PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Arenetricarbonylchromium(0) Complexes in Organic Synthesis [and Discussion]

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Arenetricarbonylchromium(0) complexes in organic synthesis

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Activation of arene rings to deprotonation and nucleophilic addition by attachment of a tricarbonylchromium unit is combined with the *ortho*-directing effects of fluorine and other substituents to generate new methods for the highly regiocontrolled synthesis of polyfunctional aromatics and benzoannulated heterocycles. With chiral oxazolone electrophiles, these reactions occur without diastereoselection although subsequent reactions of the adducts show good selectivity.

Lateral protection of protons adjacent to nitrogen and oxygen functions with bulky silane groups produces regioselective remote deprotonation by lithium bases in indole and phenol complexes. These selectivities are used to synthesize indoles functionalized in the carbocyclic ring and resorcinyl–benzofuran phytoalexins respectively.

Introduction

The attachment of a tricarbonylchromium unit to an aromatic ring results in a nett lowering of electron density within the ring and among other effects, an enhancement of the propensity of the ring to undergo both ring and benzylic deprotonation and nucleophilic addition (figure 1), or substitution if a leaving group is present (Semmelhack *et al.* 1981; Jaouen 1977).

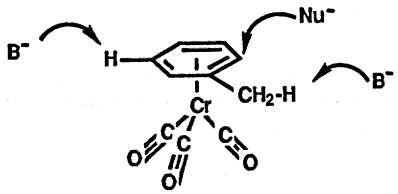
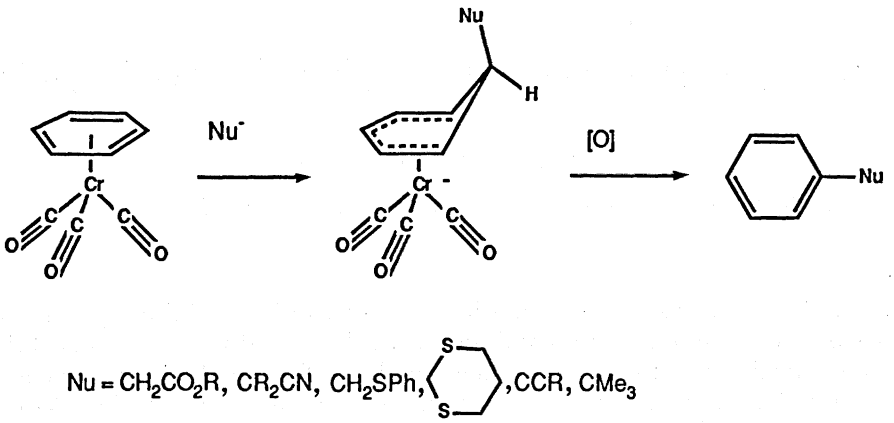
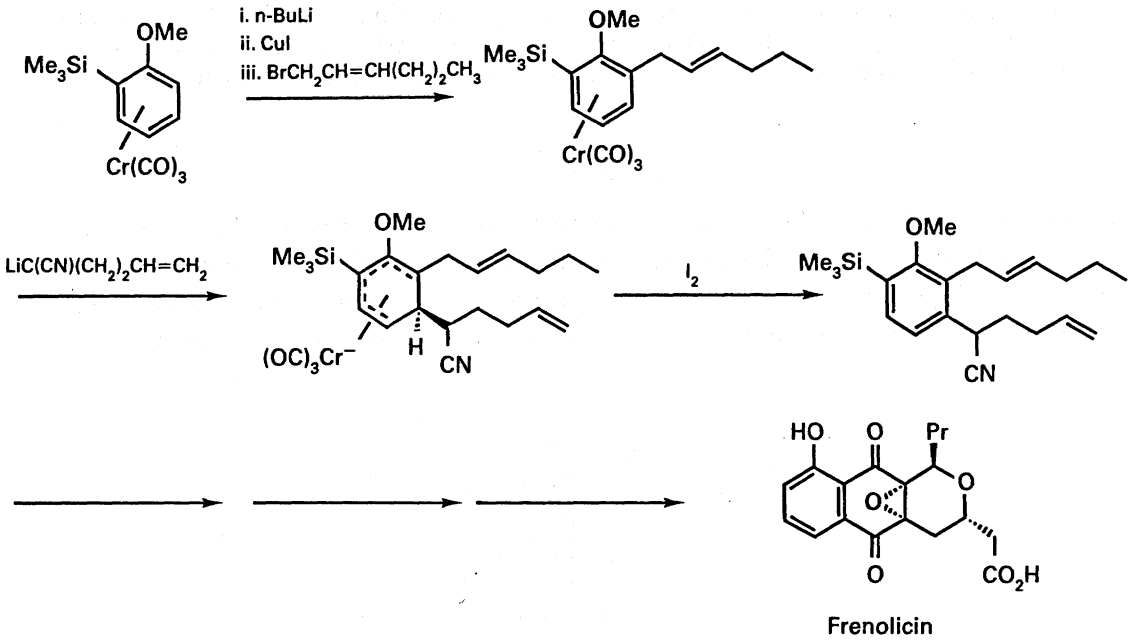


Figure 1

The latter can be used to bring about an overall substitution process because the intermediate adduct is readily rearomatized by oxidation (scheme 1). Only in rare cases, however, can the complex be regenerated, and the product of oxidation is usually the decomplexed arene. Notable applications of this approach have been reported, including the synthesis of frenolicin (Semmelhack & Zask 1983), the early stages of which are given in scheme 2. This illustrates an important feature of the chromium activation of arenes, the regiocontrol of the reactions induced or enhanced by the presence of the metal moiety. Thus for the nucleophilic addition process, a methoxy group is *meta* directing and a trimethylsilyl group is *para* directing. This regiochemistry has been related to the solid-state conformation of the tricarbonylchromium unit (Fukui *et al.* 1982), which for phenolic ethers is an orientation with one of the carbon monoxide groups eclipsing the alkoxy group. More theoretically sound molecular orbital analysis has been used to rationalize both the regiospecificities and the conformational preferences (Jackson *et al.* 1982; Hoffmann *et al.* 1978).



