Catalytic Asymmetric Synthesis of Hydroxyketones by Chemo- and Enantio-selective Alkylation of Ketoaldehydes

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Optically active hydroxyketones [up to 93% enantiomeric excess (e.e.)] were obtained from the highly chemo- and enantio-selective alkylation of ketoaldehydes with dialkylzinc reagents using (2′*S*)-(+)-diphenyl(1′-methylpyrrolidin-2′-yl)methanol (DPMPM), or (1*S*,2*R*)-(−)-, and (1*R*,2*S*)-(+)-2-(*N*,*N*-dibutylamino)-1-phenylpropan-1-ol (*N*,*N*-dibutylnorephedrine) (DBNE) as chiral catalysts.

Increasing interest has been centred on catalytic asymmetric carbon–carbon bond forming reactions.[1] Optically active hydroxyketones (**3**) are important synthetic intermediates. Chemo- and enantio-selective alkylation of the aldehyde group of prochiral ketoaldehydes (**1**), if possible, may become a versatile and direct method for synthesis of (**3**). However, most organometallic reagents such as alkyl-lithium and Grignard reagents are so nucleophilic that they usually fail to react with aldehydes chemoselectively in the presence of ketones.[2] Although the chemoselective *non-asymmetric* alkylation of aldehydes in the presence of ketones has been the subject of considerable attention,[3] no *catalytic asymmetric* synthesis of (**3**) from (**1**) has been reported.

We report the *first catalytic* asymmetric synthesis of hydroxyketones (**3**) by chemo- and enantio-selective alkylation of (**1**) with dialkylzinc reagents (**2**) using our chiral catalysts (2′*S*)-(+)-diphenyl(1′-methylpyrrolidin-2′-yl)methanol [DPMPM, (**4**)],[4] (1*S*,2*R*)-(−)-, and (1*R*,2*S*)-(+)-2-(*N*,*N*-dibutylamino)-1-phenylpropan-1-ol (*N*,*N*-dibutylnorephedrine) [DBNE, (**5**)].[5]

When 4-benzoylbenzaldehyde (**1a**) was treated with diethylzinc at 0 °C for 18 h using (+)-DPMPM (**4**) (8 mol%) as a catalyst, 4-(1-hydroxypropyl)benzophenone (**3a**) was obtained in 99% isolated yield as a result of chemoselective alkylation of the aldehyde. The enantiomeric excess (e.e.) of (**3a**) {$[\alpha]_D^{23}$ −14.5° (*c* 2.0, $CHCl_3$)} was determined to be 93%

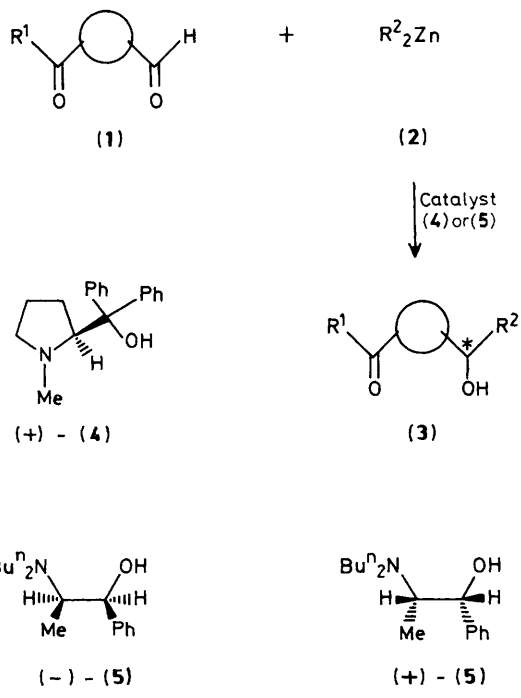
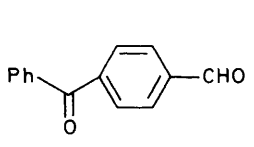


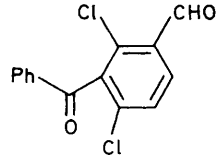
Table 1. Catalytic asymmetric synthesis of (**3a—e**).

