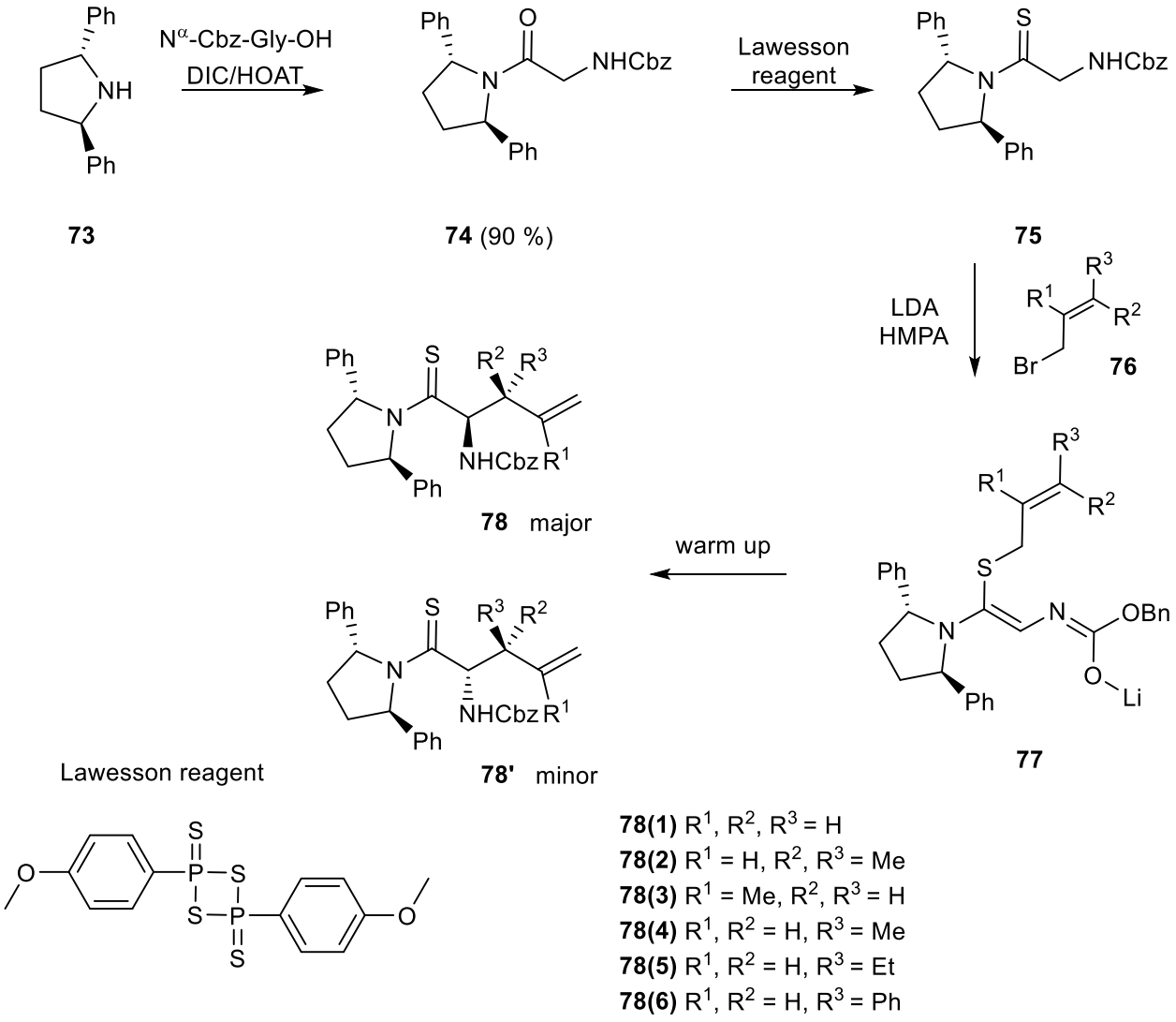


Scheme 13. The iodolactonization and zinc reduction of major *anti* products of the asymmetric Eschenmoser-Claisen rearrangement.[35]



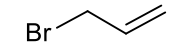
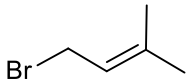
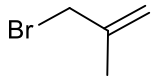
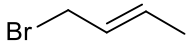
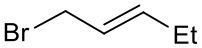
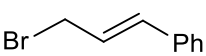
Scheme 14. Reduction/oxidation of **70(7)**.[34,35]

Further investigation by Hruby led to the use of the thio-Claisen rearrangement as a key step to prepare novel optically active *anti-β*-substituted *γ,δ*-unsaturated amino acids.[36,37] The synthesis of desired compounds began with the thio-enolate, which was made by treatment of thioamide **75** with freshly prepared LDA in THF at -78 °C and then the thio-enolate was alkylated at the sulfur position with allylic bromide (Scheme 15). In this highly selective method a bulky C_2-symmetric chiral auxiliary (2*R*,5*R*)-2,5-diphenylpyrrolidine **73** was used. The thio-Claisen rearrangement was only possible after warming up to room temperature, and in some cases, it required even higher temperatures. The reactions were carried out with the six selected allylic bromides as summarized in Table 12.[36] The results indicated that the reactions proceeded with an excellent diastereoselectivity, and in most cases only the *anti*-products were obtained. When the size of the R^3 substituent increased, there was a steric repulsion with the Cbz group, and this probably led to the decrease in diastereoselectivity (Table 12, entries 5 & 6). The authors explained this issue by modelling the transition states as proposed in Figure 8, of which **79a** was preferred for steric reasons.



Scheme 15. Production of thio-enolate dianion and asymmetric thio-Claisen rearrangement.[36]

Table 12. Results of the asymmetric thio-Claisen rearrangement[36]

Entry	Allylic bromides	T (°C)	Yield[a] (%)	*de* (%) **78:78'**[b]	*anti*/*syn* [b]
1		-78 → RT	82	>99	NA
2		-78 → reflux	66	>99	NA
3		-78 → RT	74	>99	NA
4		-78 → 40	78	>99	>99:1
5		-78 → 40	76	78	>99:1
6		-78 → RT	65	75	>73:1

[a] Isolated yield of total isomers.

[b] Determined by chiral HPLC.

