Pure & Appl. Chem., Vol. 64, No. 3, pp. 379–386, 1992.
Printed in Great Britain.

Stereoselective manipulation of acetals derived from *o*-substituted benzaldehyde chromium tricarbonyl complexes

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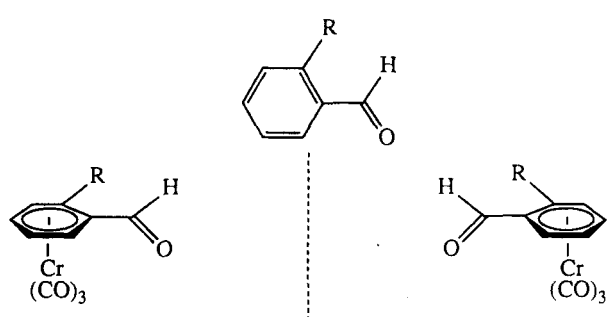
Abstract: The stereoselective syntheses of mixed acetals derived from *o*-substituted benzaldehyde chromium tricarbonyl compounds are described. These acetals are shown to undergo highly selective displacement reactions in a process which involves neighbouring group participation from the chromium tricarbonyl unit. Asymmetric syntheses of α-methyl benzylamines and 2-aryl tetrahydropyrans, *via* this methodology, are described.

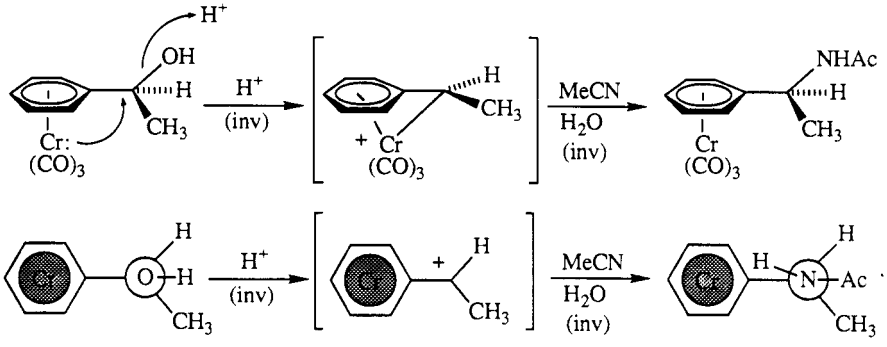
INTRODUCTION

Arene chromium tricarbonyl complexes can be synthesised from the requisite arene by treatment with a chromium tricarbonyl complex which has three coordination sites occupied by labile ligands. Under normal circumstances refluxing the arene with chromium hexacarbonyl in a suitable solvent, such as dibutyl ether, is sufficient to achieve complexation in high yield (ref. 1). It has been found that electron-rich arenes give the best yields for this process and that arenes containing either aldehydic or oxidising groups are incompatible with such a complexation procedure. Complexation under milder conditions may be achieved using either napthalene chromium tricarbonyl (ref. 2) or tris(acetonitrile) chromium tricarbonyl as chromium tricarbonyl transfer agents (ref. 3). Decomplexation is easily achieved by treatment with a variety of oxidising agents, the one most commonly employed being atmospheric oxygen (ref. 4). Thus, exposure of a diethyl ether solution of the arene chromium tricarbonyl complex to the atmosphere, in the presence of sunlight, leads to complete decomposition within twenty four hours. The liberated arene can then be isolated in very high yield by filtration and evaporation of the solvent. It is important to note that *ortho* and *meta*, unsymmetrically disubstituted arenes are prochiral; complexation of such arenes to chromium tricarbonyl leads to racemic mixtures.



Coordination of an arene to the chromium tricarbonyl moiety alters its reactivity in a manner which may be exploited for synthesis. It has been found that the chromium tricarbonyl moiety dramatically increases the stability of benzylic carbonium ions (ref. 5). This is due to electron donation from the chromium into the vacant 'p' orbital on the α-carbon, leading to substantial exocyclic double bond character. Evidence for such neighbouring group participation by the chromium comes from the Ritter reaction of (S)-(+)-1-phenethanol chromium tricarbonyl (ref. 6). Results indicate that the reaction is facile and proceeds with complete retention

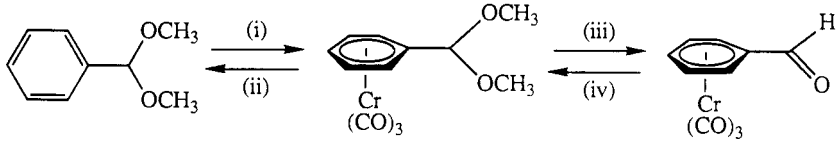
of configuration. This may be rationalised as being due to a double inversion mechanism involving neighbouring group participation from the chromium, followed by *exo* attack by the external nucleophile, acetonitrile. It also implies that the intermediate carbonium ion has conformational stability, and this is therefore in keeping with the rationale of exocyclic double bond character in these systems.



