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TRICARBONYLCHROMIUM(0) PROMOTED STEREOSELECTIVE TRANSFORMATIONS OF EPHEDRINE AND PSEUDOEPHEDRINE DERIVATIVES

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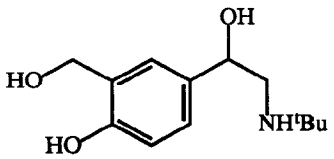
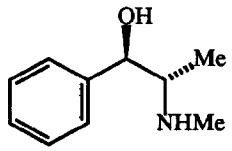
Abstract: (-)-(1*S*,2*S*)-(*N*,*O*-Dimethylephedrine)tricarbonyl chromium(0) (**6**) and (-)-(1*S*,2*R*)-(*N*,*O*-dimethylpseudoephedrine)tricarbonylchromium(0) (**22**) undergo completely stereoselective *ortho* deprotonation upon treatment with alkyllithium base, followed by addition of an electrophile. In both cases, exclusive removal of the *pro-(R)-ortho* proton was confirmed by single crystal X-ray structure analyses of the methylated products. Addition of methyllithium onto the *ortho*-formylated derivative of complex (**6**) occurs stereoselectively, the stereochemistry of the major product being confirmed by a single crystal X-ray structure determination. The results presented demonstrate an efficient transfer of chirality from a side chain onto the (arene)tricarbonylchromium(0) complex and back to a different side chain.

Introduction:

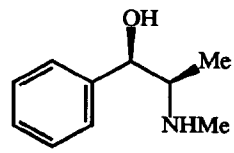
The synthesis of substituted β-amino alcohols has proved to be of considerable interest owing both to their pharmacological profiles and their potential use in asymmetric synthesis. A large number of substituted phenethanolamines have been synthesised in the search for selective α and β receptor agonists, their specificity relying upon the exact nature of the substitution pattern.[1] The bronchiodilator Salbutamol (**1**) is currently the world's twelfth best selling prescription medicine and exhibits selective β_2 agonist activity useful in the treatment of bronchial asthma.[2] The alkaloids ephedrine (**2**) and psueudoephedrine (**3**) are commercially available as either optical antipode and their derivatives have found extensive use in the field of asymmetric synthesis.[3] Their ability to serve as ligands in catalysts for the asymmetric addition of nucleophiles to aldehydes and αβ-unsaturated ketones has been documented with good stereoselectivities being observed in certain cases.[4]



(1)



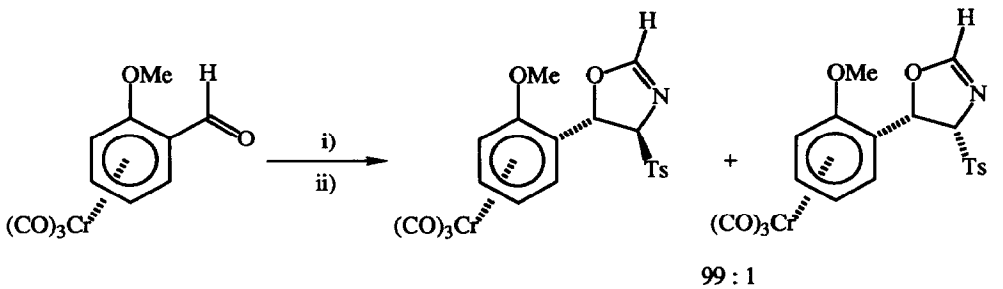
(-)-(1*R*,2*S*)-(2)



(-)-(1*R*,2*R*)-(3)

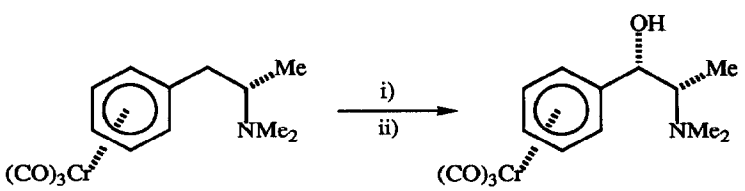
Phenethanolamines have also proved to be powerful tools in asymmetric synthesis, serving as chiral auxiliaries. For example, condensations of appropriately substituted aldehydes with derivatives of ephedrine (2) give, after crystallisation, diastereoisomerically pure oxazolidines which may be further elaborated; the new chiral centres being formed with a high degree of stereocontrol. Subsequent hydrolysis readily liberates the elaborated aldehyde and returns the homochiral amino alcohol.[5] Evans has developed an alternative strategy, employing *N*-acyl derivatives of phenethanolamine-derived oxazolidines as chiral auxiliaries, that has been widely used for the highly stereoselective formation of carbon-carbon bonds in aldol-type condensation reactions.[6]

Several recent reports in the literature concerning the syntheses of β-amino alcohols have utilised (arene)tricarbonylchromium(0) chemistry to activate an aryl aldehyde towards nucleophilic attack by trimethylsilyl cyanide,[7] or the anions of nitromethane[8] and tosyl methylisocyanate (TosMic).[9] In the latter case an oxazoline complex is obtained of high diastereoisomeric purity which after decomplexation and reduction should afford an optically active amino alcohol.



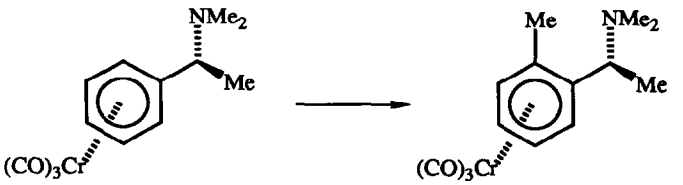
Reagents: i) TosMic, K_2CO_3, MeOH, 0°C. ii) MeCOOH

We have recently demonstrated the efficient transfer of chirality from a homobenzylic position to a benzylic position within a single side chain attached to a tricarbonylchromium(0) group.[10]

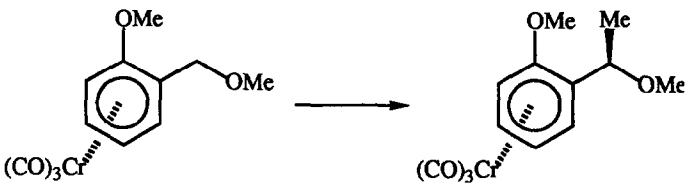


Reagents: i) BuLi, THF, -78°C. ii) MoOPH

It is also known that benzylic heteroatom substituents direct ring lithiation to an *ortho* site or promote benzylic deprotonation if suitably activated.[11,12]



Reagents: i) *t*-BuLi, THF, -78°C. ii) MeI



Reagents: i) *t*-BuLi, THF, -78°C. ii) MeI

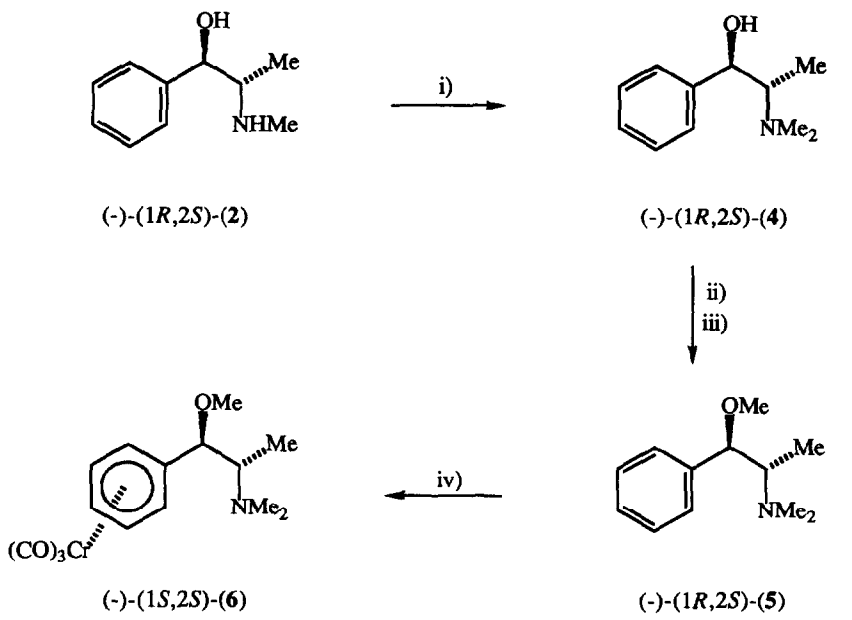
It was therefore of interest to explore the behaviour towards lithiation of a suitably substituted (arene)tricarbonylchromium(0) complex, bearing both a homobenzylic and a benzylic heteroatom substituent.

Results and discussion:

Treatment of a refluxing tetrahydrofuran solution of (-)-(1*R*,2*S*)-*N*-methylephedrine (**4**) [readily prepared from (-)-(1*R*,2*S*)-ephedrine (**2**) upon exposure to formic acid and aqueous formaldeyde at reflux] with potassium hydride followed by methyl iodide at room temperature furnished (-)-(1*R*,2*S*)-*N*,*O*-dimethylephedrine (**5**) in 63% isolated yield. Thermolysis of chromium hexacarbonyl with (**5**) in boiling dibutyl ether/THF (10:1) under a nitrogen atmosphere† gave, after work up , yellow cubes of (-)-(1*S*,2*S*)-(*N*,*O*-dimethylephedrine)tricarbonyl chromium(0) (**6**)††. A high resolution mass spectrum confirmed the identity of complex (**6**); its ^{1}H n.m.r. spectrum exhibiting the same features as that for its uncomplexed precursor (**5**), but with the aromatic proton multiplet shifted upfield (δ5.66-5.26).

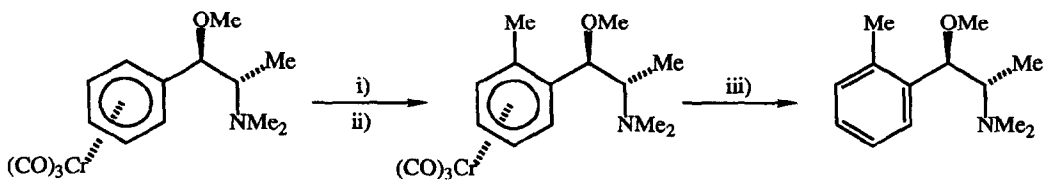
† Henceforth referred to as standard conditions for complexation.

†† The (*R*) absolute configuration in compound (**5**) becomes (*S*) upon coordination to the tricarbonylchromium(0) unit [complex (**6**)] by definition.



Reagents: i) HCOOH, CH_2O. ii) potassium hydride, THF. iii) MeI. iv) $Cr(CO)_6$, Bu_2O/THF (10:1)

Deprotonation of complex (**6**) was achieved upon treatment of a THF solution with *n*- or *t*-butyllithium at -78°C, subsequent addition of methyl iodide yielding a single compound on work up . The ^1H n.m.r. spectrum of the product exhibited signals for four contiguous aromatic protons (δ5.57-4.96) and a new three proton singlet (δ2.28), but otherwise revealed the same features as that of the starting material (**6**). The product was therefore identified as a single diastereoisomer of the *ortho*-methylated complex (-)-(*N,O,o*-trimethylephedrine)tricarbonylchromium(0) (**7**). The relative configurations within complex (**7**) were unambiguously determined as (*R,1S,2S*)[13] by a single crystal X-ray structure analysis which established that exclusive removal of the *pro-(R)-ortho* proton of complex (**6**) had occurred (Figure 1). Fractional atomic coordinates for (-)-(**12**) are given in Table 1 with selected bond lengths and angles being listed in Table 2. Decomplexation of the product (**7**) upon exposure of a diethyl ether solution to air and sunlight liberated the free arene (**8**).



