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Diastereoselective Hydrogenation of Substituted Quinolines to Enantiomerically Pure Decahydroquinolines

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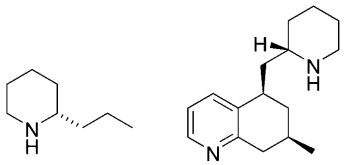
Abstract: The stereoselective hydrogenation of auxiliary-substituted quinolines was used to build up saturated and partially saturated heterocycles. In a first step, the formation and diastereoselective hydrogenation of 2-oxazolidinone-substituted quinolines to 5,6,7,8-tetrahydroquinolines is reported. In this unprecedented process, stereocenters on the carbocyclic quinoline ring were formed with a *dr* of up to 89:11. Platinum oxide as a catalyst and trifluoroacetic acid as a solvent were found to be optimal for high levels of chemo- and stereoselectivity in this step. In a second hydrogenation step, the completely saturated decahydroquinolines with 4 newly formed stereocenters were obtained with enantioselectivities of up to 99%. Rhodium on carbon as a catalyst and acetic acid as a solvent gave the best results for this hydrogenation and allowed a traceless cleavage of the chiral auxiliary. Thus, this new method allows an efficient stereoselective synthesis of valuable 5,6,7,8-tetrahydro- and decahydroquinoline products.

Keywords: asymmetric synthesis; chiral auxiliaries; decahydroquinolines; heterocycles; hydrogenation

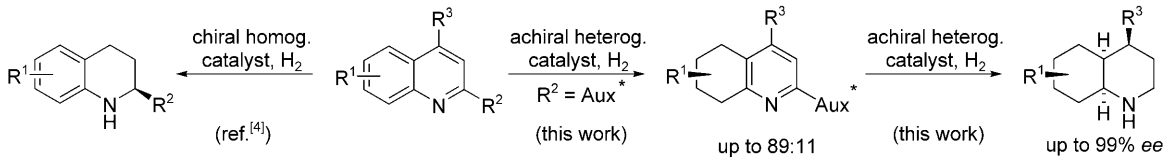
Enantiomerically pure saturated or partially saturated heterocyclic compounds are important building blocks and fragments of many biologically active compounds like coniine, the poisonous alkaloid of hemlock, or the multiply substituted *Lycopodium alkaloids*.[1] The asymmetric hydrogenation of heteroaromatic substrates presents an attractive strategy for their preparation and the last years have seen many significant contributions to this field.[2] For example, several different approaches have been reported for the asymmetric hydrogenation of pyridines: e.g., Charette



Coniine Lycoposerramine-V

et al. developed a highly selective Ir-catalyzed homogeneous hydrogenation of pyridine ylides,[3d] Zhang and Lei used a sequential combination of heterogeneous and homogeneous hydrogenation,[3c] Rueping et al. reported an organocatalytic approach employing chiral Brønsted acids, using a Hantzsch ester as the reducing agent.[3b] Whereas all these methods employ chiral, enantiomerically pure catalysts, Glorius et al. developed an efficient hydrogenation of chiral oxazolidinone-substituted pyridines using achiral heterogenous hydrogenation catalysts like $Pd(OH)_2/C$.[3e,f] In this latter reaction, the auxiliary was cleaved under the reaction conditions and fully saturated piperidines with up to 4 newly formed stereocenters and high *ee*s (85–98%) were obtained. Significantly more methods have been reported for the asymmetric (partial) hydrogenation of quinolines. Since the aromatic stabilization of the second aromatic ring in bicyclic aromatics is somewhat lower, hydrogenation of the annulated ring is significantly facilitated. Most of these methods employ homogeneous iridium, rhodium or ruthenium complexes of chiral ligands[4a–n] together with molecular hydrogen or, alternatively, chiral Brønsted acids as organocatalysts[4o,p] in transfer hydrogenations (Scheme 1).[2]

