Efficient Asymmetric Hydrogenation of Pyridines**

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Dedicated to Professor H. Martin R. Hoffmann on the occasion of his 70th birthday

Catalytic asymmetric hydrogenation has become a key technology in academic research[1] and in industry[2] owing to its generally unrivalled efficiency and selectivity.[3] Nevertheless, no satisfactory solution for the asymmetric hydrogenation of aromatic or heteroaromatic substrates according to Scheme 1 exists,[4] although these compounds are readily available and the reaction has the potential for the simultaneous creation of multiple stereocenters. Here we describe an efficient and unprecedented auxiliary-based method for the asymmetric hydrogenation of substituted pyridines (XR1 = N)[5] which enables the stereoselective formation of piperidines[6] with up to four new chiral centers (Scheme 2a).

The heterogeneous catalytic hydrogenation of pyridines is usually performed in acidic media.[7] Protonation not only activates the pyridines for hydrogenation, it also suppresses catalyst poisoning by the resulting piperidines. We reasoned that single-point attachment of chiral oxazolidinones activates the pyridines for hydrogenation, it also suppresses catalyst poisoning by the resulting piperidines. We reasoned that single-point attachment of chiral oxazolidinones]](4)[8] for ease of introduction of the auxiliary in the 2-position of the pyridine would be ideal (Scheme 2a). Moreover, it occurred to us that whereas conformation 2 should be strongly preferred for unprotonated pyridines due to dipole-moment minimization, upon protonation hydrogen bonding between the pyridinium and the oxazolidinone moiety would favor conformation 5, in which the auxiliary is oriented coplanar with the pyridine ring but rotated by 180°. Indeed, on hydrogenation the tPr substituent shields one of the diastereotopic π-faces and selective hydrogen transfer to the opposite side leads to aminal 6 (Scheme 2b).[9-10]

Substrates 2 can be readily synthesized from oxazolidinones and the corresponding 2-bromo- or chloropyridines 1 by copper catalysis (Scheme 2a).[11] Gratifyingly, hydrogenation of pyridine 2d in acetic acid under a hydrogen atmosphere of 100 bar with Pto2 as the catalyst led to the formation of (S)-3-methyl piperidine (3d) in 85% ee. Different catalysts were screened, and Pd(OH)2/C was identified as the optimum catalyst, providing 3d in 98% ee (Table 1, entry 4).[14] Importantly, the reaction does not stop at aminal 6d, but leads directly to piperidine 3d and oxazolidinone 4. Evidently traceless[15] cleavage of the auxiliary occurs under the reaction conditions, thereby combining chirality transfer from and release of the auxiliary into a single operation. We were pleased to find that after treatment of the crude reaction mixture with hydrochloric acid, separation and purification of the less soluble piperidine hydrochloride 3d and the more soluble auxiliary could be achieved efficiently by simple extraction with ether/hexanes mixtures. The piperidine hydrochloride 3d was obtained in 90% yield (98% ee) and 4 was recovered unchanged (93% yield, > 99% ee), allowing the recycling of the auxiliary.

This method for the stereoselective synthesis of piperidines has been applied successfully to a large number of substrates, whereby the oxazolidinone with a Bu group often resulted in slightly improved ee values relative to those obtained with the tPr group (Table 1).[12] Substituents in the 4-, 5- or 6-position of the 2-oxazolidinone-substituted pyridine can be used to create stereocenters at the corresponding positions (entries 1–7). Even multiple stereocenters can be generated, as exemplified by the stereoselective formation of di- and trisubstituted piperidines in near-quantitative yield and excellent enantioselectivities (entries 9, 10). As far as we know this is the first highly asymmetric hydrogenation of an aromatic compound that selectively generates three stereocenters. Under milder conditions we even succeeded in the stereoselective synthesis (> 95:5) of aminal 6j, which bears four new chiral centers (entry 11). Furthermore, functional groups on the pyridine ring are well tolerated (entries 3, 5–6). The versatility of the process can be increased still further, since hydrogenation of 2d in the presence of acetaldehyde or acetic anhydride results in the formation of the corresponding (S)-N-ethylpiperidine 7 (entries 12, 13).[16] The only present limitation concerns 3-substitution of the pyridine ring. A methyl substituent in the 3-position leads to a less reactive substrate, presumably because the oxazolidinone is rotated out of the plane of the pyridine ring thereby shielding both π-faces. Hydrogenation of 2h results in a nearly racemic product (entry 8). Finally, we were pleased to find that our method gives easy access to conine (3b), the poisonous hemlock alkaloid, in excellent yield and enantiomeric excess (entry 2).
A plausible mechanism is depicted in Scheme 3. Saturation of the pyridinium ring in 5 presumably results in the stereoselective formation of aminal 6. Disintegration of 6 into the oxazolidinone and iminium salt 8, which is in equilibrium with the respective enamion salt 9, is followed by hydrogenation of the resulting C–N or C–C double bond leading to the observed product 3 in high optical purity. The involvement of achiral 9h in the hydrogenation of 2h might explain the observed formation of nearly racemic product (entry 8).

