Tetrahedron Letters,Vol.30,No.50,pp 7095-7098,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

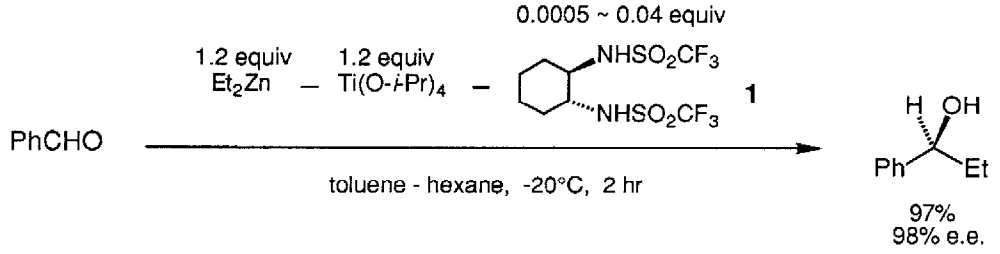
Enantioselective Alkylation of Aldehyde Catalyzed by Disulfonamide-Ti(O-*i*-Pr)$_4$-Dialkyl Zinc System

Hideyo Takahashi, Takashi Kawakita, Masato Yoshioka[1)]*,
Susumu Kobayashi and Masaji Ohno*
Faculty of Pharmaceutical Sciences, University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113, Japan

Summary: *The reaction of Et$_2$Zn-Ti(O-i-Pr)$_4$-disulfonamide **1** with various aldehydes is examined. High enantioselectivity (> 90% e.e.) is achieved using less than 0.04 equivalent of chiral disulfonamide **1**.*

An enantioselective reaction through a catalytic process is now recognized as one of the most important and challenging problems in organic synthesis.[2)] As one of the approaches to solve this problem, particularly in the case of nucleophilic addition of alkyl metal to aldehyde[3)], we became interested in modifying Lewis acids by electron-withdrawing chiral ligands rather than chiral alcohols or amines. In such a modified Lewis acid, the chiral ligand will not only provide a chiral environment but also increase the acidity of Lewis acid which we believe to be crucial to realize an efficient catalytic process. Based on this consideration we selected sulfonamide as a chiral auxiliary, and demonstrated a potential use of disulfonamide **1** in the nucleophilic addition to benzaldehyde with Et$_2$Zn-Ti(O-*i*-Pr)$_4$[4)] (Scheme 1).

Scheme 1

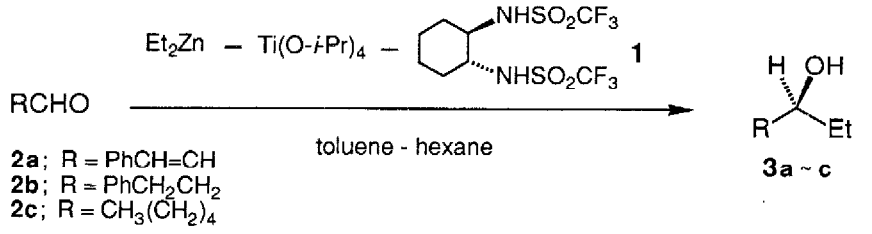


It was also found that the reaction of Et$_2$Zn-Ti(O-*i*-Pr)$_4$ and benzaldehyde proceeds very slowly without disulfonamide **1** even at room temperature (24hr for completion). Sulfonamide **1** clearly showed the activating effect, which eventually leads to the exceptionally high level of catalytic efficiency. Independent of our work, Corey recently reported the preparation of disulfonamide derivatives from (*R*,*R*)- and (*S*,*S*)-1,2-diamino-1,2-diphenylethane[2d)], and elegantly demonstrated the usefulness of disulfonamide as a chiral ligand in Diels-Alder reaction (catalytic use), aldol reaction (stoichiometric use) and allylation of aldehyde (stoichiometric use)[2d,5)].

In this paper, we will report further application of the sulfonamide **1** to other aldehydes including aliphatic ones, which has demonstrated generality of this new approach.

In contrast to benzaldehyde, cinnamaldehyde **2a** was found reactive enough at -40~-30°C with Et_2Zn-Ti(O-*i*-Pr)$_4$ even in the absence of sulfonamide. Other aldehydes such as 3-phenylpropanal **2b** and 1-hexanal **2c** also react with Et_2Zn-Ti(O-*i*-Pr)$_4$ below 0°C. Therefore, the reaction of cinnamaldehyde **2a** with chiral ethyltitanium reagent was first attempted at -50°C (1.5 hr) using 0.02 equiv of disulfonamide **1**, 1.2 equiv of Et_2Zn and 1.2 equiv of Ti(O-*i*-Pr)$_4$, and it was found that (*S*)-alcohol **3a** was obtained in 98% yield with 85% e.e.[5] (Table 1, entry 1).

