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Stereocontrolled synthesis of *N*-methyl-1,2,3,4-tetrahydroisoquinoline derivatives via chromium tricarbonyl methodologies

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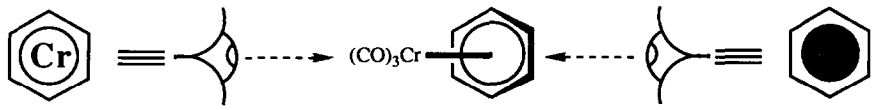
Abstract

Two chromium tricarbonyl based methods are described for the stereocontrolled synthesis of *N*-methyl-1,2,3,4-tetrahydroisoquinoline derivatives. Sequential deprotonation–alkylation reactions introduce substituents completely stereoselectively onto the 1- and 4-positions of *N*-methyl tetrahydroisoquinolines. Acid promoted cyclisations of (*N*-3,4-dimethoxybenzyl)-*N*-methyl-2-amino-1-aryl ethanol chromium tricarbonyl complexes produce, stereospecifically with retention of configuration, the corresponding 4-phenyl-*N*-methyl tetrahydroisoquinolines. These cyclisations stereochemically complement those observed for the uncomplexed series. In all cases oxidative decomplexation efficiently releases the free elaborated *N*-methyl tetrahydroisoquinoline derivatives.

Introduction

The synthesis of derivatives of substituted 1,2,3,4-tetrahydroisoquinolines * has been stimulated by their widespread natural occurrence and by the diverse range of pharmacological effects which they exhibit [1]. This review will describe our work on the use of arene chromium tricarbonyl methodologies for the stereoselective and stereospecific synthesis of a wide variety of *N*-methyl tetrahydroisoquinoline derivatives.



Scheme 1

* The descriptions 1,2,3,4 are henceforth omitted for clarity.

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$(\eta^5\text{-PhCH}_2^-)\text{Cr(CO)}_3$ $(\eta^7\text{-PhCH}_2^+)\text{Cr(CO)}_3$

Scheme 2

In arene chromium tricarbonyl complexes (Scheme 1) the bulky chromium tricarbonyl auxiliary effectively shields the coordinated face of the arene with the result that reactions generally take place with the reagents approaching the arene and benzylic positions from the unhindered, uncomplexed face.

The chromium tricarbonyl auxiliary is effective in stabilising both benzylic carbanions [2,3] and carbonium ions [4]. In each case the most significant resonance structure is the one possessing an exocyclic double bond with the charge residing on the chromium tricarbonyl moiety (Scheme 2). Both the complexed benzylic carbanion and carbonium ions are stable 18-electron species due to the ligand being bound η^5 and η^7 respectively. A consequence of the exocyclic double bond character for these ions is their configurational stability.

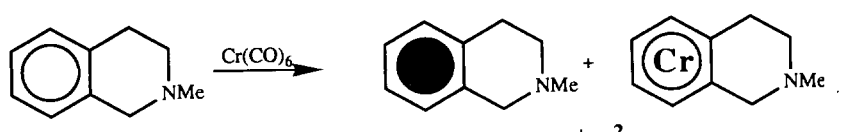
The first section of this review will describe the use of chromium tricarbonyl stabilised benzylic carbanions to stereoselectively introduce substituents onto the *N*-methyl tetrahydroisoquinoline skeleton. The second section describes the use of chromium tricarbonyl stabilised carbonium ions to effect the stereospecific formation of *N*-methyl tetrahydroisoquinolines from acyclic precursors.

Stereoselective alkylations of *N*-methyl tetrahydroisoquinoline complexes

4-Substituted N-*methyl tetrahydroisoquinolines [5]*

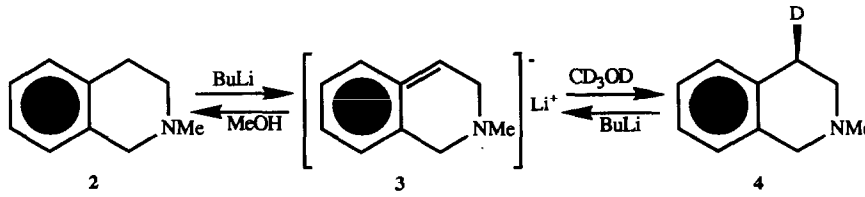
N-Methyl tetrahydroisoquinoline (**1**) is prochiral: Thermolysis of chromium hexacarbonyl in the presence of *N*-methyl tetrahydroisoquinoline produces, therefore, *N*-methyl tetrahydroisoquinoline chromium tricarbonyl (**2**; 78%) as a racemic mixture (Scheme 3). Complex **2** crystallises as bright yellow plates which, like all other similar complexes described herein, is relatively air-stable in the solid state at room temperature. These complexes may be handled in air as solids, stored indefinitely under nitrogen at $-20\,^\circ$C, but, as solutions, are best kept under nitrogen at all times.

