A New Chiral Catalyst for the Highly Enantioselective Addition of Dialkylzinc Reagents to Aliphatic Aldehydes

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Even purely aliphatic aldehydes, as well as aromatic aldehydes, were alkylated enantioselectively with dialkylzinc reagents in high enantiomeric excess using (**1**) as a chiral catalyst.

Generally, enantioselective addition of organometallic reagents to aliphatic aldehydes is less enantioselective than addition to aromatic aldehydes,[1] probably owing to the stereoelectronic effect of the aryl groups.[2]

There have been some recent reports on the enantioselective addition of dialkylzinc reagents to aldehydes using chiral catalysts.[3] However, the maximum enantiomeric excess (e.e.) for the alkylation of purely aliphatic (*i.e.*, without an aryl group or a conjugated unsaturated bond) aldehydes was 61%, in the addition of diethylzinc to heptanal.[3b] Thus the highly enantioselective catalytic asymmetric alkylation of purely aliphatic aldehydes is a challenging problem.

We now report that the new chiral catalyst (1*S*,2*R*)-(−)-2-(*N*,*N*-dibutylamino)-1-phenylpropan-1-ol (**1**), $[\alpha]_D^{25}$ −15.50° (*c* 2.00, $CHCl_3$)† catalysed the enantioselective addition of dialkylzinc reagents to purely aliphatic aldehydes to afford optically active aliphatic secondary alcohols in high enantiomeric excess (see Table 1). Thus, in the presence of a catalytic amount (6 mol%) of (**1**), 3-methylbutanal was treated with diethylzinc in hexane at 0 °C, and (*S*)-5-methylhexan-3-ol {$[\alpha]_D^{24}$ +22.10° (*c* 4.57, EtOH)} was obtained in 93% e.e. and in 92% chemical yield (entry 4).‡ Other aliphatic aldehydes, *e.g.* heptanal and nonanal, were alkylated enantioselectively with high e.e. values (entries 1—3).

The dibutylamino moiety of (**1**) is an essential part of the catalyst structure for high enantioselectivities to be achieved with aliphatic aldehydes. When methylephedrine [the dimethylamino analogue of (**1**)] was used instead of (**1**), the

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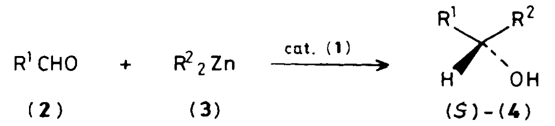
† Prepared as follows. To a suspension of (1*S*,2*R*)-(+)-norephedrine (10.0 mmol) and sodium carbonate (20.0 mmol) in ethanol (10 ml), 1-iodobutane (20.0 mmol) was added, and the mixture refluxed for 2 h, cooled to room temperature, filtered, and evaporated *in vacuo*. Column chromatography of the residue on alumina (eluant, ethyl acetate), and bulb-to-bulb distillation (170 °C bath temp.; 3 mmHg) afforded (**1**) (3.83 mmol, 38%), $[\alpha]_D^{25}$ −15.50° (*c* 2.00, $CHCl_3$). Satisfactory i.r., n.m.r., and high-resolution mass spectra were obtained.

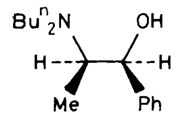
‡ *Typical procedure* (Table 1, entry 4). A mixture of 3-methylbutanal (1.00 mmol) and (**1**) (0.06 mmol) in hexane (2 ml) was stirred at room temperature for 20 min, and then cooled to 0 °C. Diethylzinc (1 M solution in hexane; 2.20 mmol) was added dropwise, then the resulting mixture was stirred at 0 °C for 16 h. The reaction was quenched with 1 M hydrochloric acid (5 ml), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (7 ml × 4). The combined organic layers were dried (Na_2SO_4) and then evaporated under reduced pressure. The residue was purified by preparative t.l.c. over silica gel (chloroform as eluant) to afford (*S*)-5-methylhexan-3-ol (0.921 mmol, 92%).

Table 1. Enantioselective addition of dialkylzinc reagents (**3**) to aldehydes (**2**) using (**1**) as catalyst.

			(*S*)-(**4**)			
Entry	R^1 in (**2**)	R^2 in (**3**)	$[\alpha]_D$ (temp./°C, *c*, solvent)	lit. $[\alpha]_D$ (temp./°C, *c*, solvent)	Yield/%[h]	E.e./%[i]
1	n-C_6H_{13}	Et	+9.07° (24, 7.17, $CHCl_3$)	+9.6° (24, 8.3, $CHCl_3$)[a]	95	88[j]
2	n-C_6H_{13}	Me	+11.15° (29, 2.09, EtOH)	+10.1° (21, 5.575, EtOH)[b]	70	100
3	n-C_8H_{17}	Et	+7.79° (26, 8.63, EtOH)	−6.22° (20, —, EtOH)[c]	95	87[j]
4	Me_2CHCH_2	Et	+22.10° (24, 4.57, EtOH)	−20.3° (21, 5.25, EtOH)[c]	92	93[j]
5	cyclo-C_6H_{11}	Et	−6.32° (25, neat)	−8.1° (30, neat)[d]	94	78
6	Ph	Et	−40.74° (26, 5.15, $CHCl_3$)	−45.45° (—, 5.15, $CHCl_3$)[e]	100	90
7	*o*-$MeOC_6H_4$	Et	−50.63° (27, 3.00, PhMe)	+47.0° (20, 1.2, PhMe)[f]	100	94[k]
8	$PhCH_2CH_2$	Et	+25.52° (25, 5.00, EtOH)	+26.8° (—, 5.0, EtOH)[g]	94	95

[a] T. Mukaiyama and K. Hojo, *Chem. Lett.*, 1976, 893. [b] R. K. Hill, *J. Am. Chem. Soc.*, 1958, **80**, 1611. [c] For the *R* isomer, 'Dictionary of Organic Compounds,' ed. J. Buckingham, Chapman and Hall, New York, 1982. [d] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 1932, **97**, 379. [e] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1914, 1115. [f] For the isomer in 87% e.e., see ref. 3d. [g] T. Sato, Y. Gotoh, Y. Wakabayashi, and T. Fujisawa, *Tetrahedron Lett.*, 1983, **24**, 4123. [h] Isolated yields of pure products. [i] Determined by the optical rotation of the product unless otherwise noted. [j] Determined by ^1H n.m.r. analysis as the corresponding (−)-α-methoxy-α-(trifluoromethyl)phenylacetate with the addition of chiral shift reagent $[Eu(fod)_3]$: J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543. [k] Configuration tentatively assigned.





(**1**)

e.e. in the ethylation of heptanal dropped considerably to 62%.

Additionally, catalyst (**1**) was also effective for aldehydes possessing phenyl groups. Thus benzaldehyde, *o*-methoxybenzaldehyde, and 3-phenylpropanal were ethylated in 90, 94, and 95% e.e. respectively (entries 6—8).

Received, 13th July 1987; Com. 988

References

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3 (a) N. Oguni and T. Omi, *Tetrahedron Lett.*, 1984, **25**, 2823; (b) M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, 1986, **108**, 6071; (c) K. Soai, A. Ookawa, K. Ogawa, and T. Kaba, *J. Chem. Soc., Chem. Commun.*, 1987, 467; (d) A. Smaardijk and H. Wynberg, *J. Org. Chem.*, 1987, **52**, 135.