Stereoselective Synthesis of α-Alkylated γ,δ-Unsaturated Amino Acids *via* Claisen Rearrangement of Chelated Enolates

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Ester enolate Claisen rearrangement of chelated *N*-protected amino acid allylic esters results in the formation of α-alkylated γ,δ-unsaturated amino acids in good yields and in a highly diastereoselective fashion.

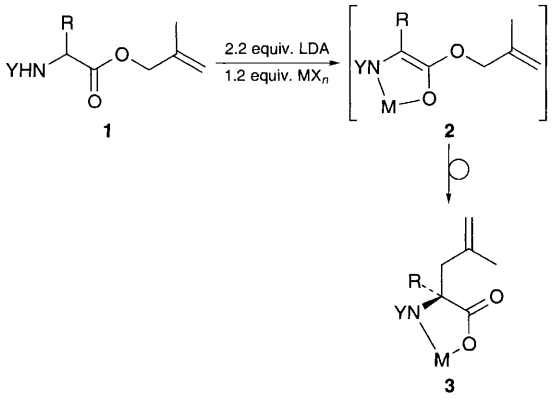
The α-alkylated amino acids are an especially interesting class of nonproteinogenic amino acids containing quaternary carbon centres,[1] particularly in view of their activity as enzyme inhibitors.[2] γ,δ-Unsaturated amino acids are also of great interest not only as naturally occurring amino acids,[3] but also as intermediates for the synthesis of complex amino acids and peptides.[4] While various methods are known for the synthesis of the α-alkylated amino acids, the sigmatropic rearrangement processes are well suited for the introduction of the unsaturated side chains.[5] The first synthesis of allylic amino acids by Claisen rearrangement was described in 1975 by Steglich.[6] The reaction proceeds *via* an oxazole intermediate and is especially suitable for the synthesis of α-alkylated allylic amino acids.[7] In 1982 the Ireland–Claisen rearrangement[8] of glycine allylic esters was studied by Bartlett and coworkers.[9] In the meantime this elegant methodology has found various applications in amino acid synthesis.[10]

Recently, we developed another variation of the ester enolate Claisen rearrangement proceeding *via* chelated allylic ester enolates.[11,12] This method is suitable for acyclic as well as cyclic allylic esters[13] and can also be applied to peptides.[14]

Herein the application of this methodology for the synthesis of sterically high demanding α-alkylated unsaturated amino acids **3** is described. Deprotonation of *N*-protected amino acid allylic esters like **1** with LDA at −78 °C and subsequent addition of metal salts (MX_n) presumably resulted in the formation of a chelated metal enolate **2** which underwent Claisen rearrangement upon warming to room temperature (Scheme 1).

In contrast to the corresponding lithium enolates, which do not show this rearrangement because they decompose during the warming, the chelate enolates are much more stable. Otherwise, the metal enolates are clearly superior to silylketene acetals, both in terms of their reactivity and selectivity.[11] The driving force for the accelerated rearrangement of the chelate enolates is probably the transformation of the high-energy ester enolate **2** into a chelate bridged, stabilised carboxylate **3**.

The influence of the protecting group Y, the side chain R, as well as the metal salt MX_n used for chelation of the ester enolate was investigated. The results are listed in Table 1. No dependence on the protecting group was observed for the rearrangement, making the method general for the synthesis of various *N*-protected amino acids and peptides.



Scheme 1

Overall, best results were obtained in the presence of zinc chloride as the chelating metal salt. Among all the other metal salts which can be employed[11] magnesium chloride gave comparable yields in many cases (entries 3 and 5). For the tryptophan derivative the yield was even higher (entries 9 and 10). This example also showed that this methodology is not restricted to amino acids with aliphatic or aromatic side chains, but can also be applied to functionalised amino acids like tryptophan or methionine (entry 11). Owing to the fixed enolate geometry, as a result of chelate formation, the rearrangement proceeded with a high degree of diastereoselectivity. This was confirmed by rearrangement of several *N*-trifluoroacetylated alanine allylic esters **4** (Scheme 2).†

Independent of the metal salt used for chelation, the rearrangement products *syn*-**5** were obtained in even higher diastereoselectivities (Table 2) in comparison to the results obtained with the corresponding glycine derivatives (R^1 = H).[11]

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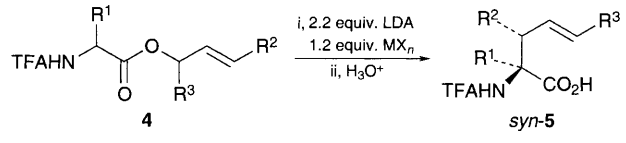
Table 1 Rearrangement of various amino acid methallyic esters **1**

Entry	Y	R	MX_n	Yield (%)[a]
1	Z	H	$ZnCl_2$	92
2	Boc	Me	$ZnCl_2$	81
3	Boc	Me	$MgCl_2$	73
4	Z	Et	$ZnCl_2$	87
5	Z	Et	$MgCl_2$	80
6	Z	Pr^i	$ZnCl_2$	39
7	Boc	Bu^i	$ZnCl_2$	62
8	Z	CH_2Ph	$ZnCl_2$	63
9	TFA	CH_2Ind[b]	$ZnCl_2$	34
10	TFA	CH_2Ind[b]	$MgCl_2$	79
11	Boc	$(CH_2)_2SMe$	$ZnCl_2$	80

[a] Isolated yield after esterification with diazomethane and flash chromatography. [b] Ind = 3-Indolyl.



Scheme 2

Table 2 Rearrangement of amino acid allylic esters **4**

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

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Footnote

† The trifluoroacetyl group was used for separation of the diastereoisomeric rearrangement products on a chiral GC column (Chira-Si-L-Val).

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