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The Asymmetric Ester Enolate Claisen Rearrangement as a Suitable Method for the Synthesis of Sterically Highly Demanding Amino Acids

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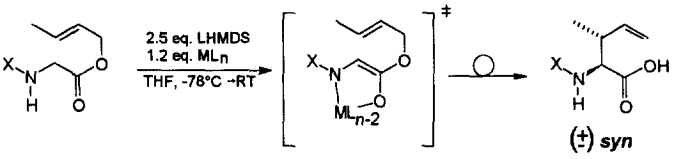
Abstract: Ester enolate Claisen rearrangement of highly substituted glycine allylic esters under the influence of chiral ligands gives rise to sterically demanding amino acids. The reaction yields amino acids with a β-quaternary carbon center in a highly diastereo- and enantioselective manner, and could be applied to a wide scope of different classes of amino acids. Copyright © 1996 Elsevier Science Ltd

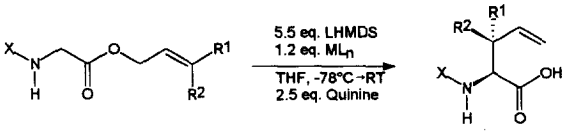
We recently developed a variation of the ester enolate Claisen rearrangement for the synthesis of γ,δ-unsaturated amino acids (Scheme 1).[1] This reaction, proceeding *via* chelate bridged allylic ester enolates, presents an alternative to the classical synthetical approaches by Steglich et al. *via* oxazole intermediates,[2] or *via* Ireland-Claisen rearrangement investigated by Bartlett and coworkers.[3]



Scheme 1: Chelate Enolate Claisen Rearrangement of Allylic Glycine Esters

This method is suitable for a wide array of substrates,[4] and can even be applied to peptides.[5] Besides the excellent yields and high diastereoselectivities found in general for this rearrangement, the intriguing idea of co-ordinating chiral ligands to the metal center of the intermediate chelate complex led us to the development of a novel stereochemical control of this reaction.[6,7] In this article, we describe our first investigations on the asymmetric chelate controlled ester enolate Claisen rearrangement to sterically highly demanding optically active amino acids.

Addition of 5.5 equiv. of LHMDS to a solution of 2.5 equiv. of quinine, a disubstituted allylic glycine ester and 1.2 equiv. of a metal salt (ML_n) in THF at -78°C results in the formation of a chiral chelated enolate. Upon warming to room temperature, this complex undergoes a Claisen rearrangement, giving rise to the γ,δ- unsaturated amino acid containing a β-quaternary carbon center[8] with high diastereo- and enantioselectivity (Scheme 2).



Scheme 2: Asymmetric Ester Enolate Claisen Rearrangement

This procedure proved to be suitable for a large scale of disubstituted glycine allylic esters, especially unsymmetrically substituted esters. Previous investigations on the possible substitution pattern of the substrates had shown, that *cis*-oriented substituents would lower the diastereoselectivity due to the steric overcrowding in the transition states involved[9]. Upon addition of quinine, Z-configured esters would not give any product expected for the rearrangement, indicating a strong steric interaction of substituent and ligand in the coordination sphere of the metal core. This could also be implied by the significant change in the simple diastereoselectivity under the influence of quinine (Table 1, entries 7 and 8). Considering these results, we chose the disubstituted allylic esters (entries 1-14) with small *cis*-oriented substituents as appropriate substrates.

The application of the rearrangement onto unsymmetrically substituted esters ($R^1 \neq R^2$) allowed us to investigate the diastereoselective generation of β-quaternary carbon centers of different classes of β-quaternary amino acids (entries 1-10). The rearrangement could also be applied to cyclic substrates (entries 11-14). Intensive screening of the rearrangement parameters gave the highest induction of chirality using a combination of $Al(OiPr)_3$ as metal salt, and the trifluoroacetyl- as (*N*)-protecting group X, the latter allowing a direct analysis of the product methyl esters by GC or HPLC.

Table 1. Asymmetric Ester Enolate Claisen Rearrangement of (*N*)-Trifluoracetyl-Glycine Allylic Esters

Entry	R^1	R^2	Yield[a] [%]	ds[b] [%]	ee[b] [%]
1	Me	Me	50	/	85
2	Et	Me	33	97	91
3	*t*Bu	Me	23	98	93
4	Cyclohexyl	Me	30	90	86
5	$(CH_2)_2$-CH=C$(CH_3)_2$	Me	51	98	85
6	Ph	Me	30	90	81
7	Naphthyl	Me	25	90	84[c]
8[d]	Naphthyl	Me	70	50	/
9	-CH_2Ph	Me	16	95	76
10	-CH_2OPh	Me	12	95	81
11	-$(CH_2)_4$-		60	/	78
12	-$(CH_2)_5$-		70	/	86
13	-$(CH_2)_6$-		45	/	82
14	-$(CH_2)_7$-		33	/	79

[a] Isolated yield after esterification with diazomethane [b] As determined by GC [c] As determined by HPLC [d] rearrangement without ligand

In summary, we have shown the asymmetric version of the ester enolate Claisen rearrangement to be a very short and attractive approach towards the synthesis of otherwise difficult to obtain γ,δ-unsaturated amino acids containing β-quaternary carbon centers. The stereochemical control of the rearrangement by addition of fully recyclable ligands of the cinchona alkaloid family allows the generation of two adjacent carbon centers in a highly enantio- and diastereoselective way.

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