Application of (η^6-Arene) Chromium Tricarbonyl Complexes in Organic Synthesis: Nucleophilic Aromatic Substitution and Lithiation

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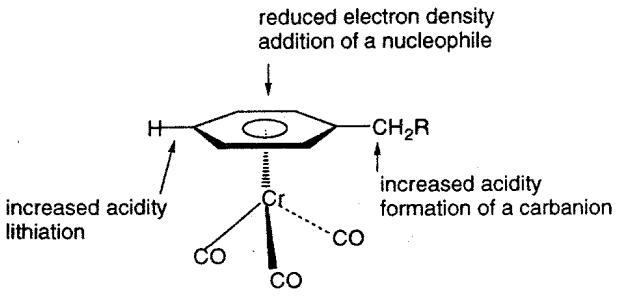
Abstract: Preparation of 2-aryl propionic acids using arene tricarbonyl chromium manganese complexes and arene cyclopentadienyl iron complexes is reported. Treatment of (η^6-arene)tricarbonylchromium complexes substituted by a leaving group X with nucleophiles and a proton source afforded new arenetricarbonylchromium complexes via HX elimination. Diastereoselective complexation of ortho - disubstituted arenes and enantioselective ortho-lithiation of arene tricarbonyl chromium complexes is described. Treatment of cationic (η^6-arene)tricarbonyl manganese with nucleophilic complexes afforded di, tri and tetranuclear complexes.

Introduction

Arene chromium tricarbonyl [1-42], and manganese tricarbonyl [43-84] π-arene complexes are widely used in the literature for several reasons. Indeed, they are easily prepared, the arene group is readily released from complexation in the case of chromium complexes and they have yet found significant application in organic synthesis. The electron withdrawing power of the $Cr(CO)_3$ entity is similar to that of the nitro group of nitrobenzene permitting an easy addition of a carbanion. Indeed, it is well known in organic chemistry that nucleophilic substitution occurs only if the arene is substituted by an activating group like NO_2 for example. Thus a large variety of carbanions can be added to the chromium and manganese complexes.

The electrophilic complexed arene ring is better able to stabilize negative charges in the case of Cr complexes. The arene protons and the benzylic protons are more acidic and are easily lithiated. The



Scheme 1. Effects on arene reactivity of metal coordination.

chromium tricarbonyl entity blocks one face of the arene directing incoming reagents to the uncomplexed face. These effects are well precedented in the literature and have been widely used in organic synthesis [27], scheme 1. This review will focus mostly on nucleophilic substitutions.

In a first part, we will describe the synthesis of 2-arylpropionic acids. This will lead us to report, new nucleophilic aromatic substitutions in organometallic chemistry. Then, we will discuss the preparation of an enantiomerically pure isoindoline. In another part, we will mention the preparation of chiral complexes. In the following paragraph, we will describe the enantioselective *ortho*-lithiation of arenetricarbonylchromium complexes and in the last part the use of such lithiated chromium complexes as nucleophiles towards cationic arenetricarbonylmanganese complexes leading to di, tri and even tetra-nuclear complexes.

Preparation of arenetricarbonylchromium complexes, which are usually yellow complexes, is easily achieved in good yield by heating the free arene with $Cr(CO)_6$ in a high boiling solvent [85-87], scheme 2. They can be prepared also [88-97] by exchange from chromium complexes of the type $Cr(CO)_3L_3$ where the ligand L can be a very labile two electrons ligand such as NH_3, [88], CH_3CN, [89-92], pyridine [90] or α-picoline [95-96] or when the ligand L_3 is naphtalene [94]. These complexes are stable in solution in an inert atmosphere but they are progressively decomposed in air. Their decoordination is achieved under very mild conditions for example by treatment with an oxidizing

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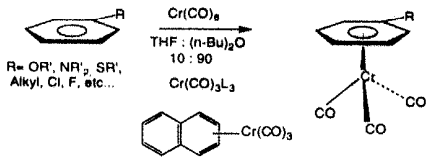
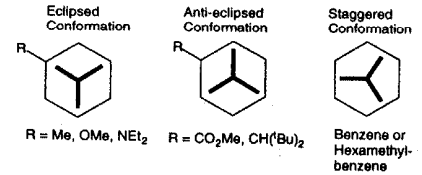
agent such as iodine or an aqueous solution of ceric ion, by addition of donor ligands (such as CO or PPh_3), by irradiation or simply by exposure to air and light [27].



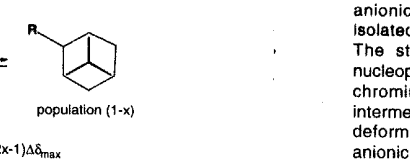
Scheme 2. Preparation of arene tricarbonyl chromium complexes.

The determination of the $Cr(CO)_3$ tripod orientation with respect to the carbons of the ring is important and is well documented in the solid state. The conformation has been shown to depend both in the solid state and in solution, mainly on electronic and steric effects of the arene substituents. First of all, in the solid state, the X-Ray structure of the benzenetricarbonylchromium complex shows that the $Cr(CO)_3$ tripod is staggered with respect to the carbons of the ring and the same conformation is also observed in the case of the complex of hexamethylbenzene. In the case of monosubstituted complexes, two eclipsed conformations are found most often : the syn eclipsed one, where R is a donor substituent, for example R being a methyl, a methoxy or a dialkylamino group and the anti-eclipsed one where R is an electron withdrawing substituent such as a carbomethoxy or a very hindered substituent such as bis-tertiobutylmethyl group, scheme 3.



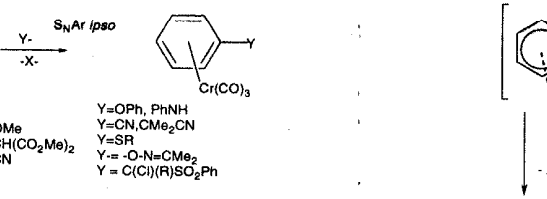
Scheme 3. Conformation of arene tricarbonyl chromium complexes in the solid state.

In solution, the conformation of the tripod can be also easily calculated if an equilibrium is considered between two conformers : one conformer eclipsing the R group and the other one anti-eclipsing the R group. If x is the population of the eclipsed conformer and (1-x) the population of the anti-eclipsed conformer, it has been shown in the literature that it is possible to calculate this population x using a simple equation : δ_3-$\delta_2 = (2x-1)\Delta\delta_{max}$ [98-103]. Indeed this population x can be calculated knowing the difference of chemical shifts δ_3-δ_2 of the *meta* and *ortho* protons H3 and H2. $\Delta\delta_{max}$ being equal in one case to the difference of chemical shifts between the 1, 3, 5 tri-methylbenzene complex adopting an eclipsed conformation and the 1, 3, 5 tri-tertiobutylbenzene complex adopting an anti-eclipsed conformation [101].



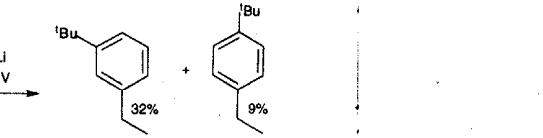
Scheme 4. Conformation of arene tricarbonyl chromium complexes in solution.

The first example of nucleophilic substitutions of chromium complexes was described by Nicholls and Whiting in 1958 and 1959 [104-105] namely the reaction of sodium methylate with chlorobenzenetricarbonylchromium to give anisoletricarbonylchromium (eq.1). This substitution has been extended to many other nucleophiles, for example N, S and C nucleophiles with the leaving group being either chlorine or fluorine [106-109].



Eq.1. *Ipso* nucleophilic aromatic substitution.