In summary, we describe a conceptually novel, practical, and efficient synthesis of optically active piperidines, an important substructure of many biologically active compounds. This process is distinguished by the fact that piperidines with multiple stereocenters can be formed in very good yields and excellent optical purities. To the best of our knowledge, this transformation unites for the first time highly selective chirality transfer and nondestructive and traceless cleavage of the chiral auxiliary in one reaction. In addition, the piperidinium hydrochloride and the auxiliary can be separated easily by extraction and the auxiliary recycled.

**Experimental Section**

Typical experimental procedure: No special care was taken to exclude air or moisture. A mixture of wet 20% Pd(OH)$_2$/C (w/w, 140 mg),...
substrate 2b (524 mg, 2 mmol), and acetic acid (15 mL) was stirred in an autoclave under a hydrogen atmosphere (100 bar) at 40°C for 22 h. The mixture was filtered through a short pad of Celite, which was subsequently washed with MeOH (15 mL). Hydrochloric acid (333 µL, 4.0 mmol) was added, and the solvent was removed by rotary evaporation until no acetic acid was left. The ee value of 3b was determined to be 95% by GC analysis of the N-trifluoroacetamide derivative of the crude reaction product. The remaining white solid was washed repeatedly with methyl tert-butyl ether/hexanes to yield hydrochloride 3b (310 mg, 95%, 96% ee) as a white solid. Evaporation of the organic phase left behind (S)-Bu-oxazolidinone (251 mg, 88%) as a white solid. All new compounds were fully characterized. The sources and types of catalysts used are given in the Supporting Information.

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[9] It is generally accepted that the hydrogen atoms are transferred to the face of the pyrimidinium ring that is adsorbed on the catalyst. Stepwise hydrogenation may give rise to partially hydrogenated species with different coordination modes. See: L. A. M. M. Barbosa, P. Sautet, J. Catal. 2003, 217, 23.

[10] In some cases the hydrogenation can be stopped at aminal 6, e.g. in the case of 6g or 6j. An investigation of their synthetic utility is ongoing and will be reported in due course.

[11] The DFT calculations for 2g and 5g are supported by comparable X-ray structures of 2e (CCDC-230262) and 5d/bf (CCDC-230264), respectively.

[12] The absolute stereochemistry of the products was determined unequivocally by comparison of optical rotation data with literature values (3a, 3b, 3d: N-Boc derivative of 3e), by X-ray analysis of 3i (CCDC-230263), 6g (CCDC-230265), 6j (CCDC-230266), and 7 (CCDC-230267) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

[13] The reaction conditions are closely related to those developed by Buchwald et al. for the amidation of aryl halides: A. Klapars, X. Huang, S. L. Buchwald, J. Am. Chem. Soc. 2002, 124, 7421. Our general protocol (Cul, ligand, K2CO3, toluene, 140 °C) varies in the choice of the optimal ligand; whereas less reactive substrates benefit from the use of N,N′-dimethylethyldiamine, phe- nanthroline proved to be superior for more reactive substrates. Catalyst screening in AcOH, 100 bar H2, 20 h ([catalyst % conversion of substrate, % ee]: 5% Ru/C [15, n.d.], PtO2 [100, 85], 10% Pt/C [100, 85], 5% Rh/C [100, 85], 0.5% Rh/4.5% Pd/C [100, 94], 10% Pd/C [100, 97], 20% Pd(OH)2/C [100, 98]. In all cases the S enantiomer is formed predominantly.


[16] Whereas the reaction with acetaldehyde can be explained as a reductive amination, the reaction with acetic anhydride is less well understood since amides seem to be tolerated under the reaction conditions (see Table 1, entry 6).