Asymmetric Alkenylation of Chiral and Prochiral Aldehydes Catalysed by Chiral or Achiral Amino Alcohols: Catalytic Diastereoselective Synthesis of Protected *erythro*-Sphingosine and Enantioselective Synthesis of Chiral Diallyl Alcohols

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Protected D-*erythro*-(2*S*,3*R*)-sphingosine was preferentially obtained by diastereoselective pentadec-1-enylation of *tert*-butyl (*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate with pentadec-1-enyl(ethyl)zinc using either (*R*)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) as a chiral catalyst or 2-(dibutylamino)ethanol as an achiral catalyst. Enantioselective alkenylation of α,β-unsaturated aldehydes using (*S*)-DPMPM as a chiral catalyst affords chiral diallyl alcohols with good enantiomeric excesses.

Sphingosine **5** and its isomers constitute an important class of compounds (gangliosides, ceramides and sphingomyelin) with multiple and potent biological activities such as cell growth and protein kinase regulation;[1] usually compound **5** is found as its D-*erythro*-(*anti*)-(2*S*,3*R*) isomer in Nature.[2] The preparation of optically active sphingosine has been reported.[3] Recently, *tert*-butyl (*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate **1** was reported as a useful chiral amino(equivalent)-aldehyde.[4] Asymmetric alkenylation (pentadec-1-enylation) of **1** may become a direct method for constructing the carbon skeleton of sphingosine. However, diastereoselective addition with diisobutyl(pentadec-1-enyl)alane is *syn*-selective (*anti*:*syn* = 1:2) affording predominantly unnatural protected *threo*(*syn*)-sphingosine **4**; we also confirmed this selectivity.[3c] Therefore, the conventional procedure requires a two-step reaction (alkynylation and the subsequent reduction) to synthesize **3** from **1**.[3a-c]

Although chiral allyl alcohols are useful synthetic intermediates the limited availability of more highly functionalised chiral diallyl alcohols[5] has restricted their use in synthesis.

Enantioselective addition of organozinc reagents to aldehydes in the presence of chiral catalysts and ligands has attracted considerable attention.[6] Recently, the preparation of alkenyl(alkyl)zinc reagent by a boron–zinc exchange reaction[7] and the catalytic enantioselective alkenylation of simple aldehydes with this reagent have been reported.†

We now report the first diastereoselective synthesis of protected D-*erythro*-(2*S*,3*R*)-sphingosine **3** by catalytic alkenylation of **1** and enantioselective synthesis of chiral diallyl alcohols **8**.

Treatment of the chiral aldehyde **1** with pentadec-1-enyl(ethyl)zinc **2**[7] in the presence of (*R*)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM)[9] (10 mol%) in toluene at 0 °C for 1.5 h gave protected sphingosine (**3** and **4**) in 52% yield (Table 1, entry 1). ^{1}H NMR (500 MHz, C_6D_6, 60 °C) analysis‡ showed that *erythro*-(*anti*)-**3** was the major product formed with good diastereoselectivity (*anti*:*syn* = 4:1). A repeat reaction in which (*S*)-DPMPM (10 mol%) was used, gave *erythro*-(*anti*)-**3** as the major product but with reduced diastereoselectivity (*anti*:*syn* = 2:1) (Table 1, entry 2). It was also found that 2-(dibutylamino)ethanol **6** (10 mol%), an achiral amino alcohol, catalyses the diastereoselective addition of **2** to **1** to afford *erythro*-(*anti*)-**3** with higher diastereoselectivity (*anti*:*syn* = 7.3:1) (Table 1, entry 3). The subsequent treatment (deprotection) of *erythro*-(*anti*)-**3** with 1 mol dm^{-3} HCl is known to afford (2*S*,3*R*)-D-*erythro*-(*anti*)-sphingosine **5**.[3c]

Treatment of (*E*)-cinnamaldehyde **7a** with hex-1-enylethylzinc **2a** in the presence of (*S*)-DPMPM (10 mol%) in toluene at 0 °C gave the chiral diallyl-alcohol, 1-phenylnona-1,4-dien-3-ol **8a** (59% yield), with 77% e.e. (Table 2, entry 1). Other chiral diallyl alcohols with 73–75% e.e.'s were also obtained (Table 2, entries 2 and 3).

Experimental

Typical Experimental Procedure (*Table 1, Entry 3*).—Cyclohexene (2.28 mmol)[7] was added to a toluene solution of

† (*S*)-DPMPM (5 mol%) catalyses the addition of oct-1-enyl(ethyl)zinc to propanal at 0 °C in *ca.* 80% e.e.[8] We observed that, in the presence of (*S*)-DPMPM (10 mol%), hex-1-enyl(ethyl)zinc adds to benzaldehyde at −30 °C to −15 °C in 64% yield with 92% e.e.

