Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 5, pp. 1039-1042, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00119-0

Ferrocenylseleno Amino Alcohols as New Catalysts for the Highly Enantioselective Alkylation of Aldehydes

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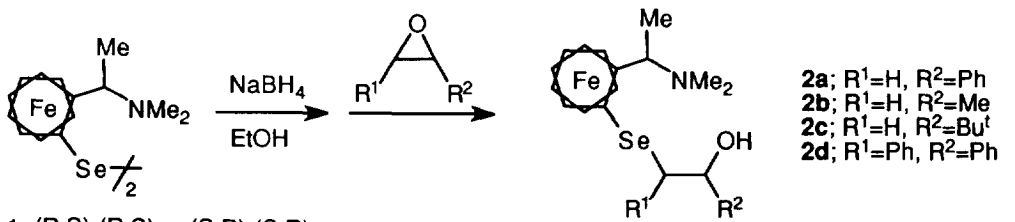
Abstract: A chiral or a diastereomeric mixture of 1-[1-(N,N-dimethylaminoethyl)-2-(2'-hydroxyalkylseleno)]-ferrocene (DASF) was easily prepared by the chiral diferrocenyldiselenide (**1**) and epoxides. DASF derivatives efficiently catalyzed the ethylation of aldehydes with diethyl zinc to give the secondary alcohols in good to excellent yield with up to 99 % ee.

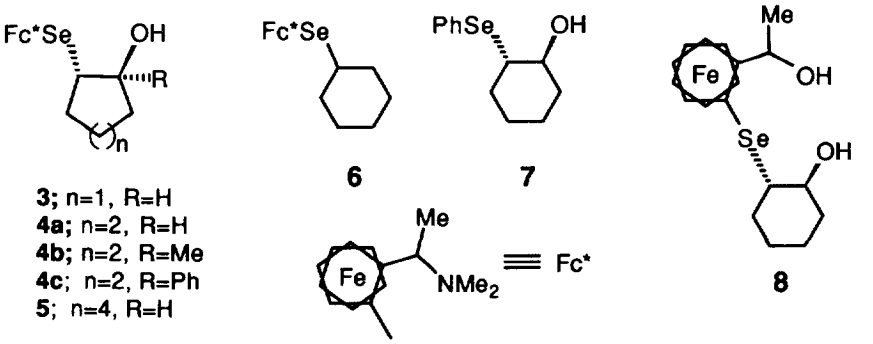
We have already demonstrated that ferrocenyl-based chiral selenium reagents were effective to achieve highly selective asymmetric organic syntheses in several examples of asymmetric reactions, e.g., selenoxide elimination,[1] a ligand of a rhodium catalyst for hydrosilylation, [2] and methoxyselenylation. [3] We have been researching the possibility of using the ferrocenyl-based selenium compounds in asymmetric organic synthesis. We designed a new chiral ferrocenylselenium-based enantioselective catalyst for ethylation of aldehydes with Et_2Zn and found some characteristic features of the catalyst. [4-5] The most striking characteristic of the catalyst is that it may be easily prepared from racemic or prochiral epoxides and used as a mixture of diastereomers.

The chiral ferrocenylselenium-based amino alcohols are readily prepared by treatment of the chiral diferrocenyldiselenide (**1**) with $NaBH_4$ in ethanol followed by addition of epoxides (Scheme I).[6] Thus, the regioselective ring opening reaction of epoxide with the ferrocenylselenolate anion, attacking at the less substituted carbon afforded 1-[1-(N,N-dimethylaminoethyl)]-2-[(2'-hydroxyalkylseleno)]ferrocene (DASF). When an optically pure epoxide was used, DASF was obtained as a single diastereomer, while when racemic or prochiral epoxide (i.e., cyclohexene oxide) was used, DASF was obtained as an approximately 1:1 mixture of diastereomers.

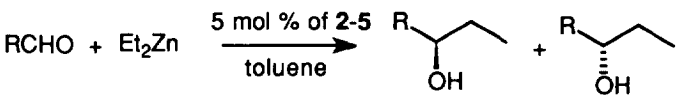
Reaction of benzaldehyde with Et_2Zn in toluene and 5 mol % of DASF (**2-5**) at room temperature for 15 h gave 1-phenyl-1-propanol in good to excellent yields with up to 94 % ee (Scheme 2). Enantiomeric excess and absolute configuration were determined by GLC analysis with a chiral capillary column (Astec, Scheme 1



1 (R,S)-(R,S) or (S,R)-(S,R)



