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KINETIC RESOLUTION *VIA* THE [2,3] STEVENS REARRANGEMENT OF EPIMERIC SIX-MEMBERED AMMONIUM YLIDES: A NEW ENTRY TO ENANTIO-ENRICHED α-AMINO ACID DERIVATIVES

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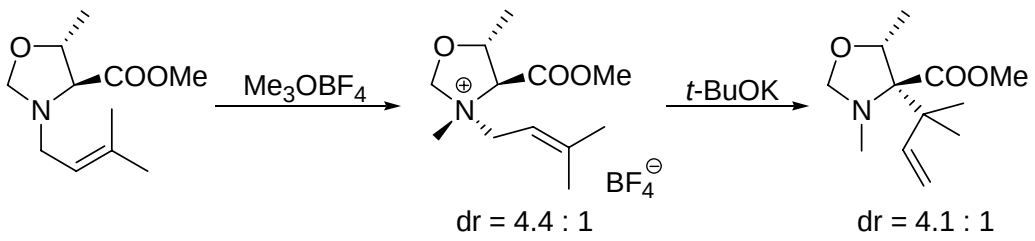
Abstract – The asymmetric [2,3] Stevens rearrangement of epimeric mixtures of *N*-allylic ammonium salts derived from (5*R*)-5-phenyl-1,4-oxazin-2-one is shown to proceed with efficient kinetic resolution to afford the unnatural α-amino acid derivatives in high enantio-purities.

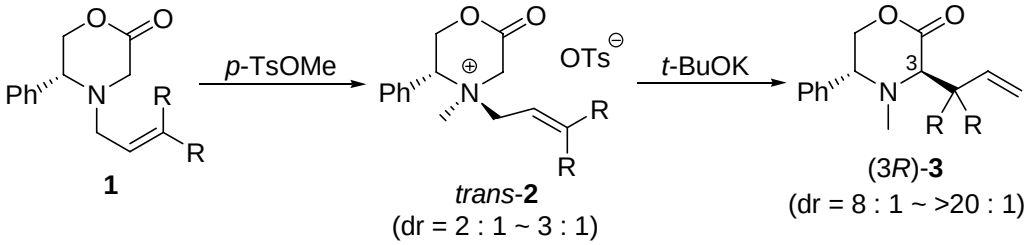
The Stevens rearrangement of ammonium ylides enjoys wide applications in organic synthesis.[1] Among several variants developed so far, the base-induced [2,3] Stevens rearrangement of quaternary *N*-allylic ammonium salts is synthetically the most attractive, since it proceeds in the concerted symmetry-allowed mechanism to provide high regio- and stereoselectivities. However, study of its asymmetric version involving the chirality transfer from nitrogen to carbon remains limited.[2,3] The West group[3] has reported that the asymmetric [2,3] Stevens rearrangement of five-membered ammonium ylides proceeds with almost complete chirality transfer as depicted by Scheme 1, wherein the overall stereoselectivity depends markedly on the stereoselectivity of the quaternarization of the tertiary amine.



Scheme 1 An example of the asymmetric [2,3] Stevens rearrangement.

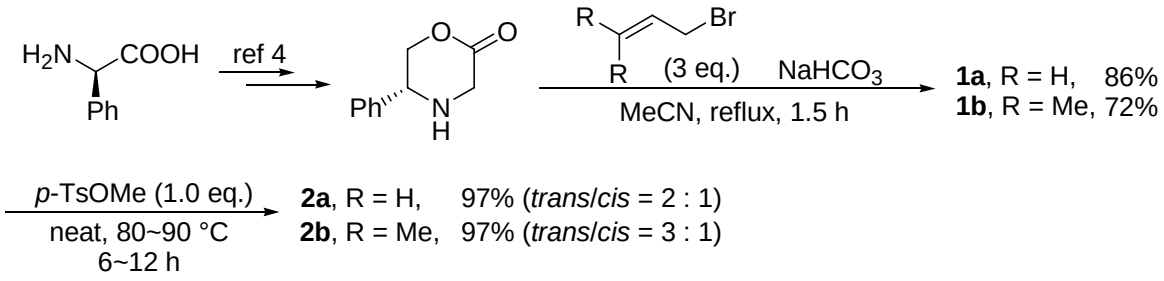
This paper is dedicated to the memory of the Emeritus Professor Knji Koga of Tokyo University.

