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Formylating Agents§

GEORGE A. OLAH,* LENA OHANNESIAN,† and MASSOUD ARVANAGHI‡

Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661

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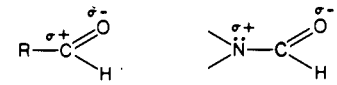
I. Introduction

The term "formyl" derives from the Latin formica (ant). In some insects like ants, formic acid is present in significant amounts in certain tissues and fluids. Formate and the formyl group have significant importance in tissue metabolism.

One carbon fragment metabolism and one carbon extension reactions have attracted extensive studies. The design of new C–C bond formation reactions and reagents in organic chemistry as well as improvement of known reactions is of continued importance. One of the major objectives of organic synthesis is finding new and improved one carbon extension reactions, since they form one of the most significant building block of molecular architecture.

One of the potentially most useful and versatile functional groups to be introduced is the formyl group. Formyl compounds owe their usefulness as synthetic intermediates to the presence of the polarizable carbon–oxygen double bond that governs their chemical reactivity. The polarizability of the formyl carbonyl group is reflected in a hard donor oxygen (hard base) and a fairly hard acceptor carbon **1a** (hard acid).



1a **1b**

Attaching the formyl group to a heteroatom bearing a nonbonded pair of electrons, such as nitrogen **1b**, will significantly affect the carbonyl carbon, rendering it softer. Formyl groups can also be readily reduced to give alcohols or oxidized to produce acids.

Interested over the years in formylation methods and formylating agents, we have reported the development of a number of such reagents and their synthetic use. In this paper we survey up to 1986 the progress of direct (one-step) formylating agents and their synthetic applications.

Recently there have been a number of reviews discussing reactions of dialdehydes in organic synthesis,[2a] carbonylation using carbon monoxide,[2b] and synthesis of carbonyl compounds using a variety of coupling reactions.[3a] With the exception of reviews on the carbonylation of organoboranes,[3b] however, direct (one-step) formylating agents have not been recently reviewed. One of us in 1964 reviewed the then available data on electrophilic Friedel–Crafts type formylations.[4] The reader is referred to this review for aspects of earlier work.

In this paper we survey progress in direct (one-step) formylating agents. The methods of preparation as well as properties and reactivities of formyl compounds will be discussed. In order to limit the scope of the dis-

† Present address: National Cancer Institute, National Institutes of Health, Frederick, MD 21701-1013.

‡ Present address: Fisher Scientific Co., Fair Lawn, NJ 07410.

§ Synthetic Methods and Reactions. 130. For part 129 see: ref 1.

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George A. Olah is the Katherine B. and Donald P. Loker Distinguished Professor of Organic Chemistry and Scientific Co-director of the Hydrocarbon Research Institute at the University of Southern California in Los Angeles, CA. He was born and educated in Hungary. Professor Olah came in 1956 first to Canada and subsequently to the United States working for Dow Chemical Co. as Research Scientist. In 1965 he became Professor and Chairman of the Chemistry Department of Western Reserve University and continued as Chairman after the merger with Case Institute of Technology until 1969. From 1967 to 1977, he held the position of C. F. Mabery Distinguished Professor of Research in Chemistry at Case Western Reserve University. In 1977 he moved to the University of Southern California to form the Hydrocarbon Research Institute together with Professor Sidney W. Benson. Professor Olah received the American Chemical Society Awards in Petroleum Chemistry in 1964 and for Creative Work in Synthetic Organic Chemistry in 1979. He was the recipient of the Baekeland Award (1967) and the Morley Medal (1970). He was given of a Guggenheim Memorial Fellowship in 1972. He was elected a member of the National Academy of Sciences in 1976 and a foreign member of the Italian National Academy of Sciences dei Lincei in 1981. He received an Alexander von Humboldt-Stiftung Award for Senior U.S. Scientists in 1979. He has held visiting professorships at the University of Toronto (Canada); The Ohio State University; University of Heidelberg (Germany); University of Colorado; Swiss Federal Institute of Technology; University of Munich (Germany); University of Strasbourg (France); and the University of London, King's College, of which he is honorary lifetime lecturer. He has been awarded many special lectureships including the FMC Lectures, Princeton University; Francis Clifford Phillips Lecturer, University of Pittsburgh; and the Centenary Lecturer, Chemical Society, London. He has served on the editorial boards of different scientific journals and was consultant to major industries in his field. Professor Olah's major research areas are in the chemistry of petroleum and hydrocarbon products and electrophilic synthetic reactions and their mechanistic chemistry. He has pioneered the chemistry of superacids, systems billions of time stronger than sulfuric acid, and of stable long-lived carbocations, the cationic species of hydrocarbons and their spectroscopic study. He has authored some 800 scientific papers, has about 100 patents to his name, and has authored (or coauthored) such widely known monographs as *Friedel–Crafts Chemistry*, *Carbonium Ions*, *Halonium Ions*, *Carbocations and Electrophilic Reactions*, *Superacids*, and *Hypercarbon Chemistry*.