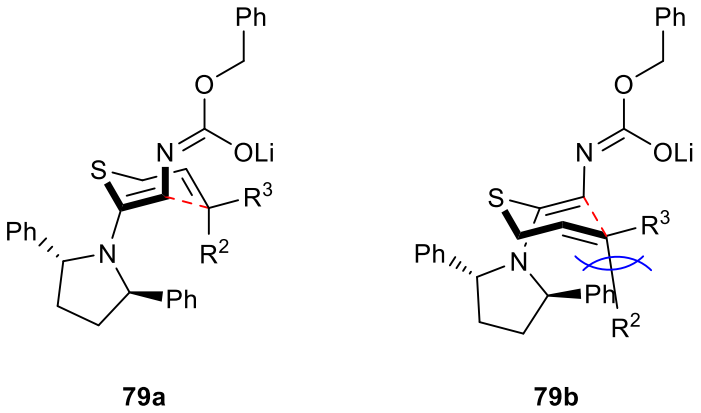
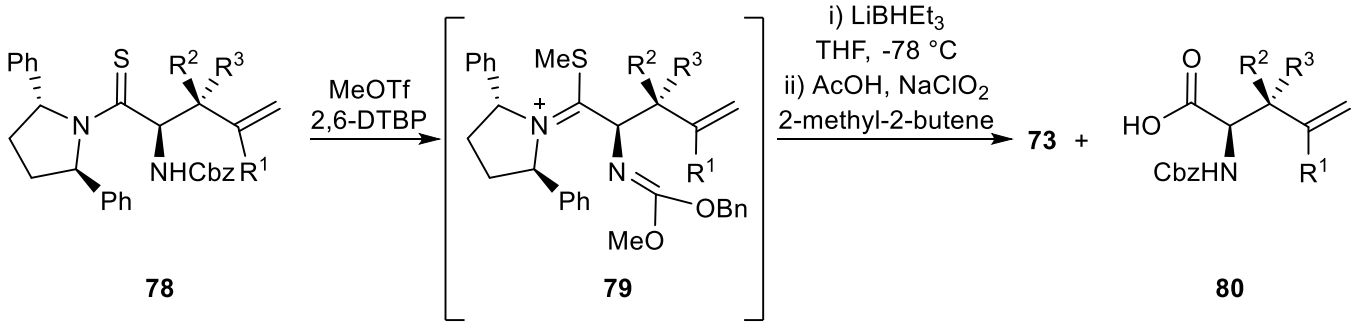


Figure 8. Proposed transition state models for thio-Claisen rearrangement.[36]

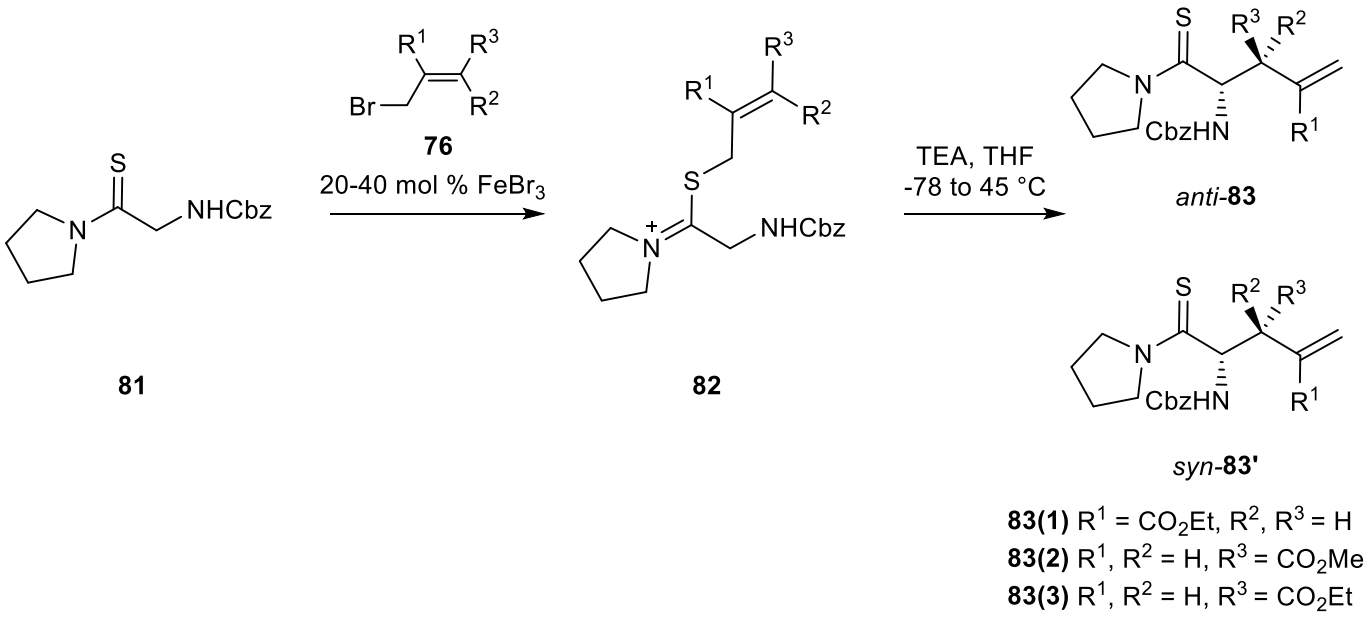
The step of removing of the chiral auxiliary consisted in one-pot alkylation-reduction-oxidation reaction. The amino thioamides were turned into amino acids with a minimal loss of the optical activity (Scheme 16).

