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Cytisine as a scaffold for *ortho*-diphenylphosphinobenzenecarboxamide ligands for Pd-catalyzed asymmetric allylic alkylation

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ABSTRACT

(−)-Cytisine has been used as a scaffold for the synthesis of three novel phosphino-benzenecarboxamide ligands. The latter were obtained from cytisine and tetrahydrocytisine, and tetrahydrodeoxocytisine thereof. The structures and conformations of the newly prepared compounds were elucidated on the basis of NMR, X-ray and DFT studies. Conformational studies in respect of hindered rotation of the amide group and the flexibility of the piperidine ring were performed. The X-ray structure of the tetrahydrocytisine-derived ligand was in agreement with the conformation in solution. The application of the ligands in Pd-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenyl-2-propenyl acetate proceeded with excellent conversions and ee's of up to 91%. The observed catalytic activity of the three ligands strongly correlated with their conformational behaviour. Additionally, a strong dependence of the enantioselectivity on the applied BSA/base system was observed.

Introduction

(1*R*,5*S*)-(−)-Cytisine **1** is a chiral natural product which belongs to the lupin alkaloid family and large amounts are easily extracted from the *Laburnum anagyroides* seeds [1]. It has been produced and marketed for over 40 years to treat tobacco dependence (Tabex®, the brand-name product of Bulgarian pharmaceutical company Sopharma AD) due to its high affinity at nicotinic acetylcholine receptors (nAChRs) of the central nervous system while displaying minimal side effects [2]. The availability of this chiral alkaloid initiated its development as a starting template for drug design and the synthesis of various substituted derivatives [3]. A comprehensive review dedicated to (−)-cytisine was published this year [4].

The most well-known naturally occurring chiral diamine used in asymmetric synthesis is (−)-sparteine (Fig. 1). O'Brian was the first one to recognize that the naturally occurring alkaloid, (−)-cytisine, is equipped with the required bispidine framework and the correct absolute configuration to serve as a (+)-sparteine mimic [5]. O'Brian and coworkers developed *N*-methyl diamine **2** (R = Me) *via* a simple three step route from extracted (−)-cytisine, and applied it as the mirror image analogue of (−)-sparteine in a number of asymmetric deprotonations [6]. Additionally, different *N*-alkylated diamines of type **2** were prepared to test the influence of the steric hindrance of various bulky substituents on the enantioselectivity [7]. Thus, application of (−)-cytisine derived diamines as (+)-sparteine surrogates in reactions of the deprotonation of *N*- and *O*-carbamates, the α-lithiation and subsequent rearrangement of epoxides, the oxidative kinetic resolution of racemic alcohols and the desymmetrization of prochiral phosphines resulted in enantioselectivities similar to the given with (−)-sparteine but in the opposite sense [7,8].

Somewhat surprisingly, in spite of the development of phosphine free palladium ligands, and the success of sparteine palladium complexes in asymmetric allylic alkylation [9], the application of structurally similar (−)-cytisine derived diamines in Pd-catalyzed asymmetric reactions, is highly underestimated. More importantly, to the best of our knowledge, modifications of (−)-cytisine to chiral phosphine ligands are not reported so far.

Since the discovery of the diamidodiphosphines by Trost and coworkers in the early 1990's, the interest in the synthesis and application of hybrid hemilabile P,O-type ligands steadily grows

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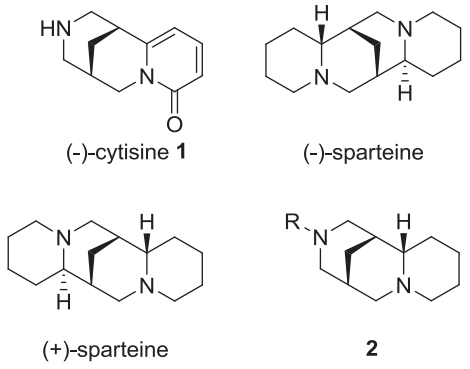


Fig. 1. (−)-Cytisine, (−)-sparteine and (+)-sparteine, and *N*-substituted tetrahydrodeoxocytisine.

through the years [10]. The phosphine-carboxamides evolved into a specific ligand platform due to their stability, ease with which they can be accessed and moreover the combination of hard and soft donor heteroatom pairs, which enables them to bind to almost any metal, generating electronic asymmetry [11]. The unambiguous proof that P,O-mode of coordination with palladium center is giving catalytically active complex [12] justify the efforts to the development and application of amido-phosphine ligands in asymmetric allylic alkylation (AAA) [13].

During the last few years, we have successfully developed and fine-tuned a number of camphane based planar chiral diphenylphosphino-ferrocenecarboxamide and diphenylphosphino-benzenecarboxamide ligands and reported their application in the palladium-catalyzed asymmetric allylic alkylation (AAA) [14]. They were found as effective ligands, affording enantioselectivities up to 92% [14c]. The use of camphane based chiral auxiliary, available by the "chiral pool"-based synthetic strategies, proved to be crucial for the asymmetric induction. Stimulated by this observations we became interested in the design and synthesis of new ligands on the base of other easily accessible polycyclic auxiliaries from the "chiral pool". (−)-Cytisine, with its bulky chiral cage and the advantage of bearing a secondary amine functionality, which could be used for the construction of amide linkage, appeared as a suitable template for further extension of our investigations.