Lena Ohannesian is an Armenian native of Iraq. She received her Ph.D. degree in 1986 from the University of Southern California under the supervision of Dr. George A. Olah and is currently a Scientist with the National Cancer Institute in Frederick, MD.

Massoud Arvanaghi, a native of Iran, obtained his Ph.D. degree in 1982 under the direction of Prof. G. A. Olah and is currently Organic Product Manager at Fisher Scientific Co., Fair Lawn, NJ.

cussion, homologation reactions that involve skeletal unit transformation to formyl group (primarily through oxidation or reduction reactions) were excluded. Only direct formylation (transformylation) will be reviewed. Synthetic procedures involving carbon–carbon bond construction to achieve the critical extension of the carbonyl group will be, however, discussed as appropriate.

The terms electrophilic and nucleophilic formylation reactions will be used throughout. We use them to differentiate between acid-catalyzed reactions of hydrocarbons with formylating agents (such as formyl fluoride) and reactions with reagents (such as *N*-formylamines) capable of formylating typical nucleophilics such as Grignard reagents and alkyllithiums.

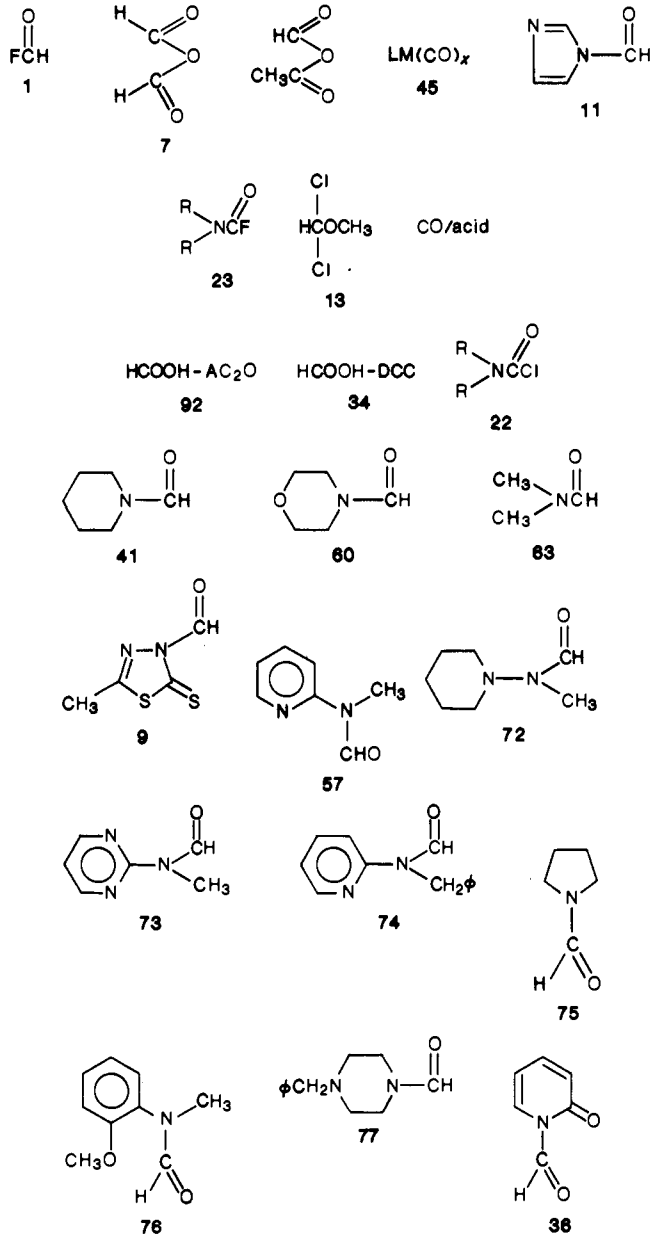
The first example of an electrophilic formylation was reported by Gattermann and Koch[5] in 1897. They extended the Friedel–Crafts acylation method to the preparation of aromatic aldehydes. Although formyl chloride was unknown at the time, they found that CO and HCl in the presence of $AlCl_3$ and cuprous chloride behave like the formyl chloride and react with toluene in a manner similar to that of other acid chlorides.[5]

Bouveault in 1904 was the first to report[6] the preparation of an aliphatic aldehyde by reacting the corresponding Grignard reagent with *N*,*N*-dimethylformamide. The reaction considered to be a nucleophilic formylation reaction, however, was not proven to be of general utility until recently, and little interest has been focused on it.