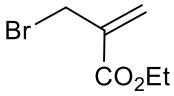
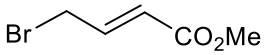
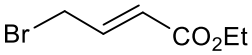


Scheme 16. Amino acids generation and chiral auxiliary recycle.[36]

Due to the fact that nature does not use the harsh reaction conditions presented in the above-described reactions (strong base LDA), Hruby et al. decided to develop a mild method to be able to obtain more structurally versatile amino acids.[37] First, the use of thioamide was found to be crucial because the resulting thioiminium ion formation should increase the acidity of the *α* proton in comparison to the NH proton. Hence, one equivalent of a weak base was enough to deprotonate the *α* proton and trigger the thio-Claisen rearrangement. Secondly, they predicted that facilitating C-Br bond breaking should improve allylation and rearrangement yields and hence a Friedel-Crafts catalyst $FeBr_3$ was applied (Table 13).[37] This mild reaction condition has given a chance to use the variety of functional group at the *β*-position. Also ester groups were successfully introduced (Table 13, entries 2 & 3). Compounds **83(2)** and **83(3)** were synthesized as diastereopure products. It can be explained based on the transition state model **84b** presented in the Figure 9. The ester carbonyl group would form a hydrogen bond with the *α*-amino group, creating a second six-membered ring to additional stabilize the transition state.[37]

Table 13. Results of new method of thio-Claisen rearrangement using Friedel-Crafts alkylation type reaction[37]



Entry	Allylic bromides	Yields **83** (%) [a]	*anti*/*syn* [b]
1		72	NA
2		82	>49:1
3		72	>49:1

[a] Isolated yield of total isomers.
[b] Determined by ^{1}H NMR.

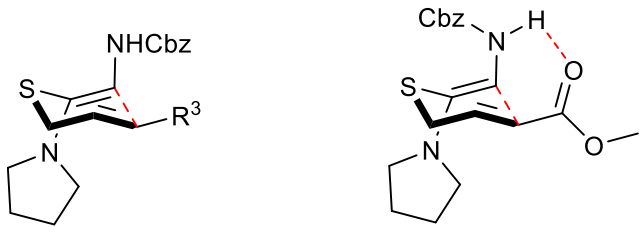
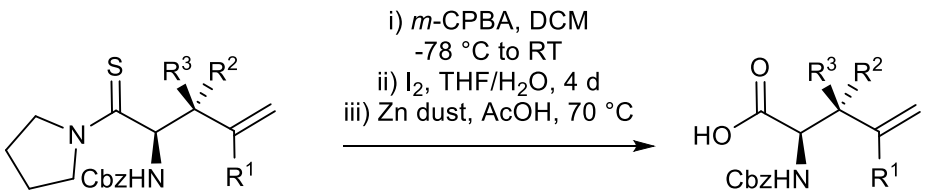


Figure 9. Proposed transition state models for thio-Claisen rearrangement.[37]

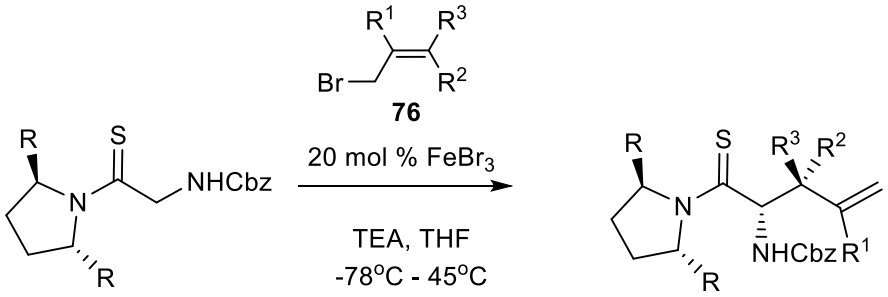
The last step was difficult due to the ester functional groups in the molecules. An oxidation-iodolactonization-reduction pathway was used to generate the target molecules (Scheme 17). During these reactions little or no epimerization was observed.[37]



83 **85**

Scheme 17. Amino acids generation.[37]

This topic is especially important due to the multifunctionality of amino acids, especially those unsaturated, which are widely used as building blocks in peptidomimetics. Encouraged by previous positive results involving the highly asymmetric Eschenmoser-Claisen rearrangement[35] and the thio-Claisen rearrangement[36,37] Hruby et al. summarized their studies in a paper from 2012.[38] In this approach, the authors also presented a combined method of applying Friedel-Crafts alkylation and the use of a three commercially available C_2-symmetric chiral auxiliary **88a-c** (Scheme 18, Table 14).



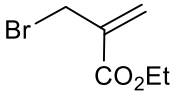
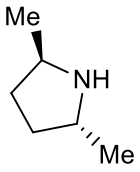
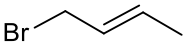
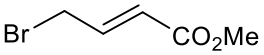
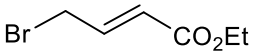
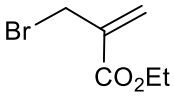
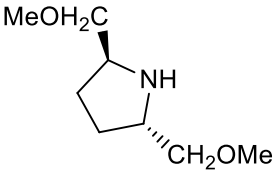
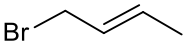
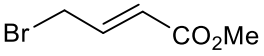
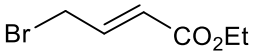
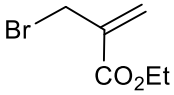
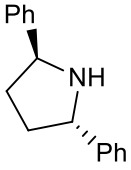
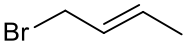
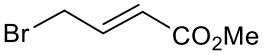
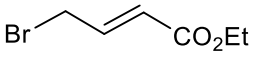
86a R = Me
86b R = CH_2OMe
86c R = Ph

87a R = Me
87b R = CH_2OMe
87c R = Ph

Scheme 18. Asymmetric thio-Claisen rearrangement with C_2-symmetric chiral auxiliaries.[38]

They noticed that the size of R group on the chiral auxiliary increased the diastereoselectivity. It was also observed that the carbonyl group in the allylic bromides resulted in the formation of the only one compound in the reaction, which confirmed their earlier findings based on the model **84b** of the transition state (Figure 9). When the C=O group is at the R^1 position, **87a(1)**, **87b(1)**, **87c(1)**, no bicyclic structure is formed and therefore no diastereoselectivity of the reaction is observed (Table 14).[38] Due to the interest of the Hruby group in the solid-phase peptide synthesis,[39] they also checked the influence of different protecting groups on diastereoselectivity. Except for Fmoc-protected amino acids, other usually applied N-protected amino acids were easily obtained with excellent optical purities.[38] For this work, they also used a three-step oxidation-iodolactonization-reduction method to convert the thioamides into the appropriate carboxylic acids. They also undertook the comparison of the ECR (Eschenmoser-Claisen rearrangement) with the TCR (thio-Claisen rearrangement) as summarized in Table 15.

