Asymmetric [1,2] Stevens Rearrangement of (S)-N-Benzylic Proline-derived Ammonium Salts under Biphasic Conditions

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The Stevens rearrangement of (*S*)-*N*-benzylic proline-derived ammonium salt with cesium hydroxide in 1,2-dichloroethane is shown to proceed with a high degree of the *N*-to-*C* chirality transmission to afford the α -substituted proline derivatives in high enantio-purities.

The [1,2] Stevens rearrangement of ammonium ylides is a useful transformation for organic synthesis since it converts a readily accessible C-N bond into a new C-C bond and hence has found applications for synthesis of α -amino acids and ketones.¹ However, its asymmetric versions remains largely unexplained probably because the rearrangement proceeds via the radical cleavage-recombination mechanism, thus leading to low stereoselectivities.² We became particularly interested in the asymmetric version which involves the transmission of a nitrogen-centered chirality to the newly-formed carbon-centered chirality. Recently, West et al. have reported that the Stevens rearrangement of the (1S,2S)-N-benzylproline methyl ester-derived ammonium salt [(1S)-1] proceeds with a moderate level (54%) of the *N*-to-*C* chirality transmission (Eq 1).³ Herein, we wish to report that this type of the [1,2] Stevens rearrangement, when performed under a proper biphasic condition, exhibits a remarkably enhanced level of the chirality transmission to afford the α -substituted proline derivatives in high enantio-purities.⁴

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For this study, we employed (*S*)-*N*-benzyl-*N*-methylproline *t*-butyl ester–derived ammonium salt [(1*S*)-**4a**] as the ylide precursor to avoid hydrolysis during the rearrangement under aqueous conditions. The requisite precursor (1*S*)-**4a** was prepared in diastereomerically pure form from (*S*)-*N*-benzylproline ester **3a**⁵ via quaternarization with methyl iodide followed by recrystallization (Scheme 1).⁶ The (1*S*)-configuration was assigned by the similarity of the NMR spectrum to that of (1*S*)-**1**.³

First, we examined the rearrangement of (1S)-4a using West's conditions (*t*-BuOK, THF, rt). The Stevens product 5a



Scheme 1. Preparation of ammonium salt (1S)-4a.



Scheme 2. Asymmetric [1,2] Stevens rearrangement using *t*-BuOK.

was obtained in 80% yield and its enantio-purity was determined to be 72% ee by chiral HPLC analysis of the amino alcohol 6a prepared by reduction of 5a with LiAlH₄ (Scheme 2).⁷ The (R)-configuration of the major product isomer was determined by comparison of the HPLC retention time of 6a with the authentic sample prepared by reduction of the known methyl ester (R)-2 with LiAlH₄.³ The observed degree of chirality transmission, albeit significantly higher than that reported for the methyl ester (1S)-1, is still unsatisfactory. In order to further improve the stereoselectivity, we next attempted the application of biphasic conditions to the present rearrangement. Thus, we carried out the rearrangement of 4a under the liquid-liquid biphasic condition using a 50% aqueous KOH solution and dichloromethane (3:1 vol %) (Table 1, Entry 1). While the selectivity was slightly improved to 86% ee, the yield was lowered (45%). Significantly, however, application of the solid-liquid biphasic condition using KOH (powder, 5 equiv.) and dichloromethane was found to provide a notably enhanced selectivity (94% ee), although the yield was still moderate (Entry 2). Interestingly, use of CsOH (solid, 5 equiv.) in the place of KOH provided an increased yield (88%), together with a slightly lower % ee (Entry 3). The best result was obtained by using CsOH as a base and 1,2-dichloroethane as a solvent to afford 73% yield and 92% ee (Entry 4).8

With the optimized biphasic procedure in hand, we carried out the rearrangements of several other N-(arylmethyl)proline

Table 1. Asymmetric [1,2] Stevens rearrangement under biphasic conditions

| | $ \begin{array}{c} & & \\ & & $ | base solvent -10 °C, 24 h | CO ₂ Bu ^t | |
|-------|---|--------------------------------------|---------------------------------|-----------------------|
| | (1 <i>S</i>)- 4a | | (<i>R</i>)- 5a | |
| Entry | Base | Solvent | Yield ^a /% | ee ^b /% |
| 1 | 50% aq. KOH | CH_2Cl_2 | 45 | 86 |
| 2 | KOH powder ^c | CH_2Cl_2 | 52 | 94 |
| 3 | CsOH solid ^c | CH_2Cl_2 | 88 | 84 |
| 4 | CsOH solid ^c | ClCH ₂ CH ₂ Cl | 73 | 92 |

^aDetermined by ¹H NMR assay using mesitylene as an internal standard. ^bDetermined by chiral HPLC analysis of **6a**. ^c5 equiv. was used.