				Hydroxyketone (**3**)[a]			
Entry	Ketoaldehyde (**1**)	R^2	Catalyst		$[\alpha]_D$ (c, solvent)	Yield (%)	E.e. (%)	Config.[b]
1	**a**	Et	(**4**)	**a**	$[\alpha]^{23}$ −14.5° (2.03, $CHCl_3$)	99	93[c]	*S*
2	**a**	Et	(−)-(**5**)	**a**	$[\alpha]^{24}$ −12.0° (2.07, $CHCl_3$)	84	91[c]	*S*
3	**a**	Bu^n	(**4**)	**b**	$[\alpha]^{21}$ −8.28° (2.21, $CHCl_3$)	64	92[c]	*S*
4	**b**	Et	(**4**)	**c**	$[\alpha]^{21}$ −34.9° (2.02, $CHCl_3$)	100	88[d]	*S*
5	**c**	Et	(−)-(**5**)	**d**	—	52	87[c]	
6	**c**	Et	(+)-(**5**)	**d**	—	48	85[c]	
7	**d**	Et	(−)-(**5**)	**e**	—	47	81[c]	

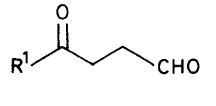
[a] Satisfactory results were obtained from n.m.r., i.r. spectroscopy and high mass spectrometric analyses. [b] Tentatively assigned based on the sense of the asymmetric induction of (**4**) and (−)-(**5**) (refs. 4 and 5a). [c] Based on h.p.l.c. analyses using a chiral column (Daicel Chiralcel OD, 250 mm; 254 nm u.v. detector). Eluant 3% propan-2-ol in hexane; flow rate 0.5 ml/min; (−)-MTPA ester of (**3a**), retention time (min), 23.6 for minor peak, 26.2 for major peak. Eluant 3% propan-2-ol in hexane; flow rate 1.0 ml/min; (−)-MTPA ester of (**3b**), retention time (min), 11.8 for minor peak, 15.6 for major peak. Eluant 5% propan-2-ol in hexane; flow rate 0.5 ml/min; (−)-MTPA ester of (**3d**) (entry 5), retention time (min), 16.2 for minor peak, 19.1 for major peak. For (−)-MTPA ester of (**3d**) (entry 6), retention time (min), 15.8 for major peak, 19.0 for minor peak. Eluant 5% propan-2-ol in hexane; flow rate 1.0 ml/min; (−)-MTPA ester of (**3e**), retention time (min), 9.1 for minor peak, 11.3 for major peak. [d] Eluant 5% propan-2-ol in hexane; flow rate 1.0 ml/min, (**3c**), retention time (min), 11.8 for minor peak, 15.6 for major peak.



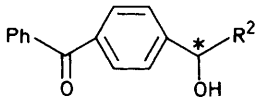
(**1a**)



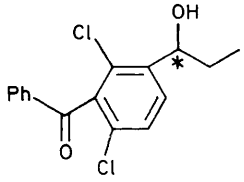
(**1b**)



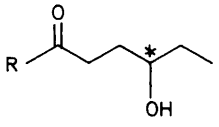
(**1c**) R^1 = Ph
(**1d**) R^1 = $PhCH_2CH_2$



(**3a**) R^2 = Et
(**3b**) R^2 = Bu^n



(**3c**)



(**3d**) R^1 = Ph
(**3e**) R^1 = $PhCH_2CH_2$

by h.p.l.c. analysis of the corresponding (−)-α-methoxy-α-(trifluoromethyl)phenylacetic (MTPA) ester[6] using a chiral column (Table 1, entry 1).† The use of (−)-DBNE (**5**) as a catalyst afforded (**3a**) in 91% e.e. (entry 2). The use of dibutylzinc instead of Et_2Zn afforded (**3b**) in 92% e.e. (entry 3). On the other hand, reaction of (**1b**) with Et_2Zn using (+)-DPMPM (**4**) gave (**3c**) in quantitative yield and 88% e.e. (entry 4).