II. Formylating Agents

In discussing the formylating agents listed in Chart I, we will center our review on recently developed reagents and systems. Previously reviewed reagents will be mentioned mainly for comparison, and the interested reader is referred to available reviews.

CHART I



Particular attention is called to a recent excellent review by Effenberger,[7] which discusses some of the available electrophilic formylating agents, as well as an earlier review by Olah and Kuhn on Friedel–Crafts type formylation.[4]

III. Electrophilic Formylating Agents

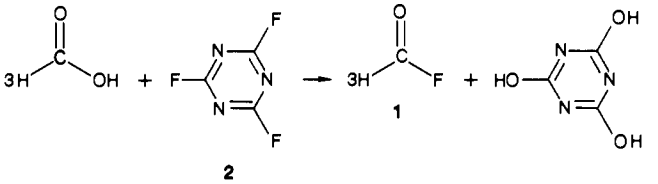
A. Formylation with Formic Acid and Its Derivatives

High reactivity and sufficient selectivity are the most important factors in successful formylations of aromatic and aliphatic systems. Of the most frequently used aromatic formylation methods, the Gattermann–Koch reaction[5] and its subsequently developed variations show the highest selectivity reflected both in the observed high toluene–benzene rate ratio, k_T/k_B (155–860), as well as in a high degree of para substitution (88.7–96%). Gross's formylation with dichloromethyl methyl ether[8a] is somewhat less selective (25 °C $AlCl_3$ in CH_3NO_2, k_T/k_B = 119; 35.8% ortho, 3.8% meta, and 60.4% para substitution), as is the Gattermann synthesis using $Zn(CN)_2$ and $AlCl_3$[4] (details in section III.B).

Although a considerable number of aldehyde synthesis and formylation methods are now known, only a few simple methods equivalent to the Friedel–Crafts ketone synthesis and acylation with acyl halides or anhydrides are available, presumably because halides and anhydrides of formic acid are considerably less stable and much less available then those of higher homologous acids. The only known stable halide of formic acid is the fluoride, which is used as an electrophilic aromatic formylating agent in the presence of Lewis acids, particularly boron trifluoride.[11] Formyl fluoride (1) was first prepared by Nesmejanov and

$$HCOOH + KF + PhCOCl \rightarrow \underset{\mathbf{1}}{HCOF} + PhCOOH + KCl$$

Kahn[9] in 1934 in 16% yield by the interaction of anhydrous formic acid, potassium fluoride, and benzoyl chloride. Mashentsev[10] prepared it in 36% yield from benzoyl fluoride and formic acid. Olah and Kuhn subsequently prepared 1[11] using KHF_2 as the fluorinating agent from formic acid and benzoyl chloride. Further improved preparation of formyl fluoride (1) by



fluorinating formic acid using cyanuric fluoride (2) in pyridine or reacting benzoyl fluoride with sodium formate allowed the extension of the utility of the reaction.[12]

Formyl fluoride and boron trifluoride form a complex at low temperature. Aluminum halides, however, due to decomposition reaction do not form a stable complex with formyl fluoride. The complex of formyl fluoride-/boron trifluoride has been used as formylating agent in electrophilic aromatic formylation reactions. It is possible to achieve a successful reaction by dissolving formyl fluoride in the aromatic solutions followed by introducing boron trifluoride as a catalyst to obtain the corresponding aldehydes.[11]

The activated complex was proposed to be HCOF·BF_3, but not the free formyl cation HCO^+. Some other Lewis acids have also been used successfully and a number of aromatic aldehydes have been prepared by this method with yields varying between 56 and 78% (Table I).[11]

Formyl fluoride was also found to react with alcohols and phenols in the presence of base (such as triethylamine) to form the corresponding formates 3. Primary

$$ROH + \underset{\mathbf{1}}{HCOF} \xrightarrow{Et_3N} \underset{\mathbf{3}}{ROC(=O)H} + HF$$

and secondary aliphatic alcohols were formylated in 73–92% yield, while benzyl alcohol and phenol gave 69% and 75% yields, respectively. Thiol formates are also readily prepared by formyl fluoride (S-formylation);[11] N-formylation is also achieved with a large variety of primary and secondary amines reacting

TABLE I. Formylation of Aromatics Using Formyl Fluoride

aromatic	product	yield, %
benzene	benzaldehyde	56
toluene	tolualdehyde	75
xylene	dimethylbenzaldehyde	78
2,4,6-trimethyl-benzene	2,4,6-trimethyl-benzaldehyde	70
2,3,4,6-tetramethyl-benzene	2,3,4,6-tetramethyl-benzaldehyde	72
naphthalene	naphthaldehyde	20, α-isomer 67, β-isomer

to give *N*-alkylformamides 4 in good to excellent yields.

