#### Asymmetric Synthesis of $(\alpha R)$ -Polyfluoroalkylated Prolinols Based on the Perfluoroalkyl-Induced **Highly Stereoselective Reduction of** Perfluoroalkyl N-Boc-pyrrolidyl Ketones

Kazumasa Funabiki,\*,\* Akitsugu Shibata,\* Hiroki Iwata,\* Keisuke Hatano,<sup>†</sup> Yasuhiro Kubota,<sup>†</sup> Kenichi Komura, Masahiro Ebihara,<sup>‡</sup> and Masaki Matsui<sup>†</sup>

Department of Materials Science and Technology and Department of Chemistry, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

funabiki@gifu-u.ac.jp

Received March 3, 2008



Reduction of the obtained chiral (S)-tert-butyl 2-(perfluoroalkanoyl)pyrrolidine-1-carboxylate with sodium borohydride or lithium aluminum hydride proceeded smoothly to give the corresponding (S)-tert-butyl 2-((R)-perfluoro-1-hydroxyalkyl)pyrrolidine-1-carboxylate in yields of 73-97% with excellent diastereoselectivities (up to >98% de), compared with the reduction of nonfluorinated (S)-tert-butyl 2-pentanoylpyrrolidine-1-carboxylate.

Considerable attention has recently been addressed to optically pure prolinol derivatives,<sup>1</sup> since these compounds are some of the most efficient organocatalysts<sup>2</sup> in catalytic asymmetric reactions, such as the Mannich reaction,<sup>3</sup> Michael (conjugate) addition,<sup>4</sup> tandem reaction,<sup>5</sup>  $\alpha$ -oxidation,<sup>6</sup> amination,<sup>7</sup>  $\alpha$ -halogenation,<sup>8</sup>  $\alpha$ -sulfenylation,<sup>9</sup>  $\alpha$ -seleneylation,<sup>10</sup>  $\alpha$ -arylation,<sup>11</sup> epoxidation,<sup>12</sup> aziridination,<sup>13</sup> aldol reaction,<sup>14</sup> ene reaction,<sup>15</sup> hetero-Diels–Alder reaction,<sup>16</sup> and 1,3-dipolar cycloaddition

<sup>†</sup> Department of Materials Science and Technology, Faculty of Engineering, Gifu University.

<sup>\*</sup> Department of Chemistry, Faculty of Engineering, Gifu University.
 (1) Reviews of the prolinol ethers: (a) Enders, D.; Klatt, M. Synthesis 1996,

1403. (b) Palomo, C.; Mielgo, A. Angew. Chem., Int. Ed. 2006, 45, 7876.

(3) A recent paper: Ibrahem, I.; Zhao, G. L.; Eriksson, L.; Córdova, A. Chem. Eur. J. 2007, 13, 683.

reaction,<sup>17</sup> and can also act as chiral ligands for the reduction of ketones,<sup>18</sup> and the alkylation<sup>19</sup> and arylation<sup>20</sup> of aldehydes. Therefore, various approaches to optically pure prolinol derivatives from commercially available L-proline have been developed over the past 30 years.<sup>21</sup>

However, to the best of our knowledge, there has been no report on the asymmetric synthesis or the use of  $\alpha$ -fluoroalky-lated optically pure prolinol derivatives,<sup>22–24</sup> despite their expected widespread applications, although some reports have described the excellent properties of  $\alpha$ -trifluoromethylated chiral aminoalcohols,<sup>25-27</sup>which could be used as ligands, chiral auxiliaries, or organocatalysts in the asymmetric addition of diethyl zinc, the asymmetric Reformatsky reaction, the asymmetric Simmons-Smith reaction, transesterification, and kinetic resolutions.

(4) Recent examples: Michael reaction : Gotoh, H.; Ishikawa, H.; Hayashi, Y. Org. Lett. 2007, 9, 5307. Conjugate addition of amines: Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G. L.; Córdova, A. Chem. Commun. 2007, 849. Conjugate addition of alcohols: Bertelsen, S.; Diner, P.; Johansen, R. L.; Jørgensen, K. A. J. Am. Chem. Soc. 2007, 129, 1536. Conjugate addition of phosphites: Maerten, E.; Cabrera, S.; Kjærsgaard, A.; Jørgensen, K. A. J. Org. Chem. 2007, 72, 8893. Conjugate addition of phosphine: Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himo, F.; Córdova, A. Angew. Chem., Int. Ed. 2007, 46, 4507. (5) A recent example: Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D.