Reagents: i) *n*- or *t*-BuLi, THF, -78°C. ii) MeI. iii) Air, sunlight

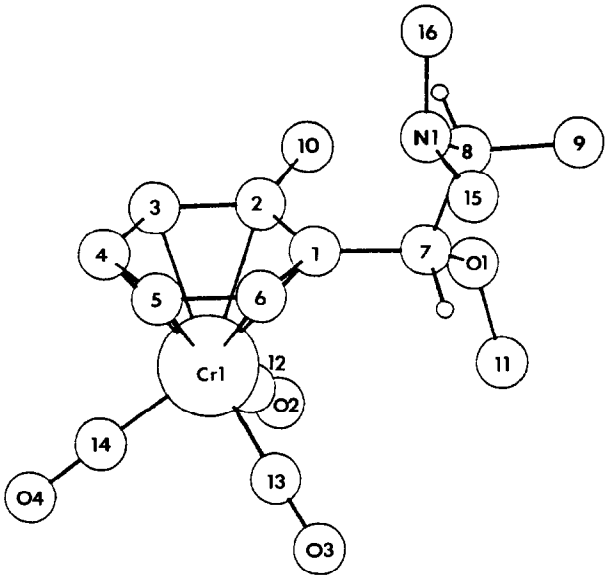


Figure 1 : X-Ray crystal structure of complex (7).

Table 1 : Fractional atomic coordinates for complex (7) with estimated standard deviations in parentheses.†

Atom	x/a	y/b	z/c
Cr(1)	3143.7(9)	-4857(1)	2833.4(9)
C(1)	2920(7)	-6089(3)	3296(8)
C(2)	4829(7)	-5850(3)	4740(8)
C(3)	4910(9)	-5228(3)	6025(8)
C(4)	3159(8)	-4874(5)	5929(7)
C(5)	1240(9)	-5116(3)	4554(9)
C(6)	1164(7)	-5718(3)	3268(9)
C(7)	2622(7)	-6750(3)	1889(8)
C(8)	2656(8)	-7500(3)	2957(8)
C(9)	2690(10)	-8169(3)	1650(10)
C(10)	6796(8)	-6226(3)	5040(10)
C(11)	3610(20)	-6471(4)	-870(10)
C(12)	1299(6)	-4812(4)	190(7)
C(13)	5177(7)	-4774(5)	1951(8)
C(14)	3028(9)	-3853(4)	2959(9)
C(15)	1470(20)	-8041(4)	5380(10)
C(16)	-970(1)	-7652(4)	2150(10)
N(1)	1036(8)	-7512(3)	3700(8)
O(1)	4116(7)	-6793(3)	1065(6)
O(2)	140(5)	-4792(4)	-1483(5)
O(3)	6445(7)	-4732(5)	1326(8)
O(4)	2913(9)	-3190(3)	3018(9)

Table 2 : Selected bond lengths (A) and angles (°) for complex (7) with estimated standard deviations in parentheses.†

Cr(1)-C(1)	2.238(4)	C(1)-C(7)	1.510(7)
Cr(1)-C(2)	2.271(5)	C(2)-C(3)	1.428(8)
Cr(1)-C(3)	2.227(5)	C(2)-C(10)	1.504(7)
Cr(1)-C(4)	2.212(4)	C(3)-C(4)	1.389(8)
Cr(1)-C(5)	2.226(5)	C(4)-C(5)	1.408(8)
Cr(1)-C(6)	2.201(4)	C(5)-C(6)	1.401(8)
Cr(1)-C(12)	1.830(4)	C(7-C(8)	1.536(6)
Cr(1)-C(13)	1.818(5)	C(7)-O(1)	1.421(6)
Cr(1)-C(14)	1.797(5)	C(8)-C(9)	1.524(8)
C(12)-O(2)	1.156(5)	C(8)-N(1)	1.463(7)
C(13)-O(3)	1.169(6)	C(11)-O(1)	1.409(8)
C(14)-O(4)	1.189(7)	C(15)-N(1)	1.459(9)
C(1)-C(2)	1.417(6)	C(16)-N(1)	1.453(9)
C(1)-C(6)	1.421(7)		
C(13)-Cr(1)-C(12)	89.5(2)	C(5)-C(6)-C(1)	123.1(5)
C(14)-Cr(1)-C(12)	88.8(3)	C(8)-C(7)-C(1)	112.3(4)
C(14)-Cr(1)-C(13)	89.7(3)	O(1)-C(7)-C(1)	112.9(4)
C(1)-Cr(1)-C(12)	97.5(2)	O(1)-C(7)-C(8)	107.2(4)
C(1)-Cr(1)-C(13)	104.3(3)	C(9)-C(8)-C(7)	112.2(5)
C(1)-Cr(1)-C(14)	164.6(2)	N(1)-C(8)-C(7)	109.7(4)
C(6)-C(1)-C(2)	118.0(4)	N(1)-C(8)-C(9)	115.1(4)
C(7)-C(1)-C(2)	124.0(4)	C(15)-N(1)-C(8)	111.7(6)
C(7)-C(1)-C(6)	117.8(4)	C(16)-N(1)-C(8)	114.9(5)
C(3)-C(2)-C(1)	118.8(5)	C(16)-N(1)-C(15)	109.7(6)
C(10)-C(2)-C(1)	123.8(5)	C(11)-O(1)-C(7)	116.4(5)
C(10)-C(2)-C(3)	117.4(5)	O(2)-C(12)-Cr(1)	179.3(6)
C(4)-C(3)-C(2)	121.3(5)	O(3)-C(13)-Cr(1)	177.8(6)
C(5)-C(4)-C(3)	120.9(6)	O(4)-C(14)-Cr(1)	178.7(6)
C(6)-C(5)-C(4)	117.7(5)		

The stereoselectivity observed in the lithiation of complex (6) must be influenced by the configuration of one or both of the chiral centres present. Coordination of lithium would be expected to occur preferentially to the nitrogen lone pair but examination of models suggests that the directionality of base coordinated to the homobenzylic heteroatom substituent offers no significant preference for the removal of one or the other of the

† Thermal parameters and bond lengths and angles are available on request from the Cambridge Crystallographic Data Centre.

two diastereotopic *ortho* protons. However, bidentate chelation of both nitrogen and oxygen atoms to lithium would generate a five-membered chelate that now offers a significant difference in the transition states that lead to *ortho* deprotonation *via* chelation of the base to the remaining oxygen lone pair. Newman projections along the C_{α}-C_{ipso} bond (Figure 2) reveal that transition states leading to the removal of the *pro-(R)-ortho* proton have the α-proton proximal to the large tricarbonylchromium(0) group whereas those leading to the removal of the *pro-(S)-ortho* proton place the bulky five-membered chelate proximal to the tricarbonylchromium(0) group, which causes an adverse steric interaction between the β-methyl substituent and the tricarbonylchromium(0) moiety. The transition states leading to the removal of the *pro-(R)-ortho* proton are therefore expected to be favoured, resulting in the observed stereoselectivity after addition of methyl iodide.

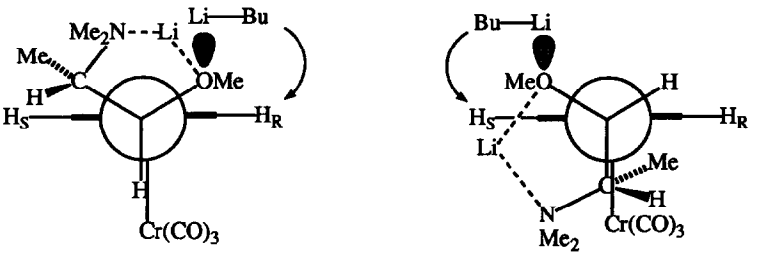


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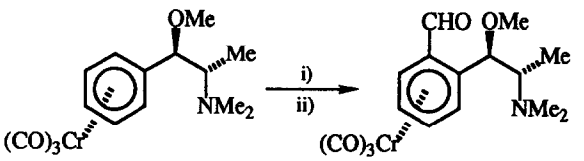
Figure 2 : Possible transition state conformations for deprotonation of complex (**6**).

In a similar fashion, treatment of the anion derived from complex (**6**) with DMF or ethyl formate, gave an exclusive product, the ^{1}H n.m.r. spectrum of which again revealed four contiguous aromatic protons together with a low field one proton singlet (δ10.11). An infra red stretch of 1675 cm^{-1} and a molecular ion *m/z* 358 (M^++1) was consistent with the *ortho*-formylated complex (**9**), the relative stereochemistry being assigned by analogy with that of complex (**7**) and subsequently confirmed (*vide infra*).

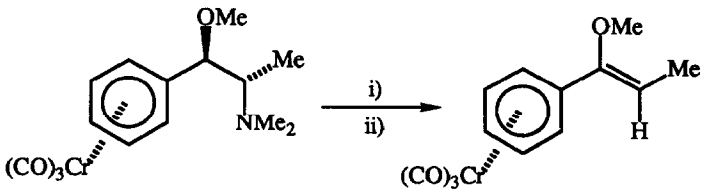


(-)-(1*S*,2*S*)-(**6**) (-)-(*R*,1*S*,2*S*)-(**9**)

Reagents: i) *n*- or *t*-BuLi, THF, -78°C. ii) DMF or HCOOEt

Attempts at trapping the anion derived from complex (**6**) with ethylene oxide resulted in the recovery of starting material. Addition of boron trifluoride etherate to the reaction mixture in an attempt to enhance the electrophilicity of the epoxide led to the isolation, after chromatography, of a red oil which was crystallised from pentane at low temperature. The ^{1}H n.m.r. spectrum of the product exhibited a highfield three proton doublet, (δ1.83) a three proton singlet (δ3.75) and a six proton multiplet (δ5.65-5.34) consistent with the enol

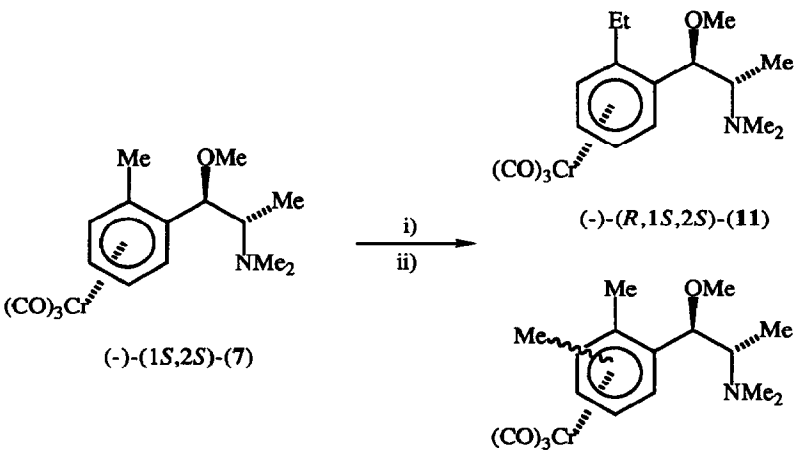
ether complex (**10**). An nOe difference spectroscopic analysis indicated that the probable geometry about the double bond was *Z*, since irradiation of the methoxyl singlet gave enhancements to both the methyl doublet (5%) and aromatic protons (11.2%), whilst separate irradiation of the methyl doublet resonance enhanced only the methoxyl singlet (3.7%) with no apparent enhancement of any aromatic protons. A high resolution mass spectrum confirmed the identity of complex (**10**). Presumably, addition of boron trifluoride causes any *ortho*-lithiated chelate to be broken up. Subsequent equilibration to give a benzylic carbanion may result in a *syn* elimination of the amine function promoted by coordination of the Lewis acid to the nitrogen lone pair.



