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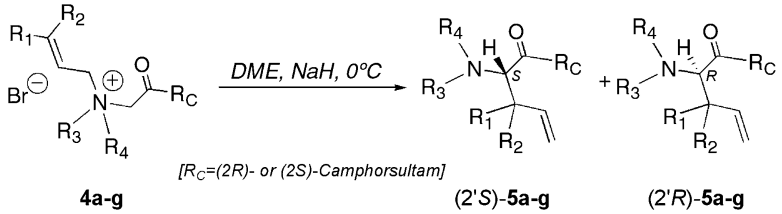

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Asymmetric [2,3]-Rearrangement of Glycine-Derived Allyl Ammonium Ylids

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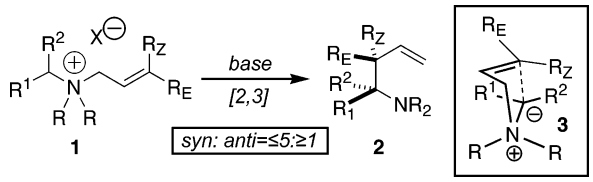
Rearrangement processes are very effective tools for organic synthesis because of the inherently high efficiency of the reactions; furthermore, these transformations often proceed with high levels of stereocontrol. Since their discovery in the late 1960s, the [2,3]-rearrangement reactions of allylic ammonium salts have received much attention:[1] the original reports of Baldwin concerning sulfonium ylids were extrapolated by Ollis et al., the process revolving around the preparation of *N*-allyl-*N*,*N*-dialkylammonium salts **1**, which react at ambient temperatures to give homoallyamines **2**, via the intermediacy of ylids **3** (Scheme 1). Where suitable electron-stabilizing substituents (R^1) are present (especially R^1 = acyl), the ylids may be isolated and characterized[2] and have also been prepared in situ by reaction of allylamines with diazo compounds.[3] Although these rearrangements frequently proceed in good yield, the stereoselectivity of the reactions is often mediocre, especially by modern standards.[1a,4]

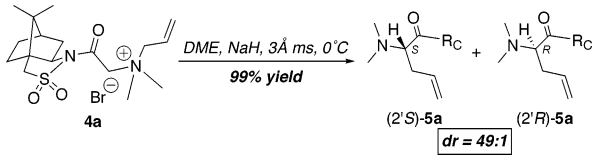
In contrast, the rearrangement of *cyclic* ylids is well-known to be a highly stereoselective process, and we have described the use of *N*-methyltetrahydropyridine-derived ester-stabilized ylids (a reaction previously described to be unfeasible[5]) to prepare a range of cis-configured proline analogues.[6] We have recently turned our attention to the design and execution of stereoselective *acyclic* ammonium ylid rearrangements, with a specific focus on obtaining an enantioselective method. Given the potent biological properties of allyl glycines,[7] any such methodology that would allow a highly stereoselective rearrangement of glycine-derived acyclic ammonium ylids (**2**, $R^1 = CO_2R$) would represent a significant advancement. We here report the preliminary results of our investigations into the asymmetric rearrangements of chiral derivatives of *N*-allyl glycine salts, which reveal that allyl glycine derivatives may indeed be prepared via [2,3]-rearrangement, with excellent enantiocontrol.

Though a modern paradigm, the use of chiral catalysis in this type of ammonium ylid rearrangement is restricted for a number of reasons, the most important being the fact that the nitrogen atom must be quaternized in these ylids, thereby precluding any ligation from the nitrogen lone pair to a chiral catalyst. This limitation to the development of chiral catalysis has recently been tackled by the use of Lewis acid complexation to generate ammonium ylids in situ,[8] but the methodology is far from mature. For these reasons, the use of a chiral auxiliary is indicated to be an appropriate synthetic choice. We first chose to examine the reactions of *N*-allyl glycine salts bearing a pendant Oppolzer camphorsultam auxiliary, and we were gratified to observe that the [2,3]-rearrangement of *N*′,*N*′,*N*′-allyldimethyl glycinoyl (2*R*)-sultam **4a** proceeded in high yield at 0 °C. Moreover, allyl glycine derivative **5a** was obtained with a high level of diastereoselectivity, in favor of the (2′*S*)-isomer[9] (dr = 49:1) (Scheme 2).

Scheme 1. [2,3]-Rearrangement of Acyclic Allyl Ammonium Ylids: Mediocre Stereoselectivity



Scheme 2. [2,3]-Rearrangement of Allyldimethyl Ammonium Sultam Ylid: A Highly Diastereoselective Reaction



The reaction proved to be a general one, with the rearrangements of salts **4b**−**g** all proceeding smoothly at 0 °C. Once again, high levels of diastereoselectivity were observed in the process, giving a range of allyl glycine derivatives (Table 1) with excellent diastereocontrol. Where terminal substitution of the allyl group was present (Table 1, entries 5 and 8), syn:anti ratios were high: syn-configured 3-substituted allyl glycines were obtained as virtually the only observable products. These allyl glycines are not easily accessible by other routes, and the stereoselectivity of the [2,3]-rearrangement is vastly improved compared to achiral reactions (vide supra).