Angew. Chem., Int. Ed. 2007, 46, 4922. (6) Ibrahem, I.; Zhao, G. L.; Sundén, H.; Córdova, A. Tetrahedron Lett. 2006,

47. 4659.

(7) A recent example: Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, B.; Jørgensen, K. A. J. Am. Chem. Soc. 2006, 128, 12973.
(8) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen,

K. A. Angew. Chem., Int. Ed. 2005, 44, 3703, and ref 7.

(9) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. Angew. Chem., Int. Ed. 2005, 44, 794.

(10) (a) Sunden, H.; Rios, R.; Córdova, A. Tetrahedron Lett. 2007, 48, 7865. (b) Tiecco, M.; Carlone, A.; Sternative, S.; Marini, F.; Bartoli, G.; Melchiorre, P. Angew. Chem., Int. Ed. 2007, 46, 6882

(11) Alemán, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A. Angew. Chem., Int. Ed. 2007, 46, 5520.

(12) A recent example: Li, Y.; Liu, X.; Yang, Y.; Zhao, G. J. Org. Chem. 2007, 72, 288.

(13) Vesely, J.; Ibrahem, I.; Zhao, G. L.; Rios, R.; Córdova, A. Angew. Chem., Int. Ed. 2007, 46, 778.

(14) Zhong, G.; Fan, J.; Barbas, C. F. Tetrahedron Lett. 2004, 45, 5681.

(15) Gotoh, H.; Masui, R.; Ogino, H.; Shoji, M.; Hayashi, Y. Angew. Chem., Int. Ed. 2006, 45, 6853.

(16) Juhl, K.; Jørgensen, K. A. Angew. Chem., Int. Ed. 2003, 42, 1498.

(17) A recent example: Ibrahem, I.; Rios, R.; Vesely, J.; Córdova, A. Tetrahedon Lett. 2007, 48, 6252.

(18) Selected reviews: Deloux, L.; Srebnik, M. Chem. Rev. 1993, 93, 763. Corey, E. J.; Helal, C. J. Angew. Chem., Int. Ed. 1998, 37, 1986.

(19) A review: (a) Soai, K.; Niwa, S. Chem. Rev 1992, 92, 833. Selected examples: (b) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. J. Am. Chem. Soc. 1987, 109, 7111. (c) Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K.;

 Yang, L.; Wong, K.-Y. Tetrahedron: Asymmetry 1999, 10, 133.
 (20) Wu, X.; Liu, X.; Zhao, G. Tetrahedron: Asymmetry 2005, 16, 2299. (21) A recent example: Bejjani, J.; Chemla, F.; Audouin, M. J. Org. Chem.

2003. 68. 9747. (22)  $\alpha,\alpha$ -Bis(4-perfluoroalkylphenyl)prolinol derivatives: (a) Chu, Q.; Yu, M. S.; Curran, D. P. Org. Lett. **2008**, *10*, 749. (b) Zu, L.; Li, H.; Wang, J.; Yu, X.; Wang, W. Tetahedron Lett. **2006**, *47*, 5131. (c) Dalicsek, Z.; Pollreisz, F.; Gömöry, Á.; Soós, T. Org. Lett. **2005**, *7*, 3243. (d) Park, J. K.; Lee, H. G.; Bolm, C.; Kim, B. M. Chem. Eur. J. 2005, 11, 945.

(23) a,a-Bis(perfluorohexylethyl)prolinol: Goushi, S.; Funabiki, K.; Ohta, M.; Hatano, K.; Matsui, M. Tetrahderon 2007, 63, 4061.

(24) 2-Trifluoromethylprolinol: Chaume, G.; Severen, V. M.-C.; Marinkovic, S.; Brigaud, T. Org. Lett. 2006, 8, 6123.

(25) (a) Katagiri, T.; Fujiwara, Y.; Takahashi, S.; Ozaki, N.; Uneyama, K. Chem. Commun. 2002, 986. (b) Fujiwara, Y.; Katagiri, T.; Uneyama, K. Tetrahedron Lett. 2003, 44, 6161. (c) Katagiri, T.; Iguchi, N.; Kawate, T.; Takahashi, S.; Uneyama, K. Tetrahedron: Asymmetry 2006, 17, 1157.

