



TETRAHEDRON: ASYMMETRY REPORT NUMBER 21

Prospects for Stereocontrol in the Reduction of Aromatic Compounds

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1. Introduction

This review is designed to outline the possibilities for stereoselective chemical transformations that exist when aromatic compounds are subjected to reduction. Examination of the literature reveals the existence of a multitude of chemical reagents which are capable of reducing aromatic compounds to their saturated or partially-saturated derivatives. Clearly, when highly-substituted aromatic compounds are subjected to these conditions several stereogenic centres may be created, and it is this area that will be scrutinised by this review. The fact that aromatic compounds are so important to the chemical community has meant that a fearsome amount of knowledge regarding the synthesis of such compounds has been amassed. Indeed, the purpose of this review is to persuade the reader that in order to prepare many unsaturated cyclic compounds in a stereodefined manner, it may prove to be efficient to construct an appropriately substituted aromatic precursor and then reduce it in a stereoselective fashion.

We have decided to examine each major class of aromatic compound separately. However, while looking at the reduction of any given aromatic compound, several distinct methods of achieving stereocontrol during reduction can be defined. For example, in reducing a substituted aromatic compound that does not contain any stereogenic centres, the possibility for relative stereochemical induction is large, but that for absolute induction is generally poor (**Figure 1**). In these cases chiral reducing agents, which have not been subject to widespread use in the reduction of aromatic compounds, may prove to be a useful method of controlling the absolute and relative stereochemistry of the reduced products. However, if the arene to be reduced does contain elements of chirality then of course, enantiopure and diastereoisomerically pure material may be obtained from a reduction reaction (**Figure 1**). In this regard it should be noted that the temporary attachment of chiral auxiliaries to aromatic derivatives has been utilised successfully for the preparation of many enantiopure cyclohexane derivatives (*vide infra*).

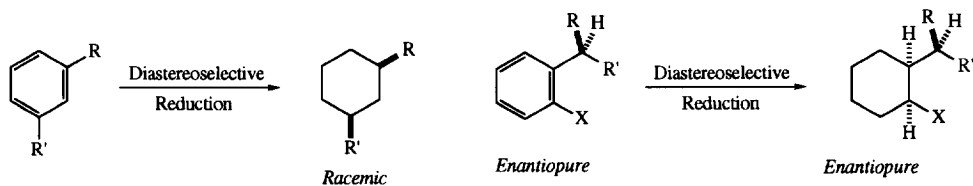


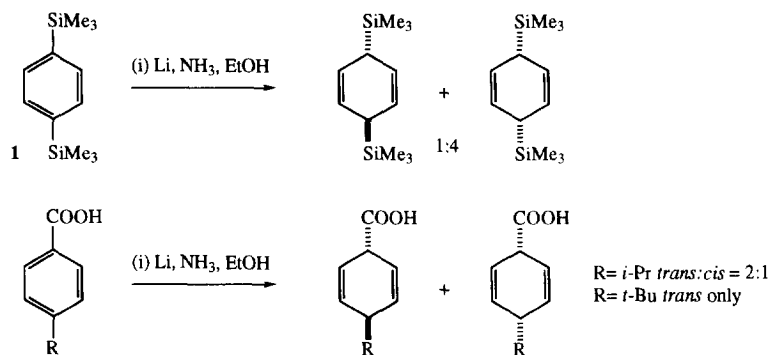
Figure 1

2. Reduction of Benzenoid Compounds

2.1 Dissolving Metal Reduction

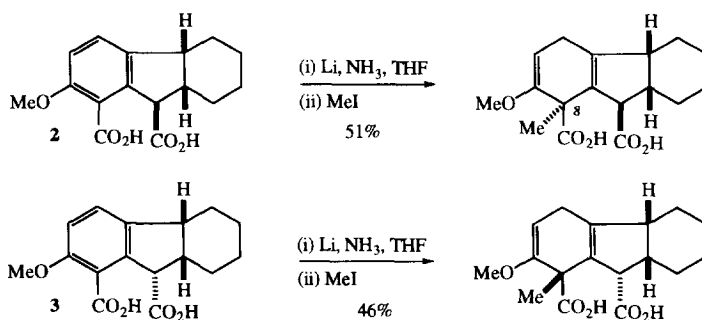
The Birch reduction is probably the most powerful method available for the partial reduction of aromatic rings, and numerous benzenoid compounds have been subjected to reducing conditions that include a group I (or group II) metal and ammonia.¹ As far as prochiral arenes are concerned, then it is normally only *para*-disubstituted aromatics that will present opportunities for stereoselection in the Birch reduction. Unfortunately, reduction at a substituted position on a benzene ring can be quite difficult to achieve, and therefore most of the examples that fall into this category also contain activating groups on the benzene nucleus. However, the effect that steric hindrance can play in controlling stereochemistry across a six-membered ring is nicely illustrated by consideration of the reduction products from 1,4-di(trimethylsilyl)benzene (**1**, **Scheme 1**).² Presumably, the stereochemistry-determining step is protonation of the anion formed after addition of two electrons and a proton to the aromatic system; assuming that this anion reacts *via* a planar conformation, then protonation can be seen to

take place from the face opposite the bulky TMS group (this leads to a predominance of the *cis* product). Unfortunately, this stereochemical argument does not hold for the reduction of *para*-substituted benzoic acids (Scheme 1), and upon reduction the opposite facial selectivity is observed (with a magnitude that appears to be dependent on the size of the *para* substituent).³ This variance may be a consequence of the different conformations imposed on the anion by the substituent directly attached to the anionic centre (*i.e.* TMS or COOH), which translates into differing transition state energies for formation of the *cis* and *trans* diastereoisomers.



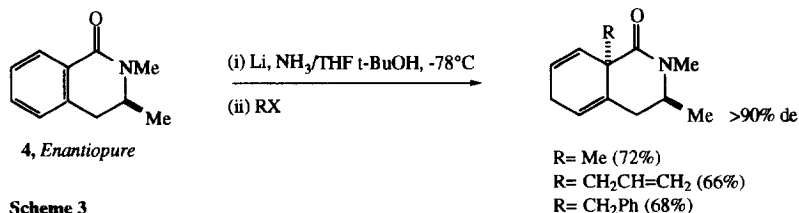
Scheme 1

There are many examples of Birch reductions performed upon chiral substrates that are stereoselective as a consequence of facially selective protonation or alkylation. Elegant studies by House on reduction of the acid derivatives **2** and **3**, which are model compounds designed to test synthetic routes to the Gibberellins (Scheme 2), showed that reductive methylation at C-8 always occurred from the face of the enolate that was opposite to the carboxylate group at C-9 (presumably for steric reasons).⁴

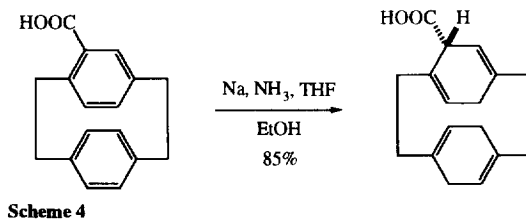


Scheme 2

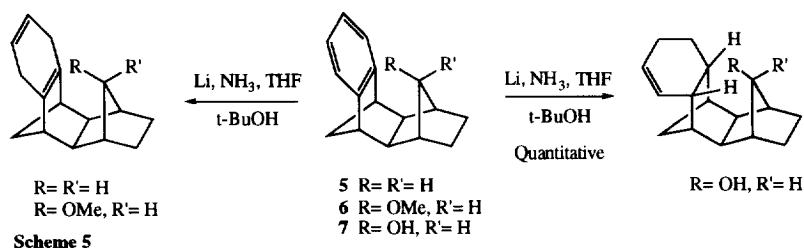
Moreover, reductive alkylation of **4**, which was obtained enantiopure from ephedrine, has also been shown to occur in a highly defined manner (Scheme 3).⁵ The enolate resulting from reduction with lithium in ammonia was capable of reacting with a variety of electrophiles in a stereoselective sense: it is worth noting that the N-methyl substituent plays a crucial role by influencing the C-2 methyl group to relieve A^(1,2) strain, adopt a pseudo-axial position and thus effectively shield one face of the enolate.



Marshall has studied the Birch reduction of a series of [2.2] paracyclophane carboxylic acids and discovered that a tetrahydro product was formed in a highly regioselective and diastereoselective manner (**Scheme 4**).⁶ Reduction of the activated 'upper deck' occurred first, with the carboxylate enolate being protonated kinetically from the top face, thus putting the carboxylic acid group in a pseudo equatorial position on the cyclohexadiene ring; reduction of the 'lower deck' then followed to give the staggered diene.

