# Enantioselective Addition of Diethylzinc to Aryl Aldehydes Catalyzed by ADPD Imine Catalysts

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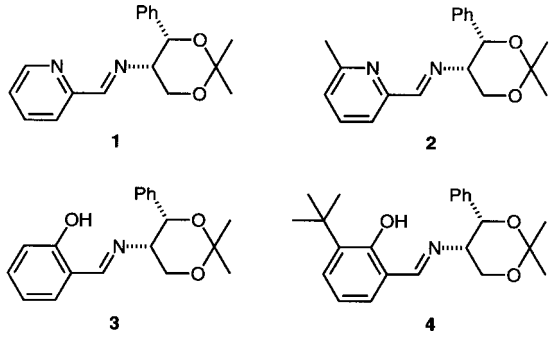
*Received 18 May 1998*

**Abstract:** The use of chiral imines **1-4** prepared from (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (ADPD) in the enantioselective addition of diethylzinc to aryl aldehydes is reported. Secondary aryl alcohols are obtained up to 85% *ee* in good yields.

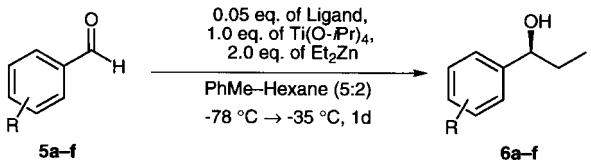
Enantioselective carbon-carbon bond formation is one of the most important methods in organic synthesis.[2] Recently the catalytic enantioselective addition of diethylzinc to aldehydes using various chiral β-amino alcohols has been reported.[3] However, only a few examples of this reaction have been reported using ligands which have imine skeleton such as the salen type ligands,[4] the diimine which are located in the core part of the ligands[5] and the benzaldehyde imine of primary amino alcohol which was created *in vitro*.[6]

(4*S*,5*S*)-(+)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane (ADPD) is a chiral amine which has a dioxane skeleton with a Ph group as a shield. We previously reported the enantioselective synthesis of chiral aldehydes using ADPD as a chiral auxiliary.[7] Enders reported the asymmetric synthesis using the *N*-Me derivative.[8] So ADPD is one of the useful chiral amines. But, in the catalytic asymmetric synthesis, to our knowledge only ADPD derivative was applied to a catalyst in the enantioselective intramolecular *Stetter* reaction.[9]

Herein, we report the enantioselective addition of diethylzinc to aryl aldehydes such as benzaldehyde using ADPD imines **1–4**. These imines **1–4**[10] were easily prepared from ADPD and corresponding aldehydes such as 2-pyridinecarboxaldehyde, 6-methyl-2-pyridinecarboxaldehyde, 2-hydroxybenzaldehyde, and 3-*tert*-butyl-2-hydroxybenzaldehyde[11] under MS 3A.




**Figure**




Enantioselective addition of diethylzinc to benzaldehyde was carried out using 5 mol% of these imines **1–4**.[12] These results are presented in Table 1. When pyridine-imine type catalysts **1** and **2** were used, the reactions were slow and (*S*)-phenylpropanol was obtained in low or moderate enantioselectivities (entries 1 and 3). When the excess of Ti(O-*i*-Pr)$_4$ was added, the reaction was accelerated and the enantioselectivity was increased (entries 2 and 4) (Figure). Lithiated 2-hydroxybenzaldehyde ADPD imine **3** was used as a ligand, the yield was raised up to 93% and the enantioselectivity was increased (entry 5 vs 6). Using 3-*tert*-butyl-2-hydroxybenzaldehyde ADPD imine **4** which has a bulky substituent such as a *tert*-butyl group at 3-position, the enantioselectivity was better than ligand **3** (entries 5 vs 7 and 6 vs 8). In the absence of Ti(O-*i*-Pr)$_4$ or *n*-BuLi, the yield and the enantioselectivity were decreased (entries 9 and 10). On the other hand, when *t*-BuLi was used instead of *n*-BuLi as lithiated reagent, enantioselectivity was not observed (entry 11).

