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Reversible addition of carbon nucleophiles to some nitrogen-substituted η^6-arenetricarbonylchromium(0) compounds

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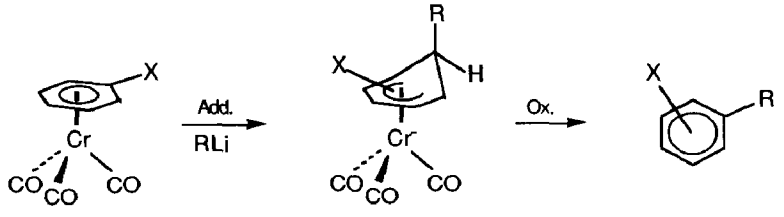
Abstract

A study has been made of the nucleophilic addition/oxidation reactions of η^6-1-methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium(0) (**1**), η^6-1-methylindolinetricarbonylchromium(0) (**2**), and η^6-2-*N*,*N*-dimethylaminotoluenetricarbonylchromium(0) (**3**) with the nucleophiles 2-lithio-2-methyl-propionitrile (**A**), 2-lithioacetonitrile (**B**) and 2-lithio-2-methyl-1,3-dithiane (**C**). The regioselectivity in the addition of stabilized nucleophiles is time- and temperature-dependent, indicating the onset of thermodynamic control in prolonged/high temperature reactions. The addition is reversible, as indicated by crossover experiments with benzene-$Cr(CO)_3$, the rate for dissociation of the C–C bond being strongly dependent on both the structure of the intermediate η^5-cyclohexadienyltricarbonylchromium anions as well as the structure of the nucleophile. The regioselectivity of the addition/oxidation reaction can be optimized by an appropriate choice of reaction conditions for each of the compounds **1**, **2** and **3**.

The addition of carbon nucleophiles to η^6-arenetricarbonylchromium(0) compounds and subsequent oxidation has become a useful method for introducing substituents in positions not accessible by electrophilic substitution [1,2].



However, initial observations by us and by others point to a rather complex reaction mechanism for addition of carbon nucleophiles to arenetricarbonylchromium substrates. The formation of the intermediate anion can be reversible, and thus the possibility of competition between kinetic and thermodynamic control

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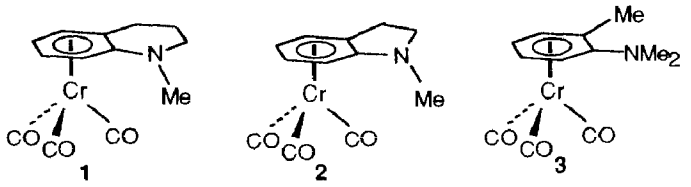
arises [3,4]. If the factors controlling the reaction can be revealed and controlled, the choice between kinetic and thermodynamic control could open up new synthetic possibilities and allow better prediction of the regioselectivity.

In order to explore this idea we have treated three related nitrogen-substituted arenetricarbonylchromium compounds with three different carbon nucleophiles. The chromium compounds studied were η^6-1-methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium(0) (**1**), η^6-1-methylindolinetricarbonylchromium(0) (**2**), and η^6-2-*N*,*N*-dimethylaminotoluenetricarbonylchromium(0) (**3**).



The nucleophiles 2-lithio-2-methylpropionitrile (**A**), and 2-lithioacetonitrile (**B**), have similar reactivities but different steric requirements, while 2-lithio-2-methyl-1,3-dithiane (**C**) is a more reactive nucleophile [2,5]. In this investigation we have tried to evaluate the various factors that control the substitution pattern in the products, and have compared our experimental results with data from EHT calculations.

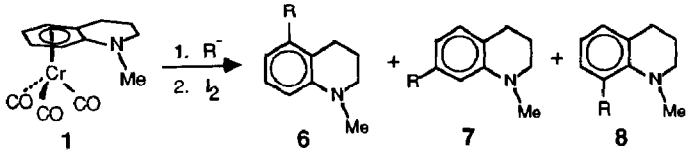
Reactions and results

The chromium complexes **1**, **2**, and **3** were prepared from the corresponding arene and hexacarbonylchromium according to standard procedures [6]. Complexes **1** and **2** were also prepared by methylation of η^6-1,2,3,4-tetrahydroquinolinetricarbonylchromium(0) (**4**), and η^6-indolinetricarbonylchromium(0) (**5**), obtained from $Cr(CO)_6$ and tetrahydroquinoline or indoline, respectively.

The reactions of complexes **1**, **2** and **3** with the nucleophiles 2-lithio-2-methylpropionitrile (**A**), 2-lithioacetonitrile (**B**), and 2-lithio-2-methyl-1,3-dithiane (**C**), were performed in THF under an inert atmosphere. After addition of the arene-$Cr(CO)_3$ complex to a solution of the nucleophile at $-78\,^\circ C$ the mixture was left to stir. In some of the reactions the temperature was raised and maintained for a defined period before being lowered to $-78\,^\circ C$. The intermediate η^5-cyclohexadienyl-$Cr(CO)_3$ anions were then oxidized with an excess of iodine. The temperature of all solutions was carefully monitored before the additions. With the temperature of the cooling baths being $-78\,^\circ C$ the temperature of the reacting solutions were $-70\,^\circ C$. The crude product mixtures were analysed by GC-MS, and the relative ratios of regioisomeric products determined from the RIC (reduced ion current) signal. The results are summarized in Table 1, in which the combined yield refers to isolated yields of mixtures of the regioisomers after flash chromatography. The reactions and the regioisomeric products obtained are summarized in Schemes 1–3.

As can be seen from Table 1, compounds **1**, **2**, and **3** react with 2-lithio-2-methylpropionitrile (**A**) to give high yields of substituted arenes, **6A–14A**, after oxidation. Three regioisomeric products are obtained from each arene-$Cr(CO)_3$ compound, in relative amounts that were found to be time- and temperature-dependent in some cases. Very high regioselectivities are obtained in the reaction between **1** or **3** with **A** for prolonged reaction times at higher temperatures, whereas the best regioselectiv-

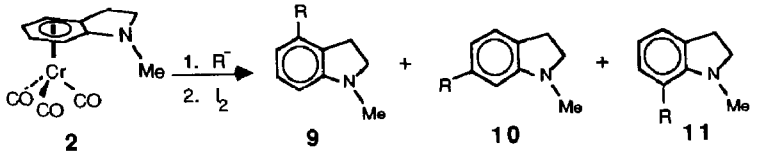
ity in the reaction between **2** and **A** is obtained at low temperature with short reaction times.



1 6 7 8

A: R = $C(CH_3)_2CN$
B: R = CH_2CN

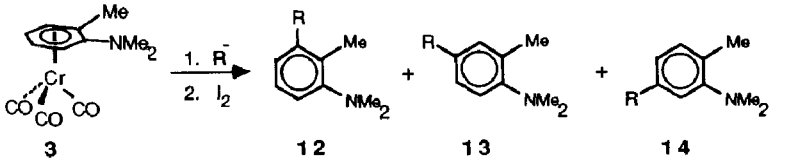
Scheme 1



2 9 10 11

A: R = $C(CH_3)_2CN$
C: R = 2-methyl-1,3-dithianyl

Scheme 2



3 12 13 14

A: R = $C(CH_3)_2CN$
B: R = CH_2CN
C: R = 2-methyl-1,3-dithianyl

Scheme 3

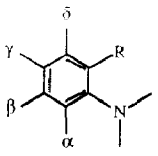
The major isomer obtained from **1**, i.e. product **7A** (97%), is formed by attack at the β position relative to nitrogen, while the major products **9A** (78%) and **13A** (80%) formed from **2** and **3** are the result of addition at the δ and γ positions, respectively.

With nucleophiles **B** and **C**, the addition/oxidation reaction was not quantitative, as unreacted starting materials were always recovered. Some of the 1-methylindoline was oxidized to 1-methylindole, and Table 1 shows the combined yields. The reactions with **B** and **C** show high selectivity for addition to the δ position. The relative ratios of regioisomeric products from **B** were not strongly influenced by the reaction time or temperature. With nucleophile **C** and **2** or **3** no changes in relative ratios of regioisomers were observed irrespective of time or temperature. In the reaction between **1** and **C** a major part of the starting material was recovered as 1-methyl-1,2,3,4-tetrahydroquinoline.