Table 1



entry	aldehyde **2** R	**1** (equiv)	Ti(O-*i*-Pr)$_4$ (equiv)	Et_2Zn (equiv)	temp (°C)	time (hr)	yield (%)	e.e.[6] (%)
1	PhCH=CH	0.02	1.2	1.2	-50	1.5	98	85
2		0.02	0.6	1.2	-50	4	78	89
3		0.02	1.2	2.2	-50	2	96	88
4		0.02	0.6	2.2	-50	3	99	92 a)
5		0.02	0.3	2.2	-50	6.5	85	99
6		0.02	0.3	1.1	-50	6.5	49	83
7		0.005	0.3	2.2	-50	3.5	67	88
8	$Ph(CH_2)_2$	0.04	1.2	2.2	0	6	quant	90 b)
9		0.04	0.6	2.2	0	6	quant	92
10		0.01	0.6	2.2	0	4.5	95	92
11		0.0005	0.6	2.2	0	4.5	93	71
12	$CH_3(CH_2)_4$	0.04	1.2	2.2	-20	6	62	99 c)
13		0.04	0.6	2.2	-20	5	78	99
14		0.02	0.6	2.2	-20	7	64	98
15		0.005	0.6	2.2	-20	6.5	74	93

a) $[\alpha]_D^{25}$ -5.4° (*c* 2.46, $CHCl_3$) [lit. $[\alpha]_D^{22}$ -5.7° (*c* 1.00, $CHCl_3$) as 96% e.e.[3a)]].

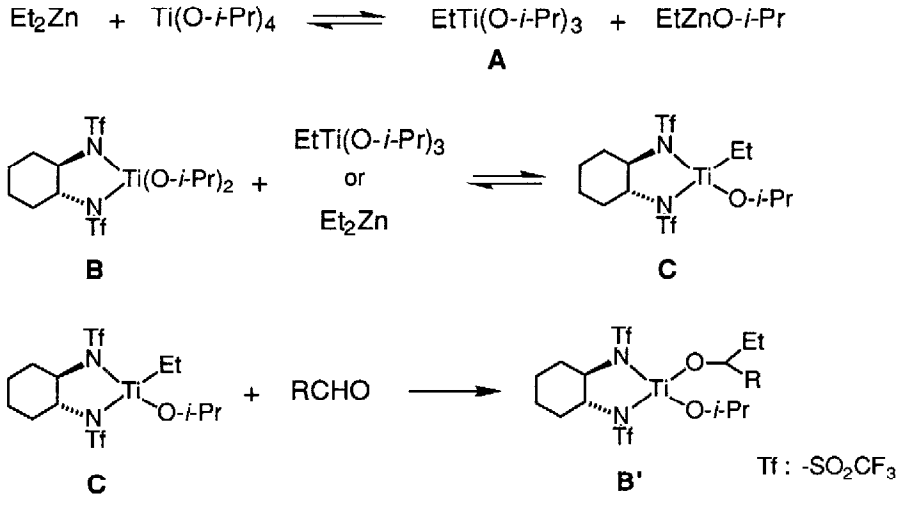
b) $[\alpha]_D^{25}$ +23.3° (*c* 3.99, EtOH) [lit. $[\alpha]_D^{25}$ +25.52° (*c* 5.00, EtOH) as 95% e.e.[3b)]; $[\alpha]_D^{22}$ +23.9° (*c* 1.44, EtOH) as 90% e.e.[3a)]].

c) $[\alpha]_D^{25}$ +12.3° (*c* 1.24, Et_2O) [lit. $[\alpha]_D^{25}$ +12.9° (*c* 6, $CHCl_3$) as 100% e.e.[7)]].

The relatively low enantiomeric excess was assumed to be due to the competitive path involving an achiral ethyltitanium reagent (A in Scheme 2) capable to be a catalyst in the case of such a reactive aldehyde. Therefore, we have carried out the reaction changing the amounts of Ti(O-*i*-Pr)$_4$ and Et_2Zn. As shown in Table 1, the enantiomeric excess increases as expected with decreasing the amount of Ti(O-*i*-Pr)$_4$, and **2a** was formed in 99% e.e. when 0.3 equiv of Ti(O-*i*-Pr)$_4$ and 2.2 equiv of Et_2Zn were used (entry 5). The use of less than 0.3 equiv of Ti(O-*i*-Pr)$_4$ was found not practical because prolonged reaction time was necessary for completion of the reaction. The results (entry 1~6) also indicate that an excess use of Et_2Zn (2.2 equiv) results in a higher enantiomeric excess (compare entry 1*vs* 3, 2*vs* 4, and 5*vs* 6). From these results, 2.2 equiv of Et_2Zn was employed in the following experiments. When 0.005 equiv of disulfonamide **1** was used, the reaction did not complete in 3.5 hr, and **3a** was isolated in 67% yield with slightly decreased enantiomeric excess (entry 7).

