Chromium directed regio- and stereocontrol: a new chapter in aromatic natural product synthesis

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Abstract – The sequence of *ortho*-directing abilities of a series of aryl functionalities in arenetricarbonylchromium(0) complexes has been shown to be different to that in the uncomplexed arenes. The kinetic resolution of the lithiated complexes with homochiral oxazolidinones has been rationalised *via* a transition state model and applied to the stereocontrolled synthesis of a series of highly functionalised, homochiral phenethylamines.

INTRODUCTION

The many studies of the chemistry of the aromatic ligands of arenetricarbonylchromuim(0) complexes have established the patterns of reactivity expressed in Figure 1[1]. The attachment of a tricarbonylchromium unit to one face of an aromatic ring modifies the chemistry of that ring both electronically and spatially.
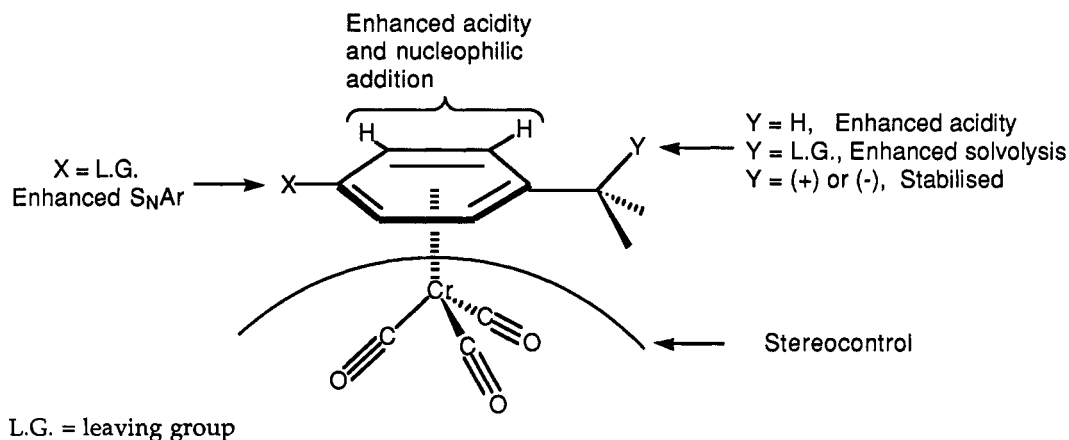

L.G. = leaving group

Figure 1

The general effect of the metal carbonyl moiety is that of electron withdrawal, resulting in enhanced acidities of the ring and benzylic protons and an increased propensity to aromatic nucleophilic addition and substitution.
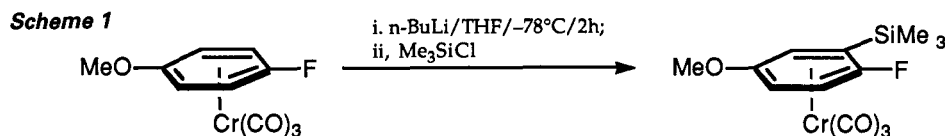
Spatially, the metal occupies one face of the ring and the attack of any reagent on the ring or at a benzylic site is constrained to an approach only from the side *anti* to the metal. More subtly, such a benzylic attack and the ionisation of a benzylic leaving group has been shown to exhibit a strong stereoelectronic preference and occurs precisely antiperiplanar to the metal atom[2].

This report will concentrate on two aspects of these attributes, ring deprotonation and stereocontrol, and show how new synthetic strategies can be developed as a consequence of the attachment of the metal.

REGIOCONTROL: DIRECTED LITHIATION

The very extensive studies of directed lithiation in aromatic compounds[3] has resulted in the development of an order of directing abilities for the many functional groups which show this phenomenon (see later).
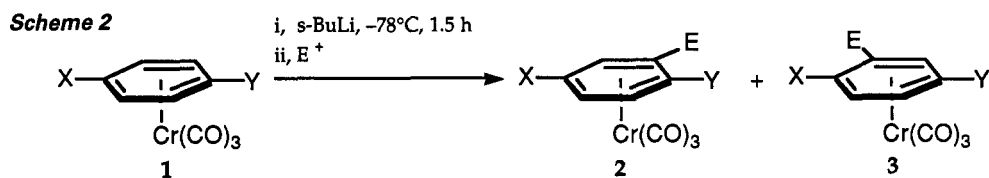
During our earlier studies an unexpected observation was made that the chromium complex of *p*-fluoroanisole was lithiated at –78°C exclusively *ortho* to the fluorine atom (Scheme 1)[4]

Scheme 1

MeO—⟨ ⟩—F
    |
   Cr(CO)$_3$

i. n-BuLi/THF/–78°C/2h;
ii, Me$_3$SiCl
$\longrightarrow$

MeO—⟨ ⟩—SiMe$_3$
          —F
    |
   Cr(CO)$_3$

In uncomplexed arenes, fluorine is reportedly a poor *ortho* directing group[5] and in our hands, under the above conditions, *p*-fluoroanisole gave a 1 : 1 ratio of the monosubstitution products.

