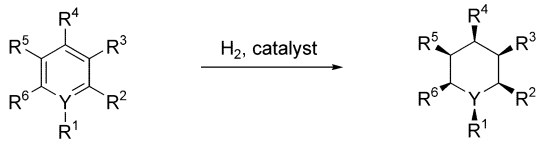
Asymmetric Synthesis

Efficient Asymmetric Hydrogenation of Pyridines**

Frank Glorius, Nick Spielkamp, Sigrid Holle, Richard Goddard, and Christian W. Lehmann*

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



Scheme 1. Stereoselective hydrogenation of (hetero)aromatic compounds ($YR^1 = CR^1$, N).

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 ($YR^1 =$ N),[5] which enables the stereoselective formation of piperidines[6] with up to four new chiral centers in a single operation (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 **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 *i*Pr 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).[13] Gratifyingly, hydrogenation of pyridine **2d** in acetic acid under a hydrogen atmosphere of 100 bar with PtO_2 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 piperidinium 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 *t*Bu group often resulted in slightly improved *ee* values relative to those obtained with the *i*Pr 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 coniine (**3b**), the poisonous hemlock alkaloid, in excellent yield and enantiomeric excess (entry 2).

[*] Dr. F. Glorius, N. Spielkamp, S. Holle, Dr. R. Goddard,[+] Dr. C. W. Lehmann[+]
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2994
E-mail: glorius@mpi-muelheim.mpg.de

[+] X-Ray structure analyses.

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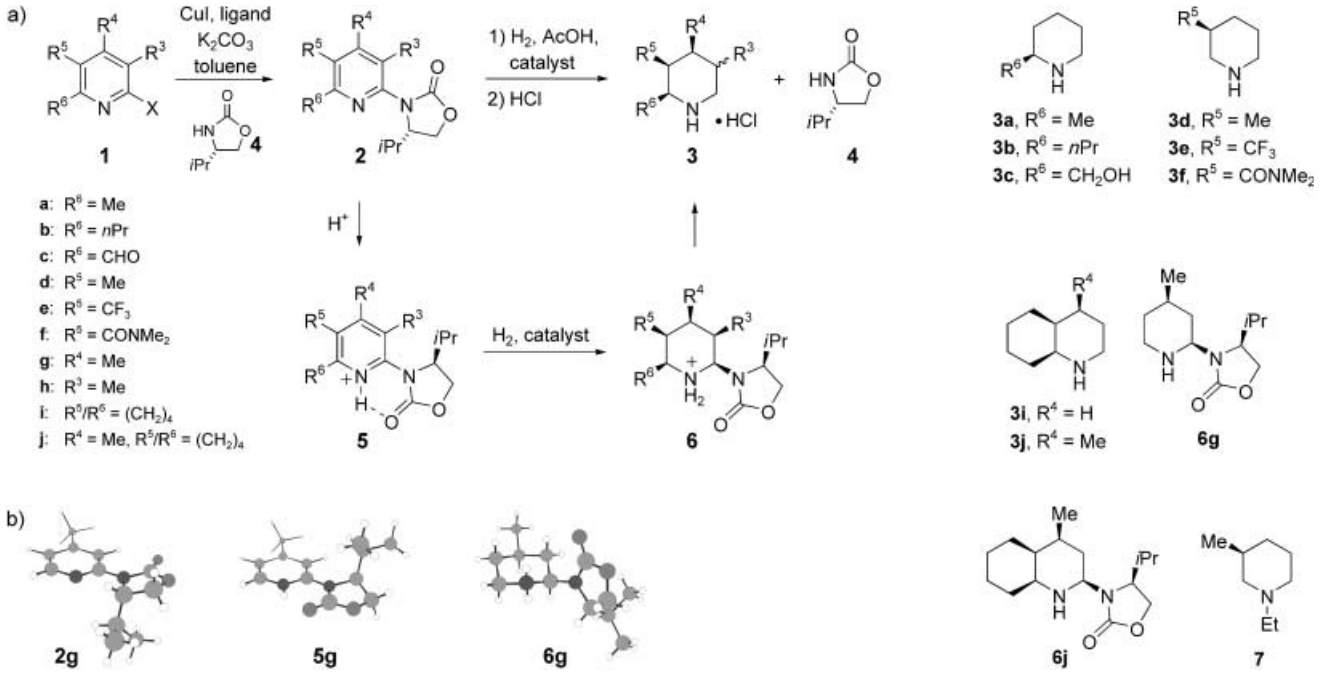


