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1,3-Asymmetric Induction in Enolate Alkylation Reactions of N-Protected γ-Amino Acid Derivatives

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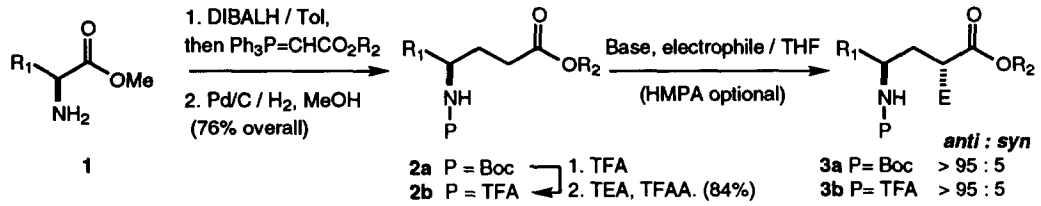
Abstract: *Dianions derived from N-TFA and N-Boc γ-amino acid esters and amides undergo highly stereoselective α-alkylation reactions. The roles of HMPA, of the cation, the electrophile, and of steric factors were studied.* Copyright © 1996 Elsevier Science Ltd

Unnatural amino acids have assumed an important role in the design and synthesis of pharmacologically relevant molecules[1]. In this regard, access to C-alkylated enantiomerically pure amino acid derivatives presents a challenge in stereocontrolled synthesis, particularly in acyclic systems. 1,2-Asymmetric induction in the alkylation of β-hydroxy[2] and β-amino[3] ester enolates has been well established in the literature. There are somewhat fewer examples involving 1,3- and 1,4-asymmetric induction in the C-allylation of γ- and δ-hydroxy carboxylic acid esters.[4,5] In the amino acid series, alkylations of aspartate derivatives are well documented,[6] while examples reporting γ-alkylations of glutamate derivatives present divergent stereoselectivities depending on the nature of the N-substituent and the ester groups.[7a,b] In previous work in our laboratory on the stereocontrolled reactions with dianions of aspartates and glutamates,[8a] we showed that hydroxylation and methylation[8b] of the glutamate dianion intermediate resulted in the *anti*-substituted isomer (1,3-asymmetric induction).[9] More recently, we have shown that the free radical α-allylation of β-,γ-, and ω-amino acid ester derivatives could be achieved with a remarkably high level of stereocontrol through H-bonded intermediates.[10] In connection with these and earlier studies, we have developed an alternate general method of alkylating dianions of γ-N-protected amino acid esters and amides resulting in unprecedented levels of 1,3-asymmetric induction in such systems (Scheme 1).

Scheme 1



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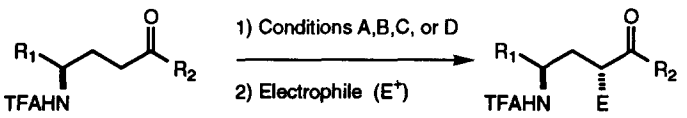
The required N-Boc or N-TFA γ-amino acid derivatives were prepared from the readily available α-amino acids by a simple homologation protocol as illustrated in Scheme 1.

Table 1 1,3-Asymmetric induction in the enolate alkylation of N-TFA γ-amino acid derivatives



Entry	R_1	R_2	E^+	Conditions[a]	Ratio[b]	Yield[d] (%)
1	Bn	OMe	allyl bromide	A	>95:5	73
2	Bn	OMe	benzyl bromide	A	>95:5	80
3	Bn	OMe	methyl iodide	A	>95:5	80
4	Bn	OMe	cinnamyl bromide	A	>95:5	90[e]
5	Bn	NMe_2	allyl bromide	B	>95:5	66[e]
6	iPr	NOMe(Me)	allyl bromide	C	>95:5	45
7	iPr	OMe	allyl bromide	A	>95:5	77
8	Me	OMe	allyl bromide	A	>95:5	85
9	Me	OTMSi ethyl	cinnamyl bromide	A	>95:5	63
10	iBu	OMe	allyl bromide	A	>95:5[c]	81
11	iBu	OMe	allyl bromide	D	>95:5	83

