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Transformations of β-Dicarbonyl Compounds by Reactions of Their Transition Metal Complexes with Carbon and Oxygen Electrophiles

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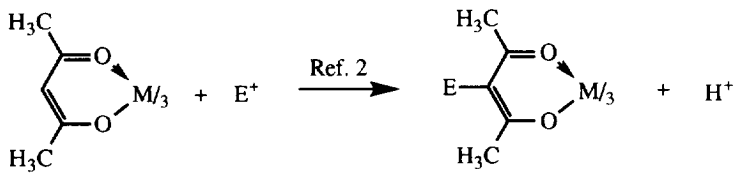
Contents

1.- INTRODUCTION

Transition metal complexes of β-dicarbonyl compounds have attracted the interest of both the organic and inorganic chemical communities.[1] However, whilst their interesting reactivity has been disseminated among organic and inorganic journals no systematic coverage in the form of a review has been attempted. In 1965 Collman published a review, mostly on his own work, emphasizing that transition metal complexes of pentane-2,4-dione (acetylacetone, acacH), mainly those of Rh(III), Co(III) and Cr(III), react with electrophiles (E^+) to afford complexes in which the central hydrogen atom of the ligands had been replaced by E (Scheme 1).[2] The range of electrophiles E was very broad, but only a few C-C bond forming reactions such as chloromethylations, acylations and Mannich-type reactions, were included. A feature of the reactions described by Collman is that the complex was not broken down during the reaction. In this sense the Collman reactions were reminiscent of the well known electrophilic substitutions on aromatic rings. This could lead one to believe that the rings present in transition metal complexes of β-dicarbonyl compounds are aromatic. However, their NMR behaviour[3] did not support this view.



E = I, Br, Cl, SCN, SAr, SCl, NO_2, CH_2Cl, CH_2NMe_2, COR, CHO
M = Rh, Co, Cr

SCHEME 1

Transition metal complexes of β-dicarbonyl compounds and their solutions are neutral according to the Brønsted definition, and their solubility in organic solvents is also high or significant. The parent β-dicarbonyl compounds are very reactive species in alkylations, acylations, Michael additions, Knoevenagel condensations and related reactions. However, a stoichiometric amount of base is required for alkylations and acylations and base catalysis is required for Michael additions and Knoevenagel condensations. This imposes some limitations since starting materials or final products sensitive to basic media can not be used in these very important synthetic methods.[4,5] Fortunately, transition metal complexes of β-dicarbonyl compounds react with carbon

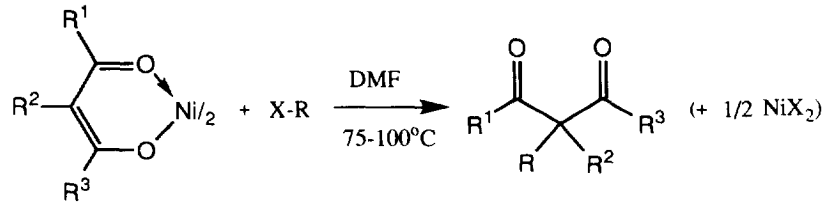
electrophiles, which provides essentially neutral reaction media compatible with a vast array of reagents and final products. Also, complexes of transition metals with an odd number of electrons, facilitates radical pathways which permit alkylation with alkyl halides that are inert under non-radical conditions. These aspects of the use of transition metal complexes of β-dicarbonyl compounds in synthetic organic methodology will be covered in the present report. It is the opinion of the authors that important advances in this field are waiting to be uncovered by the imagination of researchers.

2.- ALKYLATION

2.1.- *Stoichiometric Version. The Use of Ni, Co, Cu, and Zn Complexes. Preparation of Severely Hindered β-Diketones.*

The Ni(II) complexes, **1**, of acetylacetone and other β-dicarbonyl compounds react with alkyl halides in hot DMF to afford C-alkylation products **2** (Table 1). Allylic (Runs 9-11), benzylic (Runs 1-6), propargylic (Run 14) and α-carbonylic (Runs 12-13) halides were active. This includes halides very sensitive to basic media such as chloroacetone (Run 13). Other alkyl halides gave less interesting results.

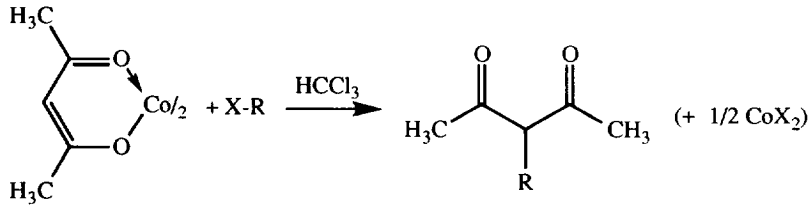
Table 1.- Reactions of Ni(II) complexes of β-Dicarbonyl Compounds with Alkyl Halides.



1 **2**

Run	R^1	R^2	R^3	1	R-X	% 2	Ref.
1	Me	H	Me	**1a**	$PhCH_2Br$	69	6,7
2	Me	H	Me	**1a**	$PhCH_2Cl$	32	6,7
3	Me	H	Me	**1a**	$4\text{-}O_2NPhCH_2Cl$	18	7
4	Me	Me	Me	**1b**	$PhCH_2Br$	17	7
5	Me	H	OMe	**1c**	$PhCH_2Br$	35	7
6	Me	H	Ph	**1d**	$PhCH_2Br$	61	7
7	Ph	H	Ph	**1e**	$PhCH_2Br$	-	7
8	Me	H	Me	**1a**	PhCH(Me)Br	3	7
9	Me	H	Me	**1a**	$MeOCOCH{=}CHCH_2Br$	65	6,7
10	Me	H	Me	**1a**	$MeOCOCH{=}C(Me)CH_2Br$	54	7
11	Me	H	Me	**1a**	$(MeCOO)_2CH{=}CHCH_2Br$	53	7,8
12	Me	H	Me	**1a**	$MeOCOCH_2Br$	53	6,7
13	Me	H	Me	**1a**	$MeCOCH_2Cl$	30	6,7
14	Me	H	Me	**1a**	$HC{\equiv}CCH_2Br$	22	7
15	Me	H	Me	**1a**	$n\text{-}C_3H_7I$	8	6,7
16	Me	H	Me	**1a**	$n\text{-}C_4H_9Br$	17	6,7
17	Me	H	Me	**1a**	$n\text{-}C_8H_{17}Br$	8	7
18	Me	H	Me	**1a**	$n\text{-}C_{16}H_{33}Br$	4	7
19	Me	H	Me	**1a**	Me_2CHBr	-	7

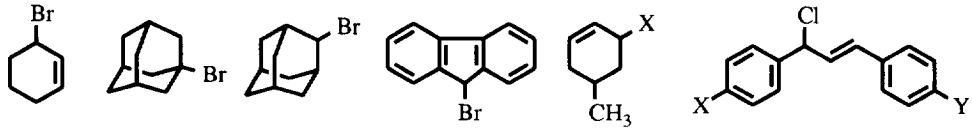
Table 2.- Reactions of $Co(acac)_2$, **3a**, with Alkyl Halides.



3a **2**

Run	R-X	Conditions	% 2	Ref.
1	$PhCH_2Br$	Reflux	53	8
2	$PhCH_2Br$	a	89	11
3	4-$MeOPhCH_2Br$	Reflux	88	9
4	4-$MeOPhCH_2Br$	a	87	11
5	4-O_2NPhCH_2Br	Reflux	6	9
6	4-O_2NPhCH_2Br	a	72	11
7	4-O_2NPhCH_2Cl	a	-	11
8	Ph_2CHBr	Reflux	97	8
9	Ph_3CCl	Reflux	29	8
10	PhCH(Me)Br	Reflux	94	8
11	PhCH(Me)Br	a	65	11
12	$PhC(Me)_2Br$	Room temp	14	8
13	$Me_2C=CCH_2Cl$	Reflux	76	8
14	$Me_2C=CCH_2Br$	a	87	11
15	$(MeCOO)_2CHCH=CHCH_2Br$	90°C	8	8
16	3-Bromocyclohexene, **4**	100°C	75	14
17	MeCH(Br)CH=CHMe	100°C	58	14
18	1-Bromoadamantane, **5**	b	81	9,10
19	1-Bromoadamantane, **5**	a	68	11
20	2-Bromoadamantane, **6**	c	21	14
21	Me_3CBr	Reflux	4	8
22	Me_3Cl	100°C	15	14
23	9-Bromofluorene, **7**	Reflux	d	12
24	**8**[e]	80°C	90[f]	19
25	**9**[g]	120°C	71[h]	19
26	**10**[i]	100°C	88[j]	19

[a] A solution in chloroform was driven to dryness at 120°C; [b] In refluxing chlorobenzene; [c] In 1,1,2,2-tetrachloroethane at 185°C; [d] Not disclosed;[e] *cis/trans* = 25:75; [f] *cis/trans* = 15:85; [g] *cis/trans* = 46:54; [h] *cis/trans* = 18:82;[i] **10a/10b** = 40:60; [j] **a/b** = 56:44



