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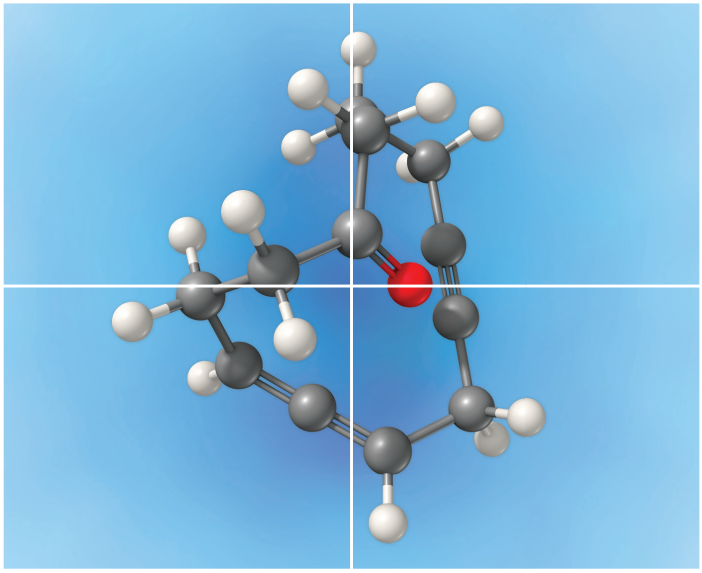

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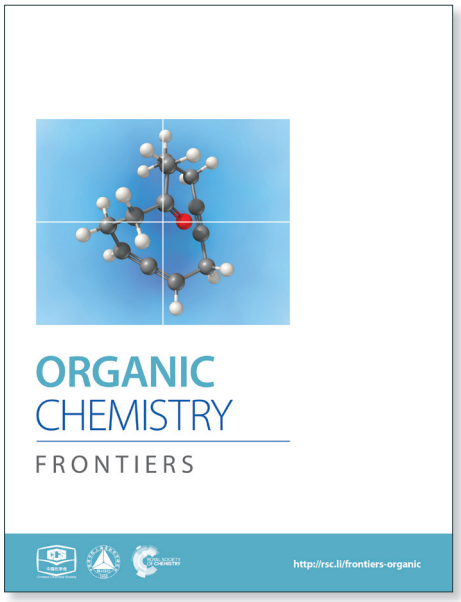

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Asymmetric synthesis of (αS)-polyfluoroalkylated *N*-Boc-prolinols by the diethyl zinc-induced asymmetric Meerwein-Ponndorf-Verley reduction of perfluoroalkyl *N*-Boc-pyrrolidyl ketones

Kazumasa Funabiki,* Hiroki Iwata, Yosuke Yano, Yasuhiro Kubota, and Masaki Matsui

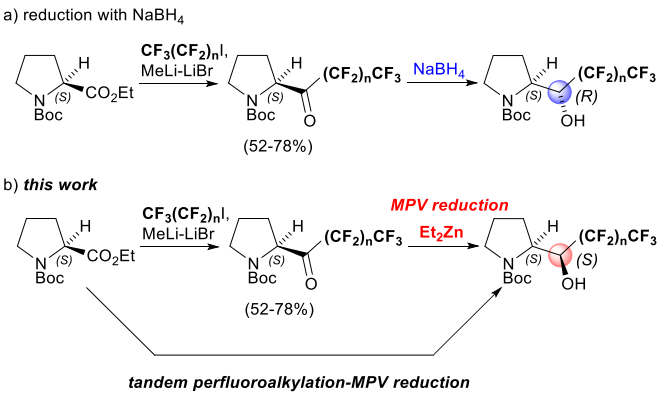
The reduction of perfluoroalkyl *N*-Boc-pyrrolidyl ketones with diethyl zinc was investigated. As a result, asymmetric Meerwein-Ponndorf-Verley reduction of perfluoroalkyl *N*-Boc-pyrrolidyl ketones proceeded smoothly with the use of 5 equiv. of diethyl zinc as a reducing agent in hexane at room temperature to give (α*S*)-polyfluoroalkylated *N*-Boc-prolinols in good yields (31-73%) with high diastereomer ratios (up to α*R*/α*S* = 7/93). The absolute configuration at the α-position of the major diastereomer is opposite that obtained by the reduction of *N*-Boc-pyrrolidyl ketone with $NaBH_4$ in ethanol. Furthermore, we also achieved the tandem perfluorobutylation-MPV reduction of *N*-Boc-proline ethyl ester to give (αS)-perfluorobutylated *N*-Boc-prolinol as a sole diastereomer in 45% yield.

