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Substrate Induced Diastereoselective Hydrogenation/Reduction of Arenes and Heteroarenes

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Chiral, either racemic or optically pure, substituted cylohexanes, piperidines, tetrahydrofurans and pyrrolidines can be prepared by the diastereoselective hydrogenation/reduction of the corresponding aromatic and heteroaromatic precursors, exploiting the presence of one or more stereocenters present in the ring substituent(s), where the sense and level of asymmetric induction can be the result of different factors: the rigidity or flexibility of the substrate, the presence of a proper functionality in the lateral substituent which can stabilize a particular conformation of the molecule, especially in pyridine and furan derivatives, the nature of the catalyst or the reducing system, and the experimental conditions.

1. Introduction

The reduction of properly substituted aromatic and heteroaromatic rings leads to the corresponding partially or totally saturated carbocyclic and heterocyclic compounds with one or more ring carbon stereocenters. Stereocontrol in these reductions is important because substituted saturated rings with defined configuration are common structural features of biologically or pharmacologically active molecules. The relative configuration of one or more newly formed stereocenter(s) in the saturated ring (simple diastereoselectivity) is dependent on the reduction method, which include: a) electron transfer from an active metal, b) dihydrogen addition or c) hydride attack. On the other hand, control of the absolute stereochemistry can be achieved by one of three general methodologies. Asymmetric induction can be provided by a stereocenter present in a ring substituent, whose configuration will be preserved in subsequent transformations leading to the desired target compound (substrate induced diastereoselectivity). By this strategy, it is also possible to start from a racemic compound, in this case only the relative stereochemistry of old and new stereocenters can be controlled, and after separation of diastereomers a resolution step must be performed to obtain the desired optically active target. In a second approach, a chiral, configurationally pure functional group can be introduced temporarily in the substituent of the aromatic ring and it is then removed after the stereocontrolled reduction step (auxiliary induced diastereoselectivity). A third option, which is in principle more advantageous, is the use of a chiral catalytic system (reagent induced stereoselectivity). In this case a chiral ligand is generally used to coordinates the transition metal center, so forming a soluble complex (homogeneous catalysis). Alternatively using a heterogeneous supported catalyst, the chiral ligand can be bound to either the metal or the insoluble support.

An early review that appeared in 1996 was concerned with dissolving metal reduction and catalytic hydrogenation of arenes and heteroarenes.[1] The auxiliary induced, diastereoselective heterogeneous hydrogenation of arenes was reviewed in 1998 for substituted benzene and furan derivatives.[2] More recently, methods for the asymmetric hydrogenation of benzene, pyridine, pyrrole and furan derivatives with homogeneous and heterogeneous catalysts have been reviewed.[3] All these reviews only covered the items of auxiliary- and reagent-induced stereoselective hydrogenations. On the other hand, at our knowledge, an exhaustive survey of diastereoselective reductions performed on chiral aromatic substrates, either racemic or optically active, has never appeared in the literature, apart a review in 2000 dealing with the synthesis of enantiopure indolizidines from pyrrole building blocks, that includes the diastereoselective hydrogenation of pyrroles bearing stereodefined *N*-substituents derived from natural α-amino acids.[4] Examples of substrate induced diastereoselective hydrogenations of aromatic compounds were also included in the Pinel's review in 2003. Thus, we aimed to provide to the readers a possibly exhaustive survey of the known methods, mainly the catalytic heterogeneous hydrogenation, for the reduction of substituted benzene, pyridine, pyrrole and furan derivatives, all bearing at least one stereocenter in the ring substituent. This search has allowed to get useful information on the factors affecting the diastereoselectivity, and, possibly, to choose the most convenient and effective methodology to get the desired chiral target.

A convenient synthetic strategy to achieve the stereoselective reduction of (hetero)aromatic rings exploits the asymmetric induction of a stereocenter already present in a

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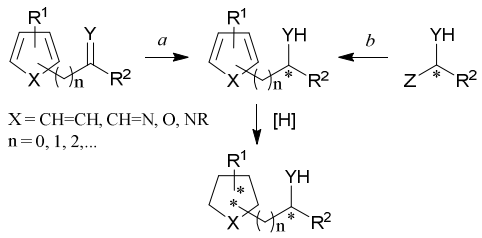


Scheme 1

ring substituent (Scheme 1). Such an intermediate can be obtained by the proper transformation of a prochiral group present in the ring substituent (route *a*), e.g. by reduction of a carbonyl or an imine function in a stereoselective fashion (auxiliary-induced diastereoselectivity or reagent-induced stereoselectivity). The stereo-inducing asymmetric center can be also created *in situ* during the hydrogenation process, provided that the prochiral functional group is reduced prior to the arene ring. Alternatively, the crucial intermediate can be prepared by transformation of an optically active molecule while retaining the innate stereochemistry (ex-chiral pool synthesis, route *b*). Both routes *a* and *b* usually lead to mixtures of diastereoisomers which can be separated by crystallization or chromatographic techniques. The isolated diastereomers are enantiomerically pure when the induced stereocenter in the precursor is configurationally pure. On the other hand, when the chiral substrate or intermediate is racemic, a resolution process must be applied to the diastereoisomers of the reduced product to obtain optically active/pure compounds.

In this review we report the hydrogenation of both racemic and optically pure compounds possessing arene or heteroarene rings. Examples, even recently reported, where the configuration of the reduced products were not determined are reported for sake of knowledge. The steps required for the preparation of the crucial intermediate to be reduced, or the final target of the overall synthetic sequence, are not always illustrated, apart for special cases.

This review is divided in sections according to the nature of the aromatic ring which undergoes reduction in the crucial intermediate, even if this is not isolated in a multistep process: benzene, pyridine, furan, and pyrrole. The asymmetric hydrogenation of thiophene derivatives is apparently not achievable because of catalyst poisoning by sulfur compounds. The reduction of the (hetero)arene rings is achieved most often by heterogeneous hydrogenation with traditional catalysts, e.g. Adams platinum catalyst (PtO_2 being reduced *in situ* to Pt), Raney nickel or noble metals supported on a variety of inorganic matrices, as this protocol presents the advantage of the ready separation of the catalyst from organic materials and drastically reduces the contamination of the isolated organic products by a metal species. Other methods, e.g. dissolving metal, borane and borohydride reductions, and other novel methods are eventually reported for comparison to traditional hydrogenation reactions. In all Schemes the crucial experimental conditions (catalyst or reducing agent, solvent, H_2 pressure, temperature) are reported, allowing comparison between different methods. If not otherwise stated, reactions were performed at 1 atmosphere and room temperature.

2. Steric, haptophilic and conformational effects in the hydrogenation of benzene derivatives

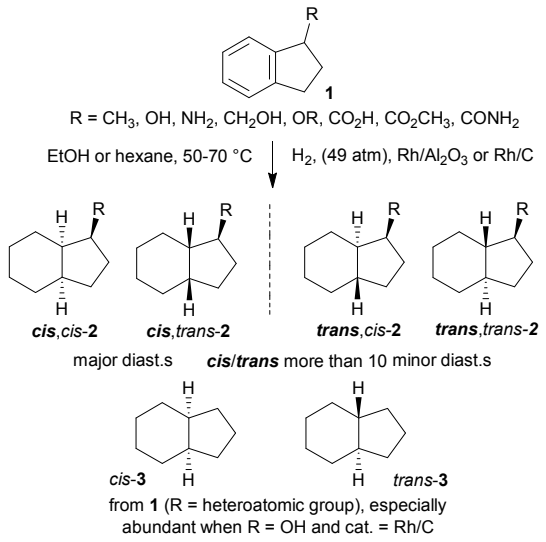
2.1. Substituted indanes

Hydrogenation of a series of racemic indanes bearing a substituent on the partially saturated ring were performed using heterogeneous rhodium catalysts (5% Rh/C or 5% Rh/Al_2O_3) under 49 atm of H_2 pressure at room temperature in ethanol or *n*-hexane as the solvent (Scheme 2 and Table 1).[5] Four diastereomers of the fully saturated products were obtained when using Rh/C as the catalyst in ethanol, and deoxygenated products **3** were largely or in part formed from 1-indanylmethanol (entries 3 and 4), 1-indanol (entries 6 and 9) and the corresponding propyl ether (entry 17). This side reaction could be largely or almost completely avoided in the presence of triethylamine (entry 7) or aqueous bases, although at the expense of the activity of the catalyst, and when using Rh/Al_2O_3 as catalyst (entries 5, 10, 11, 15 and 16), especially in *n*-hexane as the solvent. On the other hand, hydrogenolysis of the C-N bond in 1-aminoindane was not observed.

Owing to the approximate planarity of the substrates and their rigidity, as well as the close proximity of the stereogenic center to the prochiral arene sp^2-carbons, the influence of the substituent on the relative configuration of the newly formed stereocenters could be easily appreciated. The stereochemical outcomes of the hydrogenation reactions were scarcely affected by the substrate/catalyst ratio and the hydrogen pressure. The fully saturated products **2** had prevalently the ***cis*** ring junction of the fused rings, as expected, with a *cis* selectivity of the substituent generally higher than 91%. On the other hand, the relative configuration of the substituted carbon and the contiguous stereocenter was not affected by either the catalyst and the solvent, whereas the nature of the R substituent had a relevant role.

The so called "catalyst hindrance" had been previously proposed by Linstead to explain the outcomes of hydrogenation reactions performed on compounds containing one or more aromatic rings.[6] This means that the adsorption of the arene moiety on the catalyst surface is affected by the hindrance between the molecule and the catalyst. In other words, the molecule faces the catalyst from the side which allows a better adsorption owing to reduced repulsive steric interactions of the lateral substituents. Subsequent uptake of hydrogen atoms occurs to the same π face adsorbed to the catalyst surface. In the case of compounds of general structure **1**, adsorption of the arene ring is expected to take place preferentially to the less hindered face as depicted in Figure 1.

Steric effects of the substituent R would direct the addition of hydrogen to the π face *anti* to it (model **I**) and as a consequence the diastereomer ***cis***,*cis*-**2** would predominate.



Scheme 2

Conversely, the ability of the substituent to interact positively with the metal or the support, also termed "haptophilicity", would direct the hydrogen addition to the π face *syn* to the substituent (model **II**) producing the diastereomer ***cis***,*trans*-**2**. As a matter of fact, a moderate selectivity in favour of ***cis***,*cis*-**2** was observed in the case of 1-methylindane (entries 1 and 2) (Table 1), but the diastereomeric ratio was reduced in the reactions of 1-indanylmethanol and 1-indanol, where the steric effect were balanced by the haptophilicity of the OH group (entries 3-7, 9 and 11). Steric effects were predominant in case of OR, OH, CO_2H, CO_2Me, $CONH_2$ substituents and formation of ***cis***,*cis*-**2** was enhanced increasing the bulkiness of the substituent (entries 15-20). Conversely, ***cis***,*trans*-**2** was mainly produced by hydrogenation of 1-indanol in the presence of aqueous KOH (entry 8), and especially in the hydrogenation of 1-aminoindane where ***cis***,*trans*-**2** was produced almost exclusively (entries 12 and 13)

It is noteworthy that the haptophilicity of the hydroxy group towards the catalyst was only mild, in contrast to what was previously observed in the hydrogenation of highly hindered unsaturated alcohols.[7] This was explained by the stronger adsorption of the arene ring on rhodium with respect to the alkene, so that the interaction of hydroxy group with rhodium is relatively less important for indanol and indanylmethanol. Instead, amino group strongly interacts with the metal surface, resulting in high selectivity towards the *cis*,*trans*-**2** but also reducing the activity of the catalyst, therefore hydrogenation was conducted at 70 °C. The addition of inorganic bases in the hydrogenation of 1-indanol with Rh/C in EtOH reduced the hydrogenolysis reaction but also the activity of the catalyst. Moreover, the nature of the cation of the bases employed affected the diastereoselectivity, as the amount of *cis,trans*-**2** increased with increasing the size of the cation from Li to K, however, a convincing explanation of this effect was not provided.

Table 1. Hydrogenation of compounds **1**.[a]

Entry	**1** (R)	Catalyst	Solvent	**3** (Yield%)	***cis*-2** (Yield %)	***cis***,*cis*/ ***cis***,*trans*
1	Me	Rh/Al_2O_3	EtOH	-	92	64:36
2	Me	Rh/C	EtOH	-	93	63:37
3	CH_2OH	Rh/C	EtOH	30	70	45:55
4	CH_2OH	Rh/C	*n*-hexane	16	82	47:53
5	CH_2OH	Rh/Al_2O_3	EtOH	1	97	47:53
6	OH	Rh/C	EtOH	77	19	59:41
7	OH	Rh/C	EtOH[b]	-	97	50:50
8	**OH**	**Rh/C**	**EtOH**[c]	-	**89**	**15:85**
9	OH	Rh/C	*n*-hexane	42	55	47:53
10	OH	Rh/Al_2O_3	EtOH	10	88	65:35
11	OH	Rh/Al_2O_3	*n*-hexane	3	96	57:43
12	**NH_2**	**Rh/C**	**EtOH**[d]	-	**100**	**2:98**
13	**NH_2**	**Rh/Al_2O_3**	**EtOH**[d]	-	**100**	**1.5:98.5**
14	**NH_2**	Rh/Al_2O_3	EtOH[e]	-	90	32:68
15	**OMe**	**Rh/Al_2O_3**	**EtOH**	**4**	**91**	**88:12**
16	**OPr**	**Rh/Al_2O_3**	**EtOH**	**7**	**88**	**92:8**
17	OPr	Rh/C	EtOH	78	19	81:19
18	CO_2H	Rh/Al_2O_3	EtOH	-	e	84:16
19	CO_2Me	Rh/Al_2O_3	EtOH		e	85:15
20	$CONH_2$	Rh/Al_2O_3	EtOH		e	81:19

[a] **1**/Rh molar ratio 117 to 154, 49 atm of H_2 room temperature. [b] In the presence of Et_3N (Et_3N/Rh = 10). [c] In the presence of KOH (KOH/Rh = 6/1). [d] **1**/Rh = 77/1, 70 °C. [e] Reaction performed on the hydrochloride salt. [f] Yield higher than 92%.

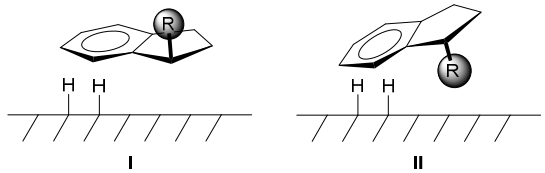
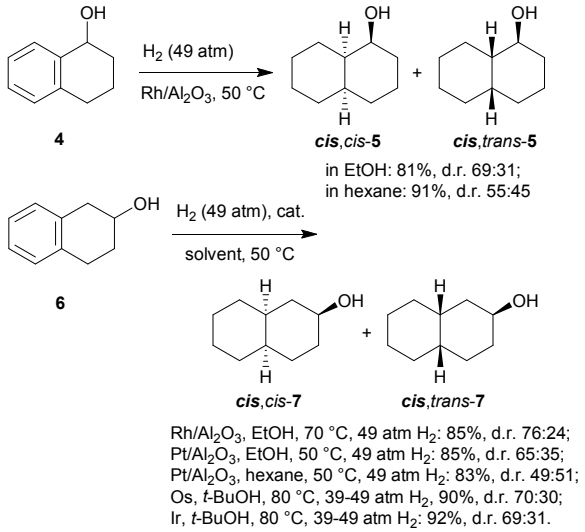


Figure 1

2.2. Tetrahydronaphthalene and octahydrophenanthrene derivatives

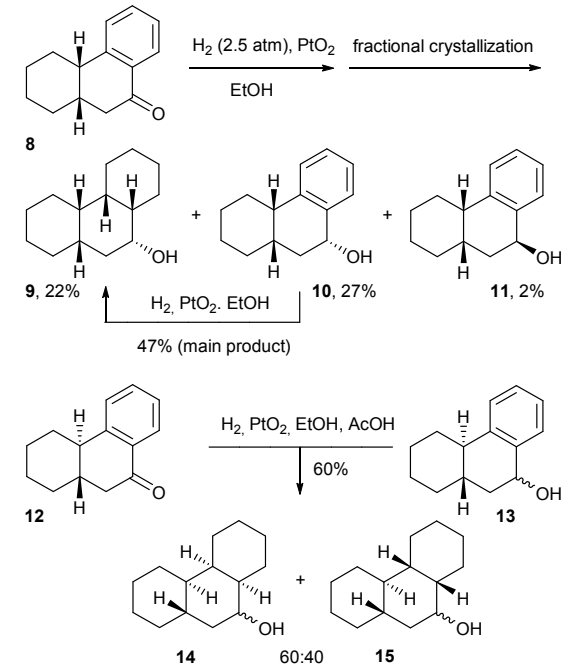
The analogous study was performed in the same paper for the hydrogenation of 1-tetralol (**4**) to 1-decalol (**5**) and of 2-tetralol (**6**) to 2-decalol (**7**) (Scheme 3, only the prevalent diastereomers are shown). Results of hydrogenation of 1-tetralol (**4**) were similar to those obtained with 1-indanol. 2-Tetralol (**6**) had been previously hydrogenated using noble metals: Ru, Rh, Pd/C, Os, Ir and Pt. The hydrogenations were carried out at different temperatures and pressures and the relative amounts of the four diastereomeric decalols and decalins were determined. The ***cis***,*cis*-diastereomers were generally prevalent in the mixtures, and Rh, Os and Ir catalysts afforded the highest ***cis***,*cis*/***cis***,*trans* ratios. [8] Interestingly, ***cis***,*cis*-**7** was obtained with greater d.r. (76:24) from 2-naphthol using Rh. In this case the reaction proceeded mainly through formation of 2-decalone.[8] Moreover, it was earlier reported that hydrogenation of 2-naphthol over Raney-nickel at 150 °C proceeded through competitive pathways involving preliminary reduction of one or the other benzene ring, but only the intermediate 2-tetralol (**6**) underwent further reduction to decalol (**7**) with undetermined diastereoselectivity and then hydrogenolysis to decaline.[9]



Scheme 3

Cis-9-keto-as-octahydrophenanthrene **8** was hydrogenated over Pt Adams catalyst to produce a mixture of compounds from which three compounds were isolated by repeated fractional crystallizations: the fully hydrogenated alcohol **9** with the *cis*,*syn*,*cis* configuration of the three fused cyclohexane rings and partially hydrogenated alcohols **10** and **11**, the latter being present in minor amount (Scheme 4).

It is likely that the carbonyl group underwent reduction prior than the benzene ring. As a matter of fact, hydrogenation of the isolated product **10** in the same conditions afforded mainly compound **9**, consequently, the hydrogenation of the benzene ring had occurred *anti* to the OH substituent.



Scheme 4

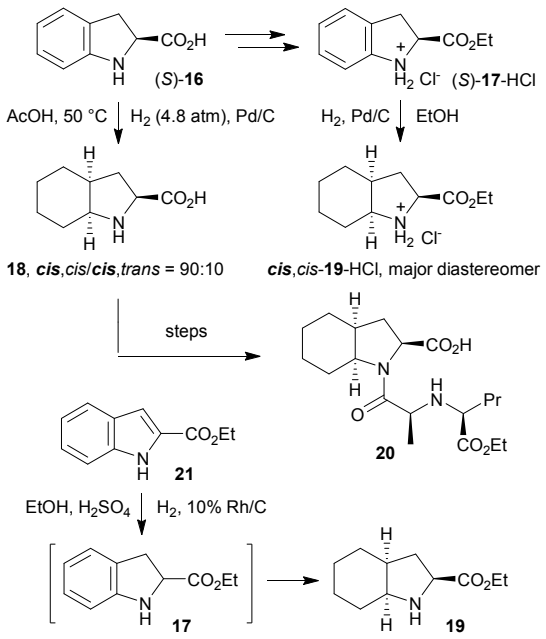
Probably, the steric hindrance of the external cyclohexane ring predominated over the haptophilic effect of the hydroxyl group.[10] Almost thirty years later, the same reaction was repeated by another group and a perhydrogenated alcohol was isolated in 36% yield by crystallization. It had the same melting point of the alcohol **9** previously described, but the configuration of C9 was not assigned. Moreover, a mixture of perhydrophenanthrenes (*cis*/*trans* 4:1) was formed by hydrogenolysis of the benzylic C-O bond.[11] On the other hand, hydrogenation of the *trans*-fused tricyclic ketone **12** gave a 60:40 mixture of *trans*,*syn*,*syn* and *trans*,*anti*,*syn* secondary alcohols **14** and **15**, respectively, which were epimeric at C9, because a satisfactory differentiation of the benzene diastereofaces was not possible. A mixture of compounds **14** and **15** with approximately the same ratio was also obtained by hydrogenation of the epimeric alcohols **13**.[12]

2.3. Indoline, isoindoline, isobenzofuran, and 1,2,3,4-tetrahydroquinoline, -isoquiniline and benzoquinoline derivatives.