SCHEME 1

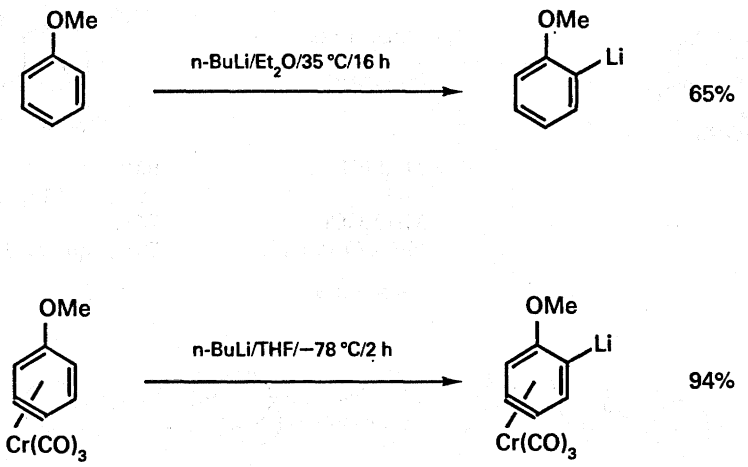


SCHEME 2

Although the overall process depicted in scheme 1 represents a valuable method for the arylation of carbon nucleophiles, the activation method is limited to a single resultant substitution step and is inefficient in its use of the chromium activator. It is the objective of the remainder of this paper to demonstrate the multiple and diverse use of the activator in sequential reactions that result in the synthesis of polyfunctional molecules and natural products.

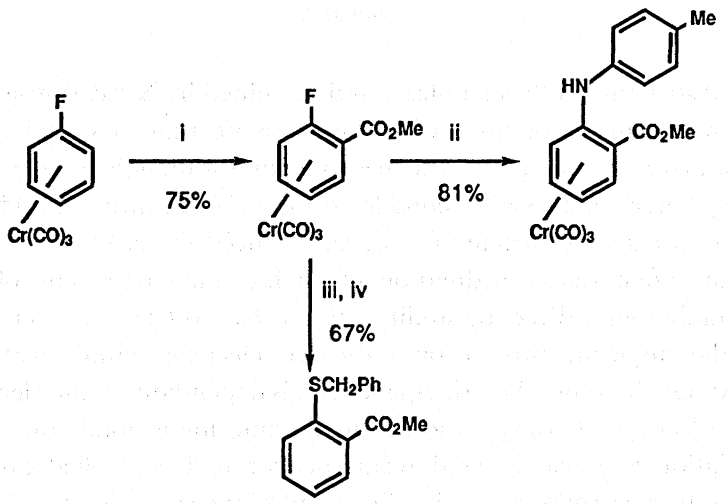
DISCUSSION

A qualitative estimate of the level of activation of a complexed ring to deprotonation is given by the comparison of the lithiation of anisole (*n*-BuLi/ether/36 °C/16 h/65%) (Finnegan & Altschuld 1967) and of its tricarbonylchromium complex (*n*-BuLi/THF/−78 °C/⩽2 h/94%) (Scheme 3) (Semmelhack *et al.* 1979).



SCHEME 3

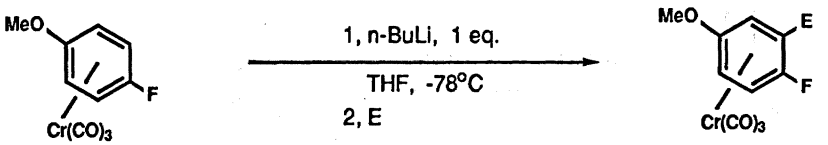
As expected, lithiation occurs *ortho* to the electronegative oxygen function. Similarly, fluorobenzene complex is readily lithiated (Semmelhack *et al.* 1979) under the same conditions to give a 2-lithio-species that is stable up to *ca.* −20 °C and that does not collapse to a benzyne complex. For this substrate, the additional reactivity exists of the chromium promoted nucleophilic substitution of the fluorine atom and a sequence of lithiation – electrophilic quench – nucleophilic substitution gives an overall general 1,2-disubstitution process with complete regiocontrol (scheme 4).



i, n-BuLi / MeO_2CCl; ii, 4-$MeC_6H_4NH_2$; iii, $PhCH_2SNa$; iv, $h\nu$ / air

SCHEME 4

In the uncomplexed arenes, the reported order of directing abilities of these two functions is OR > F (Wakefield 1974). It was surprising to find therefore that lithiation of 4-fluoroanisole complex gave substitution 98% or more adjacent to the fluorine atom (Gilday & Widdowson 1986*a*). None of the other isomer could be detected. In the one case where some disubstitution was observed (reaction with methyl iodide), both of the introduced groups were *ortho* to fluorine (scheme 5). The reason for this reversal of regiospecificity became apparent



E = Me_3SiCl	93%
MeI	72% (+15% 2,6-Di)
MeO_2CCl	75%
PhNCO (2 eq.)	72% (quinazoline)

SCHEME 5

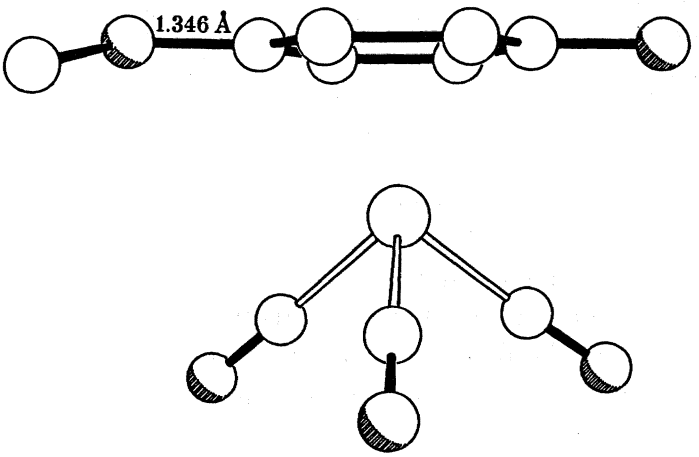


FIGURE 2

when the detailed structure of the complex was determined by X-ray diffraction (figure 2). The methoxy group was almost coplanar with the aromatic ring as would be expected for the conjugation of an oxygen lone pair with the arene and although the C—F bond length was normal for an aryl fluoride, the C—O bond length was significantly (0.2 Å†) shorter. It is clear therefore that the tricarbonylchromium unit has reduced the electron density on the oxygen atom to such an extent that coordination of an incoming base, one of the major factors normally determining *ortho*-directing ability (Jones *et al.* 1963), has been largely eliminated. Activation of the adjacent proton by inductive electron withdrawal, the other major determinant that now becomes the principal effect, is dependant on the electronegativity of the directing group (Jones *et al.* 1963), and in this the fluorine is dominant.