Scheme 2



Chiraldex, B-PH, 30 m) by comparing with an authentic sample. The results are shown in Table 1. The single isomer of **2a**, e.g., (R, S)-(R)-**2a**, was prepared from (R, S)-(R, S)-**1** and (R)-styrene oxide.[7] Similarly, the (R, S)-(S), (S, R)-(R), or (S, R)-(S) isomer of **2a** was obtained by combination of the each isomer of **1** with (R)- or (S)- styrene oxide. (R, S)-(R)-**2a** effectively catalyzed the reaction and afforded (R)-1-phenyl-1-propanol in good yield with 55 % ee (entry 1). (R, S)-(S)-**2a** also catalyzed the reaction to give the (R)-alcohol in 19 % ee. A mixture of diastereomers (R, S)-(±)-**2a** gave (R)-alcohol in 48 % ee. The use of (S, R)-(R), (S, R)-(S), or (S, R)-(±)-**2a** produced the (S)-alcohol in 20-39% ee. Regardless of the stereochemistry of the asymmetric carbon bearing the hydroxyl group of the catalyst, the sense of the enantioselectivity was constant. From these results it may be concluded that the sense of enantioselectivity depended on only the configuration of the ferrocenylselenium moiety; the (R, S)-ferrocenylselenium group gives the (R)-alcohol while the (S, R)- group gives the (S)-alcohols. The absolute configuration of the alcohol carbon did not participate in the asymmetric induction. Thus, a diastereomeric mixture may be used for the reaction as long as the single diastereomer of **1** was used.

Several acyclic and cyclic derivatives of DASF (**2b-2d**, **3**, **4a-4c**, and **5**) were prepared and their catalytic activities and selectivities in the enantioselective ethylation tested. Each compound is an approximately 1:1 of diastereomers. Throughout these experiments, it was confirmed again that the enantioselectivities depended on stereochemistry of the ferrocenylselenium part of the catalyst. Among DASF derivatives examined, the compound **4a** prepared from (R, S)- or (S, R)-**1** and cyclohexene oxide revealed to be the best catalyst for enantioselective ethylation, giving up to 94 % ee (entries 11-12).[8] Six-membered ring size was critical for achieving a high enantioselectivity. A smaller or larger membered ring derivatives such as compound **3** or **5** afforded product with a lower selectivity (entries 10 and 15). By using **4b** or **4c** that introduces methyl or phenyl group to **4a**, enantioselectivity dropped to 24-36 % ee (entries 13-14). The sulfur and tellurium analogue of **4a** also catalyzed the reaction to afford the alcohol but with lower selectivity (52 and 46 % ee, respectively).

Table 1. Enantioselective Addition of Et_2Zn to Benzaldehyde Catalyzed by 1-[1-(N,N-dimethylaminoethyl)-2-(2'-hydroxyalkylseleno)]ferrocene (DASF)[a]

Entry	Catalyst[b]	Config of DASF	Yield(%)[c]	ee(%)[d]	Config
1	**2a**	(R, S)-(R)	85	55	R
2	**2a**	(R, S)-(S)	57	19	R
3	**2a**	(R, S)-(±)	72	48	R
4	**2a**	(S, R)-(R)	39	20	S
5	**2a**	(S, R)-(S)	54	39	S
6	**2a**	(S, R)-(±)	67	31	S
7	**2b**[e]	(R, S)	62	24	R
8	**2c**[e]	(R, S)	60	0	-
9	**2d**[e]	(R, S)	98	35	R
10	**3**[e]	(R, S)	72	25	R
11	**4a**[e]	(R, S)	98	94	R
12	**4a**[e]	(S, R)	90	80	S
13	**4b**[e]	(R, S)	51	36	R
14	**4c**[e]	(R, S)	25	24	R
15	**5**[e]	(S, R)	85	22	S
16	**6**	(R, S)	52	0	-
17	**7**	-	8	0	-
18	**8**[e]	(R, S)	7	0	-

a) Reaction was carried out at room temperature for 15 h in toluene. b) 5 mol % of DASF was used. c) GLC yield. d) GC: Astec, Chiraldex B-PH , 30 m. e) A 1:1 mixture of diastereomers.

Table 2 Reaction of Aldehydes with Et_2Zn Catalyzed by **4a**[a]

Entry	Aldehyde (R in RCHO)	Yield(%)[b]	ee(%)[c]	Config
1	4-$CH_3C_6H_4$	93	91	R
2	4-$CH_3OC_6H_4$	95	99	R
3	4-ClC_6H_4	98	87	R
4	1-Naphtyl	88	74	R
5	$PhCH_2CH_2$	96	86[d]	R
6	C_6H_{13}	91	71	R

a) Reaction was carried out at room temperature for 15 h in toluene using 5 mol % of **4a** . b) GLC yield. c) GC:Astec, Chiraldex B-PH , 30 m. d) GC: Astec, Chiraldex G-TA , 30 m.