Catalytic hydrogenation was carried out on both the enantiomers of 2-indolinecarboxylic acid, e.g. (*S*)-**16**, using Pd/C in acetic acid, and the enantiomers of perhydroindole carboxylic acid, e.g. (*S*)-**18**, were obtained with d.r. 90:10 (Scheme 5). Compound (*S*)-**18** was then converted to the corresponding *t*-butyl ester, whose purity was found superior to 98% by capillary GC of the derived (-)-camphanamide. The acid ***cis***,*cis*-**18** and its *t*-butyl ester were converted to Perindopril (**20**) and Perindoprilate, which are inhibitor of Angiotensin Converting Enzyme (ACE). Interestingly, the activity was found dependent on the chirality of the ring junction.[13] The hydrochloride of the ethyl ester (*S*)-**17**-HCl was hydrogenated with Pd/C in EtOH to produce the hexahydro derivative *cis*,*cis*-**19**, which was purified by crystallization from ethyl acetate.[14] Racemic 2-indolinecarboxylic acid (*rac*-**16**) was conveniently hydrogenated over PtO_2 at atmospheric pressure in acetic acid at 60 °C, however, the diastereoselectivity was not improved, and the enantiomerically pure saturated acid ***cis***,*cis*-**18** was isolated in 70% yield by crystallization.[15]

The preparation of racemic ethyl octahydroindole-2-carboxylate (*rac*-**19**) was also accomplished by hydrogenation of ethyl 2-indolecarboxylate (**21**) using 10% Rh/C in EtOH in the presence of H_2SO_4. The reaction proceeded through the dihydro derivative *rac*-**17** and gave *rac*-**19** in good yield with high purity, although the exact d.r. was not furnished. Resolution was then accomplished either on the corresponding 4-bromobenzamide *via* formation of the diastereomeric salt with (*S*)-1-phenylethylamine, and on the *t*-butyl ester *via* formation of the L-tartrate salt.[16]

Consiglio reported the hydrogenation of 3-propyl-3*H*-isobenzofuran-2-one (**22**) with Rh/C in EtOH at room temperature (Scheme 6). Complete conversion to the saturated product **23** was observed. By shifting to Rh/Al_2O_3 or changing the catalyst/substrate molar ratio or the H_2 pressure, the d.r. (***cis***,*cis*/***cis***,*trans*) did not change significantly.

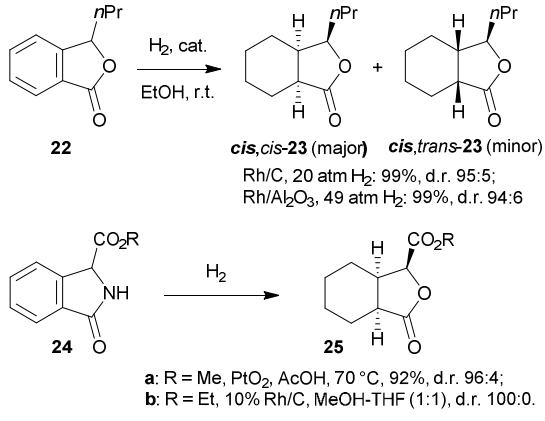


Scheme 5

A cyclohexene intermediate, presumably with the alkene double bond conjugated to the ester, was detected during the hydrogenation; moreover, the d.r. slightly increased as the reaction proceeded, suggesting that the intermediate was hydrogenated more selectively than the parent arene.[5a] Comparable high value of diastereoselectivity was obtained in the hydrogenation of isoindolin-1-one carboxylic acid methyl ester (**24a**) performed at atmospheric pressure in acetic acid at 70 °C using PtO_2 as catalyst. The octahydroisoindole derivative **25a** was obtained in 92% yield with a ***cis***,*cis*/***cis***,*trans* ratio 96:4.[15] A better procedure, however, was the hydrogenation with Rh/C, as the ethyl ester **24b** could be selectively reduced to ***cis***,*cis*-**25b** at room temperature.

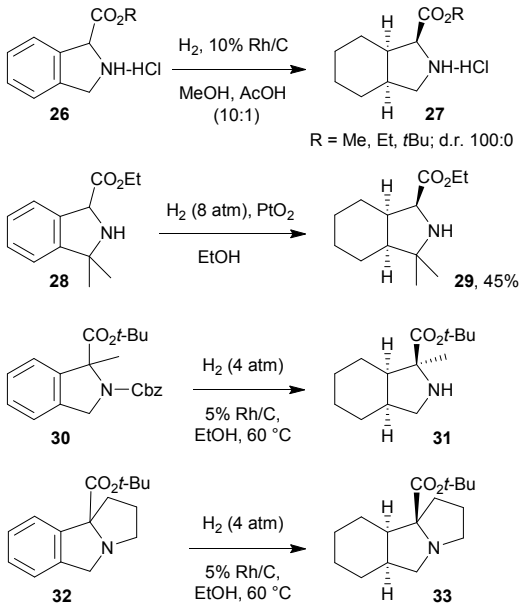
The analogous hydrogenation of the hydrochlorides of isoindolecarboxylic acid esters **26** with Rh/C catalyst afforded the saturated products **27** with complete stereocontrol (Scheme 7).[16] PtO_2 was again employed to hydrogenate the more substituted isoindole derivative **28** and the ***cis***,*cis* diastereoisomer **29** was obtained in moderate yield with almost complete stereocontrol. These perhydroindole derivatives are [*c*]-fused bicyclic proline analogues that are essential scaffolds in the synthesis of more complex molecules which display a variety of pharmacological activities.[17]

Even more impressive is the complete stereocontrol that was obtained in the hydrogenation of isoindoline derivatives **30** and **32** where the ring stereocenter bears two different substituents, an alkyl and a *tert*-butoxycarbonyl group, although more drastic conditions were required.[18] Addition of hydrogen took place exclusively to the π side shielded by the less bulky alkyl substituent, so forming the corresponding bicyclic and tricyclic saturated compounds **31** and **33**, respectively.

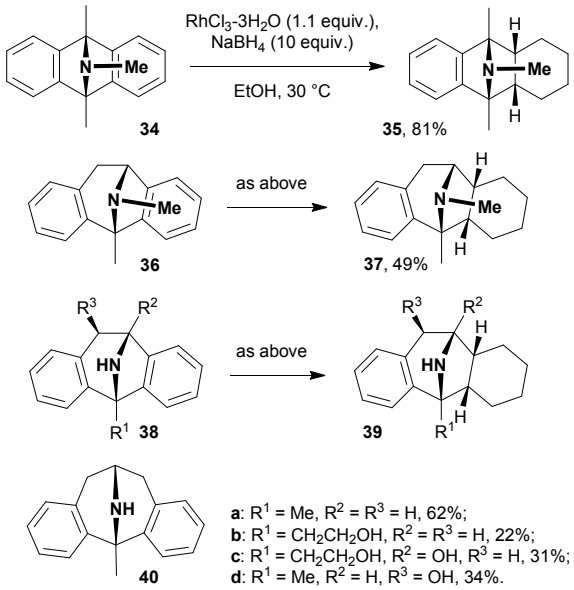


Scheme 6

Nitrogen-bridged dibenzocycloalkanes are potent antagonists of the *N*-methyl-D-aspartate (NMDA) in a subclass of glutamate receptors. In order to evaluate the relative importance of the aromatic rings for antagonist activity, a number of partially and totally reduced derivatives were prepared. The best method found was the reduction with an excess of sodium borohydride in the presence of a stoichiometric amount of rhodium trichloride, working in ethanol at room temperature. Starting from anthracen-9,10-imine **34** the partially reduced compound **35** was obtained in 81% yield with complete stereocontrol by *syn* addition of hydrogen to the less hindered face of the benzene ring, the one shielded by nitrogen (Scheme 8). Moreover, cycloheptenimines **36** and **38** underwent reduction principally at the isoindole moiety to give mainly the products **37** and **39** in low to moderate yields. Instead, reduction failed in the cases of the *N*-Boc derivative of **38a** and was very sluggish with the eight-membered dibenzo compound **40**. On the other hand,



Scheme 7

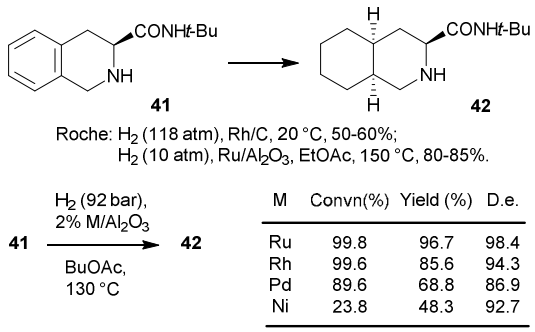


Scheme 8

high pressure hydrogenations of the acetate salt of **38a** over Rh/Al_2O_3 (101 atm of H_2, EtOH, 60 °C) or Raney-Ni (101 atm, 150 °C, EtOH) gave mixtures of products coming from partial and total hydrogenation of one or the other aromatic ring. Moreover, Birch-type reductions by Li/*n*PrNH$_2$ with or without *i*PrOH gave dihydro- and tetrahydro derivatives.[19]

Catalytic heterogeneous hydrogenation was exploited in industrial processes for the preparation of optically pure decahydroisoquinoline-3-carboxamide (DHIQ, **42**) (Scheme 9). 1,2,3,4-Tetrahydroisoquinoline-3-*t*-butylcarboxamide (**41**) was prepared from (*S*)-phenylalanine by two different synthetic sequences and was then hydrogenated under high-pressure in the presence of Rh/C to give a mixture of isomers out of which the prevalent (*S*,*S*,*S*)-decahydroamide **42** was recovered by crystallization with an overall yield of 17-20% (7 steps). A three steps route from (*S*)-phenylalanine was then optimized, where the hydrogenation step was also improved using a ruthenium catalyst in more forcing conditions requiring a "trickle-bed-reactor", which provided 94% selectivity of the desired stereoisomer.[20]

Later, the hydrogenation of **41** was investigated using supported metals evaluating the effect of several factors: metal precursor, catalyst support, solvent, method of catalyst preparation and reaction conditions. The alumina-supported catalysts were prepared from metal salts by the impregnation and incipient wetness method, then dried at 200 °C for 2.5 h, calcined at 500 °C for 3 h in air, and reduced with H_2 prior to the addition of the substrate. Four diastereomers with preserved 3*S* configuration of the innate stereocenter were mainly formed together with minor amounts of the 3*R*-diastereomers, coming from *in situ* racemization, and decomposition products. In optimized conditions, alumina-supported 2% Ru, Rh, Ni and Pd catalysts were very selective towards the formation of **42** and Ru/Al_2O_3 gave the best performance.[21]



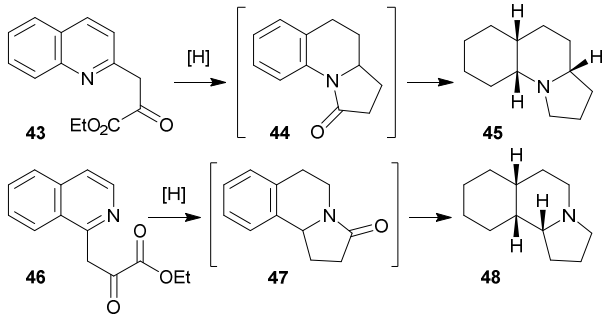
M	Convn(%)	Yield (%)	D.e.
Ru	99.8	96.7	98.4
Rh	99.6	85.6	94.3
Pd	89.6	68.8	86.9
Ni	23.8	48.3	92.7

Scheme 9

The reductive condensation of quinoline- and isoquinoline-substituted pyruvates was described as early as in 1950 by hydrogenation over copper chromite in very severe conditions (200-300 atm., up to 265 °C in dioxane). For example, the quinoline derivative **43** was reduced to **45** in 66% yield.[22] It was correctly supposed that the reaction had proceeded through the intermediate **44**, but the relative configuration of the stereocenters could not be demonstrated, although a single diastereoisomer was predominantly obtained. Similarly, the reductive condensation of the isoquinoline compound **46** afforded the tricyclic isomeric compound **48** in 66% yield through **47** (Scheme 10). Other tricyclic and tetracyclic systems were similarly prepared.

On the basis of the stereochemical outcomes of the reactions we have previously described, it is likely that compounds **45** and **48** have the *cis*,*syn* relative configuration of the three stereocenters, since they are formed in consecutive steps, and the first formed stereocenters in **44** and **47** would affect the stereoselective hydrogenation of the benzene ring. It is worth noting that other metal catalysts and milder conditions might be used to achieve the same transformations, see next Schemes 20 and 21.

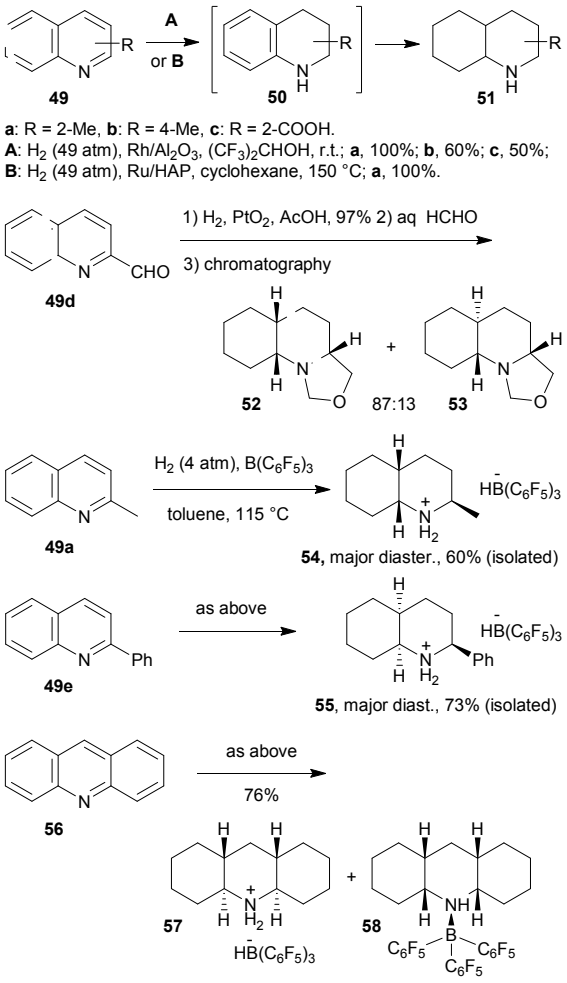
Partial hydrogenation of quinolines, isoquinolines and phenylpyridines occurs predominantly or exclusively at the pyridine ring when using heterogeneous catalysts, however, a preferential. very slow reduction of the benzene ring occurs using PtO_2 catalyst in strongly acidic medium, preferably trifluoroacetic acid.[23] A solvent dependent regioselectivity was observed in the hydrogenation of substituted quinolines **49a-c** using rhodium on alumina (Scheme 11): in methanol the



Scheme 10

1,2,3,4-tetrahydro derivatives **50** were selectively obtained, whereas in hexafluoroisopropanol the reduction proceeded to give the decahydro derivatives **51**.[24] An alternative procedure involved hydroxyapatite (HAP)-supported ruthenium catalyst in more severe conditions.[25] The chiral center formed in the intermediate **50** would have affected the configuration of the novel stereocenters formed in the successive benzene ring hydrogenation, however, the degree of diastereoselectivity was not determined in both papers. Instead, after complete hydrogenation of 2-quinolinealdehyde **49d** the crude product was converted to the diastereomeric tricyclic aminals **52** and **53**, which were separated by chromatography, and their relative stereochemistry was assigned by ^{1}H NMR studies.

Metal-free hydrogenation of aniline and pyridine rings in the presence of *tris*(pentafluorophenyl)borane in toluene at high temperature gave saturated ammonium *tris*(hexafluorophenyl)hydrogenoborates (Scheme 11).[26] Mechanistically, the initially formed amine-borane complex activates heterolysis of hydrogen to give an ammonium hydridoborate complex. A series of bicyclic and tricyclic azaheterocycles were hydrogenated under 3 atm of H_2 pressure in refluxing toluene and the products were structurally identified by X-ray crystallography Unexpectedly, the hydrogenations of 2-methylquinoline **49a** and 2-phenylquinoline **49e** gave opposite stereochemical outcomes: the corresponding products **54** and **55** showed prevalently the *cis*-fusion of the two rings, but the relative configuration of the piperidine C2-substituted stereocenter was opposite. Assuming that the pyridine ring was reduced first, the subsequent hydrogenation of the benzene ring was apparently affected by the shape or bulkiness of the phenyl substituent. Furthermore, acridine **56** was converted to a mixture of products from which the *trans*,*syn*,*trans* salt **57** crystallized, whereas the Lewis acid-base complex **58** with the *cis*,*syn*,*cis* configuration was isolated from the mother liquor.



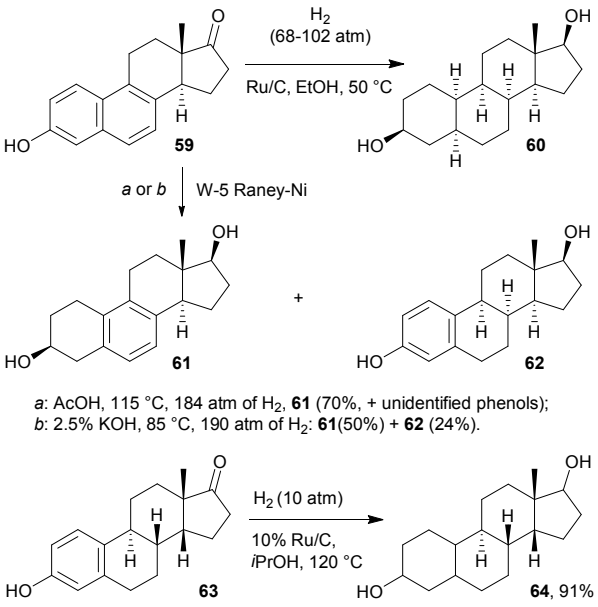
Scheme 11

2.4. Phenol and naphthol derivatives

Hydrogenation of naphthols can occur on either the benzene or the phenol ring depending on the nature of the catalyst used and on the reaction conditions. Hydrogenation of equilenin (**59**), a non-classical steroid containing the β-naphthol moiety, was performed using different catalysts. The use of PtO_2 in acidic medium led to reduction of the phenol A-ring with concomitant C-O bond hydrogenolysis, as well as reduction of the carbonyl group in ring D. Hydrogenolysis could be avoided using nickel and ruthenium catalysts (Scheme 12). Complete reduction of **59** to 5α,8α,9α,10α-estrane-3β,17β-diol (**60**) using Ru/C was reported in a patent.[27] The use of W-5 Raney-Ni in acetic acid afforded good yield of the 3β,17β-diol **61** together with minor amounts of unidentified phenolic compounds, whereas in basic conditions reduction of the benzene ring also occurred significantly, and compound **62** was isolated in addition to the main product **61**. However, the presence of other diastereomers in the reaction mixtures cannot be excluded.[28]

Recently, efficient and practical hydrogenation procedures for arenes and heteroarenes have been reported exploiting Rh/C and Ru/C in *i*PrOH at ordinary to medium pressures in neutral conditions. Among the substrates examined, compound **63** was effectively converted to the saturated derivative **64**, but the configuration of the newly formed stereocenters could not be determined (Scheme 12). Similarly, 1-naphthol was hydrogenated to 1-decalol with undetermined diastereoselectivity.[29]

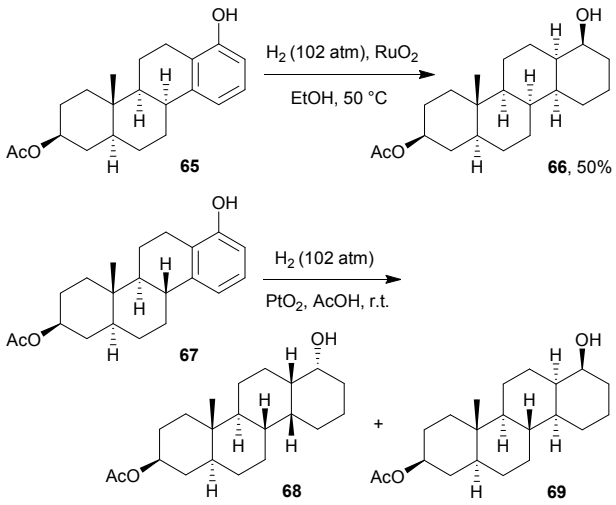
The hydrogenation of the phenolic steroid compound **65** was preferably accomplished with RuO_2 because extensive hydrogenolysis of the 17-hydroxy group occurred using PtO_2in acetic acid (Scheme 13). A single diastereomer **66** was isolated in over 50% yield, and the diastereoselectivity was explained considering that approach by the catalyst to the β side of the arene group is severely hindered by the concave bending of the molecule at the B/C ring juncture. The outcome of hydrogenation of the diastereomeric substrate **67** over PtO_2, although occurring with concomitant hydrogenolysis, provides information on the influence of the substrate structure on the diastereoselectivity. In that reaction two main products were isolated, **68** (24% isolated yield, prevalent) and **69**,



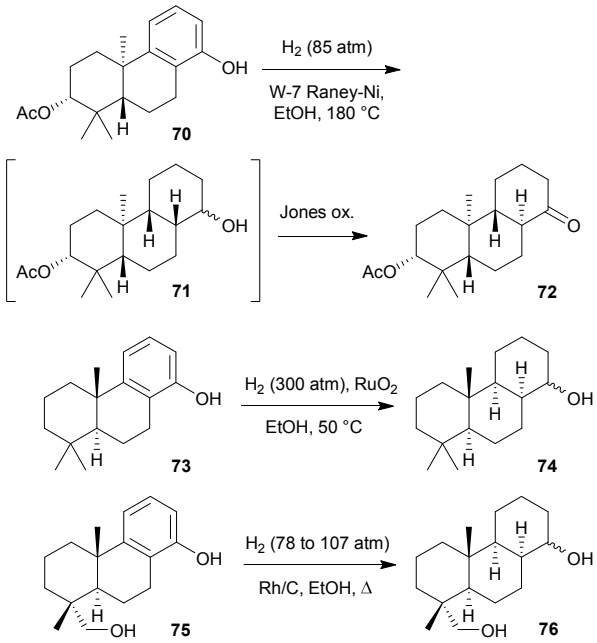
Scheme 12

demonstrating that a complete diastereoselectivity cannot be obtained in the hydrogenation of the aromatic D-ring when adjacent saturated B- and C-rings have a *trans* junction.[30]