4 **5** **6** **7** **8**, X= Br; **9**, X= Cl **10a**, X= Cl, Y= NO_2; **10b**, X= NO_2, Y= Cl

$Co(Acac)_2$, **3a**, reacts with a broad selection of alkyl halides in chloroform at refluxing or higher temperature to give 3-alkylpentane-2,4-diones, **2** (Table 2).[8-12,14,19] Several benzylic (Runs 1-12), and allylic (Runs 13-17, 24-26) halides gave very good results. Several points are remarkable:

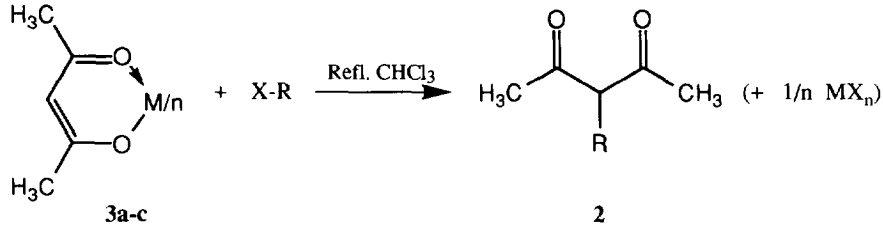
1.- Benzyl bromides featuring electron-withdrawing and electron-donating substituents are good substrates (Runs 1-12). The success with 4-nitrobenzyl bromide depends on the reaction conditions (Runs 5 and 6); higher temperatures and higher concentrations trigger a radical-initiated chain organometallic mechanism which broadens the scope of the method.[11,18,19]

2.- Alkyl halides that easily undergo dehydrohalogenation such as 1-bromo-1-phenylethane (Run 11), 2-bromo-2-phenylpropane (Run 12) and t-butyl iodide (Run 22) give from moderate to very good results.

3.- Complex **3a** is alkylated by inert halides such 1-bromoadamantane, **5**, (Runs 18, 19), 2-bromoadamantane, **6**, (Run 20) and 9-bromofluorene, **7**, (Run 23) under the forcing conditions needed for the radical-initiated mechanism to operate.

The similar reactivity of $Co(acac)_2$, **3a**, $Co(acac)_3$, **3b**, and $Zn(acac)_2$, **3c**, towards several alkyl halides is summarized in Table 3. Co(III) and Zn(II) are d^6 and d^{10} species, prone to react through non-radical mechanisms. Therefore, it was concluded that Co(II), a d^7 species, reacts in refluxing chloroform and at concentrations below ca. 0.5M by non-radical initiated mechanisms.

Table 3.- Yields of Products **2** Using Different Metal Complexes, **3a-c**



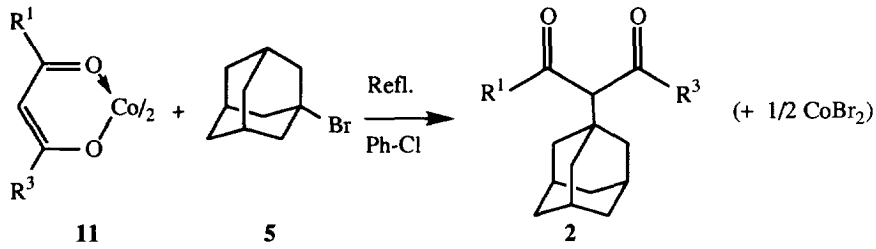
3a-c **2**

Run	R-X	$Co(acac)_2$ (3a)	$Co(acac)_3$ (3b)	$Zn(acac)_2$ (3c)	Ref.
1	$PhCH_2Br$	53	59	65	8,9
2	$4\text{-}MeOPhCH_2Br$	88	77	a	9
3	$4\text{-}O_2NPhCH_2Br$	6	0	0	9
4	Ph_2CHBr	97	96	87	9
5	Ph_3CCl	29	a	18	8,9
6	PhCH(Me)Br	75	58	61	9
7	1-Bromoadamantane, **5**	81[b]	a	75[b]	9,10

[a] Not performed; [b] In refluxing chlorobenzene

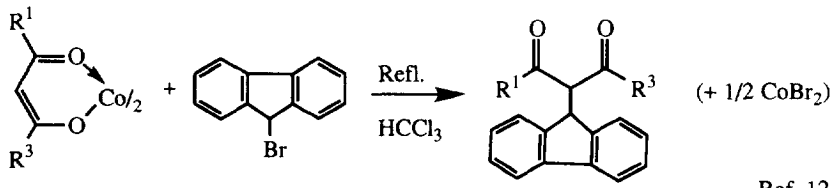
The extension of the Co(II)-based alkylation method to the complexes **11** of several diketones is described in Table 4 and in Scheme 2. Thus, alkylations with 1-bromoadamantane, **5**, (Table 4) and with 9-bromofluorene, **7**, (Scheme 2) gave excellent results despite of the final product **2** being, in some cases, sterically hindered.

Table 4.- Reactions of Co(II) Complexes of β-Dicarbonyl Compounds with 1-Bromoadamantane, **5**.



11 **5** **2**

Run	R^1	R^3	11	Yield(%)	Ref.
1	Me	Me	**11a=3a**	81	9,10
2	Me	Ph	**11b**	89	9,10
3	Ph	Ph	**11c**	80	9,10
4	t-Bu	t-Bu	**11d**	31	10
5	Me	OEt	**11e**	38	9,10



11b: R^1= Me; R^3= Ph

11f: R^1= Me; R^3= t-Bu

7

2

R^1= Me; R^3= Ph

R^1=Me; R^3=t-Bu

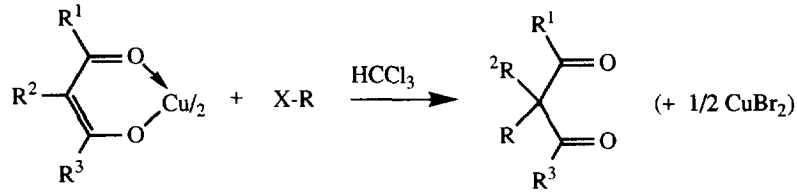
Ref. 12

SCHEME 2

Copper(II) complexes of β-diketones are also excellent alkylation substrates (Table 5) towards benzylic (Runs 1,2,8,9,14), allylic (Runs 3,4,10), and other (Runs 5-7,11-14) halides. Cu(II) is a d^9 species and reacts in general by radical-initiated mechanisms. All but two runs (13 and 14) of Table 5 contain examples in which the central position of the complex is substituted (R^2 = Me or Et). Indeed Cu(II) complexes are very useful to prepare severely hindered β-diketones such as those of Scheme 3 containing the 1-adamantyl radical. It should be noted that two of them feature two consecutive quaternary centers. Copper(II) bromide, the other product of the reaction is itself a brominating agent for activated positions such as intercarbonylic methine groups (Scheme 4). This imposes a limitation when using complexes **12** (R^2 = H) which does not exist for the Co(II) complexes since cobalt(II) halides are not halogenating agents.

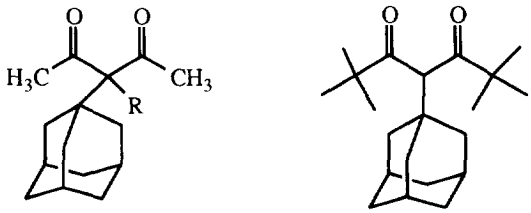
Apart from the contribution of our group, early attempts to use Cu(II) complexes for alkylation reactions were not very successful and required the presence of base,[20] probably to prevent the detrimental effect of the HX formed according to Scheme 4.

Table 5.- Reactions of Cu(II) Complexes of β-Dicarbonyl Compounds with Alkyl Halides.



