

Enantioselective Synthesis of a Chiral C_3 -Symmetric Bridgehead Amine

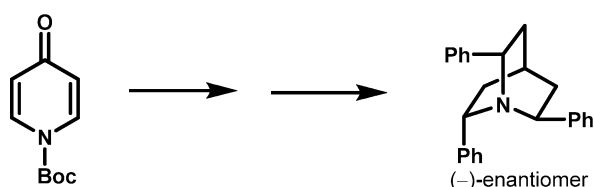
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ABSTRACT



An efficient enantioselective synthesis of the above C_3 -symmetric chiral quinuclidine starting with *N*-*tert*-butoxycarbonyl-4-pyridone has been developed.

The use of C_2 -symmetric compounds as chiral reagents or ligands for metal complexes has had a major impact on the field of enantioselective synthesis. In contrast, there has been little attention to C_3 -symmetric compounds.^{1,2} We describe herein an enantioselective route to the C_3 -symmetric bridgehead tertiary amine **1** (see below), a hitherto unknown quinuclidine derivative that is potentially useful for a number of catalytic enantioselective applications. For instance, as a quaternary ammonium salt, it could serve as phase transfer catalyst for enantioselective C–C bond formation by enolate alkylation, adol reaction or Micheal addition. The possible effectiveness of this approach is suggested by the mechanistic model that has been developed for the enantioselective reactions catalyzed by *N*-9-anthracenylmethylcinchona alkaloid salts.³

Some time ago we described the synthesis of a related diphenylquinuclidine **2** by the process summarized in Scheme 1, which utilizes a Diels–Alder reaction to form the intermediate **3**. The enantiomers of the racemic amine **2** were readily separated by recrystallization of the diastereomeric

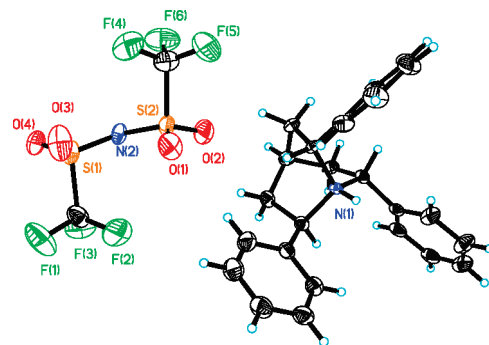


Figure 1. X-ray crystallographic structure for the salt of the (+)-enantiomer of **1** with Tf_2NH .

salt mixture formed with 1 equiv of (–)-camphor-10-sulfonic acid.⁴ An enantioselective synthesis of quinuclidine **2** was not investigated in this earlier work.

We now report an efficient enantioselective synthesis of **1** by the pathway that is outlined in Scheme 2. The 4-piperidone **4** (prepared from 4-hydroxypyridine and (*t*-BuOCO)₂O in *t*-BuOH)⁵ and $\text{RhCl}(\text{S})\text{-BINAP}$ in THF at –40 °C were treated with PhZnCl and Me_3SiCl , and the

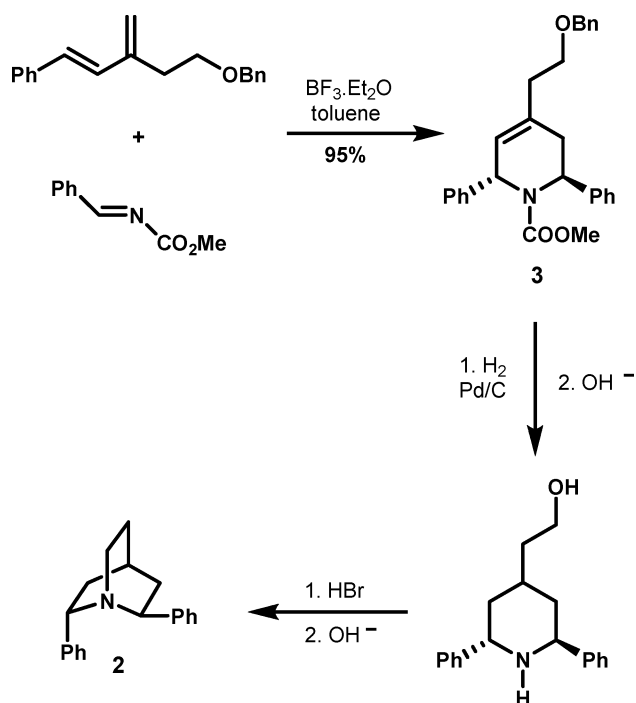
(1) For a review see: Moberg, C. *Angew. Chem., Int. Ed.* **1998**, 37, 248.