Hydrogenation of racemic 3α-acetoxy-14-hydroxy-4α,4β,10α-trimethyl-1,2,3,4,5,6,7,10-octahydrophenanthrene (**70**) with Raney-Ni in ethanol followed gave the intermediate alcohol **71** which was oxidized to the acetoxy ketone **72** in overall 50% yield after crystallization of the crude (Scheme 14). The *trans* configuration of hydrogen atoms in the newly formed stereocenters in **72**, presumably derived from racemization of the α to carbonyl stereocenter after the oxidation step, assuming that the *cis* configuration had been prevalently obtained in the hydrogenation step. Addition of



Scheme 13



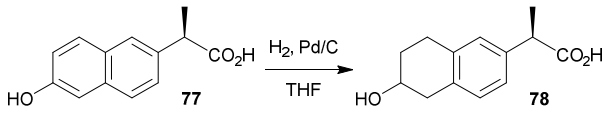
Scheme 14

hydrogen occurred to the less hindered arene face, *anti* to the angular 10-methyl substituent, so forming the intermediate **71**. On the other hand, the configuration of the 14-OH-substituted stereocenter in **71** was lost in the oxidation step.[31] This result corresponds to the outcome of the recently described hydrogenation of analogous arene **73**, which was converted to **74** using RuO_2 as the catalyst.[32] The same stereochemical outcome should be expected for the hydrogenation of substrate **75**, although the configuration of the newly formed stereocenters in the product **76** was not assigned.[33]

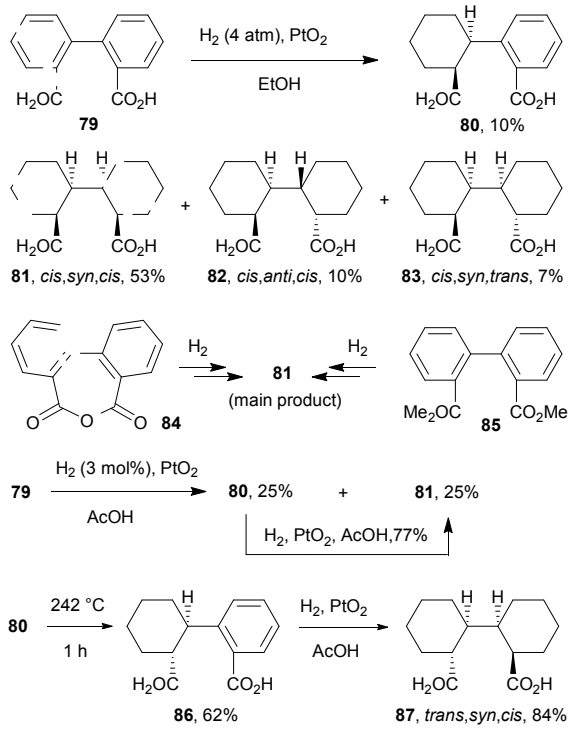
Selective hydrogenation of the phenolic ring of optically active Naproxene derivative **77** was obtained with Pd/C in THF affording compound **78** with undetermined diastereoselectivity (Scheme 15).[34]

2.5. Substituted biphenyls

The catalytic hydrogenation of "diphenic acid" **79** over PtO_2 mainly gave the perhydrodiacid **81** with *cis,syn,cis* stereochemistry together with minor amounts of diastereomers **81** and **82** and semihydrogenated compound **83** (Scheme 16).[35] The saturated diacid **81** was also the prevalent product obtained by hydrogenating the corresponding anhydride **84** and diester **85**, indicating that either acid and diester underwent hydrogenation in the coiled conformation. Hydrogenation of **79** was found more rapid in acetic acid than in ethanol; when it was stopped after 3 moles of hydrogen had



Scheme 15



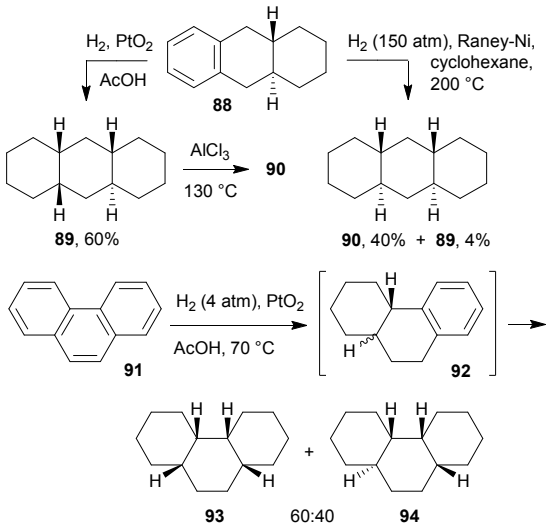
Scheme 16

been consumed, a mixture of unreacted starting material, *cis*-half-hydrogenated acid **80** and perhydroacid **81** were obtained.[36] Moreover, hydrogenation of isolated **80** in the same conditions gave the same perhydrogenated acid **81** in good yield. The latter compound could be thermally converted to its *trans* isomer **86**, whose hydrogenation gave the *trans*,*cis*,*syn*-perhydrogenated acid **87** in good yield.

2.6. Polynuclear aromatic hydrocarbons

Hydrogenation of C_2-symmetric *trans-as*-octahydroanthracene **88** with platinum in acetic acid gave the perhydroanthracene **89** by the usual *syn* addition process, whereas the use of Raney-nickel under severe conditions occurred mainly by the *anti* addition mechanism so affording **90**. Heating with powdered aluminum trichloride caused the isomerization of **89** to the more stable diastereomer **90** (Scheme 17).[37]

It was observed that the hydrogenation of fused polycyclic aromatic compounds (e.g. fluorene, anthtracene, phenanthrene, pyrene, acridine, carbazole, dibenzofuran, and others) develops through ring by ring saturation steps. Moreover, alternative sequences of ring hydrogenation steps were observed in the hydrogenation of polycylic aromatic compounds, where the relative reaction rates and hence the selectivity were dependent on the nature of the catalyst.[38] Consequently, after one or more rings of polycyclic arenes have been reduced and depending on the hydrogenation sequence, the diastereoselectivity in the successive ring hydrogenation is affected by the previously formed stereocenters. Thus, mixtures of diastereomers with different relative configurations at the

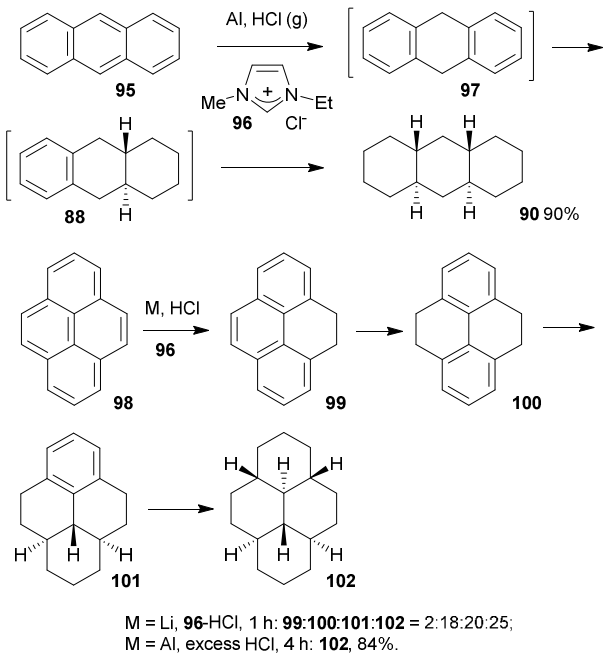


Scheme 17

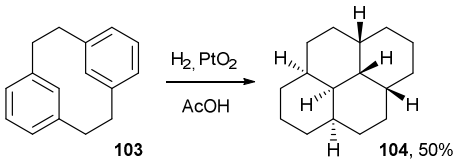
ring junctions can be formed, even if it is assumed that hydrogen uptake mainly occurs in *syn* fashion on every single double bond. Different procedures have been reported, some of them being novel: Raney-nickel and copper chromite,[39] Raney-Ni,[40] supported noble metals,[41] Al powder plus noble metals on carbon,[42] Ni-Mo on alumina[38] ruthenium black.[38] However, only in a limited number of cases the stereochemistry and ratio of diastereomeric products have been reported in those reports. For example, diastereomeric perhydrophenanthrenes **93** and **94** were obtained with an unexpected 60:40 ratio by hydrogenation of phenanthrene **91** using platinum catalyst in acetic acid at 70 °C, where the reaction is supposed to proceed *via* the intermediate octahydro derivative **92**.[11]

Dissolving metal reduction of anthracene (**95**) and pyrene (**98**) in ionic liquid was described (Scheme 18).[43] For the complete reduction of anthracene to the *trans*,*syn*,*trans*-perhydroanthracene **90**, it was found that aluminum as the electropositive metal, and gaseous hydrochloric acid as the proton source in 1-ethyl-3-methylimidazolium chloride ([emim]Cl) (**96**) afforded the best result. The intermediates **97** and **89** were detected at partial conversions. Analogously the complete hydrogenation of pyrene (**98**) to all-*trans*-**102** occurred *via* the intermediates **99**, **100** and **101**. In that conditions, aluminum trichloride formed as by-product precipitates and leaves largely unaffected the ionic liquid. Differing from common Birch reduction, this method does not lead to unconjugated double bond system. On the other hand, the hydrogenation of pyrene over Raney-Ni under 90 atm of H_2 pressure in ethanol at 140 °C produced a mixture of five diastereomers.

Noteworthy, the hydrogenation of [2.2]metacyclophane (**103**) over PtO_2 in acetic acid at normal pressure afforded selectively the *cis*,*cis*,*anti*,*cis*,*cis*-perhydropyrene **104** in 50% yield by a transannular cyclization (Scheme 19).[44]



Scheme 18



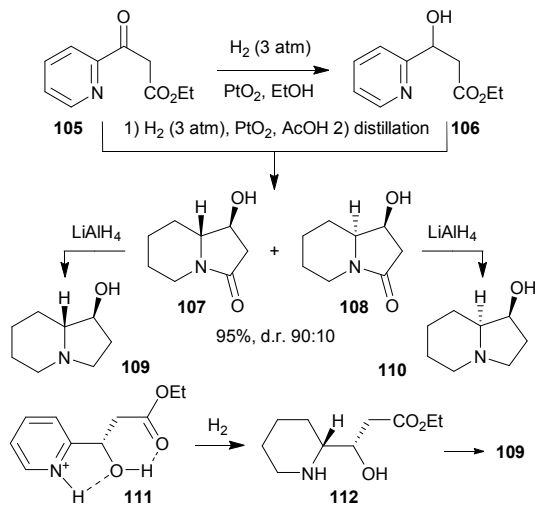
Scheme 19

3. Hydrogenation of pyridine derivatives

3.1. Hydroxyalkyl-substituted pyridines and quinolines

The hydrogenation of ethyl 3-(2-pyridyl)-3-oxopropionate (**105**) with PtO_2 in ethanol led exclusively to the secondary alcohol **106**. On the other hand, hydrogenation of either **105** and **106** with the same catalyst in acetic acid yielded almost quantitatively, after distillation of the crude, a mixture of diastereomeric bicyclic lactams **107** and **108** in 90:10 ratio. These compounds were then reduced with lithium aluminum hydride to the corresponding diastereomers of 1-hydroxyoctahydropyrrocoline **109** and **110** (Scheme 20).[45] The configuration of the two diastereomers **107** and **108** could be assigned because the m.p. (174-176 °C) of the picrate salt of **108** was almost identical to the value (176-178 °C) of the picrate salt derived by the authentic compound obtained by hydrogenation of the precursor ketone which was expected to have axial OH substituent.[46] Moreover, the reported m.p. 156-158 °C of the picrate of **107** was close to the value of the authentic compound more recently synthesized by different routes.[47]

The diastereoselectivity achieved in the hydrogenation of the pyridine derivatives **105** and **106** can be likely attributed to the preferred, relatively rigid conformation of the protonated

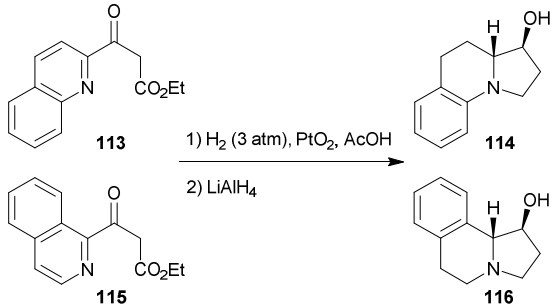


Scheme 20

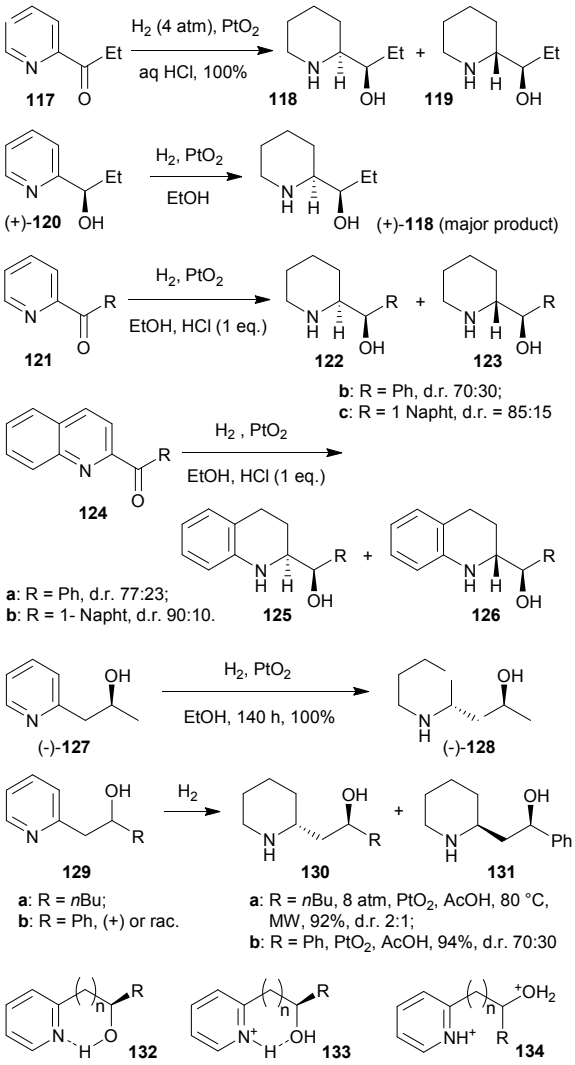
pyridine-alcohol, depicted in structure **111**, where hydrogen bonds are easily attained between the OH and ester, and most importantly, NH^+ and OH groups. Consequently, the hydrogen uptake is expected to occur preferentially to the less hindered face of the pyridine ring, leading to **112** and then **107**.

Analogous quinoline and isoquinoline derivatives **113** and **115** were hydrogenated in the same conditions and the partially hydrogenated tetrahydroquinolines spontaneously underwent cyclization at room temperature to give the corresponding tricyclic lactams, isolated as pure diastereomers after crystallization, which were then reduced to the compounds **114** and **116** using lithium aluminum hydride (Scheme 21).[48]

Hydrogenation of the 2-pyridyl ketone **117** with Adams catalyst in aqueous hydrochloric acid gave quantitatively a mixture of the two diastereomers of the 2-piperidylalcohol, **118** and **119**.[49] Later, racemic 1-(2-pyridyl)propanol **120** was synthesized and then resolved and the two enantiomers were distinctly hydrogenated in ethanol with good diastereoselectivity. Both natural and unnatural conhydrine (+)- and (-)-**118**, respectively, were so obtained (Scheme 22).[50]



Scheme 21



Scheme 22

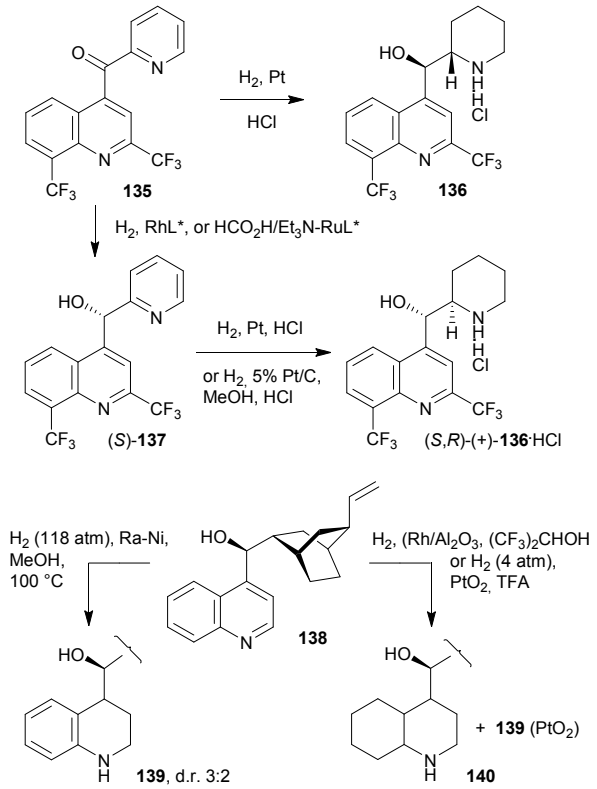
Aryl 2-pyridyl ketones **121** were hydrogenated with the same Pt catalyst but in the presence of one equivalent of hydrochloric acid to obtain mixtures of 2-piperidinyl alcohols **122** and **123** with moderate to high diastereoselectivity with prevalence of the *erythro* diastereomers **122**. The analogous hydrogenation of aryl 2-quinolyl ketones gave the corresponding alcohols **125** and **126** with slightly better diastereoselectivity.[23b] The hydrogenation of α-substituted-α-phenyl-2-pyridylmethanols with PtO_2 and Pd/C in acidic medium was also reported to give piperidines with undetermined diastereoselectivity.[51]

Similarly, the enantiomers of 1-(2-pyridyl)-2-propanol **127** were hydrogenated over PtO_2 in ethanol[52] or acetic acid.[53] Unnatural sedridine (-)-**128**, for example, was formed from (-)-**127** with excellent diastereoselectivity working in methanol, but very long time was required for a complete conversion. The use of microwave accelerated the hydrogenation reaction of compound **129a**, performed in otherwise similar conditions, afforded the piperidine derivative **130a**, but the diastereoselectivity was reduced.[54]

(*S*)-1-Phenyl-2-(2-pyridyl)ethanol (**129b**), which was prepared by lipase-mediated kinetic resolution of the acetate or by enantioselective reduction of the corresponding ketone, was hydrogenated over PtO_2 in acetic acid to the mixture of norsedamine (**131**) and norallosedamine (**132**) with moderate diastereoselectivity.[55] When the same reaction was later repeated by other authors on racemic **130**, the reduced products were converted to sedamine and *allo*-sedamine.[56]

The origin of the diastereoselectivity in the hydrogenation of hydroxyalkyl-substituted pyridines in ethanol was envisioned in the rigid conformations of the substrates or their protonated form, e.g. **133** and **134**, due to the intramolecular hydrogen bonding. In this cases, hydrogen is transferred from the catalyst surface to the side of the molecule remote to the alkyl substituent. In highly acidic conditions, where also the alcoholic group should be protonated, the substrates would adopt a non-rigid conformation causing loss of stereocontrol in the hydrogenation reactions. Moreover, increasing the bulkiness of the R substituent, higher temperatures are also required for the hydrogenation reactions, and this may have a detrimental effect on the diastereoselectivity.

Racemic Mefloquine (Lariam®) (**136**) was prepared by heterogeneous hydrogenation of 2-pyridyl ketone **135**.[57] The enantioselective synthesis of both enantiomers of **136** was later investigated at Hoffmann-La Roche (Scheme 23).[58] The strategy comprised the preliminary enantioselective reduction of the ketone **135** to the secondary alcohol, e.g. (*S*)-**137** by homogeneous hydrogenation with chiral Rh-diphosphine



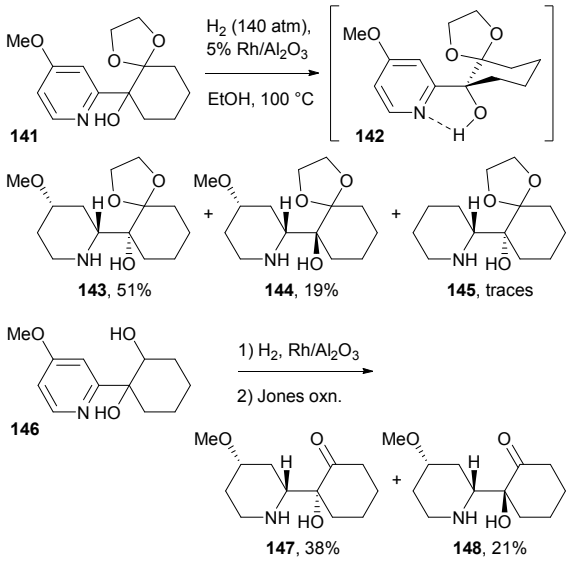
Scheme 23

complexes. The best ligand was an unsymmetrical diphosphine which afforded 92% e.e. in optimized conditions. Both enantiomers of **137** were then obtained pure by crystallization and further submitted to heterogeneous hydrogenation of the pyridine ring over Pt catalyst in hydrochloric acid. (*S*)-**137** Was reduced to (*S*,*R*)-(+)-**136**-HCl, which confirms the sense of asymmetric induction previously reported in hydrogenation of analogous substrates. It is noteworthy that the unsubstituted pyridine ring was chemoselectively reduced in the presence of the substituted quinoline ring. Asymmetric reduction of ketone **135** to (*S*)-**137** with 96% e.e. was successively achieved employing the transfer hydrogenation with formic acid as hydrogen source and a different chiral ruthenium catalyst, then hydrogenation of the pyridine ring was achieved with 5% Pt/C under 1 atm of H_2 pressure in MeOH-37% HCl mixture at room temperature. In that conditions the conversion was complete and (+)-mefloquine hydrochloride ((*S*,*R*)-**136**-HCl) was obtained with 98% e.e. accompanied by the (*S*,*S*)-epimer (d.r. 85:15), then, after purification, it was isolated with 58% yield and 99% e.e..[59]

It must be pointed out that the Hoffman-La Roche researchers attributed the *R* configuration to the alcohol **137**, and consequently the wrong configuration to (+)-metofloquine. The correct configuration of (+)-metofloquine **136** is depicted in Scheme 25; it was unambiguously determined by an alternative synthesis from commercially available (*S*)-(-)-1-Boc-piperidinecarboxylic acid without affecting the chiral center.[60] Other procedures for the heterogeneous catalytic reduction of **137** to mefloquine **136** have been reported in patents, for example employing Rh and Pt catalysts in acidic medium in the presence of bromide anion.[61]

The hydrogenation of the quinoline moiety of compound **138** was affected by the nature of the catalyst (Scheme 23). The pyridine ring was exclusively hydrogenated using Raney-nickel so affording **139** as a mixture of the two diastereomers in 3:2 ratio, whose configuration at C4 was not determined. On the other hand, hydrogenation with PtO_2 gave a mixture of the partially and fully reduced compounds **139** and **140** as mixtures of diastereomers with undetermined configuration.[62] Compound **140** was instead formed exclusively by using rhodium catalyst in hexafluoroisopropanol.[23b]

The catalytic hydrogenation of the substituted pyridine **141** bearing a quaternary hydroxy-substituted carbon stereocenter was performed en route to a useful intermediate for the synthesis of securitrinine and related alkaloids (Scheme 24).[63] In the presence or 5% rhodium on alumina the hydrogenation proceeded slowly to give two main piperidines **143** and **144** in 51% and 19% yield, respectively, and trace amounts of the deoxygenated piperidine **145**.

