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FACILE SYNTHESIS OF ENANTIOPURE *trans*-2,3-DIPHENYL-1,4-DIAZABICYCLO[2.2.2]OCTANE

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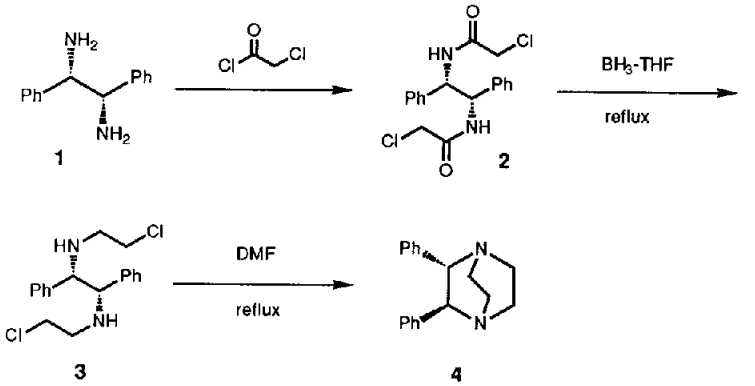
Summary: An efficient synthesis of enantiopure *trans*-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (*trans*-2,3-diphenyl-DABCO) from enantiopure stilbene diamine is reported.

Recently, 1,4-Diazabicyclo[2.2.2]octane (DABCO)-catalyzed reactions have received much attention for the synthesis of multifunctional molecules,[2] while the utility of chiral amine catalysts[3] is increasing with the growing importance of asymmetric synthesis. So far, however, no approaches to the synthesis of substituted chiral DABCO's have been reported. On the other hand, application of functionalized 1,2-diamines in modern asymmetric synthesis is expanding,[4] and practical syntheses of chiral 1,2-diamines have started to appear in the literature. In particular, the synthesis of enantiopure stilbene diamine is well established beginning with the catalytic asymmetric dihydroxylation of *trans*-stilbene.[4, 5]

As a starting point to develop some new chemistry of Chiral DABCO's (e.g. uses as chiral ligands or bases), we report here a facile synthesis of enantiopure *trans*-2,3-diphenyl-DABCO 4[6, 7] from enantiopure stilbene diamine 1.



To a solution of enantiopure (*S,S*)-stilbene diamine **1** (500 mg, 2.36 mmol), DMAP (10 mg), and Et_3N (1.6 mL) in CH_2Cl_2 (10 mL), chloroacetyl chloride (798 mg, 3 equiv) was added dropwise at 5 °C,[8] and stirred at room temperature for 3 h. The reaction mixture was cooled to -5 °C and filtered. The precipitate was washed with cold water and dried to give **2** (843 mg).[9]

Reduction of **2** (843 mg crude mixture) was performed at reflux with 1 M BH_3-THF (9.22 mL, 9.22 mmol)[10] in dry THF (20 mL) for 2 h. Methanol (5 mL) was added at 0 °C to quench the excess BH_3 and the reaction mixture was concentrated under vacuum. Dilute HCl (40 mL of 5%

aqueous) and CH_2Cl_2 (10mL) were added, and the mixture was shaken well. The phases were separated and the organic phase was discarded. The aqueous phase was made basic by aqueous NaOH and extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated to give **3** (477 mg, 60% yield from **1**) as an oil.

Cyclization of **3** (477 mg, 1.41 mmol) in refluxing DMF (5 mL) for 4 h, followed by solvent removal *in vacuo* and flash column chromatography gave enantiopure **4** (235 mg, 63% yield).[11, 12]

DABCO's possess a unique structure, featuring two nucleophilic and strongly basic nitrogens. The synthesis and utilization of chiral DABCO's for catalytic asymmetric synthesis is currently under investigation in our laboratory.

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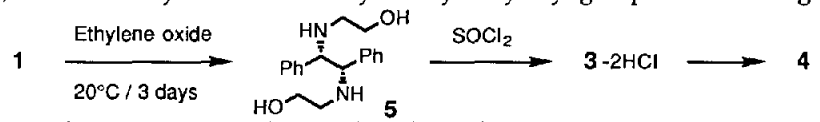
References and note

1. On leave from Mitsui Toatsu Chemicals, Inc., Japan.
2. (a) D. Basavaiah, T. K. Bharathi, and V. V. L. Gowriswari, *Tetrahedron Lett.* **1987**, *28*, 4351; (b) P. Auvray, P. Knochel, and J. F. Normant, *Tetrahedron Lett.* **1986**, *27*, 5095 and references therein; (c) H. Amri and J. Villieras, *Tetrahedron Lett.* **1986**, *27*, 4307; (d) H. M. R. Hoffmann and J. Rabe, *Angew. Chem. Int. Ed. Engl.*, **1983**, *22*, 795.
3. For example, see review by K. Tomioka, *Synthesis*, **1990**, 541.
4. R. Oi and K. B. Sharpless, *Tetrahedron Lett.*, in press, and references therein.
5. (a) B. B. Lohray and J. R. Ahuja, *J. Chem. Soc., Chem. Commun.*, **1991**, 95; (b) D. P. A. Iuliano, C. Rosini, and P. Salvadori, *Synthesis*, **1990**, 1023.
6. The synthesis of racemic-**4** is reported in the Russian literature (G. V. Shishkin, I. I. Naumenko, I. L. Anieimova, D. B. Yudina, and V. G. Storozhenko, *Khim. Geterotsikl. Soedin.*, **1982**, *1*, 95.) as follows. However, we were unable to reproduce the first step (**1** -> **5**); it seems tricky to introduce only one hydroxyethyl group on each nitrogen.



7. Except for the procedure that we describe in this paper, several other approaches, e.g., condensation of **1** with 1,2-dibromoethane or reaction with glyoxal in the presence of $NaBH_3CN$, were unsuccessful.
8. The reaction was rapid even at lower temperatures, but the precipitatation of **2** prevents stirring at temperatures lower than 5 °C, since solubility of **2** drops dramatically at lower temperature.
9. Futher purification of **2** can be perfomed by filtration through a short column (SiO_2, CH_2Cl_2) followed by recrystalyzation (EtOAc-Hexane).
10. $LiAlH_4$ reduction did not give **3**.
11. Physical data for **4** is as follows: b.p. = 167 °C (0.8 mm); $[\alpha]^{25}_D$ = +93.1° (*c* 4.34, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.48 -7.25 (m, 10H), 4.16 (s, 2H), 3.03 - 2.97 (m, 4H), 2.83 - 2.73 (m, 2H), 2.65 - 2.57 (m, 2H); IR (KBr pellet) 1044, 1070, 1084, 1449, 1494, 1598, 1762, 1812, 1885, 1949, 3027, 3056, 3081 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 82.02; H, 7.55; N, 10.89.
12. No peak for the minor enantiomer was visible by ^{1}H NMR in the presence of a chiral shift reagent (Eu[hfbc]$_3$).

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