We next investigated which parts of the compound **4a** participate in achieving a high enantioselectivity. We prepared a few catalysts that were eliminated a certain functional group from **4a**. The absence of hydroxyl group in the catalyst (compound **6**) resulted in no enantioselectivity (entry 16). The Hydroxyl group in **4a** should play an important role in the asymmetric induction. The compound **7** was a simple β-hydroxyphenylselenium compound, which showed little catalytic activity (entry 17). The compound **8** was the derivative of **4a** of which dimethylamino group was replaced by hydroxyl group with retention of configuration. The compound **8** did not act as a catalyst for the reaction (entry 18). From these results, dimethylamino group was necessary to have a catalytic activity. We may conclude that presence of both hydroxyl and the dimethylamino groups are essential to design an efficient catalyst.

Table 2 shows the typical results of enantioselective addition of Et_2Zn to aldehydes other than benzaldehyde catalyzed by **4a**. High enantioselectivities up to 99% ee were observed for aromatic and aliphatic aldehydes.

A representative experimental procedure is as follows. Under nitrogen atmosphere, to a solution of 44 mg (0.1 mmol, 5 mol %) of **4a** in 10 ml of dry toluene was added 1.0 M hexane solution of Et_2Zn (2.5 ml, 2.5 mmol) at 0 °C. After 10 min, benzaldehyde (0.20 g, 2 mmol) was added to the resulting solution at room temperature and stirred for 15 h. The reaction was quenched by addition of diluted HCl. The aqueous layer was extracted with diethyl ether (20 ml X 2), washed with brine and dried ($MgSO_4$). [9] GLC analysis of the ether solution revealed the presence of 1-phenyl-1-propanol.

Acknowledgment. The authors wish to thank Saneyoshi Scholarship Foundation for partial financial support of this work.

References and Notes

1. Nishibayashi, Y.; Singh, J. D.; Uemura, S.; Fukuzawa, S. *Tetrahedron Lett.* **1994**, *35*, 3115.
2. Nishibayashi, Y.; Singh, J. D.; Segawa, K.; Fukuzawa, S.; Uemura, S. *J. Chem. Soc. Chem. Commun.* **1994**, 1375.
3. Fukuzawa, S.; Kasugahara, Y.; Uemura, S. *Tetrahedron Lett.* **1994**, *35*, 9403.
4. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
5. Noyori, R. "Asymmetric Catalysis in Organic Synthesis", John Wiley, New York, 1994, Chap 5.
6. Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
7. ^{1}H NMR ($CDCl_3$, 400 MHz) for (R,S)-(R)-**2a**, δ 1.34 (d, 3H), 2.03 (s, 6H), 2.64 (dd, 1H, 10.7, 12.5 Hz, CHSe), 3.04 (dd, 1H, 2.2. 12.5 Hz, CHSe), 4.0-4.5 (several peaks including C*H*OH and C*H*NMe_2, 10H), 7.25 (s, 5H). Anal. Calcd. for $C_{22}H_{27}NOSeFe$. C, 57.91; H, 5.96; N, 3.07. Found. C, 57.57; H, 6.11; N, 2.99.
8. ^{1}H NMR ($CDCl_3$, 400 MHz) for a mixture of diastereomers of (R,S)-**4a**, δ 1.0-2.0 (m, 11H including C*H*$_3$CHNMe_2), 2.15 (s, 1.5H), 2.17 (s, 1.5H), 2.49 (dt, 0.5H, J=3.6, 9.7 Hz, CHSe), 2.67 (dt, 0.5H, J=4.0, 9.5 Hz, CHSe), 3.47 (dt, 1H, 4.1, 10.0 Hz, C*H*OH), 4.1-4.5 (several peaks including C*H*NMe_2, 9H). Anal. Calcd. for $C_{20}H_{29}NOSeFe$. C, 55.32; H, 6.73; N, 3.23. Found. C, 54.82; H, 6.87; N, 2.81.
9. The catalyst **4a** was extracted into the acid solution. The acid solution was slightly alkalized with solid Na_2CO_3 and **4a** was extracted from the alkaline solution by CH_2Cl_2. The catalyst **4a** was then recovered and reusable after purification by column chromatography on Al_2O_3.

(*Received in Japan* 10 *March* 1995; *accepted* 14 *April* 1995)