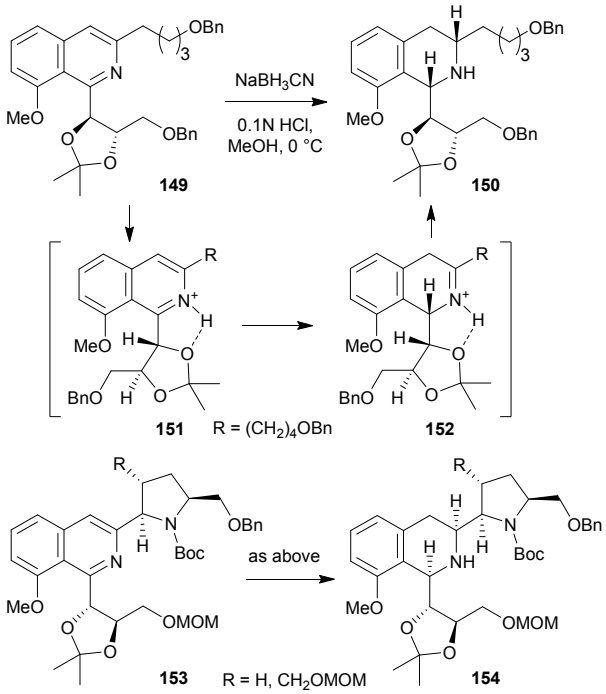


Scheme 24

The formation of the major diastereomer **143** was explained considering that addition of hydrogen took place from the less hindered pyridine face of the conformer **142** which features the O-H---N hydrogen bond. When hydrogenation was carried out on the pyridine diol **146**, a lower level of diastereoselectivity was achieved, as the diastereomeric ketones **147** and **148** were obtained in 38% and 21% yields, respectively, after subsequent Jones oxidation following chromatographic separation.

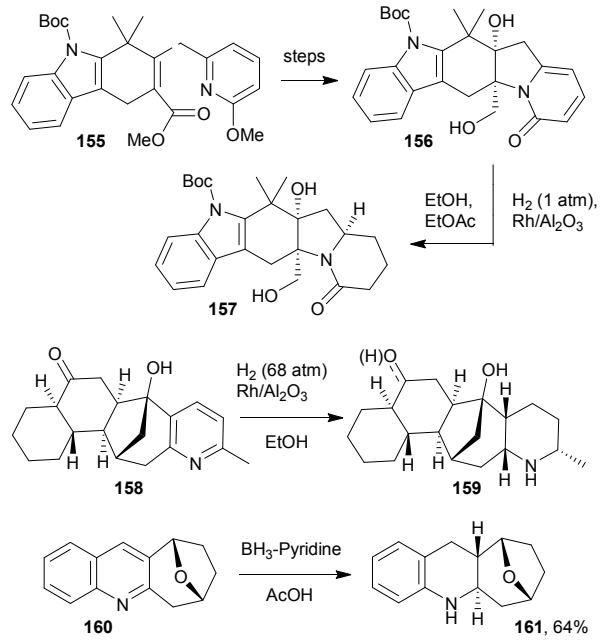
Isoquinolines can be easily reduced to tetrahydro-derivatives with sodium cyanoborohydride in acidic medium. For example, the chiral isoquinoline **149** synthesized from L-threose was converted to the tetrahydroderivative **150** in high yield with complete diastereoselectivity (Scheme 25). The reaction proceeds through consecutive reduction steps: in both of them, hydride attack occurs at the less hindered faces of iminium ions **151** and **152** in their rigid conformation resulting from hydrogen bonding.[64] Similarly, the isoquinoline **153** derived from D-threose was reduced with complete diastereoselectivity to the tetrahydroisoquinoline **154**.[65]

It has been recently reported that hydrogenation of the pyridine-2-one moiety in racemic compound **156**, available from precursor **155** by reduction, epoxidation and cyclization steps, with Rh/Al_2O_3 at atmospheric pressure occurred with good level of diastereoselectivity, although the precise d.r. was not provided (Scheme 26).[66] The configuration of product **157** was determined by single-crystal X-ray analysis, demonstrating that hydrogen uptake had occurred to the π face *syn* to the hydroxy groups. This result suggests a positive interaction of the OH function with the catalyst surface.



Scheme 25

On the contrary, only steric factors affected the diastereoselective addition of hydrogen to the pyridine ring in the complex molecule **158**, to give the piperidine derivative **159** with concomitant partial reduction of the ketone.[67] Moreover, borane-pyridine complex was used to reduce the substituted quinoline **160** to a mixture of tetrahydro derivatives, where **161** was prevalent (d.r. 64:6:12).[68]



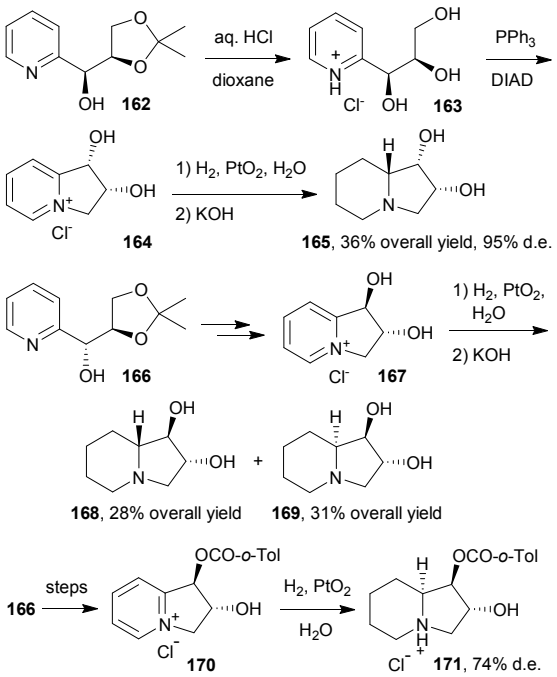
Scheme 26

3.2. *N*-Alkylpyridinium, and hydroxy-substituted indolizinium and quinolizinium salts

Several syntheses of lentiginosine derivatives have been accomplished exploiting the diastereoselective hydrogenation of the pyridine ring present in chiral substituted pyridines. An original approach involved the preparation of intermediate dihydroxy-substituted indolizinium salts (Scheme 27).[69] The reaction of 2-pyridyllithium with (*R*)-2,3-*O*-isopropylidene glyceraldehyde gave a 2.3:1 mixture of diastereomeric alcohols **162** and **166** which were separated by column chromatography. Rather than going on by hydrogenation of the pyridine ring and subsequent ring closure step, it was chosen to follow the alternative route which involves successive deprotection, cyclization and hydrogenation steps.

Mitsunobu-type cyclization of the intermediate salt **163** took place efficiently avoiding any protection and purification steps. Hydrogenation of the obtained *cis*-disubstituted pyridinium salt **164** over Pt catalyst led to the indolizidine hydrochloride with excellent yield and diastereoselectivity (d.r>95%), then basic treatment gave 1-*epi*-lentiginosine **165** with overall 36% yield based on the starting 2-bromopyridine.

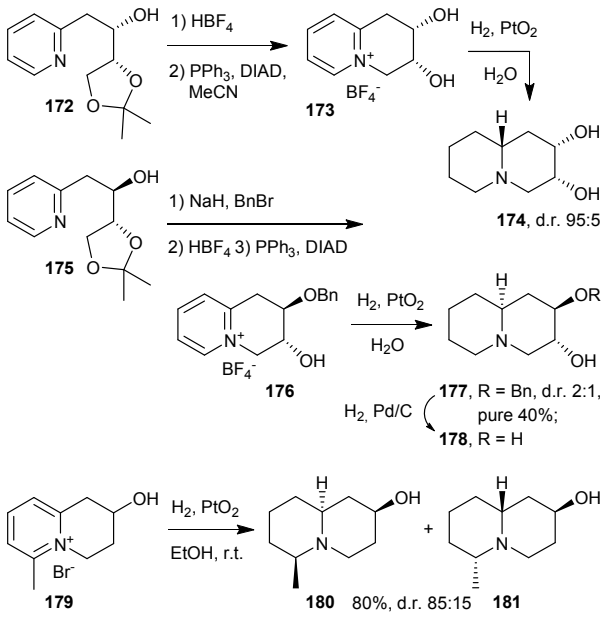
On the other hand, hydrogenation of the *trans*-disubstituted salt **167**, available from the alcohol **166,** gave a mixture of (-)-lentiginosine **168** and the 8a-*epi*-isomer **169** in almost equal amounts. However, the diastereoselectivity was improved by protecting the free hydroxy function of **166** as *o*-toluoyl derivative **170**, then the hydrogenation of the latter afforded **171** with 74% d.r, owing to the steric effect of the ester group.



Scheme 27

The same strategy was applied to synthesize dihydroxyquinolizidines (Scheme 28).[70] The addition of 2-pyridylmethyllithium to D-glyceraldehyde acetonide gave a mixture of alcohols **172** and **175** in a 3:1 ratio, and these diastereomers were separated and submitted to cyclization-reduction sequence. Deprotection was effected using aqueous tetrafluoroboric acid-diethyl ether complex, the nature of counter anion being crucial in the next step. The dihdroxyquinolizinium salt **173** was prepared modifying the cyclization procedure, but in optimized conditions a 1:1 ratio of **172** and **173** was obtained. Separation of the products was difficult, so the crude material was submitted to Pt-catalyzed hydrogenation, which proceeded with 90% of d.e. in favour of compound **174**. On the other hand, the pyridine **175** was preliminarily benzylated to give **176**, aiming to improve the diastereoselectivity and to facilitate the separation of diastereomeric products. Actually, the cyclization was not improved, but the salt **176** was easily purified. Then, the hydrogenation provided a 2:1 mixture of quinolizidines. The prevalent one **177** was isolated pure in 40% yield and then debenzylated to give the dihydroxyquinolizidine **178**. Attempts to improve the diastereoselectivity of the hydrogenation step in modified experimental conditions met with no success. Instead, hydrogenation of 2-hydroxy-6-methyl-1,2,3,4-tetrahydroquinolizinium bromide **179** took place efficiently with better diastereoselectivity, affording the saturated compounds **180** and **181** in 85:15 ratio.[71]

From these results, it appears that the hydrogenation of quinolizinium salts is less satisfactory with respect to the indolizinium salts, owing to the greater flexibility of the (6+6) fused bicyclic system. In all cases hydrogen addition occurred prevalently to the less hindered face of the positively charged ring, *anti* to the hydroxy or alkoxy substituents present in the saturated ring, demonstrating that the haptophilicity effect of the OH group was not operative in hydrogenation of positively charged aromatic heterocycles.



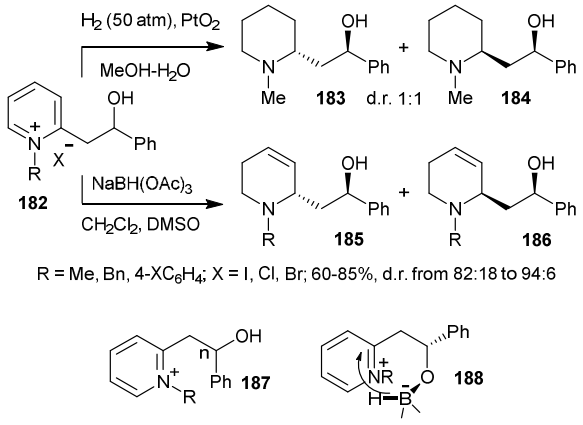
Scheme 28

Pd/C-catalyzed hydrogenation of a *N*-substituted pyridinium salt bearing 1-hydroxyalkyl substituent occurred with no diastereoselectivity.[53,72] For example, the piperidines **183** and **184** were formed in equal amounts from the *N*-methylpyridium salt **182** (R = Me).[53] High levels of diastereoselectivity (d.r. up to 94:6) have been instead obtained by reducing a few pyridinium salts **185** to the tetrahydropyridines **185** and **186** with sodium triacetoxyborohydride (Scheme 29).[73] *N*-Alkylpyridinium salts adopt non rigid conformations such as **187** and this explains the complete absence of stereocontrol in their metal-catalyzed hydrogenation reactions. On the other hand, it is likely that reduction of the same pyridinium salts by the borohydride reagent takes place through the intermediate alkoxy borohydride **188**, where a strong ionic, intramolecular interaction N^+---B^- forces the hydride to attack the C=N double bond through a six membered cyclic transition state.

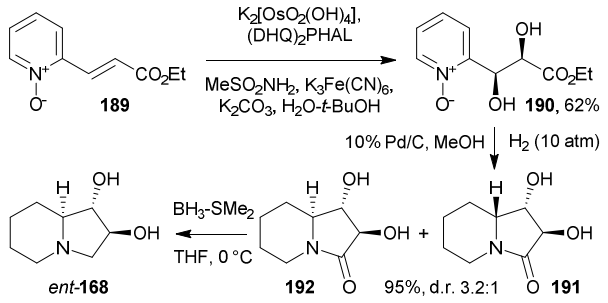
3.3. Hydroxyalkyl-substituted pyridine N-oxides

Total synthesis of (+)-lentiginosine was achieved starting from 3-(pyridine-2-yl)acrylate N-oxide **190**, on which asymmetric Sharpless dihydroxylation was performed as the key step to prepare the diol **191** with almost complete stereoselectivity (Scheme 30). As a matter of fact, dihydroxylation of the pyridyl acrylate was not successful, hence the nitrogen atom was protected as the oxide **189**. Dioxylation of the latter gave the diol **190** and subsequent catalytic hydrogenation with Pd/C under 10 atm of hydrogen pressure afforded the bicyclic saturated compound as a mixture of diastereomers **191** and **192** in high yield with moderate diastereoselectivity. The pure isomer **192** was isolated by crystallization in 43% yield and then reduced with borane dimethyl sulfide complex to (+)-lentiginosine (*ent*-**168**) in 20% overall yield.[74]

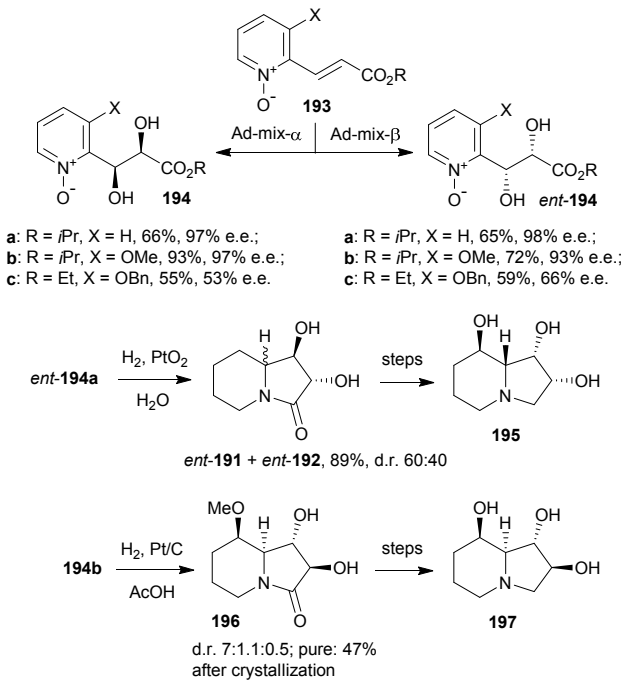
The same strategy was later adopted by Reiser to synthesize alkaloids from the *N*-oxides of 3-(pyridin-2-yl)acrylates **193** (Scheme 31).[75] Isopropyl acrylates gave better



Scheme 29



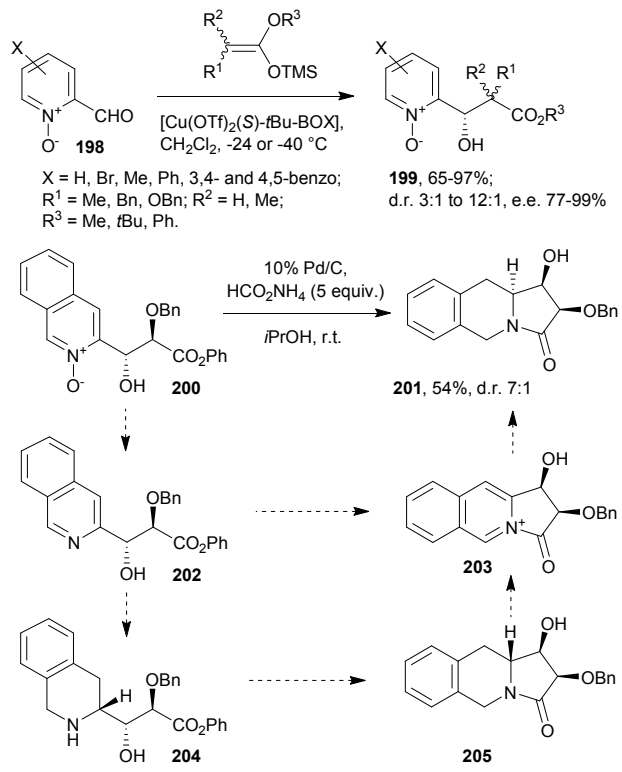
Scheme 30



Scheme 31

yields and/or enantioselectivities than ethyl esters in the asymmetric dihydroxylation reactions, which were also affected by the nature of the C3-pyridine substituent. Both enantiomers of diols **194** were prepared, including **194a** and *ent*-**194a**, which lacked the substituent on the pyridine ring. (-)-Swainsonine **195** was synthesized from diol *ent*-**194a**, whose hydrogenation gave a mixture of diastereomers *ent*-**191** and *ent*-**192** in 60:40 ratio. However, the configuration of the stereocenter at the ring junction was non influential in the following steps, which include inversion of configuration of the C1 stereocenter. Moreover, hydrogenation of methoxypyridine-diol **194b** was used to synthesize (-)-2,8*a*-di-*epi*-swainsonine **197** through the intermediate **196**. In this case, the diastereoselectivity in the hydrogenation step was good and this was explained by the authors as the consequence of positive interactions of the metal with both (pyridine)methoxy and (propanoate)-C3-hydroxy groups. However, it should be observed that such interactions, particularly the Pt-OH interactions, were not operative in hydrogenations of analogous pyridinium salts, where the stereochemical outcomes were generally influenced by repulsive steric effects. Moreover, the mechanism of hydrogenation of the pyridine *N*-oxide has not been elucidated, and at the moment it is not clear if hydrogenation of the aromatic ring takes place onto the pyridine *N*-oxide or through the preliminary deoxygenation to pyridine, or via a bicyclic pyridinium salt (see further). It is also difficult to foresee the more stable conformations of either the pyridine *N*-oxide and the corresponding pyridine, because the two hydroxy functions can participate in many hydrogen bonds with adjacent *N*-oxide, methoxy and carbonyl groups.