It became necessary to determine, therefore, whether this was peculiar to fluorine or whether and how the directing abilities of other groups were modified upon complexation by chromium and we examined complexes containing a range of *ortho* directing groups.

A series of *para* disubstituted arene complexes (1) were synthesised and lithiated under standardised conditions (Scheme 2) and reacted with chlorotrimethylsilane which we had established as an efficient quench for the lithio- species[4].

Scheme 2

X—⟨ ⟩—Y
    |
   Cr(CO)$_3$
    1

i, s-BuLi, –78°C, 1.5 h
ii, E$^+$
$\longrightarrow$

X—⟨ ⟩—Y
      E
    |
   Cr(CO)$_3$
    2

+

X—⟨ ⟩—Y
   E
    |
   Cr(CO)$_3$
    3

E$^+$ = Me$_3$SiCl unless otherwise stated

X = -NMe$_2$, -CH$_2$NMe$_2$, -CH$_2$OMe, -NHCO^{t}Bu, -OMe, -CONHPh

Y = -F, -OMe

Many of these were run, together with control experiments on the uncomplexed arenes[6], and some notable examples are given in Figure 2. Thus *p*-dimethylaminomethylanisole complex (1, X = CH$_2$NMe$_2$, Y = OMe) gave a 1 : 1 mixture of the monosilylated products, yet the uncomplexed arene was substituted exclusively *ortho* to the aminomethyl group. In contrast, *p*-t-butoxycarbonylaminoanisole (1, X = NHCO$_2$Bu^t, Y = OMe) gave a very similar product distribution whether complexed or not.

A clue to the possible reason for the differences comes from the X-ray analysis of the solid
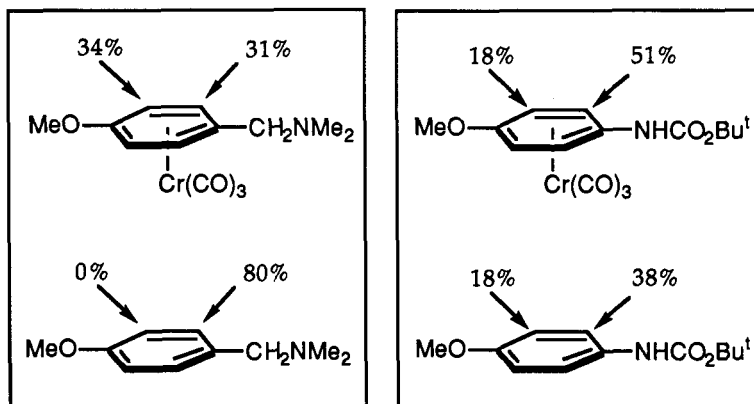
34%   31%

MeO—⟨ ⟩—CH$_2$NMe$_2$
    |
   Cr(CO)$_3$

18%   51%

MeO—⟨ ⟩—NHCO$_2$Bu^t
    |
   Cr(CO)$_3$

0%   80%

MeO—⟨ ⟩—CH$_2$NMe$_2$

18%   38%

MeO—⟨ ⟩—NHCO$_2$Bu^t

Figure 2

state structures of the *p*-fluoroanisole complex and related compounds. These show that the methoxy group of (1, X = F, Y = OMe) is almost in the plane of the aryl ring and that whilst the C–F bond length (1.351Å) is comparable to that of uncomplexed aryl fluorides (1.35Å)[7], the aryl C–O bond is slightly shortened (1.346Å, *cf* uncomplexed aryl methyl ethers, ≈ 1.36Å[8]) indicative of increased double bond character in the complex and hence enhanced positive character to the oxygen atom. Furthermore, it is known that aryl amine complexes exhibit a pronounced shortening of the C–N bond upon complexation[9] (≈1.4Å to ≈1.35Å).