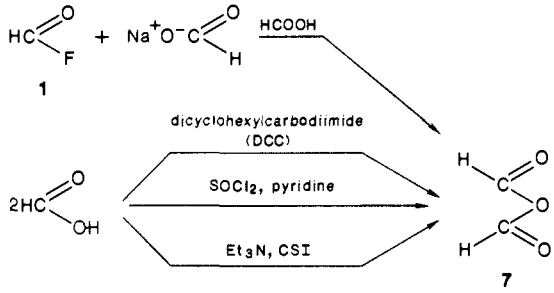
$$2R^1R^2NH + \underset{1}{HCOF} \rightarrow \underset{4}{R^1R^2NCHO} + R^1R^2NH\cdot HF$$

$$N(CH_3)_3 + \underset{1}{HCOF} \rightarrow N(CH_3)_3\cdot \underset{5}{HF} + CO$$

$$C_6H_5N + \underset{1}{HCOF} \rightarrow C_6H_5N\cdot \underset{6}{HF} + CO$$

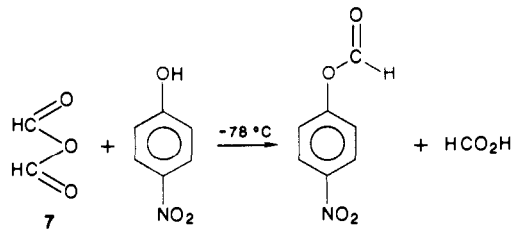
Tertiary amines do not react with formyl fluoride to form the corresponding formylium salts **5** and **6**, but give elimination of carbon monoxide with formation of the amine hydrofluorides.

Although formyl fluoride reacts with Grignard reagents to give formylated products, the reaction is generally not satisfactory.[11] Carboxylic acid salts were found to react with formyl fluoride to form the corresponding mixed carboxylic formic anhydrides.[11] Even the elusive formic anhydride **7** itself was prepared by



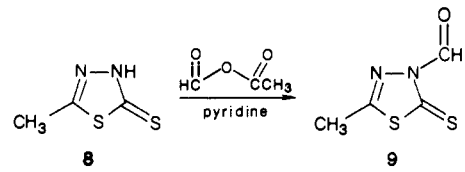
the reaction of **1** with sodium formate at −78 °C.[11] Formic anhydride **7** was further obtained by using three different reagents[13] via condensation (dehydration) reactions.

It was found that solutions of formic anhydride can serve as formylating agent. O-formylation was obtained upon reacting **7** with *p*-nitrophenol to give *p*-nitrophenyl formate in good yield.[13] Attempts to try to



formylate aromatics failed due to the instability of the anhydride above −40 °C and the difficulty of carrying these reactions in the presence of acid catalysts which lead to the decomposition of formic anhydride even at low temperatures.

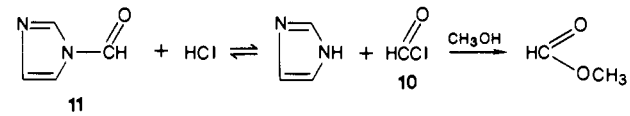
Mixed anhydrides of formic acid with higher homologous acids such as acetic formic anhydride are well-known and stable.[11] Acetic formic anhydride prepared by the reaction of formic acid with acetic anhydride is a suitable formylating agent to produce *N*-formyl derivatives of the corresponding amines.[14] 4-Formyl-2-methyl-1,3,4-thiadiazoline-5-thione (**9**) is easily prepared from 2-methyl-1,3,4-thiadiazoline-5-thione (**8**) and acetic formic anhydride by using a catalytic amount of pyridine in acetone or tetrahydrofuran in 75% yield.[15] By careful control of the reaction



8 **9**

conditions, predominantly N-formylation takes place. Olah et al. have also attempted using the acetic formic anhydride as a Friedel–Crafts formylating agent. The observed reaction, however, was always exclusive acetylation of the aromatics accompanied by carbon monoxide evolution.[11]

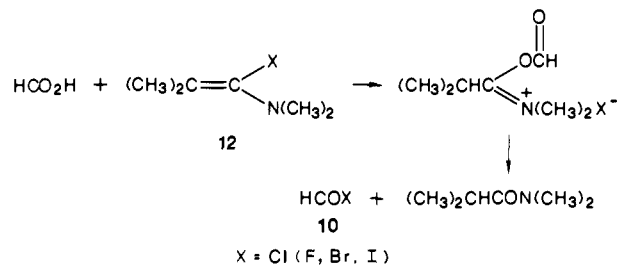
Krauskopf and Rolefson[16a] have claimed the first preparation of formyl chloride by the high-temperature photochlorination of formaldehyde; however, the results were not unequivocal.[16b] Staab et al. should be credited[17] with the intermediate preparation of the elusive formyl chloride (**10**) by passing HCl into a solution of 1-formylimidazole (**11**) in $CHCl_3$ at −60 °C. No