The effect of added ligands was studied in a series of experiments in which **1** was treated with **A** in the presence of 4 equivalents of HMPA for various times. The relative ratio of isomeric products remained constant and was observed to be 1/55/44 (α, β, δ). In another set of experiments, equimolar amounts of **1** and **A**

Table 1

Relative ratios of products from nucleophilic addition/oxidation of *N*-methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium(0) (**1**), *N*-methylindolinetricarbonylchromium(0) (**2**), and 2-*N*,*N*-dimethylaminotoluenetricarbonylchromium(0) (**3**), Nucleophiles: 2-lithio-2-methylpropionitrile (**A**), 2-lithioacetonitrile (**B**), and 2-lithio-2-methyl-1,3-dithiane (**C**). Relative ratios were obtained by GC-MS analyses. The regioisomeric products are shown in order of elution from the capillary GC column. Combined isolated yields are those after flash chromatography of crude product mixtures. α, β, γ, δ refer to positions on the arene ring relative to nitrogen



Cr-complex	Nu	React. temperature (°C) [c]	Reaction time	Relative yield of isomers				Combined yield (%)	Recovered starting material (%)
				α	β	γ	δ		
1	**A**	−78	1 min	1	64	–	35		
1	**A**	−78	2 min	1	66	–	33	82	9
1	**A**	−78	6 min	0	73	–	27		
1	**A**	−78	10 min	1	81	–	18	71	20 [d]
1	**A**	−78	2 h	0	84	–	16	71	26 [d]
1	**A**	−78	8.6 h	1	97	–	2		
1	**A**	+20	44 h	3	93	–	4	96	
1	**A**	−78	2 min	1	55	–	44 [a]		
1	**A**	−78	15 min	2	54	–	44 [a]		
1	**A**	−78	22 h	2	54	–	44 [a]		
1	**B**	−78	22 h	0	18	–	82	17	65
2	**A**	−78	24 h	3	19	–	78	77	10 [b]
2	**A**	−20	24 h	4	37	–	59	58	42 [b]
2	**A**	−21	144 h	19	29	–	52	79	20 [b]
2	**A**	+22	3 h	5	39	–	56	26	45 [b]
2	**C**	−78	2 h	4	0	–	96	69	
3	**A**	−78	2.5 h	–	32	32	36	79	
3	**A**	−78	24 h	–	30	40	30	100	
3	**A**	−50	24 h	–	8	81	11	85	
3	**A**	−20	24 h	–	12	78	10	100	
3	**B**	−78	24 h	–	9	1	90	51	2
3	**B**	−40	24 h	–	3	4	93	46	21
3	**C**	−78	4 h	–	25	10	65	56	
3	**C**	−30	2.5 h	–	25	10	65	51	

[a] In the presence of 4 eq. of HMPA. [b] 1-Methylindole. [c] Temperature of the cooling bath. [c] Temperature of the cooling bath. [d] Quench time 15 min.

were allowed to react in THF at −78°C for 30 min and 1 equivalent of benzenetricarbonylchromium(0), (**15**), was then added. The mixture was stirred at −40°C for 3 h before oxidation with I_2. The substituted benzene product, 2-methyl-2-phenylpropionitrile was isolated in 56% yield, together with 1-methyl-1,2,3,4-tetrahydroquinoline, 84%.

Structure determination

The mixtures of regioisomeric products obtained after flash chromatography of the crude product mixtures were exposed to repeated medium pressure liquid chromatography or preparative thin layer chromatography to achieve separation of isomers.

The substitution pattern for the three isomers obtained from the reaction between **1** and **A** was determined from the ^1H and ^{13}C NMR spectra (see the Experimental part). The patterns of proton coupling for two of the isomers indicate substitution α or δ to nitrogen, while the proton coupling of the third isomer is consistent with substitution β or γ to nitrogen.

The proton chemical shifts were used for a preliminary differentiation between α versus δ or β versus γ substitution, but the final assignment was based on the ^{13}C NMR spectra. The chemical shifts for the aromatic ring carbons for the three isomers were compared with calculated ^{13}C NMR chemical shifts for the four possible isomers obtained based on the chemical shifts for 1-methyl-1,2,3,4-tetrahydroquinoline and substituent chemical shifts (SCS) for the 2-cyano-2-propyl substituent [7]. The shifts for 1-methyltetrahydroquinoline were assigned by comparison with the published spectrum for 1,2,3,4-tetrahydroquinoline [8]. The major product was thus found to be the 7-substituted isomer (**7A**), resulting from addition at the β position relative to nitrogen, and the second major product was assigned structure **6A** formed by addition at the position δ relative to nitrogen. Further support for stucture **8A** for the minor isomer was provided by the observation that the signals from the *N*-methyl group were shifted 0.10–0.15 ppm upfield relative to those for the 5- and 7-substituted isomers or 1-methyltetrahydroquinoline itself, owing to steric interference between the *N*-methyl group and the substituent in the 8-position.

The substitution patterns for the products obtained from reactions of **2** or **3** with **A**, and **1** or **3** with **B**, were assigned on the basis of their ^1H and ^{13}C NMR spectra and comparison with structures **6A**, **7A** and **8A**.

The ^1H NMR spectra for the two isomers obtained from the reaction between **2** and **C** correspond to substitution in the α and δ position. The major isomer was assigned the structure **11C** (δ substitution) by analogy with the main product obtained from the reaction between **2** and 2-lithio-1,3-dithiane [9]. The substitution patterns for the three isomers obtained from **3** and **C** were tentatively assigned on the basis of ^1H NMR chemical shifts and coupling patterns.

The reaction between **2** and **A** has been erroneously reported to give the 4- and 7-substituted products **9A** and **11A** in relative ratio 75/25 [9]. Comparison of ^1H NMR spectra shows that the correct assignment should be the 4- and 6-substituted isomers **9A** and **10A**.

Calculations

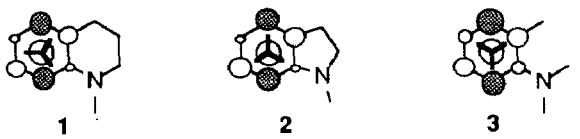
Experimental results from the kinetically controlled additions of carbon nucleophiles to arenetricarbonylchromium compounds have been correlated to calculated properties of the compounds. Thus the coefficients of the lowest arene-centred unoccupied orbital of the Cr compound may determine the site of attack [9,10]. On the other hand the site of attack may be determined by electronic effects

or the conformation adopted by the $Cr(CO)_3$ unit [11], both of these affecting the charge distribution within the compound. The effects of a donor substituent and the $Cr(CO)_3$ conformation may operate in concert.

To be able to discuss our results in these terms we have carried out some Extended Hückel (EHT) calculations on the three arenetricarbonylchromium compounds **1**, **2** and **3**. Fully optimized geometries were not calculated; instead we started with molecular mechanics calculations (Allinger's MMPI) on the parent arene and then added the $Cr(CO)_3$ unit in four different orientations, as shown, with the Cr–CO bonds either eclipsing the ring carbons, **16** and **18**, or bisecting the C–C bonds, **17** and **19**.

16 **17** **18** **19**

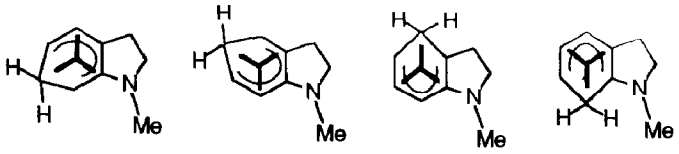
The total energies of the different conformations show some small variations, depending on the orientation of the $Cr(CO)_3$ unit, e.g. conformers **16** and **17** have the lowest energy for **1**, but conformer **16** for **2**. The energy differences between the conformers of **3** are slightly larger, with a minimum for **18**. The coefficients for the arene-centred LUMOs are shown below for the low-energy conformations.



1 **2** **3**

The LUMO coefficients are largest in the α and γ positions relative to nitrogen, and slightly smaller for the β position in **1** and **2**, indicating that *ortho* and *meta* substitution relative to nitrogen should be favoured in a frontier orbital controlled reaction. In **3** the nodal properties of the arene-centred LUMO are different, and the coefficient at the γ position is only slightly smaller than that at the β carbon. This is a consequence of the orientation of the dimethylamino substituent in **3** relative to that of the *N*-methyl groups in **1** or **2**. According to the MMPI calculations for the parent arenes, the nitrogen lone pair electrons in **1** and **2** are oriented parallel to the arene π-orbitals to allow maximum overlap whereas the nitrogen lone pair in **3** is orthogonal to the arene π-system, pointing towards the neighbouring methyl group. The geometries obtained for the arenes were used for the EHT calculations for the Cr compounds after comparison with available data on the structures of arene-$Cr(CO)_3$ compounds [12].

In the case of thermodynamic control of the product distribution the relative ratio of regioisomers should reflect the relative stabilities of the intermediate cyclohexadienyltricarbonylchromium anions. In order to correlate the observed regioselectivity with the relative stabilities of the anion intermediates, EHT calculations were performed on a model system. Hydride ion was used as the nucleophile adding to the four positions on arene$Cr(CO)_3$ (**2**) and the conformation of the $Cr(CO)_3$ unit was varied. Comparison of the four possible intermediate anions indicates the following order of increasing one-electron energies including repulsion: attack at 6-position < 5-position < 4-position < 7-position.



For each intermediate anion a minimum for the total energy is obtained for a conformation in which the $Cr(CO)_3$ unit is eclipsing three ring carbons, one of the carbons being the sp^3 carbon carrying the nucleophile (see above). The energy difference between the most and the least favoured conformation was 34 kJ/mol, indicating a definite barrier to rotation of the $Cr(CO)_3$ unit.