Optically active 2-(hydroxyalkyl)pyridine *N*-oxides **194** were synthesized with moderate to good diastereoselectivities and generally excellent enantioselectivities by bis(oxazoline)-copper catalyzed aldol reactions, of substituted pyridine *N*-oxide 2-carbaldehydes **198** with silyl enol ethers or ketene silyl acetals. (Scheme 32).[76] Conversely, the reaction performed on the *O*-benzyl protection and reduction of the lactam carbonyl were then performed. 2-Pyridinealdehyde gave a racemic product. *Syn*- and *anti*-**199** were easily separated by column chromatography and the 2*R*,3*S* configuration of one of them was determined to be by X-ray analysis. Particularly, optically pure compound **200** was submitted to catalytic hydrogenation aiming to prepare the corresponding indolizidine derivative. In this case, the hydrogenation was carried out in isopropanol at room temperature using ammonium formate as hydrogen



Scheme 32

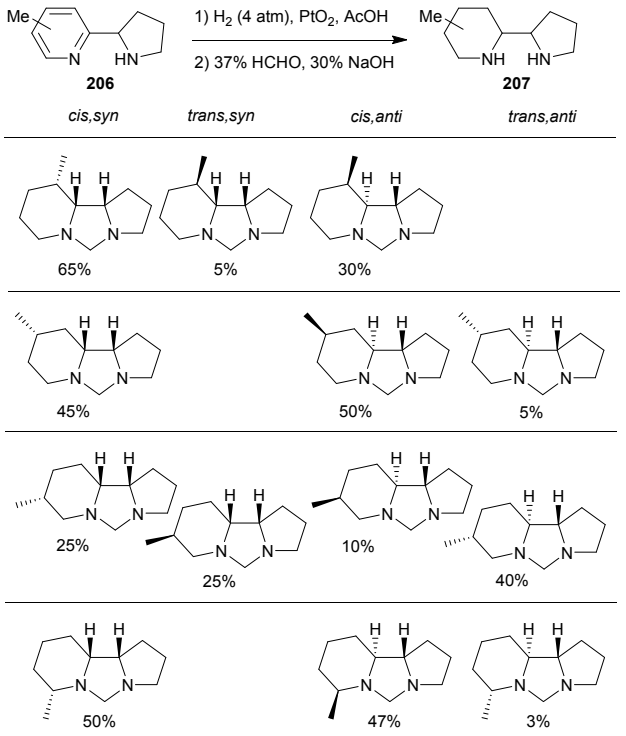
source and Pd/C as the catalyst, so obtaining the tricyclic lactam **201** in a satisfactory yield with 7:1 diastereomeric ratio. Removal of

Aiming to explain the high level of stereocontrol, the bicyclic pyridinium ion **203**, coming from the preliminary deoxygenation of the oxide **200** to the pyridine **202**, was proposed as the crucial intermediate, which should undergo hydrogen addition to the less hindered face, so affording **201**. This result is in agreement to the outcome of the hydrogenation of the bicyclic pyridinium salt **164** to **165** described in Scheme 27. Instead, would hydrogenation had taken place on the pyridine derivative **202**, the intermediate piperidine **204** with opposite configuration of the newly created stereocenter should have been obtained, considering the outcomes of the hydrogenations of analogous pyridines described in Schemes 21 and 22, and final cyclization step should have produced the diastereomeric lactam **205**. Since the possibility to reduce the pyridine *N*-oxides to the corresponding pyridines by reaction with indium metal in protic medium was demonstrated on a single substrate **199**, the deoxygenation of **200** and analogous available oxides **199**, followed by hydrogenation would give support to the proposed mechanism.

3.4. Aminoalkyl-substituted pyridines, quinolines and *N*-alkylpyridinium salts

(2-Pyrrolidinyl)pyridines **206** bearing a methyl substituent on different positions of the pyridine ring were hydrogenated over Adams catalyst in acetic acid to prepare the substituted 2-(2-pyrrolidinyl)piperidines **207**. Owing to the free rotation of the C2-C2' bond, as a consequence of the disruption of the N-H---N hydrogen bond in the acidic medium, the 2-(2-pyrrolidinyl)piperidines **207** were obtained as mixtures of diastereomers (Scheme 33). The composition of the diastereomeric mixtures were determined after their conversion to the corresponding tricyclic aminals by reaction with formaldehyde. The number and ratio of diastereomers were affected by the position of the methyl substituent. A 70:30 ratio of *syn* and *anti* diastereomers of 1-methylperhydropyrrolopyridoimidazole was unexpectedly formed and the *cis,syn* compound was largely predominant (first row). In all other cases, an approximately 1:1 ratio of *syn* and *anti* diastereomers was obtained. Surprisingly, in the hydrogenation of the 3-methyl derivative, the *trans,anti*-3-methylperhydropyrrolopyridoimidazole was unexpectedly formed in larger amount (40%) than any other diastereomer (third row).[77]

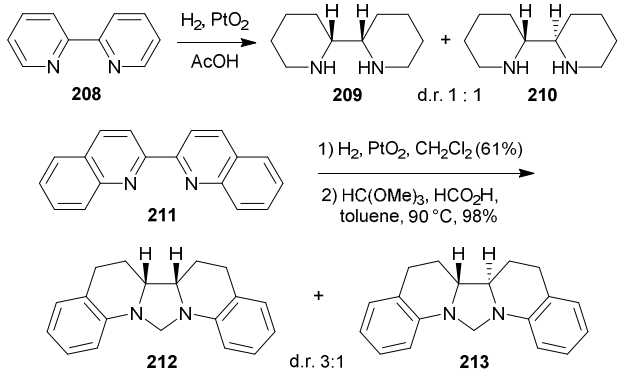
As the hydrogenation of fused polynuclear aromatic compounds proceeds by consecutive single ring hydrogenations, after reduction of the first ring, where one or more stereocenters are created, the following ring hydrogenation(s) can occur with a certain degree of diastereoselectivity. For example, reduction of 2,2'-bipyridine **208** has been accomplished by different methods, including hydrogenation with PtO_2 as the catalyst[78] and reduction with sodium in ethanol[79] and nickel-aluminum alloy in basic



Scheme 33

medium.[80] In all cases were obtained almost equal amounts of the *meso*- and *d,l*-diastereomers, which could be separated via formation of their hydrochloride salts. Optical resolution of the enantiomers was reported, too.[81] Particularly, the catalytic hydrogenation afforded a 1:1 mixture of *meso*- and *d,l*-diastereomers **209** and **210**, respectively (Scheme 34).

The stereochemical outcome indicates that *syn* addition of hydrogen occurred equally to both *syn* and *anti* conformations of diprotonated bipyridyl adsorbed on the catalyst surface. On the other hand, it was stated that hydrogenation of bisquinoline **211** was affected by the experimental conditions, although details were not provided; it was only reported that the use of PtO_2 in dichloromethane afforded a 3:1 mixture of *meso*- and *d,l*-diastereomers, as determined after conversion of the mixture to the cyclic aminals **212** and **213**.[82]



Scheme 34

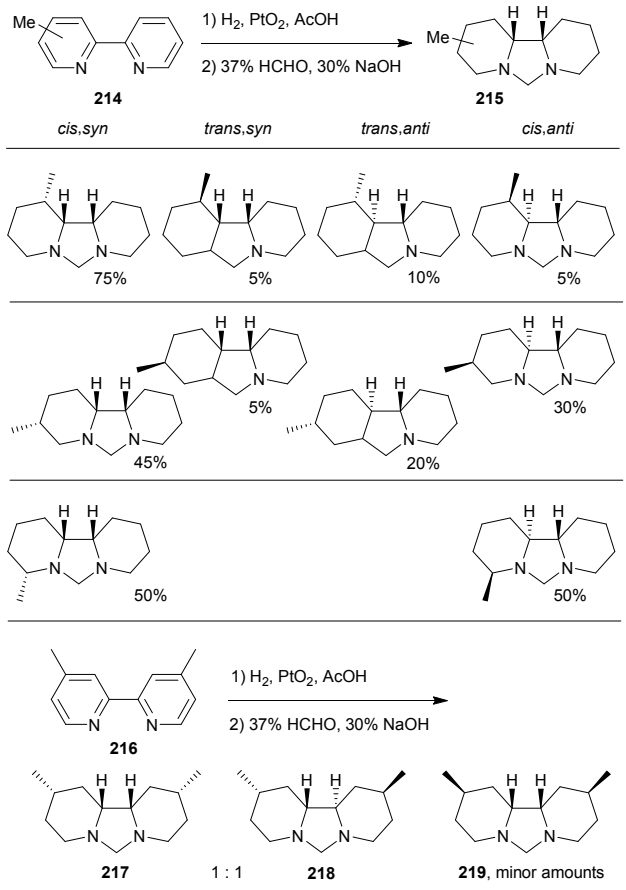
Hydrogenation of mono-substituted bipyridines **214** afforded two to four diastereomers **215** depending on the substitution pattern (Scheme 35). The relative amounts, configurations and preferred conformations of the products were determined after conversion to tricylic aminals by condensation with formaldehyde.[83] It is noteworthy that *syn* and *anti* diastereomers of **215** were formed in almost equal amounts, apart in the hydrogenation of 4-methylbipyridine (first row), where the *cis,syn* diastereomer accounted for 75% of the mixture. In the analogous hydrogenation of 4,4'-dimethyl-2,2'-bipyridine 211 a 1:1 ratio of the *cis,syn,cis*-diastereomer **217** and *cis,anti,cis*-diastereomer **218** was obtained together with minor amounts of the *trans,syn,trans*-diastereomer **219** (Scheme 35).

A recently reported metal-free hydrogenation of aromatic nitrogen heterocycles and anilines exploits the *in situ* formation of frustrated Lewis pairs. For example, 2,6-disubstituted pyridines were stereoselectively reduced to the *cis*-piperidines in toluene at 100 °C under 59 atm of hydrogen pressure in the presence of catalytic amounts of di(pentafluorophenyl)borane and pentafluorophenylethene or perfluoroalkylethene. Reduction of substituted 2,2'-bypyridyls was also investigated: hydrogenation of a single ring was observed with 6,6'-dimethyl derivative **220** so forming **216** by *syn* addition, whereas reduction of the 6,6'-ditolyl derivative **222** afforded the *meso*-perhydrogenated product **223** with almost complete diastereoselectivity (Scheme 36).[84]

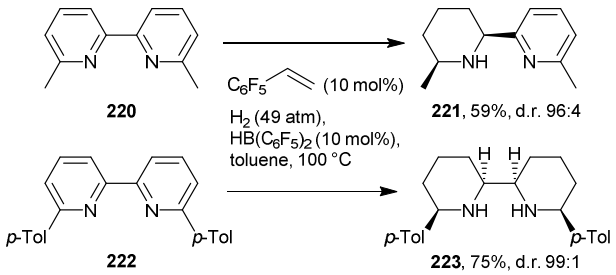
Diquat (**224**) is a bipyridinium herbicide that is used in both field and orchard crops and for control of aquatic weeds and can contaminate irrigation and domestic water. An analytical method for detection of Diquat involves the complete hydrogenation over Adams' catalyst in methanol or aqueous hydrochloric acid, extraction with organic solvent and analysis by GLC. By this way the *cis* and *trans* perhydro derivatives **226** and **227**, respectively, were formed in 65:35 ratio (Scheme 37). Considering the planar rigid structure of Diquat, the formation of the relevant amount of the *anti* diastereomer may appear surprising, however, it can be considered that the semi-hydrogenated intermediate **225** can assume the more stable flat conformation with *trans*-fused hydrogenated rings which can undergo hydrogen uptake on both faces of the pyridinium ring.[85] Prevalence of the *trans* diastereomer **227** was instead obtained using the nickel chloride-sodium borohydride reducing system, and the configuration of the two diastereomers was confirmed by X-ray crystal structure of the corresponding dihydrochlorides.[86] Discrepant *trans*/*cis* ratios were reported by other authors who used the same reducing system, ranging from 95:5[87] to ca. 25:75.[88]

3.5. 5,6,7,8-Tetrahydroquinolines

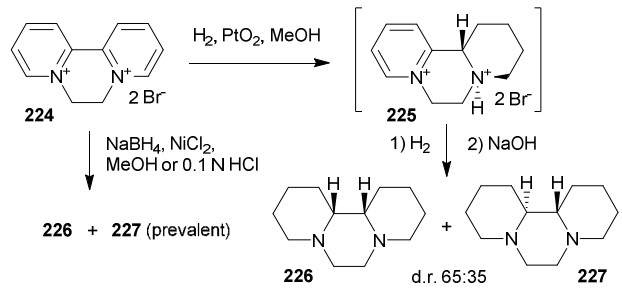
In a recently reported asymmetric synthesis of decahydroquinolines the auxiliary-induced strategy was used to hydrogenate the substituted benzene ring of quinolines **228** to give the intermediate tetrahydroquinolines **230** and **231** (Scheme 38).[89] Hydrogenation was carried out using PtO_2 as the catalyst in trifluoroacetic acid (TFA) at room temperature and 20 atm of H_2 pressure. Best results in terms of conversion and diastereoselectivity (d.r. up to 89:11) were obtained with the *i*Pr-substituted auxiliary. The sense of asymmetric induction was explained by considering the rigid structure of the protonated substrate, where a hydrogen bond is formed between the protonated pyridine and the auxilary's carbonyl group, as shown in structure **229**. Hence, the substrate is adsorbed onto the surface of the catalyst at the less hindered face, *anti* to the oxazolidinone substituent, and receives hydrogens at the same face to give **230** as the main product.



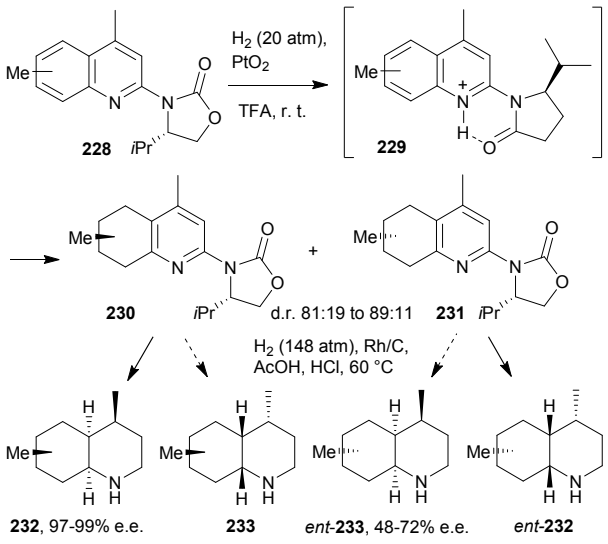
Scheme 35



Scheme 36



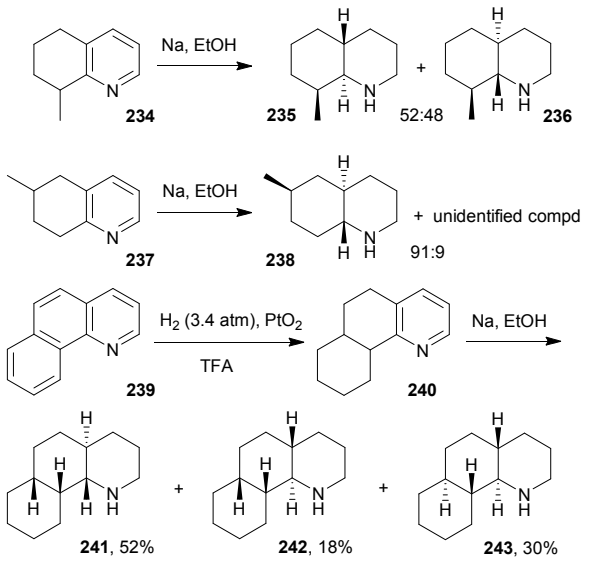
Scheme 37



Scheme 38

The subsequent hydrogenation of the 4-methyl-substituted pyridine ring of the diastereomers **230** and **231** was carried out with Rh/C as the catalyst in more severe conditions and gave the decahydro derivatives **232** and **233** and occurred with concomitant cleavage of the chiral auxiliary. In this reaction, the diastereoselectivity was controlled by either the chiral oxazolidinone (auxiliary induced diastereoselectivity, AID) and the stereogenic center previously introduced in the carbocyclic ring (substrate induced diastereoselectivity, SID). As a matter of fact, the power of the auxiliary's stereocenter was stronger than the one of the carbocyclic stereocenter. However, it was observed that when the carbocyclic methyl substituent was oriented as in **230** the highest levels of enantioselectivity were obtained because the SID enforced (matched) the AID.

Hydrogenation of mono- and disubstituted quinolines by Raney-Ni required severe conditions (120 atm., 180 °C) and produced mixture of *cis*- and *trans*-fused diastereomers, sometimes with very low efficiency.[90] Reduction with sodium in ethanol is an alternative method to obtain piperidines from pyridines and it has been applied to the reduction of 5,6,7,8-tetrahydroquinolines bearing substituent(s), hence stereocenter(s), on the saturated ring. However, mixture of two diastereomeric *trans*-fused bicyclic compounds are often obtained, e.g., compounds **235** and **236** were formed in comparable amounts from 8-methyl-5,6,7,8-tetrahydroquinoline **234**. An exception was found in the reduction



Scheme 39

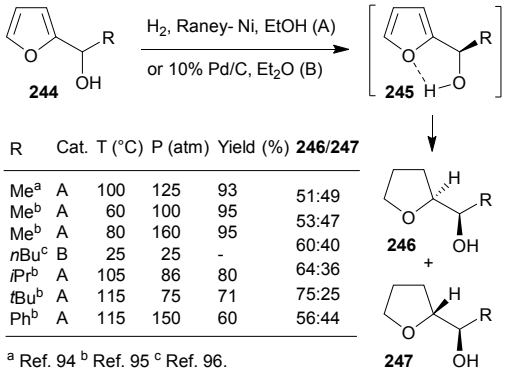
of the 6-methyl derivative **237** from which a single 6-methyldecahydroquinoline **238** was obtained together with a minor amount of an unidentified compound. Moreover, reduction of the tricyclic compound **240** afforded a mixture of three totally reduced compounds **241**, **242** and **243**. Presumably, the presence of the diastereomer **240** with *trans*-fusion of the two carbocyclic rings is due to incomplete stereoselectivity in the partial hydrogenation of the aromatic precursor benzo[*h*]quinoline (**239**).[91]

4. Hydrogenation of furan derivatives

4.1. Hydroxyalkyl- and acylfurans

Hydrogenation of the furan ring in the presence of Pt black derived from PtO_2 catalysts or copper chromite required severe experimental conditions, i.e. high temperature and hydrogen pressure, and was often accompanied by side reactions, such as hydrogenolysis of one or both C-O bonds and/or hydrogenolysis of benzylic C-O and C-N bonds when present.[92] Raney-Ni allowed a rapid hydrogenation of alkyl- and phenyl(2-furyl)carbinols **244** to the tetrahydrofuran derivatives in 80-90% yield at relatively low temperatures and pressures, typically 60-80 °C and 80 atm of hydrogen pressure.[93] In these reports the diastereoselectivity was not assessed, although it is clear that mixtures of diastereomers must have been produced, and the degree of stereocontrol is dependent on the distance between the stereocenters.

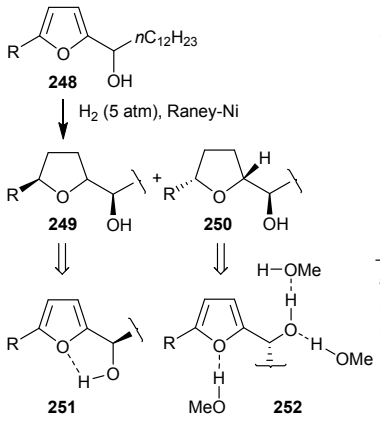
1-(2-Furyl)ethanol **244** (R = Me) was hydrogenated over Raney-Ni in ethanol at 100 °C under 125 atmospheres of hydrogen pressure, and the tetrahydro derivatives **246** and **247** were isolated in 65% and 35% yield, respectively, by distillation (Scheme 41).[94] The preferred formation of the higher boiling *erythro* diastereomer **246** was induced by the planar rigid conformation adopted by the furfuryl alcohol moiety due to the intramolecular hydrogen bond, see structure **245**,



R	Cat.	T (°C)	P (atm)	Yield (%)	246/247
Me[a]	A	100	125	93	51:49
Me[b]	A	60	100	95	53:47
Me[b]	A	80	160	95	60:40
*n*Bu[c]	B	25	25	-	64:36
*i*Pr[b]	A	105	86	80	75:25
*t*Bu[b]	A	115	75	71	75:25
Ph[b]	A	115	150	60	56:44

[a] Ref. 94 [b] Ref. 95 [c] Ref. 96.

Scheme 40



R	Solvent	249/250
H	*n*BuOH	73:27
H	*n*PrOH	71:29
H	EtOH	66:34
H	MeOH	53:47
Me	*i*PrOH	**85:15**
Me	EtOH	68:32
Me	MeOH	**37:63**
$CH(OEt)_2$	*i*PrOH	79:21
$CH(OEt)_2$	EtOH	64:36
$CH(OEt)_2$	MeOH	**14:87**

[a] The ratio 67/33 was reported in a different table in the same paper.

Scheme 41

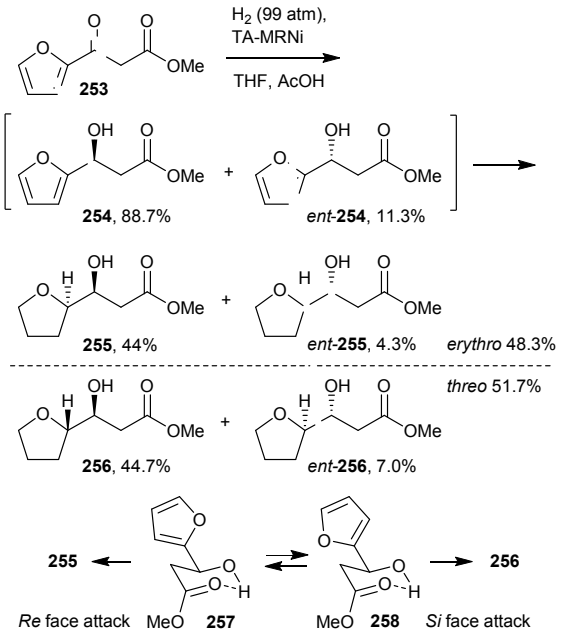
consequently the molecule is adsorbed on the heterogeneous catalyst surface by the less hindered face which then undergoes hydrogen addition.

