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AMINOHALOBORANE IN ORGANIC SYNTHESIS. VI.[1] A SIMPLE ENANTIOSELECTIVE ALDOL SYNTHESIS

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Summary A simple asymmetric aldol condensation of acetophenone and benzaldehydes was performed via chiral vinylaminodichloroborane. The enatioselectivity was compared with that by a similar method using magnesium and lithium.

Recently, Enders and his co-workers[2] reported the first regiospecific and enantioselective aldol synthesis, which consists of a reaction series involving lithiation of chiral hydrazones followed by addition of carbonyl compounds, silylation of the condensation products and oxidative hydrolysis. We will describe here a much simpler enantioselective aldol synthesis as an extension of our simple directed aldol reaction using N-cyclohexylvinylaminodichloroborane.[3]

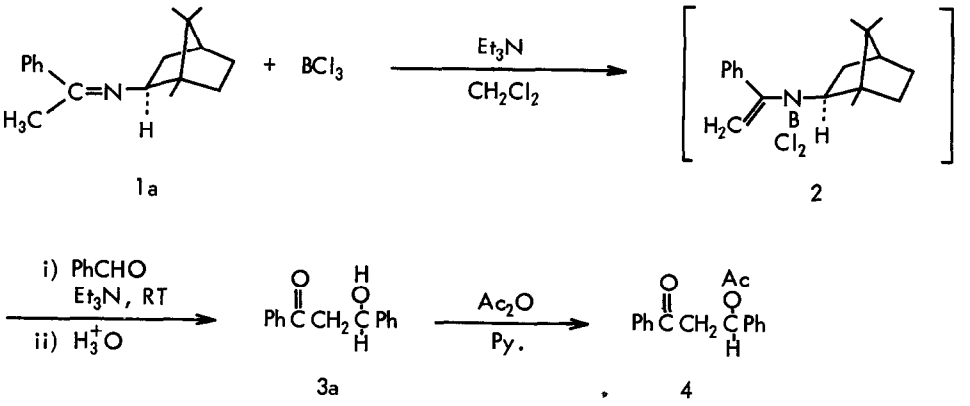
Namely, (S)-(-)-N-(α-methylbenzyliden)isobornylamine (1a) was treated with boron trichloride in the presence of 2.5 equivalents of triethylamine in dichloromethane followed by addition of benzaldehyde. The reaction proceeded presumably via chiral vinylaminodichloroborane 2. The optical purity (47.7%) and absolute configuration (R) of the aldol product (3a) obtained after acidic work-up followed by chromatography were determined by comparing the specific rotation of the corresponding acetyl derivative (4) with that of an authentic sample[4] having the R configuration.

The similar reaction of chiral imines 1a, 1b[5] or 1c with p-nitrobenzaldehyde and comparison of the reaction (run 2) with that using magnesium (run 3) and lithium (run 4) were carried out as shown in the Table. As noted, the best enantioselectivity observed was obtained by using boron atom and this may be rationalized by assuming that boron can provide more rigid intermediates by stronger coordination ability to carbonyl oxygen and facilitate the carbon-carbon bond formation in a more concerted manner. However, the opposite enantioselectivity in run 4 and the poor enentioselectivity in run 5 can not be clearly understood at present.

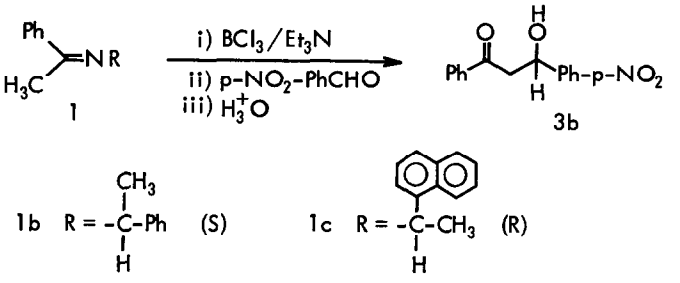
EXPERIMENTAL

(S)-(-)-N-(α-Methylbenzyliden)isobornylamine (1a)

A solution of isobornylamine [11 g, 71.2 mmol, $[\alpha]_D^{26}$ -46.4 (c 3, EtOH)] and acetophenone (8.6 g, 71.2 mmol) in dry benzene (100 mL) was refluxed in the presence of molecular sieves (4A, 30 g) with a Dean-Stark apparatus for 17 h. The molecular sieves were filtered off and washed with benzene. The combined filtrate was concentrated and the residue was distilled



Enantioselective Aldol Reaction of Acetophenone



Run	Chiral imine	Chiral aldol (3b)		
		% yield[a]	% ee[b]	$[\alpha]_D^{26}$ (c 1, $CHCl_3$)
1	1a	33.8	41.5	+27.1
2	1b[5]	41.5	34.5	+22.5
3	1b	6.3	19.1	-12.5
4	1b	15.2	7.0	+4.6
5	1c	29.9	2.5	+1.64

[a] Isolated yield based on the chiral imine used.

[b] Calculated from the optically pure aldol, mp 128-129°C (ether), $[\alpha]_D$ +65.3 (c 1, $CHCl_3$). The sample was obtained by repeated recrystallization (x6, from ether) of the product in run 2 until the sample showed no further absorption due to the antipodal benzylic methine proton in the NMR spectrum with the shift reagent tris [3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium (III).

giving 1a (15.5 g, 85%). Bp 107-108° (0.065 mmHg). $[\alpha]_D^{26}$ -129.6° (c 1, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}N$: C, 84.65; H, 9.87; N, 5.48. Found: C, 84.79; H, 9.96; N, 5.50. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1631 (-N=C). NMR ($CDCl_3$) δ: 0.85, 0.87, 1.18 (9H, s x 3, CH_3 of i-bornyl group), 2.10 (3H, s, -N=C$\langle_{CH_3}$), 3.50 (1H, m, $\rangle$C<u>H</u>-N=), 7.17-7.97 (5H, m, -Ph).