(-)-(1*S*,2*S*)-(**6**) (**10**)

Reagents: i) *t*-BuLi, THF, -78°C. ii) Ethylene oxide, $BF_3.OMe_2$

Treatment of a THF solution of complex (**7**) with *t*-butyllithium at -78°C followed by addition of methyl iodide gave, after work up , an inseparable mixture as a yellow oil. ^1H n.m.r. spectroscopic analysis revealed that the mixture comprised of at least three different compounds, one of which possessed two multiplets integrating to three protons (δ2.87-2.72, δ2.46-2.39) and a three proton triplet (δ1.25, J 7.4Hz) characteristic of an ethyl group. The mixture was therefore assigned as (*R*,1*S*,2*S*)-(*N*,*O*-dimethyl-*o*-ethyl-ephedrine)tricarbonylchromium(0) (**11**) and two ring methylated isomers in the approximate ratio 45:35:20. Use of butyllithium as the base afforded similar results.

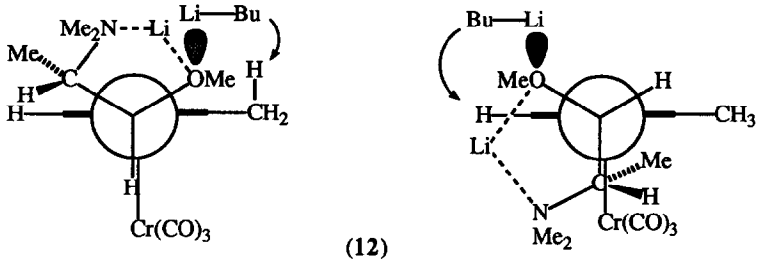


(-)-(*R*,1*S*,2*S*)-(**11**)

(-)-(1*S*,2*S*)-(**7**)

Reagents: i) *n*- or *t*-BuLi, THF, -78°C. ii) MeI

In the case of complex (-)-(**7**), initial coordination of the base to the remaining oxygen lone pair of the five-membered chelate (**12**) may result in deprotonation of the aryl methyl group or the *ortho* proton. The preponderance of complex (**11**) in the methylation of the anion derived from complex (**7**) indicates that deprotonation of the aryl methyl group is the most facile process whilst the removal of the remaining *ortho* proton is disfavoured owing to the adverse steric compression between the β-methyl substituent and the tricarbonylchromium(0) moiety or the aryl methyl substituent (Figure 3).



(**12**)

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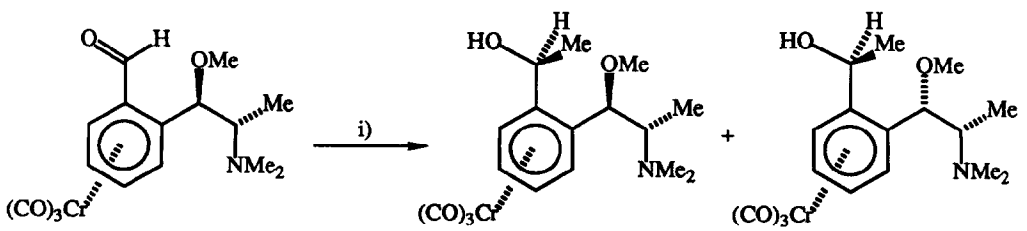
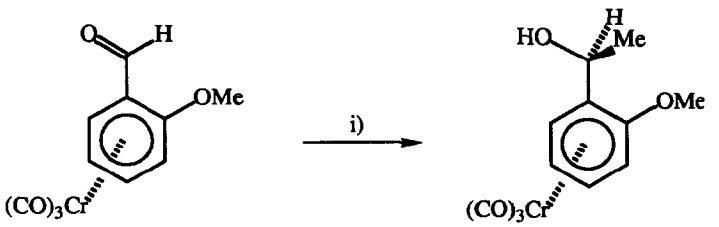
Figure 3 : Possible transition state conformations for deprotonation of complex (**7**).

A THF solution of complex (**9**) at -78°C was treated with excess methyllithium producing an immediate colour change from red to yellow, indicative of addition to the aldehyde. ^{1}H n.m.r. spectoscopic analysis of the crude product revealed the presence of two sets of peaks in the approximate ratio 86:14, each of which included two methyl doublets. Two recrystallisations from diethyl ether/hexane furnished the major component as a single diastereoisomer as yellow needles. The relative stereochemistry of the product (**13**) was initially assigned by analogy with the documented reactivity of (*o*-anisaldehyde)tricarbonylchromium(0) (**14**), which yields the secondary alcohol complex (**15**) as a single diastereoisomer upon treatment with methylmagnesium iodide.[14] A subsequent single crystal X-ray structure determination of the major product unambiguously proved the relative stereochemistry within complex (-)-(**13**) (Figure 4), thereby confirming the initial assignment of complex (**9**). Furthermore, a Flack enantiopole refinement[15] indicated that the absolute stereochemistry of (-)-(**13**) was that shown, consistent with the known absolute stereochemistry of the starting material.[16] Fractional atomic coordinates for (-)-(**13**) are given in Table 3 with selected bond lengths and angles being listed in Table 4.



(+)-(*R*,1*S*,2*S*)-(**9**) (-)-(**13**) (Major) (-)-(**16**) (Minor)

Reagents: i) MeLi, THF, -78°C



(14) **(15)**

Reagents: i) MeMgI, THF, -78°C

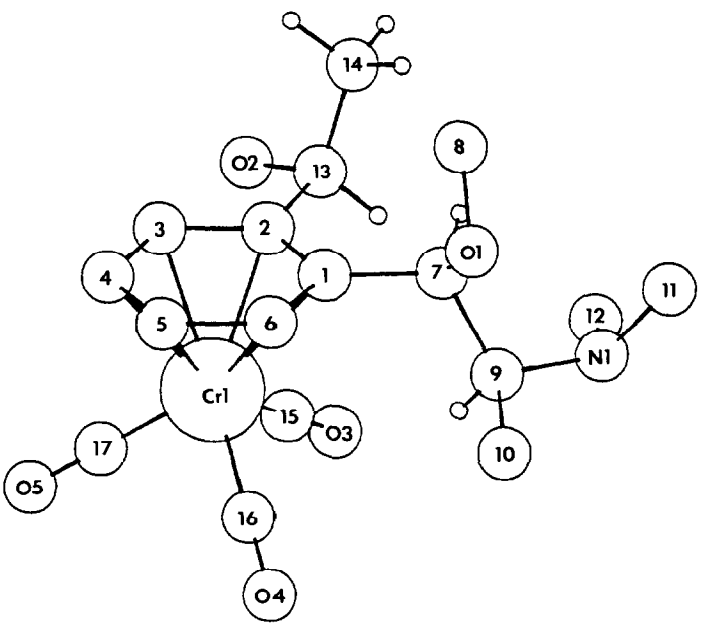


Figure 4 : X-Ray crystal structure of complex (-)-(**13**).

The formation of complex (-)-(**13**) as the major product is consistent with the formyl group of complex (+)-(**9**) adopting a conformation coplanar with the aromatic ring, with the carbonyl oxygen being placed *anti* to the bulky *ortho* substituent on steric and dipole grounds.[17] Addition of methyllithium may only occur from the unhindered *exo* face generating the new chiral centre with good stereocontrol. That chelation control was not operating was concluded as a result of an identical reaction performed in the presence of the chelating reagent TMEDA, which did not significantly alter the ratio of products.

Table 3 : Fractional atomic coordinates ($x10^4$) for complex (-)-(**13**) with estimated standard deviations in parentheses.

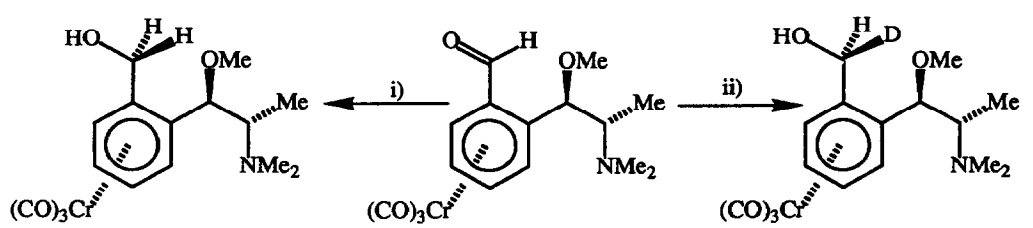
Atom	x/a	y/b	z/c
Cr(1)	1278(1)	7293.7(8)	3833.1(7)
C(1)	1309(8)	7668(4)	2447(4)
C(2)	1251(9)	6601(4)	2547(4)
C(3)	80(9)	6176(5)	3033(5)
C(4)	-996(9)	6781(6)	3438(5)
C(5)	-963(9)	7847(5)	3348(5)
C(6)	206(9)	8266(5)	2853(4)
C(7)	2479(9)	8219(5)	1877(4)
C(8)	859(12)	8640(7)	715(6)
C(9)	3841(9)	8721(5)	2353(4)
C(10)	3483(10)	9775(5)	2683(5)
C(11)	5109(10)	9147(7)	984(6)
C(12)	6003(10)	7778(6)	1828(7)
C(13)	2350(10)	5896(5)	2107(5)
C(14)	1881(11)	5742(6)	1189(6)
C(15)	945(9)	6655(6)	4847(5)
C(16)	1775(9)	8451(6)	4415(5)
C(17)	3273(9)	6879(5)	3886(5)
N(1)	5248(8)	8759(5)	1835(4)
O(1)	1733(6)	8992(3)	1400(3)
O(2)	2299(7)	4942(3)	2530(4)
O(3)	756(8)	6251(5)	5490(4)
O(4)	2040(8)	9187(4)	4772(4)
O(5)	4533(8)	6619(4)	3912(5)

The relative configurations within the minor product were tentatively assigned as the complex (**16**) epimeric at the benzylic position, since addition of nucleophiles to *ortho*-substituted benzaldehyde complexes are observed to occur with a high degree of stereocontrol.[18] The formation of complex (**16**) as the minor product may be a consequence of the enhanced acidity of the benzylic proton of (+)-(**9**) since it is equivalent to a vinylogous aldehyde. Benzylic deprotonation and subsequent reprotonation from the opposite face followed by addition of the nucleophile to the aldehyde would generate complex (**16**).

Table 4 : Selected bond lengths (A) and angles (°) for complex (-)-(**13**) with estimated standard deviations in parentheses.

