Arene Chromium Tricarbonyl Stabilised Benzylic Carbocations

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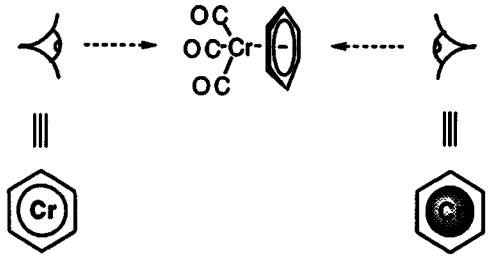
Abstract: The ability of the chromium tricarbonyl unit to stabilise benzylic carbocations and oxonium ions is described. We have investigated the use of arene chromium tricarbonyl complexes as chiral auxiliaries for asymmetric synthesis. The synthesis of homochiral tetrahydroisoquinolines, tetrahydrobenzazepines, and 2-aryltetrahydropyrans *via* intramolecular cyclisation of a nucleophile onto chromium tricarbonyl stabilised benzylic carbocations and oxonium ions is described.

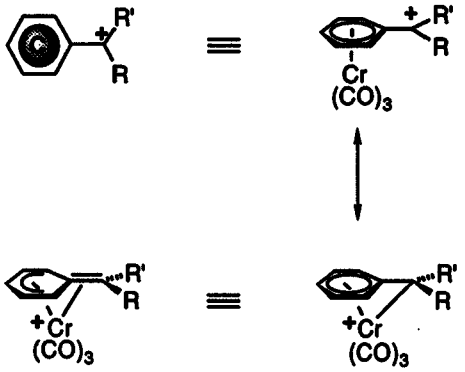
1. Introduction

The use of arene chromium tricarbonyl complexes within organic synthesis is widespread. This is due to the fact that they are synthetically equivalent to the free arene, yet possess markedly different chemical properties. Complexation of an arene ring to the chromium tricarbonyl unit is easily accomplished and is high yielding in most cases.[1] Oxidative removal of the transition metal occurs readily upon exposure of an ether solution of the complex to atmospheric oxygen and sunlight. A 1-2 or 1-3-unsymmetrically disubstituted arene is prochiral and therefore the corresponding chromium tricarbonyl compounds are chiral; we have exploited this property to allow the use of such compounds as chiral auxiliaries.



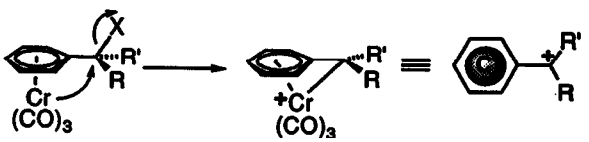
One of the most important modifications of reactivity that coordination of an arene to the chromium tricarbonyl unit imparts onto an arene is the enhanced stability of benzylic carbocations.[1] Such a stabilisation has its origins in a delocalisation of the positive charge from the benzylic carbon onto the transition metal, due to overlap between filled d-orbitals on the chromium and the empty p-orbital on the benzylic carbon. This can be represented by the resonance structures shown below, although some of these show the transition metal bound in an η^7 mode to the benzyl ligand, it is important to note that each obeys the 18 electron rule.

From this bonding picture it can be observed that a stabilised benzylic carbocation incorporates a substantial amount of exocyclic double bond character and this in turn implies that rotation about the C_α-C_{ipso} bond will be restricted. Such a phenomenon has important ramifications for the use of arene chromium tricarbonyl complexes as chiral auxiliaries.



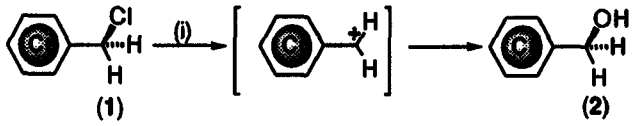
A rate increase, relative to the uncomplexed arene, is observed for a process that involves formation of a chromium tricarbonyl stabilised benzylic carbocation in the rate determining step. This is a manifestation of product-like transition states for ionisation of leaving groups in the benzylic position. The chromium tricarbonyl moiety acts, *via* neighbouring group participation, to stabilise the build-up of positive charge in such a transition state.

If one considers the nature of this neighbouring group participation by the transition metal then it appears that there must be certain stereoelectronic requirements for ionisation of leaving groups at the benzylic position. In order that there is maximum overlap between the d-orbitals on the chromium and the σ^*-orbital of the leaving group an arrangement whereby the nucleofuge lies *anti* to chromium should best facilitate transition metal promoted ionisation. This constraint becomes stereochemically important when there is a stereogenic centre at the benzylic position and will be discussed later.



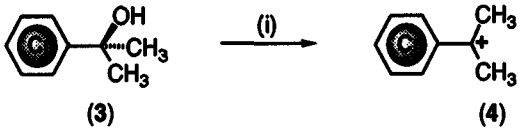
2. Evidence for Chromium Tricarbonyl Stabilisation of Benzylic Carbocations

Evidence for the increased rate of formation of these chromium tricarbonyl stabilised carbocations was first accumulated when it was discovered that benzyl chloride chromium tricarbonyl solvolysed $\approx 10^5$ times faster than the free arene under S_N1 conditions (**Scheme 1**).[2]



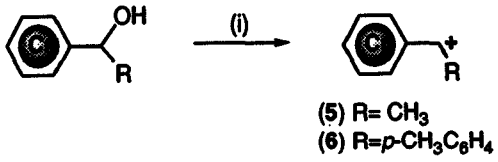
Scheme 1. Reagents: (i) H_2O, Acetone.

The rate enhancement observed over that of benzyl chloride was postulated to arise from the rapid formation of a chromium tricarbonyl stabilised benzylic carbocation in the rate determining step. A series of measurements of the rates of solvolysis of such carbocations, which was correlated to their thermodynamic stabilities, indicated that their stability was indeed more than would be expected from the influence of the arene alone. The effect of the transition metal in delocalising the positive charge was considered to be approximately equal to that imparted by another aromatic ring.[3] Full spectroscopic characterisation of the transition metal stabilised cation (**4**) was obtained by Olah *et al* when they recorded its ^1H and ^{13}C nmr spectra (**Scheme 2**).[4] The nature of the stabilising interaction was concluded to arise from an overlap of filled d-orbitals on the chromium metal centre with the LUMO of the cationic arene ligand; this has the effect of delocalising a substantial amount of the positive charge onto the transition metal.



Scheme 2. Reagents: (i) FSO_3H-SO_2.