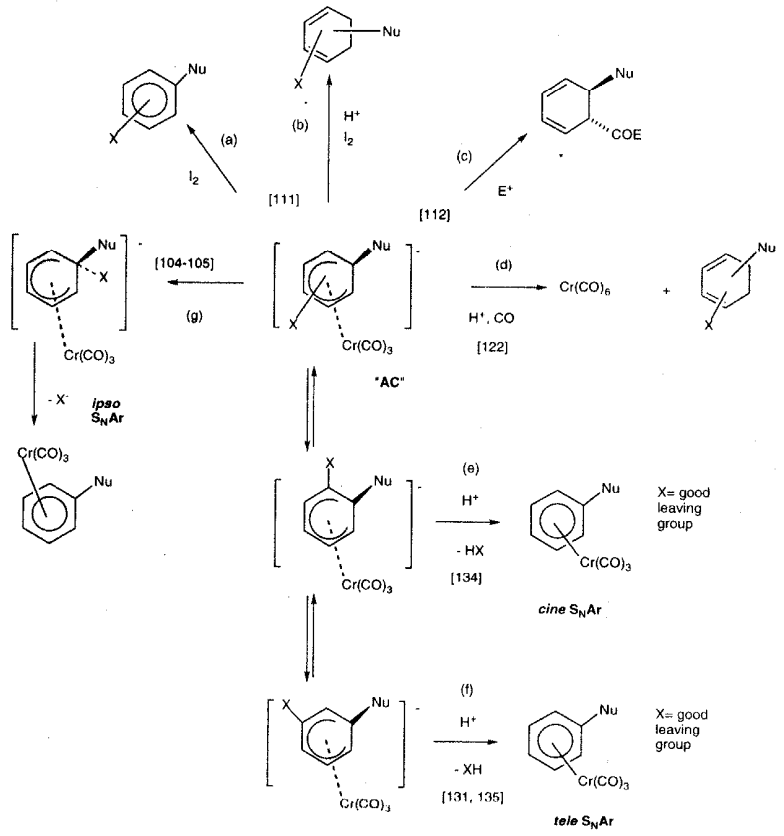
It was only in 1973 that the first reaction of a carbanion with a non-halogenated chromium complex was investigated (eq.2). Indeed, Card and Trahanovsky showed that reaction of tertiobutyllithium with ethylbenzenetricarbonylchromium followed by oxidation with ceric ions afforded two isomeric 3 and 4-tertiobutyl ethyl benzene in yields of 32 and 9 per cent [110].



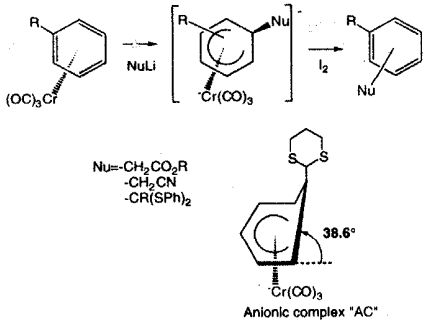
Eq.2. Addition of a nucleophile to a non-halogenated arene tricarbonyl chromium complex.

In the eighties, Semmelhack et al. have extended this reaction to many other nucleophiles, such as anions α to nitriles, α to esters and the lithium salt of 1,3 dithiane [111] eq.3. Thus substituted arenes could be obtained after oxidation with iodine (Scheme 5, path a). In the case of the lithium salt of 1,3-dithiane, the anionic complex " **AC** " was stable enough to be isolated and studied by X-Ray crystallography, eq.3. The structure shows on the one hand, that the nucleophile adds to the arene trans with respect to the chromium entity and on the other hand that the intermediate is an η^5-cyclohexadienyl complex. The deformation from planarity is 38.6 degrees. If the anionic complex "**AC**" was treated with an excess of acid and iodine, it was possible to obtain functionnalized cyclohexadienes (Scheme 5, path b).

Reaction of the anionic complex "**AC**" with some electrophiles can give *trans* disubstituted cyclohexadienes (scheme 5, path c). These reactions have been extended into an asymmetric version [112-121]. Treatment of the anionic complex with acid under CO atmosphere yields also isomeric substituted cyclohexadienes (Scheme 5, path d), and $Cr(CO)_6$ is recovered [122]. It can be used in order to prepare arenetricarbonylchromium complexes [122] (scheme 5, path d). In this case, we have never succeeded to isolate (η^4-cyclohexadiene)chromium complexes. The



Scheme 5. Nucleophilic addition of a nucleophile to arene tricarbonyl chromium complex.



Eq.3. Addition of nucleophiles to arene tricarbonyl chromium complexes.

formation of the cyclohexadienes involved (η^5-cyclohexadienyl)chromium-hydrides after acidic treatment of the anionic complex (the presence of an agostic bond is not excluded).

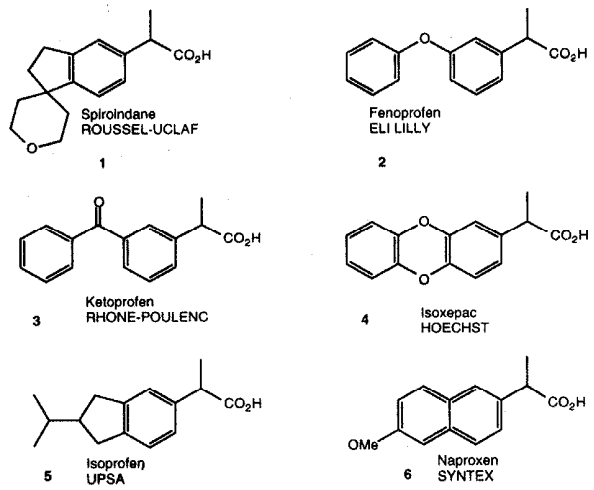
In the cases (a), (b) and (c), the chromium was lost but we will see, *vide infra*, that in some cases the $Cr(CO)_3$ remained coordinated to the arene ring (scheme 5, paths e and f) [131, 134, 135]. Some applications of chromium complexes in the synthesis of compounds which are difficult to obtain by classical methods are now presented.

Preparation of 2-Aryl Propionic Acids

Preparation of a Spiroindane Derivative

We were interested in the synthesis of 2-aryl propionic acids derivatives, which are well known anti-inflammatory reagents, scheme 6. For example, the spiroindane **1** from Roussel-Uclaf, fenoprofen **2** from Eli Lilly, ketoprofen **3** from Rhône-Poulenc, isoxepac **4** from Hoechst, isoprofen **5** from UPSA and naproxen **6** from Syntex present a 2-aryl propionic acid structure. We have achieved the synthesis of some of these acids and a precursor of ketoprofen. But we will describe in this review only two examples : the synthesis of the spiroindane **1** and of fenoprofen **2**.

For this purpose, we used the spiroindane **7** (Scheme 7) which was prepared in a large scale by Roussel-Uclaf, a pharmaceutical company [102]. Then we have coordinated this spiroindane **7** in a good yield using $Cr(CO)_6$. We reacted the lithium salt of propionitrile to **8** and we obtained the isomeric mixture of nitriles **9** whose oxidation gave the free arenes **10**. Hydrolysis of **10** gave the isomeric 2-aryl propionic acids **1**. High pressure liquid chromatography showed that the major isomer was the one which corresponded to the addition of the nucleophile to the C5 carbon. We undertook the same study at -78°C and at 0°C and we observed the same regioselectivity. Even, by changing the solvant THF with a mixture of THF : HMPT, we obtained again the same regioselectivity [102], in a good agreement with a reaction under kinetic control.



Scheme 6. 2-arylpropionic acids having anti-inflammatory properties.

In some particular cases, Kündig et al. described thermodynamic control of the regioselectivity in the addition of particular carbanions to (arene)tricarbonylchromium complexes by using nice double crossover experiments [123].

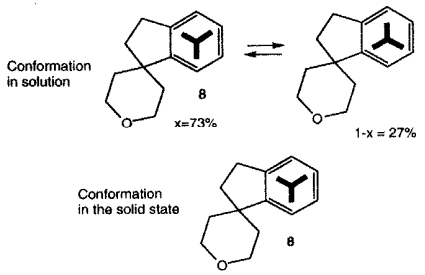
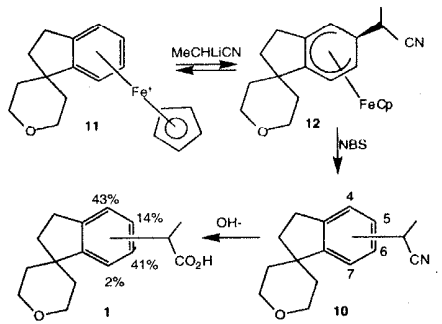


Fig. (1). Conformational studies of arene tricarbonyl chromium complexes **27**, **31** and **33**.

