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One-pot tandem cyclization of enantiopure asymmetric *cis*-2,5-disubstituted pyrrolidines: Facile access to chiral 10-heteroazatriquinanes

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Full Research Paper

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Abstract

A series of chiral 10-heteroazatriquinanes were synthesized from enantiopure asymmetric *cis*-2,5-disubstituted pyrrolidines through a one-pot tandem cyclization procedure. The structures and configurations of these new chiral 10-heteroazatriquinanes are confirmed by X-ray single-crystal diffraction analysis.

Introduction

The azatriquinane derivatives are an important substance class in organic chemistry containing nitrogen and three fused five-membered rings [1-3]. Due to the unique rigid bowl-shaped structure with one noninversible electron lone pair at the bottom of the central nitrogen ("*centro*-N") atom, 10-azatriquinane analogues are used as efficient chelation reagents of metal cations [4,5]. Mascal and colleagues [6] described the first synthesis of 10-azatriquinane (**1**) from dimethyl 3,3'-(1*H*-pyrrole-2,5-diyl)dipropanoic acid in five steps, and the reactivity of **1** was also investigated. 10-azatriquinane (**1**) is very active because of its high basicity. The X-ray structure of **1**·HBF_4 revealed that the *centro*-N is pyramidalized. 10-azatriquinacene (**2**), an unsaturated analogue of **1**, was attractive due to its high proton affinity [7]. Recently, Mascal [8] and colleagues have developed a series of 10-azatriquinanes as a C_{3v}-symmetric platform for tripodal metal complexes and calixiform scaffolds (Figure 1).

Previously, we established a facile access to enantiopure asymmetric *cis*-2,5-disustituted pyrrolidines **4** from commercially available starting materials diethyl *meso*-2,5-dibromoadipate and (*S*)-(−)-1-phenylethylamine (Figure 2) [9]. The preparations of compounds **5a**, **5b**, **6a** and **6b** were also reported in [9], but our previously published structures for compounds **5a** and **5b** were not completely correct, because the B–N dative bonds were missing. The aim of the following procedures was to

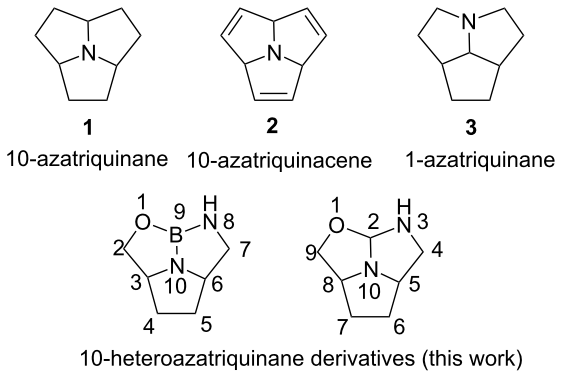
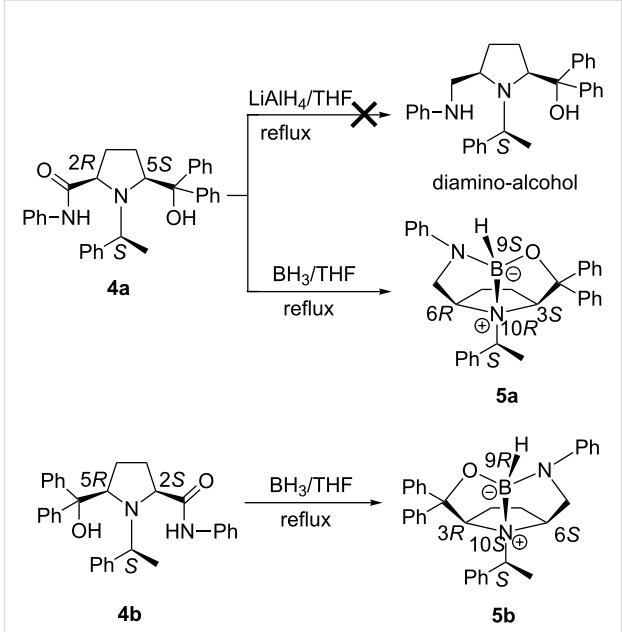


