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Efficient synthesis of optically active α-quaternary amino acids by highly diastereoselective [2,3]-rearrangement of allylic ammonium ylides†

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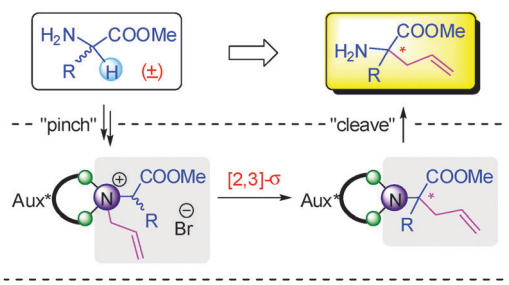
A pincer-like chiral auxiliary strategy for synthesizing various optically active α,α-disubstituted amino acids in high yields with excellent enantioselectivities is described.

α,α-Disubstituted α-amino acids bearing a quaternary carbon stereocenter at the α-position are an intriguing class of non-natural amino acids of particular interest in bioorganic and medicinal chemistry. They are often incorporated into peptides in place of the natural amino acids for conformational constraint and structural stability studies to understand the remarkable protein flexibility and bioactivity changes.[1] In addition, α,α-disubstituted α-amino acids constitute a key structural motif in natural products and bioactive compounds.[2] Due to their great importance, numerous attempts have been made by synthetic organic chemists in the past decades to develop efficient methodologies for the synthesis of these valuable, optically active compounds.[3–5] Among the wide range of strategies employed, asymmetric rearrangement processes, despite being comparatively less well documented,[3j,5] have proven to be one of the most powerful approaches in terms of excellent intrinsic reaction efficiency and stereoselectivity control. However, these rearrangement methods have frequently suffered from limited reaction scopes and many requisite substrates required multistep syntheses.

[2,3]-rearrangement of allylic ammonium ylids is an elegant method to afford homoallylic tertiary amines.[6] To our knowledge, the use of this protocol for asymmetric synthesis of α-amino acids has only been rarely reported. In 2005,[7] a significant advancement was achieved by Sweeney and co-workers with the successful preparation of enantioenriched allyl glycine derivatives *via* highly diastereoselective [2,3]-rearrangement of *N*,*N*,*N*-allyldimethyl glycine salts bearing a pendant Oppolzer camphorsultam auxiliary. However, the rather unique substrate specificity as well as the difficulties in the removal and rupture of *N*,*N*-dimethyl groups severely hamper it's practical application. Besides, the use of a bulky auxiliary simultaneously retarded the formation of ammonium salts (it generally takes more than 72 h with allyl iodide). In another example,[8] Somfai and co-workers cleverly developed a BBr_3/sulfonamide-mediated asymmetric [2,3]-rearrangement, however, the prospect of chiral catalysis in this type of rearrangement reaction remains elusive due to the lack of coordination between a quaternary nitrogen and a chiral catalyst. Moreover, with respect to stereoselective [2,3]-rearrangement of allylic ammonium ylids for constructing more challenging α-quaternary amino acids, there have been no reports in the literature. Herein, we[9] present a novel chiral auxiliary approach that addresses these issues, giving access to various functionalized α,α-disubstituted α-amino acids in a highly stereoselective manner.

As depicted in Scheme 1, we envisioned an unprecedented chiral auxiliary strategy, in which a suitably functionalized chiral auxiliary unit is attached to the substrate amine moiety in a pincer-like manner. Notably, this strategy would offer several significant advantages. We can expect that the incorporation of a chiral auxiliary more close to the rearrangement center would result in advanced reaction stereoselectivity. We also reasoned that this design, with tertiary amine in a ring structure, should potentially reduce the difficulties in forming the quaternary ammonium salt.[10] Most importantly, the key design element is that many commercially available, unprotected, racemic α-amino acid esters could be directly used as the starting substrates for further structural elaboration.

To carry out the idea, we thought of binding an axially chiral C_2-symmetric 2,2′-dimethyl-1,1′-binaphthyl bridge, as the auxiliary, to the amine nitrogen atom. As shown in Scheme 2, we first conducted reactions with a series of commercially available L/racemic α-amino acid methyl ester



Scheme 1 "*Pinch to work*" auxiliary strategy for constructing α-quaternary amino acids from unprotected racemic α-amino acid esters.