Discussion

Reversibility

As reported previously the addition of nucleophile **A** to **1** is a fast reaction, and is complete within one or two minutes at −78° C. The change in the relative ratios of regioisomeric products **6**, **7** and **8** from 35/64/1 after 1 minute to 2/97/1 after a few hours has been interpreted as reflecting a change in relative ratios of regioisomeric η^5-cyclohexadienyltricarbonylchromium anion intermediates [3]. The ratio during the first few minutes is assumed to reflect fairly closely the outcome of kinetic control of the nucleophilic addition to **1**, while the change in relative ratio of **6**, **7** and **8** indicates the onset of thermodynamic control. After prolonged reaction times an equilibrium is reached, the 7-substituted isomer **7** then being strongly favoured.

The reactions between **A** and **2** or **3** show similar variations in relative ratios of regioisomeric products, indicating equilibration of intermediate anions, but at substantially lower rates, as seen from Table 1. Upon addition of **A** to **2** the ratio of the product substituted β to nitrogen is again increased on equilibration, while the γ-substituted product is favoured at equilibrium for the addition of **A** to **3**.

Equilibration of cyclohexadienyl $Cr(CO)_3$ anion intermediates has been suggested previously [13] and also demonstrated in a few cases. There is some precedent in the nucleophilic addition to η^6-chlorobenzenetricarbonylchromium, for which the product distribution depends on the reaction time, ultimately leading to substitution of chlorine [14]. Kündig et al. have reported a similar observation of equilibration of intermediate anions from the addition of nitrile-stabilized anions to η^6-1,4-dimethoxynaphthalenetricarbonylchromium [4].

The mechanism for the equilibration of intermediate anions has been discussed by us [3] and by Kündig [4,5]. An equilibrium may be reached via an intramolecular rearrangement of the intermediate anions or via an intermolecular process, involving reversibility of the nucleophilic addition to the arene-$Cr(CO)_3$.

$$\text{AreneCr(CO)}_3 + \text{Nu}^- \rightleftharpoons \text{Intermediates} \xrightarrow{\text{ox.}} \text{Arene-Nu}$$

As seen from Table 1 the presence of HMPA during the reaction between **1** and **A** reduces the rate of equilibration of intermediate anions to a point at which it cannot be observed at −78° C. We assume that the relative ratios of isomeric products obtained, 44/55/1, closely reflects the kinetically-controlled formation of regioisomeric intermediate anions .

A few studies of the structure of α-nitrile "carbanions" have been reported. 2-Lithio-2-phenylacetonitrile has been found to adopt a dimeric structure in THF at 18.5°C [15]. In the solid state its TMEDA complex is a dimer, with two lithium atoms bridging the two nitrogen atoms of the nitrile groups [16]. 2-Lithio-2-methylpropionitrile in THF can be assumed to adopt a similar dimeric structure in which Li atoms are bonded to nitrogen. The effect exerted by HMPA can be understood in terms of complexation to lithium to leave a high-energy "naked" isobutyronitrile anion. Solvation of lithium would not be expected to exert a large influence on an intramolecular rearrangement process, but in a reversible process, the dissociation of the C–C bond leading to the regeneration of the nucleophile, would be less favourable in the presence of HMPA. An analogous observation was made by Kündig, who reported a 300-fold decrease in the rate of equilibration in the reaction of 1,4-dimethoxynaphthalene-$Cr(CO)_3$ upon addition of HMPA [5].

Further support for the reversibiltiy of the nucleophilic addition is obtained from the crossover experiment in which benzene-$Cr(CO)_3$ (**15**) was added to the mixture of intermediate anions obtained from addition of **A** to **1**. The complete transfer of the substituent 1-cyano-1-methylethyl to benzene with regeneration of 1-methyltetrahydroquinoline (89% recovered), is consistent with the dissociation of the C–C bond to generate a low but constant concentration of **A**, which then reacts with benzene-$Cr(CO)_3$, as in Scheme 4. Similar crossover experiments involving addition of benzene-$Cr(CO)_3$ (**15**), to the mixture from reactions of **3** with **A** led to incomplete transfer of the nucleophile to the benzene ring.

Kinetic control

The coefficients calculated for the lowest unoccupied arene-centred orbitals for **1**, **2** and **3** suggest that the nucleophilic addition should preferentially occur at the positions α and δ relative to nitrogen, these having the largest coefficients.

The electronic effect of the nitrogen substituent in the arene-$Cr(CO)_3$ compounds **1**, **2** and **3** would be expected to induce a charge distribution in the ground state that leaves a net positive charge on the carbons *meta* to the nitrogen. Thus in a reaction under charge control the products from addition at β and δ would be expected.

Both models predict addition at the δ position, but differ for the other positions. As seen from Table 1, the small nucleophile **B** preferentially attacks the δ position. The observed result may be equally well interpreted in terms of frontier orbital control or charge control, but does not correlate well with either model. However, the reaction between **C** and **2** can be interpreted as the result of steric effects balancing orbital control leading to 96% addition to the δ position, in analogy with results obtained for the reaction of **2** with 2-lithio-1,3-dithiane reported previously [10].

The larger nucleophile **A** shows less preference for the δ position under kinetic control. In the addition of **A** to **1** the position β is favoured over δ, with α relatively untouched. That the addition is directed to the positions *meta* to nitrogen indicates charge control rather than orbital control.

The differences observed for **1**, **2** and **3** in their reactions with **A** can be related to the stereochemistry of the arenes and the conformation of the $Cr(CO)_3$ unit. The ^1H NMR spectra (Fig. 1) are very similar for the aromatic regions of **1** and **2**, while the spectrum for **3** is different. In **1** and **2** the protons α and γ relative to nitrogen are shifted more strongly upfield relative to protons β and δ by complexation of the

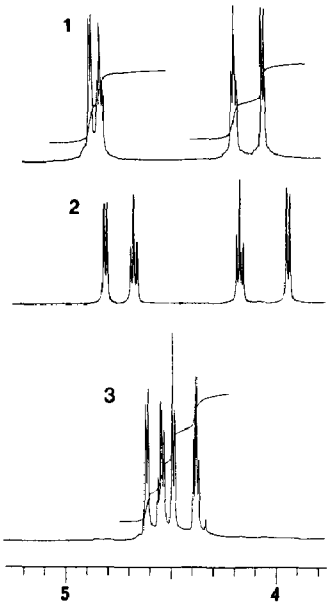


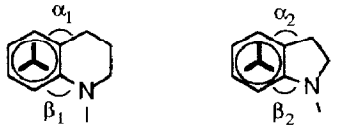
Fig. 1. ^1H NMR signals for aromatic protons in *N*-methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium (**1**), *N*-methylindolinetricarbonylchromium (**2**), *N,N*-dimethyltoluenetricarbonylchromium (**3**).

arene to the $Cr(CO)_3$ unit. The observed shifts for **1** and **2** correlate well with a preferred conformation of the rotor $Cr(CO)_3$ having Cr–CO bonds eclipsing the carbons in the β and δ positions as well as nitrogen, and with conjugation of the nitrogen with the arene π-system [17]. These structures for **1** and **2** are in good agreement with the conformations indicated by our EHT calculations, and also with solid state structures reported for toluidine-$Cr(CO)_3$ [18] and *N,N*-diethylaniline-$Cr(CO)_3$ [19], in which the $Cr(CO)_3$ eclipses the nitrogen atom. In the latter compound there is strong conjugative interaction between the N-substituent and the arene ring, as revealed by the short C–N distance (1.357 Å) [20].

Albright et al. [11] have demonstrated the correlation between the site for nucleophilic addition and the conformation of the $Cr(CO)_3$ rotor, with eclipsed carbons being preferentially attacked by nucleophiles. Including second order perturbations, Albright has shown that the LUMO coefficients on the eclipsed carbons become larger relative to results obtained from EHT calculations alone. Thus both charge and overlap control arguments operate in the same direction (*meta* to nitrogen) for the early stages of the reactions of **1** and **2**.

For compound **3** the arene proton chemical shifts are fairly similar (see Fig. 1), indicating a different conformation for the $Cr(CO)_3$ unit, in agreement with the results of our EHT calculations (see above). In **3** the α and γ positions are much less shielded compared to those in **1** or **2**, and appear close to the β and δ protons. As can be seen from Table 1, three positions react, to give roughly equal amounts of **12A**, **13A**, and **14A**, on addition of **A** to **3**. Rose et al. have pointed out the correlation between the shielding of the arene protons in arene-$Cr(CO)_3$ and the site for attack by nucleophiles, addition taking place at the less shielded positions [20], in good agreement with our observations.

The difference in regioselectivity between **1** and **2** in their reactions with **A** can be related to differences in geometries. From our molecular mechanics calculations we can see that the angles between the fused rings are larger in the indoline than in the tetrahydroquinoline. Consequently, attack at the δ position in **1** is sterically more hindered than in **2**, thus favouring attack at the β position by the large nucleophile **A**.