In all our cases, the addition reaction occured under kinetic control because our reactions were performed at low temperature (usually -78°C) with stabilized carbanions and we never observed significant changes by performing the reaction with HMPA [102]. We calculated the population x of the conformer eclipsing the C5 carbon. This population is 73 % in solution. We realized also the X-Ray structure of this complex which indicated an eclipsed C5 carbon with respect to the chromium carbon in the solid state (Fig.1). We concluded that in our case the major isomer was obtained by an addition of the stabilized carbanion on a carbon which was eclipsed by a chromium-carbonyl bond. We studied other cases and we reached the same conclusion (scheme 7) [102].

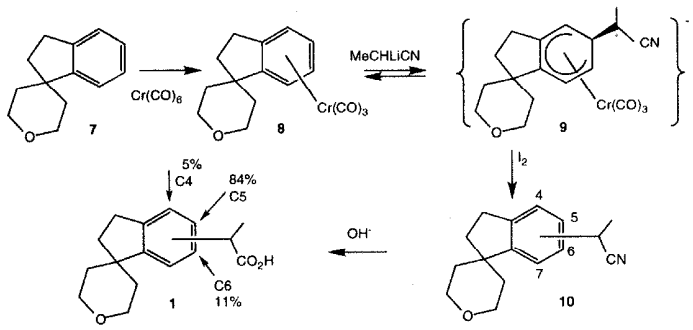
We undertook the same study with the cationic iron complex **11**. Addition of propionitrile carbanion gave neutral isomeric η^5-cyclohexadienyl complexes **12**. Oxidation with N-bromosuccinimide in benzene removed the iron and a mixture of nitrile was recovered. Hydrolysis of the nitriles gave the isomeric 2-aryl propionic acids. Again, high pressure liquid chromatography showed that the major isomers were the C4 and the C6 isomers which present no pharmaceutical properties (scheme 8) [124].



Scheme 8. Preparation of 2-aryl propionic acids using arene cyclopentadienyl iron complexes.

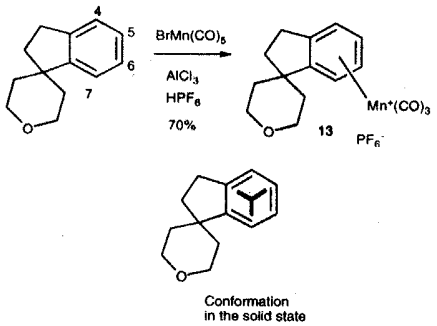
The sandwich structure of the η^5, η^6 complex **11** was obtained [125]. So, we would like to point out that without a C3 symmetry of the organometallic moiety, we did not observe a good regioselectivity of the addition of a carbanion on a particular carbon of the arene ring.

The same study with another cationic complex, the spiroindane tricarbonyl manganese complex **13**, was



Scheme 7. Preparation of 2-arylpropionic acids using arene tricarbonyl chromium complexes.

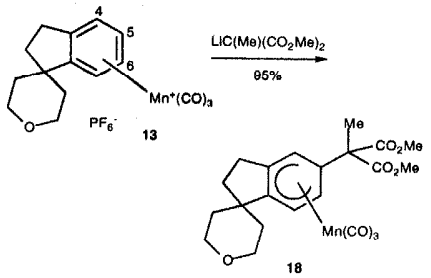
undertaken. This complex can be obtained in 70 % yield using pentacarbonylmanganese bromide, aluminium chloride and hexafluorophosphoric acid (scheme 9).



Scheme 9. Preparation of the spiroindane complex 13.

In the solid state, the conformation of the tripod also avoided the bulky spiro substituent [126]. But, unexpectedely the regioselectivity of the same carbanion, the propionitrile carbanion afforded the four isomers **14-17** (scheme 10).

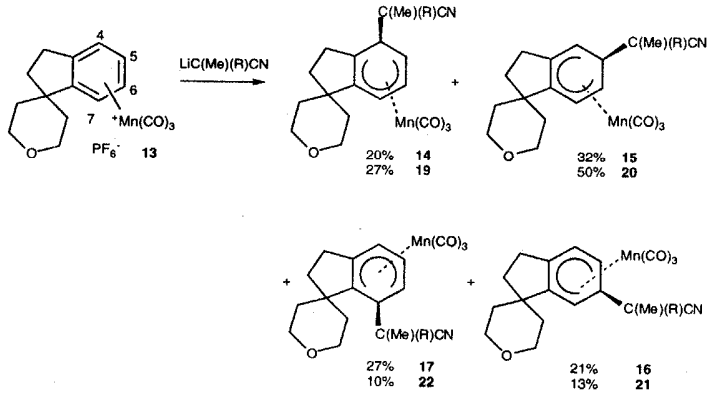
In this case, the complex is so reactive, so electrophilic that even the C7 carbon is reached by the nucleophile. We succeeded to obtain only one regioisomer **18** almost quantitativaly by using a tertiary carbanion (eq.4) [126]. The methyl malonate derivative being a good precursor of propionic acid, this is another way to obtain 2-arylpropionic acids.



Eq. 4. Addition of methylmalonate carbanion to a spiroindane manganese complex.

We did also the reaction with isobutyronitrile carbanion and the student who performed this reaction observed two different kind of crystals on the flask, good enough for X-Ray cristallography. Thus he obtained the two η^5-cyclohexadienyl structures **19** and **20**. The first one showed an addition of the nucleophile at the C4 carbon and the second at the C5 carbon [126] (scheme 10). The regioselectivity of the addition of this nucleophile was not good: indeed complexes **19, 20, 21** and **22** were obtained in the following proportions 27/50/13/10 [127].

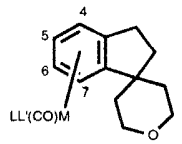
We decided to decrease the electrophilicity of the arene ring by displacing one or two CO ligands by one or two phosphito ligands. And we observed effectively that the less electrophilic complex **24**, (scheme 11) with one carbon monoxide and two phosphito ligands, can react with propionitrile carbanion giving 81 % of



Scheme 10. Addition of nitrile carbanions to arene tricarbonyl manganese complexes.

Table 1. ^{1}H NMR Data of Spiroindane Complexes

	L	L'	H4	H5	H6	H7
M=Mn$^+$	CO	CO	6.74	7.12	6.60	7.21
	CO	$P(OEt)_3$	6.32	6.53	6.13	6.77
	$P(OEt)_3$	$P(OEt)_3$	5.81(a)	5.81	5.81	5.81
M=Cr	CO	CO	5.50	5.74	5.33	5.87



(a) m, not resolved

addition of the nucleophile to the C5 carbon [128]. It is worthy to note that a good regioselectivity is obtained when the protons are shielded! In other words we observed the same regioselectivity in this case and in the case of the tricarbonyl chromium complex. We did not observe a good regioselectivity with complex **23** bearing two CO ligands and one phosphito ligand, probably because the electrophilicity of the arene ring is still too high [128].

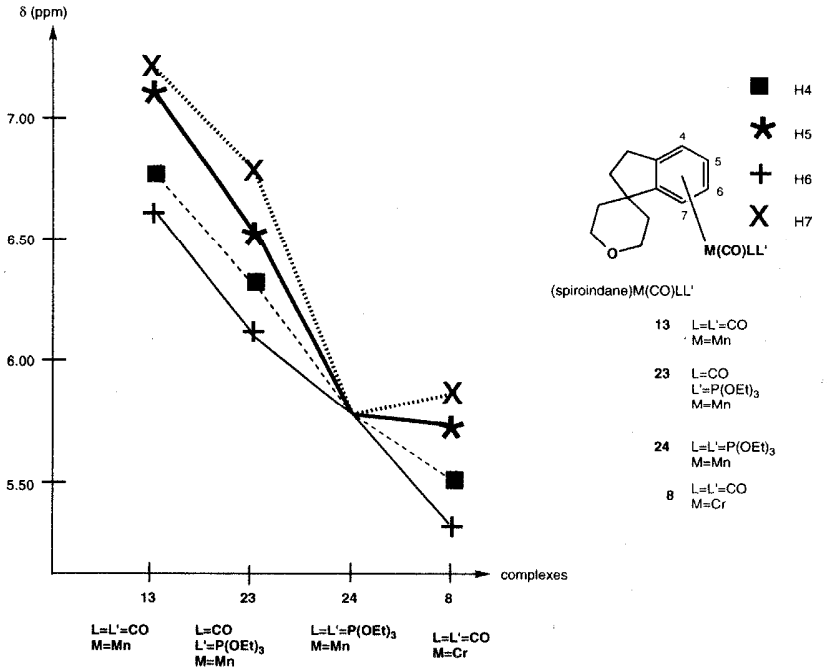
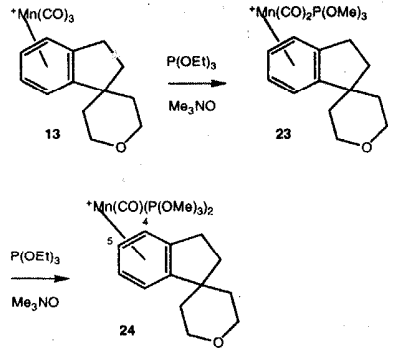


Fig. (2). Aromatic proton chemical shifts of spiroindane complexes.