We describe here how this facet of benzylic carbonium ion stability may be utilized in asymmetric synthesis methodology by using the arene chromium tricarbonyl moiety as a chiral auxiliary and the acetal funcationality as a precursor for subsequent manipulations.

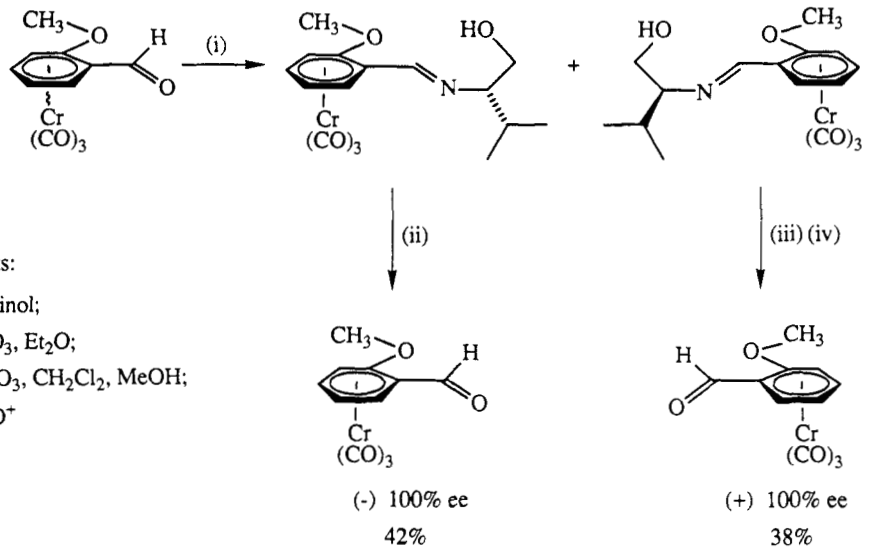
PREPARATION OF CHROMIUM TRICARBONYL COMPLEXED BENZALDEHYDE DERIVATIVES

Direct treatment of substituted benzaldehydes with chromium hexacarbonyl under thermolysis conditions gives very poor yields of the corresponding arene chromium tricarbonyl complexes (ref. 7). It is therefore desirable to protect the aldehyde functionality prior to complexation. Using the acetal functionality in this role leads to a protecting group that allows high yielding complexation, the possibility of subsequent displacement reactions and facile deprotection.



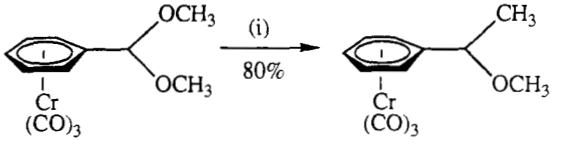
Reagents: (i) $Cr(CO)_6$, Bu_2O; (ii) O_2, hv, Et_2O; (iii) H_3O^+; (iv) $(CH_3O)_3CH$, H^+.

As mentioned earlier, complexation of a prochiral arene to the chromium tricarbonyl unit necessarily results in a racemic mixture and in order to obtain homochiral material resolution is required. Although several methods of resolving arene chromium tricarbonyl complexes have appeared in the literature (ref. 8), we find the most convenient procedure for resolving *o*-substituted benzaldehyde chromium tricarbonyl complexes to be one involving formation of oxazolidine/imine derivatives from L-valinol (ref. 9). Thus, absorption of (±)-*o*-anisaldehyde chromium tricarbonyl onto a L-valinol-doped alumina chromatography column, followed by elution, gives two very distinct fractions. There are collected and hydrolysed with hydrochloric acid to give each enantiomer of *o*-anisaldehyde chromium tricarbonyl in high yield and in homochiral form. It is proposed that of the two diastereomeric imines formed initially in this reaction, only one is converted to the corresponding oxazolidine form on exposure to alumina, while the other is hydrolysed. The former yields a relatively stable *cis*-1,3-disubstituted oxazolidine while the latter would produce a less stable *trans*-isomer. In addition to *o*-anisaldehyde chromium tricarbonyl other *o*-substituents on the aromatic ring are amenable to this resolution methodology (ref. 10), making it a general procedure for this class of compounds.