Introduction

Meerwein-Ponndorf-Verley (MPV) reduction is a classic reaction in organic synthesis. The MPV reduction of ketones normally requires metal alkoxides, e.g., alkali metal and aluminium alkoxides.[1] Although there are a few successful examples of MPV reduction using diethyl zinc (Et_2Zn),[2] there have been no reports on stereoselective MPV reduction with Et_2Zn.

On the other hand, considerable attention has been focused on prolinol derivative-catalyzed asymmetric synthesis, since prolinol derivatives are some of the most important and versatile asymmetric organocatalysts in catalytic asymmetric reactions.[3] Although α-trifluoromethylated aminoalcohols have been used as chiral ligands,[4] a chiral auxiliary,[5] and organocatalysts,[6] there have been few reports on asymmetric synthesis or the use of α-fluoroalkylated optically pure prolinol derivatives.[7]

Recently, we developed (α*R*)-polyfluoroalkylated prolinols based on the perfluoroalkyl-induced highly stereoselective reduction of perfluoroalkyl *N*-Boc-pyrrolidyl ketones with sodium borohydride ($NaBH_4$) (a, Scheme 1).[7a] In this paper, we describe not only the complementary synthesis of (α*S*)-polyfluoroalkylated prolinols by the asymmetric MPV-type reduction of perfluoroalkyl *N*-Boc-pyrrolidyl ketones with Et_2Zn, but also the one-pot asymmetric synthesis of (α*S*)-polyfluoroalkylated prolinols by the tandem perfluorobutylation-asymmetric MPV-type reduction[8] of *N*-Boc proline ethyl ester (b, Scheme 1).

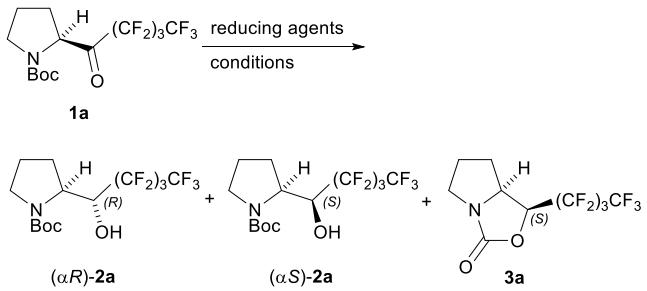


Scheme 1 Complementary synthesis of (α*R*)- and (α*S*)-polyfluoroalkylated prolinols

Results and discussion

As shown in Table 1, treatment of perfluorobutyl *N*-Boc-pyrrolidyl ketone (**1a**) with 5 equiv. of Et_2Zn in hexane at 0 °C gave α-polyfluorobutylated prolinol **2a** in 29% yield as a mixture of stereoisomers with an α*R* : α*S* ratio of 29:71, together with recovery of the starting ketone **1a** (54%) (entry 2).

Table 1 Screening of the asymmetric MPV-type reduction conditions.



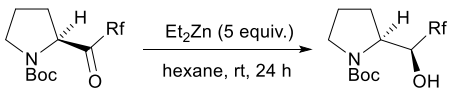
Entry	Reducing agents (equiv.)	Solvent	Conditions	Yield (%)	$\alpha R : \alpha S$[a]
1[b]	$NaBH_4$ (3)	EtOH	rt, 7 h	**2a** (78)[c]	>99 : <1
2	Et_2Zn (5)	hexane	0 °C, 24 h	**2a** (29)[c], **1a** (54)	29 : 71
3	Et_2Zn (5)	hexane	rt, 24 h	**2a** (73)[c]	8 : 92
4	Et_2Zn (2)	hexane	rt, 24 h	**2a** (41)[c], **1a** (46)	8 : 92
5	*i*-Pr_2Zn (5)	hexane	rt, 24 h	**2a** (74)[c]	17 : 83
6	Et_2Zn (5)	hexane	reflux	**2a** (57)[c], **3a** (13)	14 : 86

[a] Determined by GC analysis. [b] Previous work. See, ref. 7a.
[c] Isolated yields of of both diastereomer.

