Rearrangement

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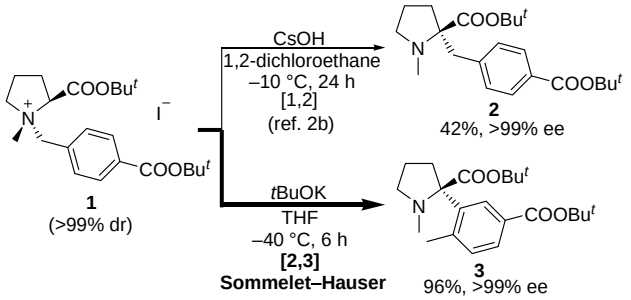
Asymmetric Sommelet–Hauser Rearrangement of *N*-Benzylic Ammonium Salts

Eiji Tayama and Hiroshi Kimura*

Graduate School of Science and Technology, Niigata University, Niigata 950-2181, Japan

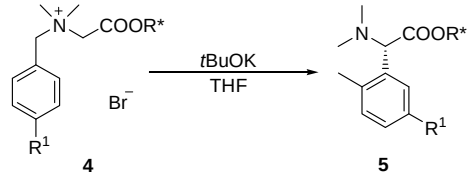
The Stevens and Sommelet–Hauser rearrangement of ammonium ylides are known as useful transformations for organic synthesis because they convert a readily accessible C–N bond into a new C–C bond.[1] The Stevens rearrangement has been widely used for the asymmetric synthesis of α-amino acid derivatives,[2,3] whereas the Sommelet–Hauser rearrangement is much less common because the Sommelet–Hauser rearrangement usually competes with the [1,2] Stevens rearrangement.[4] For example, the base-induced rearrangement of carbonyl-stabilized ammonium ylides such as *N*-benzylic-α-amino ester-derived ammonium ylides 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 wish to report the unique example of the Sommelet–Hauser rearrangement of carbonyl-stabilized ammonium ylides which are not accompanied by the [1,2] Stevens rearrangement to a detectable extent.



Scheme 1. The [1,2] Stevens vs. Sommelet–Hauser Rearrangement

Recently, we have reported that the [1,2] Stevens rearrangement of (1*S*, 2*S*)-*N*-(4-*tert*-butoxycarbonyl)benzyl proline *tert*-butyl ester-derived ammonium salt (**1**) proceeds with a perfect level (>99%) of the *N*-to-*C* chirality transmission 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 (concerted [2,3] sigmatropic process) proceeded exclusively to give the corresponding α-arylproline[6] derivative **3** in 96% yield. The ^{1}H NMR analysis of **3** showed a newly singlet peak as benzylic methyl protons (δ 2.27 in $CDCl_3$), three proton integrals as aromatic protons, and disappearance of the benzylic methylene protons. The enantiomeric excess (ee) was determined to be >99% ee 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 the analogy with the reported examples of [2,3] Stevens rearrangement of proline-derived ammonium salts.[2d, 2e]

Table 1. Asymmetric Sommelet–Hauser Rearrangement of *para*-Substituted-*N*-Benzylic Ammonium Salts **4**[a]



4 **5**

[R* = (–)-8-phenylmenthyl]

Entry	R^1		*T* [°C]	Time [h]	Yield [%][b]	Dr[c]
1	COOBu^t	**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), *t*BuOK (1.2 equiv) in THF (0.1 M) under an argon atmosphere. [b] Isolated yield. [c] Dr = 2*S*/2*R*. Determined by ^{1}H NMR assay of the crude product.

With the method in hand, we carried out the rearrangement of various types of *N*-benzylic-*N*,*N*-dimethylglycine (–)-8-phenylmenthol ester-derived ammonium bromide **4**[8] that might afford the α-arylglycine 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 perfect level of diastereoselectivity (entry 1, 2*S*/2*R* = >98:2).[10,11] Such and such [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 (entry 2), however, the diastereoselectivity was lowered (2*S*/2*R* = 87:13) because of epimerization of the rearrangement product **5b**.[13] Thus, we carried out the reaction at a lower temperature (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

[*] Dr. Eiji Tayama* and Hiroshi Kimura
Graduate School of Science and Technology
Niigata University
Niigata 950-2181, Japan
Fax: (+81)-25-262-7741
E-mail: tayama@gs.niigata-u.ac.jp

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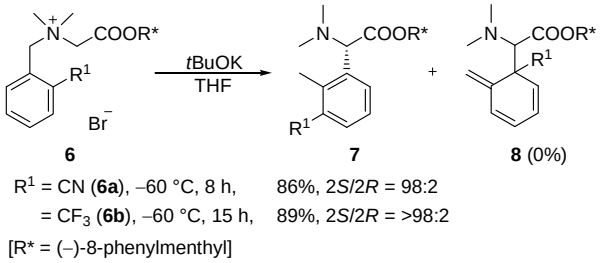
the scope and limitation of the present procedure, we prepared a series of *para*-substituted substrates **4** and carried out their reactions (entries 3–9). The methoxycarbonyl (**4c**), benzoyl (**4d**), and trifluoromethyl (**4e**) derivatives also afforded the [2,3] rearrangement products **5c**–**5e** in excellent yields and diastereoselectivities. It is worth noting that the electron-withdrawing *para*-substituent accelerates the Sommelet–Hauser rearrangement. In fact, the rearrangement of the simple benzyl derivative **4f** (entry 7, R^1 = H) at –60 °C did not give the rearrangement product. However, when the reaction was carried out at –40 °C (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** (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 (*S*)-authentic sample prepared via diastereoselective addition of 2-methylphenylmagnesium bromide to *N*-Boc-iminoacetate of (–)-8-phenylmenthol.[14] Other configurations of **5a**–**5e** were assigned by the analogy with (*S*)-**5f**.

