ASYMMETRIC SYNTHESIS OF VARIOUS CHIRAL 5-PYRIMIDYL-ALKANOLS BY THE ENANTIOSELECTIVE ALKYLATION OF PYRIMIDINE-5-CARBALDEHYDES WITH DIALKYLZINCS IN THE PRESENCE OF CHIRAL AMINO ALCOHOLS

Takanori Shibata, Tadakatsu Hayase, Yasuyuki Aiba, Hayami Tabira, and Kenso Soai*

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo, 162 Japan

Abstract - (1S, 2R)-N,N-Dibutylnorephedrine catalyzes the enantioselective addition of dialkylzincs to various pyrimidine-5-carbaldehydes. Ethylation and butylation proceed with high enantioselectivities (up to 94% e.e.) to give optically active secondary 5-pyrimidyl alkanols.

Pyrimidine ring[1] is the parent skeleton of cytosine, thymine, and uracil which are constituents of nucleic acids. There are many medicinally active compounds which include pyrimidine ring. To our knowledge, however, almost no example is reported where chiral pyrimidyl alkanols are synthesized. On the other hand, we have comprehensively examined[2] the asymmetric synthesis of optically active secondary alcohols by the enantioselective alkylations of aldehydes with dialkylzincs in the presence of catalytic amount of amino alcohols as chiral catalysts. It is not only because secondary alcohols themselves are included in various natural products, but because hydroxyl group is easily transformed into other functionalities. This paper discloses the application of our method for the preparation of various optically active 5-pyrimidyl alkanols.

Firstly, an enantioselective ethylation of 2-methylpyrimidine-5-carbaldehyde (**1a**) by diethylzinc was examined in the presence of a catalytic amount (20 mol%) of (1S, 2R)-N,N-dibutylnorephedrine (**3**) (DBNE).[3] However, the e.e. of the obtained pyrimidyl alkanol (**2a**) was low (Table 1, Entry 1). But the increase of the amount of the chiral catalyst (1S, 2R)-DBNE (**3**) to 50 mol% dramatically improved the enantioselectivity of the asymmetric ethylation (85% e.e.) (Entry 2).

Next, the enantioselectivities of various chiral catalysts, such as (1S,2R)-2-morpholino-1-phenylpropan-1-ol (**4**) (MOPEP),[4] (1R,2S)-N-vinylbenzylephedrine (**5**) (VBE),[5] (S)-diphenyl(1-methylpyrrolidin-2-methanol (**6**) (DPMPM),[6] were examined (Entries 3-5). As a result, (1S, 2R)-DBNE (**3**) was proved to be the most effective chiral catalyst in the enantioselective ethylation of aldehyde (**1a**) (Entry 2).

Using 50 mol% of (1S,2R)-DBNE (3) as a chiral catalyst, various pyrimidine-5-carbaldehydes (**1a-d**)

This paper is dedicated to the memory of the late Professor Shun-ichi Yamada.

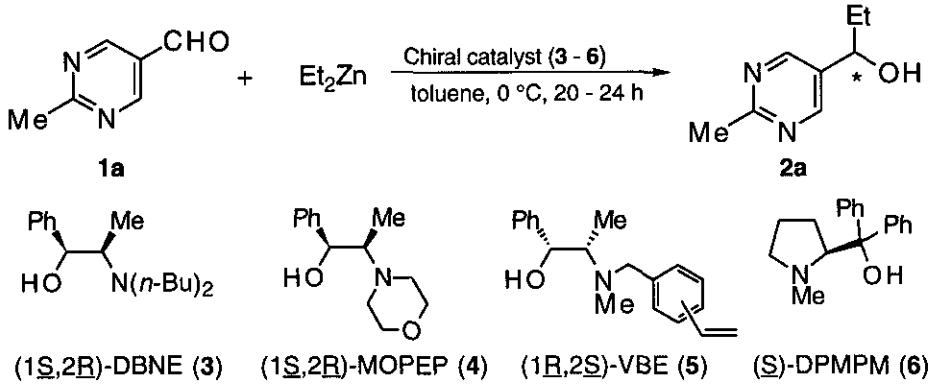

Table 1. Enantioselective ethylation of **1a** using chiral amino alcohols (**3** - **6**)