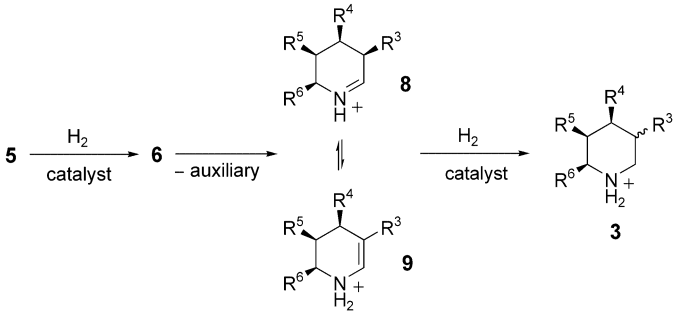
Scheme 2. a) Synthesis and asymmetric hydrogenation of oxazolidinone-substituted substrates **2** (X = Br, Cl). b) DFT-generated structures **2g** and **5g**[11] and X-ray structure **6g** (chloride anion omitted for clarity).[12]

Table 1: Asymmetric hydrogenation of oxazolidinone-substituted pyridines **2** according to Scheme 2.[a]

Entry	2	Prod. (HCl salt)	Cat.	*T* [°C]	*t* [h]	Yield [%]	*ee*[b] [%]
1	**a**	**3a**	$Pd(OH)_2/C$	50	22	93	91
2	**b**[n]	**3b**	$Pd(OH)_2/C$	40	22	95	95
3	**c**[c, n]	**3c**	$Pd(OH)_2/C$	25	20	64[d]	97
4	**d**	**3d**	$Pd(OH)_2/C$	25, 65[e]	24, 3[e]	90	98
5	**e**[n]	**3e**	$Pd(OH)_2/C$	25	26	93	95
6	**f**[n]	**3f**	$Pd(OH)_2/C$	45	22	92	85
7[f,g]	**g**	**6g**	PtO_2	25	20	87	> 95:5[h]
8	**h**	**3d**	Rh/C	25	72	100[i]	4
9	**i**[n]	**3i**	Rh/Pd/C	40	22	94[k]	96
10[f]	**j**	**3j**	Rh/C	40, 75	24, 18	92[k]	94
11	**j**	**6j**	Rh/Pd/C	40	40	63	> 95:5[h]
12[l]	**d**	**7**	$Pd(OH)_2/C$	25	22	87	93
13[m]	**d**	**7**	$Pd(OH)_2/C$	25	22	81	95

[a] General conditions: 2-mmol scale, AcOH (0.13 M), 100 bar H_2. [b] Enantiomeric excess determined by GC analysis of the *N*-trifluoroacetamide derivatives of the crude reaction products. [c] R^6 = CHO. [d] Product purified as *N*-Boc derivative. [e] 25 °C for 24 h, then 65 °C for 3 h. [f] 150 bar H_2. [g] Conc. hydrochloric acid (6 equiv) and MeOH used as solvent. [h] Diastereoselectivity determined by NMR. [i] Conversion, determined by GC-MS. [k] *syn*/*anti* > 100:1. [l] MeCHO (4 equiv) added. [m] Ac_2O (4 equiv) added. [n] In these cases, the catalyst **4** with a *t*Bu group instead of the *i*Pr group was used.

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**,[9] which is in equilibrium with the respective enaminium 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



Scheme 3. Probable mechanism for the asymmetric hydrogenation giving piperidinium salts **3**.

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*)-*t*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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Keywords: asymmetric synthesis · chiral auxiliaries · heterogeneous catalysis · hydrogenation · piperidines

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[9] It is generally accepted that the hydrogen atoms are transferred to the face of the pyridinium 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 **2c** (CCDC-230262) and **5d**/BF_4 (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 **3c**), by X-ray-analysis of **3i** (CCDC-230263), **6g** (CCDC-230265), **6j** (CCDC-230266), and **7** (CCDC-230267). CCDC 230262–230267 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 (CuI, ligand, K_2CO_3, toluene, 140 °C) varies in the choice of the optimal ligand: whereas less reactive substrates benefited from the use of *N*,*N*′-dimethylethylendiamine, phenanthroline proved to be superior for more reactive substrates.

[14] Catalyst screening in AcOH, 100 bar H_2, 20 h (catalyst [% conversion of substrate, % *ee*]): 5% Ru/C [15, n.d.], PtO_2 [100, 85], 10% Pt/C [100, 85], 5% Rh/C [100, 86], 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.

[15] Cleavage of a chiral auxiliary often leaves behind an undesired functional group, whereas in this case, a C–H bond is formed on the parent molecule. The term "traceless cleavage" is usually used in the context of traceless linkers: S. Bräse, S. Dahmen, *Chem. Eur. J.* **2000**, *6*, 1899.

[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).