Deprotonation of *N*-methyl tetrahydroisoquinoline chromium tricarbonyl (**2**) with butyllithium at $-78\,^\circ$C occurred completely regioselectively at the 4-position to generate the anion **3** as an incarnidine solution. Quenching the anion **3** with deuteriomethanol gave the 4-*exo*-deuterio derivative, complex **4**, as a single dia-

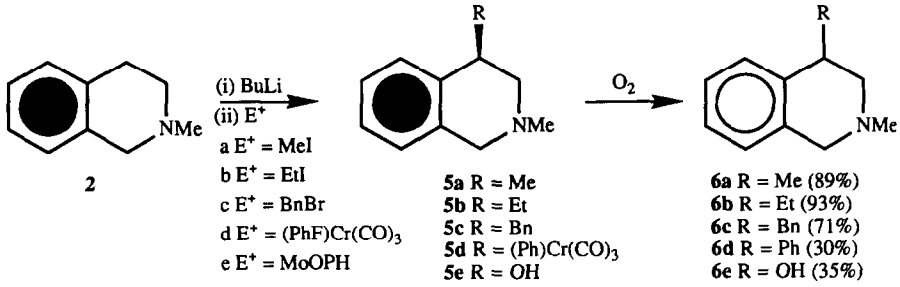


1 ± - 2

Scheme 3



Scheme 4



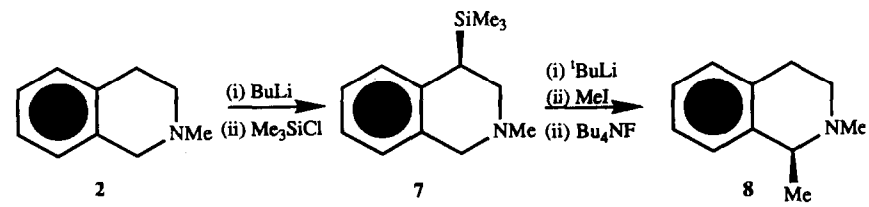
Scheme 5

stereoisomer (Scheme 4). Deprotonation–protonation of complex **4** completely removed the deuterium from **4** and regenerated the parent complex **2**. Thus both the deprotonation and electrophilic trapping steps are completely stereoselective: The 4-*exo*-proton is removed and replaced by the electrophile, in this case a deuteron, with retention of configuration. Both the regio- and stereoselectivities of the deprotonation step can be understood in terms of chelation of the butyllithium to the nitrogen lone pair directing the base to remove the pseudo-axial 4-*exo*-proton.

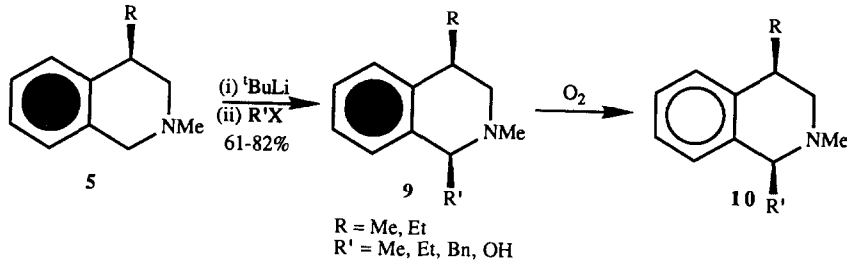
Addition of the appropriate electrophiles to anion **3** allows the completely stereoselective introduction of alkyl, phenyl and hydroxyl groups into the 4-*exo*-position generating complexes **5** (Scheme 5). Exposure of ether solutions of the thus elaborated complexes **5** to air and sunlight liberates the 4-substituted *N*-methyl tetrahydroisoquinolines **6** in essentially quantitative yield.

1-Substituted N*-methyl tetrahydroisoquinolines [6]*

The introduction of substituents into the 1-*exo*-position of complex **2** may be achieved by protecting the 4-*exo*-position with the trimethylsilyl group (Scheme 6). Thus deprotonation of **2** with butyllithium and trapping of the resultant anion **3** with trimethylsilylchloride generates complex **7** stereoselectively. Deprotonation of **7**



