Pergamon

Tetrahedron Letters, Vol. 35, No. 26, pp. 4539-4540, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00855-8

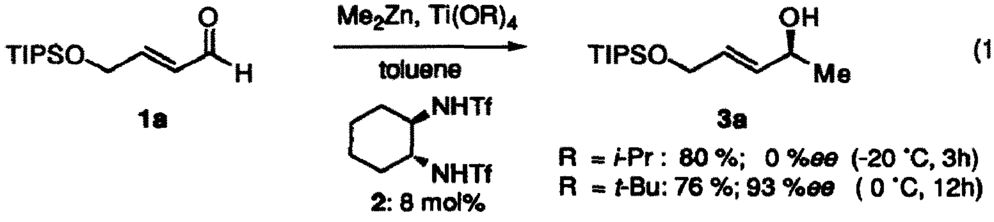
Dramatic Titanium Alkoxide Effect in the Catalytic Enantioselective Addition of Dialkylzincs to Aldehydes.

Stefan Nowotny, Stephan Vettel and Paul Knochel*

Fachbereich Chemie der Philipps-Universität Marburg
D - 35032 Marburg, Germany

Summary: The use of Ti(O*t*-Bu)$_4$, or related bulky titanium(IV) alkoxides, as cocatalysts instead of Ti(O*i*-Pr)$_4$ in the enantioselective addition of dimethylzinc to aldehydes in the presence of the catalyst **2** (8 mol%) leads to a dramatic improvement of the enantioselectivity (0%*ee* to 93%*ee*). The scope and the limitations of this effect are described.

We have recently reported that various dialkylzincs prepared via an iodine-zinc exchange,[1] add with high enantioselectivity to aldehydes **1** in the presence of Ti(O*i*-Pr)$_4$ (1-2 equiv) and the catalyst **2** (5-8 mol%) leading to secondary alcohols.[2] The addition to unsaturated aldehydes affords polyfunctional allylic alcohols (3) which are useful chiral building blocks.[3] Unfortunately, the addition of dialkylzincs to β-monosubstituted-α,β-unsaturated aldehydes proceeds with only 80-82%*ee* (entry 1 of table 1), and better results are only obtained with α-substituted unsaturated aldehydes.[3b] We have also noticed that Me$_2$Zn, which is a highly reactive and sterically non-demanding dialkylzinc, adds to unsaturated aldehydes with mediocre enantioselectivity. Thus, the addition of Me$_2$Zn to the aldehyde **1a** produces the allylic alcohol **3a** in 80% but 0%*ee*. After much experimentation, we have found that by replacing Ti(O*i*-Pr)$_4$ with Ti(O*t*-Bu)$_4$,[4] a dramatic enhancement of the enantioselectivity is observed and the product **3a** is now obtained in 76% yield and 93%*ee* (eq 1).

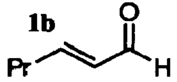
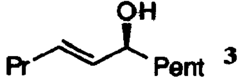
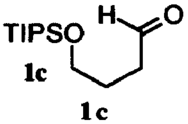
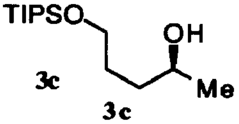
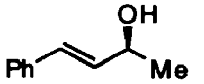
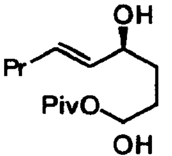
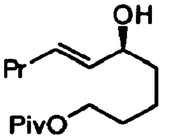


1a **2**: 8 mol% **3a** (1)

R = *i*-Pr : 80 %; 0 %*ee* (-20 °C, 3h)
R = *t*-Bu: 76 %; 93 %*ee* (0 °C, 12h)

This stereoselectivity improvement obtained by using a more bulky titanium alkoxide has some generality and other aldehydes, such as **1c** or **1d**, add Me$_2$Zn in the presence of Ti(O*i*-Pr)$_4$ with 55%*ee* and 25%*ee* respectively, whereas in the presence of Ti(O*t*-Bu)$_4$ the allylic alcohols **3c** and **3d** are obtained with 92%*ee* and 89%*ee* respectively (entries 2-5). A more systematic study on the influence of the titanium(IV) alkoxide on the enantioselectivity shows that titanium(IV) *t*-butoxide also gives excellent results for the addition of Pent$_2$Zn to (*E*)-2-hexenal (92%*ee* compared to 82%*ee* using Ti(O*i*-Pr)$_4$; entries 1 and 6). The use of bulky ligands also allows the enantioselective additions at higher temperature. By running the reaction using Ti(O*t*-Bu)$_4$ at 0 °C instead of -20 °C an enantioselectivity of 95%*ee* is obtained (entry 6). Besides Ti(O*t*-Bu)$_4$, Ti(OCH(Et)$_2$)$_4$ gives also excellent results (entry 8), however, the use of the less sterically demanding Ti(OPh)$_4$ gives only a mediocre enantioselectivity (entry 9). The addition of *functionalized* diorganozincs in the presence of Ti(O*t*-Bu)$_4$ is less efficient and requires long reaction times (2-4 days at 0 °C) and leads to the alcohols **3e** and **3f** in moderate yields but good enantioselectivity (93%*ee* and 86%*ee* respectively, entries 10 and 11). The present study clearly shows that the low steric hindrance of a small diorganozinc or unhindered aldehyde can be compensated by the use of a bulky titanium alkoxide. Further studies for improving the enantioselectivity are underway.[6]

