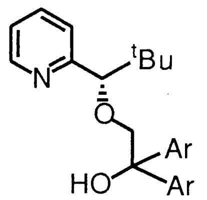
CHEMISTRY LETTERS, pp. 1337-1340, 1994.

Chiral Pyridyl Alcohol-Promoted Highly Enantioselective and Rapid Addition of Dialkylzinc to Pyridinecarboxaldehydes

Miyuki ISHIZAKI and Osamu HOSHINO*
Faculty of Pharmaceutical Sciences, Science University of Tokyo, Shinjuku-ku, Tokyo 162

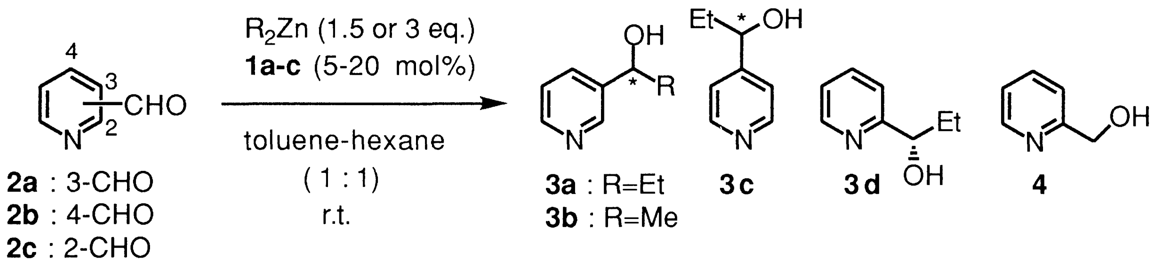
Optically active 1-(2-, 3-, and 4-pyridyl)propanols and 1-(3-pyridyl)ethanol were synthesized in good to high enantiomeric excesses (up to 88% e.e.) and in a short reaction time by catalyzed asymmetric addition of dialkylzinc to pyridine-2-, 3- and 4-carboxaldehydes and 6-bromopyridine-2-carboxaldehyde in the presence of tridentate chiral 2-[2,2-dimethyl-1-(2-pyridyl)propoxy]-1,1-diarylethanols.

Optically active pyridylalkanols can serve not only as useful intermediates in organic syntheses[1)] but also as chiral ligands[2a-e)] or reagents[2f-j)] in asymmetric reactions. Therefore, there are numerous reports concerning highly enantioselective syntheses of optically active pyridylalkanols by means of asymmetric reduction[3a-c)] of the corresponding ketones or of asymmetric addition[3d,e)] to pyridinecarboxaldehydes with stoichiometric amount of chiral organometallic reagents at low temperature. However, only a few reports[4,5)] on enantioselective catalyzed addition of pyridinecarboxaldehydes with dialkylzinc have appeared so far.



1a: Ar = α-Naphthyl
1b: Ar = β-Naphthyl
1c: Ar = Ph

Recently, we have reported that tridentate chiral pyridyl alcohols (**1**) can catalyze highly enantioselective and rapid addition of dialkylzinc to aromatic and aliphatic aldehydes.[6)] The findings suggested that the ligands (**1**) might catalyze effectively addition of dialkylzinc to pyridinecarboxaldehydes, in which because the pyridylalkanol formed *in situ* acts as a catalyst,[4)] the enantioselectivity is poor. Here, we report highly enantioselective and rapid addition of dialkylzinc to pyridinecarboxaldehydes (**2**) using catalytic amounts (5-20



Scheme 1.

Table 1. Asymmetric addition of dialkylzinc to pyridinecarboxaldehydes (**2a-c**) in the presence of (*S*)-**1a-c**[a)]

Entry	Aldehyde	Ligand mol%	R	Time sec	Product	Yield[b)] %	E.e.[c)] %
1	**2a**	**1a**(5)	Et	180	**3a**	73	76
2	**2a**	**1a**(10)	Et	30	**3a**	75	85
3	**2a**	**1a**(20)	Et	30	**3a**	79	86
4[d)]	**2a**	**1a**(10)	Et	30	**3a**	77	88[e)]
5[d)]	**2a**	**1b**(10)	Et	30	**3a**	76	88
6[d)]	**2a**	**1c**(10)	Et	30	**3a**	75	88
7	**2a**	**1a**(10)	Me	1h	**3b**	70	85(*S*)[f)]
8	**2b**	**1a**(10)	Et	30	**3c**	79	81
9[d)]	**2b**	**1a**(10)	Et	30	**3c**	73	83[g)]
10	**2c**	**1a**(10)	Et	30	**3d**	58(24)	0
11[d)]	**2c**	**1a**(10)	Et	30	**3d**	47(23)	10(*S*)[h)]