12a-e **2**

Run	R^1	R^2	R^3	12	X-R	Conditions	% 2	Ref.
1	Me	Me	Me	**12a**	$BrCH_2Ph$	100-115°C	80	13,15
2	Me	Me	Me	**12a**	$BrCHPh_2$	100-115°C	44	13,15
3	Me	Me	Me	**12a**	$BrCH_2CH{=}CH_2$	100-115°C	88	13,15
4	Me	Me	Me	**12a**	3-Bromocyclohexene, **4**	50°C	56	16
5	Me	Me	Me	**12a**	1-Br-adamantane, **5**	100-115°C	25	13,15
6	Me	Et	Me	**12b**	1-Br-adamantane, **5**	100°C	31	15
7	Me	Me	Me	**12a**	9-Br-fluorene, **7**	100-115°C	65	13,15
8	Me	Me	Ph	**12c**	$BrCH_2Ph$	100-115°C	43	13,15
9	Me	Me	Ph	**12c**	$BrCHPh_2$	100-115°C	76	13,15
10	Me	Me	Ph	**12c**	$BrCH_2CH{=}CH_2$	100-115°C	30	13,15
11	Me	Me	Ph	**12c**	1-Br-adamantane, **5**	100-115°C	1	13,15
12	Me	Me	Ph	**12c**	9-Br-fluorene, **7**	100-115°C	30	13,15
13	tBu	H	tBu	**12d**	1-Br-adamantane, **5**	160°C	31	15
14	Me	H	Me	**12e**	$BrCHPh_2$	Reflux	77	17

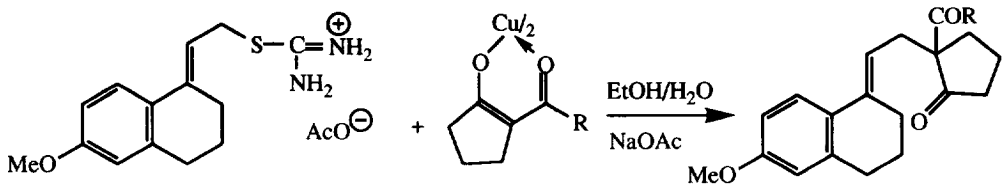


R=Me, Et

SCHEME 3

SCHEME 4

More significant were the results of Johnson and coworkers[21] (Scheme 5). Thus, the sulfur leaving groups give rise to products containing Cu-S bonds which are inert towards activated positions. This strategy was used to convert allylic sulfide **13** into stereoids precursors **14a,b**.

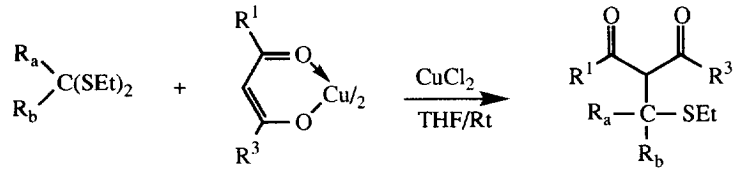


13 **12i**: R= Me; **12j**: R= OMe **14a,b**

Ref. 21

SCHEME 5

Further examples of the reactivity of Cu(II) complexes **12** towards alkylating agents possesing sulfur-based leaving groups are the reactions with dithioacetals or dithioketals **15** to afford products **16** (Scheme 6).[22] The role of $CuCl_2$ is to coordinate one sulfur atom to activate it as the leaving group.



15 **12** **16**

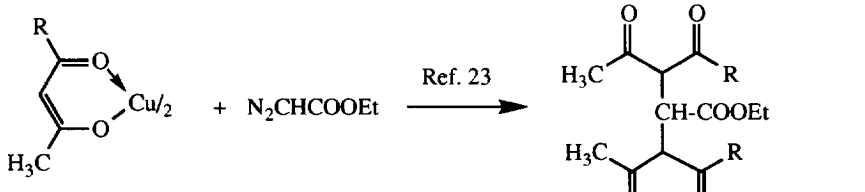
15a: R_a= R_b= Ph
15b: R_a= H; R_b= Ph
15c: R_a= H; R_b= SEt

12e: R^1= R^3= Me
12f: R^1= R^3= Ph
12g: R^1= Me; R^3= OEt

Ref. 22

SCHEME 6

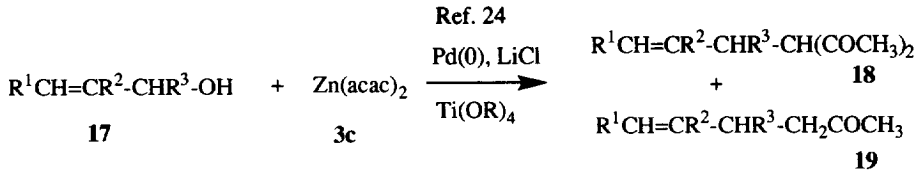
$Cu(Acac)_2$, **12e**, has been extensively used as catalyst in the decomposition of diazo-compounds to nitrogen and carbene species. In studying the fate of the ligand acac, it was found that complexes **12e,g** react with ethyl diazoacetate, **20**, to afford compounds **21** (Scheme 7).[23]



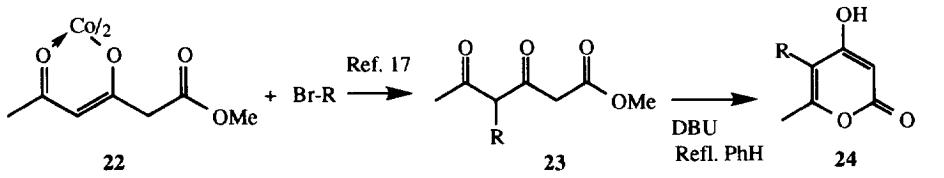
12e: R= Me; **12g**: R= OEt **20** **21e**: R= Me; **21g**: R= OEt

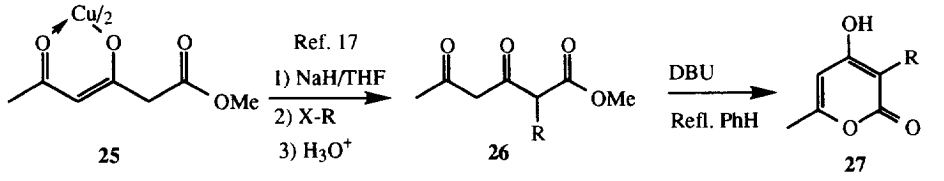
SCHEME 7

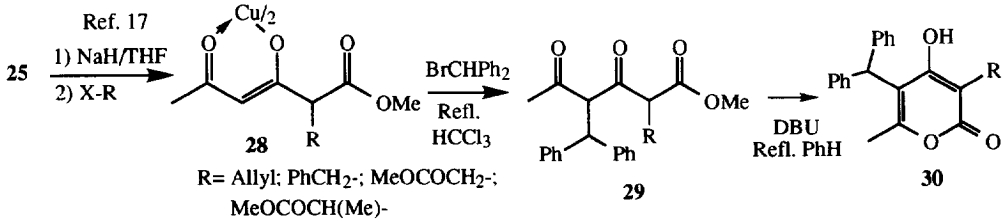
Non-radical mechanisms are probably involved in the conversion of allylic alcohols, **17**, into diketones **18** by zinc(II) complex **3c** under palladium catalysis (Scheme 8).[24] Allyl alcohols are normally bad substrates in Pd(0)-catalyzed chemistry.[25]

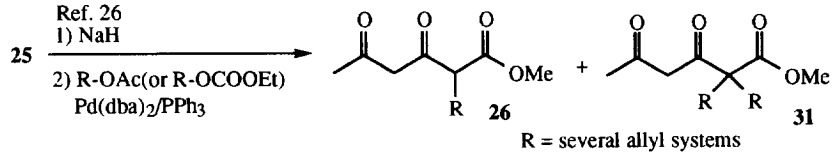


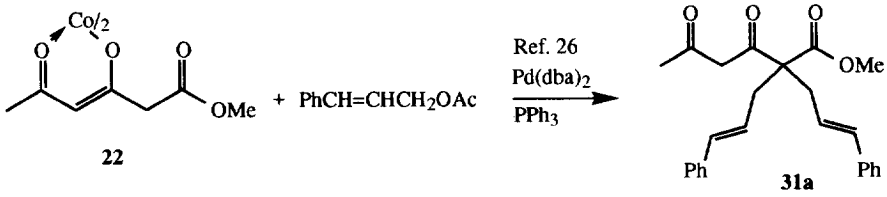
SCHEME 8











SCHEME 9

2.2.- *Regioselective Alkylation of a Polyketide Model through Activation and Protection by Co and by Cu Respectively.*

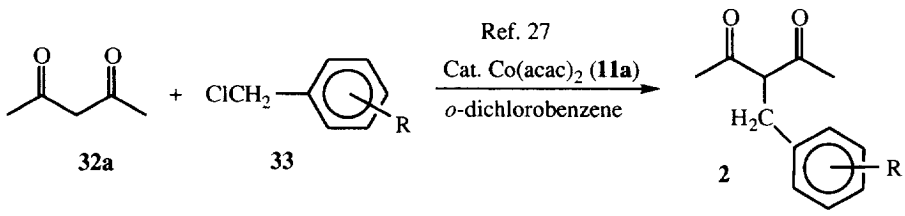
Regioselective alkylation of the polyketide model methyl 3,5-dioxohexanoate can be achieved through its Co(II) and Cu(II) complexes **22** and **25** (Scheme 9).[17] Regioselective alkylation on Co(II) complex **22** affords methyl 4-alkyl-3,5-dioxohexanoates, **23**, probably through radical-initiated mechanisms. Diketoesters **23** were cyclized to 5-alkyl-4-hydroxy-6-methyl-2-pyrones **24**.

