Enantioselective Syntheses of 2-Substituted Pyrrolidines from Allylamines by Domino Hydroformylation–Condensation: Short Syntheses of (*S*)-Nicotine and the Alkaloid 225C

Pierre Dübon, Andreas Farwick, Günter Helmchen*

Organisch-Chemisches Institut der Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
Fax +49(6221)544205; E-mail: g.helmchen@oci.uni-heidelberg.de

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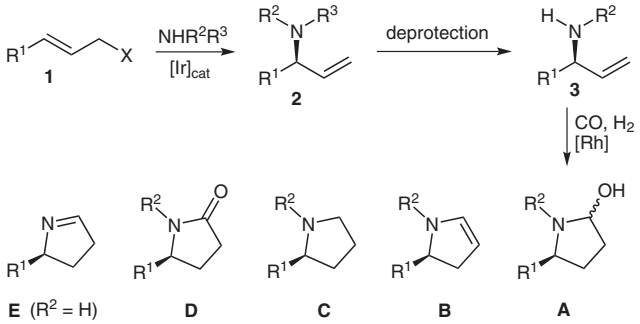
Abstract: Short routes to chiral 2-substituted pyrrolidines based on rhodium-catalyzed hydroformylations of allylamines and their *N*-alkyl and *N*-acyl derivatives, which were prepared by asymmetric allylic substitutions, are described. The outcome of the hydroformylation reaction was controlled by the substituent at nitrogen, not by the substituent at carbon. In the case of *N*-alkylallylamines in situ reduction to the pyrrolidines occurred, with *N*-acyl derivatives hemiaminals and with primary amines cyclic imines were formed. Very short syntheses of (*S*)-nicotine and the alkaloid 225C are presented.

Key words: domino reactions, hydroformylation, pyrrolidines, alkaloids, cyclizations

Over the last few years, the iridium-catalyzed allylic substitution has been developed into a tool for organic synthesis that allows chiral allylamines to be prepared in great variety with high enantioselectivity (Scheme 1).[1] Given these compounds with tailor-made, readily removable N-protection, they were used as starting compounds of ring-forming reactions.[2,3] We have now explored their use as substrates of the hydroformylation reaction.[4] In the case of secondary amines **3** (cf. Scheme 1), the aldehydes so produced undergo spontaneous cyclization, elimination, and sometimes also reduction, namely, a so-called hydroaminomethylation. This sequence of reactions is well known for the intermolecular case;[5] intramolecular reactions have been studied in particular with homoallylamine derivatives yielding piperidines.[6]

Due to the starting materials, our work was directed at 2-substituted pyrrolidines,[7] particularly pyrrolidine alkaloids and potential organocatalysts. One point of concern was racemization, which is not possible for homoallylamines, but could be marked with allylamines if the hydroformylation reaction was reversible. Therefore, enantiomeric excesses of starting materials and products were carefully determined. Furthermore, the outcome of the seemingly straightforward hydroformylation turned out to be a function of subtle details of structure, catalyst, and reaction conditions (cf. Scheme 1).[8] For example, an attempt to prepare nicotine via hydroformylation of the allylamine **3d** (R^1 = 3-pyridyl, R^2 = Me) met with complete failure, because under standard conditions, using Xantphos or Biphephos (Figure 1) as ligands, mixtures of a pyrrolidine of type **C** and a lactam of type **D** were formed. This result was an incentive to study the hydroformylation of allylamine derivatives in detail. As a result, very short and selective syntheses of pyrrolidines of types **A**, **C**, and **E** possessing high enantiomeric purity are now available via hydroformylation.

The rhodium-catalyzed cyclization reactions were probed with catalysts prepared from $Rh(acac)(CO)_2$ and several ligands; the best results were obtained with Xantphos and Biphephos (Figure 1). These ligands have indeed previously given particularly good results with respect to the *n*/iso ratio, which for 1-octene was 52:1 (Xantphos)[9] and 40:1 (Biphephos).[10] Biphephos has excelled in hydroformylations of a large variety of functionalized alkenes. In our own screening experiments no superior ligand was found.