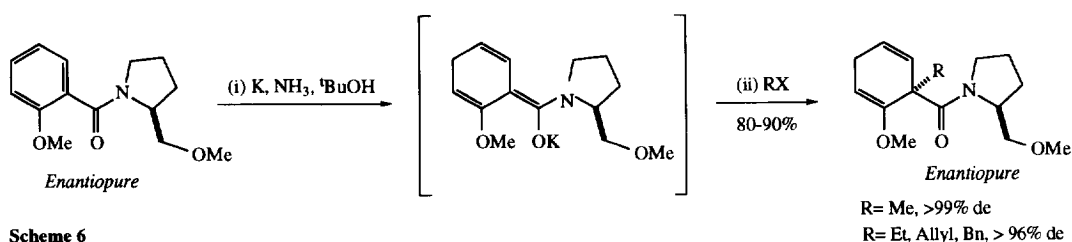


Paddon-Row has reported a nice example of a stereoselective Birch reduction which relies upon an intramolecular protonation reaction (**Scheme 5**).⁷ Reduction of compounds **5** and **6** gave the expected 1,4 dihydro compounds, whereas reduction of **7** proceeded (rapidly) to the fused cyclohexene with *cis* stereochemistry (**Scheme 5**). This effect was ascribed to proton transfer between the hydroxyl group and the C-8a (and eventually C10a) carbon of the radical anion formed after addition of an electron to the aromatic system: such a mechanism effectively explained the unusual stereochemistry and regiochemistry of reduction, together with the considerable rate increase that was observed when comparing the reduction of the methyl ether to that of the alcohol. Other examples of intramolecular protonation affecting stereoselectivity in the Birch reduction have also been noted.⁸

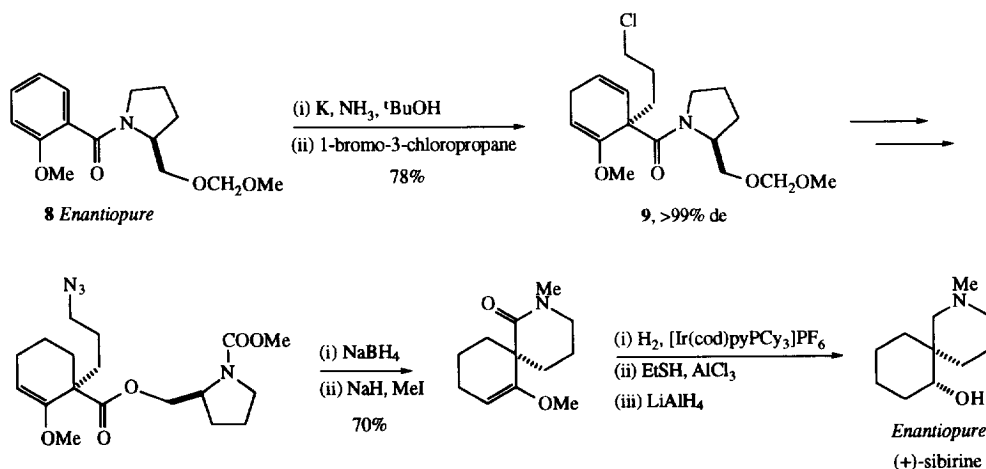


As far as stereocontrol with chiral auxiliaries is concerned, A. G. Schultz has made significant contributions by developing methods for the production of enantiopure materials from the Birch reduction of benzoic acid derivatives.⁹ Schultz utilised the amide derived from *O*-methyl prolinol and a series of aromatic

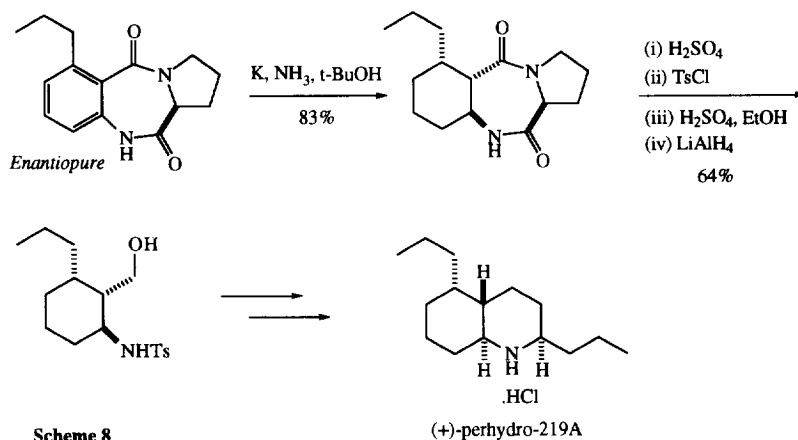
carboxylic acids in the Birch reduction and found that the aromatic ring may be reduced with a variety of group I metals.¹⁰ Moreover, the enolate that resulted from reduction in the presence of one equivalent of proton source (*t*-butyl alcohol) reacted with electrophiles in a highly stereoselective fashion (**Scheme 6**). The structure of the enolate intermediate has been probed and it was suggested that chelation between the aromatic OMe group and the enolate oxygen is important (note that if the *ortho*-methoxy group is replaced by an *ortho*-methyl group then formation of the opposing enolate geometry is suspected, as opposite facial selectivity is observed upon reaction with electrophiles).¹¹ As is probably the case with most enolate reactions, the presence of aggregated enolate assemblies was deemed to be important in defining the steric environment around the nucleophilic centre: indeed, ammonia seems to play a crucial role in holding together the proposed dimeric enolate structures and facilitating the highly stereoselective enolate quench.¹¹



Schultz has used this chemistry to good effect in the synthesis of several natural products, including (+)-sibirine (a spirocyclic alkaloid isolated from *Nitraria schobere*, **Scheme 7**).¹² The absolute stereochemistry of the sequence was assured by the utilisation of an enantiopure amide derived from prolinol and *o*-anisic acid. Of course, the key step was a reductive alkylation utilising bromochloropropane as the electrophile; this occurred with a diastereoselectivity greater than the detection limits of the experiment (**8**→**9**, >99% de, **Scheme 7**). Another intriguing step in the sequence was an amide-directed hydrogenation of an enol ether, using [Ir(cod)pyPCy₃]PF₆ as the catalyst,¹³ which set up the correct stereochemistry for the C-1 hydroxyl group.



Extensions of this methodology have been reported in which the aromatic ring is completely reduced and stereocontrol is achieved at up to three positions around the aromatic ring by utilisation of excess metal and a proton source.¹⁴ As in most Birch reductions, the presence of excess proton sources tends to lead to over-reduction of the initially formed 1,4-dihydro compound, as it may be isomerised under basic conditions and any conjugated products are subsequently reduced further. In the example shown in **Scheme 8**, the acidic proton on the amide is removed during the reduction and this provides impetus for further reduction by the metal in the manner described earlier. The exact mechanism of what is obviously a complicated process remains unclear, however, it does provide a nice example of the utility of stereocontrolled synthesis of saturated six-membered rings from their aromatic precursors, and is of direct use in the synthesis of (+)-perhydro-219A.¹⁵



2.2 Hydrogenation Methods

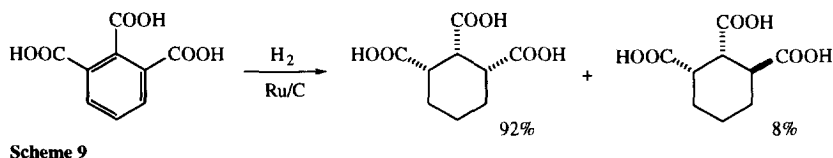
Reduction of a benzene nucleus to the fully saturated cyclohexane derivative may be accomplished with hydrogen under the catalysis of a number of different transition metals and in both heterogeneous and (to a lesser extent) homogeneous phases.¹⁶ As might be expected, use of this protocol leads to a predominance of the *cis*-substituted isomers and reactions are good to moderately stereoselective depending on the substitution pattern of the arene (exemplified here with reduction of the isomeric xylenes in **Table 1**).¹⁷ Of course, the nature of the catalyst, carrier, solvent, temperature and pressure all have a bearing on the degree of stereochemical induction. One clear trend that can be delineated from this table is that the level of stereochemical control to be expected from hydrogenation of a substituted benzene is reduced as the substituents on the arene are positioned further apart.

Arene	Temperature	Initial Pressure	<i>cis:trans</i> ratio of product
<i>ortho</i> -Xylene	35°C	280 cm	95:5
<i>meta</i> -Xylene	35°C	280 cm	86:14
<i>para</i> -Xylene	35°C	280 cm	75:25

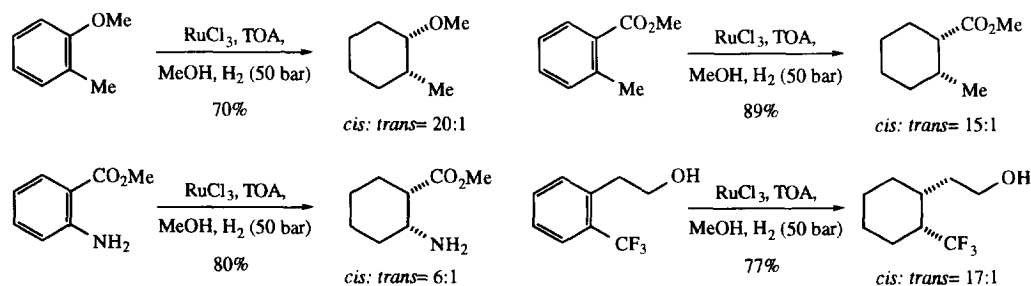
Table 1: Hydrogenation of isomeric xylenes with platinum-oxide catalyst

Early studies by Linstead who investigated the metal-catalysed *cis* addition of hydrogen to a series of aromatic compounds, led him to postulate that *cis* addition of hydrogen to each of the carbon atoms of an aromatic compound will only occur during a single period of adsorption onto the catalyst surface.¹⁸ Desorption of any partially reduced species will lead to alkenes and dienes which may then be readsorbed and therefore hydrogenated: however, this readsorption process need not occur from the same face as the first hydrogenation and so apparent *trans* hydrogenation may be observed. Endorsement of this proposal was provided by Siegel and by Schuetz who showed that the *cis* selectivity of catalytic hydrogenation of a series of xylenes increased with increasing pressure and decreasing temperature (presumably, an increase in pressure accelerates the uptake of hydrogen by the arene during a single period of adsorption).¹⁹ Isomerisation of the reduced products under low temperature conditions was an unreasonable mechanism for formation of all but very small quantities of the *trans* isomers: however at high temperatures reversible hydrogen addition is encouraged and the result is isomerisation.