11 **10**

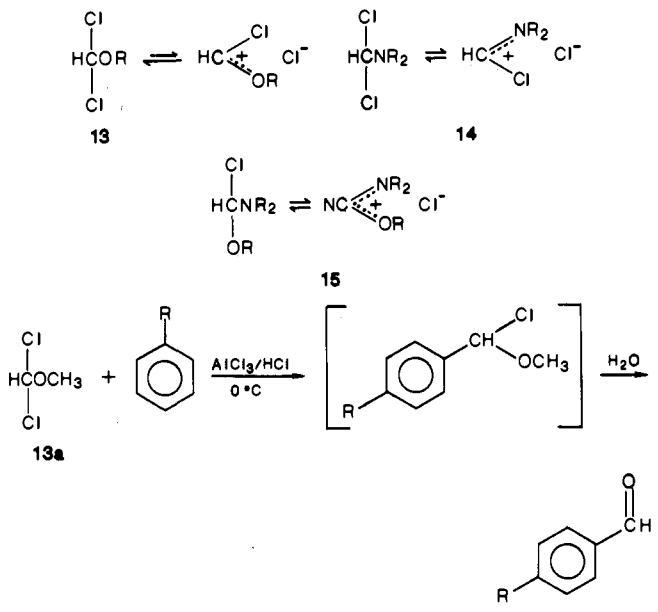
physical data of the unstable compound were given since it was immediately trapped by methanol, giving methyl formate at −60 °C. The facile decarbonylation of the expected formyl cation HCO^+ would make C-formylations with formyl chloride difficult.

Ghosez et al. reported[18] an improved preparation of formyl chloride (as well as of formyl fluoride, and even the bromide and iodide) by reacting formic acid with tetramethyl-α-halogeno enamines at or below room temperature in high yield under neutral conditions.



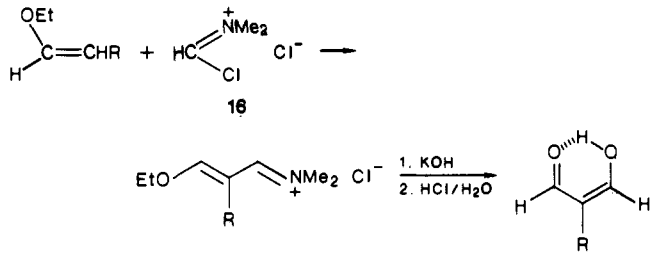
Formyl chloride was again detected only by its conversion to methyl formate (other formyl halides were converted into formanilide).

Dichloromethyl ethers and dichloromethylamines can act as formyl chloride equivalents for the formylation of aromatics and olefins. The nature of the substituent determines the reactivity of the formylating agent as the electrophilicity of the formyl carbon is decreased. The reactivity decreases for electrophilic formylation reaction in the order **13** > **14** > **15**. α,α-Dichlorodimethyl ether (**13a**) is used to formylate benzene or slightly activated arenes in the presence of a Friedel–

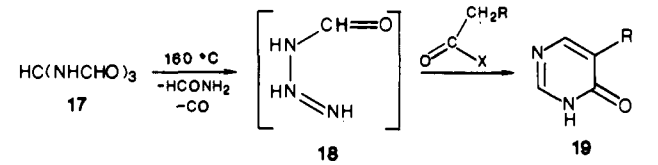


Crafts catalyst. Benzene is formylated in 37% and toluene in 80% yield.[8b]

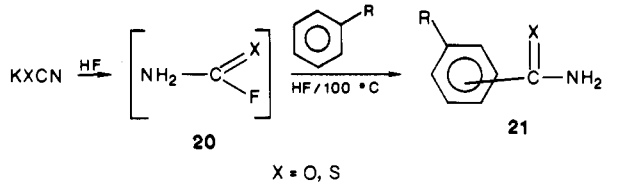
In the case of reactive arenes, the α,α-dichlorotrialkylamines **16** (chloromethyliminium chloride) can be used as formylating agents without Friedel–Crafts catalysis. The Vilsmeier–Haack–Arnold formylation of



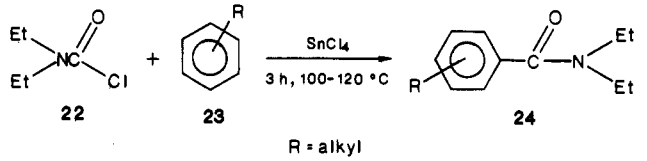
the activated olefins (enol ethers, acetates, and enamines) have also been carried out with this reagent.[19] This provides an important synthetic route for the synthesis of polycarbonyl compounds such as malondialdehyde (an important synthon). Orthoamides of formic acid, on the other hand, are less electrophilic than their oxygen analogues and therefore cannot be used for aromatic formylation. They are, however, suitable for formylating aliphatic carbaniones.[20] Orthoformic acid derivatives as well as *N,N',N''*-methylidynetriformamide (**17**) are also used as formylating agents in the field of heterocyclic synthesis, the amide component of these reagents incorporating into the skeleton of the heterocyclic compounds.[21] This method is of particular interest in the synthesis of purines and pyrimidines **19**. Effenberger discusses the reaction in more detail.[7]



