ORGANIC LETTERS

2009
Vol. 11, No. 4
919−921

# Asymmetric Lewis Acid Mediated [1,2]-Rearrangement of Proline-Derived Ammonium Ylides

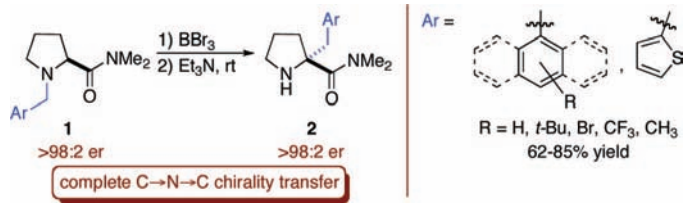
**Pavel Tuzina[†] and Peter Somfai*[,†,‡]**

*Organic Chemistry, KTH Chemical Science and Engineering, SE-100 44 Stockholm, Sweden, and Institute of Technology, University of Tartu, Nooruse 1, 50411 Tartu, Estonia*

*somfai@kth.se*

**Received December 15, 2008**

## ABSTRACT




**The first example of asymmetric Lewis acid mediated [1,2]-rearrangement of *N*-benzylic proline amides to form quaternary proline derivatives is reported. The presented reaction is shown to proceed with remarkable high C→N→C chirality transfer. Various quaternary proline derivatives have been prepared in good to excellent yields and high enantiomeric purity.**

The physical and chemical properties of specific amino acid side chains determine the three-dimensional structure of peptides and will therefore also affect their biological properties. Nevertheless, the application of native peptides is sometimes limited by inadequate selectivity for a certain receptor, enzymatic instability, or simply lack of bioavailability.[1] Incorporation of rigid amino acids into peptide structures is one of the most commonly utilized methods for developing peptidomimetics.[2] Such modification often provides lowering of conformational freedom, thus protecting peptides from proteolytic degradation and sometimes even improving selectivity and potency.[3] Proline analogues are of current interest, as proline is a crucial element in nucleating the secondary structures of peptides and thus influences their overall biological activity. It has also been shown that quaternary proline derivatives have potential as modulators of proline conformational constraint.[4] Moreover, their use extends into the design of new organocatalysts and auxiliaries for asymmetric synthesis.[5] To further expand the area, it is necessary to have ready access to various enantiomerically pure α-substituted prolines.

Several methods for stereoselective synthesis of quaternary prolines have been reported and typically rely on α-functionalization of L-proline itself.[6] Although synthetic strategies based on sigmatropic rearrangements are known, they have

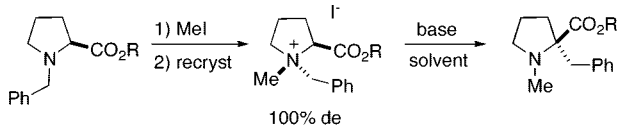
[†] KTH Chemical Science and Engineering.
[‡] University of Tartu.

(1) Adessi, C.; Soto, C. *Curr. Med. Chem.* **2002**, *9*, 963–978.
(2) For reviews on peptidomimetic chemistry, see: (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. (c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.
(3) See, for example: (a) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. *Curr. Med. Chem.* **2004**, *11*, 2785–2798. (b) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers (Pept. Sci.)* **2001**, *60*, 396–419. (c) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. *Biopolymers (Pept. Sci.)* **1997**, *43*, 219–266.
(4) Coleman, D. R., Jr.; Ren, Z.; Mandal, P. K.; Cameron, A. G.; Dyer, G. A.; Muranjan, S.; Campbell, M.; Chen, X.; McMurray, J. S. *J. Med. Chem.* **2005**, *48*, 6661–6670.
(5) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007.
(6) For recent reviews on quaternary proline derivatives, see: (a) Karoyan, P.; Sagan, S.; Lequin, O.; Quancard, J.; Lavielle, S.; Chassaing, G. *Targets Heterocycl. Syst.* **2004**, *8*, 216–273. (b) Calaza, M. I.; Cativiela, C. *Eur. J. Org. Chem.* **2008**, 3427–3448.

