JOC*Note*

Asymmetric Synthesis of (α*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,[†] Yasuhiro Kubota,[†] Kenichi Komura,[†] Masahiro Ebihara,[‡] and Masaki Matsui[†]

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

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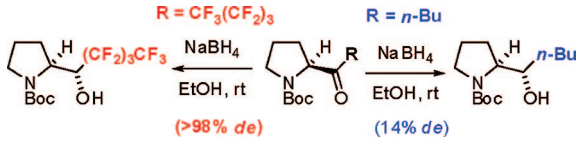

Reduction of the obtained chiral (*S*)-*tert*-butyl 2-(perfluoroalkanoyl)pyrrolidine-1-carboxylate with sodium borohydride or lithium aluminum hydride proceeded smoothly to give the corresponding (*S*)-*tert*-butyl 2-((*R*)-perfluoro-1-hydroxyalkyl)pyrrolidine-1-carboxylate in yields of 73−97% with excellent 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,[1] since these compounds are some of the most efficient organocatalysts[2] in catalytic asymmetric reactions, such as the Mannich reaction,[3] Michael (conjugate) addition,[4] tandem reaction,[5] α-oxidation,[6] amination,[7] α-halogenation,[8] α-sulfenylation,[9] α-seleneylation,[10] α-arylation,[11] epoxidation,[12] aziridination,[13] aldol reaction,[14] ene reaction,[15] hetero-Diels−Alder reaction,[16] and 1,3-dipolar cycloaddition reaction,[17] and can also act as chiral ligands for the reduction of ketones,[18] and the alkylation[19] and arylation[20] of aldehydes. Therefore, various approaches to optically pure prolinol derivatives from commercially available L-proline have been developed over the past 30 years.[21]

However, to the best of our knowledge, there has been no report on the asymmetric synthesis or the use of α-fluoroalkylated optically pure prolinol derivatives,[22–24] despite their expected widespread applications, although some reports have described the excellent properties of α-trifluoromethylated chiral aminoalcohols,[25–27]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.

† Department of Materials Science and Technology, Faculty of Engineering, Gifu University.

‡ Department of Chemistry, Faculty of Engineering, Gifu University.

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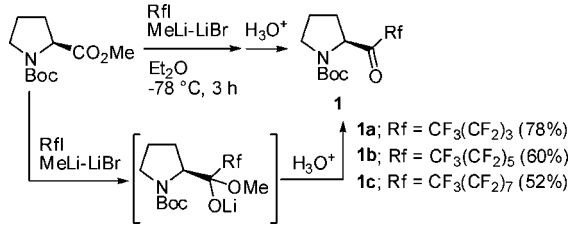
SCHEME 1. Synthesis of Perfluoroalkylated *N*-Boc-pyrrolidyl Ketones 1



On the other hand, the reduction of *N*-alkoxycarbonyl,[28] *N*-alkoxycarbonyl-*N*-alkyl,[29] or *N*,*N*-dialkyl α-amino ketones[30] 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[28a,31] on the nature of the transition state, including the relationship between the substituents on the nitrogen atom and the stereoselectivity.

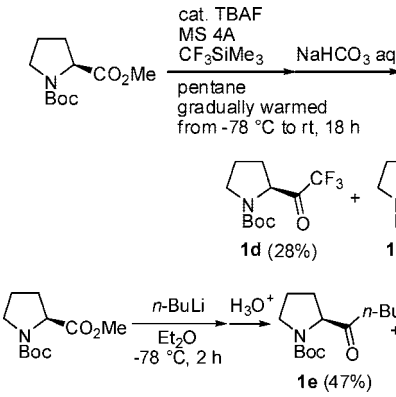
We describe here the first asymmetric synthesis of (α*R*)-perfluoroalkylated prolinol derivatives based on the perfluoroalkyl-controlled highly stereoselective reduction of the corresponding perfluoroalkyl *N*-*tert*-butoxycarbonyl (Boc)-pyrrolidyl ketones, which is one of the most promising routes to access (α*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,[32] 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-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluorononanoyl)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).[33] 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-α,α-di*n*-butylprolinol (**2**) in 41% yield (eq 2).