Figure 1: The structures of azatriquinanes and azatriquinacene.

obtain several novel bifunctional *N*-hetereocyclic carbenes (NHCs) [10-14] from compounds **4** through three steps, including reduction, debenzylation and cyclization (Scheme 1), but this failed. However, we have found a novel one-pot tandem cyclization of these enantiopure asymmetric *cis*-2,5-disubstituted pyrrolidines to produce chiral trisubstituted 10-heteroazatriquinane derivatives. To the best of our knowledge, there is very little research on the synthesis of 10-heteroazatriquinanes, and the chiral 10-heteroazatriquinanes are unknown up to now.



Scheme 2: The reduction of amides **4** by $LiAlH_4$ and BH_3·THF.

Results and Discussion

For the reduction of highly hindered amides **4**, the system of $LiAlH_4$ in anhydrous THF was found to be useless even upon heating under reflux for 18 h under an inert atmosphere, and no desired diamino-alcohols were obtained after workup. However, **4a** reacted smoothly with BH_3 to give white crystals after chromatographic purification (Scheme 2). The X-ray single-crystal diffraction analysis established that the reduction product **5a** (Figure 3) was formed with a rigid 10-heteroaza-

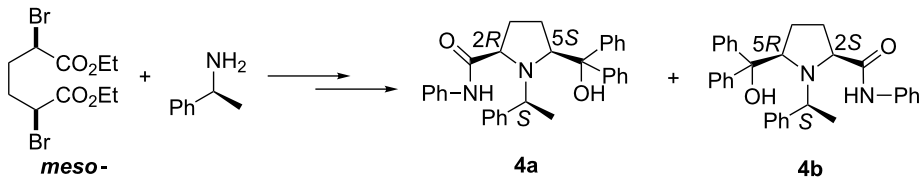
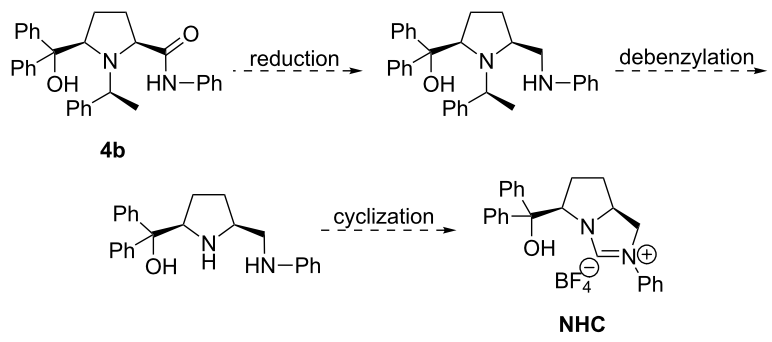


Figure 2: The synthesis of **4** (*previous work*).



Scheme 1: The designed synthetic route to a hydroxy NHC from **4b**.