$\alpha_1 < \alpha_2$

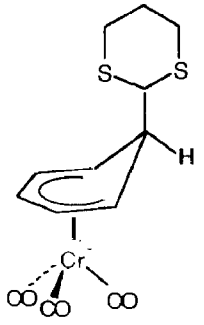
$\beta_1 < \beta_2$

The observed differences in reactivity and regioselectivity for the nucleophiles **A**, **B** and **C** are in good agreement with observations reported previously [2a,10a].

Thermodynamic control

The product distributions obtained from thermodynamically-controlled reactions are expected to reflect the relative stabilities of the intermediate isomeric η^5-cyclohexadienyltricarbonylchromium anions; charge distribution, electronic and steric interactions being major factors influencing the stability.

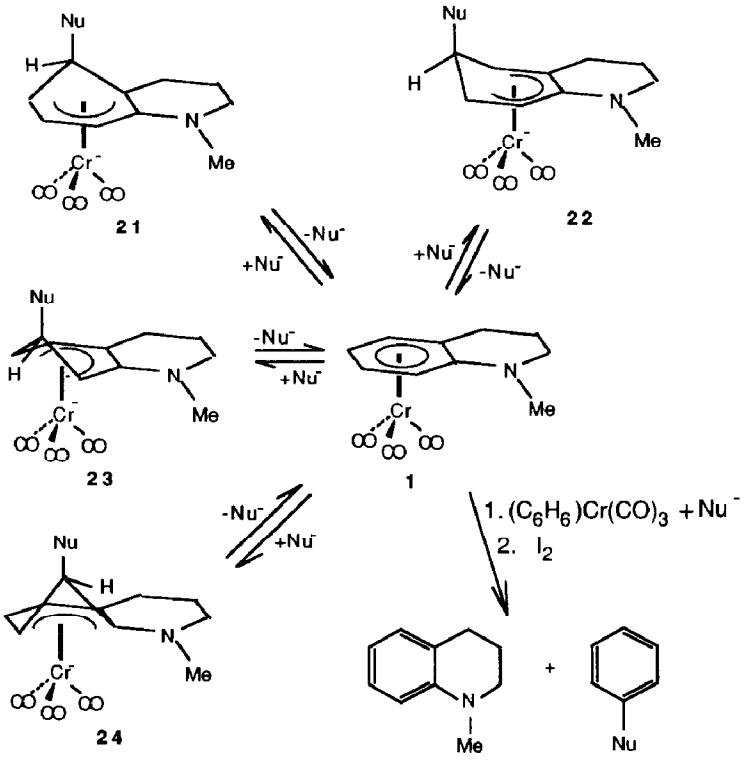
Our discussion of the factors determining the equilibria is based on some assumptions regarding the probable structures of the intermediate anions. The nucleophile attacks from the side *exo* to the $Cr(CO)_3$ group, in analogy with the solid state structure reported for the intermediate **20** formed from addition of 2-lithio-1,3-dithiane to **15** [13b]. In **20** the $Cr(CO)_3$ rotor had adopted a conformation eclipsing the sp^3 carbon, thereby minimizing charge repulsions.



20

The regioisomeric η^5-cyclohexadienyl-$Cr(CO)_3$ anions formed in the addition of nucleophiles to **1**, **2**, or **3** can be assumed to have structures corresponding to **21**, **22**, **23**, and **24**, Scheme 4, by analogy with **20**. According to calculations by Hoffmann et al. the barrier to rotation of the $Cr(CO)_3$ unit is high in this type of cyclopolyene-ML_3 complex compared with that in the parent benzene-$Cr(CO)_3$, for which the rotational barrier is negligible [21]. Our results obtained for the hydride model system (see above) agree well with their findings and support the suggested structure for the intermediates, i.e. with a CrCO unit eclipsing the sp^3-carbon.

Addition to the β and δ positions relative to nitrogen is favoured by formation of anions with minimized charge repulsions as well as minimum destabilizing electronic interactions with the nitrogen substituent. Thus nucleophilic additions under thermodynamic control should show a strong preference for formation of



Scheme 4

products substituted in the *meta* position relative to the donor nitrogen substituent. The difference between the two *meta* positions β and δ, with addition at β favoured at equilibrium, can be related to steric crowding in the δ position as discussed above, with steric interactions being more severe in additions to **1** than to **2**.

According to our EHT calculations on the four possible intermediate anions, the products from attack at the β and γ positions would be expected from reactions under thermodynamic control, these intermediate anions being favoured by the absence of steric interactions. The absence of any products from attack of a nucleophile at the γ carbon of **1** or **2** may indicate that the intermediates are not fully equilibrated, the formation of the γ-substituted intermediate being exceedingly slow. However in the reaction of **3** with **A**, **B** or **C** products from addition to the γ position are observed. Thermodynamic control of the addition of the bulky nucleophile **A** to **3** gives the γ-substituted isomer as the major product, in good agreement with the calculated relative stabilities for the intermediate anions.

That benzene-$Cr(CO)_3$ can be used as a trapping agent in the crossover experiments indicates that the nitrogen substituent in the intermediates **21**, **23** and **24** has a destabilizing effect on these anions. The benzene-$Cr(CO)_3$ adduct should thus be favoured.

The difference between the nucleophiles, with reactions of **A** being easily reversible, those with **B** involving very slow equilibration and **C** giving practically irreversible reactions, can be related to differences in the total energies of the structures as well as the energy of their respective HOMOs [10a].

Conclusion

By variation of reaction conditions it is possible to optimize the regioselectivity of the nucleophilic addition of stabilized nucleophiles to 1,2-disubstituted arene-$Cr(CO)_3$ compounds.

The regioselectivity of the nucleophilic addition under kinetic control can best be rationalized in terms of a balance of orbital control and charge control, depending on the structure of the arene-$Cr(CO)_3$ as well as of the nucleophile. The regioselectivity of attack on the arene should be controlled not only by the substituent on the arene but also by the conformation of the $Cr(CO)_3$ unit. Arene carbons which are eclipsed by a Cr–CO bond are preferentially attacked by the nucleophiles. The nucleophilic addition is sensitive to steric interactions, the least hindered of the eclipsed positions being preferentially attacked.

At thermodynamic control the equilibrium composition is determined by steric and electronic interactions in the intermediate anions.

Experimental

All reactions were carried out under a slightly positive argon pressure. Tetrahydrofuran, diethyl ether, dioxane, and pentane were freshly distilled from sodium benzophenoneketyl. Dibutyl ether was distilled from sodium (dispersion in paraffin).

^1H NMR spectra were recorded on 270 MHz (Bruker WH-270), 400 MHz (Varian XL-400) or 500 MHz (Bruker WH-500) spectrometers with TMS as internal standard. IR spectra were recorded on a Perkin–Elmer 197 spectrophotometer. Gas chromatographic/mass spectrometric analysis were performed with a Finnigan 1020 GC/MS instrument using a capillary column.

For preparative thin layer chromatography commercial TLC plates, silica gel Merck 60 F_{254}, were used, while flash chromatography was carried out on silica gel Merck 60 (230–400 mesh).

Melting points were determined on a Mettler FP5-Olympus BH apparatus.

Preparation of η^6-arenetricarbonylchromium(0) compounds

*1-Methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium (**1**)*

A 100 ml three-necked flask equipped with a magnetic stirring bar and an air-condenser, and containing 1-methyl-1,2,3,4-tetrahydroquinoline (2.08 g, 14.1 mmol) and chromium hexacarbonyl (3.01 g, 13.7 mmol) was evacuated and filled with argon. Dry dioxane, 50 ml, was added and three freeze-pump-thaw cycles were carried out before the mixture was heated under reflux. The temperature was maintained at 101 °C for four days, and the color of the solution was monitored. A strong yellow color shows the formation of the Cr compound. The mixture was cooled and dioxane evaporated. The crude product was dissolved in benzene, filtered through Florisil, and the benzene evaporated. Recrystallisation from a benzene/hexane mixture followed by sublimation gave 3.02 g of **1** (78% yield), m.p. 135 °C, IR ($CHCl_3$): ν 3020(s), 1960(s), 1865(vs), 1550(m), 960(vs) cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ 2.15 (3H, s, NCH_3), 2.59 (1H, m, H(2)), 2.34 (1H, m, H′(2)), 1.49 (1H, m, H(3)), 1.21 (1H, m, H′(3)), 2.14 (1H, m, H(4)), 1.82 (1H, m, H′(4)), 4.89 (1H, d, J_{56} 6.1 Hz, H(5)), 4.22 (1H, dd, J_{67} 5.9 Hz, H(6)), 4.85 (1H, dd, J_{78} 7.0 Hz, H(7)), 4.09 (1H, d, H(8)). ^{13}C NMR (125.75 MHz, C_6D_6): δ 38.0 (NCH_3), 50.0

(C(2)), 21.4 (C(3)), 26.5 (C(4)), 91.0 (C(4a)) 73.4 (aryl-C), 82.5 (aryl-C), 95.5 (aryl-C), 98.0 (aryl-C), 132.2 (C(8a)), 235.8 (CO).