‡ Determined by ^{1}H NMR (500 MHz, C_6D_6, 60 °C) analysis. *erythro*-(*anti*)-**3**, δ 4.285 (br s); *threo*-(*syn*)-**4**, 4.391 (t, *J* 7.0); see ref. 3(*c*).

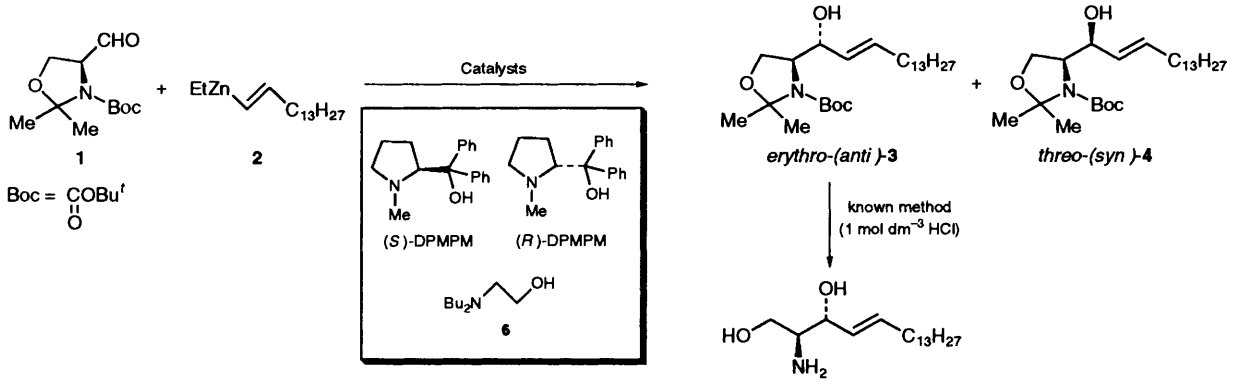


Table 1 Diastereoselective addition of pentadec-1-enyl(ethyl)zinc **2** to the chiral aldehyde **1** with DPMPM as a chiral catalyst or with 2-(dibutylamino)ethanol **6** as an achiral catalyst

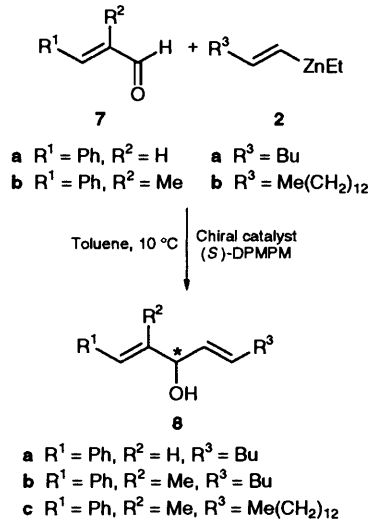
Entry	Chiral catalyst	Yield (%)	*erythro*-(*anti*)-**3**:*threo*-(*syn*)-**4**[a]
1	(*R*)-DPMPM	52	4:1
2	(*S*)-DPMPM	51	2:1
3	2-(Dibutylamino)ethanol **6**	50	7.3:1

[a] See footnote ‡.

Table 2 Catalytic enantioselective synthesis of the chiral diallyl alcohol **8** with (*S*)-DPMPM as a chiral catalyst

Entry	Aldehyde **7**	Alkenylzinc **2**	Diallyl alcohol **8** $[\alpha]_D$[a] (*T*/°C, *c*, benzene)	Yield (%)[b]	E.e. (% e.e.)[c]
1	**7a**	**2a**	**8a** +39.8 (24, 2.0)	59	77
2	**7b**	**2a**	**8b** +9.4 (22, 1.3)	56	75
3	**7b**	**2b**	**8c** +13.7 (24, 1.3)	39	73

[a] In units of 10^{-1} deg cm^2 g^{-1}. [b] Isolated yields. All new compounds gave satisfactory results for NMR, IR and high MS measurements. [c] Determined by HPLC analyses using a chiral column (Chiralcel OD).



borane–dimethyl sulfide complex (2 mol dm^{-3}; 0.55 cm^3, 1.1 mmol) at 0 °C. The mixture was stirred for 3 h at 0 °C, after which pentadec-1-yne (1.14 mmol) was added to it. After being stirred for 1 h, the mixture was cooled to −25 °C and Et_2Zn (1 mol dm^{-3} toluene solution; 1.2 mmol) and 2-(dibutylamino)ethanol (0.012 g, 0.07 mmol) in toluene (2 cm^3) were added to it. The mixture was then placed in an ice-bath and the chiral aldehyde **1** (0.181 g, 0.74 mmol) in toluene (2 cm^3) was added to it. The mixture was stirred for 1.5 h, after which it was treated with saturated aq. NH_4Cl (15 cm^3) to quench the reaction. The mixture was then extracted with AcOEt (3 × 15 cm^3) and the combined extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by silica gel TLC (developing solvent: hexane–ethyl acetate, 3:1) afforded **3** and **4** (0.164 g; total yield 50%).