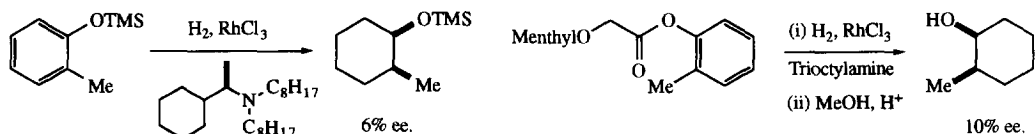
Examination of the literature reveals that a variety of functionalised arenes may be readily hydrogenated, and in most cases the *cis*-substituted isomer predominates. For example, the hydrogenation of substituted benzoic acids and anilines appears to proceed with good *cis* stereoselectivity, while that of phenols is poor (presumably this is a consequence of the formation and rehydrogenation of cyclohexanones *in situ*).¹⁶ Some functional groups are more compatible with hydrogenation conditions than others, and it appears that for any given substrate an optimum set of reaction conditions must be sought. However, some spectacular examples of stereoselective reactions can be found (Scheme 9).²⁰



Recently, a promising method for the reduction of aromatics has come to our attention which involves hydrogenation at a pressure of 50 bar, with catalysis by ruthenium trichloride and use of trioctylamine (TOA) as a phase transfer agent (Scheme 10).²¹ This method is tolerant of the epoxide and ester functionalities and produces excellent *cis* selectivity upon reduction of a variety of *ortho*-substituted benzenes. These examples also serve to illustrate how the stereoselectivity of hydrogenation is dependent on the nature of the substituents attached to the arene.



The same authors have also investigated the use of covalently bound chiral auxiliaries and chiral phase transfer reagents as a method of making enantiopure cyclohexane derivatives (**Scheme 11**).²² Although novel and promising, these results indicate that much work must be done before heterogeneous catalysis becomes a viable method for obtaining reduced aromatics in enantiomerically pure form.

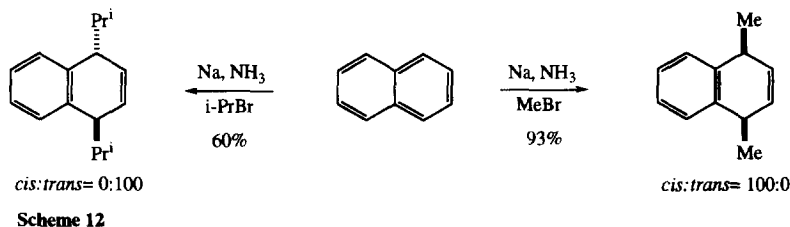


Scheme 11

3. Polynuclear Benzenoid Aromatics

3.1 Dissolving metal reductions

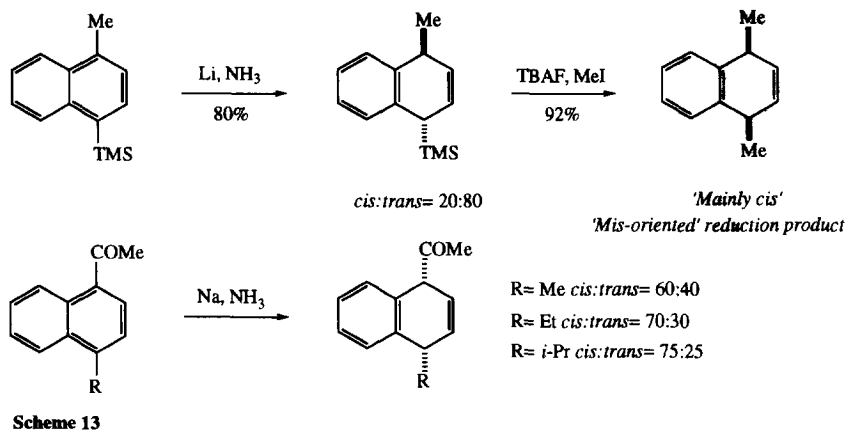
If one subjects a substituted naphthalene to reduction under the action of a dissolving metal, the unsubstituted ring tends to be reduced first, and it often proves difficult to reduce the ring that bears a substituent and hence form stereoisomers (unless of course, the substituents are activating, *vide infra*). A method which is equivalent to inducing reduction in the more substituted ring of a naphthalene does appear if one omits addition of a proton source (*i.e.* *tert*-butanol) to the metal/ammonia mixture: this enables the subsequently formed dianion to react with a carbon electrophile and a reductive alkylation ensues (**Scheme 12**).²³ The potential utility and stereochemical issues raised by this reductive alkylation have been investigated by Rabideau, who discovered that the stereochemistry of the dialkylated products was crucially dependent upon the electrophile used: methyl bromide led to a completely *cis* selective process, ethyl bromide was essentially non-selective, and *iso*-propyl bromide participated in a *trans* selective dialkylation (**Scheme 12**).²⁴ The stereochemical issues raised by this work are similar to those described elsewhere (see **Scheme 1** and **Figure 2**) and again, the stereochemistry of the final alkylation step appears to be determined by the degree of folding exhibited by the substituted anion as it reacts with an electrophile.



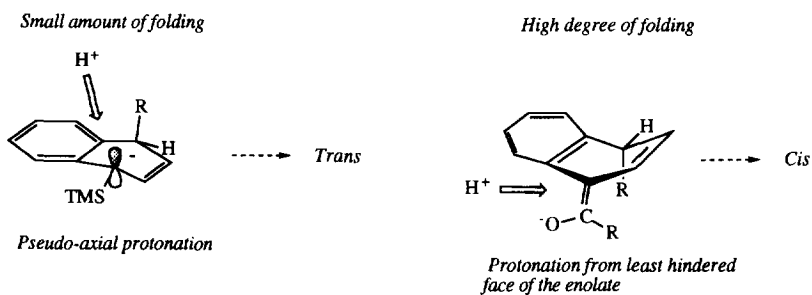
Scheme 12

When one of the two rings of naphthalene is substituted by an activating group then any subsequent reduction is directed towards the more electron deficient ring. An elegant method of harnessing this effect to obtain the 'mis-oriented' reduction product uses a removable activating group (namely trimethylsilyl) and has been reported by Rabideau (**Scheme 13**).²⁵ Removal of the directing group using TBAF generates the mis-oriented reduction product and moreover, the TMS group may be replaced with an alkyl group by harnessing the combination of anhydrous TBAF with an electrophile (**Scheme 13**).²⁵

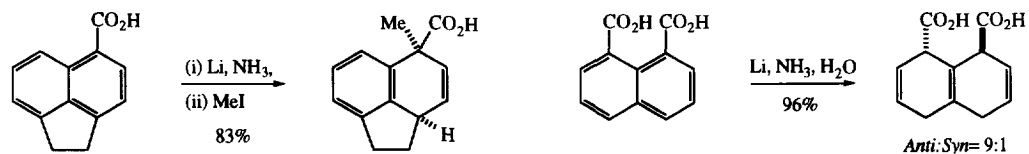
Naturally, the use of more traditional activating groups which contain a carbonyl attached to the naphthalene nucleus has also been investigated and duly reported (**Scheme 13**).²⁶



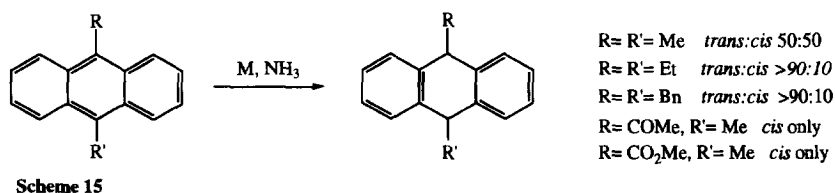
Unfortunately, prediction of the stereochemistry that is to be expected from the reduction (and reductive alkylation) of such polynuclear aromatics remains difficult, as it is the conformation of the anion undergoing final protonation that appears to be the controlling factor: isomerisation of the reduced products is not normally an issue because this process inevitably leads to the formation of conjugated products. As might be expected, the conformations of these anions are heavily dependent upon the substituents attached to them, and there appears to be a large difference in the degree of folding as exhibited by anions stabilised by π -stabilising groups compared to those substituted by alkyl or TMS groups (**Figure 2**).



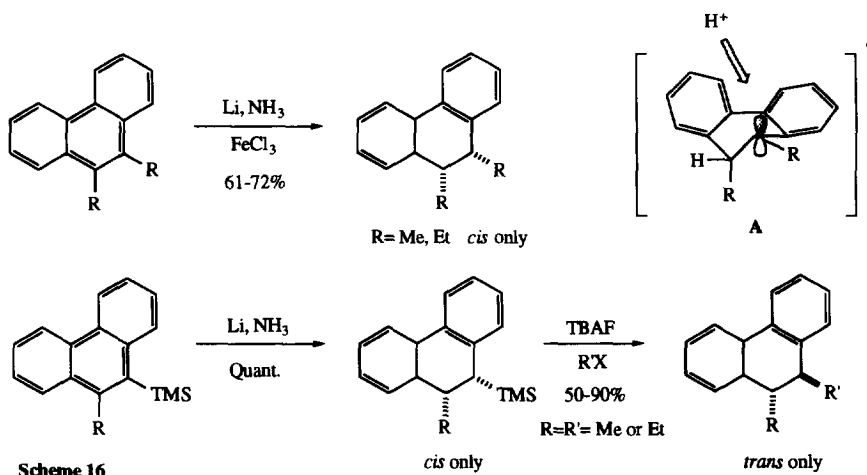
The stereochemical outcome that is to be expected from reduction of a tricyclic²⁷ or *peri*-substituted naphthalenes²⁸ is easier to rationalise, with protonation and alkylation adjacent to the carbonyl occurring from the least hindered face of the enolate (**Scheme 14**).