Directed lithiation is a widely used technique for regiocontrolled aromatic substitution (Gschwend & Rodriguez 1979) and this adjustment of the relative roles of the directing effects has important implications in synthesis. We sought therefore to assess the relative directing abilities of a number of standard directing groups when substituted in the rings of complexed arenes. Thus competitive lithiations were set up via 1,4-disubstituted arene complexes and the relative activating efficiencies of the substituents assessed by a lithiation (*s*-BuLi) – silation (Me_3SiCl) sequence. Two examples are given in scheme 6.

The fluorine group totally dominates a dimethylbenzylamine group even though in the uncomplexed analogue the reverse is true and the dimethylbenzylamine is dominant. This is an

† 1 Å = 10^{-10} m = 10^{-1} nm.

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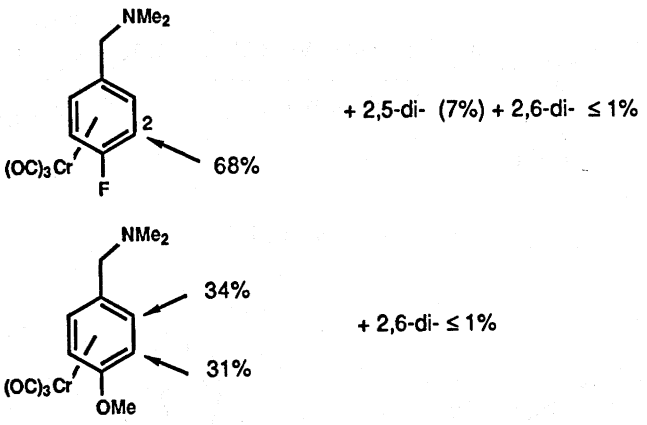

SCHEME 6

electronically isolated *ortho*-directing group, which should not be significantly affected by the presence of the metal. Therefore there must be more subtle activation processes at work than just the dimunition of the coordination effect proposed above. However, it is clear that directing abilities in complexes are dominated by inductive effects and coordination effects are less important. The order of directing abilities of our total list now becomes

$$F > NHCOBu^t > OMe \approx CH_2NMe_2 > CH_2OMe (> NR_2, SR)$$

compared with the reported sequence (Wakefield 1974) for uncomplexed arenes

$$CONHR > CONR_2 > NHCOBu^t > CH_2NMe_2 > OMe > F > NR_2 \approx SR.$$

The electron-withdrawing groups (typically $CONHBu^t$), which are *ortho* directing, generally render the ring so electron deficient that ring addition of the alkyllithium bases becomes the dominant process. Nevertheless, lithiation of a 2-fluoro-*N*-phenylbenzamide complex with LDA and chlorosilane quench gave silylation *ortho* to the fluorine atom (57%) as the only detectable substitution product (Gilday & Widdowson 1986*b*). The order of directing abilities can now be extended, albeit relating to somewhat different conditions, to

$$F > CONHPh.$$

It was shown above that fluorobenzene complex is a useful synthon for 1,2-disubstituted arene synthesis. A combination of the reactivities used there and the new order of directing abilities gives access to polyfunctional arenes with precise and varied regiocontrol dependant upon the sequence in which the different features are applied. Thus 3-fluoroanisole complex can be lithiated at C-2, quenched with chlorotrimethylsilane, lithiated again at C-4 and quenched with methyl iodide to give, in good yield (89%), and in a 'one-pot' process, a 1,2,3,4-tetrasubstituted benzene is the sole isomer (scheme 7) (Gilday & Widdowson 1986*b*).

Contiguous polyfunctional arrays like this are not easy to assemble by conventional synthesis yet this chemistry allows further easy elaboration (scheme 8).

Thus desilylation (tetrabutylammonium fluoride in THF) gives a 1,3,4-trisubstituted array, and nucleophilic displacement of the fluoro-group with pyrrolidine or benzylthiolate gives

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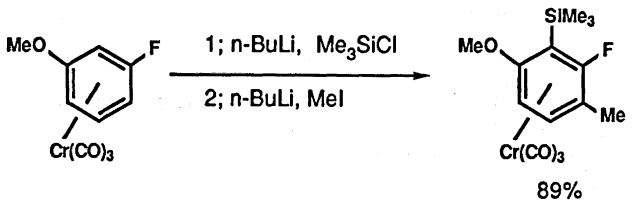
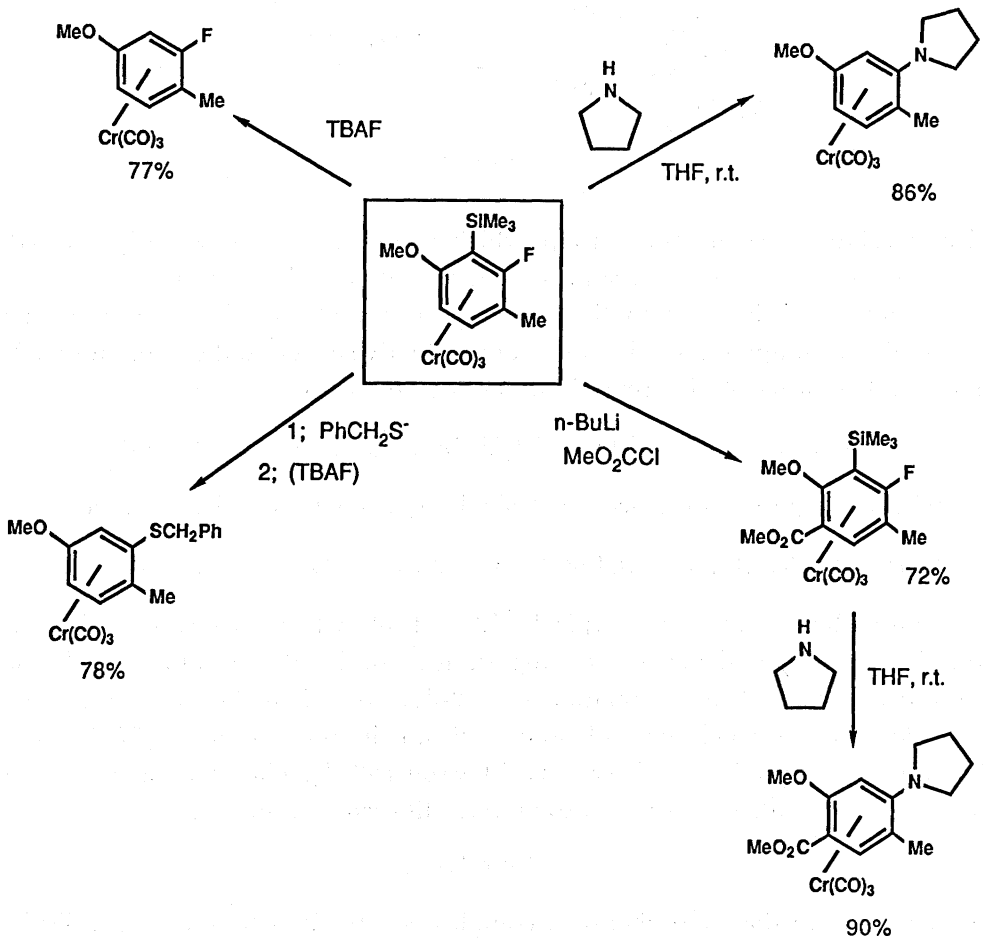


