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Novel Supramolecular Palladium Catalyst for the Asymmetric Reduction of Imines in Aqueous Media

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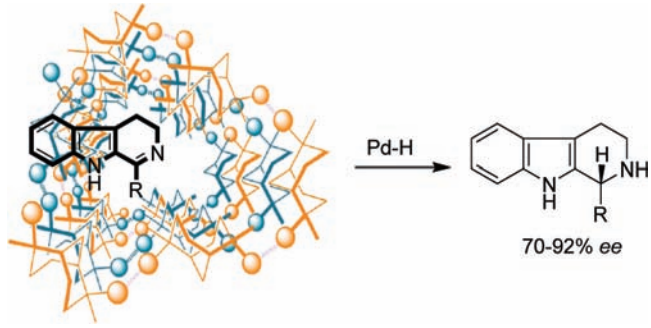
ABSTRACT



A novel approach to the asymmetric reduction of dihydro-β-carboline derivatives to the corresponding tetrahydro-β-carbolines is described based on the supramolecular lyophilized complex formed from β-cyclodextrin/imines as an enzyme mimetic and palladium hydride as the reducing agent. The methodology allowed us to develop a short and efficient preparation of (*R*)-harmicine and (*R*)-deplancheine alkaloids in high overall yields and *ee* of 89 and 90%, respectively.

Drug chirality is now a major theme in the design, discovery, development, launching and marketing of new drugs and stereochemistry is an essential dimension in pharmacology. In past decades, the pharmacopoeia was dominated by racemates, but since the emergence of new technologies in the 1990s that allowed the preparation of pure enantiomers in significant quantities, the awareness and interest in the stereochemistry of drug action has increased. Perhaps part of the interest in chirality is the fascination with the elegance of the underlying concepts. However, the most important motivation for developing enantiomers has been a genuine desire to improve efficacy and reduce adverse effects of drugs through exploitation of stereospecific differences in pharmacodynamics and pharmacokinetics.

Based on this concept, we pursued the development of an efficient methodology for the stereoselective synthesis of structurally complex compounds. Numerous methods for the synthesis of optically active amines are known, few being based on catalytic asymmetric synthesis. Among the most popular is the asymmetric hydrogenation of ketimines or enamides using chiral Rh(I), Ir(I), or Ru(II) complexes.[1] A particularly efficient method for the reduction of dihydro-

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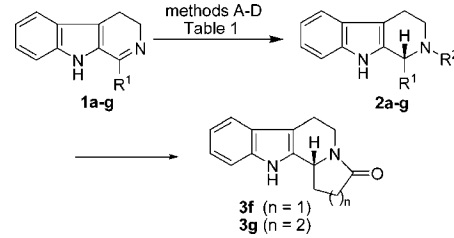
β-carbolines is the asymmetric transfer hydrogenation.[1] During the course of our total synthesis of the alkaloid Quinolactacin B, the opportunity arouse to investigate a new approach to the asymmetric reduction of dihydro-β-carbolines through a host−guest mediated process based on CD(host)/$PdCl_2$(guest)-Et_3SiH (hydride source).[2]

We used β-CD as cocatalyst in the reaction as it is a mild and efficient biomimetic catalysts in various transformations.[1,2] Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. CDs catalyze reactions via supramolecular arrangement involving reversible formation of host/guest complexes by noncovalent bonding. Complexation depends on the size, shape, and hydrophobicity of the guest molecule.