Scheme 11. Displacement of CO ligands by phosphito ligands.

By ^{1}H NMR, we observed a shielding of the aromatic protons by displacing one CO ligand by one or two phosphito ligands (Fig.2). We observed the same shielding in other cases and we will point out the simplest case : the case of benzene (Fig.3). The six protons of benzenetricarbonyl manganese resonated at 6.92 ppm. The six protons of benzene tricarbonyl chromium resonated at 5.62 ppm. So, there was a difference of 1.3 ppm of chemical shifts between these two complexes. If we displaced one CO by one phosphito ligand, the six protons were shielded and resonated at 6.49 and if we displaced two CO by two phosphito ligands, the six protons were again shielded and resonated at 5.90 which is a chemical shift that we can compare with the 5.62 chemical shift of the Cr complex (Fig.3). We observed analogous data by ^{13}C NMR (Fig.4). The carbons of the carbonyls of benzene chromium tricarbonyl resonate at 234.4 ppm although those of the manganese complex **26** resonate at 216.3 ppm [128].

Preparation of 2-(3'-Phenoxy-phenyl) Propionic Acid

In the case of diphenylether chromium tricarbonyl complex **27** which was obtained in good yield using chromiumhexacarbonyl and diphenylether, we added a nucleophile at -78° C. After treatment with iodine, the organic compound **28** was formed. The nucleophiles that we have tried are primary, secondary or tertiary

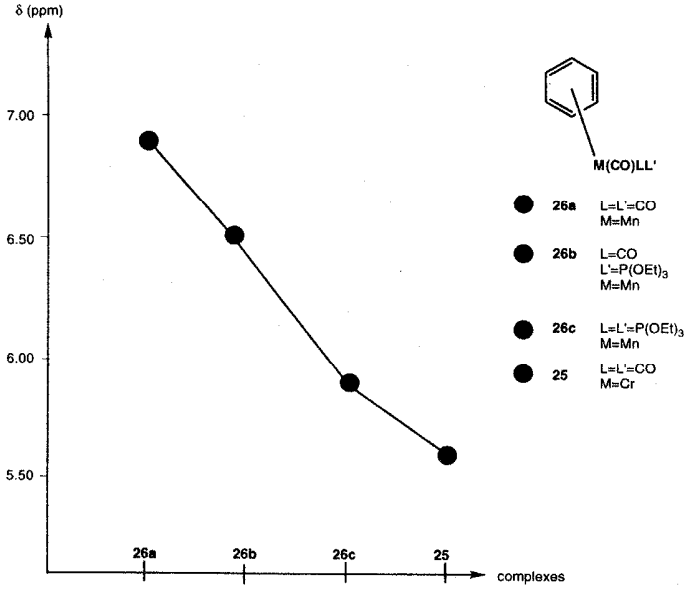


Fig. (3). Aromatic proton chemical shifts of benzene (ML_3) complexes.

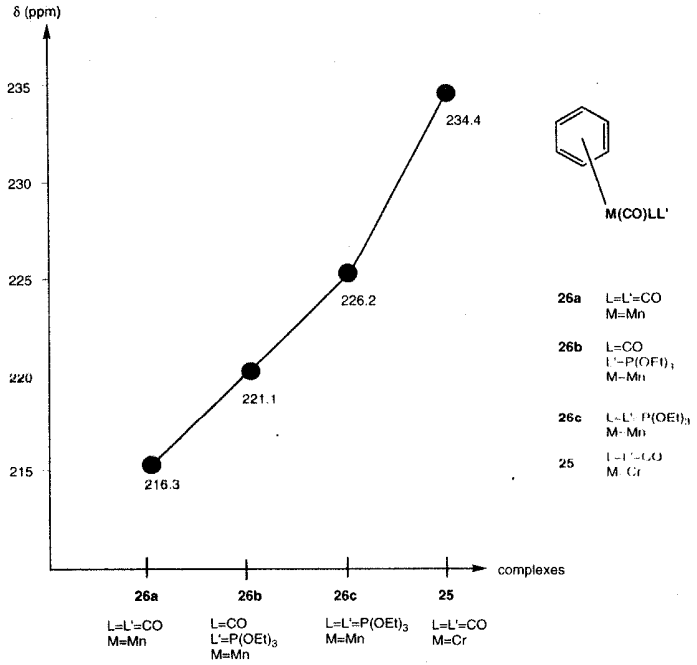


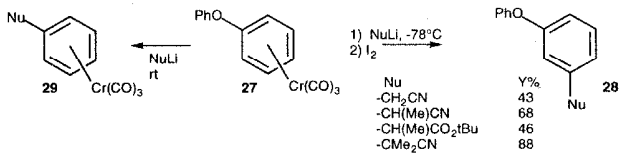
Fig. (4). Carbonyl carbon chemical shifts of benzene (ML_3) complexes.

stabilized carbanions. In the case of nitriles or esters, hydrolysis gave rise to the acids.

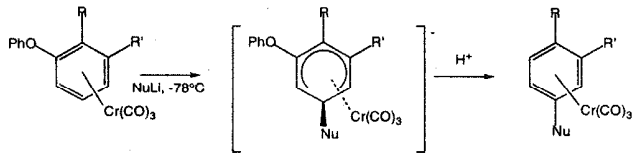
Addition of propionitrile carbanion to the diphenylether chromium tricarbonyl complex **27** at - 78° C followed by iodine oxidation and hydrolysis of the nitrile gave the free arene **28** in 68% yield. In the same conditions, addition of acetonitrile carbanion, propionic ethyl ester carbanion and isobutyronitrile carbanion gave the disubstituted arene in respectively 43, 46 and 88% yield. A better yield with a tertiary carbanion, was always observed because no side reaction can occur on the carbon α to the ester or the nitrile : no acidic hydrogen. Addition of propionitrile carbanion to the diphenylethertricarbonylchromium complex **27** at - 78° C followed by warming slowly to 5 °C the reaction mixture produces a complex **29** due to an *ipso* S_NAr reaction of the phenoxy group by the nucleophile (eq.5) [129].

Indirect Nucleophilic Aromatic Subtitutions

If we treated complex **27** with the carbanion Nu$^-$ at - 78°C and then with acid at - 78° C, we obtained a new



Eq. 5. Addition of stabilized carbanions to diphenylether tricarbonyl chromium **27**.

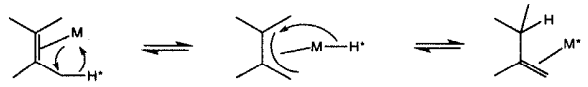


27 R=R'=H
31 R=Me, R'=H
33 R=R'=Me

30 R=R'=H
32 R=Me, R'=H
34 R=R'=Me

Eq.6. Addition of a stabilized carbanion to diphenyl ether tricarbonyl chromium complexes **27**, **31** and **33**.

complex **30** without phenoxy group (eq.6) [129-131]. So we repeated this reaction with the *ortho*-methyldiphenylether complex **31** and we obtained a *para*-disubstituted complex **32** with loss of the phenoxy group. We isolated as a minor complex a *meta*-disubstituted arene. So, in order to avoid this by-product, we did the same reaction with 2,3-dimethyldiphenylether complex **33** and we isolated a 1,2,4 trisubstituted complex **34** (eq. 6). Before describing the mechanism of this reaction, we would like to remind the isomerization of a double bond.



