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Catalytic Enantioselective Protonation of a Samarium Enolate with Fluorous Chiral and Achiral Proton Sources in Fluorous Biphasic Systems

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Abstract: *Enantioselectivities near maximum values were obtained in the catalytic reaction by a rapid addition of a fluorous achiral alcohol (Rfh_3C-OH) to the reaction mixture: for DHPEX in Rfh_3C-OH/THF solid-liquid biphase system and for a fluorous chiral alcohol in THF/FC-72 liquid-liquid biphase system.* © 1998 Elsevier Science Ltd. All rights reserved.

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Curran and coworkers have demonstrated that $(C_6F_{13}CH_2CH_2)_3SnH$ and $(C_6F_{13}CH_2CH_2CH_2)_3SnH$ show similar reactivity to the original tin hydride bearing hydrocarbon chains and that the fluorous products were cleanly separated from the nonfluorous products by simple extraction procedure with the use of a fluorous solvent such as FC-72 and standard organic solvent such as chloroform.[1]

Horváth and Rábai[2] have referred to the promising nature of fluorous biphase systems (FBS) for catalytic asymmetric reactions. However, there was no report on a catalytic asymmetric reaction in FBS when we started to investigate the catalytic enantioselective protonation in the biphase system. Very recently, Pozzi and coworkers have reported the catalytic asymmetric epoxidation of alkenes in FBS for the first time with the use of chiral salen Mn complexes bearing perfluorinated side chains.[3]

On the other hand, Takeuchi and coworkers have investigated the catalytic enantioselective protonation of a samarium enolate by using C_2-symmetric chiral diol (DHPEX) as a catalyst and trityl alcohol as an achiral proton source for regenerating the catalyst in the reaction mixture. High enantioselectivity (*93% ee*) was obtained when trityl alcohol was added very slowly to the reaction mixture *over a period of 26 h at -45 ℃*. However, when trityl alcohol was added to the reaction mixture within 1 h, the enantiomeric excess was lower than 67%ee.[4]

Thus, we hypothesized that a FBS (THF and FC-72) could be effective for the catalytic enantioselective protonation reaction: chiral and achiral alcohols which have long fluorous chains are planned to be used for the reaction shown in Scheme 1. If most of the achiral alcohol remains in FC-72 (F_3C-$(CF_2)_4$-CF_3) and the chiral alcohol and/or its conjugate base shuttles between THF and FC-72, *the achiral alcohol need not be added*

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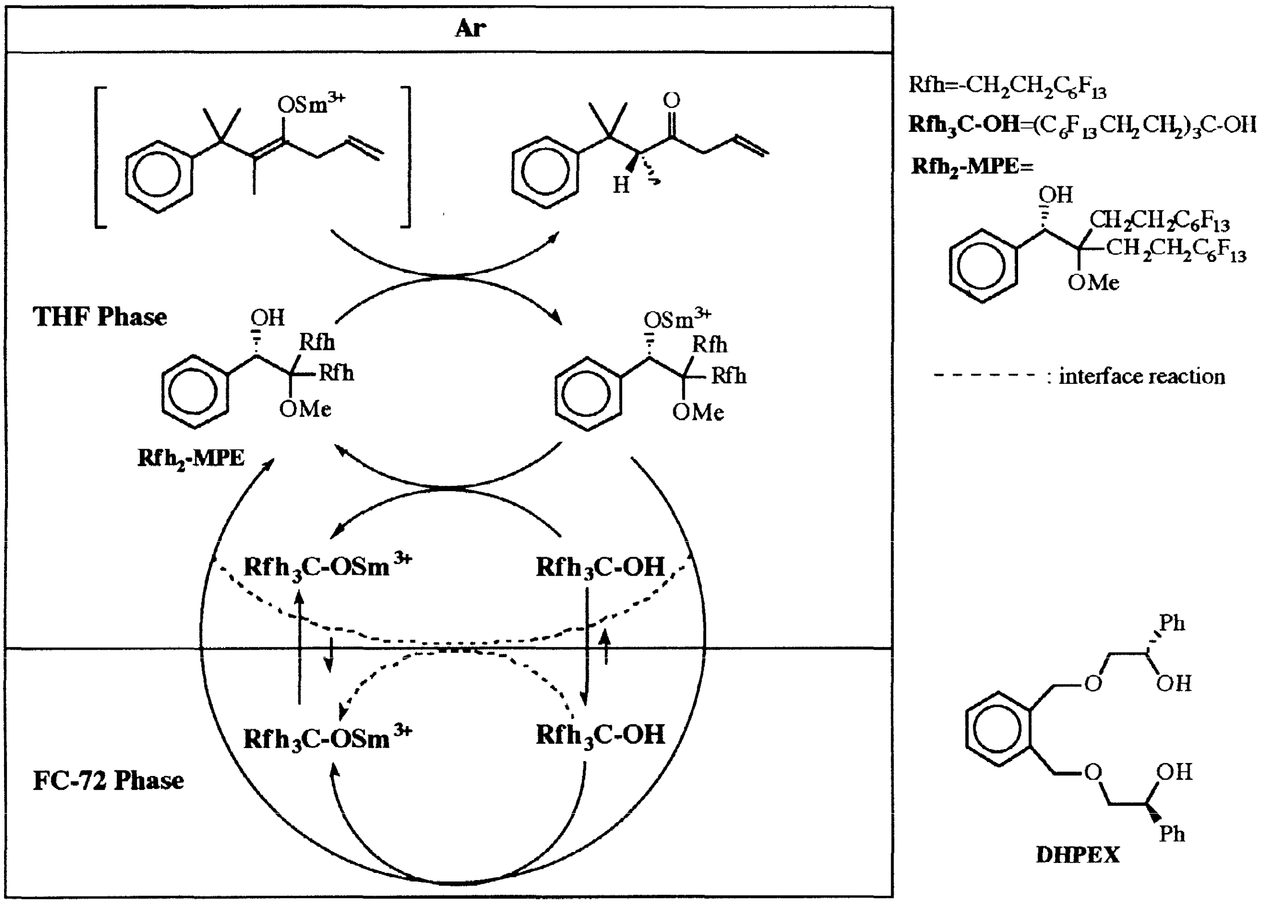
slowly from the outside of the reaction mixture. For this purpose, (*S*)-2-bis-[(perfluorohexyl)ethyl]-2-methoxy-1-phenylethanol (Rfh_2-MPE) and tris-[(perfluorohexyl)ethyl]methanol (Rfh_3C-OH) were prepared from a commercially available or known precursors[5] by Grignard reactions. The approximate partition coefficients of the alcohols between THF and FC-72 were determined from the amounts dissolved in each solvent to be 4.2:1 for the Rfh_2-MPE at room temperature, and 1:10 and 1:23 for the Rfh_3C-OH at room temperature and at -45 °C, respectively.