10.1021/ol8028803 CCC: $40.75 
**Published on Web 01/15/2009**

not enjoyed yet much attention.[7] Recently, West and Glaeske reported a study on chirality transfer in [1,2]-Stevens rearrangement[8] of diastereomerically pure cyclic ammonium salts,[9] and the technique was further improved by Tayama et al. by employing solid−liquid biphasic reaction conditions (Scheme 1).[10] In this approach a stereoselective quaterniza-

**Scheme 1.** Chirality Transfer in the [1,2]-Stevens Rearrangement of Ammonium Salts



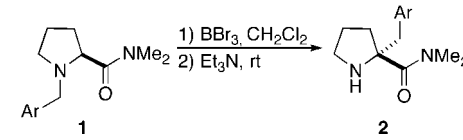

West et al.: R= Me; 73% yield, 54% ee
Tayama et al.: R= *t*-Bu; 73% yield, 92% ee

tion of the nitrogen nucleus is followed by chirality transfer from nitrogen to the forming quaternary stereocenter, thus accounting for the observed product. The main drawback with this methodology is accessing the pure diastereomer of the ammonium salt, requiring stereoselective quaternization with methyl iodide followed by several recrystallizations and ultimately yielding the pure diastereomer in low yields. It has also been noted that the level of N→C chirality transfer depends not only on the reaction conditions but also on the *N*-benzyl moiety, thus limiting the scope of the process. In addition, the products are in all cases N-methylated, making further derivatization of this functionality difficult.

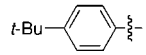
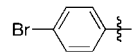
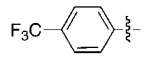
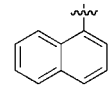
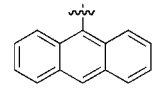
We recently described novel $BBr_3$-mediated [1,2]-Stevens rearrangement of glycine derivatives.[11] As an extension of this investigation, it was of interest to develop an asymmetric Lewis acid mediated [1,2]-shift of proline derivatives, which would involve successive C→N→C chirality transfers.[12] Such a strategy makes use of chirality already present in the substrate and should, in principle, not require chiral reagents or auxiliaries. With this reaction design, enantioenriched *N*-H proline derivatives having a quaternary α-stereocenter should be available, and herein we disclose our results.

Initial efforts were directed toward identifying optimal rearrangement conditions using compound **1a** as the model substrate (Table 1, entry 1).[13] After some experimentation it was found that complexation of **1a** with $BBr_3$ followed by addition of $Et_3N$ and stirring at RT for 1 h gave the

**Table 1.** Asymmetric [1,2]-Stevens Rearrangement of Substituted Proline Amides **1**[a]



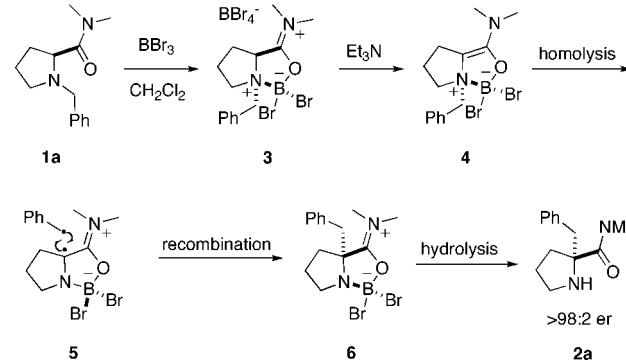

**1** **2**

| entry | Ar | *t* [h] | product | yield [%][b] | er[c] |
|---|---|---|---|---|---|
| 1 |  | 1 | **2a** | 85[d] | >98:2 |
| 2 |  | 1 | **2b** | 82 | >98:2 |
| 3 |  | 1 | **2c** | 76 | >98:2 |
| 4 |  | 1 | **2d** | 82 | >98:2 |
| 5 |  | 1 | **2e** | 81 | >98:2 |
| 6 |  | 2 | **2f** | 81 | >98:2 |
| 7 |  | 4 | **2g** | 62 | >98:2 |
| 8 |  | 1 | **2h** | 79 | >98:2 |