Scheme 6



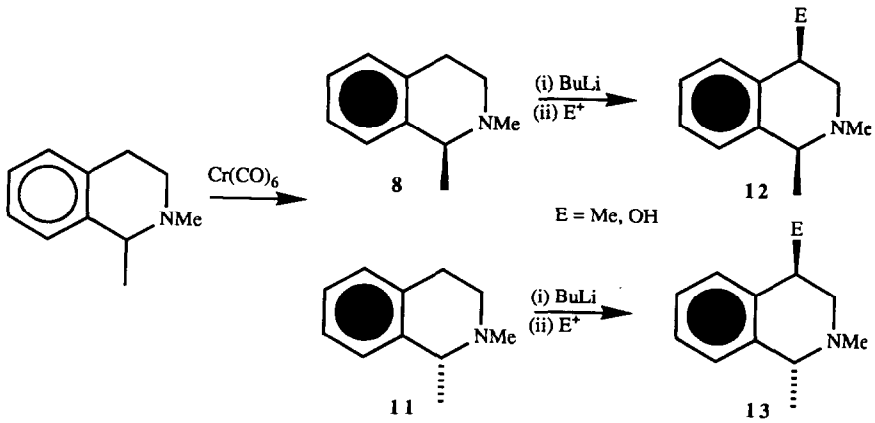
Scheme 7

with t-butyllithium is completely regioselective for the 1-position and quenching the thus generated carbanion with methyl iodide gave the corresponding 1-*exo*-methyl derivative **8** as a single diastereoisomer. Desilylation with fluoride generated *N*,1-*exo*-dimethyl tetrahydroisoquinoline chromium tricarbonyl (**8**) diastereoisomerically pure.

1,4-Disubstituted N-*methyl tetrahydroisoquinolines [6]*

Regioselective 1-deprotonation with t-butyllithium of the 4-*exo*-alkyl complexes **5**, prepared above, followed by electrophilic quenching of the thus generated anion results in the completely stereoselective introduction of substituents into the 1-*exo* position (Scheme 7). On oxidative decomplexation the corresponding *cis*-1,4-disubstituted *N*-methyl tetrahydroisoquinolines (**10**) are liberated quantitatively as single diastereoisomers.

Thermolysis of chromium hexacarbonyl with *N*,1-dimethyl tetrahydroisoquinoline gave a 75 : 25 mixture of the 1-*exo*-methyl complex **8** and the 1-*endo*-methyl complex **11**. After separation, deprotonation followed by electrophilic quench introduces a substituent into the 4-*exo*-position of **8** and **11** to generate complexes **12** and **13** respectively (Scheme 8). Decomplexation of complexes **12** and **13** results in the formation of *cis*- and *trans*-1,4-disubstituted *N*-methyl tetrahydroisoquinolines respectively.

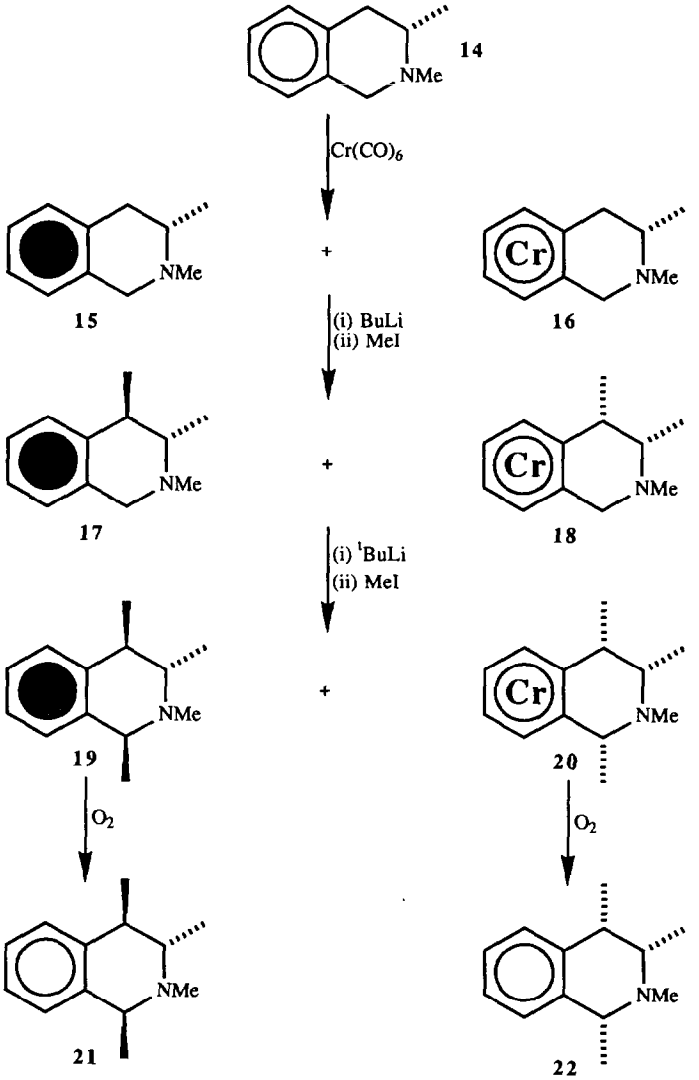


Scheme 8

Homochiral 1,N,3,4-tetramethyl tetrahydroisoquinolines [7]