Entry[a]	Chiral Catalyst	Yield (%)	e.e. (%)[b]	Configuration[c]
1[d]	(1S,2R)-DBNE (**3**)	92	38	S
2	(1S,2R)-DBNE (**3**)	90	85	S
3	(1S,2R)-MOPEP (**4**)	85	81	S
4	(1R,2S)-VBE (**5**)	83	66	R
5	(S)-DPMPM (**6**)	81	68	S

[a] Unless otherwise noted, molar ratio was as follows. Chiral catalyst : **1a** : Et_2Zn = 0.5 : 1.0 : 3.0. [b] Determined by HPLC analysis using a chiral column. [c] Absolute configuration was estimated by the new Mosher method (ref. 7). [d] Molar ratio was as follows. Chiral catalyst : **1a** . Et_2Zn = 0.2 : 1.0 : 3.0.

were submitted to the enantioselective ethylation by diethylzinc (Table 2). The substituents on the 2-position of the pyrimidine ring influenced on the enantioselectivity of alkylation, that is, 2-substituted pyrimidine-5-carbaldehydes (**1a**), (**1c**), and (**1d**) possessing bulky groups were alkylated with higher enantioselectivities than unsubstituted pyrimidine-5-carbaldehydes (**1b**) (Entries 2-4). Especially, the enantioselective ethylation of 2-phenylpyrimidine-5-carbaldehyde (**1d**) proceeded in the highest chemical and optical yield (93%, 91% e.e.) (Entry 4).

We then examined the enantioselective butylation by dibutylzinc under the same reaction conditions as described in the preceding paragraph. Asymmetric butylations of various pyrimidine-5-carbaldehydes proceeded with higher enantioselectivities than those of the ethylation, that is, the corresponding 5-pyrimidyl alkanols (**7a**), (**7b**), and (**7d**) with 81-94% e.e. were obtained (Table 3). Especially, in the enantioselective butylation of **1d** possessing a phenyl substituent at 2-position, the butylated product (**7d**) was obtained with the highest enantioselectivity of 94% e.e. (Entry 3). This is probably because the non-catalyzed butylation is hard to proceed by the less reactive dibutylzinc as an alkylating reagent.

We recently reported that chiral 5-pyrimidyl alkanols are effective asymmetric autocatalysts[8] in the enantioselective alkylation by dialkylzinc. This paper disclosed a general synthetic tool for the preparation of optically active 5-pyrimidyl alkanols which may have promising utilities.

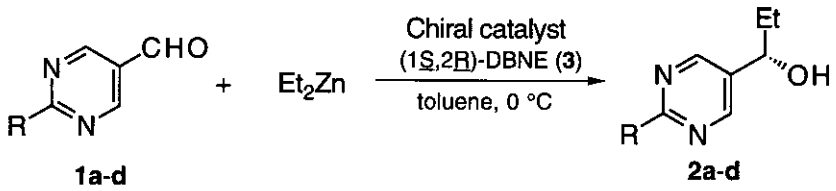

Table 2. Enantioselective ethylation of various pyrimidine-5-carbaldehydes (**1a-d**)

Entry[a]	R	Time (h)	2	Yield (%)	e.e. (%)[b]
1	H (**1b**)	3	**2b**	68	64 (S)[c]
2	Me (**1a**)	28	**2a**	90	85 (S)[d]
3	Et (**1c**)	32	**2c**	81	86 (S)[c]
4	Ph (**1d**)	36	**2d**	93	91 (S)[c]

[a] Molar ratio. Chiral catalyst **3** : **1a-d** : Et_2Zn = 0.5 : 1.0 : 3.0 [b] Determined by HPLC analysis using a chiral column. [c] Absolute configuration was estimated by the analogy with **2a**.
[d] Absolute configuration was estimated by the new Mosher method (ref. 7).

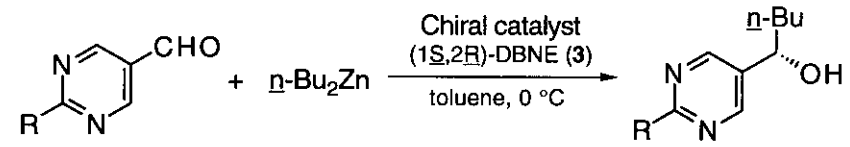

Table 3. Enantioselective butylation of **1a, b, d** using (1S,2R)-DBNE (**3**)

Entry[a]	R	Time (h)	7	Yield (%)	e.e. (%)[b]
1	H (**1b**)	32	**7b**	79	81 (S)[c]
2	Me (**1a**)	71	**7a**	81	91 (S)[d]
3	Ph (**1d**)	38	**7d**	72	94 (S)[c]