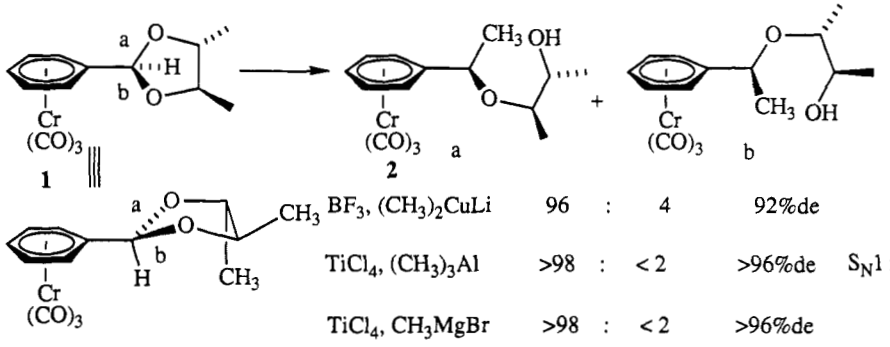
ASYMMETRIC SYNTHESIS OF α-METHYL BENZYLAMINES

Treatment of the dimethyl acetal of benzaldehyde chromium tricarbonyl with titanium tetrachloride and trimethylaluminium gave methyl-(1-phenylethyl)ether chromium tricarbonyl in 80% yield (ref. 11). This reaction proceeds *via* activation of the acetal by the Lewis acid, followed by nucleophilic attack.

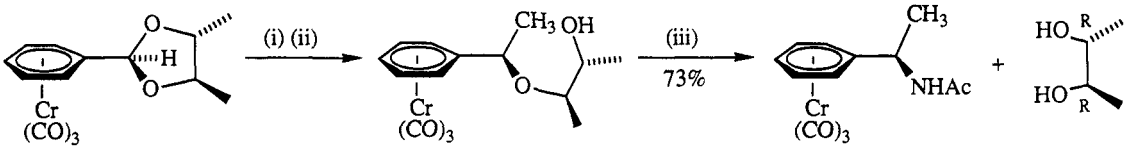


Reagents: (i) $TiCl_4$, $(CH_3)_3Al$, CH_2Cl_2, -78° C, 10 min.

This methodology was extended to include the opening of cyclic acetals derived from (RR)-2,3-butane diol (ref. 12). Thus treatment of the cyclic acetal **1** with titanium tetrachloride and trimethylaluminium gave a single diastereomer of ether **2**. In common with the uncomplexed reaction, formation of **2** involves cleavage of the pro-R acetal C-O bond, thus relieving steric compression present in the acetal. In contrast to the uncomplexed case, the conversion of **1** to **2** proceeds with retention of configuration, which is consistent with a double inversion mechanism involving cleavage of the acetal C-O bond by the chromium tricarbonyl moiety and subsequent *exo* attack by the carbon nucleophile.



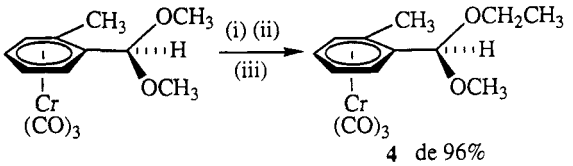
As well as dramatically improving, and reversing, the diastereoselectivity of this reaction when compared to that observed for the uncomplexed system (ref. 13), the transition metal also facilitiates the non-destructive removal of the butane diol auxiliary. By subjecting complex **2** to Ritter conditions the amide **3** was obtained in both high yield and homochiral form. As described earlier, this reaction proceeds with complete retention of configuration (ref. 11).