1,2,3,4-Tetrahydroquinolinetricarbonylchromium(0) (**4**)

A 100 ml flask equipped with an air condenser, magnetic stirring and an argon inlet was charged with $Cr(CO)_6$ (2.26 g, 10.3 mmol). The flask was evacuated and then filled with argon. Dioxane (50 ml) and 1,2,3,4-tetrahydroquinoline (1.4 ml, 10.4 mmol) were added. After two freeze-pump-thaw cycles the mixture was heated under reflux and the temperature maintained at ca. 115 °C for 3 days. Upon cooling to room temperature the remaining $Cr(CO)_6$ and any Cr^{3+} salts crystallised out, and were removed by filtration through Florisil. Evaporation of the dioxane afforded 2.63 g, 93%, crude product. After recrystallization from hexane/ether beautiful yellow crystals of 1,2,3,4-tetrahydroquinolinetricarbonylchromium (**4**) were obtained, m.p. 147 °C. IR ($CHCl_3$): ν 3680, 3620, 3020, 1955, 1865, 1525 cm^{-1}. ^1H NMR (270 MHz, C_6D_6)δ: 2.42 (1H, s, NH), 2.51 (1H, m, H(2)), 2.25 (1H, m, H'(2)), 1.47 (1H, m, H(3)), 1.15 (1H, m, H'(3)), 2.04 (1H, m, H(4)), 1.80 (1H, m, H'(4)), 4.80 (1H, d, J_{56} 6.8 Hz, H(5)), 4.10 (1H, dd, J_{67} Hz, H(6)), 4.75 (1H, dd, H(7)), 3.90 (1H, d, J_{78} 7.2 Hz, H(8)). ^{13}C NMR (100.60 MHz, C_6D_6): δ 40.7 (C(2)), 21.0 (C(3)), 25.9 (C(4)), 90.2 (C(4a)), 97.8 (aryl-C), 95.4 (aryl-C), 82.5 (aryl-C), 76.0 (aryl-C), 130,4 (C(8a)) 235.8 (CO).

Methylation of 1,2,3,4-tetrahydroquinolinetricarbonylchromium to **1**

1,2,3,4-Tetrahydroquinolinetricarbonylchromium (**4**) (751 mg, 2.8 mmol) was placed in a 50 ml 2-necked flask equipped with magnetic stirring bar, argon inlet, and a rubber septum. The flask was evacuated and then filled with argon. A suspension of sodium hydride (ca. 50% in oil, 247 mg, ca. 5 mmol NaH) and iodomethane (0.43 ml, 6.9 mmol) in 20 ml THF was prepared separately and added from a syringe to **4** [9]. Some gas evolution was observed and the mixture was stirred at room temperature until gas evolution ceased. After 70 min the reaction was quenched by pouring the mixture on to ice. After extraction with 2 × 30 ml ether the combined ethereal extracts were washed with water (2 × 30 ml), dried over $MgSO_4$ then evaporated to leave a yellow complex, 743 mg, 92%, which after recrystallization from $CHCl_3$ afforded 675 mg of pure complex **1** in 85% yield.

1-Methylindolinetricarbonylchromium(0) (**2**)

A 250 ml one-necked flask equipped with magnetic stirring bar and air condenser was charged with 1-methylindoline (2.94 g, 22.1 mmol) and $Cr(CO)_6$ (5.00 g, 22.7 mmol). The flask was evacuated and then filled with argon. Dibutyl ether (90 ml) and THF (10 ml) were added and three freeze-pump-thaw cycles carried out before heating to reflux [6a]. After maintaining the reaction at reflux for 20 h the mixture was cooled and the solvent evaporated. The crude product was dissolved in diethyl ether and filtered through Florisil. Recrystallization from a diethyl ether/pentane mixture and cooling to −78 °C afforded 5.32 g of the yellow product **2** in 90% yield, m.p. 106 °C, lit. [9] m.p. 113–115 °C. IR ($CHCl_3$): ν 3000, 1940, 1870, 1850 cm^{-1}. ^1H NMR (270 MHz, C_6D_6): δ 2.09 (3H, s, NCH_3), 2.80 (1H, ddd, H(2)), 2.67 (1H, m, H'(2)), 2.08 (2H, m, H(3)), 4.83 (1H, d, J_{45} 6.0 Hz, H(4)), 4.20 (1H, dd, J_{56} 7.0 Hz, H(5)), 4.69 (1H, dd, H(6)), 3.97 (1H, dd, J_{67} 6.6 Hz, H(7)). ^{13}C NMR (100.60 MHz, C_6D_6): δ 34.3 (NCH_3), 53.6 (C(2)), 27.5 (C(3)), 99.4 (C(3a)), 71.7 (aryl-C),

83.7 (aryl-C), 92.5 (aryl-C), 94.0 (aryl-C), 135.9 (C(7a), 234.9 (CO).

Indolinetricarbonylchromium(0) (**5**)

A 250 ml flask equipped as above was charged with indoline (9.10 g, 76.4 mmol), $Cr(CO)_6$ (10.0 g, 45.4 mmol), dibutyl ether (150 ml) and THF (15 ml). After three freeze-pump-thaw cycles the solution was heated under reflux for 4 days before being cooled to room temperature. The solvents were evaporated and the crude yellow mixture dissolved in diethyl ether. After filtration through Florisil the ether was evaporated and the product recrystallized from ether/pentane giving 11.35 g of **5** in 98% yield, m.p. 106 °C. IR: 3380, 3000, 1940, 1855 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ 2.29 (1H, b, NH), 2.66 (1H, m, H(2)), 3.02 (1H, m, H'(2)), 2.07 (2H, m, H(3)), 4.85 (1H, d, J_{45} 6.2 Hz, H(4)), 4.11 (1H, dd, J_{56} 6.4 Hz, H(5)), 4.71 (1H, dd, J_{67} 6.2 Hz, H(6)), 4.10 (1H, d, H(7)). ^{13}C NMR (100.60 MHz, C_6D_6): δ 45.7 (C(2)), 28.1 (C(3)), 98.2 (C(3a)), 73.1 (aryl-C), 83.5 (aryl-C), 92.8 (aryl-C), 94.5 (aryl-C), 134.2 (C(7a)), 235.3 (CO).

1-Methylindolinetricarbonylchromium (**2**) *from indolinetricarbonylchromium* (**5**)

Compound **5** (3.00 g, 11.8 mmol) and sodium hydride (NaH washed with pentane, 0.56 g, 23.5 mmol) were placed in a flask under argon. THF (50 ml) and iodomethane (5.00 g, 35.3 mmol) were added at −78 °C. The mixture was stirred under argon while the temperature was raised to ca 20 °C. After 20 h the temperature was lowered to −78 °C and 20 ml water (degassed) and 20 ml ether were added. After stirring at room temperature the organic layer was separated and the aqueous phase extracted with ether. The combined ether solutions were evaporated and the solid residue was recrystallized from ether/pentane. Yellow crystals were obtained at −78 °C.

1-Methylindolinetricarbonylchromium, 2.87 g, was obtained in 91% yield.

2-Dimethylaminotoluenetricarbonylchromium(0) (**3**)

To a 500 ml one-necked flask equipped with magnetic stirring and an air condenser was added 2-dimethylaminotoluene (9.61 g, 71.1 mmol) and $Cr(CO)_6$ (15.18 g, 69.0 mmol). After evacuation the system was filled with nitrogen and 140 ml dry dioxane added. After two freeze-pump-thaw cycles the mixture was heated under reflux with stirring for 4 days, and then cooled to room temperature and the dioxane evaporated. The crude product was dissolved in benzene and filtered through Florisil to remove remaining $Cr(CO)_6$. After evaporation of benzene and sublimation of the crude product (10.7 Pa, 85–90 °C) 8.44 g, 45% yield of **3** was isolated, m.p. 76–77 °C. IR: 3010, 2940, 1950, 1860 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ 2.14 (6H, s, NCH_3), 1.82 (3H, s, aryl-CH_3), 4.62 (1H, d, J_{34} 6.6 Hz, H(3)), 4.39 (1H, dd, J_{45} 6.0 Hz, H(4)), 4.55 (1H, dd, J_{56} 6.2 Hz, H(5)), 4.50 (1H, d, H(6)). ^{13}C NMR (125.75 MHz, C_6D_6): δ 18.4 (aryl-CH_3), 43.3 (NCH_3), 104.5 (C(1)), 133.3 (C(2)), 82.8 (aryl-C), 89.4 (aryl-C), 91.1 (aryl-C), 95.8 (aryl-C), 234.6 (CO).