Herein we wish to report a different type of the asymmetric [2,3] Stevens rearrangement using an epimeric mixture of the six-membered ammonium salt (**2**) as the ylide precursor which proceeds with efficient kinetic resolution to afford the unnatural α-amino acid derivatives (**3**) in high enantio-purities (Scheme 2).



Scheme 2

The requisite ammonium salts (**2**) were prepared from (5*R*)-5-phenyl-1,4-oxazin-2-one which was derived from D-phenylglycine in two steps (Scheme 3).[4] After *N*-allylation under the standard conditions, the resulting tertiary amines (**1**) were quaternarized by methyl tosylate. The ammonium salts were obtained as an epimeric mixture of *trans*- and *cis*-**2** (*trans*/*cis* = 2:1 for **2a** and 3:1 for **2b**). The configuration of the major ammonium salt (*trans*-**2a**) was assigned from the confirmed configuration of the rearrangement product [(3*R*)-**3a**] on the reasonable assumption that the chirality transfer from N to C takes place on the same face.[3] The *trans*/*cis* ratio of **2a** was determined by ^{1}H-NMR ($CDCl_3$) spectral assay (*N*-CH_3 peak, δ 3.24 ppm for the *trans*-isomer and 3.07 ppm for the *cis*-isomer).

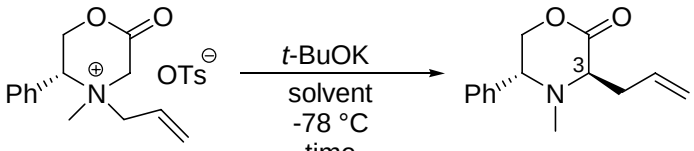


Scheme 3 Preparation of the quaternary ammonium salts (**2**).

Treatment of the epimeric mixture of ammonium salts (**2a**) (*trans*/*cis* = 2:1) with 1.0 equiv. of *t*-BuOK in THF at -78 ºC for 22 h was found to give the corresponding [2,3] shifted product [(3*R*)- and (3*S*)-**3a**] in 30 % yield as a 7:1 mixture of the stereoisomers (Table 1, entry 1). The ratio of (3*R*)/(3*S*) could be determined by ^{1}H-NMR ($CDCl_3$) spectral assay [*N*-CH_3 peak, δ 2.30 ppm for (3*R*)-**3a** and 2.17 ppm for (3*S*)-**3a**]. It is noteworthy that the observed stereoisomeric ratio of the product is significantly higher than that of the substrate used. Given the reasonable postulate that the [2,3] sigmatropic shift proceeds in completely suprafacial fashion [i.e., *trans*-**2a** to (3*R*)-**3a** and *cis*-**2a** to (3*S*)-**3a**], this observation

strongly suggests that during the rearrangement kinetic resolution occurs to an appreciable extent. Table 1 shows the yields and stereoselectivities observed under various conditions. Of special interest is that the use of THF-DME instead of THF alone provided a comparable or higher stereoselectivity at a higher conversion (entries 2, 3). The best result was obtained using THF-DME (1:2).[6,7]

Table 1 The [2,3] Stevens rearrangement of the ammonium salt (**2a**).



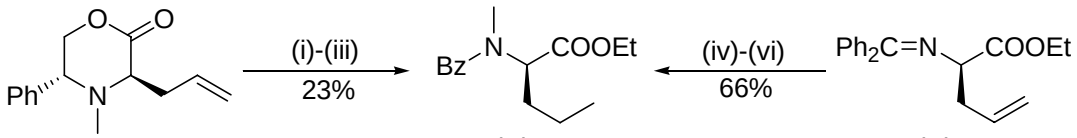
2a
(*trans*/*cis* = 2 : 1)

(3*R*)-**3a**

entry	*t*-BuOK (eq.)	solvent	time (h)	yield (%)[a]	ratio[b] (3*R*)/(3*S*)
1	1.0	THF	22	30	7 : 1
2	1.0	THF-DME (1:1)	22	34	8 : 1
3	1.0	THF-DME (1:2)	22	44	7 : 1
4	1.0	DME	22	55	5 : 1
5	1.0	THF-DME (1:2)	2	13	5 : 1
6	1.0	THF-DME (1:2)	48	44	7 : 1
7	0.6	THF-DME (1:2)	22	17	6 : 1

[a] Isolated yield. [b] Determined by ^{1}H-NMR spectroscopy.