Table 1. Secondary alcohols obtained by the addition of dialkylzincs to aldehydes in the presence of various titanium alkoxides and a catalytic amount of **2** at -20 °C.

Entry	aldehyde	R_2Zn R	titanium alkoxide	product	yield[a] (%)	ee[b] (%)
1	**1b** 	Pent	Ti(O*i*-Pr)$_4$	 3b	92	82
2	**1c** 	Me	Ti(O*i*-Pr)$_4$	 3c	94	55
3	**1c**	Me	Ti(O*t*-Bu)$_4$	**3c**	79	92[c]
4	 **1d**	Me	Ti(O*i*-Pr)$_4$	 3d	97	25
5	**1d**	Me	Ti(O*t*-Bu)$_4$	**3d**	66	89[c]
6	**1b**	Pent	Ti(O*t*-Bu)$_4$	**3b**	83	92 (95)[d]
7	**1b**	Pent	Ti(OSiMe$_3$)$_4$	**3b**	69	88
8	**1b**	Pent	Ti(OCH(Et)$_2$)$_4$	**3b**	94	95[d]
9	**1b**	Pent	Ti(OPh)$_4$	**3b**	84	20
10	**1b**	(CH$_2$)$_3$OPiv	Ti(O*t*-Bu)$_4$	 3e	49	93[c]
11	**1b**	(CH$_2$)$_4$OPiv	Ti(O*t*-Bu)$_4$	 3f	58	86[c]

[a] Isolated yield of analytically pure products. [b] Determined by preparing the corresponding *O*-acetylmandelates using (*S*)-(+)-*O*-acetylmandelic acid. [c] The reaction temperature was 0 °C. [d] The reaction temperature was 20 °C.

Acknowledgment

We thank the Fonds der Chemischen Industrie, the DFG (SFB 260) for generous support of this research and Witco (Bergkamen), BASF AG (Ludwigshafen) for generous gift of chemicals.

References and Notes.

1. Rozema, M.J.; AchyuthaRao, S.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956.
2. (a) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657. (b) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095. (c) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691.
3. (a) Brieden, W.; Ostwald, R.; Knochel, P. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 582. (b) Rozema, M.J.; Eisenberg, C.; Lütjens, H.; Ostwald, R.; Belyk, K.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 3115.
4. (a) Bradley, D.C.; Thomas, I.M. *J. Chem. Soc.* **1959**, 3404. (b) Rust, J.B.; Takimoto, H.H.; Denault, G.C. *J. Org. Chem.* **1960**, *25*, 2040.
5. The effect of chiral titanium alkoxides using TADDOL as catalyst has been studied: Seebach, D.; Plattner, D.A.; Beck, A.K.; Wang, Y.M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171.
6. *Typical procedure* (entry 6). A 20 mL three-neck flask equipped with an argon inlet, a thermometer and a septum cap was charged with the catalyst **2** (0.139 g, 0.37 mmol), Ti(O*t*-Bu)$_4$ (3.51 g, 10.3 mmol) and toluene (10 mL). The reaction mixture was heated to 50 °C for 0.5 h. After cooling to rt, Pent$_2$Zn (2.49 g, 12.0 mmol) was added, followed after 0.5 h by **1a** (0.45 g, 4.58 mmol) was added. GC analysis indicates the completion of the reaction after 1 h. The reaction mixture was worked up as usual and the resulting residual oil was purified by chromatography (hexanes : ether 4 : 1). The pure alcohol **3b** (0.65 g, 3.82 mmol, 83%) was obtained as a colorless oil (95 %*ee*; $[\alpha]_D$ = +0.55 (c = 7.3, benzene)).

(*Received in Germany* 22 *April* 1994; *accepted* 27 *April* 1994)