Addition of 2-lithio-2-methylpropionitrile (**A**) *to 1-methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium* (**1**)

A system of three 3-necked flasks connected via teflon tubes was set up. In flask 1, equipped with an argon/vacuum inlet, rubber septum and magnetic stirrer under argon, 2-lithio-2-methylpropionitrile (1.34 mmol) was prepared by addition of

2-methylpropionitrile (0.13 ml, 1.40 mmol) to lithium diisopropylamide (prepared from 1.6 *M* butyllithium, 0.83 ml, 1.34 mmol, and diisopropylamine, 0.21 ml, 1.46 mmol, in 10 ml of THF at −78° C) [2a] in THF at −78° C. The mixture was stirred for 20 min at −78° C. A solution of complex **1** (0.344 g, 1.21 mmol) in 10 ml THF was added rapidly by transfer via a teflon tube by a positive argon pressure from flask 2 kept at −78° C. The mixture was stirred at −78° C for 2 min and then a solution of I_2 (1.54 g, 6.1 mmol) in 10 ml THF at −78° C was introduced under pressure into the reaction flask. After 2 h stirring the mixture was added to a solution of Na_2SO_3. The aqueous layer was extracted three times with ether and the ether fraction washed with aq. $NaHCO_3$ and aq. NaCl. The combined ether fractions were dried, filtered through Celite and evaporated to give 264 mg of crude product.

GC-MS analysis showed the presence of three regiosomeric products, M^+ 214 (base peak) in relative ratio 1/75/24 in order of elution from the GC capillary column. No starting material was observed. The combined yield of regioisomers after flash chromatography was 82.2%.

The structures of the three regioisomers were determined from their ^1H (500 MHz) and ^{13}C NMR (125.75 MHz) spectra. The ^{13}C NMR spectra for the isomers were compared with calculated spectra using the ^{13}C NMR data for 1-methyltetrahydroquinoline and substituent chemical shifts, SCS, for the 2-methyl-2-propionitrile group [8].

Isomer **8A**: 8-(1-cyano-1-methylethyl)-1-methyl-1,2,3,4-tetrahydroquinoline. ^1H NMR (500 MHz, $CDCl_3$): δ 2.75 (3H, s, NCH_3), 3.03 (2H, t, J_{23} 6.4 Hz, H(2)), 2.04 (2H, m, H(3)), 2.87 (2H, t, J_{34} 7.4 Hz, H(4)), 7.1 (1H, m, H(5)), 7.0 (2H, m, H(6), H(7)), 1.80 (6H, s, $2CH_3$). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 49.74 (C(1)), 43.92 (C(2)), 25.26 (C(3)), 29.68 (C(4)), 129.20 (C(5)), 123.58 (C(6)), 124.54 (C(7)), 135.25, 136.26 (C(8), C(10)), 149.17 (C(9)), 34.41 (C(11)), 29.56 (C(12)), 125.94 (C(13)). MS: *m/z* 214 (*M*, 90%), 199 (40%), 174 (100%), 160 (90%), 144 (45%).

Isomer **7A**: 7-(1-cyano-1-methylethyl)-1-methyl-1,2,3,4-tetrahdyroquinoline. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.91 (3H, s, NCH_3), 3.22 (2H, t, *J* 5.7 Hz, H_2), 1.95 (2H, m, H(3)), 2.72 (2H, t, *J* 6.4 Hz, H(4)), 6.92 (1H, d, J_{56} 7.7 Hz, H(5)), 6.63 (1H, dd, *J* 7.7, 1.8, H(6)), 6.66 (1H, d, J_{68} 1.8 Hz, H(8)), 1.69 (6H, s, $2CH_3$). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 51.16 (C(1)), 38.92 (C(2)), 22.23 (C(3)), 27.38 (C(4)), 129.01 (C(5)), 112.10 (C(6)), 140.27 (C(7)), 107.50 (C(8)), 146.78 (C(9)), 122.18 (C(10)), 37.18 (C(11)), 29.22 (C(12)), 126.89 (C(13)). MS: *m/z* 214 (*M*, 100%), 199 (20%), 144 (20%). HRMS: Found 214.145 ± 0.003, calc. for $C_{14}H_{18}N_2$ 214.147.

Isomer **6A**: 5-(1-cyano-1-methylethyl)-1-methyl-1,2,3,4-tetrahydroquinoline: ^1H NMR (500 MHz, $CDCl_3$): δ 2.90 (3H, s, NCH_3), 3.25 (2H, t, *J* 6.4 Hz, H(2)), 1.98 (2H, q, H(3)), 3.03 (2H, t, *J* 6.2, H(4)), 6.62 (1H, d, *J* 7.5 Hz, H(6) or H(8)), 6.63 (1H, d, *J* 7.9 Hz, H(6) or H(8)), 7.09 (1H, dd, H(7)), 1.75 (6H, s, $2CH_3$). ^{13}C NMR (125.75 MHz , $CDCl_3$): δ 50.61 (C(1)), 39.32 (C(2)), 22.35 (C(3)), 25.61 (C(4)), 137.28 (C(5)), 112.44 (C(6)), 126.96 (C(7)), 111.16 (C(8)), 147.82 (C(9)), 122.78 (C(10)), 34.47 (C(11)), 28.68 (C(12)), 125.05 (C(13)). MS: *m/z* 214 (*M*, 100%), 199 (20%), 144 (30%).

This experiment was repeated several times varying the reaction time from 1 min to several hours. The relative ratios of regioisomeric products were determined from GC-MS data using the RIC signal (reduced ion current). The nucleophilic addition was complete within a few minutes at −78° C. Relative ratios of regioisomeric

products were found to vary with reaction time. A few examples have been summarised in Table 1.

In some experiments the oxidation with I_2 was allowed only 15 min. The time for oxidation did not influence the relative ratios of products.

Medium pressure liquid chromatography, MPLC, silica gel with hexane/ether as eluent separated the minor isomer, **8A**, from the other two. Isomer **7A** and **6A** could be separated after repetitive MPLC with slicing of the fraction containing **7A** and **6A**. Isomer **6A** was obtained by collecting the very front of the eluting fraction containing the mixture while isomer **7A** was isolated by collecting the tail of the eluting peak.

*Addition of 2-lithio-2-methylpropionitrile (**A**) to 1-methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium (**1**) at 20°C*

To a solution of 2-lithio-2-methylpropionitrile (1.1 mmol) in 5 ml THF was added a solution of **1** (0.284 g, 1.00 mmol) in 6 ml of THF at −78°C. After stirring for 10 min the cooling bath was removed and the temperature was raised to room temperature and the mixture was left with stirring for 44 h. The color of the solution changed from yellow to orange. The mixture was cooled to −78°C before quenching with a cold solution of I_2 (0.81 g, 3.2 mmol) in 10 ml of THF. After the usual work-up a crude product oil was obtained, 205 mg, 96%. GC analysis of the oil showed < 3% of 1-methyl-1,2,3,4-tetrahydroquinoline. Three regioisomeric products in relative ratio 3/93/4 (order of elution from GC) were observed. GC-MS showed the same molecular ion M^+ 214 (base peak) for the three products. No by-products could be detected.

*Addition of 2-lithio-2-methylpropionitrile (**A**) to 1-methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium (**1**) in the presence of HMPA*

The reaction was carried out using three 3-necked flasks connected by teflon tubes as described above. To a solution of 2-lithio-2-methylpropionitrile (1.4 mmol, from 2-methylpropionitrile, 0.13 ml, 1.43 mmol) in 10 ml THF was added 1 ml of HMPA (6.2 mmol) at −78°C. After stirring for 15 min a solution of complex **1** (0.329 g, 1.2 mmol) in 10 ml THF (−78°C) was transferred to the reaction flask and stirring continued for 22 h at −78°C before addition of a cold solution of I_2 (1.77g, 7.0 mmol) in 10 ml THF. The crude product after work-up was analysed by GC-MS. No starting material was observed. Three regioisomeric products in relative ratios 2/54/44 (order of elution) were observed, M^+ 214 (base peak).

This experiment was repeated with various reaction times: 2 min, 15 min , 22 h. In all cases the same relative ratios of regioisomers were obtained, cf. Table 1.

*Addition of 2-lithio-2-methylpropionitrile (**A**) to 1-methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium (**1**) followed by addition of benzenetricarbonylchromium*

A system of four 3-necked flasks connected with Teflon tubes was set up as above. To a solution of 2-lithio-2-methylpropionitrile (1.21 mmol, from 0.13 ml 2-methylpropionitrile) in 10 ml THF was added a cold solution of **1** (0.344 g, 1.21 mmol, −78°C) in 10 ml of THF. The mixture was stirred for 30 min at −78°C before addition of a solution of benzenetricarbonylchromium (0.260 g, 1.21 mmol, −78°C) in 10 ml THF at −78°C. After stirring at −40°C for 3 h the reaction was quenched by addition of I_2 (3.2 g, 6.3 mmol) in 10 ml THF. After work-up 0.195 g

of crude product was isolated. GC-MS analysis showed the presence of 1-methyl-1,2,3,4-tetrahydroquinoline and 2-methyl-2-phenylpropionitrile but no trace of **6A**, **7A** or **8A**. Flash chromatography of the crude product afforded 0.099 g of 2-methyl-2-phenylpropionitrile (yield 56%) and 0.15 g 1-methyl-1,2,3,4-tetrahydroquinoline (recovered 84%).

2-Methyl-2-phenylpropionitrile. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.45 (2H, d, J_{23} 7.7 Hz, H(2), H(6)), 7.36 (2H, dd, H(3), H(5)), 7.29 (1H, d, J_{34} 7.7 Hz, H(4)). MS: m/z 145 (M, 30%), 130 (100%), 103 (60%), 77 (25%).