(2) C_3 -Symmetric compounds have one three-fold axis of rotation and no other axis of rotation.

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Scheme 1. Synthesis of Diphenylquinicidine 2



mixture was brought to 0 °C and maintained there for 48 h. Extractive isolation and chromatography on silica gel (1:2 EtOAc–hexanes) afforded **5** in 91% yield and 98.7% ee.⁶ Addition of the α,β -enone **5** in THF to a THF solution of the reagent from 2 equiv of PhMgBr and 1 equiv of CuI at 0 °C gave after 2 h at 0 °C, extractive isolation, and column chromatography on silica gel the *trans*-2,6-diphenyl piperidone derivative **6** in 82% yield as a colorless solid, mp 178–179 °C, $[\alpha]_D^{23} +117$ (*c* 0.70, CHCl₃).⁷ Reaction of phenylethynyl-cerium with **6** at –78 °C provided alcohol **7** in 95% yield as a yellow foam (515 mg, yield 95%) after silica column chromatographic purification. The alcohol **7** was then treated with a catalytic amount of MoO₂(acac)₂, AuCl(PPh₃), and AgOTf in toluene at rt for 5 h.⁸ Extractive isolation and chromatography on silica gel (1:6 EtOAc–hexanes) produced the conjugated ketone **8** in 92% yield. Reduction of **8** with NaBH₄ in the presence of CoCl₂ in methanol at 23 °C for 20 h afforded the saturated alcohol **9** in 81% yield as a colorless foam. Treatment of the Boc-protected amino alcohol **9** with 48% hydrobromic acid at 23 °C for 18 h led to aminobromide **10** in 88% yield as a mixture of two diastereomers. Both isomers underwent cyclization by heating with sodium bicarbonate in toluene at 115 °C for 12 h and then, after addition of tetrabutyl ammonium iodide, further heating at 115 °C for 6 h to form (–)-**1** in 76% yield; colorless solid, mp 208–209 °C, $[\alpha]_D^{23} -437$ (*c* 0.53, CHCl₃).

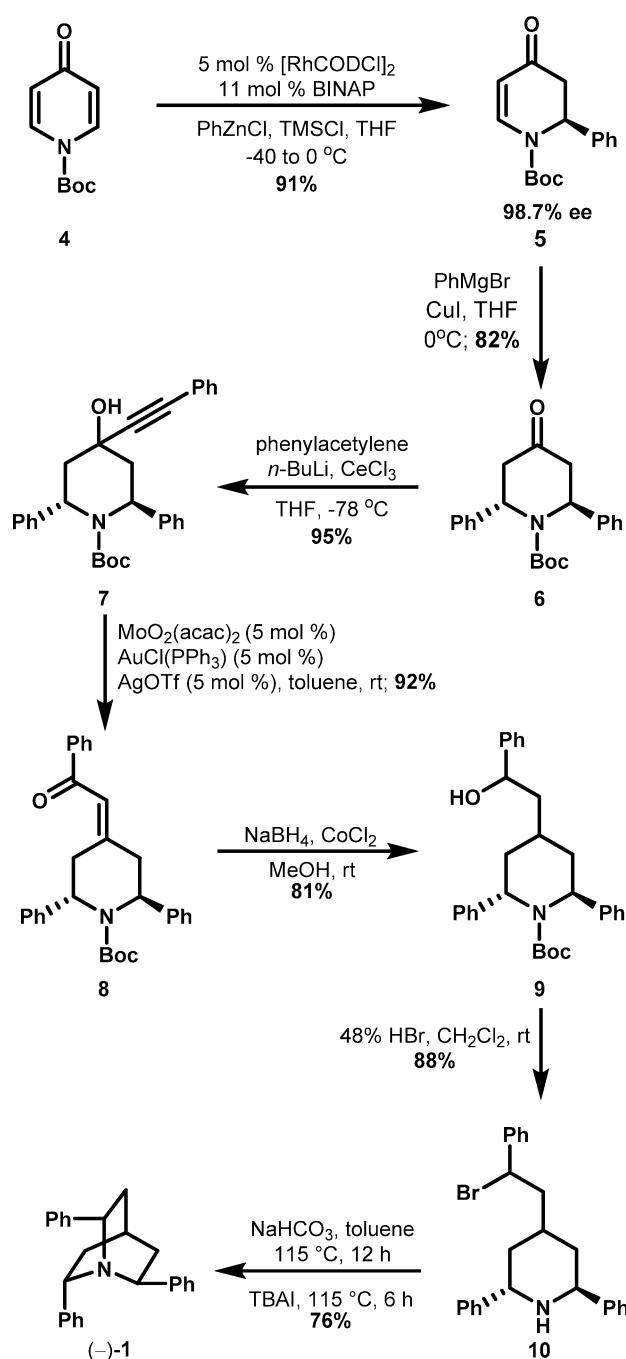
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(6) (a) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, 126, 6240. (b) Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, 7, 5317.