In sharp contrast, copper protects the diketone moiety in complex **25**, and alkylations under conventional conditions produce diketoesters **26** which were cyclized to 3-alkyl-4-hydroxy-6-methyl-2-pyrones, **27**. An example of Cu both protecting and activating a β-diketone function is the non-radical conversion of complex **25** into complexes **28** (protection of the diketone; avoiding the hydrolysis step, complexes **28** are isolated) followed by radical-initiated reaction of **28** with benzhydryl bromide (activation of the diketone) to afford **29**.

The protection of the diketone through the copper complex, **25**, and through the Co complex **22** has been used in the Pd-catalyzed ionic allylation to afford diketoesters **26** and **31**.[26]

2.3.- *Catalytic Alkylations.*

The most clear catalytic version of the cobalt-mediated alkylation of β-diketones has been reported by a Chinese group.[27] The reaction of acetylacetone, **32a**, with several benzyl chlorides, **33**, under $Co(acac)_2$, **11a**, catalysis in hot dichlorobenzene affords alkylated products **2** (Scheme 10). The authors suggest a catalytic cycle of two steps. In the first one, the catalyst is alkylated in the Collman manner to afford the Co(II) complex of the final product plus HCl. The second step is the ligand scrambling to regenerate the catalyst **11a** and to liberate **2**. However, no proof for this cycle is given.



32a **33** **2**

1) $1/2\ Co(acac)_2 + ClCH_2Ar \longrightarrow 1/2\ [CH_3COC(CH_2Ar)COCH_3]_2\ Co + HCl$

2) $1/2\ [CH_3COC(CH_2Ar)COCH_3]_2\ Co + CH_3COCH_2COCH_3 \longrightarrow 1/2\ Co(acac)_2 + CH_3COCH(CH_2Ar)COCH_3$

SCHEME 10

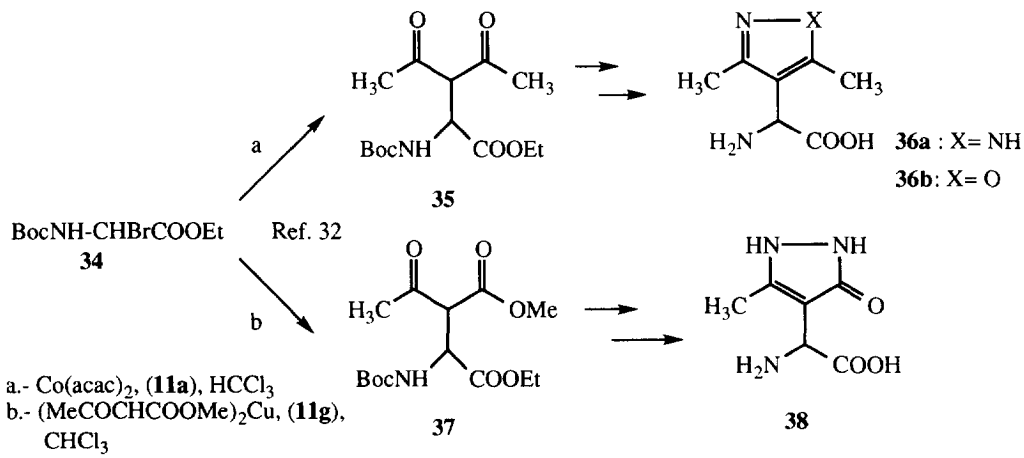
Other catalytic versions have been also published.[28]

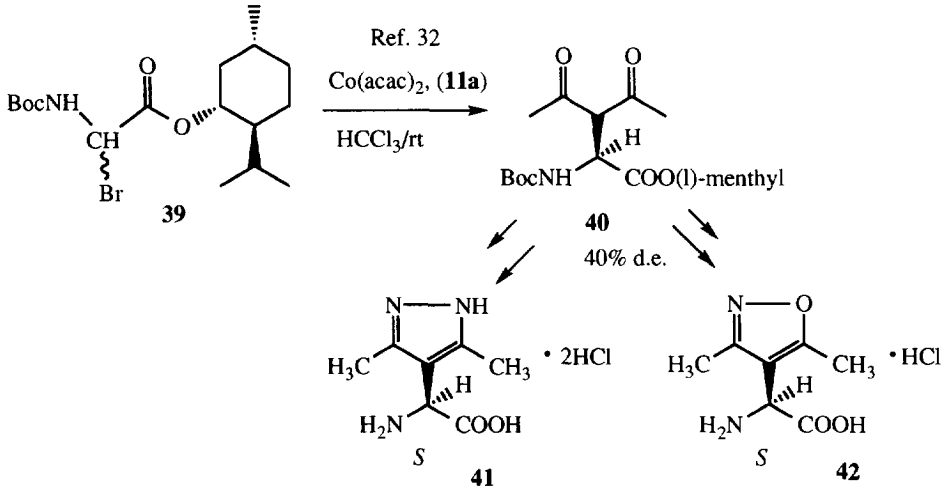
C-Allylations of β-dicarbonyl compounds with allylic substrates are catalyzed by Cu(I) species.[29,30] The authors suggest an activation of the allylic substrate by the copper species rather than an activation of the β-dicarbonyl compound.

Finally, it has been reported that allylic acetates react with diketones under anhydrous cobalt(II) chloride catalysis.[31a] However, in our hands the reaction between cinnamyl acetate and acetylacetone under these conditions failed.[31b]

2.4.- *Induction of Enantioselectivity at the Electrophile. The Preparation of Homochiral Heterocyclic Amino Acids.*

The glycine derivative **34** (Scheme 11) is the precursor of a stabilized capto-dative radical. Its reactions with $Co(acac)_2$, **11a**, and with the Co(II) complex of methyl acetoacetate, **11g**, afford compounds **35** and **37**, which were further converted into the heterocyclic amino acids **36** and **38**.[32] The chiral version is also given in Scheme 11. Thus, the mixture of compounds **39** reacts with **11a** to afford **40** with a diastereoisomeric excess of 40% (25% overall yield of enantiopure **40** after recrystallization). Reactions of **40** with hydrazine and with hydroxylamine followed by deprotection afford the enantiomerically pure amino acids **41** and **42**.



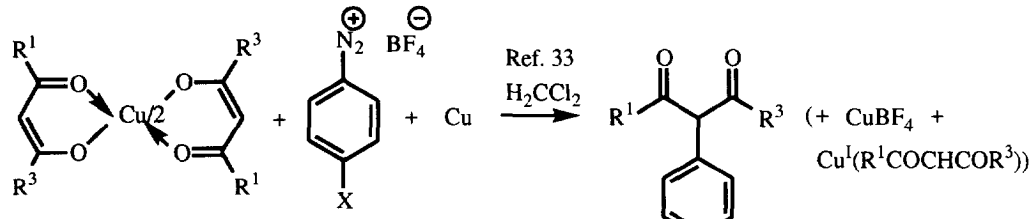


SCHEME 11

3.- ARYLATION

3.1.- *Arylation of β-Diketones at C-α. The Use of Cu(II) Complexes.*

The reactions of Cu(II) complexes **12** with arenediazonium tetrafluoroborates in the presence of one equivalent of copper powder affords aryldiketones **44**, and probably copper(I) tetrafluoroborate and copper(I) diketonate (Scheme 12).[33] Again, severely hindered diketones were obtained by a free-radical based, copper-mediated reaction.



12d: $R^1 = R^3$ = t-Bu
12e: $R^1 = R^3$ = Me
12f: $R^1 = R^3$ = Ph
12h: R^1 = Me; R^3 = Ph

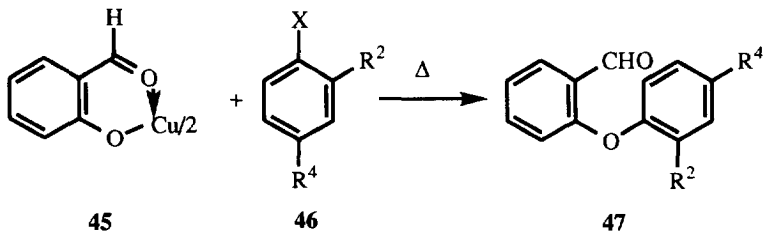
43

44

SCHEME 12

3.2.- *Arylation at Oxygen of the Copper Complex of Salicylaldehyde,* **45**.

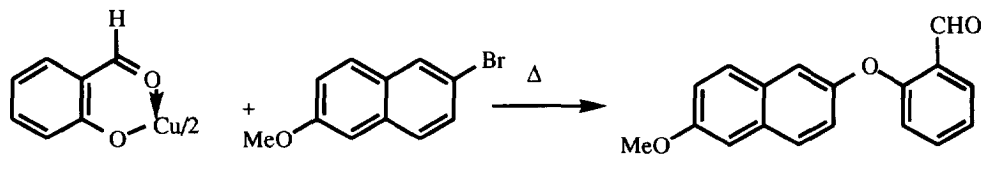
In a much earlier work, it was reported that the Cu complex of salicylaldehyde, **45**, reacts under strong thermal conditions with aryl bromides and iodides, **46** and **48**, to afford ethers **47** and **49** (Scheme 13).[34,35] In sharp contrast with almost all other reactions covered in this review, this arylation takes place at the phenolic oxygen atom of salicylaldehyde.