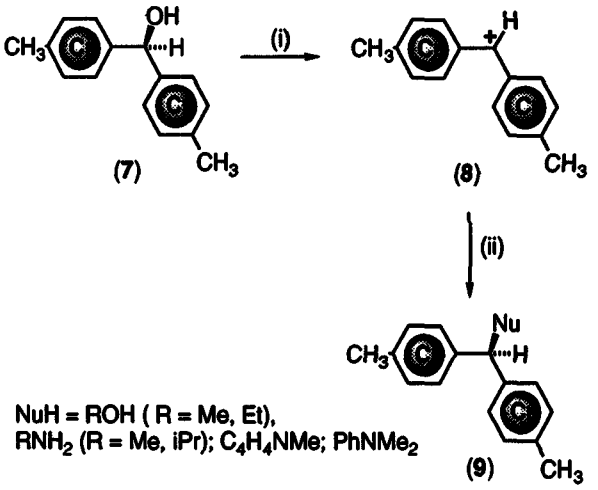
This view was further reinforced by the ^{13}C nmr studies that were carried out on the cations (**5**) and (**6**), (**Scheme 3**), which clearly demonstrated the inequivalence of both the *ortho* and *meta* carbons of the complexed arenes as a consequence of restricted rotation about the Cα-Cipso bond.[5]



Scheme 3. Reagents: (i) FSO_3H.

Seyferth *et al* utilised complex (**7**) to obtain the doubly stabilised cation (**8**) as dark blue crystals, which were analysed spectroscopically (**Scheme 4**).[6] Numerous trapping experiments showed that this cation could be captured by most reasonably nucleophilic species to give the benzylically substituted derivatives in good yields. This indicated that such cations, once generated, could be used in a synthetically useful manner.

The properties exhibited by such complexes, as shown above, make arene chromium tricarbonyl complexes ideal tools for the selective generation of stereogenic centres, i.e. chiral auxiliaries. With this emphasis the following sections will illustrate how such goals have been realised. There are three distinct arrangements whereby stereocontrol within the arene chromium tricarbonyl compound can be achieved:



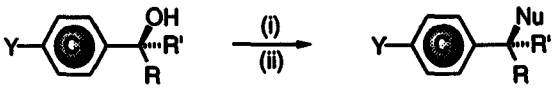
Scheme 4. Reagents: (i) HPF_6; (ii) NuH.

3. Acyclic Systems without *ortho* Substitution

The lack of an *ortho* substituent on the arene ring is significant as it removes any external influence upon the conformation of the benzylic cation. Restricted rotation about the Cα-Cipso bond means that these species, once formed, should be configurationally stable. Nucleophilic attack onto the cation will occur from the *exo* face, opposite to the bulky chromium tricarbonyl group. If the leaving group was ionised whilst positioned *anti* to the transition metal, as a consequence of neighbouring group participation, then a double inversion mechanism should be in operation.

3.1 Carbocations

We performed preliminary experiments which showed that the carbocations derived from the acyclic derivatives shown below could be captured by a large variety of nucleophiles, such as alcohols,[7] amines,[7] thiols,[8] and Grignard reagents[9] with yields ranging from 23-92% (**Scheme 5**). However, the consequences of a double inversion mechanism were outside the scope of these studies because the starting material was either achiral (R= R') or racemic.

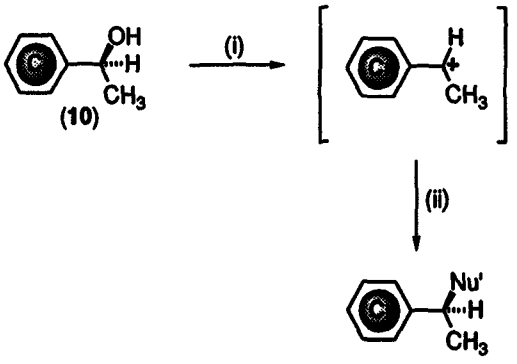


Y=H, OCH_3.
R= H, CH_3.
R'= H, CH_3, C_6H_5.

NuH= ROH (R= CH_3, C_2H_5);
$(CH_3)_2NH$;
RNH_2 (R= CH_3, H);
C_2H_5SH;
BuMgBr.

Scheme 5. Reagents: (i) HPF_6 or HBF_4; (ii) NuH.

The arene chromium tricarbonyl moiety was found to be particularly effective in promoting the Ritter reaction, i.e. the addition of a nitrile to a carbocation to generate, after hydrolysis, an amide.[10] Not only did complexation to the transition metal increase the range of benzylic alcohols that underwent the Ritter reaction but it also expanded the range of nitriles that could be used successfully under these conditions (e.g. PrCN, $ClCH_2CN$). A leading study by Jaouen and Top, demonstrated that reaction of the optically active alcohol (**10**) with sulphuric acid and acetonitrile as the solvent, lead to complete retention of configuration; unfortunately this was not the case with other nucleophiles that were examined (**Scheme 6**).[11] Presumably, this is a consequence of the fact that they were not employed in the role of solvent for these reactions and therefore reacted at a slower rate with any cationic intermediate, allowing it time to racemise by rotation about the Cα-Cipso bond.

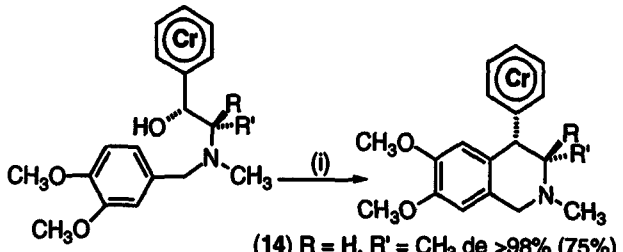


(10)

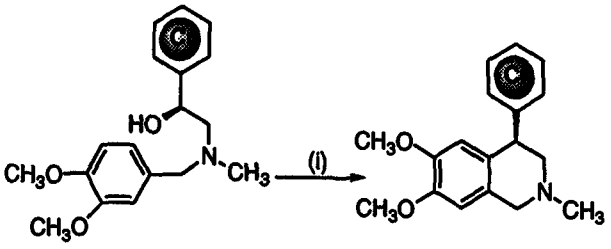
(11) Nu= CH_3CN, Nu'= CH_3CONH, 100% Retention.
(12) Nu= CH_3OH, Nu'= OCH_3, 72% Retention.
(13) Nu= H_2O, Nu'= OH, 47% Retention.

Scheme 6. Reagents (i) H_2SO_4 (ii) Nu.

We also established that the double inversion process occurred when the nucleophile operated in an intramolecular sense. This enabled the asymmetric synthesis of several, pharmacologically important, tetrahydroisoquinoline[12] and tetrahydrobenzazepine[13] derivatives *via* a cyclisation reaction of homochiral benzyl alcohols that is generally both unselective and inefficient in the absence of the transition metal (**Scheme 7/8**). In all cases, removal of the transition metal was quantitative, leading to homochiral material.

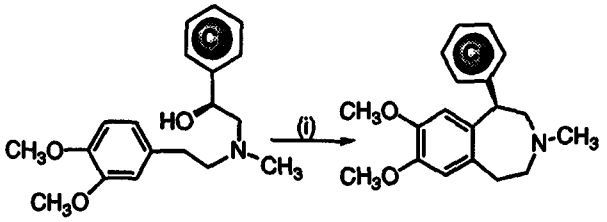


(14) R = H, R' = CH_3 de >98% (75%)
(15) R = CH_3, R' = H de >98% (95%)



(16) ee >98% (67%)

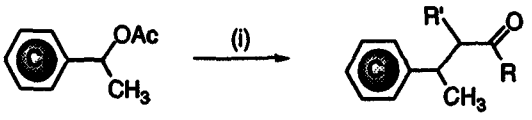
Scheme 7. Reagents: (i) HBF_4.