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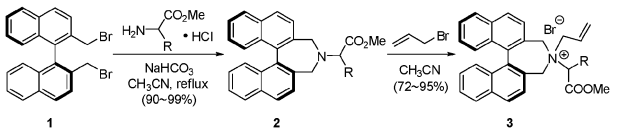


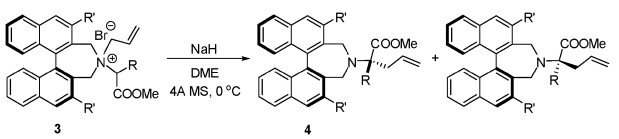
Scheme 2 Synthesis of quaternary ammonium salts, **3**.

hydrochloride salts with (*R*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl (**1**). After screening several reaction conditions, we found that tertiary amines, **2**, could be prepared in over 90% yields using $NaHCO_3$ as the base in refluxing CH_3CN. Subsequently, these tertiary amines were subjected to reaction with allylbromide. As expected, the corresponding quaternary ammonium salts, **3**, were formed in good to excellent yields under very mild conditions using CH_3CN as the solvent at room temperature.

With quaternary ammonium salts **3** in hand, we chose several to evaluate their [2,3]-sigmatropic rearrangement for optimal conditions (see ESI†). After careful studies on solvent, temperature and base, we found that the reaction proceeded smoothly in the presence of 1.5 equiv. of NaH in DME at 0 °C. When **3b** (R = Me) was employed, the desired α-quaternary amino acid product, **4b**, was obtained in 92% yield with 85% de (Table 1, entry 3). Notably, when the sterically more demanding substrate **3c** (R = Bn), derived from phenylalanine, was examined under the same conditions, we were pleased to find that both excellent yield (92%) and diastereoselectivity (98% de) were achieved (entry 5).

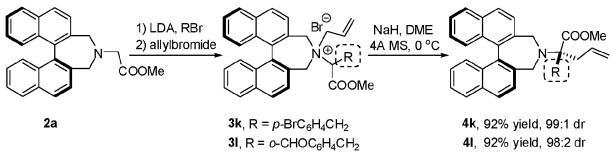
With these promising results, we then turned our attention to investigate the substrate generality of the reaction. A wide range of natural α-amino acid derived quaternary ammonium salts bearing different R substituents with diverse steric and electronic properties were examined. As shown in Table 1, the reaction was found to be general, and it appears that α-allylation of various commercial available α-amino acids, including leucine,

Table 1 Asymmetric [2,3]-rearrangement of allylic ammonium salts derived from different natural amino acids[a]



Entry	3	R′	R	4	Yield[b] (%)	de[c]
1[d]	**3a**	H	H	**4a**	76	76[f]
2[d]	**3a′**	Ph	H	**4a′**	68	96
3	**3b**	H	Me	**4b**	92	85
4	**3b′**	Ph	Me	**4b′**	90	96
5	**3c**	H	Bn	**4c**	92	98
6	**3d**	H	$CH_2CH(CH_3)_2$	**4d**	95	>98
7	**3e**	H	CH_2CH_2Ph	**4e**	97	>98
8	**3f**	H	$CH_2CH_2SCH_3$	**4f**	88	>98
9	**3g**	H	CH_2OMOM	**4g**	78	98
10[e]	**3h**	H	4-$OHC_6H_4CH_2$	**4h**	85	96
11[e]	**3i**	H	1H-indol-3-methylene	**4i**	91	>98
12	**3j**	H	Ph	**4j**	92	>98

[a] Unless otherwise mentioned, all reactions were performed on 0.1 mmol scale with 1.5 equiv. of NaH and 100 mg of 4 Å molecular sieves in 5 mL of DME at 0 °C. [b] Yield of isolated product. [c] Determined by ^1H NMR and LC–MS. [d] With 1 equiv. of NaH. [e] With 2.5 equiv. of NaH. [f] Product **4a** with >95% de was obtained after a single crystallization of its HBr salt from CH_2Cl_2/MTBE.



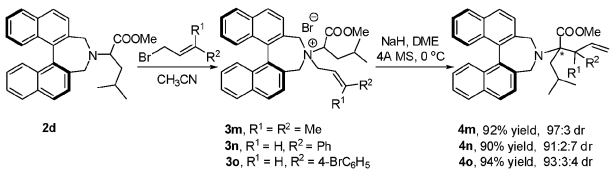
Scheme 3 Expanding the reaction scope with a combined strategy.

homophenylalanine, methionine, serine, tyrosine, tryptophan and phenylglycine, were all successfully carried out, giving the corresponding products in good yields and with excellent diastereoselectivities (>95% de) (entries 5–8, 10–15). It is noteworthy that unprotected phenolic OH in the tyrosine moiety and indole NH in the tryptophan moiety are well tolerated in the current transformation. In these cases, the use of 2.5 equiv. of NaH was required to ensure good yields. Gratifyingly, for the substrates bearing less sterically hindered R, such as that derived from alanine (**3b**, R = Me), the de could be substantially improved by using modified ammonium salt **3b′**, in which two phenyl substituents were introduced at the 3 and 3′ positions of the chiral binaphthyl auxiliary. This protocol was shown to be efficient for the synthesis of α-monosubstituted amino acids, such as allylglycine, as well (entry 2). The absolute stereochemistry of the major diastereomer was determined as indicated by the X-ray crystallographic analysis[11] of **4a** (entry 1) and **4k** (in Scheme 3).