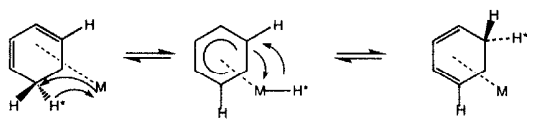
35 **36** **37**

Fig. (5). Isomerisation of an olefin coordinated to a metal.

It is well known that isomerization of the double bond of an allylic complex **35** for example occurs easily by an oxidative addition of the metal to the carbon-hydrogen bond (Fig.5). The new π-allyl chromium-hydride complex **36** is formed. At this stage, a reductive elimination of the metal by a migration of the hydride to the other carbon gives the other olefin **37**. This isomerization involves a 1,3-hydride migration. In the case of a diolefin, the same migration can occur and isomerization involves a 1,5-hydride migration. Thus oxidative addition of the metal to the carbon-hydrogen of complex **38** gives an η^5-cyclohexadienyl complex with a metal-hydride bond **39**. The hydride can migrate and a reductive elimination affords an isomeric η^4-cyclohexadiene **40**. In other words η^4-cyclohexadienes isomers **38** and **40** are in equilibrium (Fig.6).

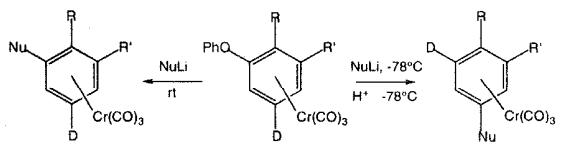
In our case in order to know more about the mechanism of our reaction, we prepared the diphenylethertricarbonylchromium complex **41** (eq. 7) substituted by two methyl groups at the C-2 and C-3 positions in order to avoid addition of the nucleophile to the C3 carbon and labelled by a deuterium at the C5 position [129-131]. Complex **41** treated with NuLi (Me_2CLiCN for example) and CF_3CO_2D generated complex **42** (eq. 7).

We called this reaction a *tele*-substitution [131]. Indeed, according to IUPAC recommendations, the term *tele*-substitution is used to denote reactions in which the entering group takes up a position more than one atom away from the atom to which the leaving group is attached [132]. To be more precise, we called it *tele-meta* substitution [131]. It is worthy to note the



38 **39** **40**

Fig. (6). Isomerisation of a 1-3-cyclohexadiene coordinated to a metal.



43 **41** **42**

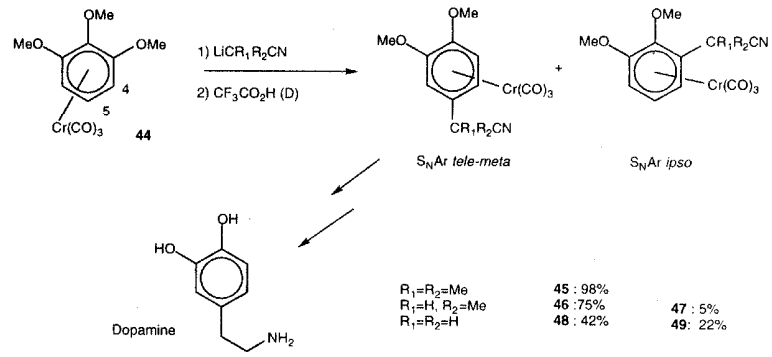
Eq. 7. *Ipso* and *tele-meta* nucleophilic aromatic subtitutions.

role of the temperature, indeed treatment of complexes **41** with NuLi (2-lithio-isobutyronitrile for example) at -78°C followed by warming at 25°C gave complex **43** *via* an *ipso* nucleophilic aromatic substitution (eq. 7).

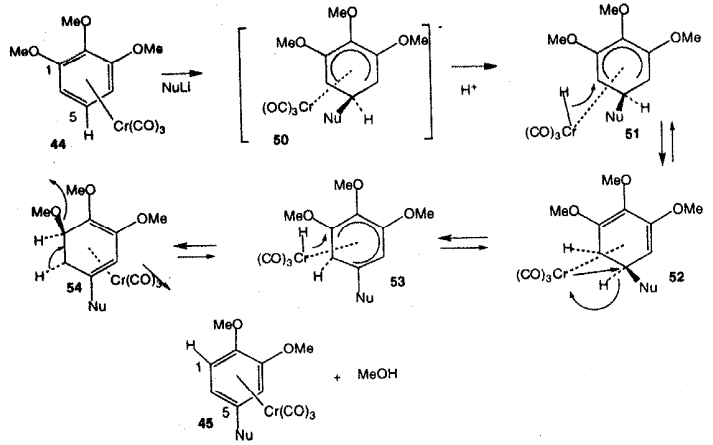
We decided to apply this reaction in order to prepare dopamine derivatives (eq.8). For this purpose, we reacted 1,2,3-trimethoxybenzene tricarbonyl chromium complex **44** with carbanions and then with trifluoroacetic acid. We observed in the case of a tertiary carbanion the formation of only one complex **45**. A *tele-meta* S_NAr occured, and the nucleophile reacted, as expected, on the C5 carbon. Indeed, the H5 proton resonated at the lowest field and the carbon C5 was eclipsed by a chromium carbonyl bond. In the case of a secondary carbanion, the major product is still the complex obtained via a *tele* subtitution **46** but a minor complex **47** was observed. The formation of which can easily be explained by an *ipso* addition of the nucleophile to the carbon bearing an external methoxy group. And in the case of acetonitrile carbanion, we obtained 42 % of the *tele-meta* substitution product **48** and 22 % of the *ipso* substitution product **49** (eq. 8) [133].

The mechanism of the formation of complex **45** is described in the scheme 12. First, *meta*-addition of the nucleophile Nu^- gave the anionic intermediate **50**. Protonation of this anion afforded the chromium hydride **51** which can migrate in order to give an (η^4-cyclohexadiene) chromium **52**. Isomerization occured via another (η^5-cyclohexadienyl) complex **53** and another (η^4-cyclohexadiene) **54**. At this stage, anti-periplanar methoxy group and hydrogen can be eliminated. This represented the driving force of this reaction with rearomatization of the cycle via a 1,5-hydrogen migration [133]. We wondered if it might be possible to find some reactions which would correspond this time to the addition of the carbanion *ortho* or *para* to the leaving group.

To promote an *ortho* attack, we chose the *para*-chlorotoluene complex **55** (eq.9), in the hope of adding the nucleophile *ortho* to the leaving group. Reaction of isobutylnitrile carbanion, for example, followed by acidic treatment at -78°C led to the *meta*-disubstituted complex **56** corresponding to an addition in the position *ortho* to the leaving group : this is a *cine* S_NAr (eq. 9) [134]. The term "*cine* substitution" is used in accordance with IUPAC recommendations to denote

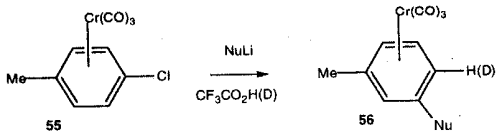


Eq. 8. Preparation of 4-substituted veratrole derivatives.



Scheme 12. Mechanism of the *tele-meta* S_NAr.

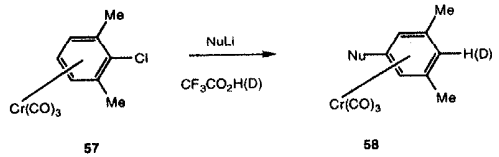
reactions in which the entering group takes up a position *ortho* to the leaving group [132]. If deuterated acid was used, there was incorporation of a deuterium atom on the carbon which bore the leaving group.



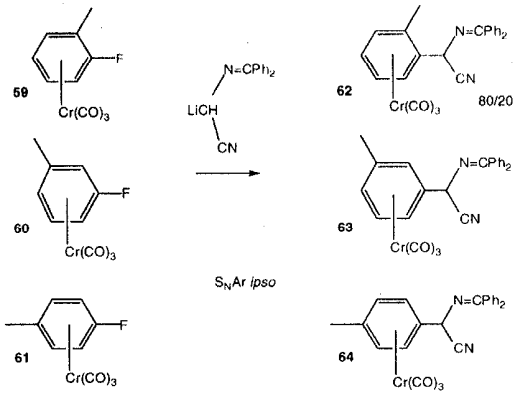
Eq. 9. *Cine* nucleophilic aromatic substitution.