Table 14. Results of Asymmetric thio-Claisen rearrangement with C_2-symmetric chiral auxiliaries[38]

Entry	Allylic bromides	Chiral auxiliary	Yield[a] (%)	*anti*/*syn*[b]	*de* (%)[c]
1		 **88a**	64	NA	56[e]
2			62	17:1[d]	78[d]
3			86	99:1[e]	99[e]
4			83	99:1[e]	99[e]
1		 **88b**	54	NA	90[e]
2			52	30:1[e]	88[e]
3			64	99:1[e]	99[e]
4			65	99:1[e]	99[e]
1		 **88c**	60	NA	67[e]
2			58	99:1[e]	91[e]
3			63	99:1[e]	99[e]
4			70	99:1[e]	99[e]

[a]Isolated yield of total isomers.

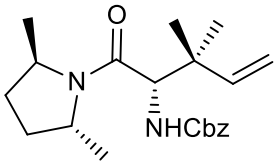
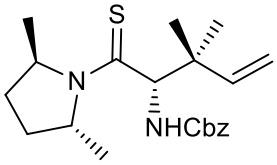
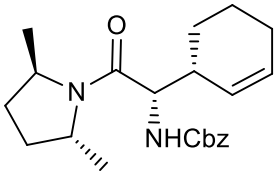
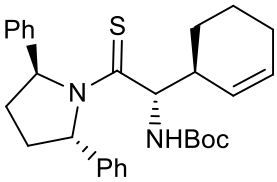
[b]*Anti*: 2*S*,3*S* and 2*R*,3*R*, *Syn*: 2*S*,3*R* and 2*R*,3*S.*

[c] Diastereomeric excess between two *anti* isomers: *anti* major 2*S*,3*S*; *anti* minor 2*R*,3*R.*

[d] Determined by weight.

[e] Determined by chiral HPLC.

Table 15. Results of comparing ECR and TCR diastereoselectivities[38]

Compounds	Yield (%)	*anti*/*syn* [b]	*de* (%) [c]
 **89**	81 [f]	NA	49 [f]
 **90**	66 [a]	NA	99 [d]
 **91**	32 [a]	- [e]	- [e]
 **92**	44 [a]	99:1 [d]	99 [d]

[a] Isolated yield of total isomers.
[b] *Anti*: 2*S*,3*S* and 2*R*,3*R*, Syn: 2*S*,3*R* and 2*R*,3*S.*
[c] Diastereomeric excess between two *anti* isomers: *anti* major 2*S*,3*S*; *anti* minor 2*R*,3*R.*
[d] Determined by chiral HPLC.
[e] Inseparable diastereomeric mixtures.
[f] Results from previous publications.

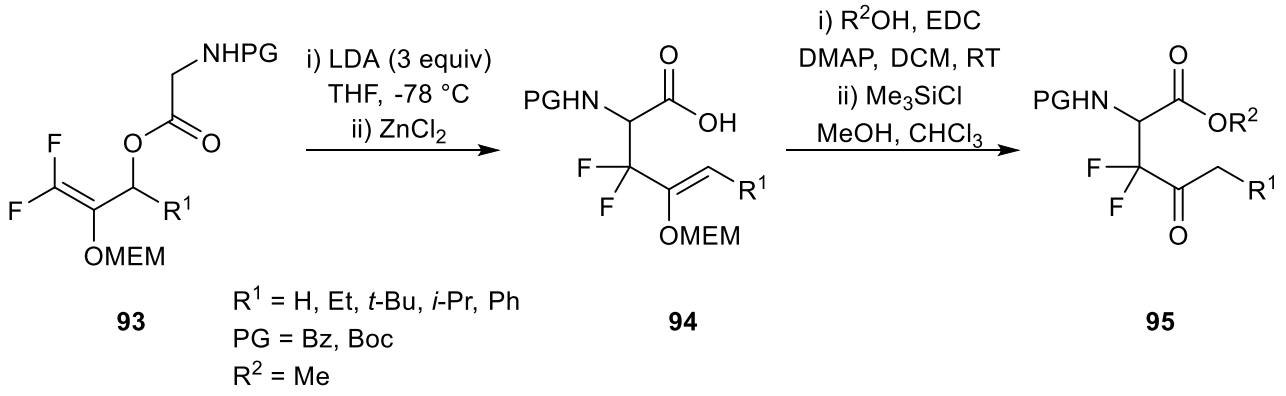
In summary, the thio-Claisen reaction using catalytic $FeBr_3$ in the alkylation step may be a commonly used method. The mild reaction conditions make it suitable for compounds with various substituents as well as protecting groups.

4. Application of Claisen Rearrangement to the Synthesis of Fluorine-containing *γ,δ*-Unsaturated Amino Acids

In this review we would like also to show that there are several examples of the use of Claisen rearrangement to obtain fluorine-containing amino acids. Fluorine is not one of the favourite elements that nature applies to construct organic matter. However, it is such a valuable construction material for the synthesis of biologically active compounds that the chemists use the available tools to receive organofluorine compounds.[40,41] The