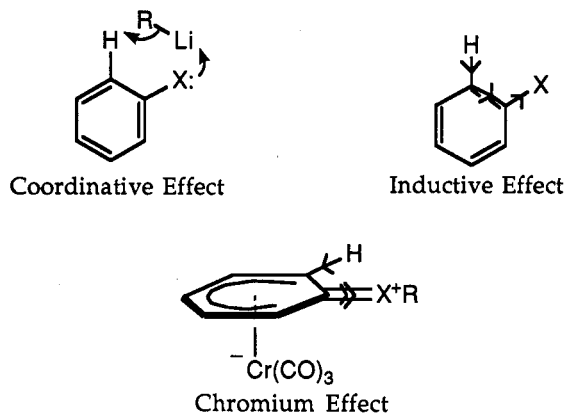Coordinative Effect   Inductive Effect

Chromium Effect

Figure 3

Directed *ortho* lithiations are generally ascribed to a combination of two effects, the coordination of the incoming base and the inductive labilisation of the adjacent ring proton by the electron withdrawing substituent (Figure 3)[10]. These both enhance the kinetic acidities of the ring protons. Fluorine in aryl fluorides is non-coordinating towards incoming bases[10] and the strong back donation from the fluorine non-bonding electrons to the aryl ring, cited as the reason for the short C–F bond length[11], would tend to counteract the inductive effect of the fluorine atom by enhancing the electron density on the ring.

As judged by the X-ray data, the C–F bond length is unchanged on complexation to the metal. In the sequence from fluorine to nitrogen, the increasing bond shortening upon complexation indicates an increasing back donation and a progressive reduction in the coordinating ability of the heteroatoms.

In contrast, the effect in the σ framework will be to increase the the inductive effect more especially as the negative charge is not located on the ring but remote from it on the metal carbonyl unit. Thus there appears to be a particular 'chromium effect' (Figure 3), a twofold modification of the reactivity which differs from the consequence of adding a competitive ligand such as *N,N,N'N'*-tetramethylethylenediamine (TMEDA)[12]. This explains why the methoxy group in *p*-dimethylaminomethylanisole complex shows comparable activation to the aminomethyl group, even though the latter is a more powerful director in the parent arene in the presence of TMEDA[12].

The secondary amide group is one of the most powerful *ortho* directors in aromatic systems[13]. The aromatic ring of the *o*-fluorobenzanilide complex proved to be so electron deficient that kinetic lithiation with alkyl lithiums was not possible. Addition of the alkyl anion to the ring was the only process observable. However, lithiation under thermodynamic conditions with lithium diisopropylamide was possible. Quenching of the anion with chlorotrimethylsilane gave silylation next to fluorine as the only detectable substitution product (Scheme 3).
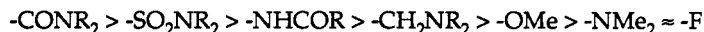
Scheme 3
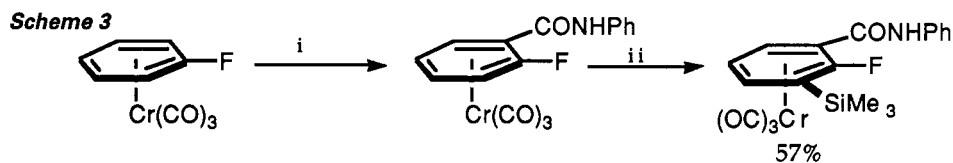
i; n-BuLi/THF/–78°C, PhNCO.

ii; LDA(2eq.)/THF/–78°C, Me₃SiCl.

Based upon these results, we can now construct a new order of directing abilities for the complexes:—

$$-F > (-CONHR) > -NHCOR > -CH_2NR_2 \approx -OMe \gg -CH_2OMe > -NR_2, -SR$$

compared with:—

$$-CONR_2 > -SO_2NR_2 > -NHCOR > -CH_2NR_2 > -OMe > -NMe_2 \approx -F$$

for the uncomplexed arenes.

The use and power of this new order has been illustrated by the synthesis of polyfunctionalised aromatics from *o-*, *m-* and *p*-fluoroanisole complexes[4] and provided new strategies for the synthesis of highly functionalised aromatic natural products and related compounds as exemplified by the phytoalexins of *Morus* spp.[14] and the functionalised β-phenethylamines as set out below.