Cr(1)-C(1)	2.238(6)	C(1)-C(2)	1.425(8)
Cr(1)-C(2)	2.224(6)	C(1)-C(6)	1.40(1)
Cr(1)-C(3)	2.211(7)	C(2)-C(3)	1.40(1)
Cr(1)-C(4)	2.196(8)	C(3)-C(4)	1.39(1)
Cr(1)-C(5)	2.231(7)	C(4)-C(5)	1.421(9)
Cr(1)-C(6)	2.220(7)	C(5)-C(6)	1.40(1)
Cr(1)-C(15)	1.831(8)	C(15)-O(3)	1.157(9)
Cr(1)-C(16)	1.840(8)	C(16)-O(4)	1.150(9)
Cr(1)-C(17)	1.834(8)	C(17)-O(5)	1.16(1)
C(16)-Cr(1)-C(15)	89.4(4)	C(6)-C(5)-C(4)	117.7(7)
C(17)-Cr(1)-C(15)	88.5(4)	C(5)-C(6)-C(1)	122.1(6)
C(17)-Cr(1)-C(16)	90.2(3)	O(1)-C(7)-C(1)	110.0(6)
C(6)-C(1)-C(2)	119.1(7)	O(1)-C(7)-C(9)	107.2(5)
C(7)-C(1)-C(2)	123.9(6)	O(2)-C(13)-C(2)	108.4(6)
C(7)-C(1)-C(6)	116.9(5)	O(2)-C(13)-C(14)	108.4(6)
C(3)-C(2)-C(1)	119.2(7)	O(3)-C(15)-Cr(1)	179.0(8)
C(4)-C(3)-C(2)	120.9(6)	O(4)-C(16)-Cr(1)	177.8(7)
C(5)-C(4)-C(3)	121.0(8)	O(5)-C(17)-Cr(1)	179.4(9)

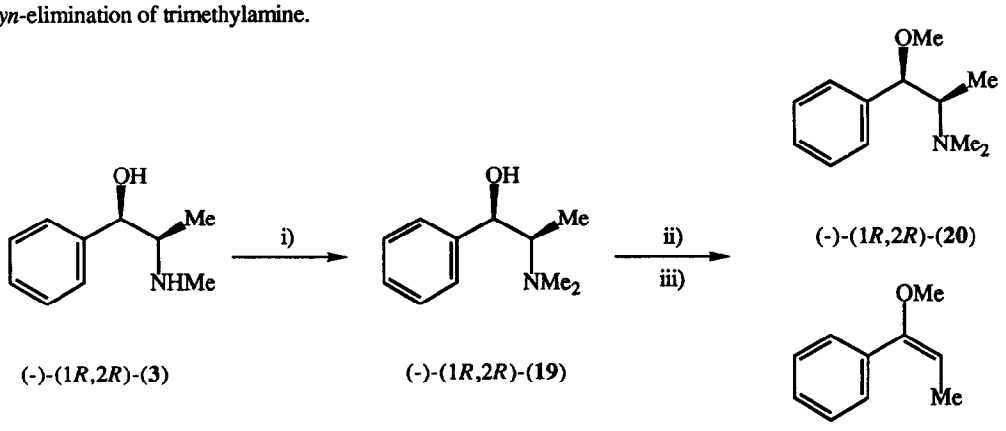
A solution of aldehyde (+)-(**9**) was treated with sodium borohydride to afford the corresponding alcohol complex (-)-(**17**) as a yellow solid. The structure of the product followed from comparison of its ^{1}H n.m.r. spectrum with that of (+)-(**9**) which exhibited a new AB system (δ4.83, 4.16) and the disappearance of the low field formyl proton resonance. A molecular ion *m/z* 360 (M^++1) in the mass spectrum and an elemental analysis were both consistent with the assigned structure. In a similar manner sodium borodeuteride reduction of (+)-(**9**) gave complex (**18**) that showed good deuterium incorporation according to its mass spectrum in comparison to that of complex (-)-(**17**). Owing to the similarity in the ^{1}H n.m.r. spectra of (-)-(**17**) and (**18**) the diastereoselectivity of this reduction could not be assessed although it appeared to be high. In addition, there was no evidence to suggest the formation of the benzylically epimeric complex.



(-)-(**17**) (+)-(**9**) (**18**)

Reagents: i) $NaBH_4$, THF, 20°C. ii) $NaBD_4$, THF, 20°C

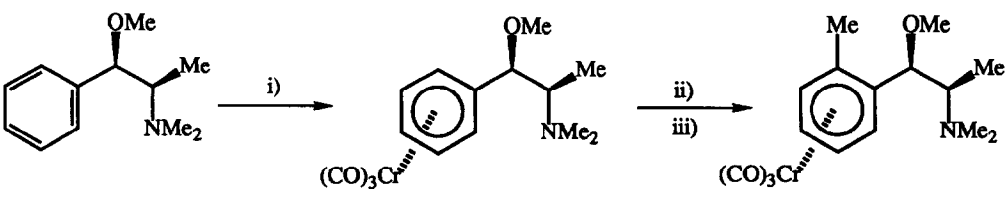
In order to determine the relative importance of the two chiral centres in the above reactions, attention was turned to the epimeric pseudoephedrine series. (-)-(1*R*,2*R*)-Pseudoephedrine (**3**) was *N*-methylated upon exposure to formic acid and formaldehyde furnishing (-)-(1*R*,2*R*)-*N*-methylpseudoephedrine (**19**) as a white solid. Treatment of a refluxing THF solution of (-)-(**19**) with potassium hydride followed by methyl iodide at room temperature led to the isolation of two products. The major component was identified as the desired (-)-(1*R*,2*R*)-*N*,*O*-dimethylpseudoephedrine (**20**) whilst the minor product was found to be *E*-α-methoxy-β-methylstyrene (**21**), the geometry of which was assigned on the basis of an nOe difference spectroscopic analysis involving the irradiation of the methoxyl protons of (**21**). The latter compound presumably arises as a consequence of *N*-methylation of (-)-(**20**) with excess methyl iodide followed by deprotonation of one of the *N*-methyl substituents by excess potassium hydride followed by an intramolecular *syn*-elimination of trimethylamine.



(-)-(1*R*,2*R*)-(**3**) (-)-(1*R*,2*R*)-(**19**) (-)-(1*R*,2*R*)-(**20**) *E*-(**21**)

Reagents: i) HCOOH, CH_2O. ii) potassium hydride, THF. iii) MeI

Thermolysis of hexacarbonylchromium(0) with (**20**) under standard conditions afforded (-)-(1*S*,2*R*)-(*N*,*O*-dimethylpseudoephedrine)tricarbonylchromium(0) (**22**) as a yellow solid. Deprotonation of complex (22), achieved upon treatment with butyllithium and subsequent addition of methyl iodide, again furnished a single diastereoisomer in essentially quantitative yield. The ^1H n.m.r. spectrum of the product was similar to that of the starting material but contained an aromatic multiplet that displayed signals for four contiguous aromatic protons (δ5.58-4.96) and an additional three proton singlet (δ2.33), consistent with the *ortho*-methylated complex (**23**).



(-)-(1*R*,2*R*)-(**20**) (-)-(1*S*,2*R*)-(**22**) (-)-(*R*,1*S*,2*R*)-(**23**)

Reagents: i) $Cr(CO)_6$, Bu_2O/THF (10:1). ii) BuLi, THF, -78°C. iii) MeI

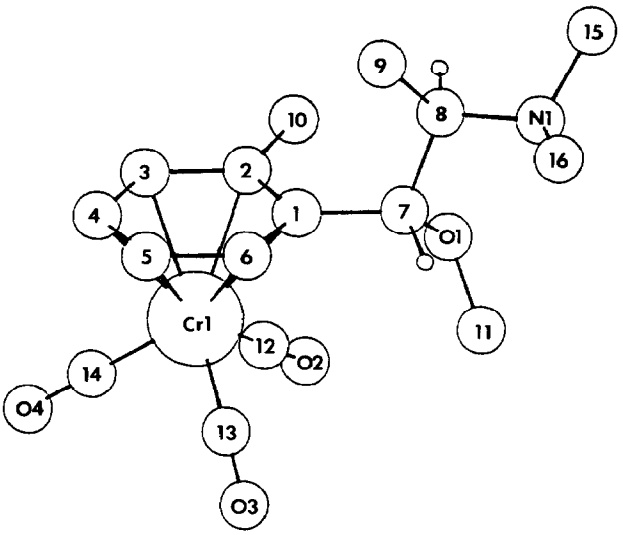


Figure 5 : X-Ray structure of complex (**23**).

Table 5 : Fractional atomic coordinates ($x10^4$) for complex (**23**) with estimated standard deviations in parentheses.

Atom	x/a	y/b	z/c
Cr(1)	2141(2)	-1102(1)	2213.6(7)
C(1)	3698(10)	-616(7)	1242(5)
C(2)	3538(11)	-1773(7)	1232(5)
C(3)	1872(13)	-2237(9)	1258(5)
C(4)	473(14)	-1559(14)	1285 (6)
C(5)	626(12)	-417(12)	1281(6)
C(6)	2268(12)	54(9)	1269(5)
C(7)	5379(10)	6(6)	1163(4)
C(8)	6094(10)	-66(7)	373(4)
C(9)	4757(13)	94(9)	-241(5)
C(10)	4997(12)	-2568(7)	1173(6)
C(11)	6842(12)	223(9)	2302(5)
C(12)	687(11)	-1848(8)	2828(5)
C(13)	1917(12)	134(8)	2794(5)
C(14)	3885(12)	-1622(8)	2787(5)
C(15)	7047(15)	1878(7)	227(6)
C(16)	8687(13)	398(10)	-285(5)
N(1)	7495(9)	723(5)	305(4)
O(1)	6592(7)	-431(4)	1657(3)
O(2)	-188(10)	-2340(7)	3227(4)
O(3)	1756(13)	918(7)	3177(4)
O(4)	4956(10)	-1967(8)	3148(4)

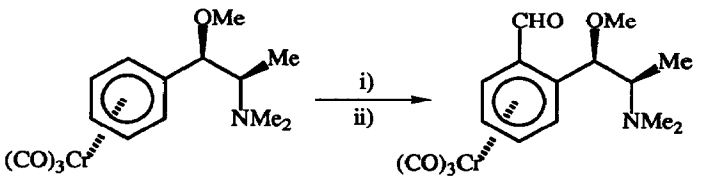
The relative configurations within the product (23) were unambiguously determined by a single crystal X-ray structure determination which established that exclusive substitution of the *pro-(R)-ortho* proton of complex (22) for a methyl group had occurred to give (-)-(*R*,1*S*,2*R*)-(*N*,*O*,*o*-trimethylpseudoephedrine)tricarbonylchromium(0) (23) (Figure 5). Fractional atomic coordinates for complex (23) are given in Table 5 with selected bond lengths and angles being listed in Table 6.

Table 6 : Selected bond lengths (A) and angles (°) for complex (23) with estimated standard deviations in parentheses.