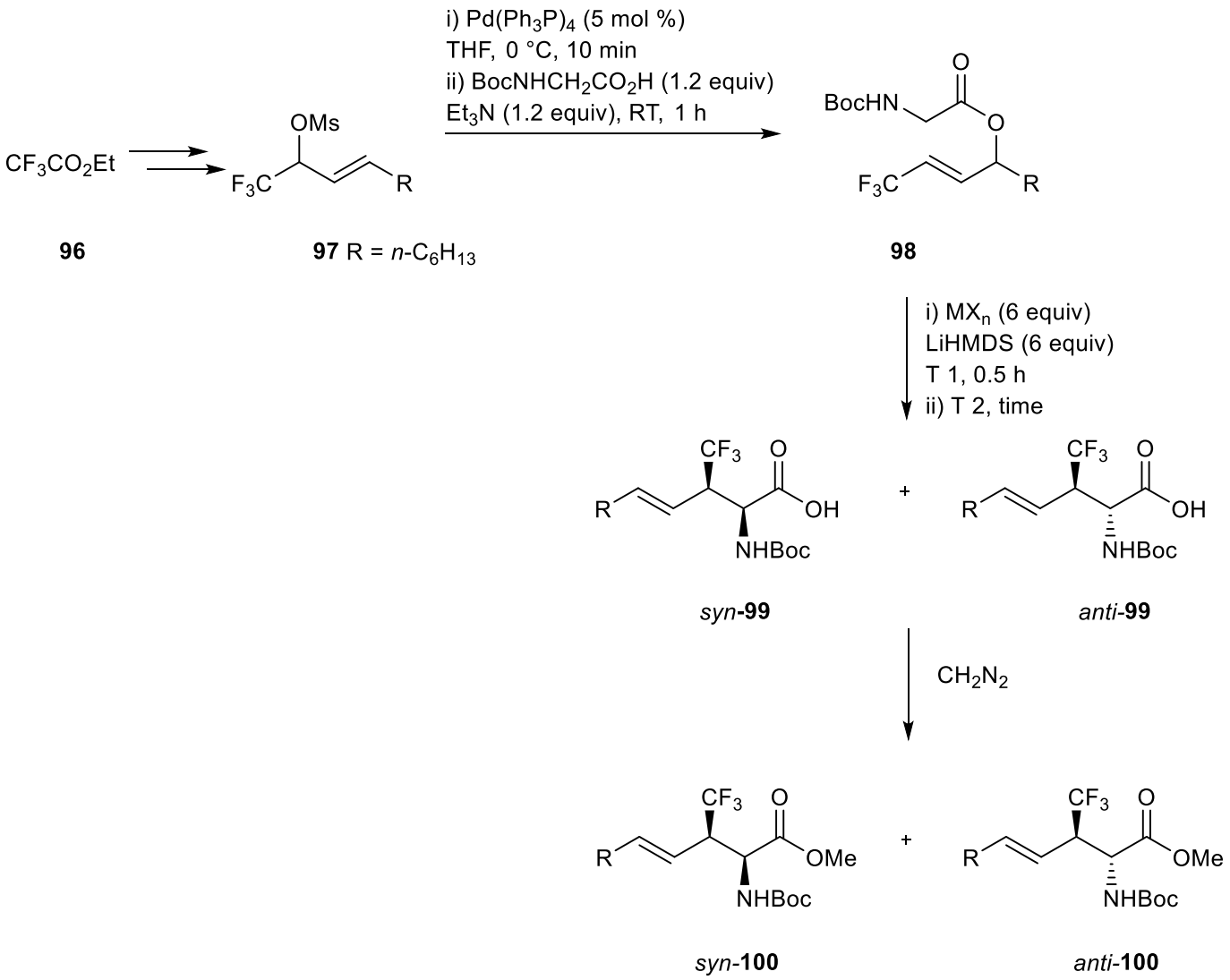
direct fluorination and the methods employing fluorinated building blocks are knowable ways for their preparation.[42,43] These intermolecular reactions are multistage and involve quite drastic reaction conditions. The intramolecular rearrangement reaction such as Claisen rearrangement or related [3,3]-sigmatropic rearrangements might be an interesting alternative route. Rearrangement reactions belong to the most often used transformations, especially for the synthesis of fluorine-containing unsaturated amino acids. This class of non-proteinogenic amino acids is particularly important because their non-fluorinated counterparts have relevant features: act as a potent inhibitors of enzymes[44] or participate in the synthesis of peptidomimetics or peptides.[45]

In 1998 Percy and Prime applied first the Kazmaier's methodology to the synthesis of fluorinated compounds.[46] The N-protected *γ,γ*-difluorinated glycinate esters **93** were rearranged with $ZnCl_2$ to yield *β,β*-difluoro-*α*-aminio acids **94** (Scheme 19). The rearranged acid was the only product of the reaction, what was revealed by both ^{19}F and ^{1}H NMR spectroscopy.



Scheme 19. A short route to the *β,β*-difluoro-*α*-aminio acids via chelated [3,3]-rearrangement.[46]

The optically active *β*-fluoroalkylated *γ,δ*-unsaturated amino acids were synthesized by sequential Pd-catalyzed allylic substitution and Ireland-Claisen rearrangement by Konno et al.[47] The glycine allyl ester **98** was generated readily from the mesylate **97** by the Pd-catalyzed allylic substitution reaction presented below (Scheme 20).[48]



Scheme 20. The combination reactions of Pd-catalyzed allylic substitution and Ireland-Claisen rearrangement.[47]

Experiment showed that the allylic substitution reaction of fluorinated allyl mesylate with *N*-Boc glycine gave neither the regioisomer **101**, the stereoisomer **102** nor the allylamine derivative **103** (Figure 10).[47]

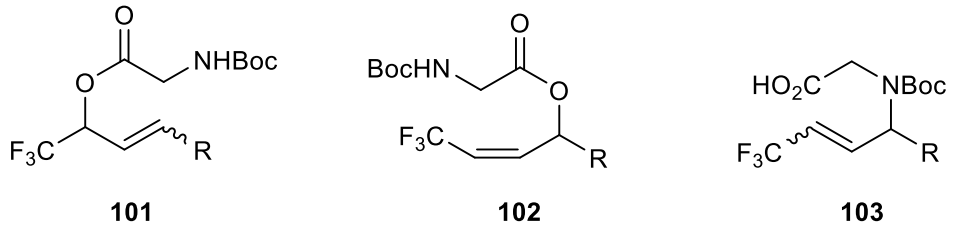


Figure 10. The feasible products of the palladium-catalyzed allylic substitution reaction.[47]

The next step, the Ireland-Claisen rearrangement required investigation (Scheme 20, Table 16). Bartlett and Barstow reported in 1982 that non-fluorinated glycine crotyl ester underwent Ireland-Claisen rearrangement stereoselectively and with good yield.[49] Herein, the products *syn*-**99** and *anti*-**99** were formed

as a diastereomeric mixture in a 62:38 ratio and in unsatisfactory 48% yield (Table 16, entry 1). Stirring the mixture heated at reflux for 6 h led to a marked increase of the yield (94%) but the stereoselectivity remained moderate (Table 16, entry 3). The reaction without TMSCl gave excellent diastereoselectivity, but did not lead to an acceptable yield (Table 16, entry 4).