The results of 3-phenylpropanal **2b** and 1-hexanal **2c** are also summarized in Table 1. It should be emphasized that excellent enantioselectivity was achieved in the case of 1-hexanal **2c** (entry 13).

Scheme 2



Although the exact structures of the active species are not clear at present, probable mechanism is shown in Scheme 2. We assume that chiral ethyltitanium reagent (C) is a key species in the present system. Alkyltitanium reagent is known to react with aldehyde[8]. Chiral ethyltitanium species C might initially be generated by the reaction of chiral titanate B[9] and achiral ethyltiatanium species A[10], and further be regenerated from dialkoxytitanate B' establishing the catalytic cycle. Alternatively, direct formation of chiral ethyltitanium species C from B (or B') and Et_2Zn is also possible.

It should be concluded that disulfonamide **1**-Ti(O-*i*-Pr)$_4$-R_2Zn is an excellent system for a catalytic and enantioselective alkylation of aldehydes. Furthermore, we believe that the concept of modifying a Lewis acid with chiral disulfonamide ligand is promising in developing catalytic and enantioselective reactions.

Acknowledgment: This work was financially supported in part by a Grant-in-Aid for Scientific Research (No.01649003) from the Ministry of Education, Science, and Culture of Japan.

References and Notes:

1. Present address: Seiwa Kasei Co., Ltd., 1-2-14, Nunoichi-cho, Higashiosaka, Osaka 579, Japan.
2. Diels-Alder reaction: a) K. Furuta, Y. Miwa, K. Iwanaga, and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 6254 (1988). b) K. Furuta, S. Shimizu, Y. Miwa, and H. Yamamoto, *J. Org. Chem.*, **54**, 1483 (1989). c) K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989). d) E. J. Corey, R. Imwinkelried, S. Pikul, and Y. B. Xiang, *ibid.*, **111**, 5493 (1989).
   Aldol reaction: e) Y. Ito, M. Sawamura, and T. Hayashi, *ibid.*, **108**, 6405 (1986).
   Ene reaction: f) K. Maruoka, Y. Hoshino, T. Shirasaka, and H. Yamamoto, *Tetrahedron Lett.*, **29**, 3967 (1988). g) K. Mikami, M. Terada, and T. Nakai, *J. Am. Chem. Soc.*, **111**, 1940 (1989).
   Reduction: h) E. J. Corey, R. K. Bakshi, and S. Shibata, *ibid.*, **109**, 5551 (1987).
   i) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, and R. Noyori, *ibid.*, **110**, 629 (1988). j) U. Leutenegger, A. Madin, and A. Pfaltz, *Angew. Chem. Int. Ed. Engl.*, **28**, 60 (1989).
3. a) M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, **108**, 6071 (1986).
   b) K. Soai, S. Yokoyama, K. Ebihara, and T. Hayasaka, *J. Chem. Soc., Chem. Commun.*, **1987**, 1690.
4. M. Yoshioka, T. Kawakita, and M. Ohno, *Tetrahedron Lett.*, **30**, 1657 (1989).
5. E. J. Corey, C.-M. Yu, and S. S. Kim, *J. Am. Chem. Soc.*, **111**, 5495 (1989).
6. Enantiomeric excess of **3a** and **3b** was determined directly by HPLC using DAICEL CHIRALCEL OK (eluent; 1% isopropanol in hexane for **3a**, and 2% isopropanol in hexane for **3b**), and that of **3c** was determined by HPLC using DAICEL CHIRALPAK OT(+) (eluent; methanol) after converting **3b** to its benzoate.
7. G. Kirchner, M. P. Scollar, and A. M. Klibanov, *J. Am. Chem. Soc.*, **107**, 7072 (1985).
8. a) B. Weidmann and D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **22**, 31 (1983).
   b) M. T. Reetz, "Organotitanium Reagents in Organic Synthesis," Springer-Verlag, Berlin, 1986.
   c) M. T. Reetz, T. Kükenhhöhner, and P. Weinig, *Tetrahedron Lett.*, **27**, 5711 (1986).
9. Prior to the addition of Et_2Zn and aldehyde, chiral titanate B is prepared *in situ* by mixing disulfonamide **1** and $Ti(O\text{-}i\text{-}Pr)_4$ in toluene at 40°C for 20 min.
10. Although ethyltitanium species (A) is drawn as a monomeric structure in Scheme 2, ^{1}H-NMR experiments suggest that ethyltitanium exists in a rather complicated polymeric form with Et_2Zn, $Ti(O\text{-}i\text{-}Pr)_4$ and/or $EtZn(O\text{-}i\text{-}Pr)$ depending on the ratio of Et_2Zn and $Ti(O\text{-}i\text{-}Pr)_4$.

(Received in Japan 16 September 1989)