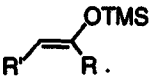
(17) ee >98% (76%)

Scheme 8. Reagents: (i) HBF_4.

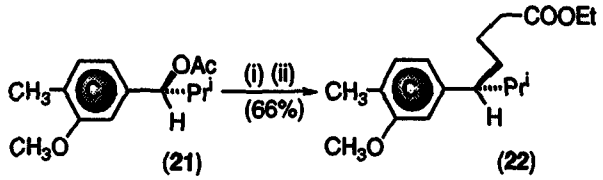
The role of Lewis acids in promoting ionisation of similar derivatives has also been explored. Initially Reetz *et al*, generated a stabilised carbocation from a benzylic acetate utilising zinc chloride.[14] This cation was then trapped with a series of trimethylsilyl enol ethers (**Scheme 9**). Although a double inversion mechanism was suspected, the use of racemic material prevented any definite conclusions.



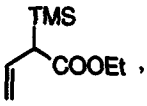
(18) R= CH_3, R'= H (84%)
(19) R= ^tBu, R'= H (82%)
(20) R= R'= $(CH_2)_4$ (68%)

Scheme 9. Reagents: (i) $ZnCl_2$, 

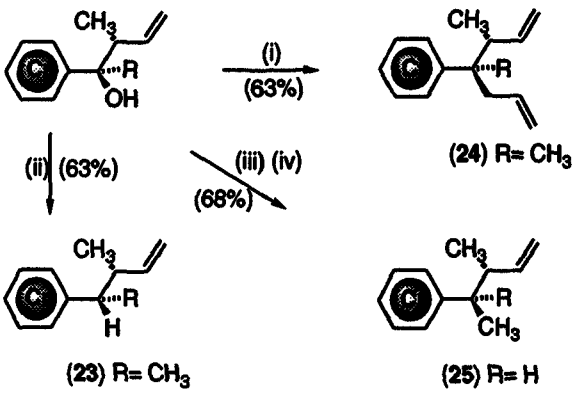
Uemura studied systems containing stereogenic elements that were additional to that at the benzylic centre, thus allowing the categorisation of any displacement process by a study of the *diastereoselectivity* of these reactions. In all cases the observed products were consistent with the operation of a double inversion mechanism leading to overall retention (**Schemes 10/11**).[15]



(21) (22)

Scheme 10. Reagents: (i)  , $BF_3.OEt_2$; (ii) PtO_2/H_2.

The presence of additional stereogenic centres on the arene side chain does not peturb the double inversion mechanism as outlined in **Scheme 11**.[16]



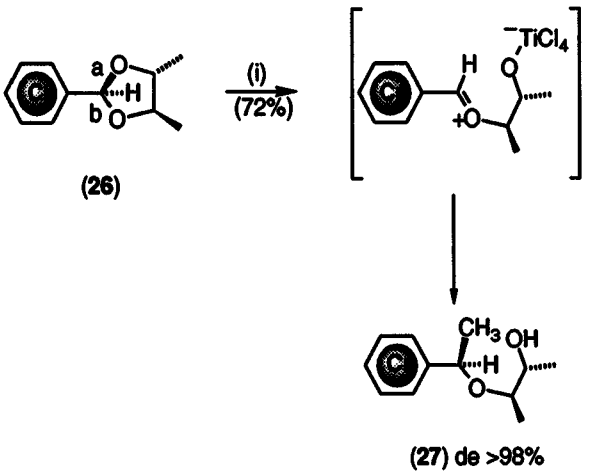
(23) R= CH_3 (25) R= H

Scheme 11. Reagents: (i) CH_2=$CHCH_2Si(CH_3)_3/BF_3.OEt_2$; (ii) Et_3SiH/ TFA; (iii) Ac_2O; (iv) Me_3Al.

3.2 Oxonium Ions

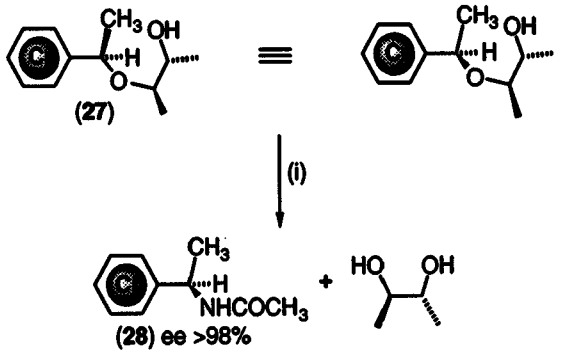
We also investigated the reactions of novel chromium tricarbonyl stabilised benzylic oxonium ions and observed the operation of a double inversion mechanism. The constraints outlined earlier for ionisation at the benzylic centre and subsequent quenching of the cationic intermediate appear to apply. Ionisation of the (*R,R*)-butane-2,3-diol derived acetal (**26**) with a Lewis acid, followed by reaction with trimethylaluminium generated the complex (**27**) with complete selectivity (**Scheme 12**).[17]

The involvement of a double inversion mechanism was deduced by consideration of the relative stereochemistry within (**27**). This



Scheme 12. Reagents: (i) $TiCl_4$, -95°C; (ii) $(CH_3)_3Al$.

conclusively shows that the product is not that expected from a S_N2 displacement of the pro-*R* acetal oxygen (bond a) by the organometallic nucleophile, as was observed in the case of the free arene.[17] Rather, this bond had been broken by participation from the chromium, and the resulting oxonium ion attacked from the *exo* face. It was now possible to remove the auxiliary non-destructively and in so doing synthesise homochiral N-acetyl-1-phenylethylamine, using Ritter methodology (**Scheme 13**).



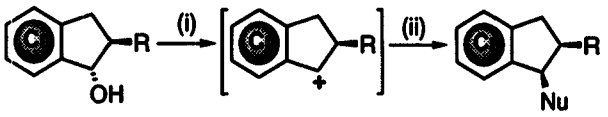
Scheme 13. Reagents: (i) H_2SO_4, MeCN, H_2O.

4. Bicyclic Complexes

Arene chromium tricarbonyl complexes, which are fused to a second ring, provide another opportunity for stereocontrolled reactions. A stabilised, cationic intermediate, generated at the benzylic position has only one possible conformation, as a consequence of the constraints of the ring. Nucleophilic attack on such intermediates occurs exclusively from the *exo* (uncomplexed) face and this has allowed the synthesis of a wide range of substituted derivatives. To date, studies have been confined to stabilised carbocations contained within 5 or 6 membered rings.