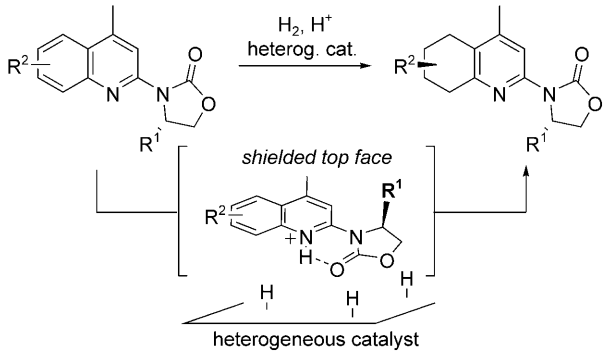
However, despite these advances in the area of asymmetric hydrogenation of (hetero)aromatics, many challenges remain. For example, the asymmetric hydrogenation of benzene rings is still an unsolved, though important task. Consequently, whereas the asymmetric hydrogenation of substituted quinolines to 1,2,3,4-tetrahydroquinolines with a newly formed



Scheme 1. Asymmetric homogeneous hydrogenation of quinolines.

stereocenter in the 2-position has been reported several times,[4] the asymmetric hydrogenation of quinolines to 5,6,7,8-tetrahydroquinolines or to enantiomerically pure decahydroquinolines with stereocenters in the cyclohexane ring fragment has not been described to the best of our knowledge. Herein we report the first (asymmetric) hydrogenation of auxiliary-substituted quinolines to selectively form chiral 5,6,7,8-tetrahydroquinolines. Furthermore, the successive hydrogenation leading to enantiomerically pure decahydroquinolines with a total of 4 stereocenters, 3 of them in the cyclohexane ring fragment is described (Scheme 1).

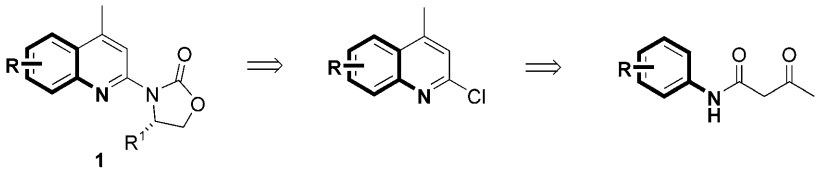
We reasoned that an auxiliary-based approach could lead to high levels of stereoselectivity in building up stereocenters on the benzene ring[2d,e] of the quinoline system. The hydrogenation of 2-oxazolidinone-substituted quinolines seemed attractive. In acidic media, a hydrogen bond should result in a rigid structure, in which the top face would be shielded by the R^1 substituent of the chiral auxiliary (Scheme 2). The bottom face would be accessible for adsorption to the heterogeneous catalyst and would thus receive the hydrogen atoms, resulting in the stereoselective formation of a new stereocenter.[3f] The required substrates **1** were prepared starting from commercially



Scheme 2. Asymmetric heterogeneous hydrogenation of pyridines – mode of action of the chiral auxiliary.[3f]

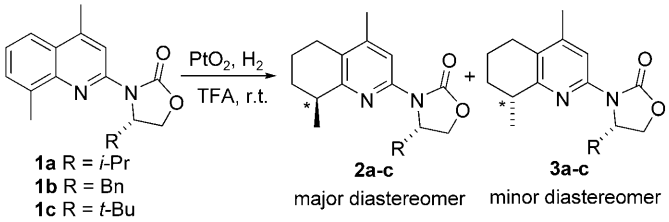
available anilines through the corresponding acetoacetanilides and 2-haloquinolines (Scheme 3).[5,6]

Our goal was to develop methods for the partial hydrogenation to 5,6,7,8-tetrahydroquinolines as well as the hydrogenation to the fully saturated decahydroquinolines. Our study commenced with the partial hydrogenation of 4,8-dimethyl-2-oxazolidinone-substituted quinoline **1a**. It was unclear whether the highly regioselective hydrogenation of the carbocyclic ring of the quinolines would be possible, but some literature reports were promising.[7] Screening of different reaction parameters revealed the catalyst and especially the solvent to be critical factors for the selectivity of the hydrogenation of the benzene ring. Gratifyingly, Adam's catalyst (PtO_2) and the solvent trifluoroacetic acid (TFA) were found to be optimal to provide high levels of reactivity and selectivity for the desired hydrogenation to the 5,6,7,8-tetrahydroquinoline **2a** (Table 1).[6] After 20 h reaction time under these reaction conditions with a hydrogen pressure of 20 bar, complete and selective conversion to the desired 5,6,7,8-tetrahydroquinolines in a diastereomeric ratio of 89:11 was observed (entry 3). When the less acidic AcOH was used as a solvent the chemoselectivity of the reaction was decreased and partial hydrogenation of the pyridine ring occurred (not shown).[6] Furthermore, an H_2 pressure of 5 bar was still found to be sufficient for complete conversion and the selectivity of the reaction was not affected by different H_2 pressures between 1 and 70 bar (entries 1–4). Amazingly, and unlike in many other applications of oxazolidinones,[8] the isopropyl group proved to be the best substituent on the chiral auxiliary for obtaining high selectivities in this transformation. Benzyl- and *tert*-butyl-substituted oxazolidinones were significantly less selective (entries 5–7). This is attractive, since the *i*-Pr-substituted auxiliary is stable under the hydrogenation conditions (unlike the benzyl derivative) and can be synthesized from the naturally occurring and cheap amino acid L-valine.



