Tetrahedron: Asymmetry Vol. 3, No. 3, pp. 359-360, 1992
Printed in Great Britain

0957-4166/92 $3.00+.00
Pergamon Press plc

Synthesis of (2S,5S)-2,5-Bis(phenylmethyl) -1,4-diazabicyclo[2.2.2]octane

Kenso Soai,* Atsushi Oshio, and Hideharu Yoneyama
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Shinjuku, Tokyo 162, Japan

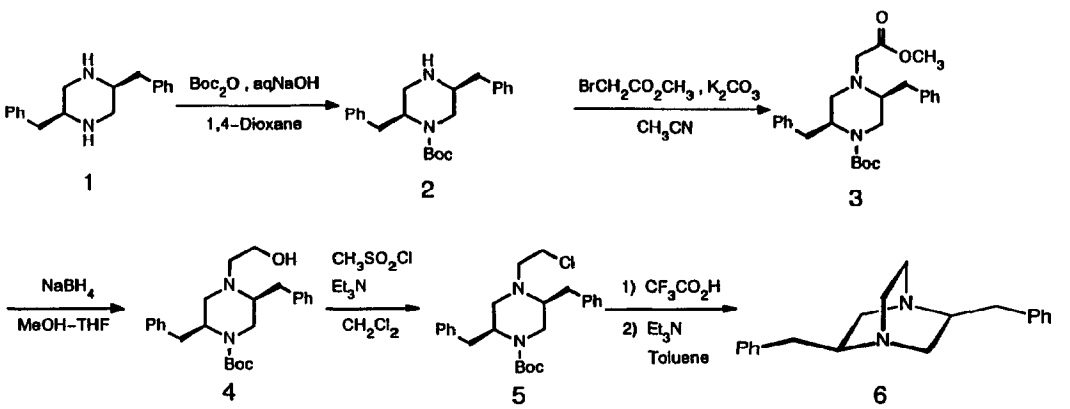
(*Received* 28 *January* 1992)

Abstract: (2S,5S)-2,5-Bis(phenylmethyl)-1,4-diazabicyclo [2.2.2]octane [(2S, 5S)-bis(phenylmethyl)-DABCO] (6), a potentially useful chiral catalyst for asymmetric syntheses, was synthesized from a chiral piperazine.

1,4-Diazabicyclo[2.2.2]octane (DABCO) is known as a strong base with two nucleophilic nitrogen atoms at the bridgehead positions. It has been used as a base catalyst in organic reactions.[1] If the chiral derivatives of DABCO are synthesized, they become potentially enantioselective chiral catalysts for the asymmetric syntheses. However, only very few reports have appeared on the synthesis of chiral 2,3-disubstituted DABCO derivatives.[2] Meanwhile, we reported the enantioselective addition of dialkylzincs to aldehydes using chiral piperazines as chiral catalysts.[3]

We now wish to report the synthesis of a 2,5-disubstituted optically active DABCO derivative, (2S,5S)-2,5-bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane (6).

Reaction of (2S,5S)-bis(phenylmethyl)piperazine (1),[3,4] prepared from (S)-phenylalanine, with di-tert-butyl dicarbonate (Boc_2O) in aq. NaOH and 1,4-dioxane gave a monoprotected piperazine 2 (39%). Treatment of 2 with methyl bromoacetate in acetonitrile in the presence of potassium carbonate (r.t., 22 hr) afforded 3 in 78%. The methyl ester of 3 was reduced chemoselectively with sodium borohydride[5] by the dropwise addition of a small amount of MeOH to a THF solution of 3 at 45-50 °C. Aminoalcohol 4 was obtained in 60% yield as a colorless crystalline solid (m.p. 80-81 °C, $[\alpha]^{25}_{D}$ +25.8 (c 5.49, MeOH)). The subsequent reaction of 4 with methanesulfonyl chloride and triethylamine in dichloromethane (r.t., 21 hr) did not



afford the corresponding mesylate but gave exclusively the chloride 5 in 72%. The steric bulkiness of the phenylmethyl group may be the reason for this conversion. (When the two phenylmethyl substituents were not present, the corresponding normal mesylate was obtained.)[6] The Boc group of 5 was removed in trifluoroacetic acid (r. t., 1 hr). The cyclization to the chiral DABCO (6) was performed by heating in toluene in the presence of triethylamine at 80-90 °C for 3 hr. Purification by alumina gel TLC afforded 6[7] ($[\alpha]^{24}_{D}$ +104.1 (c 4.06, MeOH)) as an oil in 56% from 5.

The use of 6 as an chiral catalyst in enantioselective reactions is in progress in our laboratories.

References

1. Review: S. E. Drewes and G. H. P. Roos, Tetrahedron, 1988, 44, 4653.
2. (a) R. Oi and K. B. Sharpless, Tetrahedron Lett., 1991, 32, 4853; (b) T. Oishi and M. Hirama, The 61st National Meeting of the Chemical Society of Japan, Yokohama, 1991; Paper 2D142.
3. a) K. Soai, S. Niwa, Y. Yamada, and H. Inoue, Tetrahedron Lett., 1987, 28, 4841; b) S. Niwa and K. Soai, J. Chem. Soc., Perkin Trans., 1, 1991, 2717.
4. K. Soai, H. Hayashi, and H. Hasegawa, Heterocycles, 1986, 24, 1287.
5. K. Soai, H. Oyamada, and M. Takase, Bull. Chem. Soc. Jpn., 1984, 57, 2327; K. Soai, H. Oyamada, M. Takase, and A. Ookawa, ibid., 1984, 57, 1948.
6. For the conversion of alcohols to chlorides using tosyl chloride, N,N-dimethylaminopyridine, and triethylamine, see C. K. Hwang, W. S. Li, and K. C. Nicolaou, Tetrahedron Lett., 1984, 25, 2295.
7. ^{1}H-NMR, δ(ppm) 7.28 (s, 10H), 3.25-2.23 (m, 14H); IR (neat) 3080, 3050, 2950, 2880, 1620, 1510, 1460, 1380, 1330, 1260, 1180, 1160, 1080, 760, 710 cm^{-1}; High resolution MS, m/z calcd for $C_{20}H_{24}N_2$ 292.1941, found 292.1931.