The (3*R*)-configuration of the major product was assigned as follows (Scheme 4). According to the reported method,[4] **3a** was first converted to *N*-benzoyl-*N*-methyl-α-*n*-propylglycine ethyl ester (**4a**) which was then chromatographically correlated with the (*R*)-authentic sample independently prepared from Schiff-base protected (*R*)-α-allylglycine ethyl ester (**5a**)[5]: HPLC analysis (Daicel Chiralpak AD-H, Hex/EtOH = 70:30, 0.50 mL/min), t_R = 11.4 min for the (*R*)-isomer and 14.6 min for the (*S*)-isomer.



(3*R*)-**3a**
> 99% de

(*R*)-**4a**

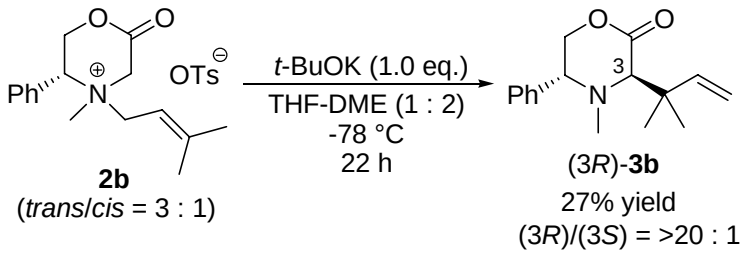
(*R*)-**5a**
96% ee

(i) 1N HCl, EtOH, reflux. (ii) 10% Pd-C, H_2 (1 atm), EtOH, rt. (iii) BzCl, *aq*. $NaHCO_3$, THF, 0 °C to rt. (iv) 1N HCl, THF, rt then BzCl, $NaHCO_3$, 0 °C to rt. (v) Ag_2O, MeI, DMF, rt. (vi) 10% Pd-C, H_2 (1 atm), EtOAc, rt.

Scheme 4

Next, a similar rearrangement of the *N*-prenylammonium salt (**2b**) was examined (Scheme 5). This rearrangement is of special value, since it would ultimately afford the α-*tert*-alkylamino acids which are

otherwise difficult to obtain. Thus, a mixture of *trans*- and *cis*-**2b** (3:1) was rearranged under the same conditions as described in entry 3 (Table 1). Rather surprisingly, product (**3b**) was obtained as almost single enantiomer, although the yield was rather low. The dramatic improvement of the stereoselectivity reveals that kinetic resolution during the rearrangement of **2b** occurs with higher efficiency, compared with the aforementioned case of *N*-allyl analogue (**2a**).



2b
(*trans*/*cis* = 3 : 1)

Scheme 5 The [2,3] Stevens rearrangement of **2b**.

In summary, we have shown that the asymmetric [2,3] Stevens rearrangement of the epimeric six-membered ammonium ylides proceeds with efficient kinetic resolution to afford the unnatural α-amino acid derivatives in high enantio-purities. Further studies on different types of the asymmetric Stevens rearrangement are underway.

ACKNOWLEDGEMENTS

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6. **The [2,3] Stevens rearrangement of an epimeric mixture of *trans*- and *cis*-ammonium *p*-toluenesulfonate (2a):** To a 2:1 epimeric mixture of **2a** (210 mg, 0.52 mmol) in THF (1.7 mL) and DME (3.4 mL) was added *t*-BuOK (58 mg, 0.52 mmol) in one portion at -78 ºC with stirring. After stirring for 22 h at the same temperature, the resulting mixture was quenched with saturated

aqueous NH_4Cl. The mixture was treated with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 8:1 as eluent) to give (3*R*)-**3a** (colorless oil, 46 mg, 38 %) and (3*S*)-**3a** (colorless oil, 6 mg, 6 %).

7. To describe that our method is kinetic resolution not stereoselective protonation, epimerization of the rearrangement product (**3a**) was examined. A solution of **3a** [(3*R*)/(3*S*) = 6 : 1] in THF was treated with *t*-BuOK (1.1 equiv.) at -78 ºC for 2 h. The epimerized starting material **3a** was recovered in 34 % yield. The ratio was changed from (3*R*)/(3*S*) = 6 : 1 to 1 : 9. This result indicates that the epimerization of (3*R*)-**3a** gave another isomer [(3*S*)-**3a**] preferably.