ENANTIOSELECTIVE ADDITION OF DIALKYLZINCS TO PYRIDINECARBALDEHYDE IN THE PRESENCE OF CHIRAL AMINOALCOHOLS : ASYMMETRIC SYNTHESIS OF PYRIDYLALKYL ALCOHOLS

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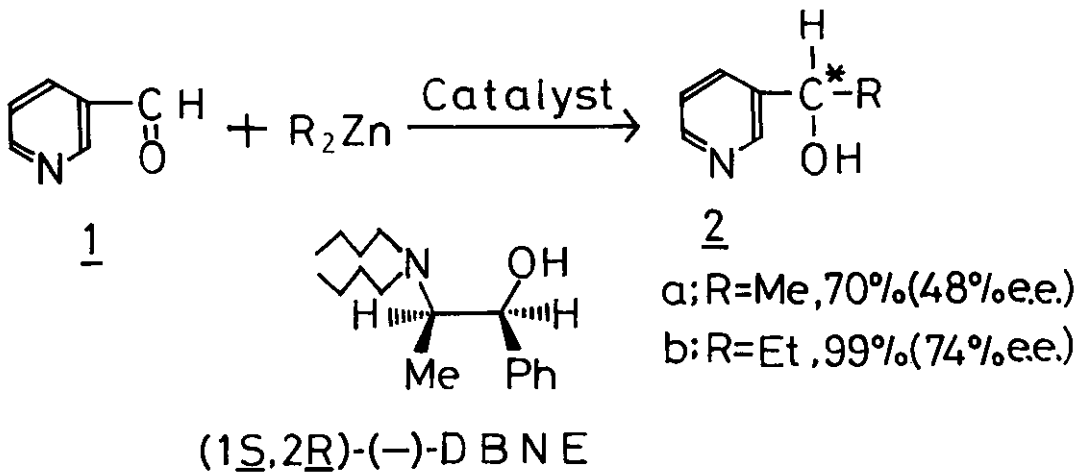
Abstract —— 1-(3-Pyridyl)ethanol and -propanol were synthesized in moderate to good enantiomeric excesses by the enantioselective addition of dialkylzincs to nicotinaldehyde using N,N-dibutylnorephedrine as chiral catalyst.

Optically active pyridylalkyl alcohols are important synthetic intermediates.[1] Asymmetric reduction of acylpyridines by biochemical[1a,2] and chemical[3] methods has been reported. However, biochemical reduction can afford only one enantiomer and it is difficult to obtain the enantiomer of the opposite configuration. On the other hand, chemical methods require stoichiometric amount of chiral auxiliaries and enantiomeric excesses (e.e.) of the most of the chemical reductions range from



low to moderate. We recently reported asymmetric reduction of acetylpyridines by lithium borohydride modified with (R,R')-N,N'-dibenzoylcystine and ethanol.[4] To our knowledge, no method has been reported on the catalytic asymmetric synthesis of pyridylalkyl alcohols by enantioselective alkylation of pyridinecarbaldehyde.

During our continuing study on the enantioselective addition of dialkylzincs to aldehydes using chiral catalysts,[5] we found that pyridylalkyl alcohols are synthesized in moderate to good e.e. by asymmetric alkylation of pyridinecarbaldehyde with dialkylzincs using chiral amino alcohol as a catalyst.

When nicotinaldehyde (**1**) was treated with Et_2Zn in hexane in the presence of (1S,2R)-(-)-N,N-dibutylnorephedrine (DBNE) (mol ratio to aldehyde = 0.05), (-)-1-(3-pyridyl)propanol (**2b**) was obtained in 93% yield (37% e.e.).[6] Unlike the reaction with other simple aldehydes such as benzaldehyde,[5b] it was found that e.e. of **2b** increased according to the increase of the mol ratio of DBNE to **1**. When the ratio was 0.75, **2b** [$[\alpha]^{24}_D$ -26.11° (c 1.49, MeOH)] was obtained in 99% yield and in 74% e.e. (determined by hplc analysis of MTPA ester using chiral column).

One of the advantages of the present alkylation method over the conventional reduction method is its easy access to other pyridylalkylalcohols by merely changing the structure of R_2Zn. Thus by using Me_2Zn instead of Et_2Zn, (S)-1-(3-pyridyl)ethanol (**2a**) [$[\alpha]^{25}_D$ -12.25° (c 1.42, MeOH)] was obtained in 70% yield and in 48% e.e. [determined by hplc analysis of (-)-MTPA ester using chiral column]. Though no experimentation has been attempted, it is very likely that (R)-(+)-(**2a**) and (+)-(**2b**) can be synthesized by using (1R,2S)-(+)-DBNE (norephedrine is readily available in either enantiometric form).

In a typical experiment, nicotinaldehyde (**1**) (0.057g, 0.05ml, 0.53 mmol) was added to a hexane (0.5 ml) solution of DBNE (0.102g, 0.38 mmol). The mixture was cooled to 0 °C, and Et_2Zn (1.4 ml of 1 M hexane solution) was added. The mixture was stirred for 1 h at room temperature and quenched with 1 M HCl. Saturated aqueous sodium bicarbonate was added until the mixture became alkaline, and the resulting white precipitate was filtered off using Celite. The filtrate was extracted with ethyl acetate, and the organic layer was dried over Na_2SO_4. After the evaporation of solvent under reduced pressure, the residue was purified on silica gel tlc (developing solvent, EtOAc). **2b** (0.070g) was obtained in 99% yield. E.e. was determined as 74% e.e. based on hplc analysis of the corresponding (-)-MTPA ester using chiral column (Daicel Chiralcel OD), eluent:

10% 2-propanol in hexane, uv- detector (254 nm), 1.0 ml / min, retention time for the minor isomer 7.6 min, for the major isomer 9.2 min. High ms, Found(m/z) 137.0843. Calcd for $C_8H_{11}ON$: 137.0847.

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6. The effect of chiral catalyst was examined in the same reaction conditions except the reaction temperature (0 °C). (S)-(+)-Diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM)[5a,d] and (R)-3-quinuclidinol (85% e.e.) afforded **2b** in 22 and 17% e.e. respectively.

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