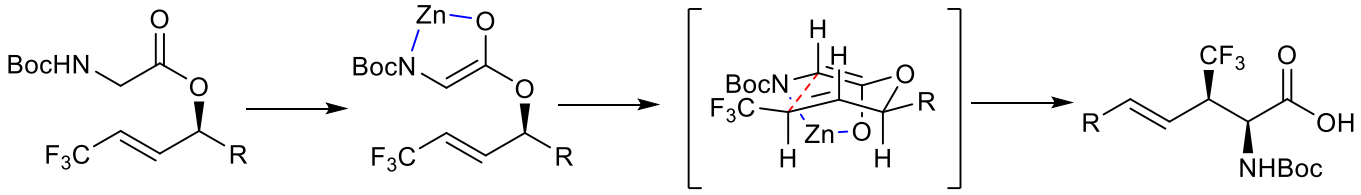
Table 16. Investigation of the reaction conditions[47]

Entry	MX_n	T 1 (°C)	T 2 (°C)	Time (h)	Yield of **99** (%)[a]	Yield of **98** (%)[a]	Diastereomeric ratio
1	TMSCl	-78	RT	6	48	44	62:38
2	TMSCl	-78	RT	20	45	55	54:46
3	TMSCl	-78	reflux	6	94	2	73:27
4	-	-78	RT	20	49	23	100:0
5	TMSCl	0	RT	20	62	32	96:4
6	TMSCl	0	reflux	6	84	9	91:9
7	TMSCl	0	reflux	15	84	11	90:10
8[b]	TMSCl	0	reflux	6	79	4	94:6
9	$ZnCl_2$	0	reflux	6	82	14	100:0
10	$ZnCl_2$•TMEDA	0	reflux	6	71	22	100:0

[a] Determined by ^{19}F NMR.

[b] Glycine was used instead of Boc-glycine.

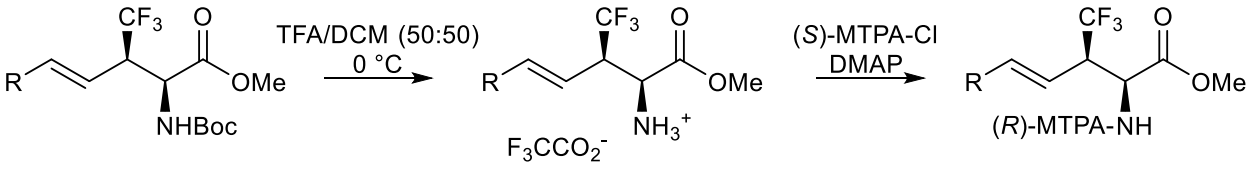
Kazmaier et al.,[10] findings that the bidentate chelation in the enolate by using $ZnCl_2$ brings a marked enhancement of thermal stability and that the Ireland-Claisen rearrangement proceeds stereoselectively (Table 16, entry 9) can be represented by the mechanism depicted in Scheme 21. Treatment of the glycine allyl ester with $ZnCl_2$ gave in the stereoselective manner the (*Z*)-enolate **98** (Int-A). A stereoselective Ireland-Claisen rearrangement via the energetically stable six-membered cyclic transition state **98** (Int-B), where the *R* group takes the equatorial position, resulted in the desired *β*-trifluoromethylated amino acid **99** with (2*S*,3*R*)-configuration.[47]



98 **98** Int-A **98** Int-B **99**

Scheme 21. The mechanism of the Ireland-Claisen rearrangement.[47]

The rearranged product **100** was then stirred for several hours at 0 °C with TFA and DCM (50:50 v:v) to deprotect the NH group. The TFA salt **104** was treated with Mosher's acid chloride and DMAP to give the MTPA-amide **105** with 92% diastereomeric access (Scheme 22).



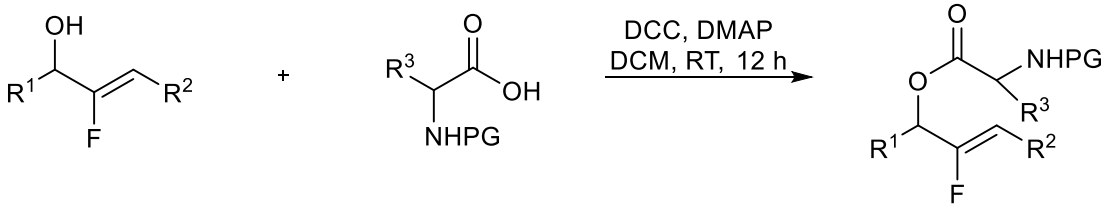
100 (R = *n*-C_6H_{13}) **104** **105** 92% *de*

Scheme 22. Removing of the Boc group.

The above presented method also served as a good way for the preparation of chiral amino acids with other fluoroalkylated groups (-CF_2H, -CF_2CF_3) at the *β* position.[47]

The synthesis of *γ*-fluoro-*γ,δ*-unsaturated *α*-amino acids was described by Haufe research group in 2005.[50] The Kazmaier variant of the Ireland-Claisen rearrangement with minor modifications constituted an essential stage of this approach. Fluorinated allylic esters of glycine **107** and (*R,S*)-alanine **108** were prepared according to the method earlier described independently by two groups[51-52] (Table 17). This procedure gave the best results with Boc-amino acids (esters **109** and **110**). The fluoroallyl alcohols used in this reaction were prepared via allylic hydroxylation of vinyl fluorides.[53]

Table 17. Synthesis of amino acid 2-fluoroallylic esters **109-112**[50]

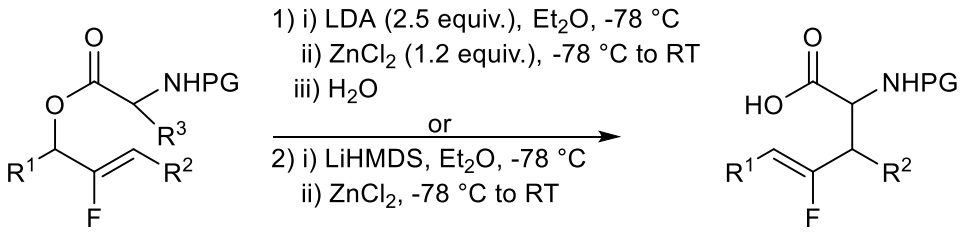


106 **107, 108** **109-112**

Entry	R^1	R^2	R^3	PG	Yields (%)
1	C_3H_7	H	H	Boc	**109a** (80)
2	C_3H_7	H	Me	Boc	**110a** (69)
3	C_7H_{15}	H	H	Boc	**109b** (94)
4	C_7H_{15}	H	Me	Boc	**110b** (96)
5	$C_{13}H_{27}$	H	H	Boc	**109c** (92)
6	$C_{13}H_{27}$	H	Me	Boc	**110c** (100)
7	H	C_7H_{15}	H	Boc	**110d** (97)
8	H	H	H	Boc	**110e** (96)
9	H	H	Me	Boc	**110f** (88)
10	C_3H_7	H	H	TFA	**111a** (33)
11	C_7H_{15}	H	H	TFA	**111b** (54)
12	$C_{13}H_{27}$	H	H	TFA	**111c** (51)
13	H	H	H	TFA	**111e** (57)
14	C_3H_7	H	Me	TFA	**112a** (29)
15	C_7H_{15}	H	Me	TFA	**112b** (50)
16	$C_{13}H_{27}$	H	Me	TFA	**112c** (26)
17	H	H	Me	TFA	**112f** (35)

