Stereoselective Rearrangements

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Asymmetric Sommelet–Hauser Rearrangement of *N*-Benzylic Ammonium Salts**

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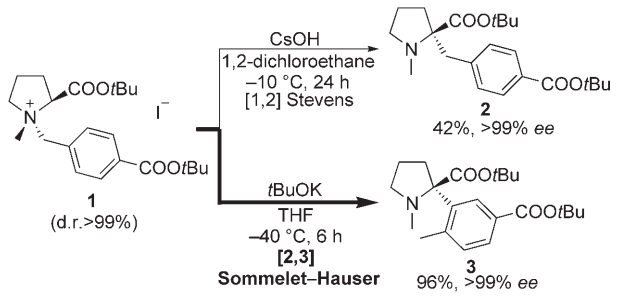
The Stevens and Sommelet–Hauser rearrangements of ammonium ylides are known as useful transformations for organic synthesis because they convert a readily accessible C–N bond into a new C–C bond.[1] The Stevens rearrangement has been widely used for the asymmetric synthesis of α-amino acid derivatives,[2,3] whereas the Sommelet–Hauser rearrangement is much less common because it usually competes with the [1,2] Stevens rearrangement.[4] For example, the base-induced rearrangement of carbonyl-stabilized ammonium ylides such as those derived from *N*-benzylic α-amino esters almost exclusively undergoes the [1,2] Stevens rearrangement to give the α-benzylated amino acid derivatives. For these reasons, synthetic applications of the Sommelet–Hauser rearrangement and its asymmetric versions have been limited.[5] Herein, we report a unique example of a Sommelet–Hauser rearrangement of carbonyl-stabilized ammonium ylides that is not accompanied by the [1,2] Stevens rearrangement to a detectable extent.

Recently, we reported that the [1,2] Stevens rearrangement of ammonium salt **1**, which is derived from (2*S*)-*N*-(4-*tert*-butoxycarbonyl)benzyl proline *tert*-butyl ester, proceeds with a perfect level (greater than 99%) of N-to-C chirality transfer to give the α-benzylated proline *tert*-butyl ester **2** (Scheme 1).[2b] However, when the rearrangement was performed in THF at −40 °C using potassium *tert*-butoxide (1.5 equiv) as a base, the Sommelet–Hauser rearrangement

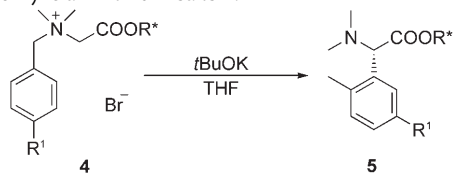


Scheme 1. The [1,2] Stevens versus Sommelet–Hauser rearrangement.

(concerted [2,3] sigmatropic process) proceeded exclusively to give the corresponding α-aryl proline[6] derivative **3** in 96% yield. The ^{1}H NMR analysis of **3** showed a new singlet peak from benzylic methyl protons ($\delta = 2.27$ ppm in $CDCl_3$), three proton signals from aromatic protons, and the disappearance of the benzylic methylene protons. The enantiomeric excess was determined to be greater than 99% by chiral HPLC analysis after reduction of **3** to the amino alcohol with lithium aluminum hydride.[7] The *R* configuration of **3** was assigned by analogy with the reported examples of [2,3] Stevens rearrangement of proline-derived ammonium salts.[2d,e]

With this method in hand, we carried out the rearrangement of various types of ammonium bromide **4**[8], derived from *N*-benzylic-*N*,*N*-dimethylglycine (−)-8-phenylmenthol ester, that might afford the α-aryl glycine derivative **5** (Table 1).[9] As expected, the rearrangement of *para*-*tert*-butoxycarbonyl derivative **4a** with potassium *tert*-butoxide at −40 °C gave the α-aryl *N*,*N*-dimethylglycine ester **5a** in 95% yield with a high level of diastereoselectivity (Table 1, entry 1, 2*S*/2*R* > 98:2),[10,11] and the [1,2] Stevens rearrangement product was not observed.[12] Next, we carried out the reaction of a *para*-cyano derivative **4b** under the same conditions (Table 1, entry 2); however, the diastereoselectivity was lower (2*S*/2*R* = 87:13) because of epimerization of the rearrangement product **5b**.[13] Thus, we carried out the reaction at a

Table 1: Asymmetric Sommelet–Hauser rearrangement of *para*-substituted *N*-benzylic ammonium salts **4**.[a]



