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The effect of transition metal benzyl and propargyl species on the behavior of steroidal hormones

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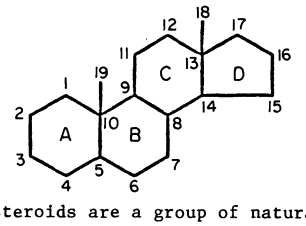
Abstract - The activation of positions adjacent to a transition metal coordinated organic ligand (e.g.arene, alkyne) can be taken to advantage in organic chemistry. Particularly, this methodology allows regio and stereospecific functionalisation in steroidal hormones as well as access to suspected efficient and selective affinity markers.

INTRODUCTION

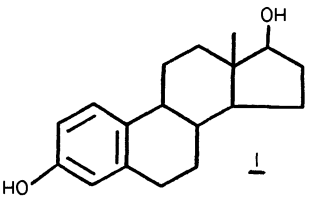
The incorporation of organometallic moieties into biologically important molecules is a field of burgeoning importance. For example, in the area of bioorganometallic chemistry, significant advances are emerging. Thus, we have discussed the use of steroidal hormones labelled with metal carbonyls to assay receptor sites (1). This concept is based not only on the ability of the hormone to recognize its specific receptor but also on the fact that the metal carbonyls absorb strongly in the infrared region in the range 2100-1850cm^{-1} ; this frequency range coincides with a window in which the proteins do not absorb. Although the concentrations of hormones encountered in biological systems are of the order of only a few femtomoles per milligram of protein, such levels of metal carbonyl substituted hormones can be detected using Fourier transform infrared spectroscopy. This technique may thus provide a viable means for monitoring the hormone dependance of breast cancer whilst avoiding the use of radioactivity and its associated inconveniences. The attachment of organo-transition metal moieties into molecules to exploit their spectroscopic properties for analytical purposes can, in principle, be applied not only to the animal but also to the vegetable and mineral kingdoms One would have to satisfy the criteria that some organo-metallic chemistry be possible for the appropriate precursors and also that the products of reaction be reasonably stable. In the case at hand, it is important that the organometallic derivatives of the hormones retain their ability to recognize their specific receptor sites. These new applications of transition-metal chemistry are based on the present, highly-developed state of this field whichs offers the opportunity to synthesize and exploit a rich and versatile new class of tailor-made organometallic complexes. In the present report we will show how the study of the biochemistry of steroidal oestrogens benefits from a fundamental understanding of the synthesis and electronic properties of model arene chromium tricarbonyl complexes and related species. In steroid chemistry (scheme 1), metal carbonyl fragments have already been used for the temporary protection of particular functional groups so that another portion of the molecule could be modified. For example, complexation of the diene unit in the B ring of ergosterol by a Fe(CO)3 group allowed the hydrogenation of the exocyclic double bond at C-22 ; subsequent removal of the tricarbonyliron fragment regenerated the diene unit (2). Likewise, modification of steroidal sidechains has been elegantly accomplished via allyl-palladium intermediates (3). As far as aromatic steroids (scheme 2) are concerned, the attachment of a Cr(CO)3 moiety allows both analytical (1) and chemical applications. Thus, owing to the activation of benzylic positions mediated by Cr(CO)3 units this temporary arene complexation has been used to carry out a series of useful regio- and stereospecifif functionalisations (4).

Scheme 1



The steroids are a group of naturally occuring organic compounds and their synthetic derivatives, all of which are characterized by a basic skeleton consisting of three six-membered rings and one five-membered ring.

Scheme 2



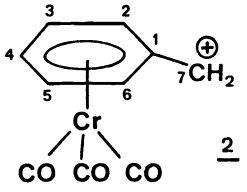
1 = Estradiol, the archetype of the estrogens, with an aromatic A ring. The intimate involvement of these steroids in the cause of certain cancer (such as breast cancers) is now well established (5).

ACTIVATION OF BENZYLIC POSITIONS MEDIATED BY $Cr(CO)_3$ UNITS

Among the transition metal arene complexes, arene tricarbonyl chromium derivatives appear as the leading series for stoichiometric organic synthesis (6). This situation exists not only because the complexation and decomplexation steps are simple and almost quantitative (7) (8) in this series but also because the chemical properties of the arene are significantly alterated on complexation. The recognized changes in arene reactivity that have been observed when a metal is coordinated with the arene π-system are summarized as follows : stabilisation of side-chain cation sites, enhanced kinetic acidity of the benzylic protons, stereoelectronic effects of the coordinated metal units, enhanced acidity of arene ring hydrogen substituents, nucleophilic aromatic addition and substitution reactions. The organic modifications occurring directly on the ring have already been reviewed (9).

For some years, many papers have been concerned with the capacity of the tricarbonyl-chromium (o) moiety to stabilize anions (10) or cations (11) at the benzylic position. This hermaphroditic particularity unique in organomatallic chemistry, enlarges the synthetic potential of these species in organic synthesis but requires the outline of an explanation.

Scheme 3



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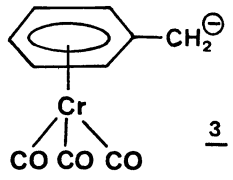
The remarkable stability of the coordinated benzyl cation 2 arises via back-bonding from the chromium dx^2-y^2 orbital into the non-bonding π-orbital of the benzyl ligand.

Scheme 4

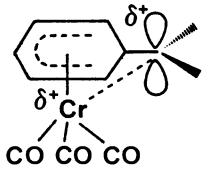


3

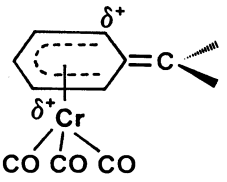
The electron withdrawal occurs primarily from the ring σ-orbitals. The charge-stabilizing effect of the $Cr(CO)_3$ group is via inductive or σ-framework interactions rather than a resonance pathway.

Spectroscopic evidence confirms the greater thermodynamic stability of $[(benzyl)Cr(CO)3]^+$ 2 compared with the free benzyl cation (pk_{R+} = -11.8 and <17.3, respectively) (12). Because of the ubiquity of this situation in organometallic chemistry (Table 1), this problem has attracted considerable attention. Two fundamentally different stabilization mechanisms (based largely on analogy with the related α-ferrocenyl carbenium ions (13) (14) have been proposed (15) : a) neighbouring group participation (d-orbital bridging) in which there is direct interaction between a filled metal d orbital and a vacant p orbital on the carbenium ion (scheme 5) :

Scheme 5



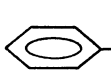
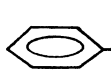
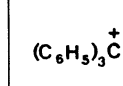
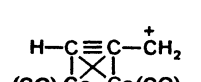
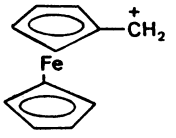
Scheme 6



b) metal-ring σ-π delocalization in which the α-carbenium ion is stabilized by π-conjugation with the ring (scheme 6).

However, INDO molecular orbital calculations suggest that the stabilisation arises via yet another mechanism, which leads to an overall change in the structure of the benzyl moiety (16) ; namely via backbonding from the chromium $d_{x^2-y^2}$ orbital into the non-bonding π-orbital of the benzyl ligand. The C(7) atom is the most strongly affected since the vacant non-bonding orbital Ψ_n has a high location on this site (62%). The remainder of the back-donation occurs almost equally to C(2), C(4) and C(6). It is probable that bending of ca. 40° of the C(7) atom towards the chromium might occur since this configuration was more stable than the planar structure by ca. 150KJ.mol^{-1}. The above stabilization mechanism resembles a neighbouring group interaction. However, it does not involve specific bond formation between the metal and C(7), but rather overlap with the benzyl ring as a whole.

TABLE 1. pK_{R^+} values for some stable carbenium ions

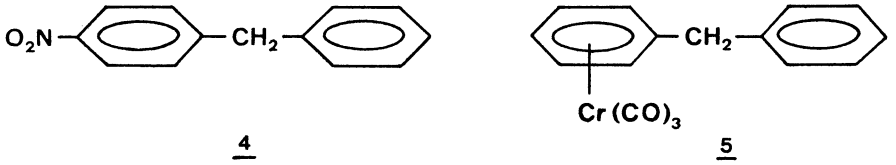
carbenium ion					
pK_{R^+}	$<$-17.3 (17)	-11.8 (12)	-6.6 (17)	-6.8 (18)	-1.5 (13)

The pK's for ionisation of alcohols in aqueous sulfuric acid were determined spectrophotometrically by the method of Deno and coworkers (17) (e.g. pK_{R^+} of Ph_2CH^+ = -13.4).

On the basis of reactivity patterns (19) (20), dipole moment data (21), and the close similarity of the pKa's of p-nitro-phenyl-and chromium tricarbonyl complexed phenylacetic acids (19a), Cr(CO)3 was regarded as having a similar electron-withdrawing effect to that of a p-nitro group. However the degree of this analogy should be carefully examined and the exact nature of the electron-withdrawing effect of the Cr(CO)3 group has been recently appreciated (22).

The kinetics and thermodynamic acidities of the Cr(CO)3 or p-nitro substituted di-and triphenylmethanes have been measured in methanol-dimethyl sulfoxide solutions. The kinetic acidifying influence of a single tricarbonyl chromium (o) group 5 has been found to be greater than that of a single p-nitro substituent 4 in these molecules by a factor of 3-4 but the acidifying effect of the tricarbonylchromium (o) group is not cumulative and steric effects become increasingly evident in these complexed molecules. The thermodynamic acidities of the nitro-substituted aromatics are greater of some orders of magnitude than those of their Cr(CO)3-complexed analogues, in accord with the greater charge delocalization in their carbanions by the nitro group. These data are in accord with those of Ceccon for base-catalyzed eliminations, from $p\text{-}NO_2$-substituted, or Cr(CO)3-complexed, 2-phenylethyl derivatives where he found the influence of a $p\text{-}NO_2$ group to be much greater (i.e. accelerating) than that of the Cr(CO)3 group toward E_2 eliminations (23). These results strongly support an interpretation that the charge-stabilizing effect of the Cr(CO)3 group is via inductive or σ-frame work interactions rather than a resonance pathway.

Scheme 7



4 5

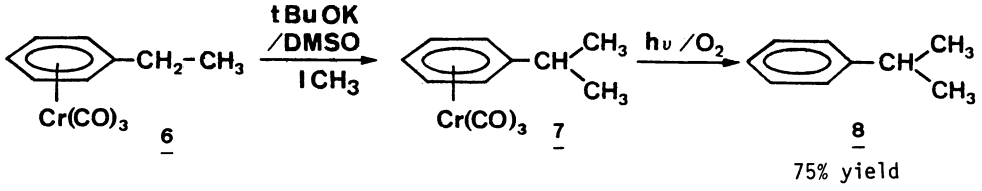
The kinetic acidifying effect of one $Cr(CO)_3$ group is greater than that of one $p\text{-}NO_2$ group in diphenylmethane by a factor of 3-4. Comparison of the estimated thermodynamic acidity for 4, with the experimental values for 5 yields K ratio of 4/5 of ca 40:1 indicating that the $p\text{-}NO_2$ group has a greater thermodynamic effect than one $Cr(CO)_3$ group in diphenylmethane (22).