Scheme 1 Products potentially formed by hydroformylation of an allylamine

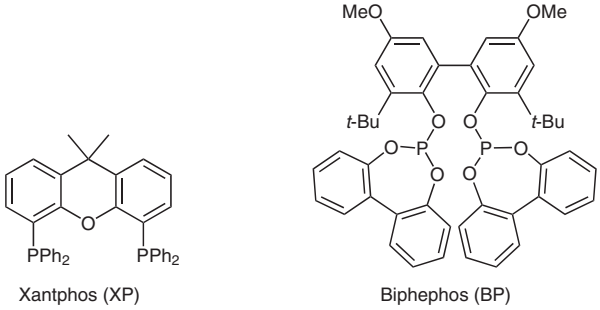


Figure 1 Ligands used for rhodium-catalyzed hydroformylation reactions

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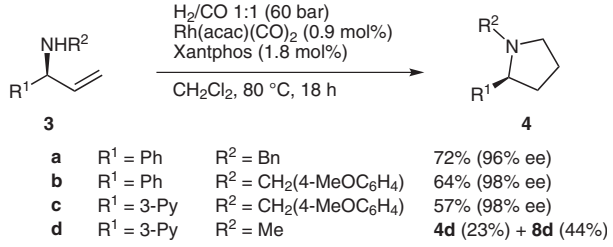
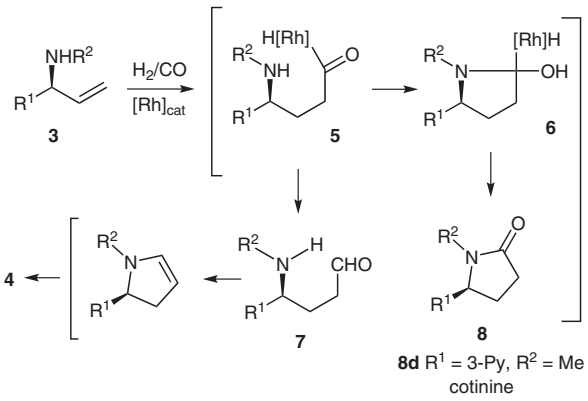
First, the *N*-benzyl- and N-(*p*-methoxyphenyl)methylallylamines **3a–c**, prepared by standard Ir-catalyzed allylic amination,[11] were probed using conditions published by Eilbracht et al. (Scheme 2).[12] The aforementioned intramolecular hydroaminomethylation gave the 2-substituted pyrrolidines **4a–c** in 57–72% yield. Careful determination of the enantiomeric excess of the starting materials and the products showed that racemization had not occurred.[13]



Scheme 2 Domino hydroformylation–reductive amination

The substrate **3d**, as was mentioned above, proved problematic. With Xantphos as ligand in a variety of experiments the major product was the lactam cotinine (**8d**), also a tobacco alkaloid (Scheme 3). This compound is presumably formed via the rhodium complex **6** by β-H elimination. Lactams as hydroformylation products have previously been observed.[5b,6b]

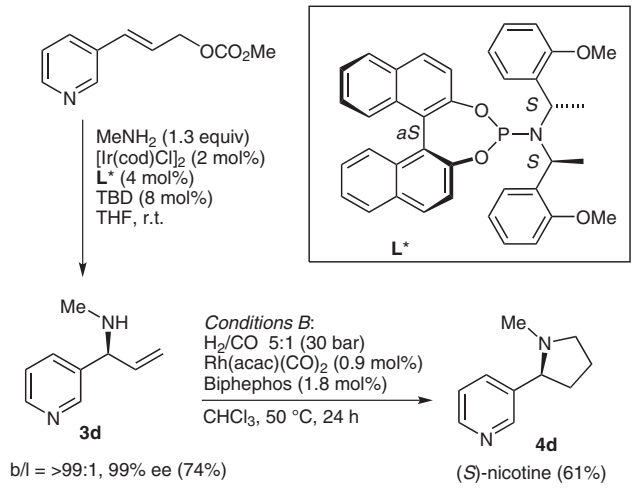


Scheme 3 Intermediates of the domino-hydroformylation–reductive amination

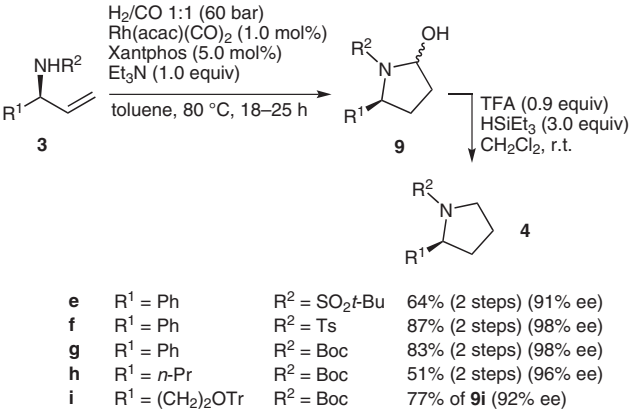
In order to accelerate the hydrogenation step, the partial pressure of hydrogen was increased (H_2/CO = 5:1). Furthermore, the phosphite Biphephos was used as ligand, which induces higher activity than Xantphos. This allowed decrease of the reaction pressure (30 bar) and temperature (50 °C). Under optimized conditions (B, Scheme 4)[14] (*S*)-nicotine (**6d**) was obtained in 61% yield, not contaminated by cotinine, with 99% ee, that is, without racemization. This route constitutes a very short synthesis of (*S*)-nicotine.[15,16]

As second class of substrates *N*-sulfonyl- (**3e**,**f**) and *N*-acyl-allylamines (**3g–i**) were investigated (Scheme 5). These were prepared using salt-free conditions of the Ir-catalyzed allylic substitution and partial N-deprotection.[11c,17–19] The course of the hydroformylation of these compounds, using slightly modified conditions A (cf. Scheme 2), was different from that with *N*-alkyl-allylamines (Scheme 5). Hemiaminals **9** were produced after cyclization of the intermediary aldehydes.[20] The isolated yields of the hemiaminals **9** were good to excellent. Racemization did not occur. The hemiaminals were reduced with TFA and $HSiEt_3$ to give 2-substituted pyrrolidines **4** in yields of 51–87% (over two steps, Scheme 5).