To further expand the scope of the present 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 perfect levels of diastereoselectivity. Such and such other [2,3] rearrangement product **8** was not detected.

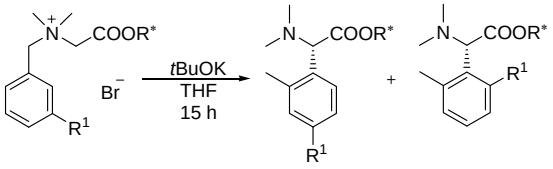


Scheme 2. Asymmetric Sommelet–Hauser Rearrangement of *ortho*-Substituted-*N*-Benzylic Ammonium Salt **6**

Finally, we carried out the rearrangement of the *meta*-substituted-*N*-benzylic ammonium salts (Table 2). The rearrangement of *meta*-cyano derivative **9a** (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 (entry 2) gave the corresponding 2,4-disubstituted regioisomer **10b** in only 20% yield. When we carried out the reaction at –40 °C (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 in DMSO-d_6 for **10a**, δ 7.26 in benzene-d_6 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** (Figure 1).

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 *N*-benzylic proline-derived ammonium salt or *N*-benzylic glycine (–)-8-phenylmenthol ester-derived ammonium salt 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.

Table 2. Asymmetric Sommelet–Hauser Rearrangement of *meta*-Substituted-*N*-Benzylic Ammonium Salt **9**[a]



Entry	R^1		*T* [°C]	Yield[b] (Dr)[c] **10**	Yield[b] (Dr)[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), *t*BuOK (1.2 equiv) in THF (0.1 M) under an argon atmosphere. [b] Isolated yield. [c] Dr = 2*S*/2*R*. Determined by ^{1}H NMR assay of the crude product. [d] Determined by ^{1}H NMR assay of the crude product.

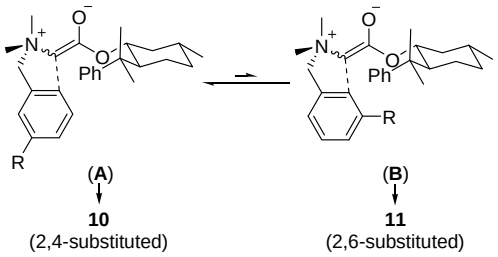


Figure 1. Proposed Mechanism of the Asymmetric Sommelet–Hauser Rearrangement of *meta*-Substituted-*N*-Benzylic Ammonium Salt **9**

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 1.0 M THF solution of potassium *tert*-butoxide (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 as eluent) 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. For more details, see the Supporting Information.

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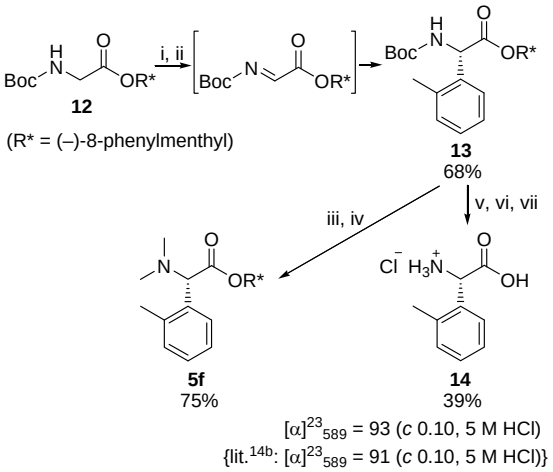
[10] To confirm that the selectivity is determined in rearrangement step, we carried out the reaction of **4a** using less amount of *t*BuOK (0.50 equiv). The rearrangement product **5a** was obtained in 45% yield with the similar diastereoselectivity (2*S*/2*R* = 98:2).

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

[12] When the reaction was carried out in CH_2Cl_2–50% *aq*. KOH at 0 °C for 1 h, the corresponding [1,2] Stevens rearrangement product was obtained as a major product (49% yield, dr = 4:1) with a small amount of **5a** (4% yield, 2*S*/2*R* = 1.5:1). The mechanistic origin about the competition of Sommelet–Hauser and [1,2] Stevens rearrangement is unclear at present. Further studies were nessesary to discuss.

[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 diastereomer ratio was changed to 2*S*/2*R* = 85:15. The diastereomixture was treated with *t*BuOK (0.2 equiv) at –60 °C for 8 h, the **5b** was recovered in 90% yield with the same diastereomer 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**) by diastereoselective addition of 2-methylphenylmagnesium bromide to *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. Then, the compound **13** was converted to (*S*)-**5f** by deprotection and *N*-dimethylation [(iii) TFA, CH_2Cl_2, RT; (iv) *aq*. HCHO, $NaBH_3CN$, AcOH, CH_3CN, RT]. The absolute configration of **13** was determined after conversion to (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 $[\alpha]^{23}_{589}$ = 93 with that of the known (*S*)-**14** {$[\alpha]^{23}_{589}$ = 91 (*c* 0.10, 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 $LiAlH_4$ reduction. For example, reduction of **5f** with $LiAlH_4$ (Et_2O, reflux) gave (*S*)-2-(dimethylamino)-2-(2-methylphenyl)ethanol in 87% yield without racemisation. For more details, see the Supporting Information.