In a similar experiment, the reaction of γ-ketoaldehyde (**1c**)[7] with Et_2Zn using (−)-DBNE (**5**) afforded optically active γ-hydroxyketone (**3d**) in 87% e.e.(entry 5). The γ-hydroxyketone is the product of a homoaldol reaction. To the best of our knowledge, no catalytic asymmetric synthesis of γ-hydroxyketones has been reported. DBNE is available in either enantiomeric form; therefore the hydroxyketone of either enantiomeric form can be synthesised by using the appropriate enantiomer of DBNE. Thus, using (+)-DBNE (**5**), the opposite enantiomer of (**3d**) was obtained in 85% e.e. (entry 6).‡ In addition, even the aliphatic§ ketoaldehyde (**1d**) was ethylated enantioselectively to afford (**3e**) in 81% e.e. (entry 7).¶

† (+)-DPMPM (**4**) (0.08 mmol, 8 mol%) in toluene (1 ml) was added to a toluene solution (1 ml) of (**1a**) (210 mg, 1.00 mmol) at 0 °C. After 20 min of stirring, Et_2Zn (2.2 mmol, 2.2 ml of 1 M hexane solution) was added. The reaction mixture was stirred at 0 °C for 18 h and quenched with 1 M HCl. The mixture was extracted with dichloromethane, and the extract was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel t.l.c. [$CHCl_3$–MeOH (50 : 1 v/v) as eluant]. (**3a**) was obtained in 99% yield and 93% e.e.

‡ The order of the elution of the major peak of (**3d**) from entry 5 in h.p.l.c. analysis was opposite to that from entry 4. See footnote b in Table 1.

§ 'Aliphatic' signifies no aromatic substituents at the α,α' positions with respect to carbonyl.

¶ *Note added in proof:* Addition of dialkylzinc to aldehyde is usually very sluggish (B. Marx, E. H.-Basch, and P. Freon, *C. R. Hebd. Seances Acad. Sci., Ser. C*, 1967, **264**, 527). Mukaiyama *et al.* reported that chiral β-aminoalcohol catalyses the addition of Et_2Zn to benzaldehyde to afford 1-phenylpropanol in 76% (T. Sato, K. Soai, K. Suzuki, and T. Mukaiyama, *Chem. Lett.*, 1978, 601; T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, *J. Am. Chem. Soc.*, 1979, **101**, 1455). For the enantioselective addition of dialkylzinc reagents to aldehydes using chiral β-aminoalcohol catalysts, see refs. 4, 5a, and N. Oguni and T. Omi, *Tetrahedron Lett.*, 1984, **25**, 2823; M. Kitamura, S. Suga, and R. Noyori, *J. Am. Chem. Soc.*, 1986, **108**, 6071; Ab. A. Smaardijk and H. Wynberg, *J. Org. Chem.*, 1987, **52**, 135; P. A. Chaloner and S. A. R. Perera, *Tetrahedron Lett.*, 1987, **28**, 3013; E. J. Corey and F. Hannon, *ibid.*, 1987, **28**, 5233, 5237; K. Soai, M. Nishi, and Y. Ito, *Chem. Lett.*, 1987, 2405; G. Muchow, Y. Vannoorenberghe, and G. Buono, *Tetrahedron Lett.*, 1987, **28**, 6163; S. Itsuno and J. M. J. Frechet, *J. Org. Chem.*, 1987, **52**, 4142; K. Soai, S. Niwa, and M. Watanabe, *ibid.*, 1988, **53**, 927; *J. Chem. Soc., Perkin Trans. 1*, 1989, 109; W. Oppolzer and R. N. Radinov, *Tetrahedron Lett.*, 1988, **29**, 5645; N. Oguni, Y. Matsuda, and T. Kaneko, *J. Am. Chem. Soc.*, 1988, **110**, 7877; K. Soai, *Yuki Gosei Kagaku Kyokaishi*, 1989, **47**, 11. For the reaction using chiral piperazine catalysts, see K. Soai, S. Niwa, Y. Yamada, and H. Inoue, *Tetrahedron Lett.*, 1987, **28**, 4841. For the enantioselective addition to functionalised aldehydes, K. Soai, S. Yokoyama, T. Hayasaka, and K. Ebihara, *Chem. Lett.*, 1988, 843; K. Soai and S. Niwa, *ibid.*, 1989, 481.

As described, the present results open up a direct method of obtaining optically active hydroxyketones.

Received, 7th December 1988; Com. 8/04842H

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