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

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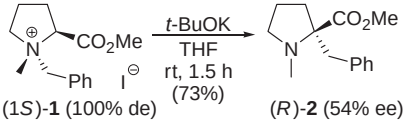
The Stevens rearrangement of (*S*)-*N*-benzylic proline-derived ammonium salt with cesium hydroxide in 1,2-dichloroethane is shown to proceed with a high degree of the *N*-to-*C* chirality transmission to afford the α-substituted proline derivatives in high enantio-purities.

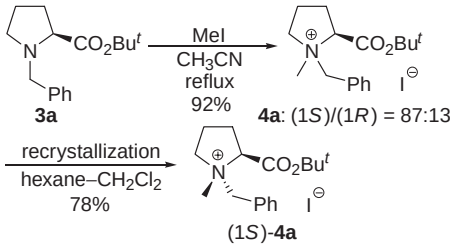
The [1,2] Stevens rearrangement of ammonium ylides is a useful transformation for organic synthesis since it converts a readily accessible C–N bond into a new C–C bond and hence has found applications for synthesis of α-amino acids and ketones.[1] However, its asymmetric versions remains largely unexplained 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 (1*S*,2*S*)-*N*-benzylproline methyl ester–derived ammonium salt [(1*S*)-**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]



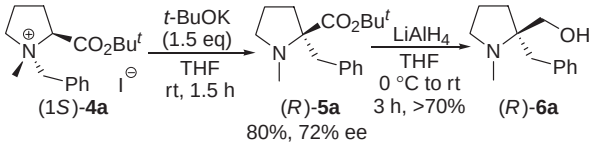
(1*S*)-**1** (100% de) (*R*)-**2** (54% ee) (1)

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 (1*S*)-**4a** using West's conditions (*t*-BuOK, THF, rt). The Stevens product **5a**



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

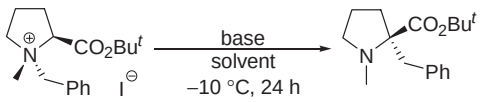


Scheme 2. Asymmetric [1,2] Stevens rearrangement using *t*-BuOK.

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 $LiAlH_4$ (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 $LiAlH_4$.[3] The observed degree of chirality transmission, albeit significantly higher than that reported for the methyl ester (1*S*)-**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

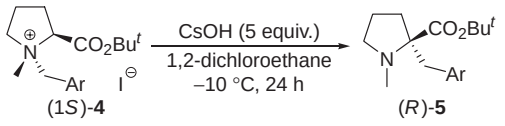
Table 1. Asymmetric [1,2] Stevens rearrangement under biphasic conditions



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]	$ClCH_2CH_2Cl$	73	92

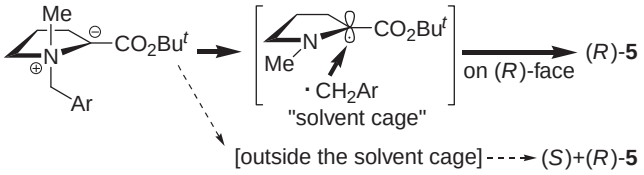
[a]Determined by ^1H NMR assay using mesitylene as an internal standard. [b]Determined by chiral HPLC analysis of **6a**. [c]5 equiv. was used.

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



Entry	Ar	Product	Yield/%[a]	ee/%[b]
1	4-Me-Ph	**b**	77	84
2	4-MeO-Ph	**c**	56	86
3	4-F-Ph	**d**	69	90
4[c]	4-^{t}BuOCOPh	**e**	42[d]	>99

[a]Determined by ^{1}H NMR assay using mesitylene or diphenylmethane as an internal standard. [b]Determined by chiral HPLC analysis after reduction of **5** with $LiAlH_4$. [c]Performed at 0 °C. [d]*t*-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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5 Prepared from Cbz-L-proline in three steps: (i) isobutene, cat. H_2SO_4, CH_2Cl_2, rt. (ii) H_2 (1 atm), 10% Pd–C, EtOAc, rt. (iii) $PhCH_2Cl$, $NaHCO_3$, CH_3CN, 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; $[\alpha]_D^{25} = -20.2°$ ($c = 1.00$, MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69–7.65 (m, 2H, Ph), 7.53–7.42 (m, 3H, Ph), 5.41 (d, 1H, $J = 12.7$ Hz, CH_2Ph), 5.22 (dd, 1H, $J = 10.5$, 9.2 Hz, $CHCO_2Bu^t$), 5.12 (d, 1H, $J = 12.7$ Hz, CH_2Ph), 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, CH_3), 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, ^{t}Bu); ^{13}C NMR (68 MHz, $CDCl_3$) 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 $C_{17}H_{26}INO_2$: 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.

8 Reaction procedure: To a solution of (1*S*)-**4a** (180 mg, 0.447 mmol) in 1,2-dichloroethane (5 mL) was added CsOH (0.37 g, 2.5 mmol) in one portion at −10 °C under a nitrogen atmosphere. After stirring for 24 h at the same temperature, the resulting mixture was diluted with H_2O and extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. The yield of (*R*)-**5a** was determined by ^{1}H NMR 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). $[\alpha]_D^{22} = 8.4°$ ($c = 1.00$, EtOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27–7.15 (m, 5H, Ph), 3.27 (d, 1H, $J = 13.2$ Hz, CH_2Ph), 3.06–2.99 (m, 1H, 5-H), 2.65 (d, 1H, $J = 13.2$ Hz, CH_2Ph), 2.70–2.58 (m, 1H, 5-H), 2.46 (s, 3H, CH_3), 2.06–1.93 (m, 1H, 3- or 4-H), 1.81–1.53 (m, 3H, 3- and 4-H), 1.45 (s, 9H, ^{t}Bu); ^{13}C NMR (68 MHz, $CDCl_3$) 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 $C_{17}H_{25}NO_2$: 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 $LiAlH_4$ in THF [Daicel CHIRALPAK AD-H, Hex/EtOH = 85:15, 0.50 mL/min, $t_R = 15.7$ min for the (*S*)-isomer and 18.4 min for the (*R*)-isomer].

9 Recrystallization solvents: Hex/CH_2Cl_2 for **4b** and **4d**, Hex/THF for **4c**, and Hex/CH_2Cl_2/PhH for **4e**.

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