Then to promote a *para* substitution, we protected the positions 2 and 6 of chlorobenzene tricarbonylchromium complex by preparing complex **57** (eq.10). The addition of a nucleophile was forced to occur on the C5 carbon and we recovered complex **58** after acidic treatment. This is a *tele* S_NAr [135], to be more precise, we called it a *tele-para* S_NAr (eq.10). If deuterated trifluoroacetic acid was used, there was incorporation of deuterium on the carbon which bore the leaving group. We will not go into the mechanism of this substitution, it involved the same intermediates as those invoked in the previous examples. In all the cases, the $Cr(CO)_3$ entity was preserved and thus a second functionnalization was possible. The free arene and $Cr(CO)_6$ can be recovered, if the final complex was treated under CO atmosphere. So, we have described a trilogy of reactions, namely *cine*, *tele-meta* and *tele-para* substitutions, by adding a nucleophile and then an acid to complexes substituted by a good leaving group. The nucleophile added at a position *ortho*, *meta* or *para* to the leaving group.

We mostly used stabilized carbanions such as those of α to nitriles or α to esters or α to dithianyl groups. But we checked also the reactivity of other carbanions



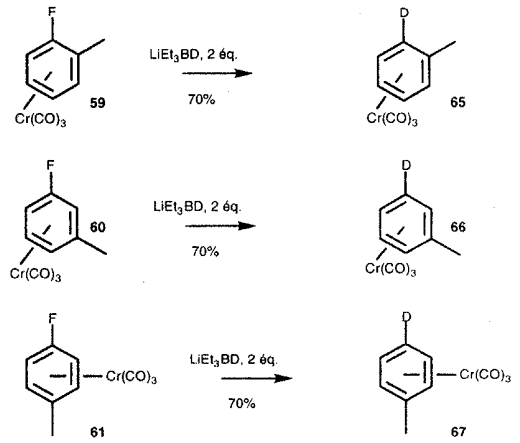
Eq. 10. *Para-tele* nucleophilic aromatic substitution.



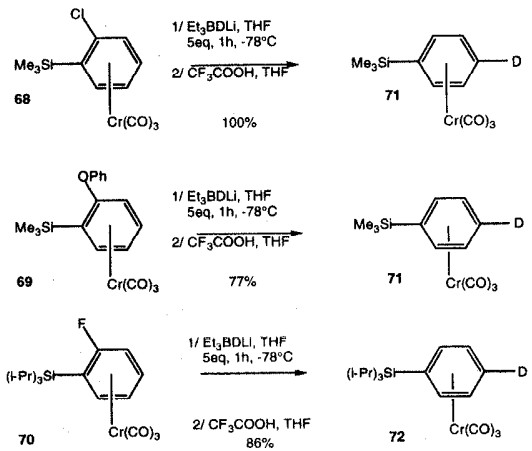
Scheme 13. Addition of a stabilized carbanion to fluoroarene complexes.

in particular the iminoesters or iminonitriles carbanions (scheme 13 towards halogenated chromium complexes. In the case of *ortho* **59**, *meta* **60** or *para* **61** fluorotoluene complexes, we obtained the corresponding *ortho* **62**, *meta* **63** or *para* **64** disubstituted complexes using *ipso* addition conditions. Hydrolysis of the iminonitriles gave the corresponding aminonitriles with the $Cr(CO)_3$ entity still coordinated on the arene [136]. In the case of the *ortho* disubstituted complex **59**, we obtained two diastereoisomers in an 80/20 ratio. Indeed, there is a first chiral center which is the benzylic center and a second one due to the planar chirality of the arene complex (scheme 13) [136].

We would like now to report the reactivity of a very simple nucleophile, namely an hydride. Does an hydride react with an arenetricarbonylchromium complex and, if so, what is the regioselectivity of this addition ? If lithiumtriethylborodeuteride was used in the case of the *ortho*, *meta* and *para* fluoro toluene complexes **59-61** (scheme 14), *ipso* addtion of the hydride took place and toluene complexes **65-67** with a deuterium at the *para*, *meta* and *ortho* positions with



Scheme 14. Addition of hydride to *ortho* -substituted complexes.



Scheme 15. Addition of hydride to *ortho*-substituted trialkylsilyl complexes.

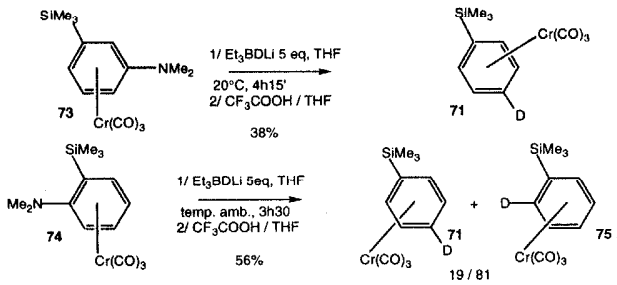
respect to the methyl group were obtained. Indeed, fluoroarene complexes were so reactive that *ipso* addition occured even at low temperature [137] (scheme 14).

If lithiumtriethylborodeuteride and trifluoroacetic acid were used in the case of three *ortho* disubstituted complexes bearing a bulky group such as a trialkylsilyl group **68-70**, we observed a *tele* substitution with the departure of the chloride atom (or the phenoxy group) giving **71** or of the fluoride atom giving **72** (scheme 15). A *meta* addition of the deuteride took place [137]. In this case, *ipso* substitution of the fluoride did not occur for steric reasons.

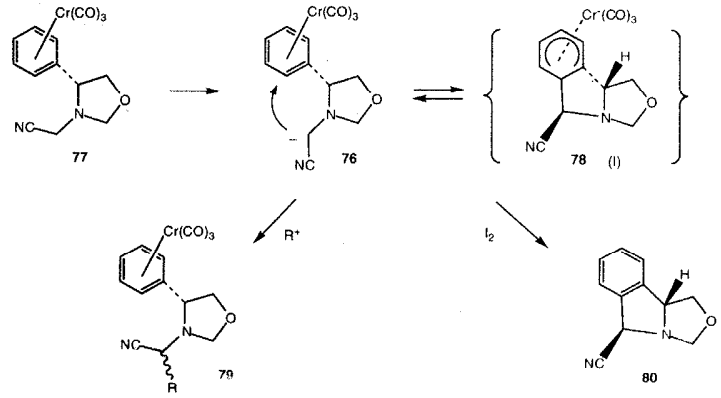
We wanted then to study the cleavage of the carbon-nitrogen bond which is known to be difficult to realize in organic chemistry. Although, this reaction did not give good yields (scheme 16), we observed in the case of *meta*-trimethylsilyl-dimethylamino derivative **73** a *cine* substitution and in the case of *ortho*-trimethylsilyl dimethylamino complex **74** two *tele meta* substitutions affording respectively the *para*-deuterotrimethylsilyl complex **71** and the *ortho* deutero-trimethylsilyl complex **75.** We never succeeded to cleave a C-S bond of complexes of diphenylthioether derivatives [138].

Preparation of Enantiomerically Pure Isoindoline

We have described that (η^6-arene)tricarbonyl chromium complexes react with carbanions derived



Scheme 16. Cleavage of the carbon-nitrogen bond : addition of hydride to aniline derivatives.

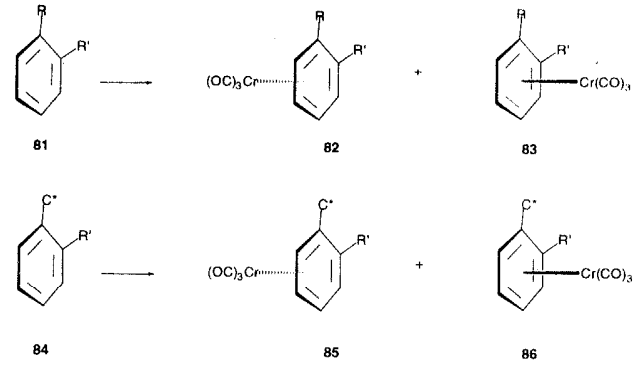


Eq.11. Preparation of iso-indoline derivatives.