^{1}H and ^{13}C NMR analyses revealed that atropisomers of the *N*-Boc-pyrrolidyl ketones **1** arose from the carbamate moiety.[34]



These ratios were 63:37 for perfluorobutylated ketone **1a** and 58:42 for *n*-butylated **1e** in $CDCl_3$, 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 (+)-α-methoxy-α-(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 (+)-α-methoxy-α-(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*-Boc-pyrrolidyl ketone **1a** was added to an ethanol solution of sodium borohydride ($NaBH_4$) 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 (α*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 (α*R*)-perfluorohexylated and (α*R*)-perfluorooctylated *N*-Boc-prolinols (α*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).[35] 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 α-trifluoromethylated *N*-Boc-prolinol (α*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 (α*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

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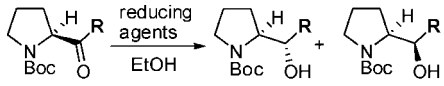
TABLE 1. Asymmetric Reduction of Perfluoroalkylated, Trifluoromethylated, and *n*-Butylated *N*-Boc-pyrrolidyl Ketones 1



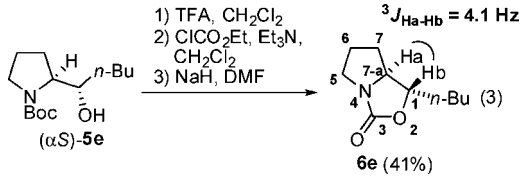
1a : R = $CF_3(CF_2)_3$
1b : R = $CF_3(CF_2)_5$
1c : R = $CF_3(CF_2)_7$
1d : R = CF_3
1e : R = *n*-Bu

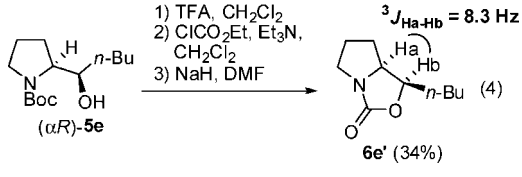
entry	1	reducing agents[a]	conditions	5, yield (%)[b] (αR:αS)
1	**1a**	$NaBH_4$	rt, 7 h[c]	**5a** 78% (>99: <1)
2	**1b**	$NaBH_4$	rt, 7 h[c]	**5b** 77% (>99: <1)
3	**1c**	$NaBH_4$	rt, 7 h[c]	**5c** 73% (>99: <1)
4[d]	**1d**	$NaBH_4$	rt, 7 h[c]	**5d** 83% (85: 15)
5[e]	**1d**	$NaBH_4$	0 °C to rt[f]	**5d** 92% (96: 4)
6[e]	**1d**	$NaBH_4$	−78 to 0 °C[g]	**5d** 97% (98: 2)
7	**1e**	$NaBH_4$	rt, 7 h[c]	**5e** 96% (43: 57)
8	**1e**	$NaBH_4$	−78 to 0 °C[g]	**5e** 88% (24: 76)
9[h]	**1a**	$LiAlH_4$	−78 to 0 °C[g]	**5a** 77% (>99: <1)

[a] Two equivalents was used. [b] Yields of isolated products. [c] An ethanol solution of **1** was added at 0 °C. [d] A mixture of the ketone **1d** and the ketone hydrate (56:44) was used. [e] A mixture of the ketone **1d** and the ketone hydrate (40:60) was used. [f] The reaction mixture was gradually warmed over 7 h. [g] The reaction mixture was gradually warmed over 6 h. [h] 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 (α*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 ^{1}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 ($^3J_{Ha\text{-}Hb}$ = 4.1 Hz) than that of **6e′** ($^3J_{Ha\text{-}Hb}$ = 8.3 Hz), according to the reported values.[21,28]





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 = $CF_3(CF_2)_3$, $^3J_{Ha\text{-}Hb}$ = 4.3 Hz; **6d**; Rf = CF_3, $^3J_{Ha\text{-}Hb}$ = 3.3 Hz) are similar to those of *n*-butylated *anti*-oxazolidinone **6e**. The stereochemical assignment of *N*-Boc-α-perfluorobutyl prolinol **5a** could also be determined to be 2*S*,α*R* by X-ray analysis, as shown in the Supporting Information.

