Regiocontrolled Lithiation of Arenetricarbonylchromium(0) Complexes: *meta*-Substitution of Phenols and Anilines

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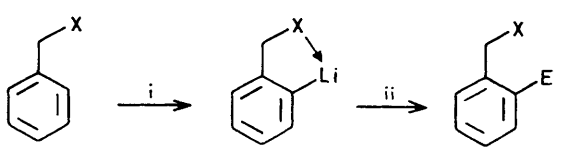
Tri-isopropylsilyl ethers of phenol- and aniline-tricarbonylchromium(0) complexes are lithiated predominantly *meta* to the heteroatom and subsequent reaction with suitable electrophiles produces overall *meta*-electrophilic substitution of phenols and anilines.

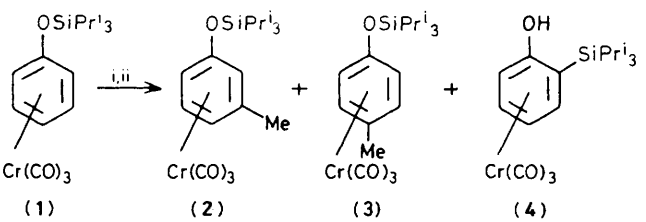
The development of chelation controlled lithiation of aromatic rings (as Scheme 1) has resulted in a wealth of new, regioselective syntheses of polysubstituted aromatic compounds.[1] Chelation control necessarily produces the usually less accessible *ortho* substitution product and this selectivity is one of the major strengths of the technique.

Recently we reported[2] lithiations of η^6-indoletricarbonylchromium(0) complexes in which lithiation was directed to a remote site by the use of bulky protecting groups (lateral protection). We now report the application of this principle to simple systems in a manner which allows overall electrophilic substitution *meta* to an oxygen or nitrogen function and thereby allows access to previously unattainable substitutions.

In order to achieve efficient lateral protection, we have previously demonstrated[2] the greater efficiency of the triisopropylsilyl group over the more commonly used t-butyldimethylsilyl analogue. Accordingly (η^6-tri-isopropylsiloxybenzene)tricarbonylchromium(0), (**1**)† (67% yield from phenol) was lithiated (Scheme 2) and the lithio-species quenched with methyl iodide to give mono-methylated products (78%) which consisted of the *m*- and *p*-methyl derivatives (**2**) and (**3**) in a ratio of 10:1 respectively (by n.m.r. analysis). In addition a small quantity (3%) of *o*-tri-isopropylsilylphenol was formed, presumably by silicon transfer to an *ortho*-lithiated intermediate. In a comparable experiment, the t-butyldimethylsilyl analogue gave only 40% of the *m*-methylated product. Independently of us, 40% of this product



Scheme 1. i, RLi; ii, E^+.



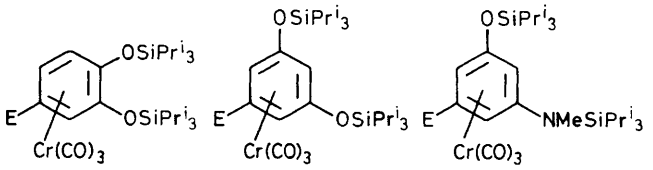
Scheme 2. i, Bu^{t}Li (2 equiv.), tetrahydrofuran, −78 °C, 1.5 h; ii, MeI.

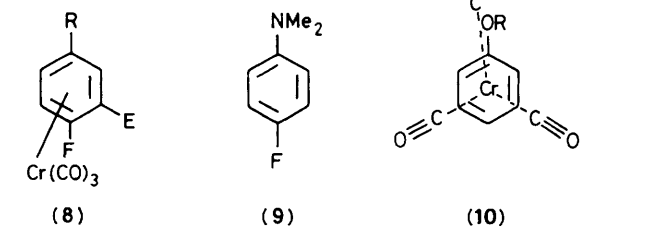
† All new compounds have been fully characterised by elemental and spectral analysis.

Table 1. Lithiation of arenetricarbonylchromium(0) complexes.