4.1 (6-5) Ring Systems

The most commonly encountered derivatives are those of indanol chromium tricarbonyl, which can exist as either the *endo* or *exo* diastereoisomer. Direct complexation of indanol gives predominantly the *endo* isomer in a process mediated by the hydroxy group. Similarly, the reduction of indanone chromium tricarbonyl also produces the *endo* isomer, as hydride attack occurs from the sterically least hindered *exo* face. Consequently nearly all the studies that have been undertaken on these systems have been concerned with the *endo* isomer. In these cases, loss of a benzylic leaving group from the *exo* face, is clearly not possible and rather a mechanism which involves *endo* ionisation is in operation. Attack onto the resulting cation from the *exo* face, as described previously, results in an *inversion* at the benzylic centre (**Scheme 14**).[10,18] Substitution on the *exo* face (R= CH_3) does not influence the stereochemical outcome of these reactions. Although these reactions are assumed to proceed *via* a S_N1 mechanism, the observed products are also consistant with a S_N2 displacement.

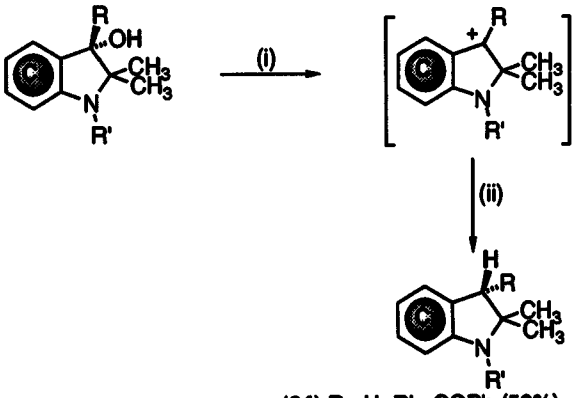


(**29**) R= H, NuH= CH_3OH (79%)
(**30**) R= H, NuH= H_2O (55%)
(**31**) R= H, Nu= CH_3CONH (89%)
(**32**) R= CH_3, NuH= CH_3OH
(**33**) R= CH_3, NuH= H_2O

Scheme 14. Reagents: (i) H_2SO_4;
(ii) NuH (CH_3OH, H_2O and CH_3CN).

It is interesting to note that, for these types of reaction, displacement of the *exo* isomer has been shown to be substantially faster than for the *endo* isomer.[10b] This is in accord with the notion of a transition metal assisted ionisation as the stereoelectronic constraints for neighbouring group participation by the chromium tricarbonyl unit can be only be achieved in the former case.

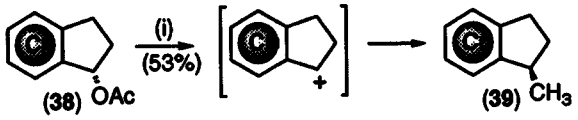
Subjecting the indoline chromium tricarbonyl derivatives shown in **Scheme 15** to protic acid and subsequently quenching with hydride anion also demonstrated the substitution of OH with inversion.[19] Interestingly, when these experiments were performed on the free arene, the sole product arose from a 1-2 methyl shift, followed by aromatisation to an indole derivative.



(**34**) R= H, R'= COPh (52%)
(**35**) R= H, R'= CH_2Ph (89%)
(**36**) R= CH_3, R'= COPh (65%)
(**37**) R= CH_3, R'= CH_2Ph (60%)

Scheme 15. Reagents: (i) HPF_6 or CF_3CO_2H; (ii) $(C_2H_5)_3SiH$.

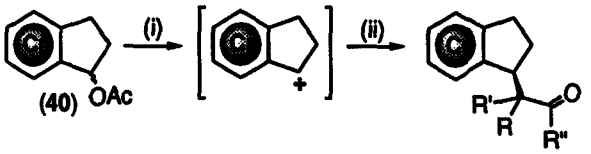
A similar displacement, utilising a Lewis acid, was performed on the *endo* indanol acetate (**38**). In this example the organoaluminium reagent acts as both a Lewis acid and a nucleophile (**Scheme 16**).[20]



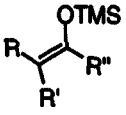
Scheme 16. Reagents: (i) $(CH_3)_3Al$.

An epimeric mixture of *exo* and *endo* acetates was employed by Reetz *et al*, who effected ionisation with zinc chloride.[21] Subsequent nucleophilic attack with a series of trimethylsilyl enol ethers gave the *exo* substituted isomers exclusively (**Scheme 17**). This behaviour was

explained by considering that the two epimers behave in a convergent manner, both giving the same carbocation upon *endo* or *exo* loss of the acetate group.

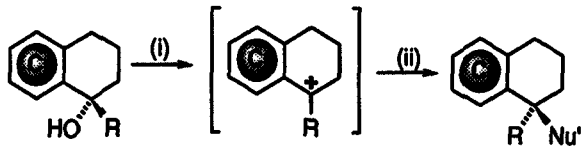


(41) R= R'= H, R"= t-Bu (76%)
(42) R= R'= CH_3, R"=OCH_3 (76%)
(43) R= R'= H, R"= CH_3 (76%)

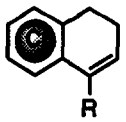
Scheme 17. Reagents: (i) $ZnCl_2$; (ii) 

4.2 (6-6) Ring Systems

A more extensive study has been made on the (6-6) fused ring system, with most derivatives based on tetralol chromium tricarbonyl. These complexes exhibit the same behaviour, with respect to stereocontrol, as the (6-5) systems discussed earlier. Initial experiments established that the carbocation derived from *endo* tetralol chromium tricarbonyl could be captured, from the *exo* face, by electron rich arenes.[22] However, additional substitution at the Cα position, which would have allowed the synthesis of chiral quarternary centres (R=CH_3, **Scheme 18**), curtailed substitution and elimination became the predominant pathway.



(44) R=H, NuH= $(CH_3O)_2C_6H_4$, (74%).
(45) R=H, NuH= $(CH_3O)_3C_6H_3$, (80%).



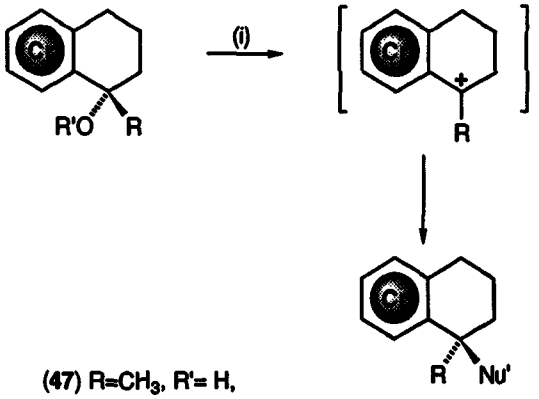
(46) R=CH_3, NuH= 1,2,3-$(CH_3O)_3C_6H_3$ (90%).

Scheme 18. Reagents: (i) HBF_4; (ii) NuH.

The problem of elimination could be circumvented by employing stronger nucleophiles and the methodology was therefore extended by using both organometallics and organosilanes as nucleophilic species (**Scheme 19**).[20] In all cases the stereoselectivity of the reactions appeared to be complete. This methodology provides an asymmetric synthesis of quarternary centres.