Cr(1)-C(1)	2.218(9)	C(1)-C(7)	1.54(1)
Cr(1)-C(2)	2.232(9)	C(2)-C(3)	1.44(1)
Cr(1)-C(3)	2.196(9)	C(2)-C(10)	1.50(1)
Cr(1)-C(4)	2.20(1)	C(3)-C(4)	1.38(2)
Cr(1)-C(5)	2.22(1)	C(4)-C(5)	1.37(2)
Cr(1)-C(6)	2.186(9)	C(5)-C(6)	1.42(1)
Cr(1)-C(12)	1.830(9)	C(7)-C(8)	1.530(9)
Cr(1)-C(13)	1.81(1)	C(7)-O(1)	1.411(8)
Cr(1)-C(14)	1.84(1)	C(8)-C(9)	1.54(1)
C(12)-O(2)	1.16(1)	C(8)-N(1)	1.46(1)
C(13)-O(3)	1.17(1)	C(11)-O(1)	1.411(9)
C(14)-O(4)	1.15(1)	C(15)-N(1)	1.43(1)
C(1)-C(2)	1.38(1)	C(16)-N(1)	1.47(1)
C(1)-C(6)	1.39(1)		

C(13)-Cr(1)-C(12)	89.1(4)	C(5)-C(6)-C(1)	121.8(9)
C(14)-Cr(1)-C(12)	88.7(4)	C(8)-C(7)-C(1)	112.5(6)
C(14)-Cr(1)-C(13)	91.5(4)	O(1)-C(7)-C(1)	111.2(6)
C(1)-Cr(1)-C(12)	162.7(4)	O(1)-C(7)-C(8)	107.9(6)
C(1)-Cr(1)-C(13)	107.2(3)	C(9)-C(8)-C(7)	113.4(7)
C(1)-Cr(1)-C(14)	96.1(4)	N(1)-C(8)-C(7)	109.0(6)
C(6)-C(1)-C(2)	119.7(9)	N(1)-C(8)-C(9)	112.7(7)
C(7)-C(1)-C(2)	124.0(8)	C(15)-N(1)-C(8)	115.9(8)
C(7)-C(1)-C(6)	116.2(7)	C(16)-N(1)-C(8)	112.5(7)
C(3)-C(2)-C(1)	117.8(9)	C(16)-N(1)-C(15)	110.1(7)
C(10)-C(2)-C(1)	123.8(8)	C(11)-O(1)-C(7)	114.2(6)
C(10)-C(2)-C(3)	118.3(8)	O(2)-C(12)-Cr(1)	177.7(9)
C(4)-C(3)-C(2)	121.5(9)	O(3)-C(13)-Cr(1)	178.8(8)
C(5)-C(4)-C(3)	120.8(11)	O(4)-C(14)-Cr(1)	178.6(9)
C(6)-C(5)-C(4)	118.3(10)		

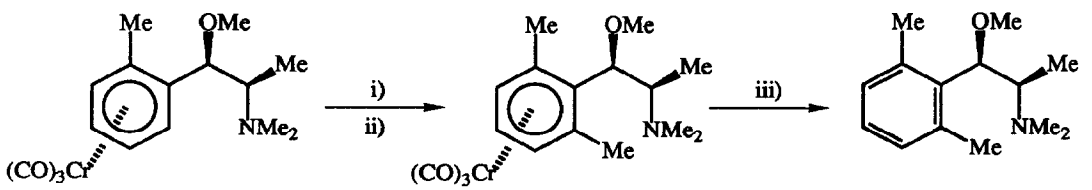
The stereoselectivity observed in the methylation of complex (**22**) may again be rationalised in terms of bidentate chelation of both oxygen and nitrogen atoms to lithium. Subsequent chelation of base to the remaining oxygen lone pair permits removal of the *pro-(R)-ortho* proton (*vide supra*) (Figure 2). Treatment of the anion derived from (-)-(**22**) with DMF or ethyl formate, furnished (+)-(**24**) as a single diastereoisomer, the stereochemistry being assigned by analogy with the previously described reactions.



(-)-(1*S*,2*R*)-(**22**) (+)-(*R*,1*S*,2*R*)-(**24**)

Reagents: i) *t*-BuLi, THF, -78°C. ii) DMF or HCOOEt

Methylation of complex (-)-(**23**) was achieved upon sequential treatment with *t*-butyllithium and methyl iodide to give a single product after work up. ^{1}H n.m.r. spectroscopic analysis of the product revealed the presence of three contiguous aromatic protons (δ5.58-4.84) and two aryl methyl proton singlets (δ2.42, 2.28) consistent with the ring methylated complex (**25**). Oxidative decomplexation liberated the corresponding free arene (**26**).



(-)-(*R*,1*S*,2*R*)-(**23**) (+)-(**25**) (**26**)

Reagents: i) *t*-BuLi, THF, -78°C. ii) MeI. iii) Air, sunlight

In contrast to the non-selective methylation of the *ortho*-methylated complex (-)-(**7**), the methylation of complex (-)-(**23**) is observed to be completely stereoselective furnishing complex (+)-(**25**) as a single diastereoisomer. This may be rationalised by again invoking bidentate chelation of both oxygen and nitrogen atoms to lithium to form a five-membered chelate. Subsequent coordination of the base to the remaining oxygen lone pair may now permit the stereoselective removal of the *ortho* proton without adverse steric interaction of the β-methyl substituent with the tricarbonylchromium(0) moiety or aryl methyl group, as would be expected for the epimeric complex (-)-(**7**) (Figure 6). The rate of deprotonation *via* this mechanism is presumably much faster than deprotonation of the aromatic methyl group which would necessitate an unfavourable seven-membered transition state.

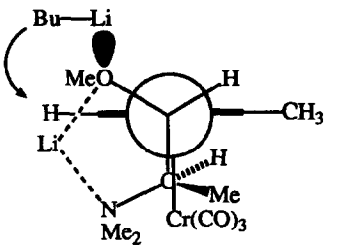
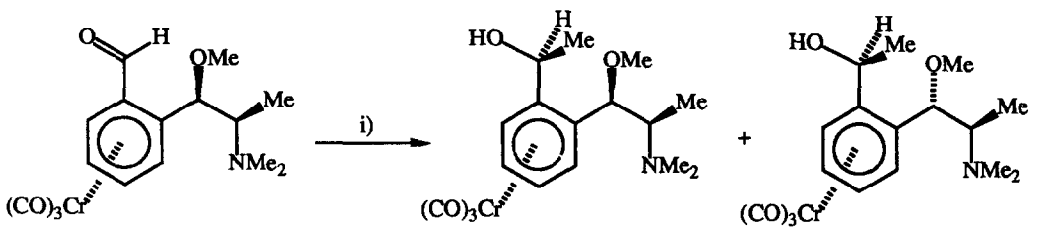


Figure 6 : Possible transition state conformation for deprotonation of complex (**23**).

Addition of methyllithium to complex (+)-(**24**) gave two products in the approximate ratio 86:14 which could not be separated. The major component was assigned as complex (**27**) by analogy with the previously described reaction of the ephedrine-derived complex (+)-(**9**) whilst the minor component was assigned as the benzylically epimerised addition product.



(+)-(*R*,1*S*,2*S*)-(**24**) (**27**) (Major) (Minor)

Reagents: i) MeLi, THF, -78°C

Summary:

(-)-(1*S*,2*S*)-(*N*,*O*-Dimethylephedrine)tricarbonyl chromium(0) (**6**) and (-)-(1*S*,2*R*)-(*N*,*O*-dimethylpseudoephedrine)tricarbonylchromium(0) (**22**) undergo completely stereoselective *ortho* deprotonation upon treatment with alkyllithium base, followed by addition of an electrophile. In both cases, exclusive removal of the *pro-(R)-ortho* proton was confirmed by single crystal X-ray structure analyses of the methylated products. Attack of nucleophiles onto the *ortho*-formylated derivatives of complexes (**6**) and (**22**) occurs stereoselectively. The stereochemistry of the major product in each case is consistent with attack of the nucleophile onto the formyl group in a transition state which places the carbonyl oxygen *anti* to the ethanolamine side chain. These results demonstrate an efficient transfer of chirality from a side chain onto the (arene)tricarbonylchromium(0) complex and back to a different side chain.

Experimental:

General experimental procedures - All reactions involving (arene)tricarbonylchromium(0) complexes, their preparation and purification were carried out under a nitrogen atmosphere using standard vacuum line techniques[19] and all solvents were deoxygenated prior to use. THF was freshly distilled from sodium benzophenone ketyl under nitrogen prior to use, Bu_2O was sodium dried and distilled from CaH_2 under nitrogen. CH_2Cl_2 was freshly distilled from CaH_2 under nitrogen prior to use. Petroleum ether refers to that fraction which boils in the range 40-60°C and was redistilled prior to use. Removal of all solvents was carried out under reduced pressure and all commercial reagents were purified (where necessary) according to standard techniques.[20] Hexacarbonylchromium(0) was purchased from Strem Chemicals and was steam distilled before use. Butyllithium was used as a 1.65M solution in hexanes, *t*-butyllithium was used as either a 1.97M, 2.62M or a 4.28M solution in pentane and methyllithium was used as a 1.0M or a 1.4M solution in Et_2O. Flash chromatography was performed on SiO_2 (Merck, 40-60μm) and Grade V Al_2O_3 refers to alumina (Grade I) that has been deactivated by the addition of water (10%, v/v). ^1H n.m.r. spectra were obtained as $CDCl_3$ solutions at 300MHz (unless otherwise stated) using a Bruker WH300 instrument. ^{13}C n.m.r. spectra were obtained as $CDCl_3$ solutions at 62.9MHz (unless otherwise stated) using a Bruker AM250 instrument. ^2H n.m.r. spectra were obtained as $CHCl_3$ solutions at 38.4MHz using the same instrument. I.r. spectra were obtained as $CHCl_3$ solutions (unless otherwise stated) using a Perkin-Elmer 781 Infrared Spectrophotometer and were calibrated against polystyrene (1601cm^{-1}). A Perkin-Elmer 241 Polarimeter was used to measure optical rotations. Melting points were obtained using a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were obtained on a V.G. Micromass ZAB 1F instrument using Electron Impact or Chemical Ionisation techniques. All calculations for X-ray crystal structure determinations were performed on the Chemical Crystallography VAX11/750 computer using the CRYSTALS software package incorporating SHELXS[21] and MULTAN80[22]

General complexation procedure - A deoxygenated mixture of the relevant arene and hexacarbonylchromium(0) in Bu_2O and THF (ratio 10:1) was heated at reflux under a nitrogen atmosphere until the onset of decomplexation (10-30h).[23] The cooled solution was filtered and evaporated and the residue subjected to column chromatography. The corresponding tricarbonylchromium(0) complex was invariably isolated as a yellow solid and further purified where necessary by recrystallisation.

General decomplexation procedure - A solution of the relevant complex in Et_2O (10mg ml^{-1}) was allowed to stand in air and sunlight until the yellow solution became colourless (24-48h). The precipitated chromium residues were removed by filtration (celite) and the filtrate evaporated to furnish the free arene. Further purification (where necessary) was achieved by crystallisation or chromatography.

(-)-(1S,2S)-(N,O-Dimethylephedrine)tricarbonylchromium(0) (6) - A mixture of (-)-(1*R*,2*S*)-ephedrine (2) (80.0g, 484mmol) and formic acid (98-100%, 500ml) was treated with formaldehyde (37% aqueous solution, 500ml) and the mixture heated at reflux (3h). The acid was removed under reduced pressure, the solution basified (NaOH) and the aqueous phase extracted (Et_2O). The combined extracts were evaporated and the solid obtained recrystallised from MeOH to give (-)-(1*R*,2*S*)-*N*-methylephedrine (4) as colourless needles (74.15g, 85%), m.p. 85-86°C (lit.[24] 87-88°C). A portion of this material (65.44g, 365 mmol) in THF (200ml) was added dropwise to a stirred suspension of potassium hydride (43.8g, 1.09mol) in THF (200ml).