When we consider reduction of the anthracene and phenanthrene nuclei, the factors behind any stereochemical preferences become even more complex. For example, reduction of a series of 9,10-disubstituted anthracenes shows us that either the *cis* or the *trans* product may predominate in the reaction (Scheme 15).²⁹ In keeping with the general model outlined earlier (Figure 2), it seems that a carbonyl-substituted anion displays considerably more folding than one substituted by a small alkyl group (such extra folding appears to lead to formation of the *cis* product): such differences in conformation may be attributed to the extra allylic strain experienced between the exocyclic double bond of the enolate and the *peri* hydrogens, compared to that between an alkyl substituent and the same *peri* hydrogens. However, the fact that the different types of anion may attack an electrophile along different trajectories, or even that enolate protonation may take place on oxygen followed by rearrangement, must not be overlooked as influencing factors in the stereochemistry determining step.

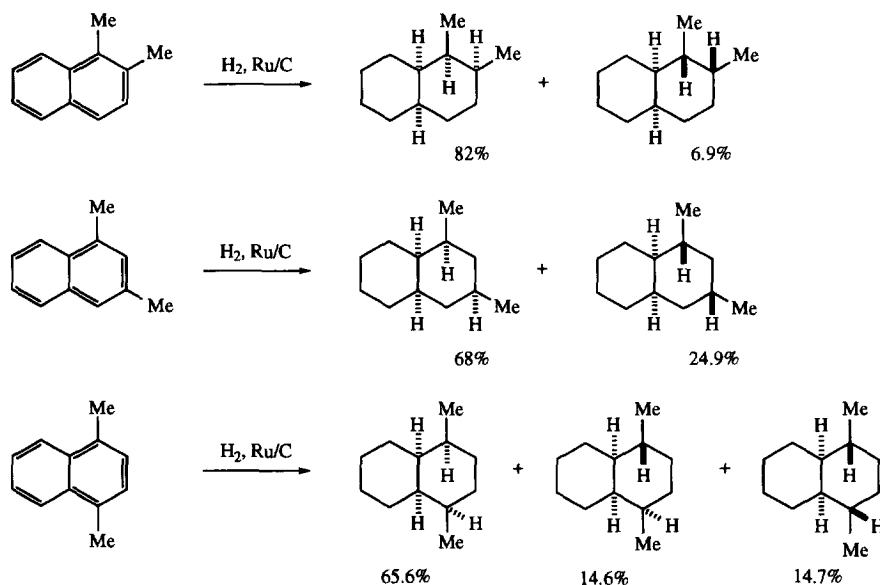


The phenanthrene system is also susceptible to dissolving metal reduction, and 9,10-disubstituted phenanthrenes have been observed to give exclusively the *cis* dihydro-products,³⁰ the stereochemical outcome of these reactions may be rationalised by invoking addition of a proton source to the top face of the anion A, which is placed in a conformation that minimises allylic strain (Scheme 16). When performing reduction of the phenanthrene system, ferric chloride must be added to the reaction mixture to prevent over-reduction (it appears that the iron may aid in removal of excess lithium). If a *trans* diastereoisomer of the dihydrophenanthrene system is desired, it can be prepared by reduction of the 9-trimethylsilyl-10-alkyl derivative (this protocol gives the *cis* isomer and moreover, the TMS group seems to prevent over-reduction).³¹ Removal of the silyl group with dry TBAF, in the presence of an electrophile, results in formation of the *trans* diastereoisomer, presumably via an S_E2 type reaction.

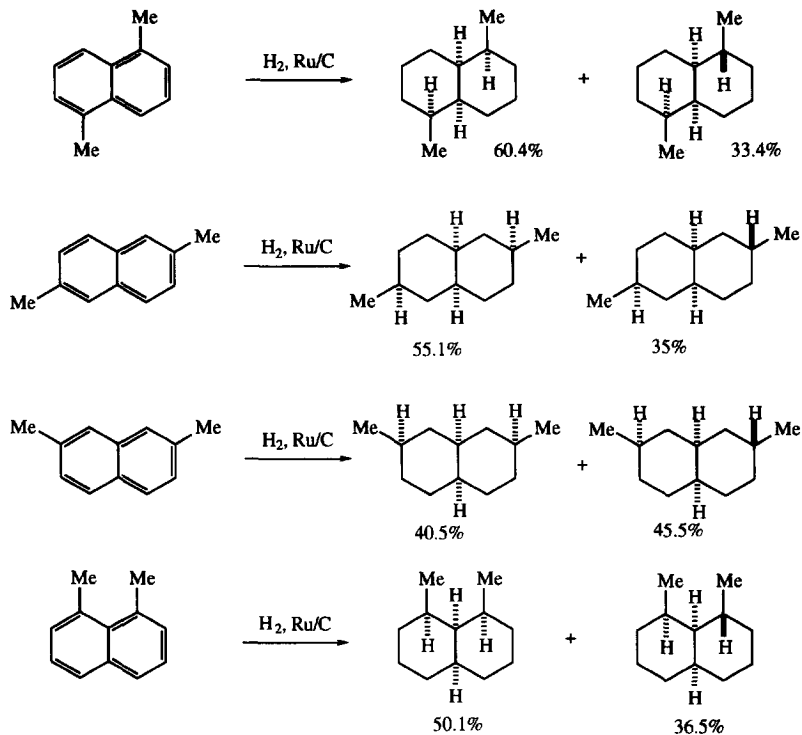


3.2 Hydrogenation Methods

The full and partial hydrogenation of naphthalene derivatives has received considerable study;³² it should be recognised that the complete hydrogenation of naphthalene can result in the formation of two diastereoisomers. However, if a fully substituted naphthalene were subjected to hydrogenation then a maximum of ten stereogenic centres could be created (one should also consider the possibility of partial reduction and the regiochemistry of this process) and so the situation becomes highly complicated. While naphthalene itself is hydrogenated to *cis*-decalin with >95% selectivity under Ru catalysis,³³ **Scheme 17** illustrates the distribution of stereoisomers that are to be expected from the complete hydrogenation of dimethyl-substituted naphthalenes (small amounts of other isomers are also formed but these have been omitted for clarity).³³ For comparative purposes, the catalyst has been maintained at Ru on carbon, although the isomer ratios do vary with the metal that is used in this role.



As the substituents on the naphthalene ring become more distant, the ability to control relative stereochemistry diminishes (**Scheme 18**); in keeping with the mechanism outlined earlier, isomers that appear to have been hydrogenated in a *trans* fashion probably arise from desorption of partially hydrogenated derivatives followed by (non facially selective) rehydrogenation.

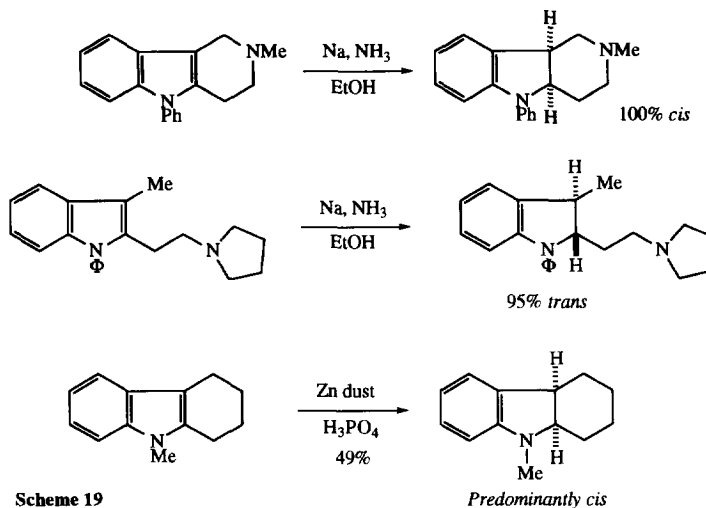


As far as the hydrogenation of other polycyclic aromatic compounds are concerned, there is less data to examine. However, the hydrogenation of phenanthrene has been shown to give predominantly the *cis-syn-cis* isomer when Adam's catalyst is used in the presence of acetic acid.³⁴

4. The Stereoselective Reduction of Indoles

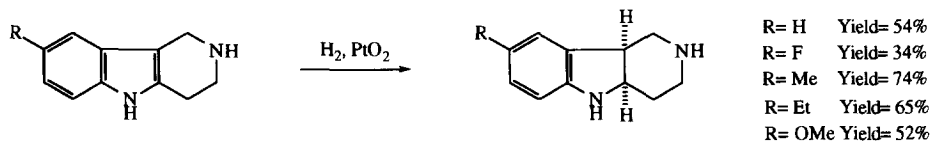
4.1 Metal-Promoted Reductions

The dissolving metal reduction of indoles has been reported to give partial reduction in either of the two rings, depending on the reaction conditions that are employed. Indoles that are substituted at the C-2 and C-3 positions are capable of producing stereoisomeric products upon partial reduction of the heterocyclic ring, and a few examples of the stereocontrolled reduction of substituted indoles are outlined below (**Scheme 19**):³⁵ these results were explained by assuming that in each case the thermodynamically more stable reduction product was formed, although this was not proven. In addition, it should be noted that the reduction of N-methyl-1,2,3,4-tetrahydrocarbazole with zinc and phosphoric acid has been reported to yield the *cis* reduction product (**Scheme 19**).³⁶