As described, protected *erythro*-sphingosine has been synthesized by diastereoselective alkenylation of a chiral aldehyde with chiral or achiral amino alcohols as catalysts. Chiral diallyl alcohols were also obtained by the enantioselective alkenylation of prochiral α,β-unsaturated aldehydes using DPMPM as a chiral catalyst.

References

1 Y. A. Hannun, C. R. Loomis, A. H. Merrill, Jr. and R. M. Bell, *J. Biol. Chem.*, 1986, **261**, 12604; M. Y. Pushkareva, V. A. Khan, A. V. Alesenko, N. Sahyoun and Y. A. Hannun, *J. Biol. Chem.*, 1992, **267**, 15246; R. A. Sabbadini, R. Betto, A. Teresi, G. Fachechi Cassano and G. Salviati, *J. Biol. Chem.*, 1992, **267**, 15475; L. R. Ballou, C. P. Chao, M. A. Holness, S. C. Barker and R. Raghow, *J. Biol. Chem.*, 1992, **267**, 20044; S. Tanabe, T. Tamaki and Y. Wada, *Thromb. Res.*, 1992, **67**, 115. For reviews, T. Hori and M. Sugita, *Progr. Lipid Res.*, 1993, **32**, 25; S. Spiegel, A. Olivera and R. O. Carlson, *Adv. Lipid Res.*, 1993, **25**, 105; S. Chatterjee, *Adv. Lipid Res.*, 1993, **26**, 25.

2 K. A. Karlsson, *Nature*, 1960, **188**, 312.

3 (*a*) P. Herold, *Helv. Chim. Acta*, 1988, **71**, 354; (*b*) S. Nimkar, D. Menaldino, A. H. Merrill and D. Liotta, *Tetrahedron Lett.*, 1988, **29**, 3037; (*c*) P. Garner, J. M. Park and E. Malecki, *J. Org. Chem.*, 1988, **53**, 4395; (*d*) A. Dondoni, G. Fantin, M. Fogagnolo, A. Medica, *J. Chem. Soc., Chem. Commun.*, 1988, 10; (*e*) H. Newman, *J. Am. Chem. Soc.*, 1973, **95**, 4098; (*f*) K. Mori and Y. Funaki, *Tetrahedron*, 1985, **41**, 2379; (*g*) P. Tkaczuk and E. R. Thornton, *J. Org. Chem.*, 1981, **46**, 4393; (*h*) R. H. Boutin and H. Rapoport, *J. Org. Chem.*, 1986, **51**, 5320; (*i*) J. S. Yadav, D. Vidyanand and D. Rajagepal, *Tetrahedron Lett.*, 1993, **34**, 1191; (*j*) K. Koike, M. Sugimoto, Y. Nakahara and T. Ogawa, *Glycoconjugate J.*, 1985, **2**, 105; (*k*) Y. Ito, M. Sawamura and T. Hayashi, *Tetrahedron Lett.*, 1988, **29**, 239; (*l*) P. Somfai and R. Olsson, *Tetrahedron*, 1993, **49**, 6645; (*m*) For a review, H. S. Byun and R. Bittman, *Phospholipids Handbook*, ed. g. Cevc, Dekkar, New York, 1993, p. 97.

4 P. Garner and J. M. Park, *J. Org. Chem.*, 1987, **52**, 2361. For diastereoselective addition of a simple vinyl-metal reagent, see R. S. Coleman and A. J. Carpenter, *Tetrahedron Lett.*, 1992, **33**, 1697; P. Garner and J. M. Park, *J. Org. Chem.*, 1988, **53**, 2979.

5 Kinetic resolution, K. B. Sharpless, C. H. Behrens, T. Katsuki, A. W. M. Lee, V. S. Martin, M. Taketani, S. M. Viti, F. J. Walker and S. S. Woodard, *Pure Appl. Chem.*, 1983, **55**, 589.

6 For recent reviews, K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833; R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49.

7 M. Srebnik, *Tetrahedron Lett.*, 1991, **32**, 2449.

8 W. Oppolzer and R. N. Radinov, *Helv. Chim. Acta*, 1992, **75**, 170.

9 K. Soai, A. Ookawa, T. Kaba and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111.

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