STEREOCONTROL: KINETIC RESOLUTION

1,2-Diheterofunctionalised benzenetricarbonylchromium(0) complexes are asymmetric but not readily obtained in homochiral form[15]. We sought to assess their potential for diastereoselection in their reaction with chiral reagents (Scheme 4).

Seebach's chiral 5-oxazolidinones[16] were the chosen reagents because of the diversity of their potential for natural product and bioactive molecule synthesis. In the event, successful reaction required the use of an equivalent of a Lewis acid and of the many studied, boron trifluoride etherate proved to be the most effective. Without this, the lithiated complex simply deprotonated the substrate. It is presumed that the much less basic boron ate complex is the reacting species. In addition, it was found necessary to use a more bulky acyl group on N-3 in order to avoid attack at the amide carbonyl group.
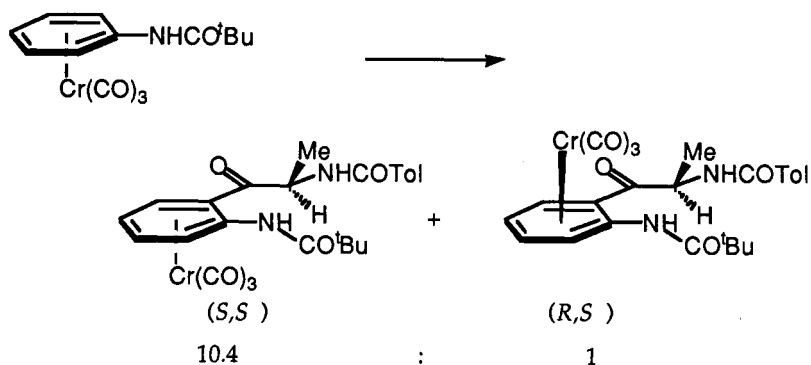
Scheme 4

R, (S)
R*X = chiral reagent
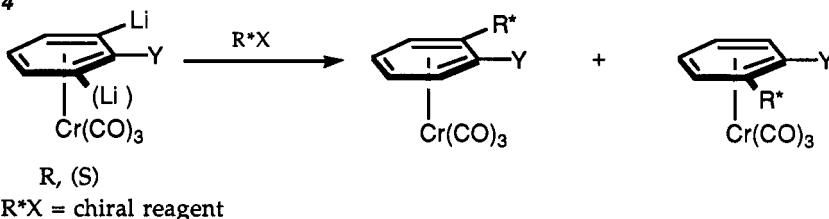
The reaction of 2-lithiofluorobenzene complex with the alanine derived *syn*-oxazolidinone (Scheme 5) gave the adducts in 69 – 80% yield without diastereoselection. The structures of these complexes were determined by a single crystal X-ray analysis of the (*S,S*) isomer.