(26) Wayman, K. A.; Sammakia, T. Org. Lett. 2003, 5, 4105.
 (27) (a) Notte, G. T.; Sammakia, T.; Steel, P. J. J. Am. Chem. Soc. 2005, 127, 13502. (b) Notte, G. T.; Sammakia, T. J. Am. Chem. Soc. 2006, 128, 4230.

<sup>(2)</sup> Recent reviews on organocatalysis: ref 1b and: (a) Dalko, P. I.; Moisan, L. Angew. Chem., Int. Ed. 2001, 40, 3726. (b) List, B. Synlett 2001, 1675. (c) List, B. Tetrahedron 2002, 58, 2481. (d) Dalko, P. I.; Moisan, L. Angew. Chem., Int. Ed. 2004, 43, 5138. (e) Special Issue, Acc. Chem. Res. 2004, 37, No. 8. (f) Berkessel, A.; Gröger, H. Asymmetric Organocatalysis; Wiley-VCH: Weinheim, Germany, 2005. (g) Seayad, J.; List, B. Org. Biomol. Chem. 2005, 3, 719. (h) Lelais, G.; MacMillan, D. W. C. Aldrichim. Acta 2006, 39, 79. (i) List, B. Chem. Commun. 2006, 819. (j) Marigo, M.; Jørgensen, K. A. Chem. Commun. 2006, 2001. (k) Guillena, G.; Ramon, D. J. Tetrahedron: Asymmetry 2006, 17, 1465. (1) Taylor, M. S.; Jacobsen, E. N. Angew. Chem., Int. Ed. 2006, 45, 1520. (m) Connon, S. J. Chem. Eur. J. 2006, 12, 5418. (n) Akiyama, T.; Itoh, J.; Fuchibe, K. Adv. Synth. Catal. 2006, 348, 999.

### JOCNote

SCHEME 1. Synthesis of Perfluoroalkylated *N*-Boc-pyrrolidyl Ketones 1



On the other hand, the reduction of *N*-alkoxycarbonyl,<sup>28</sup> *N*-alkoxycarbonyl-*N*-alkyl,<sup>29</sup> or *N*,*N*-dialkyl  $\alpha$ -amino ketones<sup>30</sup> with various reducing agents has become one of the most reliable and efficient methods for the stereoselective synthesis of 1,2-aminoalcohols. There have been some systematic studies<sup>28a,31</sup> on the nature of the transition state, including the relationship between the substituents on the nitrogen atom and the stereoselectivity.

We describe here the first asymmetric synthesis of  $(\alpha R)$ -perfluoroalkylated prolinol derivatives based on the perfluoroalkyl-controlled highly stereoselective reduction of the corresponding perfluoroalkyl *N-tert*-butoxycarbonyl (Boc)-pyrrolidyl ketones, which is one of the most promising routes to access  $(\alpha R)$ -perfluoroalkyl prolinol derivatives.

Methyl (*S*)-*N*-Boc-pyrrolidine-2-carboxylate was reacted with perfluoroalkyllithiums, prepared in situ from perfluorobutyl, perfluorohexyl, and perfluorooctyl iodides and methyllithium—lithium bromide complex,<sup>32</sup> to produce only (*S*)-*tert*-butyl 2-(2,2,3,3,4,4,5,5,5-nonafluoropentanoyl)pyrrolidine-1-carboxylate (**1a**), (*S*)-*tert*-butyl 2-(2,2,3,3,4,4,5,-5,6,6,7,7,7-tridecafluoroheptanoyl)pyrrolidine-1-carboxylate (**1b**), and (*S*)-*tert*-butyl 2-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9heptadecafluorononanoyl)pyrrolidine-1-carboxylate (**1c**) in respective yields of 78%, 60%, and 52%, via hydrolysis of the stable lithium hemiketal intermediate (Scheme 1).

(*S*)-*tert*-Butyl 2-(2,2,2-trifluoroacetyl)pyrrolidine-1-carboxylate (**1d**) was obtained in 28% yield via the trifluoromethylation of ester with trifluoromethyltrimethylsilane in the presence of a catalytic amount (3 mol %) of tetrabutylammonium fluoride (TBAF) in pentane, together with ketone **1d** hydrate in 40% yield (eq 1).<sup>33</sup> Trifluoromethylation occurred predominantly at the carbonyl carbon of the methoxycarbonyl group.