R^2	R^4
H	H
OMe	H
H	OMe
H	Me
H	NO_2

45 **46** **47**

Ref. 34 and 35

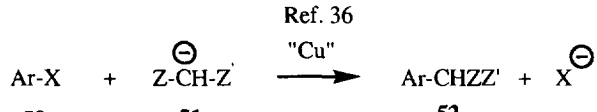


45 **48** **49**

SCHEME 13

3.3.- *C-Arylations of β-Dicarbonyl Compounds under Cu Catalysis.*

This topic (Scheme 14) has been already reviewed[36] and will not be treated further here.



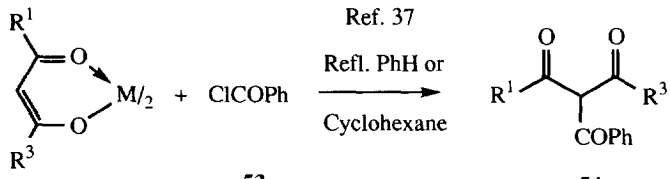
SCHEME 14

4.- ACYLATION

4.1.- *Acylation of β-Diketones. The Use of Ni(II), Cu(II), and Zn(II) Complexes.*

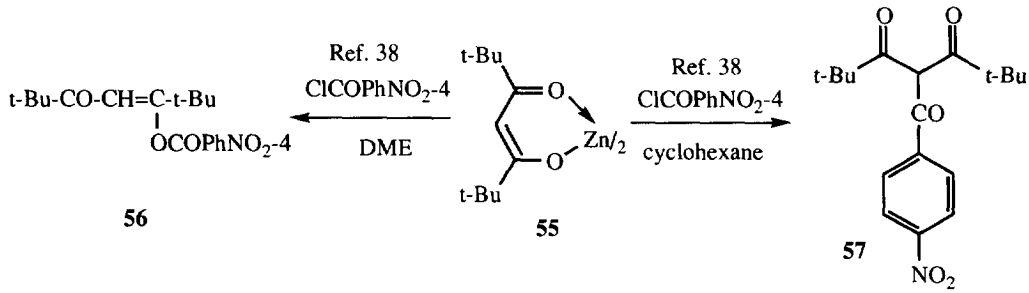
The benzoylation of the Ni(II) and Cu(II) complexes of many diketones is achieved as indicated in Scheme 15, by treatment with benzoyl chloride, **53**, in refluxing benzene or cyclohexane.[37] Under these conditions the complex is broken, which makes these reactions different from those reported by Collman.[2]

However, the outcome of the reaction of the zinc(II) complex **55** of 2,2,6,6-tetramethylheptane-3,5-dione (dipivaloylmethane) with 4-nitrobenzoyl chloride depends on the solvent. Thus, in cyclohexane the product of C-acylation, **57**, was isolated, whereas in dimethoxyethane the enol ester **56** was formed (Scheme 15).[38]



M= Ni $R^1 = R^3$ = Me (**1a**), Pr, i-Pr, t-Bu, CH_2-t-Bu

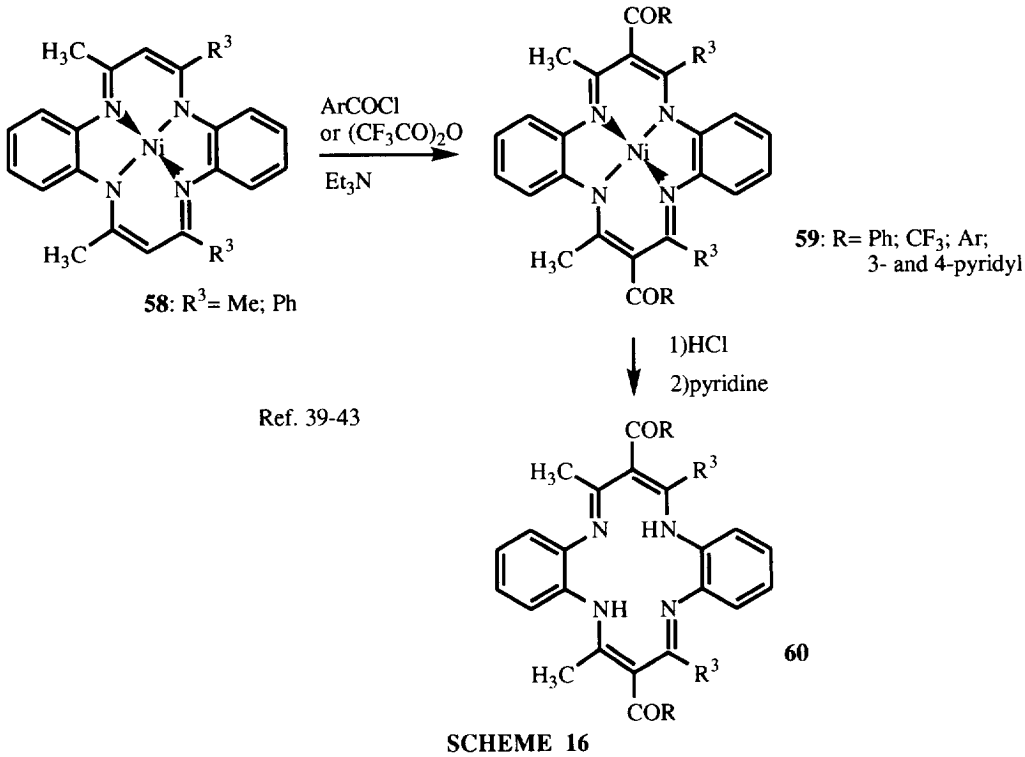
M= Cu $R^1 = R^3$ = Me (**12e**), Pr, i-Pr, t-Bu (**12d**), CH_2-t-Bu



SCHEME 15

4.2.- *Acylation of the Ethylenediamine Imines of β-Diketones. The Use of Ni(II) Complexes.*

The Ni(II) complexes **58** (Scheme 16) of the Schiff bases from *o*-phenylenediamine are acylated at the central C-α with a variety of acid chlorides and with trifluoroacetic anhydride to afford the new complexes **59**.[39-43] The reaction seems to be quite general, and it requires one equivalent of triethylamine. Liberation of the acylated ligand is achieved by consecutive treatments with HCl and pyridine.



58: R^3= Me; Ph

59: R= Ph; CF_3; Ar; 3- and 4-pyridyl

60

SCHEME 16

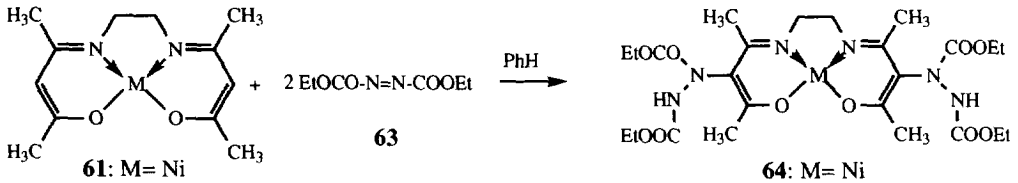
5.- MICHAEL-TYPE ADDITIONS

5.1.- *Stoichiometric Version.*

In one of the first papers of an important series, Nelson and coworkers reported the Michael-type addition of the Ni(II) and Cu(II) complexes **61** and **62** to Michael acceptors such as diethyl azodicarboxylate, **63**, and dimethyl acetylenedicarboxylate, **66** (Scheme 17).[44] The complexes were not broken down during the process, which occurred in benzene under neutral conditions. This paper was followed by the report of the same type of reaction directly on $Ni(acac)_2$, **1a**, (Scheme 18).[45] Thus, under very mild conditions, complexes **69** and **70** were easily formed and isolated in a neutral medium.

5.2.- *Catalytic Versions.*

A real improvement was published some years later, when the method was made catalytic by Nelson[46] and others.[47] Thus, several β-dicarbonyl compounds, **32**, react with a vast array of Michael acceptors in neutral medium under $Ni(acac)_2$ catalysis.[46] All β-dicarbonyls and Michael acceptors used are collected in Scheme 19. The dicarbonyls include a diketone, a ketoester, a ketoamide and a diester. In Scheme 20 the mechanism proposed by the authors[46] is represented. They suggest a catalytic cycle of two steps: the Ni(II) complex, **1**, of the dicarbonyl compound, formed by ligand scrambling from **1a** adds to the Michael acceptor, **72**, to afford complex **73**. This is equivalent to an electrophilic substitution. A scrambling of ligand between **73** and unreacted **32**, regenerates **1** and gives rise to the final product **71**. The mechanistic proposal has in its favour the preservation of the Ni(II) complex in reacting with Michael acceptors (See Scheme 18). This makes step 1 of the mechanistic cycle possible. However, it is hard to accept without further evidence that products such as diethyl malonate form complexes in situ so easily. In any case, irrespective of the mechanism this is a very useful synthetic method.