Herein, we report a practical synthesis of new chiral phosphino-benzenecarboxamide ligands on the base of the (−)-cytisine scaffold, and their application in Pd-catalyzed asymmetric allylic alkylation. Elucidation of the structures is made on the base of NMR, X-ray and DFT studies. To the best of our knowledge this is the first example of chiral phosphino-carboxamide ligands based on (−)-cytisine as a chiral auxiliary.

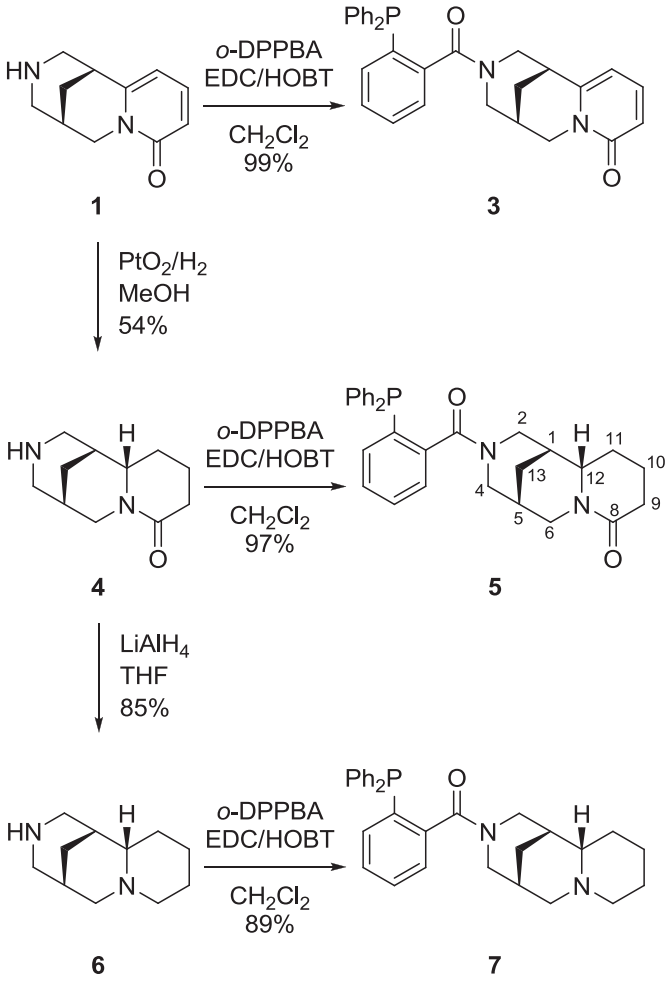
Results and discussion

(1*R*,5*S*)-(−)-Cytisine, tetrahydrocytisine and tetrahydrodeoxocytisine were selected as key starting compounds for the synthesis of the desired phosphino-benzenecarboxamide ligands. Cytisine is obtained by extraction from the Laburnum anagyroides seeds and was donated by the pharmaceutical company Sopharma AD. The latter two compounds were prepared subsequently from cytisine as described below.

Ligand **3** was easily obtained by condensation of *ortho*-diphenylphosphinobenzoic acid (*o*-DPPBA) with (−)-cytisine **1** in dry CH_2Cl_2 in the presence of *N*-[-3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBT) [15]. The phosphine-amide **3** was isolated as air stable white solid in quantitative yield after flash column chromatography (Scheme 1).

Ligand **5** was synthesized from tetrahydrocytisine, which was prepared *via* hydrogenation of the pyridone functionality of (−)-cytisine **1**. Thus, reaction of **1** in methanol with hydrogen, at atmospheric pressure, and platinum (IV) oxide (Adams' catalyst) resulted in the formation of lactam **4** in 54% yield after chromatography (Scheme 1) [8b]. The condensation of *o*-DPPBA with tetrahydrocytisine **4**, following the already described procedure, afforded the corresponding amido-phosphine ligand **5** in excellent yield after flash column chromatography. Compound **5** was isolated as a single diastereoisomer and the absolute configuration of the newly formed stereogenic center, C-12, was unequivocally assigned as (*S*) by X-ray crystallography. As shown in Figire 2, H-12 is *cis* to the methylene bridge connecting carbons C-1 and C-5. This is in accordance with the previously reported pyridone hydrogenation of (−)-cytisine **1** proceeding at the less sterically hindered *exo* face [16].

Finally, the reduction of lactam **4** with excess of lithium aluminum hydride in refluxing THF gave tetrahydrodeoxocytisine **6** (Scheme 1). The crude diamine **6** was obtained in 85% yield and used immediately in the next step without purification. Formation of the amide linkage was accomplished by applying the EDC/HOBT/o-DPPBA coupling procedure. The desired ligand **7** was isolated as a single diastereoisomer in 89% yield after flash column chromatography. Based on the known absolute configuration of **5**, the



Scheme 1. Synthesis of diphenylphosphino-benzenecarboxamide ligands **3**, **5** and **7**.