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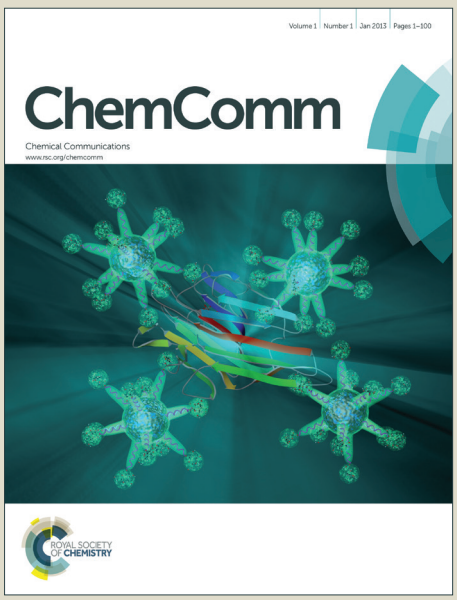





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# Double axial chirality promoted asymmetric [2,3] Stevens rearrangement of *N*-cinnamyl L-alanine amide-derived ammonium ylides

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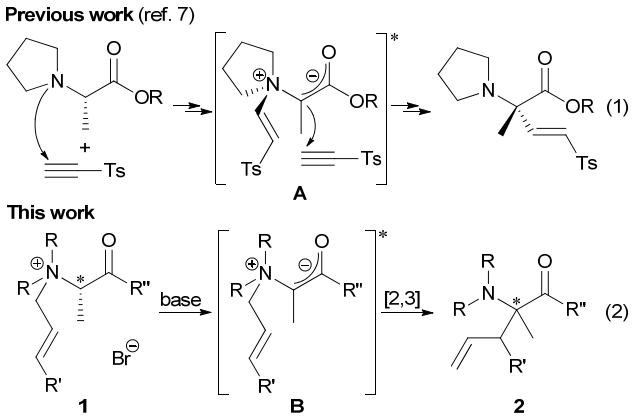
**The base-induced asymmetric [2,3] Stevens rearrangement of *N*-cinnamyl tetraalkylammonium ylides derived from L-alanine amides proceeds via a double axially chiral intermediate to afford the corresponding α-substituted alanine derivatives with high enantio- and diastereoselectivities.**

The base-induced [2,3] Stevens rearrangement of *N*-allylic tetraalkylammonium ylides is a useful transformation for organic synthesis because it converts a readily accessible C–N bond into a new C–C bond. The rearrangement has been applied to the synthesis of unnatural amino acid derivatives because it proceeds via a concerted symmetry-allowed mechanism to yield the corresponding products with high stereoselectivities.[1] However, the asymmetric version of the rearrangement remains limited. The asymmetric [2,3] Stevens rearrangement has been achieved using stoichiometric sources of chirality, such as a chiral auxiliary[2] or N-to-C chirality transmission of *N*-chiral tetraalkylammonium ylides.[3] In a similar protocol, chiral Lewis acid-mediated [2,3] sigmatropic rearrangement of *N*-allylic tertiary amines has also been reported.[4] These methods require removal of the chiral auxiliary after the reaction or preparation of enantiomerically enriched *N*-chiral tetraalkylammonium salts as substrates. This disadvantage limits the scope of substrates and products. Therefore, the development of other methods for the asymmetric rearrangement is needed. Very recently, a chiral isothiourea-catalyzed asymmetric [2,3] rearrangement was reported by Smith's group[5] to solve the limitation. Herein, we report the asymmetric [2,3] Stevens rearrangement via memory of chirality as another protocol for the use of α-amino acid as the chirality source.[6]