4.2 Hydrogenation of Indoles

The indole nucleus appears to be rather resistant to hydrogenation and, moreover, it seems that either of the two rings may be saturated depending on the conditions that are employed and the substitution pattern of the indole that is reduced. Indeed, the presence of a substituent on one of the two rings tends to encourage reduction of the other, thus avoiding the issue of diastereoselection! Therefore, examples of stereocontrolled hydrogenation in these systems are rare and most involve reduction of tricyclic indole derivatives (Scheme 20).³⁷



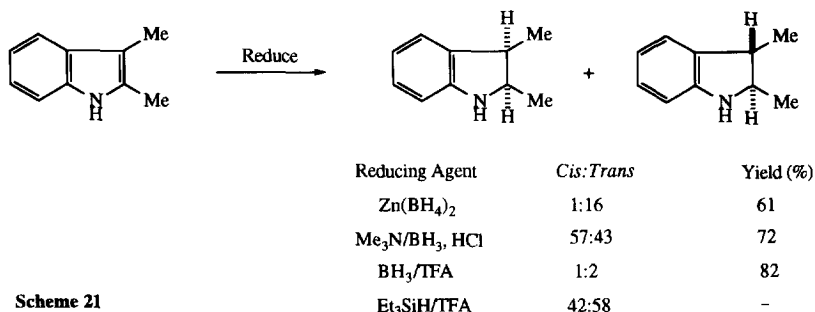
Scheme 20

4.3 Reduction of Indoles Using Hydride Sources

Extensive studies have shown that the 2,3 double bond of indoles may be reduced under the action of a wide variety of reducing agents which are formally hydride sources:³⁸ however, in most cases it is necessary to add acid to the reaction mixture so as to protonate the indole (forming an indolenium ion) and hence increase its reactivity towards a nucleophile. Hence, the best results have been obtained with hydride sources that are stable to acid (*vide infra*). Of course, when 2,3-disubstituted indoles are subjected to such reducing conditions the possibility of stereochemical discrimination arises, and the stereoselectivity of reduction of such compounds is found to be highly dependent on the structure of the indole and also the nature of the reductant: in many cases it is possible to obtain stereochemically complementary results by variation of the reducing agent.

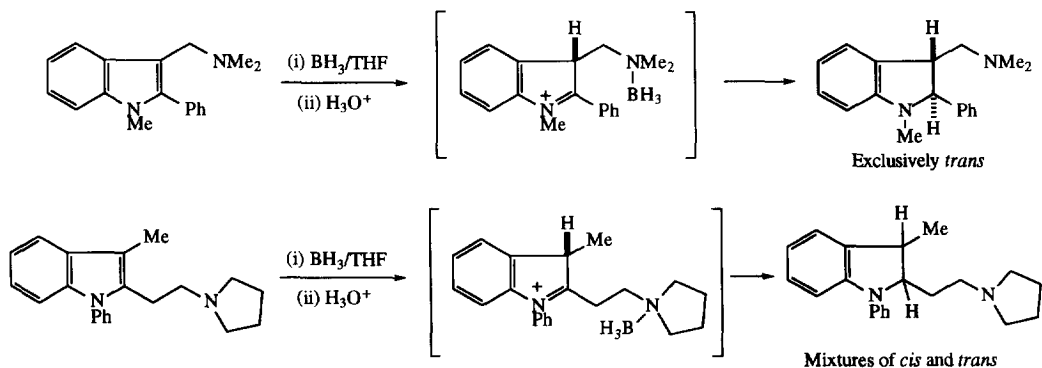
2,3-Disubstitued indoles in which the substituents do not form part of another ring are a class of compounds that are difficult to reduce stereoselectively. Under most reducing conditions, mixtures of both the

cis and *trans* isomers are formed (exemplified with 2,3-dimethyl indole, **Scheme 21**).³⁹ However, it does appear to be possible to obtain the *trans* isomer selectively if zinc borohydride is used as the reducing agent.⁴⁰



Scheme 21

If one of the substituents on the C-2 or C-3 position of an indole contains a basic nitrogen, reduction becomes more complex as co-ordination between the amine and the reducing agent is possible. In practice this normally leads towards selective formation of the *trans* isomer (**Scheme 22**).⁴¹ Presumably, the stereochemical outcome of this reaction is a consequence of initial complexation between the amine and the borane, followed by protonation of the C2-3 double bond at C-3. The amine-borane complex then delivers hydride intramolecularly to the C-2 position forming the *trans* compound. The fact that reduction occurs non-stereoselectively if the trimethylamine-borane complex is used as the reductant supports this hypothesis. Interestingly, if the substitution pattern is reversed (*i.e.* the amino alkyl substituent positioned on C-2) then the side chain is attached to the indolenium ion *via* a trigonal carbon: intramolecular hydride delivery is therefore less stereoselective, and mixtures of *cis* and *trans* isomers are formed depending on the exact reducing conditions that are employed (**Scheme 22**).⁴¹



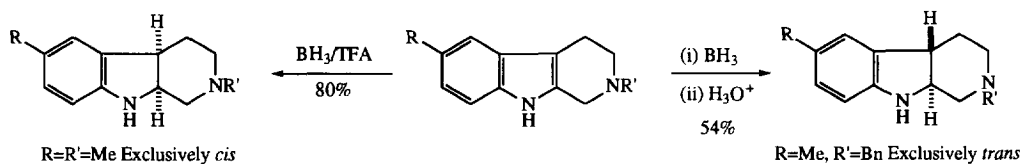
Scheme 22

Ionic hydrogenation of indoles which contain a bulky substituent at the C-3 position has been shown to lead to the *cis* isomer. Presumably, the intermediate indolenium ion is reduced by hydride attack from triethylsilane *via* the less hindered face (**Scheme 23**).⁴²



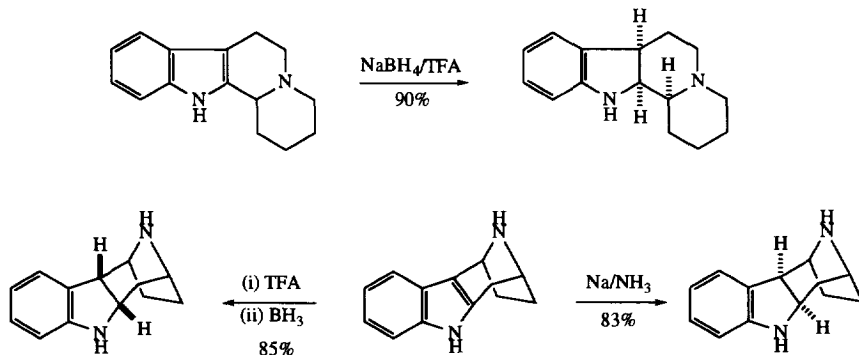
Scheme 23

When alkyl substituents on the C-2 and C-3 positions of the indole form part of a nitrogen-containing ring then the stereochemical outcome of reduction can be controlled by the choice of reagents (Scheme 24).⁴³ A satisfactory explanation of these results takes into account the possibility of an amine directed hydride delivery that provides the *trans* compound under neutral conditions but not under acidic conditions as the amine is protonated. Removal of the nitrogen atom from the non-aromatic ring leaves the tetrahydrocarbazole skeleton, and here the 2,3-double bond is reduced with *cis* selectivity under a variety of conditions (e.g. BH_3/TFA , $\text{Zn}(\text{BH}_4)_2$, $\text{HCl}/\text{Me}_3\text{N}-\text{BH}_3$).³⁸⁻⁴³



Scheme 24

Many other structures which contain the indole nucleus may be reduced stereoselectively under a variety of conditions, and the reactions shown in Scheme 25 exemplify this point. It may be seen from the latter example that the choice of reducing conditions is paramount in determining the stereochemical outcome of such reductions.⁴⁴

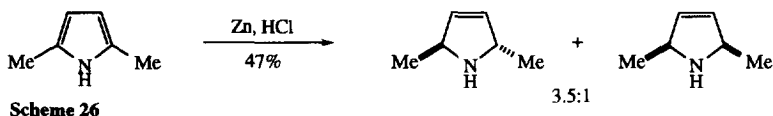


Scheme 25

5. The Reduction of Pyrroles

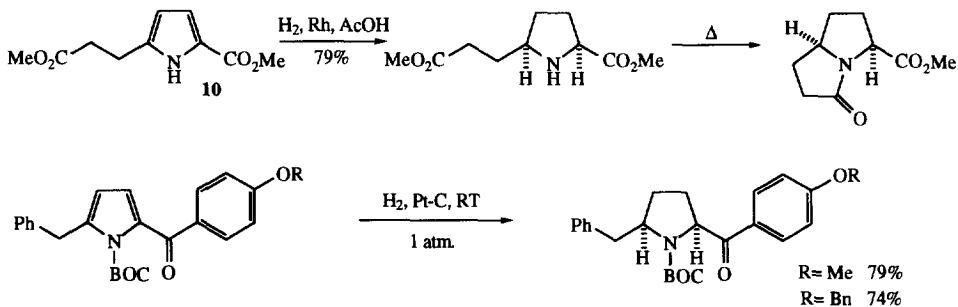
5.1 Metal-Promoted Reduction

Reduction of the pyrrole nucleus under Birch type conditions appears to be unknown,⁴⁵ and we are aware of only one metal-promoted reaction that is capable of performing this task, namely, zinc in acetic acid.⁴⁶ However, the prospects for stereocontrolled synthesis of the pyrroline isomers thus formed are not good, as reduction of 2,5-dimethylpyrrole under these conditions gives a 3.5:1 mixture of the *trans* and *cis* isomers (Scheme 26).⁴⁶