*Addition of lithioacetonitrile (**B**) to 1-methyl-1,2,3,4-tetrahydroquinolinetricarbonylchromium (**1**)*

A system of three 3-necked flasks was set up as above. **B** was prepared by addition of butyllithium (1.6 *M*, 0.97 ml, 1.5 mmol) to a solution of acetonitrile (0.10 ml, 1.8 mmol) in 10 ml THF at −78°C. After stirring for 30 min a solution of **1** (0.40 g, 1.4 mmol) in 10 ml THF (−78°C) was added and the mixture was left with stirring for 22 h at −78°C. A white suspension which initially formed disappeared during the reaction. The reaction was quenched by addition of a cold solution of I_2 (1.79 g, 7.1 mmol) in 10 ml of THF. After the normal work-up with satd. aq. Na_2SO_3 and aq. NaCl extractions the crude product, 0.274 g, was analysed by GC-MS. > 50% 1-methyl-1,2,3,4-tetrahydroquinoline remained unreacted. Two regioisomeric products were formed in relative ratios 18/82. Flash chromatography afforded two fractions, 0.135 g of 1-methyl-1,2,3,4-tetrahydroquinoline, 65% recovered, and 0.052 g of a mixture of two isomeric products, 17% yield. MS for both isomers show M^+ 186 and base peak 185. The NMR spectrum was recorded for the mixture of regioisomers.

*5-Cyanomethyl-1-methyl-1,2,3,4-tetrahydroquinoline (**6B**) major isomer.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.89 (3H, s, NCH_3), 3.22 (2H, t, J_{23} 5.6 Hz, H(2)), 2.03 (2H, m, H(3)), 2.69 (2H, t, J_{34} 6.5 Hz, H(4)), 6.60 or 6.67 (1H, d J_{67} 7.4 Hz, H(6)), 7.08 (1H, dd, H(7)), 6.60 or 6.67 (1H, d, J_{78} 7.4 Hz, H(8)), 3.57 (2H, s, CH_2CN). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 39.6 (NCH_3), 50.6 (NCH_2), 21.9 (CH_2), 22.0 (CH_2), 24.3 (CH_2), 111.4 (CH), 116.9 (CH), 127.2 (CH), 128.2 (CH), 117.8 (C), 120.7 (C), 147.4 (C). MS: *m/z* 186 (*M*, 85%), 185 (100%), 158 (20%), 144 (30%), 130 (20%).

*7-Cyanomethyl-1-methyl-1,2,3,4-tetrahydroquinoline (**7B**), minor isomer.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.89 (3H, s, NCH_3), 3.23 (2H, t, H(2)), 1.96 (2H, m, H(3)), 2.74 (2H, t, H(4)), 6.91 (1H, d, J_{56} 7.4 Hz, H(5)), 6.51 (1H, d, H(6)), 6.47 (1H, s, H(8)), 3.64 (2H, s, CH_2CN). MS: *m/z* 186 (*M*, 80%), 185 (100%), 144 (20%), 130 (20%).

*Addition of 2-lithio-2-methylpropionitrile (**A**) to 1-methylindolinetricarbonylchromium (**2**)*

A system of three 3-necked flasks was set up as above. A cold solution of 1-methylindolinetricarbonylchromium (**2**) (0.400 g, 1.49 mmol) in 10 ml THF was added to a solution of **A** (1.7 mmol, prepared from 2-methylpropionitrile, 0.13 ml, 1.7 mmol) in 10 ml of THF at −78°C. The mixture was stirred at −78°C for 24 h before addition of a cold solution of I_2 (1.89 g, 7.4 mmol) in 10 ml THF. After the normal work-up 0.35 g of crude product was obtained. GC-MS analysis showed < 10% 1-methylindoline together with 1-methylindole. Three regioisomeric products

were observed in the relative ratio 3/19/78 in order of elution from the GC column. After flash chromatography three fractions were obtained: (a) 8 mg of 1-methylindole, 4%, (b) 11 mg of 1-methylindoline, 5% and (c) 229 mg of a mixture of three regioisomeric products, M^+ 200. This mixture was chromatographed on preparative TLC plates with pentane/ether as eluent. The isomers separated after repeated chromatography.

This reaction was repeated several times at various temperatures and reaction times as reported in Table 1. The Cr-complex **2** was added at −78°C and the mixture stirred for ca. 10 min before the temperature was raised. The reaction mixture was cooled to −78°C before quenching with I_2. In situ oxidation of 1-methylindoline to 1-methylindole was observed in serveral cases.

7-(1-Cyano-1-methylethyl)-1-methyl-indoline (***11A***). ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.00 (3H, s, NCH_3), 3.40 (2H, t, J_{23} 8.1 Hz, H(2)), 2.98 (2H, t, H(3)), 7.12 (1H, d, J_{45} 7.6 Hz, H(4)), 6.85 (1H, dd, H(5)), 7.12 (1H, d, J_{56} 7.6 Hz, H(6)), 1.84 (6H, s, CH_3).

MS: m/z 200 (M, 75%), 183 (65%), 172 (100%), 158 (50%), 115 (45%).

6-(1-Cyano-1-methylethyl)-1-methyl-indoline (***10A***). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.78 (3H, s, NCH_3), 3.35 (2H, t, J_{23} 8.2 Hz, H(2)), 2.93 (2H, t, H_3), 7.05 (1H, d, J_{45} 7.6 Hz, H(4)), 6.73 (1H, dd, H(5)), 6.53 (1H, d, J_{57} 1.8 Hz, H(7)), 1.71 (6H, s, CH_3). MS: *m/z* 200 (*M*, 95%), 183 (100%), 131 (90%), 115 (25%), 77 (25%).

4-(1-Cyano-1-methylethyl)-1-methyl-indoline (***9A***). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.77 (3H, s, NCH_3), 3.35 (2H, t, J_{23} 7.3 Hz, H(2)), 3.21 (2H, t, H(3)), 6.65 (1H, d, J_{56} 8.0 Hz, H(5)), 7.11 (1H, dd, H(6)), 6.46 (1H, d, J_{67} 7.8 Hz, H(7)), 1.73 (6H, s, CH_3). MS: *m/z* 200 (*M*, 100%), 185 (50%), 169 (75%), 146 (60%), 115 (30%).

Addition of 2-lithio-2-methyl-1,3-dithiane (***C***) *to 1-methylindolinetricarbonylchromium* (***2***)

A system of three 3-necked flasks was set up as above. **C** was prepared by addition of butyllithium (1.6 *M*, 1.11 ml, 1.78 mmol) to 2-methyl-1,3-dithiane (0.23 ml, 1.93 mmol) in 10 ml of THF at −78°C. The mixture was stirred for 2 h at −25°C. After cooling to −78°C a cold solution of **2** (0.40 g, 1.5 mmol) in 10 ml THF was added and the mixture stirred for 2 h before quenching with a cold solution of I_2 (1.89 g, 7.4 mmol) in 10 ml THF. After stirring for 2.5 h the mixture was added to a solution of Na_2SO_3. The aqueous layer was extracted three times with ether and the ether fraction washed with aq. $NaHCO_3$ and aq. NaCl. The aqueous fractions were extracted with ether and the combined ether fractions dried, filtered through celite and evaporated to give 492 mg of crude product. GC-MS analysis of the crude product showed some 1-methylindoline and 2-methyl-1,3-dithiane together with two regioisomeric products in relative ratio 4/96 in order of elution, M^+ 265. After flash chromatography (ether/pentane 3/97) four fractions were isolated: (a) 68 mg of 2-methyl-1,3-dithiane, (b), 119 mg 1-methylindoline (with some solvent), (c) 250 mg of the major regioisomer, 63.4% yield, (d) 20 mg of minor isomer, 5.1% yield.

Minor isomer. MS: *m/z* 265 (*M*, 65%), 191 (100%), 157 (45%), 115 (35%), 59 (50%); assigned to be 1-methyl-7-(2-methyl-1,3-dithian-2-yl)indoline (**11C**).

^{1}H NMR of major isomer (270 MHz, $CDCl_3$): δ 2.76 (3H, s, NCH_3), 3.35 (2H, s, NCH_2), 3.23 (2H, s, aryl-CH_2), 2.79 (4H, m, SCH_2), 1.95 (2H, m, CH_2), 7.28 (1H, d, J_{56} 8.3 Hz, H(5)), 7.12 (1H, dd, H(6)), 6.46 (1H, d, J_{67} 7.8 Hz, H(7)). MS: *m/z*

265 (*M*, 40%), 190 (80%), 158 (100%), 132 (30%), 115 (35%), 59 (60%); interpreted to be 1-methyl-4-(2-methyl-1,3-ditian-2-yl)indoline (**9C**) after comparison with lit. data [9].