Interestingly, the absolute configuration at the α-position of the major diastereomer produced by MPV reduction is opposite that obtained by the reduction of perfluorobutylated *N*-Boc-pyrrolidyl ketone **1a** with $NaBH_4$ in ethanol, as reported previously (entry 1).[7a] MPV reduction of the ketone **1a** with Et_2Zn at room temperature resulted in a large increase in the yield (73%) of prolinol **2a** with a much better diastereomer ratio ($\alpha R/\alpha S$ = 92/8) (entry 2). The diastereomers of **2a** are separable by normal column chromatography with silica gel. However, two conformational isomers of (α*S*)-**2a** that arise from an amide moiety were observed by NMR. Employment of 2 equiv. of Et_2Zn gave **2a** in only 41% yield, together with the 46% recovery of the starting ketone **1a** (entry 4). The use of di-*iso*-propyl zinc (*i*-Pr_2Zn) in place of Et_2Zn lowered the isomer ratio from 8/92 to 17/83 (entry 5). A higher reaction temperature gave both a lower diastereomer ratio (14/86) and a lower yield (57%), together with 1-perfluoroalkylated oxazolidinone **3a** in 13% yield, which was produced via the cyclization of (α*S*)-**2a** (entry 6). Based on these results, the optimized reaction conditions are given in entry 2, which requires 5 equiv of Et_2Zn at room temperature.

Based on the screening of the reaction conditions in Table 1, other perfluoroalkyl *N*-Boc-pyrrolidyl ketones **1b,c,d** carrying perfluorohexyl, perfluorooctyl, and trifluoromethyl groups were examined (Table 2). Perfluorohexylated and perfluorooctylated *N*-Boc-pyrrolidyl ketone **1b,c** participated nicely in the MPV reduction with 5 equiv. of Et_2Zn to give the corresponding α-polyfluorohexylated and perfluorooctylated prolinols **2b,c** in 67-70% yields with $\alpha R/\alpha S$ isomer ratios of 7-8/92-93. The reaction of trifluoromethylated *N*-Boc-pyrrolidyl ketone **1d** containing ketone hydrate did not smoothly proceed to give the corresponding α-trifluoromethylated prolinol **2d** in 31% yield as a mixture of stereoisomers with an $\alpha R : \alpha S$ ratio of 8:92, together with recovery of the starting ketone **1a** containing its hydrare (41%) (entry 4).

Table 2 Et_2Zn-induced MPV-type asymmetric reduction of perfluoroalkyl *N*-Boc-pyrrolidyl ketones (**1**).



1a : Rf = $CF_3(CF_2)_3$
1b : Rf = $CF_3(CF_2)_5$
1c : Rf = $CF_3(CF_2)_7$
1d : Rf = CF_3[a]

Entry	Rf	Product	Yield (%)	$\alpha R : \alpha S$[b]
1	$CF_3(CF_2)_3$	**2a**	73	8 : 92
2	$CF_3(CF_2)_5$	**2b**	70	7 : 93
3	$CF_3(CF_2)_7$	**2c**	67	8 : 92
4	CF_3	**2d**	31[c]	8 : 92

[a] The mixture of ketone **1d** / ketone hydrate (59/41) was used. [b] Determined by GC analysis. [c] The mixture of ketone **1d**/ketone hydrate (87/13) was recovered in 41% yield.

The stereochemistries at the α-position of α-perfluorobutylated prolinol (**2a**) produced by MPV reduction with Et_2Zn could be confirmed to be *S* based on the vicinal coupling constant of the obtained 1-perfluorobutylated oxazolidinone **3a.** The coupling constant between two protons at C-7-a and C1 of the obtained 1-perfluorobutylated oxazolidinone **3a** was 7.9 Hz, which is similar to that previously reported for *n*-butylated oxazolidinone (1*S*)-**4**, as shown in Figure 1.[7a] The stereochemical assignments for the other α-polyfluorobutylated prolinols **2b,c** were made by comparison of the chemical shifts in ^{19}F NMR to those of α*R*- and α*S*-**2a**.