1 **2** de > 98% **3** ee > 98%

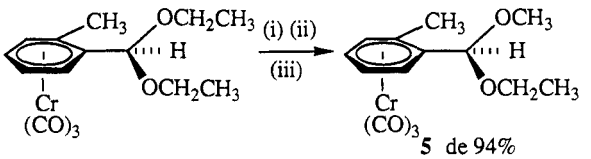
Reagents: (i) $TiCl_4$; (ii) $(CH_3)_3Al$; (iii) H_2SO_4, MeCN, H_2O

Subjecting *o*-tolualdehyde dimethyl acetal chromium tricarbonyl to titanium tetrachloride and triethylamine, followed by quenching with ethanol, generated the mixed acetal **4** with excellent diastereoselectivity. The other diastereomer **5** could be synthesised, again highly stereoselectively, by trapping the activated diethyl acetal with methanol. The relative stereochemistry within **4** and **5** is that expected for a double inversion mechanism and was assigned on the basis of ^1H nmr spectroscopic analysis.



4 de 96%

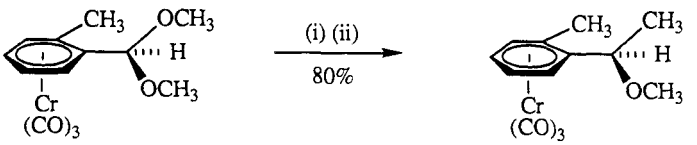
Reagents: (i) $TiCl_4$, -78°C; (ii) NEt_3; (iii) CH_3CH_2OH



5 de 94%

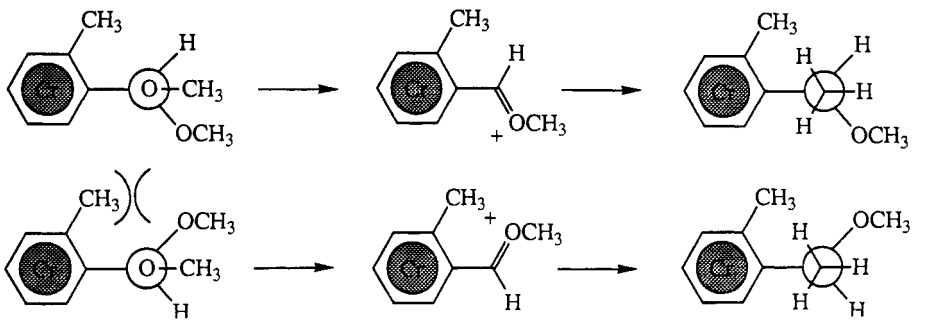
Reagents: (i) $TiCl_4$, -78°C; (ii) NEt_3; (iii) CH_3OH

It was found that treatment of *o*-tolualdehyde dimethyl acetal chromium tricarbonyl with titanium tetrachloride, followed by trimethylaluminium, produced complex **6** as a single diastereomer (ref. 14). These reactions are thought to proceed by ionisation of the dimethyl acetal to give a chromium-stabilised oxonium ion. This adopts a conformation whereby the oxonium ion lies in the plane of the aromatic ring but *anti* to the bulky *o*-substituent in order to minimise non-bonded interactions. The nucleophile then attacks from the *exo* face, away from the large chromium tricarbonyl unit, to generate complex **6** stereoselectively.



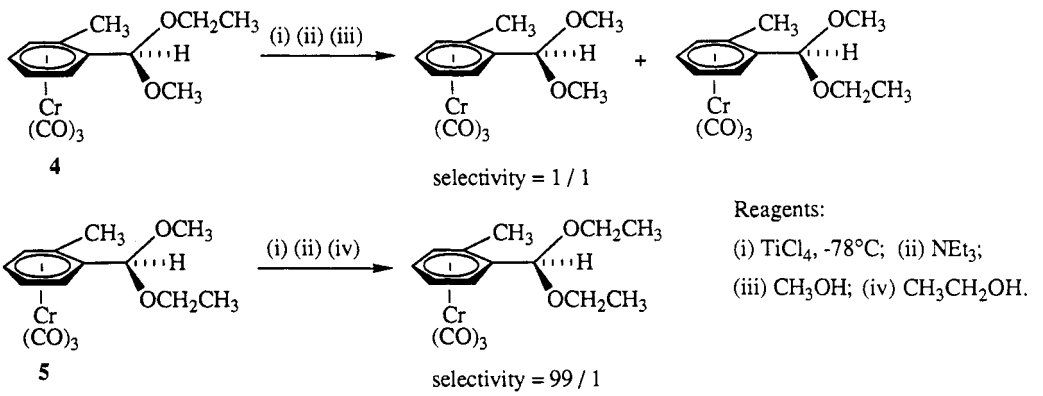
Reagents: (i) $TiCl_4$; (ii) $(CH_3)_3Al$. **6** de ≥ 99%