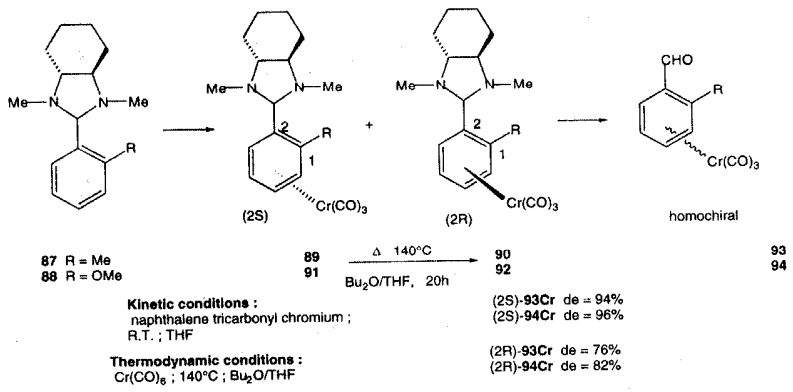
from alkyl nitriles for example to give negatively charged η^5 intermediates. Some intramolecular examples are known, but no case has been described for γ cyano arenes, nor for heterocyclic systems. We tried to know more about the stereochemical control during alkylation of the anionic intermediate **76** (obtained by deprotonation of the arene complex **77**) which is in equilibrium with the tricyclic anionic complex **78** (eq.11) [139]. Oxidative trapping-decomplexation of **78** with an excess of iodine gave complex **80** as a single R stereoisomer in about 20 % yield [139]. This represented an unprecedented intramolecular *ortho* directed cyclization of a (γ-cyanoarene) chromium complex. Treated with MeI, the anionic complex **76** gave complex **79** in 68 % (40 % de with the major diastereoisomer S having the S configuration at the new chiral center).

Diastereoselective Complexation of *Ortho*-disubstituted Arenes

We are coming now to a different aspect of these complexes. The goal to reach was to know if it should be possible to do some diastereoselective complexations of *ortho* substituted benzaldehyde. Indeed several asymmetric synthesis are based on the use of optically pure *ortho*-substituted complexes [140-154]. So, we tried to prepare such *ortho*-



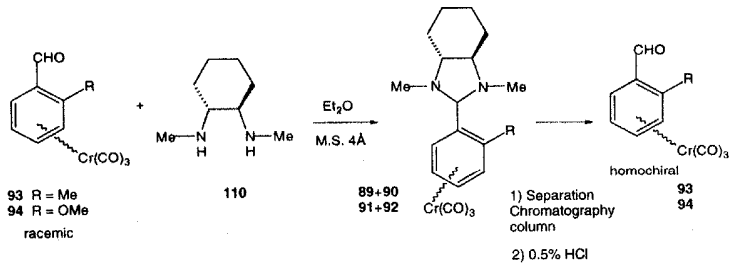
Scheme 17. Complexation of *ortho*-substituted arenes.



Scheme 18. Diastereoselective complexation : of *ortho*-substituted chiral aminals.

substituted benzaldehyde derivatives using chiral diamines with a C2 axis of symmetry as protecting groups. The (R,R), 1,2-bis(N-methylamino)cyclohexane was found to be the best diamine for this study. In the case of an *ortho*-disubstituted complex **81** it is easy to see that the $Cr(CO)_3$ entity can coordinate the arene ring under or above the plane of the arene. Thus, two enantiomeric complexes **82** and **83** can be obtained (chiral planarity) (scheme 17). If R is a chiral substituent (such as a chiral aminal), then the complexation of the arene **84** gives rise to the formation of two diastereoisomers **85** and **86** [155].

We wanted to know if it was possible by choosing the appropriate experimental conditions, to introduce selectively the chromium atom on one face or on the other one of the arene ? We found that chromation can be realized under very mild conditions using naphthalene chromium tricarbonyl complex at room temperature with a 94% enantiomeric excess in the case of the toluene complex **87** and with a 96% enantiomeric excess in the case of the anisole derivative **88** (scheme 18). Using thermodynamic conditions, with $Cr(CO)_6$ at 140°C in a mixture of dibutylether and tetrahydrofuran, we obtained after hydrolysis the homochiral benzaldehydes **93 and 94** in 76 and 82 % ee. But now the opposite diastereoisomer was the major one. This inversion of selectivity is unprecedented in the literature [155]. Thus for the first time, an efficient method exists for the enantioselective introduction of the chromiumtricarbonyl moiety on aromatic aldehydes. In the case of anisole derivatives, the two diastereoisomers can be studied by ^1H NMR. The aminalic proton of the R diastereoisomer resonated at 4.6 ppm and the aminalic proton of the S diastereoisomer at 3.9 ppm. The X-Ray structure of one aminal was obtained and showed as expected an eclipsed methoxy group with respect to a chromium carbonyl bond [156].



Eq. 12. Resolution of benzaldehydetricarbonyl chromium complexes.

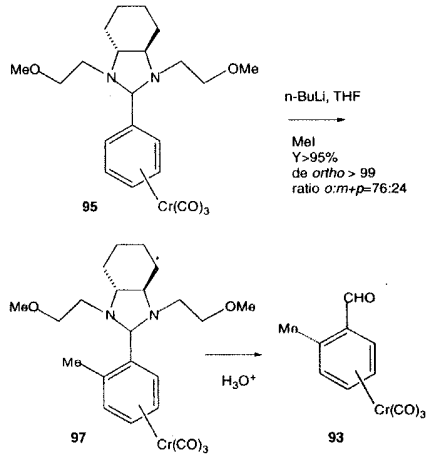
In the same study we used a racemic mixture of *ortho* substituted benzaldehydes to condense the chiral 1,2-diaminocyclohexane diamine. At room temperature, it was possible to obtain the yellow diastereoisomers **89, 90, 91** and **92** which could be separated on a silica gel chromatography column and hydrolyzed in order to get the homochiral benzaldehydes **93** and **94** (eq.12). This result showed that a chiral diamine is an efficient tool of resolution of a racemic mixture of *ortho* substituted benzaldehyde complexes.

Enantioselective *Ortho*-lithiation of Arene Chromium Tricarbonyl Complexes

Chiral chromium tricarbonyl arene complexes are known to be useful synthons in asymmetric synthesis [148-164]. Selective *o*-metallation versus *o'*-metallation of arene chromium tricarbonyl complexes led to highly diastereoselective preparation of *o*-substituted arene complexes [157-164]. In the case of acetals, the main problem lies in the difficulties in the preparation of these complexes and in the final hydrolysis step because extensive decomplexation occurs [162-164].

In view of the synthesis of enantiomerically pure ortho-substituted benzaldehyde chromium complexes, we used chiral aminals in light of the ease of preparation and hydrolysis of these compounds. Thus the asymmetric *ortho* lithiation of aminals of benzaldehyde tricarbonyl chromium complexes (from diamines **96, 99, 101, 103** represented Fig.7) showed that the best regioisomeric composition was attained with the aminal **95** using the diamine **96**; lithiation quenching with MeI and hydrolysis of the aminal **97** back to the aldehyde afforded a single enantiomer of the *o*-substituted benzaldehyde complex **93** (eq. 13).

In all the cases, the selectivity of *o*-metallation versus *o'*-metallation was total in Et_2O or in THF. This regioselectivity in the case of **95** is ascribed to the bidentate structure of the oxygen of the side chain and of the nitrogen of the imidazoline ring.



Eq. 13. Enantioselective lithiation.

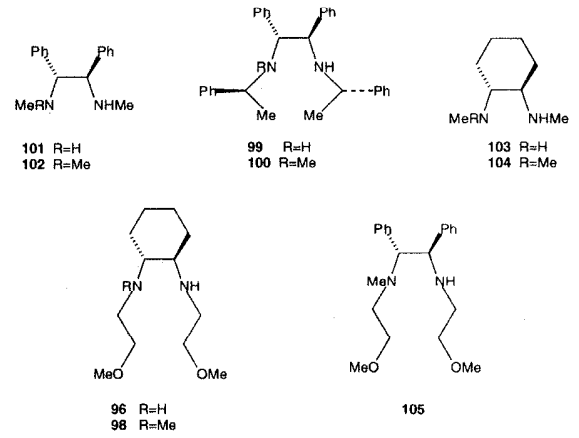
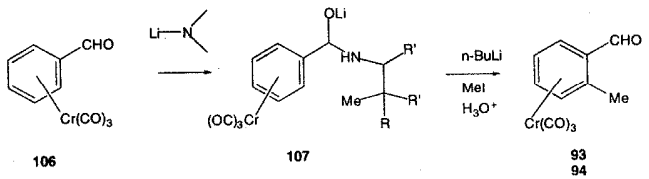


Fig. (7). Enantioselective formation of *ortho*-substituted benzaldehydes complexes.