[a] Molar ratio. Chiral catalyst **3** : **1a, b, d** : n-Bu_2Zn = 0.5· 1 0 : 3.0 [b] Determined by HPLC analysis using a chiral column. [c] Absolute configuration was estimated by the analogy with **7a**.
[d] Absolute configuration was estimated by the new Mosher method (ref. 7)

EXPERIMENTAL

General. Optical rotation was measured by Jasco DIP-1000 polarimeter. IR spectra were recorded with Horiba FT210 spectrophotometer. ^1H NMR spectra (300 MHz) were measured with Bruker DPX300 spectrometer using tetramethylsilane as the internal standard and $CDCl_3$ was used as solvent. High-resolution mass spectra (HRMS) were obtained with JEOL JMS-SX102A mass spectrometer.

Toluene was distilled from calcium hydride and dried over Molecular Sieves 4A (MS 4A). Pyrimidine-5-carbaldehydes (**1a**),[9] (**1b**),[10] and (**1d**)[9] were prepared according to the literature methods. All reactions were carried out under an argon atmosphere.

2-Ethylpyrimidine-5-carbaldehyde (1c). **1c** was prepared by the literature method[9] except that ethylamidine hydrochloride was employed instead of acetamidine. Yield 75%. IR (neat) 1709 cm^{-1}; ^1H NMR δ= 1.41 (t, J= 7.6 Hz, 3H), 3.11 (q, J= 7.6 Hz, 2H), 9.11 (s, 2H), 10.13 (s, 1H); HRMS Found m/z 136.0635. Calcd for $C_7H_8N_2O$: M, 136.0637.

General procedure for the enantioselective alkylation of pyrimidine-5-carbaldehydes (1a-d) using (1S,2R)-DBNE (3) as a chiral catalyst. A mixture of a toluene solution (4 mL) of (1S,2R)-DBNE (**3**) (131.7 mg, 0.50 mmol) and 1 M toluene solution of dialkylzinc (3.0 mL, 3.0 mmol) was stirred for 20 min at 0 ℃. Then pyrimidine-5-carbaldehydes (**1a-d**) (1.00 mmol) was added in a toluene solution (3 mL) at 0 ℃. The reaction mixture was stirred at 0 ℃ for the appropriate time cited in the Tables. The reaction was quenched by the successive addition of 1 M HCl (5 mL) and sat. aq. $NaHCO_3$ (15 mL) at 0 ℃. The mixture was filtered using celite and the filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressures. Purification of the crude residue on silica gel TLC gave the corresponding pyrimidyl alkanols (**2a-d**), (**7a**, **b**, and **d**).

(S)-(-)-1-[5-(2-Methylpyrimidyl)]propan-1-ol (2a). Pale yellow oil. Optical purity was determined to be 85% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OG: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time (min) 18.0 for the major isomer, 21.7 for the minor isomer). $[\alpha]^{22}_D$ -32.88° (*c* 1.96, $CHCl_3$); IR (neat) 3417 cm^{-1}; ^1H NMR δ= 0.95 (t, J= 7.4 Hz, 3H), 1.26-1.89 (dq, J_d= 6.5 Hz, J_q= 7.4 Hz, 2H), 2.68 (s, 3H), 3.83 (br s, 1H), 4.64 (dd, J= 6.5, 6.5 Hz, 1H), 8.57 (s, 2H); HRMS Found m/z 152.0960. Calcd for $C_8H_{12}N_2O$: M, 152.0951.

(S)-(-)-1-(5-Pyrimidyl)propan-1-ol (2b). Pale yellow oil. Optical purity was determined to be 64% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 3% 2-propanol in hexane, flow rate: 0.7 mL/min, retention time (min) 45.0 for the major isomer, 55.9 for the minor isomer). $[\alpha]^{23}_D$ -31.72° (*c* 2.36, $CHCl_3$); IR (neat) 3340 cm^{-1}; ^1H NMR δ= 0.98 (t, J= 7.4 Hz, 3H), 1.78-1.93 (m, 2H), 2.87 (br s, 1H), 4.71 (dd, J= 5.6, 5.6 Hz, 1H), 8.73 (s, 2H),9.11(s, 1H); HRMS Found m/z 138.0791 Calcd for $C_7H_{10}N_2O$: M, 138.0794.