Asymmetric Supramolecular Reduction of Dihydro-β-carbolines. The search for novel enantioselective imine reduction methods was inspired by the cyclodextrin (CD)/$NaBH_4$ asymmetric reduction of carbonyl compounds which however provided poor *ee*% when applied to imines.[2,3] Based on our previous preliminary results,[2] we initially investigated the supramolecular induction of chirality in the reduction of dihydro-β-carbolines promoted by the β-cyclodextrin/$PdCl_2$-Et_3SiH catalytic system. Our choice of dihydro-β-carbolines as substrates was dictated by our interest to apply the methodology to the asymmetric total synthesis of some indole alkaloids and also because it would allow us to compare our results with those provided by the Noyori asymmetric transfer hydrogenation which is based on the utilization of ruthenium(II)-DPEN complexes and is carried out in the presence of HCO_2H-Et_3N azeotropic mixture.[2b,4,5] Despite its effectiveness of the reduction of dihydro-β-carbolines, we considered to be of interest to develop alternatives, particularly those based on a different concept such as the use of a chiral host−guest complex in aqueous media.

The methodology developed in our laboratory is based on β-cyclodextrin host−guest chiral complexes.[6] Previously, we have described the CD/imine complexes reduction employing $NaBH_4$ as the reducing agent but the corresponding amines were obtained with low enantiomeric excess (*ee* 25%).[2a] However, we noticed that when lyophilized host−guest complexes of β-CD and $PdCl_2$ were used, considerably higher *ee*% values were obtained in the reduction of dihydro-β-carbolines. A representative protocol used was: overnight $PdCl_2$/β-CD (1:2 molar ratio) complex formation in aqueous Na_2CO_3 solution (0.2 mol/L), followed by lyophilization of the resulting mixture. The lyophilized powder was resuspended in water and a solution of imines **1a**−**g** in CH_2Cl_2 was added (method A, Table 1). Finally, the solution was kept at 0 °C and Et_3SiH was added dropwise. After 12 h, (*R*)-amines **2a**−**g** were obtained in good to excellent yields (78−95%) and good *ee*% values (70−92%).

Table 1. β-Cyclodextrin Mediated Reduction of Imines **1** to Amines **2**



entry	R	method A[a] *ee*% (yield %)	method B[b] *ee*% (yield %)	method C[c] *ee*% (yield %)	method D[d] *ee*% (yield %)
a	Me (**1a**)	92 (92)	90 (95)	80 (90)	95 (96)
b	Et (**1b**)	78 (94)	83 (94)	76 (75)	92 (90)
c	^{i}Pr (**1c**)	70 (82)	70 (92)	70 (80)	94 (98)
d	1-pentenyl (**1d**)	76 (80)	70 (93)	70 (80)	92 (90)
e	Ph (**1e**)	90 (85)	88 (90)	80 (90)	92 (98)
f	$(CH_2)_2CO_2Me$ (**1f**)	89 (95)	89 (86)	76 (75)	90 (85)
g	$(CH_2)_3CO_2Me$ (**1g**)	90 (80)	85 (82)	–	92 (84)

[a] Method A: $PdCl_2$/CD then imine and Et_3SiH. [b] Method B: Imine (**1**)/CD then $PdCl_2$ and Et_3SiH. [c] Method C: Imine (**1**)/CD then $NaBH_4$. [d] Method D: TsDPEN-Ru(II) complex, HCO_2H/Et_3N, DMF, rt, 12 h.

To test whether the order of addition might influence the *ee%* values, we added $PdCl_2$ followed by Et_3SiH in the resuspended lyophilized complex imine/β-CD in water (method B, Table 1). The *ee%* values were slightly lower than previously observed in method A. Another protocol tested was based on β-CD/imine complex formation, following the same steps described above, but using $NaBH_4$ as reducing agent (method C, Table 1). (*R*)-Amines **2a**−**g** were obtained in *ee%* values around 70−80% and excellent yields. Finally, Noyori asymmetric hydrogenation with (*S*,*S*)−TsDPEN-Ru(II) catalyst (method D, Table 1) was used to compare the *ee%* values and determine the absolute configuration of the newly formed stereogenic center in methods A-C. The *ee%* values were determined by chiral HPLC (Welk-01 column, 90:10:0.1 hexanes/isopropanol/diisopropyl-amine; 0,8 mL/min, λ 263 nm).