Scheme 5
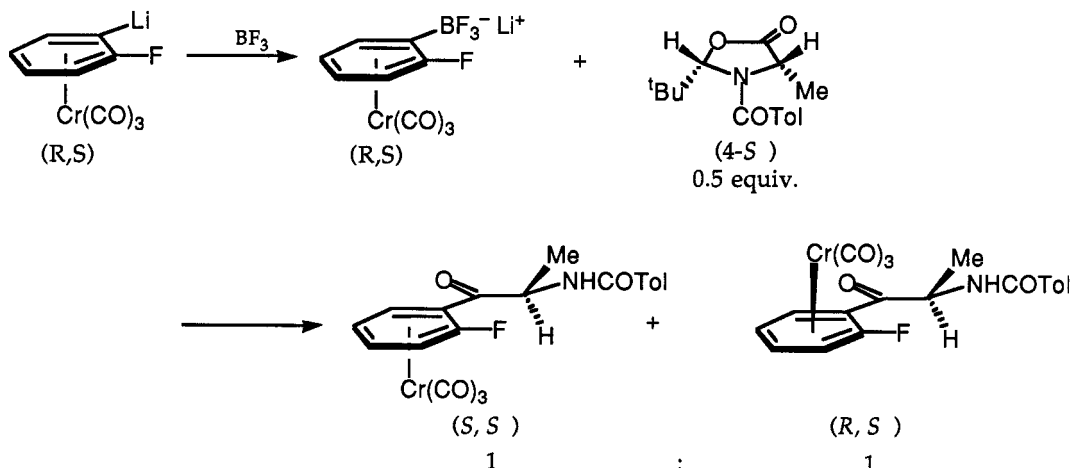
With more bulky *ortho* directing groups, the diastereoselection increased markedly. Thus 2-lithioanisole complex gave a 3 : 1 ratio of diastereomers and the 2-lithiopivalamidobenzene complex a 10.4 : 1 (Scheme 6), the structures of which were determined by chemical correlation with the single crystal X-ray analysis of the analogous 2-fluoro- complex above.
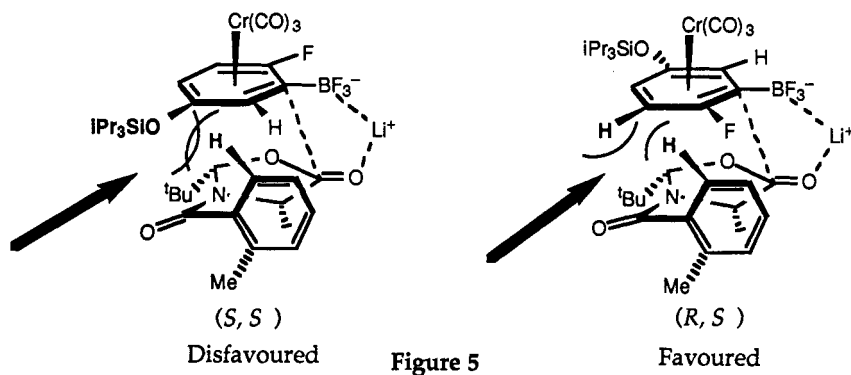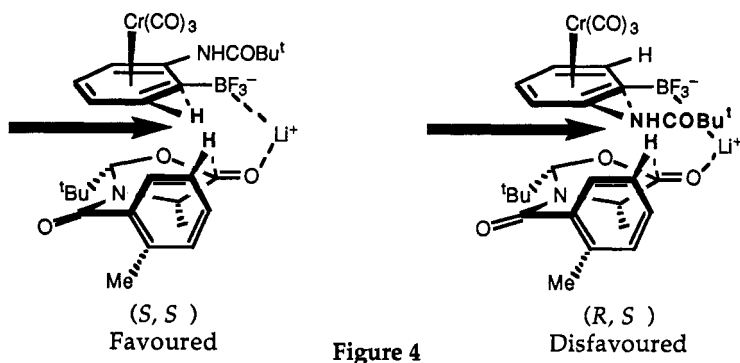
Scheme 6

(S,S)

10.4 : 1 (R,S)

Although stereodifferentiation by a large group adjacent to lithium can be readily appreciated, more surprising was the observation of stereodifferentiation by a remote large group (Scheme 7).

Scheme 7

(R,S)   0.5 equiv.

64%

(S,S)   (R,S)

1 : 10
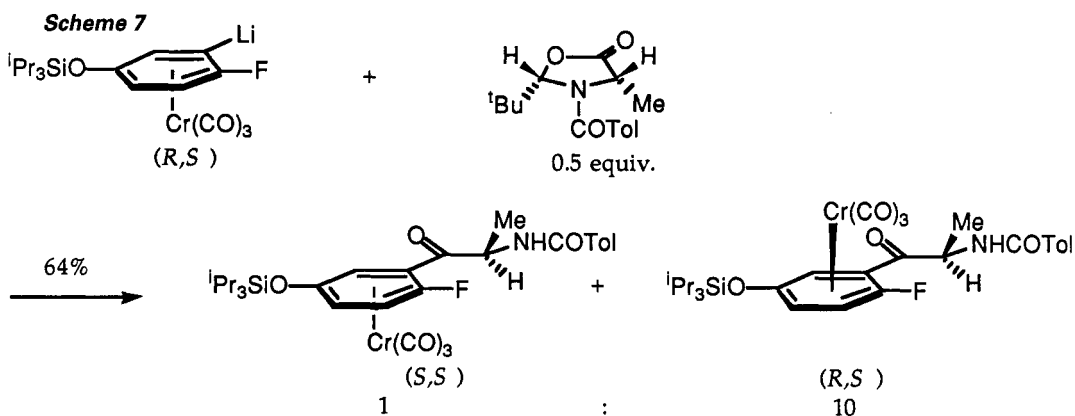
All of these results can be rationalised in terms of the transition states given in Figures 4 and 5.