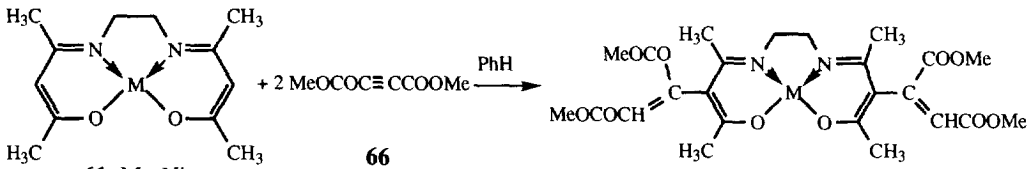


61: M= Ni
62: M= Cu

63

64: M= Ni
65: M= Cu

Ref. 44

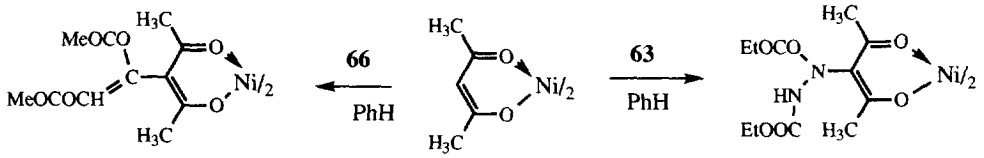


61: M= Ni
62: M= Cu

66

67: M= Ni
68: M= Cu

SCHEME 17



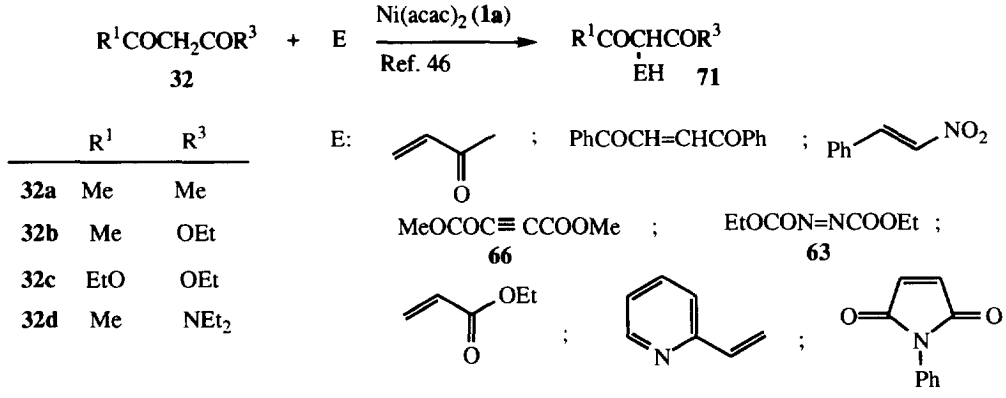
70

1a

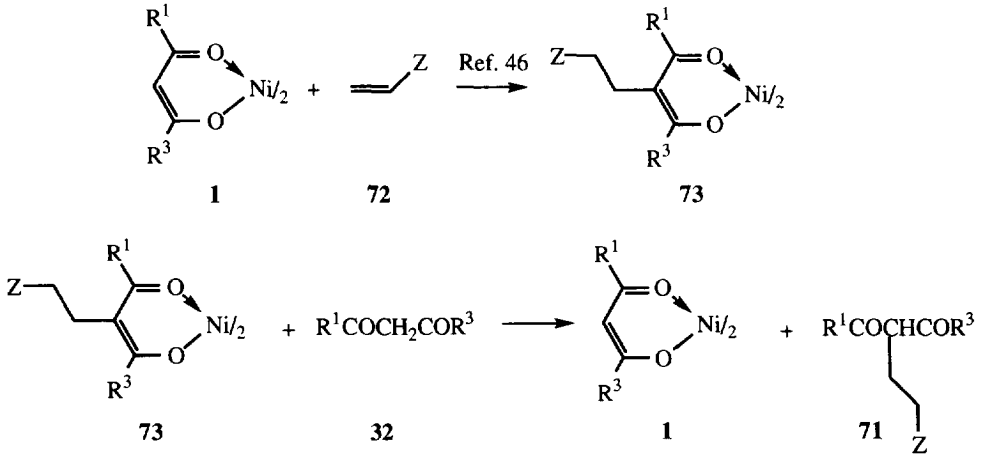
69

Ref. 45

SCHEME 18

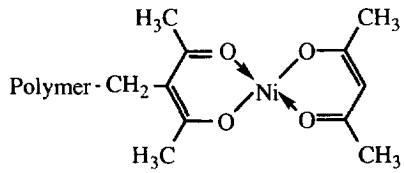


SCHEME 19

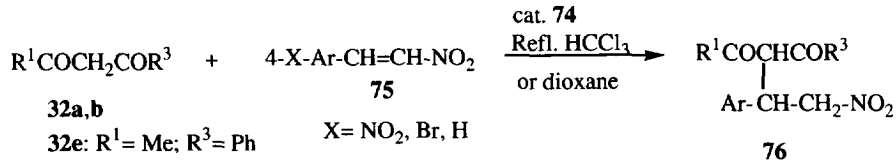


SCHEME 20

The Nelson method has been modified by other authors incorporating the catalysts in the form of a polymer, **74**, easily separable from the reaction medium and reusable at least once more (Scheme 21).[48]



Ref. 48



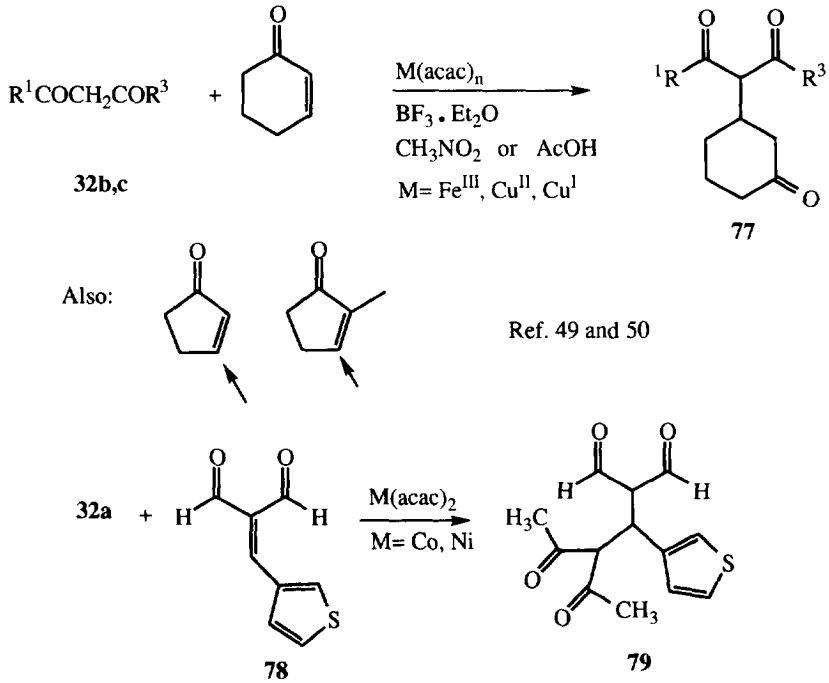
SCHEME 21

The method of Nelson is very useful for a series of Michael acceptors not very sterically hindered. If a Lewis acid such as boron trifluoride etherate is introduced to activate the acceptor, the reaction becomes useful for cyclohexenone and cyclopentenone (Scheme 22).[49,50] Other catalysts different from **1a** are also useful, including the Fe(III), Cu(II) and Cu(I) complexes of acetylacetone.[49, 50]

5.3.- *Induction of Enantioselectivity in Michael-type Reactions.*

Some efforts have been devoted to the generation of enantioselectivity in Michael-type reactions of β-ketoesters catalyzed either by $Co(acac)_2$, **11a**, in the presence of enantiopure ligand diamines[51-53] or by Cu(II) complexes of enantiopure ligands.[54,55] Since the mechanism proposed for these reactions involves the incorporation of the nucleophilic β-ketoester into the coordination sphere of the metal in a chiral environment, the inclusion in this report is justified.

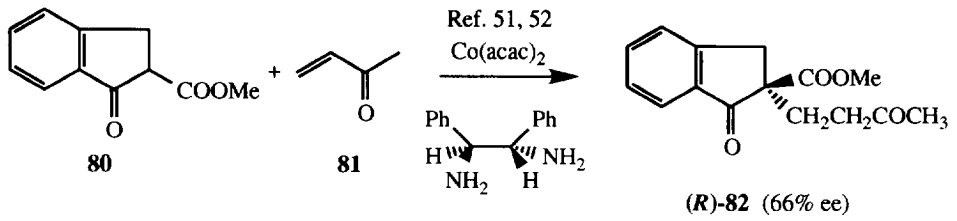
The best example of the work by the group of Brunner and coworkers[51,52] is shown in Scheme 23. The reaction of the cyclic diketoester **80** with 3-buten-2-one, **81**, in the presence of catalytic amounts of $Co(acac)_2$ and (1*S*,2*S*)-1,2-diphenylethanediamine affords (***R***)-**82** in 66% enantiomeric excess. The authors suggest the incorporation of **80** into the coordinating sphere of the cobalt atom in a chiral environment.