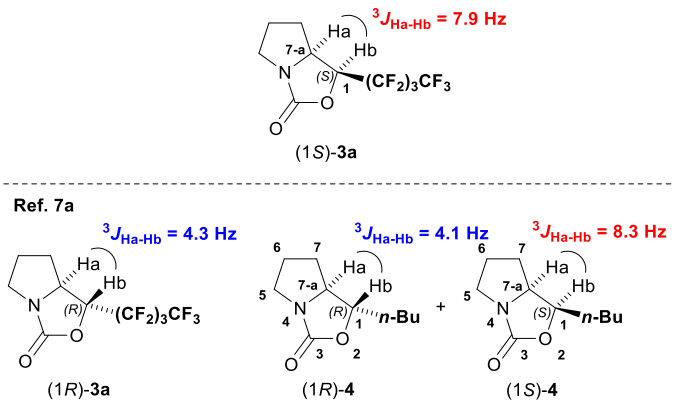


Figure 1.

Based on the absolute stereochemistry at the α-carbon of (α*S*)-perfluorobutylated prolinol ((α*S*)-**2a**), a proposed transition state

(**TS**) is shown in Figure 2. A hydride transfers from an ethyl group of Et_2Zn to perfluoroalkyl *N*-Boc-pyrrolidyl ketone **1** through a transition state (**TS**), where not only chelation between zinc metal and two oxygen atoms of two carbonyl groups of ketone and Boc groups **1** but also the steric repulsion between bulkier *N*-Boc-pyrrolidyl and ethyl groups are crucial.

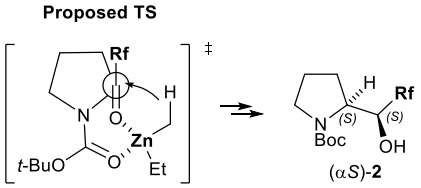
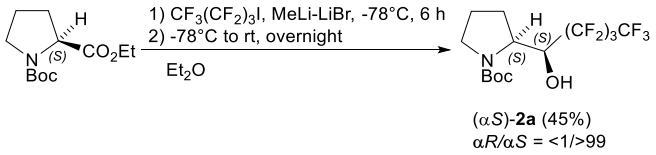


Figure 2. A proposed transition state

Finally, the one-pot asymmetric synthesis of (α*S*)-perfluoroalkylated *N*-Boc-prolinol (α*S*)-**2a** through tandem perfluoroalkylation-MPV reduction of *N*-Boc proline ethyl ester was examined (Scheme 2). After *N*-Boc-proline ethyl ester was subjected to perfluorobutylation by the reaction of iodoperfluorobutane with a methyllithium-lithium bromide complex for 6 h at −78 ℃, the resultant mixture was gradually warmed to room temperature overnight. Consequently, the one-pot tandem perfluorobutylation-MPV reduction successfully proceeded to give the (α*S*)-perfluorobutylated *N*-Boc-prolinol (α*S*)-**2a** as a sole diastereomer in 45% yield.



Scheme 2 One-pot tandem perfluoroalkylation-MPV reduction of *N*-Boc proline ethyl ester leading to (α*S*)-perfluoroalkylated *N*-Boc-prolinol **2a**

Conclusions

In conclusion, we have developed an asymmetric Meerwein-Ponndorf-Verley reduction of perfluoroalkyl *N*-Boc-pyrrolidyl ketones with the use of 5 equiv. of Et_2Zn as a reducing agent to give (α*S*)-polyfluoroalkylated *N*-Boc-prolinols in good yields (31-73%) with high diastereomer ratios (up to α*R*/α*S* = 8/92). This method represents a complementary asymmetric synthesis of (α*S*)-polyfluoroalkylated *N*-Boc-prolinols, since the absolute configuration of at the α-position of the major diastereomer is opposite that obtained by the reduction of *N*-Boc-pyrrolidyl ketone with $NaBH_4$ in ethanol. Furthermore, we have also achieved the tandem perfluorobutylation-MPV reduction of *N*-Boc-proline ethyl ester to give (α*S*)-perfluorobutylated *N*-Boc-prolinol (α*S*)-**2a** as a sole diastereomer in 45% yield.

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Notes and references

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