Scheme 3. Retrosynthesis of the substrates.[6]

Table 1. Influence of hydrogen pressure and the substituent of the chiral auxiliary.[a]



Entry	Substrate	Pressure [bar]	*dr* **2**:**3**[b]
1	**1a**	1	89:11[c]
2	**1a**	5	89:11
3	**1a**	20	89:11
4	**1a**	70	89:11
5	**1b**	5	82:18[d]
6	**1b**	20	79:21
7	**1c**	20	84:16

[a] *General procedure:* **1** (40 mg), PtO_2 (8 mg, 20 wt%), and TFA (1 mL) were stirred in an autoclave under a hydrogen atmosphere at room temperature for 20 h. In each case, unless otherwise mentioned, clean reactions and full conversion was obtained.
[b] *dr* determined by GC.
[c] Incomplete conversion.
[d] 54 h reaction time.

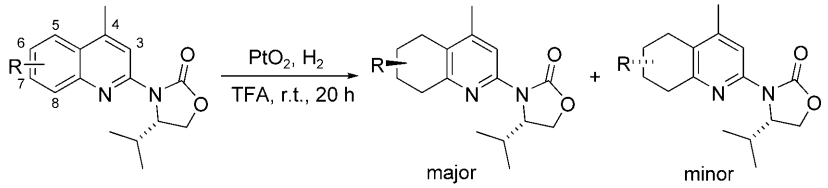
Differently substituted quinolines **1** were hydrogenated under the optimized conditions (Table 2). The determination of the diastereomeric ratio was slightly more complicated for products **2/3d** and **2/3e**. The two stereocenters are separated by 6 or 7 bonds and the diastereomers – obviously behaving more like enantiomers – could not be separated by using GC or HPLC with columns containing achiral phases; on NMR no baseline resolution was achieved. Only by using a column with a chiral stationary phase could a separation be achieved. The results show a decrease of selectivity the more bonds are located between the newly formed stereocenters and the chiral auxiliary (entry 1: 5 bonds, entry 3: 7 bonds). In all cases one main diastereomer (**2**) formed preferentially.

To analyze the stereochemistry of the products, the minor diastereomer **3a** was isolated in pure form and crystallized. Its structure, and consequently also the one of the major diastereomer **2a**, was unequivocally proven by single crystal X-ray analysis (Figure 1).[9]

The methyl-substituted tetrahydroquinolines **2** were further hydrogenated to the decahydroquinolines. Gratifyingly, traceless cleavage[10] of the chiral auxiliary occurred in the course of the reaction. Optimization of the reaction conditions showed Rh/C as a catalyst, acetic acid as solvent at 150 bar and elevated temperatures to be optimal. The results are shown in Table 3.

The decahydroquinolines could be isolated as the corresponding hydrochlorides in 72–99% yield. As expected, the hydrogenation is highly *cis*-selective and the diastereomeric ratio of the products depends on the *dr* of the starting material. The *ee* of the major diastereomer was found to be very high in each case (97–99% *ee*), whereas the *ee* of the minor diastereomer was only moderate. One reason for the latter observation might be the influence of the initially formed stereocenter in the 6-, 7- or 8-position (matched/mismatched case). However, the directing

Table 2. Hydrogenation of differently methyl-substituted quinolines.[a]



Entry	Substrate	Isolated Yield[b]	*dr* **2**:**3**
1	**1a**	95%	89:11[c]
2	**1d**	91%	86:14[d]
3	**1e**	99%	81:19[d]
4	**1f**	94%	78:10:5:7[d]

[a] *General procedure:* substrate (300 mg), PtO_2 (60 mg, 20 wt%) and TFA (3 mL) were stirred in an autoclave under a hydrogen atmosphere (20 bar) at room temperature for 20 h.
[b] After purification by column chromatography.
[c] Determined by GC.
[d] Determined by HPLC using a Chiralcel AD-H column.