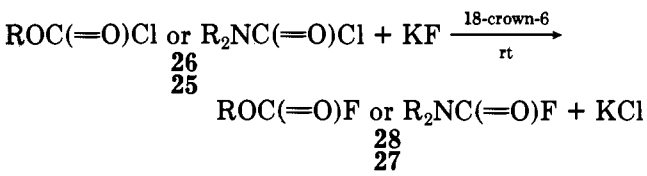
Only a brief mention of the reaction of carbamoyl halides is included in this section due to its relevance to the foregoing discussion. The carboxamidation of arenes (for a review see ref 4), i.e., the Gattermann amide synthesis, presents some preparative problems since in situ preparation of carbamoyl chloride is difficult to handle. Carbamoyl fluoride (**20**) has been used



for the preparation of benzamides **21**.[22] Carboxamidation of alkylarenes with *N,N*-diethylcarbamoyl chloride (**22**) is less complicated and gives better yields.[23]



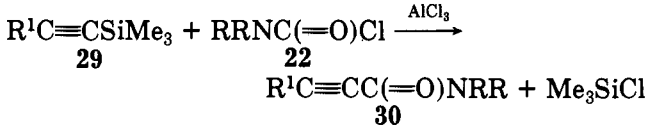
Methods for the preparation of enol carbonates and carbamates have been reported. Alkyl fluoroformates ROCOF or tertiary carbamoyl fluorides R_2NCOF are easily prepared by reacting the corresponding carbamoyl chlorides **26** or chloroformate **25** with KF acti-



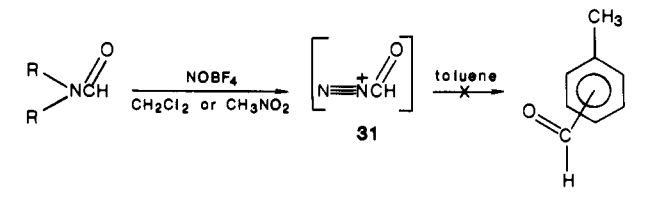
vated by phase-transfer agent 18-crown-6 (ca. 5 mol %) at room temperature (Table II). As alkyl chloroformates are known to decompose at more elevated temperature the phase-transfer-catalyzed process is preferred. Products such as **27** and **28** are distilled from the reaction mixture.[24]

Fluoroformates can also be prepared from the corresponding alcohols (amines) with COF_2 or COFCl,[25] but these reagents are less accessible.

An extention to the available formylation methodology is the use of trimethylsilane reagents. Amide linkages have been prepared by the reaction of acetylenic trimethylsilanes and carbamoyl chlorides in the presence of a Lewis acid.[26] The simplicity of this reaction makes it an attractive synthetic method.



Attempts were made to effect formylations of aromatics via in situ formed formyldiazonium ion (**31**) in



the reaction of formamides with NO^+ salts. All attempts, however, so far have been unsuccessful, as the formyldiazonium ion readily loses CO.[27]

TABLE II. Fluoroformates, Carbamoyl Fluorides, and Acyl Fluorides Prepared from Their Respective Chlorides

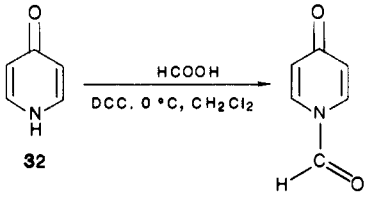
RCOF prod., R =	yield, %	KF equiv	18-C-6, mol %	temp, °C	time, h	bp (found) °C/Torr
$MeCH_2O$	89	1.6	6	0	68	55–57/760
Me_2CHO	95	1.6	6	13	47	66–70/760
Me_2CHCH_2O	91	1.3	4	rt[a]	45	92–93/760
$MeCH_2CH_2CH_2O$	84	1.8	8	rt[a]	13	99–100/760
c-$C_6H_{11}O$	89	1.5	9	70	4	52–53/21
cholesteryl-3-O	89	3.9	15	rt[a]	53	mp 112–113
PhO	80	1.6	6	15–19	144	60–64/120
Me_2N	95	1.3	4	rt[a]	27	65–70/80
N-piperidino	88	1.9	5	rt[a]	31	75–77/10
N-morpholino	97	2.9	6	rt[a]	68	60–65/2
$MeCH_2CH_2$	90	1.4	4	rt[a]	27	66–67/760
phenyl	90	2.1	7	rt[a]	234	56–57/20

[a] Room temperature.