Homochiral (enantiomerically pure) 3*S*-methyl *N*-methyl tetrahydroisoquinoline (**14**) is readily available via a Bischler–Napieralski ring closure of (+)-amphetamine. Thermolysis of chromium hexacarbonyl in the presence of **14** gave a 40:60 mixture of the *endo*- and *exo*-complexes **15** and **16** (Scheme 9). This mixture was subjected to butyllithium and methyl iodide to effect regio- and stereoselective 4-*exo*-methylation and generate a 40:60 mixture of complexes **17** and **18**. Further regio- and stereoselective 1-*exo*-methylation was achieved by sequential treatment with t-butyllithium and methyl iodide.

The structures of complexes **19** and **20** were initially assigned on the assumption that the *exo* complex **16** was the major diastereoisomer in the initial complexation



Scheme 9

reaction and that all the stereoselective methylations placed the methyl substituents in the *exo*-positions relative to the chromium tricarbonyl. These tentative assignments were reinforced by extensive NOE data and finally unambiguously confirmed by an X-ray crystal structure on complex **20**.

Complexes **19** and **20** were separable by chromatography. Oxidative decomplexation of complex **19** gave homochiral (−)-(1*S*,3*S*,4*R*)-1,2,3,4-tetramethyl tetrahydroisoquinoline (**21**) while decomplexation of **20** gave homochiral (+)-(1*R*,3*S*,4*S*)-1,2,3,4-tetramethyl tetrahydroisoquinoline (**22**). Both **21** and **22** were diastereoisomerically pure and their homochirality derives from the homochirality of the starting amphetamine.

*(8*R*)- and (8*S*)-methylcanadine [8]*

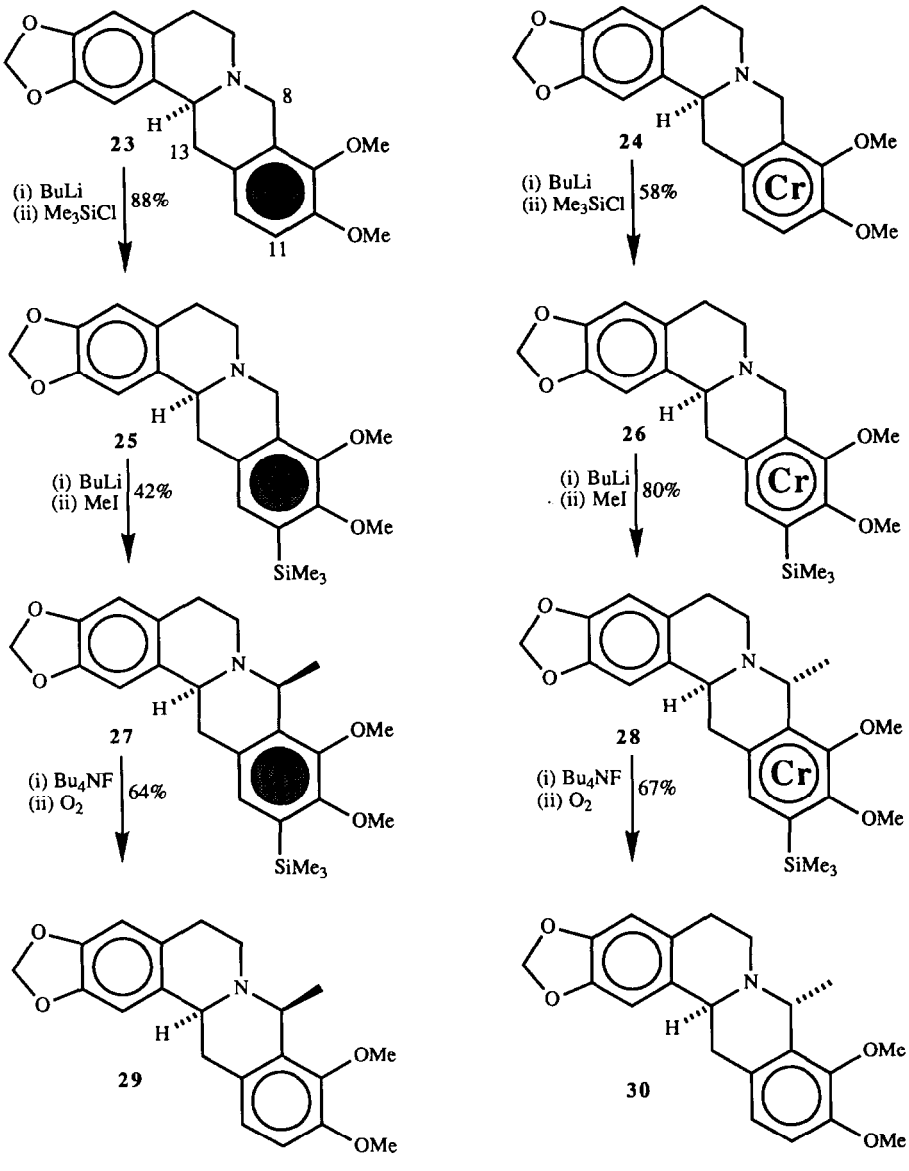
The protoberberines, for example canadine, are a widespread class of alkaloids based on the tetrahydroisoquinoline skeleton. Both enantiomers of canadine occur naturally; (−)-canadine is obtained from *Hydrastis canadensis* while (+)-canadine comes from *Corydalis tuberosa*. Racemic canadine may be prepared from reduction of berberine. Complexation of (−)-canadine to chromium tricarbonyl in the usual way gave a readily separable 40 : 60 mixture of two of the four possible canadine chromium tricarbonyl complexes (Scheme 10). ^{1}H NMR analysis established that completely regioselective complexation in favour of the dimethoxy ring over the methylenedioxy ring had occurred and that the complexes were the diastereoisomers **23** and **24**. The stereochemistry of the minor diastereoisomer **23**, and hence of **24**, was unambiguously established by an X-ray crystal structure analysis.