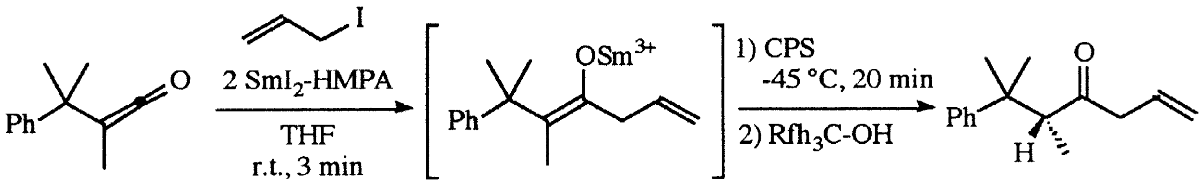


Scheme 1

At first, a stoichiometric enantioselective protonation of the samarium enolate was carried out by using Rfh_2-MPE to give 66% ee at -45 °C as shown in Entry 1 of Table 1. Therefore, the maximum enantiomeric excess of the catalytic enantioselective reaction should be 66%.

Next, we examined the three different types of catalytic reaction by two different modes of addition of Rfh_3C-OH to the reaction mixture and two different types of solvent system: (A) slow addition (6 h) of THF solution of Rfh_3C-OH in THF, (B) rapid addition of THF solution of Rfh_3C-OH within 1 min at the begining of the catalytic reaction in THF, and (C) rapid addition of FC-72 solution of Rfh_3C-OH within 1 min at the begining of the catalytic reaction in THF/FC-72 biphase system. Among these, the enantiomeric excess was highest in the biphase system (Entry 4) and lowest in the slow addition method in THF (Entry 2). The tendency did not change when the molar ratio of Rfh_3C-OH to the substrate was increased to 2.0 and 2.8: the enantioselectivities were 8-11% higher in THF/FC-72 biphase system than in THF (Entries 3-8).[6] From the

Table 1. Stoichiometric and Catalytic Enantioselective Protonations of the Samarium Enolate with the Use of Rfh_2-MPE and/or Rfh_3C-OH.