The mixture was heated at reflux (20h) and the cooled solution (<0°C) treated with MeI (25ml, 402mmol). The mixture was stirred (20°C, 1h) and MeOH (40ml) cautiously added. The product was filtered (celite) and evaporated to leave a pale yellow oil. Distillation under reduced pressure gave (-)-(1*R*,2*S*)-*N*,*O*-dimethylephedrine (**5**) as a colourless oil (44.0g, 62%) (87°C, 0.06mm Hg), $[\alpha]_D^{20}$ -30.3 (*c* 1.32 in MeOH); (Found: C, 74.8; H, 10.0; N, 7.3. $C_{12}H_{19}NO$ requires C, 74.6; H, 9.9; N, 7.25%); $\nu_{max.}$ 2821 (OCH_3), 2779 [$N(CH_3)_2$], 1088 (COC) cm^{-1}; δ_H 7.48-7.22 (5H, m, Ph), 4.36 (1H, d, J 4.3Hz, PhCH), 3.28 (3H, s, OCH_3), 2.62 (1H, m, CHMe), 2.38 [6H, s, $N(CH_3)_2$], 0.99 (3H, d, J 6.6Hz, $CHCH_3$); δ_C 129.01-125.73 (6C), 84.52, 65.09, 56.58, 41.68 (2C), 7.97; *m/z* 194 (M^++1) . A portion of this material (0.500g, 2.59mmol) and hexacarbonylchromium(0) (0.854g, 3.88mmol) in Bu_2O (50ml) and THF (5ml) were reacted according to the standard complexation procedure to give a yellow solid. Recrystallisation from Et_2O/petroleum ether gave the *title compound* as yellow plates (0.362g, 44%), m.p. 81-82°C; $[\alpha]_D^{20}$ -73.0 (*c* 1.12 in $CHCl_3$); $\nu_{max.}$ 2813 (OCH_3), 2781 [$N(CH_3)_2$], 1969 and 1887 (C≡O), 1099 (COC) cm^{-1}; δ_H 5.66-5.26 [5H, m, $(CO)_3CrPh$]; 4.00 [1H, d, J 4.4Hz, $(CO)_3CrPhCH(OMe)$], 3.58 (3H, s, OCH_3), 2.55 (1H, dq, J 4.4 and 6.8Hz, CHMe), 2.31 [6H, s, $N(CH_3)_2$], 0.97 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 329 (M^+) (Found: *m/z* 329.0719. $C_{15}H_{19}NO_4Cr$ requires *m/z* 329.0719).

(-)-(R,1S,2S)-(N,O,o-Trimethylephedrine)tricarbonylchromium(0) (7) - To a stirred solution of (-)-(1*S*,2*S*)-(*N*,*O*-dimethylephedrine)tricarbonylchromium(0) (**6**) (0.231g, 0.70mmol) in THF (15ml) at -78°C was added *t*-butyllithium (0.39ml, 0.77mmol) and the solution stirred (-78°C, 2h). Methyl iodide (0.07ml, 1.05mmol) was added and stirring continued (-78°C, 2h). After addition of MeOH (1ml), the solution was warmed and evaporated to a yellow oil. Column chromatography (Al_2O_3 Grade V, Et_2O) gave on evaporation of the solvent and recrystallisation from CH_2Cl_2/petroleum ether, the *title compound* as yellow needles (0.182g, 76%), m.p. 89-90°C; $[\alpha]_{546}^{20}$ -50.0 (*c* 1.00 in $CHCl_3$); $\nu_{max.}$ 2815 (OCH_3), 2792 [$N(CH_3)_2$], 1967 and 1889br (C≡O), 1132 (COC) cm^{-1}; δ_H 5.57-4.96 [4H, m, $(CO)_3CrC_6H_4$], 3.90 [1H, brs, $(CO)_3CrC_6H_4CH(OMe)$], 3.37 (3H, s, OCH_3), 2.84 (1H, qu, J 6.3Hz, CHMe), 2.28 [3H, s, $(CO)_3CrC_6H_4CH_3$], 2.26 [6H, s, $N(CH_3)_2$], 1.10 (3H, d, J 6.6Hz, $CHCH_3$); *m/z* 343 (M^+) (Found: *m/z* 343.0875. $C_{16}H_{21}NO_4Cr$ requires *m/z* 343.0876).

X-Ray crystal structure analysis of (-)-(R,1S,2S)-(N,O,o-trimethylephedrine)tricarbonylchromium(0) (7) - Crystal data for the X-ray structure analysis of complex (-)-(**7**) were measured using an Enraf-Nonius CAD4-F 4-circle diffractometer and are presented below. Graphite monochromated Cu-Kα X-radiation [(Cu-Kα)=1.5418A] using the ω/2θ scan technique was used to collect reflection intensities out to a Bragg angle of θ=75°. The space group was determined unambiguously as a result of the structure analysis but initially indicated by the optical activity of the sample compound. The unit cell parameters were determined by least-squares refinement, the setting angles of 25 accurately centred reflections being used for this purpose. The omega scan angle was calculated from [1.10+(0.14tanθ)]° and increased by 25% on each side for background determination. The scan speed was varied from 1.0 to 6.7° min^{-1} depending upon intensity. Several standard reflections were measured every hour during data collection and showed no appreciable variation with time. The data were corrected for Lorentz and polarisation effects.[25] An absorption correction was also applied to obtain correct relative intensities. Crystal data for (-)-(**7**); $C_{16}H_{21}CrNO_4$, *M* 343.340, monoclinic, space group P 2_1, **a** 7.205(1), **b** 17.845(3), **c** 7.158(3) A, β 113.49(2)°, U 844.1 A^3, D_{calc} 1.35 gcm^{-3}, Z 2, μ(Cu-Kα) 60.0cm^{-1}. The crystal used for data collection was yellow in colour and of approximate

dimensions 0.30 by 0.45 by 0.90 mm. Number of independent reflections measured 1655, number with $I>3\sigma(I)$ 1647; R-factor 0.042; weighted R-factor 0.056; absorption corrections, maximium 1.96, minimum 1.00. The structure was solved by direct methods and electron-density Fourier synthesis. The structure was refined by large-block, least-squares which included parameters for atomic coordinates, temperature factors (anisotropic for non-hydrogen atoms), an overall scale factor and an extinction parameter. Reflections were weighted by applying a 3 term Chebychev series of the form $w = [1095.4t_0(X) + 1489.4t_1(X) + 441.5t_2(X)]$ where $X = F_o/F_{max}$. Final Fourier synthesis showed no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors.

(-)-(1R,2S)-N,O,o-Trimethylephedrine (8) - (-)-(*R*,1*S*,2*S*)-(*N*,*O*,*o*-Trimethylephedrine)tricarbonylchromium(0) (**7**) (0.031g, 0.09mmol) in diethyl ether was decomplexed according to the general procedure (72h), to give the *title compound* as a clear, colourless oil (0.011g, 58%); δ_H 7.40-7.15 (4H, m, C_6H_4), 4.73 (1H, d, J 2.1Hz, C_6H_4CH), 3.24 (3H, s, OCH_3), 2.44 [6H, s, $N(CH_3)_2$], 2.65 (1H, dq, J 2.1 and 6.8Hz, CHMe) 2.35 (3H, s, $C_6H_4CH_3$), 1.01 (3H, d, J 6.8Hz, $CHCH_3$); δ_C 138.50, 135.37, 130.55, 126.96, 125.79, 80.94, 77.20, 62.91, 56.53, 41.85, 7.49; *m/z* 208 (M^++1).

(+)-(R,1S,2S)-(o-Formyl-N,O-dimethylephedrine)tricarbonylchromium(0) (9) - To a stirred solution of (-)-(1*S*,2*S*)-(*N*,*O*-dimethylephedrine)tricarbonylchromium(0) (**6**) (0.549g, 1.67mmol) in THF (40ml) at -78°C was added *t*-butyllithium (0.65ml, 1.70mmol) and the solution stirred (-78°C, 2h). Ethyl formate (1.5ml, 18.6mmol) was added and stirring continued (-78°C, 6.75h). After addition of MeOH (1ml) the red solution was warmed and evaporated. Column chromatography [Al_2O_3 Grade V, CH_2Cl_2/MeOH (10:1)] gave a red fraction as an oil that solidified on standing. ^1H n.m.r. spectroscopy of the crude material revealed the presence of the *title compound* and the starting material in the ratio 75:25 [0.425g, 71% (96% based on recovered starting material)]. Recrystallisation from Et_2O/hexane gave a pure sample for characterisation, m.p. 113-115°C; $[\alpha]_D^{20}$ +392.8 (*c* 0.14 in $CHCl_3$); (Found: C, 53.5; H, 5.5; N, 3.6. $C_{16}H_{19}CrNO_5$ requires C, 53.8; H, 5.4; N, 3.9%); $\nu_{max.}$ 1970 and 1890 (C≡O), 1675 (C=O) cm^{-1}; δ_H 10.11 (1H, s, CHO), 5.90-5.18 [4H, m, $(CO)_3CrC_6H_4$], 3.85 [1H, d, J 4.4Hz, $(CO)_3CrC_6H_4CH(OMe)$], 3.57 (3H, s, OCH_3), 3.00 (1H, dq, J 4.3 and 7.0Hz, CHMe), 2.13 [6H, s, $N(CH_3)_2$], 1.01 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 358 (M^++1). The use of butyllithium as the base or DMF as the electrophile also furnished the *title compound* along with recovery of some starting material.

Z-(α-Methoxy-β-methylstyrene)tricarbonylchromium(0) (10) - A stirred solution of (-)-(1*S*,2*S*)-(*N*,*O*-dimethylephedrine)tricarbonylchromium(0) (**6**) (0.606g, 1.84mmol) in THF (30ml) at -78°C was treated with *t*-butyllithium (0.77ml, 2.02mmol) and the solution stirred (-78°C, 2h). Ethylene oxide (excess) and $BF_3.OMe_2$ (0.23ml, 1.84mmol) was added and stirring continued (-78°C, 2h). After addition of MeOH (4ml) the mixture was evaporated and the residue purified by column chromatography (Al_2O_3 Grade V, Et_2O) to furnish the *title compound* as a red oil. Crystallisation from pentane gave a pure sample as slender needles, $\nu_{max.}$ 1960 and 1895 (C≡O) cm^{-1}; δ_H 5.65-5.34 [6H, m, $(CO)_3CrPh$ and CHMe], 3.75 (3H, s, OCH_3), 1.83 (3H, d, J 7.0Hz, $CHCH_3$); *m/z* 284 (M^+) (Found: *m/z* 284.0140. $C_{13}H_{12}CrO_4$ requires *m/z* 284.0141). Differential nOe experiments were performed on complex (**10**) as $CDCl_3$ solutions at 300MHz. Irradiation of the methyl doublet gave an enhancement to the methoxyl singlet (3.7%) whilst separate irradiation of the methoxyl singlet gave enhancements to both the methyl doublet (5%) and to the aromatic

protons (11.2%). These results are consistent with Z geometry about the double bond.

Methylation of (-)-(R,1S,2S)-(N,O,o-trimethylephedrine)tricarbonylchromium(0) (7) using t-butyllithium - To a stirred solution of (-)-(*R*,1*S*,2*S*)-(*N*,*O*,*o*-trimethylephedrine)tricarbonylchromium(0) (**7**) (0.300g, 0.88mmol) in THF (12ml) at -78°C was added *t*-butyllithium (0.21ml, 0.90mmol) and the solution stirred (-78°C, 2h). Methyl iodide (0.310g, 2.18mmol) was added and stirring continued (-78°C, 2h). After addition of MeOH (1ml), the solution was warmed and evaporated to an orange oil. Column chromatography (Al_2O_3 Grade V, Et_2O) gave, after removal of the solvent, a mixture of (*R*,1*S*,2*S*)-(*N*,*O*-dimethyl-*o*-ethylephedrine)tricarbonylchromium(0) (**11**) and two unassigned ring methylated isomers in ratio 45:35:20 (0.309g, 98%). (500MHz) (**11**) δ_H 5.56-4.91 [4H, m, $(CO)_3CrC_6H_4$], 3.84 [1H, d, J 4.5Hz, $(CO)_3CrC_6H_4CH(OMe)$], 3.35 (3H, s, OCH_3), 2.87-2.82, 2.46-2.39 (3H, 2m, CH_2Me, CHMe), 2.28 [6H, s, $N(CH_3)_2$], 1.25 (3H, t, J 7.4Hz, CH_2CH_3), 1.10 (3H, d, J 6.5Hz, $CHCH_3$); (300MHz) major ring methylated isomer: δ_H 3.30 (3H, s, OCH_3), 2.28, 2.21 [6H, 2s, $(CO)_3CrC_6H_3(CH_3)_2$], 2.27 [6H, s, $N(CH_3)_2$], 1.13 (3H, d, J 6.6Hz, $CHCH_3$); (300MHz) minor ring methylated isomer: δ_H 3.39 (3H, s, OCH_3), 2.27 [6H, s, $N(CH_3)_2$], 2.23, 2.13 [2s, 6H, $(CO)_3CrC_6H_3CH_3$]. Repeating the reaction using butyllithium gave identical results.