Entry no.	Substrate	Base[a]	Electrophile	Product	Yield[b] (%)
1	(5), E = H	Bu^nLi	MeI	(5), E = Me	71
2	"	LDA	"	"	77
3	"	Bu^nLi	Me_3SiCl	(5), E = $SiMe_3$	87
4	"	"	MeO_2CCl[c]	(5), E = CO_2Me	83
5	(6), E = H	"	MeI	(6), E = Me	74
6	"	LDA	"	"	77
7	"	Bu^nLi	Me_3SiCl	(6), E = $SiMe_3$	67
8	"	"	MeO_2CCl[c]	(6), E = CO_2Me	80
9	(7), E = H	Bu^nLi[d,e]	MeI	(7), E = Me	85
10	"	LDA[d]	"	"	80
11	"	Bu^nLi[d,e]	Me_3SiCl	(7), E = $SiMe_3$	85
12	(8), E = H, R = $NMeSiPr^i_3$	"	MeI	(8), E = Me, R = $NMeSiPr^i_3$	90
13	"	"	Me_3SiCl	(8), E = $SiMe_3$, R = $NMeSiPr^i_3$	83
14	"	"	MeO_2CCl[f]	(8), E = CO_2Me, R = $NMeSiPr^i_3$	83
15	(8), E = H, R = $OSiPr^i_3$	Bu^nLi	MeI	(8), E = Me, R = $OSiPr^i_3$	65
16	"	"	MeO_2CCl[c]	(8), E = CO_2Me, R = $OSiPr^i_3$	74

[a] 2 Equiv. used, reaction conditions: 1.5 h, −78 °C. [b] Isolated after column chromatography. [c] Quenched at −78 °C. [d] Reaction conditions: 2 h, −60 °C. [e] 1 Equiv. *N,N,N′,N′*-tetramethylethylenediamine added. [f] Quenched at −60 °C.





together with 35% of the *o*-silylated analogue of (**4**) has recently been recorded.[3] Other bases [lithium di-isopropylamide (LDA), Bu^nLi, lithium 2,2,6,6-tetramethylpiperidide (LTMP)] gave similar product distributions from (**1**) in yields of 53% (LTMP) to 77% (LDA). In a control experiment, the uncomplexed tri-isopropylsilyl ether was allowed to react with n-butyl-lithium in diethyl ether at room temperature for 24 h and the resulting solution quenched with methyl iodide. After 1 h, work up gave only starting materials.

The lithiation reaction has been extended to other phenols and the results are given in Table 1. In each case, lithiation occurred in high yield at a position *meta* to oxygen or nitrogen. This contrasts with lithiation of the unhindered, uncomplexed species which invariably lithiate at a site adjacent to the heteroatom.[1]

Of particular note is the lithiation of the resorcinol and *m*-aminophenol derivatives (**6**) and (**7**) (Entries 5—11) which are electrophilically substituted exclusively in the 5-position. The only other direct access to such substitution is by nucleophilic addition to the analogous methyl ether complexes.[4] Lithiation adjacent to fluorine in the *p*-fluoroaniline complex (**8**, R = $NMeSiPr^i_3$, E = H) (Entries 12—14) again contrasts with the reaction of the unprotected uncomplexed material (**9**) which lithiates predominantly *ortho* to the nitrogen function. The analogous phenol complex (**8**, R = $OSiPr^i_3$, E = H) similarly lithiates exclusively *ortho* to fluorine (Entries 15, 16). Since fluorine is readily displaced by a range of nucleophiles,[5] these complexes allow a complete reversal of normal reactivity with *m*-electrophilic and *p*-nucleophilic substitution in the phenol and aniline series.

The origin of the regioselectivity is not known with certainty but would accord with an extension of current theories of electrophilic and nucleophilic additions to such complexes.[6] Thus the conformation of the tricarbonylchromium moiety, normally eclipsed [as (**10**)] for ether complexes[4,6] correlates with an electron deficiency at the eclipsed ring carbon atoms, which in turn promotes either nucleophilic attack or deprotonation at these centres, depending on the reagent used. Chelation of the lithium base by carbonyl oxygen has also been suggested.[7] The normally dominant inductive labilisation of the *ortho*-protons[1,8] would be effectively negated in these kinetic deprotonations by the bulk of the protecting group.

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