Addition of 2-lithio-2-methylpropionitrile (A) to 2-dimethylaminotoluenetricarbonylchromium (3)

A system of three 3-necked flasks was set up as above. A cold solution of 2-dimethylaminotoluenetricarbonylchromium (**3**) (0.400 g, 1.47 mmol) in 10 ml of THF was added to a solution of A (1.7 mmol, from 2-methylpropionitrile, 0.16 ml, 1.77 mmol) in 10 ml of THF at −78° C. The mixture was stirred at −78° C for 2.5 h before quenching by addition of a cold solution of I_2 (1.87 g, 7.4 mmol) in 10 ml THF. After normal work-up 0.386 g of crude product was obtained. GC-MS analysis showed no traces of starting materials. Three regioisomeric products, M^+ 202, in relative ratio 32/32/36 (in order of elution from GC column) were observed. After flash chromatography one fraction, 0.236 g, containing three regioisomers was obtained in 79% combined isolated yield. This mixture was chromatographed on preparative TLC plates with pentane/ether as eluent. The isomers separated after repeated chromatography.

The reaction was repeated with variation of reaction time and temperature. Results are given in Table 1. The reaction at −50° C, 24 h, gave 0.336 g of crude product. GC-MS analysis showed the three isomers in relative ratio 8/81/11. Flash chromatography gave 0.252 g, 85% isolated yield of the major isomer interpreted to be 2-methyl-2-(3-dimethylamino-4-methylphenyl)-propionitrile.

2-Methyl-2-(3-dimethylamino-4-methylphenyl)propionitrile (***14A***). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.34 (3H, s, aryl-CH_3), 2.70 (6H, s, NCH_3), 1.69 (6H, s, CH_3), 7.12 (1H, d, J_{26} = 2.0 Hz, H(2)), 7.00 (1H, dd, H(6)), 7.15 (1H, d, J_{56} = 7.9 Hz, H(5)). MS: *m/z* 202 (*M*, 30%), 187 (100%), 171 (20%)

2-Methyl-2-(4-dimethylamino-3-methylphenyl)proprionitrile (***13A***). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.31 (3H, s, aryl-CH_3), 2.73 (6H, s, NCH_3), 1.71 (6H, s, CH_3), 7.01 (1H, d, J_{56} = 6.5 Hz, H(5)), 7.22 (1H, d, H(6)), 7.24 (1H, s, H(2)). MS: *m/z* 202 (*M*, 90%), 187 (100%), 171 (60%), 115 (20%).

2-Methyl-2-(3-dimethylamino-2-methylphenyl)propionitrile (***12A***). ^{1}H NMR (270 MHz, $CDCl^3$) δ: 2.61 (3H, s, aryl-CH_3), 2.68 (6H, s, NCH_3), 1.79 (6H, s, CH_3), 7.03 (1H, d, aryl-H), 7.09 (1H, d, aryl-H), 7.18 (1H, dd, J_{45} = 7.7 Hz, J_{56} = 7.7 Hz, H(5)).

MS: *m/z* 202 (*M*, 100%), 187 (80%), 172 (30%), 162 (25%), 118 (50%).

Addition of lithioacetonitrile (B) to 2-dimethylaminotoluenetricarbonylchromium (3)

A system of three 3-necked flasks was set up as above. A cold solution of **3** (0.400 g, 1.47 mmol) in 10 ml of THF was added to a cold solution of **B** (1.7 mmol, prepared from acetonitrile, 0.1 ml, 1.9 mmol, and butyllithium, 1.6 *M*, 1.1 ml, 1.77 mmol) in 10 ml THF at −78° C. The mixture was stirred for 24 h at −78° C followed by addition of a cold solution of I_2 (1.87 g, 7.4 mmol) in 10 ml THF. After 4 h the mixture was treated with aqueous Na_2SO_3 until remaining I_2 had been removed. The aqeous phase was worked up and 0.264 g of crude product was isolated. GC-MS analysis showed some 2-dimethylaminotoluene together with three regioisomeric products, M^+ 174, in relative ratio 9/1/90. Flash chromatography gave three fractions: (a) 4 mg of 2-dimethylaminotoluene, 2% recovered, (b) 11 mg

of one minor isomer in 4% isolated yield, and (c) 120 mg of the major isomer in 47% isolated yield.

2-(3-Dimethylamino-4-methylphenyl)acetonitrile (***14B***). ^{1}H NMR (270 MHz, $CDCl_3$) of minor isomer: δ 2.34 (3H, s, aryl-CH_3), 2.81 (6H, s, NCH_3), 3.76 (2H, s, CH_2), 7.07 (1H, d, J_{56} 6.9 Hz, H(5)), 7.21 (1H, dd, H(6)), 7.07 (1H, d, J_{26} 2.5 Hz, H(2)). MS: *m/z* 174 (*M*, 40%), 146 (95%), 132 (100%), 117 (50%), 77 (70%), 58 (80%).

2-(4-Dimethylamino-3-methylphenyl)acetonitrile (***13B***). MS: *m/z* 174 (*M*, 80%), 173 (80%), 159 (100%), 143 (35%), 117 (40%), 103 (45%), 91 (60%), 77 (45%).

2-(3-Dimethylamino-2-methylphenyl)acetonitrile (***12B***). ^{1}H NMR (270 MHz, $CDCl_3$) of major isomer, δ: 2.30 (3H, s, aryl-CH_3), 2.68 (6H, s, NCH_3), 3.65 (2H, s, CH_2CN), 7.05 (1H, d, aryl-H), 7.05 (1H, d, aryl-H), 7.17 (1H, dd, *J* 7.1 Hz, *J* 8.9 Hz, H(5)). MS: *m/z* 174 (*M*, 75%), 173 (80%), 159(100%), 143 (40%), 132 (45%), 103 (50%), 77 (50%), 73 (50%).

Addition of 2-lithio-2-methyl-1,3-dithiane (***C***) *to 2-dimethylaminotoluenetricarbonylchromium* (**3**)

A system of three 3-necked flasks was set up as above. A cold solution of **3** (0.400 g, 1.47 mmol) in 10 ml of THF was added to a cold solution of **C** (2.9 mmol, prepared from 1.6 *M* butyllithium, 1.8 ml, 2.94 mmol and 2-methyl-1,3-dithiane, 0.39 ml, 3.24 mmol at 0 °C) in 10 ml of THF at −78 °C. The temperature was raised to −30 °C and the mixture was stirred for 2.5 h before cooling to −78 °C and addition of a cold solution of I_2 (2.25 g, 8.9 mmol) in 10 ml of THF. After usual work-up the crude product was analysed by GC-MS showing some 2-methyl-1,3-dithiane, 2-dimethylaminotoluene together with three regioisomeric products in relative ratio 25/10/65 (in order of elution from the GC column) M^+ 267. Flash chromatography gave three fractions: (a) 0.3 g of a mixture of 2-methyl-1,3-dithiane and 2-dimethylaminotoluene, (b) 84 mg of the major isomer in 21% combined yield, and (c) 118 mg of a mixture of the two minor regioisomers in 30% combined yield.

2-Methyl-2-(3-dimethylamino-4-methylphenyl)-1,3-ditiane (***14C***). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.67 (6H, s, NCH_3), 2.25 (3H, s, aryl-CH_3), 1.80 (3H, s, CH_3), 2.69 (4H, m, SCH_2), 1.82 (2H, m, CH_2), 7.56 (1H, d, J_{26} 3.0 Hz, H(2)), 7.08 (1H, d, J_{56} 8.2 Hz, H(5)), 7.42 (1H, dd, H(6)). MS: *m/z* 267 (*M*, 100%), 193 (100%), 178 (35%), 162 (30%).

2-Methyl-2-(4-dimethylamino-3-methylphenyl)-1,3-dithiane (***13C***). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.66 (6H, s, NCH_3), 2.28 (3H, s, aryl-CH_3), 1.74 (3H, s, CH_3), 2.90 (4H, m, SCH_2), 1.82 (2H, m, CH_2), 7.60 (1H, s, H(2)), 6.92 (1H, d, J_{56} 8.0 Hz, H(5)), 7.58 (1H, d, H(6)). MS: *m/z* 267 (*M*, 60%), 193 (100%), 178 (30%), 160 (60%).

2-Methyl-2-(3-dimethylamino-2-methylphenyl)-1,3-dithiane (***12C***). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.67 (6H, s, NCH_3), 2.74 (3H, s, aryl-CH_3), 2.10 (3H, s, CH_3), 1.99 (2H, m, CH_2), 2.77 (2H, m, SCH_2), 2.92 (2H, m, SCH'_2), 7.07 (1H, d, J_{45} 7.9 Hz, H(4)), 7.17 (1H, dd, H(5)), 7.73 (1H, d, J_{56} 7.9 Hz, H(6)). MS: *m/z* 267 (*M*, 60 %), 192 (70%), 178 (100%), 163 (30%), 115 (30%).

Calculations

The molecular mechanics calculations were performed by use of Allinger's MMPI program and a standard set of parameters. Extended Hückel calculations [22] were

performed by use of Hoffmann's standard parameters on geometries obtained from the MMPI calculations [23]. The distance (1.7 Å) between the Cr atom and the arene ring centre was obtained from X-ray structure analysis of the related compounds η^6-1-methoxyindanetricarbonylchromium(0) [24].

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