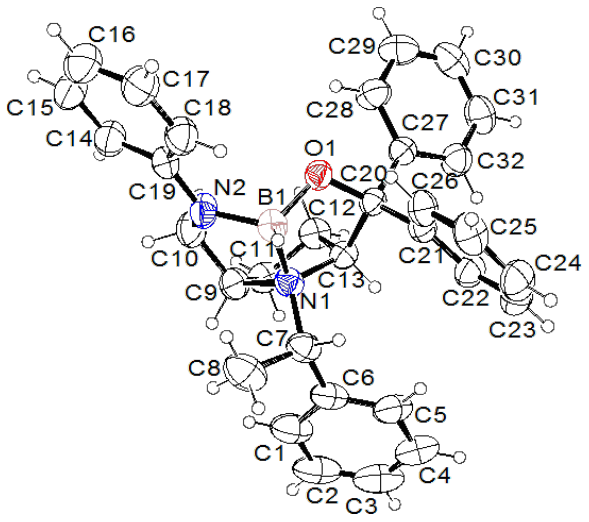
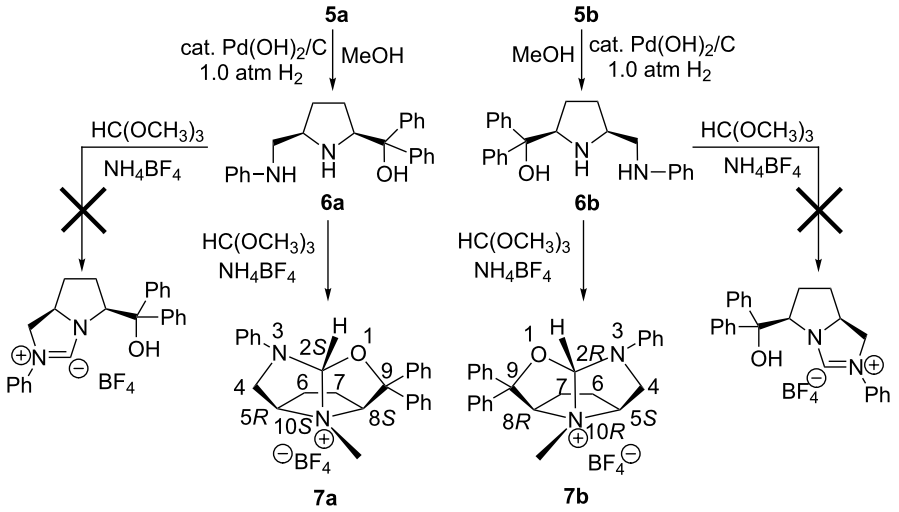


Figure 3: X-ray crystal structure of compound **5a**.

quinane skeleton through an intramolecular Lewis acid–base pair interaction [15-18]. Three five-membered rings are fused to give a very stable bowl-shaped tricyclic system with five stereogenic centers, especially for one chiral nitrogen center and one chiral boron center. The configurations of the stereogenic centers in **5a** are deduced from the configuration of the chiral auxiliary (*S*)-(−)-1-phenylethylamine to be *S*, 3*S*, 6*R*, 9*S* (chiral B atom) and 10*R* (chiral N atom), respectively. This novel tandem reduction/cyclization was made possible by the *cis*-configuration of the starting 2,5-disubstituted pyrrolidine **4a**. Following the same procedure, 10-heteroazaquinane **5b** was obtained in good yield (87%), and the configurations of **5b** were assigned to be *S*, 3*R*, 6*S*, 9*R* (chiral B atom) and 10*S* (chiral N atom), respectively. Compounds **5a** and **5b** are diastereomers.

In the presence of a catalytic amount of $Pd(OH)_2/C$, under 1.0 atm of hydrogen, the above 10-heteroazaquinane derivatives **5** were converted into enantiopure asymmetric *cis*-2,5-disubstituted pyrrolidines **6** in good yields with a diamino-alcohol skeleton. In this process, both *N*-debenzylation and a ring-opening reaction occurred. Diamino-alcohols **6a** and **6b** are enantiomers, and they can serve as precursors for the synthesis of hydroxy *N*-heterocyclic carbenes. Following the reported procedure for the preparation of *N*-heterocyclic carbenes [19,20], the enantiopure pyrrolidine **6b** and NH_4BF_4 in $HC(OCH_3)_3$ is heated to 80 °C for 2 h, the light yellow crystals were obtained in good yield after workup (Scheme 3). The same result was obtained by heating the mixture of **6b**, NH_4BF_4 and $HC(OCH_3)_3$ in anhydrous toluene under reflux.