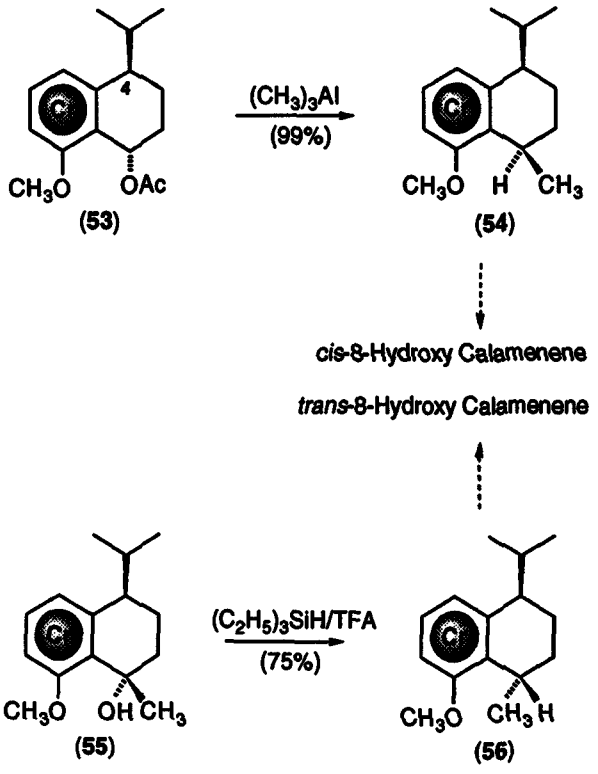
The occurrence of the tetrahydronaphthalene unit in nature has allowed chromium tricarbonyl methodology to be used in the synthesis of several natural products. Most notable in this regard have been Uemura's efforts directed towards the synthesis of substituted calamenenes and of dihydroxyserrulatic acid. The syntheses of both *cis* and *trans* isomers of 8-hydroxy calamenenes illustrate the wide application of this methodology.[23] It is noteworthy that the bulky isopropyl group on C-4 does not interfere with nucleophilic attack on the *exo* face (**Scheme 20**).

A similar sequence of reactions on the 7-methoxy substituted derivatives of (53) and (55) enabled the selective syntheses of *cis*- and *trans*-7-hydroxy calamenene.[24]



(47) R=CH_3, R'= H,
Reagents: (i) TFA/$(C_2H_5)_3SiH$; Nu'= H.
(48) R=H, R'= Ac,
Reagents: (i) $(CH_3)_3Al$; Nu'= CH_3 (99%).
(49) R=H, R'= H,
Reagents: (i) $(CH_3)_3Al/TiCl_4$; Nu'= CH_3 (60%).
(50) R=H, R'= CH_3,
Reagents: (i) $(CH_3)_3Al/TiCl_4$; Nu'= CH_3 (92%).
(51) R=H, R'= Ac, Reagents: (i) CH_2=$CHCH_2Si(CH_3)_3$/ $TiCl_4$; Nu'= CH_2CH=CH_2 (95%).
(52) R=CH_3, R'= H, Reagents: (i) $HCCCH_2Si(CH_3)_3$/ $BF_3.OEt_2$; Nu'= CH=C=CH_2 (95%).

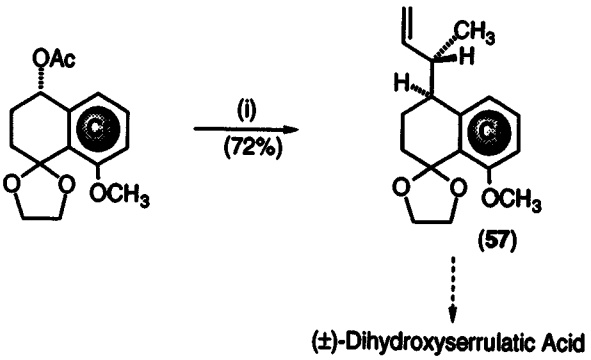
Scheme 19



Scheme 20

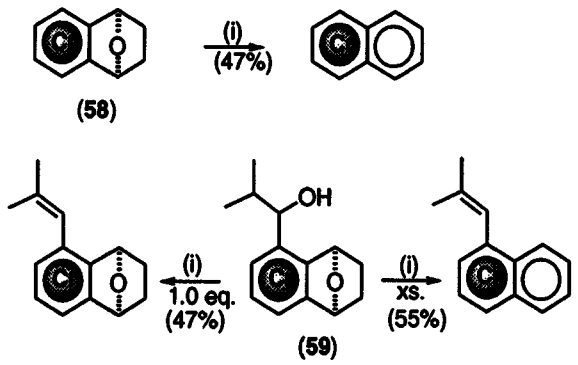
One of the key steps in a recent synthesis of dihydroxyserrulatic acid involved the generation of a chromium tricarbonyl stabilised benzylic carbocation and its diastereoselective reaction with an allyl silane thus forming stereoselectively two contiguous stereogenic centres (**Scheme 21**).[25]

An efficient synthesis of naphthalene chromium tricarbonyl, which is a useful chromium tricarbonyl transfer agent, has recently been reported.[26] Treatment of (58) with an excess of HBF_4 lead to a double elimination reaction which yielded the aromatised complex in



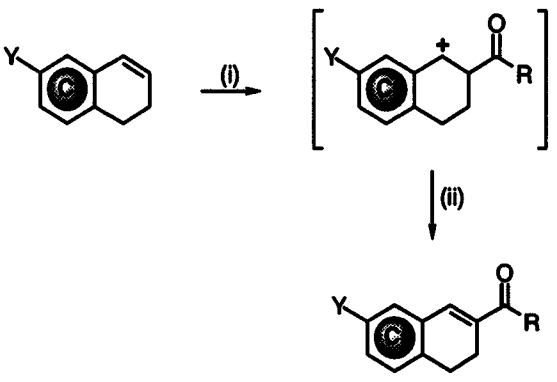
Scheme 21.
Reagents: (i): E-$CH_3CH{=}CHCH_2Si(CH_3)_3/BF_3.OEt_2$.

47% yield (**Scheme 22**). Further chemistry of (**58**) was also investigated and the substituted complex (**59**) could be partially or fully dehydrated in the presence of HBF_4.



Scheme 22. Reagents: (i) HBF_4.

The Friedel-Crafts acylation of several dihydronaphthalene chromium tricarbonyl complexes has been explored. During the course of these reactions, acylation of the olefin lead to the formation of a chromium tricarbonyl stabilised cation, which was eliminated to give the conjugated enone upon addition of a nucleophile (**Scheme 23**).[27]



(**60**) Y=H, R= CH_3 (65%)
(**61**) Y=H, R= Ph (42%)
(**62**) Y=H, R= $CH{=}CHCH_3$ (45%)
(**63**) Y=OCH_3, R= CH_3 (61%)

Scheme 23.
Reagents: (i) $RCOAlCl_4$; (ii) H_2O, CH_3OH, or CH_3CN.