The ester reacted with *n*-butyllithium (*n*-BuLi) to produce (*S*)-*tert*-butyl 2-pentanoylpyrrolidine-1-carboxylate (**1e**) in 47% yield, together with *N*-Boc- $\alpha$ , $\alpha$ -din-butylprolinol (**2**) in 41% yield (eq 2).

<sup>1</sup>H and <sup>13</sup>C NMR analyses revealed that atropisomers of the *N*-Boc-pyrrolidyl ketones **1** arose from the carbamate moiety.<sup>34</sup>



These ratios were 63:37 for perfluorobutylated ketone **1a** and 58:42 for *n*-butylated **1e** in CDCl<sub>3</sub>, respectively. The ratios of the atropisomers of **1a,e** were not significantly different. To determine the enantiomeric purity of the perfluorobutyl *N*-Boc-pyrrolidyl ketone **1a0**, we performed GC and NMR analyses of the crude reaction mixture of (+)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid ((+)-MTPA) amide derivative **4**, which was obtained via a second perfluorobutylation of the perfluorobutyl *N*-Boc-pyrrolidyl ketone **1a** giving bis(perfluorobutyl) *N*-Boc-prolinol **3**, cleavage of the Boc group by trifluoroacetic acid (TFA), and condensation with (+)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl chloride in the presence of sodium hydroxide (see the Supporting Information). Consequently, the enantiomeric purity of perfluorobutyl *N*-Boc-pyrrolidyl ketone **1a** was found to be >99% ee.

Interestingly, when the resulting perfluorobutyl N-Bocpyrrolidyl ketone 1a was added to an ethanol solution of sodium borohydride (NaBH<sub>4</sub>) at 0 °C and the mixture was stirred at room temperature for 7 h, reduction of the ketone 1a proceeded smoothly to produce the corresponding alcohol ( $\alpha R$ )-5a in 78% yield as a single diastereomer (Table 1, entry 1). Perfluorohexyl and perfluorooctyl N-Boc-pyrrolidyl ketones 1b,c could also participate in the reduction at room temperature to give the corresponding  $(\alpha R)$ -perfluorohexylated and  $(\alpha R)$ -perfluorooctylated N-Boc-prolinols ( $\alpha R$ )-**5b,c** in respective yields of 77% and 73% (entries 2 and 3). Use of a mixture of the trifluoromethylated ketone 1d and its hydrate under the same reaction conditions resulted in a decrease in diastereoselectivity (dr = 85:15) (entry 4).<sup>35</sup> A lower reaction temperature was very effective for increasing the diastereoselectivity of 5d in the reduction of a mixture of the trifluoromethylated ketone 1d and its hydrate to give  $\alpha$ -trifluoromethylated N-Boc-prolinol ( $\alpha R$ )-5d in yields of 92-97% with excellent diastereoselectivities (92-96% de) (entries 5 and 6). The hydrate of trifluoromethylated ketone 1d is probably likely to be reduced via the in situ generation of the ketone 1d to give the  $(\alpha R)$ -trifluoromethylated prolinol 5d with high diastereoselectivity. In contrast, the reduction of fluorine-free (S)-tert-butyl 2-pentanoylpyrrolidine-1-carboxylate (1e) gave the corresponding prolinol 5e with extremely low to moderate diastereoselectivities (14-52% de), even at a lower reaction temperature (-78 to 0 °C) (entries 7

<sup>(28) (</sup>a) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. J. Org. Chem. 2002, 67, 1045. (b) Harris, B. D.; Bhat, K. L.; Joullie, M. M. Tetrahedron Lett. 1987, 28, 2837.

<sup>(29)</sup> Reduction of N-Boc-protected secondary amino ketones: Chung, S.-K.; Lee, J.-M. *Tetrahedron: Asymmetry* **1999**, *10*, 1441. Nishida, A.; Sorimachi, H.; Iwaida, M.; Matsumizu, M.; Kawate, T.; Nakagawa, M. *Synlett* **1998**, 389. Koskinen, A. M. P.; Koskinen, P. M. *Tetrahedron Lett.* **1993**, *34*, 6765.

<sup>(30)</sup> Reetz, M. T.; Drewes, M. W.; Mattews, B. R.; Lennick, K. J. Chem. Soc., Chem. Commun. 1989, 1474. Lagu, B. R.; Liotta, D. C. Tetrahedron Lett. 1994, 35, 547.