Kawase et al. reported that the reduction of α-*N*-*alkoxycarbonyl*-*N*-alkylamino trifluoromethylated ketones with $NaBH_4$ in ethanol at room temperature gave the corresponding *syn*-β-amino-α-trifluoromethyl alcohols in good to excellent yields with excellent *syn*-selectivities.[35b] In the literature, *syn*-selectivities have been explained by the Felkin−Anh transition state model. This excellent *syn*-selectivity in the reduction of α-*dibenzyl*amino trifluoromethyl ketones with $NaBH_4$ in a mixture of solvent methanol and THF at −20 °C to give the corresponding β-dibenzylamino-α-trifluoromethyl alcohol has also been reported by Pedrosa et al.[35a] 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] ≫ *n*-butyl (E_s = 0.39).

In conclusion, chiral perfluoroalkyl *N*-Boc-pyrrolidyl ketones could be prepared by reacting methyl (*S*)-*N*-Boc-pyrrolidine-2-carboxylate and perfluoroalkyllithium reagents prepared from perfluoroalkyl iodides and methyllithium−lithium bromide complex. Trifluoromethyl *N*-Boc-pyrrolidyl ketone could also be obtained by reacting methyl (*S*)-*N*-Boc-pyrrolidine-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 $NaBH_4$ and LAH. This method provides the first efficient and asymmetric access to (α*R*)-perfluoroalkylated prolinols. Further studies on the asymmetric synthesis of α-perfluoroalkylated prolinols carrying a quaternary carbon center at the α-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 $NaBH_4$ (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_2O (3 × 30 mL). The organic layer was washed with brine (70 mL), dried over Na_2SO_4, and concentrated by distillation under reduced pressure. Purification of the residue by silica gel

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

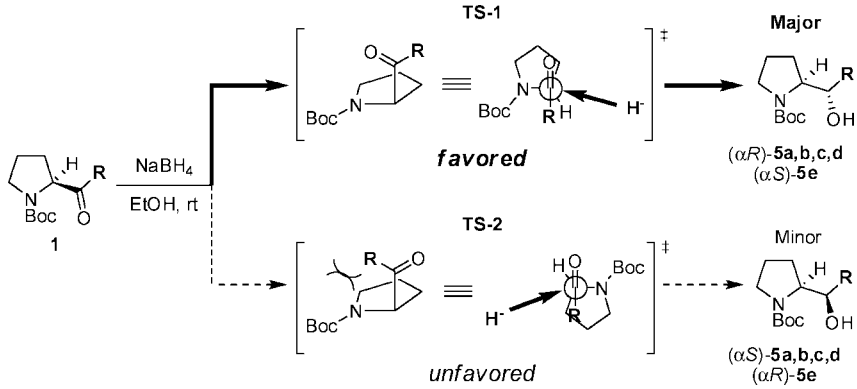


FIGURE 1. Proposed transition state.

column chromatography (hexane−CH_2Cl_2 = 1:2) gave (α*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 ((α*R*)-5a). *Rf* 0.33 (hexane−CH_2Cl_2 = 1:2); mp 74.6−75.3 °C; $[\alpha]^{25}_D$ −19.9 (*c* 1.00, $CHCl_3$); IR (KBr) 3250 (OH), 1682 (C=O) cm^{-1}; HRMS (FAB) found *m*/*z* 420.1212, calcd for $C_{14}H_{19}F_9NO_3$ (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. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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); ^{19}F NMR (372 MHz, $CDCl_3$) 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).

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Supporting Information Available: Detailed procedures and characterization of all of the compounds, ^{1}H and ^{13}C NMR spectra for **1a**−**d**, **2**, **3**, **4**, (α*R*)-**5a**−**e**, (α*S*)-**5d**,**e**, **6a**,**c**,**d**, and **6c′**, and crystallographic data for compound (α*R*)-**5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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