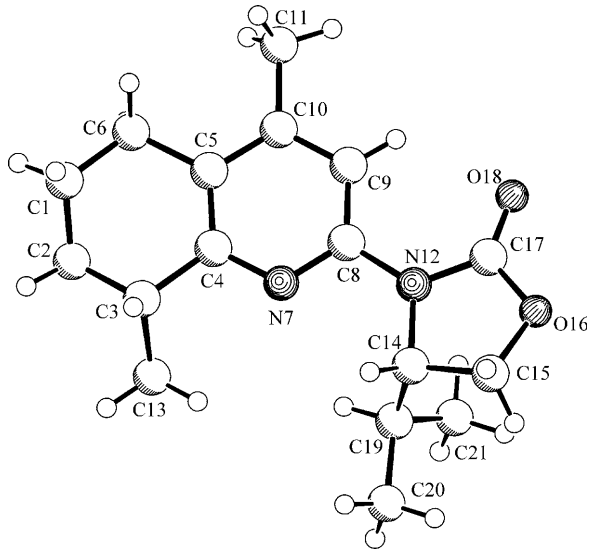


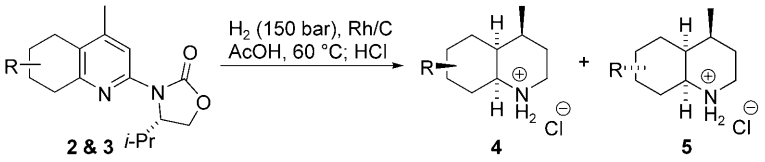
Figure 1. Crystal structure of the minor diastereomer **3a**.

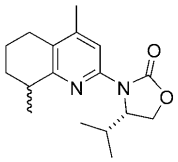
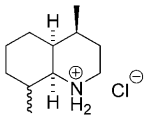
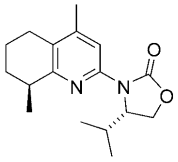
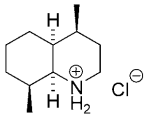
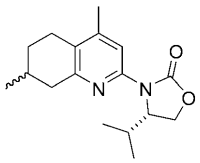
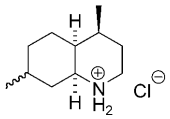
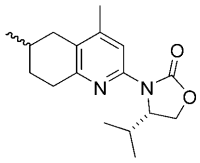
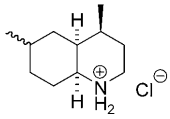
power of the chiral auxiliary is still stronger than the one of the methyl group and the stereochemical outcome of the reaction can be explained by Horeau's principle[11] as shown in Scheme 4.

To prove the relative and absolute stereochemistry, one of the products, **4a**, was crystallized and examined by single crystal structural analysis. The structure of decahydroquinoline·HCl **4a** is shown in Figure 2.[9]

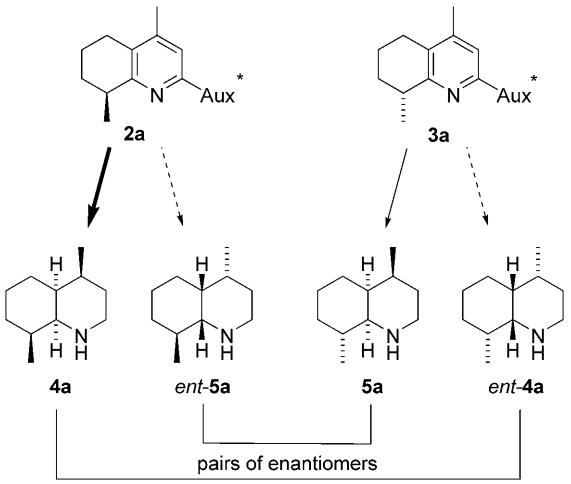
In conclusion, we have demonstrated a new and, arguably, the first strategy for the stereoselective formation of chiral 5,6,7,8-tetrahydro- and decahydroquinolines with newly formed stereocenters in the cyclohexane ring. Remarkably, in these cases the chiral auxiliary can influence the formation of a new stereocenter over a wide distance, namely 5 to 7 bonds away from its own stereocenter. Whereas the known hydrogenation methods are limited to the formation of 1,2,3,4-tetrahydroquinolines mostly with a stereocenter in the 2-position only, our method was demonstrated to

Table 3. Second hydrogenation step to decahydroquinolines.