Remarkably, hydroformylations of *N*-acyl-homoallylamines in aprotic solvents, using Biphephos as ligand, yield aldehydes or *N*-acyl-dehydropiperidines (i.e., enamines), according to Ojima et al.[6c,d] These authors also reported that elimination of water from corresponding hemiaminals under acidic conditions is facile. Under the same conditions, the hemiaminals **9** did not react. Thus, the rate of elimination of water likely is the cause of the differing reaction modes of *N*-alkyl- and *N*-acyl-allylamines.

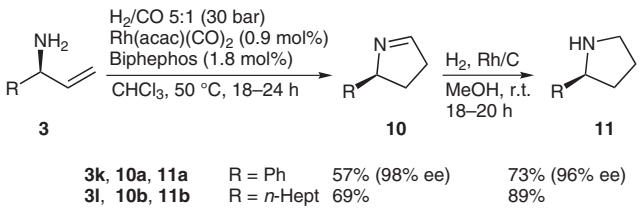


Scheme 4 Enantioselective synthesis of (*S*)-nicotine (preparation of L* according to Alexakis et al.).[21] The designations b and l refer to the branched (**3d**) and linear product, respectively, of the allylic amination.



Scheme 5 Hydroformylation of *N*-sulfonyl- and *N*-acyl-allylamines

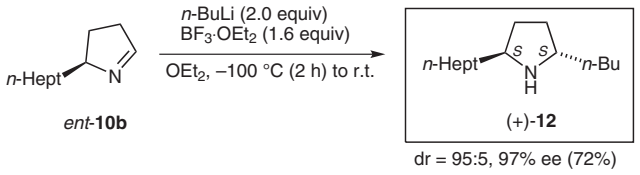
Finally, N-unprotected primary allylamines were subjected to the hydroformylation reaction (Scheme 6). Under standard hydroformylation conditions [Xantphos, 60 bar, H_2/CO (1:1), CH_2Cl_2 or toluene, 80 °C, 24 h] conversion was low. Under the conditions B optimized for nicotine [Biphephos, 30 bar, H_2/CO (5:1), $CHCl_3$] the imines **10a** and **10b** were formed in good yield; reductive amination did not occur (GC-MS).[22]



Scheme 6 Hydroformylation–cyclization of primary allylamines

Hydrogenation of the imines **10** was carried out with Rh/C as catalyst (methanol, r.t., 1 atm of H_2). The enantiomeric excess decreased slightly, from 98% (**10a**) to 96% (**11a**, Scheme 6). In contrast, with Pd/C as catalyst under otherwise identical conditions the ee decreased to 90%.

The cyclic imines **10** are of interest for syntheses of biologically active compounds. We have used *ent*-**10b** for a short synthesis of the alkaloid 225C [(+)-**12**], a constituent of the venom of the fire-ant *Solenopsis fugax*.[23] Introduction of the *n*-Bu group by addition of *n*-BuLi was an obvious route (Scheme 7). The addition of a nucleophile to an imine generally requires the presence of an electron-withdrawing N-substituent[24] or addition of a Lewis acid.[25] Following a procedure by Nakagawa et al.,[25b] a solution of *ent*-**10b** in toluene was cooled to –78 °C, treated with $BF_3{\times}OEt_2$ (1.6 equiv) and then with *n*-BuLi (2 equiv, 1.6 M in *n*-hexane). The addition proceeded with a low dr of 66:34 (*trans*/*cis*). However, with diethyl ether as solvent at –100 °C using *n*-BuLi, which was precooled[26] to the same temperature, an excellent dr of 95:5 resulted.



Scheme 7 Application of a cyclic imine in the synthesis of an alkaloid

In summary, we present short routes to chiral 2-substituted pyrrolidines[27] based on rhodium-catalyzed hydroformylations of allylamines, which were derived from asymmetric allylic substitutions. The outcome of the hydroformylation reaction was found to be controlled by the nature of the substituent at nitrogen, fortunately not by the substituent at carbon. In the case of *N*-alkylallylamines in situ reduction to the pyrrolidines occurred, with *N*-acyl derivatives hemiaminals and with primary amines cyclic imines were formed. The insight gained allowed very short syntheses of (*S*)-nicotine and the alkaloid 225C to be carried out.

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(14) **General Procedure for the Rh-Catalyzed Hydroformylation–Reduction (cf. Conditions B, Scheme 4)**
A cylindrical glass vessel (2.5 × 7 cm) with a perforated snap on lid was charged with $Rh(acac)(CO)_2$ (2.3 mg, 9.0 μmol), Biphephos (18 μmol), and a soln of the allylic amine (1.0 mmol) in $CHCl_3$ (10 mL/mmol). The vessel was placed in an autoclave, which was pressurized (30 bar) with H_2/CO (5:1); oxygen was removed by flushing twice with the gas mixture. The autoclave was then heated for 18–24 h at 50 °C. The resulting brown mixture was analyzed by GC-MS. The solvent was removed in vacuo and the residue subjected to flash chromatography on SiO_2.

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