(S, S)
Favoured

Figure 4

(R, S)
Disfavoured

(S, S)
Disfavoured

Figure 5

(R, S)
Favoured

Access to these homochiral complexes allowed application of benzylic stereocontrolled reactions of chromium tricarbonyl complexes to a chira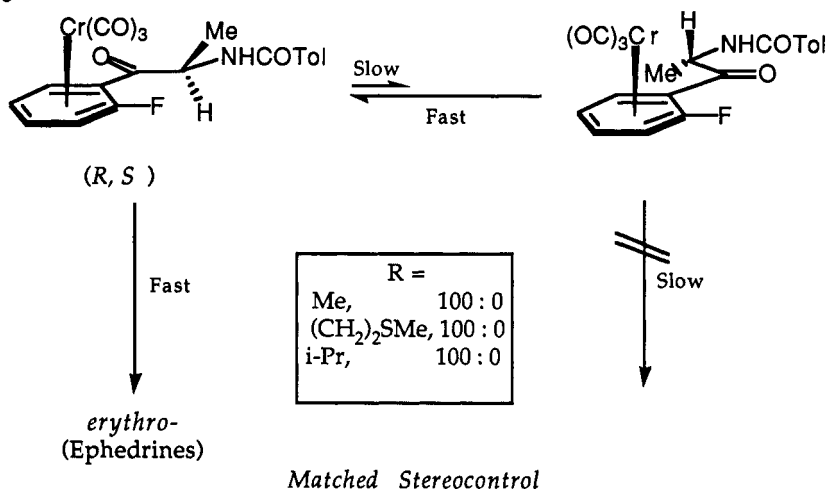l synthesis of ephedrines (Scheme 8). Thus the (R, S)- isomer gave a single diastereomer with the *erythro*- configuration.

Scheme 8

$$KBH_4/MeOH/THF/H_2O$$
r.t. , 1.5h
79%
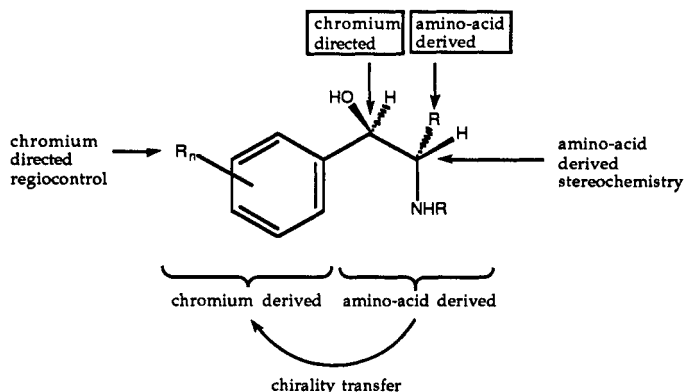
(R, S)

(R, S, S)
Ephedrines
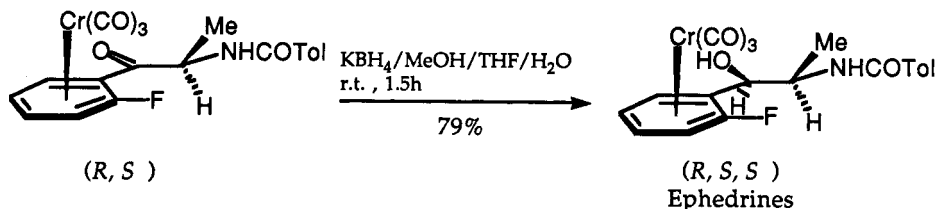
The fact that the chromium unit is known to control completely the stereochemistry of reactions at the benzylic site[2], taken together with our observation that larger side chains (from methionine or valine) on the oxazolidinone served to diminish the proportion of the *threo* (ψ-ephedrine) series from the reduction of the (S, S)- isomer, shows that the reaction occurs *via* an equilibrating pair of conformers (Scheme 9).

Scheme 9

(R, S)

Slow
Fast

Fast

R =	
Me,	100 : 0
$(CH_2)_2SMe$,	100 : 0
i-Pr,	100 : 0

Slow

erythro-
(Ephedrines)

Matched Stereocontrol

These results can be summarised as shown in Figure 6.

chromium directed | amino-acid derived

chromium directed regiocontrol

amino-acid derived stereochemistry

chromium derived   amino-acid derived

chirality transfer

Figure 6

Thus we have reached the first stage of a programme of natural product and related compound synthesis. By a combination of the two features described here, the potential exists to synthesise a wide range of highly functionalised homochiral phenethylamines. The chromium complexes are also being applied to the synthesis of more phytoalexins, and a range of indolic alkaloids and antibiotics[17].

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