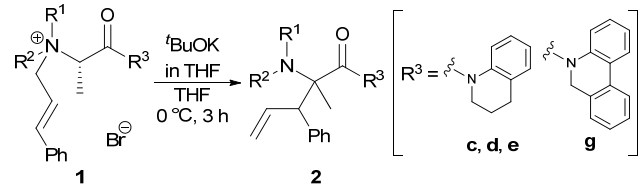
Recently, we reported the asymmetric α-2-tosylethenylation of *N*,*N*-dialkyl-L-amino acid esters via formation of non-racemic intermediate **A**, which arises from the axial chirality between tetraalkylammonium cation and α-carbon to carbonyl (Scheme 1, eq. 1).[7] This result encouraged us to pursue asymmetric Stevens rearrangements, which proceed via formation of the corresponding intermediate **B**, for the structural design of tetraalkylammonium salt **1** (eq. 2). Therefore, we selected an *N*-cinnamyl substituent as a migrating group and prepared *N*-cinnamyl pyrrolidinyl-L-alanine cyclohexyl ester-derived ammonium salt **1a** because it has a structure similar to the *N*-tosylethenyl substituent in **A** (three-atom chain with an aromatic moiety). The base-induced [2,3] Stevens rearrangement of **1a** with 1.2 equivalents of potassium *tert*-butoxide in THF at 0 °C afforded the corresponding product **2a** in 51% yield as a single diastereomer. However, no asymmetric induction was observed (Table 1, entry 1). To take advantage of the asymmetric induction, we next attempted the rearrangement of pyrrolidine amide derivative **1b** because the amide moiety was previously used for asymmetric α-alkylation via memory of chirality[8] or chiral Lewis acid-mediated asymmetric [2,3] sigmatropic rearrangement.[4] However, the reaction also resulted in almost no selectivity (Entry 2). We thought that asymmetric induction would be obtained by introducing additional axial chirality from the amide moiety. Therefore, we decided to use 1,2,3,4-tetrahydroquinoline amide as an analogue of 1-naphthyl carbonyl. This structure was used for asymmetric α-alkylation via memory of chirality.[9] We prepared **1c** and performed the reaction under the same conditions. The desired product **2c** was obtained in 74% yield with 42% ee (Entry 3) as judged by chiral HPLC. The asymmetric induction was improved to 71% ee using piperidinyl derivative **1d** (Entry 4).[10] However, the use of *N*,*N*-dimethyl




**Scheme 1** Planning of asymmetric [2,3] Stevens rearrangement via memory of chirality (eq. 2) based on our previous work (eq. 1).

derivative **1e** resulted in lower enantioselectivity (Entry 5, 30% ee). These results may indicate that the asymmetric induction was improved by the double axial chirality between the N–C(α) bond and the CO–N bond. To investigate the additional structural requirements, we prepared amides **1f**–**1k** and carried out their reactions. Use of indoline amide **1f** as an analogue for **1d** resulted in no asymmetric induction (Entry 6, 4% ee). The rearrangement of phenanthridine amide **1g**, which is known as a readily removable amide,[11] afforded **2g** in a similar yield with improved enantioselectivity (Entry 7, 81% ee). The reaction of *N*-methylaniline amide **1h** as an acyclic aromatic amide did not afford desired product **2h** due to undesirable [1,2] Stevens rearrangement at the piperidinyl ring (Entry 8).[12] The use of a bulky tertiary amide, such as *N*-diphenylmethyl-*N*-methyl amide **1i**, did not result in asymmetric induction (Entry 9). Interestingly, although the rearrangement of Weinreb amide **1j** did not exhibit any enantioselectivity (Entry 10), *O*-*tert*-butyl analogue **1k** yielded **2k** in 26% yield with 64% ee (Entry 11). We tested analogous bases and other solvents, such as solid potassium *tert*-butoxide, sodium *tert*-butoxide in THF, or potassium bis(trimethylsilyl)amide (KHMDS), dichloromethane, *tert*-butyl methyl ether, acetonitrile, DMF, DMSO, and *tert*-butanol did not observe improvements.[13]

**Table 1** Effects of *N*,*N*-substituents and amide moieties.



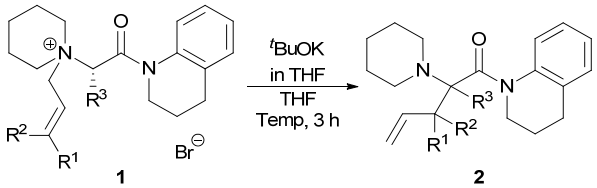

**1** **2**

| Entry | $R^1$ | $R^2$ | $R^3$ | | Yield (%)[a,b] | Ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | $-(CH_2)_4-$ | | O$^c$Hex | **a** | 51 | 0 |
| 2 | $-(CH_2)_4-$ | | pyrrolidin-1-yl | **b** | 52 | < 7[e] |
| 3 | $-(CH_2)_4-$ | | 3,4-dihydroquinolin-1(2*H*)-yl | **c** | 74 | 42 |
| 4 | $-(CH_2)_5-$ | | 3,4-dihydroquinolin-1(2*H*)-yl | **d** | 71 | 71 |
| 5 | Me | Me | 3,4-dihydroquinolin-1(2*H*)-yl | **e** | 60 | 30 |
| 6 | $-(CH_2)_5-$ | | indolin-1-yl | **f** | 56 | 4 |
| 7 | $-(CH_2)_5-$ | | 5,6-dihydrophenanthridin-5-yl | **g** | 65 | 81 |
| 8 | $-(CH_2)_5-$ | | N(Me)Ph | **h** | 0[d] | – |
| 9 | $-(CH_2)_5-$ | | N(Me)CHPh$_2$ | **i** | 58 | < 7[e] |
| 10 | $-(CH_2)_5-$ | | N(Me)OMe | **j** | 31 | < 2[e] |
| 11 | $-(CH_2)_5-$ | | N(Me)O$^t$Bu | **k** | 26 | 64 |