[a] All reactions were performed using **1** (0.4−0.6 mmol), $BBr_3$ (2 equiv), and $Et_3N$ (5 equiv) in $CH_2Cl_2$ (0.2 M) in a nitrogen atmosphere. [b] Yield of isolated product. [c] The er was determined by HPLC of **2** using a Chiracel OD-H column. [d] 97% yield when determined by $^1H$ NMR spectroscopy using 1-methylnaphthalene as an internal standard.

corresponding product **2a** in good yield and excellent er.[14] The high level of C→N→C chirality transfer can be explained by in situ formation of the rigid bicyclic complex **3** (Scheme 2). Treatment of amide **1a** with $BBr_3$ results in

**Scheme 2.** Proposed Mechanism for the [1,2]-Shift of **1a**




**1a** **3** **4** **5** **6** **2a**

(7) For an example of ester−enolate Claisen rearrangement in synthesis of quaternary prolines, see: (a) Sakaguchi, K.; Yamamoto, M.; Watanabe, Y.; Ohfune, Y. *Tetrahedron Lett.* **2007**, *48*, 4821–4824. (b) Sakaguchi, K.; Fujita, M.; Suzuki, H.; Higashino, M.; Ohfune, Y. *Tetrahedron Lett.* **2000**, *41*, 6589–6592.

(8) For reviews on Stevens rearrangement, see: (a) Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043–1062. (b) Pine, S. H. *Org. React. (NY)* **1970**, *18*, 403–464. (c) Lepley, A. R.; Giumanini, A. G. *Mechanisms of Molecular Migrations*; Thygarajan, B. S., Ed.; Interscience: New York, 1971; Vol. 3, pp 297−440. (d) Markó, I. E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 913−973.

(9) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31–33.

(10) Tayama, E.; Nanbara, S.; Nakai, T. *Chem. Lett.* **2006**, *35*, 478–479.

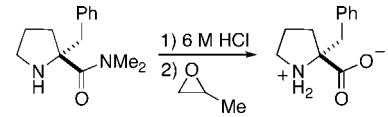
(11) Tuzina, P.; Somfai, P. *Tetrahedron Lett.* **2007**, *48*, 4947–4949.

(12) For the chirality transfer via a chiral borane−amine adduct in alkylation of (*S*)-*N*-benzylproline methyl ester, see: Ferey, V.; Vedrenne, P.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **1996**, *61*, 7244–7245, and references therein.

coordination of the Lewis acid *cis* to the amide moiety[15] which is followed by formation of structure **3**,[16] resulting in an efficient transfer of chirality from the α-carbon to the nitrogen nucleus. Subsequent deprotonation of **3** with $Et_3N$ provides ylide **4**, which suffers a homolytic cleavage of the C−N bond (see structure **5**) and then a radical recombination to form complex **6**. Although the bicyclic structure in **5** is achiral, efficient N→C chirality transfer is secured by selective migration of the benzyl radical on the α-face. Finally, hydrolysis of **6** gives **2a**, the absolute stereochemistry of which is identical to the starting material **1a**.[17] To define the scope and limitation of the rearrangement, proline derivatives **1b**−**h** were prepared and subjected to the optimized reaction conditions. Substrates **1b**−**d**, having different electronic properties, smoothly provided the enantioenriched amides **2b**−**d** in excellent yields (entries 2−4). Increasing the steric hindrance in the ortho position, as in derivative **1e**, provided the corresponding product **2e** in excellent yield and selectivity (entry 5). When employing 1-naphthyl derivative **1f**, prolonged reaction time was necessary to achieve full conversion to **2f** (entry 6). The more sterically demanding **1g**, having a 9-anthracenyl moiety, provided the corresponding quaternary amino acid derivative **2g**, although in a somewhat lower isolated yield (entry 7). This, then, should provide an efficient entry to novel fluorescent amino acid derivatives, compounds of current interest.[18] Interestingly, employing thiophene derivative **1h** provides the novel amino acid derivative **2h** in good isolated yield, illustrating the generality of the presented methodology (entry 8).[19]