 <sup>(31)</sup> Ookawa, A.; Soai, K. J. Chem. Soc., Perkin Trans. 1987, 1, 1465.
 (32) Uno, H.; Shiraishi, Y.; Simokawa, K.; Suzuki, H. Chem. Lett. 1987, 1153.

<sup>(33)</sup> Wiedemann, J.; Heiner, T.; Mloston, G.; Prakash, G. K. S.; Olah, G. A. Angew. Chem., Int. Ed. **1998**, *37*, 820.

<sup>(34)</sup> Tetrahedron Symposium-in-print on Axially Chiral Amides: Clayden, J., Ed. *Tetrahedron* **2004**, *60*, 4325.

<sup>(35)</sup> Diastereoselective reduction of the α-protected amino trifluoromethylated ketones: (a) Andrés, J. M. Pedrosa, R. Pérez-Encabo, A. Eur. J. Org. Chem. 200471558. (b) Kawase, M.; Hirabayashi, M.; Kumakura, H.; Saito, S.; Yamamoto, K. *Chem. Pharm. Bull.* **2000**, *48*, 114. (c) Peet, N. P. Burkhart, J. P. Angelastro, M. R. Giroux, E. L. Mehdi, S. Bey, P. Kolb, M. Neises, B. Schirlin, D. J. Med. Chem. 199033394. Non-stereoselective reduction of the α-protected amino perfluoroalkylated ketones: (d) Omote, M.; Eto, Y.; Tarui, A.; Sato, K.; Ando, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2768.

# JOC Note

 TABLE 1.
 Asymmetric Reduction of Perfluoroalkylated,

 Trifluoromethylated, and *n*-Butylated *N*-Boc-pyrrolidyl Ketones 1

N Boc O EtOH		
1a: R = $CF_3(CF_2)_3$ 1b: R = $CF_3(CF_2)_5$ 1c: R = $CF_3(CF_2)_7$ 1d: R = $CF_3$ 1o: R = $n$ Ru	(α <i>R</i> )-5a,b,c,d (αS)-5e	(αS)- <b>5a,b,c,c</b> (α <i>R</i> )- <b>5e</b>

entry	1	reducing agents <sup>a</sup>	conditions	<b>5</b> , yield $(\%)^b$ ( $\alpha R:\alpha S$ )
1	1a	NaBH <sub>4</sub>	rt, 7 h <sup>c</sup>	<b>5a</b> 78% (>99: <1)
2	1b	$NaBH_4$	rt, 7 h <sup>c</sup>	<b>5b</b> 77% (>99: <1)
3	1c	$NaBH_4$	rt, 7 h <sup>c</sup>	<b>5c</b> 73% (>99: <1)
$4^d$	1d	$NaBH_4$	rt, 7 h $^c$	5d 83% (85: 15)
$5^e$	1d	NaBH <sub>4</sub>	0 °C to $rt^{f}$	5d 92% (96: 4)
$6^e$	1d	$NaBH_4$	-78 to 0 °C <sup>g</sup>	5d 97% (98: 2)
7	1e	$NaBH_4$	rt, 7 h $^c$	5e 96% (43: 57)
8	1e	$NaBH_4$	-78 to 0 °C <sup>g</sup>	5e 88% (24: 76)
$9^h$	1a	LiAlH <sub>4</sub>	-78 to 0 °C <sup>g</sup>	<b>5a</b> 77% (>99: <1)

<sup>*a*</sup> Two equivalents was used. <sup>*b*</sup> Yields of isolated products. <sup>*c*</sup> An ethanol solution of **1** was added at 0 °C. <sup>*d*</sup> A mixture of the ketone **1d** and the ketone hydrate (56:44) was used. <sup>*e*</sup> A mixture of the ketone **1d** and the ketone hydrate (40:60) was used. <sup>*f*</sup> The reaction mixture was gradually warmed over 7 h. <sup>*g*</sup> The reaction mixture was gradually warmed over 6 h. <sup>*h*</sup> THF was used as a solvent.

and 8). With regard to other reducing agents, when perfluorobutylated ketone **1a** was added to a tetrahydrofuran (THF) solution of lithium aluminum hydride (LAH) at -78 °C and the resulting mixture was gradually warmed to 0 °C over 6 h, reduction of the ketone **1a** proceeded smoothly to give the prolinol ( $\alpha R$ )-**5a** in 77% yield with the same excellent diastereoselectivity (entry 9).

