Pergamon

Tetrahedron Letters 43 (2002) 687–689

TETRAHEDRON
LETTERS

# α-Hydroxy carboxylic acids: new ligands for diethylzinc additions to aldehydes

Tomasz Bauer* and Joanna Tarasiuk

*Department of Chemistry, Warsaw University, Pasteura 1, PL-02-093 Warsaw, Poland*

Received 2 October 2001; revised 15 November 2001; accepted 21 November 2001

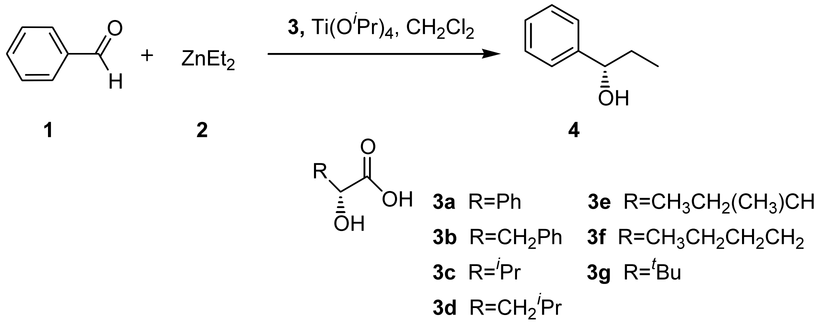
---

**Abstract**—The first examples of the enantioselective titanium-mediated diethylzinc additions to benzaldehyde catalyzed by optically active α-hydroxy acids are presented. (*S*)-1-Phenylpropanol has been obtained in up to 86% enantiomeric excess. © 2002 Elsevier Science Ltd. All rights reserved.

---

An enantioselective organometallic addition reaction to aldehydes is a valuable method for the synthesis of optically active secondary alcohols. Although several efficient catalysts have so far been developed, asymmetric addition reaction of diethylzinc to aldehydes has remained a challenge.

Various types of chiral ligands can be used as ligands for such additions. Since 1986, when DAIB was introduced by Noyori,[1] the amount of very useful and efficient dialkylamino alcohols has grown dramatically,[2] and now includes not only dialkylamino alcohols but also amino thiols,[3] oxazolines[4–6] and even diols, such as TADDOLs[7,8] and BINOLs.[9–11] Further progress in enantioselective additions to aldehydes was achieved, when Ohno and co-workers reported diethylzinc additions in the presence of titanium tetraisopropoxide and chiral bissulfonamide as the ligand.[12] Since then, extensive synthetic studies were conducted and α-hydroxy sulfonamides and bissulfonamides were proven as very efficient ligands for additions of dialkylzincs.[13–17] Albeit the exact mechanism of the process is so far not known, recent structural and mechanistic investigations showed that the active catalytic intermediates could be an ethyltitanium species derived from the transfer of an ethyl group from zinc to titanium or a bimetallic species containing an ethylzinc compound.[15] Both ligand accelerated diethylzinc additions and alkyltitanium additions to carbonyl compounds exhibit excellent chemoselectivity.[18] For mixtures of aldehydes and ketones, only addition to the aldehyde carbonyl group is observed whilst ketones remain intact. This led us to the conclusion that carboxylic acids can serve as ligands in $Ti(O\textit{i}Pr)_4$-catalyzed additions of diethylzinc to aldehydes. As a second coordination site, we have chosen the hydroxy group so that our ligands belong to the readily accessible family of α-hydroxy acids.



**Scheme 1.** Diethylzinc addition to benzaldehyde in the presence of α-hydroxy acids as chiral ligands.

---

*Keywords*: diethylzinc; titanium tetraisopropoxide; α-hydroxy acid; benzaldehyde; enantioselective.

* Corresponding author. Tel.: (+48-22)-822-02-11, ext. 273; fax: (+48-22)-822-59-96; e-mail: tbauer@chem.uw.edu.pl

PII: S0040-4039(01)02220-1

**Table 1.** Enantioselective addition of diethylzinc to benzaldehyde with α-hydroxy acids as chiral ligands

| Entry | Ligand | Mol% | Temp. (°C) | Yield (%) | ee (%)[a,b] |
|---|---|---|---|---|---|
| 1 | **3a** | 20 | rt | 88 | 77 (*S*) |
| 2 | **3a** | 40 | rt | 88 | 79 (*S*) |
| 3 | **3a** | 60 | rt | 89 | 80 (*S*) |
| 4 | **3a** | 80 | rt | 85 | 80 (*S*) |
| 5 | **3a** | 100 | rt | 84 | 80 (*S*) |
| 6 | **3a** | 20 | 0 | 87 | 80 (*S*) |
| 7 | **3a** | 20 | −20 | 62 | 76 (*S*) |
| 8 | **3a** | 20 | −78 | No reaction | – |
| 9 | **3b** | 20 | rt | 80 | 85 (*S*) |
| 10 | **3c** | 20 | rt | 85 | 85 (*S*) |
| 11 | **3d** | 20 | rt | 73 | 80 (*S*) |
| 12 | **3e** | 20 | rt | 71 | 83 (*S*) |
| 13 | **3f** | 20 | rt | 88 | 77 (*S*) |
| 14 | **3g** | 20 | rt | 80 | 86 (*S*) |

[a] Determined by HPLC analysis using a Daicel Chiracel OD column.