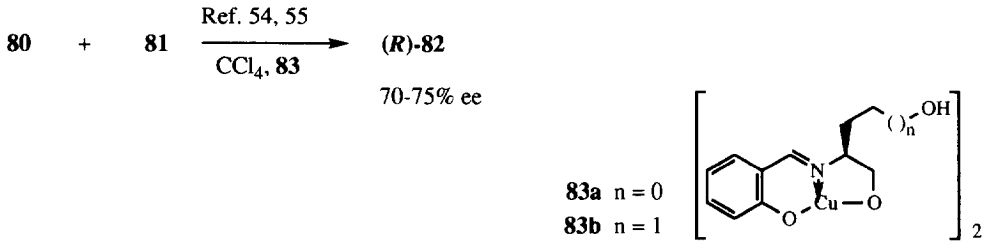


SCHEME 22

The best examples of the different approach followed by Desimoni and coworkers[54,55] are also shown in Scheme 23. The reaction between **80** and **81** in tetrachloromethane at temperatures below 0°C in the presence of the chiral complexes **83** gives (***R***)-**82** in 70-75% enantiomeric excess.

No good results have been obtained with open chain ketoesters.





SCHEME 23

6.- REACTIONS WITH ISOCYANATES, CYANIDES, ALDEHYDES AND OTHER ELECTROPHILES

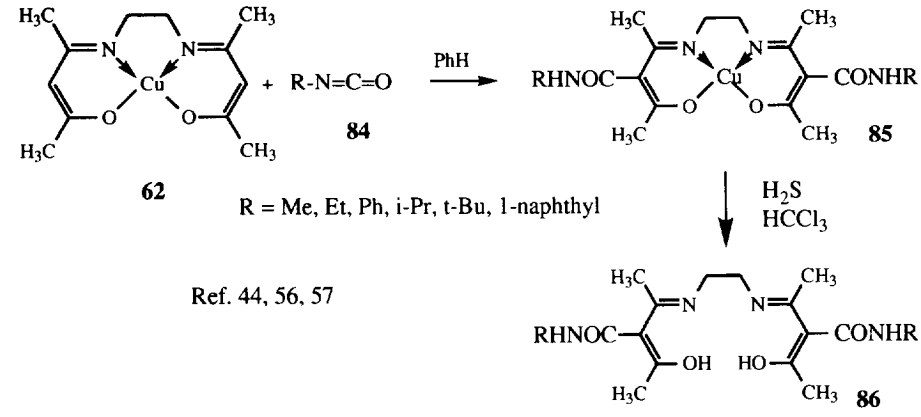
6.1.- *Reactions with Isocyanates. Stoichiometric Versions.*

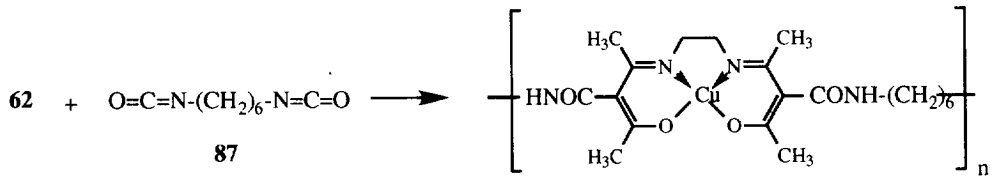
Nelson and coworkers have studied the reactions of the ethylenediamine complex **62** with several alkyl and aryl isocyanates, **84**, to afford complexes **85** (Scheme 24).[44,56,57] As in the case of the Michael additions, the structure of the complexes was mantained in these reactions which should be considered as electrophilic substitutions. The free ligands **86** can be liberated by treatment with H_2S in chloroform. The reaction of **62** with hexane-1,6-diisocyanate, **87** gives rise to polymer **88**.

These results were soon followed by similar reactions with the Ni(II) complex **1a**, which upon treatment with alkyl, aryl, and sulfonylisocyanates, afford complexes **89** (Scheme 25).[45] Again, the free ligands **90** are liberated with H_2S in chloroform. These results parallel those obtained by the same group in the field of Michael-type additions.

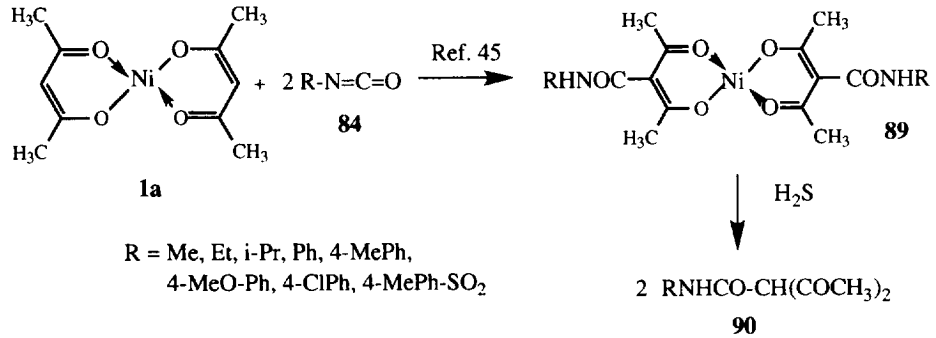
6.2.- *Reactions with Isocyanates. Catalytic Versions.*

Following the same pathway as the conjugate additions, the reactions with isocyanates were later made catalytic by Nelson and coworkers. Thus, the reactions of acetylacetone **32a** with several isocyanates, **84**, under catalysis by $Ni(acac)_2$, **1a**, afford compounds **90** (Scheme 26).[45] The proposed mechanism is also shown in Scheme 26. It consists of two steps, the first one of which is the reaction of the catalysts **1a** with the isocyanate to afford product **89**, thereby maintaining the complex structure as in the reactions of Scheme 25. The second step is a ligand scrambling to regenerate the catalyst and yields the final product **90**.

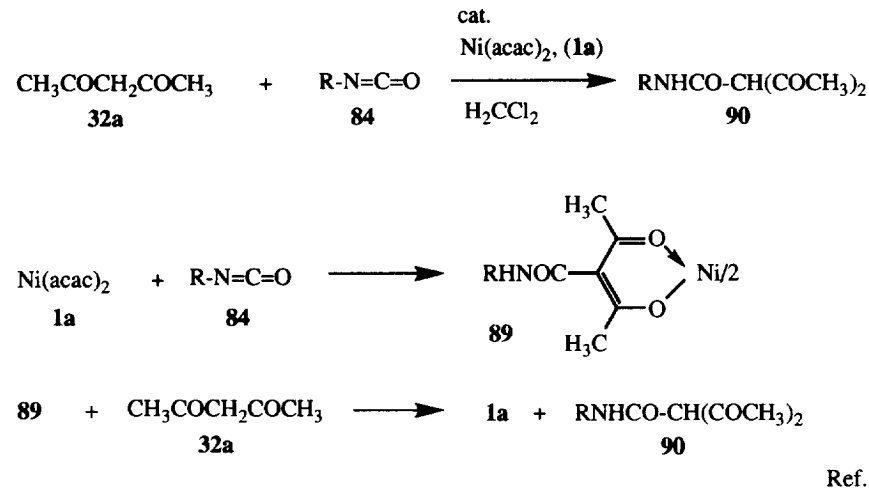




SCHEME 24



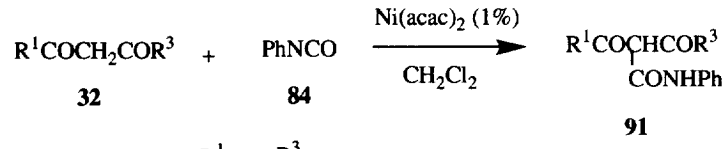
SCHEME 25



Ref. 45

SCHEME 26

An extension of this reaction to many β-dicarbonyl compounds, **32**, to give products **91** has been also reported and is summarized in Scheme 27.[58]



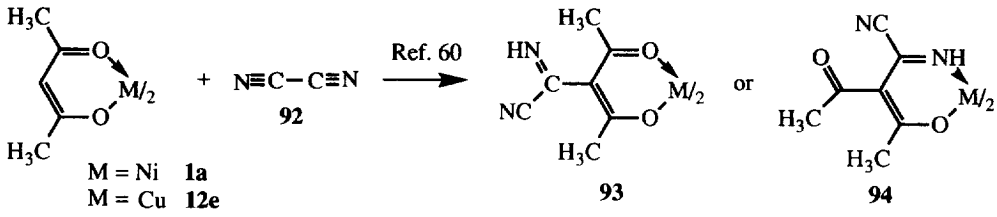
	R^1	R^3
32b	Me	OEt
32e	Me	Ph
32f	Ph	Ph
32g	Me	NHPh
32h	t-Bu	t-Bu
32i	t-Bu	Me
32j	t-Bu	Et