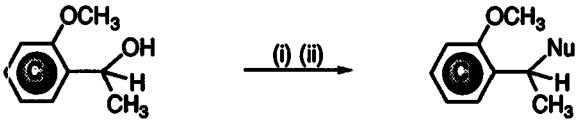
5 *ortho* Substituted Acyclic Compounds

The presence of a substituent on the arene, *ortho* to a benzylic carbocation, has a profound effect upon reactivity of the carbocation.

Any stabilised carbocationic intermediate potentially has access to two distinct conformations, whereby each of the groups on the carbocation centre is disposed either *syn* or *anti* to the *ortho* group. Allylic strain destabilises the *syn* confomer with respect to the *anti*, and, in some cases, interconversion is observed.

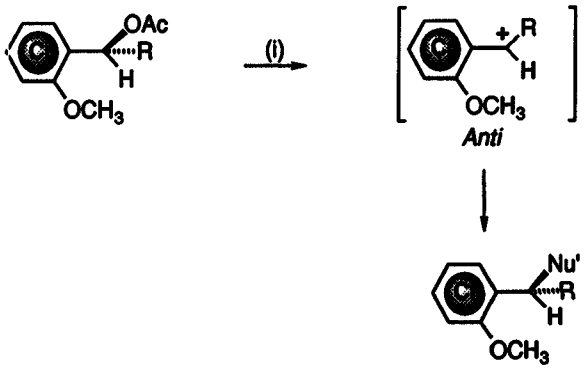
5.1 Carbocations

Carbocations derived from various *ortho*-substituted benzylic alcohols have received much attention. Experiments on the *ortho*-methoxyphenethanol complex shown below, indicated that it could be ionised with a protic acid and the subsequently formed carbocation successfully quenched by a variety of nucleophiles, such as electron rich arenes and β-dicarbonyl compounds (**Scheme 24**).[22] The stereochemical consequences of such reactions were not, however, fully elaborated.

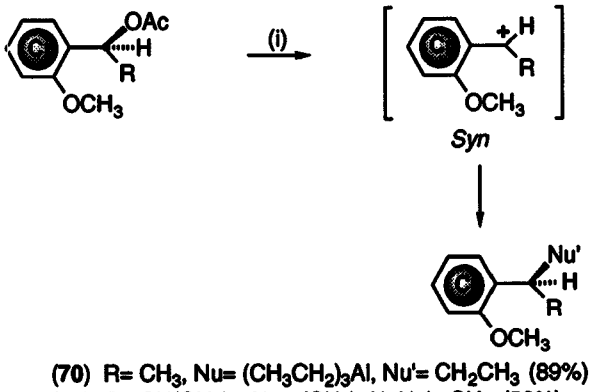


(**64**) NuH= 1,2-$(CH_3O)_2C_6H_4$ (74%)
(**65**) NuH= 1,2,3-$(CH_3O)_3C_6H_3$ (80%)
(**66**) NuH= $CH_2(COCH_3)_2$ (73%)
(**67**) NuH= $CH_2(COCH_3)CO_2CH_3$ (81%)

Scheme 24. Reagents: (i) HBF_4; (ii) NuH.



(**68**) R= CH_3, Nu= $(CH_3CH_2)_3Al$, Nu'= CH_2CH_3 (86%)
(**69**) R= $CH(CH_3)_2$, Nu= $(CH_3)_3Al$, Nu'= CH_3 (74%)

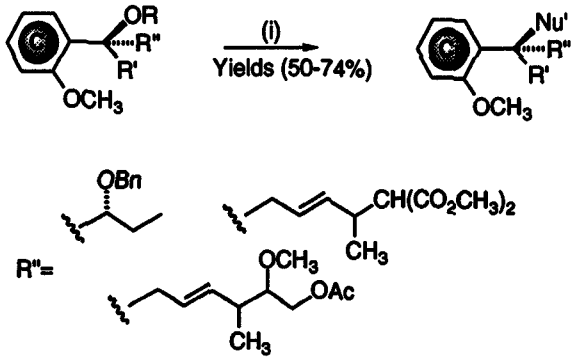


(**70**) R= CH_3, Nu= $(CH_3CH_2)_3Al$, Nu'= CH_2CH_3 (89%)
(**71**) R= $CH(CH_3)_2$, Nu= $(CH_3)_3Al$, Nu'= CH_3 (53%)

Scheme 25. Reagents: (i) Nu.

Experiments on the two diastereoisomerically pure acetates in **Scheme 25**, showed that each was stereospecifically converted into the substituted derivatives shown. Organoaluminium reagents were used both to generate and to trap benzylic carbocation intermediates. The relative stereochemistry formed during these reactions indicated that a double inversion mechanism was occurring.[28] Loss of the *acetate group from the exo face implied that one diastereoisomer* formed a carbocation in the *anti* conformation while ionisation of the other diastereoisomer gave rise to the *syn* carbocation. Although each of these carbocations appears to be conformationally stable (and the selectivity of the nucleophilic quench complete) the relatively low yield recorded for complex (**71**) is attributed to the severe steric interaction between the isopropyl and methoxy groups in the intermediate *syn* cation.

Such mechanistic behaviour has been shown to be valid for a wide range of substrates. The examples outlined below indicate the two types of reaction that have proved to be most successful, i.e. substitution of OR (R= OAc or H) by organoaluminium and silicon *hydride nucleophiles (A and B respectively, Scheme 26).*[29,30,31]

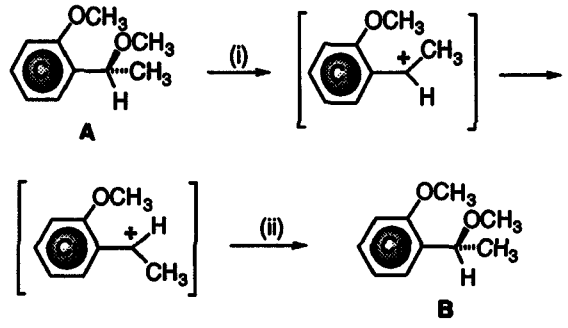


A R= OAc, R'= H, Nu= $(CH_3)_3Al$, Nu'= CH_3

B R= H, R'= CH_3, Nu= $(CH_3CH_2)_3SiH/BF_3OEt_2$, Nu'= H

Scheme 26. Reagents: (i) Nu.

We have observed the epimerisation of chromium tricarbonyl stabilised carbocations to their most stable *anti* conformers at higher *temperatures. The series of experiments outlined in Scheme 27 show* that almost complete conversion from the *syn* to the *anti* conformer occurs at 40°C.[32]



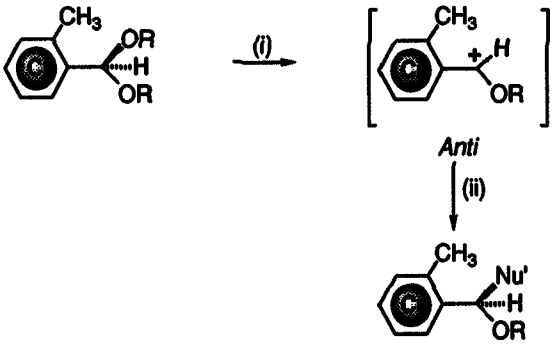
Time before adition of MeOH	Temp.°C	Ratio A/B
3 min	0	41 : 59
4 min	20	8 : 92
4 min	40	6 : 94

Scheme 27. Reagents: (i) $HBF_4.OMe_2$; (ii) MeOH.