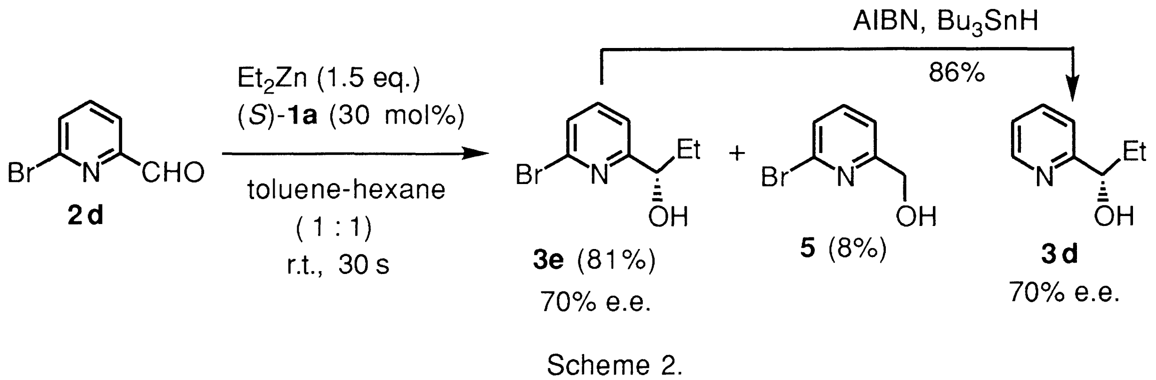
a) All reactions were carried out in a 1 : 3 mixture of aldehydes and R_2Zn in toluene-hexane at room temperature, unless otherwise noted. b) Isolated yield (value in parenthesis is yield of **4**). c) Determined by HPLC analyses using CHIRALCEL OD or OJ (DAICEL) of the corresponding (-)-MTPA ester for **3a** or acetates for **3b** and **3c**. d) A 1 : 1.5 mixture of aldehydes and Et_2Zn was used. e) $[\alpha]_D^{28}$ -41.4° (c 2.1, MeOH). Absolute configuration was not determined. f) $[\alpha]_D^{29}$ -42.7° (c 1.6, MeOH) {Lit.[3a] $[\alpha]_D^{25}$ 35.06° (c 0.88, MeOH) for 87% e.e. of (*R*)-**3b**}. g) $[\alpha]_D^{29}$ -41.1° (c 2.0, EtOH). h) $[\alpha]_D^{26}$ -6.4° (c 1.8, EtOH) {Lit.[7] $[\alpha]_D^{25}$ 38.0° (c 1.68, MeOH) for 52.1% e.e. of (*R*)-**3d**}.

mol%) of the ligands (**1**) at ambient temperature (Scheme 1).

First, we examined amount of the ligand (*S*)-**1a** effective for enantioselectivity in the reaction of pyridine-3-carboxaldehyde (**2a**) with diethylzinc (Et_2Zn) (Table 1, entries 1-3). Employment of more than 10 mol% of (*S*)-**1a** was found to give (-)-1-(3-pyridyl)propanol (**3a**)[5] in similar enantiomeric excess (85-86% e.e.) for 30 sec (entries 2, 3). Hence, 10 mol% of the ligand was used in the following reaction. Treatment of **2b** with Et_2Zn using (*S*)-**1a** gave **3c**[7] in 81% e.e. (entry 8), whereas that of **2c** gave racemic **3d**[8] (entry 10). It is not surprising at the latter result by taking into consideration that the reaction of **2a**, **2b**, and **2c** with Et_2Zn in the absence of the ligand (**1a**) for 30 sec afforded **3a** (12%), **3c** (53%), and **3d** (56%) and **4** (33%), respectively. It would be attributed to the chemical behavior of the carbonyl groups at the 4- and 2-positions activated by the inter- and intra-molecular chelation of the nitrogen atom in the pyridine ring with Zn atom of Et_2Zn that the rapid reaction of **2b** and **2c** took place in the similar extent.

Next, effect of equivalent of Et_2Zn on enantioselectivity was examined. Even when 1.5 eq. of Et_2Zn was used, the reaction of **2a** smoothly proceeded to furnish **3a** in 88% e.e. (entry 4). The reaction of **2c** with 1.5 eq. of Et_2Zn using **1a**, however, led to **3d** in only 10% e.e. (entry 11). Other ligands (**1b**,**c**) gave also satisfactory results (entries 5, 6). Furthermore, high enantioselectivity (85% e.e.) was obtained by the reaction of **2a** with Me_2Zn using (*S*)-**1a** (entry 7).