[a] Isolated yield. [b] Obtained as a single diastereomer. [c] Determined by HPLC analysis using a chiral column. [d] [1,2] Stevens rearrangement at the piperidinyl ring afforded **9** (see, ref. 12). [e] Not baseline separation in HPLC.

To define the scope and limitations of the present asymmetric [2,3] Stevens rearrangement, we prepared various types of *N*-allylic-L-amino acid amide-derived ammonium salts **1l**–**1s** and performed their rearrangements (Table 2). The reaction of *para*-substituted-cinnamyl derivatives **1l**–**1n** resulted in the corresponding [2,3] rearrangement product **2l**–**2n** at the same levels of the enantio-enriched form (Entries 1–3). Interestingly, the rearrangement of *Z*-cinnamyl derivative **1o** (*E*/*Z* = 15/85) created **2d** with 16% ee (Entry 4). The same diastereomer derived from *E*-cinnamyl derivative **1d** (Table 1, entry 4) was obtained as a major product (ca. 9/1 dr). The use of *N*-(hex-2-en-1-yl)- or *N*-allyl derivatives **1p** or **1q** resulted in no asymmetric induction (Entries 5 and 6). The ee of **2d** improved (up to 91% ee) when the rearrangement was performed at a lower temperature (Entries 7–11, –40 to –92 °C). The L-phenylalanine and leucine derivatives **1r** and **1s**, did not afford the corresponding [2,3] Stevens rearrangement products **2** (Entries 12–13) due to the same undesirable [1,2] Stevens rearrangement at the piperidinyl ring in the reaction with **1h**, which is depicted in Table 1.

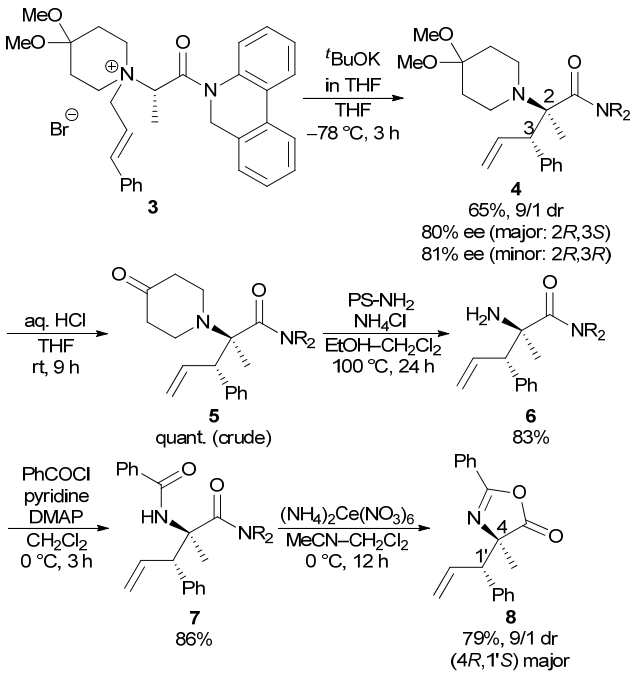
**Table 2** Effects of migrating group and temperature.