STEREOSPECIFIC ELECTROPHILIC ATTACK AT BENZYLIC POSITION VIA $Cr(CO)_3$ ACTIVATION

As a consequence of the electron-withdrawing effect of the Cr(CO)3 moiety, temporary complexation of an arene substrate increases its susceptibility to proton abstraction from a carbon chain.This increased tendency towards anion formation thus permits electrophilic attack of substrates for which free ligands have little or no reactivity.

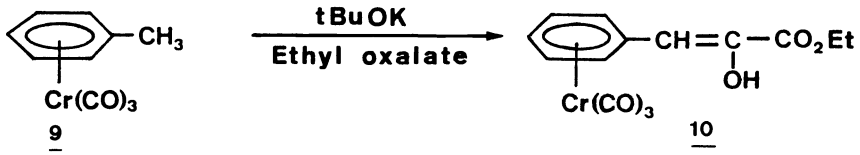
We have reported some years ago that C6H5iPr 8 is obtained in 75% yield from the complex Cr(CO)3(PhEt) 6 by use of methyl iodide and tert-butyl potassium oxide in dimethyl sulfoxide (scheme 8) (24) (25). Moreover, in a rigid system, e.g. complexed indane, the exclusive exo substitution of hydrogens bonded to a carbon in the ring α-position occurs (26).

Scheme 8



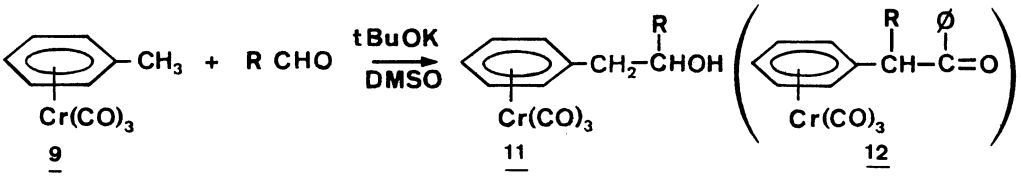
Several examples of functionalisation of aromatic benzylic positions(10e) (27) by using the Cr(CO)3 activating effect have appeared in the recent literature. scheme 9 shows, as example, the synthesis of phenyl ethyl pyruvate trapped in its enolic form by a Cr(CO)3 moiety (28). The reaction of tBuOK with toluene Cr(CO)3 9 in the presence of an equimolar amount of ethyl oxalate gives rise to the stable enol 10 in good yields (78%). Phenylpyruvate derivatives are involved in mechanistically puzzling enzymatic liver reactions (29).

Scheme 9



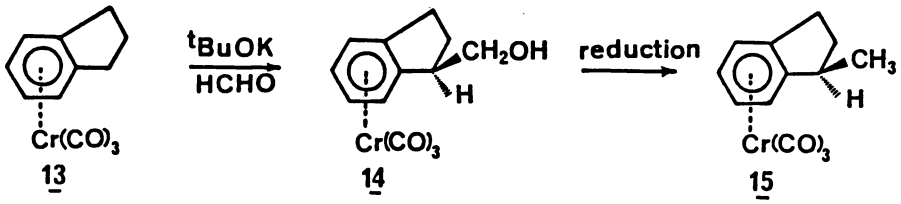
When aldehydes are used instead of ethyl oxalate, the complexed alcohols are obtained (scheme 10) (30) (4). To perform this functionalisation reaction, the carbonyl reagent should not possess enolic protons. Thus benzaldehyde and formaldehyde can be used but with $(CD_3)_2CO$ solely α-deuteriated complexes are isolated owing to the occurrence of a proton exchange. Interestingly , depending on the solvent (THF instead of DMSO) this reaction can lead to the Oppenauer-Woodward oxidation product 12 (31).

Scheme 10



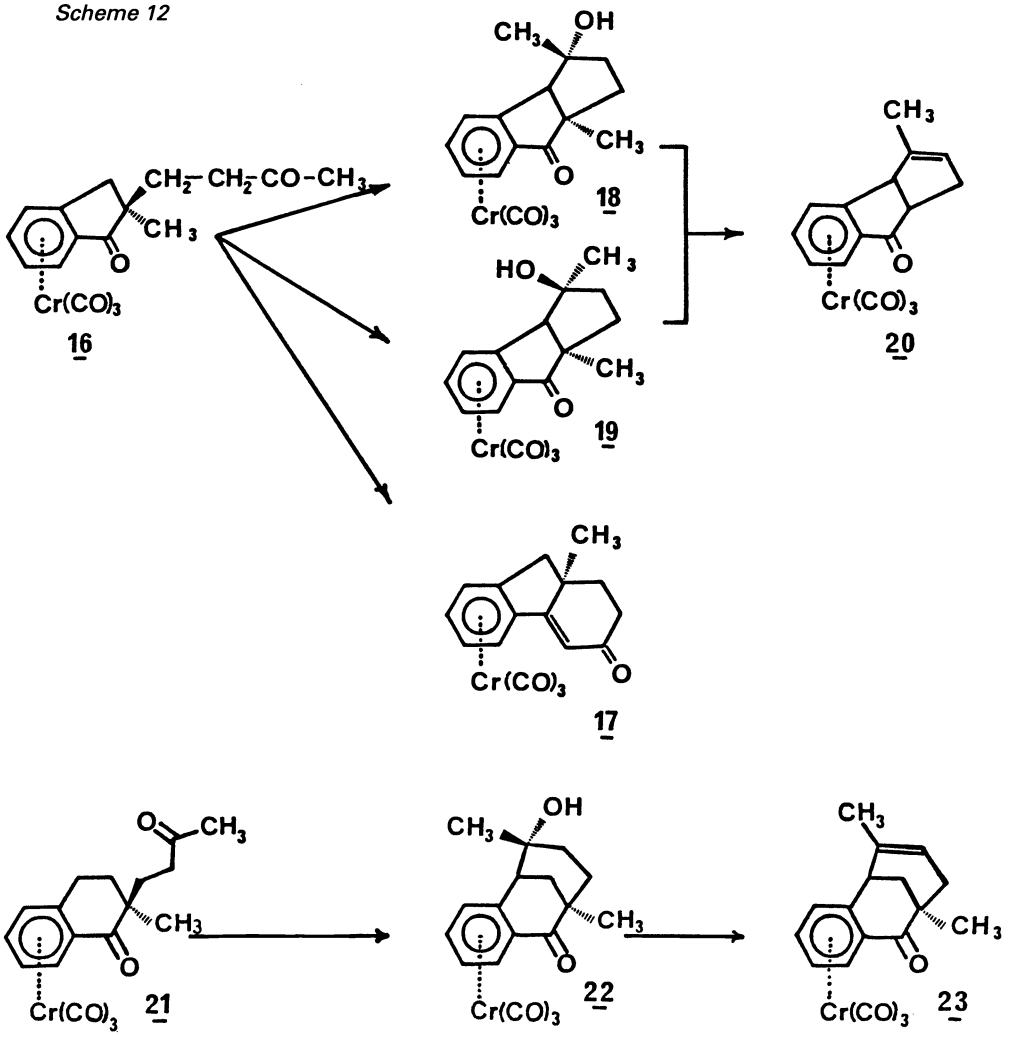
The stereochemical course of the reaction was studied as follows. To the carbanion derived from indane chromium tricarbonyl 13, formaldehyde was added. (scheme 11). After treatment, only one isomer of (1-hydroxymethyl indane)- Cr(CO)3 14 was obtained in 60% yield. After addition of toluene-p-sulfonyl chloride and reduction with $LiAlH_4$, the (1-methylindane) Cr(CO)3 15 was characterized and compared with an authentic sample. Therefore, the attack by formaldehyde is stereospecific in an exo fashion due to the stereoelectronic effect of the bulky tripod.

Scheme 11



Actually, the first stereospecific functionalization at the benzylic site was reported in 1976 by Jaouen and Meyer (32) (33) in an unusual preparation of chiral benzobicyclic ring systems (scheme 12).

Scheme 12



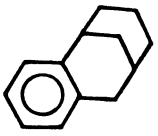
The ketone 16, with the shown absolute configuration, underwent two concurrent cyclizations. The first one led to the expected diastereomeric α-enone 17 whereas the second ring formation which is predominant (>90%), yielded two products 18 and 19 (ratio $^{18}/_{19} = {}^{45}/_{55}$). The assignment of the stereochemistry in these complexes was elucidated on spectroscopic evidence.

The unusual annulation in 16, resulting from attack of the linear ketone in an exo fashion at the benzylic group rather than classical attack at the cyclic ketone, can be explained by considering the activation of the methylene protons in the α position of an arene coordinated to Cr(CO)3. In 16, the oxobutyl group is free from the steric hindrance of $Cr(CO)_3$ and an attack on the activated exo benzylic hydrogen is possible. Of course, by changing the position of the substituents adjacent to the ketone function in 16 (CH_3 in exo position), solely the normal conjugated α-enone was obtained because the endo benzylic hydrogen is not activated.

Upon treatment with $SOCl_2$ in pyridine the keto alcohols 18 and 19 were converted by dehydration into the same non conjugated enone 20 in 90% yield.

This annulation reaction was also applied to the tetralone derivatives. Annulation of the endo methyl isomer 21 led to complex 22 as the major product (>95%). This keto alcohol was constructed specifically by the unusual cyclization process producing a new six-membered ring.This process can then be used to reach the skeleton 24, already mentioned in the synthesis of polycyclic compounds (34).

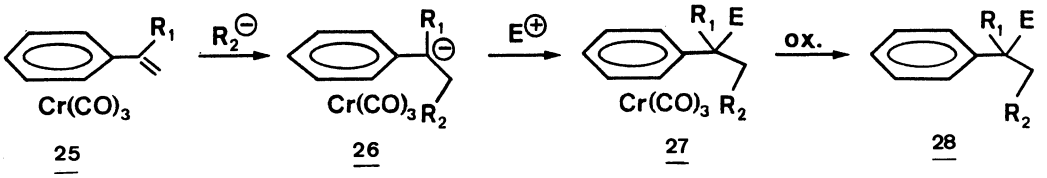
Scheme 13



24

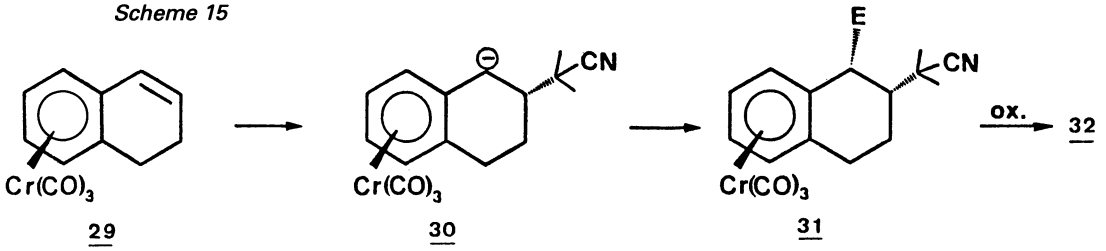
It was also recognized that nucleophilic addition to the β position of an η^6-styrene ligand generates the stabilized benzyl anion (35) (36) (scheme 14).

Scheme 14



A variety of nucleophiles, electrophiles, and styrene-type ligands participated smoothly in the conversion represented above. The dihydronaphtalene complex 29 provides an example of the excellent stereochemical control in reactions of rings fused to arene - Cr(CO)3 complexes. (scheme 15).

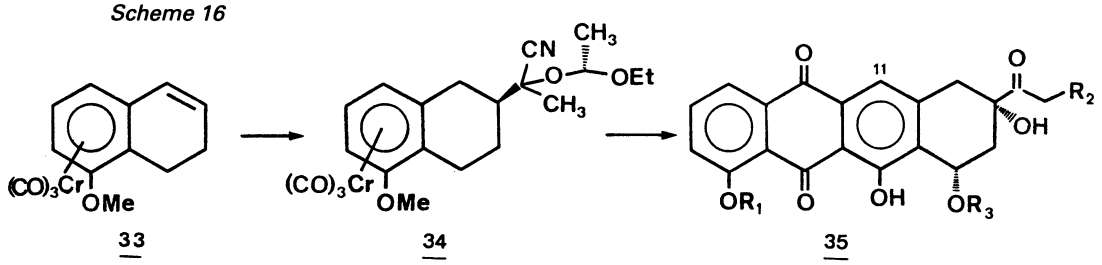
Scheme 15



Reaction with 2-lithio-2 methyl propionitrile proceeded rapidly at 0°C. Addition of electrophiles E^+ gave mainly the adduct 31. The cis orientation shows the well-established tendency for exo attack in the reactions of rigid bicyclic arene Cr(CO)3 complexes.

The behavior of (η^6-styrene) Cr(CO)3 as equivalent to a Michael acceptor, in which nucleophilic addition occurs at the β position of the styrene ligand, was turned to advantage in the synthesis of 11-deoxyanthracyclinone 35 (scheme 16) (37).

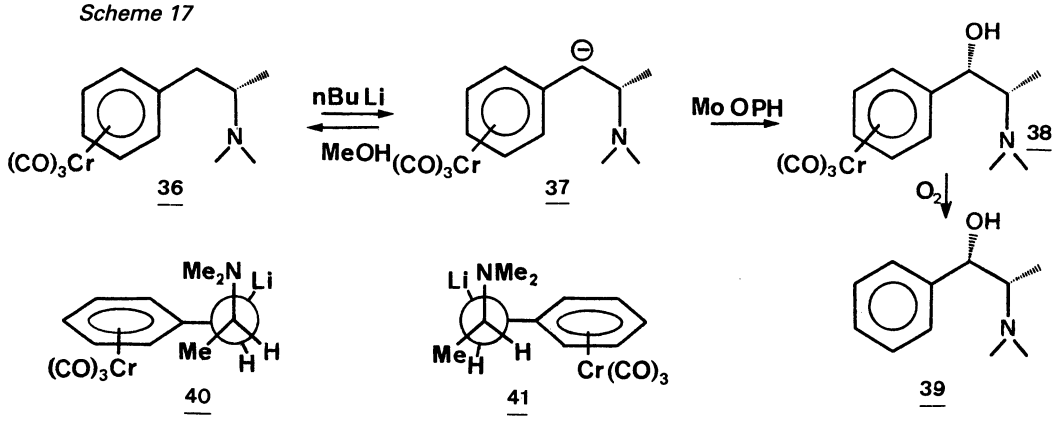
Scheme 16



Interestingly, these benzylic substitutions are stereospecific even in open chain series. For example, the coordinated N,N-dimethyl-amphetamine 36 after treatment with nBuLi at -78°C can be trapped by electrophiles, such as MoOPH , to yield the complex 38 (38). The decomplexation by exposure of ether solutions to air and sunlight (8) liberates N-methylpseudoephedrine 39. This stereospecific substitution with retention of configuration presumably originates from unfavourable steric interactions between the 1-methyl group and the phenylchromium tricarbonyl moiety leading to formation of 40. Such unfavourable interactions

are avoided in transition states leading to removal of the pro-R hydrogen and formation of 41.

Scheme 17

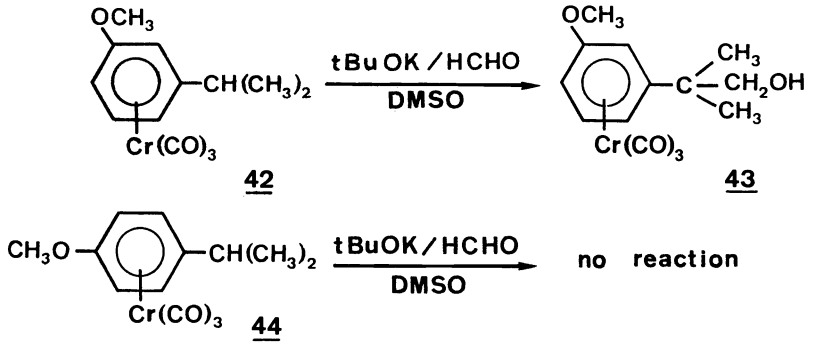


REGIOSPECIFIC FUNCTIONALIZATION OF BENZYLIC SITES BY TRICARBONYL CHROMIUM ARENE COMPLEXATION

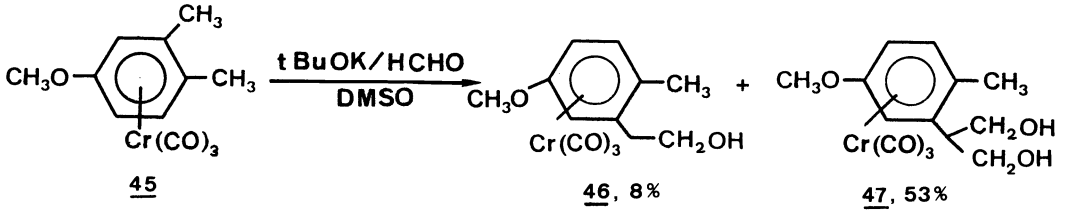
Several reports have appeared in the literature on substituent effects in electrophilic (39) and nucleophilic (40) direct addition to the aromatic ring of arene-chromium tricarbonyl complexes. The dominance of conformational effects in directing the attack of both electrophilic and nucleophilic reagents has been established (41) (42) (43).

Owing to the importance of regioselectivity in aromatic synthesis, the behavior of tricarbonyl (alkyl benzene) chromium complexes bearing electron-donating and electron-withdrawing arene substituents has been examined (44) (4). As a model reaction, the behavior of stabilized benzyl anions, generated by t.BuOK, in the presence of formaldehyde has been particularly analyzed. The selection of results listed in schemes 18, 19, 21 shows a striking difference in the comportment of the complexes depending on the position of the substituents.

Scheme 18



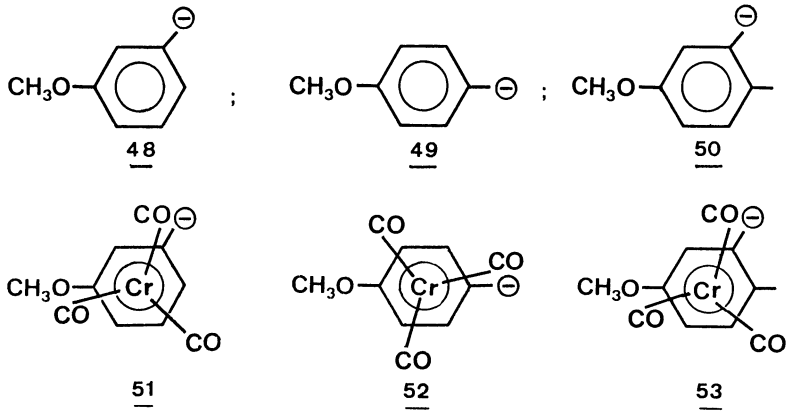
Scheme 19



In scheme 18, the meta alkyl substrates are much more reactive than the para alkyl compounds. While, in the first example 42, the yield of isolated product 43, is superior to 65%, the second compound 44 appears to be inert. Interestingly, when the two potential sites of attack (namely the meta and para positions with respect to the methoxy substituent) are present in the same molecule 45, only products bearing the methyl hydroxy group at the meta α-carbon 46, 47 were produced (scheme 19).

In contrast to previous regioselectivity reports, in the reaction studied here no attack on the ring has been detected. Extended Hückel calculations have shown that the conformational effect of the tripod is, in the present case, a minor phenomenon (45). The difference in stability of the generated carbanions 48 and 49 (and 51, 52) appears the important factor to be taken into account. Therefore, the encountered regioselectivity is a purely arenic phenomenon. For example, in the free ligands, the hypothetical species 48 appears to be more stable than 49 by about 3 Kcal/mole. Interestingly the same difference in stability exists between 51 and 52 whatever the conformation of the Cr(CO)3 unit. Similarly, 50 and 53 were found to be the most stable trisubstituted anions for electronic reasons.

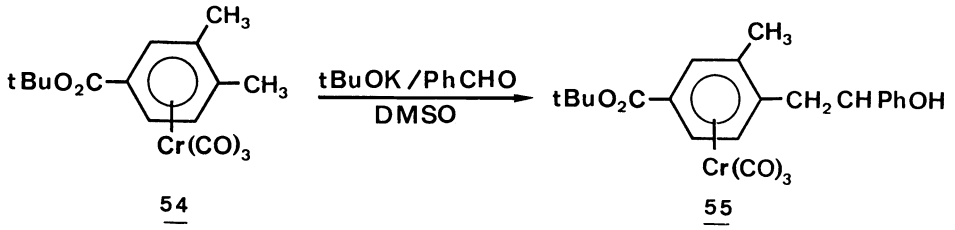
Scheme 20



The role of the Cr(CO)3 moiety is to favor the generation of the carbanion but this unit does not modify strongly the electronic effects of the substituants such that they are established in the free ligands. The regioselectivity results are quite compatible with the electronic properties of the methoxy substituent which possesses an electron-withdrawing inductive effect and an electron-donating resonance potential.

Similarly, the effects of electron-withdrawing substituents (e.g. an ester function) on benzylic functionalization are in accord with the above explanation (scheme 21).

Scheme 21

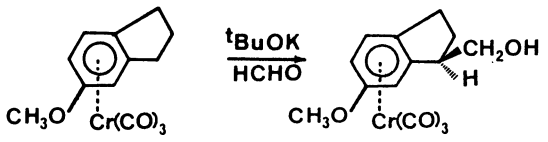


For example, tricarbonyl (tButyl 3,4-dimethylbenzoate) chromium 54 promoted the attachment of the CRHOH group exclusively at the 4-methyl group 55, while the 3-methyl group remained unchanged (44). This para activation reflects the selective acidifying influence of an ester function exalted by the Cr(CO)3 unit.

REGIOSPECIFIC AND STEREOSPECIFIC FUNCTIONALIZATION OF ESTRADIOL DERIVATIVES VIA $Cr(CO)_3$ COMPLEXES

The possibility of regiospecific and stereospecific functionalization of extra arenic sites in a natural product mediated by an organometallic temporary activation technique becomes apparent from the synthetic pathway shown in scheme 22.

Scheme 22



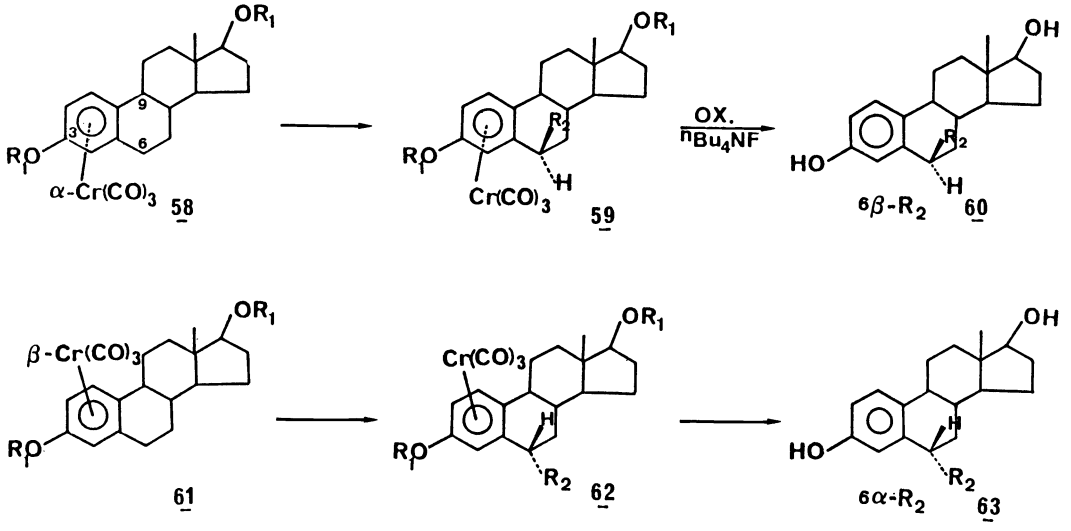
56 57

This diagram is indeed particularly demonstrative of the stereochemical scope of the reaction since the alicyclic complex 57, obtained in good yields (95%), results from both a regiospecific and stereospecific addition of the carbonyl compound to the exo position (4). Obvious substrates to begin with, for the examination of the possible extension of this methodology to natural products, may be selected among the estrogen derivatives (scheme 1, scheme 2).

The biological activity of steroidal hormones, such as estrogens, depends upon their interaction with certain high affinity binding proteins, called receptors, that are found in the cells of target tissues. The interaction between a steroid and its receptor is of high affinity and is characterized by a high degree of stereospecificity. Therefore, it is not surprising that small alterations in the structure of certain estrogens often affect the receptor binding affinity of these compounds and their biological potency.

The attachment of cytotoxic moieties to natural estrogens in order to carry them into hormone sensitive cells is a major goal in cancer chemotherapy because most antitumor agents suffer from a lack of specificity (45). Alkyl substituents have been suggested as suitable probes in the search for appropriate positions in the estradiol molecule that would be reasonably tolerant to fairly large adducts (46). Thus, 17α , 11β positions can accomodate structural modifications but there is a lack of information concerning other parts of the skeleton (47). In order to explore the effect of the modification of the estradiol 6-position, a versatile new synthetic pathway has to be found. It was tempting to exploit for this purpose the original features of the above reaction.

Scheme 23



R_1= -SiMe$_2$t.Bu

R_2= a: -CH$_3$
b: -CH(CH$_3$)$_2$
c: -n.C$_{12}$H$_{25}$

The suitably protected estradiol α and β derivatives (depending on the location of the tripod on the α and β side of the molecules) have been prepared by conventional routes (48). The identification of the diastereomers 58 and 61 has been ascertained both by chemical correlation with a $Cr(CO)_2CS$ estradiol complex on which an X-Ray structural analysis has been performed and by high field NMR spectroscopy (49).

The alkylation reaction has been studied with the pair of diastereomers 58 and 61 (scheme 23). For this purpose, it was necessary to replace the base t.BuOK by $(Me_3Si)_2NNa$ to avoid removal of the protecting groups. The α complexed compound 58 led to products with the alkyl groups exclusively in the 6-position of the hormone and anti with respect to the Cr(CO)3 moiety. A similar regio- and stereospecificity resulted from the reaction of the β-diastereomers 61 giving rise to 6-α alkylated complexes. It is worth noticing that for this β location of the tripod, the 6 and 9 benzylic sites of the complexed hormones are available for proton abstraction but only products corresponding to attack at the 6-position have been observed. Therefore, the results obtained with the above model molecules are directly transferable to more complex derivatives such as estrogens. Finally, decomplexation of 59 and 62 by exposure to sunlight and air (8), followed by deprotection with Bu_4^nNF furnished the 6-alkyl substituted hormones 60 and 63 in 60-80% yields.

Starting from the pair of diastereomers 58 and 61, it appears that a range of 6-substituted estradiols with completely controlled stereochemistry is readily accessible. Previously, this class of compounds was not generally accessible.

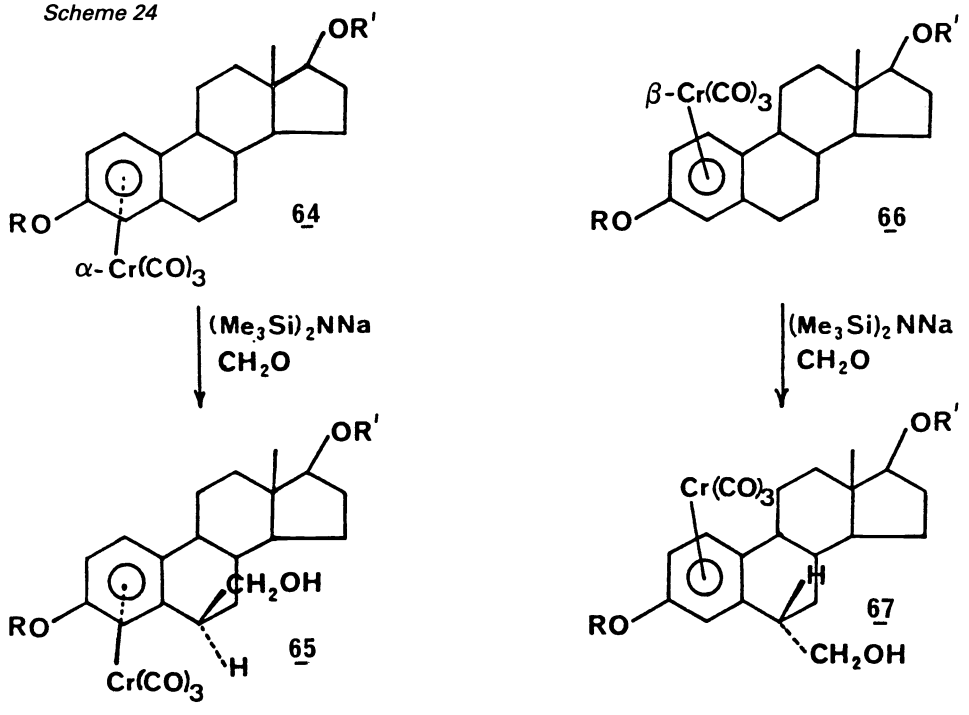
The availability of these alkyl estrogens has allowed receptor binding assays(RBA) to be performed using tritium labeled estradiol as a tracer and lamb uterine cytosol as a source of estradiol receptor (Table 2) (48).

TABLE 2. Relative binding affinity (R.B.A.) of estradiol and its 6-substituted derivatives

Compounds	R.B.A.%
Estradiol (E_2)	100
6α-Me E_2	31
6α-iPr E_2	11.4
6β-iPr E_2	1.6
6α-$nC_{12}H_{25}$-E_2	< 0.1

These data show a clear discrimination between the α- and β- alkyl derivatives. While the β site appears more sensitive to steric hindrance, the 6α-alkyl substitution leads to products that maintain a reasonable affinity for the receptor providing the attached groups are not too bulky. Therefore, it seems possible to attach alkylating groups at the 6-position and still preserve some degree of affinity for the receptor.

Scheme 24



The functionalization reaction has been studied on both 64 and 66 (4). Once again, a regio- and stereospecific reaction takes place whichever the starting diastereomer (scheme 24). Products such as 65 and 67, for which the Cr(CO)3 group can be removed without detriment to the organic molecule (8), might be valuable precursors in current endocrinology problems such as designed fixation of cytotoxic groups, γ-emitting estrogen and affinity markers (50).

NUCLEOPHILIC ATTACK ON α-CARBENIUM IONS OF ORGANOMETALLIC COMPLEXES OF TRANSITION METALS

The remarkable stabilization of α-carbenium ions of organometallic complexes of transition metals is the most constant characteristic of these series (11) (51). While several studies have been devoted to the fundamental problem of elucidating the nature of this stabilization, the exploitation of this property in organic synthesis has scarcely been touched upon with the notable exception of several reports by the groups of Jaouen and Nicholas (52) (53).

Although several organometallic series, for example, the ferrocenyl system, have been shown to allow ready accessibility of the α-carbenium ions, the intrinsic interest of the ultimate products to the synthetic organic chemists is not very compelling. However, in other series such as the benchrotrenes, the interest is much greater since each arene can theoretically be compared to its complexed analogue. Furthermore, the regeneration of the purely organic products presents no difficulties. Nevertheless, this latter series is characterized by the difficult accessibility of their stable carbenium ions, and this has militated against their strategic use in synthesis. Indeed, the first attempt (11e) at isolation of an α-carbenium ion in the arene chromium tricarbonyl series, viz., $(OC)_3CrC_6H_5CH_2^+$, was unsuccessful. For a long time this initial problem could not be surmounted,until Seyferth et al. (11c) showed that the carbenium ion is sufficiently stable to be isolated only when two arene rings are complexed as in $(OC)_3CrC_6H_5C^+HC_6H_5Cr(CO)_3$.

Concurrently, our work on the α-carbenium ions of arenechromium tricarbonyls (54) has shown that even when they cannot be isolated they can be turned to synthetic advantage . By performing in situ reactions under adequate conditions, one can use these α-carbenium complexes despite their relatively short lifetimes. Indeed, the action of methanol or an amine on primary, secondary, or tertiary carbocations readily leads to the formation of ethers or amines.(54) This approach is also applicable to the Ritter reaction, as shown in the following equation.

$$(\eta^6\text{-}R_1C_6H_4CR^2R^3OH)Cr(CO)_3 + R^4CN \xrightarrow[-15°C]{H_2SO_4} (\eta^6\text{-}R^1C_6H_4CR^2R^3NHCOR^4)Cr(CO)_3$$

68 **69**

The Ritter reaction (55), which involves the reaction of nitrile on a carbenium ion, giving rise to an amide can be considerably improved even from primary alcohol precursors by using metal stabilized carbenium ions intermediates (56) (57). However, an excessive stabilization can inhibit the reactivity.

This temporary complexation method may be easily extended to other organometallic systems of synthetic interest, for example (prop-2-ynylic alcohol) $Co_2(CO)_6$ (57). Since the activating unit is introduced (58) and removed (59) efficiently under mild conditions, these complexes appear to be ideally suited for utilization as electrophilic propynyl synthons.

Scheme 25

$$H-C\equiv C-CH_2OH \xrightarrow[CH_3CN]{H^+} H-C\equiv C-CH_2NHCOCH_3$$

$Co_2(CO)_6$ $Co_2(CO)_6$

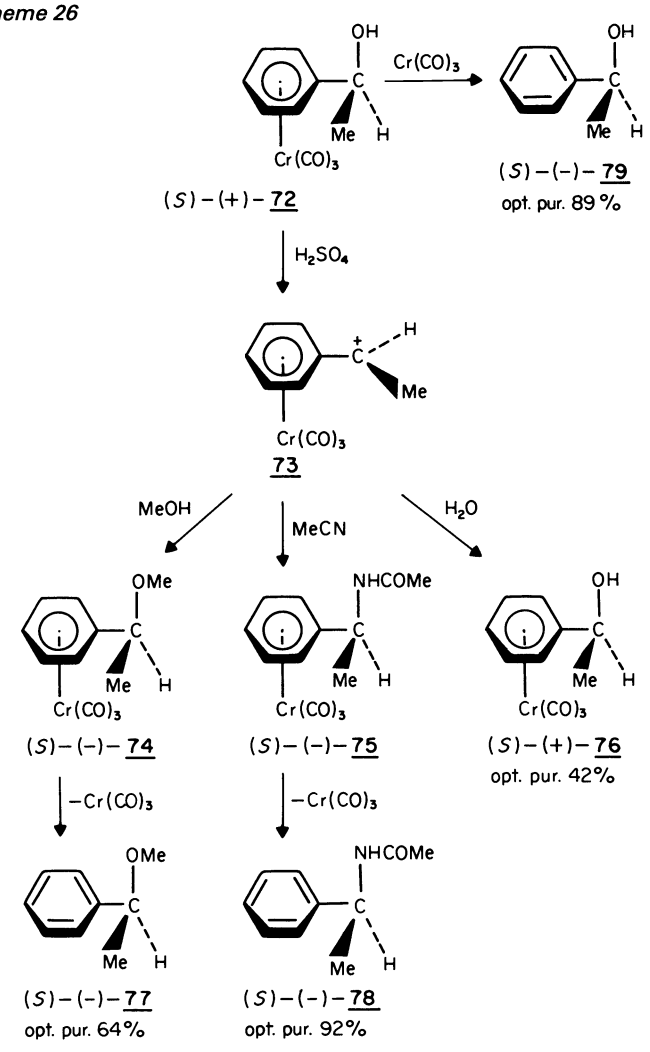
70 **71**

Reaction of the cation derived from the primary alcohol 70 with MeCN led to 71 in a similar manner to the Cr(CO)3 series (scheme 25). Acid-catalyzed rearrangements which are troublesome with uncomplexed propynylic alcohols are avoided in this reaction (60).

In the organometallic series a number of interesting stereochemical features arise. It is known that the incorporation of a Cr(CO)3 moiety imposes a three-dimensional structure on the molecule, and this can be profitably utilized in asymmetric transformations. Various attempts at alkylation via chiral alcohols have run into problems of racemisation and so total stereochemical control could not be maintained (61).

This has been attributed to the formation of planar carbenium ion intermediates. It is now possible, even with open-chain compounds, to realize asymmetric transformation with a high degree of retention of configuration by using Cr(CO)3 intermediates (scheme 25) (62).

Scheme 26

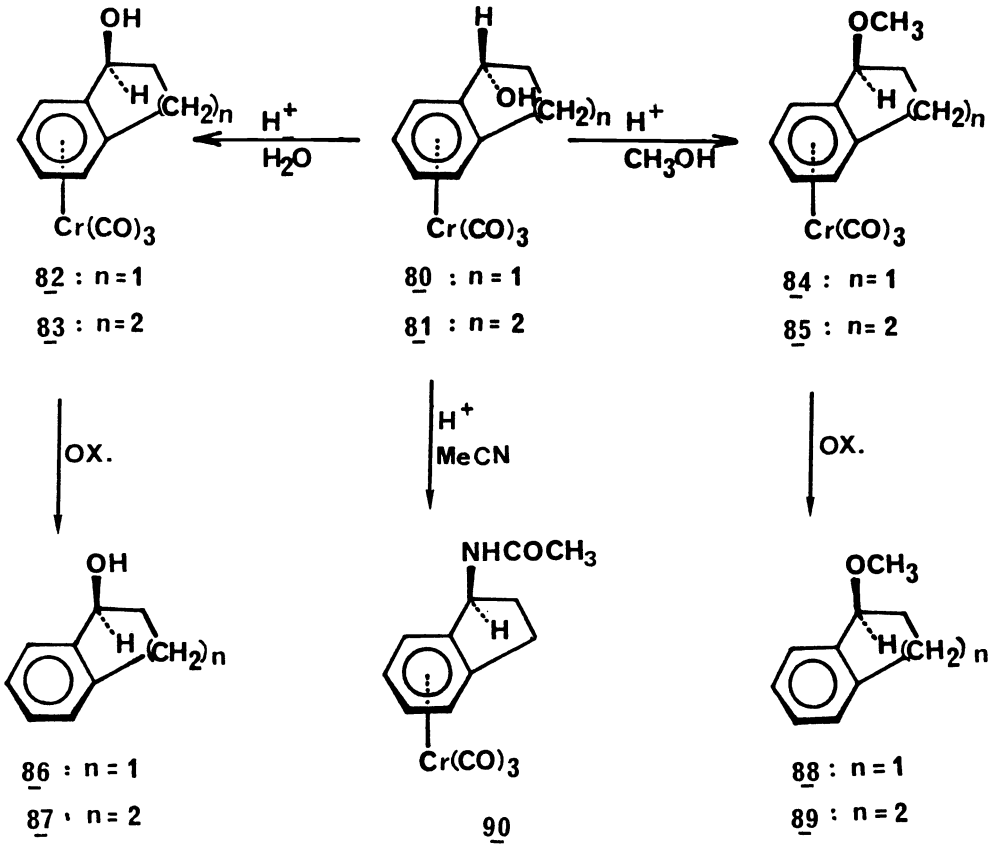


(S) (+) (1-phenyl-1-hydroxyethyl) chromium tricarbonyl 72 of optical purity 89% reacts with MeOH,H_2O and MeCN leading respectively to 74, 76 and 75 with both retention of configuration and high conservation of optical purity. It is remarkable that in the case of acetonitrile the amide (S)(-) 75 is obtained quantitatively with practically 100% retention of configuration. The extent of racemisation may depend on the rate of reaction of the nucleophile with the carbenium ion.

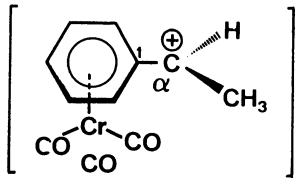
As a comparison, scheme 27 depicts the same reactions when applied to cyclic compounds (63). All these examples show a total inversion of the configuration at the chiral 1-position. There is reason to question the complete change in stereochemistry observed when one examines the rigid series (indanol, tetralol, inversion) and the open series (phenylethanol, retention).

There is no contradiction between these facts. In the indanol 80 , or in the tetralol 81, the hydroxyl is essentially fixed in the endo position, and the generation of the carbenium ion can only occur upon departure of this moiety, giving unequivocally a structure which

Scheme 27



could only lead to the amide 90, the ether 84 or the alcohol 82, by a stereospecifically exo attack; this type of attack normally occurs in this series, as shown in scheme 27. A different situation obtains in the open series where the OH group could adopt either an endo or exo position. Even if the endo conformation is favored in solution, it is clear that, by virtue of either the steric protection or the anchimeric assistance afforded by the Cr(CO)3 group, the rate of formation of the carbenium ion is very greatly accelerated when the OH is exo, thus preferentially generating the carbenium ion 73. A rapid stereospecific exo attack by the nucleophile, in a manner identical with the preceding case, now leads to the isolated product.

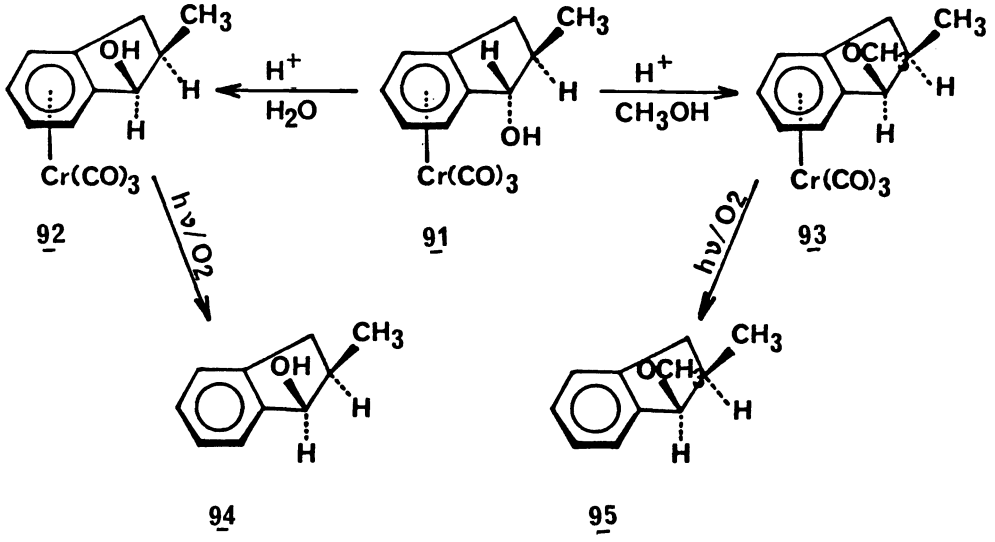


73

We note also that for an ion such as 73 the difficulty of rotation about the C1-Cα bond has been analyzed by NMR spectroscopy (11d). The observed exo attack by nucleophiles on the carbenium ion-Cr(CO)3 complexes may be rationalized in the following way. If we reasonably suppose the bent structural distortion occurs in the benzene-Cr(CO)3 complexes, then endo attack is sterically congested, and exo attack will be the favored mode.

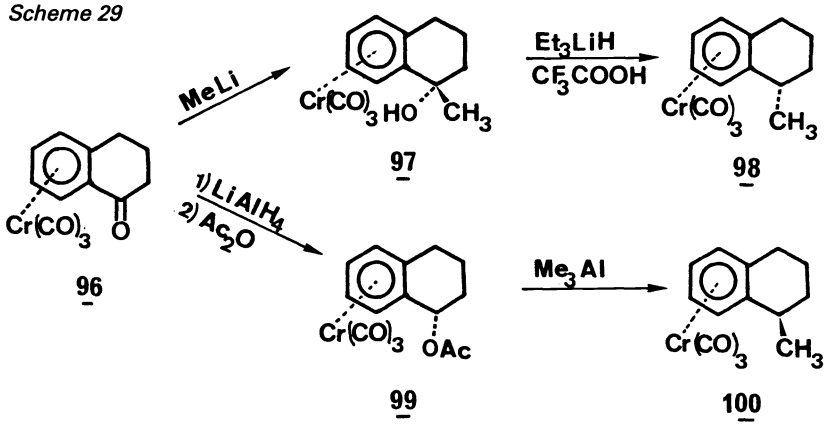
The presence of an exo alkyl substituent on the alicyclic ring does not affect the selectivity of the reaction (63). Scheme 28 shows how a trans structure in an organic ligand 91 may be converted to cis configuration 92 and 93.

Scheme 28



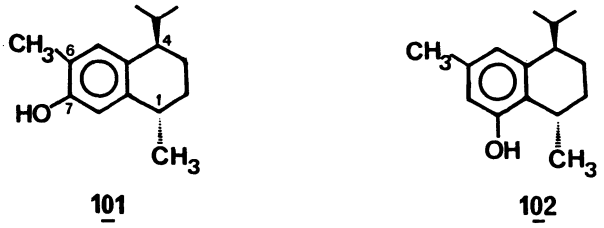
A similar methodology has been elegantly used by Uemura etal. (scheme 29) (64). It has been possible to obtain stereoselectively either endo or exo-isomers from a common α-tetralone 96 or α-indanone. The p-endo methyl complex 98 was prepared by an excess of triethylsilane and trifluoroacetic acid via stereoselective exo-hydride displacement (32). While the endo-acetate complex 99 was converted into a (1-exo-methyltetralin)-Cr(CO)3 100 via exo-methyl attack on the carbocation by treatment with Me_3Al.

Scheme 29



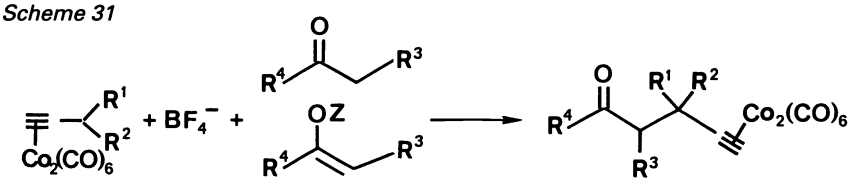
The model reactions provided the key for the stereo- and regioselective synthesis of 7- and 8- hydroxycalamenenes 101, 102 (scheme 30). (65).

Scheme 30



Cobalt-complexed propargyl cations 103 exhibit a similar behavior to that of chromium-complexed benzyl cations since regio- and stereoselective syntheses of organic products are attainable in this way. For example, these highly stable carbenium ions ($pKR^+ \simeq -6.8$) flanked by $Co_2(CO)_6$ moieties alkylate ketones regiospecifically as well as trimethylsilyl enol ethers and enol acetates (scheme 31) (66).

Scheme 31



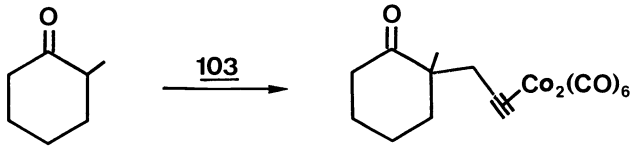
103 104

a: $R^1 = R^2 = H$
b: $R^1 = H, R^2 = Ph$
c: $R^1 = R^2 = CH_3$

$Z = SiMe_3, COMe$

The key features of this reaction are 1) the generally good yields of exclusively monoalkylated products which are obtained and 2) the remarkable regioselectivity found in reactions with asymmetrical ketones (scheme 32). The regioselectivity observed is qualitatively as expected for attack of the electrophilic complex on the thermodynamically favored, more highly substituted enol. However, the degree of selectivity is exceptional ($\geqslant 95\%$)

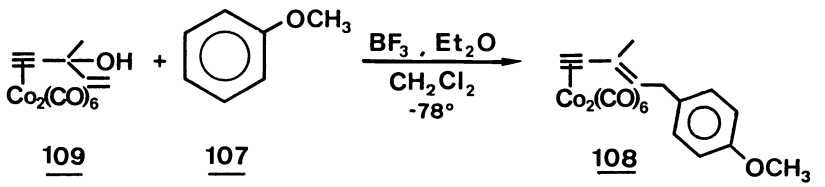
Scheme 32



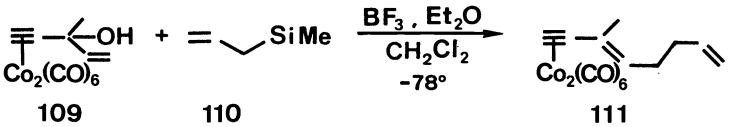
105 106

New regio- and stereoselective coupling reactions leading to E-1,3- enyne derivatives are depicted in scheme 33 (67).

Scheme 33



109 107 108

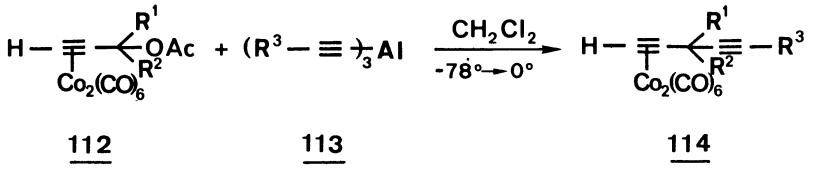


109 110 111

The encountered high E-selectivity for the production of enyne complexes contrasts with previous reports (68). The considerable steric bulk of the $Co_2(CO)_6$ moiety clearly exhibiting isomeric mixtures plays a critical role in determining the stereochemical course of the present reactions.

Similarly, a general, highly selective route to skipped (1,4) diynes 114 is provided by the reactions of (propargyl acetate) $Co_2(CO)_6$ complexes 112 with trialkynyl alanes 113 and subsequent demetalation (69) (scheme 34).

Scheme 34

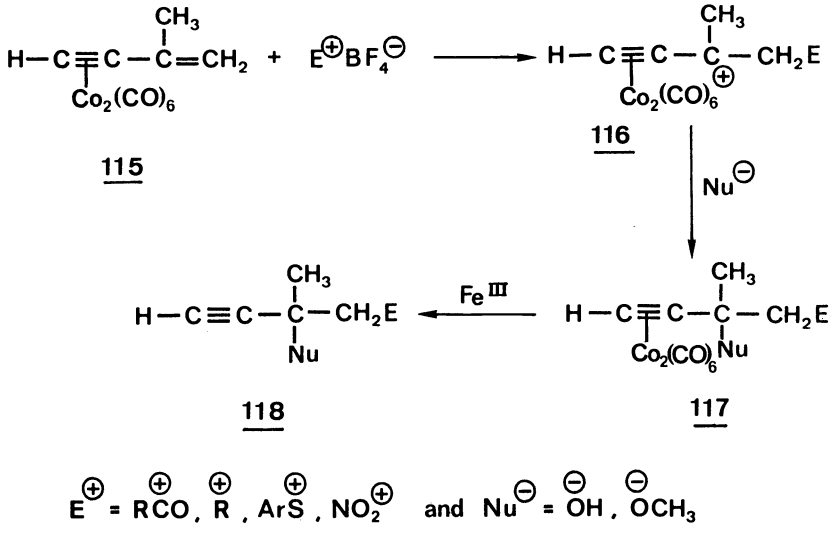


112 113 114

From these examples and previous ones (70) (71) (72), it is clear that the coupling of (propargyl) dicobalt hexacarbonyl cations with a variety of nucleophiles (aromatics, β-dicarbonyls, ketones and enol derivatives, allylsilanes etc...) appears to be an efficient propargylation method, free from the allenic by products associated with reactions of typical propargyl electrophiles (73). This result combined with the ready introduction and removal (vide supra) of the $Co_2(CO)_6$ moiety under mild conditions single out this approach as the preferred method in most instances for introduction of the synthetically versatile propargyl function.

Finally, recent papers report that the dicobalt hexacarbonyl complex of the enyne isopropinylacetylene 115 is effective in permitting stepwise AdE reactions to the double bond via stabilization of the intermediate carbenium ion 116 (scheme 35) (74) (75).

Scheme 35



115 116 117 118

$E^{\oplus}$ = RCO, R, ArS, $NO_2^{\oplus}$ and $Nu^{\ominus}$ = OH, OCH_3

Very stable propargyl cations can be obtained upon protonation of cobalt complexes of conjugated enynes. This route suggested the possibility of using these complexes of enynes as a method for the discrete introduction of electrophiles via the AdE pathway. The interaction of the cation complex with a nucleophile, and a subsequent decomplexation,lead to products of net addition of E^+ and Nu^- across the double bond of 115. Curiously, these results are relevant to our biochemical results (vide infra).

PERSPECTIVES AND CONCLUSION

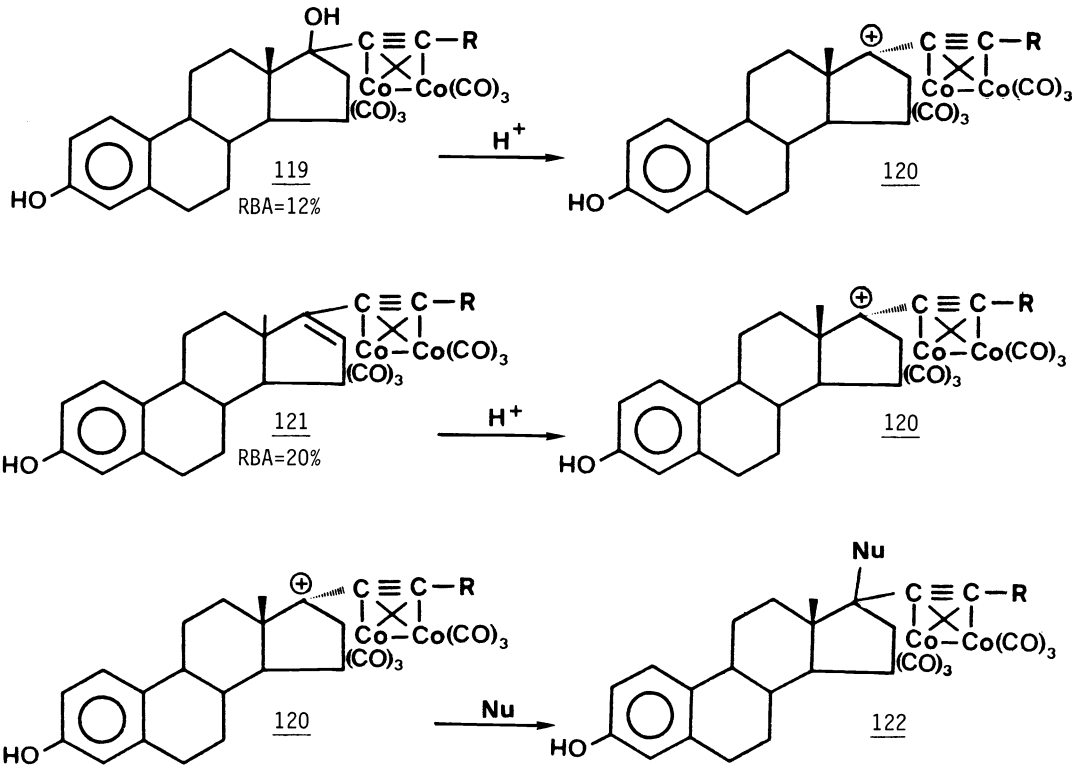
The original behavior of the carbon atoms adjacent to organometallic π-complexes may provide novel applications of these species beyond the area of organic synthesis and into bioorganometallic.

Affinity labeling, the process by which binding proteins may be covalently labeled by reactive ligand analogs, is a labeling method with potentially high selectivity (77) since it allows

the labeling of a selected binding protein in a mixture to the exclusion of other non-binding proteins. This researched selectivity may enable affinity labeling to be used to label receptors for hormones and neurotransmitters in fractionated preparations or complex intact systems (78).

Receptor labelling may be approached by using agents based both on photoreactive and on electrophilic functions. These two strategies complement one another. Photoaffinity labelling is generally considered better suited to achieve highly selective labeling ; however the efficiency of this technique is often quite low. In contrast, electrophilic agents may label receptors efficiently, but may do so with low selectivity because of their inherent reactivity (79). The organometallic approach may help develop a new generation of efficient and selective affinity labels which combine the advantages of the two previous strategies. The approach outlined here is based on both the remarkable stability of organometallic α-carbenium ions and the supposed existence of an acidic estrogen-binding site (80).

Scheme 36



The important functions for the binding of estradiol derivatives to the estrogen receptor site are the 3- and 17- hydroxy groups. By using organometallics, the chemical properties of these functions are significantly altered (see Table 1 for pkR^+ values) while maintaining a reasonable recognition capacity for the receptor (see scheme 36 for the relative binding affinity (RBA) values, determined as before). The generation of carbenium ions from complexes such as 119 and 121 is straightforward, even at low temperature, in acidic medium and is characterized by an instantaneous change in coloration of the complexes.

Furthermore, our studies have shown that these relatively stable transient species are quite reactive in presence of nucleophiles, such as amines, alcohols etc..., leading to a new covalent C-N, C-O, bond with controlled stereochemistry at the 17 position (no mixture of diastereomers). These particularities can be taken to advantage in biochemistry owing to the importance of the 17 position in the estrogen series.

The interaction of these complexes 119 - 121 with the estrogen receptors has been ass yed indirectly by exchange assays (79) in order to evaluate the efficiency and selectivity of these candidate agents. However, since the measurement and the attachment efficiency and selectivity of affinity probes available in radiolabeled form is straightforward, we have prepared radioactive 119* labelled by ^{14}CO. The CO exchange reaction provided a product 119* with a specific activity(S.A.) of 51 mC/mMole.

In lamb uterine cytosol preparations, a species that might be the estrogen receptor is rapidly labeled in a covalent fashion when the cytosol preparations are exposed to (^{14}CO) Cobalt carbonyl propynyl estradiol 119[x]. A few fold excess of this product suffices to covalently label the receptor quantitatively with only very limited labeling of non receptor proteins. These preliminary experiments require further confirmations but are quite consistent with the recognized properties of these organometallic units. They suggest indeed that the alcohol (or alkene) functions are being selectively activated in the estrogen binding site, presumably by accepting a proton to form a highly reactive carbenium ion which then alkylates a nearly nucleophilic group. Our complexes show some similarity with (Z)-(1- 4-(2-[N-aziridinyl] ethoxy) phenyl])-1,3-diphenyl-1-butene, an electrophilic analogue of the antiestrogen tamoxifen (80). Thus, the covalent labeling process with the organometallic hormones resembles, in a way, the behavior of enzyme suicide inactivations, which become activated selectively in the active site of enzymes by specific catalytic processes (81).

Fine-tuned affinity markers can be obtained by changing the 17α-organometallic units. These species will prove to be useful in a wide varieties of studies of receptor structures, physicochemical properties and subcellular localization. They will also provide new approches for assaying the receptor (presence of M-CO markers) and for studying receptor dynamics and function.

Acknowledgement

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REFERENCES

1. a)G.Jaouen, A.Vessières, S.Top, A.A.Ismail, I.S.Butler, C.R.Acad.Sc.Paris sér II.,298, 683 (1984).
   b)G.Jaouen, A.Vessières, S.Top, A.A.Ismail, I.S.Butler, J.Amer.Chem.Soc., in press (1985)
2. D.H.R. Barton and H.Patin, J.Chem.Soc.Perkin I,829 (1976).
3. B.H.Trost, T.R.Verhoenen, J.Amer.Chem.Soc., 102, 4743 (1980).
4. G.Jaouen, S.Top, A.Laconi, D.Couturier, J.Brocard, J.Amer.Chem.Soc., 106, 2207 (1984).
5. See for example, W.L.Mc Guire, Progress in Cancer Research and Therapy ., 25, p.29 Raven Press, New-York (1983).
6. G.Jaouen, in Transition Metal Organometallics In Organic Synthesis, 2, p.65-120, Academic Press, New-York (1978).
7. G.Jaouen, Ann. N.Y.Acad.Sci., 295, 59 (1977).
8. G.Jaouen, R.Dabard, Tetrahedron Letters,1015 (1971).
9. M.F. Semmelhack, Pure Appl.Chem., 53, 2379 (1981).
10. a) K.M.Nicholas, R.C.Kerber, E.I.Stiefel, Inorg.Chem.,10, 1519 (1971).
    b) A.N.Nesmeyanov, N.A.Ustynyuk, L.G.Makarova, S.Andre, Yu.A.Ustynyuk, L.N.Novikova, Yu.N.Luzikov, J.Organometal.Chem., 154, 45 (1978).
    c) M.F.Semmelhack, H.T.Hall, R.Farina, M.Yoshifuji, G.Clark, T.Bargar, K.Hirotsu, J.Clardy, J.Amer.Chem.Soc., 101, 3535 (1979) and references therein.
    d) R.J.Card and W.S.Trahanovsky, J.Org.Chem., 45, 2555 (1980)
    e) G.Jaouen, S.Top, M.J.Mc Glinchey, J.Organometal.Chem., 195, C5 (1980).
    f) A.Ceccon, A.Gambaro, G.Agostini, A.Kenzo, J.Organometal.Chem., 217, 79 (1981).
    g) A.Ceccon, A.Gambaro, A.M.Romanin, A.Venzo, Chem.Commun., 907 (1982).
    h) S.Top, G.Jaouen, B.G.Sayer, M.J.Mc Glinchey. J.Amer.Chem.Soc., 105, 6426 (1983).
11. a) M.Cais, Organometal.Chem.Rev., 1, 435 (1966).
    b) L.Haynes, R.Pettit in Carbonium ions., G.A.Olah and P.V.R.Schleyer, Eds., vol 5,Wiley, N.Y. (1975).
    c) D.Seyferth, J.S.Merola, C.S.Eschbach, J.Amer.Chem.Soc., 100, 4124 (1978).
    d) M.Acampora, A.Ceccon, M.Dalfarra, G.Giacometti, G.Rigatti, J.C.S.Perkin Trans., 2, 483 (1977).
    e) J.D.Holmes, D.A.K.Jones, R.Pettit, J.Organometal.Chem., 4, 324 (1965).
    f) S.P.Gubin, V.S.Khandkarova, A.Z.Kreindlin, J.Organometal.Chem., 64, 229 (1974).
12. D.K.Wells, W.S.Trahanovsky, J.Amer.Chem.Soc., 91, 5870 (1969).
13. J.H.Richards, E.A.Hills, J.Amer.Chem.Soc., 83, 4216 (1961) and references therein.
14. T.G.Traylor, J.C.Ware, J.Amer.Chem.Soc., 89, 2304 (1967) and references therein.
15. a) R.S.Bly, R.L.Veazey, J.Amer.Chem.Soc., 91, 4221 (1969).
    b) R.S.Bly, R.A.Mateer, K.K.Tse, R.L.Veazey, J.Org.Chem., 38, 1518 (1973).
16. D.W.Clack, L.A.P.Kane-Maguire, J.Organometal.Chem., 145, 201 (1978).
17. a) N.C.Deno, J.J.Jaruzelski, A.Schriesheim, J.Amer.Chem.Soc., 77, 3044 (1955).
    b) N.C.Deno, P.T.Groves, J.J.Jaruzelski, N.N.Lugasch, J.Amer.Chem.Soc., 82, 4719 (1960).

18. R.E.Connor, K.M.Nicholas, J.Organometal.Chem., 125, C45 (1977).
19. a) B.Nicholls, M.C.Whiting, J.Chem.Soc., 551 (1959).
    b) D.A.Brown, J.R.Raju, J.Chem.Soc.,(A), 40 (1966).
20. A.C.Knipe, S.J.Mc Guiness, W.E.Watts, J.Chem.Soc., Perkin Trans. 2, 193 (1981).
21. E.W.Randall, L.E.Sutton, Proc.Chem.Soc., 93 (1959).
22. F.Terrier, P.G.Farrell, J.Lelièvre, S.Top, G.Jaouen, Organometallics, in press (1985).
23. A.Ceccon, G.Catelani, J.Organometal.Chem., 72, 179 (1974).
24. G.Jaouen, A.Meyer, G.Simonneaux, Chem.Commun., 813 (1975).
25. G.Simonneaux, G.Jaouen, Tetrahedron, 35, 2249 (1979).
26. W.Trahanovsky, R.J.Card, J.Amer.Chem.Soc., 94, 2897 (1972).
27. a) S.Top, G.Jaouen, M.J.Mc Glinchey, Chem.Commun., 643 (1980).
    b) S.G.Davies, N.J.Holman, C.A.Laughton, B.E.Mobbs, Chem.Commun., 1316 (1983).
28. a) B.Caro, J.Y.Le Bihan, J.P.Guillot, S.Top, G.Jaouen, Chem.Commun., 602 (1984).
    b) J.F.Halet, J.Y.Saillard, B.Caro, J.Y.Le Bihan, S.Top, G.Jaouen, J.Organometal.Chem., 267, C37 (1984).
29. a) B.L.Goodwin, Tyrosine Catabolism., Oxford University Press, Oxford, (1972).
    b) S.Lindstedt, M.Rundgren, Biochem.Biophys.Acta, 704, 66 (1982); J.Biol.Chem., 257,1922 (1982).
30. a) J.Lebibi, J.Brocard, D.Couturier, Bull.Soc.Chim.Fr., II, 357 (1982).
    b) J.Brocard, J.Lebibi, D.Couturier, Chem.Commun., 1264 (1981).
31. M.C.Sénéchal-Tocquer, D.Sénéchal, J.Y.Le Bihan, D.Gentric, B.Caro, J.Organometal.Chem., in press (1985).
32. G.Jaouen, A.Meyer, Tetrahedron Letters., 3547 (1976).
33. A.Meyer, O.Hofer, J.Amer.Chem.Soc., 102, 4410 (1980).
34. a) W.Baker, W.G.Leeds, J.Chem.Soc., 974 (1948).
    b) J.W.Cook, C.L. Hewett, J.Chem.Soc., 62 (1936).
    c) B.L.Shapiro, M.J.Shapiro, J.Org.Chem., 41, 1522 (1972).
    d) J.C.Bardhan, R.C.Banerjee, J.Chem.Soc., 1809 (1956).
35. M.F.Semmelhack, W.Seufert, L.Keller, J.Amer.Chem.Soc., 102, 6586 (1980).
36. G.R.Knox, D.G.Leppard, P.L.Pauson, W.E.Watts, J.Organometal.Chem., 34, 347 (1972).
37. M.Uemura, T.Minami, Y.Hagoshi, Chem.Commun., 1193 (1984).
38. J.Biagg, S.G.Davies, Chem.Commun., 653 (1985).
39. a) W.R.Jackson, W.B.Jennings, Chem.Commun., 824 (1966).
    b) D.E.F.Gracey, W.R.Jackson, W.B.Jennings, Chem.Commun., 366 (1968).
40. a) M.F.Semmelhack, G.R.Clark, R.Farina, M.Saerman, J.Amer.Chem.Soc., 101, 217 (1979).
    b) M.F.Semmelhack, G.R.Clark, J.L.Garcia, J.J.Harrison, Y.Thebtaranouth, W.Wulff, A.Yamashita, Tetrahedron., 37, 3957 (1981).
41. W.R.Jackson, I.D.Rae, M.G.Wong, M.F.Semmelhack, J.Garcia, Chem.Commun., 1359 (1982).
42. T.A.Albright, B.K.Carpenter, Inorg.Chem., 19, 3092 (1980).
43. A.Solladié-Cavallo, J.Suffert, Org.Magn.Reson., 14, 426 (1980).
44. J.Brocard, A.Laconi, D.Couturier, S.Top, G.Jaouen, Chem.Commun., 475 (1984).
45. J.Y.Saillard, personal communication.
46. For a recent review see : J.A.Katzenellenbogen, B.S.Katzenellenbogen, Breast Cancer Research and Treatment, 2, 347 (1982).
47. F.J.Zeelen, E.W.Bergink, in Cytotoxic Estrogens in Hormone Receptive Tumors., Academic Press, p.39 et sq. (1980).
48. G.Teutsch, in Adrenal Steroid Antagonism., Walter de Gruyter, Berlin, New-York, p.43 et sq. (1984) and references therein.
49. S.Top, A.Vessières, J.P.Abjean, G.Jaouen, Chem.Commun., 428 (1984).
50. S.Top, G.Jaouen, A.Vessières, J.P.Abjean, D.Davoust, C.A.Rodger, B.G.Sayer, M.J.Mc Glinchey, Organometallics, in press (1985).
51. a) D.F. Heiman, S.G.Senderoff, J.Katzenellenbogen, R.J.Neeley, J.Med.Chem., 23, 994 (1980).
    b) J.K.Mazaitis, R.E.Gibson, T.Komai, W.C.Eckelman, B.Francis, R.C.Reba, J.Nucl.Med.,21, 142 (1980).
    c) S.S.Simons Jr., E.B.Thompson, Biochem.Actions Horm.,9, 221 (1982).
52. W.E.Watts, J.Organomet.Chem.Libr., 7, (1979).
53. S.Top, B.Caro, G.Jaouen, Tetrahedron Letters., 787 (1978).
54. R.F.Lockwood, K.M.Nicholas, Tetrahedron Letters., 4163 (1977).
55. S.Top, G.Jaouen, J.Organometal.Chem., 197, 199 (1980).
56. L.I.Krimen, D.J.Cotta, Org.React., 17, 213 (1969).
57. S.Top, G.Jaouen, Chem.Commun. 224 (1979).
58. S.Top, G.Jaouen, J.Org.Chem., 46, 78 (1981).
59. R.S.Dickson, P.J.Froser, Adv.Organomet.Chem., 12, 323 (1974).
60. a) K.M.Nicholas, R.Pettit, Tetrahedron Letters., 3475 (1971).
    b) D.Seyferth, A.Wehman, J.Amer.Chem.Soc., 92, 5520 (1970).
61. J.H.Wotiz in Chemistry of Acetylenes., Marcel Dekker, New-York, 365-424 (1969).
62. See for example : a) C.C.Price, M.Lund, J.Amer.Chem.Soc.,62, 3105 (1940).
    b) R.L.Burnell Jr., S.Archer, J.Amer.Chem.Soc., 64, 1032 (1942).
    c) H.Hart, H.S.Eleuteris, J.Amer.Chem.Soc., 76, 516 (1954).
63. S.Top, G.Jaouen, M.J.Mc Glinchey, Chem. Commun., 1110 (1980).
64. S.Top, A.Meyer, G.Jaouen, Tetrahedron Letters., 37, 3537 (1979).
65. M.Uemura, K.Isobe, Y.Hayoshi,J. Org. Chem., in press (1985).
66. M.Uemura, K.Isobe, Y.Hayoshi, Chem. Letters., 91 (1985).

67. K.M.Nicholas, M.Mulvaney, M.Bayer, J.Amer.Chem.Soc., 102, 2508 (1980).
68. S.Padmanabhan, K.M.Nicholas, Tetrahedron Letters., 23, 2555 (1982).
69. a) J.E.Anderson, Tetrahedron Letters., 46, 4079 (1975).
b) E.R.H.Jones, J.T.Mc Combie, J.Chem.Soc., 261 (1943).
c) E.A.Evans, C.J.Timmons, Nature., 177, 1167 (1956).
d) F.Le Bihan, P.Maitte, C.R.Acad.Sc.Paris., Ser.C, 272, 695 (1971).
e) S.Bancel, P.Cresson, C.R.Acad.Sc.Paris., Ser.C, 270, 2161 (1970).
f) J.Corbier, P.Cresson, C.R.Acad.Sc.Paris., Ser.C, 272, 695 (1971).
70. S.Padmanabhan, K.M.Nicholas, Tetrahedron Letters., 24, 2239 (1983).
71. H.D.Hodes, K.M.Nicholas, Tetrahedron Letters., 4349 (1978).
72. K.E.O'Boyle, K.M.Nicholas, Tetrahedron Letters., 1595 (1980).
73. S.Padmanabhan, K.M.Nicholas, J.Organometal.Chem., 212, 115 (1981).
74. a) L.Brouin, M.C.Faroux, O.Riobé, Bull.Soc.Chim.Fr., 2320 (1960).
b) G.Fontaine, C.André, J.Jolivet, P.Maitte, Bull.Soc.Chim.Fr., 1447 (1963).
c) J.H.Wotiz, J.Amer.Chem.Soc., 72, 1639 (1950) and 73, 693 (1951).
d) E.J.Corey and H.A.Kirst, Tetrahedron Letters., 5041 (1968).
75. W.A.Smit, A.A.Schegolev, A.S.Gybin, G.S.Mikaelian, R.Caple, Synthesis., 887 (1984).
76. A.A.Schegolev, W.A.Smit, Y.B.Kalgan, M.Z.Krimer, R.Caple, Tetrahedron Letters., 23,4419 (1982).
77. W.B.Jakoby, M.Wilchek (eds) Methods Enzymol. 46, entire volume (1977).
78. J.A.Katzenellenbogen in "Biochemical Actions of Hormones" (G.Litwack, ed.) Vol.IV, chap.1, Academic Press, N.Y., (1977).
79. For a recent review see : J.A.Katzenellenbogen, B.S.Katzenellenbogen, in "Vitamines and Hormones" Vol 41, p.213 et sq., (1984), Academic Press Inc.
80. J.A. Katzenellenbogen, K.E. Carlson, D.F. Heiman, D.W. Robertson, L.L. Wei, B.S. Katzenellenbogen, J.Biol.Chem., 258, 3487 (1983).
81. C.Walsh, Tetrahedron, 38, 871-909.