Entry	R^1	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]
1	COO*t*Bu (**a**)	−40	4	95	>98:2
2	CN (**b**)	−40	4	84	87:13
3	CN (**b**)	−60	8	82	97:3
4	$COOCH_3$ (**c**)	−60	8	85	>98:2
5	COPh (**d**)	−60	8	82	>98:2
6	CF_3 (**e**)	−60	15	93	>98:2
7	H (**f**)	−60	15	0	–
8	H (**f**)	−40	15	46	>98:2
9	OCH_3 (**g**)	−40	15	0	–

[a] All reactions were performed using **4** (0.20–0.30 mmol) and *t*BuOK (1.2 equiv) in THF (0.1 M) in an argon atmosphere. R* = (−)-8-phenylmenthyl. [b] Yield of isolated product. [c] d.r. = 2*S*/2*R*; determined by ^{1}H NMR analysis of the crude product.

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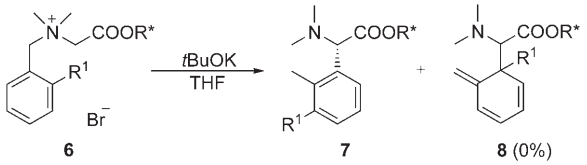
lower temperature (Table 1, entry 3, −60 °C) to minimize epimerization, and the corresponding rearrangement product **5b** was obtained in 82% yield with excellent diastereoselectivity (2*S*/2*R* = 97:3). To define the scope and limitation of this procedure, we prepared a series of *para*-substituted substrates **4** and carried out their reactions (Table 1, entries 3–9). The methoxycarbonyl (**4c**), benzoyl (**4d**), and trifluoromethyl (**4e**) derivatives also afforded the [2,3] rearrangement products **5c–e** in excellent yields and diastereoselectivities. It is worth noting that the electron-withdrawing *para* substituent accelerates the Sommelet–Hauser rearrangement. In fact, rearrangement of the simple benzyl derivative **4f** (Table 1, entry 7, R^1 = H) at −60 °C did not give the rearrangement product. However, when the reaction was carried out at −40 °C (Table 1, entry 8), the corresponding rearrangement product **5f** was obtained in 46% yield with comparable selectivity (2*S*/2*R* > 98:2). The rearrangement of the *para*-methoxybenzyl derivative **4g** (Table 1, entry 9, R^1 = OMe) failed even at −40 °C. The *S* configuration of the product **5f** was determined by ^{1}H NMR comparison of the authentic *S* sample prepared by diastereoselective addition of 2-methylphenylmagnesium bromide to the *N*-Boc-iminoacetate of (−)-8-phenylmenthol.[14] Other configurations of **5a–e** were assigned by analogy with (*S*)-**5f**.

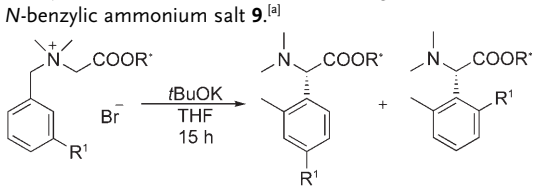
To further expand the scope of the asymmetric Sommelet–Hauser rearrangement, we examined the rearrangement of the *ortho*-substituted *N*-benzylic ammonium salts **6a** (R^1 = CN) and **6b** ($R^1 = CF_3$) with potassium *tert*-butoxide (Scheme 2). Interestingly, the [2,3] rearrangement products **7a** and **7b** were obtained in excellent yields with high levels of diastereoselectivity, and the other [2,3] rearrangement product **8** was not detected.



Scheme 2. Asymmetric Sommelet–Hauser rearrangement of *ortho*-substituted *N*-benzylic ammonium salt **6**. R* = (−)-8-phenylmenthyl.

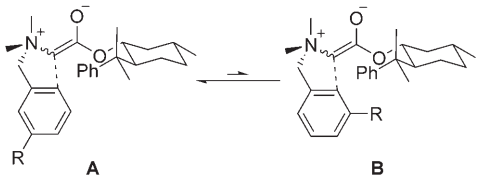
Finally, we carried out the rearrangement of the *meta*-substituted *N*-benzylic ammonium salts (Table 2). The rearrangement of *meta*-cyano derivative **9a** (Table 2, entry 1) was found to afford a mixture of the 2,4-disubstituted regioisomer **10a** in 63% yield along with the other regioisomer **11a** in 6% yield with excellent diastereoselectivities. However, the rearrangement of *meta*-trifluoromethyl derivative **9b** at −60 °C (Table 2, entry 2) gave the corresponding 2,4-disubstituted regioisomer **10b** in only 20% yield. When we carried out the reaction at −40 °C (Table 2, entry 3), **10b** was obtained in 90% yield (2*S*/2*R* > 98:2) as the only detectable regioisomer. The assignments of **10** and **11** were made by ^{1}H NMR analysis; the 2,4-disubstituted regioisomer **10** showed a singlet peak of an aromatic proton (3-H: δ = 7.64 ppm in [D$_6$]DMSO for **10a**, δ = 7.26 ppm in [D$_6$]benzene for **10b**), but the 2,6-disubstituted regioisomer **11** did not. The regioselectivity observed here may be rationalized by assuming that the intermediate **A** leading to **10** is sterically more favorable than **B** (Scheme 3).