SCHEME 7



SCHEME 8

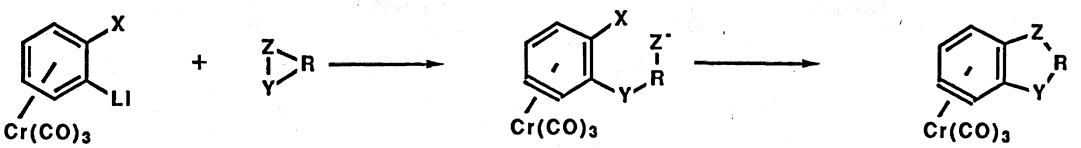
alternate 1,3,4-arrays by both substitution and desilylation (by the liberated fluoride ion). Further lithiation of the tetrasubstituted intermediate will now occur *ortho* to the methoxy group because the fluorine-directed sites are blocked, and an electrophilic quench (methyl chloroformate) produces a pentasubstituted benzene, isomerically pure, and in good yield (72%). Again, nucleophilic displacement of fluorine gives concommitant desilylation and in this case a specific 1,2,4,5-tetrasubstituted benzene results (90%).

This group of reactions, directed lithiation with electrophilic quench, nucleophilic displacement and silane blocking–fluoride deblocking, all with precisely controlled regiochemistries can be carried out in any order and present a powerful means for the synthesis of specific polysubstituted aromatics.

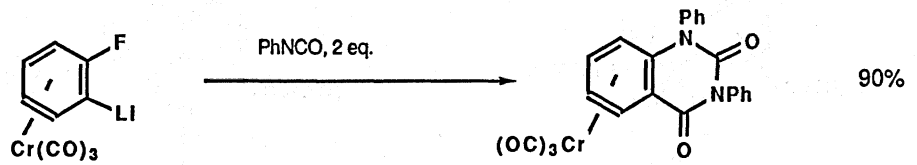
All the above reactions involved intermolecular attack of separate electrophiles and nucleophiles on the lithiated fluorobenzene complexes, yet it is possible to envisage the two reagents combined in a latent bifunctional species that will react in an intramolecular fashion with a 2-lithiofluorobenzene complex so as to form, *in situ*, a benzoannulated product (scheme 9).

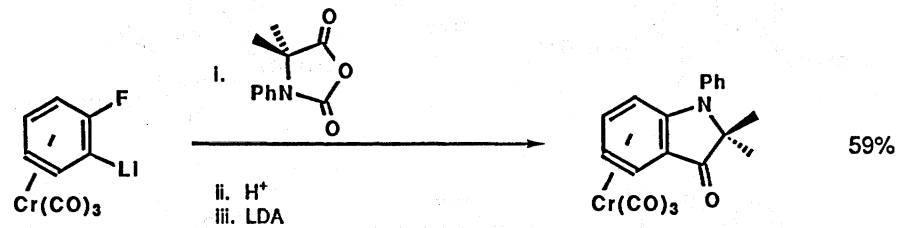
In practice there is a precedent for this process in the formation of benzoxepinone from 2-lithiofluorobenzene and butyrolactone (Semmelhack *et al.* 1979) but in general, enolisable carbonyl reagents are inefficient reactants which tend to proton quench the lithio-species. However, aprotic substrates such as isocyanates, non-enolizable *N*-carboxyanhydrides, azlactones and related compounds readily undergo the cycloannulation reaction (scheme 10) to produce, in high yield, the corresponding 1,3-diphenylquinoxaline and indoxyl complexes respectively (Ghavshou & Widdowson 1983).

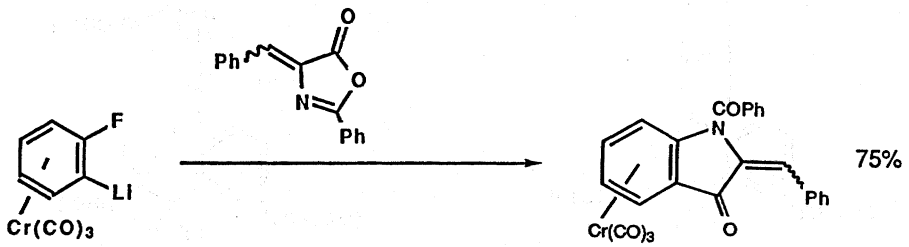
The 2-lithiofluorobenzene complex is chiral and the possibility existed that reaction with an enantiomerically pure substrate would result in a diastereoselective process. In the event, the fluorine atom is not large enough relative to hydrogen to bring about any differentiation and