5.2 Hydrogenation of Pyrroles

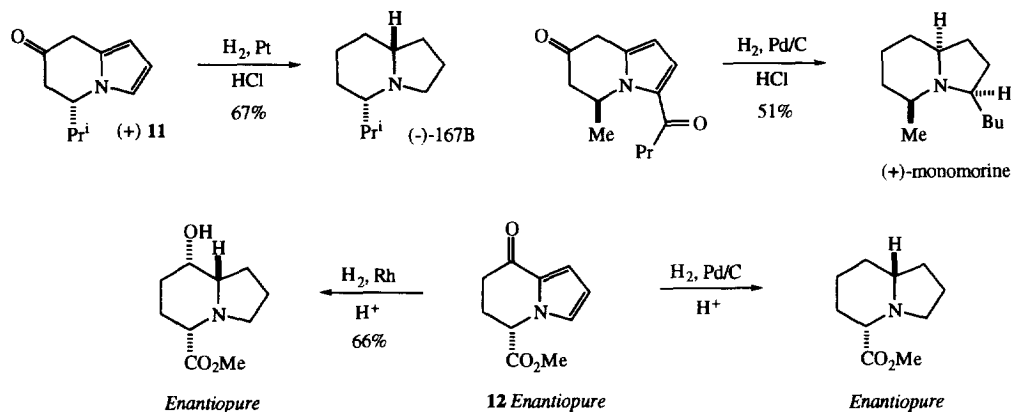
The pyrrole nucleus is rather resistant to hydrogenation and reduction of this heterocycle normally requires vigorous conditions; the use of an acidic medium is also found to be beneficial, as it removes basic amine functionality from the medium and in so doing reduces its poisoning effect on the catalyst. As far as stereoselective reductions of pyrroles are concerned, there appear to be relatively few examples of *cis* hydrogenation to yield substituted pyrrolidines. As expected, hydrogenation of 2,5-dimethyl pyrrole with a series of transition metal catalysts furnishes predominantly the *cis* 2,5-dimethylpyrrolidine.⁴⁷ During a synthesis of pyrrolizine carboxylic acid derivatives as possible agents for the inhibition of the angiotensin converting enzyme, Turner found that the disubstituted pyrrole carboxylic acid derivative **10** could be hydrogenated with high stereoselectivity (Scheme 27).⁴⁸ Rapoport has described a very similar reaction during an approach to Anatoxin *a*.⁴⁸ If one subjects an electron-deficient pyrrole to hydrogenation conditions, then complete and stereoselective reduction of the heterocycle can be accomplished at room temperature and under one atmosphere of hydrogen, provided that either rhodium or platinum on carbon is used as catalyst (Scheme 27).⁴⁹



Scheme 27

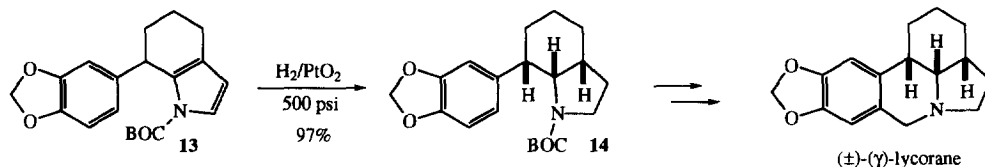
There have been a series of papers published recently which detail the hydrogenation of bicyclic pyrroles which contain a bridgehead nitrogen. Indeed, such a reaction has proven to be instrumental in allowing preparation of a series of naturally occurring pyrrolizidine and indolizidine alkaloids in enantiomerically pure form (Scheme 28).⁵⁰ Key reductions and the corresponding natural product targets are adumbrated below

(Scheme 28). It may be seen from these results that substituents on the non-aromatic ring are capable of influencing the face of the pyrrole that is adsorbed onto the metal surface and therefore reduced. Additionally, benzylic carbonyl groups are susceptible to either complete or partial reduction under the conditions required to reduce the pyrrole nucleus.



Scheme 28

Another example of diastereoselective hydrogenation of a highly substituted pyrrole was reported by Angle and co-workers during their recent synthesis of (\pm)-(γ)-lycorane (Scheme 29).⁵¹ In this case it was interesting to note that the pendant aromatic ring was not reduced at all under the conditions that were employed (13 \rightarrow 14, Scheme 29).

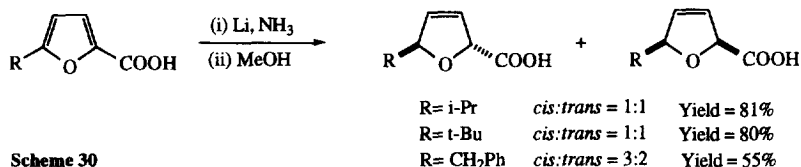


Scheme 29

6. Reduction of Furans

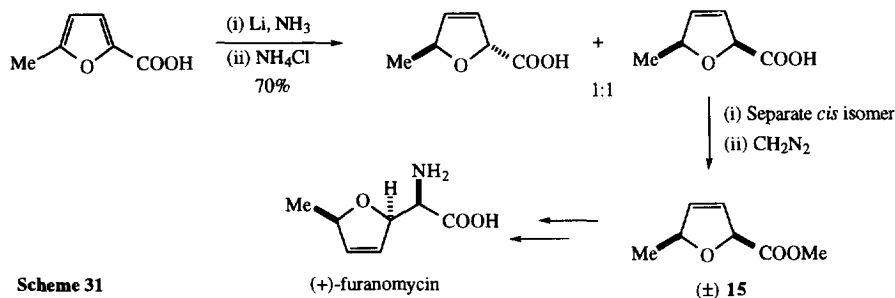
6.1 Reduction with Dissolving Metals

In contrast to the reduction of pyrroles, furans can be partially reduced under Birch type conditions provided that an electron withdrawing group (in practise this is a carboxylic acid) is attached to the nucleus to prevent ring opening side reactions.⁵² Unfortunately, the prospects for the stereocontrolled synthesis of dihydrofurans *via* this methodology are not promising, as equal mixtures of *cis* and *trans* isomers result from reduction of 2-5 disubstituted furans (Scheme 30).⁵³

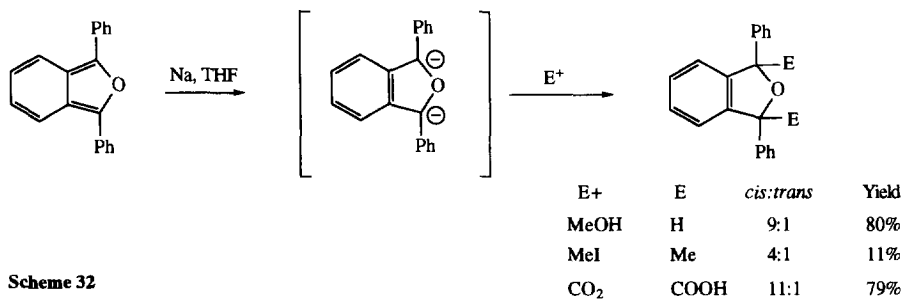


Scheme 30

Provided one is willing to separate the diastereoisomers thus formed, this approach can be used in natural product synthesis, as illustrated by Joullié and co-workers in their preparation of the antibiotic (+)-furanomycin:⁵⁴ note that enantiomeric purity of the final product was ensured by performing a resolution on a derivative of **15** (Scheme 31).

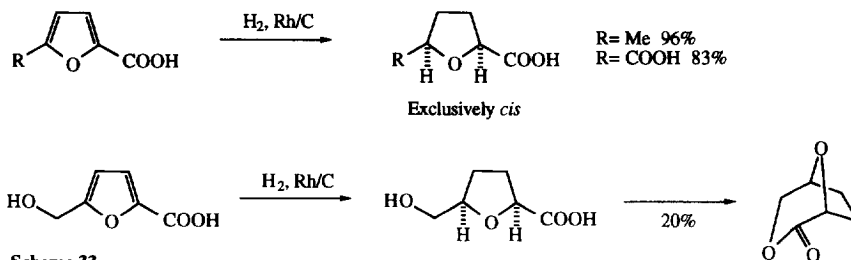


Bearing in mind their relationship to furans, the reduction of isobenzofurans will also be considered at this juncture. James Smith and co-workers have studied the dissolving metal reduction of the 1,3-diphenyl derivative of this heterocycle and discovered that selectivity in favour of the *cis* isomer was attainable.⁵⁵ This particular heterocycle was thought to be capable of sustaining a dianion when treated with a reactive group I metal in THF, and so reductive alkylation and carboxylation became a device for controlling the resulting stereochemistry around the heterocyclic nucleus (Scheme 32). The highest stereoselectivities were observed with sodium as the electron source; unfortunately the presence of co-solvents (*e.g.* HMPA, TMEDA) only served to reduce the levels of stereocontrol. Diastereofacial selectivity was proposed to originate from the conformation of the dianion formed from the addition of two electrons to the heterocycle: this preferred to react in a manner which kept the two phenyl groups in a pseudo-equatorial arrangement thus ensuring formation of the *cis* stereoisomer.