Finally, hydrolysis of amides **2** to the corresponding amino acids was briefly investigated. Subjecting **2a** to 6 M HCl gave the corresponding hydrochloride salt, which was subsequently treated with propylene oxide.[20] After standard purification (*S*)-α-benzylproline (**7**) was isolated in 67% yield and >98:2 er (Scheme 3), which also confirmed the absolute configuration of **2a**.[21]

**Scheme 3.** Hydrolysis of **2a**




In conclusion, the first example of asymmetric Lewis acid mediated [1,2]-Stevens rearrangement was developed. This reaction serves as an efficient method for the preparation of proline derivatives having a quaternary stereocenter. The transformation is operationally simple and proceeds in good to excellent yields and with retention of the stereochemical purity of the starting material. In one case, it has been shown that the rearrangement product can be easily hydrolyzed into the corresponding amino acid.

**Acknowledgment.** This work was financially supported by the Royal Institute of Technology, the Swedish Research Council, and the Knut and Alice Wallenberg foundation.

**Supporting Information Available:** Experimental procedures and spectroscopic characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8028803

(13) Compound **1a** was prepared from commercially available *N*,*N*-dimethyl L-prolineamide.

(14) Similar rearrangement at 60 °C gave **2a** in 82% yield and 90:10 er.

(15) This is believed to arise from a preferential N pyramidal form, in which the substituent on nitrogen and the C-2 substituent are trans disposed. See: Vedejs, E.; Arco, M. J.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831–4837.

(16) Blid, J.; Brandt, P.; Somfai, P. *J. Org. Chem.* **2004**, *69*, 3043–3049. For the case with chiral Lewis acid, see: (a) Blid, J.; Panknin, O.; Tuzina, P.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 1294. (b) Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, *127*, 9352.

(17) The enantiomeric ratio of **2a** was determined by HPLC using a Chiracel OD-H column.

(18) For fluorescent anthracene-based amino acid derivatives, see: Kohta, S.; Shah, V. R.; Mishra, P. P.; Datta, A. *Amino Acids* **2007**, *35*, 169−173. For a study on efficient incorporation of fluorescent nonnatural amino acids, see: (a) Doi, Y.; Ohtsuki, T.; Shimizu, Y.; Ueda, T.; Sisido, M. *J. Am. Chem. Soc.* **2007**, *129*, 14458–14462. (b) Hohsaka, T.; Kajihara, D.; Ashizuka, Y.; Murakami, H.; Sisido, M. *J. Am. Chem. Soc.* **1999**, *121*, 34.

(19) Only one example of [1,2]-Stevens rearrangement of an ammonium salt containing a thienylmethyl moiety has been reported. See: Kocharyan, S. T.; Karapetyan, V. E.; Churkina, N. P. *Russ. J. Gen. Chem.* **2000**, *70*, 1094–1097.

(20) MacQuarrie-Hunter, S.; Carlier, P. R. *Org. Lett.* **2005**, *7*, 5305–5308.

(21) The assignment was confirmed by comparison of the sign of **7** $[\alpha]^{23}_D$ −21.2 (*c* 0.27, $H_2O$) with that of the known (*S*)-**7** ($[\alpha]^{20}_D$ −18.1 (*c* 0.27, $H_2O$)). See: Genin, M. J.; Baures, P. W.; Johnson, R. L. *Tetrahedron Lett.* **1994**, *35*, 4967–4968.