SCHEME 9



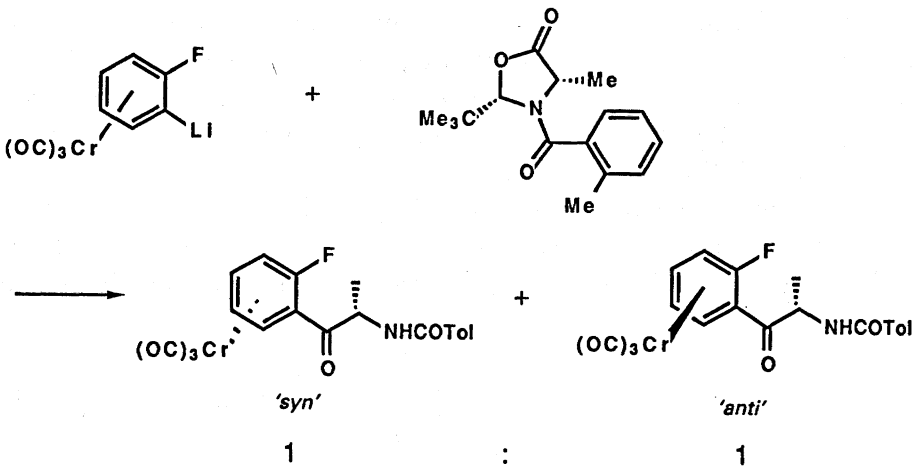




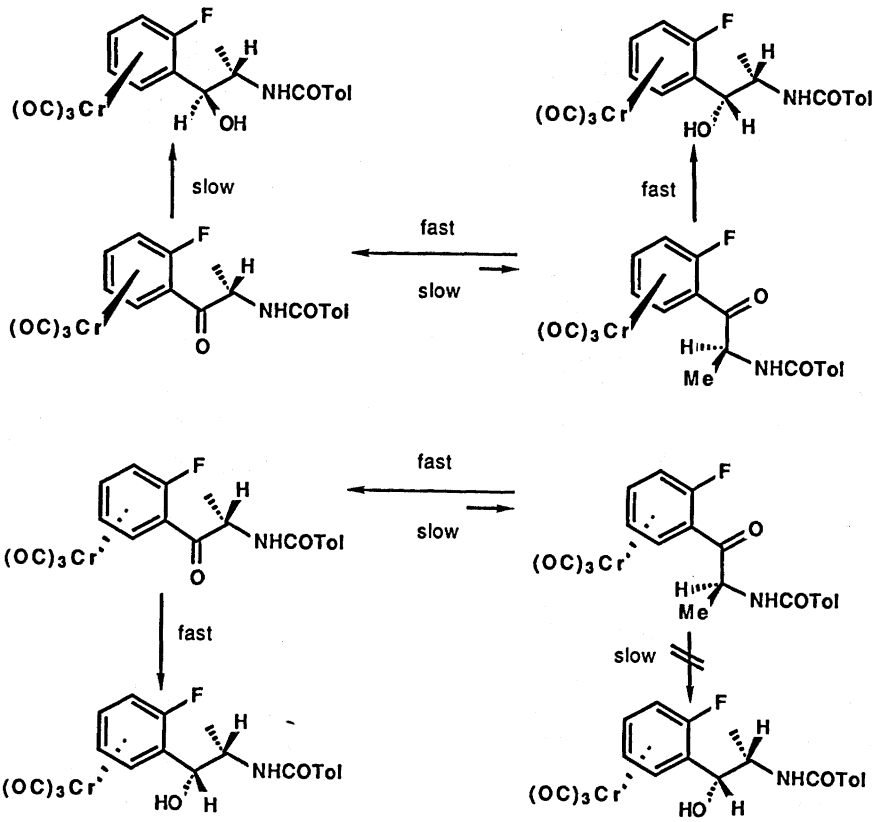
SCHEME 10

the boron trifluoride etherate catalysed reaction of the complex with the 2-*S*-4-*S*-oxazolidinone (Seebach & Fadel 1985) (scheme 11) under a variety of conditions, including the use of a large excess of the complex, always gave a 1:1 proportion of the diastereomers.

In contrast, potassium borohydride reduction of the diastereomers showed pronounced stereoselectivities (scheme 12) that result from conformational preferences dictated by the fluorine atom.



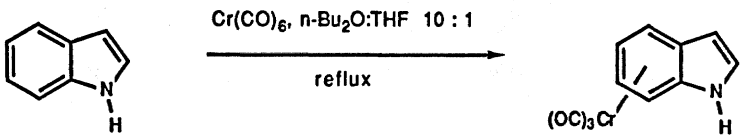
Scheme 11



Scheme 12

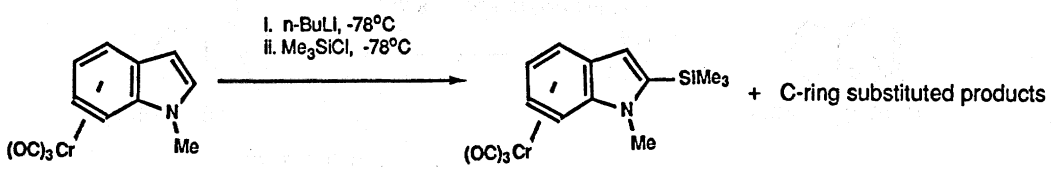
Indole has been known for many years to coordinate a tricarbonylchromium unit on the carbocyclic ring (Fischer *et al.* 1968) (scheme 13).

This raises the interesting possibility of using such complexes to directly substitute this ring at the normally inaccessible 4-, 5-, 6- or 7-positions and avoid the necessity for total ring synthesis. The indole complex itself is unstable and first studies were made on the *N*-methylindole complex. Lithiation under the usual conditions followed by chlorotrimethylsilane quench gave predominantly the 2-silylated complex (60%) (scheme 14) together with minor amounts of C-ring substituted products (Nechvatal & Widdowson 1982).



85%

SCHEME 13



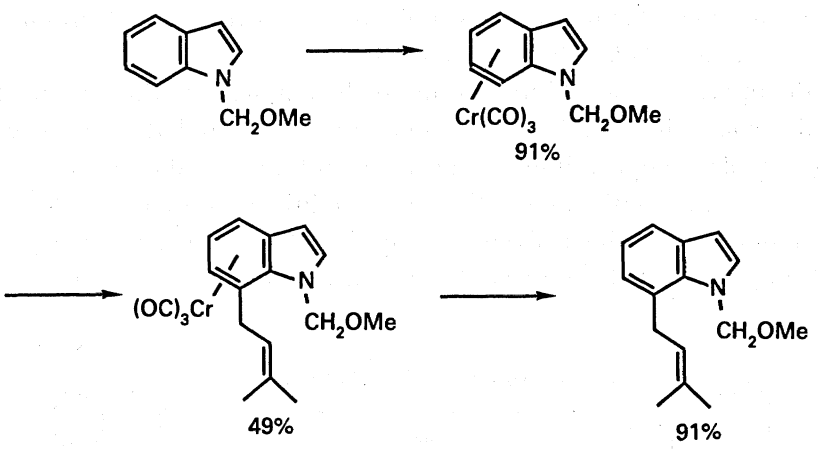
60% 15%

SCHEME 14

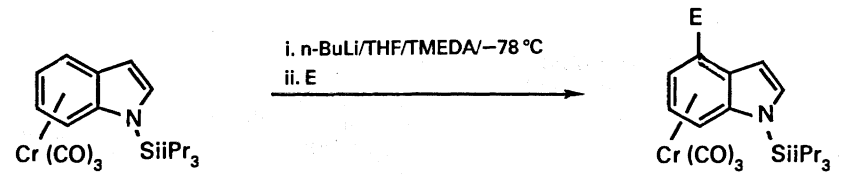
Further lithiation of the 2-trimethylsilylindole complex gave a 1:4 mixture of 4- and 7-substitution and in an attempt to maximize the regiocontrol, a directing ligand was incorporated into the *N*-protecting group. Thus lithiation of the 1-methoxymethylindole-complex followed by quenching with prenyl bromide gave a 49% isolated yield of the 7-substituted product, with no 4-substitution detectable. The overall process to 1-methoxymethyl-7-prenylindole was achieved in 41% yield (Nechvatal & Widdowson 1982) (scheme 15).