For both diastereoisomers **23** and **24** deprotonation with butyllithium occurs completely regioselectively at the 11-position and hence this position had to be protected by trapping the 11-aryl anions with trimethylsilylchloride, thus generating complexes **25** and **26** respectively (Scheme 10). The acidity of the aryl C-11 proton is enhanced by the adjacent electronegative methoxyl group. Deprotonation of **25** and **26** was expected to occur at C-13, this being the position equivalent to the 4-position of the previously studied tetrahydroisoquinoline complexes. However in both cases regioselective deprotonation at C-8 occurred to yield, after quenching with methyl iodide, the *exo*-8-methyl complexes **27** and **28** respectively. Presumably introduction of the C-11 trimethylsilyl group stabilises the C-8 anion relative to the C-13 anion. The electron withdrawing nature of the chromium tricarbonyl moiety makes the fluoride induced desilylations of **27** and **28** facile. Subsequent oxidative decomplexations releases (−)-8*S*-methylcanadine (**29**) and (−)-8*R*-methylcanadine (**30**) respectively.

Stereospecific syntheses of 4-phenyl N*-methyl tetrahydroisoquinolines*

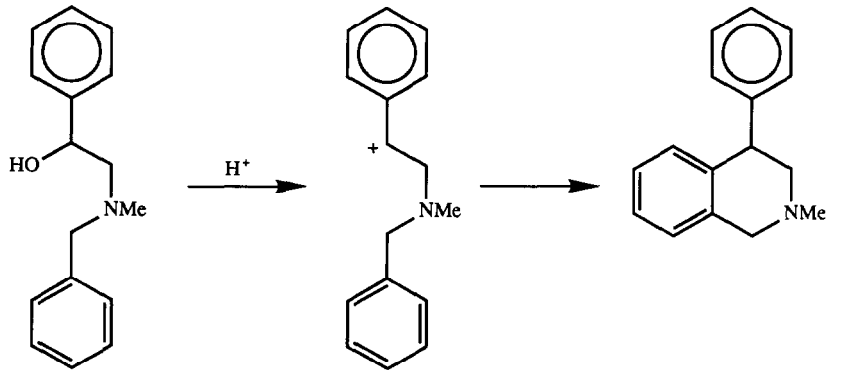
The potent pharmacological activity exhibited by 4-aryl tetrahydroisoquinolines has stimulated particular interest in their synthesis. Although a limited number of 4-aryl tetrahydroisoquinolines had been prepared in homochiral form by classical resolution procedures their direct synthesis had not been reported. Generally, the synthesis of 4-aryl tetrahydroisoquinolines is achieved by the strong acid, high temperature cyclisation of 2-benzylamino-1-aryl ethanols (Scheme 11).