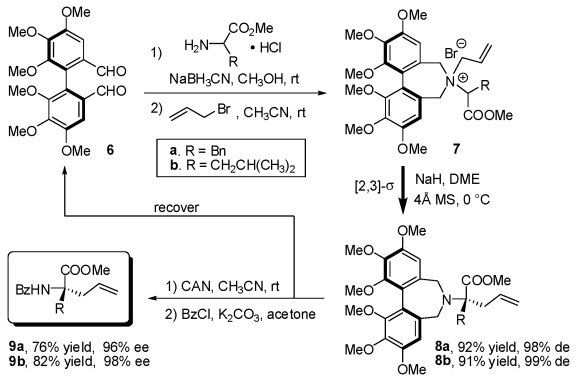
The scope of the reaction was further explored to synthesize more challenging and structurally exceptional α-quaternary amino acids. As illustrated in Scheme 3, a combined strategy was successfully employed to convert binaphthyl amine **2a** to diastereomerically enriched α,α-disubstituted products by sequential α-alkylation, allylation and [2,3]-rearrangement. Since the ammonium salt (**3**) unavoidably undergoes α-racemization upon treatment with NaH, the stereochemical information gained from the first alkylation has no impact on the final reaction stereoselectivity. Accordingly, in the examples of **4k** and **4l**, stereogenic quaternary carbon centers with very high levels of stereocontrol were efficiently constructed *via* rearrangement processes. It is also notable that tolerated functionality, such as bromine or aldehyde, would be useful for further elaboration.

Moreover, the advantage of the present approach was further demonstrated by the application to the synthesis of otherwise-more-difficult-to-access α-quaternary α-amino acids. As shown in Scheme 4, three differently substituted allyl ammonium salts (**3m**, **3n** and **3o**) underwent [2,3]-rearrangement smoothly under standard conditions to give α-quaternary leucine derivatives in good yields and with high diastereoselectivities. Thus, the reaction substrate scope is largely expanded, indicating the great compatibility and efficiency of the method.

Removal of the chiral binaphthyl auxiliary can be accomplished under hydrogenation conditions (H_2, Pd/C) to afford



Scheme 4 Expanding the reaction scope with other allyl reagents.



Scheme 5 An alternative auxiliary approach to highly optically active α-allyl α-quaternary amino acids.

the corresponding quaternary carbon-containing α-amino acids in high yields without loss of the optical purities.[12]

Despite that the allylic double bond can be pre-elaborated or derivatized before hydrogenation,[13] we realized that it is necessary to identify an alternative, equally effective chiral auxiliary that could be easily removed while preserving the alkene functionality in the molecule. For this purpose, we investigated the use a of more electron-rich, axially chiral dial **6**[14] (98% ee, Scheme 5). Similarly, we found that the allyl ammonium salts represented by **7a** and **7b**, formed from phenylalanine and leucine, were capable of efficient [2,3]-rearrangement under the above same conditions, furnishing products **8a** and **8b** in high yields as well as excellent diastereoselectivities. Significantly, the auxiliary was cleanly removed by oxidative debenzylation with cerium(IV) ammonium nitrate (CAN), and highly enantiomerically enriched (*R*)-allyl phenylalanine (**9a**) and (*S*)-allyl leucine (**9b**) were satisfactorily accessed.

In summary, we have developed an unprecedented, unique chiral auxiliary strategy to access various highly optically active α,α-disubstituted quaternary amino acids, including structurally exceptional and functionalized ones through an efficient, stereospecific [2,3]-sigmatropic rearrangement process under very simple and mild conditions. A particularly remarkable design element is that many commercially available unprotected racemic amino acid esters could be directly used as the starting substrates for α-allylation with great stereocontrol. Given the broad scope and generality, and high efficiency for creation of all-carbon quaternary stereocenters, this method is expected to be of great interest and to have significant applications in organic synthesis.

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11 CCDC 865414 (**4a**.HBr) and 865415 (**4k**) contain the supplementary crystallographic data.

12 See ESI† for details. It is worth noting that the auxiliary derivative (2,2′-dimethyl-1,1′-binapthene) can be recovered in over 90% yield, and reused after bromination with NBS.

13 For example, double bond elaboration of product **4d** *via* Heck reaction with either electron-rich or electron-poor aryl iodide was successfully performed, see ESI† for details.

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