[b] Configuration of the major enantiomer in parentheses.

In order to confirm the considerations presented above, we decided to use commercially available (*S*)-mandelic acid as a ligand and benzaldehyde as a model carbonyl compound. The reaction was conducted at room temperature in methylene chloride in the presence of 0.2 equiv. of mandelic acid, 3 equiv. of diethylzinc and 1.4 equiv. of titanium tetraisopropoxide. The reaction proceeded very cleanly; we were very pleased to observe almost 50% conversion after 4 h. The reaction was stirred overnight, and after TLC showed complete conversion, quenched with aqueous hydrochloric acid. The mixture was extracted with ethyl acetate, washed with brine and dried over anhydrous magnesium sulfate. Flash chromatography using methylene chloride as eluent gave 1-phenylpropanol in 88% yield. The enantiomeric excess 77% ee in favor of the product with 1*S* configuration was determined by HPLC using a Chiracel OD column. Encouraged by this result, we prepared series of optically active α-hydroxy acids **3b–g** by diazotization of α-amino acids[19] and used them as ligands for the addition to benzaldehyde (Scheme 1). Also, the influence of the amount of the catalyst and temperature on the enantioselectivity of the reaction catalyzed by (*S*)-mandelic acid was studied. The results are summarized in Table 1.

The results presented in Table 1 need some comments. Asymmetric induction is only slightly dependent on the amount of the chiral catalyst and it increased from 77 to 80% for 20 and 100 mol%, respectively (entries 1–5). The reaction conducted at lower temperatures also shows only a modest influence of the temperature on the ee. As expected, the enantioselectivity depends on the bulkiness of the R substituent in acid **3** and the highest was obtained for (*S*)-2-hydroxy-3,3-dimethyl butyric acid **3g** (entry 14, R = $^t$Bu).

To the best of out knowledge, we have presented here the first example of diethylzinc addition to an aldehyde catalyzed by α-hydroxy acids. We believe, that due to the availability of substituted carboxylic acids, our findings open new possibilities for the enantioselective additions to aldehydes. Further investigations on more selective α-hydroxy acids, the application of α-amino acids and the generality of the method are in progress in our laboratory.

## Acknowledgements

Financial support from the State Commitee for Scientific Research (Grant 3 T09A 039 16) is gratefully acknowledged.

## References

1. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072.
2. For reviews see: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
3. Kang, J.; Kim, D. S.; Kim, J. I. *Synlett* **1994**, 842–844.
4. Falorni, M.; Collu, C.; Conti, S.; Giacomelli, G. *Tetrahedron: Asymmetry* **1996**, *7*, 293–299.
5. Aurich, H. G.; Biesemeier, F.; Geiger, M.; Harms, K. *Liebiegs Ann./Recl.* **1997**, 423.
6. Seebach, D.; Pichota, A.; Beck, A. K.; Pinkerton, A. B.; Litz, T.; Karjalainen, J.; Gramlich, V. *Org. Lett.* **1999**, *1*, 55–58.
7. Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99–101.
8. Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Ganter, C.; Gawley, R. E.; Kuehnle, F. N.; Tuleja, J.; Wang, J. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071–2210.
9. Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236.
10. Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585–589.
11. Kitajima, H.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207–217.
12. Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691–5700.

13. Knochel, P.; Perea, J.; Almena, J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275–8319.
14. Hwang, C.-D.; Uang, B.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3979–3984.
15. Paquette, L. A.; Zhou, R. *J. Org. Chem.* **1999**, *64*, 7929–7934.
16. Ito, K.; Kimura, Y.; Okamura, H.; Katsuki, T. *Synlett* **1992**, 573–574.
17. Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423–6424.
18. Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986.
19. **3b**,**3d**, **3f**: Degerbeck, F.; Fransson, B.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc.*, *Perkin Trans 1* **1993**, 11–14; **3c**: Cahiez, G.; Metais, E. *Tetrahedron Lett.* **1995**, *36*, 6449–6452; **3e**: Lloyd-Williams, P.; Monerris, P.; Gonzales, I.; Jou, G.; Giralt, E. *J. Chem. Soc.*, *Perkin Trans 1* **1994**, 1969–1994; **3g**: Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499–2506.