These experiments clearly indicate that any oxonium ion, derived from these acetals, is trapped in a diastereoselective manner by a variety of nucleophiles. The mixed acetals that were generated by this procedure were used as mechanistic probes, to determine whether or not the ionisation of the acetals was stereoselective. We expected that, in the absence of complicating factors, the chromium tricarbonyl moiety would exhibit a penchant for ionising only one of the two alkoxy groups within the acetal. Considering the Newman projections looking along each of the two acetal O-C bonds in the conformations necessary for chromium assisted ionisation and assuming that ionisation will be preferred such that the 'leaving group' will lie antiperiplanar with respect to the arene centroid to chromium axis, ionisation of one of the alkoxy groups



will lead to a crowded oxonium ion, involving steric repulsion between the remaining oxygen and the *o*-substituent, while loss of the other oxygen will lead to a more favourable oxonium ion lacking any severe steric interactions.

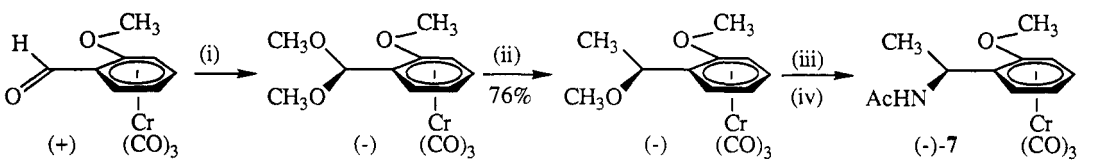
This rationale predicts that compound **4** will prefer to lose an ethoxy group and compound **5** a methoxy group. The exchange reaction on **4** proved essentially non-selective, while that on **5** was essentially completely stereoselective. Presumably the Lewis acid prefers to bind to the more accessible methoxy oxygen which promotes the inherent stereoselectivity in the ionisation of **5** but conflicts in the reaction of **4**.



4

5

Starting from homochiral *o*-anisaldehyde chromium tricarbonyl the secondary amide **7** was prepared with an initial diastereomeric excess of 90%, increased to 100% after one crystallisation. The stereochemical integrity is compromised somewhat in the Ritter reaction: Apparently the presence of the *o*-substitutent disturbs the double inversion mechanism, possibly by encouraging epimerisation of the intermediate carbocation (ref. 14).

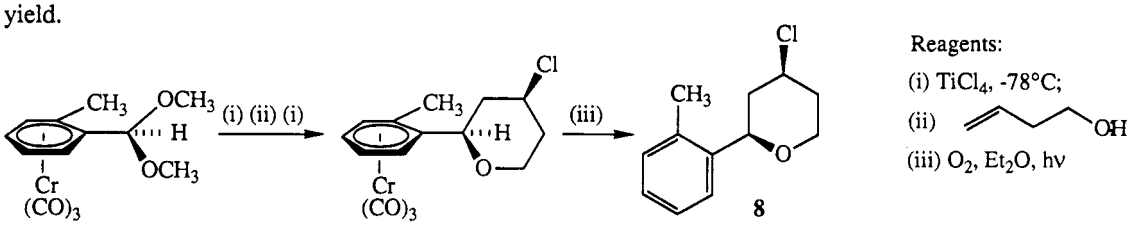


Reagents: (i) $CeCl_3$, MeOH, $(CH_3O)_3CH$; (ii) $TiCl_4$, $(CH_3)_3Al$, -78°C; (iii) H_2SO_4, MeCN; (iv) H_2O.

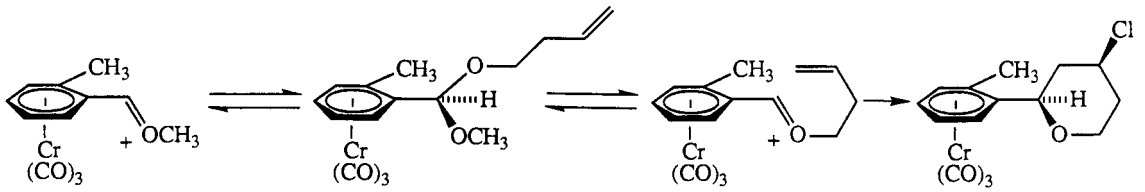
ASYMMETRIC SYNTHESIS OF 2-ARYL TETRAHYDROPYRANS

It was decided to extend this methodology to the synthesis of substituted tetrahydropyrans *via* an oxonium induced cyclisation (ref. 15). Activating the dimethyl acetal of *o*-tolualdehyde chromium tricarbonyl with titanium tetrachloride, quenching the oxonium ion thus formed with a homoallylic alcohol, and subsequent

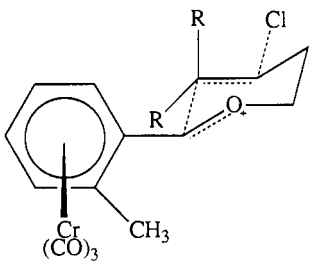
treatment with further Lewis acid gave, after 24 h at -78° and decomplexation the cyclised product **8** in 95% yield.