The reason why with **2c** the enantioselectivity was poor seemed to be due to facile intramolecular chelation of Et_2Zn between the nitrogen atom and a carbonyl group in **2c**, accelerating non-catalyzed reaction.[4] Based on the assumption, introduction of an electonwithdrawing group at the 6-position of the pyridine ring could suppress intramolecular chelation because of both steric effect and reduced basicity of the pyridine ring. The reaction of 6-bromopyridine-2-carboxaldehyde (**2d**)[9] with Et_2Zn in the presence of 30 mol% of (*S*)-**1a** was carried out to furnish in 70% e.e.[10] **3e**[7] along with **5** (8%), as expected. Radical mediated reduction of **3e** smoothly proceeded to give **3d** in 86% yield without loss of optical purity. Thus, catalytic asymmetric synthesis of (-)-**3d** was accomplished in two steps (Scheme 2).



Scheme 2.

In summary, tridentate chiral pyridyl alcohols (**1**) were proved to be effective as a catalyst for rapid alkylation of pyridinecarboxaldehydes.

References

1) J. Deeter, J. Frazier, G. Staten, M. Stazak, and L. Wiegel, *Tetrahedron Lett.*, **31**, 7101 (1991); R. A. Farr, N. P. Peet, and M. S. Kang, *ibid.*, **31**, 7109 (1991); M. R. Uskokovic, R. E. Lewis, J. J. Partridge, C. W. Despreaux, and D. L. Pruess, *J. Am. Chem. Soc.*, **101**, 6742 (1979).

2) a) C. Bolm, M. Zehnder, and D. Bur, *Angew. Chem., Int. Ed. Engl.*, **29**, 205 (1990); b) G. Chelucci, S. Conti, M. Falorni, and G. Giacomelli, *Tetrahedron Lett.*, **47**, 8251 (1991); c) C. Bolm, M. Ewald, M. Felder, and G. Schlingloff, *Chem. Ber.*, **125**, 1169 (1992); d) M. Falorni and G. Giacomelli, *Gazz. Chim. Itall.*, **122**, 339 (1992); e) G. Chelucci, M. Falorni, G. Giacomelli, and F. Soccolini, *Tetrahedron*, **48**, 8993 (1992); f) A. Frank and C. Rüchardt, *Chem. Lett.*, **1984**, 1431; g) C. Rüchardt, H. Gärtner, and U. Salz, *Angew. Chem., Int. Ed. Engl.*, **23**, 162 (1984); h) U. Salz and C. Rüchardt, *Chem. Ber.*, **117**, 3457 (1984); i) R. Chinchilla, C. Nájera, M. Yus, and A. Heumann, *Tetrahedron: Asymmetry*, **2**, 101 (1991); j) A. Mazon, C. Nájera, M. Yus, and A. Heumann, *ibid.*, **3**, 1455 (1992).

3) a) K. Soai, S. Niwa, and T. Kobayashi, *J. Chem. Soc., Chem. Commun.*, **1987**, 881; b) M. M. Midland, J. I. McLoughlin, and J. Gabriel, *J. Org. Chem.*, **54**, 159 (1989); c) H. C. Brown, J. Chandrasekharam, and P. V. Ramachandran, *ibid.*, **55**, 6328 (1990); d) U. S. Racherla and H. C. Brown, *ibid.*, **56**, 401 (1991); e) U. S. Racherla, Y. Liao, and H. C. Brown, *ibid.*, **57**, 6614 (1992).

4) K. Soai, S. Niwa, and H. Hori, *J. Chem. Soc., Chem. Commun.*, **1990**, 982.

5) Asymmetric addition of Et_2Zn or Me_2Zn to pyridine-3-carboxaldehyde (**2a**) using nearly stoichiometric amount (75 mol%) of (-)-*N*,*N*-dibutylnorephedrine has been reported to give the corresponding alcohols in 74 or 48% e.e. K. Soai, H. Hori, and S. Niwa, *Heterocycles*, **29**, 2065 (1989).

6) M. Ishizaki, K. Fujita, M. Shimamoto, and O. Hoshino, *Tetrahedron: Asymmetry*, **5**, 411 (1994).

7) All new compounds gave satisfactory chemical or high-resolution mass spectral analysis.

8) A. Ohno, J. Nakai, and K. Nakamura, *Bull. Chem. Soc. Jpn.*, **54**, 3482 (1981).

9) J. E. Parks, B. E. Wargner, and R. H. Holm, *Inorg. Chem.*, **10**, 2472 (1971).

10) The reaction of **2d** with 10 or 20 mol% of (*S*)-**1a** gave **3e** in 50 or 62% e.e., respectively.

(Received April 20, 1994)