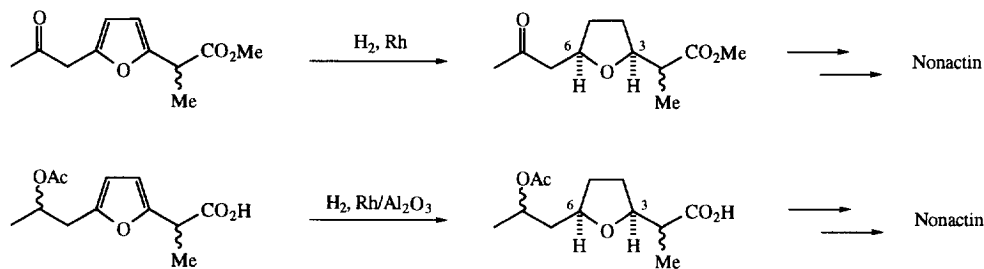
6.2 Hydrogenation of Furans

Despite the large amount of literature surrounding the hydrogenation and hydrogenolysis of furans, the concept of using stereoselective reduction of highly substituted furans as a route to naturally occurring tetrahydrofuran derivatives has received relatively little attention.⁵⁶ Moreover, if a rhodium catalyst is utilised during hydrogenation, the persistent problem of ring opening appears to be circumvented and stereoselective *cis* addition of hydrogen can be encouraged (Scheme 33).⁵⁷



Scheme 33

A few research groups have successfully utilised the stereoselective hydrogenation of furans in the arena of natural product synthesis, while in pursuit of nonactin (**Scheme 34**).⁵⁸ While, in each case, the hydrogenation step was capable of generating the required *cis* stereochemistry at C-3 and C-6 of the natural product fragment, the presence of stereogenic centres on the furan substituents proved to be an ineffective method of controlling the relative proportions of the two *cis* isomers that can be formed, and mixtures of diastereoisomers ensued.

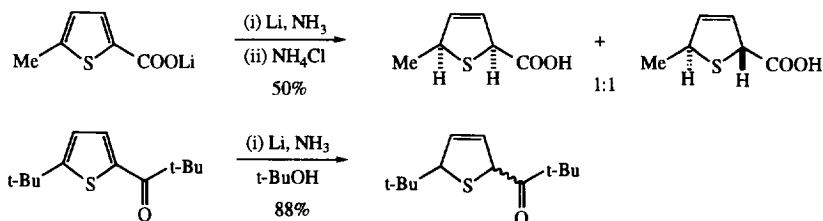


Scheme 34

7. Reduction of Thiophenes

7.1 Reduction with Dissolving Metals

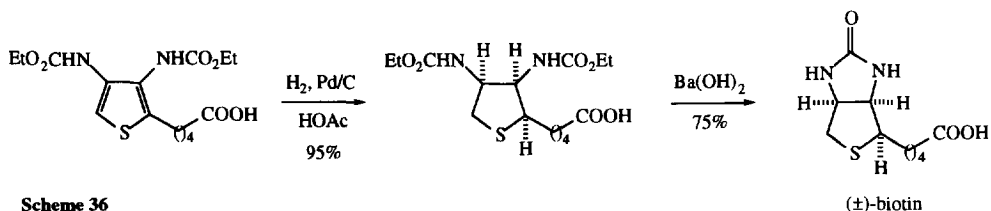
In a manner analogous to that of furan, the dissolving metal reduction of thiophenes is complicated by the issue of ring-opening but can be accomplished if a sufficiently anion-stabilising group is positioned on the heterocycle nucleus (*i.e.* acyl or carboxylate functionality):⁵⁹ we are not aware of any stereochemical discrimination during the reduction of disubstituted thiophenes, and formation of diastereoisomeric mixtures are the norm (**Scheme 35**).⁶⁰



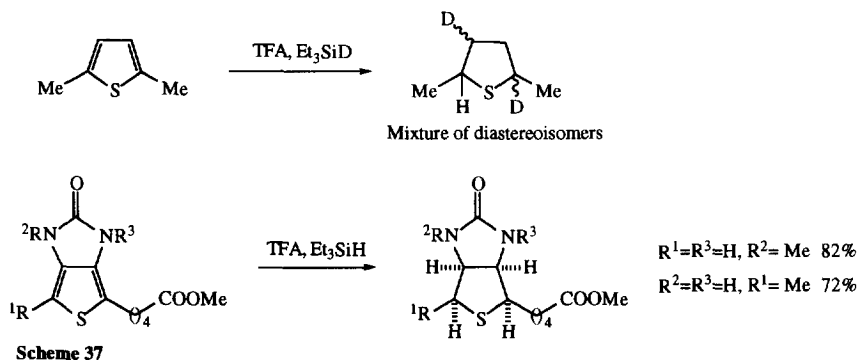
Scheme 35

7.2 Hydrogenation of Thiophenes

The hydrogenation of thiophenes with a heterogeneous transition metal catalyst is hindered by the ability of sulfur to bind onto the catalyst surface and in so doing halt the reaction. Nevertheless, an example of stereoselective *cis*-hydrogenation of a tri-substituted thiophene was reported by Confalone and co-workers during their elegant synthesis of biotin (**Scheme 36**).⁶¹



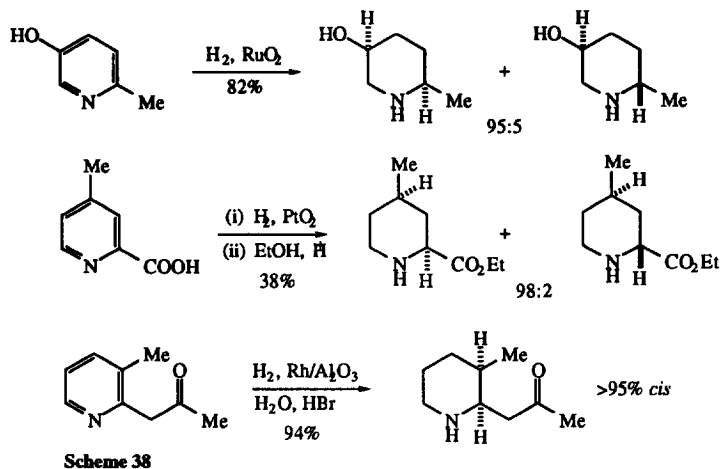
Indeed, it is possible to accomplish the hydrogenation of thiophenes under 'ionic' conditions (H^+ , Et_3SiH). Reduction of 2,5-dimethyl thiophene under conditions which led to the incorporation of deuterium (TFA, Et_3SiD) did not lead to any stereochemical discrimination at the two newly formed stereogenic centres, but did yield important information about the mechanism of this type of reduction (**Scheme 37**).⁶² However, if the substituents on the thiophene ring are adjacent to one another then good stereochemical control in favour of the *cis* isomer may be obtained; biotin precursors similar to those outlined above have therefore been reduced stereoselectively under ionic hydrogenation conditions (**Scheme 37**).⁶³



8. The Reduction of Pyridines and Pyridinium Ions

8.1 Hydrogenation of Pyridines

Substituted pyridines are susceptible to hydrogenation under a variety of conditions and, in a manner analogous to their benzene counterparts, yield predominantly the *cis* substituted diastereoisomers (**Scheme 38**).⁶⁴ Indeed, the levels of stereocontrol that are attainable seem to surpass those observed in the benzenoid series and high diastereoselectivities are the norm: **Scheme 38** describes a series of selective hydrogenations which show that several functional groups are compatible with such reducing conditions and that hydrogenation of pyridines with a variety of substitution patterns is feasible.⁶⁵

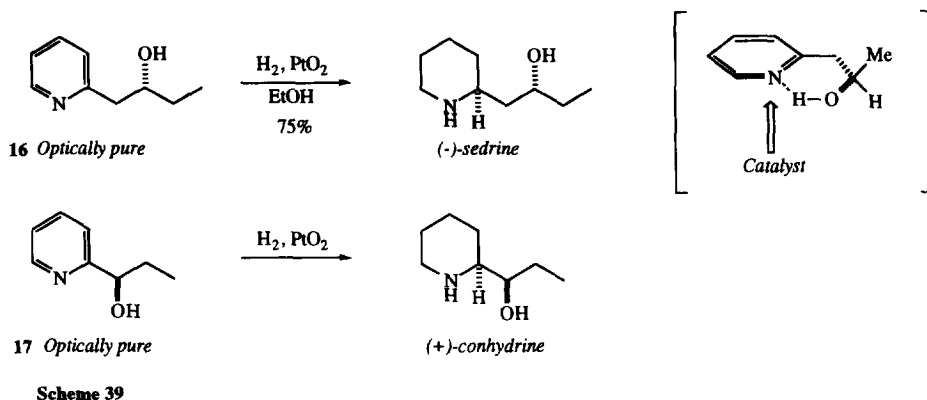


As might be predicted, hydrogenation of substituted pyridinium ions is also a *cis* selective process; good to excellent levels of stereochemical control are attainable (Table 2).⁶⁶

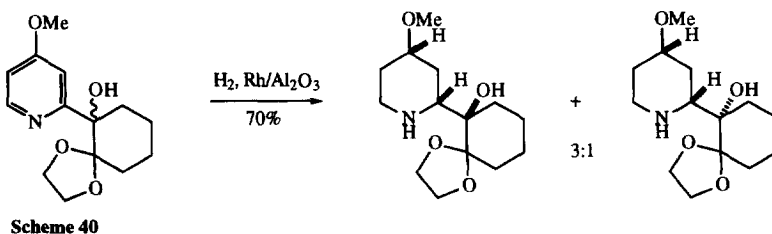
Substituent	<i>cis:trans</i>	Substituent	<i>cis:trans</i>
2,3-dimethyl	99:1	2,6-dimethyl	82:18
2,4-dimethyl	96:4	3,5-dimethyl	70:30
2,5-dimethyl	65:35	3,4-dimethyl	100:0

Table 2: *cis:trans* Ratios of the exhaustive hydrogenation products of substituted N-methyl pyridinium iodides (1 atmosphere of hydrogen and PtO₂ catalyst).