Entry	Substrate	*dr*	Product	*dr* **4**:**5**[b,c]	*ee*[d]	Isolated yield of the hydrochlorides **4** and **5**
1		89:11		87:13	99% (**4a**); 72% (**5a**)	81%[e]
2				>97:3	>99% (**4a**)	99%
3		88:12		85:15	97% (**4d**); 48% (**5d**)	72%[f]
4		81:19		79:21	97% (**4e**); 68% (**5e**)	86%

[a] *General procedure:* substrate (200 mg), catalyst (20–25 wt%) and acetic acid (3 mL) were stirred in an autoclave under a hydrogen pressure (150 bar) at 60 °C for 60–84 h.
[b] Diastereomeric ratio of the crude product was determined by GC analysis.
[c] Other diastereomers <5%.
[d] *ee* determined by chiral GC.
[e] 48% yield, if only major diastereomer **4** was isolated.
[f] Only the major diastereomer **4** was isolated.



Scheme 4. Plausible explanation for the selectivities obtained in the hydrogenation to decahydroquinolines.

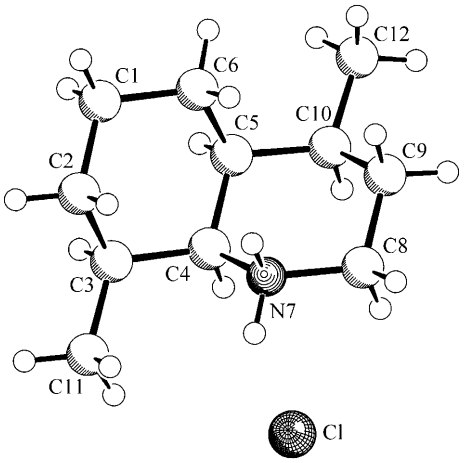


Figure 2. Single crystal structure of decahydroquinoline **4a**.

work for building up stereocenters in the 5-, 6-, 7- and 8-positions of the tetrahydroquinoline ring system. Furthermore, the auxiliary can be cleaved traceless-ly[10] in a second hydrogenation step, resulting in the formation of the corresponding decahydroquinolines with up to 99% *ee*, containing up to 4 stereocenters. The development of efficient hydrogenation methods for the asymmetric formation of heterocyclic compounds is ongoing in our laboratories.

Experimental Section

General Procedure for the Hydrogenation of 2-Auxiliary-Substituted Quinolines to 5,6,7,8-Tetrahydroquinolines

A mixture of substituted (*S*)-3-(quinoline-2-yl)-4-isopropyloxazolidinone (300 mg), platinum oxide (60 mg, 20 wt%) and trifluoroacetic acid (3 mL) was stirred in an autoclave under a hydrogen atmosphere (20 bar) at room temperature for 20 h. After releasing the hydrogen pressure, the reaction mixture was filtered through celite to remove the catalyst. The filtrate was concentrated under reduced pressure. The residue was taken up with MTBE (30 mL) and the organic layer was washed with saturated aqueous Na_2CO_3 solution. The aqueous layer was extracted with MTBE (2×30 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography or recrystallization.

General Procedure for the Hydrogenation of 5,6,7,8-Tetrahydroquinolines to Decahydroquinolines

A mixture of 5,6,7,8-tetrahydroquinoline (200 mg), Rh/C (40 mg, containing 5 wt% Rh) and acetic acid (3 mL) was stirred in an autoclave under a hydrogen atmosphere (150 bar) at 60 °C for 60 to 84 h. After releasing the hydrogen pressure, the reaction mixture was filtered through celite. 3 mL of HCl in MeOH ($c=1$ mol/L) were added to the filtrate. The filtrate was concentrated under reduced pressure. The crude product was taken up with a small amount of CH_2Cl_2, washed with saturated aqueous Na_2CO_3 solution, dried over Na_2SO_4 and purified by flash chromatography (CH_2Cl_2/MeOH, 10:1→5:1, height: 5 cm). Before the solvent was removed, an excess of HCl was added to convert the volatile products into non-volatile hydrochloride derivatives.

Acknowledgements

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