As shown in eqs 3 and 4, the relative configurations of **5** could be determined by the vicinal coupling constants of the oxazolidinones **6** in <sup>1</sup>H NMR after prolinols **5** were converted into oxazolidinones **6** (**6e**, 41%; **6e**', 34%) via cleavage of the Boc group, reprotection by the ethoxycarbonyl group, and cyclization in the presence of sodium hydride (NaH) as a base. Direct conversion of the prolinols **5** to the oxazolidinones **6** was very sluggish, probably because of the steric hindrance of the *t*-Bu group. *n*-Butylated oxazolidinone **6e**, whose vicinal protons at C-1 and C-7-a are situated in an *anti* arrangement, has a smaller coupling constant (<sup>3</sup>J<sub>Ha-Hb</sub> = 4.1 Hz) than that of **6e**' (<sup>3</sup>J<sub>Ha-Hb</sub> = 8.3 Hz), according to the reported values.<sup>21,28</sup>



Consequently, the structure of the obtained 1-perfluoroalkylated oxazolidinones **6a,d** (**6a**, 28% from **5a**; **6d**, 32% from **5d**) could also be assigned to be *anti*, since the vicinal coupling constants (**6a**, Rf = CF<sub>3</sub>(CF<sub>2</sub>)<sub>3</sub>,  ${}^{3}J_{\text{Ha-Hb}} = 4.3$  Hz; **6d**; Rf = CF<sub>3</sub>,  ${}^{3}J_{\text{Ha-Hb}} = 3.3$  Hz) are similar to those of *n*-butylated *anti*oxazolidinone **6e**. The stereochemical assignment of *N*-Boc- $\alpha$ - perfluorobutyl prolinol **5a** could also be determined to be  $2S,\alpha R$  by X-ray analysis, as shown in the Supporting Information.

Kawase et al. reported that the reduction of  $\alpha$ -N-alkoxycarbonyl-N-alkylamino trifluoromethylated ketones with NaBH<sub>4</sub> in ethanol at room temperature gave the corresponding syn- $\beta$ -amino- $\alpha$ -trifluoromethyl alcohols in good to excellent yields with excellent syn-selectivities.<sup>35b</sup> In the literature, syn-selectivities have been explained by the Felkin-Anh transition state model. This excellent syn-selectivity in the reduction of  $\alpha$ -dibenzylamino trifluoromethyl ketones with NaBH<sub>4</sub> in a mixture of solvent methanol and THF at -20 °C to give the corresponding  $\beta$ -dibenzylamino- $\alpha$ -trifluoromethyl alcohol has also been reported by Pedrosa et al.<sup>35a</sup> On the basis of these reports as well as the results of the X-ray analysis of 5a and the stereochemical assignment of the oxazolidinones **6a**,**d**, the reduction of perfluoroalkyl N-Boc-pyrrolidyl ketones 1 proceeds via the Felkin-Anh transition state TS-1, as shown in Figure 1.

Good to excellent diastereoselectivities were observed in the reduction of perfluoroalkyl *N*-Boc-pyrrolidyl ketones **1a**–**d** even at room temperature, since the steric repulsion between the perfluoroalkyl group and the pyrrolidine ring should be much greater than that with *n*-butylated ketone **1e**. Thus, the diastereoselectivities may depend on the bulkiness of the perfluoroalkyl or *n*-butyl groups, which are in the following order: perfluorooctyl = perfluorohexyl = perfluorobutyl > trifluoromethyl (steric effect constant  $(E_s) = 1.16)^{36} \gg n$ -butyl  $(E_s = 0.39)$ .