Several other features are also noteworthy. First, the reactions are predictable in terms of asymmetric control: (2*R*)-configured auxiliary delivers predominantly (*2′S*)-configured products, while the use of the (2*S*)-auxiliary gives (*2′R*)-products. Second, allyl migration is favored over benzyl migration (Stevens [1,2]-rearrangement, see entry 4). Finally, the yields of rearrangement only suffered when the allyl subunit was α-branched (as with cyclohex-2-enyl salt **4h**, Scheme 3). In the latter reaction, a complex mixture of products was obtained, which complicated the stereochemical assignments. Thus, all four possible diastereoisomers were observed (for the first time in these reactions) (anti:syn = 14:86), but the enantioselectivity of this rearrangement was virtually nonexistent. Given that the yield of this rearrangements was also <50%, it may be the case that the presence of asymmetry adjacent to the ammonium group is now exerting an influence and that there is a difference in the rate of rearrangement of the N-diastereoisomers in this more sterically demanding process.

It seems that the juxtaposition of the asymmetric auxiliary and the nucleophilic carbon atom is not absolutely necessary for stereoselective reaction. Thus, an isomeric ylid (**6**) in which the chiral auxiliary was attached to the allylic substituent (rather than the glycine moiety) also underwent rearrangement in excellent yield and with high stereoselectivity, to give β-ethenyl aspartate derivative

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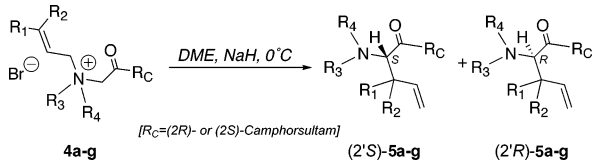
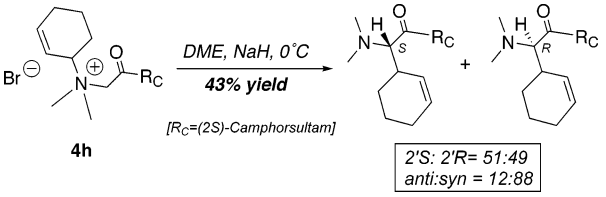
Table 1. [2,3]-Rearrangement of Allyldimethyl Ammonium Sultam Ylids (**4a**−**g**): A Highly Stereoselective Reaction



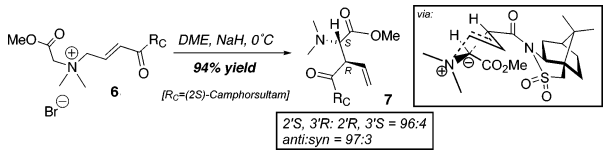
entry	salt	R^1	R^2	R^3	R^4	yield **5** (%)	anti:syn	2′*R*:2′*S*
1	**4a**[b]	H	H	Me	Me	99		2:98[a]
2	**4b**[c,d]	H	H	Me	allyl	99		97:3[e]
3	**4c**[c,d]	H	H	allyl	allyl	86		97:3[e]
4	**4d**[d]	H	H	Bn	allyl	80		>99:1[e]
5	**4e**[d]	Me	H	Me	Me	86	>99:1	96:4[a]
7	**4f**[d]	Me	Me	Me	Me	70		97:3[a]
8	**4g**[d]	MeO_2C	H	Me	Me	64[f]	>99:1	>99:1[a]

[a] Absolute stereochemistry was assigned using X-ray crystallography. [b] R_C = (2*R*)-camphorsultam. [c] Iodide salt used. [d] R_C = (2*S*)-camphorsultam. [e] Stereochemistry assigned by analogy and/or chemical correlation. [f] Trace amount of [1,2]-product also observed.

Scheme 3 . [2,3]-Rearrangement of 2-Cycloxenyl Ylid **4h**



Scheme 4 . [2,3]-Rearrangement of 4-(Aminocrotonoyl)sultam Ylid **6**: A Highly Stereoselective Reaction

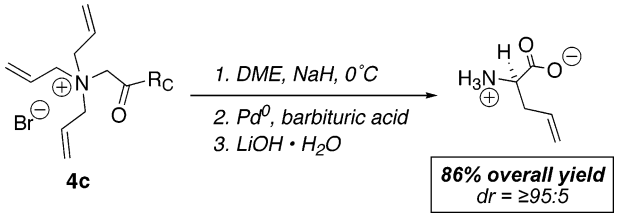


7 (Scheme 4; the absolute stereochemistry of **7** was determined by X-ray crystallography).

Finally, we have used this reaction to accomplish a new and efficient asymmetric synthesis of (*R*)-allyl glycine. Thus, salt **4c** underwent rearrangement[10] (Table 1, entry 3, dr = 32:1), deallylation,[11] and saponification,[12] yielding (*R*)-(+)-allylglycine ($[\alpha]_D^{20}$ +32;[13] cf. lit. 37.2[14a] and 33.5[14b]) in high overall yield (Scheme 5). This process represents an efficient synthesis of this important nonproteinogenic amino acid and exemplifies the inherent utility of these [2,3]-rearrangements.

In summary, we have reported the first asymmetric [2,3]-sigmatropic rearrangements of simple allylic ammonium ylids. A range of substituted compounds have been used to generate a collection of structurally diverse, densely functionalized allyl glycine derivatives in generally good yields and with high diastereo- and enantioselectivity. We have exploited this methodology to execute a highly efficient synthesis of (*R*)-allylglycine. Given the importance

Scheme 5 . Efficient Enantioselective Synthesis of (*R*)-Allyl Glycine via Asymmetric [2,3]-Rearrangement



of these amino acid derivatives, we believe that this protocol will find widespread use in the synthesis of biologically significant compounds.

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Note Added after ASAP Publication. Due to a production error, the numbers in the first column of Table 1 were incorrect in the version published ASAP on December 21, 2004. The table was corrected for final print and Web publication, and the correct version was posted on January 5, 2005.

Supporting Information Available: X-ray structures, experimental procedures, and data for key compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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