a. Conditions: A) 2.2 eq. LDA, 3 mol. eq. HMPA, THF, -78°C. B) 2.2 eq. LDA, -78°C -> 0°C -> -78°C, 1.1. eq. nBuLi. C) 2.2 eq. KHMDS, THF, -78°C. D) NaHMDS, HMPA, THF, -78°C. b. Ratios determined by ^1H NMR of the products after chromatographic purification; essentially one isomer was detected in all cases. c. Ratio verified by HPLC d. Yield of isolated product after chromatography. e. X-ray crystal structure

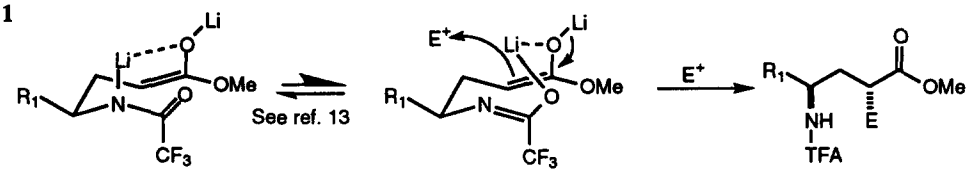
Table 1 shows the results of alkylation of enolates of methyl esters, TMSi ethyl esters, N,N-dimethyl amides and N-methyl-N-methoxy amides of N-trifluoroacetyl γ-amino acids. Excellent levels of 1,3-asymmetric induction were observed with four representative amino acids. The use of LDA and HMPA was preferred in the case of esters, while LDA/BuLi proved to be best for N,N-dimethylamide derivatives (entry 5). Optimal results with the N-methyl-N-methoxy amide derivative were achieved with KHMDS in THF (no HMPA), although the yield of isolated alkylated product was modest (Table 1, entry 6).

The absolute stereochemistry of the major products in entries 4 and 5 was determined by single crystal X-ray analysis. In all other cases the *anti* configuration is inferred from these results. Entries 1-4 demonstrate the diverse types and sizes of electrophiles that can be used resulting in excellent stereoselectivities. Entries 1,7,8, and 10 show that the the selectivity of this reaction is independent of the steric bulk of the terminal R_1 group. When the reaction is carried out on amides, the yields decrease significantly due to either the difficulty in generating the dianion as in the case of a N,N-dimethylamide (Table 1, entry 5), or to side-reactions as in the case of the Weinreb amide derivative (Table 1, entry 6).

Interestingly, the ratio of isomers did not change when the nature of the cation was varied in the ester examples (Table 1, entry 11). Moreover, addition of HMPA did not seem to affect the level of asymmetric induction as the ratio of isomers remained unchanged. The reactions were also faster compared to when LDA alone was used. Narasaka and coworkers[4] observed the same behavior in the alkylation of γ-hydroxy *t*-butyl esters in the presence of HMPA. They suggested a chelated transition state in which stereochemical bias was

possibly due to lithium-π-olefin coordination, based on an original observation by Posner *et al.*[11] However, the conclusions of Gu *et al* [7a] and North *et al* [7b] with regard to the nature of the transition states in the alkylations of dianions of N-Cbz and N-*p*-nitrobenzoyl glutamate esters are contradictory. Although it is difficult to propose a definitive transition state model to explain our results, it is clear that the stereochemical outcome of the alkylation reactions is not affected by the introduction of HMPA, by a change in the nature of the cation, or by the relative size of the electrophile (Table 1). The disruptive role of HMPA in the case of ordered Zimmerman-Traxler[12] type transition states may be minimized in our case by the presence of highly coordinated dianionic species involving the two charged sites as shown in Figure 1. The addition of HMPA may simply aid in loosening higher aggregates in THF, without disrupting the strong coordination in the individual dianionic species.