Table 2: Asymmetric Sommelet–Hauser rearrangement of *meta*-substituted *N*-benzylic ammonium salt **9**.[a]



Entry	R^1	*T* [°C]	Yield [%][b] (d.r.)[c] **10**	Yield [%][b] (d.r.)[c] **11**
1	CN (**a**)	−60	63 (>98:2)	6 (>98:2)
2	CF_3 (**b**)	−60	20[d] (>98:2)	0
3	CF_3 (**b**)	−40	90 (>98:2)	0

[a] All reactions were performed using **9** (0.20–0.30 mmol) and *t*BuOK (1.2 equiv) in THF (0.1 M) in an argon atmosphere. R* = (−)-8-phenylmenthyl. [b] Yield of isolated product. [c] d.r. = 2*S*/2*R*; determined by ^{1}H NMR analysis of the crude product. [d] Determined by ^{1}H NMR analysis of the crude product.



Scheme 3. Proposed intermediates in the asymmetric Sommelet–Hauser rearrangement of *meta*-substituted *N*-benzylic ammonium salt **9**. Intermediate **A** leads to compound **10** (2,4-substituted), whereas intermeidate **B** leads to compound **11** (2,6-substituted).

In conclusion, we have reported the asymmetric rearrangement of *N*-benzylic ammonium ylides that undergo exclusively the Sommelet–Hauser rearrangement ([2,3] sigmatropic shift). The rearrangement of an ammonium salt derived from *N*-benzylic proline or *N*-benzylic glycine (−)-8-phenylmenthol ester is shown to proceed with remarkably high levels of stereoselectivity. The method provides unique and efficient access to optically active α-aryl amino acid derivatives[15] and expands the synthetic scope of the Sommelet–Hauser rearrangement.

Experimental Section

Representative procedure: A solution of **4a** (123 mg, 0.209 mmol) in THF (2.1 mL) was cooled to −40 °C and treated with a solution of potassium *tert*-butoxide in THF (1.0 M, 0.25 mL, 0.25 mmol). The mixture was stirred for 4 h at the same temperature under an argon atmosphere. The resulting mixture was added to stirred ice-cold saturated aqueous ammonium chloride, and the mixture was

extracted with ether. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 7:1 to 4:1) gave **5a** (101 mg, 95%) as a colorless gum.

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[7] Reaction conditions: $LiAlH_4$, THF, 0 °C to RT, 85% yield. Only one *tert*-butyl ester on the aromatic ring was reduced. For more details, see the Supporting Information.

[8] Prepared from (−)-8-phenylmenthol: i) $BrCH_2COOH$, *p*-TsOH, PhH, reflux; ii) *N*,*N*-dimethylbenzylic amine, CH_3CN, RT; Ts = toluene-*p*-sulfonyl. For more details, see the Supporting Information.

[9] Recent examples of asymmetric synthesis of α-aryl glycine derivatives: a) M. A. Beenen, D. J. Weix, J. A. Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 6304–6305; b) G. Shang, Q. Yang, X. Zhang, *Angew. Chem.* **2006**, *118*, 6508–6510; *Angew. Chem. Int. Ed.* **2006**, *45*, 6360–6362; c) H. Y. Ku, J. Jung, S. H. Kim, H. Y. Kim, K. H. Ahn, S. G. Kim, *Tetrahedron: Asymmetry* **2006**, *17*, 1111–1115; d) S. Shirakawa, R. Berger, J. L. Leighton, *J. Am. Chem. Soc.* **2005**, *127*, 2858–2859; e) J. C. D. Le, B. L. Pagenkopf, *J. Org. Chem.* **2004**, *69*, 4177–4180; f) C. S. Ge, Y. J. Chen, D. Wang, *Synlett* **2002**, 37–42.