**Table 1.** Enantioselective Addition of Diethylzinc to Benzaldehyde **5a**

| Entry | Ligand | Additive | Reaction time | Yield / %[a] | %*ee*[b] |
|---|---|---|---|---|---|
| 1 | **1** | non | 48 h | 20 | 10 |
| 2 | **1** | Ti(O-*i*-Pr)$_4$ | 24 h | 20 | 40 |
| 3 | **2** | non | 48 h | 35 | 52 |
| 4 | **2** | Ti(O-*i*-Pr)$_4$ | 24 h | 48 | 57 |
| 5 | **3** | non | 48 h | 78 | 25 |
| 6 | **3** | Ti(O-*i*-Pr)$_4$, *n*-BuLi | 24 h | 93 | 30 |
| 7 | **4** | non | 48 h | 48 | 71 |
| 8 | **4** | Ti(O-*i*-Pr)$_4$, *n*-BuLi | 24 h | 94 | 82 |
| 9 | **4** | Ti(O-*i*-Pr)$_4$ | 24 h | 33 | 7 |
| 10 | **4** | *n*-BuLi | 24 h | 12 | 27 |
| 11 | **4** | Ti(O-*i*-Pr)$_4$, *t*-BuLi | 24 h | 72 | 2 |

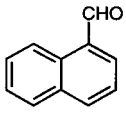
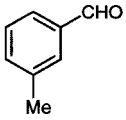
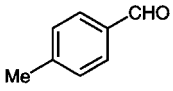
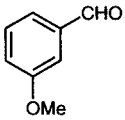
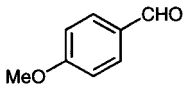
[a] Determined by GLC. [b] Determined by GLC with chiral column

Finally, using lithiated ADPD imine **4** as a catalyst, enantioselective addition of diethylzinc promoted by excess of Ti(O-*i*-Pr)$_4$ to various aryl aldehydes was carried out. These results are presented in the Table 2. For example 3-methylbenzaldehyde (**5c**) was used as an aryl aldehyde, α-ethyl-3-methylbenzylalcohol was obtained in high yield and enantioselectivity (up to 85% *ee*) (entry 2).

In summary, we reported a convenient synthesis of novel ADPD imines and a diethylzinc addition to various aryl aldehydes using these imines in moderate to high enantioselectivities.

***Typical Procedure for the Enantioselective Addition of Diethylzinc to Aryl Aldehydes***. To a solution of ADPD imine **4** (0.05 mmol, 0.018 g) in toluene (5 mL), *n*-butyl lithium (0.05 mmol, 0.03 mL of 1.6 M solution in hexane) was added and the mixture was stirred at -78 °C under an argon atmosphere for 20 min. Then, Ti(O-*i*-Pr)$_4$ (1.0 mmol, 0.28 mL)

**Table 2.** Enantioselective Addition of Diethylzinc to Aryl Aaldehyde **5b–f** Using Lithiated Chiral Ligand **4**

| Entry | Aryl Aldehyde | | Yield / %[a] | %*ee*[b] |
|---|---|---|---|---|
| 1 |  | **5b** | 82 | 78 |
| 2 |  | **5c** | 88 | 85 |
| 3 |  | **5d** | 92 | 81 |
| 4 |  | **5e** | 91 | 82 |
| 5 |  | **5f** | 93 | 80 |

[a] Determined by GLC. [b] Determined by HPLC with chiral column

was added. After 20 min, diethylzinc (2 mmol, 2 mL of 1 M solution in hexane) was added and stirring was continued for 1 h. After warming to -35° C, benzaldehyde (1.0 mmol, 0.10 mL) was added and the mixture was stirred for 24 h at -35° C. The reaction mixture was quenched with 2 M hydrochloric acid, and then extracted with ether. The organic layers were washed with sat. $NaHCO_3$ aq. and brine, and dried over $MgSO_4$ anhydrous. The solvent was evaporated and the residue was purified by TLC (hexane:EtOAc=4:1). The *ee* values were determined by GLC with a Chrompack CP-Cyclodextrin-B-236-M-19 column (0.25mm i.d. x 50m) and HPLC with a Chiralcel OD column. The absolute configuration of alcohols was determined by the comparison of the optical rotation of literature data.[13]

**References and Notes**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(2) Seyden-Penne, J. in *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons, Inc., New York, **1995**.

(3) a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. b) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49.

(4) Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. *Terahedron Lett.* **1996**, *37*, 4613.

(5) Suzuki, T.; Hirokawa, Y.; Ohtake, K.; Shibata, T.; Soai, K. *Terahedron: Aymmetry* **1997**, *8*, 4033.

(6) Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S, Fréchet, J. M. J. *J. Org. Chem.* **1990**, *55*, 304.

(7) Mino, T.; Saitoh, M.; Yamashita, M. *J. Org. Chem.* **1997**, *62*, 3981.

(8) Enders, D.; Kirchhoff, J. *Acros Organics Acta* **1996**, *2*, 10 and references cited therein.

(9) Enders, D.; Breuer, K.; Runsink, J. *Helv. Chem. Acta* **1996**, *79*, 1899.