Entry	CPS[a] (mol *equiv*[b])	mol *equiv* of Rfh_3C-OH (addition method)	Solvent System	React. Temp.	React. Time (h)	Yield (%)	% ee[c]
1	Rfh_2-MPE (1.6)	-	THF	-45 °C	2	56	66
2	Rfh_2-MPE (0.16)	1.0 (A)	THF	-45 °C r.t.	6 0.5	51	43
3	Rfh_2-MPE (0.16)	1.0 (B)	THF	-45 °C r.t.	6 0.5	65	52
4	Rfh_2-MPE (0.16)	1.0 (C)	THF/FC-72[d]	-45 °C r.t.	6 0.5	59	60
5	Rfh_2-MPE (0.16)	2.0 (B)	THF	-45 °C r.t.	6 0.5	65	47
6	Rfh_2-MPE (0.16)	2.0 (C)	THF/FC-72[d]	-45 °C r.t.	6 0.5	59	58
7	Rfh_2-MPE (0.16)	2.8 (B)	THF	-45 °C r.t.	6 0.5	62	44
8	Rfh_2-MPE (0.16)	2.8 (C)	THF/FC-72[d]	-45 °C r.t.	6 0.5	57	54
9	DHPEX (0.16)	1.0 (B)	THF	-45 °C r.t.	6 0.5	57	90
10	DHPEX (0.16)	1.0 (C)	THF/FC-72	-45 °C r.t.	6 0.5	55	89

[a] CPS : Chiral proton source. [b] Molar equivalent based on 1 molar equivalent of substrate. [c] Determined by HPLC analysis using DAICEL CHIRALCEL OD on the hydrogenated sample of the reaction product. [d] The amount of FC-72 were 4 mL, 6 mL and 8 mL in Entries 4, 6 and 8, respectively.

results, it is clear that the biphase system is more effective than in THF single solvent system *(60% ee and 52% ee in Entries 4 and 3 correspond to 91% and 79% of the maximum value, 66% ee in Entry 1)*. In order to check the effect due to the fluorous side chain of Rfh_2-MPE in the biphase system, we finally examined the catalytic reaction by using DHPEX as the catalyst and Rfh_3C-OH by rapid addition methods, (B) and (C). Surprisingly, high enantioselectivity (90% ee; Entry 9) similar to that in the slow addition of trityl alcohol (93% ee; 26 h)[4] was obtained in THF. This seems to be brought about by the low solubility of Rfh_3C-OH in THF at -45 °C. When the Rfh_3C-OH solution in THF (402 mg/3 ml) was cooled to -45 °C or added to the reaction mixture at -45 °C, the solutions became cloudy because of the precipitates of Rfh_3C-OH. Therefore, the reaction conditions are actually solid (Rfh_3C-OH) and liquid (THF) biphase system and must be similar to those reported by Koga[7]: sparingly soluble achiral proton sources, thus resembling slow addition conditions in spite of the quick addition of them, were used for their enantioselective protonation to get high enantioselectivity.

The enantiomeric excess in THF/FC-72 biphase system (89% ee; Entry 10) was not higher than that in Rfh$_3$C-OH/THF biphase system (Entry 9), although almost the same value implies that THF/FC-72 biphase system also worked well. In THF/FC-72 biphase systems, both THF and FC-72 phases were homogeneous throughout the reaction. Since DHPEX has no fluorous side chains, the conjugate base of DHPEX is considered to be protonated by Rfh$_3$C-OH in THF and/or at the interface between THF and FC-72 in the similar effectiveness to in Entry 9.

The small but clear difference in enantioselectivities between the THF/FC-72 and the Rfh$_3$C-OH/THF biphase systems in Entries 3-8, which were obtained only by a vigorous stirring of the reaction mixture and were confirmed by repeated experiments, demonstrates that the conjugate base of Rfh$_2$-MPE was protonated by Rfh$_3$C-OH more effectively in THF/FC-72 biphase system probably not only in THF but also in FC-72 and/or at the interface, compared to in Rfh$_3$C-OH/THF biphase system. The small value of the difference are reasonable judging from the partition coefficient of Rfh$_2$-MPE.

Thus, we have established the novel method to get the enantioselectivities near the maximum values in the catalytic reaction by the rapid addition of the fluorous achiral proton source: Rfh$_3$C-OH was effective both for DHPEX and for Rfh$_2$-MPE in Rfh$_3$C-OH/THF solid-liquid biphase system and in THF/FC-72 liquid-liquid biphase system, respectively.

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6. After degassed in vacuo at -78 °C, FC-72 was treated by SmI$_2$ solution to remove O$_2$. The samarium enolate was prepared from the ketene (66.4 mg, 0.381 mmol) by the procedure described in Ref. 4. To the reaction mixture was added a solution of Rfh$_2$-MPE (51.5 mg, 0.061 mmol) in THF (3 mL) and after the reaction at -45 °C for 20 min, was added a solution of Rfh$_3$C-OH (402 mg, 0.376 mmol) in FC-72 (4 mL). After vigorous stirring for 6 h at -45 °C and then 30 min at room temperature, the reaction was quenched by 0.1 M HCl and then extracted Rfh$_3$C-OH with FC-72 (10 mLx4) and the THF-H$_2$O layer was treated by usual work-up followed by PTLC to give the desired product (48.4 mg, 59%, 60% ee) and Rfh$_2$-MPE. From the FC-72 solution Rfh$_3$C-OH was recovered quantitatively in almost pure state.
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