The use of the $PdCl_2$/β-CD/Et_3SiH protocol (method A) provided good enantiomeric excesses, particularly for dihydro-β-carbolines **1a** and **1e**−**g**. In these particular examples, the supramolecular reducing condition (method A) performed

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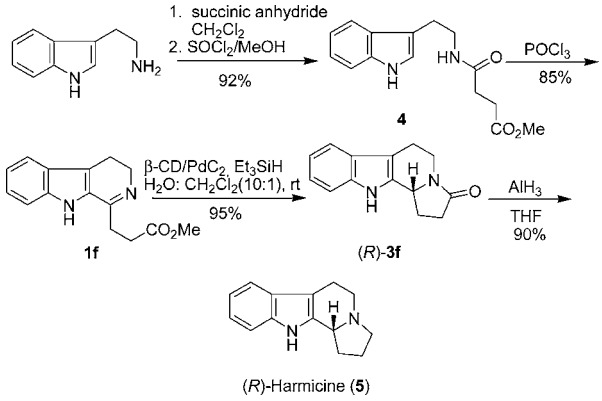
as well as the Noyori asymmetric transfer hydrogenation (method D) regarding the enantiomeric excess and therefore it constitutes a novel asset in the asymmetric catalytic reduction of prochiral dihydro-β-carbolines. In the last two examples (**1f** and **1g**), the asymmetric reduction was followed by a spontaneous lactamization step affording the corresponding tetracyclic lactams **3f** and **3g**.

Harmicine. The above methodology allowed us to develop a short and efficient preparation of the indoloquinolizidine alkaloid (*R*)-harmicine (**5**), isolated from the leaf extracts of *Kopsia griffithii*, which is reported to display strong antileishmania activity in preliminary screening.[7] Recently, Ohsawa reported the synthesis of *ent*-**3** and assigned *R* absolute configuration to the natural product based on a 11-step protocol from the β-carboline precursor.[8]

The requisite amide **4** was straightforwardly prepared from tryptamine and succinic anhydride in 92% yield (Scheme 1). Following the same approach which was successfully

Scheme 1. Supramolecular Approach to the Synthesis of (*R*)-Harmicine (**5**)



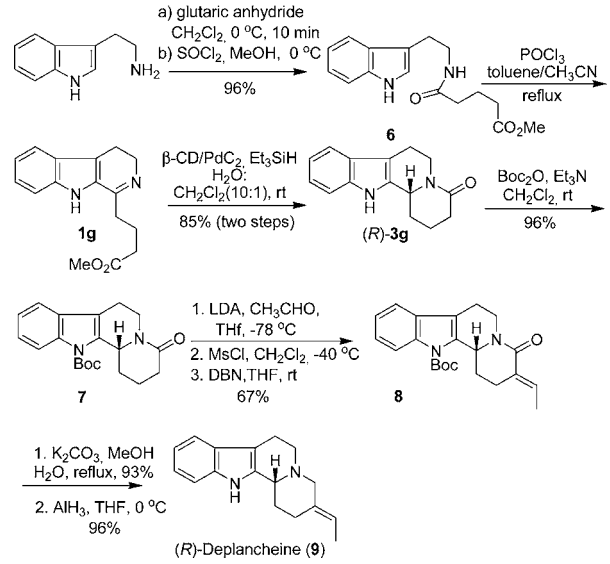
employed in the total synthesis of arborescidines A, B and D,[5b] Bischler-Napieralski cyclization promoted by phosphorus oxychloride provided dihydro-β-carboline (**1f**) in 85% yield which was submitted to the supramolecular reduction conditions described above (Table 1, method A) to afford lactam **3f** in 95% yield and 89% *ee* after spontaneous lactamization. This result compares favorably with those obtained using the Noyori protocol (85% yield and 90% enantiomeric excess, Table 1, method D). The total synthesis of (*R*)-harmicine was thus accomplished in 5 steps and 67% overall yield from tryptamine and succinic anhydride after reduction of lactam **2f** with recently prepared alane soln. in THF.