It had been generally assumed that these cyclisations would proceed via a benzylic carbonium ion with the resultant lose of all stereochemical information to produce racemic products. We reasoned that if these cyclisations could be induced

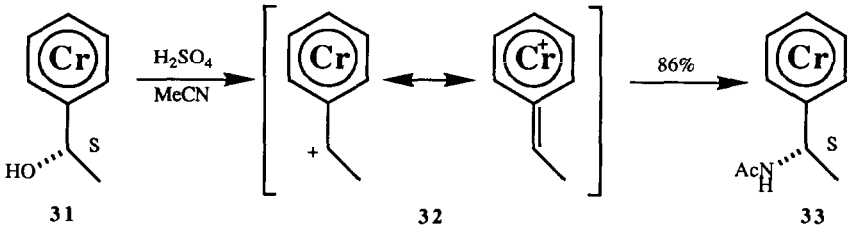


Scheme 10

under milder conditions then the benzylamino group might act as a neighbouring group, participating in the ionisation of the benzyl alcohol function. Such participation would result in inversion of configuration at the benzylic centre thus maintaining its stereochemical integrity. Two mechanisms were considered as reasonable for the cyclisation involving either the *ortho* carbon or the *ipso* carbon acting as the nucleophile towards the benzyl alcohol carbon or carbonium ion. The former would result in direct closure to the skeleton of the product tetrahydroisoquinoline whereas the latter would involve prior formation of a *spiro* intermediate followed by rearrangement. The stereochemical consequences of both mechanisms are the same,



Scheme 11



31 32 33

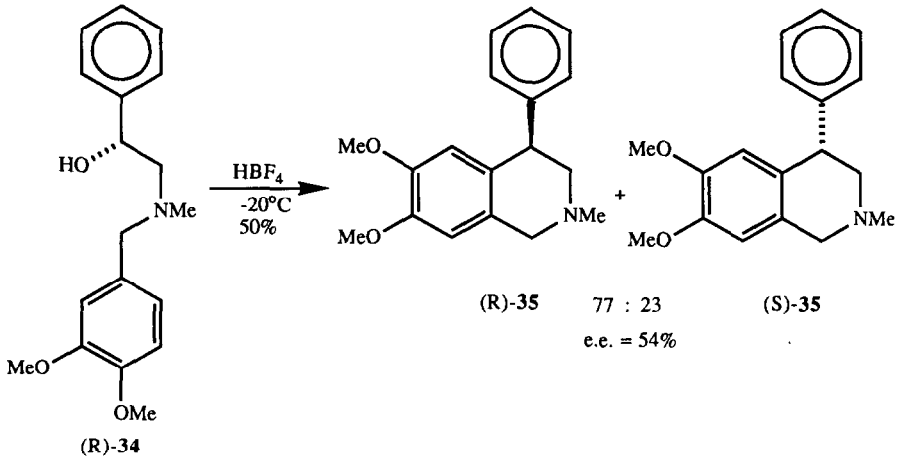
Scheme 12

racemisation for the carbonium ion process but inversion for the neighbouring group process. In order to facilitate the neighbouring group pathway, and thus promote stereochemical inversion, 3,4-dimethoxybenzylamino derivatives were chosen for study; the 3-methoxy group to promote the nucleophilicity of the 6-carbon and the 4-methoxy group to promote the nucleophilicity of the *ipso*-carbon.

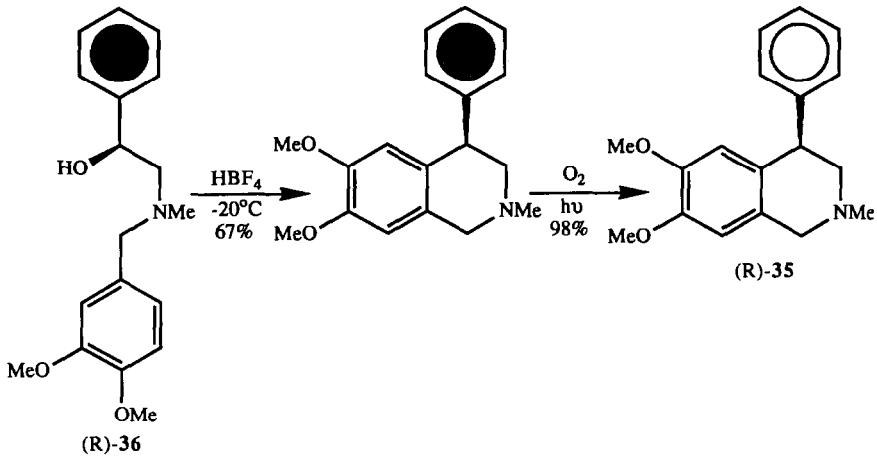
The Ritter reaction performed on phenethanol chromium tricarbonyl is known to proceed with complete retention of configuration (Scheme 12) [9]. This stereospecificity is consistent with a chromium lone pair participating in the ionisation of the benzyl alcohol function of **31** to give the chromium stabilised and stereochemically intact intermediate **32** which is trapped from the uncoordinated face by acetonitrile to give **33**. This double inversion mechanism explains the stereospecific retention of configuration. Furthermore, chromium tricarbonyl stabilised benzylic carbonium ions have been trapped intermolecularly with electron rich arenes [10]. Application of this chromium tricarbonyl methodology to the acid promoted cyclisations of 2-benzylamino-1-aryl ethanols was expected, therefore, to result in retention of configuration for the formation of tetrahydroisoquinoline products. It would thus complement the anticipated neighbouring group participation with inversion on the same substrates.