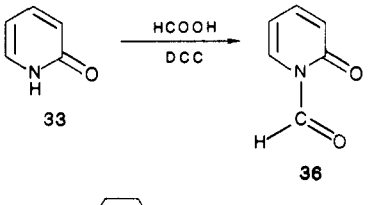
TABLE III. Electrophilic Formylation of Toluene and Benzene

formylation agent	catalyst	solvent	temp, °C	k_T/k_B	% tolualdehydes[31] ortho	meta	para
CO	$HF–SbF_5$	SO_2ClF	−95	1.6	45.2	2.7	52.1
HCOF	BF_3	excess aromatics	25	34.6	43.3	3.5	53.2
HCN–HCl	$AlCl_3$	excess aromatics	25	49.1	39.9	3.7	56.4
$Zn(CN)_2$–HCl	$AlCl_3$	CH_3NO_2	25	92.8	38.7	3.5	57.8
$Zn(CN)_2$–HCl	$AlCl_3$	excess aromatics	50	128	34.3	1.8	63.9
Cl_2CHOCH_3	$AlCl_3$	CH_3NO_2	25	119	35.8	3.8	60.4
CO + HCl	$AlCl_3Cu_2Cl_2$	excess aromatics	25	155	8.6	2.7	88.7
CO + HCl	$AlCl_3$	excess aromatics	0	319	6.6	0.8	92.6
CO + HF	BF_3	excess aromatics	0	860	3.5	0.5	96.0
CO	CF_3SO_3H/SbF_5 (1:1)	Freon-113	25	15	4.5	1.7	93.8[32]
CO	CF_3SO_3H/HF (1:1)/BF_3		25	21	5.5	4.2	91.3[32]

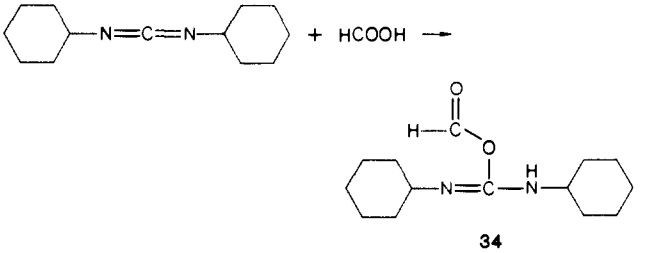
Formic acid is also used as a formylating agent in conjunction with some dehydrating agents, making the carboxylic carbon more electrophilic. N-formylation in pyridones **32** and **33** is easily achieved by using formic acid and dicyclohexylcarbodiimide (DCC) at 0 °C.[28]



32 **35**



33 **36**



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Intermediate **34** resulting from reacting formic acid with DCC may be involved in the reaction. *N*-Formylamines **35** and **36** are both used for selective formylation of alcohols. **36** has been used successfully even with highly crowded alcohols, such as 17-α-hydroxyprogesterone. The reaction is carried out in CH_2Cl_2 solution below 40 °C. Above this temperature it is unstable due to rapid decarbonylation.[28]

B. Acid-Catalyzed Formylation with Carbon Monoxide

Homogeneous and heterogeneous catalytic activation of carbon monoxide is an area of continuing intensive research. Among the reactions of interest have been CO reduction by hydrogen, the water gas shift reaction, reductive carbonylation of various organic substrates,[29] and acid-catalyzed reactions.[30] Reductive carbonylation lies, however, outside the scope of our review.

The classical electrophilic formylation method using CO, the Gattermann–Koch reaction[5] ($AlCl_3$/HCl or $AlCl_3/Cu_2Cl_2$/HCl), shows the highest selectivity and reactivity, in the observed high k_T/k_B rate ratios as well in the high degree of para substitution. The Gattermann synthesis using $Zn(CN)_2$ and $AlCl_3$ shows lower selectivity. As was mentioned previously the Friedel–Crafts type formylation with formyl fluoride (**1**) (referred to sometimes as Olah's reaction[31]) gives low para selectivity. This was attributed to the fact that the $HCOF·BF_3$ system produces a more reactive electrophile ($HCOF·BF_3$ complex, but not the free formyl cation HCO^+). Superacid-catalyzed carbonylation of a large variety of aromatics has been investigated. The lowest substrate selectivity reaction was observed when HF–SbF_5-catalyzed formylation with CO in SO_2ClF solution at −95 °C was used, giving toluene/benzene rate ratio k_T/k_B = 1.6. At the same time an isomer distribution of 45.2% *o*-, 2.7% *m*-, and 52.1% *p*-tolualdehyde was obtained (Table III).