Because lithiation of the 1-methyl-2-trimethylsilylindole complex gave a mixture of 4- and 7-substitution, it was clear that if reaction at C-7 could be blocked, then 4-attack would become the major process. We resorted to the use of a lateral blocking group, for which purpose the triisopropylsilyl unit proved to be the most effective, and lithiation of the readily prepared 1-triisopropylsilylindole complex under the standard conditions followed by a chlorotrimethylsilane quench at −78 °C, gave the 4-trimethylsilyl-1-triisopropylsily indole complex in 53% isolated yield together with minor amounts (*ca.* 5%) of 5- and 6-substituted products (scheme 16). We have now produced a wide range of 4-substituted indoles by this method and a representative range is given in scheme 16. Our best estimate is that lithiation occurs at C-4 to an extent of 80% or more.

It was known from X-ray studies (Nechvatal & Widdowson 1982) that in the solid-state conformation, the N, C-4 and C-6 atoms are eclipsed by carbonyls and since C-5 may also be



SCHEME 15



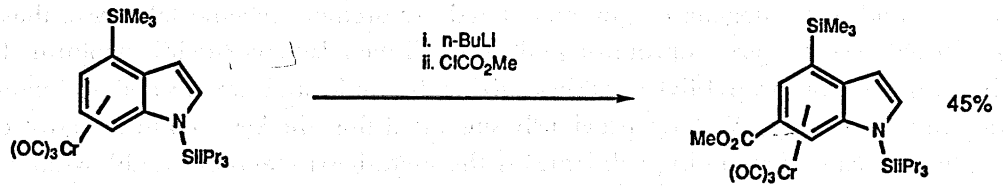
E	percentage pure	(percentage by nmr)
Me_3SiCl	53	(67)
$ClCO_2Et$	60	—
$ClCO_2Me$	59	—
PhCHO	—	(77)
$Me_2C{=}CHCH_2Br$	36	(72)

SCHEME 16

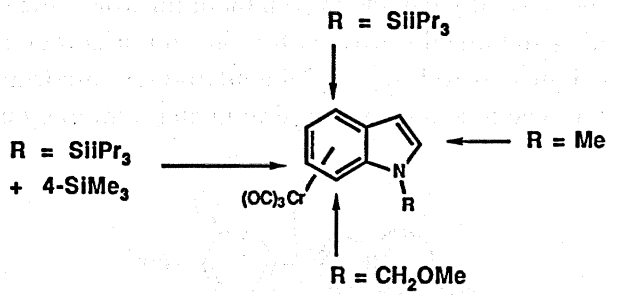
expected to be shielded, at least in part, by a non-ligating C-4 substituent, then further lithiation of a 1,4-disilylated indole complex would be expected to further lithiate at C-6. In the event, standard lithiation followed by a methyl chloroformate quench gave 45% yield of the 6-methoxycarbonyl-4-trimethylsilyl-1-triisopropylsilylindole complex together with some 1-desilated (and decomplexed) material (scheme 17).

In total, the controlled functionalization of the indole complexes, directed by the group located on N-1 is summarized in scheme 18.

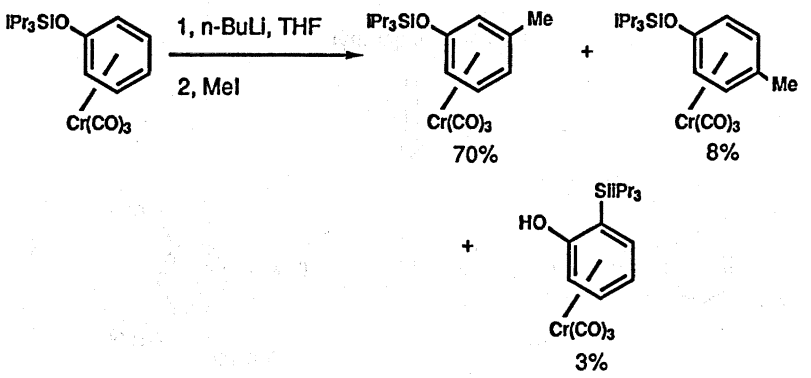
Having demonstrated the effectiveness of the triisopropylsilyl protecting group for lateral protection in the indole series, attention was turned to simple aromatics and the possibility of remote functionalization in what is normally an *ortho*-directing alkoxy systems. We considered that triisopropylsilylphenol complex would not lithiate at C-2 under kinetic conditions, and because the *meta* positions are the most electron-deficient centres, attack at these sites may be expected. Indeed, standard lithiation followed by a methyl iodide quench gave a 70% yield of the *meta*-methylated product together with 8% of *para* and 3% of the *ortho* (Masters & Widdowson 1983). In the latter case, the isolated material had undergone an intramolecular [1,3]-shift of silyl residue to give the 2-silylated phenol (scheme 19).



SCHEME 17



SCHEME 18



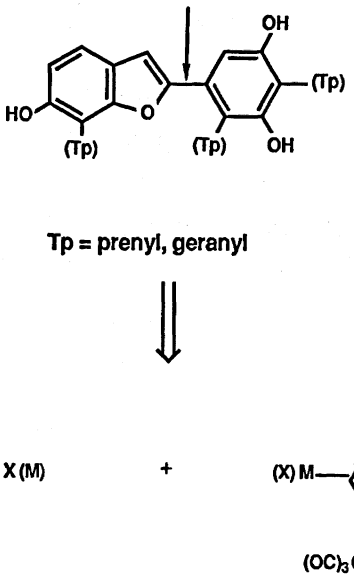
SCHEME 19

The overall process amounts to an electrophilic substitution in a phenol derivative directed *meta* to the oxygen function, a process not readily achieved by conventional means. In an extension of this, we found that the complex of *O*,*O*-bistriisopropylsilylresorcinol lithiated exclusively at C-5, and we sought to apply this regioselectivity to the synthesis of a suitable polyfunctional molecule.