5.2 Oxonium Ions

We have also investigated the reactions of stabilised oxonium ions, adjacent to arenes with *ortho* substitution. In most cases, the reaction of such oxonium ions proceeds through the more stable *anti* conformation, regardless of the conformation in which the oxonium ion was generated. This may be a consequence of a facile rotation about the C_α-C_{ipso} bond, which therefore allows the system to reach its most stable conformation before nucleophilic attack.

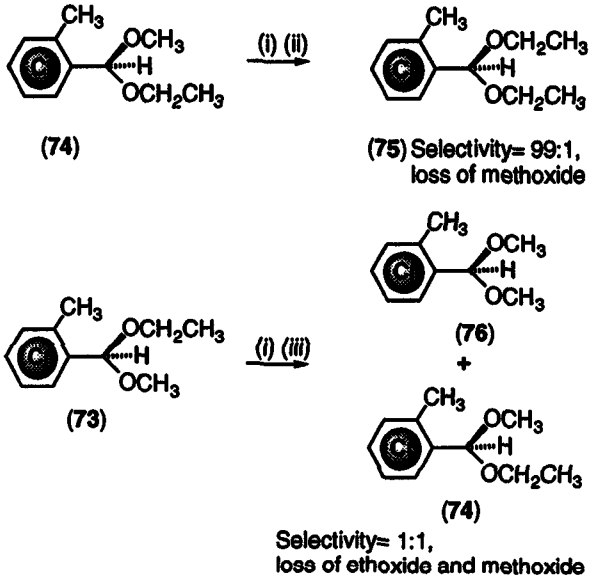
The first complexes that we studied in depth were those derived from the acetals of *o*-tolualdehyde and *o*-anisaldehyde. Treatment with a strong Lewis acid at -78°C generated an oxonium ion, which was captured by a variety of nucleophilic species, such as organometallics and alcohols, in a highly stereoselective fashion (**Scheme 28**).[33] The diastereoselectivity of such reactions was explained by invoking nucleophilic attack onto the *exo* face of an oxonium ion, in the *anti* conformation.



(72) R= Me, Nu= Me_3Al, Nu'= Me (80%) 99% de
(73) R= Me, Nu=EtOH, Nu'= OEt (85%) 96% de
(74) R= Et, Nu=MeOH, Nu'= OMe (76%) 94% de

Scheme 28. Reagents: (i) $TiCl_4$; (ii) Nu.

We investigated the reaction of the mixed acetals (**73**) and (**74**) when they were re-ionised with titanium tetrachloride, before being quenched with an alcohol (**Scheme 29**).[33] Such experiments were *designed to reveal any influence that the chromium tricarbonyl moiety* exhibited upon the ionisation of the benzylic acetals. Ionisation of (**74**) is completely selective and the sole product from the ionisation experiment is the diethyl acetal formed after loss of the methoxy

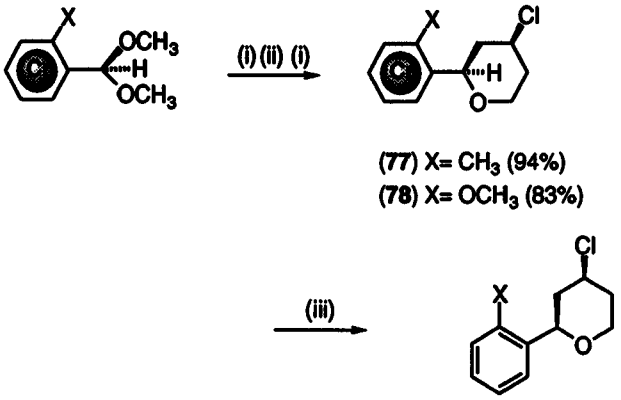


Scheme 29. Reagents: (i)$TiCl_4$;
(ii) $CH_3CH_2OH/(CH_3CH_2)_3N$; (iii) $CH_3OH/(CH_3CH_2)_3N$.

group. The transition metal exhibits a penchant for ionising the alkoxy group which produces the oxonium ion in its *anti* conformation. Unfortunately, the ionisation of (**73**) is non-selective, and the products that are observed arise from loss of both methoxide and ethoxide. This, non-selective ionisation, was rationalised by considering the bias that already exists within the ethyl methyl acetal. In the absence of any external influence, ionisation of a methoxy over an ethoxy group should be preferred as a consequence of coordination of the Lewis acid to the oxygen on the sterically more accessible methoxy group. It can be seen that the bias within the mixed acetal and that exhibited by the transition metal reinforce each other in the selective ionisation and oppose in the non-selective example.

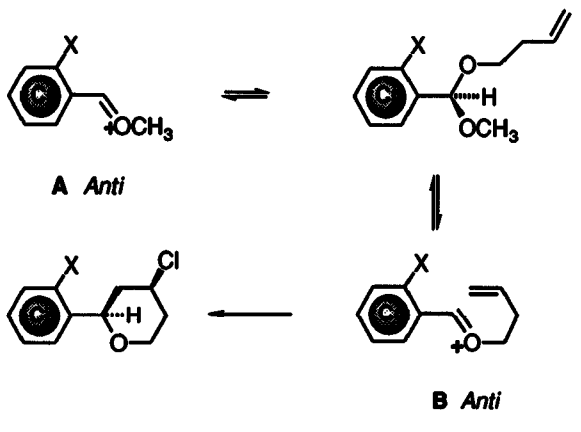
The origin of (**74**) whereby the mixed acetal (**73**) loses methoxide is uncertain. It may have occurred from the *endo* face of the molecule in order to form the stabilised oxonium ion in its *anti* conformation. Alternatively, an *exo* loss of methoxide, followed by an epimerisation of the subsequently formed *syn* oxonium ion to its *anti* conformer, prior to nucleophilic attack, would also account for the observed stereoselective formation of (**74**).

We extended this methodology by utilising cyclisation of an olefin onto an oxonium ion to enable the asymmetric synthesis of 2-aryltetrahydropyran derivatives.[34] A protocol was developed whereby the chromium tricarbonyl complexes of the dimethyl acetals of *o*-tolualdehyde and *o*-anisaldehyde, can be transformed into a tetrahydropyran in a single reaction. This involved ionising the aforementioned acetals with titanium tetrachloride, quenching the subsequently formed oxonium ion with a homoallylic alcohol and then re-ionising the mixture with a further portion of Lewis acid (**Scheme 30**). The stereoselectivity of these cyclisations was high (>96:4) and in all the examples shown, removal of the chromium tricarbonyl unit was high yielding (>90%).