(-)-(R,1S,2S,1'S)-(o-1-Hydroxyethyl-N,O-dimethylephedrine)tricarbonylchromium(0) (13) - To a stirred solution of (+)-(*R*,1*S*,2*S*)-(*o*-formyl-*N*,*O*-dimethylephedrine)tricarbonylchromium(0) (**9**) (0.037g, 0.10mmol) in THF (15ml) at -78°C was added methyllithium (1.0ml, 1.1mmol) and the solution stirred (-78°C, 6h). MeOH (2ml) was added, the solution warmed and evaporated. Column chromatography (Al_2O_3 Grade V, CH_2Cl_2) gave a yellow oil that comprised three components according to ^1H n.m.r. spectroscopy. The minor component was identified as starting material whilst the other two components (ratio 86:14) were assigned as the *title compound* (**13**) (major) and complex (**16**) (minor). Two crystallisations from Et_2O/hexane furnished a pure sample of the *title compound* as slender yellow needles, m.p. 99-100°C; $[\alpha]_D^{20}$ -32.7 (*c* 0.17 in $CHCl_3$); (Found: C, 54.9; H, 6.3; N, 3.6. $C_{17}H_{23}CrNO_5$ requires C, 54.7; H, 6.2; N, 3.75%); $\nu_{max.}$ 1965 and 1880 (C≡O) cm^{-1}; δ_H 5.69-5.13 [4H, m, $(CO)_3CrC_6H_4$], 5.01 [1H, q, J 6.3Hz, $(CO)_3CrC_6H_4CHMe$], 3.85 [1H, d, J 6.3Hz, $(CO)_3CrC_6H_4CH(OMe)$], 3.29 (3H, s, OCH_3), 3.10 (1H, br s, OH), 2.91 (1H, qu, J 6.5Hz, CHMe), 2.28 [6H, s, $N(CH_3)_2$], 1.51 (3H, d, J 6.3Hz, $CHCH_3$), 1.11 (3H, d, J 6.7Hz, $CHCH_3$); *m/z* 374 (M^++1) . A repeat experiment in the presence of TMEDA (16 equivalents) gave identical results.

X-Ray crystal structure analysis of (-)-(R,1S,2S,1'S)-(o-1-hydroxyethyl-N,O-dimethylephedrine)tricarbonylchromium(0) (13) - Crystal data for the X-ray structure analysis of complex (-)-(**13**) were measured using an Enraf-Nonius CAD4-F 4-circle diffractometer and are presented below. Graphite monochromated Cu-Kα X-radiation [(Cu-Kα)=1.5418A] using the ω/2θ scan technique was used to collect reflection intensities out to a Bragg angle of θ=75°. The space group was determined unambiguously as a result of the structure analysis but initially indicated by the optical activity of the sample compound. The unit cell parameters were determined by least-squares refinement, the setting angles of 25 accurately centred reflections being used for this purpose. The omega scan angle was calculated from [1.10+(0.14tanθ)]° and increased by 25% on each side for background determination. The scan speed was varied from 1.7 to 6.7° min^{-1} depending upon intensity. Several standard reflections were measured every hour during data collection and showed no

appreciable variation with time. The data were corrected for Lorentz and polarisation effects.[25] An absorption correction was also applied to obtain correct relative intensities. Crystal data for (-)-(**13**); $C_{17}H_{23}CrNO_5$, *M* 373.368, orthorhombic, space group P 2_1 2_1 2_1, **a** 8.761(4), **b** 13.269(3), **c** 15.744(5) A, U 1830.2 A^3, D_{calc} 1.36 gcm^{-3}, Z 4, μ(Cu-Kα) 54.3cm^{-1}. The crystal used for data collection was yellow in colour and of approximate dimensions 0.18 by 0.26 by 2.09 mm. Number of independent reflections measured 2149, number with $I>3\sigma(I)$ 1478; R-factor 0.058; weighted R-factor 0.066; absorption corrections, maximium 2.07, minimum 1.91. The structure was solved by direct methods and electron-density Fourier synthesis. The structure was refined by large-block, least-squares which included parameters for atomic coordinates, temperature factors (anisotropic for non-hydrogen atoms), an overall scale factor and an extinction parameter. Reflections were weighted by applying a 3 term Chebychev series of the form $w = [10.45\ t_0(X) - 1.312\ t_1(X) + 6.969\ t_2(X)]$ where $X = F_o/F_{max}$. Final Fourier synthesis showed no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors.

(-)-(R,1S,2S,1'S)-(o-1-Hydroxymethyl-N,O-dimethylephedrine)tricarbonylchromium(0) (17) - A stirred solution of (+)-(*R*,1*S*,2*S*)-(*o*-formyl-*N*,*O*-dimethylephedrine) tricarbonylchromium(0) (**9**) (0.091g, 0.25mmol) in THF (15ml) was treated with $NaBH_4$ (0.024g, 0.64mmol) producing a colour change from red to yellow. The solution was stirred (20°C, 3h), MeOH (5ml) added followed by addition of aqueous NH_4Cl (10ml). The solvent was evaporated, water (5ml) added and the aqueous phase extracted (Et_2O, 3x25ml). The combined extracts were purified by column chromatography [Al_2O_3 Grade V, Et_2O/petroleum ether (1:1)] to furnish the *title compound* as a yellow oil (0.060g, 66%). Crystallisation from Et_2O/petroleum ether gave a pure sample for characterisation, m.p. 115-118°C; $[\alpha]_D^{23}$ -66.2 (*c* 0.11 in $CHCl_3$); (Found: C, 53.1; H, 6.0; N, 4.2. $C_{16}H_{21}CrNO_5$ requires C, 53.5; H, 5.9; N, 3.9%); $\nu_{max.}$ 1970 and 1890 (C≡O) cm^{-1}; δ_H 5.53-5.15 [4H, m, $(CO)_3CrC_6H_4$], 4.83, 4.16 [2H, AB system, J_{AB} 12.3Hz, $(CO)_3CrC_6H_4CH_2OH$], 3.47 (3H, s, OCH_3), 3.05 (1H, dq, J 5.0 and 7.0Hz, CHMe), 2.18 [6H, s, $N(CH_3)_2$], 1.10 (3H, d, J 7.0Hz, $CHCH_3$); *m/z* 360 (M^++1). In a repeat experiment, $NaBD_4$ was used as the reducing agent to afford complex (**18**) as a yellow solid (64%). The ^1H n.m.r. spectrum of the product exhibited the same features as that of complex (-)-(**17**) except that the AB system at δ4.83, 4.16 had been replaced by a 1 proton broad singlet at δ4.16; *m/z* 361 (M^++1).

(-)-(1S,2R)-(N,O-Dimethylpseudoephedrine)tricarbonylchromium(0) (22) - A mixture of (-)-(1*R*,2*R*)-pseudoephedrine (**3**) (41.2g, 250mmol) and formic acid (98-100%, 2.50ml) was treated with formaldehyde (37% aqueous solution, 250ml) and the mixture heated at reflux (18h). The acid was removed under reduced pressure, the solution basified (NaOH) and the aqueous phase extracted (Et_2O). The combined extracts were evaporated and the residue distilled under reduced pressure to give (1*R*,2*R*)-*N*-methylpseudoephedrine (**19**) as a low melting point solid (43.1g, 96%), b.p. 81°C (0.1mmHg) (m.p. lit.[24] 29-30°C); $\nu_{max.}$ (neat) 3350br (OH), 2788 [$N(CH_3)_2$], 1605 (arene ring), 751, 702 (monosubstituted arene) cm^{-1}; δ_H 7.39-7.27 (5H, m, Ph), 5.06 [1H, br s, PhCH(OH)], 4.21 (1H, d, J 9.7Hz, PhCH), 2.58 (1H, dq, J 9.7 and 6.7Hz, CHMe), 2.31 [6H, s, $N(CH_3)_2$], 0.73 (3H, d, J 6.7Hz, $CHCH_3$). A portion of this material (4.00g, 22.3mmol) in THF (100ml) was added dropwise to a stirred suspension of potassium hydride (1.36g, 34.0mmol) in THF (100ml). The mixture was heated at reflux (3.5h) and the cooled solution (20°C) treated with methyl iodide (3.81g, 26.8mmol). The mixture was stirred (1h) and MeOH (4ml) cautiously added to give, on evaporation, a brown oily residue. Flash chromatography (SiO_2, 39:10:1 toluene:EtOH:c.NH_3) gave two fractions. Fraction one was evaporated and distilled to give *E*-α-methoxy-β-methylstyrene (**21**) as a clear, colourless oil

(0.231g, 7%), b.p. 45-48°C (0.1mmHg); δ_H 7.47-7.24 (5H, m, Ph), 5.40 (1H, q, J 6.9Hz, CHMe), 3.56 (3H, s, OCH_3), 1.82 (3H, d, J 6.9Hz, $CHCH_3$). A differential nOe experiment was performed on complex (**21**) as a $CDCl_3$ solution at 300MHz. Irradiation of δ3.56 (OCH_3) gave enhancements of δ7.47-7.24 (ArH, 5.20%) and δ5.40 (CHMe, 4.83%). Fraction two was evaporated and distilled to give (-)-(1*R*,2*R*)-*N*,*O*-dimethylpseudoephedrine (**20**) as a clear, colourless oil (3.27g, 76%), b.p. 49-53°C (0.1mmHg); $[\alpha]_D^{21}$ -98.0 (*c* 4.62 in MeOH); (Found: C, 74.3; H, 10.3; N, 7.8. $C_{12}H_{19}NO$ requires C, 74.6; H, 9.9; N, 7.25%); $\nu_{max.}$ (neat) 2808 (OCH_3), 2783 [$N(CH_3)_2$], 1599 (arene ring), 1094 (COC), 749 and 699 (monosubstituted arene) cm^{-1}; δ_H 7.36-7.27 (5H, m, Ph), 3.99 (1H, d, J 9.1Hz, PhCH), 3.15 (3H, s, OCH_3), 2.92 (1H, m, CHMe), 2.36 [6H, s, $N(CH_3)_2$], 0.61 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 194 (M^++1). A portion of this material (1.50g, 7.77mmol) and hexacarbonylchromium(0) (2.05g, 9.33mmol) in Bu_2O (55ml) and THF (5ml) were reacted according to the general complexation procedure to give a yellow solid. Recrystallisation from CH_2Cl_2/petroleum ether gave the *title compound* as yellow cubic crystals (2.11g, 83%), m.p. 73-74°C; $[\alpha]_D^{22}$ -81.0 (*c* 0.98 in $CHCl_3$); (Found: C, 54.6; H, 6.0; N, 4.5. $C_{15}H_{19}CrNO_4$ requires C, 54.7; H, 5.8; N, 4.25%); $\nu_{max.}$ (CH_2Cl_2) 2810 (OCH_3), 2778 [$N(CH_3)_2$], 1967 and 1883br (C≡O), 1086 (COC) cm^{-1}; δ_H 5.65-5.23 [5H, m, $(CO)_3CrPh$]; 3.91 [1H, d, J 4.7Hz, $(CO)_3CrPhCH(OMe)$], 3.58 (3H, s, OCH_3), 2.64 (1H, dq, J 4.7 and 6.8Hz, CHMe), 2.26 [6H, s, $N(CH_3)_2$], 0.90 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 329 (M^+).