(S)-(-)-1-[5-(2-Ethylpyrimidyl)]propan-1-ol (2c). Pale yellow oil. Optical purity was determined to be 86% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time (min) 12.4 for the major isomer, 13.2 for the minor isomer). $[\alpha]^{23}_D$ -27.21° (*c* 2.95, MeOH); IR (neat) 3311 cm^{-1}; ^1H NMR δ= 0.97 (t, J= 7.4 Hz, 3H), 1.36 (t, J= 7.6 Hz, 3H), 1.82 (dq, J_d= 6.3 Hz, J_q= 7.4 Hz, 2H), 2.45 (br s, 1H), 2.99 (q, J= 7.6 Hz, 2H), 4.67 (dd, J= 6.3, 6.3 Hz, 1H), 8.64 (s, 2H); HRMS Found m/z 166.1112. Calcd for $C_9H_{14}N_2O$: M, 166.1107.

(S)-(-)-1-[5-(2-Phenylpyrimidyl)]propan-1-ol (2d). mp 72 ℃ (recrystallized from hexane). Optical purity was determined to be 91% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 21.7 for the major isomer, 45.2 for the minor isomer). $[\alpha]^{25}_D$ -39.87° (*c* 1.00, $CHCl_3$); IR (neat) 3359 cm^{-1}; ^1H NMR δ= 0.97 (t, J= 7.4 Hz, 3H), 1.75-1.92 (dq, J_d= 6.4 Hz, J_q= 7.4 Hz, 2H), 2.57 (d, J= 3.6 Hz, 1H), 4.64-4.79 (ddd, J= 3.6, 6.4, 6.4 Hz, 1H), 7.26-7.53 (m, 3H), 8.37-8.43 (m, 2H), 8.74 (s, 2H); Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.76; H, 6.28; N, 12.97.

(S)-(-)-1-[5-(2-Methylpyrimidyl)]pentan-1-ol (7a). Pale yellow oil. Optical purity was

determined to be 81% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel AD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 15.1 for the major isomer, 27.9 for the minor isomer). $[\alpha]^{27}_{D}$ -35.48° (*c* 1.59, $CHCl_3$); IR (neat) 3351 cm^{-1}; ^1H NMR δ = 0.90 (t, J= 6.9 Hz, 3H), 1.23-1.46 (m, 4H), 1.66-1.89 (m, 2H), 2.70 (s, 3H), 3.19 (br s, 1H), 4.71 (dd, J= 6.6, 6.6 Hz, 1H), 8.59 (s, 2H); HRMS Found m/z 180.1276. Calcd for $C_{10}H_{16}N_2O$: M, 180.1264.

(S)-(-)-1-(5-Pyrimidyl)pentan-1-ol (7b). Pale yellow oil. Optical purity was determined to be 91% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OB-H: 4 x 250 mm, 254 nm UV detector, rt, eluent: 3% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time (min) 18.2 for the major isomer, 20.5 for the minor isomer). $[\alpha]^{31}_{D}$ -31.17° (*c* 2.73, $CHCl_3$); IR (neat) 3351 cm^{-1}; ^1H NMR δ= 0.90 (t, J=6.9 Hz, 3H), 1.25-1.48 (m, 4H), 1.68-1.89 (m, 2H), 3.88 (br s, 1H), 4.75 (dd, J=5.8, 7.4 Hz, 1H), 8.70 (s, 2H), 9.05 (s, 1H); HRMS Found m/z 166.1099. Calcd for $C_9H_{14}N_2O$: M, 166.1107.

(S)-(-)-1-[5-(2-Phenylpyrimidyl)]pentan-1-ol (7d). Pale yellow oil. Optical purity was determined to be 94% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time (min) 10.7 for the major isomer, 15.4 for the minor isomer). $[\alpha]^{25}_{D}$ -43.34° (*c* 5.05, $CHCl_3$); IR (neat) 3417 cm^{-1}; ^1H NMR δ= 0.88 (t, J= 6.9 Hz, 3H), 1.21-1.44 (m, 4H), 1.65-1.86 (m, 2H), 3.05 (br s, 1H), 4.67 (dd, J= 6.1, 7.2 Hz, 1H), 7.29-7.49 (m, 3H), 8.37-8.40 (m, 2H), 8.70 (s, 2H); HRMS Found m/z 242.1420. Calcd for $C_{15}H_{18}N_2O$: M, 242.1426.

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