 Table 2. CsOH-induced asymmetric [1,2] Stevens rearrangement

| | $\begin{array}{c} \overset{}{} \\ \overset{}{} \\ \overset{}{} \\ \overset{}{} \\ (1S)-4 \end{array} \xrightarrow{CO_2Bu^t} \begin{array}{c} \overset{}{} \\ \overset{\textcircled}{} \\ \overset{\textcircled}{} \\ \overset{\textcircled}{} \\ \overset{\end{array}{}} \\ \overset{\textcircled}{} \\ \overset{\end{array}{}} \\ \overset{\textcircled}{} \\ \overset{\end{array}{}} \\ \overset{\end{array}{} \\ \overset{\end{array}{}} \\ {} \\ {} \\ {} \\ {}} \\ {} \end{array} {} \\ {} \\ {} \\ {} \end{array} {} {} \\ {} \\ {} \\ {} \end{array} {} {} \end{array} {} {} \end{array} {} \overset$ | SOH (5 equiv.) 2-dichloroethane –10 °C, 24 h | CO ₂ E N (<i>R</i>)-5 | 3u ^t |
|----------------|---|--|--|-------------------|
| Entry | Ar | Product | Yield/% ^a | ee/% ^b |
| 1 | 4-Me-Ph | b | 77 | 84 |
| 2 | 4-MeO-Ph | с | 56 | 86 |
| 3 | 4-F-Ph | d | 69 | 90 |
| 4 ^c | 4- ^t BuOCOPh | e | 42 ^d | >99 |

^aDetermined by ¹H NMR assay using mesitylene or diphenylmethane as an internal standard. ^bDetermined by chiral HPLC analysis after reduction of **5** with LiAlH₄. ^cPerformed at 0 °C. ^dt-Butyl *p*-toluate was isolated in 55% yield.



Scheme 3. Pathways of the chirality transmission.

ammonium salts **4b**–**4e** which were prepared in stereo-pure form in the same way as described for **4a**.⁹ As shown in Table 2, these rearrangements afforded the corresponding α -(arylmethyl)proline *t*-butyl esters (**5b**–**5d**) with 84–90% ee in reasonable yields except for the case of **4e** where **5e** was obtained as an almost single enantiomer in only 42% yield, together with a considerable amount of *t*-butyl *p*-toluate (Entry 4).

The question arises as to why the solid-liquid biphasic condition provides such a remarkably enhanced % ee. While the exact reason cannot be advanced at present, it is safe to say that under the biphasic conditions, the recombination of the radical pair initially formed from the N-ylide occurs more rapidly in a solvent cage and hence more preferentially in the retentive fashion (on the bottom side) to give an enhanced % ee (Scheme 3). In other words, the recombination outside the solvent cage leading to a decrease in % ee would be suppressed under the biphasic conditions. The stability of the benzylic radical involved might be another factor in dictating the % ee. The more unstable benzylic radical involved is, the more rapidly the recombination would occur inside the solvent cage, thus leading to a higher % ee as actually observed in Entry 4 (Table 2), although the p-(t-butoxycarbonyl)benzyl radical is so reactive (unstable) and hence abstracts a hydrogen leading to the formation of *t*-butyl *p*-toluate as a by-product.

In summary, we demonstrated that the [1,2] Stevens rearrangement of the (*S*)-*N*-benzylic proline-derived ammonium salts, when carried out under the solid–liquid biphasic conditions, exhibits a remarkably high level of the *N*-to-*C* chirality transmission to afford the corresponding α -arylmethyl-substituted proline derivatives in high enantio-purities. Further works on other asymmetric Stevens rearrangements are underway.