(10) **1**. $[\alpha]_D^{25}$=+25.48 (*c* 1.0, $CHCl_3$); m.p. 144–145 8C; $^1$H NMR ($CDCl_3$) δ: 1.64 (*s*, 3H), 1.65 (*s*, 3H), 3.55 (*d*, *J*=2.4 Hz, 1H), 3.97 (*dd*, *J*=2.4 and 12.2 Hz, 1H), 4.47 (*dd*, *J*=3.1 and 12.2 Hz, 1H), 5.33 (*d*, *J*=2.4 Hz, 1H), 7.10–7.99 (*m*, 9H), 8.52 (*s*, 1H); $^{13}$C NMR ($CDCl_3$) δ: 19.52, 29.08, 64.97, 67.24, 74.17, 99.53, 121.33, 124.59, 126.73, 127.32, 127.90, 136.32, 138.85, 148.99, 154.52, 163.00; MS m/z (rel intensity): 281 ($M^+$-Me, 0.4).
**2**. $[\alpha]_D^{25}$=+28.68 (*c* 1.0, $CHCl_3$); m.p. 121–122 8C; $^1$H NMR ($CDCl_3$) δ: 1.64 (*s*, 3H), 1.65 (*s*, 3H) , 2.50 (*s*, 3H), 3.55 (*q*, *J*=2.7 Hz, 1H), 3.93 (*dd*, *J*=2.4 and 12.2 Hz, 1H), 4.45 (*dd*, *J*=3.0 and 12.2 Hz, 1H), 5.33 (*d*, *J*=2.4 Hz, 1H), 7.09–7.80 (*m*, 8H), 7.97 (*s*, 1H); $^{13}$C NMR ($CDCl_3$) δ: 19.58, 24.23, 29.05, 65.01, 67.63, 74.18, 99.54, 118.45, 124.22, 126.81, 127.28, 127.89, 136.57, 138.89, 153.96, 157.55, 163.19; MS m/z (rel intensity): 310 ($M^+$, 100).
**3**. $[\alpha]_D^{25}$=+39.48 (*c* 1.0, $CHCl_3$); m.p. 180–182 8C; $^1$H NMR($CDCl_3$) δ: 1.62 (*s*, 3H), 1.64 (*s*, 3H) , 3.39 (*d*, *J*=2.0 Hz, 1H), 3.97 (*dd*, *J*=2.0 and 7.8 Hz, 1H), 4.45 (*dd*, *J*=2.4 and 12.2 Hz, 1H), 5.31 (*d*, *J*=2.0 Hz, 1H), 6.73–7.87 (*m*, 9H), 7.89 (*s*, 1H); MS m/z (rel intensity): 311 ($M^+$, 1.5).
**4**. $[\alpha]_D^{25}$=+37.88 (*c* 1.0, $CHCl_3$); m.p. 107–109 8C; $^1$H NMR ($CDCl_3$) δ: 1.42 (*s*, 9H), 1.62 (*s*, 3H), 1.64 (*s*, 3H) , 3.37 (*q*, *J*=2.1 Hz, 1H), 3.99 (*dd*, *J*=2.1 and 11.9 Hz, 1H), 4.45 (*dd*, *J*=2.4 and 11.9 Hz, 1H), 5.30 (*d*, *J*=2.4 Hz, 1H), 6.66–7.28 (*m*, 8H), 7.93 (*s*, 1H); $^{13}$C NMR ($CDCl_3$) δ: 19.23, 29.28, 29.34, 34.84, 65.00, 65.57, 73.83 99.54, 117.18, 118.49, 126.38, 127.51, 128.10, 129.16, 129.61, 137.39, 138.62, 160.70, 166.03; MS m/z (rel intensity): 367 ($M^+$, 12); Anal. Calcd. for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.76; H, 8.06; N, 3.74.

(11) a) Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc. Perkin Trans. 1*, **1980**, 862. b) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515.

(12) **6a**. $[\alpha]_D^{25}$ -39.58 (*c* 1.0, $CHCl_3$); **6b**. $[\alpha]_D^{25}$ -21.48 (*c* 1.0, $CHCl_3$); **6c**. $[\alpha]_D^{25}$ -36.78 (*c* 1.0, $CHCl_3$); **6d**. $[\alpha]_D^{25}$ -34.98 (*c* 1.0, $CHCl_3$); **6e**. $[\alpha]_D^{25}$ -31.18 (*c* 1.0, $CHCl_3$); **6f**. $[\alpha]_D^{25}$ -30.48 (*c* 1.0, $CHCl_3$).

(13) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.