The diastereoselective hydrogenation of homologous 1-(2-furyl)alkanols was later investigated as a function of the substituent R, which also affected the reaction conditions required for efficient hydrogenation. [95] It could be so ascertained that the d.r. increased with increasing the bulkiness of the R substituent, although the outcomes reported for hydrogenation of R = Me does not match exactly with the previously reported data. In the case or R = Ph, partial hydrogenation of the Ph ring was also observed. In agreement with this trend, the hydrogenation of 1-(2-furyl)pentanol was later accomplished with only moderate diastereoselectivity (d.r. 60:40) using Pd/C as the catalyst, which allowed to use milder reaction conditions (25 atm. of H_2 pressure at room temperature in diethyl ether as the solvent).[96]

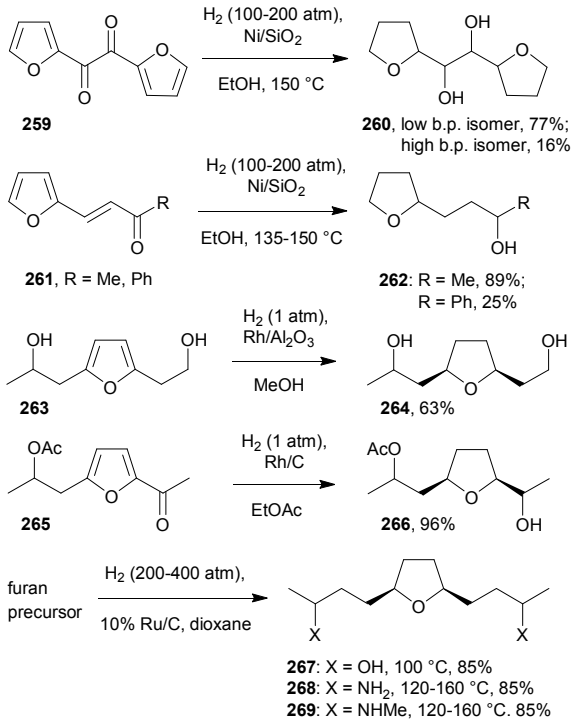
Later, the hydrogenation of 1-(2-furyl)tridecanol and two analogous alcohols **248** was investigated using Raney-Ni in different alcoholic solvents (Scheme 42).[97] It was discovered that the sense and the degree of diastereoselectivity were dependent on the solvent used, besides the nature of the furan C5-substituent. Taking the unsubstituted substrate **248** (R = H) as a model, the diastereoselectivity in favor of **249** decreased in the order: 1-butanol, 1-propanol, 2-propanol, ethanol, methanol. Moreover, the diastereomer **249** was prevalently obtained from the methyl-substituted furan, especially working in 2-propanol (d.r. 85:15). However, in methanol as the solvent, the diastereomer **250** predominated (d.r. 37:63). The same trend was observed with the substrate **248** bearing the bulkiest acetal group, in this case the highest level of diastereoselectivity was observed in methanol in favour of **250**. It was found that the pressure had a limited influence on the diastereoselectivity, as similar results were achieved working at 80 atmospheres of hydrogen pressure. Finally, in agreement with precedent reports, hydrogenation over rhodium on alumina gave unsatisfactory results.

The opposite sense of diastereoselectivity observed in different alcohols was explained by the different polarity of the solvent. In the less polar solvent 1-butanol the intramolecular hydrogen bond forces the substrate in the relatively rigid conformation **251**, so that hydrogen addition occurs to the less hindered face of furan, leading to diastereomer **249**. Conversely, in the most polar solvent methanol, the substrate assumes preferably the conformation **252** where methanol can form hydrogen bonds with either furan oxygen and the secondary alcohol, especially in the presence of the bulky substituent.

Methyl 3-(2-furyl)-3-oxopropanoate (**253**) was hydrogenated over (*R*,*R*)-tartaric acid-modified Raney-Ni (TA-MRNi) to afford a mixture of four stereoisomers **255**, *ent*-**255**, **256** and *ent*-**256** (Scheme 42).[98] The relative stereochemistry of the fully hydrogenated products was assigned knowing the stereoselectivity of the reduction of **253** with sodium borohydride, where the *threo* diastereomers were eluted first with respect to the *erythro* diastereomers in the GLC analysis. It was so determined that the hydrogenation had occurred with moderate enantioselectivity (74% of e.e.) and almost no diastereoselectivity. This result is in contrast with the stereochemical outcomes described in Scheme 40, where *erythro* diastereomers were the prevalent hydrogenated products. A possible explanation for that discrepancy is that, a hydrogen bond is preferentially formed between the hydroxy and ester functions in the intermediate furfuryl alcohol, e.g. **254**, because the furan oxygen is less basic than the carbonyl oxygen. Consequently, the (furan-C2)-C3 bond is free to rotate, see models **257** and **258**, and hydrogen can add on both faces of furan, leading to **255** and **256**, respectively. It should be observed that the furfuryl alcohols **254** and *ent*-**254** underwent hydrogenation of the furan ring on the chiral catalyst with a different degree of diastereoselectivity, as the ratio *ent*-**256**/*ent*-**255** was higher than the ratio **256**/**255**. Moreover, when substrates analogous to **253**, bearing either electron-donating or -withdrawing substituents, were submitted to the



Scheme 42



Scheme 43

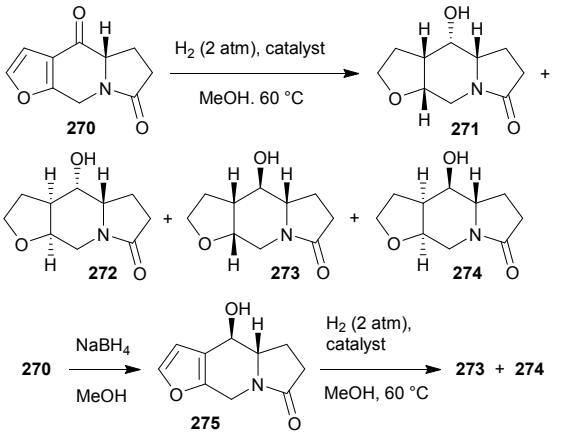
same hydrogenation conditions, only the carbonyl group was reduced, and in the most favorable case of 5-methyl-2-furyl derivative the fully hydrogenated compound was formed in low amount.

Silica-supported nickel was used to reduce 1,2-bis(2-furyl)ethanedione (**259**) under high hydrogen pressure and temperature (100-200 atm., 150 °C) to give 1,2-bis(2-tetrahydrofuryl)-1,2-ethandiol (**260**) in high yield and moderate diastereoselectivity, although the relative stereochemistry was not determined (Scheme 43). Similarly, β-(2-furyl)-α,β-unsaturated ketones **261** were reduced to β-(tetrahydro-2-furyl)alkanols **262** although formation of the phenyl-substituted product was accompanied by extensive hydrogenolysis and side reactions. [99] Analogous aldol condensation of furfural with acetone, dehydration to α,β-unsaturated products (mono- and bilateral reactions) and subsequent hydrogenation of the resulting compounds could be effected in a single process in a batch reactor over Pd/MgO-ZrO_2 (120 °C, 54 atm of H_2) to give the fully saturated products by reduction of C=C and C=O groups and furan ring, presumably with low or no diastereoselectivity.[100]

En route to nonactic acid, hydrogenation of the furan rings present in compounds **263** and **265** was carried out using supported rhodium catalysts in surprisingly mild conditions.[101] It was claimed that a single diastereoisomer **264** was formed from **263**, perhaps meaning that complete *cis* selectivity was observed in hydrogenation of the furan ring, while the relative configuration of the secondary alcohol stereocenter was not determined. Similarly, incomplete information was given about the stereochemistry of the hydrogenated product **266** from the precursor **265** (Scheme 44). Mixture of diastereomers of compounds **267-269** were presumably obtained by hydrogenation of 2,5 disubstituted furans bearing hydroxy and amino functions over Ru/C, in severe conditions, owing to the increased distance between the formed stereocenters.[102]

4.2. Functionalized fused polycyclic compounds containing the furan ring

Enantiomerically pure furan-fused indolizidinediones **270** were prepared from (*S*)-pyroglutamic acid and were converted to tetrahydrofuran-fused indolizidinols (Scheme 44). The key step is the diastereoselective hydrogenation of both carbonyl group and furan ring, which was investigated applying a number of heterogeneous catalysts. Elevated temperatures and relatively long reaction times were required for an effective reduction. All the four diastereomers **271**-**274** of the reduced product were obtained in different ratios, depending on the catalyst used. Rhodium on alumina gave the best performance providing the highest percentage of the diastereomer **271**, as compared to Raney-Ni and palladium and ruthenium catalysts.[103]
Compound **271** was unequivocally identified by X-ray crystallography, whereas the structural determination of **272**, **273** and **274** was established by means of complementary NMR analyses. On the other hand, only the diastereomers **273** and **274** were produced in hydrogenation reactions of the enantiopure alcohol **275**, which was prepared by reduction of **270** with sodium borohydride. It is noteworthy that an unsatisfactory ratio **273**/**274** (56:44) was obtained in the hydrogenation of **275** over rhodium on alumina as compared to the corresponding hydrogenation of **270** where the ratio **271**:**272** was 87:04. This implies that hydrogenation of **270** mostly occurs through the preliminary addition of hydrogen of



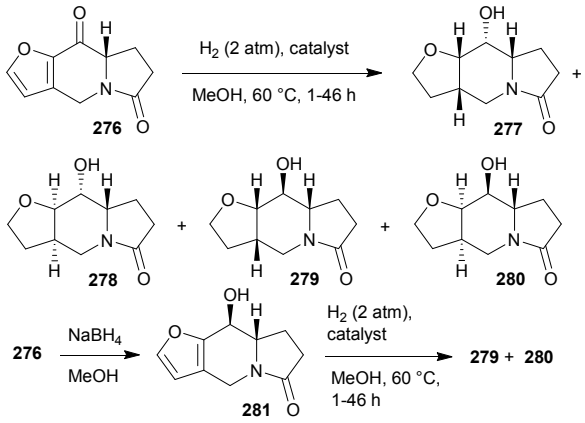
Compd	Catalyst	Time (h)	Yield (%)	271/272/273/274
270	10% Pd/C	18	99	14 : 16 : 12 : 46
270	Ra-Ni	17	98	41 : 16 : 15 : 28
270	5% Ru/C	29	99	58 : 08 : 09 : 25
270	5% Rh/Al_2O_3	22	82	87 : 04 : 03 : 06
275	10% Pd/C	02	99	39 : 61
275	Ra/Ni	04	99	64 : 36
275	5% Ru/C	45	99	30 : 70
275	5% Rh/Al_2O_3	28	95	56 : 44
275	10% Pd/C, AcOH	02	99	54 : 46
275	10% Pd/C, Et_3N	02	99	73 : 27
275	10% Pd/C, TMEDA	03	82	76 : 24

Scheme 44

the less hindered face of the alkene double bond of the O-C=C-C=O moiety, and the carbonyl group is reduced in a second step. Only moderate levels of diastereoselectivity were obtained in hydrogenation of the alcohol **260**, with any catalyst used, and the prevalence of the one or the other diastereomer was dependent on the nature of the catalyst. Moreover, in the presence of triethylamine or tetramethylethylenediamine the ratio **273**/**274** was inverted in the hydrogenation of **275** with Pd/C, presumably owing to the deprotonation of the alcohol and repulsive interaction between the alkoxide and the catalyst surface.

Similarly, hydrogenation reactions were performed on the regioisomeric ketone **276** and the alcohol **277** derived from it (Scheme 45). Scrutiny of different catalysts in hydrogenation of **276** showed the same trend observed in the hydrogenation of ketone **270** in Scheme 45, as mixtures of the four diastereomers **277**-**280** were always obtained and the highest proportion 96% of **277** was achieved using rhodium on alumina as the catalyst. On the other hand, differing from the outcomes of hydrogenation reactions of the alcohol **275** in Scheme 44 hydrogenation of the enantiomerically pure alcohol **286** occurred with good diastereoselectivity, and especially, Raney-Ni gave the highest diastereomeric ratio **279**:**280** = 93:7. The prevalent formation of **273** from **275** and of **279** from **281** is likely explained by the haptophilicity of the OH group which directs the addition of hydrogen from the same side.

Furan rings can be reduced to tetrahydro derivatives by two step sequence involving conversion to 2,5-dihydro derivative by Birch reduction and subsequent hydrogenation of the C3-C4

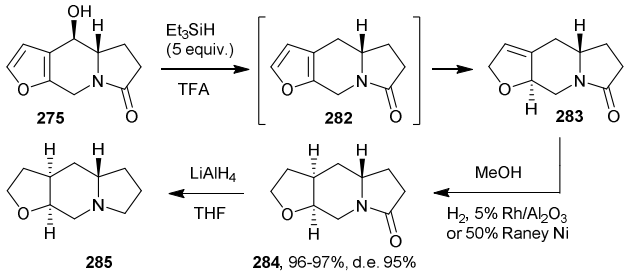


Compd	Catalyst	Time (h)	Yield (%)	277/278/279/280
276	10% Pd/C	01	90	12 : 04 : 63 : 21
276	Ra-Ni	20	98	56 : 16 : 17 : 11
276	5% Ru/C	46	99	60 : 09 : 12 : 20
276	5% Rh/Al_2O_3	46	82	96 : 00 : 01 : 03
281	10% Pd/C	15	99	77 : 24
281	Ra-Ni	22	99	93 : 0 7
281	5% Ru/C	45	95	62 : 38
281	5% Rh/Al_2O_3	42	99	75 : 25

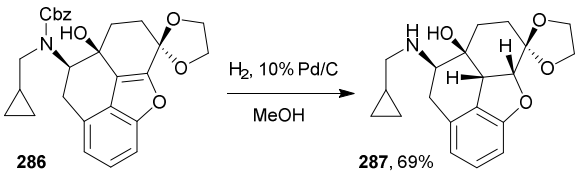
Scheme 45

double bond. As an alternative to the Birch reduction, semi-hydrogenation of compound **275** was performed with an excess of triethylsilane in trifluoroacetic acid and gave selectively the 2,5-dihydrofuran derivative **283** owing to the concomitant reductive cleavage of the benzylic C-O bond (Scheme 46). The reaction performed with one equivalent of triethylsilane gave the compound **282**, which is therefore the intermediate of **283** in the precedent reaction. The C=C double bond was then hydrogenated with rhodium on alumina or Raney-nickel in methanol to give **284** with 95% d.e., and this was followed by lactam reduction, leading ultimately to the compound **285**.[104] It should be observed that, despite the different reducing agent and apart the occurrence of hydrogenolysis pathway, the final stereochemical outcome is the same as obtained in Scheme 44.

The hydrogenation of the furan ring of the polycyclic compound **286** occurred smoothly using Pd/C in methanol under atmospheric pressure at room temperature and afforded a single diastereomer **297** (Scheme 47). The stereochemistry of the hydrogenation is hardly affected by steric factors. Instead, examination of the molecular model of



Scheme 46



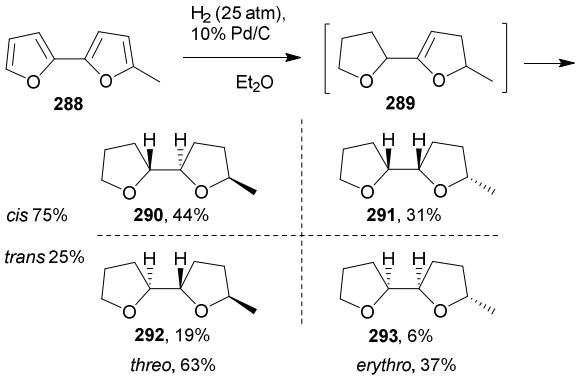
Scheme 47

286 shows the almost perpendicular orientation of the hydroxyl group with respect to the benzofuran plane, so that it is likely that hydrogen uptake occurs following the interaction of the OH group with the metal surface.[105]

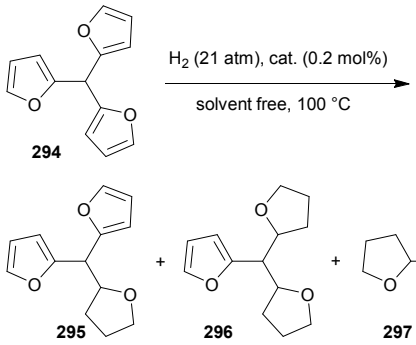
4.4. Polyfurans

The hydrogenation of 5-methyl-[2,2']bifuranyl (**288**) over Pd/C was performed at room temperature in diethyl ether under 25 atm. of hydrogen pressure (Scheme 49).[96] The hydrogenation proceeds by the initial reduction of the less substituted furan ring. As a matter of fact, the presence of high amounts of the semi hydrogenated intermediate was detected by ^{1}H NMR analysis of a sample taken during the reaction. The final mixture was composed of four diastereomers where the *threo* isomers **290** and **292** were prevalent over the *erythro* ones **291** and **293**. Also, it can be noticed that *trans*-isomers, especially **292**, were formed in relatively large amounts. This outcome can be explained assuming that reduction of the second furan ring occurred through the intermediate **289**, then the hydrogenation of the last C=C bond took place under the influence of the two previously formed stereocenters.

Tris(5-methylfyran-2-yi)methane (**294**) was submitted to hydrogenation in solvent free conditions in the presence of different heterogeneous transition metal catalysts in order to prepare tetrahydrofurfuryl ethers, which are useful as diesel additives (Scheme 50). Partial and complete hydrogenation afforded the products **295-297**, however, products derived from hydrogenolysis were also formed. In the same experimental conditions, Pd/C gave the better selectivity for tris(5-methyltetrahydrofuran-2-yl)methane (**297**), while Rh/Al_2O_3 was preferable to obtain the partially hydrogenated



Scheme 48

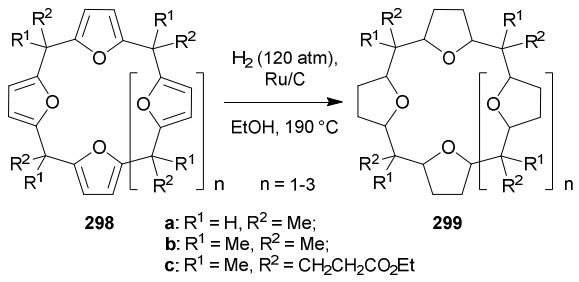


Catalyst	Convn (%)	**295** (Yield %)	**296** (Yield %)	**297** (Yield %)	Hydrogenolysis products (%)
Pd/C	100	1	11	57	31
Pd/Al_2O_3	99	2	34	38	24
Ru/C	65	34	17	3	11
Rh/C	42	30	5	1	6
Rh/Al_2O_3	100	33	58	5	4

Scheme 49

compound **296**. Higher temperature and pressure in Pd/C-catalyzed hydrogenation reactions led to increased formation of hydrogenolysis products. Two diastereomers exist for both compounds **296** and **297**, but their ratio was not estimated.[106]

Calix[n]furans **298** (n = 1-3) were prepared by condensation of furan with acetaldehyde, acetone and ethyl levulinate and were then hydrogenated in severe conditions (120-140 atm, 160-250 °C, 5-6 h) over Ru/C or Ru-Rh/C in EtOH to give the saturated macrocycles **299**, which were obtained as mixture of diastereoisomers in 15-73% yields (Scheme 50).[107] The calix[4]furan (**298b**) derived from acetone lacks stereocenters in the *meso* positions and has a more rigid conformation than higher homologues. Hence, assuming that hydrogen prevalently add *syn* to each furan ring, the issue of diastereoselectivity is reduced to the control of the relative configurations of tetrahydrofuran rings to each other in the reduced macrocycle **299b**. However, number, ratio and configuration of the obtained diastereomers were not provided.

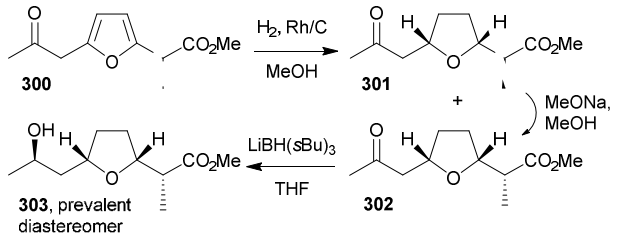


Scheme 50

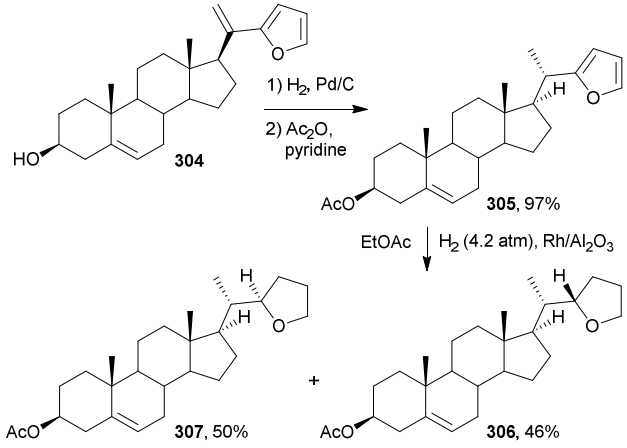
4.5. Other substituted furans

Racemic nonactic acid methyl ester **303** was synthesized by a route which comprised the *cis*-hydrogenation of the substituted furan **300** by means of rhodium on alumina Although the relative stereochemistry was not controlled and the two diastereomeric tetrahydrofuran **301** and **302** were formed in equal amount, the isomer **301** could be converted into the desired one **302** by basic treatment. Finally, reduction of the carbonyl group was achieved by reaction with tris(*sec*-butyl)borohydride which afforded the ester **303** with satisfactory diastereoselectivity (Scheme 52).[108]

The ecdysone side chain was prepared starting from pregnenolone constructing first the furan derivative **304** (Scheme 52).[109] Hydrogenation of the alkene group with palladium on carbon and acetylation of the alcohol function exclusively afforded the furan derivative **305** in excellent yield. Hydrogenation of the heterocyclic ring was instead accomplished using rhodium on alumina as the catalyst in ethyl acetate for 1 h at medium pressure of hydrogen. However, the two diastereomers **306** and **307** were obtained in comparable amounts, because of lack of conformational rigidity of the furylalkyl moiety. Longer reaction time (6 h) in the above reaction led to further reduction of the trisubstituted alkene.