Mulberry, *Morus alba*, produces a variety of phytoalexins in response to attack by certain fungi (Fukai *et al.* 1984). These compounds, the moracins and albafurans, have the basic skeleton depicted in scheme 20, the 5-(2-benzofuranyl)resorcinol system. The parent compound is moracin M, which is the 6-hydroxybenzfuranyl analogue. Other members of the series have terpenoid sidechains attached at C-2 or C-4 in the resorcinol ring or at C-5 or C-7 in the benzofuran ring system and a number of more highly functionalized analogues have been described (Fukai *et al.* 1984).

Most have not been synthesized (Binh *et al.* 1984) yet they present an ideal target for the chemistry that we have developed in this and other programmes. The crucial reaction in the synthesis would be a palladium catalysed coupling between a 2-metallated (or halogenated)

benzofuran and a 5-halogenated (or metallated) resorcinol (scheme 20) (Murahashi *et al.* 1979). Initial results were unpromising, 6-*t*-butyldiphenylsiloxy-2-iodobenzofuran failed to couple with bis(triisopropylsilyl)resorcin-5-ylzinc bromide and we needed to examine the reaction more precisely. We have previously suggested that the key step in the cross-coupling process for sterically demanding substrates is the metathesis reaction (Widdowson & Zhang 1986). The transition-state model proposed for this reaction, based on an S_E2 cyclic mechanism and shown in figure 3, requires that one aryl unit, derived from aryl halide (the left-hand ring in figure 3), be normally σ-bonded to palladium where the other (right-hand ring in figure 3) is approaching the metal centre with a face-on orientation. This means that the spatial accommodation of the two aryl rings is different and it is important to consider in which sequence to carry out the reaction to give a minimum steric interaction.



SCHEME 20

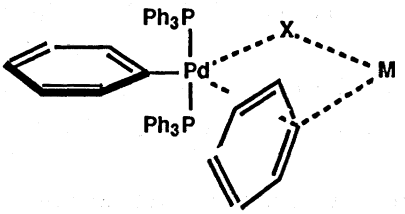
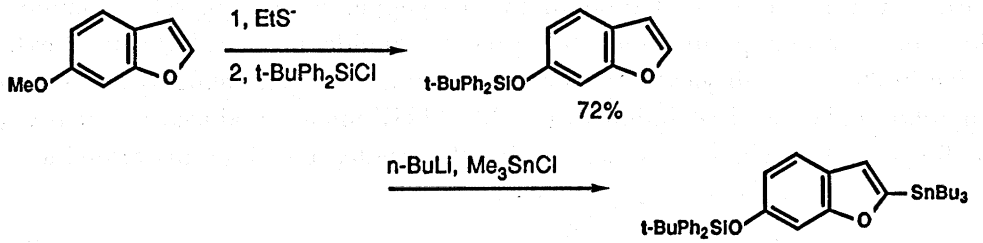


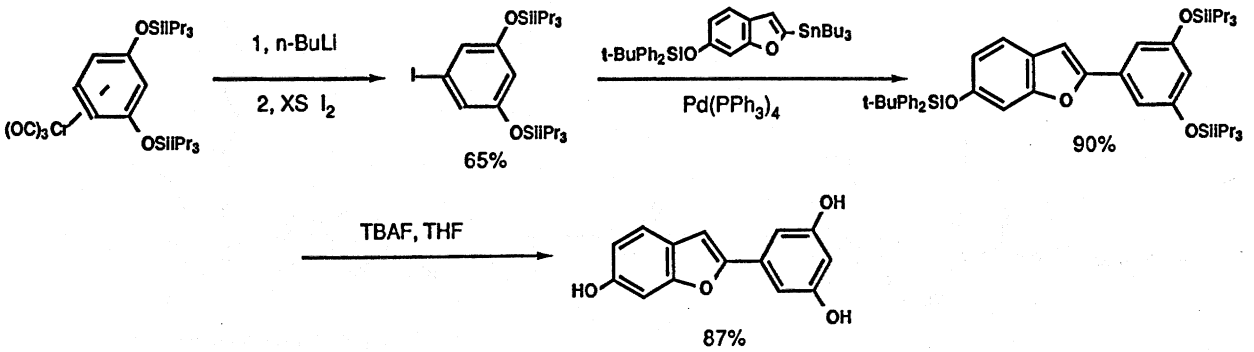
FIGURE 3

A computerized conformational analysis of the two sequences, iodobenzfuran/metallo-resorcinol or metallobenzfuran/iodoresorcinol, using CLASH, a simple spatial analysis based on Van der Waals radii and ignoring electronic effects, showed that for the tricarbonylchromium complexes, the latter sequence was much preferred. (This program was written by Dr G. Hermitage, ICI Plant Protection Division. He kindly ran the program for our putative transition states.) Consequently, we reversed our original unsuccessful approach to that shown in schemes 21 and 22 (Clough *et al.* 1987).



SCHEME 21

6-Methoxybenzfuran was demethylated with ethanethiolate ion and silylated with *t*-butyldiphenylsilyl chloride to give the silyl ether in 72% yield. Lithiation at −10 °C (*n*-BuLi/Et_2O) and a chlorotrimethylstannane quench gave the very labile 2-trimethylstannylbenzfuran in good yield, although because of its lability, the compound was not normally isolated but used immediately. For the other half, it was expedient to remove the chromium unit after iodination because our immediate target required no further functionalization. Thus resorcinol bistriisopropylsilylether complex was lithiated under standard conditions and the lithio-species quenched with an *excess* of iodine to give the 5-iodoresorcinol silyl ether (65%) (scheme 22). This was immediately coupled with a slight excess of the stannylated benzfuran using tetrakistriphenylphosphinepalladium(0) as catalyst to give a 90% yield of the coupled product. Deprotection (tetrabutylammonium fluoride in THF) then gave moracin M (87%) (Clough *et al.* 1987).