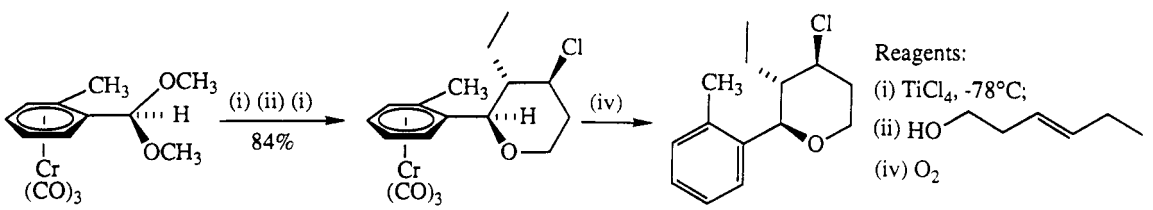
The formation of **8** is understandable in terms of initial formation of the mixed acetal followed by intramolecular trapping, by the olefin, of the oxonium ion formed by loss of the second methoxy group. As the olefin cyclises onto the oxonium ion the developing carbonium ion is trapped by a chloride ion.

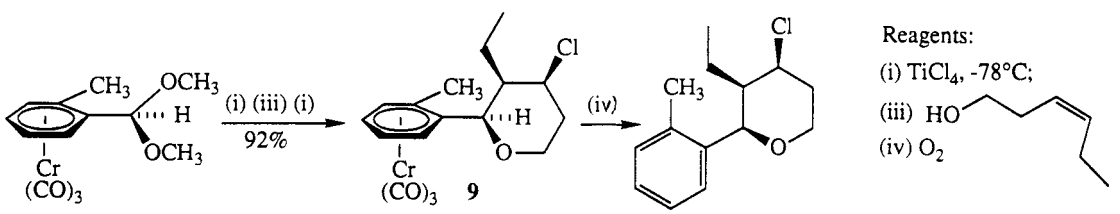


The stereoselectivity of the cyclisation may be rationalised by firstly assuming antiperiplanar addition across the double bond and secondly invoking a chair transition state in which the arene chromium tricarbonyl moiety adopts an equatorial position.



If the above analysis is correct, introduction of a substituent onto the terminal position of the double bond of the homoallylic alcohol should allow the stereospecific introduction of this substituent into the 2-position of the cyclised product. Both of the examples shown below proceeded as predicted, to yield, in each case, only the expected diastereoisomer, completely stereoselectively. Decomplexation was facile, being achieved in near quantitative yield in all cases.





The assigned stereochemistry in this series was confirmed unambiguously by a single crystal X-ray structure analysis on the *cis,cis* complex **9**.