In conclusion, chiral perfluoroalkyl N-Boc-pyrrolidyl ketones could be prepared by reacting methyl (S)-N-Bocpyrrolidine-2-carboxylate and perfluoroalkyllithium reagents prepared from perfluoroalkyl iodides and methyllithiumlithium bromide complex. Trifluoromethyl N-Boc-pyrrolidyl ketone could also be obtained by reacting methyl (S)-N-Bocpyrrolidine-2-carboxylate and trifluoromethyltrimethylsilane in the presence of a catalytic amount of tetrabutylammonium fluoride, together with trifluoromethyl N-Boc-pyrrolidyl ketone hydrate. We have achieved the perfluoroalkyl-induced highly stereoselective reduction of the resulting perfluoroalkyl N-Boc-pyrrolidyl ketones using common reducing agents, such as NaBH<sub>4</sub> and LAH. This method provides the first efficient and asymmetric access to  $(\alpha R)$ -perfluoroalkylated prolinols. Further studies on the asymmetric synthesis of  $\alpha$ -perfluoroalkylated prolinols carrying a quaternary carbon center at the  $\alpha$ -position based on the carbon-carbon bond formation of perfluoroalkyl N-Boc-pyrrolidyl ketones are now in progress.

#### **Experimental Section**

**Typical Procedure for the Reduction of Ketones.** To a solution of NaBH<sub>4</sub> (0.076 g, 2 mmol) in EtOH (5 mL) was added an EtOH solution (3 mL) of (*S*)-*tert*-butyl 2-(2,2,3,3,4,4,5,5,5-nonafluoropentanoyl)pyrrolidine-1-carboxylate (**1a**) (0.417 g, 1 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 7 h, the reaction was quenched with 10% HCl aq solution (60 mL), and then subjected to extraction with Et<sub>2</sub>O (3 × 30 mL). The organic layer was washed with brine (70 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated by distillation under reduced pressure. Purification of the residue by silica gel

<sup>(36)</sup> Tafts, K. W., Jr. Steric Effects in Organic Chemistry; Newman, M. S., Ed.; John Wiley & Sons: New York, 1956; p 556.

## JOC Note



FIGURE 1. Proposed transition state.

column chromatography (hexane $-CH_2Cl_2 = 1:2$ ) gave ( $\alpha R$ )-5a (78%, 0.325 g).

(*S*)-*tert*-Butyl 2-((*R*)-2,2,3,3,4,4,5,5,5-Nonafluoro-1-hydroxypentyl)pyrrolidine-1-carboxylate ((*αR*)-5a). *Rf* 0.33 (hexane– CH<sub>2</sub>Cl<sub>2</sub> = 1:2); mp 74.6–75.3 °C; [*α*]<sup>25</sup><sub>D</sub> –19.9 (*c* 1.00, CHCl<sub>3</sub>); IR (KBr) 3250 (OH), 1682 (C=O) cm<sup>-1</sup>; HRMS (FAB) found *m*/*z* 420.1212, calcd for C<sub>14</sub>H<sub>19</sub>F<sub>9</sub>NO<sub>3</sub> (M + H) 420.1221. Anal. Calcd for C, 40.10; H, 4.33; N, 3.34. Found: C, 39.80; H, 4.18; N, 3.35. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.39 (9H, s), 1.78–1.86 (3H, m), 1.93–2.01 (1H, m), 3.25–3.40 (2H, m), 3.85 (1H, dt, *J* = 19.9, 8.5 Hz), 4.26 (1H, t, *J* = 8.5 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 23.7 (s), 28.0 (s), 28.7 (s), 46.8 (s), 56.8 (s), 73.4–73.9 (m), 81.4 (s), 105.9–122.1 (4C, m), 158.8 (s); <sup>19</sup>F NMR (372 MHz, CDCl<sub>3</sub>) δ –52.48 to –51.66 (m, 2F), –49.96 to –47.71 (m, 2F), –46.36 to –41.03 (m, 2F), –5.73 (s, 3F). Acknowledgment. We thank Professors T. Ishihara, T. Konno, and H. Yamanaka of the Kyoto Institute of Technology for the HRMS measurements.We are grateful to Daikin Inc. for the gift of perfluoroalkyl iodides as well as Tosoh F-Tech, Inc. for the gift of trifluoromethyltrimethylsilane. K.F. also acknowledges the AJINOMOTO Award in Synthetic Organic Chemistry, Japan.

Supporting Information Available: Detailed procedures and characterization of all of the compounds, <sup>1</sup>H and <sup>13</sup>C NMR spectra for 1a-d, 2, 3, 4,  $(\alpha R)$ -5a-e,  $(\alpha S)$ -5d,e, 6a,c,d, and 6c', and crystallographic data for compound  $(\alpha R)$ -5a. This material is available free of charge via the Internet at http://pubs.acs.org. JO8004952