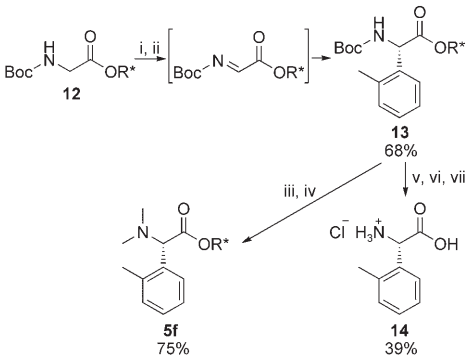
[10] To confirm that the selectivity is determined in the rearrangement step, we carried out the reaction of **4a** using a lower amount of *t*BuOK (0.50 equiv). The rearrangement product **5a** was obtained in 45% yield with a similar diastereoselectivity (2*S*/2*R* = 98:2).

[11] To confirm the 2*R* isomer of **5a**, the product **5a** (2*S*/2*R* > 98:2) was treated with excess *t*BuOK (1.5 equiv, THF, −40 °C for 4 h). Compound **5a** was recovered in 68% yield, and the diastereomeric ratio was changed to 2*S*/2*R* = 84:16. ^1H NMR analysis of the diastereomer mixture of **5a** showed two singlet peaks of the α proton ($\delta = 3.46$ ppm for the 2*S* isomer, $\delta = 4.02$ ppm for the 2*R* isomer).

[12] When the reaction was carried out in a mixture of CH_2Cl_2 and 50% aqueous KOH (volume ratio 2:1) at 0 °C for 1 h, the corresponding [1,2] Stevens rearrangement product was obtained as a major product (49% yield, d.r. = 4:1) with a small amount of **5a** (4% yield, 2*S*/2*R* = 1.5:1). The mechanistic origin of the competition of Sommelet–Hauser and [1,2] Stevens rearrangement is unclear at present; further studies are necessary.

[13] When the product **5b** (2*S*/2*R* = 97:3) was treated with *t*BuOK (0.2 equiv) in THF at −40 °C for 4 h, **5b** was recovered in 96% yield, and the diastereomeric ratio was changed to 2*S*/2*R* = 85:15. The diastereomer mixture was treated with *t*BuOK (0.2 equiv) at −60 °C for 8 h, and **5b** was recovered in 90% yield with the same diastereomeric ratio (2*S*/2*R* = 85:15).

[14] (*S*)-*N*-Boc-(2-methylphenyl)glycine (−)-8-phenylmenthol ester (**13**) was prepared from Boc-glycine (−)-8-phenylmenthol ester (**12**; R* = (−)-8-phenylmenthyl; Boc = *tert*-butoxycarbonyl) by diastereoselective addition of 2-methylphenylmagnesium bromide to the in situ prepared *N*-Boc-iminoacetate of (−)-8-phenylmenthol [i) AIBN, NBS, CCl_4, reflux; ii) 2-methylphenylmagnesium bromide, Et_2O, 0 °C to RT]; see: a) P. Ermert, J. Meyer, C. Stucki, J. Schneebeli, J. P. Obrecht, *Tetrahedron Lett.* **1988**, *29*, 1265–1268; AIBN = azobisisobutyronitrile, NBS = *N*-bromosuccinimide. Then, the compound **13** was converted into (*S*)-**5f** by deprotection and N-dimethylation [iii) TFA, CH_2Cl_2, RT; iv) aq. HCHO, $NaBH_3CN$, AcOH, CH_3CN, RT]; TFA = trifluoroacetic acid. The absolute configration of **13** was determined after conversion into (2-methylphenyl)glycine hydrochloride (**14**) [v) $LiAlH_4$, Et_2O, reflux; vi) $RuCl_3$, $NaIO_4$, CH_3CN/H_2O, RT; vii) HCl, Et_2O, RT]. The assignment was confirmed by comparison of the sign of the specific rotation of $[\alpha]_{589}^{23} = 93\ deg\,cm^3\,g^{-1}\,dm^{-1}$ with that of the known (*S*)-**14** ($[\alpha]_{589}^{23} = 91\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.10\ g\,cm^{-3}$, 5 M HCl)); see: b) C. Mellin-Morlière, D. J. Aitken, S. D. Bull, S. G. Davies, H. P. Husson, *Tetrahedron: Asymmetry* **2001**, *12*, 149–155. For more details, see the Supporting Information.



[15] The chiral auxiliary can be removed by reduction with $LiAlH_4$. For example, reduction of **5f** with $LiAlH_4$ (Et_2O, reflux) gave (*S*)-2-(dimethylamino)-2-(2-methylphenyl)ethanol in 87% yield without racemization. For more details, see the Supporting Information.