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References and Notes

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- 4 For preparations of α-substituted proline derivatives, see:
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- 5 Prepared from Cbz-L-proline in three steps: (i) isobutene, cat. H₂SO₄, CH₂Cl₂, rt. (ii) H₂ (1 atm), 10% Pd–C, EtOAc, rt. (iii) PhCH₂Cl, NaHCO₃, CH₃CN, reflux. Other substrates (**3b**–**3e**) were prepared by the same procedure using the corresponding benzylic chloride or bromide in step (iii).
- 6 Spectroscopic data; (1*S*, 2*S*)-*N*-benzyl-*N*-methylproline ammonium salt (1*S*)-**4a**; mp 155–156 °C; $[α]_D^{25} = -20.2^{\circ}$ (*c* = 1.00, MeOH); ¹H NMR (270 MHz, CDCl₃) δ 7.69–7.65 (m, 2H, Ph), 7.53–7.42 (m, 3H, Ph), 5.41 (d, 1H, *J* = 12.7 Hz, CH₂Ph), 5.22 (dd, 1H, *J* = 10.5, 9.2 Hz, CHCO₂Bu'), 5.12 (d, 1H, *J* = 12.7 Hz, CH₂Ph), 4.76 (ddd, 1H, *J* = 10.5, 10.5, 10.5 Hz, 5-H), 3.46 (ddd, 1H, *J* = 10.5, 8.4, 1.9 Hz, 5-H), 3.08 (s, 3H, CH₃), 2.81–2.68 (m, 1H, 3- or 4-H), 2.39–2.19 (m, 2H, 3- or 4-H), 2.09–1.95 (m, 1H, 3- or 4-H), 1.54 (s, 9H, 'Bu); ¹³C NMR (68 MHz, CDCl₃) δ 164.8, 132.5, 130.7, 129.2, 127.5, 85.7, 71.9, 65.9, 63.8, 44.0, 28.0, 24.6, 18.4; IR (KBr) 1744, 1148 cm⁻¹; Anal. calcd for C₁₇H₂₆INO₂: C, 50.63; H, 6.50; N, 3.47%. Found: C, 50.79; H, 6.61; N, 3.51%.
- 7 Similar rearrangements at 0 and -10 °C gave **5a** with 80% ee (71% yield) and 84% ee (91% yield), respectively.
- Reaction procedure: To a solution of (1S)-4a (180 mg, 8 0.447 mmol) in 1,2-dichloroethane (5 mL) was added CsOH (0.37 g, 2.5 mmol) in one portion at $-10 \degree \text{C}$ under a nitrogen atmosphere. After stirring for 24 h at the same temperature, the resulting mixture was diluted with H₂O and extracted with Et₂O. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. The yield of (R)-5a was determined by ¹HNMR spectroscopy of the crude product using mesitylene as an internal standard (73% yield). The pure (R)-5a was obtained after chromatography on silica gel (Hex/EtOAc = 20:1 as eluent) as a colorless oil (84.1 mg, 68% yield). $[\alpha]_D^{22} = 8.4^\circ$ (c = 1.00, EtOH); ¹H NMR (270 MHz, CDCl₃) δ 7.27–7.15 (m, 5H, Ph), 3.27 (d, 1H, $J = 13.2 \text{ Hz}, \text{ CH}_2\text{Ph}), 3.06-2.99 \text{ (m, 1H, 5-H)}, 2.65 \text{ (d, 1H, })$ $J = 13.2 \,\text{Hz}, \,\text{CH}_2\text{Ph}), \, 2.70 - 2.58 \,(\text{m}, 1\text{H}, 5 - \text{H}), \, 2.46 \,(\text{s}, 3\text{H}), \, 3.16 \,(\text{s}, 3 - 10 \,\text{Hz}), \, 3.16 \,(\text{s}, 3 - 10 \,\text{H$ CH₃), 2.06–1.93 (m, 1H, 3- or 4-H), 1.81–1.53 (m, 3H, 3and 4-H), 1.45 (s, 9H, ^tBu); ¹³C NMR (68 MHz, CDCl₃) δ 171.9, 138.0, 130.3, 127.6, 126.0, 80.9, 71.4, 54.4, 40.5, 35.5, 33.8, 28.4, 21.6; IR (film) 1714, 1160 cm⁻¹; Anal. calcd for C17H25NO2: C, 74.14; H, 9.15; N, 5.09%. Found: C, 74.23; H, 9.39; N, 5.11%. The ee was determined to be 92% ee by chiral HPLC analysis of the amino alcohol 6a which prepared by reduction of (R)-5a with LiAlH₄ in THF [Daicel CHIRALPAK AD-H, Hex/EtOH = 85:15, 0.50 mL/min, $t_{\rm R} = 15.7$ min for the (S)-isomer and 18.4 min for the (R)-isomer].
- 9 Recrystallization solvents: Hex/CH₂Cl₂ for **4b** and **4d**, Hex/THF for **4c**, and Hex/CH₂Cl₂/PhH for **4e**.