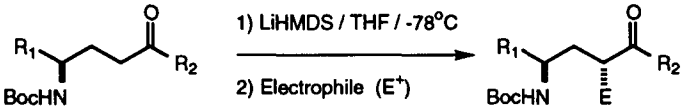
Figure 1



When attempting to hydrolyze the 2-C-allyl methyl ester in the N-TFA protected series (Table 1, entry 1) under basic conditions, lactamization occurred almost exclusively to give the corresponding 3-C-allyl pyrrolidinones. In contrast, the TMSi ester (Table 1, entry 9) can be readily cleaved (Bu_4NF / THF) without lactam formation.

In order to broaden the scope of these enolate alkylations, we extended the reactions to N-Boc derivatives with equally high stereoselectivities as shown in Table 2. In this series, LiHMDS was most effective in generating the dianion, although yields with these derivatives were somewhat less than with the corresponding N-TFA protected examples. The size of the R_1 group, and the inclusion of HMPA, did not affect the diastereomeric ratios.

Table 2 1,3-Asymmetric induction in α-alkylation of N-Boc γ-amino acid derivatives



Entry	R_1	R_2	E^+	Ratio[a]	Yield[b]
1	Me	OMe	allyl bromide	> 95:5	60
2	Me	OMe	cinnamyl bromide	> 95:5[c]	68
3	Me	OTMSi ethyl	cinnamyl bromide	> 95:5	71
4	iPr	OMe	allyl bromide	> 95:5	67
5	iPr	OMe	cinnamyl bromide	> 95:5	66

a. Ratio determined by ^1H NMR after chromatography b. Yield of isolated product c. Ratio verified by HPLC

Hydrolysis of the Boc group was easily achieved with 10 eq. TFA in CH_2Cl_2, or with 4 N HCl in dioxane, but as with the TFA series, hydrolysis of methyl esters under basic conditions also resulted in lactamization. This could be circumvented by working with the TMSi ethyl ester group which, on treatment with TBAF / THF, yields the free acid.

In summary, we have demonstrated the facile synthesis of enantiomerically pure α-alkyl-γ-amino acid chirons from readily available starting materials. This methodology is applicable to the synthesis of a wide variety of natural and unnatural products including peptides that incorporate γ-amino acids with a choice of α-functional groups. Results pertaining to the synthesis and conformations of such unnatural peptides will be communicated in due course.

Typical procedures:
1. Alkylation of γ-amino N-TFA protected ester derivatives: LDA (2.5 equiv) is transferred to a solution of substrate (1 equiv) dissolved in THF at -78°C (0.15 M total volume). After 45 min, HMPA (5 equiv) was added and the solution allowed to stir for 20 min. Electrophile (5 equiv) was then added (neat) and the reaction was stirred for 1 h and followed by TLC. Usual quench at -78°C (10% HCl) and flash column chromatography with 3:7 ethyl acetate : hexanes yielded the desired product.
2. Alkylation of γ-amino N-Boc protected ester derivatives: LiHMDS (2.6 equiv)(Aldrich; 1M in THF) is added to a solution of substrate in THF at -78°C (0.15 M total volume). After 45 min., electrophile (5 equiv) was added (neat) and reaction was stirred at -78°C for 1.5 h. Usual quench at -78°C (10% HCl) and flash column chromatography with a 3:7 ethyl acetate : hexanes yielded the desired product.
3. Alkylation of γ-amino N-Boc protected N,N-dimethyl amide derivatives: Follows procedure **1** until 30 min. have elapsed after adding base. At this point, the reaction was warmed to 0°C for 20 min. and then cooled to -78°C before adding 1.1 equiv of nBuLi. After 30 min., the warming and cooling procedure was repeated. 30 min. later the electrophile (5 equiv) was added, and worked up as in procedure **1**.
4. Alkylation of γ-amino N-Boc protected N-methyl-N-methoxy amide derivatives: Same as procedure **2** except for the use of KHMDS (1.5M in hexanes).

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