(S)-(+)-α-Methyl-N-(α-methylbenzyliden)benzylamine (1b)

1b was obtained from (S)-(-)-α-phenylethylamine [$[\alpha]_D^{25}$ -34.1 ± 0.6° (c 1.2, $CHCl_3$)] and acetophenone in a similar way to the above (58%) or according to literature 5 (82%). Bp 97-98° (0.056 mmHg). The specific rotation of our 1b was +87.0 ± 1.4° (c 0.91, $CHCl_3$), +88.1 ± 6.1° (c 1.50, benzene) and +88.3 ± 1.3° (neat, l = 0.1 cm) at 25°. Lit.[5], $[\alpha]_D^{25}$ -97.56° and $[\alpha]_D^{25}$ -98.4 (c 5.59 benzene), but the sign has been corrected (private communication from Dr. K. Harada).

(R)-(-)-N-(α-Methylbenzyliden)-1-(1-naphthyl)ethylamine (1c)

1c was obtained from (R)-(+)-α-(1-naphthyl)ethylamine [$[\alpha]_D^{27}$ +81.8 ± 0.5° (neat, l = 0.1 cm)] and acetophenone in a similar manner to the above. Yield 84.2%, bp 153-155° (0.05 mmHg), $[\alpha]_D^{26}$ -23.05 ± 2.5° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{19}N$: C, 87.87; H, 7.01; N, 5.12. Found: C, 87.72; H, 7.04; N, 5.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1632. NMR ($CDCl_3$) δ: 1.55 (0.4H, d, J = 7 Hz, syn C<u>H</u>$_3$CH$\langle$), 1.70 (2.6H, d, J = 7 Hz, anti C<u>H</u>$_3$CH$\langle$), 2.08 (2.6H, s, anti C<u>H</u>$_3$-C=N), 2.33 (0.4H, s, syn C<u>H</u>$_3$-C=N), 5.22 (0.13H, q, J = 7 Hz, syn =N-C<u>H</u>-CH_3), 5.48 (0.87H, q, J = 7 Hz, anti =N-C<u>H</u>-CH_3), 6.97-8.33 (12H, m, aromatic H) (syn and anti are tentatively assigned).

Enantioselective Condensation of Benzaldehydes with Chiral Imines (General Procedure)

i) With Boron Trichloride and Triethylamine

A solution of (S)-(-)-N-(α-methylbenzyliden)isobornylamine (1a) (2.56 g, 10 mmol) in dichloromethane (8 mL) and triethylamine (3.5 mL, 25 mmol) were added successively at -45° to a stirred solution of boron trichloride (8.8 mL of 1.15 M dichloromethane solution, 10 mmol). Next, a solution of benzaldehyde (1.06 g, 10 mmol) in dichloromethane (3 mL) was added under ice-cooling and stirring. After the suspension had been stirred for 6 h at room temperature, ice and 1 N acetic acid (20 mL) were added and the mixture was stirred for 2 h. The mixture was extracted with dichloromethane and the organic layer was washed with dil. $NaHCO_3$ solution and H_2O. After drying ($MgSO_4$) and concentration, the residue was dissolved in benzene and the solution was passed through a short SiO_2-gel layer to remove a polar fraction. The eluate was purified by chromatography (SiO_2 60, prepacked column B, Merck, $CHCl_3$:AcOEt, 100:3) giving β-hydroxy-β-phenylpropiophenone (3a), 685 mg (30.3%), $[\alpha]_D^{23}$ +16.2 ± 0.1 (c 6.613 MeOH). 3a (530 mg) was acetylated with acetic anhydride (287 mg) in pyridine (1 mL) at room temperature for 20 h. After the usual work-up, the residue was purified by chromatography in a similar manner to the above to give chalcone (48 mg) and (R)-(+)-β-acetoxy-β-phenylpropiophenone (4), 525 mg, 83.7% based on 3a. $[\alpha]_D^{22}$ +14.7 ± 0.1° (c 6.550 MeOH), 47.7% OP [Lit.,[5] $[\alpha]_D^{18}$ +30.8 ± 0.2° (c 6.457, MeOH)].

ii) With Ethylmagnesium Bromide

To a stirred THF solution of EtMgBr (6.25 mL of 0.8 M solution, 5 mmol), a solution of (S)-(+)-α-methyl-N-(α-methylbenzylidene)benzylamine (1b) (1.11 g, 5 mmol) in THF (6 mL) was added at room temperature and the solution was refluxed for 3 h under N_2. After cooling, a

solution of p-nitrobenzaldehyde (756 mg, 5 mmol) in THF (6 mL) was added to the stirred suspension at 5° and the mixture was stirred at room temperature for 5 h. Work-up and purification similar to the above gave β-hydroxy-β-p-nitrophenylpropiophenone (3b)[3] (6.3%) besides p-nitrobenzalacetophenone (10.5%, mp 164-165° from ether), p-nitrobenzylalcohol (16.7%) and recovered acetophenone (36.3%).

iii) With Lithium Diisopropylamide (LDA)

To a stirred solution of LDA (5 mmol) in ether (6 mL), a solution of 1b (1.12 g, 5 mmol) in ether (5 mL) was added at -20° under N_2 and the solution was stirred further for 45 min. The resulting suspension was cooled at -70° then a mixed solution of p-nitrobenzaldehyde (756 mg, 5 mmol) in ether (15 mL) and THF (5 mL) was added. After stirring at room temperature for 2 h, the mixture was worked up and purified in a similar manner to the above to give 3b (15.2%)

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