Deplancheine. The indolo[2,3-*a*]quinolizidine is the core structure in several indole alkaloids such as yohimbine, geissoschizine, and reserpine. (*R*)-(+)-Deplancheine (**9**), isolated from the stems and bark of *Alstonia deplanchei*[9] as well as from *Alstonia undulata*[10] and from the South American *Aspidosperma maregravianum*,[11] had its absolute configuration established by Meyers and co-workers in 1986 through the total synthesis of the (*S*)-enantiomer.[12] Due to its deceptively simple structure, deplancheine has become a preferential testing ground to evaluate the efficiency of methodologies designed for the asymmetric synthesis of alkaloids featuring the indolo[2,3-*a*]quinolizidine architecture.[13]

Our approach to the asymmetric total synthesis of (*R*)-deplancheine (**9**) was inspired by the construction of the indolo[2,3-*a*]quinolizidine core via the Bischler-Napieralski/supramolecular reduction protocol, followed by the introduction of the *E*-configured exocyclic double bond via stereoselective aldol-dehydration sequence employed in our total synthesis of homopumiliotoxin.[14]

In fact, the reaction of tryptamine with glutaric anhydride, followed by esterification with MeOH/$SOCl_2$ afforded amide **6** in 96% yield. Bischler-Napieralski cyclization and supramolecular reduction of the intermediate dihydro-β-carboline **1g** provided tetracyclic lactam **3g** in 85% overall yield (two steps) and 90% *ee*, by chiral HPLC analysis (Scheme 2). Attempts to install the exocyclic double bond in lactam

Scheme 2. Supramolecular Approach to the Synthesis of (*R*)-Deplancheine (**9**)



3g via the aldol/dehydration sequence met with failure due to the deprotonation of the indol nitrogen and its previous protection with the *terc*-butoxycarbonyl group (Boc) was required. Boc-protected lactam **7** was uneventfully prepared (96% yield) and was successfully converted to the corresponding *E* ethylydene derivative **8** in 67% overall yield, after aldol reaction of the corresponding lithium enolate with acetaldehyde, followed by mesylation and DBN elimination.[13] Boc-deprotection of **8** followed by reduction of the

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carbonyl group with alane in THF afforded (*R*)-deplancheine (**9**) in 44% overall yield from tryptamine and glutaric anhydride. The final compound proved to be identical to the natural product and to (*R*)-deplancheine (**9**) prepared via Noyori asymmetric hydrogen transfer using (*S*,*S*)-TsDPEN/Ru(II) catalyst.

The lyophilized host−guest complex involving β-CD/dihydro-β-carbolines/$PdCl_2$ and Et_3SiH provided higher %*ee* than previously reported systems using β-CD/dihydro-β-carbolines and $NaBH_4$ as the reducing agent. We have demonstrated the feasibility of this novel protocol for the asymmetric reduction of dihydro-β-carbolines with yields and %*ee* comparable to those obtained by the Noyori methodology (TsDPEN-Ru(II) complex and azeotropic HCO_2H/Et_3N). The utility of our protocol was demonstrated with the total synthesis of the indole alkaloids (*R*)-harmicine (**5**) and (*R*)-deplancheine (**9**) in 5 (67% overall yield, 89% *ee*) and 10 steps (44% overall yield, 90% *ee*), respectively. The supramolecular protocol presented here opens up several possibilities for its application to the asymmetric reduction of imines and to the total synthesis of enantiomerically enriched nitrogenated compounds.

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Supporting Information Available: Copies of the ^1H and ^{13}C NMR spectra of compounds **1a**, **1d**, **1f**, **2f**−**g**, **3**−**8**, precursor amides as well as detailed experimental procedures of all synthesized compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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