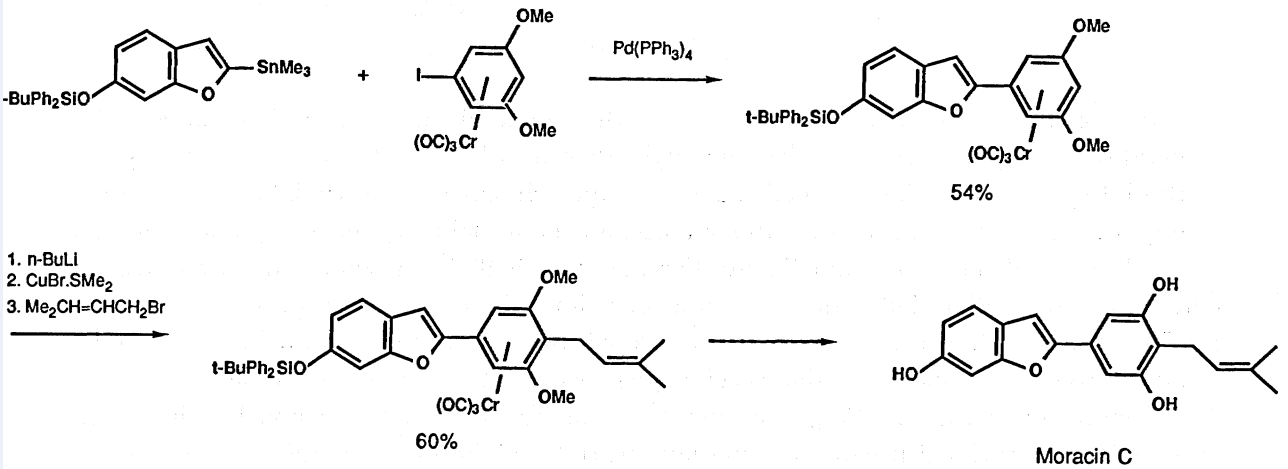
SCHEME 22

To demonstrate the versatility of the method, we wished also to retain the chromium unit through the coupling in order to facilitate prenylation or other functionalization. Accordingly, resorcinol bistriisopropylsilyl ether complex was lithiated as before and carefully quenched with one equivalent of iodine to give an 85% yield of the 5-iodoresorcinolbistriisopropylsilyl ether complex. It was soon apparent that even when run in the better sequence, the coupling was not efficient with both the bulky silyl ethers and the metal unit present (*ca.* 20% yield). Thus in a one-pot operation, the silyl ethers were removed (TBAF/THF) and the liberated phenols methylated (dimethyl sulphate) to give 5-iodoresorcinol dimethyl ether complex (80%). Coupling of this with the stannylated benzfuran (scheme 23) now gave the tricarbonylchromium complex of the 5-(2-benzfuranyl)resorcinol, as shown, in 54% yield.

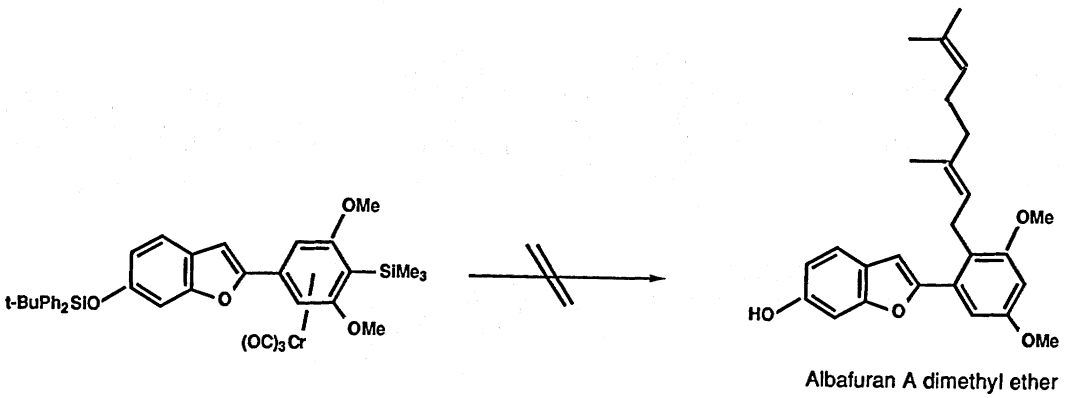
This molecule was now set up for unambiguous lithiation/substitution in the resorcinol ring.

Standard lithiation, transmetallation to the arylcopper with copper(I) bromide dimethyl sulphide complex and prenylation with prenyl bromide produced the 2-prenylresorcinol derivative in 60% overall yield, after decomplexation ($h\nu$/air). Demethylation with lithium dephenylphosphide and desilylation with TBAF/THF finally produced moracin C (50%).

One further phytoalexin was tackled by this route, the 4-geranylresorcinol analogue



SCHEME 23



SCHEME 24

albafuran A. The concept was simple. Lithiation of the resorcinol dimethylether complex as for moracin C synthesis and quenching with chlorotrimethylsilane would block and protect C-2 of the resorcinol ring and subsequent lithiation, transmetallation to the arylcopper and reaction with geranyl bromide would give the phytoalexin. In the event, a 67 % yield of geranyl substituted product was formed, but the side chain was located at C-3 of the benzfuran ring (scheme 24). In all subsequent studies, and in contrast to the fluorine directed substitutions described above, we have been unable to make a pentasubstituted resorcinol complex. If there are no alternative sites, then the lithiation of the tetrasubstituted benzene complexes used in this series does not occur at all.

The work described here has demonstrated that the attachment of a tricarbonylchromium unit to an arene ring confers novel reactivity on the arene such that new and precisely controlled regioselectivities in lithiation, both *ortho* and remotely directed, can be carried out with good efficiency and versatility. These selectivities give new insight into the nature of heteroatom directed lithiation, a process very widely used in general aromatic synthesis. The method allows rapid access to a variety of polyfunctionalized aromatics, such as occur in many natural products and bioactive molecules, which would not be readily synthesized by conventional means.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Discussion

B. T. Golding (*Department of Organic Chemistry, University of Newcastle upon Tyne, U.K.*). Has Dr Widdowson tried a chiral base for the deprotonation of fluorobenzenechromium-(tricarbonyl)?

D. A. Widdowson. The fact that the highly asymmetric oxazolone (see scheme 11) shows no discrimination between the two enatiomers of 2-lithiofluorobenzene complexes suggests that a chiral base would be equally inefficient, but we have not proved this yet. Fluorine is just too small to allow effective chiral discrimination. It is pertinent that the racemic 2-lithioanisole complex reacts with the oxazolone to produce a 3:1 diastereoselection from which it is evident that for the larger functionalities, asymmetric *ortho* deprotonation is a distinct possibility.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES