STEREOSELECTIVE FUNCTIONALIZATION AND C-C BOND FORMATION ON TRANSITION METAL TEMPLATE

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STEREOSELECTIVE FUNCTIONALIZATION AND C-C BOND FORMATION ON TRANSITION METAL TEMPLATE

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NATIONAL CHEMICAL LABORATORY

PUNE - 411 008

CERTIFICATE

*This is to certify that the work incorporated in the thesis entitled “**Stereoselective functionalization and C-C Bond Formation on Transition Metal Template**” submitted by Vishwanath M. Swamy was carried out by him under my supervision at the National Chemical Laboratory. Such material as has been obtained from other sources has been duly acknowledged in the thesis.*

Date :

National Chemical Laboratory	(Dr. Amitabha Sarkar)
Pune 411 008	Research Guide

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(Vishwanath M. Swamy)

To my Parents
and Teachers

CONTENTS

GENERAL REMARKS

1. All melting points (recorded on a Thermonik Campbell melting point apparatus) are uncorrected and are recorded on the Celsius scale.
2. IR spectra were recorded as nujol mull or chloroform, on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1600 FT-IR and ATI Mattson, UK, Model-RS-1 FT-IR, using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).
3. Proton NMR spectra were recorded using tetramethylsilane as internal reference on Bruker MSL-300 and Bruker AC-200. Chemical shifts were recorded in parts per million (δ). Abbreviations, *viz.*, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, brs = broad singlet, br = broad peak, dt=doublet of triplet and m = multiplet have been used to describe spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.
4. ^{13}C NMR spectra were recorded on Bruker MSL-300 and Bruker AC-200 instrument operating at 75.2 MHz and 50.3 MHz respectively.
5. Elemental analyses (C, H, N) were obtained on a Carlo-Erba 1100 automatic analyzer by Dr. S. Y. Kulkarni and his group at NCL.
6. Circular Dichroism data was collected on Jasco J-15 spectrophotometer in a cell of path length 1 cm and scanned from a range 250 nm to 400 nm.
7. The progress of the reaction was monitored by analytical thin layer chromatography plates precoated with silica gel 60 F_{254}(Merck). Column chromatography of chromium complexes were carried out with silica gel obtained from Merck (230-400 mesh, 9385 grade) under argon or nitrogen pressure.
8. Known compounds were characterized by IR and proton NMR.
9. Pet-ether refers to the fraction boiling between 60-80 °C.

10 All the reactions were performed under argon atmosphere.

ABBREVIATIONS

BuLi or butyllithium	*n*- Butyl Lithium in hexane
DMF	Dimethylformamide
Et_2O or ether	Diethyl ether
o	Ortho
m	Meta
p	Para
TBAB	Tetrabutylammonium bromide
THF	Tetrahydrofuran
TBAF	Tetrabutylammonium fluoride
r.t	Room temperature

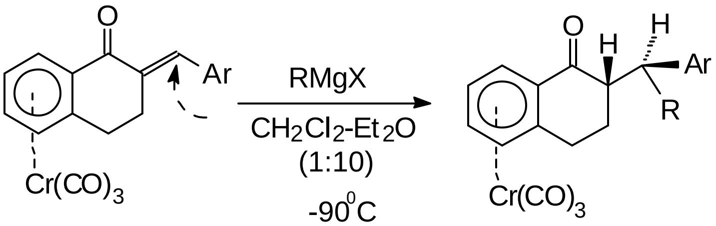
Synopsis of the thesis

Compound numbers in the synopsis are not related to the numbers in the chapters

Chapter 1 Diastereoselective conjugate addition of strong nucleophiles to 2-arylidene-1-tetralone tricarbonylchromium complexes

In a non-coordinating solvent medium, several Grignard reagents added to the enones **1a-b** in a conjugate manner rather than at the carbonyl function (Scheme–1). The stereochemistry was established unequivocally by crystal structure determination of a representative complex.

Scheme – 1



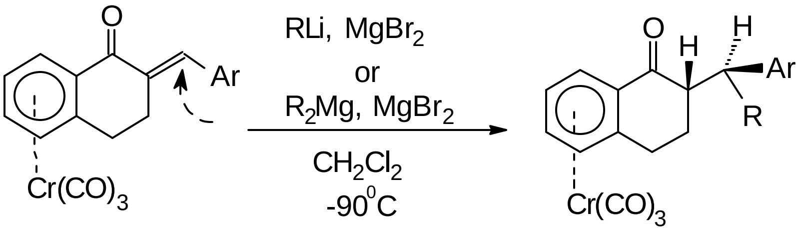
1a-b

2a-e

1a: Ar = Ph
1b: Ar = 4-Me-C_6H_4
R = Me, *n*-Bu, Ph
X = Cl, Br, I

The role of magnesium bromide was established by carrying out reactions of organolithium or salt-free organomagnesium reagents on the same substrates pretreated with $MgBr_2$ (Scheme-2).

Scheme – 2



1a-b

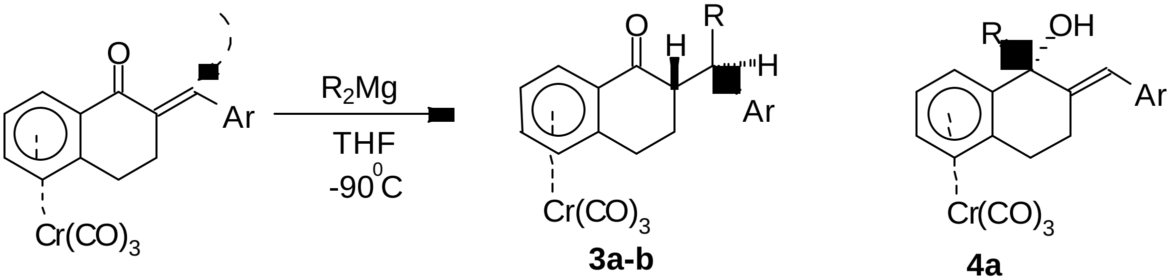
1a: Ar = Ph

1b: Ar = 4-Me-C_6H_4

R = Me, *n*-Bu, Ph

Regioselectivity of addition of diorganomagnesium reagent in the absence of a Lewis acid, was found to be dependent on the organic ligand (Scheme-3).

Scheme – 3



1a-b

3a-b

	Ar	**R**
3a	4-Me-C_6H_4	*n*-Bu
3b	4-Me-C_6H_4	Ph

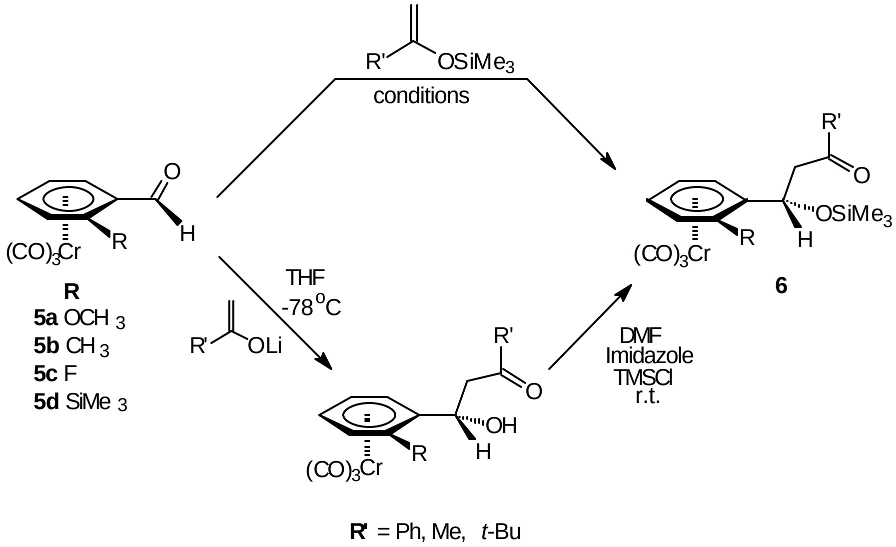
4a

	Ar	**R**
4a	4-Me-C_6H_4	Me

Chapter 2 Diastereoselective Mukaiyama aldol and related reactions of chiral arylaldehyde complexes of tricarbonylchromium

On reaction with silyl enol ethers, chiral aldehyde complexes **5a-d** yielded aldol products with high diastereoselectivity (> 95%) under a variety of conditions (Scheme-4). The isolated yields ranged from 70 to 85 % .

Scheme – 4



Conditions

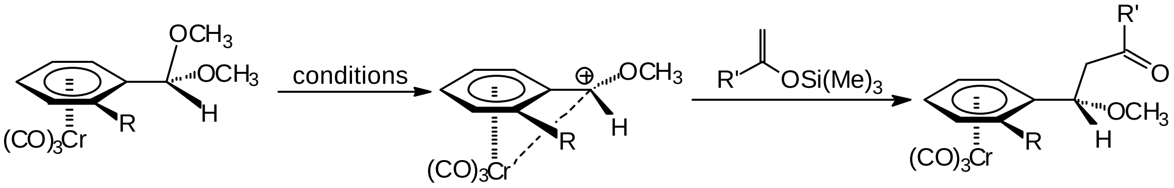
a. 10 mol% $Sc(OTf)_3$, CH_2Cl_2, r. t.

b. 10 mol% $Yb(OTf)_3$, CH_2Cl_2, r. t.

c.10 mol% TBAF, -78°C, THF

Dimethyl acetals of the aldehydes, 7a-d, yielded products with same relative stereochemistry, presumably via the confugarationally stable benzyl cationic intermediate as shown in Scheme-5.

Scheme – 5



R
7a OCH3
7b CH3
7c Cl
7d F

R' = Ph, Me,*t*-Bu

8

Conditions

a. 10 mol% $Sc(OTf)_3$, CH_2Cl_2, r. t.

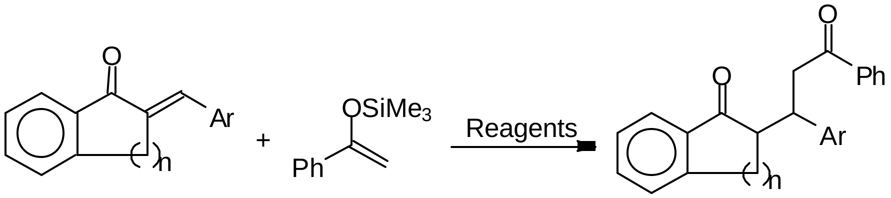
b. 10 mol% $Yb(OTf)_3$, CH_2Cl_2, r. t.

Stereochemistry of products was ascertained by crystal structure determination of representative molecules. Further stereochemical correlation between two reaction sequences was done using optically pure starting materials and comparing the CD data of products.

Chapter 3 Base induced conjugate addition of enolsilanes to enones – an alternative to Lewis acid mediated reactions

A convenient procedure for conjugate addition of silyl enol ethers to enones was developed. The reactions were performed at ambient temperature using mild, nucleophilic bases to provide 1,5 diketones of various types (Scheme-6).

Scheme – 6



	n	Ar
9a	0	Ph
9b	1	Ph
9c	1	4-OMe-C_6H_4
9d	2	Ph

10

Reagents

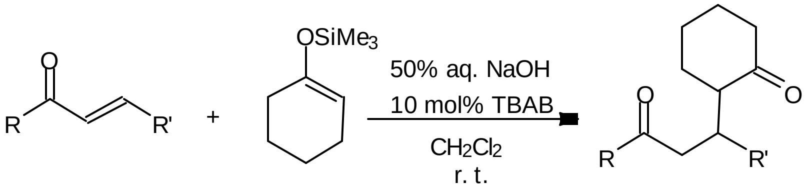
a. 50 % aq. NaOH, 10 mol% TBAB, CH_2Cl_2

b. KH, DMF

c. *t*-BuOK, THF

Cyclic silyl enol ethers also added to acyclic enone substrates under similar conditions (Scheme-7).

Scheme – 7

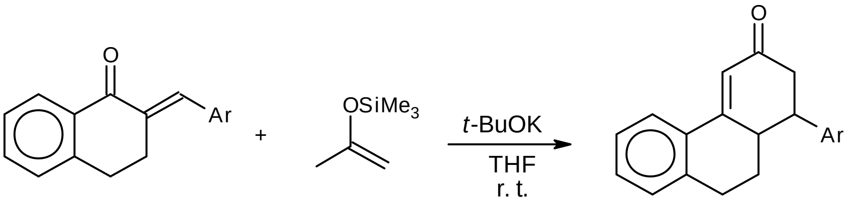


	R	R'
11a	Ph	Ph
11b	Ferrocenyl	Ph

12

This procedure was further extended to realize a convenient ring annulation (Scheme-8)

Scheme – 8



Ar
13a Ph
13b 4-Me-C_6H_4

14

Chapter - I

Diastereoselective conjugate addition of strong nucleophiles to 2-arylidene-1-tetralone tricarbonylchromium complexes

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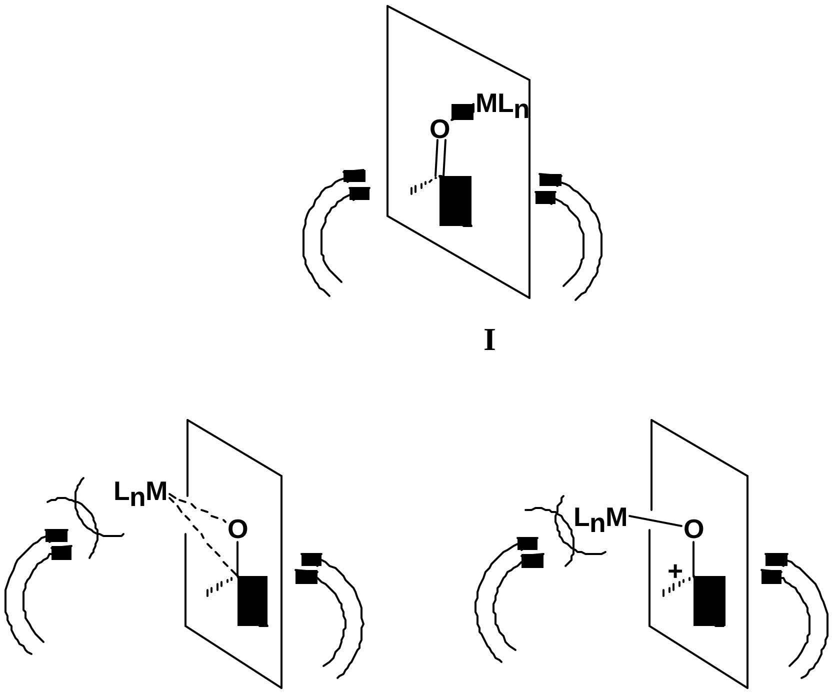
Part of this work has been published in *Tetrahedron Lett*. **1999,** *40*, 6061-6064

Introduction

Lewis acids play a prominent role in organic synthesis by virtue of their ability to activate carbonyl groups.[1] They are used as catalysts for a large number of carbon-carbon bond forming reactions.[2] A Lewis acid catalyzed reaction is characterized by a dramatically enhanced rate compared to the uncatalyzed reaction.[3] This rate enhancement is rationalized in terms of an increase in the polar character of the carbonyl group as a result of complexation with Lewis acids. The structure of the Lewis acid carbonyl complex probably has longer C-O bonds, an increased dipole moment, and a higher sp^3 character of the carbonyl oxygen. These features also influence the stereochemical outcome of the reaction.[4] The growing interest in asymmetric catalysis in carbon-carbon bond forming reaction has led to the design and synthesis of numerous chiral Lewis acids, some of which promote excellent enantioselectivity.[5]

The Lewis acid can bind to the lone pair of electrons of the carbonyl oxygen to form a σ complex **I**, which is the usual phenomenon (Figure-1). The Lewis acid can also coordinate with the π bond of the carbonyl group[6] to form an η^2 complex **II**. A third possibility is that the Lewis acid binds *in-plane* with the lone pair of electrons, and as a consequence of this, the oxygen may become sp^3 hybridized. A torsion around the C-O bond now can place the Lewis acid effectively *out-of-plane* with respect to the carbonyl plane, while the carbonyl carbon bears a positive charge and is now an activated electrophile, as represented by **III**. In terms of stereochemical consequence, structures **II** and **III** are very similar. The coordinated Lewis acid sterically hinders nucleophilic attack from one face of the carbonyl group. On the other hand, an *in-plane* bound Lewis acid, as in **I**, does not impose such π-facial discrimination[7].

Figure-1



I

II

III

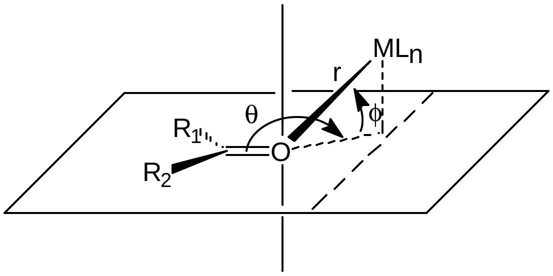
In Lewis acid mediated reactions, the steric and electronic requirements of the carbonyl ligand and its immediate neighborhood determine the mode of coordination of the Lewis acid, and consequently, governs the steric course of the reaction.

Because the stereoelectronic variables contributing to Lewis acid mediated reactions are many, it has been difficult to propose a single structural model which applies to all such reactions. A large number of studies pertaining to the structure of Lewis acid-carbonyl complexes by crystallography and NMR methods have been carried out.[8] Theoretical studies of Lewis acid carbonyl interactions indicate that cationic Lewis acids prefer a linear geometry though distortions upto 15° are noted.[9] Neutral Lewis acids, on the other hand, prefer a bent, planar geometry in the direction of one of the sp^2 hybridized lone pairs.[10] It is observed that when a

Lewis acid forms complexes with aldehydes, the Lewis acid prefers *anti* complexation with simple aldehydes and *syn* complexation with α-heterosubstituted aldehydes.[11] In case of α,β-unsaturated carbonyl complexes, the *transoid* geometry seems to be preferred since it minimizes adverse steric interactions.[12]

Between the two limiting modes of complexation, the σ complexation is more common for most main group metals, early transition metals and lanthanides whereas the π complexation is prevalent with electron rich transition metal complexes.[6] In the σ mode, the Lewis acid can be located in many different positions, defined by three variables,[8] the Lewis acid-oxygen distance, *r*, and the two angles, q and f (Figure-2) .

Figure-2

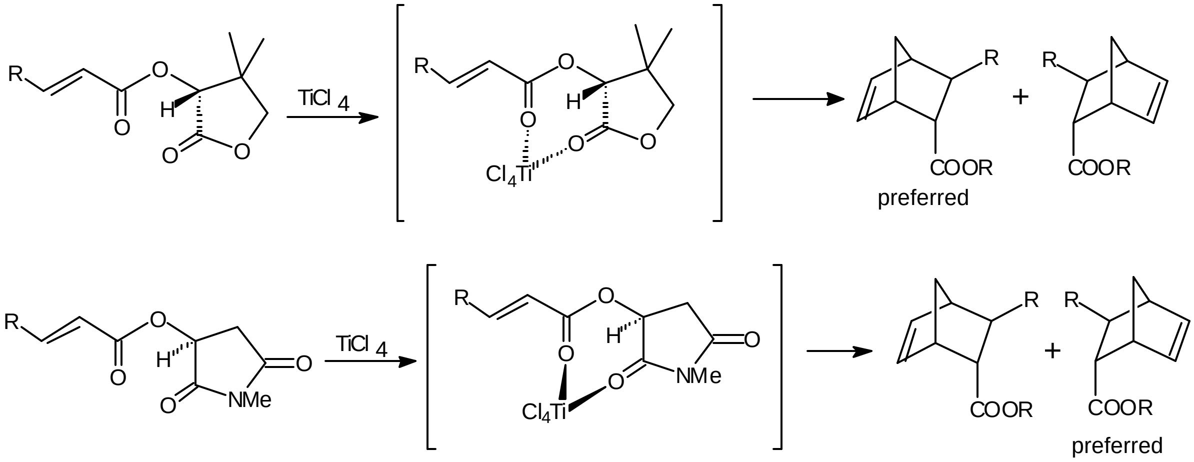


Crystal structures indicate[13] that complexes of Lewis acids with aldehydes are planar (f = 0°) and bent (q = 120° ±15°). However, in case of ketones and esters there are a few cases where the Lewis acid is complexed *out-of-plane* (φ > 0) with the carbonyl group.[14] The determining factor in such cases appears to be unfavorable steric crowding around the carbonyl group.

Attempts have been made to correlate the structure with reactivity patterns and models have been proposed to predict the outcome of individual types of reactions. The most popular among all these reactions is the Lewis acid mediated Diels-Alder reaction.[15]

Helmchen and co-workers[16] have reported an *out-of-plane* complexation of enolates with $TiCl_4$ and their effect in Diels-Alder reaction with cyclopentadiene (Scheme-1). It was postulated that the diastereofacial selectivity encountered in these reactions (>97% in favour of the major isomer) is due to a selective shielding of one face of the enolate by the $TiCl_4$.

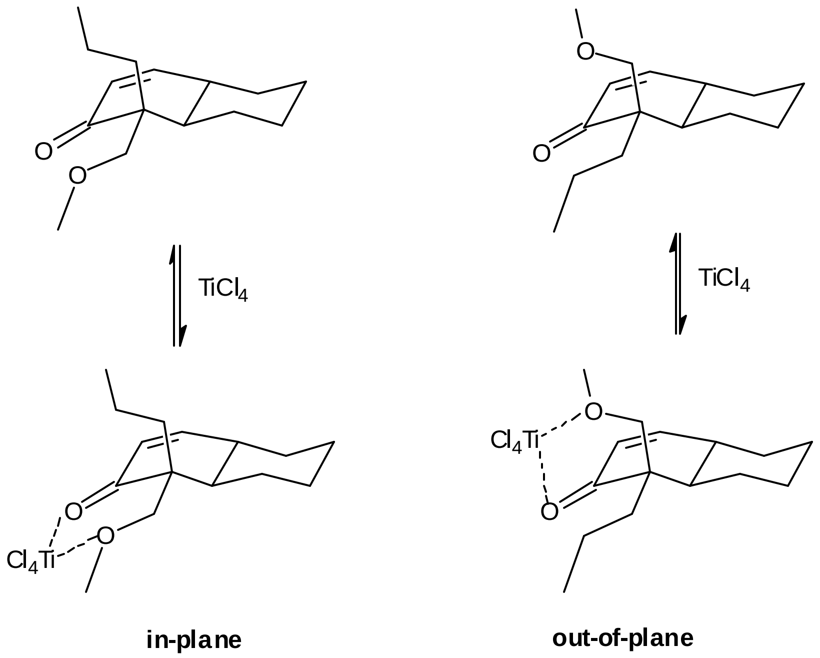
Scheme-1



In Diels-Alder reaction of fumarates with cyclopentadiene, the Lewis acid free route and the $TiCl_4$ mediated reaction afforded opposite diastereomers. The explanation stated that $TiCl_4$ was bound to the ester unit in an *out-of-plane* mode and consequently directed the diene to approach from the opposite face.

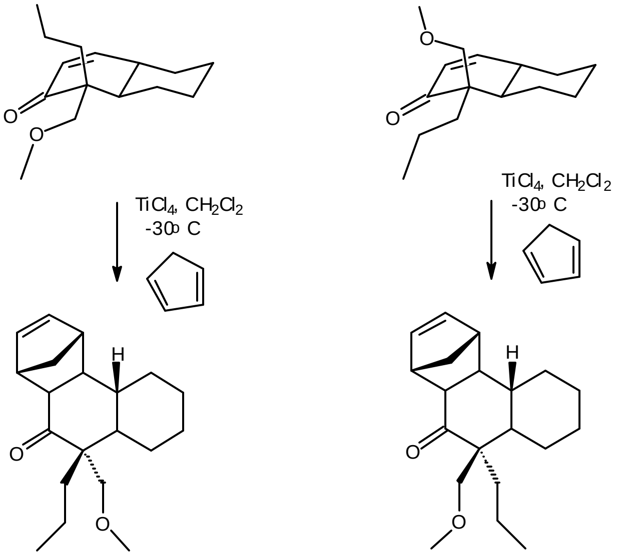
Recently, Corcoran and co-workers have illustrated that such stereocontrol can also be engineered using suitably designed enones.[17] The enones have properly positioned methoxymethyl groups to direct *in-plane* and *out-of-plane* coordination of $TiCl_4$ with the carbonyl function (Scheme-2).

Scheme-2



The two complexes formed on addition of $TiCl_4$, were isolated and characterized. Crystal structure analysis confirmed the predicted geometry of the Lewis acid-carbonyl complexes. These $TiCl_4$-complexed enones were separately treated with cyclopentadiene to form Diels-Alder adducts (Scheme-3).

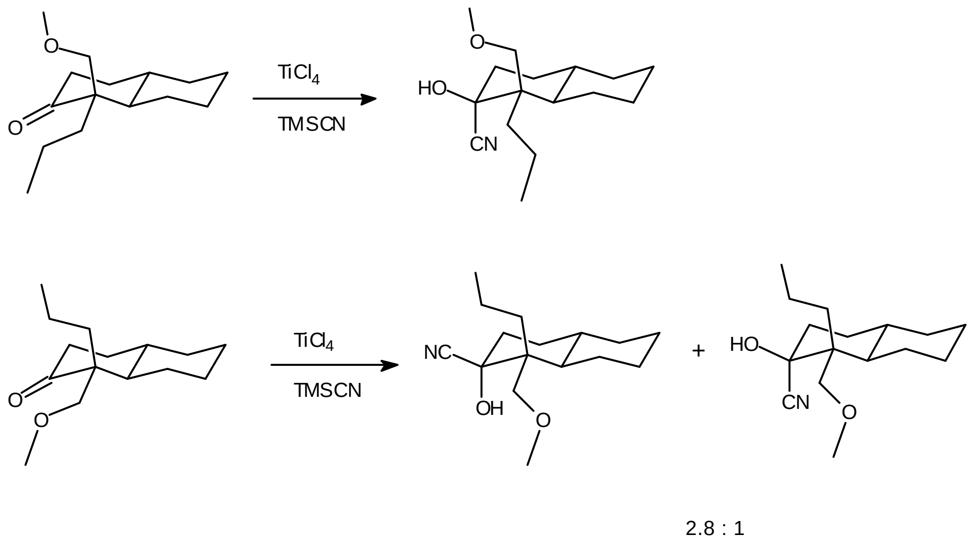
Scheme-3



The *out-of-plane* complex reacted 15 times faster than the *in-plane* complex.[18] The study shows that the former is less stable than the later by at least 6 kcal mol^{-1} which is consistent with the rate difference.

TMSCN added directly to the carbonyl group of similar substrates in presence of $TiCl_4$ to yield cyanohydrins (Scheme-4). The stereochemistry of the products depended on the stereochemistry of the alkoxy appendage.[17c]

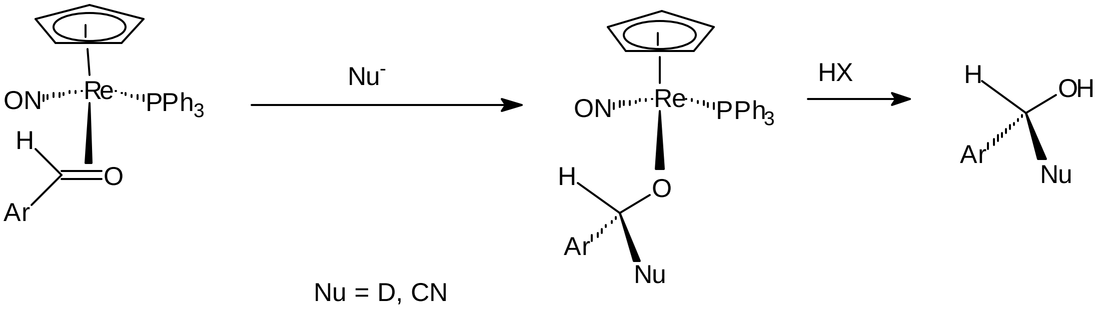
Scheme-4



In all these examples, however, the molecule has a functionality to direct $TiCl_4$ complexation with carbonyl group *in-plane* or *out-of-plane*. In substrates without such a neighboring functional group, it is much more difficult to precisely define orientation of $TiCl_4$ with respect to carbonyl group.

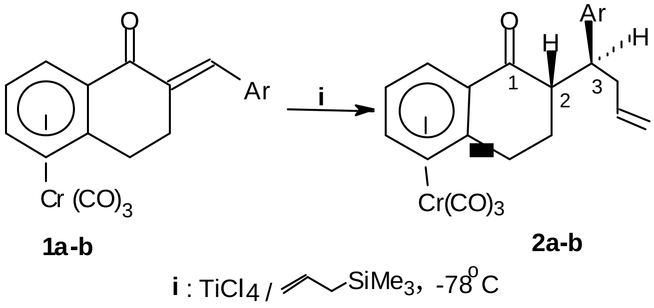
Although an *out-of-plane* coordination of the Lewis acid is expected to direct the trajectory of the incoming group,[19] reports describing such an effect are rare.[5a,b,20] Gladysz and co-workers reported η^2-coordinated complexes of aldehydes with $CpRe(NO)PPh_3$ cation.[5a,b] In enantiomerically pure form, they undergo nucleophilic additions with high enantioselectivities (Scheme-5).

Scheme-5



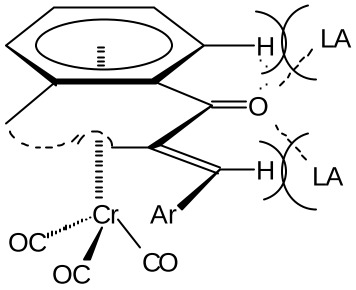
During the course of our investigations on remote stereocontrol in arenetricarbonyl chromium complexes,[21] we were perplexed by the observation of an *endo*-selective conjugate Hosomi-Sakurai allylation on 2-arylidene-1-tetralone tricarbonylchromium complexes[22] using $TiCl_4$ as the Lewis acid (Scheme-6).

Scheme-6

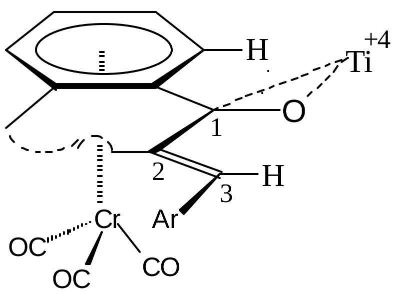


In these complexes, the chromium-complexed aromatic ring and the enone functionality are coplanar and the array of *sp*^{2} carbons form part of a rigid bicyclic system. The oxygen atom is also *sp*^{2} -hybridized, and hence the two nonbonded electron pairs on oxygen are coplanar with these carbons. In this situation, the *peri* proton of the aromatic ring as well as the olefinic proton hinder an *in-plane* approach of the Lewis acid to the oxygen atom from either direction as shown in **3a** (Figure-3). Titanium is thus forced to adopt *out-of-plane* coordination with the C=O π-bond as in **3b** (Figure-3).

Figure-3



3a



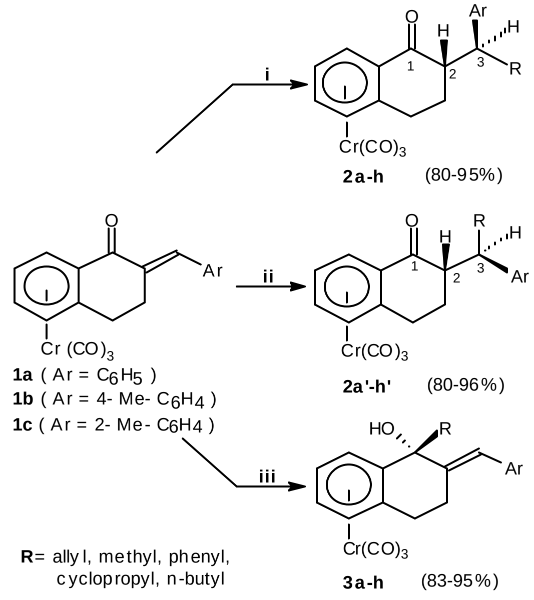
3b

Out-of-plane coordination of titanium with the CO π-bond has been structurally characterized for a simple molecule such as ethyl cinnamate.[23] Although such coordination has sometimes been described as η^2, in reality, the Ti-O distance is evidently shorter than Ti-C bond. One can even consider a single bond between Ti and a sp^3 oxygen, which in turn implies that the carbonyl carbon center is rendered cationic, and thus the enone function is activated for reaction with allyltrimethylsilane. It is likely that $TiCl_4$ would occupy the less crowded *exo* face (opposite to the tricarbonylchromium as in **3b**) and direct the allyltrimethylsilane to approach from the *endo* face of the molecule to reach C-3.

In arene tricarbonylchromium complexes, *exo*-selective functionalization[24a,24b,24c] is the normal trend. The above example of a complete reversal of stereoface selection due to out-of-plane coordination of Lewis acid, suggested a possible way of engineering *endo*-selectivity on such substrates. Initial experiments involved addition of organolithium and organomagnesium reagents to the enones in the presence of $TiCl_4$. Dichloromethane has never been the solvent of choice for reactions of alkyl lithium or Grignard reaction. However it was considered advantageous to use a non-coordinating solvent like dichloromethane[25] in this study to maximize the interaction of Lewis acid with the carbonyl group.

The reaction with organolithium or organomagnesium reagents afforded only 1,4 addition products resulting from an *endo*-selective process[26] (Scheme-7).

Scheme-7



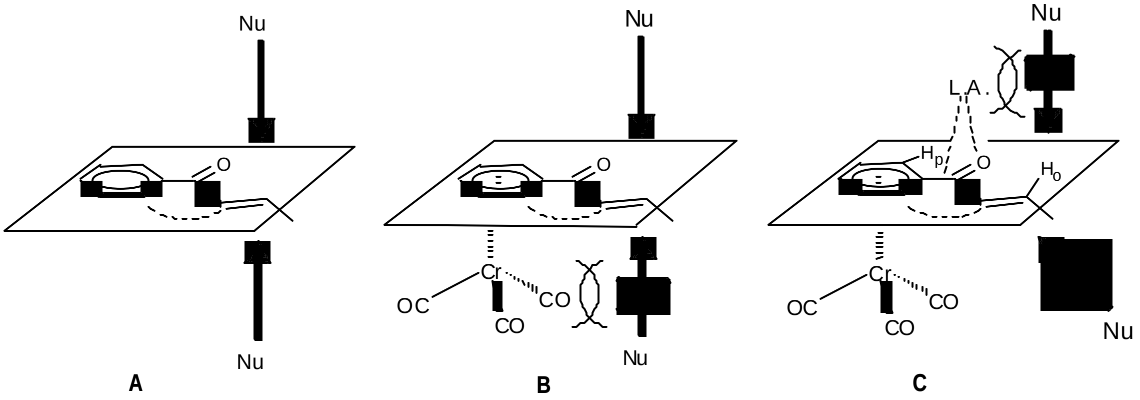
i : $TiCl_4$ -90°C 15 min ; RLi or RMgX -90°C 15 min

ii : $R_2Cu(CN)Li_2$ -78°C ~1 h

iii : RLi -90°C 30 min

Reagent approach in π-systems with conflicting stereochemical bias can be visualized with the help of Figure-4.

Figure-4



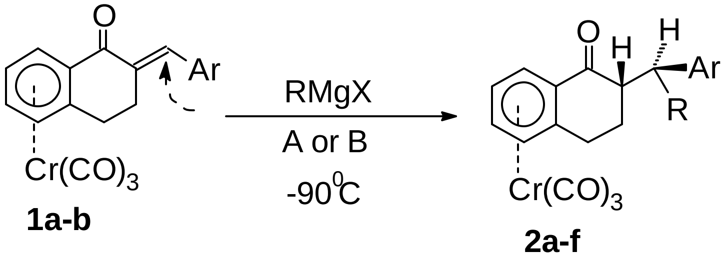
While both the faces of the enone are equally accessible to a reagent or reaction partner in structure **A**, one of the faces of **B** is blocked by metal coordination. In structure **C**, access from *endo*-face is prevented by $Cr(CO)_3$ group and in-plane coordination is discouraged by two flanking hydrogens (the *peri* proton H_p of the aromatic ring of tetralone, and the β- olefinic proton H_o) on both sides of the ketone function. The Lewis acid is therefore forced to coordinate from the *exo*-face in an out-of-plane manner. Since the Lewis acid is now placed nearer to the reacting center, nucleophilic attack is clearly disfavored from the *exo*-face, which is at a site three carbons away from the chromium complexed aromatic ring. An *endo*-selective approach by the nucleophile seems more viable.

Present Work

To ascertain the stereodirecting role of $TiCl_4$ in the Grignard reaction, it was necessary to perform the reaction of tricarbonylchromium complexes of 2-arylidene-1-tetralone without any additive as a 'blank' experiment. Since the substrates were insoluble in ether, but readily soluble in THF, Grignard reactions were carried out in THF (Scheme-8).

Surprisingly, contrary to our expectations the products obtained were all 1,4 adducts appended from the *endo* face of the molecule. This was readily confirmed by comparing the ^1H NMR spectra with those obtained earlier[26] from the $RLi/TiCl_4$ additions. The results were same when the reactions were carried out in dichloromethane as solvent and Grignard reagents prepared in diethyl ether were added to the solution.

Scheme-8



1a-b

2a-f

A = THF
B = CH_2Cl_2

1a	Ph
1b	4-Me-C_6H_4

Table-1

Entry	Ar	R	Product	Yield (%)[a]	
				A[b]	**B**[b]
1	1a	Me	**2a**	79	76
2	1b	Me	**2b**	82	84
3	1a	*n*Bu	**2c**	80	85
4	1b	*n*Bu	**2d**	85	82
5	1b	Ph	**2e**	89	88
6	1a	4-CH_3-C_6H_4	**2f**	84	82

a: Yields of pure isolated compounds, b: Grignard reagent was made in ether, the ratio of the solvent to the ether was maintained 10:1 v/v.

This result was initially puzzling because these reactions were performed without addition of any external Lewis acid. In these cases the only conceivable Lewis acid present could be the MgX_2 salt formed as a result of the Schlenck equilibrium[27] (eqn-1).

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \quad \text{---------} \quad (1)$$

In order to establish the role of $MgBr_2$, it was essential to carry out the experiments under salt free conditions and compare the results when $MgBr_2$ was added. Salt-free dialkylmagnesiums were made either by the precipitation of MgX_2 from the Grignard reagents with addition of dioxan[28a] or by treatment of organolithium reagents with $MgCl_2$.[28b] These salt-free reagents were treated with the enones at -90°C in THF. The regiochemistry of addition of dialkylmagnesium reagents is known to depend on the steric bulk of the alkyl group.[27] For smaller alkyl groups like methyl, 1,2 addition is predominant, whereas for bulkier phenyl and butyl groups 1,4 addition prevails. In our case, a similar observation was made. Dibutylmagnesium and diphenylmagnesium added in a conjugate manner from the *exo*-face (entries 1-3, Scheme-9), while addition of dimethylmagnesium yielded the 1,2-*exo* product (entries 4 and 5, Scheme-9).

Scheme-9

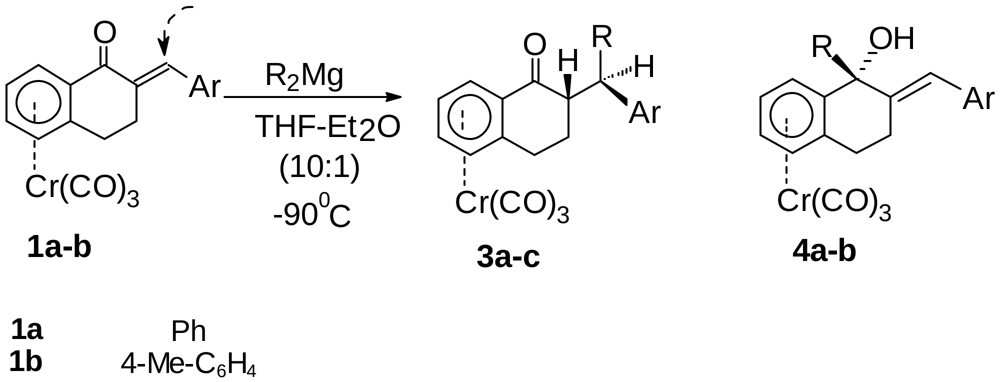


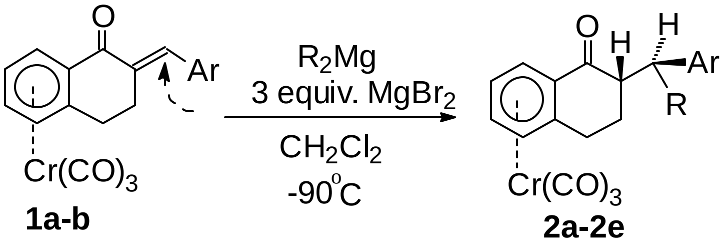
Table-2

Entry	Ar	R	Product	Yield (%)[a]
1	1a	*n*Bu	**3a**	84
2	1b	*n*Bu	**3b**	80
3	1a	Ph	**3c**	77
4	1b	Me	**4a**	84
5	1b	Me	**4b**	81

a: Yields of pure isolated compounds

These reactions were repeated with $MgBr_2$ as an additive. To maximize the coordinating effect of $MgBr_2$, with the substrates the reactions were carried out in dichloromethane. In a typical run, the solid enone and $MgBr_2$ were intimately mixed and placed in a flask with a stirrer. With stirring and cooling the mixture at -90°C, dichloromethane was added via a syringe. On addition of dichloromethane the color of the reaction mixture instantly changed to violet. To this violet solution the dialkylmagnesium reagent was added. The dialkylmagnesium reagents added in a 1,4-*endo* manner irrespective of the size of the alkyl groups. Identity of the products were satisfactorily established by comparison of their ^1H NMR spectra with those of authentic samples.

Scheme-10



1a	Ph
1b	4-Me-C_6H_4

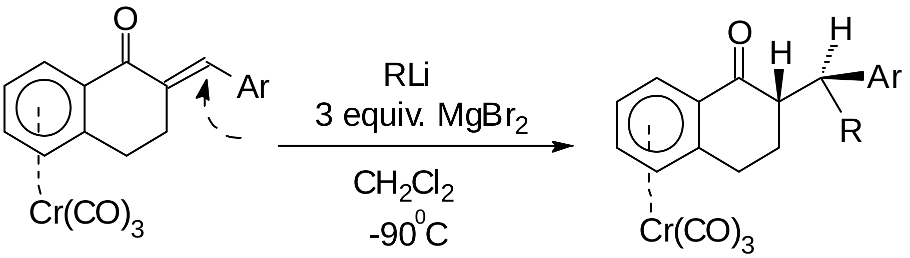
Table-3

Entry	Ar	R	Product	Yield (%)[a]
1	1a	Me	**2a**	80
2	1b	Me	**2b**	80
3	1a	*n*Bu	**2c**	86
4	1b	*n*Bu	**2d**	83
5	1b	Ph	**2e**	87

a: Yields of pure isolated compounds

The role of $MgBr_2$ was further confirmed by carrying out addition of organolithium reagents to the same substrates in presence of $MgBr_2$ as the Lewis acid (Scheme-10). In a typical run, the solid enone and $MgBr_2$ were intimately mixed and placed in a flask with a stirrer to which dichloromethane was added via a syringe with stirring and cooling the mixture at -90°C. To this violet solution the alkyllithium reagents were added at the same temperature. The reaction was complete in 10-15 minutes. The same stereoisomer of the product was obtained as with the Grignard reagents. This clearly indicated that $MgBr_2$ behaves in a manner similar to $TiCl_4$ as observed earlier.

Scheme-11



1a-b

1a	Ph
1b	4-Me-C_6H_4

Table-4

Entry	Ar	R	Product	Yield (%)[a]
1	1a	Me	**2a**	78
2	1b	Me	**2b**	80
3	1a	*n*Bu	**2c**	89
4	1b	*n*Bu	**2d**	87
5	1b	Ph	**2e**	82
6	1a	4-CH_3-C_6H_4	**2f**	88

a: Yields of pure isolated compounds

Similarity of product selectivity in presence of titanium halides and magnesium bromide, strongly implies that Mg^{2+} can also coordinate with the ketone carbonyl in an *out-of-plane* manner, and thereby direct regio- and stereoselectivity of the reaction as does the Ti^{4+} ion. *Out-of-plane* coordination has been discussed[29] mainly for ions like Ti^{4+}, Sn^{4+} and Al^{3+}, where crystal structures provided convincing evidence, or, steric outcome of relevant reactions could be explained with the help of such a model. In common perception, magnesium is not usually associated with ? -complexes. But, magnesium possesses vacant low lying *3d* orbitals, and they can participate in the formation of a ? -bond.[30] To our knowledge, this is the first convincing example of *out-of-plane* bound magnesium ion to a carbonyl function, that completely reverses the steric course of nucleophilic addition as described above. In addition, these findings underscore the importance of Schlenck equilibrium in Grignard reactions, which can either complicate interpretation of results or provide a means to design stereodivergent routes for different stereoisomers from the same substrate, as in the present case.

Summary

The experiments described in this chapter pertains to an unusual mode of coordination of Mg^{2+} ion with carbonyl group of an organic substrate, that controls stereo- and regioselection in stereochemically biased α-β-unsaturated molecules. For enones anchored on an arene tricarbonylchromium group, the trend of *exo*-selective nucleophilic 1,2-addition can be reversed in the presence of magnesium ion to *endo*-selective conjugate addition products.

Experimental

All reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents. Diethyl ether and THF were freshly distilled over sodium benzophenone ketyl. Dichloromethane was freshly distilled over P_2O_5. Aromatic aldehydes, $MgCl_2$ and $MgBr_2.OEt_2$ were purchased from Aldrich, USA, and used as received. Organolithium and organomagnesium reagents were prepared following reported procedures.[31]

General procedure for the preparation of enones (1a-b) :

Following a reported procedure the enones were prepared from 1-tetralone $Cr(CO)_3$ complex (0.5 g, 1.77 mmol), aromatic aldehydes (1.78 mmol) and KOH (0.12 g, 2.14 mmol) using Claisen-Schmidt condensation. In a typical procedure, ethanolic KOH was added dropwise to a solution of the tetralone complex and aromatic aldehyde in ethanol at room temperature. Reaction was complete within 2.5 h (TLC). The reaction mixture was diluted with water, extracted with dichloromethane and dried over sodium sulfate. Removal of solvent afforded red crystalline solid in all the cases. Enones **1a** and **1b** have been reported earlier.[32, 33]

Typical procedure for the preparation of Grignard reagent :

A two-necked flask equipped with a double surface condenser, and a septum capped dropping funnel with a pressure equalizer was cooled under argon. Magnesium turnings (264 mg, 11 mmol) and dry ether (20 ml) were taken in the reaction flask, and a solution of 10 mmol of the corresponding alkyl halide in 10 ml dry ether was added to the dropping funnel. Approximately one third of the alkyl halide solution was added and allowed to stir till the reaction mixture starts refluxing slowly. The remaining alkyl halide was then added at such a rate that reflux is maintained without external heating. After the addition was complete, the reaction mixture was stirred at room temperature for 1-2 hrs. The dropping funnel was, replaced by a septum, the reagent was then ready for use.

General Procedure for the synthesis of dialkylmagnesiums.

Procedure A:

The Grignard reagent was prepared in ether by the usual method. To this solution about 5-6 equivalents dry dioxan was added dropwise to precipitate magnesium salts. The reaction mixture was stirred for 2-3 hrs to allow complete precipitation. The precipitate was allowed to settle overnight, aliquots of the supernatant solution containing the dialkyl magnesium, were transferred by a syringe.

Procedure B:

To a suspension of magnesium chloride (10 mmol) in 20 ml of dry pet ether under argon atmosphere, the alkyllithium reagent (20 mmol) was added gradually. The reaction mixture was stirred for 3 to 4 hrs at room temperature. During the process lithium halide was precipitated, while the dialkylmagnesium remained in the solution. After the precipitate settled on standing overnight, the supernatent solution, containing the dialkylmagnesium reagent was used for further reactions.

Preparation of complexes 2a-2f from 1a-b

(A) Typical procedure for Grignard additions

To a solution of the enone (n mmol) in THF (7n ml), the Grignard reagent (1.2n mmol) in ether was added dropwise at –90 ºC with stirring. After completion of the reaction (TLC, 15 min) reaction mixture was carefully quenched with degassed methanol (2 ml) at –90 ºC. The contents were allowed to attain room temperature, diluted with saturated ammonium chloride and finally extracted with ether. The organic layer was washed with water and dried over sodium sulfate. The crude product obtained after removal of ether was purified by flash column chromatography under nitrogen.

Reactions were done on 0.5-1.0 mmol scale and isolated yields are indicated in Table-1

(B) Typical procedure for MgBr$_2$ mediated additions: (Preparation of complexes **2a-f** from **1a-b**)

Dichloromethane (5n ml) was slowly introduced to a mixture of enone (n mmol) and MgBr$_2$ (3n mmol) with stirring at –90ºC. Color of the solution became dark purple. It was stirred for 15 min and then alkyllithium/dialkylmagnesium in ether or hexane (1.2 mmol) was added. After completion of the reaction (TLC, 15 min.), the reaction mixture was quenched with degassed MeOH (2 ml), and allowed to attain room temperature. Usual work up followed by removal of the solvent afforded the crude product, which was purified by flash column chromatography.

Reactions were done on 0.5-1.0 mmol scale and isolated yields are indicated in Table-10 and Table-11.

Complex 2a

Color : Orange
mp : 124 °C, lit.[26]125 °C
IR (CHCl$_3$) : 1985, 1915, 1680 cm^{-1}
^{1}H NMR (200 MHz) : (δ, CDCl$_3$)
1.25 (d, 3H, J=7.2 Hz), 1.72-1.90 (m, 1H), 2.05 (ddd, 1H, J=21.2, 17.3, 4.15 Hz), 2.45-2.75 (m, 2H), 2.76-2.95 (m, 1H), 3.90 (ddd, 1H, J=21.2, 17.3, 4.15 Hz), 5.10 (d, 1H, J=6.5Hz), 5.35 (t, 1H, J=6.5Hz), 5.60 (t, 1H, J=6.5Hz), 6.21 (d, 1H, J=6.5Hz), 7.15-7.45 (m, 5H).

Complex 2b

Color : Red
Mp : 150-152 °C, lit.[26]: 151 °C

IR ($CHCl_3$) : 1980, 1910, 1667 cm^{-1}
^{1}H NMR : (δ, $CDCl_3$)
(200 MHz) 1.28 (d, 3H, J=7.5 Hz), 1.78-1.91 (m, 1H), 1.92-2.18 (ddd, 1H, J=21.0, 17.1, 4.2 Hz), 2.35 (s, 3H), 2.45-2.60 (m, 1H), 2.60-2.95 (m, 2H), 3.98 (ddd, 1H, J=21.0, 17.1, 4.2 Hz), 5.10 (d, 1H, J=6.4Hz), 5.34 (t, 1H, J=6.4Hz), 5.60 (t, 1H, J=6.4Hz), 6.20 (d, 1H, J=6.4Hz), 7.19 (s, 4H)

Complex 2c

Color : Red
mp : 128 °C
IR ($CHCl_3$) : 1980, 1910, 1667 cm^{-1}
^{1}H NMR : (δ, $CDCl_3$)
(200 MHz) 0.85 (t, 3H, J=7.3 Hz), 1.10-1.37(m, 3H), 1.38-1.57 (m, 4H), 1.50-1.70 (m, 2H), 1.80-2.20 (m, 4H), 2.4 (m, 1H), 2.60 (m, 2H) 3.75 (m, 1H), 5.10 (d, 1H, J=6.5 Hz), 5.30 (t, 1H, J=6.5Hz), 5.60 (t, 1H, J=6.5Hz), 6.20 (d, 1H, J=6.5Hz), 7.25 (m, 5H).
^{13}C NMR : (δ, $CDCl_3$)
(50.3 MHz) 14.13, 21.95, 22.95, 27.98, 28.50, 29.91, 30.52, 43.42, 54.70, 89.65, 90.09, 91.57, 94.84, 115.49, 126.59, 128.83, 143.17, 196.51, 233.0
Analysis: Calcd. : C=66.33, H=5.80
Observed : C=65.95, H=5.70

Complex 2d

Color : Red
mp : 138-140 °C, lit.[26]: 140 °C

IR ($CHCl_3$) : 1974, 1901, 1678cm^{-1}
^{1}H NMR : (δ, $CDCl_3$)
(200 MHz) 0.85 (t, 3H, J=7.3 Hz), 1.08-1.37(m, 3H), 1.38-1.57 (m, 2H), 1.70-1.90 (m, 2H), 1.90-2.20 (m, 2H), 2.35 (s, 3H), 2.55-3.90 (m, 2H), 3.75 (m, 1H), 5.10 (d, 1H, J=6.5 Hz), 5.30 (t, 1H, J=6.5Hz), 5.60 (t, 1H, J=6.5Hz), 6.20 (d, 1H, J=6.5Hz), 7.15 (s, 4H).

Complex 2e
Color : Orange
mp : 146-48 °C, lit.[26] : 150 °C
IR ($CHCl_3$) : 1982, 1910, 1675 cm^{-1}
^{1}H NMR : (δ, $CDCl_3$)
(200 MHz) 1.77-2.10 (m, 2H), 2.34 (s, 3H), 2.63-2.85 (m, 1H), 2.90-3.10 (m, 1H), 3.17-3.37 (m, 1H), 4.84 (d, 1H, J=7.2 Hz), 5.08 (d, 1H, J=6.5Hz), 5.25 (t, 1H, J=6.5Hz), 5.65 (t, 1H, J=6.5Hz), 6.18 (d, 1H, J=6.5Hz), 7.08-7.40 (m, 9H).

Complex 2f
Color : Red
mp : 162-164 °C, lit.[26] : 165 °C
IR ($CHCl_3$) : 1990, 1920, 1680 cm^{-1}
^{1}H NMR : (δ, $CDCl_3$)
(200 MHz) 1.75-2.15 (m, 2H), 2.30 (s, 3H), 2.65-2.82 (m, 1H), 2.90-3.11 (m, 1H), 3.20-3.38 (m, 1H), 4.82 (d, 1H, J=7.5 Hz), 5.08 (d, 1H, J=6.8 Hz), 5.22 (t, 1H, J=6.8 Hz), 5.63 (t, 1H, J=6.8 Hz), 6.18 (d, 1H, J=6.8 Hz), 7.10 (s, 4H), 7.15-7.40 (m, 5H).

Typical procedure for the reaction of dialkyl magnesium with enones (1a-1b): The solution of enone (n mmol) in THF (5n ml) was cooled to –78 °C, under argon. To this a solution of freshly prepared dialkylmagnesium was added gradually with stirring through a syringe. The solution was then allowed to stir for additional 20-30 min. After the consumption of starting material (TLC), the reaction mixture was quenched with 5 ml of degassed methanol. The reaction mixture was then allowed to attain room temperature and diluted with dichloromethane. The dichloromethane layer was washed with water, dried over sodium sulfate. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography.

Reactions were done on 0.5-1.0 mmol scale and isolated yields are indicated in Table-2.

Complex 3a

Color	:	Red
mp	:	122 °C
IR ($CHCl_3$)	:	1980, 1915, 1675 cm^{-1}
^{1}H NMR (200 MHz)	:	(δ, $CDCl_3$) 0.9(t, 3H, J=6.5 Hz), 1.25 (m, 4H), 1.8 (q, 2H, J=6.3Hz), 1.9 (m, 2H), 2.26 (q, 2H, J=6.5Hz), 1.9 (m, 3H), 2.6 (quintet, 1H, J=5.5Hz), 2.8 (t, 2H, J=5.2Hz), 3.5 (q, 1H, J=6.6Hz), 5.05 (d, 1H, J=6.3Hz), 5.25 (t, 1H, J=6.3Hz), 5.60 (t, 1H, J=6.3Hz), 6.2 (d, 1H, J=6.3Hz), 7.25 (m, 5H)
^{13}C NMR (50.3 MHz)	:	14.09, 22.84, 24.64, 27.43, 30.22, 33.35, 44.59, 52.72, 88.74, 89.21, 91.90, 94.91, 115.86, 126.66, 128.50, 128.87, 141.95, 197.50, 230.71
Analysis: (C H O Cr)	:	Calcd: C=66.33, H=5.80

($C_{25}H_{26}O_4Cr$) Observed: C=66.04, H=5.70

Complex 3b

Color : Red
mp : 108-110 °C, lit.[26] : 110 °C
IR ($CHCl_3$) : 1980, 1915, 1675 cm^{-1}
^1H NMR : (δ, $CDCl_3$)
(200 MHz) 0.85 (t, 3H, J=7.5 Hz), 1.05-1.45 (m, 5H), 1.70-1.80 (m, 2H), 1.80-2.05 (m, 1H), 2.32 (s, 3H), 2.42-2.65 (m, 1H), 2.70-2.85 (m, 2H), 3.35-3.51 (m, 1H), 5.05 (d, 1H, J=6.5 Hz), 5.20 (t, 1H, J=6.5 Hz), 5.60 (t, 1H, J=6.5 Hz), 6.20 (d, 1H, J=6.5 Hz), 7.10 (s, 4H)

Complex 3c

Color : Red
mp : 162-164 °C, lit.[26]: 164 °C
IR ($CHCl_3$) : 1990, 1920, 1680 cm^{-1}
^1H NMR : (δ, $CDCl_3$)
(200 MHz) 1.75-2.15 (m, 2H), 2.30 (s, 3H), 2.65-2.82 (m, 1H), 2.90-3.11 (m, 1H), 3.20-3.38 (m, 1H), 4.82 (d, 1H, J=7.5 Hz), 5.08 (d, 1H, J=6.8 Hz), 5.22 (t, 1H, J=6.8 Hz), 5.63 (t, 1H, J=6.8 Hz), 6.18 (d, 1H, J=6.8 Hz), 7.10 (s, 4H), 7.15-7.40 (m, 5H).

Complex 4a:

Color : : Yellow
mp : 110-112 °C, lit.[26]: 110-112 °C
IR ($CHCl_3$) : 1980, 1910, cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$) 1.65 (s, 3H), 2.01 (s, 1H), 2.59-2.75 (m, 3H), 2.85-3.15 (m, 1H), 5.20-5.54 (m, 3H), 5.90 (d, 1H, J=6.7 Hz), 7.01 (s, 4H), 7.18-7.50 (m, 5H)

Complex 4b:

Color : Yellow

mp : 90 °C, lit.[26] : 91 °C

IR ($CHCl_3$) : 3400-3600(br) 1980, 1910 cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$) 1.63 (s, 3H), 2.05 (s, 1H), 2.38 (s, 3H), 2.70 (m, 3H), 2.88-3.05 (m, 1H), 5.21-5.48 (m, 3H), 5.90 (d, 1H, J=6.6Hz), 6.98 (s, 1H), 7.19 (s, 4H)

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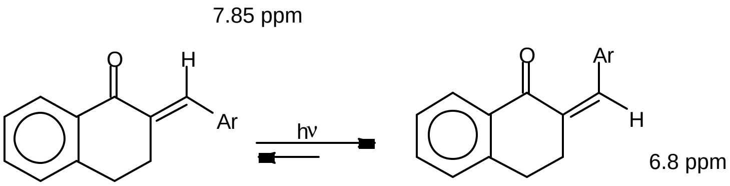
33. The stereochemistry of the double bond was further confirmed by photolysis of 2-(*p*-tolylidene)-1-tetralone at 350 nm for five hours in chloroform-*d*. It afforded a mixture of *Z* and *E* stereoisomers; the olefinic proton in each appeared at 6.8 and 7.85 ppm respectively (Scheme-18).[22]



In rigid and stereochemically defined structures such as isomeric α-benzylidenecamphors, the chemical shift of the *syn* (with respect to the carbonyl group) olefinic proton is 7.4 ppm while that of the *anti* olefinic proton is 6.45 ppm. The deshielding of *syn* olefinic proton is ascribed to the deshielding effect of the coplanar carbonyl group anisotropy. See also Kossanyi, J.; Furth, B.; Morizur, J. P. *Tetrahedron* **1970**, *26*, 395

Chapter - II

Diastereoselective Mukaiyama aldol and related reactions of chiral arylaldehyde complexes of tricarbonylchromium

Introduction

The Mukaiyama reaction[1] is a modified crossed aldol reaction where a Lewis acid is used to induce the addition of a silyl enol ether or a silyl ketene acetal to an aldehyde (Scheme-1). The reaction provides a mild method for making carbon–carbon bonds and creates new stereogenic centers with a high degree of stereochemical control. The silyl enol ethers can be synthesized[2] regioselectively on a ketone with desired geometry *(E* or *Z).*

Scheme-1

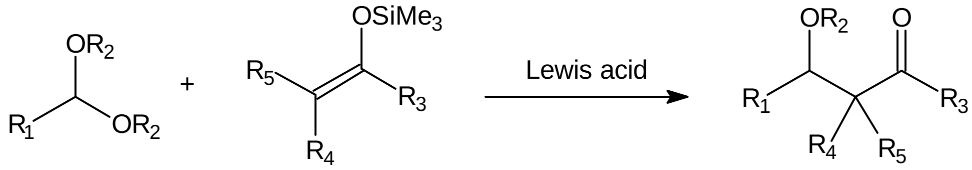
R'= H, Alkyl

R" = Alkyl, Aryl, Alkoxy, Aryloxy

Originally the Mukaiyama reaction used a stiochiometric amount of Lewis acids like $TiCl_4$, $BF_3.OEt_2$[3], etc. In order to accommodate acid sensitive functional groups on the substrates milder conditions were developed later with the use of catalytic amount of Lewis acids. Among such catalysts are TMSOTf,[4a] $Sn(OTf)_2$,[4b] Me_3SiI,[4c] Ph_3CClO_4,[4d] $SnCl_4/Ph_3CCl$,[4e] $Ph_3C(OTf)$,[4f] lanthanide triflates,[4g] Ti, Yb, and Zr triflate complexes.[4h] While many are air and moisture sensitive, the lanthanide and the scandium triflates[5] are stable to air and moisture. In fact they are even soluble in water and catalyze reactions in aqueous medium. For instance Kobayashi has reported the reaction of various silyl enol ethers with formaldehyde in aqueous medium.[6] With aldehydes which are insoluble in water, THF or acetonitrile is used as a co-solvent[7] with surfactants as phase transfer agents. As these salts are air-stable they can be accurately weighed, and their solubility in water permits effective recovery after an aqueous work-up. In this manner they can be recycled 4 to 5 times. These salts are effective as Lewis acid catalysts even when supported on a polymer or encapsulated in Nafion.[8]

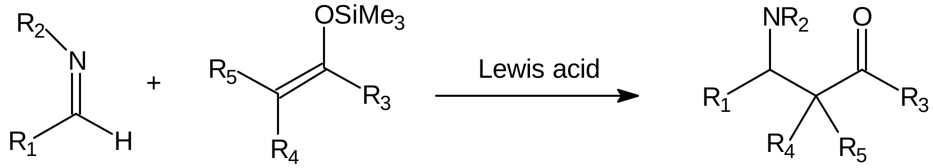
In a further modification of Mukaiyama reaction, Lewis acids have been used to catalyze addition of silyl enol ethers or silyl ketene acetals to acetals in place of aldehydes (Scheme-2). This is an important modification as sensitive aldehydes can be now protected as acetals and still be treated with the silyl enol ethers to give the β-alkoxy ketone or ester instead of the β-hydroxy ketone or ester.[9] The reactivity of the acetals is comparable with the parent aldehydes when strong Lewis acids like $TiCl_4$,[9a] or $BF_3.OEt_2$[9b] are used. However, with the triflates the acetals react sluggishly compared to the aldeydes.[10] Hence a chemoselectivity can be attained in favor of the aldehyde in presence of an acetal.

Scheme-2



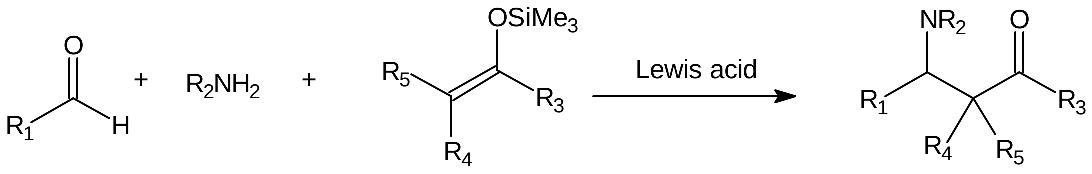
Another important extension is the addition of the silyl enol ethers and silyl ketene acetals to imines to produce β-amino ketones and β-amino esters[11a] (Scheme-3). Instead of stronger Lewis acids like $TiCl_4$, triflate and perchlorate salts have been extensively used[11b] in this reaction.

Scheme-3



Kobayashi used either ytterbium triflate, or scandium triflate to catalyze a three component reaction comprising of an aldehyde, an amine and a silyl ketene acetal to afford synthetically useful β-amino esters which can be cyclized to β-lactams[11c] (Scheme-4).

Scheme-4

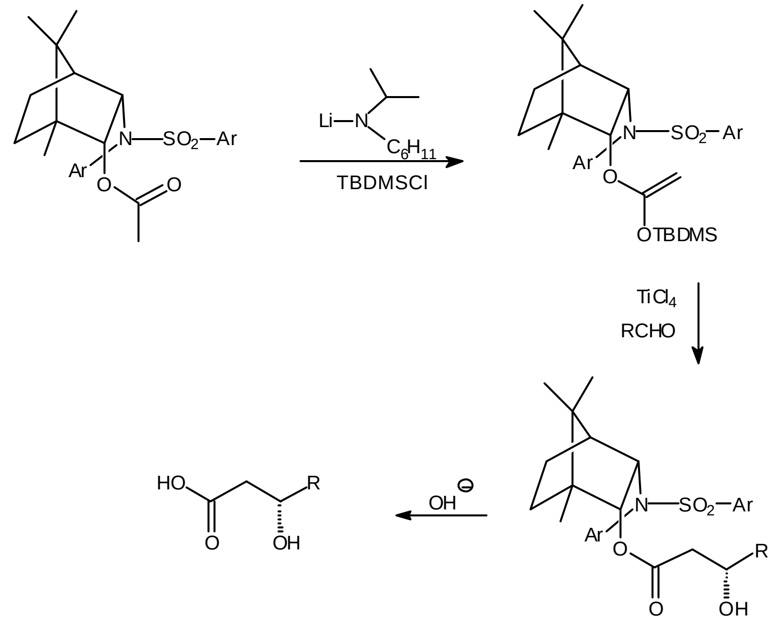


Control of stereoselectivity in these reactions can be achieved at two levels. For silyl enol ethers or ketene acetals bearing no substituent at the α-carbon, only one stereogenic center is produced. Enantioselectivity in this reaction can be attained either by the use of a chiral silyl enol ether component or a chiral aldehyde partner, or both. We consider these examples first.

A number of chiral auxiliaries have been developed to generate α-unsubstituted chiral silyl enolates. The most widely used are acetates derived from camphor derivatives, either the Helmchen type[12] or the Oppolzer[13] type (Scheme-5). In both cases, the reaction of the corresponding silyl ketene acetal with achiral aldehydes, give predominantly a single isomer (99:1). The products on hydrolysis regenerates the auxiliaries, and affords the optically pure β-hydroxy acids. It is of interest to note that lithium enolates of these acetates did not provide very high selectivity (80:20).

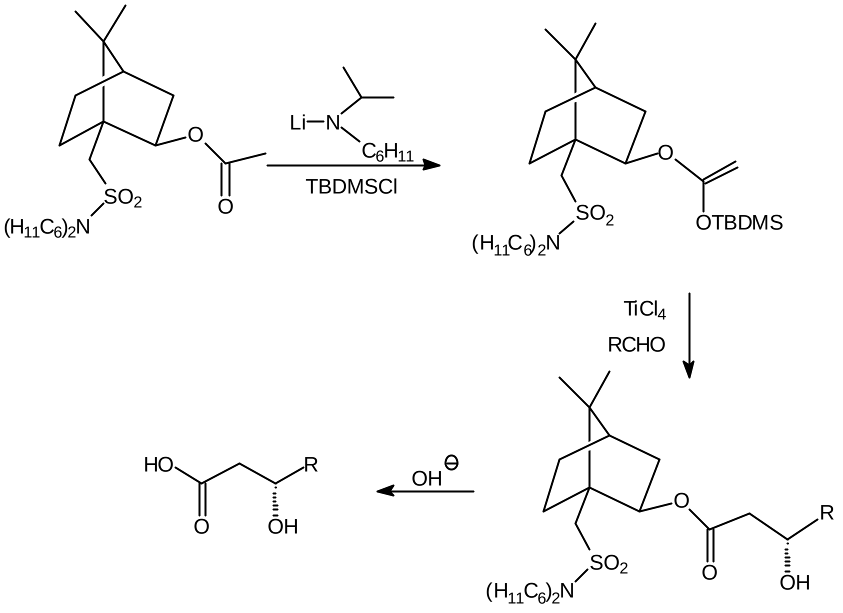
Scheme-5

Helmchen type



$R= C_2H_5, CH(CH_3)_2, CH_3(CH_2)_6, C_6H_5$

Oppolzer type

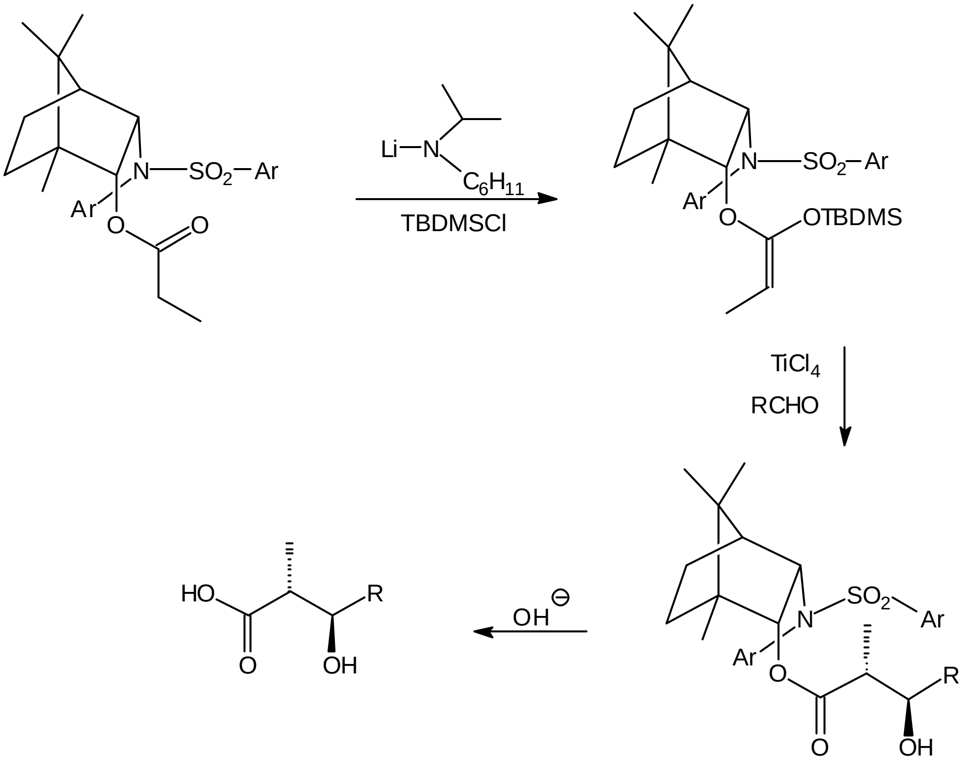


$R= C_2H_5, CH(CH_3)_2, CH_3(CH_2)_6, C_6H_5$

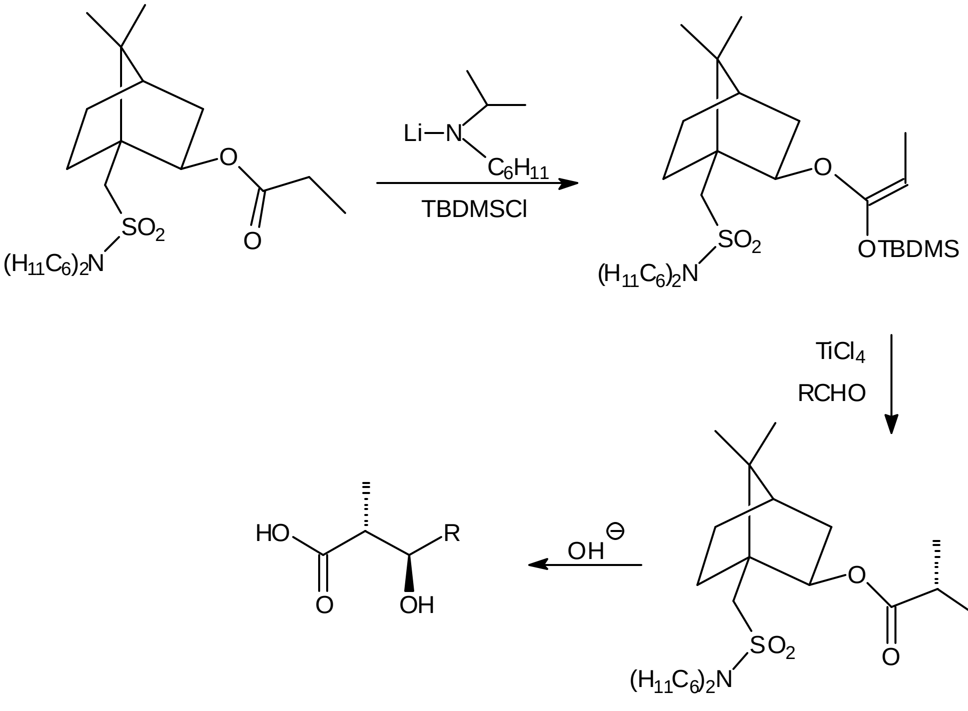
If the α-carbon of silyl ketene acetal is substituted, the product of Mukiayama reaction would contain two stereogenic centers and *syn*-*anti* selectivity becomes crucial in these reactions.

The propionates derived from the camphor auxillaries gave selectively *E*-silyl ketene acetals (Scheme-6). When treated with the achiral aldehydes, they showed a very high *anti*-selectivity.

Scheme-6

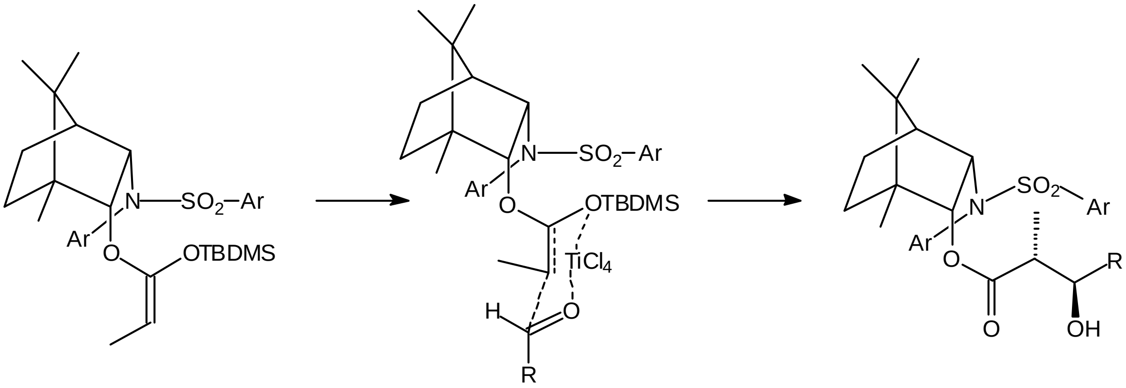


R= C_2H_5, $CH(CH_3)_2$, $CH_3(CH_2)_6$, C_6H_5

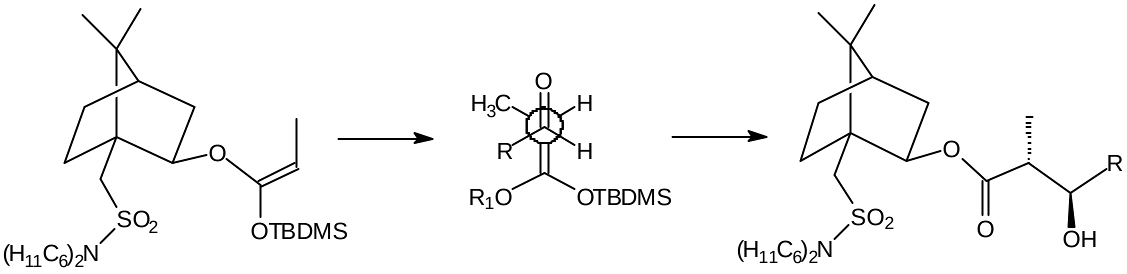


R= C_2H_5, $CH(CH_3)_2$, $CH_3(CH_2)_6$, C_6H_5

Scheme-7a



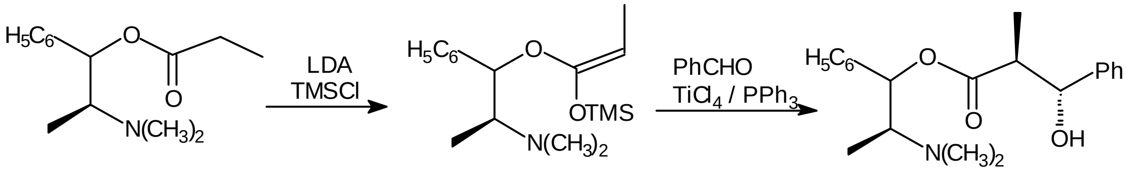
Scheme-7b



In the case of the Helmchen type derivatives, the product stereochemistry[12] was explained by a closed transition state also called the Zimmerman-Traxler intermediate (Scheme-7a), whereas for the Oppolzer type derivatives the product stereochemistry was explained[13] by an open transition state (Scheme-7b).

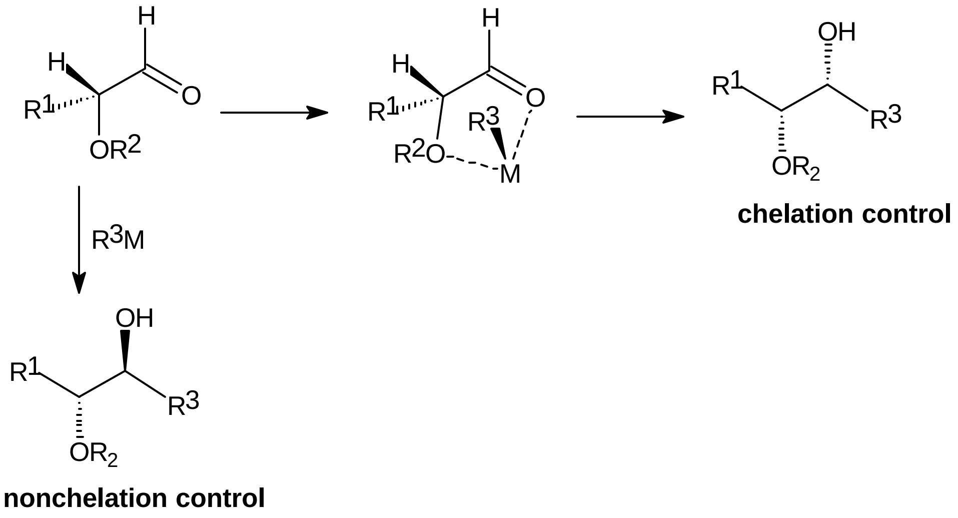
The *E*-silyl ketene acetals derived from N-methyl ephedrine[14] gave moderate selectivity (80:20) when treated with achiral aldehydes in the presence of $TiCl_4$. Intetrestingly the selectivity increased to 95:5 when a combination of $TiCl_4$ and PPh_3 was used (Scheme-8).

Scheme-8



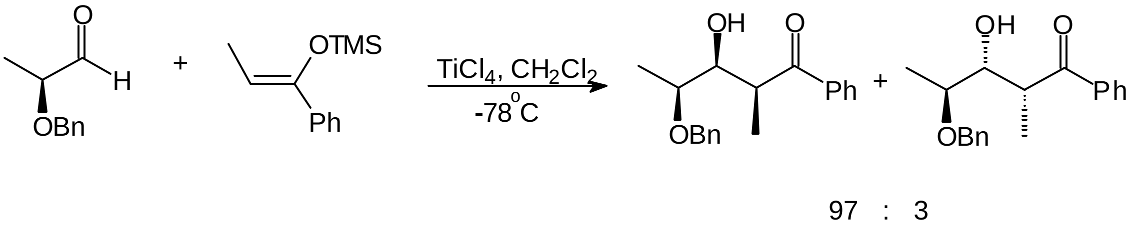
The alternative approach to ensure stereoselectivity uses enantiopure chiral aldehydes and achiral silyl enol ethers. A number of chiral aldehydes have been studied in this respect. The most extensively studied are the α-alkoxy aldehydes. In the presence or absence of Lewis acids, such substrates lead to the formation of different isomers. This is explained[15] by Cram's cyclic model (Scheme-9).

Scheme-9



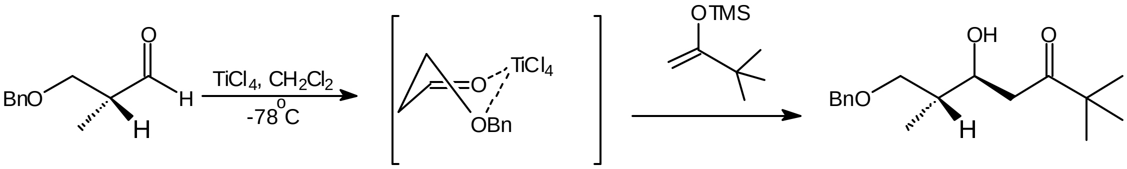
For example, a high stereoselectivity (*syn/anti*, 95:5) was observed[16a] in the $TiCl_4$ induced reaction of 2-benzyloxypropanal and different α-unsubstituted silyl enol ethers. Similarly the *Z*-enolsilane of propiophenone, gave 2,3 syn adducts[16b] with a very high selectivity. In both the cases, the product stereochemistry was explained by a chelation controlled cyclic intermediate (Scheme-10).

Scheme-10



Similarly a chelation was also indicated in a similar reaction with 3-benzyloxy-2-propanal, where a predominant formation of anti adducts (92:8) was observed [16c] (Scheme-11).

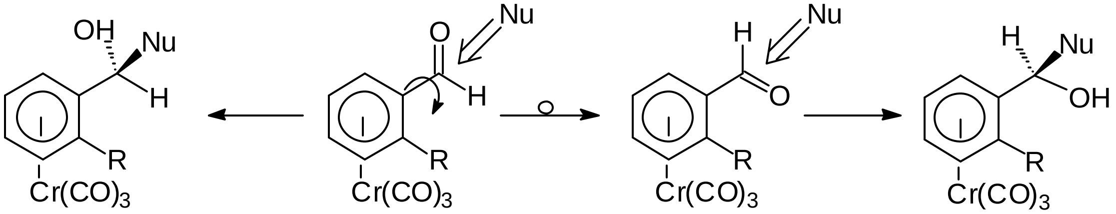
Scheme-11



Background to present work

The *ortho*-substituted benzaldehyde chromium tricarbonyl complexes possess a planar chirality and hence serve as a set of chiral aldehydes.[17] Stereoselectivity in nucleophilic addition is affected by the steric bulk of tricarbonylchromium group which, disfavors attack of the nucleophile from the *endo* face of the molecule. However, a rotation about the aryl-CO bond, leads to two conformers *syn* and *anti* with respect to the *ortho* substitiuent, and consequently exposes two different diastereofaces of the aldehyde group to *exo*-selective nucleophilic attack (Scheme–12). Stereochemistry of the product is thus dependent on *syn* or *anti* oreintation of the aldehyde group.

Scheme – 12



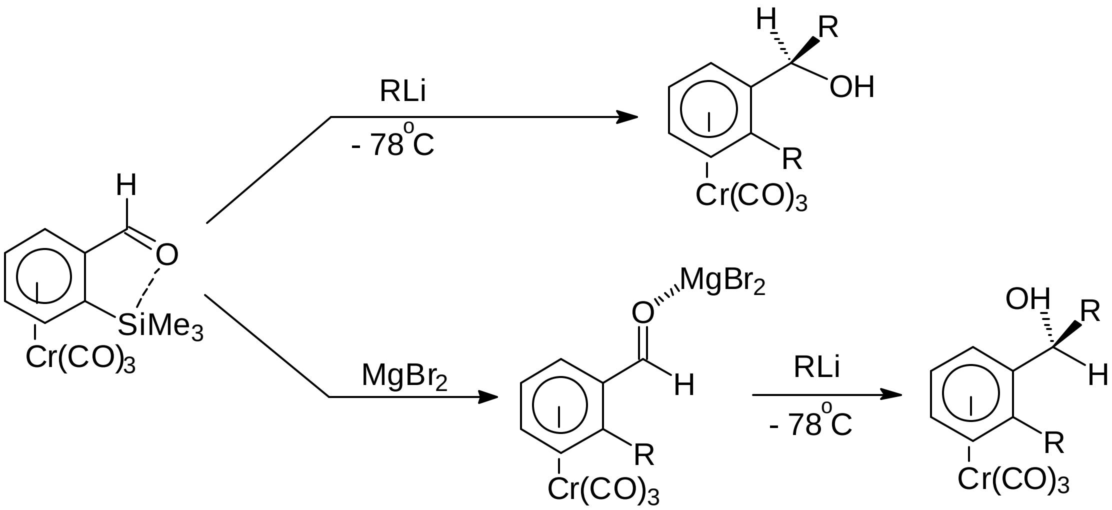
Anti *Syn*

The nature of R group at the *ortho* position can govern *syn* vs. *anti* conformational preference. For instance, if R is a bulky alkyl group, the aldehyde carbonyl prefers an *anti* conformation on steric grounds. With hetero atoms like O, F, Cl in the *ortho* position, the carbonyl prefers an *anti* conformation on electronic grounds.

However when the R group is a $SiMe_3$, it has been suggested[18] that the carbonyl oxygen is involved in a weak bonding interaction (Scheme-13) with the silicon and hence can adopt a *syn* conformation. In the presence of a Lewis acid complexing with the carbonyl oxygen, the Si-O interaction is disrupted and *anti* conformation is preferred on steric grounds.

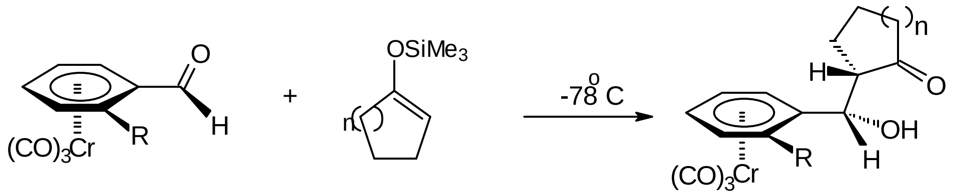
Davies supported this suggestion with extensive studies[18] on nucleophilic additions to such aldehydes (Scheme-13).

Scheme-13



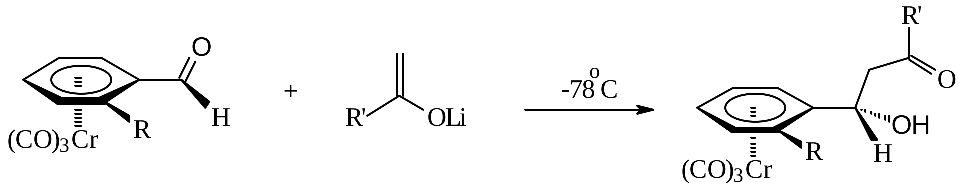
Mukai reported[19a] a *threo*-selective Mukaiyama aldol reaction between *ortho* substituted benzaldehyde tricarbonyl chromium complexes and cyclic silyl enol ethers mediated by $BF_3.OEt_2$ (Scheme-14). However, high *threo* selectivity was obtained only in the case of the *ortho* trimethylsilyl complexes. Similar selectivities were observed[19b] when α-substituted silyl ketene acetals were used, with $TiCl_4$ as the Lewis acid.

Scheme-14



On the other hand, reaction of lithium enolates of acylic ketone like acetophenone and methyl *tert*-butyl ketone with ortho subtituted benzaldehyde chromium complexes has been reported[20] to proceed with very high selectivities. The *exo* addition of the enolates presumably takes place on the *anti* conformer (Scheme-15).

Scheme-15



R	**R'**
OCH$_3$	Ph
OCH$_3$	*t*-Bu

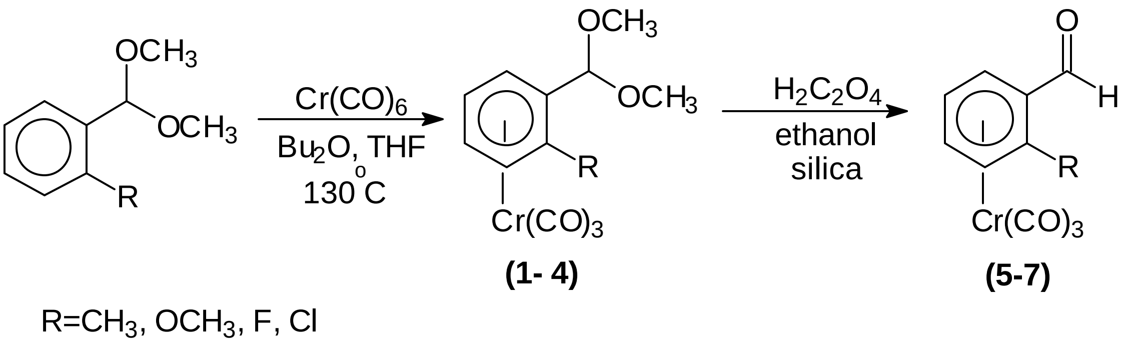
The structural assignments however, were based solely on the optical rotation data of optically active products.

These reactions form the starting point of the present investigation. It was thought of immediate interest to explore whether Mukaiyama-type reaction on these substrates using catalytic Lewis acids would proceed with high selectivity at ambient temperature. The Lewis acids considered were mainly scandium and rare earth triflates described by Kobayashi.[6a-b]

Present Work

The dimethyl acetal complexes **1-3** were prepared by the thermolysis of $Cr(CO)_6$ in the presence of the corresponding acetals (Scheme-16) in a mixture of dibutyl ether and THF (10:1) at 130°C. The aldehydes **5-7** were prepared[21a] by the deprotection of the corresponding dimethyl acetals **1-3** complexes under acidic conditions.

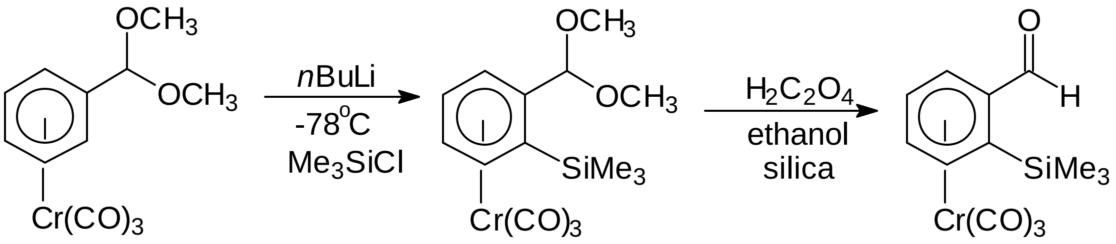
Scheme-16



R=			
	OCH_3	**1**	**5**
	CH_3	**2**	**6**
	F	**3**	**7**
	Cl	**4**	**-**

For the preparation of *ortho* trimethylsilyl aldehyde complex **8**, the trimethylsilyl group was introduced by lithiation of benzaldehyde dimethyl acetal complex at –78°C in THF followed by quenching with trimethylsilyl chloride (Scheme-17). Acidic hydrolysis of the *ortho* trimethylsilyl acetal complex[18] gave the desired substrate **8**.

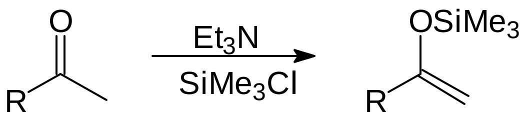
Scheme-17



(8)

Silyl enol ether of acetophenone **9** was prepared[22a] by refluxing acetophenone in DMF, with trimethylsilyl chloride and triethylamine. Reaction of pinacolone with trimethylsilylchloride using sodium hydride in THF at room temperature afforded[22a] the corresponding silyl enol ether **10**. Silyl enol ether of acetone **11** was synthesized by treating acetone with trimethylsilyl chloride in the presence of sodium iodide and triethylamine in acetonitrile.[22b] The silyl enol ethers were distilled and characterized by their ^{1}H NMR spetra. The ^{1}H NMR spectra showed a characteristic singlet at 0.3 ppm for the trimethyl silyl group and a singlet at 4.4 ppm for the olefinic protons.

Scheme-18



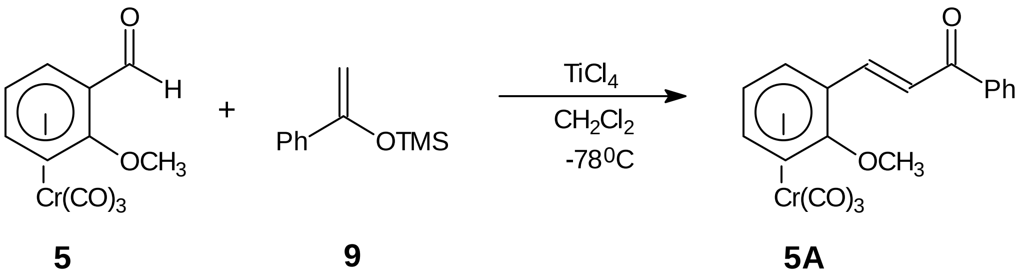
(9-11)

R = Ph, *t*Bu, CH_3

R=	Ph	**9**
	t-Bu	**10**
	CH_3	**11**

For complex **5** and silyl enol ether **9**, using the standard protocol where $TiCl_4$ is used as the Lewis acid, the product was isolated as a α,β unsaturated ketone **5A,** in 76 % yield instead of the expected β-hydroxy ketone (Scheme-19).

Scheme-19



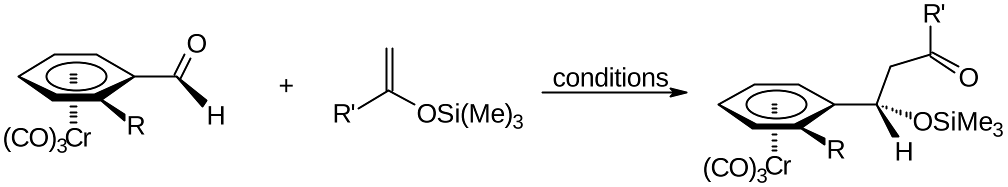
The product **5A** displays typical olefinic signals in the 1H and 13CNMR spectra.

Thus, it is likely that a stable carbocation is readily formed under the strong acidic condition and elimination ensued.

In order to obtain the aldol product it was therefore necessary to use milder Lewis acid and preferably in catalytic amount. Inspired by the work of Kobayashi,[6a-b] we employed scandium triflate for the aldol reaction of silyl enol ethers to the ortho-substituted benzaldeyde complexes **5-8**. An additional advantage of the protocol is the convenience of ambient temperature. When complex **5** and silyl ether **9** in dichloromethane was treated with 10 mol% of scandium triflate, the intense red color of the solution turned pale yellow within 15 mins to give the β-hydroxy ketone **5a** protected as a trimethylsilyl ether. This short reaction time is typical for the chromium complexes, while reaction with uncomplexed aldehydes took 12-18 hours.[4g] Enhanced electrophilicity of carbonyl functions attached to aromatic rings complexed with tricarbonyl chromium has been recorded in several other reactions.[23]

An aqueous work up, yielded the crude product which was purified by flash column chromatography with 5% acetone in pet-ether as the eluent. The purified product was identified as a single diastereomer by ^{1}H and ^{13}C NMR spectra. A sharp singlet at 0.15 ppm in the ^{1}H NMR spectrum and a signal at 2 ppm in the ^{13}C NMR spectrum indicated the presence of the $SiMe_3$ group. A signal at 200 ppm indicated the presence of a ketone carbonyl in the adduct. The results are summarized in Table-1.

Scheme-20



	Conditions
A	10 mol% $Sc(OTf)_3$, CH_2Cl_2, r.t
B	10 mol% $Yb(OTf)_3$, CH_2Cl_2, r.t
C	10 mol% $Nd(OTf)_3$, CH_2Cl_2, r.t
D	10 mol% TBAF, CH_2Cl_2, -78°C

Table-1

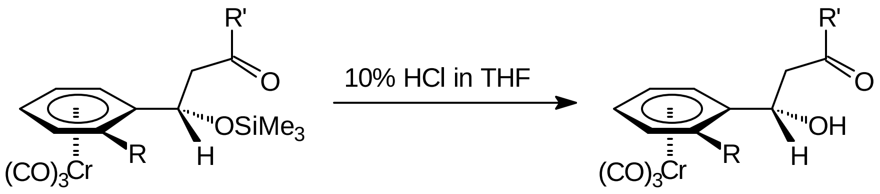
Entry	Aldehyde	Enolsilane	R	R'	Condition	Product[b]	%yield[a]
1	**5**	**9**	OCH_3	Ph	**A**	5a	**87**
2					B		**82**
3					C		**76**
4					D		**70**
5	**5**	**10**	OCH_3	*t*-Bu	A	**5b**	**80**
6					D		**72**
7	**5**	**11**	OCH_3	CH_3	A	**5c**	**85**
8					C		**81**
9	**6**	**9**	CH_3	**Ph**	A	**6a**	**82**
10					B		**84**
11	**6**	**10**	CH_3	*t*-Bu	A	**6b**	**82**
12					B		**80**
13	**6**	**11**	CH_3	CH_3	A	**6c**	**84**
14	**7**	**9**	F	Ph	A	**7a**	**83**
15					B		**78**
16	**7**	**10**	F	*t*-Bu	A	**7b**	**80**
17	**7**	**11**	F	CH_3	**A**	7c	**83**
18	**8**	**9**	$SiMe_3$	Ph	**A**	8a	**78**

In all the cases the reaction rates were comparable, and diastereomerically pure β-siloxy ketones were obtained as crystalline, yellow solids. To confirm only one diastereomer was indeed formed, ^{1}H NMR spectrum of the products were frequently recorded prior to any purification. Noteworthy was the reaction of acetone silyl enol ether **11**, which is highly moisture and acid-sensitive, generally gives very low yields of the aldol[24], under stronger acidic conditions. However, with scandium triflate, the reaction yielded the expected products with very high yields (70-85 %). Rare earth triflates catalyzed the reaction with same efficiency as scandium triflate.

A remarkable feature of the ^{1}H NMR spectra of the products (entries 5-18) was a typical AB quartet for the diastereotopic methylene protons at 3.2-3.5 ppm. The methine signal remains embedded in the region of complexed arene protons (5.0-5.5 ppm). The methylene protons of the *ortho*-methoxy substituted product **5a** appear as a multiplet in $CDCl_3$ but displays the familiar doublet of doublet pattern when recorded in C_6D_6.

As the products obtained in the triflate catalyzed aldol were all β-siloxy ketones, the silyl ether was cleaved under mild acidic conditions to give the corresponding β-hydroxy ketones to enable a direct spectral comparison with precedents [20] from the literature. Thus, the β-siloxy ketones **5a** and **5b** were treated with 10% HCl in THF at –10 to 0°C, and stirred until the consumption of the starting material (TLC). A careful aqueous work up and neutralization with $NaHCO_3$ gave the crude hydroxy ketones which, were purified by flash column chromatography with 5% acetone in pet ether as the eluent. The melting points and the ^{1}H NMR data for these products (**5a'** and **5b'**) were identical with the reported[20] values. The product stereochemistry was thus consistent with the proposal of *exo* addition to the *anti* conformer of the aldehyde.

Scheme-21



R = OCH_3
R' = Ph, *t*Bu

Table-2

Siloxy ether	R	R'	Alcohol	Yield (%)
5a	OCH_3	Ph	5a'	72
5b	OCH_3	*t*-Bu	5b'	70

Scheme-22

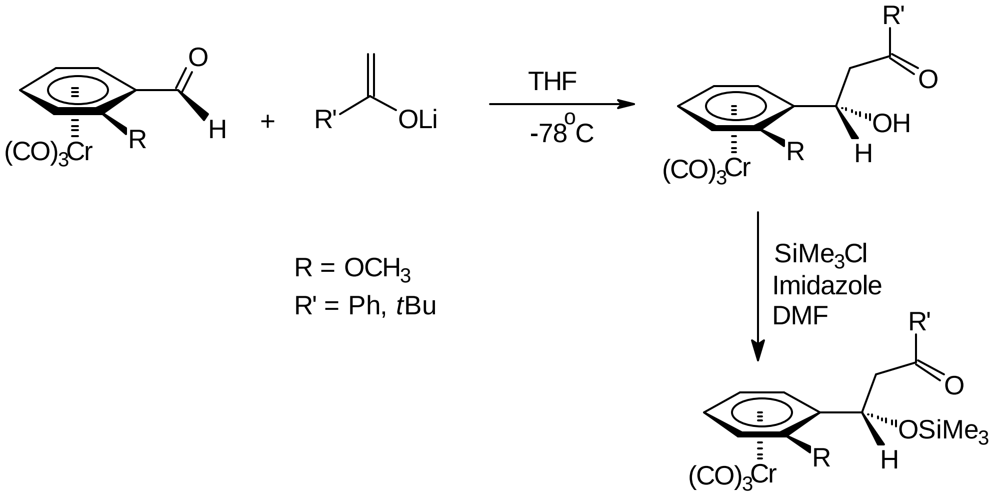


Table-3

R	R'	Alcohol	Siloxy ether	Yield (%)[a]
OCH_3	Ph	5a'	5a	68
OCH_3	*t*-Bu	5b'	5b	64

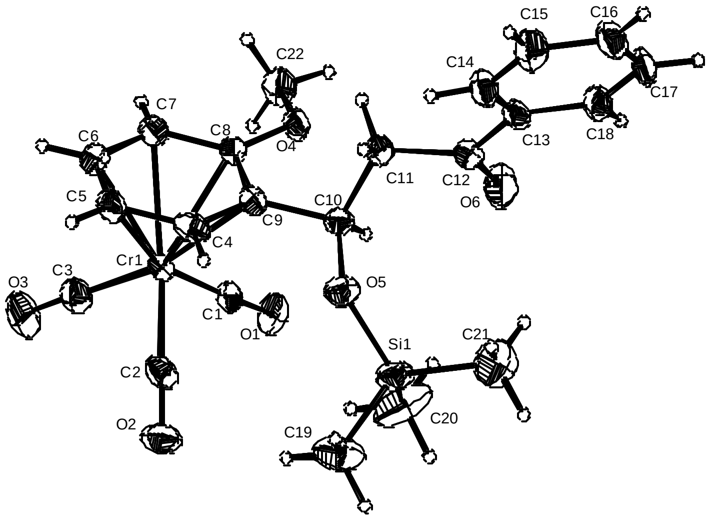
a: over yield of two steps

The hydroxy compounds (**5a'** and **5b'**) were synthesized following the reported method[20] and protected as trimethylsilyl ethers, for comparison with the siloxy ketones **5a** and **5b**.

The results also establish – I) no chelation occurs involving the OMe group and aldehyde in complex **5**; and, II) the weak Si-O interaction possible in **8** was not relevant for the reactive conformation in presence of Lewis acid.[18]

The product stereochemistry was unambiguously determined from the crystal structure analysis of a representative compound **5a** (Fig.2). The structure clearly depicts the relative stereochemistry as anticipated and discussed above.

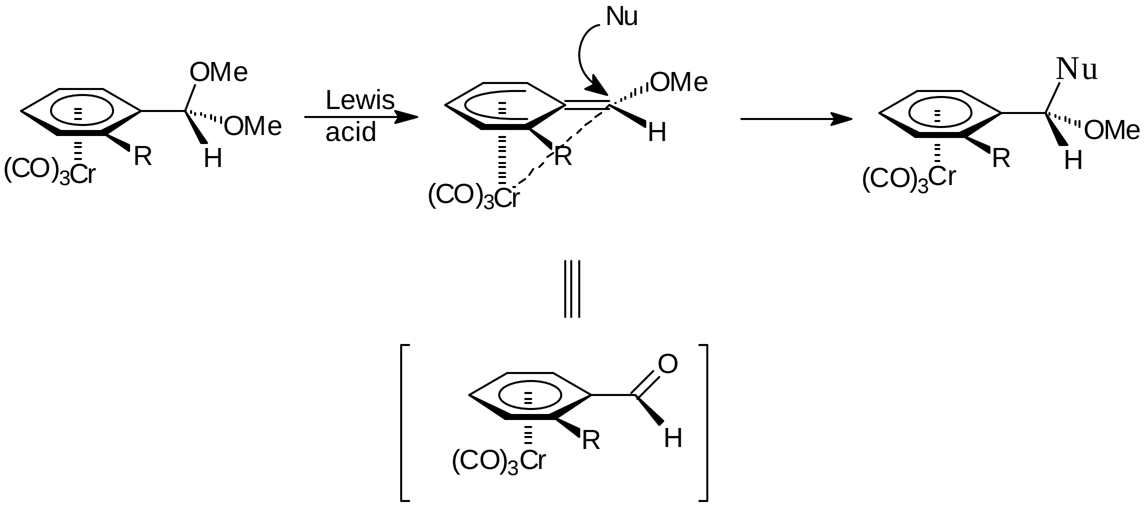
Fig-2



Single crystal X-ray structure of compound **5a**

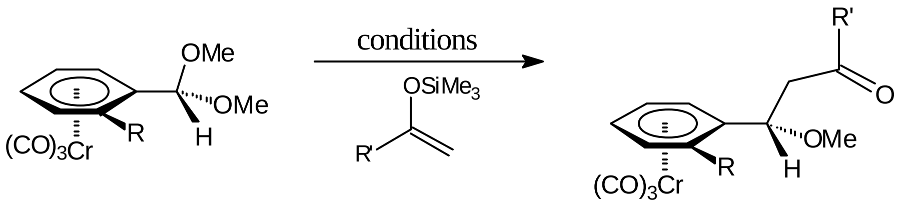
Mukaiyama has shown that even the acetals of the corresponding aldehydes react with the silyl enol ethers in a similar manner in the presence of Lewis acids.[9] The acetals, however were found to react slowly than the corresponding aldehydes. When dialkyl acetals of *ortho* substituted benzaldehyde complexes are treated with Lewis acids, the resulting carbocation is stabilized by participation of the tricarbonylchromium moiety (Scheme-23). Consequently, the rotation along the C_{aryl}-C_{ald} bond is restricted and the alkoxy group remains *anti* with respect to the *ortho* substituent on steric grounds.[24] This conformation is thus similar to the *anti* conformation of the aldehydes discussed before and nucleophilic addition from the *exo*-face should result identical product stereochemistry.

Scheme-23



The dimethyl acetal complexes **1-4** were therefore treated with the enolsilanes **9-11** in dichloromethane in the presence of scandium triflate (10mol%) at room temperature. Complete consumption of the starting material was observed within 20-30 minutes and aqueous work up followed by chromatographic purification of the crude residue furnished the diastereomerically pure products (entries 1-19, Table-4). The products were satisfactorily characterized by ^1H, ^{13}C NMR spectral and elemental analysis.

Scheme-24



R = OCH_3, CH_3, F, Cl
R' = Ph, *t*Bu, CH_3

	Conditions
A	$Sc(OTf)_3$, CH_2Cl_2
B	$Yb(OTf)_3$, CH_2Cl_2
C	TMSOTf, CH_2Cl_2

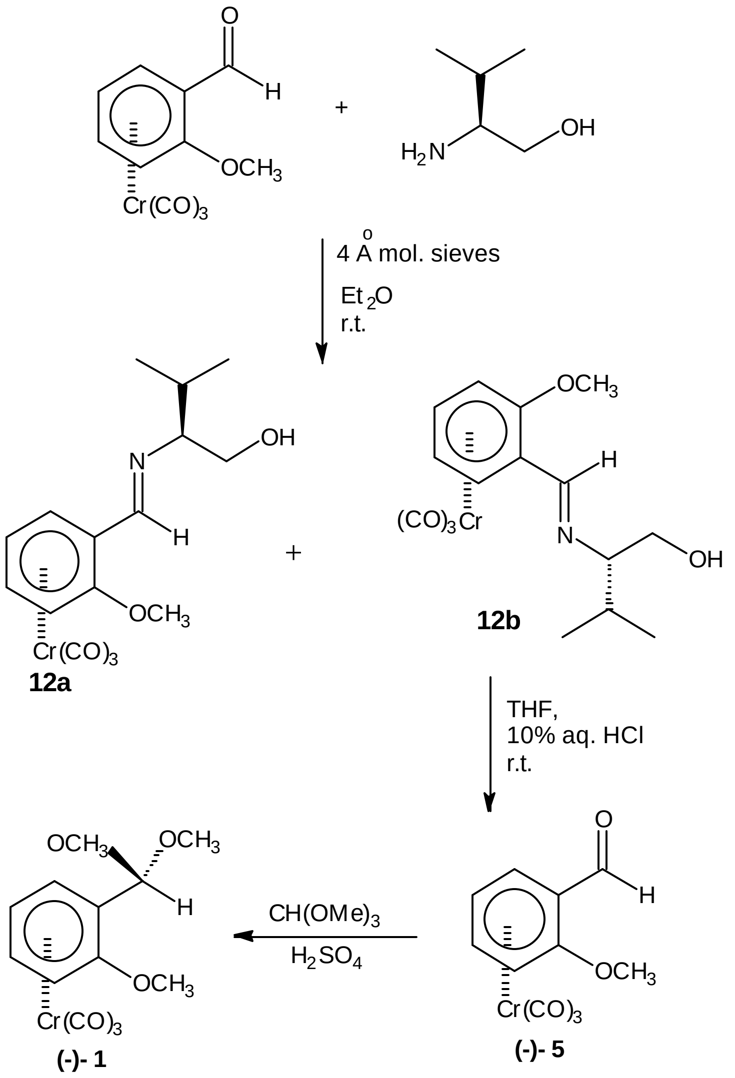
Table-4

Entry	Acetal	Enolsilane	R	R'	Condition	%yield	Product
1	**1**	**9**	OCH_3	Ph	A	82	**1a**
2					B	86	
3					C	80	
6	**1**	**11**	OCH_3	CH_3	A	84	**1c**
7					B	88	
8	**2**	**9**	CH_3	Ph	A	82	**2a**
9					B	83	
10					C	80	
11	**2**	**11**	CH_3	CH_3	A	83	**2c**
12					B	82	
13	**3**	**9**	F	Ph	A	80	**3a**
14					B	84	
15	**3**	**10**	F	*t*-Bu	A	78	**3b**
16	**3**	**11**	F	CH_3	A	88	**3c**
17	**4**	**9**	Cl	Ph	A	79	**4a**
18					B	82	
19	**4**	**10**	Cl	*t*-Bu	A	76	**4b**

The ^{1}H NMR spectral pattern of these compounds were strikingly similar in each case. There was a pair of AB quartets from 2.6 ppm to 3.5 ppm for the diastereomeric homobenzylic protons and another AB quartet for the benzylic proton, the AB quartet for the benzylic proton, being a little shielded (4.7-4.9 ppm) in the β-methoxy ketones compared to the β-silyloxy ketones (5.1-5.5 ppm). This indicated that the relative configuration of the silyloxy ketones obtained from the aldehydes and the methoxy ketones obtained from the acetals might be the same.

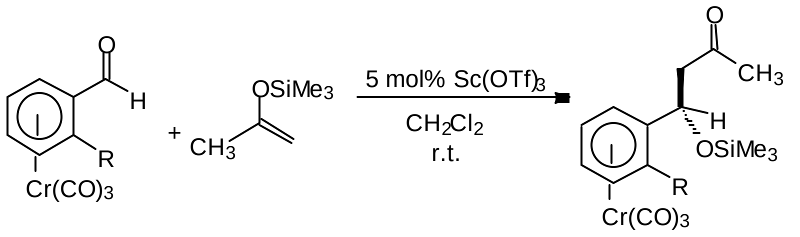
To confirm this possibility, optically pure aldehyde (–)-**5** was prepared by resolving[25] the racemic aldehyde **5** *via* diastereomeric imines **(12a and 12b)** from L-valinol and then separating the diastereomers on a basic alumina column. [26a]The imines were individually hydrolyzed to afford, as reported, a pair of optically active aldehydes. The optical purity of the aldehyde (–)-**5** was ensured by crystallization to constant rotation that matched reported values.[25] Similarly, optically pure tricarbonylchromium complex of *ortho*-anisaldehyde dimethyl acetal (–)-**1** was obtained by treating the optically pure aldehyde complex (–)-**5** with trimethylorthoformate under acidic conditions[24d] (Scheme-25).

Scheme-25



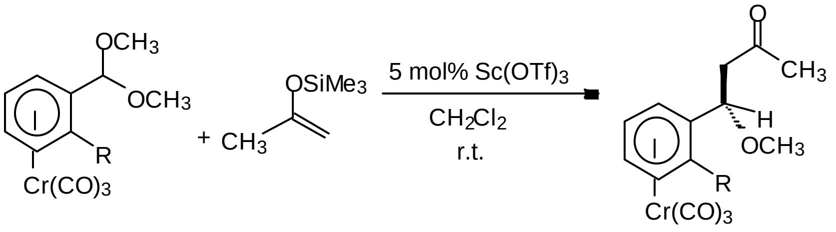
The optically pure dimethylacetal complex (–)-**1** and the *o*-anisaldehyde complex (–)-**5** were treated separately with the silyl enol ether of acetone **11** in dichloromethane with scandium triflate (10 mol%) to give the corresponding aldol products (+)-**1c** and (+)-**5c** respectively as single diastereomers. These products were purified by flash chromatography followed by crystallization (twice) to constant optical rotation.

Scheme-26a



(-)5 **11** **(+)5c**

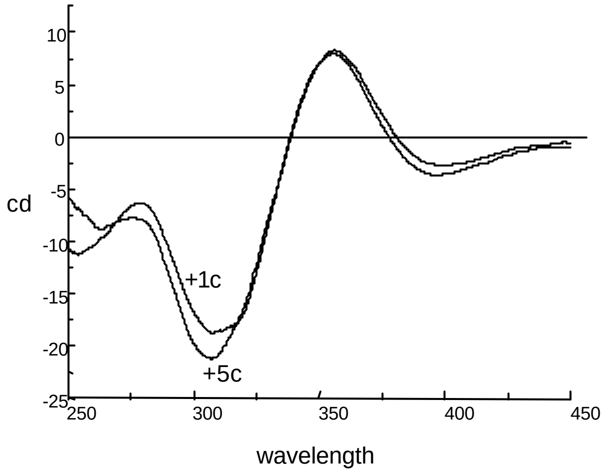
Scheme-26b



(-)1 **11** **(+)1c**

The CD spectral patterns of the two adducts, (+)-**5c** and (+)-**1c**, in chloroform showed a similar curve (Fig.3).

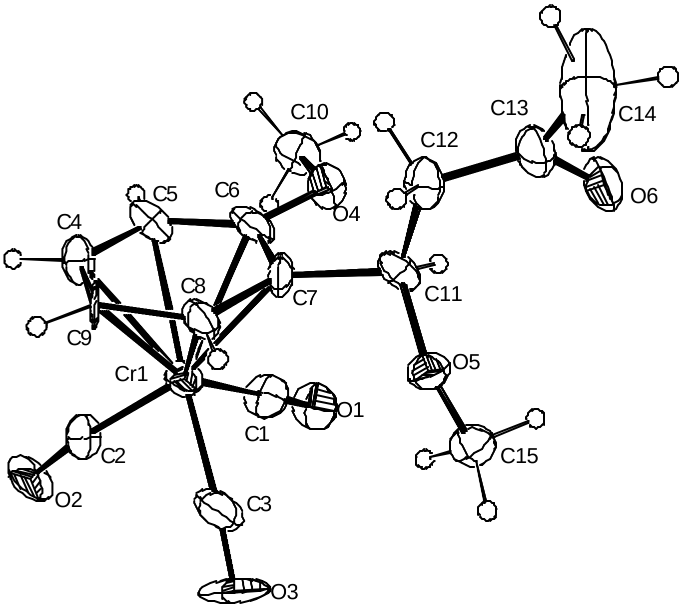
Fig-3



CD spectral patterns for compounds (+)-**1c** and (+)-**5c**

This showed that the absolute configurations of the two products at the benzylic center are similar. The absolute streochemistry was further confirmed by single crystal X-ray analysis (Fig.4) of compound **5c**.

Fig-4



Single crystal X-ray structure of compound **1c**

Summary

Addition of silyl enol ethers to tricarbonylchromium complexed, *ortho*-sustituted aromatic aldehydes has been shown to proceed with very high diastereoselectivity under triflate salt catalysis at ambient temperature. Since *ortho*-SiMe$_3$ group can be converted to variety of functional groups, this reaction should prove eminently useful in synthetic transformation of such substrates.

Experimental

All reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents. Scandium and rare earth triflate salts were prepared from reported procedures. Silyl enol ethers were also prepared according to the reported procedures.[22] The ortho substituted benzaldehyde complexes and their corresponding acetals were synthesized following reported[21] procedures.

Preparation of Compound 5A:

To a solution of the complexed aldehyde **5** (1 mmol) in dichloromethane (5 ml), titanium tetrachloride (2n mmol) was added dropwise with stirring at –78 °C. after stirring for 15 min, silyl enol ether **9** was added dropwise with stirring at the same temperature. After completion of the reaction (TLC, 30 mins), the reaction mixture was quenched with methanol at –78 °C, followed by addition of water at room temperature, and finally extracted with dichloromethane. The crude product obtained after evaporation of solvent. Purification by flash column chromatography using 10-12% acetone in pet-ether gave the compound **5A** as a red oil.

Complex 5A:

IR ($CHCl_3$)	:	1965, 1890 (br), 1685 cm^{-1}
^{1}H NMR	:	(δ, $CDCl_3$):
(200 MHz)		3.85 (s, 3H), 5.05(t, 1H, J=6.5Hz), 5.20 (d, 1H, J=6.6Hz), 5.70(t, 1H, J= 7.0Hz), 6.1(d, 1H, J=6.9Hz), 7.25 (d, 1H, J=12Hz), 7.55 (m, 3H), 7.85 (d, 1H, J=12Hz), 8.00 (d, 2H, J=7Hz)

^{13}C NMR (50.3 MHz) : (δ, CDCl$_3$): 55.85, 73.55, 84.87, 89.09, 93.09, 122.21, 127.97, 128.36, 128.55, 132.82, 137.31, 137.90, 142.65, 189.62, 232.10

Analysis for $C_{19}H_{14}O_5Cr$: Calcd.: C=60.96, H=3.77
Observed.: C=60.56, H=3.53

General Procedure for triflate salt catalyzed aldol reaction of *ortho*-substituted benzaldehyde complexes (5-8) and silyl enol ethers (9-11):

To a solution of complexed aldehyde (n mmol) and silyl enol ether (1.2n mmol) in dry dichloromethane, (0.1n mmol) triflate salt was added with stirring at room temperature. The red solution of the aldehyde instantly changed to yellow as the triflate salt is being added. After 15 minutes (TLC) the reaction mixture was diluted with dichloromethane, washed with water and dried over sodium sulfate. Evaporation of dichloromethane gave the crude product which, was purified by flash chromatography (5-10 % acetone in pet-ether).

All the reactions were done in a scale of 1-2 mmol and the yields of the isolated products are indicated in Table-3

Complex 5a:

mp : 137 °C
IR (CHCl$_3$) : 1965, 1890 (br), 1705 cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$):
0.15 (s, 9H), 3.2 (m, 2H), 3.7 (s, 3H), 4.95 (m 2H), 5.5 (t, 2H, J = 6.5Hz), 5.95 (d, 1H, J= 6.3Hz) 1H, 7.5 (m, 3H), 7.95 (d, 2H, J=6.0Hz)
(δ, C_6D_6):
0.4 (s, 9H), 2.95 (m, 4H), 31 (dd, 1H, J=16Hz, 5Hz), 4.05 (d, 1H, J=6.4Hz), 4.25 (t, 1H, J=6.4Hz), 4.75 (t, 1H, J=7.0Hz), 5.8 (m, 2H), 7.1 (m, 3H), 7.8 (d, 2H, J=6.4Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$):
0.45, 48.4, 55.95, 66.22, 73.35, 85.05, 93.04, 94.23, 105.9, 128.50, 128.82, 133.36, 137.71, 140.35, 197.35, 233.3

Analysis for $C_{22}H_{24}O_5SiCr$: Calcd. : C=58.91; H=5.39
Observed : C=58.10; H=5.09

Complex 5b:

mp : 114-115 °C

IR ($CHCl_3$) : 1970, 1890 (br) 1710 cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$):
0.2 (s, 9H), 1.1 (s, 9H), 2.65 (dd, 1H, J=17Hz, 2Hz), 2.85 (dd, 1H, J=17Hz, 8Hz), 3.75 (s, 3H), 4.90 (m,1H), 5.35 (dd, 1H, J=8Hz, 2Hz),5.5 (t, 1H, J=7.4Hz), 5.95 (d, 1H, J=6.4Hz)

^{13}C NMR (50.3 Mhz) : (δ, $CDCl_3$):
0.5, 26.16, 44.10, 46.23, 55.84, 65.22, 73.31, 85.00, 92.96, 94.14, 106.60, 140.09, 212.0, 233.30

Analysis for : Calcd. : C=56.05; H=6.58

$C_{20}H_{28}O_5SiCr$ Observed : C=55.10; H=6.15

Complex 5c

mp : 86-88 °C

IR ($CHCl_3$) : 1965, 1890 (br) 1705cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$): 0.2 (s, 9H), 2.1 (s, 3H), 2.75 (m, 2H), 3.7 (s, 1H), 4.95 (m, 2H), 5.3 (m, 1H), 5.5 (t, 1H, J=6.4Hz), 5.9 (d, 1H, J=6.4Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$): 0.35, 31.73, 52.53, 55.93, 65.63, 73.19, 84.88, 93.03, 94.33, 105.18, 140.27, 206.02, 233.36

Analysis for $C_{17}H_{22}O_5SiCr$: Calcd. : C=52.83 H=5.73
Observed : C=52.05 H=5.25

Complex 6a:.

mp : 84 °C

IR ($CHCl_3$) : 1970, 1888 (br), 1710cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$): 0.15 (s, 9H), 2.20 (s, 3H), 3.0 (dd, 1H, J=17.0, 2.0Hz), 3.45 (dd, 1H, J=17.0Hz, 8.0Hz), 5.0 (d, 1H, J=7.5Hz), 5.15 (t, 1H, J=7.3Hz), 5.45 (m, 2H), 5.95 (d, 1H, J=6.9Hz), 7.5 (m, 3H), 7.95 (d, 2H, J=6.8Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$): 0.32, 18.83, 49.45, 67.02, 88.89, 91.91, 92.09, 94.08, 106.86, 114.00, 128.47, 128.87, 133.58, 137.38, 196.96, 233.40;

Analysis for : Calcd. : C=61.09; H=5.59

$C_{22}H_{24}O_4SiCr$ Observed : C=60.65; H=5.40

Complex 6b:

mp : 90-92 °C

IR ($CHCl_3$) : 1965, 1890 (br), 1710cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$): 0.25 (s, 9H), 1.1(s, 9H), 2.1 (s, 3H) 2.5 (dd, 1H, J=16.8Hz, 3.0Hz), 2.95 (dd, 1H, J=16.8 Hz, 8.0Hz), 5.05 (d, 1H, J=6.9Hz), 5.15 (t, 1H, J=6.4Hz), 5.25 (dd, 1H, J= 8.0, 3.1 Hz), 5.45 (t, 1H J=6.9Hz), 5.8 (d, 1H, J=6.8Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$): 0.50, 18.84, 26.27, 44.2, 47.90, 66.30, 88.92, 91.98, 92.11, 94.90, 106.83, 115.57, 211.83, 233.48.

Analysis for : Calcd. : C=58.23; H=6.84

$C_{20}H_{28}O_4SiCr$ Observed : C=58.05; H=6.12

Complex 6c:

mp : 70 °C

IR ($CHCl_3$) : 1970, 1890 (br), 1705 cm^{-1} ;

^{1}H NMR (200 MHz) : (δ, $CDCl_3$): 0.20 (s, 9H), 2.2 (s, 6H), 2.6 (dd, 1H, J=16.6Hz, 2.8), (dd, 1H, J=17.0Hz, 8.0Hz), 5.0 (d, 1H, J=6.9Hz), 5.2 (m, 2H), 5.4 (t, 1H, J=6.4Hz), 5.8 (d, 1H, J=6.4Hz);

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$): 0.32, 18.75, 31.65, 53.72 66.54, 89.07, 91.97, 92.27, 94.00, 106.86, 114.50, 205.47, 233.5;

Analysis for : Calcd. : C=55.12; H=5.98

$C_{17}H_{22}O_4SiCr$ Observed : C=54.32; H=5.45

Complex 7a:.

mp : 44 °C

IR ($CHCl_3$) : 1970, 1890 (br), 1705 cm^{-1}

^1H NMR (200 MHz) : (δ, $CDCl_3$):
0.25 (s, 9H), 3.20 (dd, 1H, J=16.0Hz, 3.0Hz), 3.45 (dd, 1H, J=16.0Hz, 8.0Hz), 4.85 (bt, 1H, J=6.5 Hz), 5.3 (t, 1H, J=6.3 Hz), 5.5 (m, 2H), 5.85 (bt, 1H, J=6.4 Hz), 7.55 (m, 3H), 7.9 (d, 2H, J=7.2Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$):
0.32, 48.8, 65.51, 76.60, 85.47, 91.43, 93.27, 128.46, 128.90, 133.58, 137.32, 165.26, 196.25, 231.87

Analysis for : Calcd. : C=57.78; H=4.85; F=4.35

$C_{21}H_{21}O_4SiCrF$ Observed : C=57.12; H=4.40; F=3.95

Complex 7b:

mp : 89 °C

IR ($CHCl_3$) : 1965, 1890 (br), 1715 cm^{-1}

^1H NMR (200 MHz) : (δ, $CDCl_3$):
0.25 (s, 9H), 1.1 (s, 9H), 2.65 (dd, 1H, J=16.8Hz, 3.0Hz), 3.05 (dd, 1H, J=16.8Hz, 8.0Hz), 4.9 (dt, 1H, J=6.0Hz, 1.9Hz), 5.25 (t, 1H, J=6Hz), 5.35 (dd, 1H J=8.0Hz, 3.5Hz), 5.45 (qt, 1H, J=5.8Hz, 1.3Hz), 5.85 (t, 1H, J=6Hz)

^{13}C NMR : (δ,$CDCl_3$):
0.32, 26.10, 44.18, 46.85, 64.72, 76.90, 85.44, 91.41, 93.24, 103.0, 104.28, 211.56, 231.85

Analysis for $C_{19}H_{25}O_4SiCrF$: Calcd. : C=54.79; H=6.05, F=4.56
Observed : C=54.06; H=5.74, F=3.92

Complex 7c

mp : 119-120 °C
IR ($CHCl_3$) : 1970, 1890 (br), 1705 cm^{-1}
^{1}H NMR (200 MHz) : (δ, $CDCl_3$):
0.25 (s, 9H), 2.20 (s, 3H), 2.85 (m, 2H,), 4.85 (bt, 1H, J=6.3 Hz), 5.25 (m, 2H), 5.45 (bt, 1H), 5.80 (bt, 1H, J=6.5 Hz)
(δ, C_6D_6):
0.25 (s, 9H), 1.55 (s, 3H), 2.20 (dd, 1H, J=16.5, 8.0 Hz), 2.35 (dd, 1H, J=16.5, 2.8 Hz), 3.85 (bt, 1H, J=6.5 Hz), 4.35 (m, 2H), 5.25 (dd, 1H, J=7.4, 4 Hz), 5.45 (bt, 1H, J=6.2 Hz)
^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$):
0.22, 31.17, 52.60, 64.55, 77.05, 85.02, 90.98, 92.96, 93.11, 102.52, 102.78, 204.67, 231.43

Analysis for $C_{24}H_{30}O_4Si_2Cr$: Calcd. : **C=58.75; H=6.16**
Observed : **C=58.60; H=6.02**

Complex 8a:

mp : 119-120 °C
IR ($CHCl_3$) : 1970, 1890 (br), 1705 cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$): 0.05 (s, 9H), 0.45 (s, 9H), 2.95 (d, 1H, J=9.0Hz,), 3.5 (dd, 1H, J=17.0Hz, 8.0Hz), 5.20 (m, 1H), 5.35 (d, 1H, J=7.4Hz), 5.5 (m, 3H), 7.5 (m, 3H), 7.9 (d, 2H, J=7.0Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$): 0.72, 1.20, 51.7, 68.45, 87.96, 91.56 94.33, 96.27, 99.30, 124.37, 128.50, 128.95, 133.62, 137.56, 164.95, 196.97, 233.30

Analysis for $C_{24}H_{30}O_4Si_2Cr$:
Calcd. : **C=58.75; H=6.16**
Observed : **C=58.60; H=6.02**

General procedure for the (TBAF) catalyzed aldol reaction on the ortho substituted benzaldehyde chromium complex 5 and silyl enol ethers 9 and 10.

A solution of aldehyde (1mmol) complex **5** and silyl enol ether (1.2 mmol) in dry THF (4ml) was cooled to -78°C, to this cooled solution 1ml of 1molar tetrabutyl ammonium flouride solution in THF was added. After completion of the reaction (TLC) the reaction mixture was diluted with dry pet ether. The reaction mixture was gradually warmed to room temperature and extracted with dichloromethane. The dichloromethane layer was washed with water, dried over sodium sulfate, evaporation of dichloromethane gave the crude product, which was purified by flash column chromatography with 5% acetone in pet-ether as the eluent.

Reaction with silyl enol ether **9** gave the product **5a** in 70 % yield, whereas the reaction with slyl enol ether **10** afforded the alcohol **5b** in 72 % yield.

General Procedure for trilate salt catalysed Aldol reaction of *ortho*-substituted benzaldehyde dimethylacetal complexes and silyl enol ethers.

To a suspension of of the triflate salt (0.1n mmol) in of dry dichloromethane (2n ml), a solution of silyl enol ether (1.2n mmol) and dimethyl acetal (1n mmol) complex in 2n ml dry dichloromethane was added dropwise with stirring. After completion of the reaction (TLC), the reaction mixture was diluted with dichloromethane, washed with water and dried over sodium sulfate. Evaporation of dichloromethane gave the crude product which, was purified by flash column chromatography (5-10 % acetone in pet-ether).

All the reactions were done on a scale of 1-2 mmol and the yields of the isolated products are indicated in Table-6

Complex 1a:

mp : 94 °C

IR ($CHCl_3$) : 1970, 1890 (br), 1715 cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$): 3.15 (dd, 1H, J=17.0Hz, 3.0Hz), 3.45 (dd, 1H, J=17.0Hz, 8.0Hz), 3.6 (s, 3H), 3.75 (s, 3H), 5.0 (m, 3H,), 5.55 (t, 1H, J=6.4Hz), 5.95 (d, 1H, J=6.3Hz), 7.5 (m, 3H), 7.95 (d, 2H, J=7.0Hz);

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$): 46.51, 55.95, 59.59, 73.84, 85.11, 93.04, 94.43, 100.95, 128.32, 128.75, 133.36, 137.11, 140.35, 197.02, 233.25

Analysis for $C_{20}H_{18}O_6Cr$: Calcd. : C=59.11, H=4.46

Observed : C=58.91, H=4.26

Complex 1c:

mp : 98-99 °C

IR ($CHCl_3$) : 1940, 1820 (br), 1710 cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$): 2.2 (s, 3H), 2.7 (d, 2H, J=6.3 Hz), 3.60 (s, 3H,), 3.75 (s, 3H), 4.8 (t, 1H, J=7.3 Hz), 4.95 (t, 1H, J=6.3 Hz), 5.05 (t, 1H, J=6.3 Hz), 5.55 (t, 1H, J=6.5 Hz), 5.85 (d, 1H, J=7.0Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$): 31.51, 51.60, 56.56, 60.14, 74.18, 85.59, 93.30, 94.80, 101.07, 140.71, 206.21, 233.70

Analysis for $C_{13}H_{16}O_6Cr$: Calcd. : C=48.75, H=5.03
Observed : C=48.52, H=4.94

Complex 2a:

mp : 90-91 °C

IR ($CHCl_3$) : ($CHCl_3$):, 1970, 1890 (br), 1720 cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$): 2.15 (s, 3H), 2.95 (dd, 1H, J=17.0Hz, 3Hz), 3.45 (dd, 1H, J=17.0Hz, 8.0Hz), 3.6 (s, 3H), 4.85 (dd, 1H, J=8.0, 3.1Hz), 5.15 (d, 1H, J=7.4Hz), 5.25 (t, 3H J= 6.9Hz), 5.45 (t, 1H,), 5.85 (d, 1H), 7.5 (m, 3H), 8.0 (d, 2H, J=7.0Hz);

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$): 18.57, 47.24, 59.48, 75.08, 89.19, 92,02, 92.78, 95.06, 107.01, 110.27, 128.39, 128.86, 133.63, 136.93, 196.70, 233.39

Analysis for : Calcd. : C=61.54, H=4.64
$C_{20}H_{18}O_5Cr$ Observed : C=61.12, H=4.42

Complex 2c:

mp : 120 °C
IR ($CHCl_3$) : 1970, 1880 (br), 1710cm^{-1}
^1H NMR : (δ, $CDCl_3$):
(200 MHz) 2.2 (s, 3H), 2.25 (s, 3H), 2.55 (dd, 1H, J=16.5Hz, 2.9Hz), 2.75 (dd, 1H, J=16.8Hz, 8.2Hz), 3.6 (s, 3H), 4.65 (dd, 1H, J=8.1, 3.0 Hz), 5.10 (d, 1H, J=7.1Hz), 5.20 (t, 1H J=7.3Hz), 5.45 (t, 1H, J=6.8 Hz), 5.75 (d, 1H, J=6.4 Hz)
^{13}C NMR : (δ, $CDCl_3$):
(50.3 MHz) 19.00, 31.64, 52.25, 59.93, 75.52, 89.85, 92.49, 93.44, 95.72, 107.47, 110.32, 205.77, 233.95
Analysis for : Calcd. : C=51.31, H=5.30
$C_{13}H_{16}O_5Cr$ Found : C=51.45, H=5.25

Complex 3a:

mp : 78 °C
IR ($CHCl_3$) : 1970, 1885 (br) 1715cm^{-1}
^1H NMR : (δ, $CDCl_3$):
(200 MHz) 3.20 (dd, 1H, J=16.5Hz, 3Hz), 3.50 (dd, 1H, J=17.0Hz, 8.0Hz), 3.65 (s, 3H), 4.90 (m, 2H), 5.35 (t,1H, J=6.8Hz), 5.55 (bt, 1H J=7.2Hz), 5.80 (bt, 1H, J=7.0Hz), 7.50 (m, 3H0, 7.95 (d, 1H, J=6.8Hz)

^{13}C NMR (75.2 MHz) : (δ, CDCl$_3$):
30.39, 47.43, 60.12, 73.88, 78.78, 86.37, 92.44, 94.25, 94.34, 99.64, 99.80, 128.92, 129.46, 134.21, 137.43, 143.47, 146.98, 196.88, 232.43

Analysis for $C_{19}H_{15}O_5CrF$: Calcd. : C=57.84, H=3.84, F=4.81
Observed : C=57.61, H=3.42, F=4.03

Complex 3b:

mp : 68-70 °C
IR (CHCl$_3$) : 1970, 1890 (br), 1710 cm^{-1}
^{1}H NMR (200 MHz) : (δ, CDCl$_3$):
1.15 (s, 9H), 2.60 (dd, 1H, J=17.0Hz, 3Hz), 3.00 (dd, 1H, J=17.0Hz, 8.0Hz), 3.60 (s, 3H), 4.75 (dd, 1H, J=8Hz, 3Hz), 4.9 (bt, 1H, J=7Hz), 5.25 (t,1H, J=6.5Hz) 5.50 (m, 3H), 5.70 (bt, 1H, J=7.2Hz);
^{13}C NMR (50.3 MHz) : (δ, CDCl$_3$):
26.18, 44.37, 45.05, 59.62, 73.14, 76.64, 78.51, 81.86, 85.72, 91.82, 93.57, 93.72, 99.58, 211.70, 231.86.
Analysis for $C_{17}H_{19}O_5CrF$: Calcd. : C=54.54, H=5.11
Observed : C=54.12, H=5.03

Complex 3c:

mp : 102-103 °C
IR (CHCl$_3$) : 1970, 1890 (br), 1710 cm^{-1}

^{1}H NMR : (δ, $CDCl_3$):
(200 MHz) 2.20 (s, 3H), 2.70 (dd, 1H, J=17.0Hz, 3Hz), 2.85 (dd, 1H, J=17.0Hz, 8.0Hz), 3.60 (s, 3H) 4.7 (dd, 1H, J= 8Hz, 3Hz) 4.90 (dt, 1H, J=6.2 Hz), 5.30 (t, 1H, J=7Hz), 5.5 (qt, 1H, J=6, 2 Hz), 5.75 (bt, 1H, J=6.2Hz)
^{13}C NMR : (δ, $CDCl_3$):
(75.2 MHz) 30.84, 51.36, 59.82, 73.45, 78.41, 85.62, 91.50, 91.59, 93.30, 98.81, 99.09, 204.44, 231.66.
Analysis for : Calcd. : C=46.76, H=4.25
$C_{12}H_{13}O_5CrF$ Observed : C=45.68, H=4.02

Complex 4a:

mp : 115-116 °C
IR ($CHCl_3$) : 1965, 1888 (br) 1705cm^{-1}
^{1}H NMR : (δ, $CDCl_3$):
(200 MHz) 3.20 (dd, 1H, J=17.0Hz, 3Hz), 3.40 (dd, 1H, J=17.0Hz, 8.0Hz), 3.65 (s 3H), 5.05 (m, 2H), 5.45 (m, 2H), 5.90 (d, 1H, J=7.2Hz), 7.50 (m) 3H, 8.0 (d, 1H, J=6.8Hz)
^{13}C NMR : (δ, $CDCl_3$):
(75.2 MHz) 46.58, 59.85, 75.51, 87.77, 90.89, 93.87, 107.97, 111.48, 128.35, 128.84, 133.57, 136.91, 196.31, 231.80.
Analysis for : Calcd. : C=55.55, H=3.68
$C_{19}H_{15}O_5CrCl$ Observed : C=55.85, H=3.32

Complex 4b:

mp : 95 °C
IR ($CHCl_3$) : 1970, 1890 (br), 1710 cm^{-1}

^{1}H NMR (200 MHz) : (δ, $CDCl_3$): 1.15 (s, 9H), 2.65 (dd, 1H, J=16.8Hz, 3.2Hz), 2.90 (dd, 1H, J=17.0Hz, 7.8Hz), 3.55 (s, 3H), 4.85 (dd, 1H, J=8Hz, 3Hz), 5.05 (t, 1H, J=7Hz), 5.45 (m, 2H), 5.85 (d, 1H, J=7.2Hz);

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$): 26.76, 44.94, 45.38, 60.50, 75.94, 78.16, 88.16, 91.32, 94.31, 108.73, 111.99, 212.22, 232.35.

Analysis for $C_{17}H_{19}O_5CrF$: Calcd. : C=52.25, H=4.90
Observed : C=51.32, H=4.98

Preperation of compounds of 5a' and 5b':

(a) General procedure for the cleavage of b-siloxy ketones 5a and 5b

To a solution of ketone cooled at 0 to -10°C in THF, a solution of 10% HCl in THF was added slowly with constant stirring. The solution was allowed to stir at the same temperature for 3 hrs. After completion of the reaction (TLC), the reaction mixture was neutarlized by a solution of 10% $NaHCO_3$ and THF was removed *under vacuo*, The residue obtained was extracted with dichloromethane thrice and the combined organic layers were washed with water and dried over sodium sulfate. Removal of solvent followed by purification by column chromatography gave the pure product as yellow solid.

Reactions were done on 0.5-1.0 mmol scale and the yields of the isolated pure products are indicated in Table-2

2. Aldol reaction of Lithium enolate with aldehyde complexes:

LDA was generated from equimolar quantities of diisopropyl amine and n-BuLi at -78°C. To this an equivalent quantity of acetophenone was added at the same temperature and stirred for 1 hr. A solution of an equivalent amount of complexed aldehyde in dry THF was cooled to -78°C, to this the lithium enolate was transferred dropwise by a cannula. The color of the solution instantaneously changed from red to yellow. After completion of the reaction (TLC), degassed methanol was added to the reaction at -78°C. The reaction was warmed gradually to room temperature, and extracted with dichloromethane. The organic layer was washed with water, dried over sodium sulfate. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography with 5-10 % acetone in pet-ether as the eluent.

Reactions were done on 0.5-1mmol scale the yields of the isolated pure products are indicated in Table-5

Complex 5a':

mp : 115 °C, lit[20] mp: 117 °C

IR ($CHCl_3$) : 3400 (br), 1970, 1890 (br), 1705 cm^{-1}

^1H NMR (200 MHz) : (δ, $CDCl_3$): 3.2 (dd, 1H, J=9.0, 17 Hz), 3.30 (d, 1H, J=3.5 Hz), 3.40 (dd, 1H, J=3, 17 Hz), 3.75 (s, 3H), 4.95 (t, 1H, J=6.3 Hz), 5.06 (d, 1H, J=7.7Hz), 5.35 (m, 1H), 5.50 (t, 1H, J=6.3 Hz), 6.0 (d, 1H, J=6.2Hz), 7.50 (m, 3H), 7.95 (d, 2H, J=7.55)

Complex 5b':

mp : 102 °C, lit[20] mp: 104 °C

IR ($CHCl_3$) : 3400 (br), 1970, 1890 (br), 1700 cm^{-1}

^{1}H NMR	:	(δ, $CDCl_3$):
(200 MHz)		1.15 (s, 9H), 2.70 (dd, 1H, J=9.0, 17 Hz), 2.90 (dd, 1H, J=3, 17 Hz), 3.35 (d, 1H, J=3.5 Hz), 3.75 (s, 3H), 4.95 (t, 1H, J=6.3 Hz), 5.05 (d, 1H, J=7.7Hz), 5.20 (m, 1H), 5.50 (t, 1H, J=6.3 Hz), 5.65 (d, 1H, J=6.2Hz).

Preparation optically pure ortho anisaldehyde complex (–)-5:

L-Valinol (1.10g, 10mmol) was added to an ether solution of complex **5** (2.52 g, 10 mmol) containing an excess of 4 A° molecular seives (3 g). The mixture was stirred for 18 h and filtered through Celite. Evaporation of ether gave a orange oil. The two diastereomeric imines were seperated by column chromatography using 10 % triethylamine in ether as the eluent over basic alumina. The first fraction contained the (+) imine and the second contained the (-) imine. The two imines were independently dissolved in THF containing 1 ml of water and 6 drops of concentrated HCl. The solution was stirred at room temperature for 2 h. Removal of solvent afforded a red oil which was dissolved in dichloromethane, and washed with 10% $NaHCO_3$ solution. The organic layer was dried over sodium sulfate, removal of solvent followed by flash column chromatography with 5% acetone in pet-ether as the eluent gave a solid. Recrystalization from 10% dicloromethane in pet ether (v/v) gave the aldehyde complex (–)-**5** as a crystalline red solid in 35% yield (850 mg). The optically purity of the compound was confirmed by crystallization to constant optical rotation

$[\alpha]_D^{20} = -998$ (conc.: 0.01 g/ml $CHCl_3$)

Reported = –1008 (conc.: 0.01 g/ml $CHCl_3$)

Preparation optically pure ortho anisaldehyde dimethyl acetal complex (–)-1:

To a solution of the 378 mg (1.5 mmol) aldehyde (–)-**5** in 3 ml trimethyl orthformate, one drop of conc. sulphuric acid was added. The solution turns yellow within 10 minutes, and 2 gms of sodium carbonate is added to the solution. The reaction mixture was filtered and the filtrate was diluted with dichloromethane. The combined organic layer was washed with 10% $NaHCO_3$. Evaporation of solvent followed by column chromatography with 5% acetone in pet-ether as the eluent gave a yellow solid. Recrsytallization from 10% dicloromethane in pet ether (v/v) gave the acetal complex (–)-**1** as a crystalline yellow solid in 65 % (200 mg) yield. The optically purity of the compound confirmed by crystallization to constant optical rotation.

$[\alpha]_D^{20} = -181.6$ (conc.: 0.010 g/ml; $CHCl_3$)

Preparation of (+)-5c from optically pure (-)-5:

To a suspension of scandium triflate (25 mg, 0.05 mmol) in dichloromethane (1 ml), a solution of of the aldehyde **(-)-5**, (126 mg, 0.5 mmol) in dichloromethane (3 ml) was added gradually with stirring. The red colored solution started to change to yellow during the addition. The reaction mixture was stirred for 30 mins at room temperature, and diluted with 10 ml dichloromethane. The diluted organic layer was washed with water, and dried over sodium sulfate. Removal of solvent gave the crude product which, was purified by column chromatography with 5% acetone in pet-ether as the eluent. The product was obtained in 84% yield. The optical purity was confirmed by repeated crystallizations (twice) which gave constant optical rotation in each case.

$[\alpha]_D^{25} = +168.57$ (conc.: 0.0105 g/ml; $CHCl_3$)

Preparation of (+)-1c from optically pure (-)-1

To a suspension of scandium triflate (25mg, 0.05 mmol) in dichloromethane (1 ml), stirred under argon atmosphere, a solution of of the acetal

(-)-1 (159 mg, 0.5 mmol) in dichloromethane (3 ml) was added gradually with stirring. The reaction was stirred for 30 mins at room temperature, and diluted with 10ml dichloromethane. The diluted organic layer was washed with water, and dried over sodium sulfate. Evaporation of solvent followed by column chromatography with 5% acetone in pet-ether as the eluent, afforded the pure product as a yellow solid in 82 % yield. The optical purity was confirmed by repeated crystallizations (twice) which gave constant optical rotation in each case.

$[\alpha]_D^{25} = + 20.052$ (conc. 0.095 g/ml; $CHCl_3$)

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Chapter - III

Base induced conjugate addition of enolsilanes to enones – an alternative to Lewis acid mediated reactions

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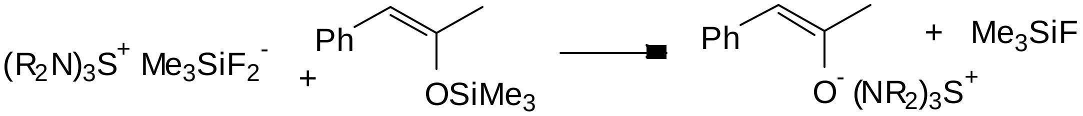
Introduction

Michael reaction is a very well known and important carbon-carbon bond forming reaction.[1] However, synthetic utility of this reaction is limited to addition of stabilized enolates such as those derived from malonates, cyanoacetates or acetoacetates. Michael reaction of simple enolates is often complicated by side reactions, which include proton transfer, self-condensation and 1,2-additions. To surmount these difficulties, modified enolates or masked enolates are employed. Silyl enol ethers and silyl ketene acetals are examples of such masked enolates.[2] Since their reactions are performed under neutral conditions, unwanted reactions like self-condensation and polycondensation are minimized.

Since the Si-F bond has significantly high bond energy compared to the Si-O or Si-C bond, fluoride ion has a very strong affinity for silicon.[3] Taking advantage of this property, fluoride reagents have been widely used for the cleavage of Si-C and Si-O bonds. In order to enhance the nucleophilic property of the fluoride ion, large and soft cations like tetraalkylammonium are used as counterions. Tetrabutylammonium fluoride and benzyl triethylammonium fluoride are frequently used as desilylating agents.[4a] Tetrabutylammonium fluoride effectively catalyzes the Mukaiyama aldol reaction, benzyl triethylammonium fluoride effects alkylation of silyl enol ethers and silyl ketene acetals and CsF is used for the addition of silyl enol ether to α-β unsaturated ketones.[4b]

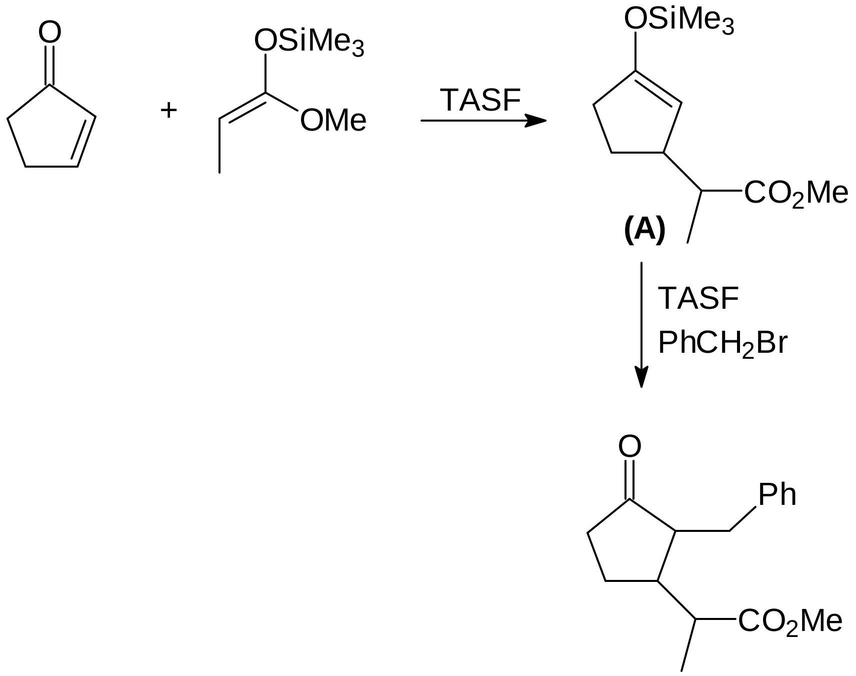
Sometimes *Tris*(dialkylamino)sulphonium difluoromethyl siliconates (TASF) have also been used as a desilylating agent[5] (Scheme-1).

Scheme-1



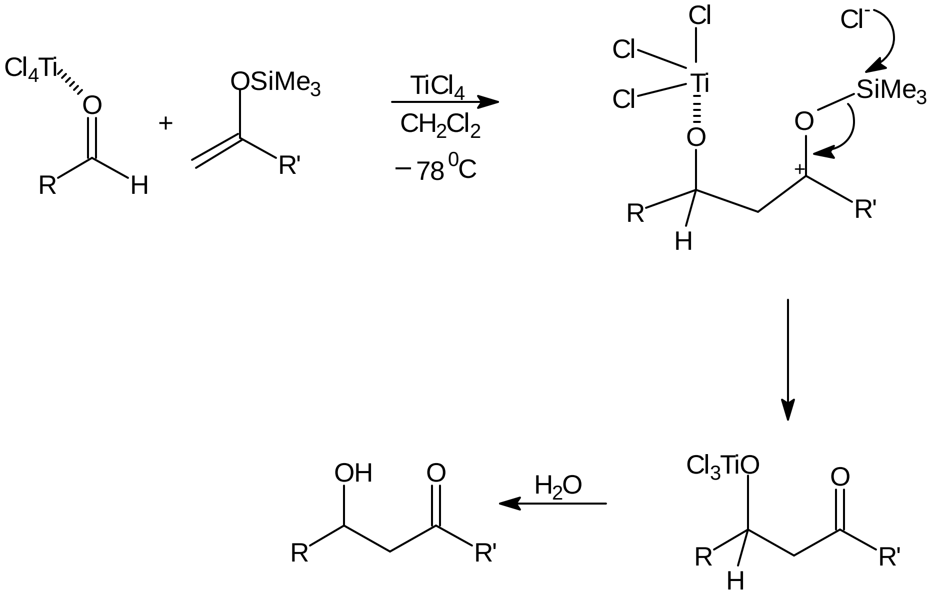
The TASF catalyzed addition of silyl ketene acetals to α-β unsaturated ketones gave silyl enol ether **A** (Scheme-2). This enol ether could be further alkylated using TASF as the catalyst.[6]

Scheme-2



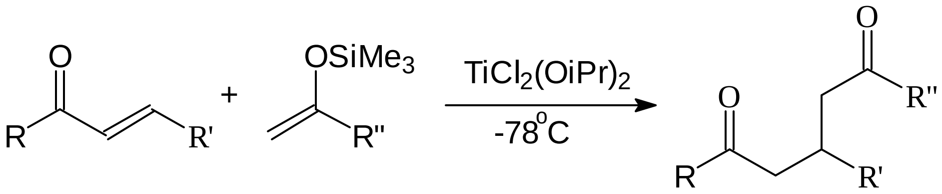
As an alternative approach, Mukaiyama[7a] employed $TiCl_4$ as a Lewis acid to activate the aldehyde so that the olefin bond of the silyl enol ether or silyl ketene acetal can now act as a nucleophile (Scheme-3). The resultant cation is stabilized by a β-silicon effect.

Scheme-3



The enones were also activated by a milder reagent $TiCl_2(OiPr)_2$ and treated with silyl enol ethers to yield 1,5 dicarbonyl compounds[7b] (Scheme-4). These are useful synthons for Robinson annulations[7c] and various heterocyclzations.[7d]

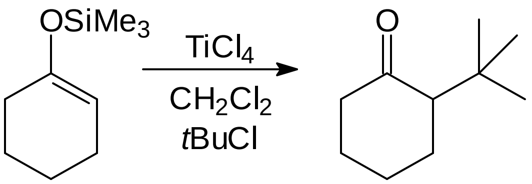
Scheme-4



Lewis acids like $BF_3.OEt_2$,[8a] $SnCl_4$,[8b] $ZnCl_2$[8c] *etc.* work equally well for similar reactions. Perchlorate[9a] and triflate[9b] salts are shown to promote the reaction when present in catalytic amounts.

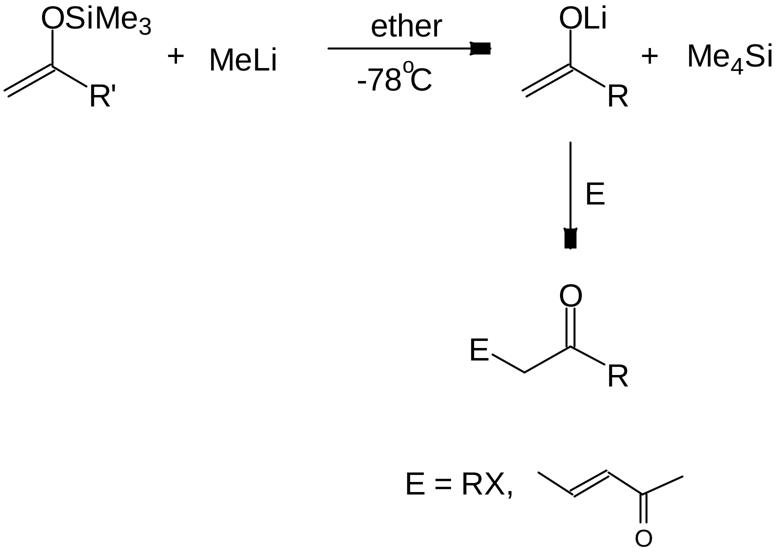
Alkylations of enolates with alkyl halides are limited only to primary and secondary alkyl halides. Chan[10a] and Reetz[10b] reported alkylation of silyl enol ethers by tertiary halides in the presence of Lewis acids (Scheme-5).

Scheme-5



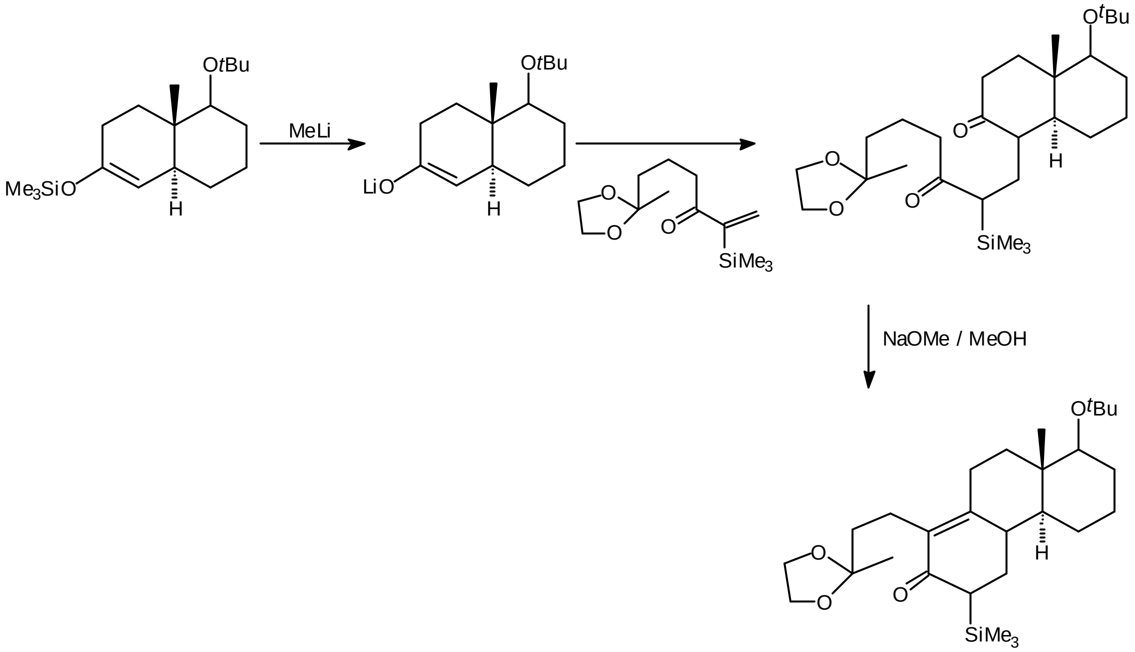
Stork[11] demonstrated that lithium enolates can be generated by treating silyl enol ethers or silyl ketene acetals with methyllithium. Methyllithium attacks the trimethylsilyl group to produce tetramethylsilane, a stable compound, and lithium enolate (Scheme-6). The lithium enolate can then be regioselectively quenched with aldehydes, alkylating agents or enones.

Scheme-6

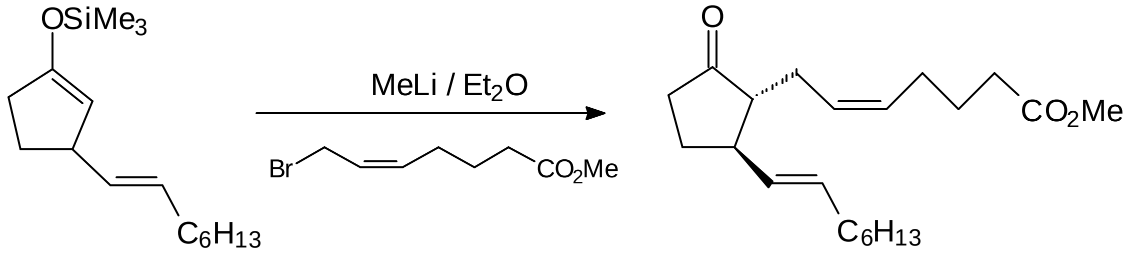


This methodology has been employed in the synthesis of various natural products, two examples of which are presented[12] in Scheme-7a and 7b.

Scheme-7a

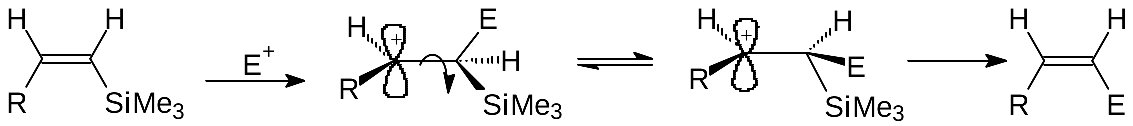


Scheme-7b



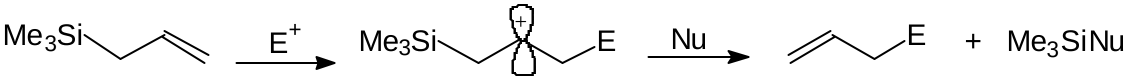
Compared to the cleavage of Si-O bond, the cleavage of Si-C bond is difficult unless the silicon is attached to a *sp*^{2} carbon or placed at an allylic position. Electrophilic cleavage of the Si-C bond is explained by the formation of a carbocation β to the silicon. For instance, in the case of vinylsilanes, addition of an electrophile generates a β-carbocation, to stabilize the carbocation, the $2p_z$ orbital containing the carbocation and the Si-C bond become coplanar by a bond rotation.[13] As a result of this the alkene formed after Si-C bond cleavage is with retention of configuration (Scheme-8).

Scheme-8



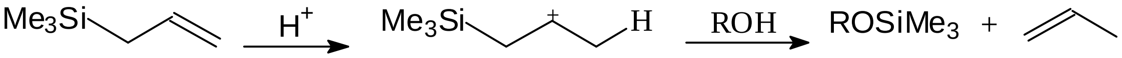
Similarly in the electrophilic substitution of allyl silanes, a β-carbocation is formed followed by the cleavage of this Si-C bond. The important feature of this addition is the relocation of the π-system[14] (Scheme-9).

Scheme-9



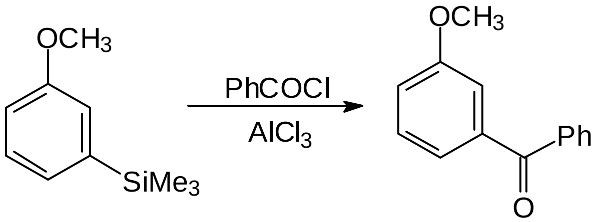
Such a carbocation intermediate derived from the allylsilanes can lead to the formation of trimethylsilyl ethers[15] (Scheme-10).

Scheme-10



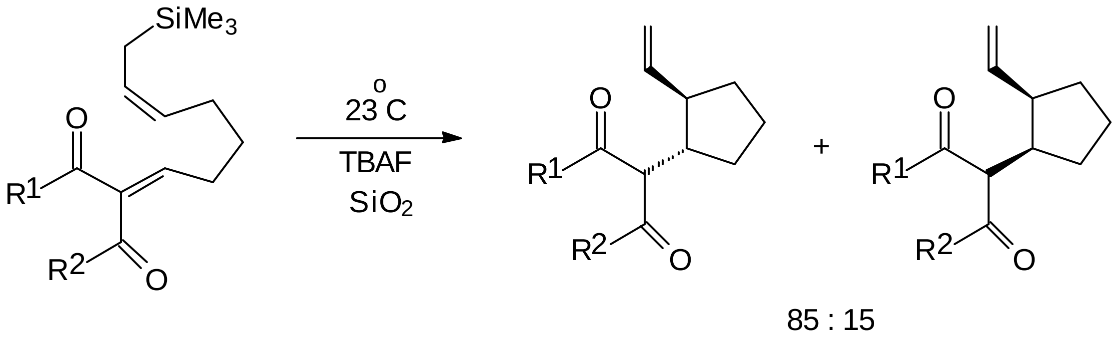
In a similar manner the *ipso* substitution on aryl silanes[16] has been demonstrated (Scheme-11).

Scheme-11



Fluoride catalyzed allylation with allylsilanes is the most common example of nucleophilic desilylation[17] (Scheme-12).

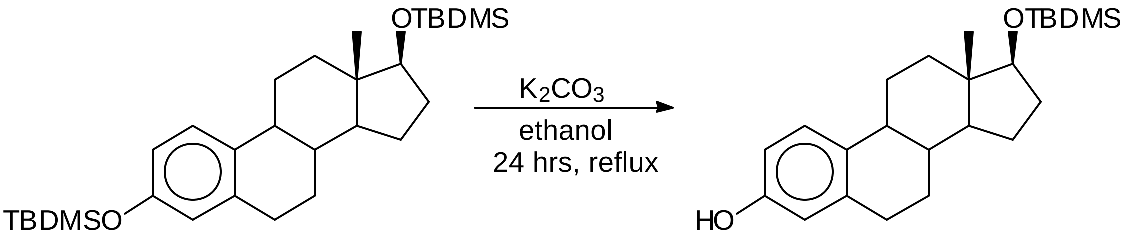
Scheme-12



A trimethylsilyl group attached to an aromatic ring deactivated by NO_2 or Cl substituents, undergoes desilylation with bases like *t*BuOK.[18] The driving force of the reaction is the stabilization of the resulting carbanion.

Also, a recent report[19] described that aryl silyl ethers can be cleaved selectively to generate phenols using K_2CO_3 in the presence of 18-Crown-6, in the presence of aliphatic silyl ether in the same molecule (Scheme-13).

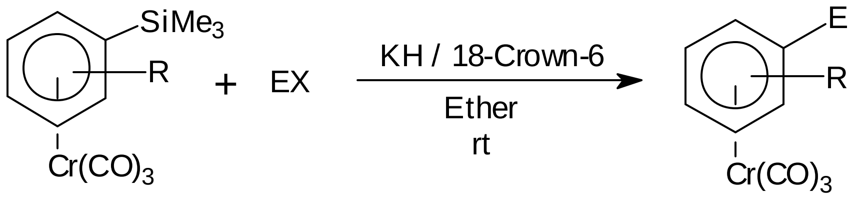
Scheme-13



Present Work

Recently it has been reported from our laboratory[20a] that the C-$SiMe_3$ bond of an electron-deficient benzene ring such as the one complexed to $Cr(CO)_3$, can be efficiently cleaved using KH or 50% aq NaOH and the resultant anion can be trapped by various electrophiles (Scheme-14).

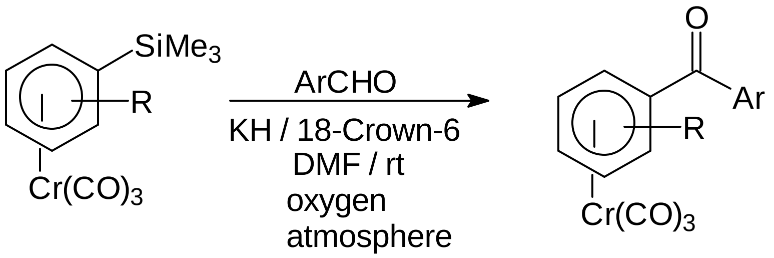
Scheme - 14



EX	**E**
DMF	CHO
$(MeO)_2CO$	CO_2Me
$(EtO)_2CO$	CO_2Et

The methodology was extended further towards the synthesis of chromium complexed, unsymmetrical biaryl ketones[20b] (Scheme-15).

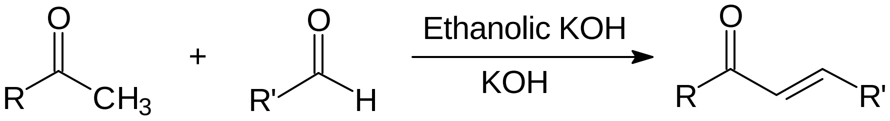
Scheme-15



The facility of the Si-C bond cleavage was attributed to the stabilization of anion on the electron deficient aromatic ring in the complexed aryl substrates. This led us to investigate the cleavage of Si-O bonds in silyl enol ethers under basic conditions in the presence of a α-β unsaturated ketones. The desilylation would then lead to the formation of corresponding enolates which, would react with enones to give 1,5-dicarbonyl compounds.

The representative enones were benzylidene derivatives of aryl ketones - cyclic and acyclic. The starting materials were made from appropriate precursors by standard methods[21] using ethanolic KOH or NaOH as base (Scheme-16a and 16b) as in Claisen-Schmidt reaction. The downfield signal for the β-proton in ^{1}H NMR spectra (7.1-7.4 ppm) were diagnostic for these compounds.[21]

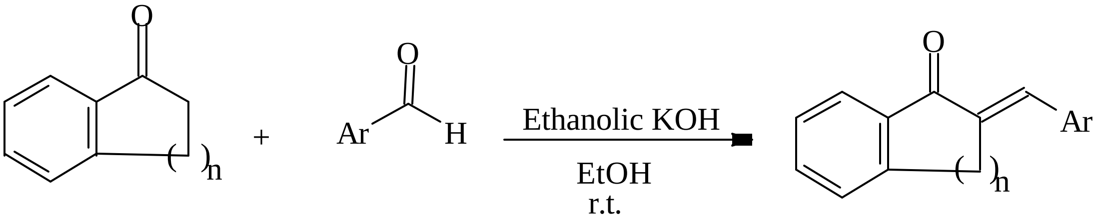
Scheme-16a



1a-c

Enone	R	R'
1a	Ph	Ph
1b	Ph	Ferrocenyl
1c	Ferrocenyl	Ph

Scheme-16b



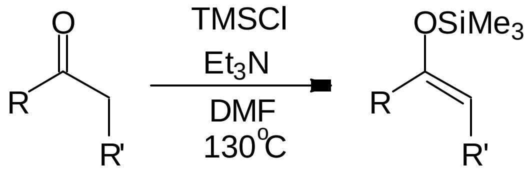
1d - g

Enone	N	Ar
1d	1	Ph
1e	1	p-anisyl
1f	2	Ph

1g	2	p-tolyl

Acetophenone silyl enol ether and cyclohexanone silyl enol ether were prepared[22] by refluxing acetophenone or cyclohexanone with triethylamine and trimethylsilyl chloride in DMF (Scheme-17). The silyl enol ethers were characterized by a sharp singlet at 0.3 ppm for the trimethylsilyl group and a signal at 4.5 ppm for the olefinic protons in their ^{1}H NMR spectra.

Scheme-17

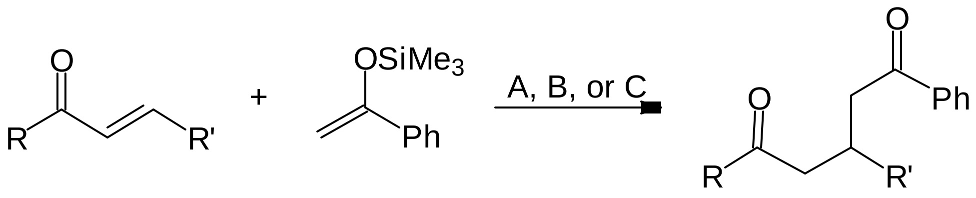


2a-b

Enolsilane	R, R'
2a	R=Ph, R' =H
2b	R- R' = -(-CH_2-)$_4$-

In our first experiment chalcone **1a** was treated with silyl enol ether **2a** in the presence of KH in DMF at room temperature. After the completion of reaction (TLC) the excess hydride was quenched by adding 2 ml of methanol. The reaction mixture was then diluted by adding dichloromethane and the organic layer was washed successively with 10% aq. HCl, water, 10% aq. sodium bicarbonate solution and water. The organic layer was then dried over sodium sulfate. Removal of solvent gave the crude product. Purification by column chromatography with 5% acetone in pet-ether as the eluent afforded the pure product which was identified as the 1,5 diketone **3a** (Table-1, entry1) by ^{1}H NMR spectral data and melting point. The ferrocenyl chalcones **1b** and **1c** gave products in a similar facility (Scheme-18, Table-1). The products were characterized satisfactorily by ^{1}H NMR and ^{13}C NMR spectra and elemental analysis.

Scheme-18



1a-c **2a** **3a-c**

A	KH/DMF, r.t
B	50 % aq. NaOH, 10 mol%TBAB, CH_2Cl_2
C	*t*-BuOK, THF, r.t

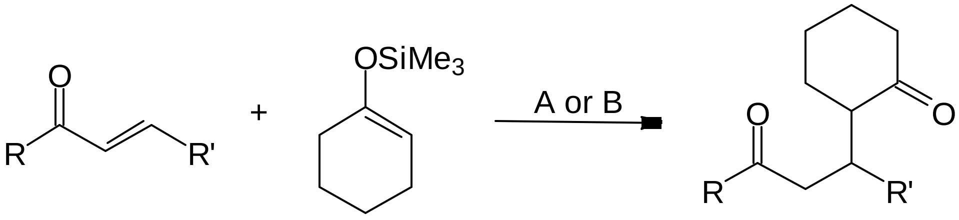
Table-1

Entry	R	R'	Product	Condition	Time (hrs)	Yield[a] (%)
1	Ph	Ph	**3a**[7b]	A	2	64
2	Ph	Ph	**3a**	B	3	77
3	Ph	Ph	**3a**	C	0.5	82
4	Ferrocenyl	Ph	**3b**	B	10	72
5	Ph	Ferrocenyl	**3c**	B	10	76

a: isolated pure products.

The chalcones **1a-b** when treated with cyclohexanone silyl enol ether **2b** under similar conditions, gave the corresponding 1,5 diketones (Scheme-19) in good yields.

Scheme-19



1a-b **2b** **3d-e**

A	KH/DMF, r.t
B	50 % aq. NaOH, 10 mol%TBAB, CH_2Cl_2

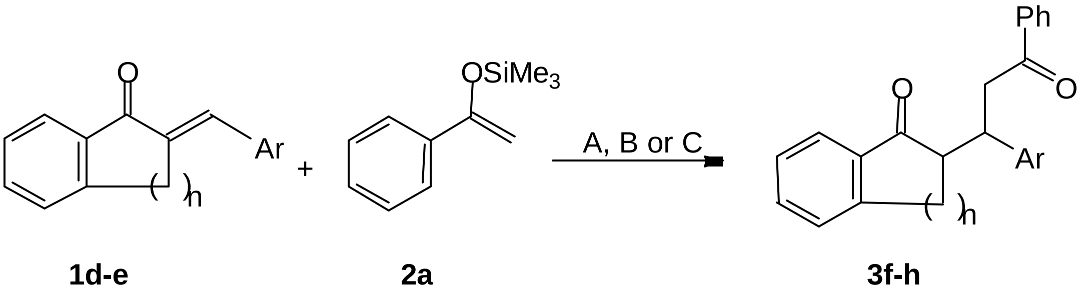
Table-2

Entry	**R**	**R'**	**Enone**	**Product**	**Condition**	**Time (hrs)**	**Yield[a] (%)**
1.	Ph	Ph	**1a**	**3d**[7b]	A	2	66
2.	Ph	Ph	**1a**	**3d**	B	4	77
3.	Ferrocenyl	Ph	**1b**	**3e**	B	10	76

a: isolated pure products.

1-Tetralone and 1-indanone benzylidenes **1d-1f** were treated with acetophenone silyl enol ther in DMF in the presence of KH to give the 1,5-diketones in good yields (Scheme-20). The conjugate addition results in the formation of two new chiral centres. Thus, a pair of diasteromers were formed which could not be seperated by column chromatography. The ^1H NMR spectrum for each of these products indicated the formation of the diastereomers in equal amounts. The ^{13}C NMR spectra also showed two peaks for most of the signals.

Scheme-20



A	KH/DMF, r.t
B	50 % aq. NaOH, 10 mol%TBAB, CH_2Cl_2
C	*t*-BuOK, THF, r.t

Table-3

Entry	**Enone**	**N**	**Ar**	**time (hrs)**	**Product**	**Conditions**	**Yield[a] (%)**
1	**1d**	1	Ph	5	**3f**	*A*	70
2	**1d**	1	Ph	4	**3f**	*B*	76
3	**1d**	1	Ph	0.5	**3f**	*C*	80
4	**1e**	1	*p* – anisyl	5	**3g**	*B*	74
5	**1f**	2	Ph	4	**3h**	*A*	62
6	**1f**	2	Ph	8	**3h**	*B*	74

a: isolated pure products.

The success of the reaction led us to investigate the reaction with other nucleophilic bases. Water was avoided in all these reactions. However, Lubinue[23] showed that the Mukaiyama reaction could be done in an aqueous medium under elevated pressure. We hence performed the reaction with 50% aq. NaOH as the base and tetrabutylammonium bromide (TBAB) as a phase transfer catalyst. Chalcone **1a** was treated with silyl enolether **2a** in the presence of 50% NaOH and 10 mol% TBAB in dichloromethane. After completion of the reaction (TLC), the reaction mixture was diluted with sufficient amount of dichloromethane and washed with 10 % aq. HCl and 10% aq. $NaHCO_3$ solution successively. The combined organic layer was dried over sodium sulfate, removal of solvent gave the crude product. Purification by column chromatography gave the pure product, which was identified as the 1,5-diketone **3a** by its melting point and ^{1}H NMR spectral features.

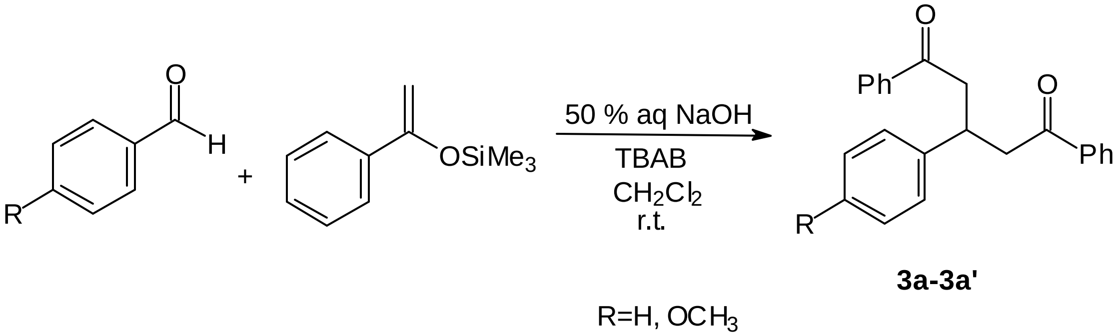
The combination of different enones **1b-f** and silyl enol ethers **2a** and **2b** worked equally well under the same conditions to give 1,5-diketones in good to moderate yields (Table-1, entries-2,4,5; Table-2, entries-2,3; Table-3, entries 2,4,6). The compounds were satisfactorily characterized by spectral data and elemental analysis.

To further investigate the scope of the reaction it was necessary to look at the reactions of other electrophiles with silyl enol ethers under similar conditions. In the first reaction, benzaldehye was treated with silyl enol ether **2a** in the presence of 50% NaOH and 10 mol% TBAB in dichloromethane. Complete consumption of the starting material was not observed even after stirring the reaction mixture overnight. After usual work up, the crude product was purified by column chromatography to furnish a pure product in 52% yield. The ^{1}H NMR spectrum of the product indicated the formation of the 1,5-diketone **3a**, instead of a β-hydroxy ketone.

The formation of a 1,5 diketone indicated that the aldol reaction did occur, but the β-hydroxy ketone eliminated water in the presence of excess base to yield chalcone, which acted as a Michael acceptor for a second molecule of silyl enol ether (Scheme-21)

The reaction was repeated with 2 mmol of acetophenone silyl enol ether **2a** and 1 mmol aldehyde to achieve a complete conversion of the starting material. A similar trend was observed when the reaction was done with *para*-anisaldehyde (Table-4)

Scheme-21



3a-3a'

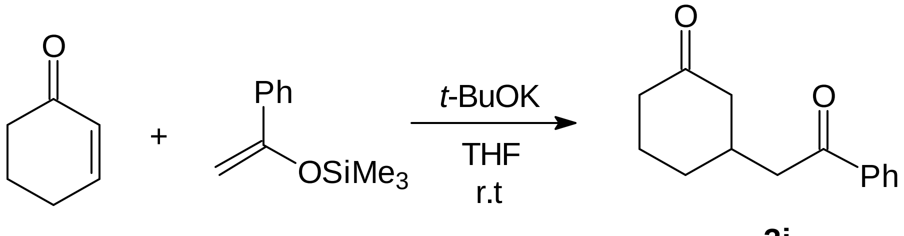
Table-4

R	Time (hrs)	Product	yield[a] %
H	6	**3a**	62
OCH_3	4	**3a'**	60

a: isolated pure products.

Methyl vinyl ketone and 2-cyclohexenone were not good substrates under these reaction conditions, a complex mixture of products resulted from their reaction. However when 2-cyclohexenone was treated with silyl enol ether, **2a** in THF in the presence of equimolar amount of *t*BuOK at room temperature, complete consumption of starting material was observed (TLC) in an hour. The reaction mixture was quenched with saturated ammonium chloride and THF was evaporated. The residue was extracted thrice with dichloromethane, the combined organic layers were washed with water and dried over sodium sulfate. Removal of solvent gave the crude product as a viscous liquid. Purification by column chromatography with 3% acetone in pet-ether gave a white solid identified as the 1,5-diketone **3i** (Scheme-22) by comparison of ^{1}H NMR data and melting point with literature value.[7b]

Scheme-22



2a

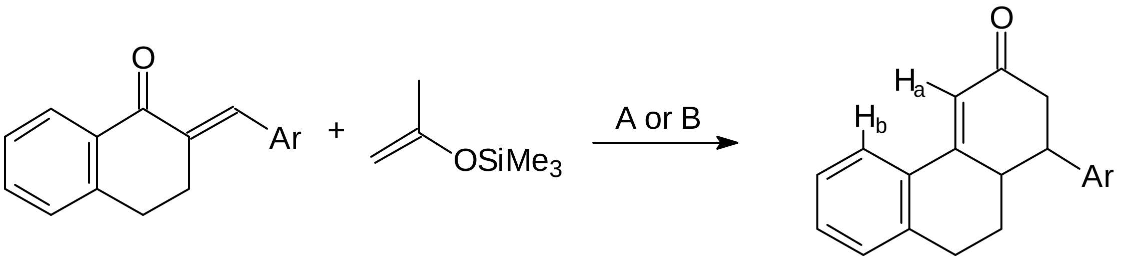
3i

The base *t*BuOK effected similar reaction with other enones as well to give the corresponding 1, 5 diketones in good yields (see Table-1, entry-1 and Table-3, entry-3).

Acetone silyl enol ether[24] is a useful synthon, which on addition to an enone in a conjugate fashion can give a 1,5 diketone that can undergo a Robinson annulation. However the acetone silyl enol ether **2c** is very sensitive to acids and hence gives very low yields of the corresponding 1,5-diketone under standard Mukaiyama conditions using strong Lewis acids.

The addition of acetone silyl enol ether using 50% aq. NaOH was not feasible bacause it involved an aqueous phase that would quench the enolate prior to reaction with the enone. Therefore, acetone silyl enol ether **2c** was treated with enone **1f** in the presence of *t*BuOK in THF as the solvent. The reaction was complete within an hour (TLC). An aqueous work up followed by purification of the crude afforded a pale yellow solid. The product was identified as the annulated product **4a** by ^{1}H NMR spectrum. A singlet at 6.8 ppm was assigned for the olefinic proton H_a. The signal for the aromatic proton H_b was shifted downfield to 8.0 ppm due to the anisotropic effect of the olefin bond. The ^{13}C NMR spectrum featured the carbonyl signal at 195 ppm for the enone carbonyl. A similar annulation was observed when the enone **1g** was treated with acetone silyl enol ether **2c** under similar conditions (Scheme-23).

Scheme-23



1f-1g **4a-4b**

A	KH/DMF, r.t
B	*t*BuOK, THF, r.t

Table-5

Entry	Enone	Ar	Conditions	Product	Yield[a] (%)
1.	**1f**	Ph	A	4a	61
2.	**1f**	*Ph*	B	4a	74
3.	**1g**	*p*-tolyl	A	4b	63
4.	**1g**	*p*-tolyl	B	4b	76

a: isolated pure products.

The yield of product dropped when KH was used as a base in DMF for the reaction (see entries 1 and 3, Table-5).

Summary

In summary, we have described a convenient alternative to Lewis acid and fluoride mediated conjugate addition of enol silyl ethers to enones, which should find wide use in the synthesis of 1,5-diketones. A second observation is the formation of 1,5 diketones starting from aromatic aldehydes under the biphasic condition of 50% aq. NaOH. However, enones with enolizable hydrogens adjacent to the ketone are not good substartes for the reaction with KH or 50% aq. NaOH. But *t*-BuOK effectively gives 1,5-diketones with 2-cyclohexenone. With acetone silyl enol ether **2c** the conjugate addition is followed by a Robinson annulation.

Experimental

1-Indanone and potassium *tert*-butoxide (*t*BuOK) were purchased from the Aldrich Chemical Company, and used as received. Tetrabutylammonium bromide (TBAB) was purchased from Merck India Ltd. and was used as received. Potassium hydride purchased from Aldrich Chemical Company as a 35% suspension in mineral oil was washed with pet-ether thrice prior to use. THF was freshly distilled over sodium benzophenone ketyl. DMF was freshly distilled over calcium hydride. Dichloromethane was freshly distilled over P_2O_5. Silyl enol ethers were synthesized following reported procedures.[22]

All the conjugate additions were worked up as described below:

The reaction mixture was quenched with saturated ammonium chloride and diluted with dichloromethane, washed with 2N HCl followed by 10% $NaHCO_3$ and brine. The combined organic layer was dried over anhydrous sodium sulfate. Evaporation of solvent gave the crude product.

General method for the preparation of enones.

A solution of the aromatic aldehyde (11 mmol) and the ketone (1-tetralone or 1-indanone, 10 mmol) was taken in 20 ml of ethanol. An ethanolic solution of KOH (10 mmol in 5 ml ethanol) was added dropwise *via* syringe. When all of the starting material was consumed (usually after 2-3 h as confirmed by TLC), solvent was removed under reduced pressure, the residue was washed with water and then extracted with dichloromethane. The dichloromethane extract was dried over anhydrous sodium sulfate. After evaporation of solvent a crude product was obtained, which was recrystallised from dichloromethane/pet ether.

Compound 1a:

Benzalacetophenone was prepared by essentially following the above procedure with the exception NaOH was used instead of KOH.

mp: 56 °C, lit.[21a] mp 57- 58 °C.

Compound 1b: Yield : 3.0 g, 85%

mp : 128-130 °C lit.[21e] mp 132 °C

IR ($CHCl_3$) : 1685, 1620, 1600

^1H NMR (200 MHz) : (δ, $CDCl_3$) 4.19 (s, 5H), 4.50, (bs, 2H), 4.60 (bs, 2H), 7.14 (d, 1H, J=15 Hz), 7.50 (m, 3H), 7.7 (d, 1H, J=15Hz)

Compound 1c: Yield : 2.9g, 83%

mp : 136-138 °C lit.[21f] mp 140-142 °C

IR ($CHCl_3$) : 1690, 1620, 1600

^1H NMR (200 MHz) : (δ, $CDCl_3$) 4.2 (s, 5H), 4.6 (d, 2H, J= 2.5Hz), 4.9 (d, 2H, J=2.5 Hz), 7.0 (d, 1H, J=12Hz), 7.4 (m, 3H), 7.8 (d, 1H, J=12Hz)

Compound 1d: Yield : 2.1 g, 85%

mp : 174–178 °C

IR ($CHCl_3$) : 1685, 1640

^1H NMR (200 MHz) : (δ, $CDCl_3$) 4.07 (s, 2H), 7.50 (m, 4H), 7.6 (m, 2H), 7.65 (m, 3H), 7.95 (d, 1H, J= 6.5 Hz)

Compound 1e: Yield : 1.80 g, 82%

mp : 132 °C

IR ($CHCl_3$) : 1690, 1620, 1600
^1H NMR : (δ, $CDCl_3$)
(200 MHz) 3.85 (s, 3H), 4.0 (s, 2H), 6.95 (d, 2H), 7.40 (dd, 1H), 7.60 (m, 4H), 7.90 (d, 2H).

Compound 1f: Yield : 2.20g, 82%

mp : 101 °C

IR ($CHCl_3$) : 1685, 1655, 1480, 1300, 705
^1H NMR : (δ, $CDCl_3$)
(200 MHz) 2.9 (t, 2H), 3.1 (t, 2H), 7.4 (m, 8H), 7.90 (s, 1H), 8.25 (d, 1H)

Compound 1g: Yield : 2.10g, 78%

mp : 120-122 °C

IR ($CHCl_3$) : 1680, 1655,
^1H NMR : (δ, $CDCl_3$)
(200 MHz) 2.40 (s, 3H), 3.0 (t, 2H, J=6.5Hz), 3.20 (t, 2H, J=6.5Hz), 7.15-7.60 (m, 7H), 7.9 (s, 1H), 8.20 (d, 1H, J=7.0Hz)

Preparation of compounds 3a-i:

A) Typical procedure for conjugate addition with KH:

To suspension of KH (1.2 mmol) in dry DMF (4 ml), silyl enol ether (1.2 mmol) and enone (1 mmol) were added successively with constant stirring. The reaction mixture was stirred at room temperature for 2-4 h. Following completion of the reaction (TLC), usual work-up afforded the crude product that was purified by column chromatography using 5% acetone in pet-ether as the eluent.

B) Typical procedure for conjugate addition with 50% aq NaOH and PTC:

To a solution of silyl enol ether (1.2 mmol) and the enone (1 mmol) in dry dichloromethane (4ml), 0.5 ml of degassed 50 % aq. NaOH and TBAB (0.10 mmol) were added successively with constant stirring. The reaction mixture was stirred at room temperature. After completion of the reaction (3-10 h, TLC), the crude product was obtained after usual work-up and it was purified by column chromatography using 5% acetone in pet ether as the eluent.

C) Typical procedure for conjugate addition with t-BuOK :

To a solution of silyl enol ether (1.0 mmol) and the enone (1.2 mmol) in THF (5 ml), solid *t*BuOK (1.1 mmol) was added with constant stirring. The reaction mixture was stirred at room temperature for 30 min to 1 h. Following completion of the reaction, the crude product obtained by usual work-up was purified by column chromatography using 5% acetone in pet-ether as the eluent.

Compound 3a:

Yield (%) : **A:** 64; **B**: 77; **C**: 82

mp : 84-86 °C, lit.[7b] 83 °C

IR ($CHCl_3$) : 1700, 1600

^{1}H NMR (200 MHz) : (δ, $CDCl_3$) 3.4 (m, 4H), 4.2 (quintet, 1H, J= 6.0 Hz), 7.2-7.6 (m, 11 H), 7.95 (d, 4H, J= 6.8 Hz)

Compound 3b:

Yield (%) : **B**: 72

mp : 110-111 °C

IR ($CHCl_3$) : 1710,

^{1}H NMR (300 MHz) : (δ, $CDCl_3$) 3.1 (d, 1H, J=7.0 Hz); 3.4 (dd, 2H, J= 12, 6Hz); 3,6 (dd, 2H, J= 12, 6 Hz); 4.0 (s, 5H); 4.4 (s, 2H); 4.6 (s, 2H); 7.10-7.85 (m, 8H); 7.9 (d, 2H, J=7 Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$) 36.72, 44.50, 45.81, 69.03, 69.13, 69.55, 72.06, 78.55, 126.55, 127.52, 127.97, 128.42, 132.88, 136.78, 144.10, 0 198.48, 202.07

Analysis for $C_{27}H_{24}O_2Fe$: Calcd. : C=74.32; H=5.54

Observed : C=73.98; H=5.41

Compound 3c:

Yield (%) : **B**: 76

mp : 120-122 °C

IR ($CHCl_3$) : 1710, 1690

^{1}H NMR (200 MHz) : (δ, $CDCl_3$) 3.10 (dd, 2H, J=11, 6.8 Hz); 3.15 (dd, 2H, J=11, 6.8 Hz); 3.80 (quintet, 1H, J=6.5 Hz); 4.2 (s, 9H), 7.5 (m, 6H), 8.0 (d, 4H, J=7Hz)

^{13}C NMR (75.2 MHz) : (δ, $CDCl_3$) 31.41, 45.03, 67.28, 67.56, 68.59, 93.08, 128.31, 128.80, 133.17, 137.34, 199.22

Analysis for $C_{27}H_{24}O_2Fe$: Calcd. : C=74.32; H=5.54

: Observed : C=73.71; H=5.36

Compound 3d

Yield (%) : **A** : 66 ; **B**: 77

mp : 132-134 °C

IR ($CHCl_3$) : 1720, 1700

^{1}H NMR (200 MHz) : (δ, $CDCl_3$)
1.25-2.1 (m, 6H); 2.35-2.6 (m, 2H); 2.8 (dt, 1H, J= 8, 3 Hz); {(3.25 and 3.5 m) 2H}; 3.75 (dt, J=7.5, 2.5Hz) and 3.95 (q, J=6 Hz), 1H; 7.15 (m, 4H); 7.5 (m, 4H), 7.9 (m, 2H).

Compound 3e

Yield (%) : **B** : 76

mp : 158 °C

IR ($CHCl_3$) : 1700, 1680

^{1}H NMR (200 MHz) : (δ, $CDCl_3$)
1.3 (m, 1H); 1.55-2.05 (m, 5H); 2.4 (m, 2H); 2.75 (dt, 1H, J= 8, 3.5Hz); {3.10, m+3.15m} 2H; 3.75 (m, 1H); {3.9 (s) + 4.1(s)} 5H; 4.4 (m, 2H); 4.7 (m, 2H); 7.25-7.4 (m, 5H)

^{13}C NMR (75.2 MHz) : (δ, $CDCl_3$)
23.43, 28.27, 31.97, 40.03, 41.77, 44.76, 55.08, 68.78, 69.05, 69.36, 71.75, 78.88, 126.40, 128.01, 128.25, 128.34, 128.52, 142.43, 201.17, 213.34

Analysis for $C_{25}H_{26}O_2Fe$:
Calcd. : C=72.47; H=6.32
Observed : C=71.83; H=6.13

Compound 3f

Yield (%) : **A**: 70 ; **B**: 76 ; **C**: 80

mp : 142-144 °C

IR (CHCl$_3$) : 1700 (b), 1610

^{1}H NMR (200 MHz) : (δ, CDCl$_3$) 2.95 (dd, 2H, J=8, 6.5 Hz); 3.8 (d, 1H, J=7.0 Hz), 3.9 (t, 1H, J=7.5Hz), 4.1 (d, 1H, J=6.90Hz), 4.5 (dd, 1H, J=7, 7.5Hz); 6.9-7.65 (m, 13H); 7.8 (d, 1H, J=7Hz)

^{13}C NMR (50.3 MHz) : (δ, CDCl$_3$) 29.81, 46.05, 52.24, 53.71, 59.85, 71.30, 124.11, 125.00, 125.41, 125.92, 126.4, 127.92, 128.60, 129.15, 134.21, 135.14, 135.42, 135.98, 136.35, 136.9, 137.5, 153.20, 155.41, 204.21, 208.15

Analysis for $C_{24}H_{20}O_2$:
Calcd. : C=84.67; H=5.92
Observed : C=84.07; H=5.36

Compound 3g

Yield (%) : **B**: 74

mp : 135-136 °C

IR (CHCl$_3$) : 1700 (b), 1610 (b)

^{1}H NMR (200 MHz) : (δ, CDCl$_3$) 2.95 (dd, 2H, J=12, 6.3 Hz); 3.65 (s, 3H), 3.70 (s, 3H), 3.80 (m, 2H); 4.0 (d, 1H, J=8.5Hz); 4.5 (dd, 1H, J= 8, 6.5 Hz); 6.75 (t, 4H, J=7Hz); 6.95-7.6 (m, 8H); 7.8 (d, 1H, J=6.8 Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$) 29.69, 46.5, 53.38, 53.71, 55.25, 58.78, 70.50, 113.79, 113.91, 123.46, 124.56, 125.43, 126.04, 127.15, 128.35, 128.47, 128.73, 129.07, 129.35, 129.63, 134.87, 135.24, 135.96, 137.48, 153.20, 156.10, 158.64, 158.87, 205.87, 208.15

Analysis for $C_{25}H_{22}O_3$: Calcd. : C=81.10; H=5.94
Observed : C=81.54; H=6.08

Compound 3h:

Yield (%) : **A**: 62 ; **B**: 74
mp ; 136-138 °C
IR ($CHCl_3$) : 1690 (b), 1600, 1590
^{1}H NMR (200 MHz) : (δ, $CDCl_3$) 2.1 (m, 2H); 2.9-3.25 (m, 3H); 3.6 (m, 2H); {4.05 (m)+4.25(m)} 1H; 7.15-7.60 (m, 11H); 8.0 (m, 3H)
^{13}C NMR (50.3MHz) : (δ, $CDCl_3$) 25.79, 26.15, 27.12, 39.56, 39.96, 41.13, 43.64, 45.03, 51.98, 53.41, 126.67, 126.75, 127.56, 127.72, 128.17, 128.32, 128.47, 128.61, 128.72, 128.86, 132.65, 132.99, 133.20, 133.49, 137.23, 142.29, 142.43, 143.68, 143.98, 198.55, 198.95, 199.06, 199.81,

Analysis for $C_{24}H_{22}O_2$: Calcd. : C=84.70; H=6.20
Observed : C=84.27; H=6.37

Compound 3i:

Yield (%) : **C**: 72

mp	:	72-73 °C, lit[7b] mp 75-76 °C
IR ($CHCl_3$)	:	1680, 1720
^1H NMR	:	(δ, $CDCl_3$)
(200 MHz)		1.45-2.95 (m, 3H); 2.00-2.70 (m, 6H); 3.0 (dd, 2H, J= 6.5, 6.0Hz), 7.5 (m, 3H); 7.95 (d, 2H, J=6.5Hz)

Typical procedure for the reaction of aromatic aldehydes with silyl enol ethers promoted by 50% aq. NaOH and 10 mol% TBAB: Preparation of compounds 3a and 3a'

To a solution of the aromatic aldehyde (1 mmol) and silyl enol ether (2 mmol) in dry dichloromethane (4 ml), 0.5 ml of 50 % aq. NaOH and TBAB (0.10 mmol) were added with constant stirring. The reaction was stirred at room temperature overnight. The crude product obtained after usual work-up was purified by column chromatography using 5% acetone in pet ether as the eluent.

Compound 3a

Yield (%)	:	62

Compound 3a'

Yield (%)	:	63
IR ($CHCl_3$)	:	1700, 1600
^1H NMR	:	(δ, $CDCl_3$)
(300 MHz)		3.15 (dd, 2H, J=16, 5.6 Hz), 3.30 (dd, 2H, J=16, 5.6 Hz), 3.70 (s, 3H), 4.0 (quintet, 1H, J=6.0 Hz), 6.8 (d, 2H, J=6.5 Hz), 7.2 (d, 2H, J=6.5 Hz), 7.5 (m, 6H), 7.95 (d, 4H, J=7Hz)

Typical procedure for reaction of 2-arylidene-1-tetralone (1g-h) with acetone silyl enol ether 2c:

A. Using KH:

A suspension of KH (2.4 mmol) was carefully added to a stirred solution of the enone (1 mmol) and acetone silyl enol ether (1.2 mmol) in DMF. The reaction mixture was stirred at room temperature for 30 min to an hour. After completion of the reaction (TLC), the crude product was isolated after usual work-up and purified by column chromatography using 10% acetone in pet-ether.

B. Using *t*BuOK:

To a solution of acetone silyl enol ether (1.2 mmol) and enone (1 mmol) in 5 ml THF, solid *t*BuOK (2.2 mmol) was added with constant stirring. Stirring was continued at room temperature for 30 min. The crude product was obtained after usual work-up, and was purified by column chromatography using 10% acetone in pet ether as the eluent.

Compound 4a:

Yield (%)	:	**A**: 63; **B**: 76
mp	:	136-138 °C
IR ($CHCl_3$)	:	1680, 1650
^{1}H NMR	:	(δ, $CDCl_3$)
(200 MHz)		1.5 (m, 1H), 1.9 (m, 1H); 2.85 (m, 5H), 3.15 (m, 1H), 6.75 (s, 1H); 7.4 (m, 8H); 7.9 (d, 1H, J=6.5Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$)
27.91, 30.11, 43.19, 45.47, 48.12, 120.67, 125.78, 126.88, 127.36, 127.76, 129.09, 129.79, 130.81, 131.59, 140.19, 142.65, 157.61, 198.96

Analysis for $C_{21}H_{20}O$: Calcd. : C=87.46, H=6.99
Observed : C=87.23, H=6.79

Compound 4b:

Yield (%) : **A** : 61; **B**: 74

mp : 150-152 °C

IR ($CHCl_3$) : 1680, 1650

^{1}H NMR (200 MHz) : (δ, $CDCl_3$)
1.4 (m, 1H), 1.9 (m, 1H), 2.35 (s, 3H), 2.55-2.85 (m, 5H), 3.0(m, 1H); 6.7 (s, 1H); 7.1-7.35 (m, 7H); 7.75 (d, 1H, J= 6.5Hz)

^{13}C NMR (50.3 MHz) : (δ, $CDCl_3$)
21.02, 27.67, 29.91, 43.03, 45.03, 47.48, 120.45, 125.56, 126.62, 127.43, 129.53, 130.59, 136.77, 139.42, 140.00, 157.54, 199.08

Analysis for $C_{20}H_{18}O$: Calcd. : C=87.25, H=6.61
Observed : C=87.10, H=6.41

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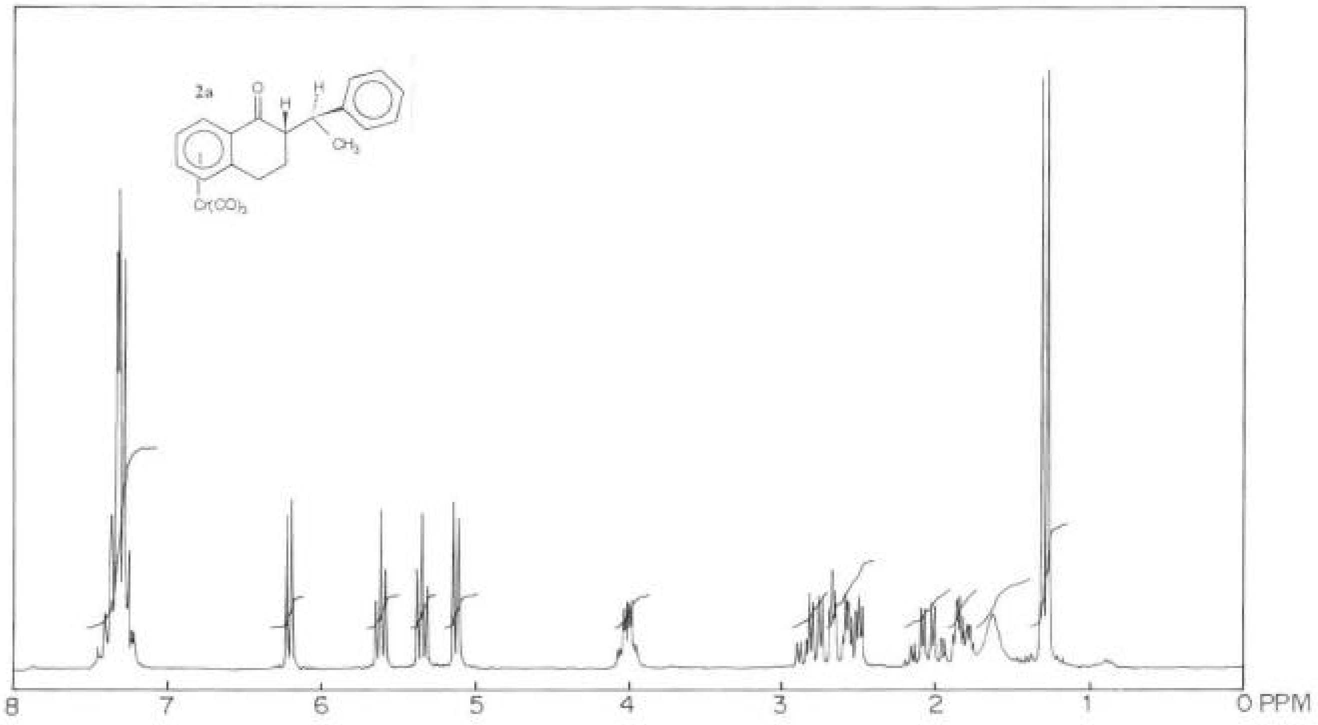
Appendix-I

Spectra of compounds - Chapter I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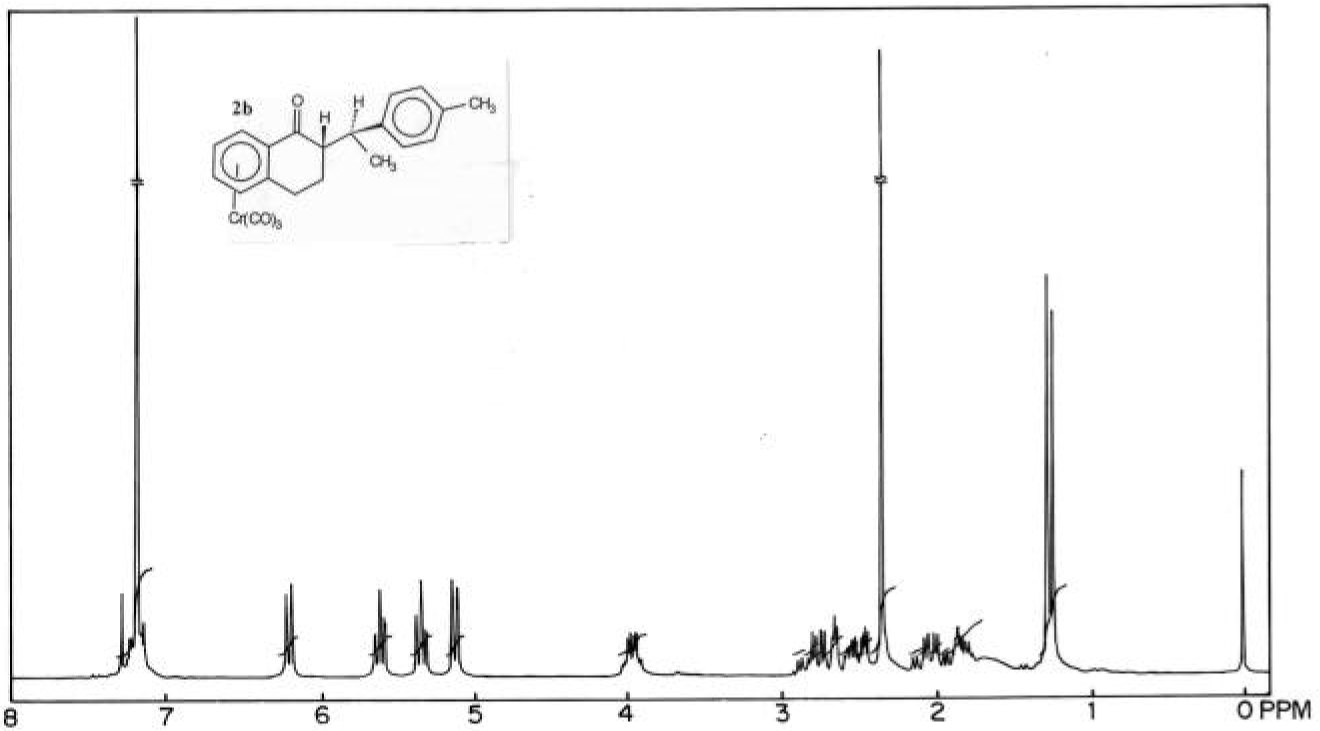
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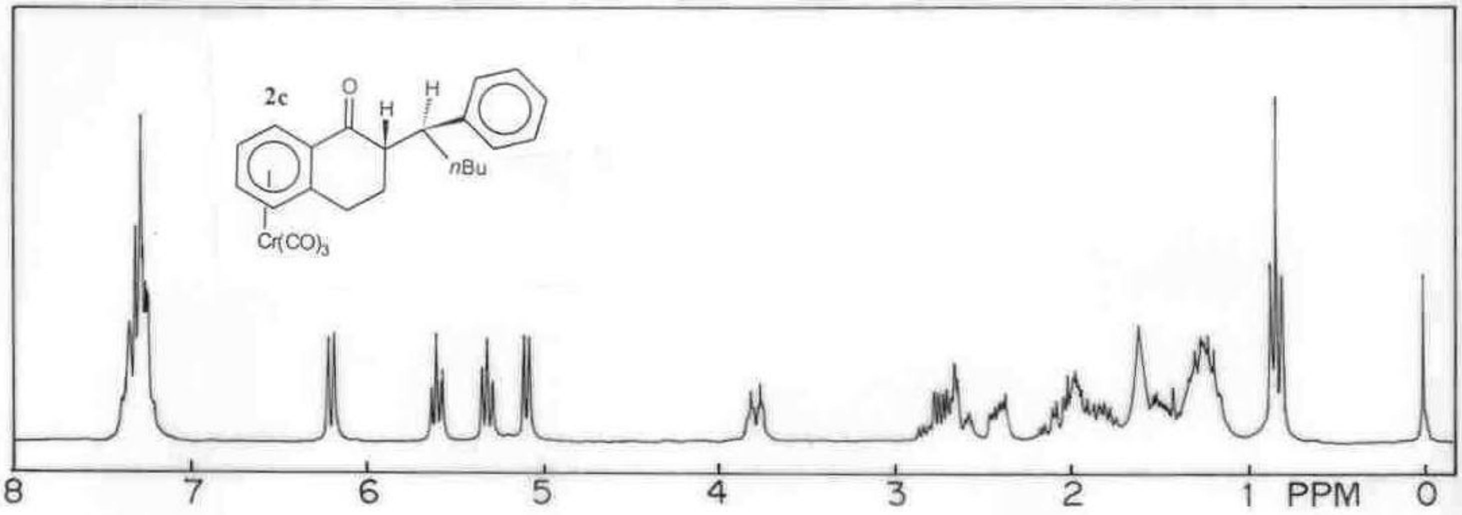
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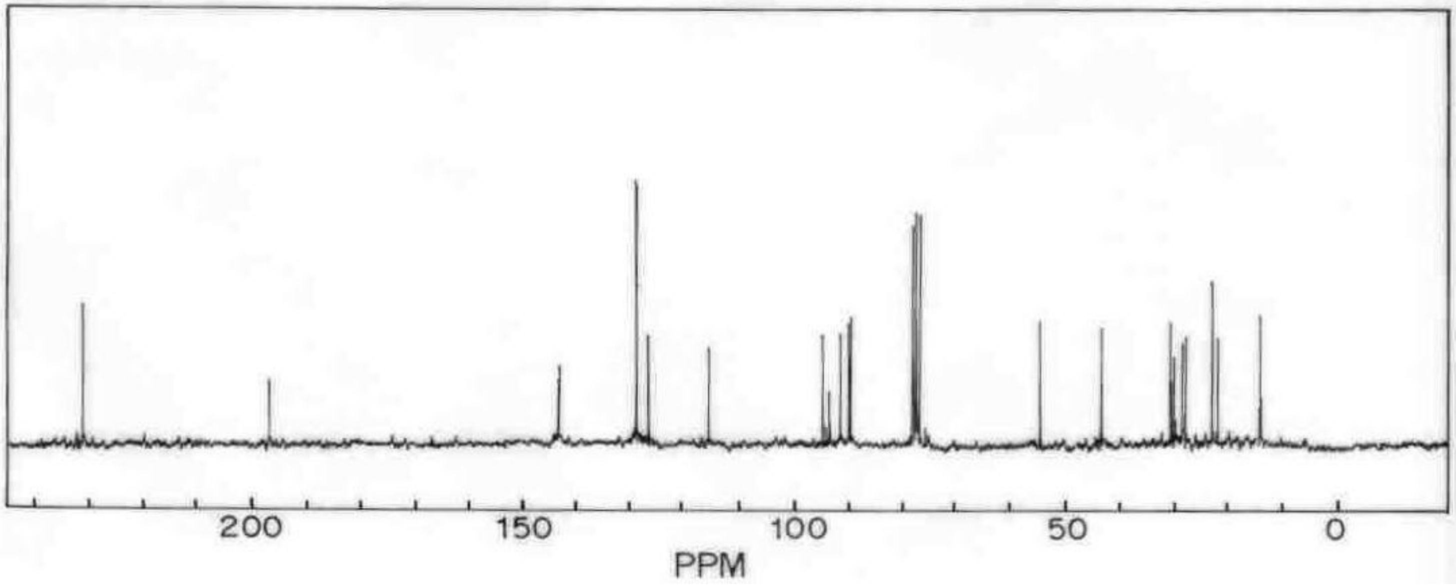
200
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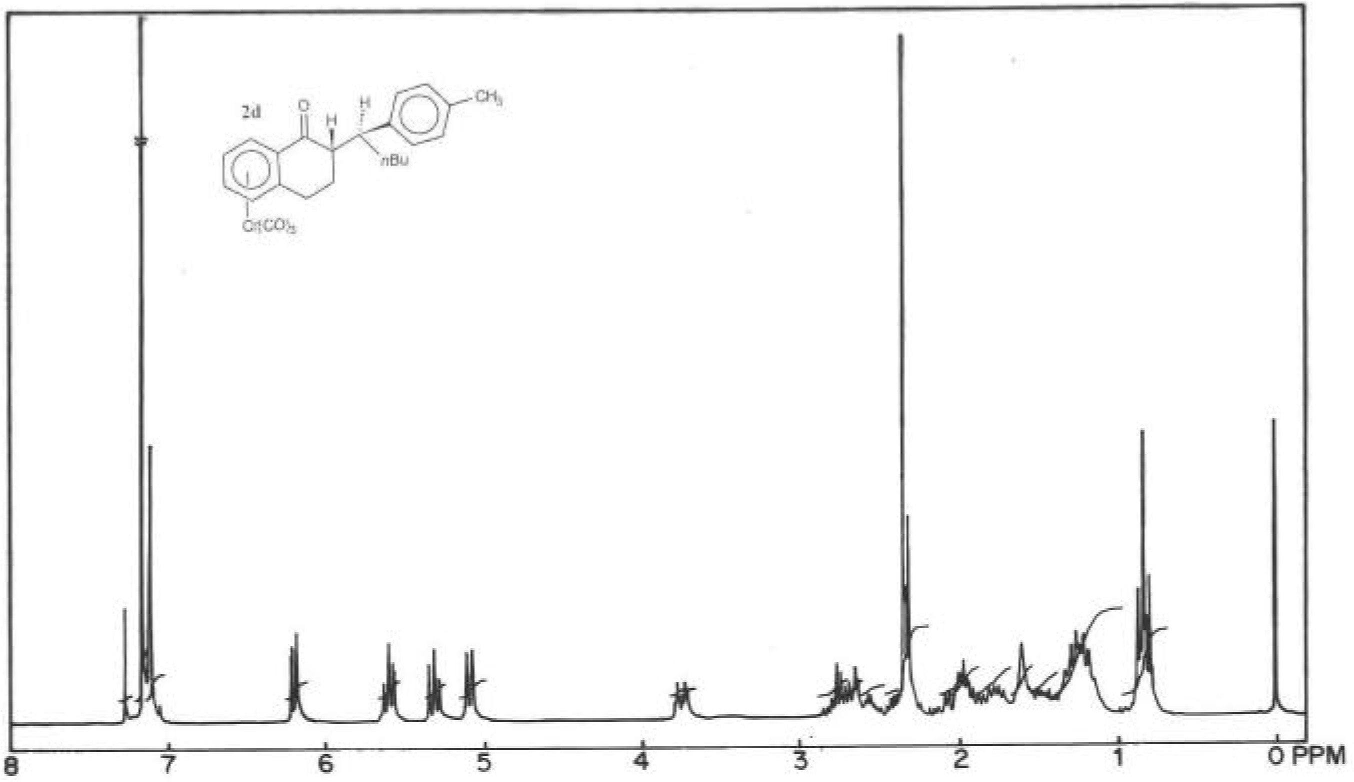
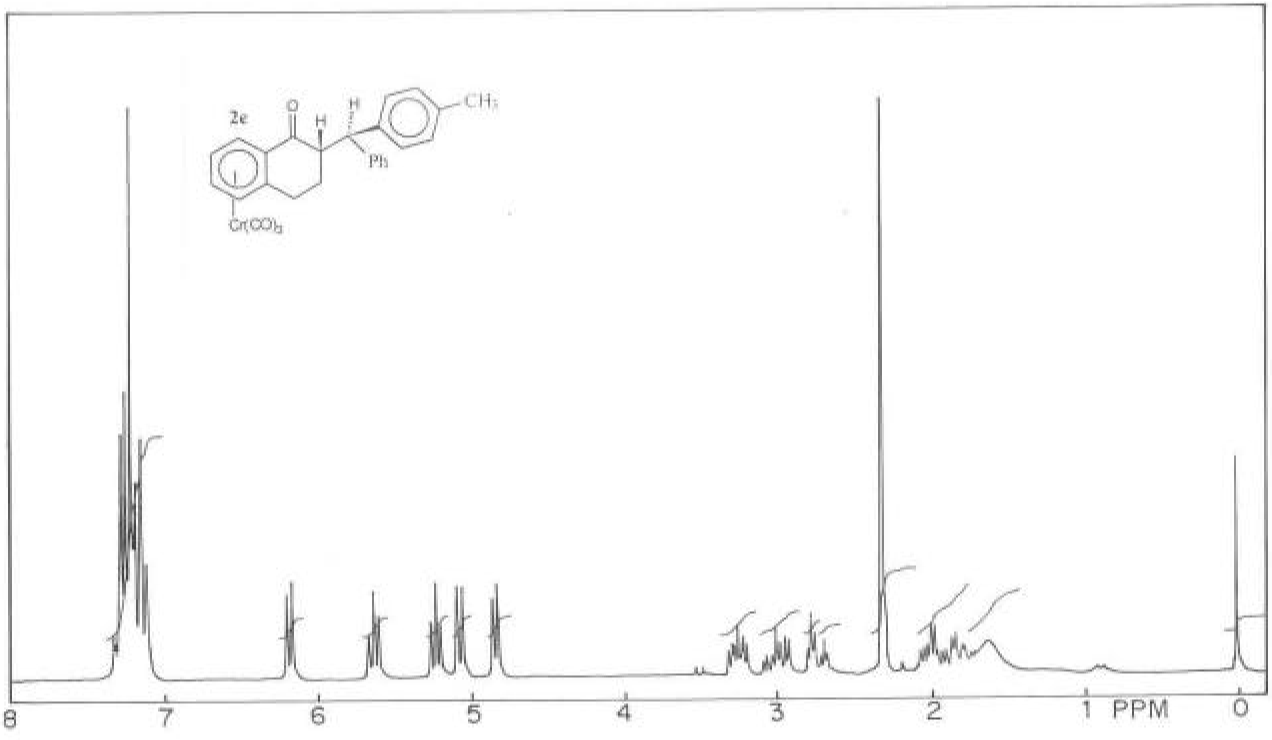
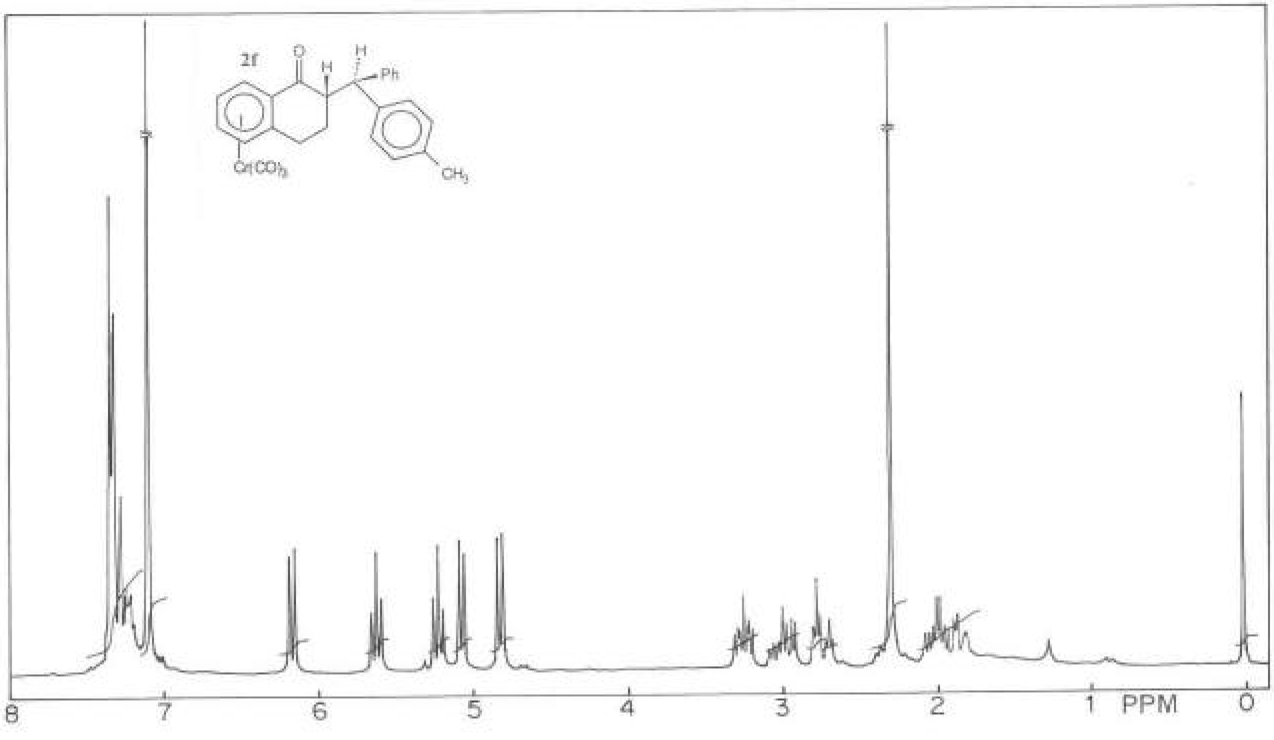
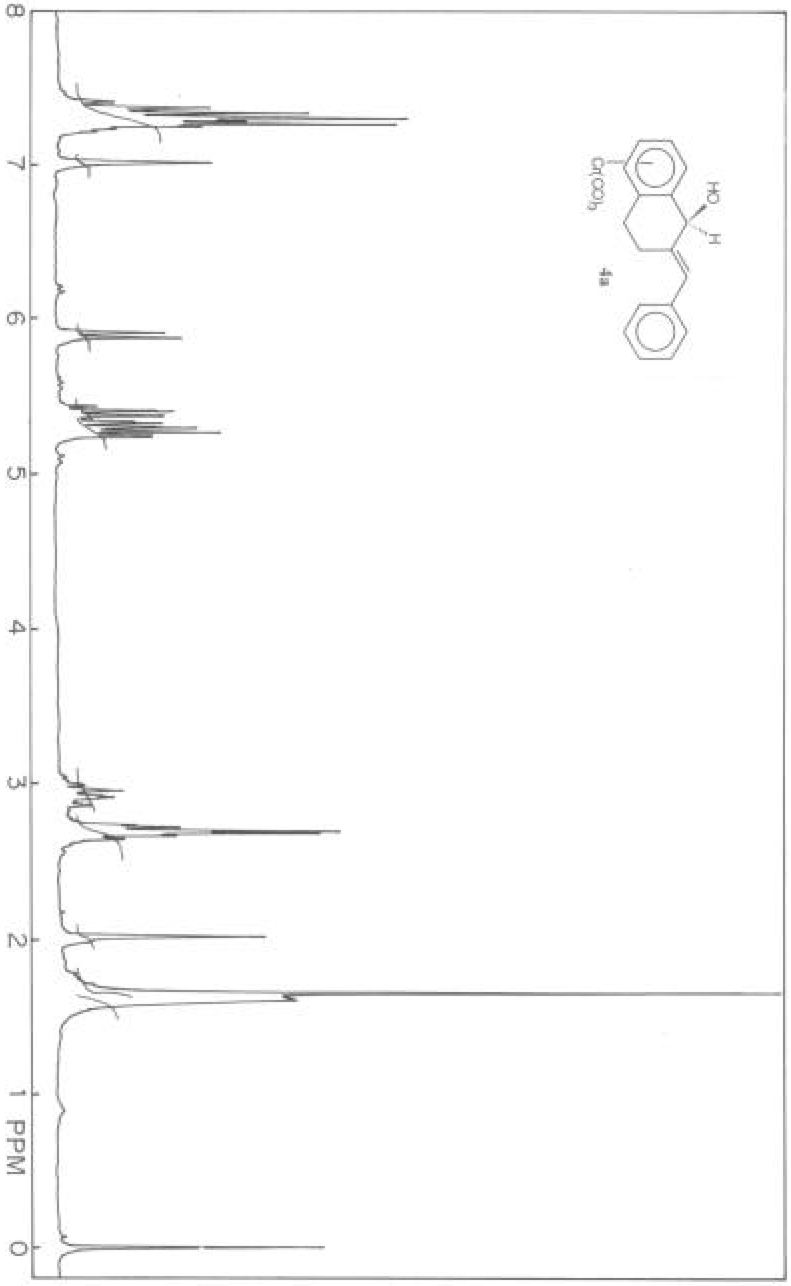
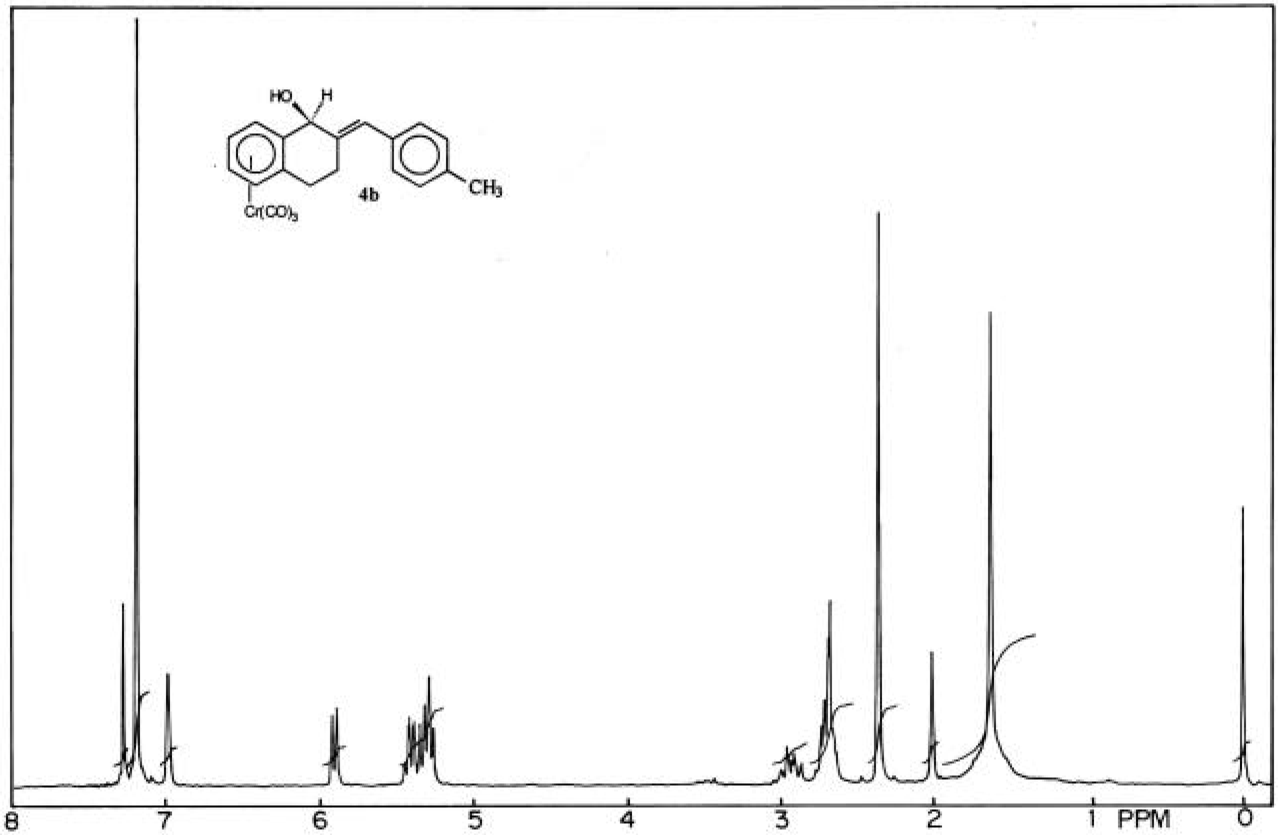
0
PPM

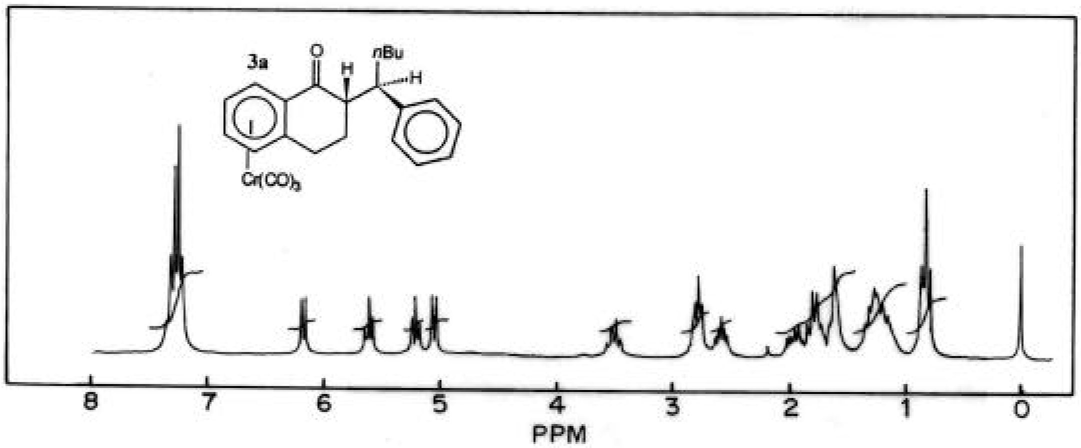

2d
O
H
H
CH3
nBu
Cr(CO)3
8
7
6
5
4
3
2
1
0 PPM

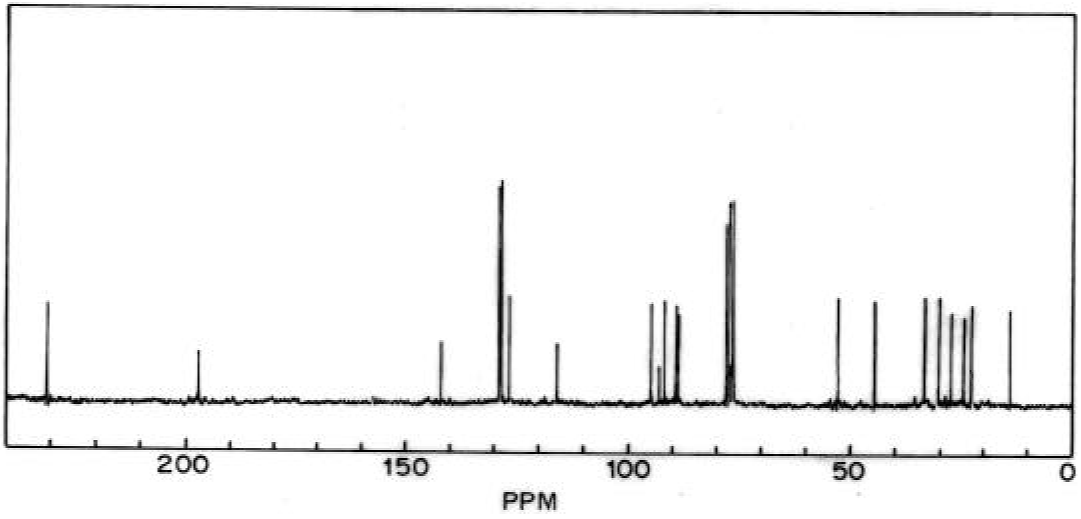

2e
O
H
H
Ph
CH3
Cr(CO)3
8
7
6
5
4
3
2
1 PPM
0

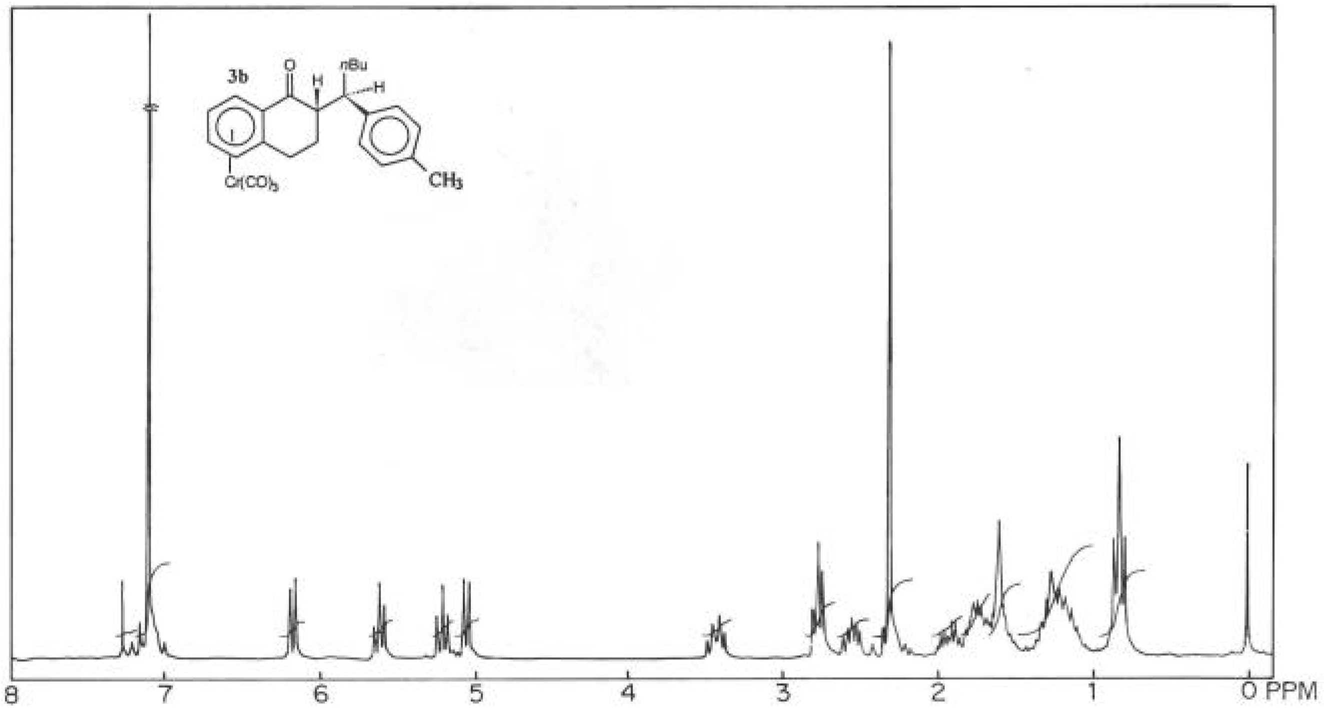

2f
O
H
H
Ph
Cr(CO)3
CH3
8
7
6
5
4
3
2
1
PPM
0


8
7
6
5
4
3
2
1 PPM
0
HO
H
Cr(CO)3
4a


HO
H
CH3
Cr(CO)3
4b
8
7
6
5
4
3
2
1 PPM
0

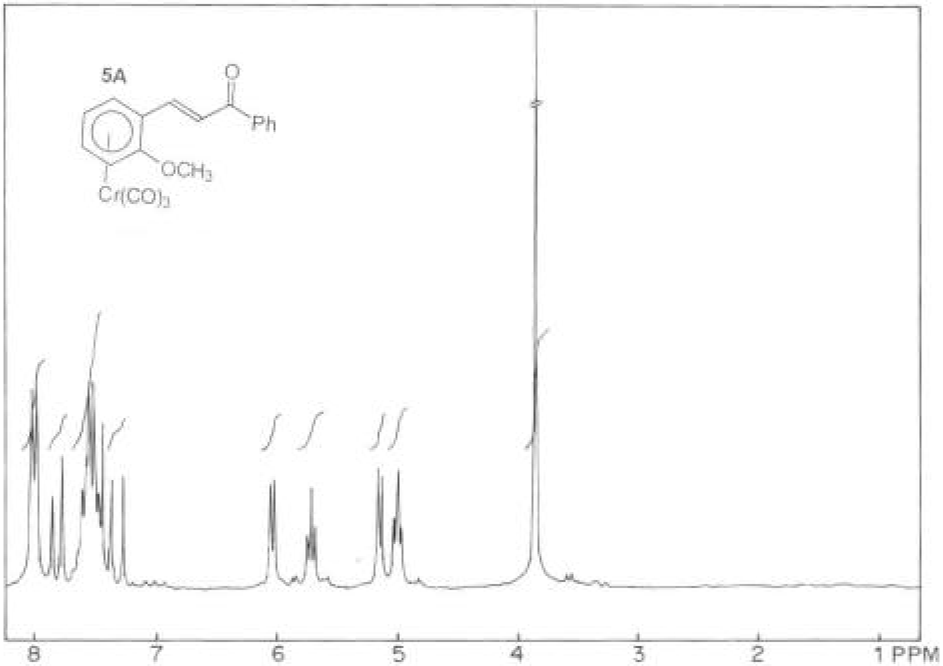

3a
O
H
nBu
H
Cr(CO)3
8
7
6
5
4
3
2
1
0
PPM

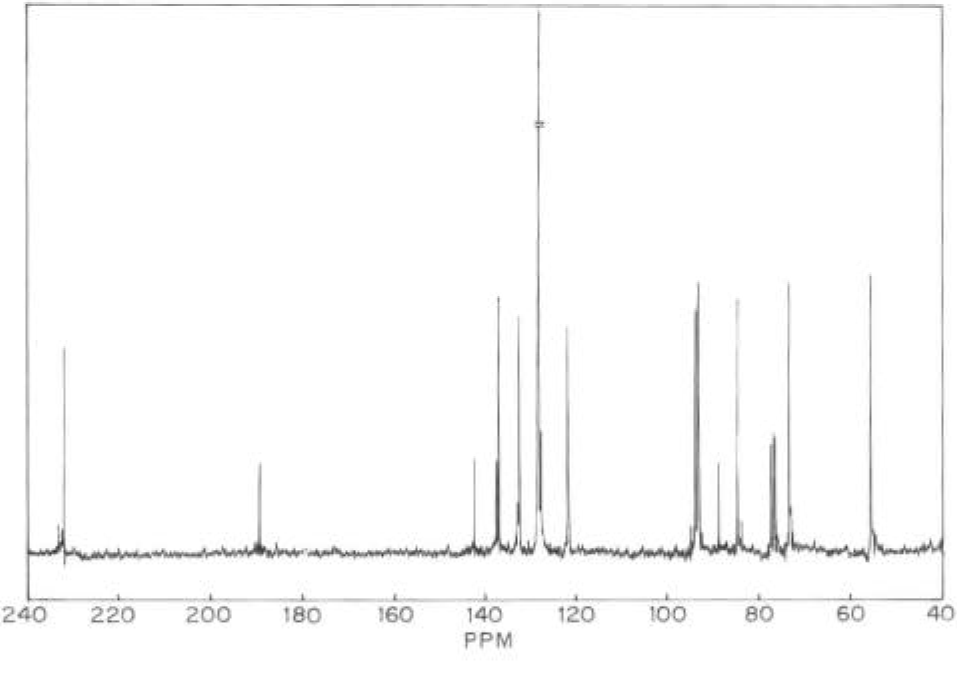

200
150
100
50
0
PPM

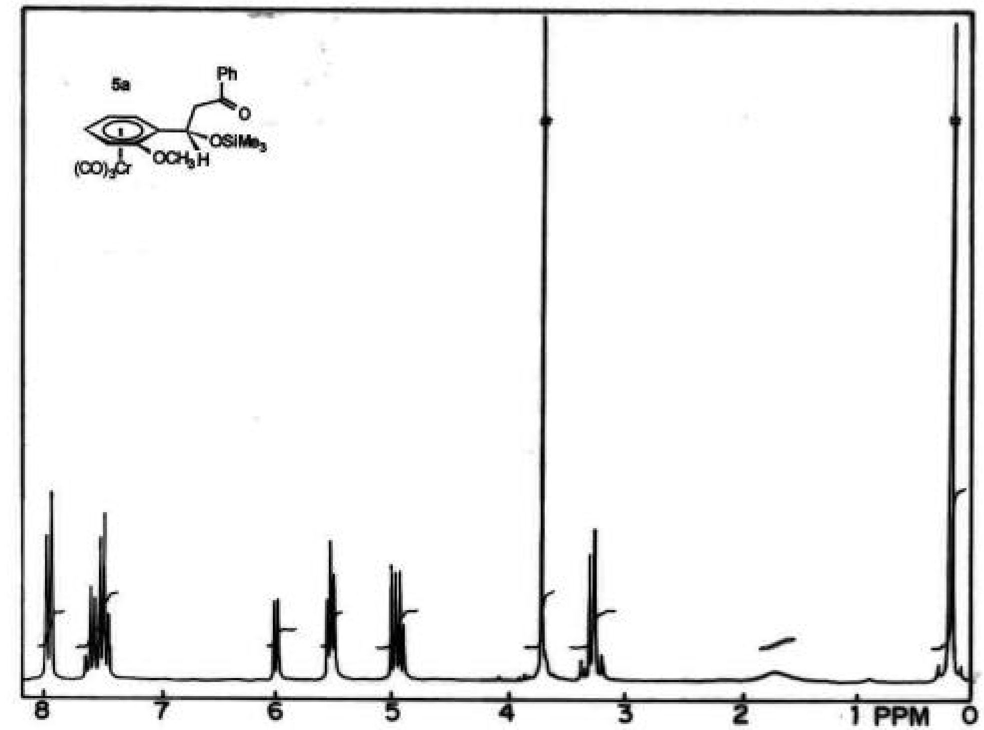

3b
O
H
nBu
H
Cr(CO)3
CH3
8
7
6
5
4
3
2
1
0 PPM

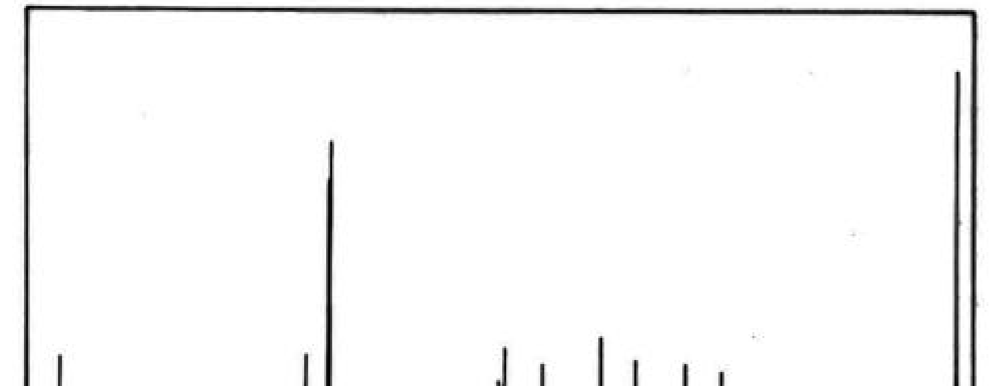
Appendix-II

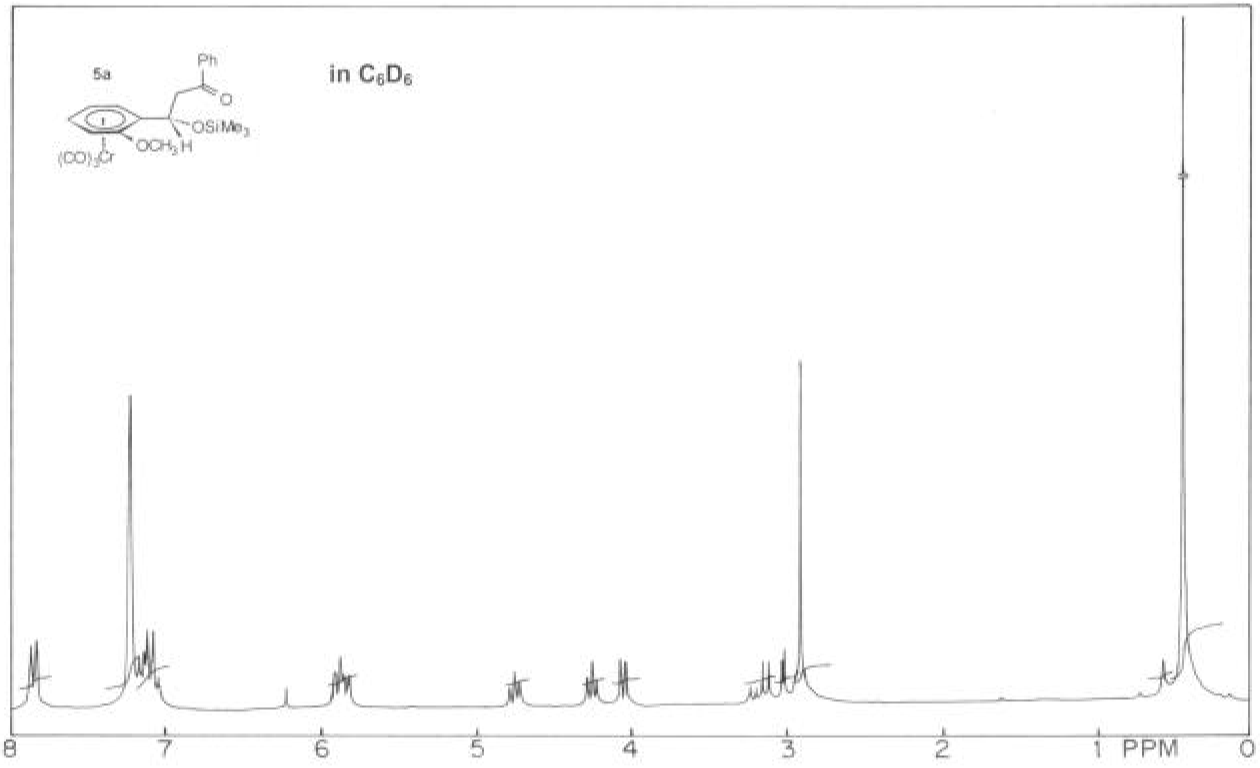
Spectra of compounds - Chapter II

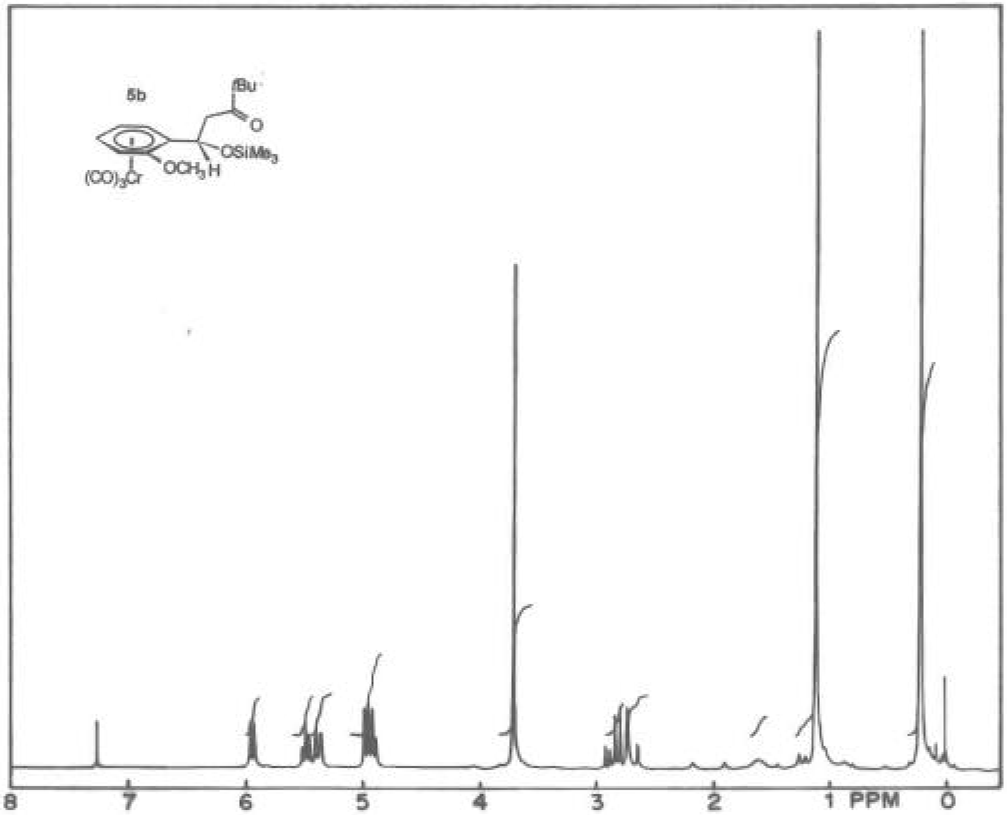

5A
O
Ph
OCH3
Cr(CO)3
8
7
6
5
4
3
2
1 PPM

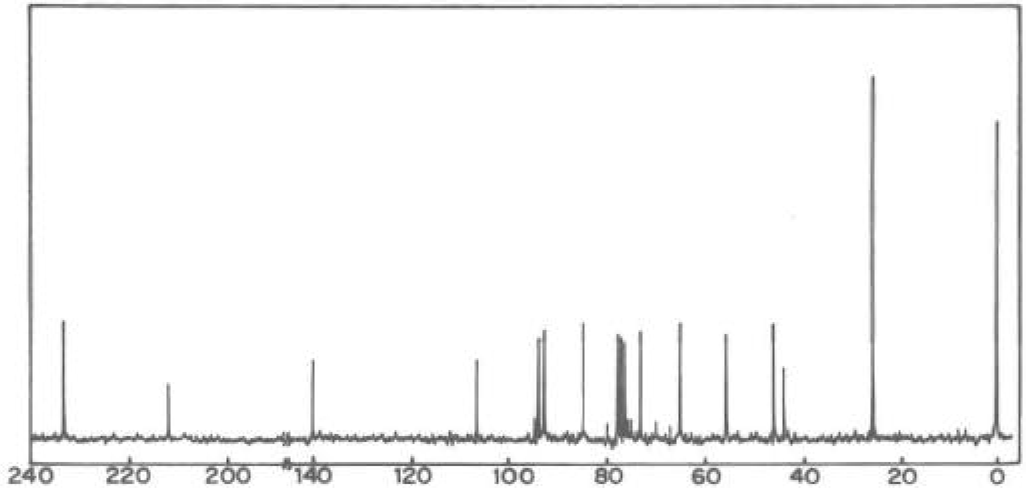

240
220
200
180
160
140
120
100
80
60
40
PPM

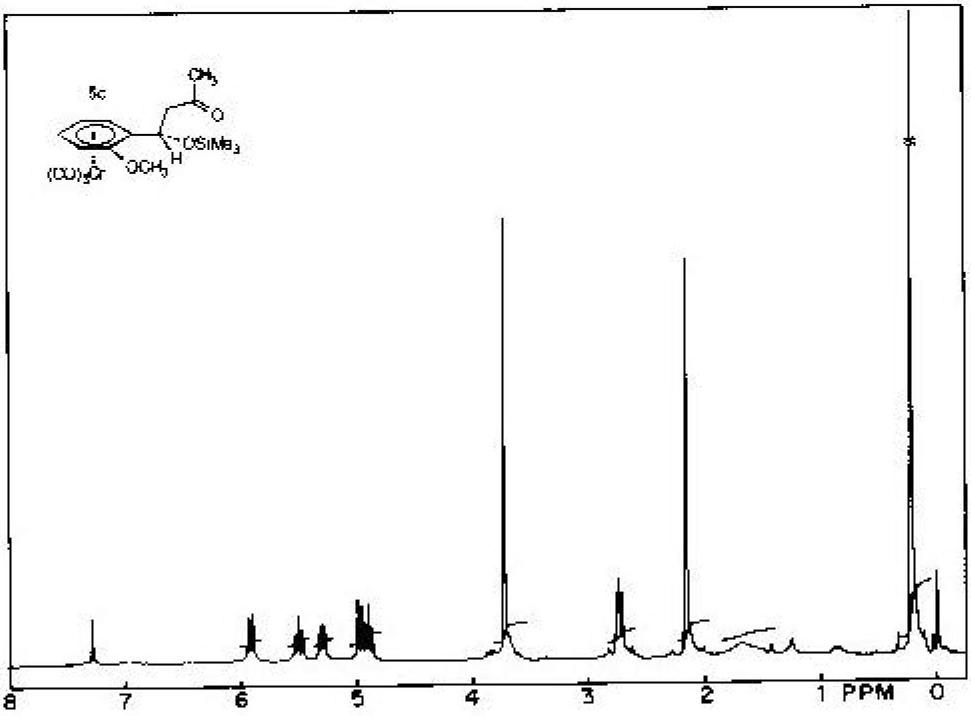

5a
Ph
O
OSiMe$_3$
(CO)$_3$Cr
OCH$_3$
H
8
7
6
5
4
3
2
1 PPM
0

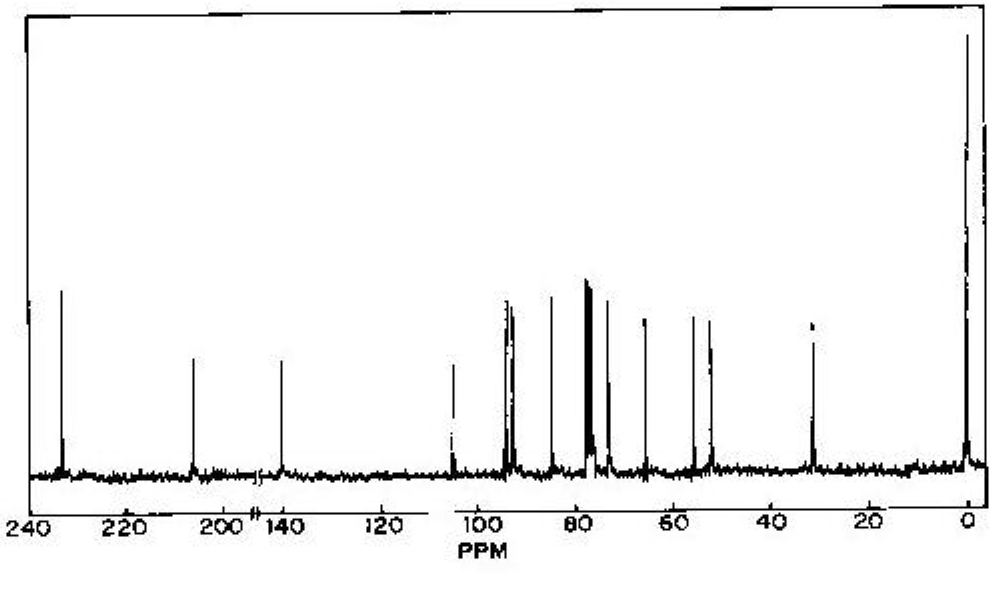

240
200
120
80
40
0
PPM

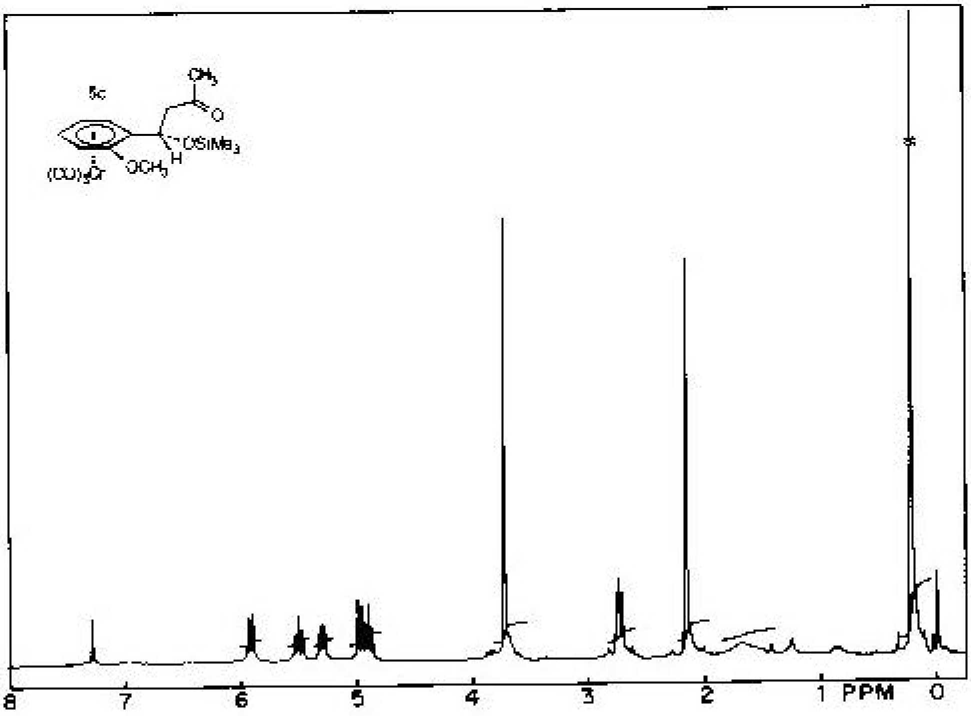

5a
Ph
O
OSiMe3
OCH3 H
(CO)3Cr
in C6D6
8
7
6
5
4
3
2
1 PPM
0


5b
tBu
O
OSiMe3
OCH3 H
(CO)3Cr
8
7
6
5
4
3
2
1 PPM
0

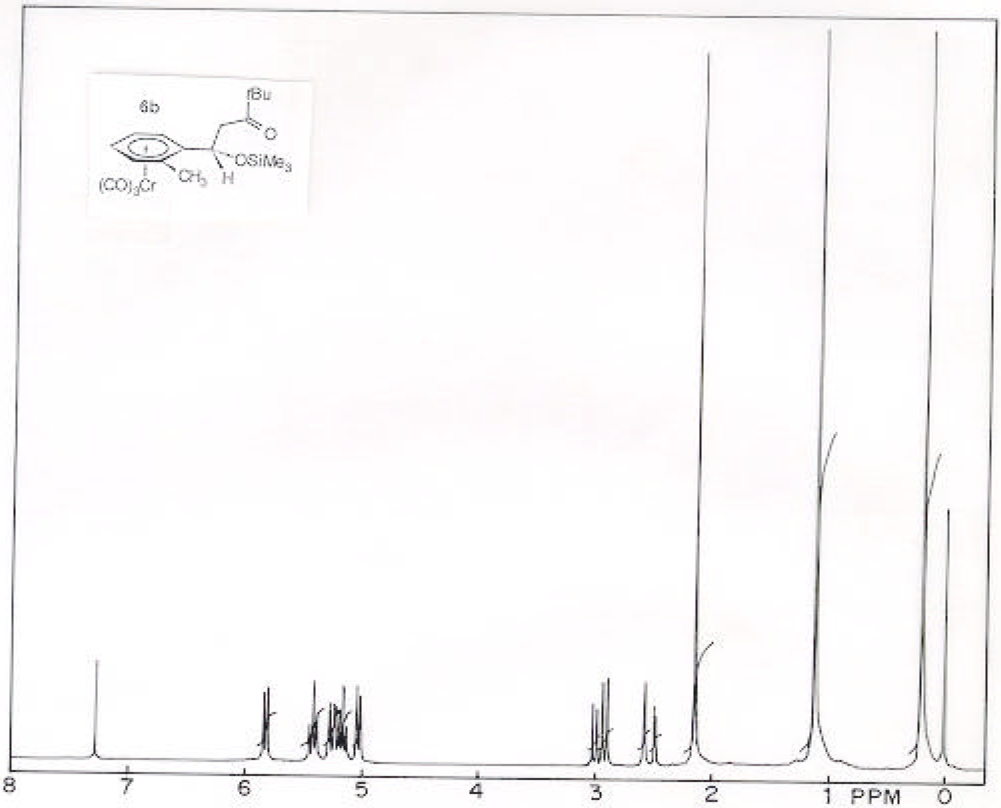

240
220
200
140
120
100
80
60
40
20
0
PPM

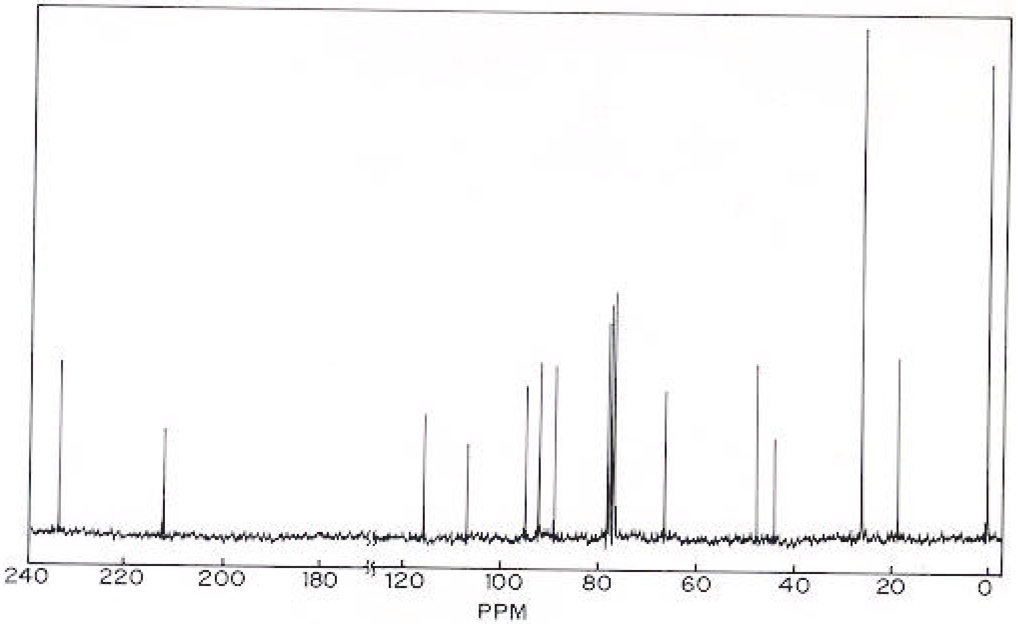

5c
CH3
O
OSiMe3
H
OCH3
(CO)3Cr
*
8
7
6
5
4
3
2
1 PPM
0

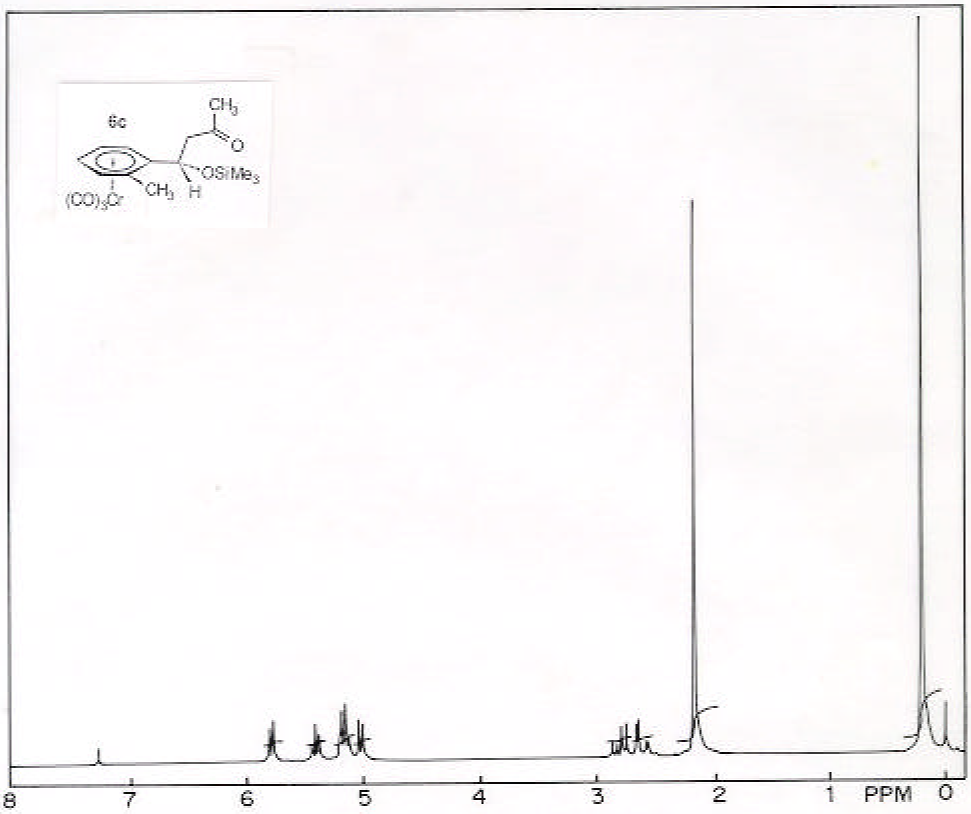

240
220
200
140
120
100
80
60
40
20
0
PPM

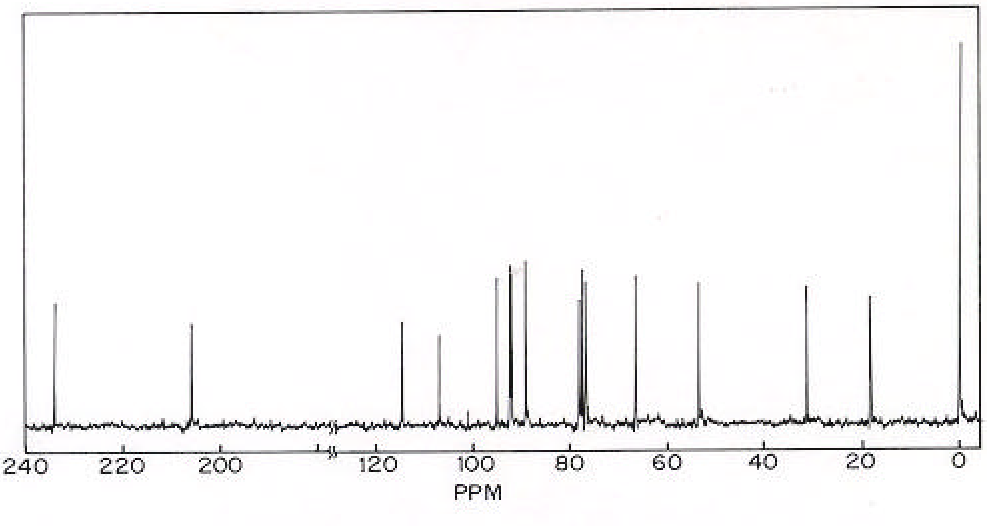

5c
CH3
O
OSiMe3
H
OCH3
(CO)3Cr
*
8
7
6
5
4
3
2
1 PPM
0

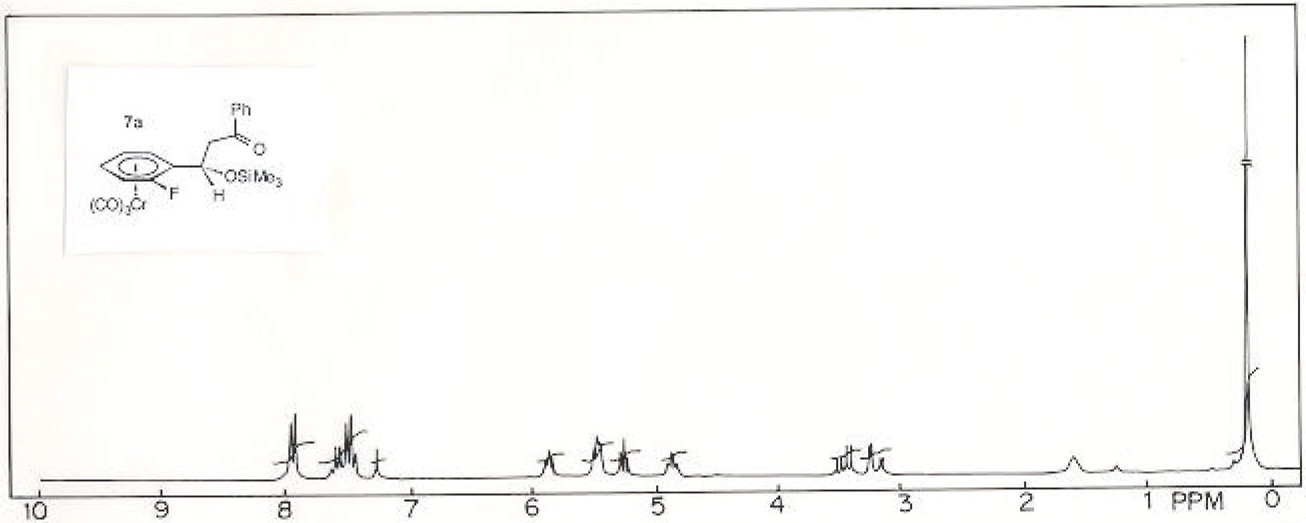

240
220
200
140
120
100
80
60
40
20
0
PPM


6b
tBu
O
OSiMe3
(CO)3Cr
CH3
H
8
7
6
5
4
3
2
1 PPM
0

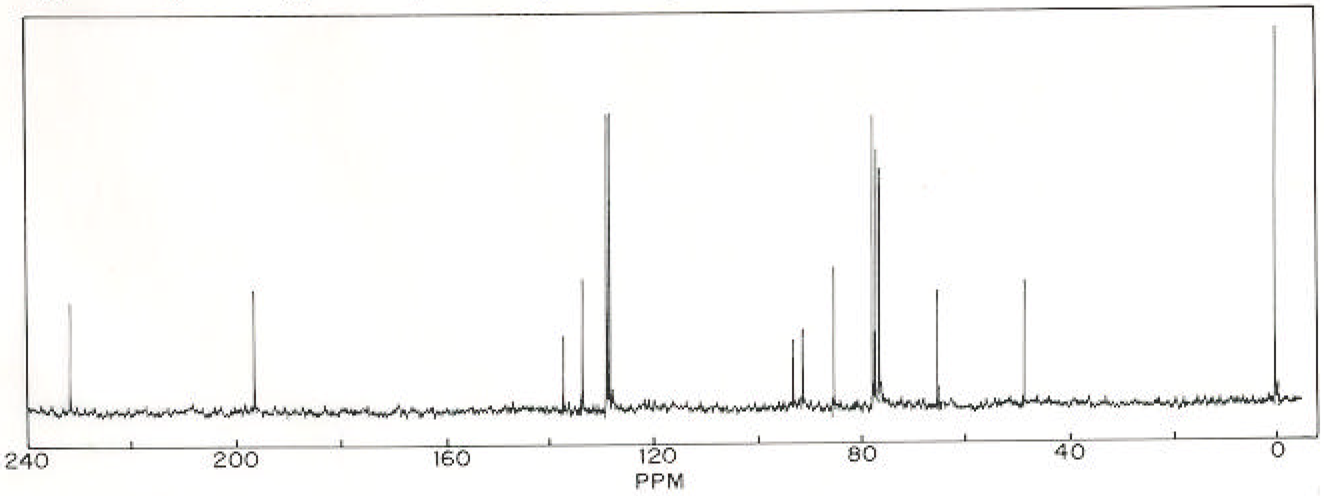

240
220
200
180
120
100
80
60
40
20
0
PPM


6c
CH3
O
OSiMe3
H
CH3
(CO)3Cr
8
7
6
5
4
3
2
1
PPM
0

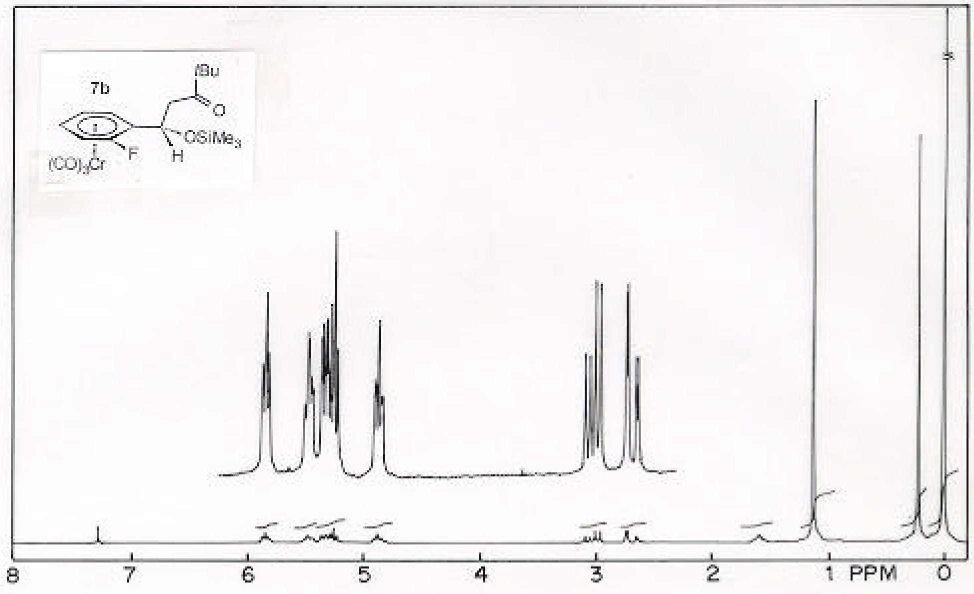

240
220
200
120
100
80
60
40
20
0
PPM

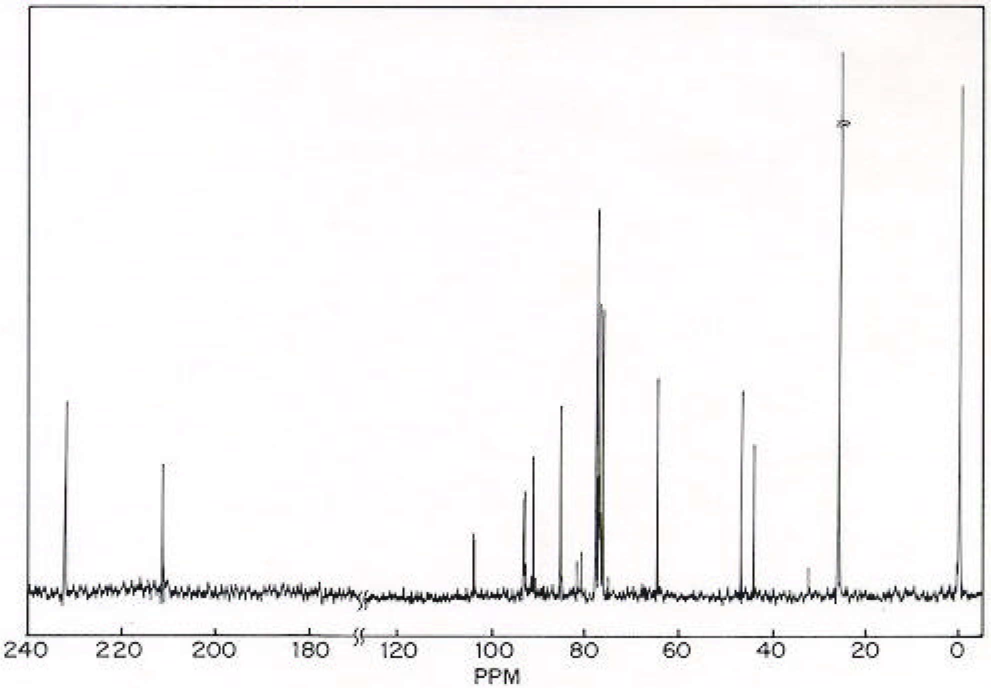

7a

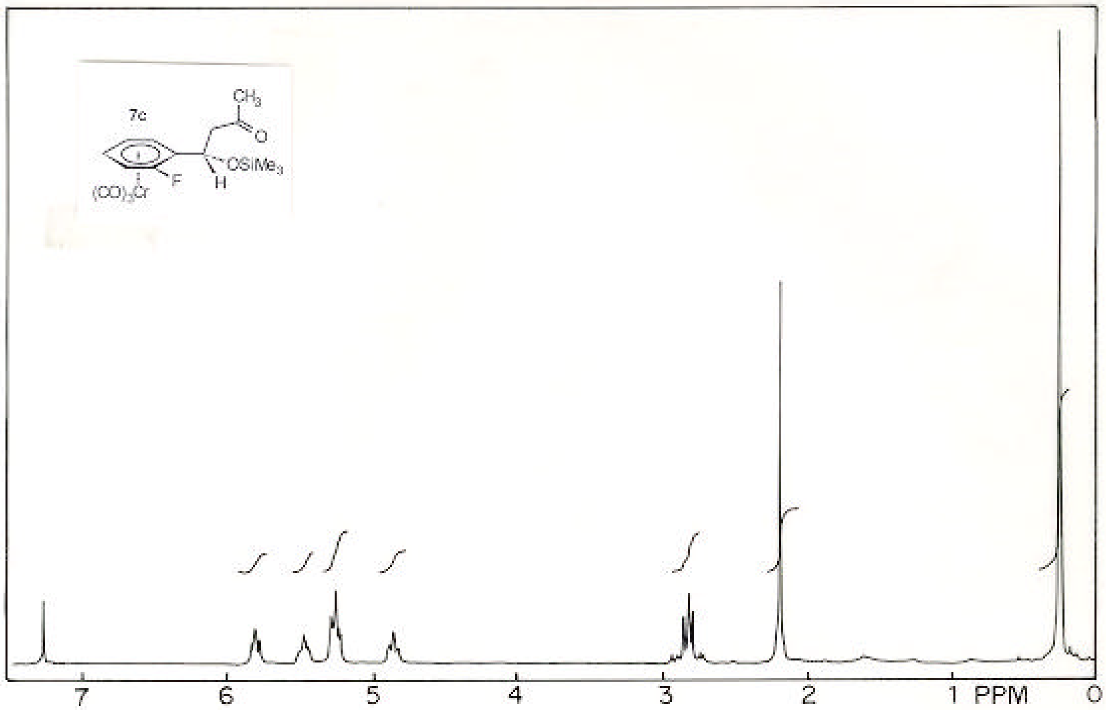
Ph
O
OSiMe3
H
F
(CO)3Cr
10
9
8
7
6
5
4
3
2
1 PPM
0

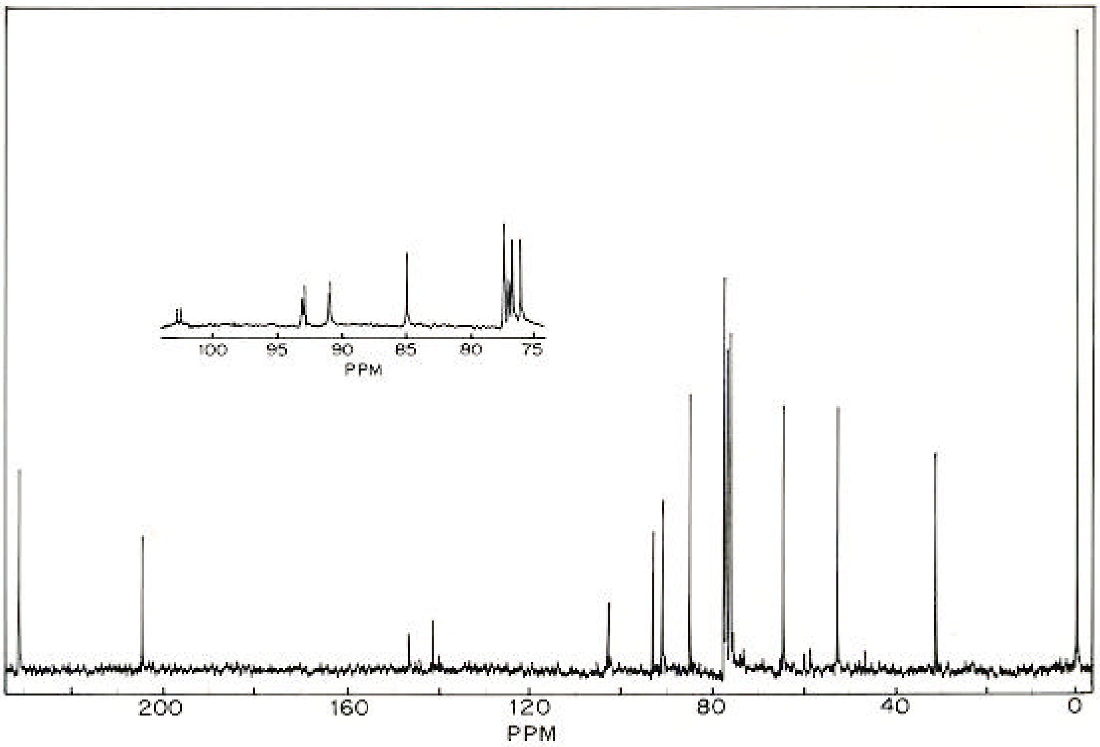


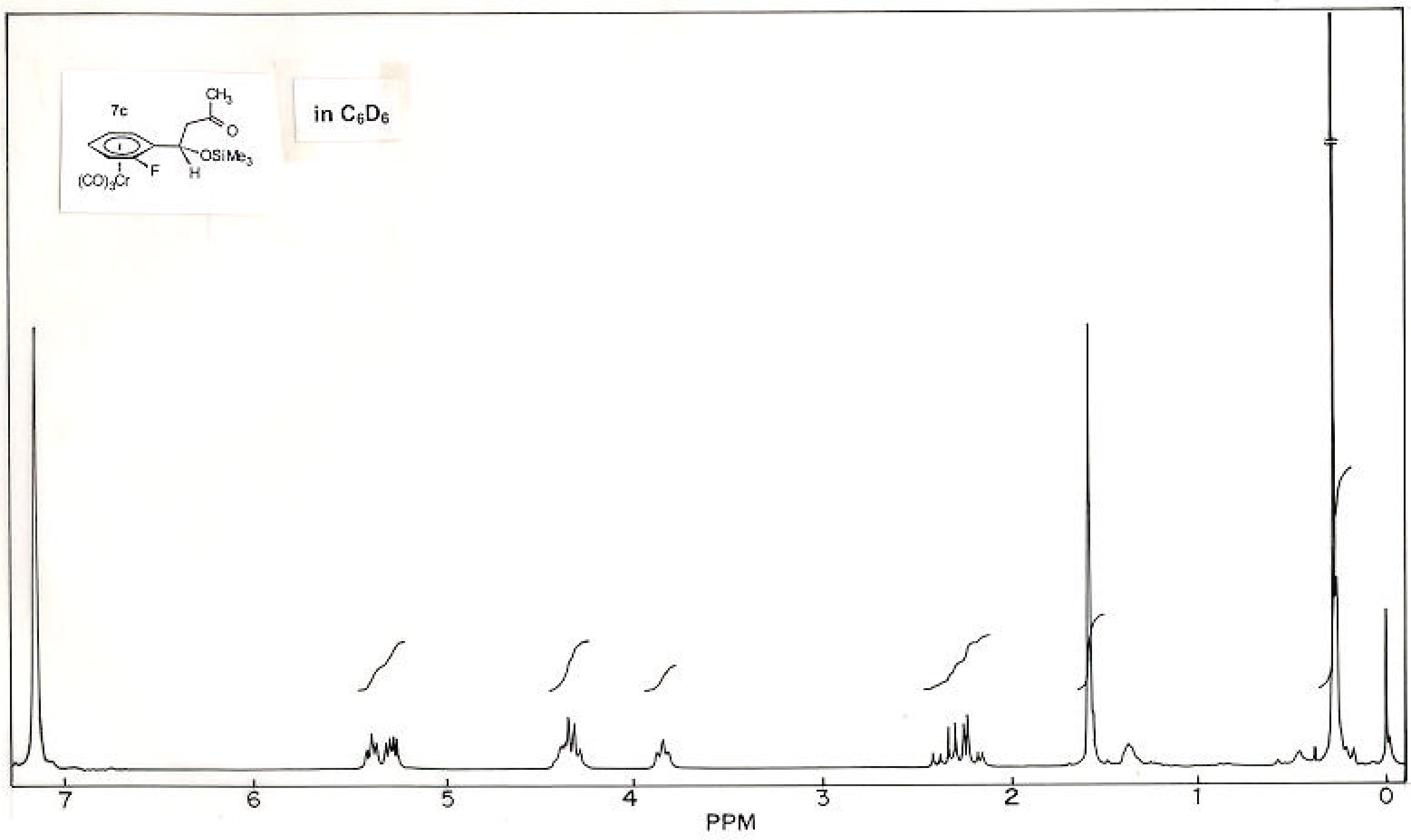
240
200
160
120
PPM
80
40
0

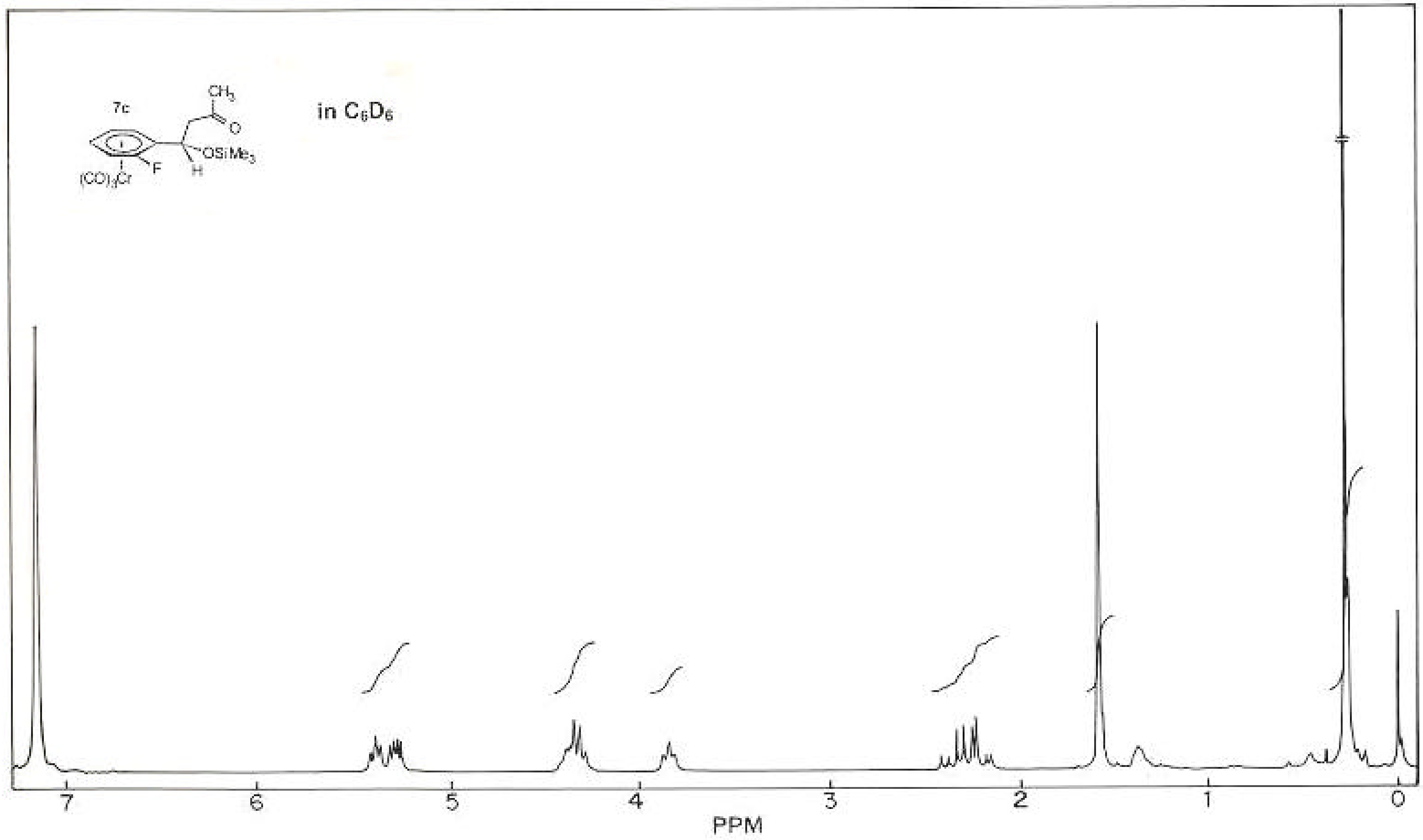

7b
tBu
O
OSiMe$_3$
H
F
(CO)$_3$Cr
8
7
6
5
4
3
2
1 PPM
0

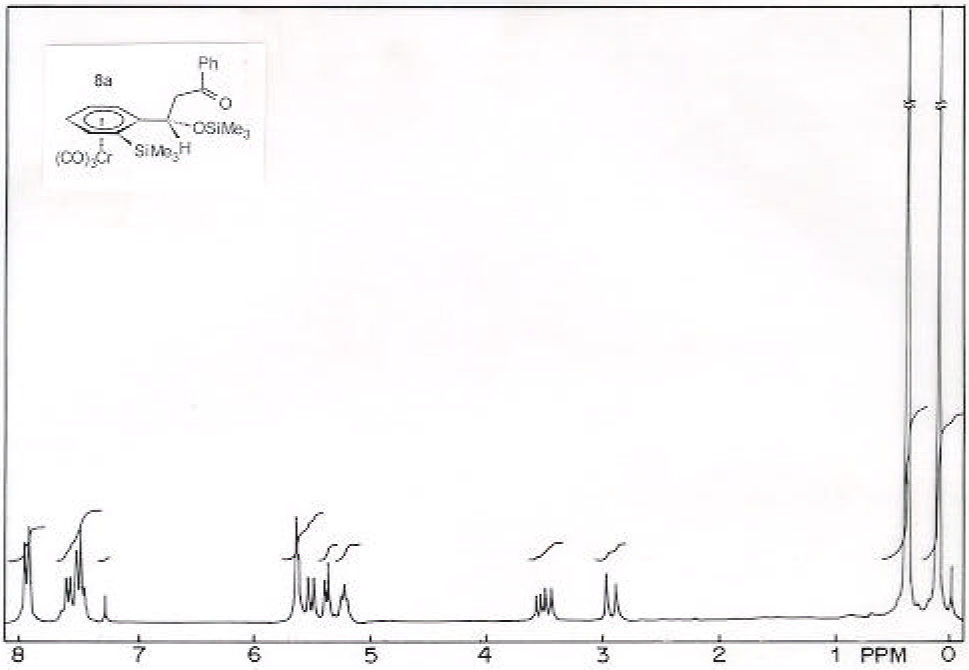

240
220
200
180
120
100
80
60
40
20
0
PPM

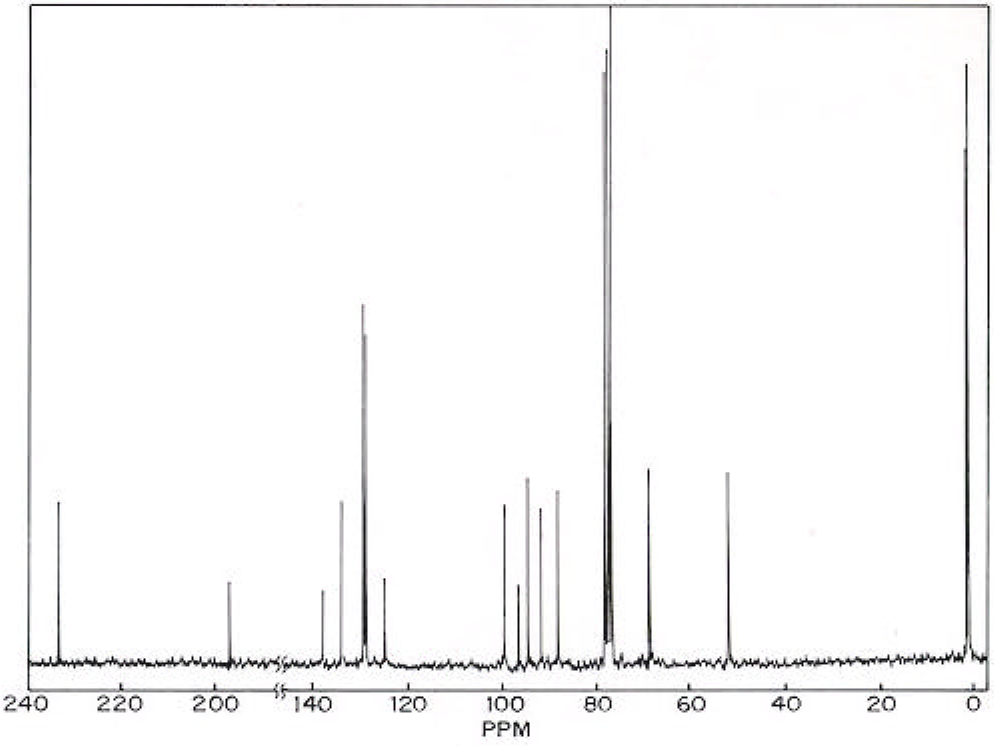

7c
CH3
O
OSiMe3
H
F
(CO)3Cr
7
6
5
4
3
2
1 PPM
0

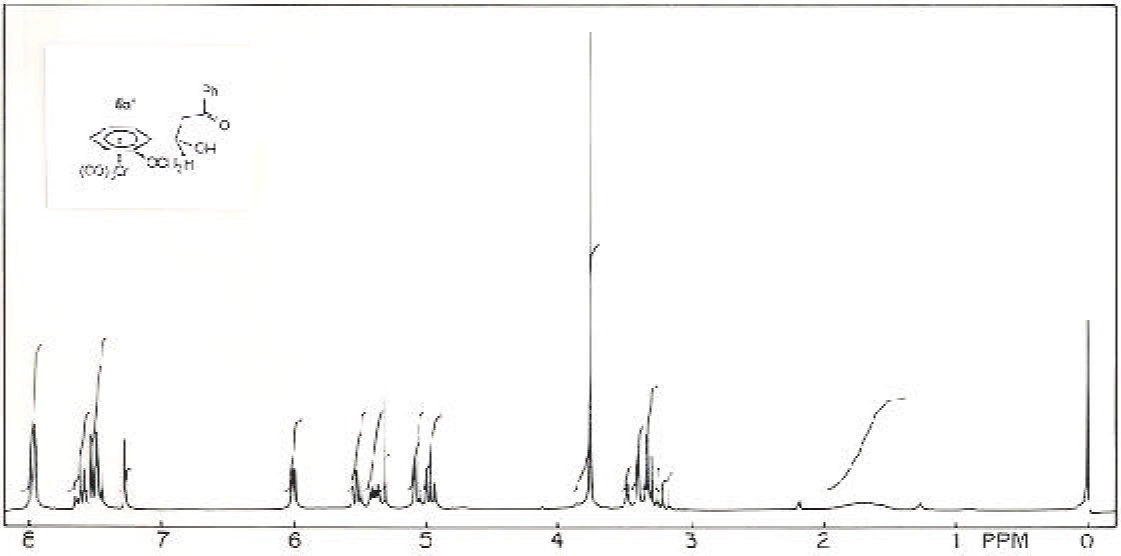

100
95
90
85
80
75
PPM
200
160
120
80
40
0
PPM

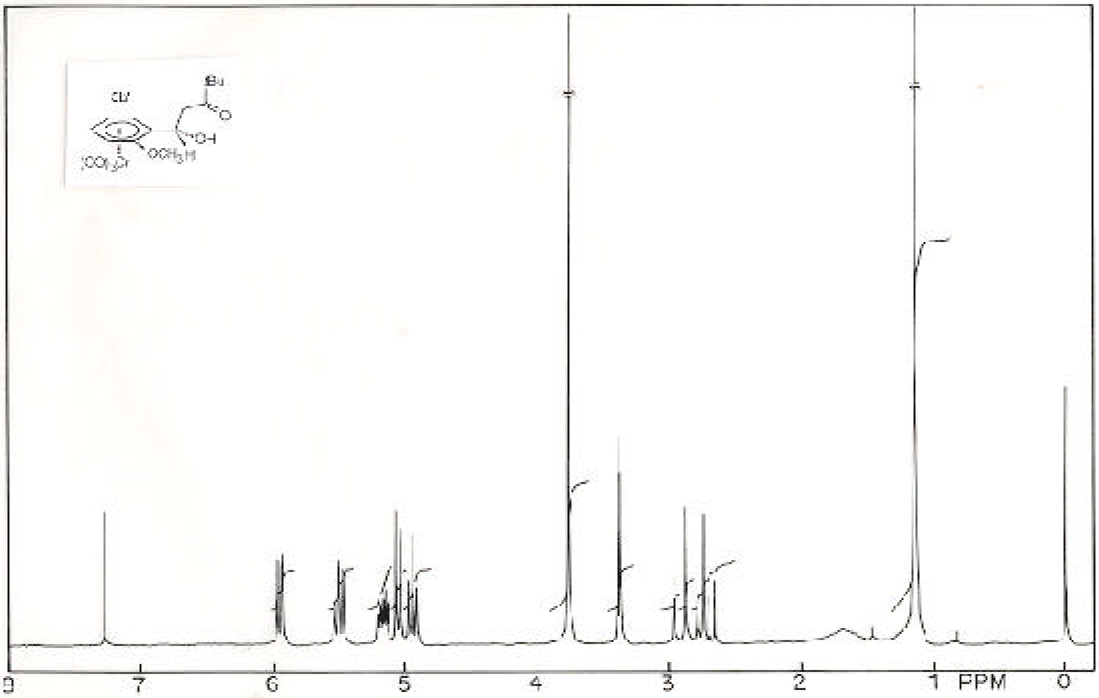

7c
CH3
O
OSiMe3
H
F
(CO)3Cr
in C6D6
7
6
5
4
3
2
1
0
PPM

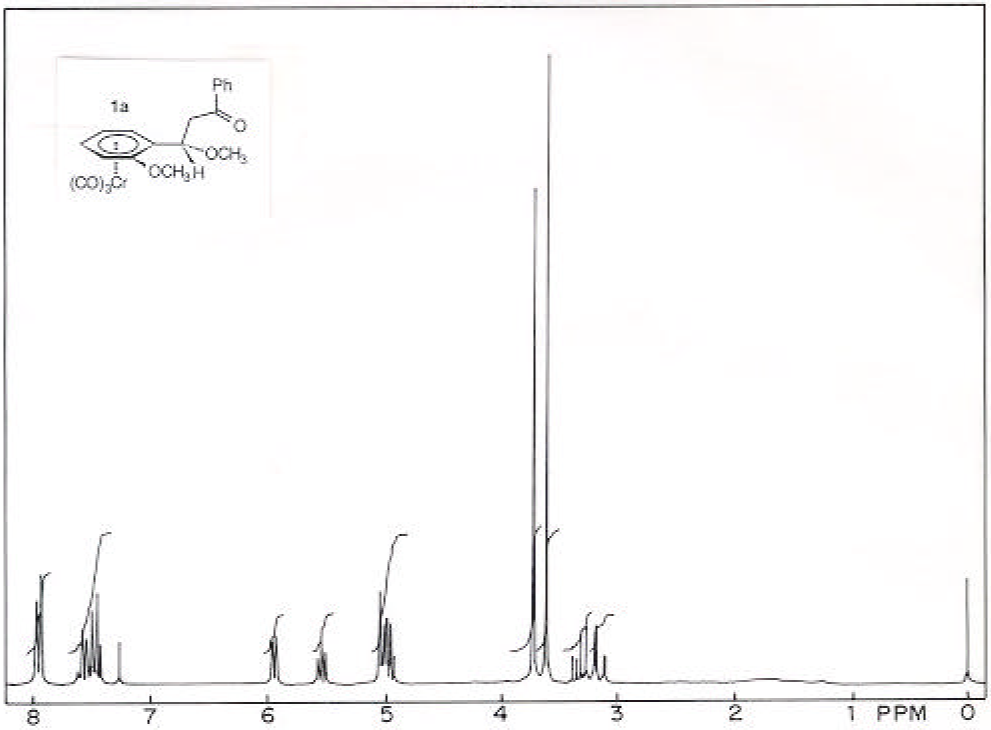

7c
CH3
O
OSiMe3
H
F
(CO)3Cr
in C6D6
7
6
5
4
3
2
1
0
PPM

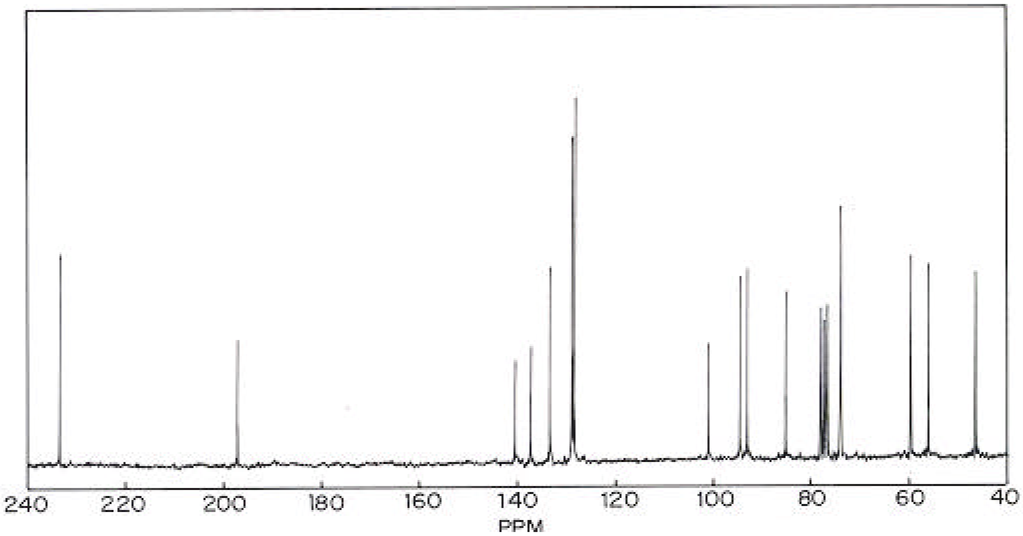

8a
Ph
O
OSiMe3
(CO)3Cr
SiMe3
H
8
7
6
5
4
3
2
1
PPM
0

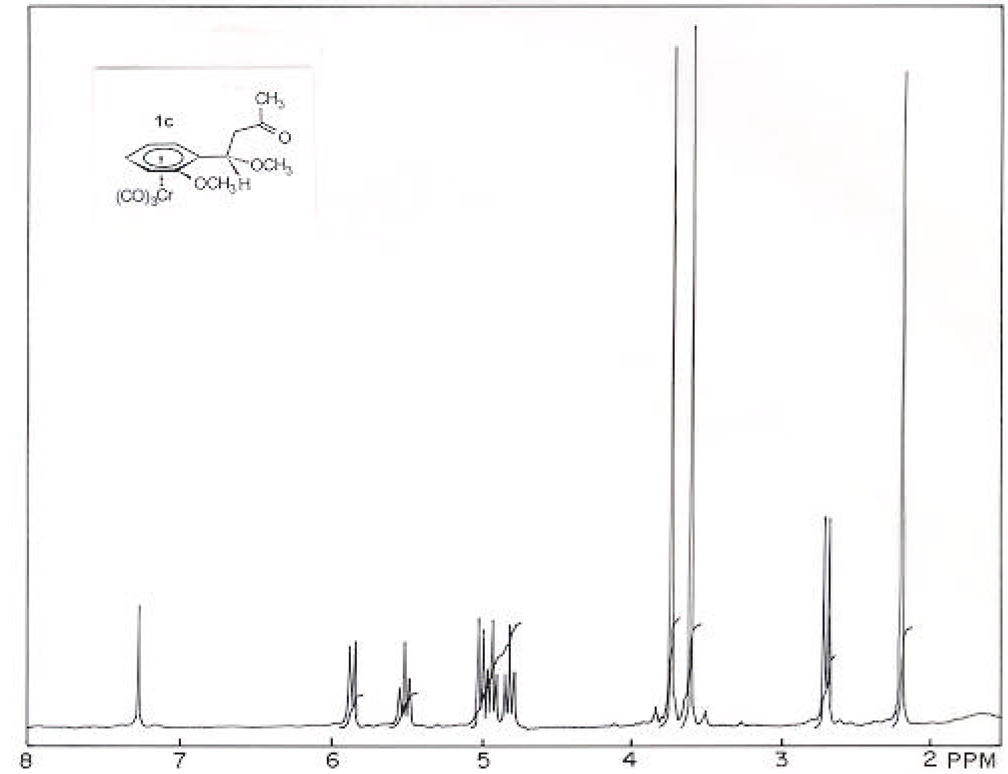

240
220
200
140
120
100
80
60
40
20
0
PPM

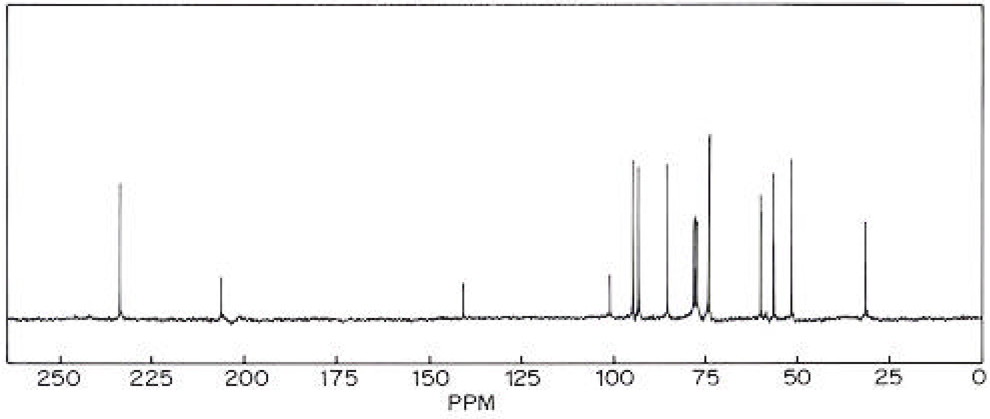

6a'
Ph
O
OH
OCH3 H
(CO)3Cr
8
7
6
5
4
3
2
1 PPM
0

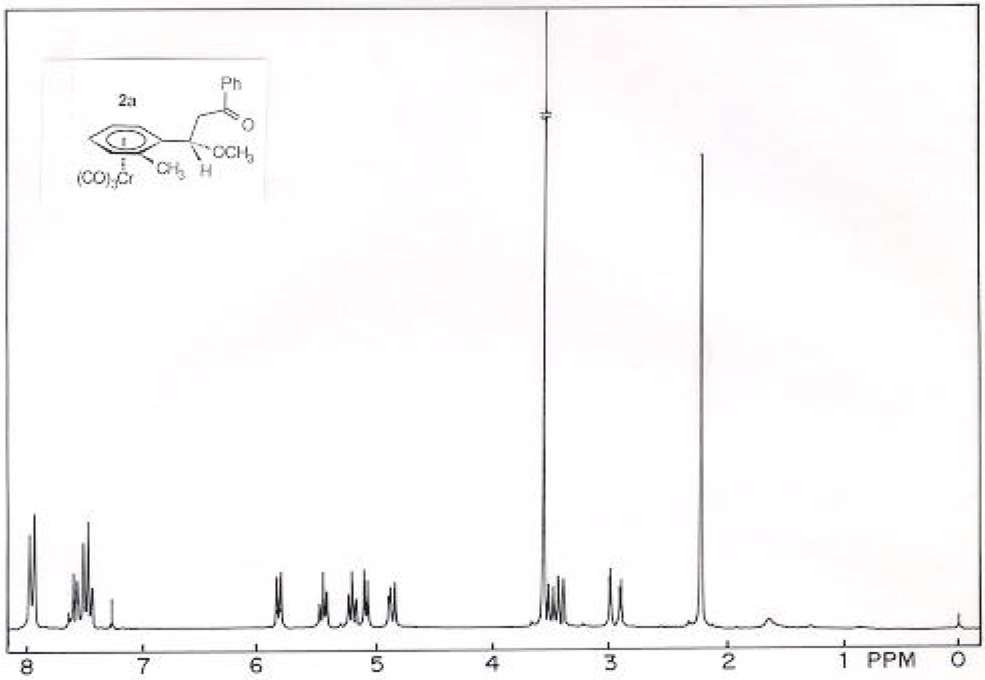

6b'
tBu
O
OH
OCH3 H
(CO)3Cr
8
7
6
5
4
3
2
1 PPM
0

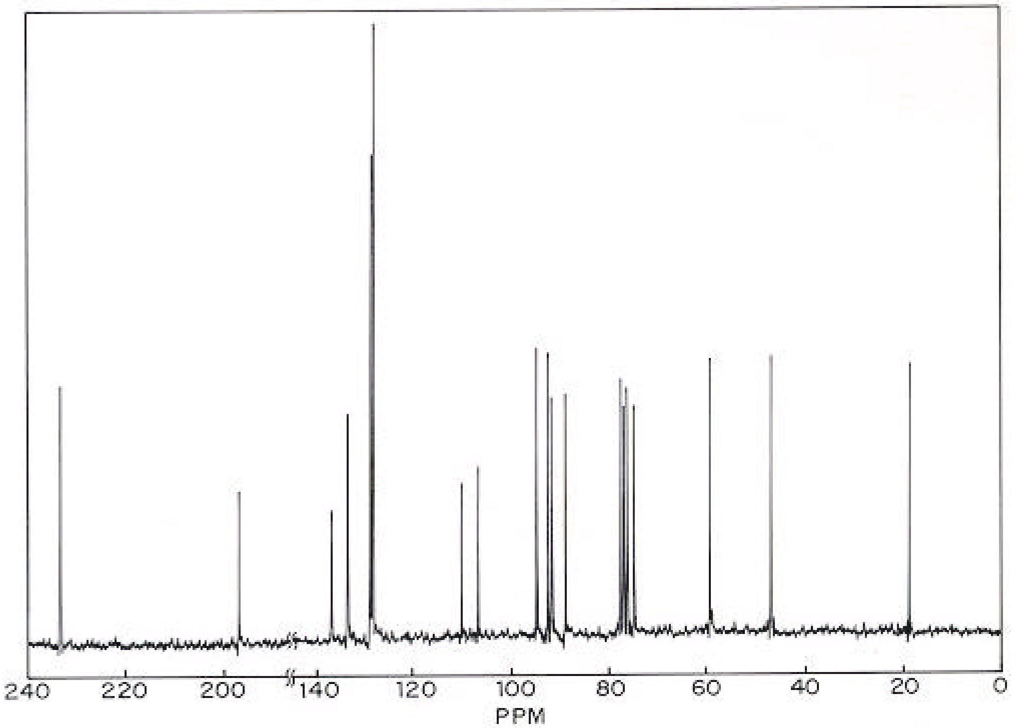

1a
Ph
O
OCH3
(CO)3Cr
OCH3
H
8
7
6
5
4
3
2
1
PPM
0

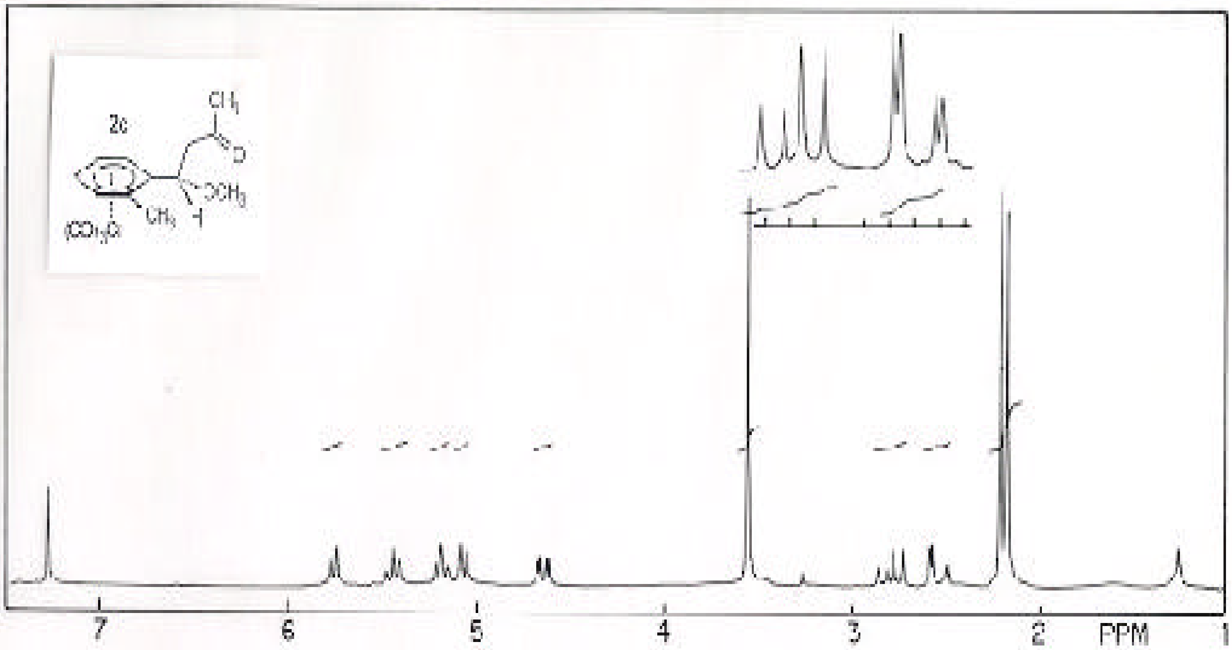

240
220
200
180
160
140
120
100
80
60
40
PPM

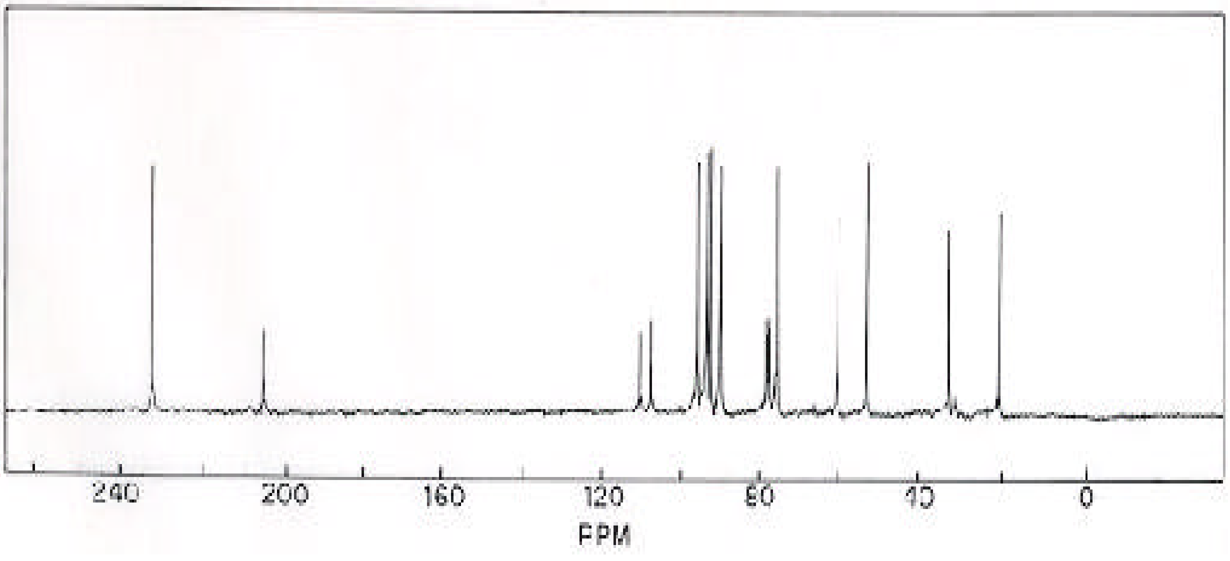

1c
CH3
O
OCH3
OCH3 H
(CO)3Cr
8
7
6
5
4
3
2 PPM

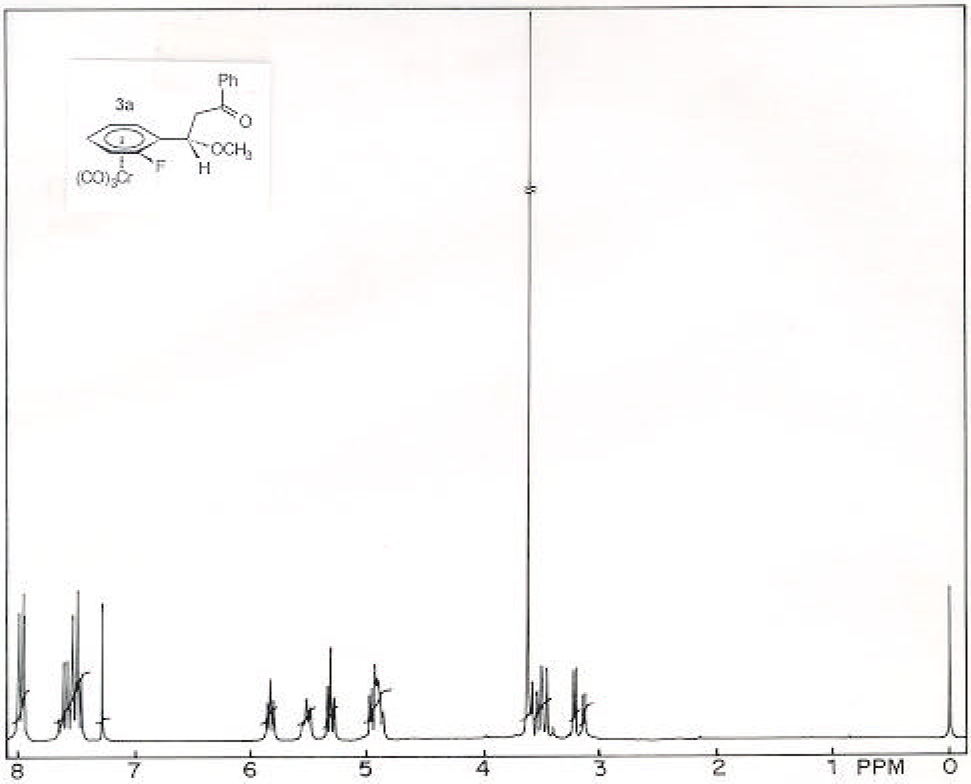

250
225
200
175
150
125
100
75
50
25
0
PPM

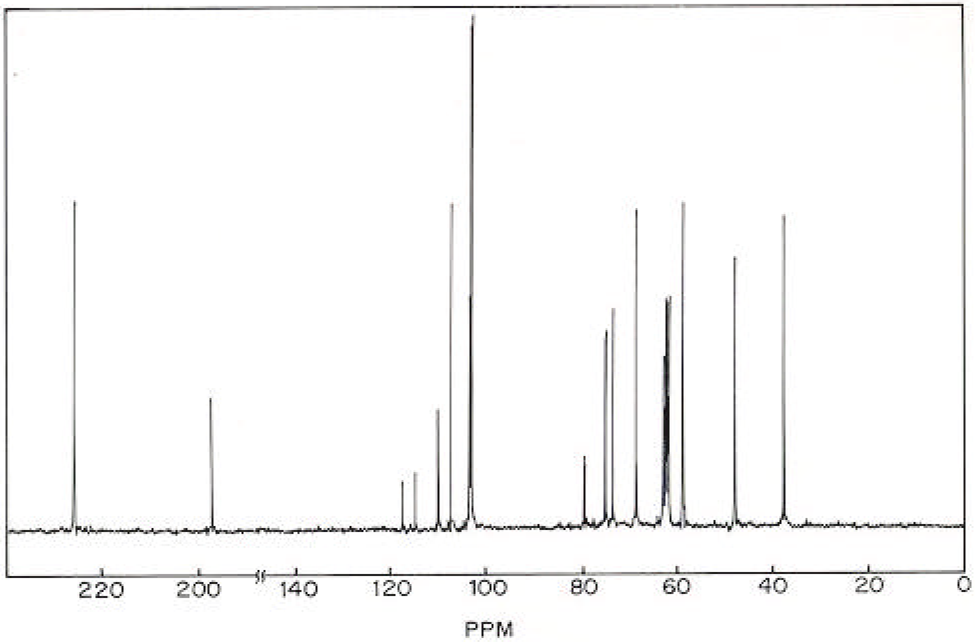

2a
Ph
O
OCH3
(CO)3Cr
CH3
H
8
7
6
5
4
3
2
1 PPM
0

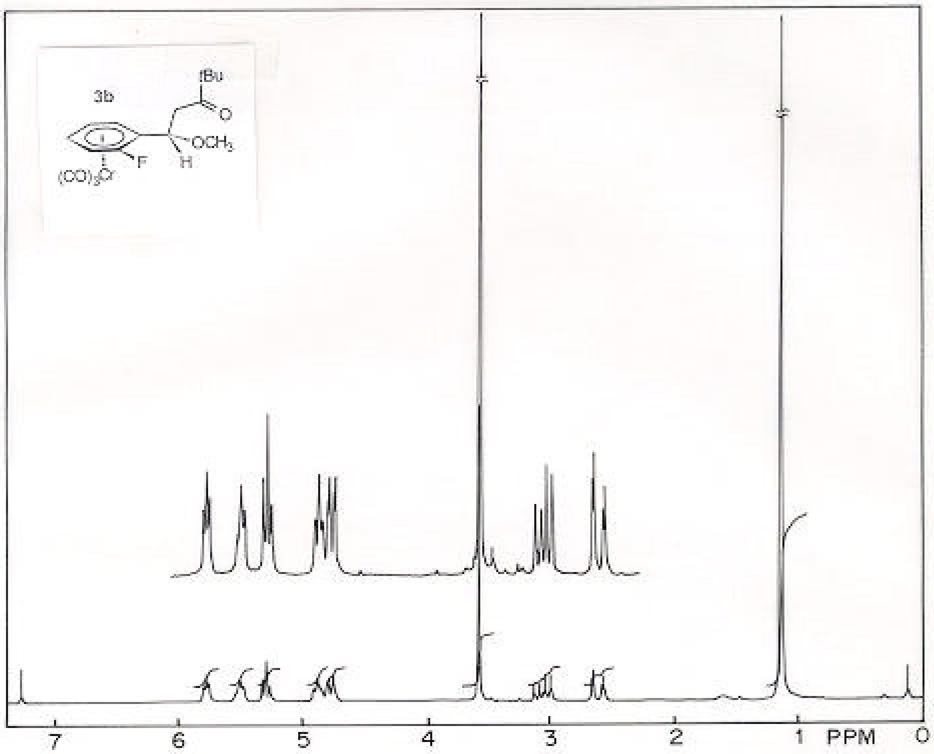

240
220
200
140
120
100
80
60
40
20
0
PPM

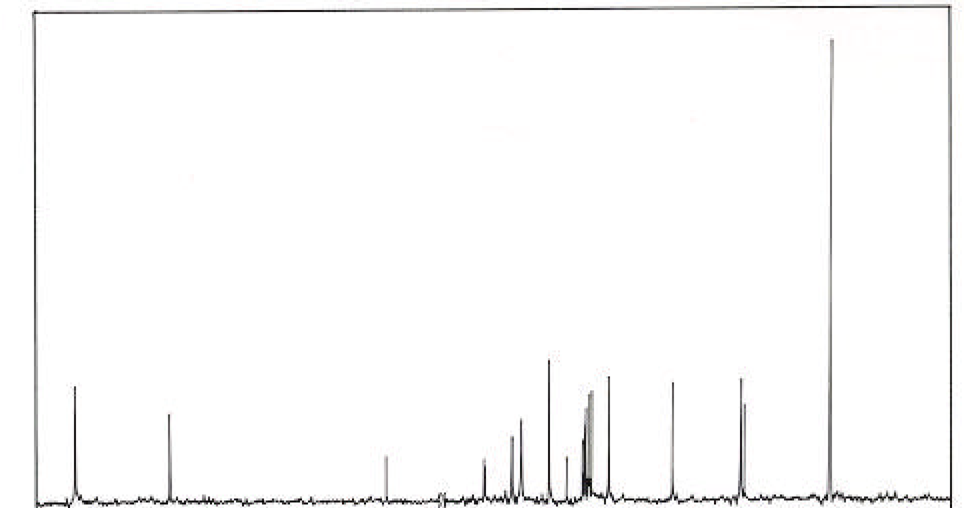

2c
CH3
O
OCH3
H
CH3
(CO)3Cr
7
6
5
4
3
2
PPM
1

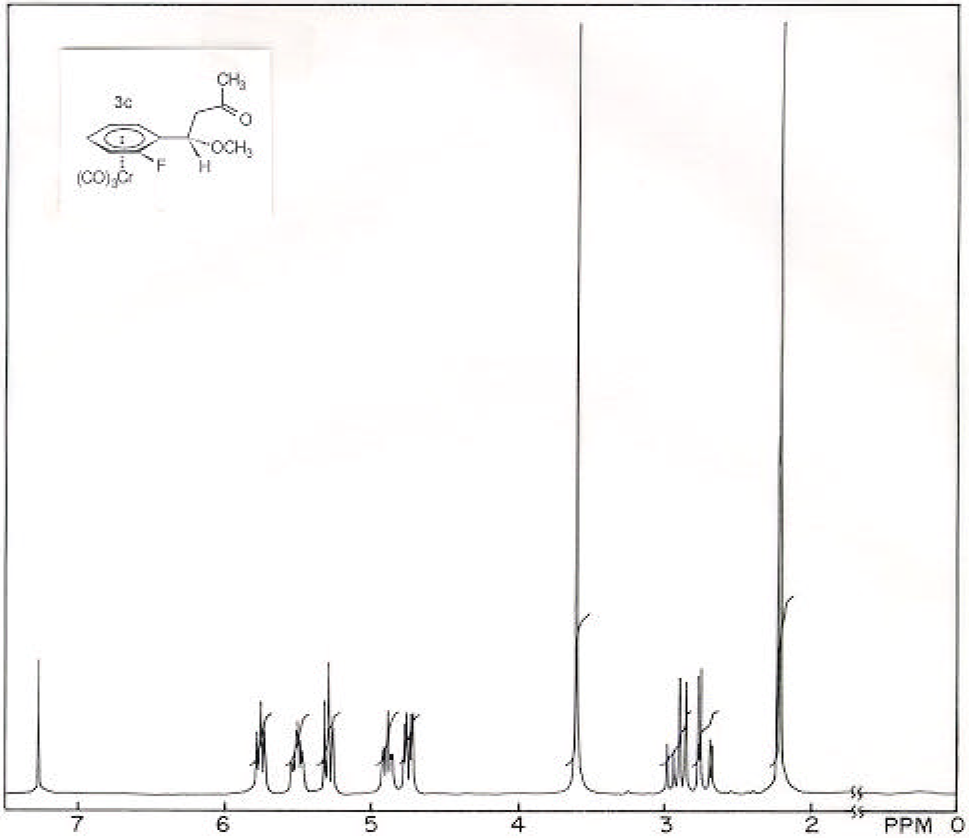

240
200
160
120
80
40
0
PPM

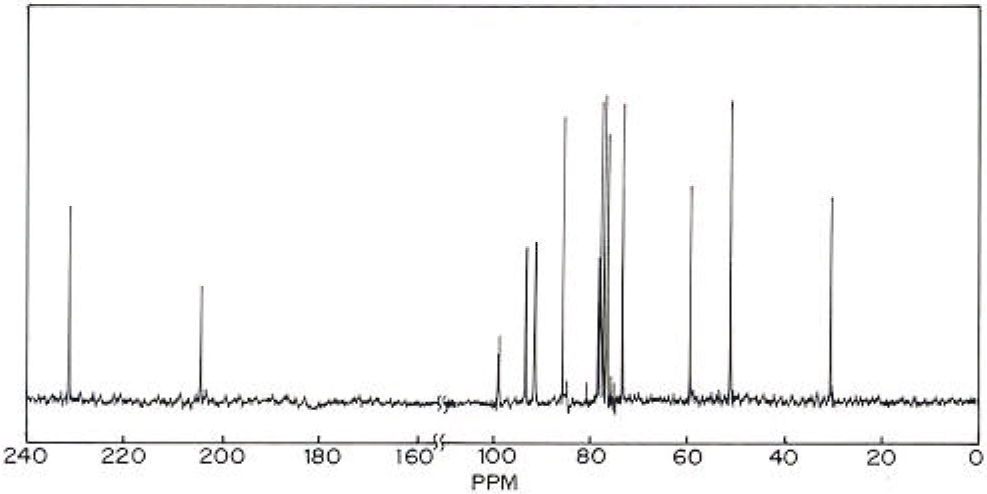

3a
Ph
O
OCH3
H
F
(CO)3Cr
8
7
6
5
4
3
2
1 PPM
0

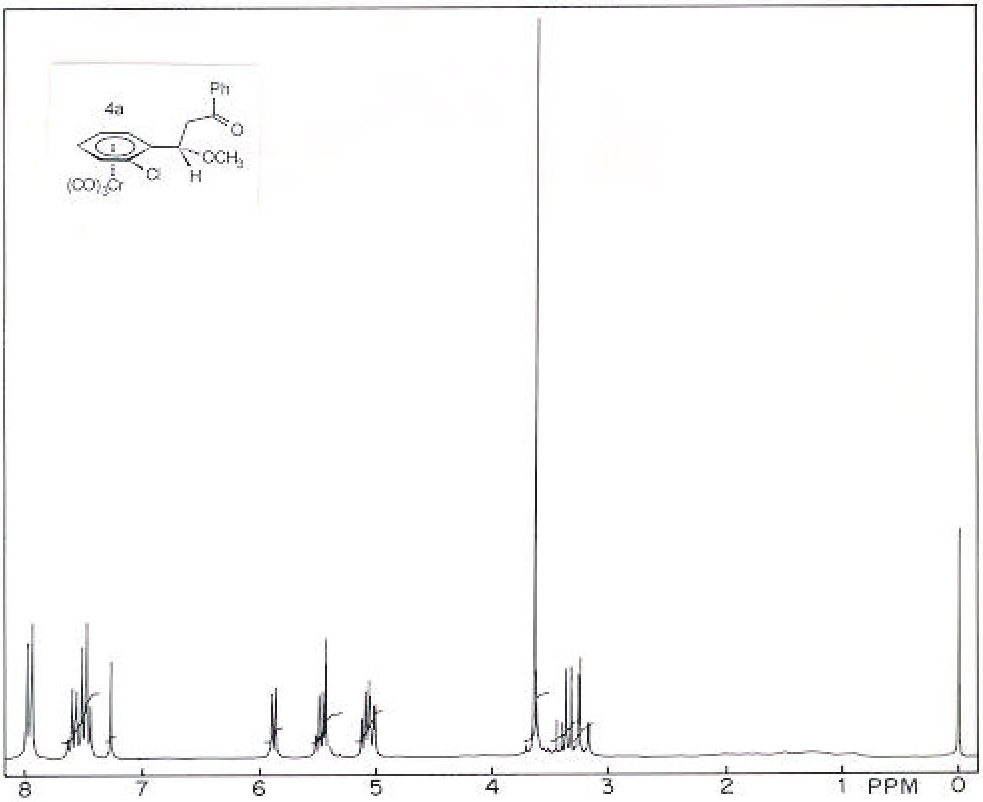

220
200
140
120
100
80
60
40
20
0
PPM

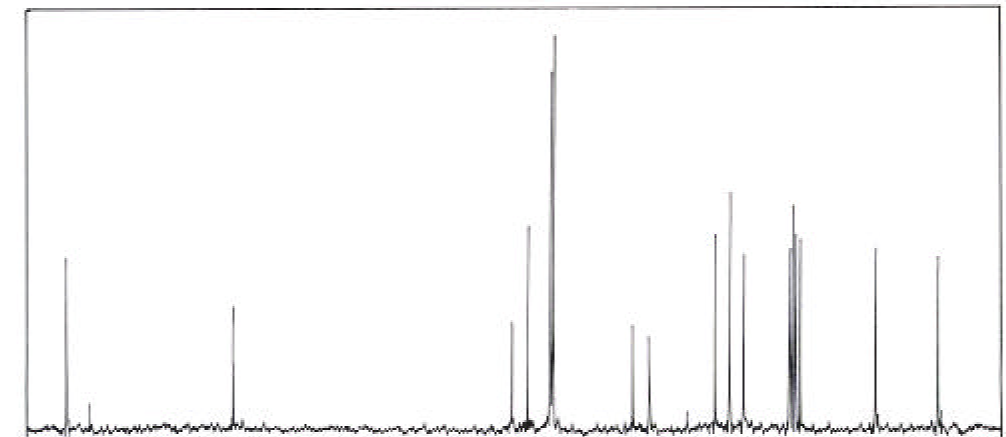

3b
tBu
O
OCH3
H
F
(CO)3Cr
7
6
5
4
3
2
1 PPM
0

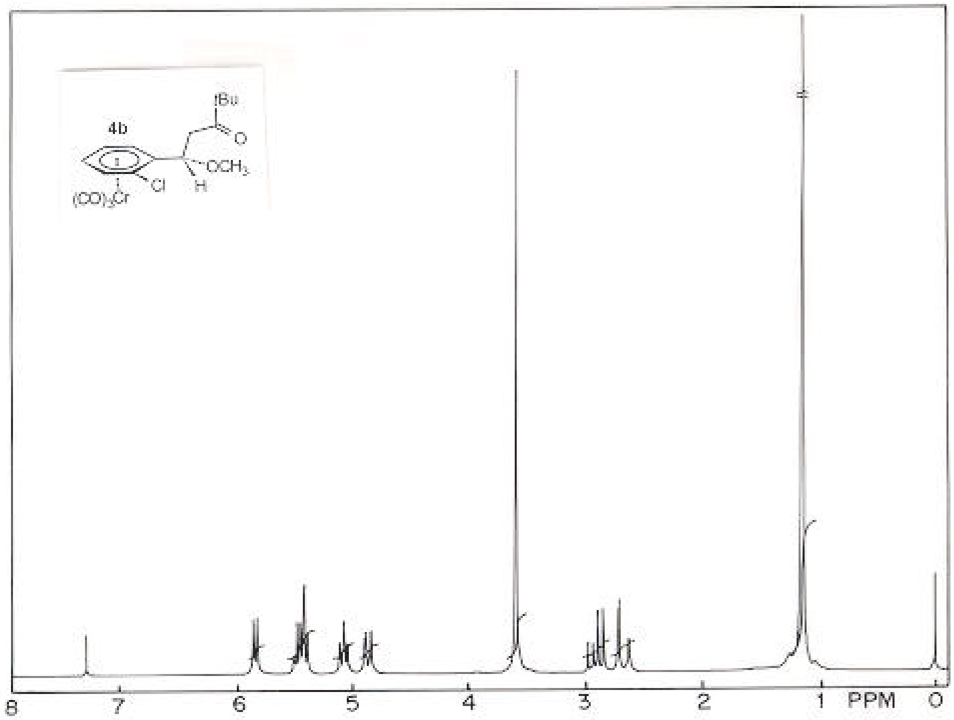

240
220
200
180
160
100
80
60
40
20
0
PPM

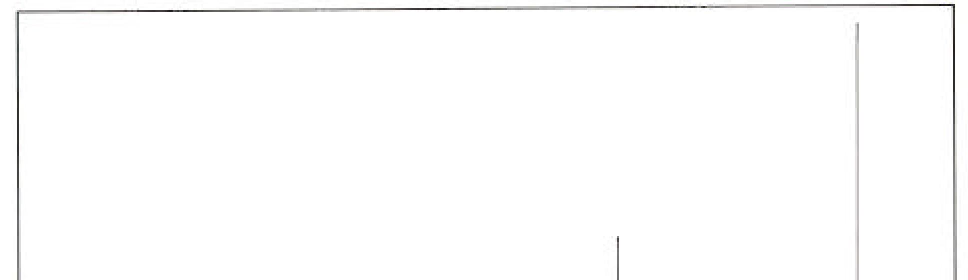

3c
CH3
O
OCH3
F
H
(CO)3Cr
7
6
5
4
3
2
PPM 0


240
220
200
180
160
100
80
60
40
20
0
PPM


4a
Ph
O
OCH$_3$
H
Cl
(CO)$_3$Cr
8
7
6
5
4
3
2
1
PPM
0

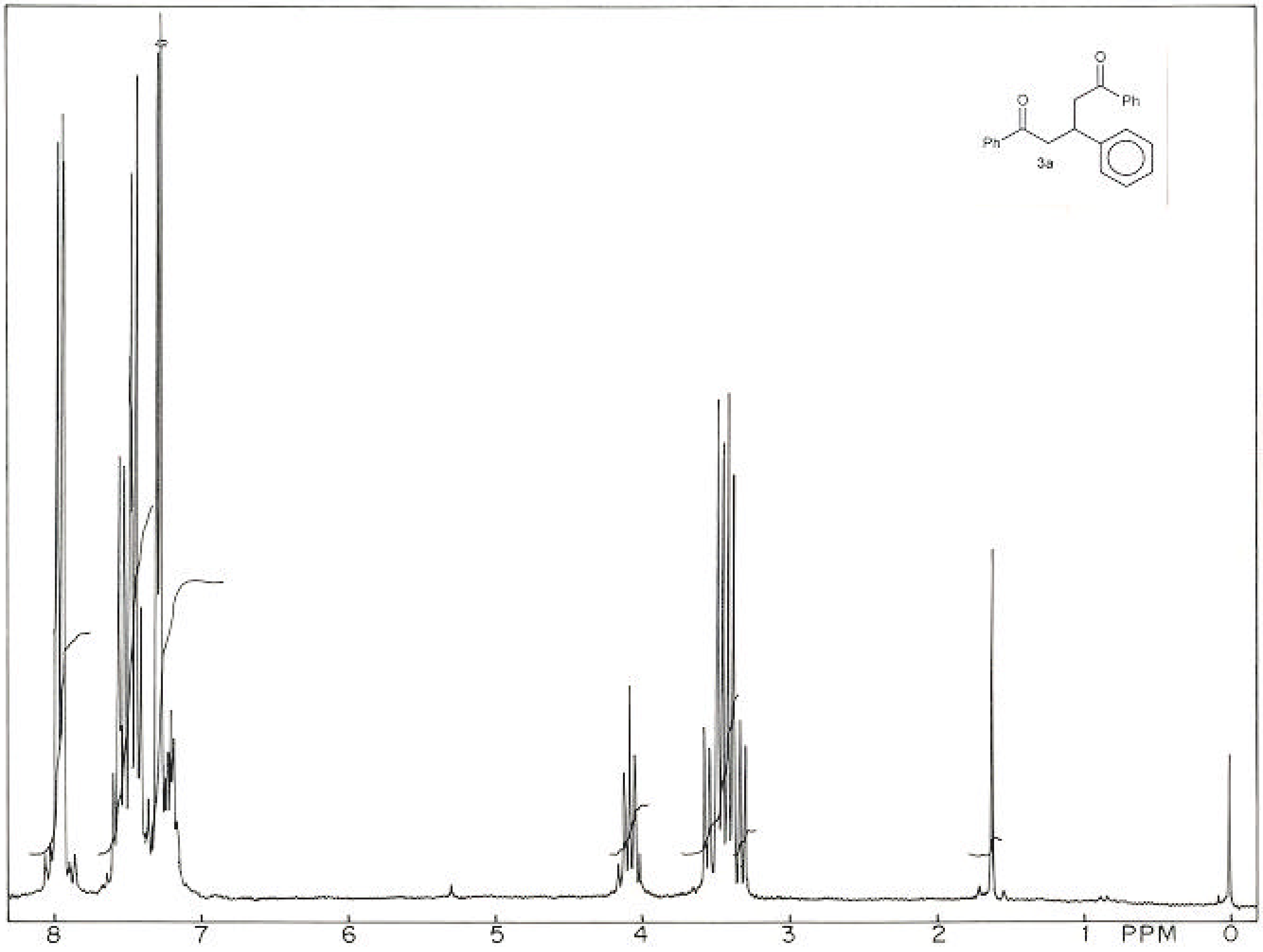

240
220
200
180
160
140
120
100
80
60
40
PPM

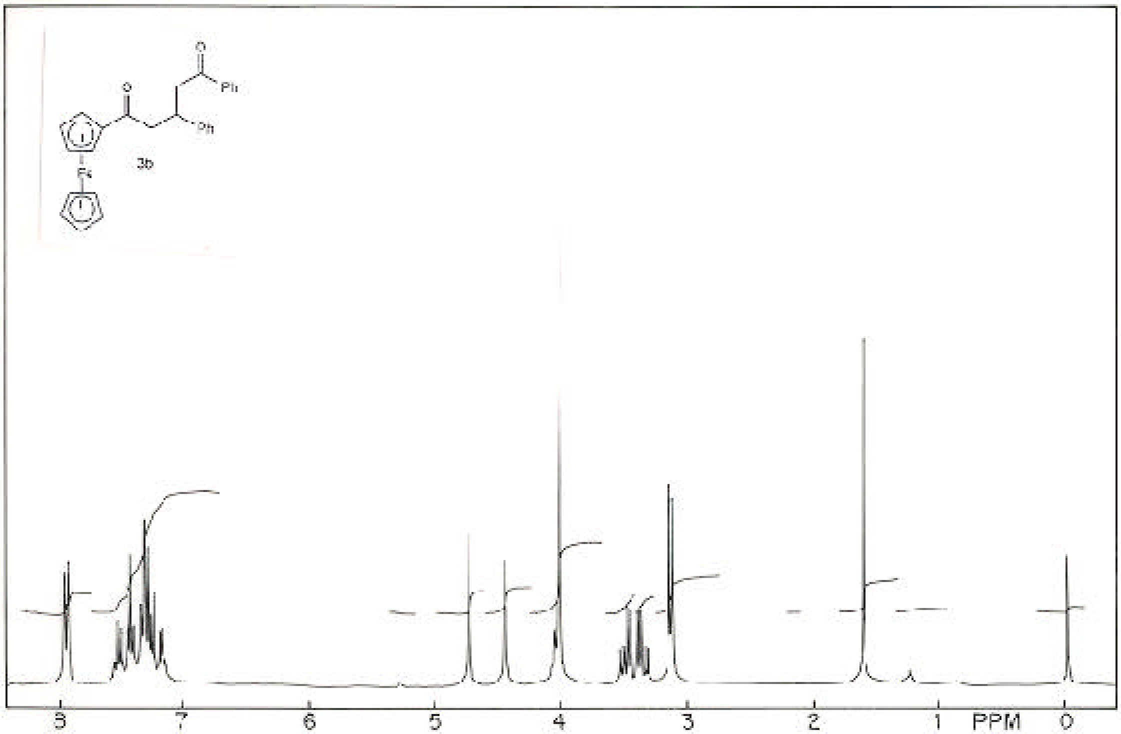

4b
tBu
O
OCH3
Cl
H
(CO)3Cr
8
7
6
5
4
3
2
1
PPM
0

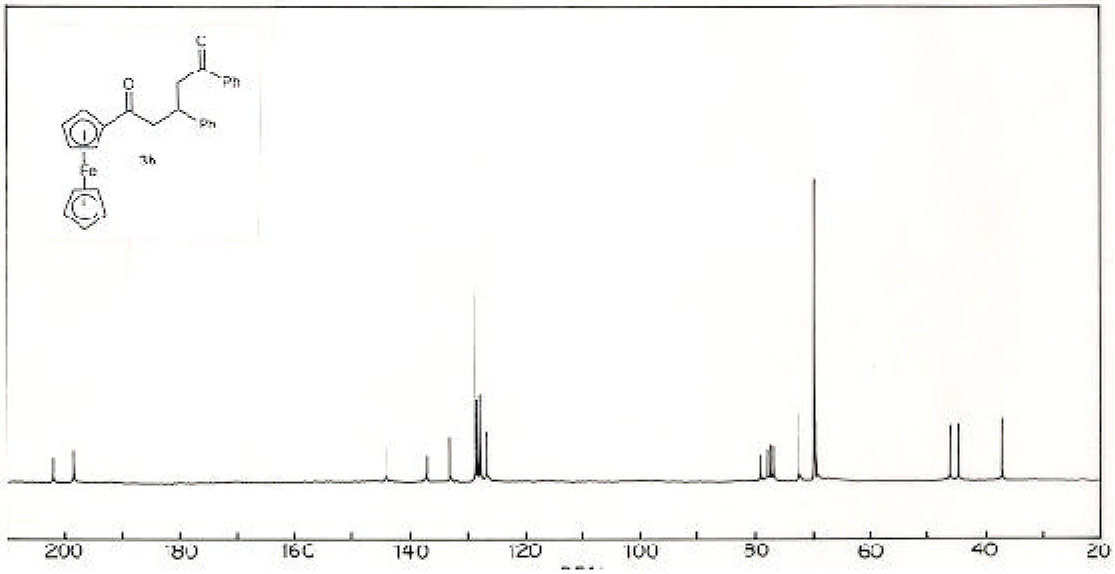

250
225
200
175
150
125
100
75
50
25
0
PPM

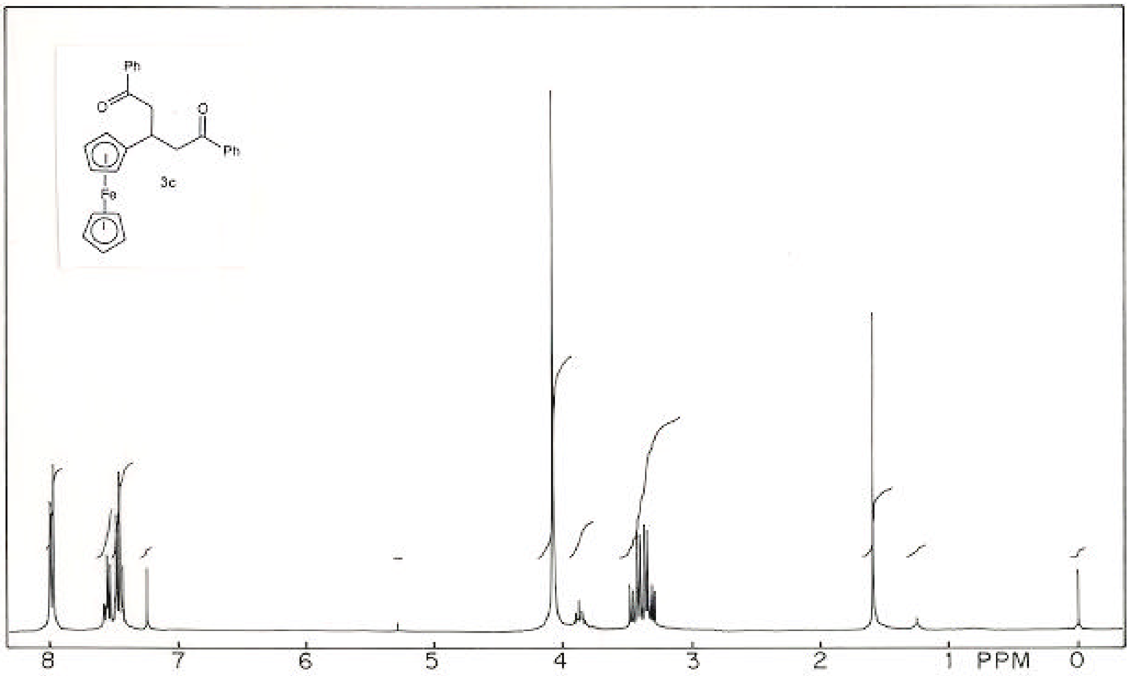
Appendix-III

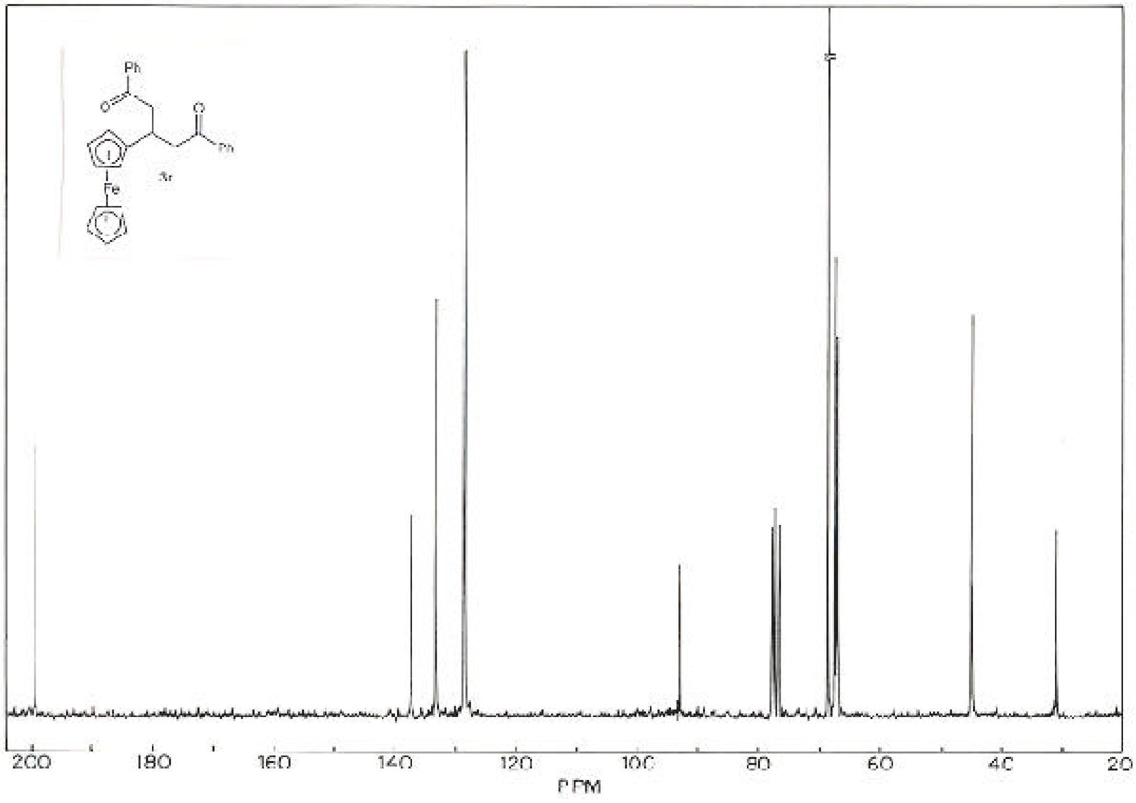
Spectra of compounds - Chapter III

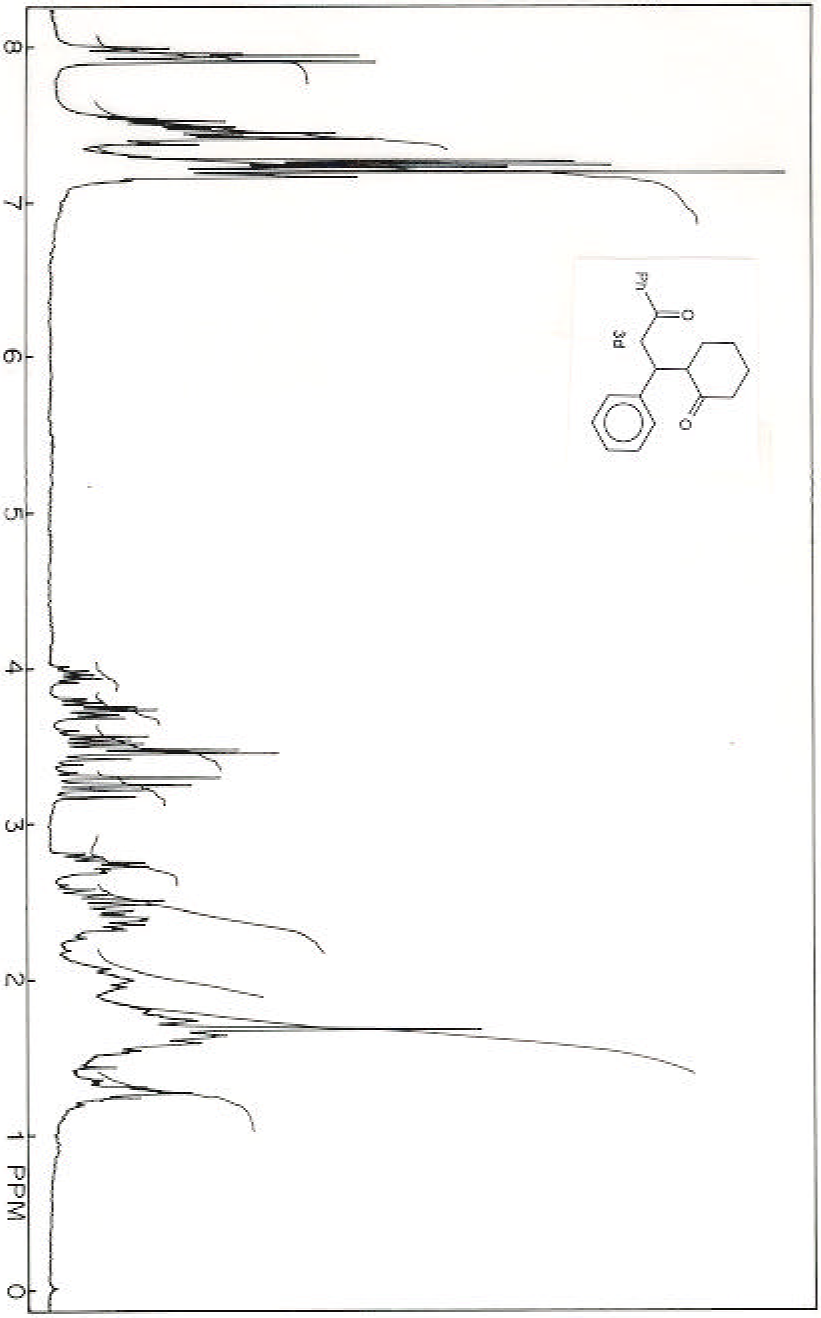

O
Ph
O
Ph
3a
8
7
6
5
4
3
2
1
PPM
0

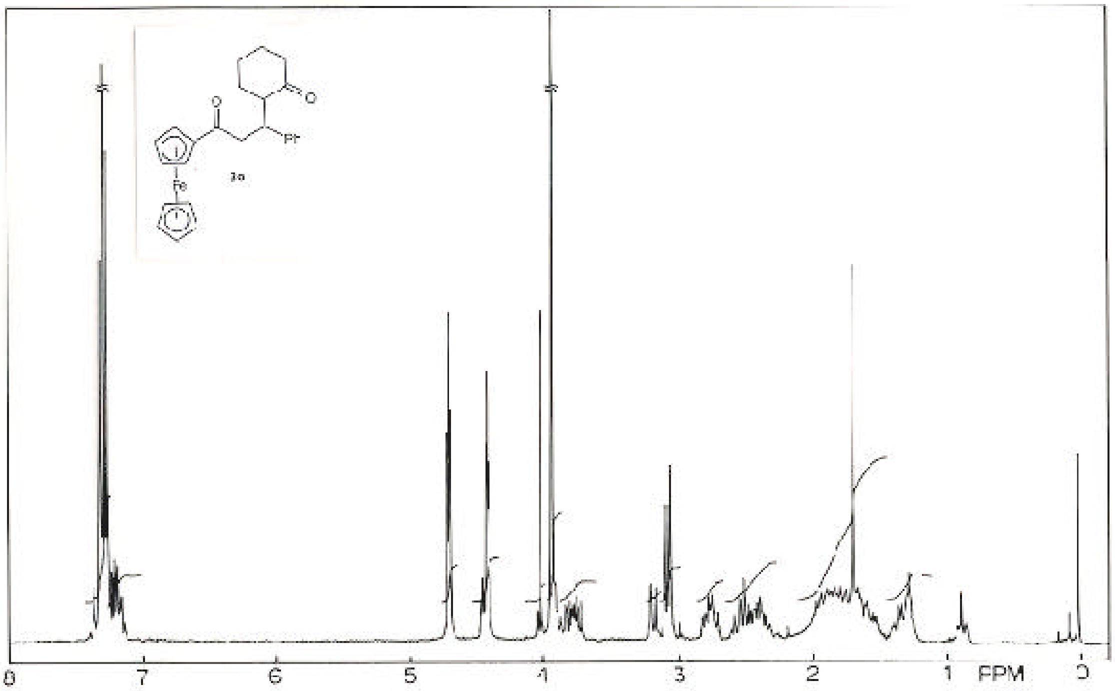

O
Ph
O
Ph
Fe
3b
8
7
6
5
4
3
2
1
PPM
0

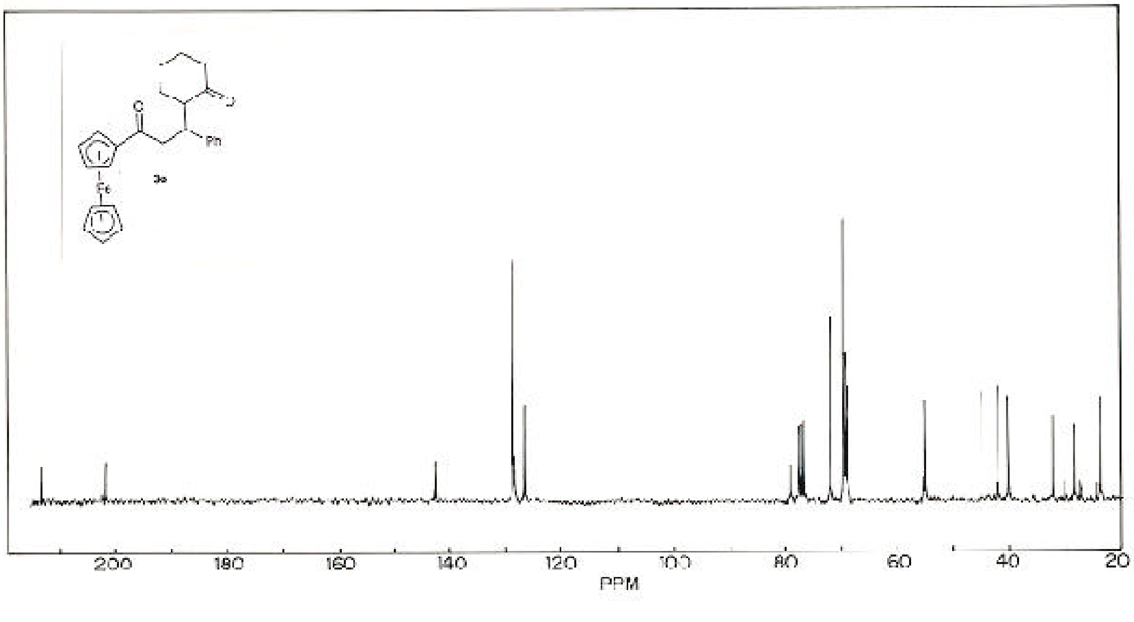

O
Ph
O
Ph
Fe
3b
200
180
160
140
120
100
80
60
40
20

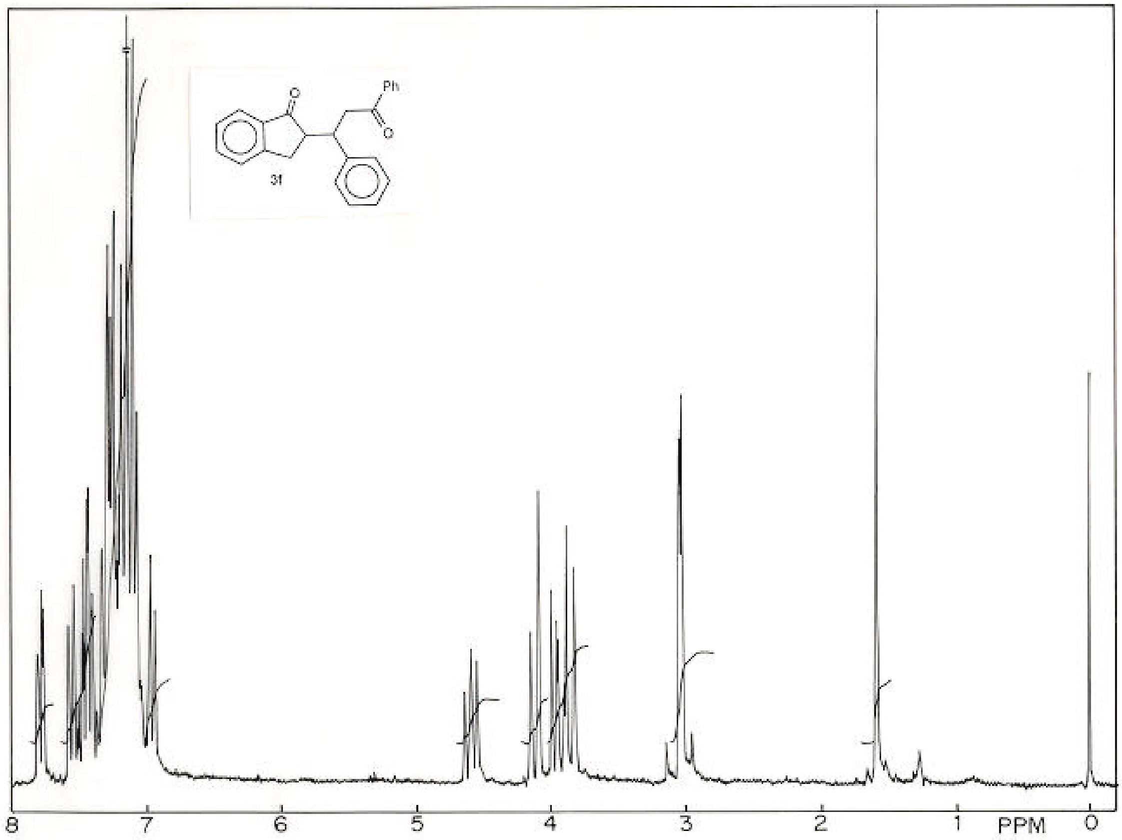

Ph
O
O
Ph
Fe
3c
8
7
6
5
4
3
2
1 PPM
0

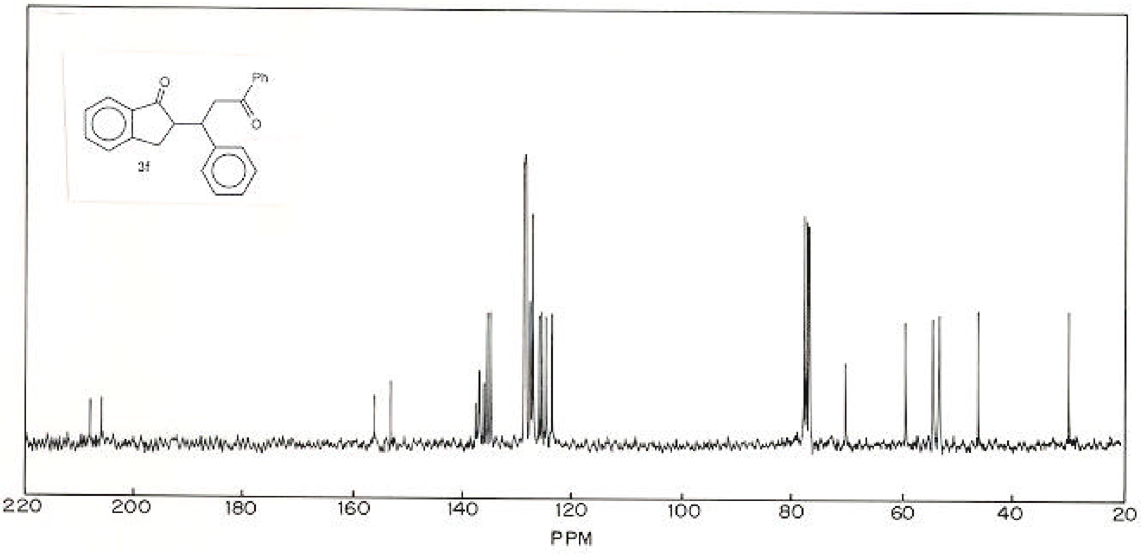

Ph
O
O
Ph
Fe
3c
200
180
160
140
120
100
80
60
40
20
PPM

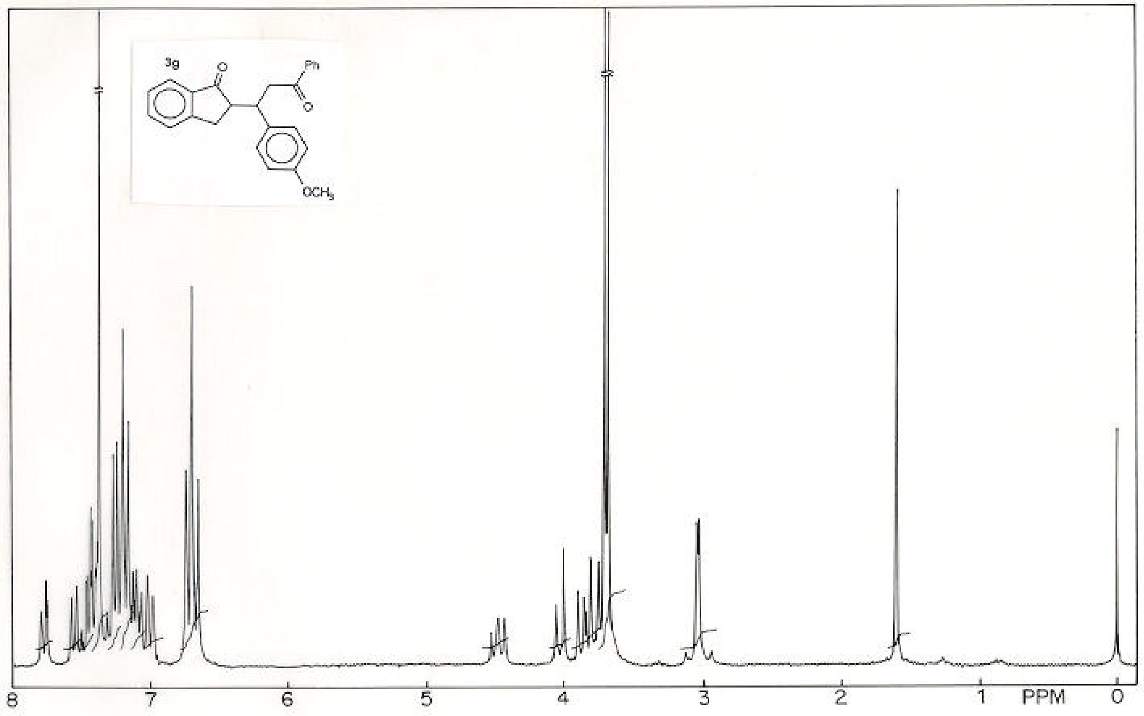

8
7
6
5
4
3
2
1 PPM
0
O
Ph
3d
O

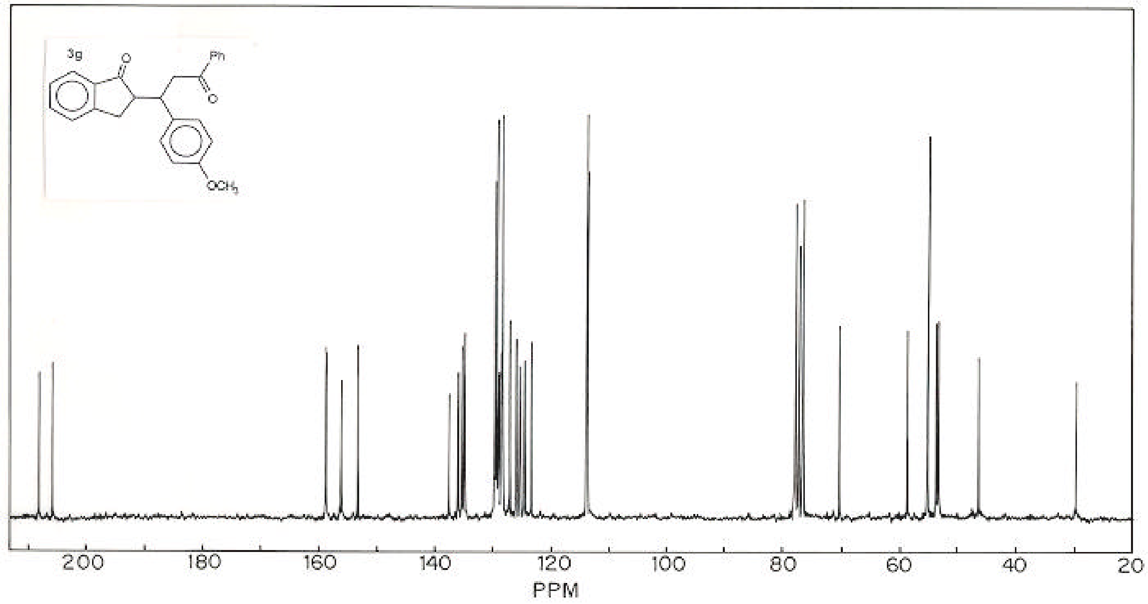

O
O
Ph
Fe
3o
8
7
6
5
4
3
2
1
PPM
0

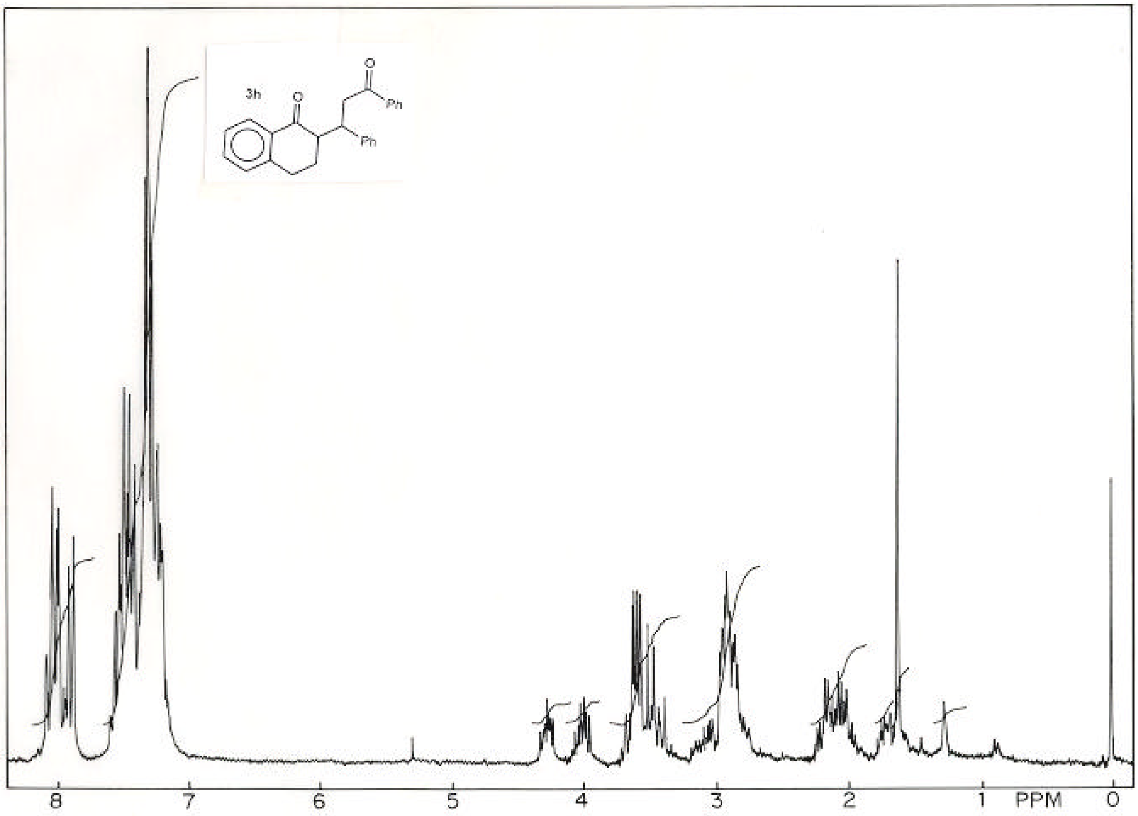

O
O
Ph
Fe
3o
200
180
160
140
120
100
80
60
40
20
PPM

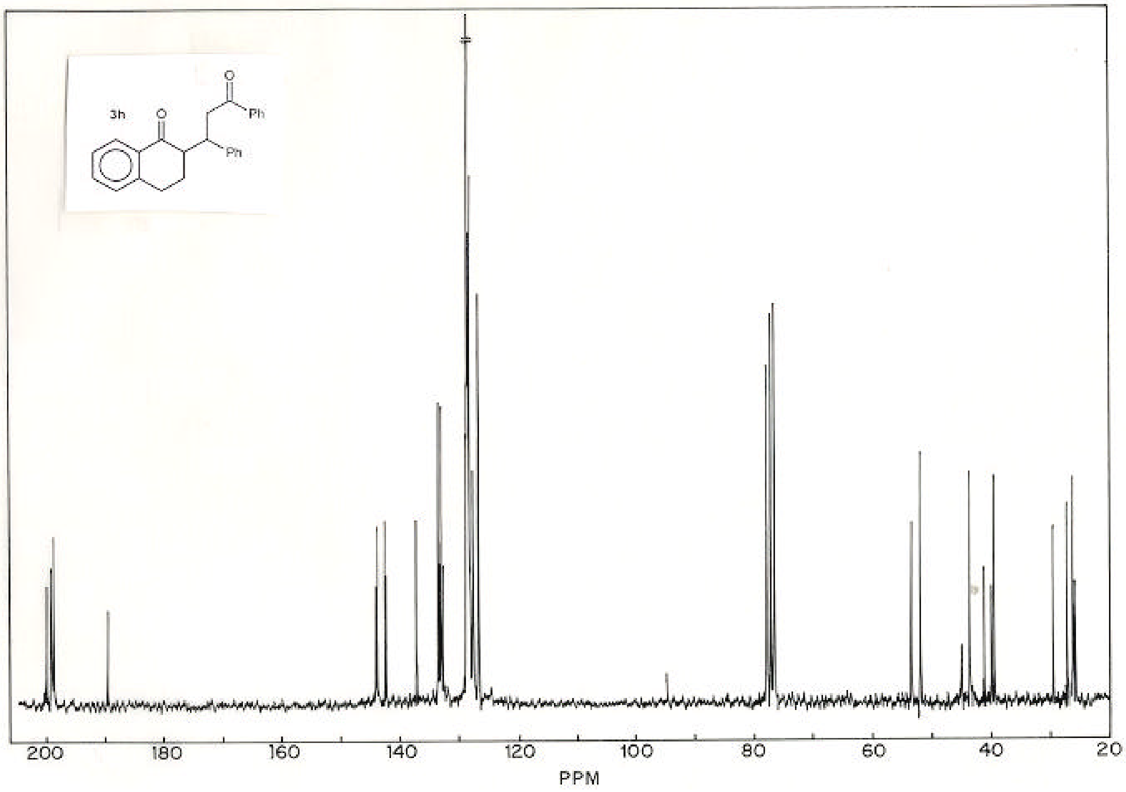

O
Ph
O
3f
8
7
6
5
4
3
2
1
PPM
0

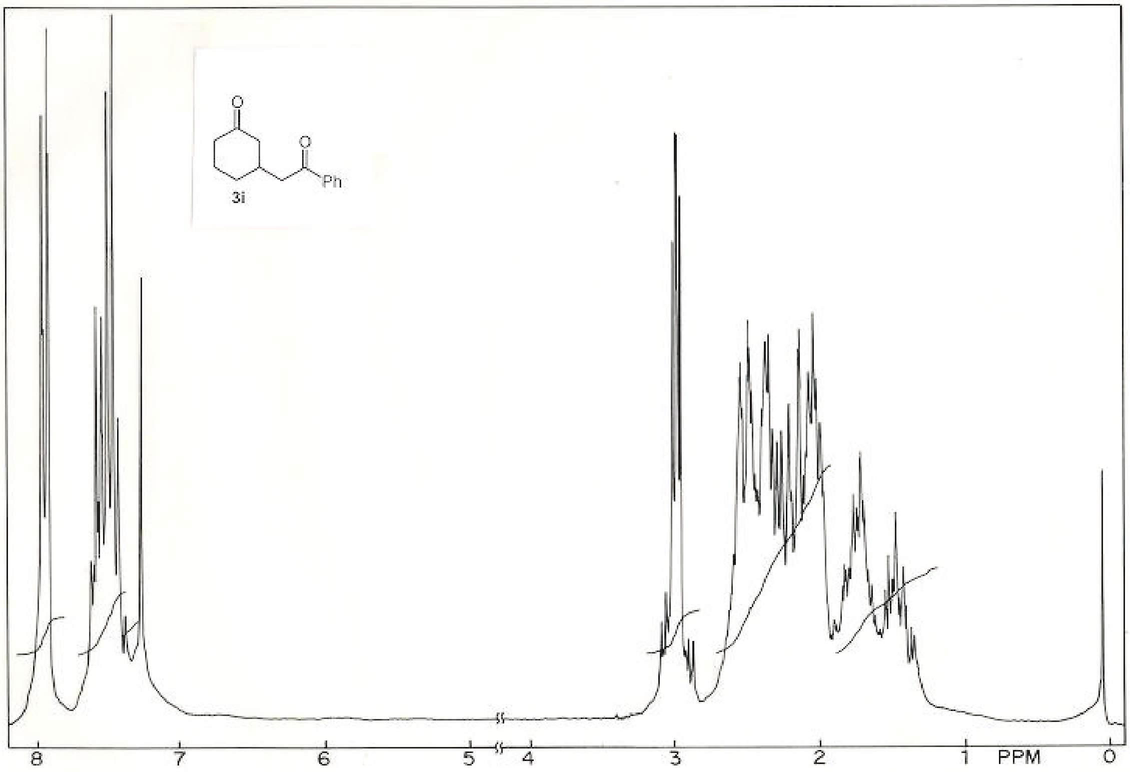

O
Ph
O
3f
220
200
180
160
140
120
100
80
60
40
20
PPM

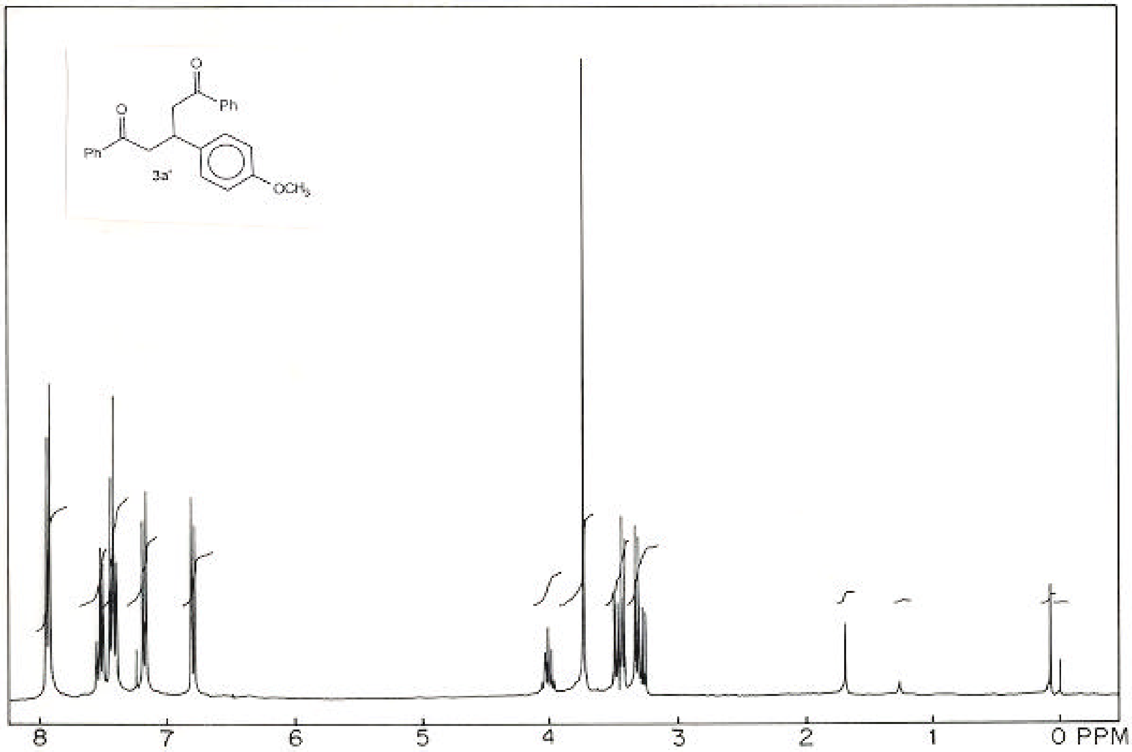

3g
O
Ph
O
OCH3
8
7
6
5
4
3
2
1
PPM
0

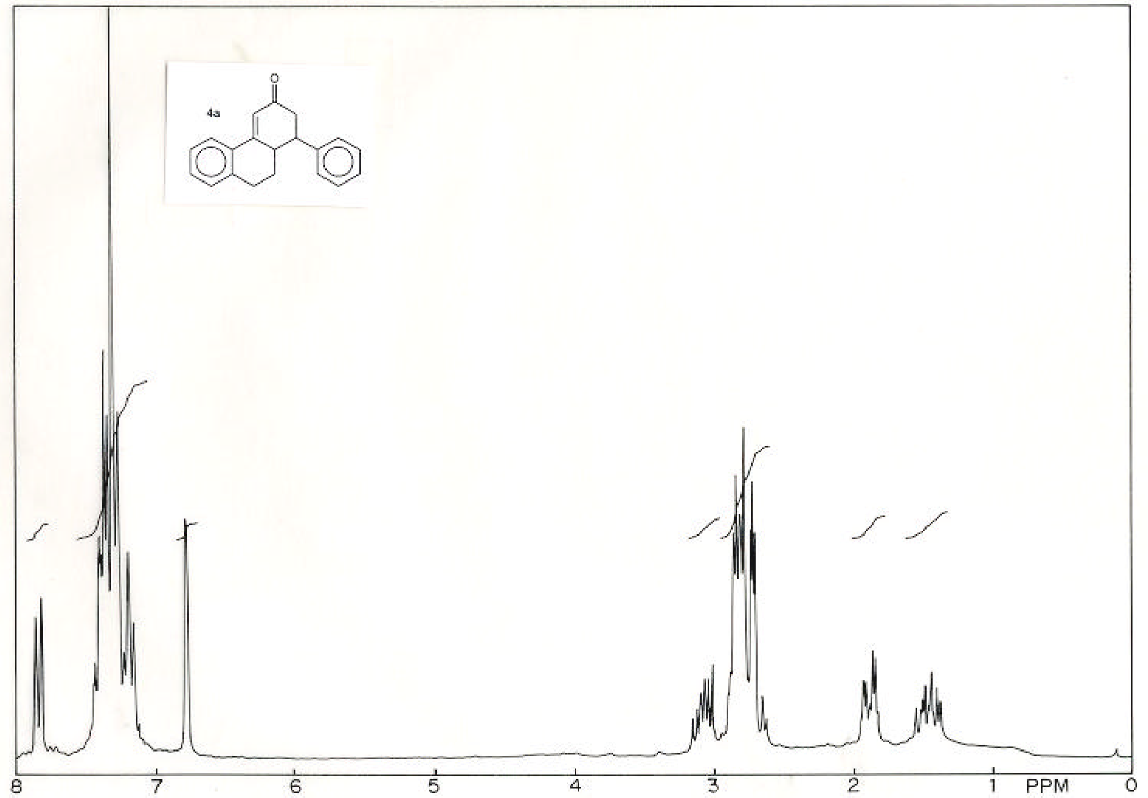

3g
O
Ph
O
OCH3
200
180
160
140
120
100
80
60
40
20
PPM

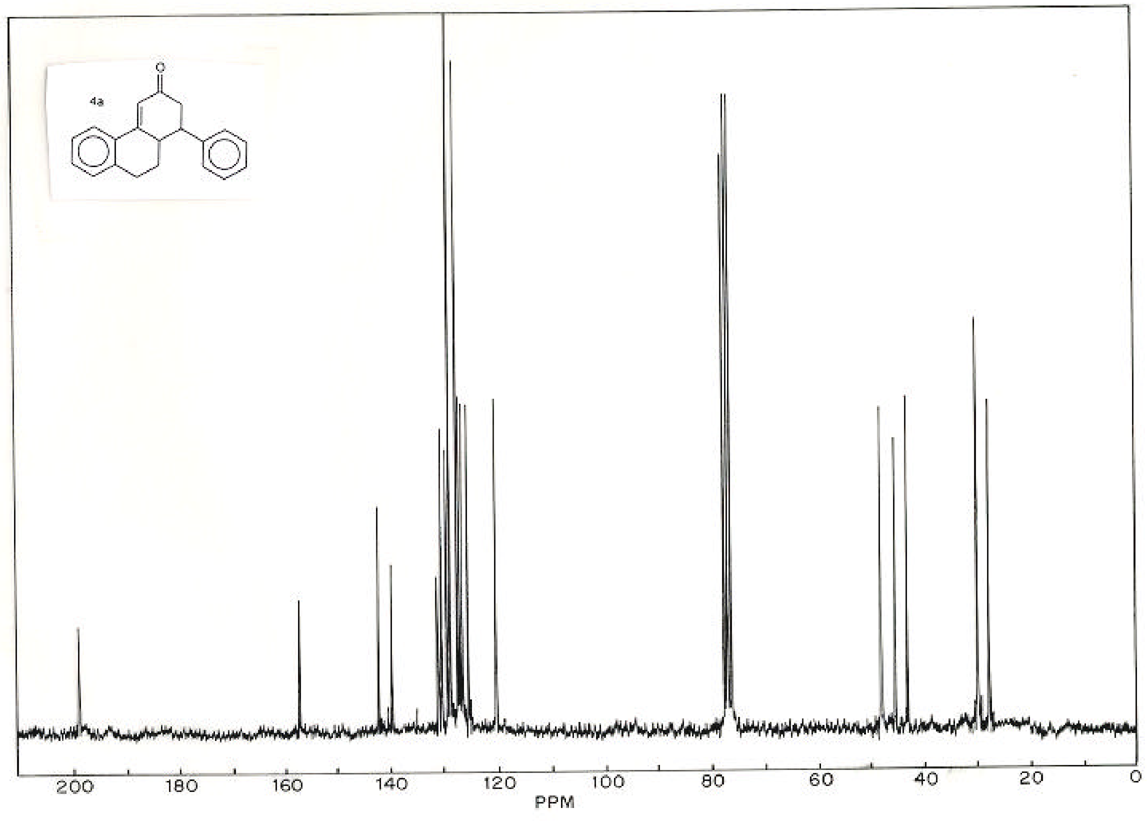

3h
O
O
Ph
Ph
8
7
6
5
4
3
2
1
PPM
0

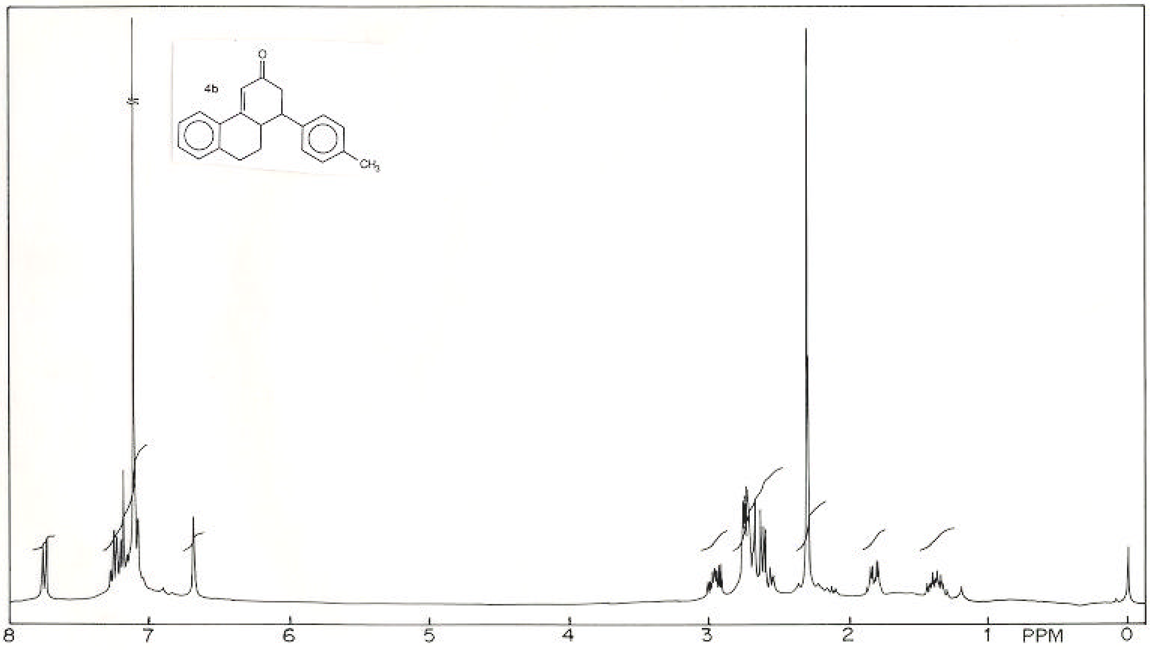

3h
O
O
Ph
Ph
200
180
160
140
120
100
80
60
40
20
PPM

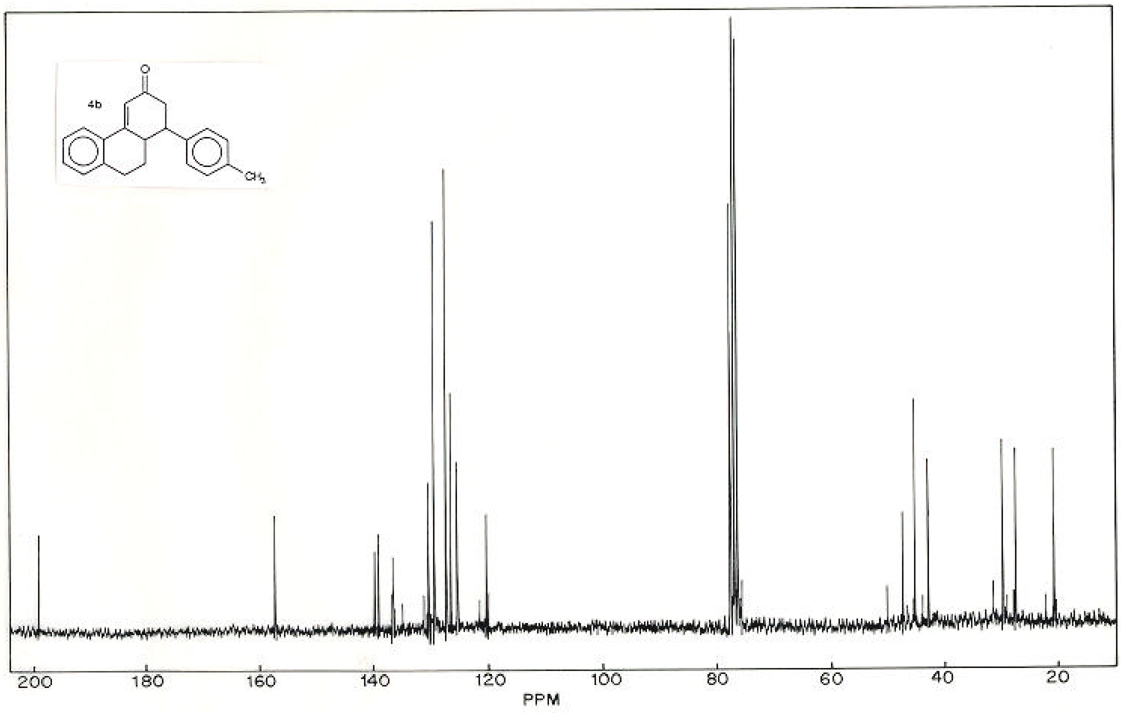

O
O
Ph
3i
8
7
6
5
4
3
2
1
PPM
0


O
Ph
O
Ph
3a'
OCH3
8
7
6
5
4
3
2
1
0 PPM


4a
O
8
7
6
5
4
3
2
1
PPM
0


4a
O
200
180
160
140
120
100
80
60
40
20
0
PPM


4b
O
CH3
8
7
6
5
4
3
2
1
PPM
0


4b
O
CH3
200
180
160
140
120
100
80
60
40
20
PPM