The rearrangement of the *γ*-fluoro-amino acid esters, obtained from Boc-glycine, failed under conditions described by Kazmaier. The substrates were either recovered almost quantitatively or the esters were hydrolyzed. However, an approach using Et_2O instead of THF enabled the rearrangement of the Boc-glycine esters **109a-c** and the *γ*-fluoro-*γ,δ*-unsaturated *α*-amino acids **113a-c** were obtained (Table 18, entries 1-3). Worthy of note was that increasing the steric demand of the R^1 substituent impacted the degree of rearrangement. The reaction of compound **113d** with R^1 = H failed (Table 18, entries 4 & 5).[50]

Table 18. Results of ester enolate Claisen rearrangement[50]



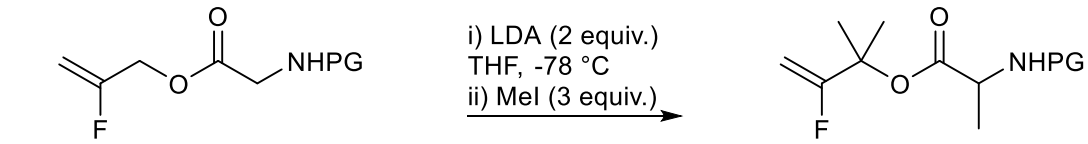
109a-e **113a-e**

Entry	Products	R^1	R^2	R^3	Yield (%) PG = Boc	Yield (%) PG = TFA[a]
1	**113a**	C_3H_7	H	H	36	41
2	**113b**	C_7H_{15}	H	H	64	45
3	**113c**	$C_{13}H_{27}$	H	H	39	41
4	**113d**[b]	H	Alkyl or H	Alkyl or H	0	0
5	**113e**[b]	Alkyl or H	Alkyl or H	Alkyl or H	0	0

[a] LiHMDS/Et_2O

[b] Starting materials were recovered

Presumably, the esters **110** of a racemic alanine, valine and phenylglycine with $R^3 \neq H$ did not rearrange because of steric reasons. These problems did not occur for non-fluorinated allylic esters tested by Kazmaier. However, Percy et al. described a similar case in Johnson-Claisen rearrangement of *β*-chloro-*γ*-fluoroallylic esters.[54] This may suggest the fluorine atom impact, which was investigated using the reaction shown below (Scheme 23). It seems preferable to deprotonate the allyl position of *β* to a fluorine substituent. The rearrangement of compounds with R^1 = H probably failed for this reason. The use of lithium hexamethyldisilyl amide (LiHMDS) was expected to avoid this problem.

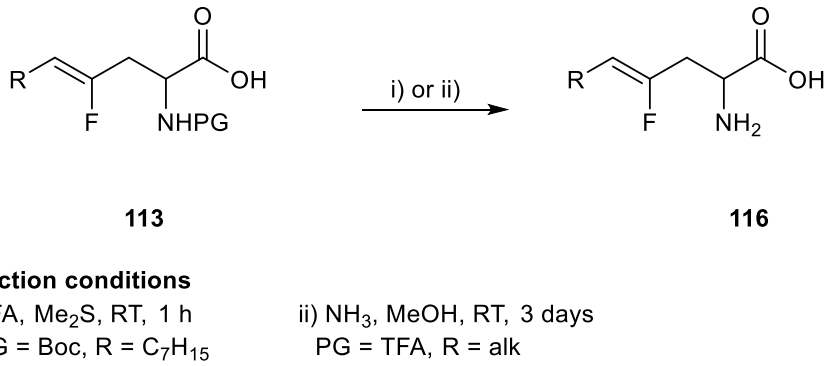


PG = Boc

114 **115** and other products

Scheme 23. Fluorine atom impact on deprotonation.[50]