(-)-(R,1S,2R)-(N,O,o-Trimethylpseudoephedrine)tricarbonylchromium(0) (23) - To a stirred solution of (-)-(1*S*,2*R*)-(*N*,*O*-dimethylpseudoephedrine)tricarbonylchromium(0) (**22**) (0.339g, 1.03mmol) in THF (15ml) at -78°C was added butyllithium (1.35ml, 2.16mmol) and the solution stirred (-78°C, 2h). Methyl iodide (0.616g, 4.34mmol) was added and stirring continued (-78°C, 2h). After addition of methanol (1ml), the solution was warmed and evaporated. Column chromatography (Al_2O_3 Grade V, Et_2O) gave on evaporation of the solvent and recrystallisation from CH_2Cl_2/petroleum ether, the *title compound* as yellow needles (0.318g, 90%, m.p. 74-75°C; $[\alpha]_D^{22}$ -60.0 (*c* 0.70 in $CHCl_3$); (Found: C, 55.7; H, 6.3; N, 3.7. $C_{16}H_{21}CrNO_4$ requires C, 56.0; H, 6.2; N, 4.1%); $\nu_{max.}$ (CH_2Cl_2) 2816 (OCH_3), 2778 [$N(CH_3)_2$] 1961 and 1880br (C≡O), 1600 (arene ring), 1089 (COC) cm^{-1}; δ_H 5.58-5.53, 5.04-4.96 [4H, 2m, $(CO)_3CrPhC_6H_4$], 3.66 [1H, d, J 7.9Hz, $(CO)_3CrPhC_6H_4CH(OMe)$], 3.51 (3H, s, OCH_3), 3.01-2.92 (1H, m, CHMe), 2.35 [6H, s, $N(CH_3)_2$], 2.33 (3H, s, $ArCH_3$), 0.91 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 344 (M^++1).

X-Ray crystal structure analysis of (-)-(R,1S,2R)-(N,O,o-trimethylpseudoephedrine)tricarbonylchromium(0) (23) - Crystal data for the X-ray structure analysis of complex (-)-(**23**) were measured using an Enraf-Nonius CAD4-F 4-circle diffractometer and are presented below. Graphite monochromated Cu-Kα X-radiation [(Cu-Kα)=1.5418A] using the ω/2θ scan technique was used to collect reflection intensities out to a Bragg angle of θ=75°. The space group was determined unambiguously as a result of the structure analysis but initially indicated by the optical activity of the sample compound. The unit cell parameters were determined by least-squares refinement, the setting angles of 25 accurately centred reflections being used for this purpose. The omega scan angle was calculated from [1.10+(0.14tanθ)]° and increased by 25% on each side for background determination. The scan speed was varied from 1.7 to 6.7° min^{-1} depending upon intensity. Several standard reflections were measured every hour during data collection and showed no appreciable variation with time. The data were corrected for Lorentz and polarisation effects.[25] An absorption correction was also applied to

obtain correct relative intensities. Crystal data for (-)-(**23**); $C_{16}H_{213}CrNO_4$, *M* 343.340, *ortho*rhombic, space group P 2_1 2_1 2_1, **a** 7.964(3), **b** 11.909(2), **c** 17.958(3) A, U 1703.2 A^3, D_{calc} 1.34 gcm^{-3}, Z 4, μ(Cu-Kα) 57.5cm^{-1}. The crystal used for data collection was yellow in colour and of approximate dimensions 0.09 by 0.11 by 0.42 mm. Number of independent reflections measured 1575, number with I>3σ(I) 1447; R-factor 0.061; weighted R-factor 0.079; absorption corrections, maximium 2.07, minimum 1.91. The structure was solved by Patterson methods and electron-density Fourier synthesis. The structure was refined by large-block, least-squares which included parameters for atomic coordinates, temperature factors (anisotropic for non-hydrogen atoms), an overall scale factor and an extinction parameter. Reflections were weighted by applying a 4 term Chebychev series of the form $w = [494.9t_o(X) + 722.5t_1(X) + 325.7t_2(X) + 96.44t_3(X)]$ where $X = F_o/F_{max}$. Final Fourier synthesis showed no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors.

(R,1S,2R)-(o-Formyl-N,O-dimethylpseudoephedrine)tricarbonylchromium(0) (24) - To a stirred solution of (-)-(1*S*,2*R*)-(*N*,*O*-dimethylpseudoephedrine)tricarbonylchromium(0) (**22**) (0.513g, 1.56mmol) in THF (40ml) at -78°C was added *t*-butyllithium (0.60ml, 1.57mmol) and the solution stirred (-78°C, 2h). Ethyl formate (1.5ml, 18.6mmol) was added and stirring continued (-78°C, 6.75h). After addition of MeOH (1ml) the red solution was warmed and evaporated. Column chromatography [Al_2O_3 Grade V, CH_2Cl_2/MeOH (10:1)] gave a red oil that, according to ^1H n.m.r. spectroscopy of the crude material comprised the *title compound* and the starting material in the ratio 26:74 [0.50g, 24% (84% based on unreacted starting material)]. Crystallisation from Et_2O/hexane gave a pure sample for characterisation, m.p. 98-100°C; $[\alpha]_D^{20}$ +220.0 (*c* 0.13 in $CHCl_3$); (Found: C, 53.9; H, 5.1; N, 3.9. $C_{16}H_{19}CrNO_5$ requires C, 53.8; H, 5.4; N, 3.9%); $\nu_{max.}$ 1975 and 1905 (C≡O), 1675 (C=O) cm^{-1}; δ_H 9.88 (1H, s, CHO), 5.85-5.26 [4H, m, $(CO)_3CrC_6H_4$], 3.76 [1H, d, J 2.6Hz, $(CO)_3CrC_6H_4CH(OMe)$], 3.64 (3H, s, OCH_3), 2.50 (1H, dq, J 2.6 and 7.0Hz, CHMe), 2.12 [6H, s, $N(CH_3)_2$], 1.20 (3H, d, J 6.8Hz, $CHCH_3$); *m/z* 358 (M^++1). The use of butyllithium as the base or DMF as the electrophile also furnished the *title compound* along with recovery of some starting material.

(+)-(1S,2R)-(N,O,o,o-Tetramethylpseudoephedrine)tricarbonylchromium(0) (25) - To a stirred solution of (-)-(*R*,1*S*,2*R*)-(*N*,*O*,*o*-trimethylpseudoephedrine)tricarbonylchromium(0) (**23**) (0.222g, 0.65mmol) in THF (8ml) at -78°C was added *t*-butyllithium (0.15ml, 0.65mmol) and the solution stirred (-78°C, 2h). Methyl iodide (0.230g, 1.62mmol) was added and stirring continued (-78°C, 2h). after addition of methanol (1ml), the solution was warmed and evaporated. Column chromatography (Al_2O_3 Grade V, Et_2O) gave, on evaporation of the solvent and recrystallisation from CH_2Cl_2/petroleum ether, the *title compound* as yellow needles (0.183g, 79%), m.p. 143-136°C; $[\alpha]_D^{21}$ +18.0 (*c* 1.01 in $CHCl_3$); (Found: C, 57.1; H, 6.6; N, 3.8. $C_{17}H_{23}CrNO_4$ requires C, 57.1; H, 6.5; N, 3.9%); $\nu_{max.}$ (CH_2Cl_2) 2820 (OCH_3), 2776 [$N(CH_3)_2$], 1960 and 1880br (C≡O), 1602 (arene ring), 1092 (COC) cm^{-1}; δ_H 5.58-4.84 [3H, m, $(CO)_3CrC_6H_3$], 4.08 [1H, d, J 9.0Hz, $(CO)_3CrC_6H_3CH(OMe)$], 3.62 (3H, s, OCH_3), 3.18-3.12 (1H, m, CHMe), 2.42, 2.28 [6H, 2s, $(CO)_3CrC_6H_3CH_3$], 2.41 [6H, s, $N(CH_3)_2$], 0.77 (3H, d, J 6.5Hz, $CHCH_3$); *m/z* 357 (M^+).

(1R,2R)-N,O,o,o-Tetramethylpseudoephedrine (26) - (+)-(1*S*,2*R*)-(*N*,*O*,*o*,*o*-Tetramethylspeudoephedrine)-tricarbonylchromium(0) (**25**) (0.071g, 0.20mmol) in diethyl ether (25ml) was decomplexed according to the general procedure (72h), to give the *title compound* as a clear, colourless oil (0.042g, 95%), δ_H ($CDCl_3$) 7.14-6.99 (3H, m, C_6H_3), 4.82 [1H, d, J 9.2Hz, $C_6H_3CH(OMe)$], 3.78-3.63 (1H, m, CHMe), 3.16 (3H, s, OCH_3), 2.77 [6H, s, $N(CH_3)_2$], 2.47, 2.39 (6H, 2s, $C_6H_3CH_3$), 0.99 (3H, d, J 6.5Hz, $CHCH_3$); δ_H (C_6D_6) 6.98-6.81 (3H, m, C_6H_3), 4.74-4.67 [1H, d, J 6.9Hz, $C_6H_3CH(OMe)$], 3.60-3.49 (1H, m, CHMe), 2.90 (3H, s, OCH_3), 2.56 [6H, s, $N(CH_3)_2$], 2.41, 2.22 (6H, 2s, $C_6H_3CH_3$), 0.88 (3H, d, J 6.9Hz, $CHCH_3$).

(R,1S,2R,1'S)-(o-1-Hydroxyethyl-N,O-dimethylpseudoephedrine)tricarbonylchromium(0) (27) - To a stirred solution of (+)-(*R*,1*S*,2*R*)-(*o*-formyl-*N*,*O*-dimethylpseudoephedrine)tricarbonylchromium(0) (**24**) (0.030g, 0.08mmol) in THF (15ml) at -78°C was added methyllithium (0.15ml, 0.23mmol) and the solution stirred (-78°C, 2h). MeOH (0.5ml) was added, the solution warmed and evaporated. Column chromatography (Al_2O_3 Grade V, CH_2Cl_2) gave a single fraction as a yellow oil (0.016g, 52%) that comprised two components in the ratio 86:14 according to ^1H n.m.r. spectroscopy of the crude material. The major product was assigned as the *title compound* by analogy with the previous reaction but all attempts at its isolation failed, δ_H 5.85-5.15 [5H, m, $(CO)_3CrC_6H_4$ and $(CO)_3CrC_6H_4CHMe$], 3.76 [1H, br s, $(CO)_3CrC_6H_4CH(OMe)$], 3.51 (3H, s, OCH_3), 2.91 (1H, qu, J 7.1Hz, CHMe), 2.34 [6H, s, $N(CH_3)_2$], 1.47 (3H, d, J 6.3Hz, $CHCH_3$), 0.93 (3H, d, J 6.9Hz, $CHCH_3$).

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