Cyclisations of halostachine derivatives [11]

On treatment with acid at $-20\,^{\circ}C$ (*R*)-*N*-3,4-dimethoxybenzyl halostachine (**34**) gave (*R*)-6,7-dimethoxy-*N*-methyl-4-phenyl tetrahydroisoquinoline (**35**) with an enantiomeric excess of 54% (Scheme 13). This corresponds to 46% of the reaction



Scheme 13



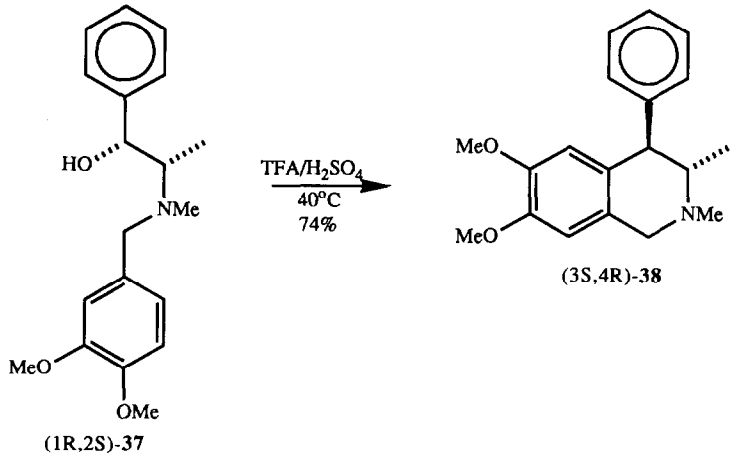
Scheme 14

proceeding via a free carbonium ion to racemic product **35** and 54% proceeding via the neighbouring group participation mechanism to inverted product (*R*)-**35**.

The equivalent cyclisation on the analogous chromium tricarbonyl complex (*R*)-**36** derived from (*S*)-halostachine gave, after oxidative decomplexation, homochiral (*R*)-**35** (Scheme 14), which corresponds, as expected, to a stereospecific process involving complete retention of configuration.

Cyclisations of ephedrine derivatives [12]

Treatment of *N*-3,4-dimethoxybenzyl ephedrine (**37**) with acid at 40 ° C produced the *trans*-tetrahydroisoquinoline **38** as a single diastereoisomer (Scheme 15). This completely stereoselective ring closure can be understood in terms of neighbouring group participation with inversion giving the *trans*-product and intramolecular trapping of the benzylic carbonium ion being controlled by the adjacent chiral centre also forming the thermodynamically most stable *trans*-product. In this case,



(1R,2S)-37

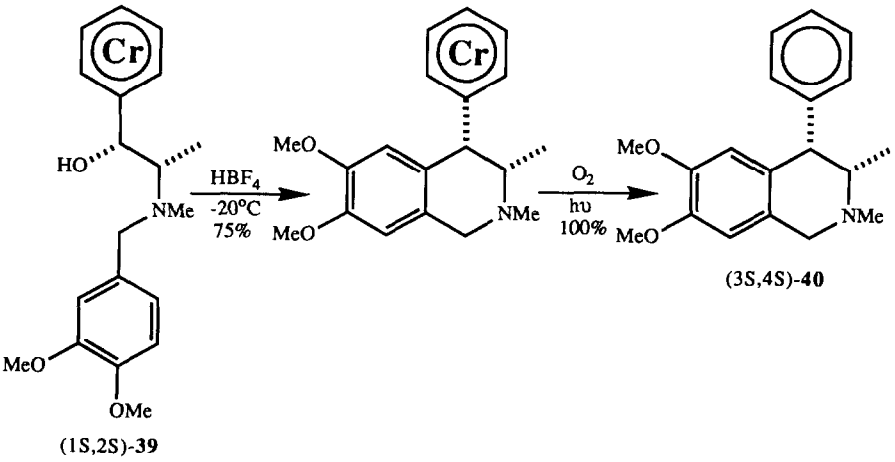
(3S,4R)-38

Scheme 15

since both mechanisms lead to the same product, their relative importance could not be established.

In complete contrast to the above cyclisation of **37**, acid treatment of **39**, the chromium tricarbonyl complex of **37** again proceeded completely stereoselectively, but after decomplexation to produce the *cis*-tetrahydroisoquinoline **40** (Scheme 16). The observed retention of configuration at the benzylic centre is consistent with the double inversion mechanism expected from initial participation of the chromium in the ionisation followed by cyclisation onto the unhindered face of the configurationally stable carbonium ion equivalent.