**1** **2**

| Entry | $R^1$ | $R^2$ | $R^3$ | | Temp (°C) | Yield (%)[a,b] | Ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | *p*-Cl-Ph | H | Me | **l** | 0 | 47 | 71 |
| 2 | *p*-Br-Ph | H | Me | **m** | 0 | 45 | 70 |
| 3 | *p*-Me-Ph | H | Me | **n** | 0 | 58 | 62 |
| 4[d] | H | Ph | Me | **o** | 0 | 54[e] | 16 |
| 5 | $^n$Pr | H | Me | **p** | 0 | 76 | 5 |
| 6 | H | H | Me | **q** | 0 | 79 | 3 |
| 7 | Ph | H | Me | **d** | –40 | 69 | 81 |
| 8 | Ph | H | Me | **d** | –78 | 75 | 89 |
| 9 | Ph | H | Me | **d** | –92 | 62 | 91 |
| 10 | *p*-Br-Ph | H | Me | **m** | –78 | 36 | 86 |
| 11 | *p*-Me-Ph | H | Me | **n** | –78 | 64 | 85 |
| 12 | Ph | H | $CH_2Ph$ | **r** | 0 | 0 | – |
| 13 | Ph | H | $^i$Bu | **s** | 0 | 0 | – |

[a] Isolated yield. [b] Unless otherwise noted, product **2** was obtained as a single diastereomer. [c] Determined by HPLC analysis using a chiral column. [d] *E*/*Z* = 15/85. [e] The same diastereomer with the reaction of **1d** (**2d**: Table 1, Entry 4) was obtained as a major product (9/1 dr).




**Scheme 2** Removal of *N*,*N*-substituent and amide moiety of **4**.

Finally, the removal of the *N*,*N*-substituent and amide moiety from the product was examined (Scheme 2). The rearrangement of 4,4-dimethoxypiperidinyl ammonium salt **3** afforded **4** in 65% yield with 9/1 dr. The enantioselectivities of the major and minor diastereomers were 80% ee and 81% ee, respectively. The piperidinyl ring, as in **4**, was removed after acid hydrolysis to aminoketone **5**. Treatment of **5** with aminomethylated polystyrene resin[14] afforded the corresponding

primary amine **6** in 83% overall yield. After *N*-benzoylation to **7** in 86% yield, the amide moiety was removed under mild oxidative conditions[11] to afford corresponding oxazolone **8** in 79% yield. The absolute configuration of the major diastereomer of **8** was determined to be (4*R*,1'*S*) by comparison of the $^1$H NMR, the value of the optical rotation, and HPLC retention time with that reported for **8**. Therefore, the absolute configuration of major diastereomer of **4** was determined to be (2*R*,3*S*).[15] The relative stereochemistry of **4** was confirmed by a single-crystal X-ray analysis of *rac*-**4** prepared from *rac*-**3**.

To discuss about the mechanism of this asymmetric induction, a single-crystal X-ray analysis of hexafluorophosphate salt of **1d** (**1d-PF$_6$**) was performed (Figure 1). The analysis showed the conformation of cinnamyl and 1,2,3,4-tetrahydroquinoline amide moieties. Thereby, we proposed that the rearrangement would proceed on the *Re*-face through the *exo* transition state (***exo* TS**) leading to the (2*R*,3*S*) isomer. The formation of *endo* transition state (***endo* TS**) leading to the (2*R*,3*R*) isomer would be inhibited by steric repulsion with the amide moiety,[16] which CO–N bond is not planar by the axial chirality.

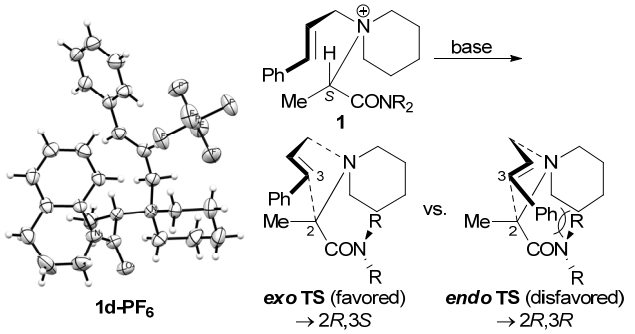



**Figure 1** Proposed transition state in the rearrangement of **1**.

In conclusion, we have reported the base-induced asymmetric [2,3] Stevens rearrangement of *N*-cinnamyl tetraalkylammonium ylides derived from L-alanine amides, which proceeds via a double axially chiral intermediate to afford the corresponding α-substituted alanine derivatives with high enantio- and diastereoselectivities. The *N*,*N*-substituents and amide moiety of the rearrangement product were successfully removed.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details (including selected NMR spectra) and crystallographic data. CCDC 995319–995320. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000000x/

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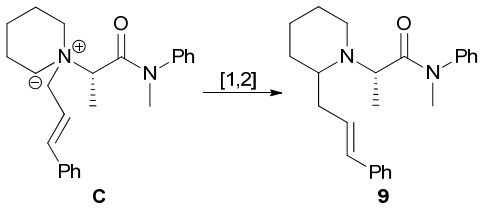


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