Scheme 51



Scheme 52

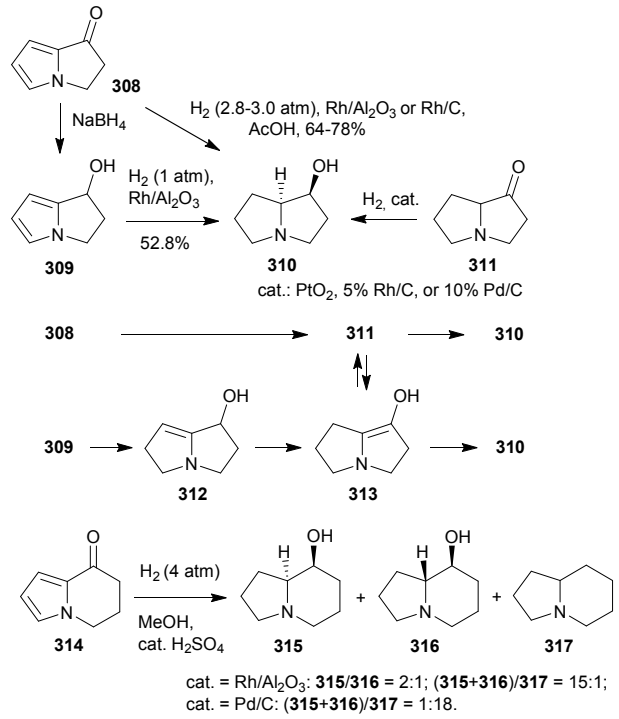
5. Pyrrole derivatives

5.1. Pyrrolizine and indolizine derivatives

2,3-Dihydropyrrolizin-1-one (**308**) was first reduced by Adams using Rh/Al_2O_3 as the catalyst in acetic acid in mild conditions to give the 1-hydroxypyrrolizidine **310**, which was also obtained by hydrogenation of 2,3-dihydropyrrolizidin-1-ol (**309**) (Scheme 54).[110] The correct configuration of **310** was later assigned by preparing the identical compound by hydrogenating **308** using Rh/C as catalyst.[111]

A 90:10 ratio of two diastereomers, where **310** was the prevalent one, was successively detected when the same reduction was repeated by other authors, who also prepared essentially pure **310** by hydrogenation of pyrrolizidin-1-one **311** over PtO_2or carbon-supported Pd and Rh catalysts.[112]

The identical stereochemical results of the hydrogenations of the pyrrole-ketone **308** and -alcohol **309** poses the problem of the mechanistic interpretation of the reactions. First of all, it was not determined which of the functional groups of **308**, ketone or pyrrole, was reduced first, as both the possible intermediates **309** and **311**, prepared by alternative routes, afforded the same final product **310**. Moreover, the stereochemistry of the hydrogenation of the pyrrole-alcohol **309** can be explained on the ground of purely steric effects, excluding any role of the "haptophilic effect" that should direct the hydrogen uptake *syn* to the hydroxy group, as observed in the hydrogenation of indanol (Section 1). However, a reaction pathway involving the consecutive formation of the partially reduced intermediates **312** and **313**, where the latter can be reduced exclusively to **310**, cannot be excluded.

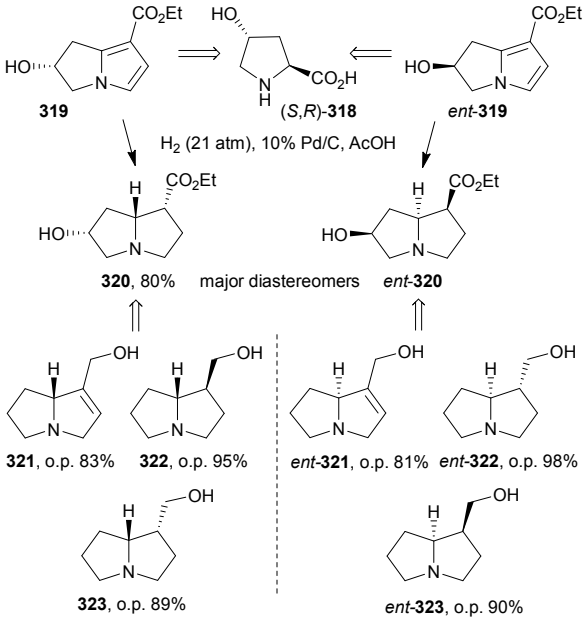


Scheme 53

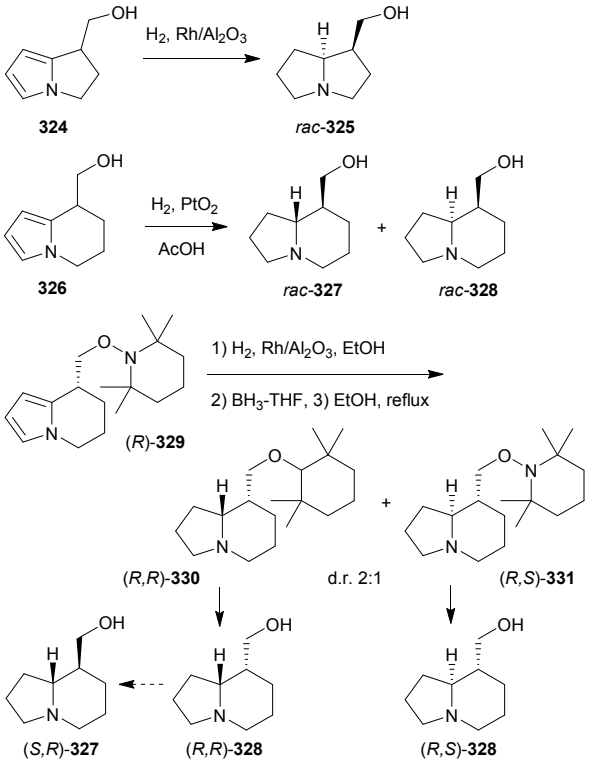
Similarly, 6,7-dihydro-5H-indolizin-8-one (**314**) was hydrogenated over Rh/Al_2O_3 by Barton to give a mixture of diastereomeric saturated alcohols **315** and **316** in quantitative yield (Scheme 54).[113] Later, a 2:1 ratio was determined for the same compounds when they were obtained in similar conditions, although being accompanied by minor amounts of octahydroindolizine **316**. Noteworthy, **317** was mainly formed when the hydrogenation of **314** was performed with Pd/C (4.4 atm, Rh/Al_2O_3,100%, undetermined d.r.).[114]

(-)-4-Hydroxy-L-proline (**318**) was converted by a sequence of steps to both enantiomers of ethyl (2*R*)-2-hydroxy, 2,3-dihydro-1*H*-pyrrolizine-7-carboxylate (**319**). Both enantiomers were then submitted to catalytic hydrogenation under moderate hydrogen pressure in acetic acid to obtain the tetrahydroderivatives **320** and *ent*-**320** in good yield with high level of diastereoselectivity, although the precise d.r. was not provided (Scheme 54). [115] From these products both enantiomers of supinidine (**321**), trachelantamidine (**322**) and isoretrodecanol (**323**) were in turn synthesized with high levels of optical purities.

(±)-Isoretronecanol (**325**) was synthesized from pyrrole by a route involving the final diastereoselective hydrogenation of the pyrrole derivative **324** over Rh/Al_2O_3 at atmospheric pressure of hydrogen (Scheme 55).[116] (±)-Tashiromine (**327**) was similarly synthesized from the corresponding pyrrole precursor **326** by hydrogenation over Adams catalyst in acetic acid, but its epimer (±)-**328** was also formed in relevant amount. *epi*-Tashiromine ((*R*,*R*)-**327**) and (-)-Tashiromine ((*R*,*S*)-**327**) were synthesized starting from L-glutamic acid by a route involving the multi-step construction of the bicyclic pyrrole derivative (*R*)-**329**, which was submitted to hydrogenation over Rh/Al_2O_3. In this case, a 2:1 ratio of the diastereomers (*R*,*R*)-**330** and (*R*,*S*)-**331** was produced, the ratio being inversed with respect to that observed in the hydrogenation of **326**,



Scheme 54



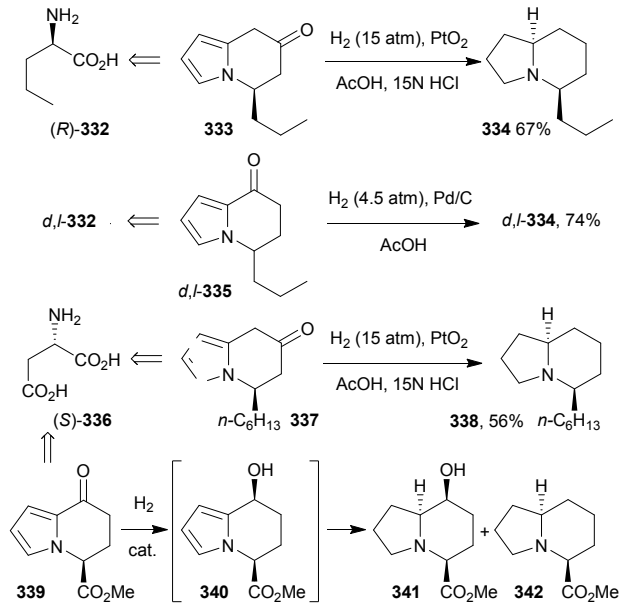
Scheme 55

because of the greater bulkiness of the ring substituent in **329**. Chromatographic separation of the diastereomers required the preliminary formation of their borane complexes to avoid formation of the *N*-oxides, then deprotection was achieved by refluxing in ethanol. (+)-Tashiromine ((*S*,*R*)-**327**) should be available from (*R*,*R*)-**328** through an epimerization process reported for the racemic compounds.[117]

Indolizidine 167B (**334**) was synthesized starting from D-norvaline (**332**) exploiting the hydrogenation of the properly substituted β-keto pyrrole **333** over PtO_2 under 15 atm. of hydrogen pressure in acidic medium, which involved the hydrogenolysis of the carbonyl group (Scheme 56). [118] An alternative route to **334** was also described where d,l-norvaline was converted to the optically pure α-keto pyrrole **335** by achiral auxiliary-induced separation of diastereomeric intermediates. In this case the hydrogenation was performed using Pd/C as the catalyst.[119]

L-Aspartic acid (**336**) was envisaged as the precursor of indolizidine alkaloids. For example, it was converted to the β-keto pyrrole **337**, whose hydrogenation-hydrogenolysis afforded the optically pure indolizidine 209D **338** (Scheme 57).[120] Moreover, **336** served to prepare the pyrrole-ketone-ester **339**, which was reduced with different catalyst in acidic media: the use of Rh/Al_2O_3 as the catalyst gave mainly the alcohol **340**, thus limiting the hydrogenolysis process leading to **341** whereas the latter compound was almost exclusively or prevalently obtained using the Pd catalyst.[121]

Based on the stereochemical outcomes, it was proposed that both the reactions with rhodium and palladium catalysts



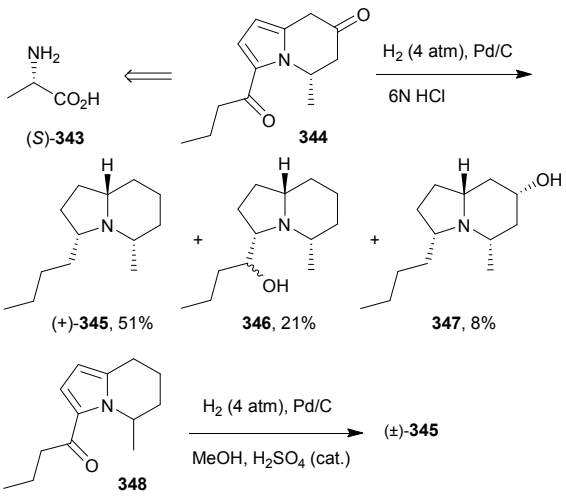
cat. = Rh/Al_2O_3, 4 atm H_2, MeOH-H_2SO_4 (cat): 100% convers., **341**/**342** = 7:1;
cat. = Pd/C, 4 atm H_2, MeOH-H_2SO_4 (cat): 100% convers., **341**/**342** = 1:18.

Scheme 56

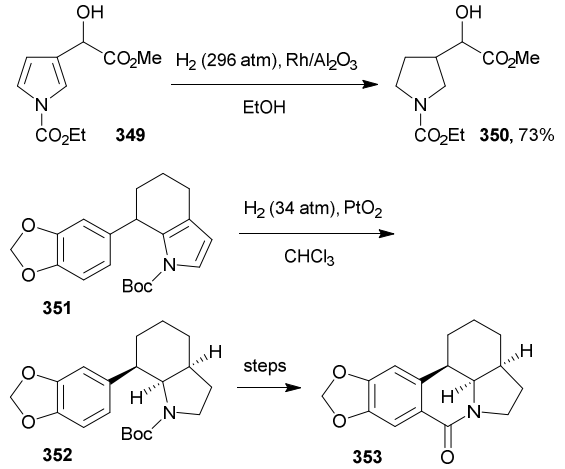
proceeded through the preliminary reduction of the carbonyl group to give the common intermediate **340**. The origin of the chemoselectivity was hen dependent on the different rates of the pyrrole ring hydrogenation with respect to the hydrogenolysis pathway, which involved the formation of an iminium ion by protonation of the OH group and loss of H_2O in the acidic medium.[122]

L-Alanine (**343**) was the chiral source to synthesize (+)-monomorine (**345**). The crucial intermediate **344** underwent hydrogenation and hydrogenolysis over Pd/C in 6N HCl giving a mixture of the desired product **345** and regioisomeric alcohols **346** and **347** in minor amounts (Scheme 57).[118] (±)-Monomorine was later synthesized from pyrrole, the last step of the synthesis was the hydrogenation of the α-keto-pyrrole **348** over Pd/C.[123] Even in the experiments described in Schemes 56 and 57 the configuration of the newly formed carbon stereocenters in the fused bicyclic products was dictated by the already present stereocenter, as hydrogen added exclusively to the less hindered faces of the pyrrole rings and carbonyl functions.

N-Alkoxycarbonyl- and *N*-acylpyrroles can be hydrogenated in relatively mild conditions. For example, (±)-α-hydroxy-3-pyrrolidineacetic acid (**350**), structurally related to β-homoproline, was prepared in good yield by hydrogenation of the pyrrolic precursor **349** using Rh/Al_2O_3 as the catalyst in ethanol (Scheme 58). The ratio of diastereomers was not reported, but a low diastereoselectivity is expected in that reaction because of the free rotation along the pyrrole-C_α bond.[124] On the other hand, the *cis*-fused octahydroindole **352**, a precursor of (±)-γ-licorane (**353**), was exclusively obtained in 97% yield by hydrogenation of the substituted *N*-Boc-pyrrole **351**over Adams catalyst in chloroform.[125]

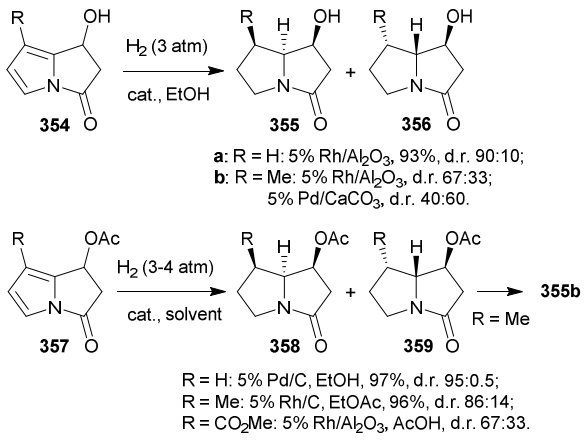


Scheme 57



Scheme 58

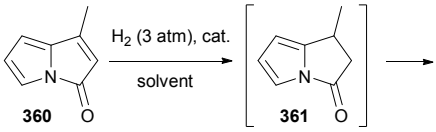
1-Hydroxy- and 1-acetoxy-1,2-dihydropyrrolizin-3-ones **354** and **357**, respectively, were hydrogenated over Rh and Pd catalysts (Scheme 59).[126] The highest ratio of the hexahydro derivatives **355** and **356** (95:5) was obtained in the absence of substituent at C-7 (R = H), either with Rh/Al_2O_3 and Pd/C in ethanol. Substitution at C-7 (R = Me, CO_2Me) markedly reduced the diastereoselectivity, and over $Pd/CaCO_3$ the ratio **355**/**356** was reversed to 40:60, suggesting that the OH group of the substrate interacted with the catalyst surface. In the case of 7-acetoxy derivative **357**, the hydrogenation was complicated by partial hydrogenolysis of the acetoxy group. Retronecanol **355b** was obtained pure from the diastereomeric mixture of compounds **358b** and **359b** by reduction with lithium aluminum hydride, followed by crystallization of the picrate salts mixture.



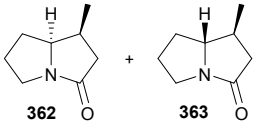
Scheme 59

The influence of catalyst and solvent on the diastereoselectivity of hydrogenation of 1-methylpyrrolizin-3-one **360** was extensively studied (Scheme 60). The highest d.r. of the pyrrolizidinones **362** and **363** was obtained with Raney-nickel, but the main product in this reaction was the 1,2-dihydro derivative **361**, so that 5% Rh/Al_2O_3 at atmospheric pressure in ethanol was chosen as the catalytic system for preparative-scale hydrogenation, that provided compounds **362** and **363** in 90:10 ratio. The methyl substituent in the intermediate **361** clearly directs the hydrogen addition to the opposite pyrrole face.

Similarly, 1-methoxycarbonylpyrrolizin-3-one (**364**) was hydrogenated en route to (±)-isoretronecanol (**369**). In the best conditions (5% Pd/C, MeOH, 3 atm of H_2) the reduced compounds **365** and **366** were obtained in 53% yield with a 91:9 ratio. The high level of diastereoselectivity can be attributed to the steric effect of the ester group on the saturated ring, but it can be at least in part due to isomerization of the intermediate **367** to the more stable isomer **368** with the exocyclic conjugated double bond.[126]



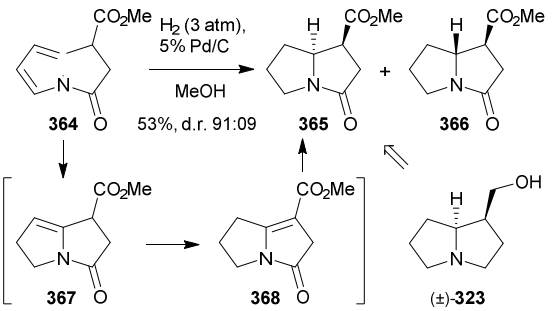
Catalyst	Solvent	362/363
5% Pd/C	hexane	82:18
5% Pd/C	EtOAc	74:26
5% Pd/C	EtOH	76:24
$Pd/CaCO_3$	AcOH	89:11
PtO_2	Hexane	85:15
PtO_2	EtOAc	78:22
5% Rh/C	AcOH	85:15
5% Rh/C	Hexane	89:11
Raney-Ni	Hexane	93:07[a]
Raney-Ni	EtOAc	94:06[a]



Catalyst	Solvent	362/363
5% Rh/Al_2O_3	Hexane	88:12
5% Rh/Al_2O_3	EtOAc	89:11
5% Rh/Al_2O_3	EtOH	91:09
5% Rh/Al_2O_3	AcOH	90:10

[a] The major product was the 1,2-dihydro derivative.

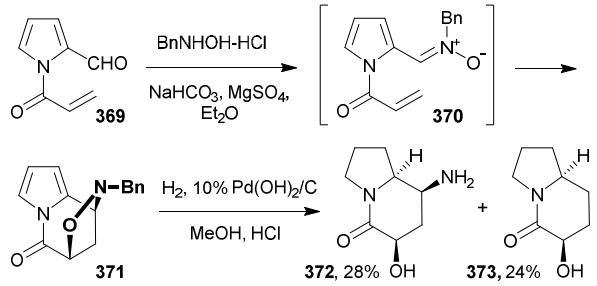
Scheme 60



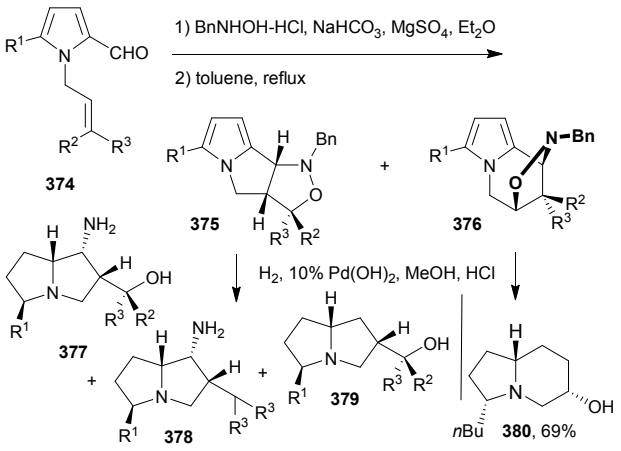
Scheme 61

The intramolecular cycloaddition of nitrones derived from 2-pyrrolaldehydes bearing unsaturated substituents was investigated as a route to pyrrolizidine and indolizidine alkaloids. For example, reaction of *N*-acryloyl-2-pyrrolaldehyde (**369**) with benzylhydroxylamine gave the cycloadduct **371** through the intermediate nitrone **370** (Scheme 61). The successive hydrogenation of the pyrrole ring of **371** was carried out over $Pd(OH)_2/C$ in methanol in the presence of hydrochloric acid and took place with concomitant hydrogenolysis of the N-O and *N*-benzyl bond and gave the polyfuctionalized compound **372** in a stereoselective manner, as hydrogen was introduced *anti* to the nitrogen functionality. However, the concomitant cleavage of the benzylic C8-N bond could not be avoided, and compound **373** was formed in comparable amount.[127]

The same procedure was the applied to *N*-alkenyl-2-pyrrolealdehydes **374** so producing a mixture of fused and bridged-ring regioisomers **375** and **376**, respectively, whose ratio was dependent on the steric property of the substituent (Scheme 62). The prevalent isomers obtained were submitted to hydrogenation in the previously used conditions to give one or two of the three compounds **377**-**379**. Particularly, the reductive deoxygenation process to give **378** occurred when benzylic and tertiary alcohol functionalities were present in the starting material, whereas **379** coming from hydrogenolysis of both benzylic C-N bond was exclusively obtained from the less substituted substrate. Likewise, the compound **380** was exclusively formed from the less substituted bridged compound **376**.