Two examples of an elegant facially directed hydrogenation have been reported by Fodor and co-workers (Scheme 39).⁶⁷ Reduction of the enantiomerically pure pyridine (16) gave a single diastereoisomer of the reduced product (enantiomerically pure sedrine). It was postulated that the conformation of the alcohol was fixed by intramolecular hydrogen-bonding (this was supported by IR experiments) and that the catalyst, and therefore the hydrogen, approached the aromatic ring from the least hindered face *anti* to the methyl group. Reduction of a similar compound (17) which contained a hydroxy group α to the pyridine nucleus was also stereoselective and enabled a synthesis of (+)-conhydrine (presumably, analogous conformational effects can be invoked to rationalise this stereoselectivity).

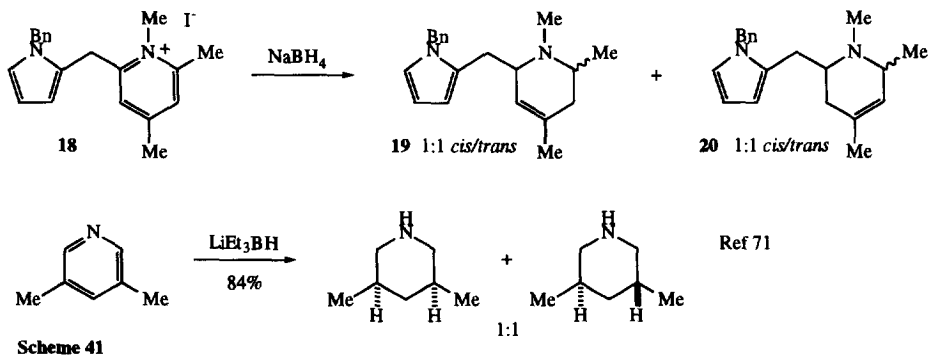


Another example of stereoselective hydrogenation which falls into this category shows us that a stereogenic centre on the *ortho* substituent of a pyridine can influence the facial selectivity of hydrogenation (again, the reactive conformation appears to be fixed by intramolecular hydrogen bonding), and the result also illustrates that the hydrogenation proceeds with *cis* stereoselectivity (**Scheme 40**).⁶⁸



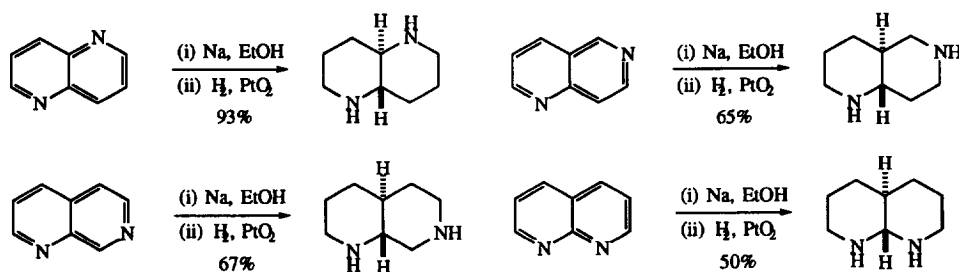
8.2 Reduction of Pyridines and Pyridinium Ions with Hydride Sources

This area is extensive and has already been the subject of two excellent reviews;⁶⁹ therefore only particularly pertinent examples will be considered. It appears that the prospects for reducing substituted pyridines in a diastereoselective manner under these conditions are poor, as exemplified by the non-selective reductions illustrated in **Scheme 41**. In fact, reduction using hydride sources is also complicated by the fact that incomplete reduction can occur and this process leads to mixtures of double bond isomers⁷⁰ in addition to the mixtures of diastereoisomers that can be formed (*e.g.* **18**→**19**+**20**, **Scheme 41**).



8.3 Sodium Metal Reduction of Naphthyridines

A series of naphthyridines have been subjected to reduction under the action of sodium metal, in ethanol, in order to scrutinise the stereochemistry of the decahydro-naphthyridines thus produced (Scheme 42).⁷² Unfortunately, the products obtained after treatment with sodium in ethanol were not fully saturated, and complete saturation was achieved by immediate treatment under hydrogenation conditions. In each case that was examined, this combination of conditions yielded the thermodynamically more stable *trans* isomer: comment on the origins of this stereoselectivity is difficult in light of the two step reduction procedure which conceals the exact stereochemistry determining step (it should be noted that attempts to produce the corresponding *cis* isomers by catalytic hydrogenation of the aromatic heterocycles proved unsatisfactory).



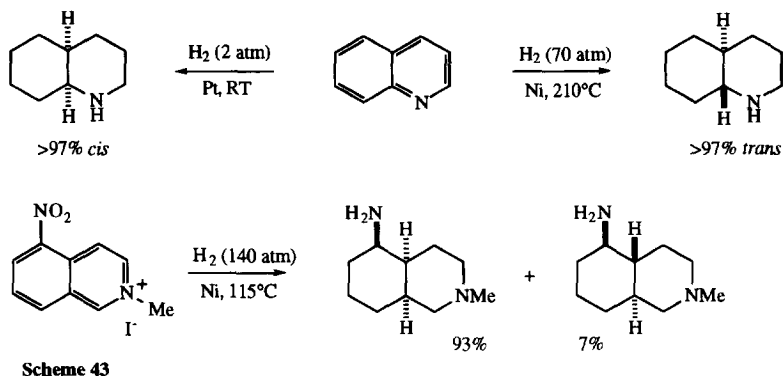
Scheme 42

9. Reduction of Miscellaneous Heterocycles

The final chapter in this review is meant to provide an outline of the stereochemical outcome that is to be expected should other heterocycles be subjected to reducing conditions. As expected, we have found reports indicating that many diverse and highly substituted heterocycles can be partially or completely reduced (mainly by hydrogenation), although it should be noted that as the number of heteroatoms in the heterocycle increases, the opportunity for stereocontrolled reduction becomes lower as a corollary of the reduced number of carbon atoms onto which one may attach a substituent!

9.1 Quinolines and Isoquinolines

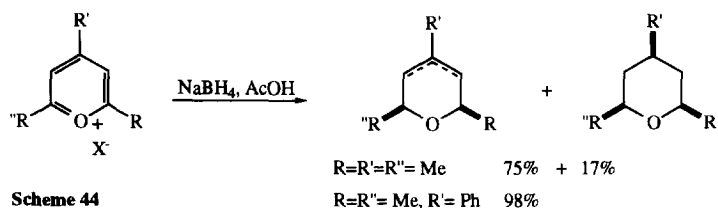
Quinolines may be hydrogenated under a variety of conditions, and selective reduction of the heterocyclic or carbocyclic ring can be accomplished by choice of the appropriate catalyst.⁷³ Exhaustive hydrogenation using platinum catalysis under mild conditions gave exclusively the *cis* isomer (Scheme 43);⁷⁴ as may be the case with a large number of hydrogenations, recourse to forcing conditions lead to the appearance of the thermodynamically more stable *trans* isomer.⁷⁵ Although isoquinolines may be completely reduced, they appear to be more resistant to hydrogenation than the corresponding quinolines and consequently much of the work concerning reduction of these heterocycles has been concerned with their quaternary salt derivatives (Scheme 43).⁷⁶



In a related study, the kinetics and stereochemistry of the reduction of acridine has been reported, and the authors discovered that both the regiochemistry and the stereochemistry of reduction was influenced by kinetic and thermodynamic factors, depending on the conditions that were employed.⁷⁷

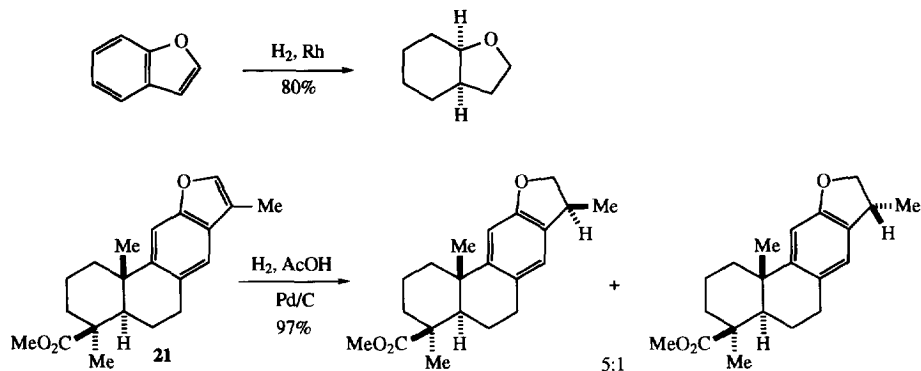
9.2 Pyrylium Salts

The reduction of pyrylium salts to their fully or partially saturated derivatives may prove to be an important route to stereochemically defined di- and tetra-hydropyrans. A study of the regiochemistry and stereochemistry to be expected from reduction of a series of substituted pyrylium salts with sodium borohydride in acetic acid has been reported:⁷⁸ while the results are complicated by the issue of electrocyclic ring opening reactions, predominance of the *cis* isomers was observed (**Scheme 44**).



9.3 Benzofurans

The benzofuran nucleus is susceptible to complete hydrogenation using a rhodium catalyst and, as expected, the *cis* diastereoisomer proves to be the major product (**Scheme 45**).⁷⁹ An example of the partial hydrogenation of a benzofuran was reported recently which described reduction of the tetracyclic nucleus illustrated below (**21**, **Scheme 45**):⁸⁰ under specific conditions, adsorption (and subsequent hydrogenation) took place predominantly from the least hindered face of the molecule, *anti* to the angular methyl group.



Scheme 45

Acknowledgments: We would like to express our gratitude to Rhône-Poulenc Rorer for a lectureship (to TJD).

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