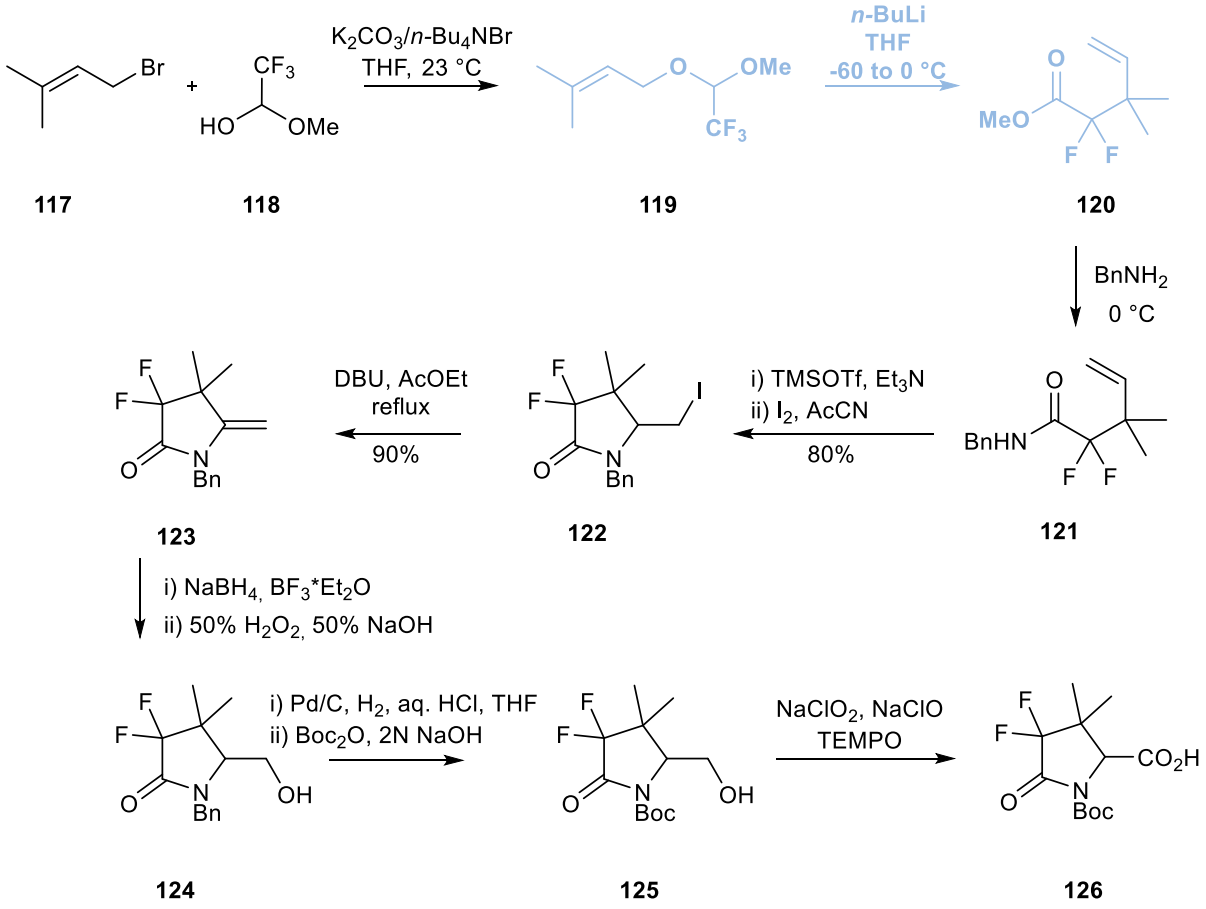
The deprotection reactions were accomplished under salt-free conditions (Scheme 24).



Scheme 24. Deprotection of *γ*-fluoro-*γ,δ*-unsaturated *α*-amino acids derivative.[50]

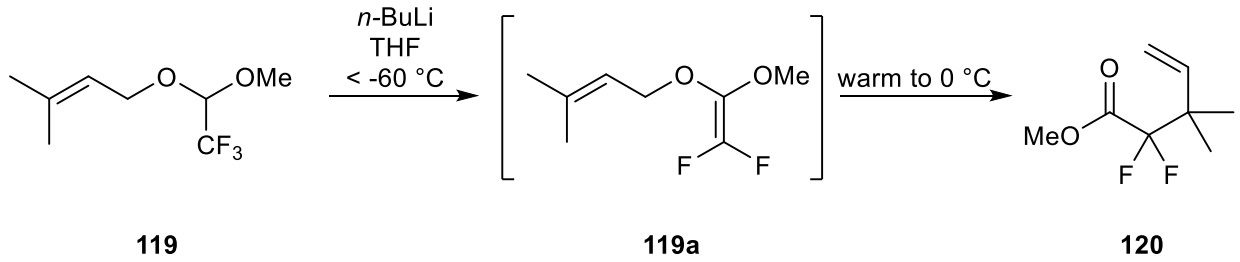
The presented research shows that there must be a balanced combination of steric and electronic effects of substituents in the *α* position to the carbonyl group and *β* to the fluorine atom to enable ester enolate Claisen rearrangement of the fluorinated esters of amino acids.[50]

Chen et al. proposed a Claisen rearrangement and iodolactamization sequence leading to the 4,4-difluoro-3,3-dimethylproline derivative **126**[55,56] (Scheme 25), whose (*S*)-enantiomer is a key building block for a number of second-generation HIV protease inhibitors.[57]



Scheme 25. Synthesis of 4,4-difluoro-3,3-dimethylproline derivative **126**.[56]

The application of a Claisen rearrangement to introduce the difluoro moiety into the molecule was a valuable alternative (Scheme 26) to the low yielding original synthesis, which required expensive and dangerous reagents (DAST and Deoxo-Fluor).[58]



119 **119a** **120**

Scheme 26. Key step of the 4,4-difluoro-3,3-dimethylproline derivative synthesis.

The preparation of non-natural and/or fluorine containing amino acids and their precursors can be a considerable effort for chemists, but their significant application primarily for medicine and pharmacy makes researchers take up this challenge. The use of a Claisen rearrangement and its variants may, due to the fact that it is an intramolecular reaction, enable the synthesis of these compounds, as presented in this paper.

5. Conclusions

Considering the quantity and quality of articles over the last 25-years which describe research on the Claisen rearrangement, we can safely assume that this topic will undergo further development. The protocol finds wide use in the synthesis of optically pure compounds needed as building blocks to prepare key compounds in bioorganic and medical chemistry. The versatility of the Claisen rearrangement was further demonstrated via the synthesis of fluorinated *γ,δ*-unsaturated amino acids that highlighted the significant influence of the fluorine atom on the properties of biomolecules.

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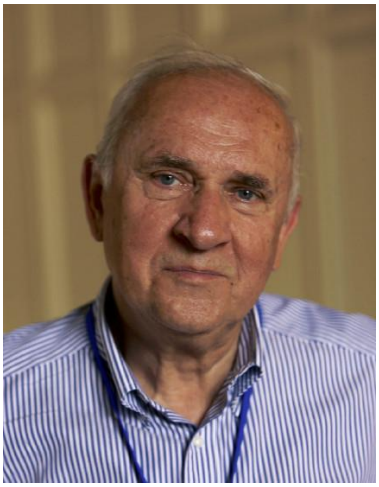

Henryk Koroniak is a Professor at Adam Mickiewicz University, Poznań, Poland. He is a Head of Department of Synthesis and Structure of Organic Compounds. His research activity includes: synthesis and structural studies of fluorine containing organic molecules, biologically active fluorochemicals, molecular modelling, and mostly fluorine influence on reactivity and structure of organic compounds. He serves presently as a Dean of Faculty of Chemistry, Adam Mickiewicz University, He was also involved is several activities related to his academic career such as Member of Polish State Committee for Scientific Research; Member of Editorial Board of Journal of Fluorine Chemistry; Editor of "On the borderline between chemistry and biology" (39 volumes up to 2019), Member of Council of The Foundation for Polish Science (FNP), Member of Fluorine Division, American Chemical Society.