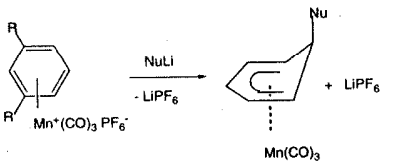


Eq.14. Preparation of chiral amino alcoolate.

The Commins method to temporarily protect an aromatic aldehyde as an amino alcoolate was used [165-166]. Indeed the amino appendage facilitates *ortho*-deprotonation. When applied to an aromatic derivative having a potential planar chirality it allows an asymmetric version (eq. 14). The diamines **98**, **100**, **102**, **104**, **105** were used (Fig.7). The asymmetric *ortho*-lithiation of benzaldehyde complexes was performed by in situ temporary protection of the aldehyde functionality giving the amino alcoolate **107**. By treating this complex **107** with n-BuLi and MeI followed by acidic hydrolysis the *ortho* -methyl benzaldehyde **93** was obtained, the ratio *ortho* : *ortho'* being 6 : 1 in 68 % yield (ee 72 %). No *meta* product was observed using the diamine **105** having the two methoxy appendages on the nitrogen atom [167].

Reactivity of Chromium Complexes as Nucleophiles Towards Cationic Arenetricarbonylmanganese Complexes

As presented before, chromium complexes are easily lithiated and it was interesting to react some of these so formed carbanions with other organometallic complexes namely electrophilic cationic arenetricarbonyl Mn complexes. Indeed it is well known that the addition of a nucleophile to an arene manganese complex affords a stable neutral (η^5-cyclohexadienyl) complex. For example the Mn complexes **26** and **108** reacted with different nucleophiles (such as chloroester carbanions, bromoester carbanions, nitriles carbanions, isonitrile esters, iminoester and iminonitrile carbanions) to give almost quantitatively stable neutral η^5-cyclohexadienyl complexes **109-115** (eq.15) [127,169-171]. The structures of some of these complexes were determined by X-Ray crystallography [171-172].

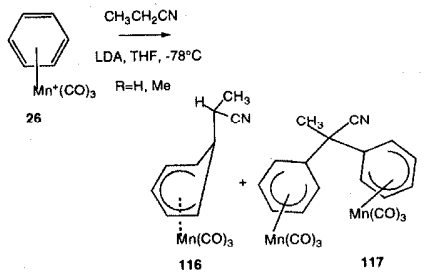


26 R=R'=H
108 R=R'=Me

109 Nu=-C(Cl)(CH3)CO2CH3
110 Nu=-C(Br)(CH3)CO2CH3
111 Nu=-C(CH3)2CN
112 Nu=-CH(CO2CH3)NC
113 Nu=-C(Y)(CN)N=CPh2 Y=H, F,Me
114 Nu=-C(Y)(CO2R)N=CPh2
115 Nu=-C(Y)(Z)SO2Ph

Eq.15. Addition of stabilized carbanions to cationic Mn complexes.

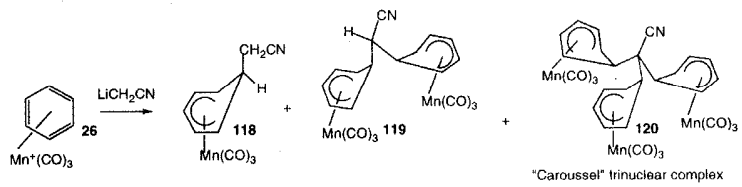
In the presence of an excess of base (for ex. LDA in eq. 16), the dinuclear complex **117** was obtained besides the mononuclear one **116**. Depending on the amounts of propionitrile and LDA, it was possible to prepare the mono **116** or the dinuclear complex **117** as the major one.



Eq. 16. Addition of propionitrile carbanion to benzene tricarbonyl manganese.

With acetonitrile carbanion, it was also possible to obtain the mono **118**, the dinuclear complex **119** whose the X-Ray structure has been realized but also the trinuclear complex **120** that we called the "caroussel like" complex (eq.17) [127, 172].

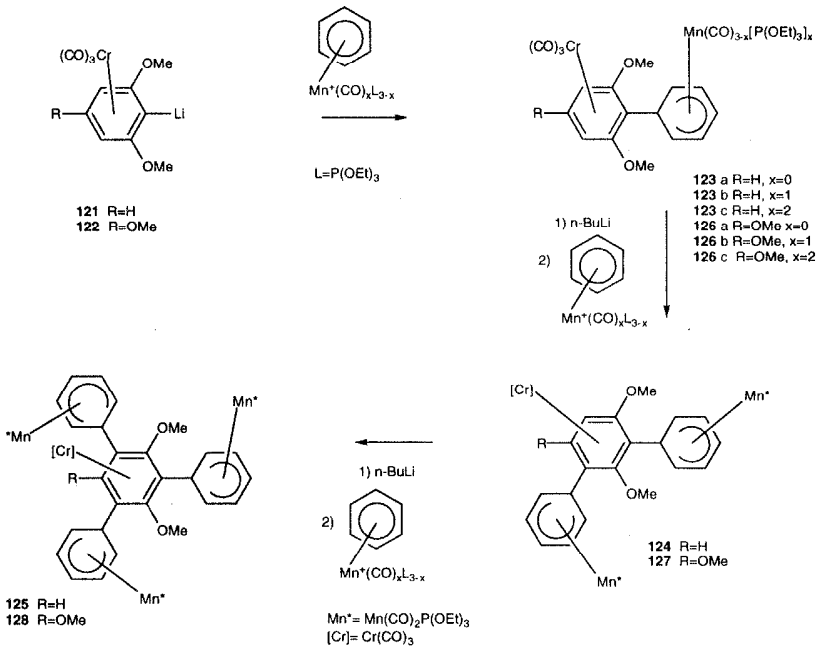
We next changed the nature of the nucleophile and we chose an aryllithium chromium complex. In order to avoid the formation of different isomers, we chose as starting material a 1,3-dimethoxybenzene chromium complex **121** (scheme 19). Indeed lithiation occurs at



Eq.17. Addition of acetonitrile carbanion to benzene tricarbonyl manganese.

the C2 carbon, and after adding a cationic Mn complex, we obtained a dinuclear complex **123**. Using the same experimental conditions, it was possible to prepare a trinuclear complex **124** (scheme 19) and then a tetranuclear complex **125**. With the 1,3,5-trimethoxy benzenetricarbonyl chromium complex **122**, we obtained in the same way complexes **126**, **127** and **128** [173-174].

In conclusion, we described that it was possible to obtain a good regioselectivity of the addition of a nucleophile to an arene-chromium complex in the case of the addition of propionitrile carbanion to a spiroindane chromium tricarbonyl complex. This can be explained by the conformation of the chromium tricarbonyl tripod with respect to the arene ring. No regioselectivity was observed in the case of the corresponding arene cyclopentadienyl iron complexes. In the case of the corresponding manganese complex, it was possible to observe a good regioselectivity if the ligands coordinated to the metal center are appropriate (less π acceptor). We described also three reactions : the *cine*, the *tele meta* and the *tele para* nucleophilic aromatic substitutions which corresponded to the



Scheme 19. Addition of aryllithium tricarbonyl chromium complexes to cationic iron complexes.

addition of a nucleophile *ortho* , *meta* and *para* to a leaving group if the reaction medium was treated with an acid after reacting with the nucleophile : - 1,5 hydride migration occured. The chromium tricarbonyl entity was preserved (a second functionalisation was possible) and depending on the nature of the R group, the regioselectivity of the addition of a nucleophile can be chosen. Diastereoselective complexation of *ortho*-substituted aminals can work efficiently by choosing the appropriate chiral aminals. Enantioselective *ortho*-lithiation of arenetricarbonyl chromium complexes was achieved by using the appropriate chiral amines to temporarily protect an aromatic aldehyde as an amino alcoolate. Finally, we showed that it was possible to synthesize new hetero di-, tri- and tetra-metallic complexes in combining the specific properties of (η^6-arene) chromium tricarbonyl complexes (easy deprotanation) and of (η^6-arene) manganese complexes (high electrophilicity).

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