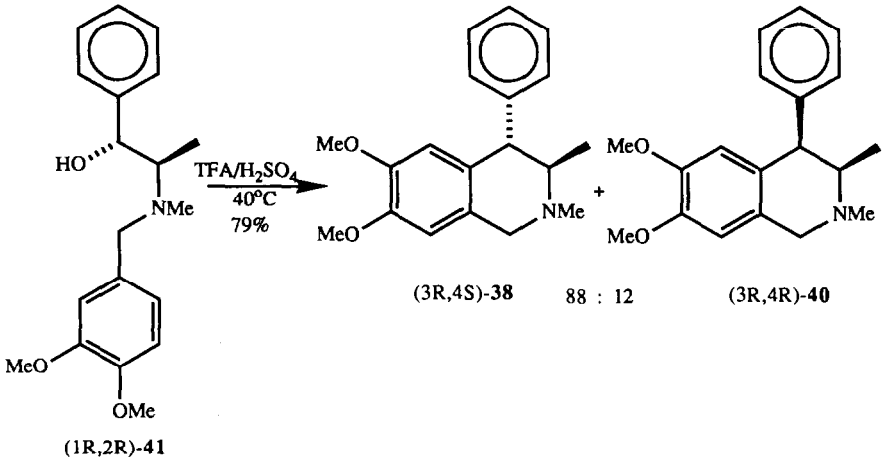
The stereochemically completely complementary cyclisations of **37** and its chromium tricarbonyl complex **39** allow the conversion of homochiral (−)-ephedrine into homochiral *trans*- and *cis*-2,3-dimethyl-4-phenyl-6,7-dimethoxytetrahydroisoquinolines **38** and **40** respectively.



(1S,2S)-39

(3S,4S)-40

Scheme 16



(3R,4S)-**38** 88 : 12 (3R,4R)-**40**

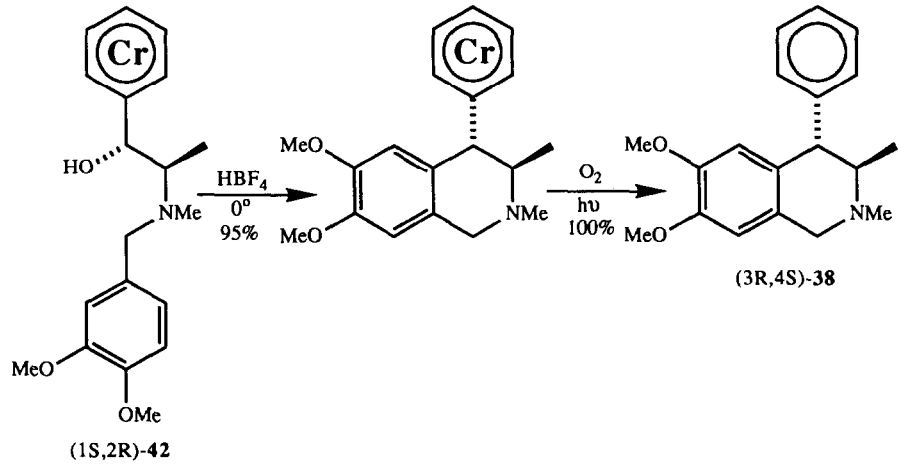
(1R,2R)-**41**

Scheme 17

Cyclisations of pseudoephedrine derivatives [12]

Acid treatment of *N*-3,4-dimethoxybenzyl pseudoephedrine (**41**) gave an inseparable 88 : 12 mixture of the *trans*- and *cis*-tetrahydroisoquinolines **38** and **40** (Scheme 17). This result is consistent with the reaction going 12% via neighbouring group participation giving the inverted less stable *cis*-diastereoisomer **40** and 88% via the benzylic carbonium ion which is trapped, as before, completely stereoselectively to the *trans*-diastereoisomer **38**.

On the other hand, acid promoted cyclisation of **42**, the chromium tricarbonyl complex of the pseudoephedrine derivative **41** was completely stereoselective to yield after decomplexation the *trans*-tetrahydroisoquinoline derivative **38** (Scheme 18). Once again the chromium tricarbonyl moiety induces complete retention of configuration during the cyclisation process.



(3R,4S)-**38**

(1S,2R)-**42**

Scheme 18

Conclusions

Tetrahydroisoquinolines may be constructed stereospecifically from *N*-methyl-2-amino-1-phenyl ethanols via methodology involving chromium tricarbonyl stabilisation of benzylic carbonium ions. Alternatively, already constructed *N*-methyl tetrahydroisoquinoline skeletons may be elaborated completely stereoselectively by exploitation of the ability of the chromium tricarbonyl moiety to stabilise benzylic carbanions.

Acknowledgements

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