To our delight, a single crystal was grown from CH_2Cl_2, suitable for X-ray diffraction analysis. It was found that the ring-closing reaction took place during the heating process following *N*-methylation to provide the rigid 1-oxo-3-aza-10-azaquinane skeleton **7b** as its ammonium salt. Compound **7b** contains four stereogenic centers, and their configurations are assigned to be 2*R*, 5*S*, 8*R* and 10*R* (chiral N atom) based on its starting material **4b** (Figure 4). Actually, $HC(OCH_3)_3$ as an efficient reagent for *C*-, *N*-, and *O*-methylation has been reported [21-24], but the mechanism of these methylations is elusive. The other chiral ammonium salt **7a** was obtained under the same



Scheme 3: One-pot tandem cyclization of **6** in the presence of $HC(OCH_3)_3$.

conditions as those for the preparation of **7b**. The chiral ammonium salts **7a** and **7b** were derived from the enantiomers **6a** and **6b**, therefore, **7a** and **7b** are also enantiomers. The configurations of **7a** are assigned to be 2*S*, 5*R*, 8*S* and 10*S* (chiral N atom).

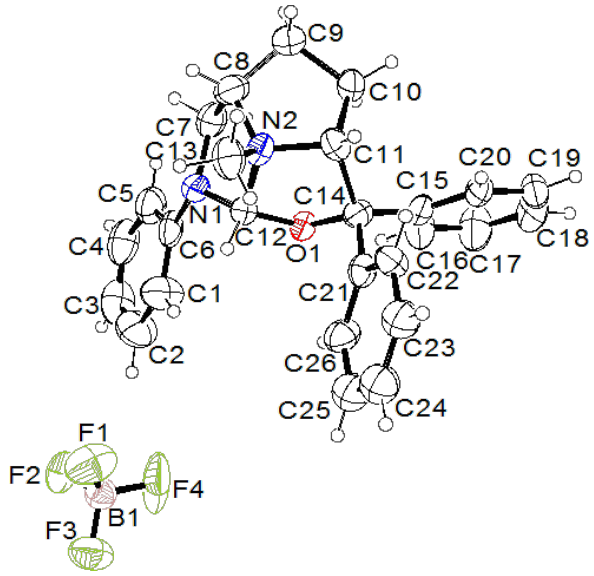
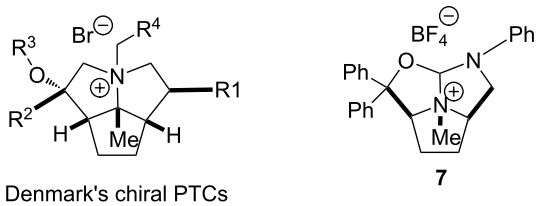


Figure 4: X-ray crystal structure of compound **7b**.

As shown in Figure 4, this 10-heteroazatriquinane **7b** possesses a rigid bowl-like molecular scaffold with a quaternary nitrogen site (N2) at the bottom of the cavity. Recently, Denmark and colleagues [25,26] have synthesized a series of chiral phase-transfer catalysts (chiral PTCs) based on a 2-azatriquinane skeleton (Figure 5), and they have investigated their catalytic activities in asymmetric alkylation reactions for producing enantiomerically enriched amino acids. The synthesis of these quaternary ammonium ions follows a diversity-oriented approach wherein the tandem inter-[4 + 2]/intra-[3 + 2] cycloaddition of nitroalkenes serves as the key transformation. The chiral ammonium salts **7** have a structure similar to the chiral PTCs of Denmark et al. The substituents in the chiral ammonium salts **7** are easily tunable, which could open a route to various chiral PTCs for organic synthesis.

Conclusion

In summary, we provide here a facile access to chiral 10-heteroazatriquinanes from enantiopure asymmetric *cis*-2,5-disubstituted pyrrolidines through one-pot tandem cyclization reactions, and their configurations are confirmed by X-ray single-crystal diffraction analysis. The applications of these novel 10-heteroazatriquinanes are currently being investigated in our laboratory.



7

Denmark's chiral PTCs
R^1 = H, Me
R^2 = Mesityl, *t*-Bu, 1-naphthyl, etc.
R^3 = H, Ph, 2-pyridyl, etc.
R^4 = Aryl

Figure 5: The structural comparison of chiral ammonium salts such as **7** with the chiral PTCs of Denmark et al.

Supporting Information

Supporting Information File 1

Full experimental details, analytical data and crystallographic information.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-32-S1.pdf]

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