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Scheme 2. Synthesis of (–)-Triphenylquinicidine 1

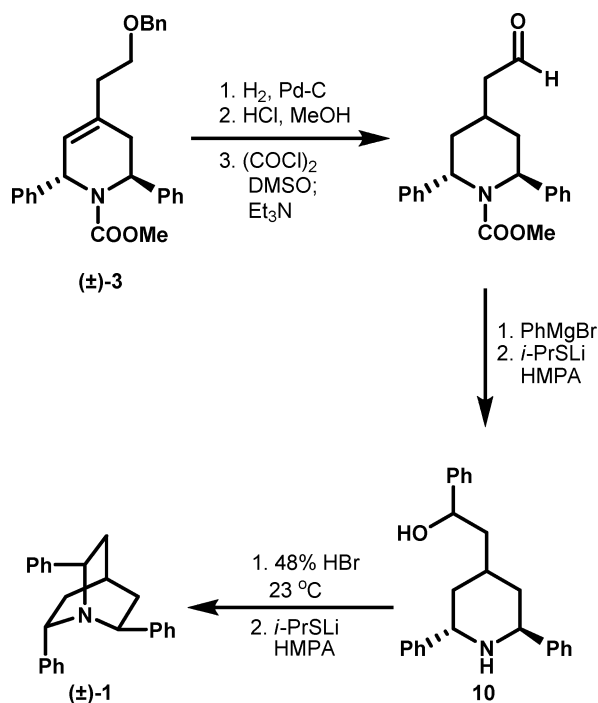


The absolute configuration of **1** obtained by the process outlined in Scheme 2 follows from the established enantio-preference in closely related examples.⁶ The assignment was confirmed by X-ray crystallographic analysis (see Figure 1).

We have also synthesized the racemate corresponding to **1** from the previously prepared Diels–Alder adduct (±)-**3** (see below and Scheme 1) by the process outlined in Scheme 3.

The enantiomeric forms of **1** are readily separated by column chromatography on a chiral OD column (Chiral Technologies) using 98:2 hexanes–*i*-PrOH for elution. The

Scheme 3. Synthesis of (±)-Triphenylquinidine 1



results of a typical separation are shown in Figure 2. The measured optical rotation of **1** were $[\alpha]^{23}_D -432 \pm 5$ (*c* 1, CHCl_3) and $[\alpha]^{23}_D +432 \pm 5$ (*c* 1, CHCl_3). The dextrorotatory enantiomer was converted to the crystalline 1:1 salt with triflimide (CF_3SO_2)₂NH. X-ray crystallographic analysis of salt of dextrorotatory **1** confirmed the structure and absolute configuration as shown in Figure 1.

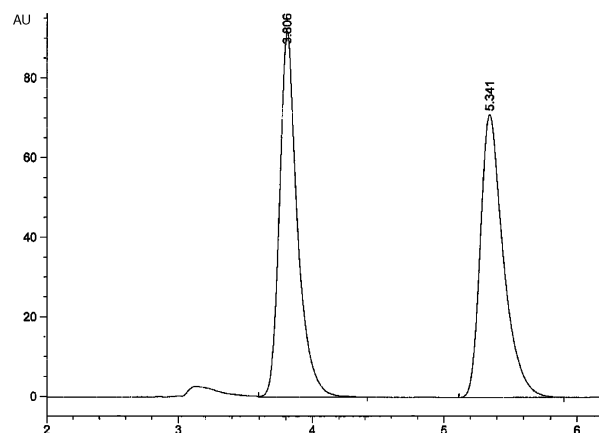


Figure 2. HPLC separation of (±)-**1**.

This general approach described for the enantioselective synthesis of **1** can be extended to a large number of analogous C_3 -symmetric amines, some of which are expected to be useful for application to catalytic enantioselective synthesis.

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Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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