(**77**) X= CH_3 (94%)
(**78**) X= OCH_3 (83%)

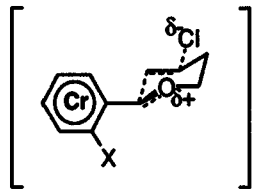
Scheme 30. Reagents: (i) $TiCl_4$; (ii) CH_2=$CHCH_2CH_2OH$; (iii) O_2/hυ.



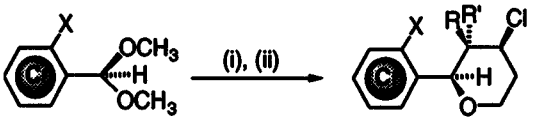
Scheme 31

A mixed methyl, homoallyl acetal is an intermediate in this reaction; this is ionised by addition of the second portion of Lewis acid. Of the two oxonium ions possible from this ionisation (**A** and **B**, **Scheme 31**) only one (**B**) can undergo cyclisation to the cyclic ether. By invoking a reversible process it is possible to allow each of the chromium tricarbonyl stabilised oxonium ions to be converted into cyclised product, irrespective of the ratio of **A**/**B** formed during ionisation of the mixed acetal.

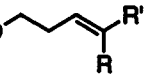
We rationalise the relative stereochemistry of the cyclised products by invoking a chair transition state with the arene chromium tricarbonyl moiety lying in an equatorial position. The olefin attacks the benzylic centre from the *exo* face, opposite to the chromium tricarbonyl unit. A *trans* addition of chloride, which originates from the Lewis acid, and the oxonium ion across the double bond, correctly predicts the presence of the equatorial halide group on C-4.



Introduction of a substituent onto the terminus of the double bond leads to the stereospecific introduction of such substitution at C-3 of the tetrahydropyran (**Scheme 32**).[35]



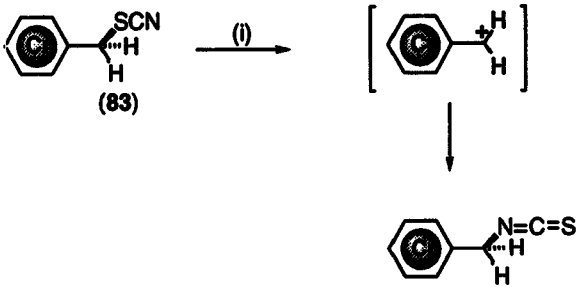
(**79**) X= CH_3, R= CH_2CH_3, R'= H (92%)
(**80**) X= CH_3, R= H, R'= CH_2CH_3 (80%)
(**81**) X= OCH_3, R= CH_2CH_3, R'= H (83%)
(**82**) X= OCH_3, R= H, R'= CH_2CH_3 (80%)

Scheme32. Reagents : (i) $TiCl_4$; (ii) 

In all of the above cyclisations the use of homochiral acetal (X= OCH_3) lead to the synthesis of homochiral tetrahydropyrans

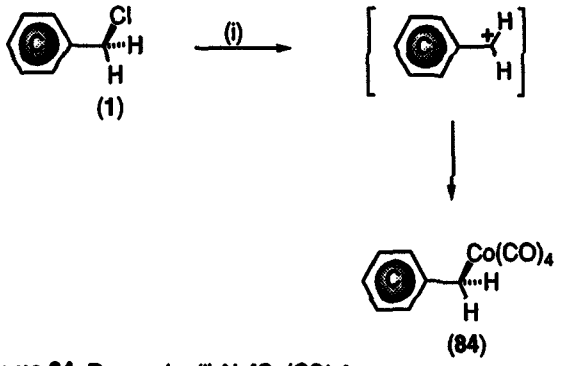
6. Miscellaneous Applications of Chromium Tricarbonyl Stabilised Carbocations

The stabilisation of benzylic carbocations by the chromium tricarbonyl unit has also found uses in a diverse range of reactions where stereoselectivity is not an important issue. For example, heating the thiocyanate (**83**) to 80°C allowed facile rearrangement to an isothiocyanate derivative (**Scheme 33**).[36] Presumably the intermediacy of a stabilised carbocation accounts for the mild conditions that are required.



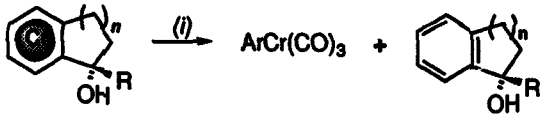
Scheme 33. Reagents: (i) Acetone.

A related synthetic sequence has allowed the isolation of η^1 benzyl-tetracarbonyl cobalt derivatives *via* treatment of benzyl chloride chromium tricarbonyl with *sodium cobalt tetracarbonyl* (**Scheme 34**).[37]

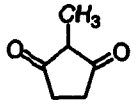


Scheme 34. Reagents: (i) $Na[Co(CO)_4]$.

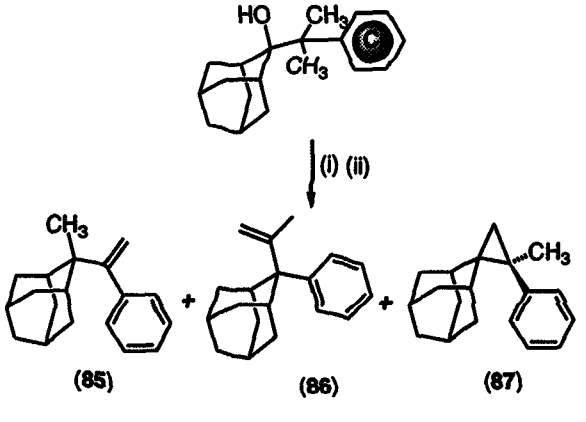
Stabilisation of a benzylic carbocation by the chromium tricarbonyl moiety introduces a substantial amount of positive charge onto the transition metal. This has the effect of weakening the arene-chromium bond and, in the presence of an aromatic nucleophile, an arene exchange reaction occurs on the chromium tricarbonyl unit.[38] This principle has been used to allow the complexation of a range of electron rich arenes. Addition of 2-methyl-cyclopentadienone, as a proton source, to the indanol and tetralol chromium tricarbonyl derivatives shown in **Scheme 35**, *generates small quantities* of cationic species which can be displaced from the chromium by a suitable arene.



R= Ph, n= 2, Ar= 3-aminotoluene (72%)
R= Ph, n= 2, Ar= 2-methoxyaniline (74%)
R= CH=CH_2, n= 2, Ar= *o*-xylene (80%)
R= CH=CH_2, n= 1, Ar= methyl 3-methoxybenzoate (35%)

Scheme 35. Reagents: (i) Arene/ 

The 2-cumyladamant-2-ol derivative shown in **Scheme 36** was synthesised by J. L. Fry *et al.* in order to study its behaviour under acidic conditions.[39] After decomplexation the major products were found to be those resulting from methyl migration to an adamantyl cation, (**85**) (**87**), and from aryl migration (**86**). It was hoped that



Scheme 36. Reagents: (i) HCl; (ii) $h\nu/O_2$.

transition metal stabilisation of the cation resulting from methyl migration, would influence the product distribution. However it was *found that this complex behaved almost identically to the analogous* compound without the chromium tricarbonyl substitution.

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