Ref. 58

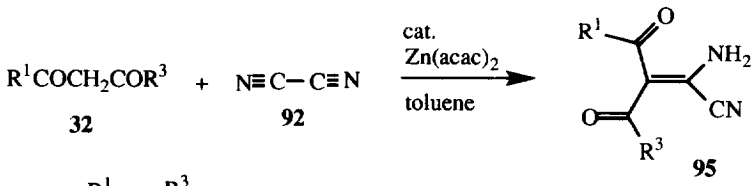
SCHEME 27

6.3.- *Reactions with Cyanides and Aldehydes.*

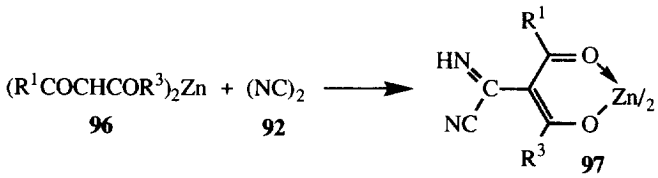
The reactions of $Ni(acac)_2$, **1a**, and of $Cu(acac)_2$, **12e**, with dicyanogen, **92**, has been investigated. They give complexes of structures **93** or **94** (Scheme 28).[60] $Zn(acac)_2$, **3c**, has been used in the catalytic version. Thus, β-dicarbonyl compounds **32** react with **92** under the Zn(II) complex catalysis. A catalytic cycle as usual has been proposed for this reaction (Scheme 29).[61]



SCHEME 28



	R^1	R^3
32a	Me	Me
32b	Me	OEt
32e	Me	Ph
32f	Ph	Ph
32h	t-Bu	t-Bu
32k	OMe	OMe
32l	Me	CF_3
32m	t-Bu	CF_3

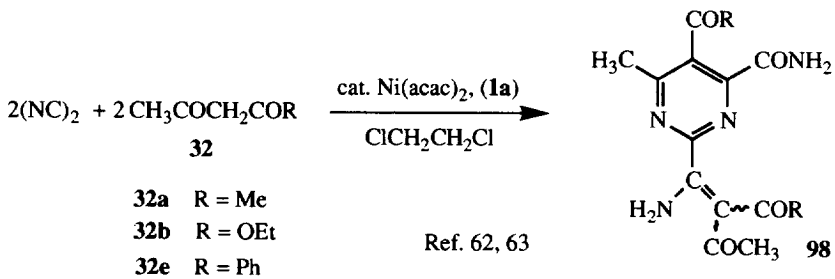


97 + **32** ⟶ **95** + **96**

Ref. 61

SCHEME 29

If $Ni(acac)_2$ is used as catalyst instead of $Zn(acac)_2$ pyrimidines **98** are obtained by a process involving two equivalents of each reagent (Scheme 30).[62,63]

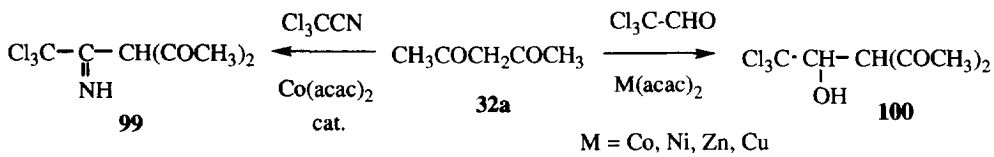


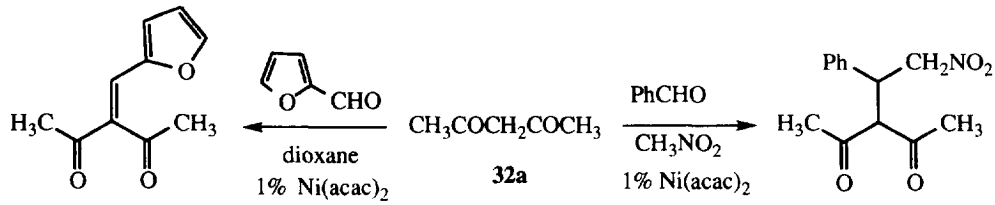
32a R = Me
32b R = OEt
32e R = Ph

Ref. 62, 63

SCHEME 30

Strongly electrophilic nitriles and aldehydes such as trichloroacetonitrile and trichloroacetaldehyde react with acetylacetone, **32a**, under $Co(acac)_2$, **11a**, catalysis to afford products **99** and **100** (Scheme 31).[59]





SCHEME 31

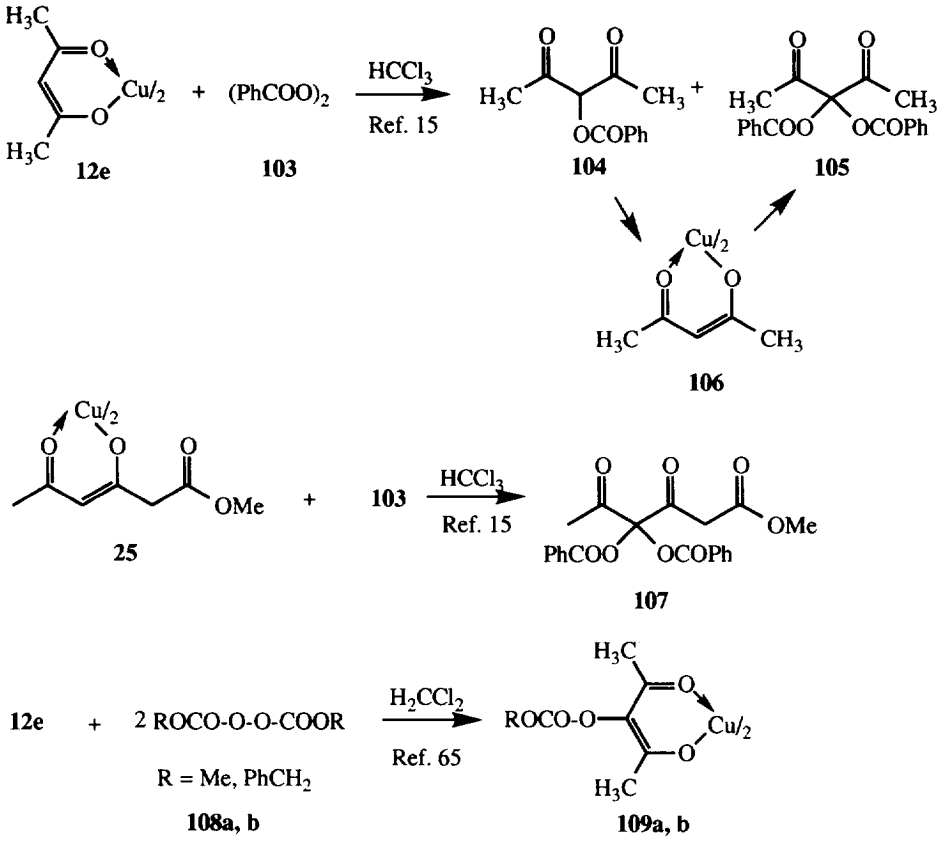
The group of Nelson has reported also the formation of **102** by the Knoevenagel-type reaction between **32a** and furfural.[46] If the reaction between **32a** and benzaldehyde is performed in nitromethane, consecutive Knoevenagel reaction and conjugate addition of nitromethane occur under $Ni(acac)_2$ catalysis to afford product **101** (Scheme 31).[46] The reactions of Scheme 31 are examples of Knoevenagel reactions performed under neutral catalysis.

7.- REACTIONS WITH OXYGEN ELECTROPHILES

7.1.- *Reactions with Peroxides.*

The first indication of the reactivity of metal complexes of β-dicarbonyl compounds with peroxides is the report of the reaction of the Cu(II) complex **12e** with benzoyl peroxide to afford compound **105** (Scheme 32).[64] In a more specific study of this reaction it has been reported that both **104** and **105** were formed in ratios depending on the stoichiometry of starting materials.[15] The Cu(II) complex, **106**, prepared from **104** was independently converted into **105**.[15] A further indication of the activation produced by the metal Cu(II) in these radical-type reactions is the regioselective reaction of complex **25** with benzoyl peroxide, **103**, to afford only **107**, the reaction product at the interketonic position.[15]

In the afore mentioned experiment the final products were the functionalized free ligands. The same result was obtained by Schank and coworkers.[65] However, these authors have reported that the reactions of the same complex **12e** with peroxydicarbonates **108a,b** afford the functionalized complexes **109a,b** in which the metal remains bound to the ligand (Scheme 32).[65]



SCHEME 32

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