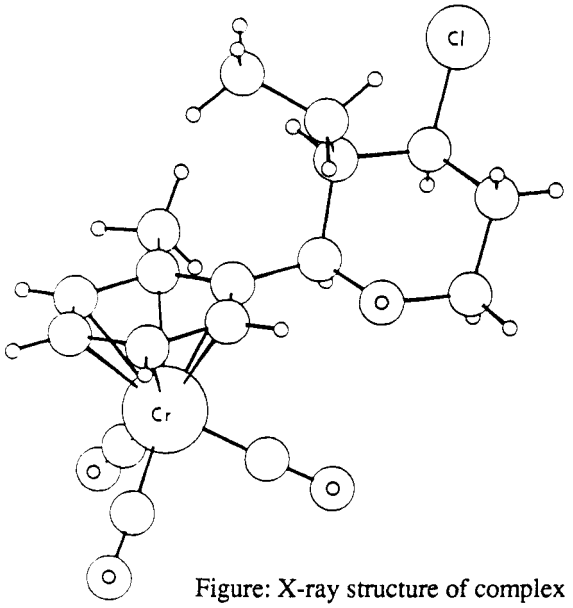
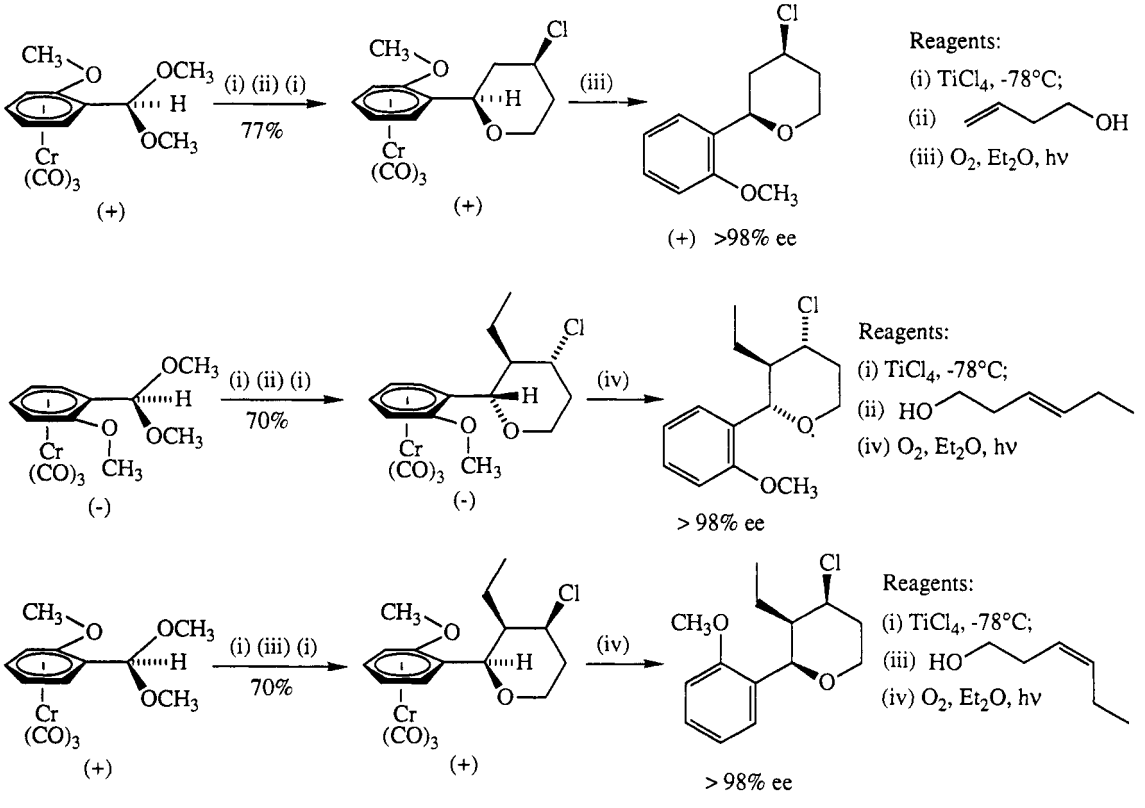


Figure: X-ray structure of complex **9**.

The oxonium ion initiated cyclisations described above were also completely stereoselective for the *o*-methoxy derivatives. Thus, starting from homochiral *o*-anisaldehyde dimethyl acetal the three tetrahydropyrans shown below were prepared (ref. 16). These were judged to be homochiral (greater than 98% e.e) by analysis of their ^1H nmr spectrum in the presence of (S)-(+)-2,2,2-trifluoro-1-(9-anthyl)ethanol; only one enantiomer being detected in comparison with each respective racemate (ref. 17).



CONCLUSION

We have demonstrated that acetals derived from benzaldehyde chromium tricarbonyl complexes can act as templates for the enantioselective synthesis of α-methyl benzylamines and 2-aryl tetrahydropyrans. In all cases, a double inversion mechanism has been shown to operate with the stereoselectivity being induced either by chirality in the alkoxy groups or in the *o*-substituted arene chromium tricarbonyl fragment.
The high yielding and extremely diastereoselective nature of all these reactions, coupled with the ease of decomplexation, shows that arene chromium tricarbonyl complexes are promising chiral auxiliaries for asymmetric synthesis.

Acknowledgement

We thank ICI Pharmaceuticals (Macclesfield) and the SERC for a CASE award (TJD), and Glaxo Group Research (Ware) for a studentship (JMJW).

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