Scheme 62



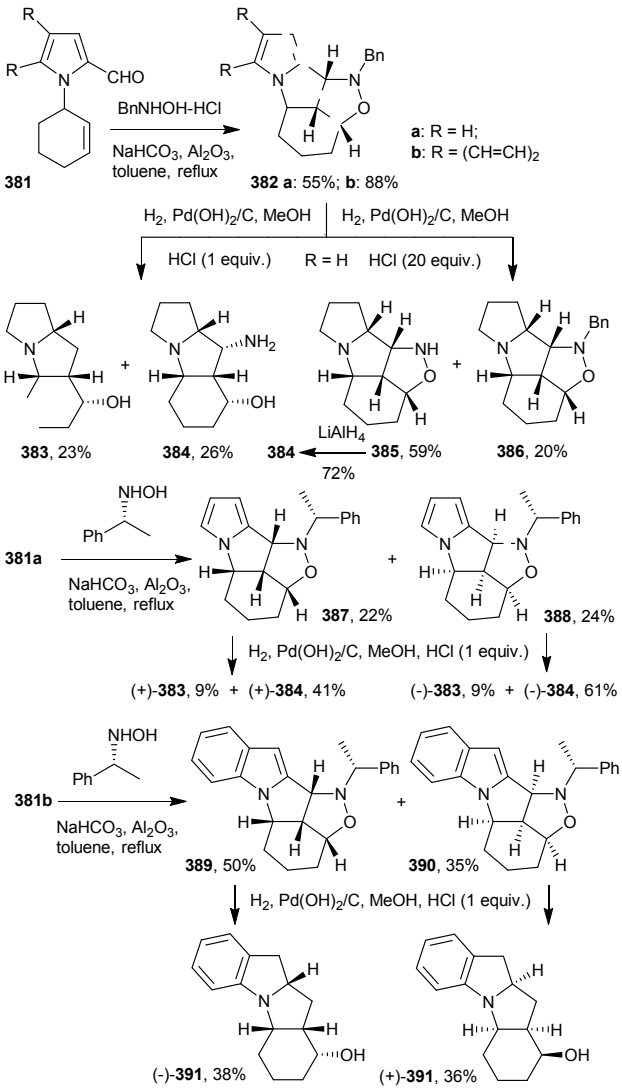
R^1	R^2	R^3	**377** (%)	**378** (%)	**379** (%)
H	H	Ph	10	34	0
H	H	*n*Pr	77	0	0
H	Me	Me	13	32	0
*n*Bu	H	H	0	0	26

Scheme 63

(*R*)-1 Phenylethylhydroxylamine was then checked as chiral auxiliary to provide access to optically active products, in this case the cycloaddition products corresponding to **375** and **376** were obtained as mixtures with low diastereoselectivity.[128]

When applied to *N*-cyclohex-3-en-1-yl-2-pyrrolealdehyde (**381a**), and 2-indolealdehyde (**381b**), the reactions with *N*-hydroxylamine proceeded with complete regio- and stereoselectivities to give the fused polycylic compounds **382a,b** in moderate to good yields. The pyrrole derivative **382a** was submitted to hydrogenation at atmospheric pressure over $Pd(OH)_2/C$ catalyst in methanol at room temperature in different conditions, so observing that the outcomes of the reactions were dependent on the acidity of the medium (Scheme 64).[129] Only cleavage of the N-O and N-benzyl bonds occurred in the absence of HCl. On the other hand, in the presence of 1 molar equivalent of HCl the pyrrole ring was reduced, but further hydrogenolysis of the benzylic C8-N bond could not be avoided, so that a mixture of tricyclic compounds **383** and **384** was obtained. Furthermore, in the presence of 20 molar equivalents of HCl the pyrrole ring of **382a** was hydrogenated preserving the tetracyclic structure and in part the *N*-benzyl substituent, giving mainly compound **385** and minor amount of **386**. The former compound was then converted to **384** by cleavage of the N-O bond with lithium aluminum hydride.

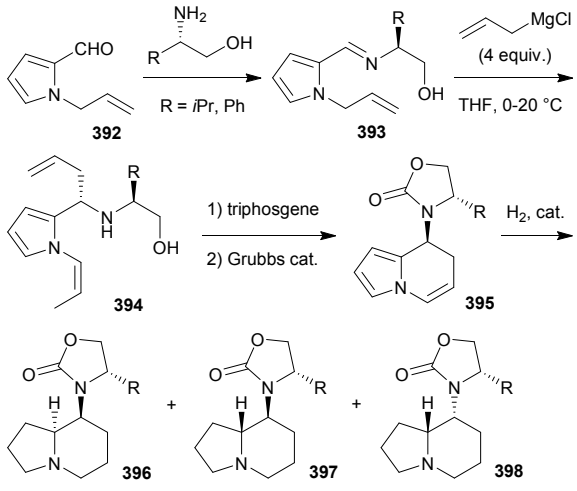
The procedure was then extended to the preparation of optically active compounds by using (*R*)-1-phenylethyamine as chiral auxiliary. Starting from the pyrrolealdehyde **382a**, the diastereomeric cycloadducts **387** and **388** were obtained with no diastereoselectivity and in low yield, and were submitted to hydrogenation in the presence of 1 molar equivalent of HCl, ultimately leading to optically pure compounds (+)- and (-)-**383** and (+)- and (-)-**384**. On the other hand, cycloadducts **389** and **390** were more effectively prepared from the indole aldehyde



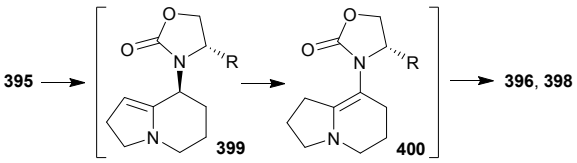
Scheme 64

382b, and were then hydrogenated with concomitant removal of the nitrogen substituent without affecting the benzene ring, so leading to the optically pure compounds (-)- and (+)-**391**.

7,8-Dihydroindolizin-8-ylamine derivatives **395** were stereoselectively synthesized from *N*-allyl-2-pyrrolealdehyde **392** and (*S*)-valinol or (*S*)-phenylglycinol, by a sequence of steps involving the intermediates **393** and **394**. The two pyrrole derivatives **395** were hydrogenated over heterogeneous Pd, Pt and Rh catalysts in methanol to find optimal conditions for the preparations of optically active saturated products (Scheme 65).[130] In all cases mixture of two or three diastereomeric compounds **396-398** were obtained with ratios dependent mainly on the nature of the catalyst. As a matter of fact, the use of Pd/C, $Pd(OH)_2/C$ and PtO_2 gave the worst results in terms of diastereoselectivity or conversion, whereas Rh/Al_2O_3 gave satisfactory performances, especially because this catalyst avoided or largely limited the formation of diastereomer **398**.



R	Catalyst	H_2 (atm)	Solvent	396/397/398	396, 397 (Yield%)
*i*Pr	5% Al_2O_3	1	MeOH	31:69;00	19, 57
*c*Hx	5% Al_2O_3	8	MeOH-AcOH (4:1)	28:69:03	24, 56
*i*Pr	5% Al_2O_3	1	MeOH-Et_3N (4:1)	22:78:00	11, 65
*i*Pr	26% Rh/Gr	1	MeOH-Et_3N (4:1)	24:76:00	11, 62
*c*Hx	26% Rh/Gr	8	MeOH	26:67:07	18, 53
*c*Hx	26% Rh/Gr	1	MeOH-AcOH (4:1)	29:66:05	19, 50

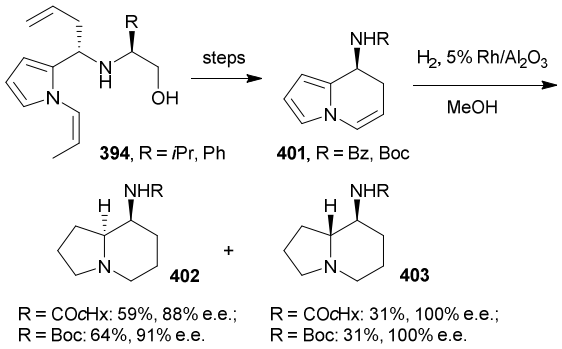


Scheme 65

Moreover, the use of rhodium on graphite (26% Rh/Gr) did not improve the reaction outcome.[131]

The diastereoselectivity was scarcely affected by the hydrogen pressure and the presence of acid or base, as well as by the nature of the R substituent (the phenyl substituent was hydrogenated to cyclohexyl). The configuration of the diastereomers **396** and **397** was determined by X-ray crystallographic studies, and demonstrated that hydrogen had added to the pyrrole face prevalently *syn* to the ring substituent, presumably due to steric reason, considering the freedom of ring substituent to rotate along the C_{ring}-N bond. On the other hand, the formation of the diastereomer **398**, in which the configuration of the originally present stereocenter is inverted, was rationalized by the mechanism involving the isomerization of the pyrroline intermediate **399** to the enediamine **400**, whose hydrogenation would lead to both **396** and **398**.

Aiming to assess the influence of the achiral *N*-substituent on the diastereoselectivity, hydrogenation reactions were carried out on the *N*-benzoyl and *N*-Boc compounds **401** prepared from the same precursors **394** by a sequence of steps (Scheme 66). The outcomes of the reactions were similar to those previously obtained from the oxazolidinone derivatives,



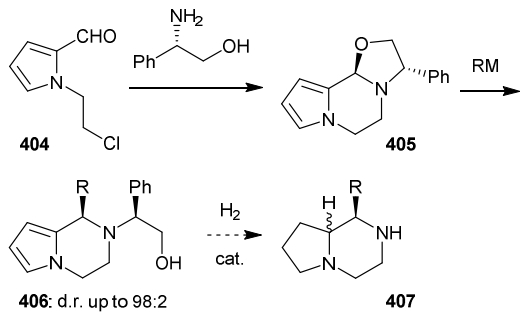
Scheme 66

although the *N*-Boc derivative performed slightly better than the *N*-benzoyl one in terms of yield, diastereoselectivity and especially optical purity of the saturated products **402** and **403**. In fact, the hydrogenation of optically pure *N*-benzoyl and *N*-Boc compounds **401** suffered from partial loss of enantiopurity, because of the occurrence of an epimerization process analogous to that described in Scheme 65. Finally, a correlation was demonstrated between compounds **397** (Scheme 65) and **403** (R = Boc).

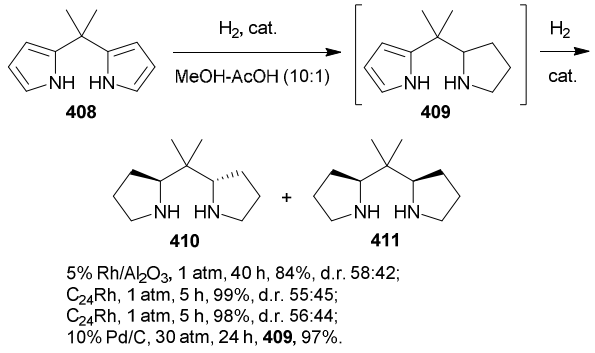
An analogous strategy was adopted to asymmetrically synthesize 1,2-disubstituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **406** (Scheme 67).[132] Several organometallic additions were performed on the oxazolidine **405** obtained by condensation of the substituted 2-pyrrolealdehyde **4044** with (*S*)-phenylglycinol, and the products **406** were obtained with moderate to excellent diastereoselectivity (d.r. up to 98:2). Hydrogenation of purified compounds **406** (R = Me, Et) under 7 atm. of H_2 resulted mainly in the cleavage of *N*-substituent and only traces of the fully hydrogenated products **407** were observed in the crude reaction mixtures. The latter compounds should be certainly obtained by using more active catalysts and/or more forcing conditions, however, this item was not pursued further by the authors.

5.2. Tethered polypyrroles

The simple dipyrrole **408**, easily available by condensation of pyrrole with acetone in acidic medium, was hydrogenated over Rh and Pd catalysts in a MeOH-AcOH mixture at different pressure (Scheme 68). After the first ring was fully reduced to the intermediate **409**, the hydrogenation of the second ring



Scheme 67



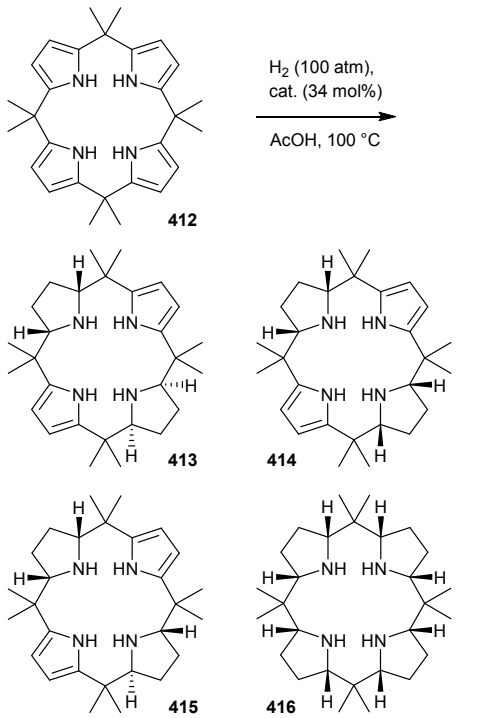
Scheme 68

afforded a mixture of the two fully reduced products **410** and **411** with low diastereoselectivity because the protonated intermediate **409-H$^+$** does not have a rigid conformation. The highest ratio 58:42 was obtained using Rh/Al_2O_3, although Rh/Gr ($C_{24}Rh$) proved to be a more active catalyst.[133]

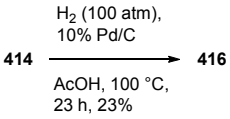
The hydrogenation of *meso*-octamethylporphyrinogen (calyx[4]pyrrole) (**412**) required very severe conditions owing to steric hindrance offered by the *meso*-substituents. Several catalysts were examined under 100 atm of H_2 pressure in acetic acid at 100 °C: 10% Pd/C, Rh/Al_2O_3, and transition metals supported on graphite, such as $C_{24}Rh$, $C_{24}Ru$ and $C_{16}Pd$(Scheme 69).[134] Four products were formed and identified by NMR and X-Ray spectroscopy. Three of them were half reduced compounds with alternating pyrrole and pyrrolidine rings with different relative stereochemistry: *cis*,*anti*,*cis* (**413**), *cis*,*syn*,*cis* (**414**), and *cis*,*trans* (**415**). The fully reduced compound with *all*,*cis* stereochemistry (**416**) was formed in minor amounts, however, it could be also obtained from the half reduced compound **414** preferably using 10% Pd/C as the catalyst. These outcomes indicated that the reduction of **412** proceeded by consecutive hydrogenations of pyrrole rings. After the first ring had been hydrogenated, the pyrrole ring opposite to the first formed pyrrolidine ring was preferably reduced to give the half reduced compounds **413**, **414** and **415**, but only **414** could be reduced to the fully saturated compound **416**.

Conclusions

The diastereoselectivity in the heterogeneous hydrogenation of aromatic and heteroaromatic rings present in chiral molecules, either racemic or optically active ones, can be rationalized taking into account one or more factors. In the case of rigid molecules, e.g. fused polycyclic compounds, steric effects direct the adsorption of the molecule on the heterogeneous catalyst surface, and consequently hydrogen addition takes place to the same, less hindered π face. Such a steric effect has been called "catalyst hindrance". However, when a hydroxyl or an amino group is present in the aliphatic skeleton, possibly near the arene ring, the diastereoselectivity is affected by the so called "haptophilic effect". This means that the approximately planar molecule is adsorbed to the catalyst surface at the π face that allows the OH group to interact with the catalyst surface. On the other hand, flexible compounds,



Catalyst	413/414/415/416
10% Pd/C	25 : 40 : 14 : 16
5% Rh/Al_2O_3	40 : 33 : 11 : 08
$C_{24}Rh$	43 : 31 : 12 : 09
$C_{24}Rh$	36 : 39 : 19 : 05
$C_{16}Pd$	27 : 34 : 17 : 06



Scheme 69

where different conformers can exist, e.g. following rotation around one or more bonds, undergo hydrogenation to the one or the other π face with a selectivity that approximately corresponds to the relative population of the conformers.

On the other hand, the diastereoselective hydrogenation of chiral pyridines and furans which bear a hydroxy group in the C2-alkyl substituent, is controlled by the capability of forming hydrogen bonds between the ring heteroatom and the protic group.

The nature of the metal catalyst and the heterogeneous matrix, the solvent and, at a lesser degree, the temperature, pressure, metal loading, can have a role on the diastereoselectivity. However, a general rule allowing the choice of the best catalyst could not be deduced after surveying the so many reports, as the same catalyst could perform differently on different aromatic substrates. Moreover, in the choice of the catalyst a balance should be made between the activity, selectivity in its wider sense, availability and mildness of the experimental conditions. Among heterogeneous supported metals, Rh/Al_2O_3 and Rh/C in methanol or acetic acetic acid often displayed superior activity/selectivity with respect to the corresponding Pd catalysts and were used efficiently for

hydrogenating any types of benzene and heteroarene derivatives at low temperature and pressure. Also, a problem encountered when using Pd catalysts is the concomitant hydrogenolysis of benzylic C-O and C-N bonds. Instead, ruthenium catalysts have been scarcely used, and mainly on benzene derivatives. On the other hand, the use of Raney-Ni, although selective in some cases, is limited by the very severe experimental conditions required.

Alternatively, zero-valent transition metals can be formed *in situ* from high-valence precursors. Most importantly, the Adams catalyst PtO_2 in alcoholic or acidic medium has been often exploited for the efficient and selective hydrogenation of benzene, pyridine and pyrrole derivatives in mild conditions. Noteworthy, the $RhCl_3$-$NaBH_4$ system, which avoids the use of hydrogen pressure, gave a superior diastereoselectivity than Rh/Al_2O_3-H_2 in the reduction of nitrogen-bridged dibenzocycloalkanes (Scheme 8), however it should be noted that a stoichiometric amount of the rhodium salt was used and diastereoselective reductions on different substrates have not been reported at our knowledge.

Homogeneous reducing systems, e.g. alkali metals in ethanol or ammonia/amines (Birch reduction), and borane and borohydride reagents are appealing alternative to the heterogeneous hydrogenation of arenes and heteroarenes. However, a comparison of the diastereoselectivities offered by heterogeneous vs. homogeneous methods have been scarcely reported in the literature. It should be considered that the homogeneous reduction of fused polycyclic aromatic compounds, e.g. naphthalene, anthracene, quinoline and acridine derivatives, are often complementary, not alternative, to heterogeneous hydrogenation methods, because *trans*- and mainly *cis*-fused bicyclic compounds are formed, respectively. Moreover, lack of diastereoselectivity induced by a chiral substituent was almost always observed, when determined. In fact, the reduction of chiral substituted 5,6,7,8-tetrahydroquinolines by sodium in ethanol in most cases gave mixtures of diastereomers (Scheme 39). However other newly discovered reducing systems were more satisfactory. For example, reduction of phenanthrene and pyrene by Al-HCl_{gas}-ionic liquid occurred with high diastereoselectivity (Scheme 18).

Pyridines are particularly suited for homogenous reduction, and examples of highly diastereoselective, although partial, reductions of quinolines and *N*-alkylpyridinium salts by borohydride reagents are reported in Schemes 25 and 29, respectively. A novel method of metal-free hydrogenation of pyridine and aniline rings has been described using hydrogen pressure in the presence of tris(pentafluorophenyl)borane, and for substituted quinolines and acridine the stereochemical outcomes were unexpectedly different for each substrate (Scheme 11). Moreover, a similar protocol, but using di(pentafluorophenyl)borane allowed to reduce a 6,6'-disubstituted-2,2'-bipyridyl to the single *meso* diastereomer by *syn* addition of hydrogen to both rings (Scheme 36).

The furan ring is often resistant to hydrogenation, and the choice between the mainly used catalysts Raney-Ni, Rh/Al_2O_3 and Pd/C was dependent on the substrate structure. Homogeneous reduction with triethylsilane has been exploited to achieve the partial hydrogenation of substituted furans to the 2,5-dihydro derivatives, but the hydrogenolysis of benzylic C-O bond was a parallel pathway (Scheme 46).

Hydrogenation of the pyrrole ring can be accomplished in mild conditions only when it brings an acyl substituent and/or in acidic conditions, mostly using rhodium and palladium catalysts.

The hydrogenation of the aromatic ring present in chiral molecules can be a useful method for the stereoselective synthesis of substituted cyclohexanes, piperidines, tetrahydrofurans and pyrrolidines. It has been exploited to prepare natural compounds, taking advantage of the presence of stereogenic center(s) in the aromatic ring substituent(s). In order to prepare optically active/pure substituted carbocyclic or heterocyclic compounds, one can exploit the asymmetric induction of a stereocenter present in the crucial intermediate to be hydrogenated ("substrate induced diastereoselectivity"). This intermediate can be prepared from an easily available, optically pure starting material ("ex-chiral pool synthesis"), or by the asymmetric transformation of a prochiral precursor ("reagent induced stereoselectivity" or "auxiliary induced diastereoselectivity").

When the (hetero)aromatic ring presents two or more substituents, or in the case of fused polycyclic aromatic compounds, two or more stereocenters are simultaneously formed in the hydrogenation step. In this case, one must take into account that their relative *cis* or *trans* stereochemistry will be dependent on the reducing method.

Considering that more and more efficient hydrogenation methods/catalysts are being developed, it is conceivable that the hydrogenation of chiral arenes and heteroarenes can be used as the crucial step in novel projected multi-step asymmetric synthesis of natural, biologically and pharmacologically active compounds

Acknowledgements

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