Under the superacidic conditions studied, CO is protonated to give the rapidly equilibrating (with the solvent acid system) protosolvated formyl cation, an

TABLE IV. Superacid-Catalyzed Formylation of Arenes with CO at Atmospheric Pressure and 0 °C

substrate	superacid system	% yield of aldehyde (% disproportion products)
C_6H_5Me	CF_3SO_3H/SbF_5 (1:1)/Freon-113	59 (0)
C_6H_5Me	CF_3SO_3H/HF (5:1)/BF_3/Freon-113	79 (0)
o-$C_6H_4Me_2$	CF_3SO_3H/HF (5:1)/BF_3/Freon-113	44 (12)
m-$C_6H_4Me_2$	CF_3SO_3H/HF (5:1)/BF_3/Freon-113	56 (8)
p-$C_6H_4Me_2$	CF_3SO_3H/HF (5:1)/BF_3/Freon-113	54 (15)
C_6H_5Et	CF_3SO_3H/HF (5:1)/BF_3/Freon-113	78 (20)

obviously very reactive electrophilic reagent. When the reaction is carried out at 0 °C and only excess aromatics are used as solvent, the para regioselectivity becomes much higher, giving an isomer distribution of 7.5% *o*-, 2.8% *m*-, and 89.8% *p*-tolualdehyde.

The formylation of hexadeuteriobenzene (C_6D_6) with HCOF–BF_3 shows a kinetic hydrogen isotope effect of k_H/k_D = 2.68, on the basis of comparison of the reactivity of $C_6H_6/CH_3C_6H_5$ and $C_6D_6/CH_3C_6H_5$. This isotope effect is similar to that observed in Friedel–Crafts acetylation and propionylation reactions and indicates that the proton elimination step is at least partially rate determining. The low substrate selectivity formylation with CO/HF/SbF_5, however, shows no primary isotope effect.[30]

Trifluoromethanesulfonic acid catalyzed carbonylation of aromatics, including benzene, xylene, mesitylene, and ethylbenzene, with carbon monoxide is investigated under comparable reaction conditions.[32] The yield of aromatic aldehydes increases with increasing acidity of the catalyst system. Under atmospheric pressure and at 0 °C CF_3SO_3H/HF/BF_3 and CF_3SO_3H/SbF_5 give high yield of aldehydes (Table IV). Comparable conversions, with CF_3SO_3H/TaF_5 and CF_3SO_3H, are obtained by using CO pressure and excess acid (Table V). Moreover, the reaction of toluene with CF_3SO_3H under CO pressure (1200 psi) requires a large excess of the acid, and isomeric ditolylmethanes are produced, via the intermediate formation of dimethyl alcohol, together with traces of tritolylmethane. The amount of byproducts formed has a direct correlation with the steric requirement of the aromatic compound (18–20% for toluene, 3–5% for xylenes, and none for mesitylene). The para-substitution selectivity with CF_3SO_3H/HF/BF_3 and CF_3SO_3H/SbF_5 is comparable to that observed in conventional Gattermann–Koch reaction with $AlCl_3$/HCl or $AlCl_3/Cu_2Cl_2$/HCl, whereas that observed in the reaction of HCOF/BF_3 was lower.[32]

For a long while Friedel–Crafts acylations were considered to give almost exclusively para substitution of toluene. The reason accounting for this fact was considered to be steric. Our increasingly better understanding of the mechanism of electrophilic aromatic substitution indicated that this is not necessarily the only reason. Para substitution is greatly favored if the transition state of highest energy of the reaction is intermediate arenium ion (σ-complex) like, where a para methyl group is more stabilizing than an ortho group (and much more than a meta group). When, however, the highest transition state becomes increasingly "early" on the reaction path, the ratio of ortho/para substitution increases. Meta substitution always stays relatively low, generally less than 5–6%, varying with the reactivity of the reagent within this limit. It is interesting to examine the same pattern in the electrophilic formylation reactions (Table III). In these reactions the involved substituting agents are obviously less space demanding than those of other acylation reactions. Steric effects consequently cannot be a very significant factor affecting selectivity, which is primarily reflected in the changing ortho/para isomer ratio. The methyl group always remains a predominantly ortho–para directing substituent, even in very low substrate selectivity reactions, and the meta isomer does not increase above 4%.

IV. Carbonylation of Organometallic Reagents

Carbonylation of organometallic reagents with carbon monoxide has been reviewed recently.[2] Therefore, we will discuss only some reactions of direct interest to the context of the present review.

Seyferth and Hui reported[33a] a procedure for the direct nucleophilic 1,4-acylation of α,β-unsaturated ketones and aldehydes. In this process the carbonylation at atmospheric pressure of "higher order" cuprates of type $R_2(CN)CuLi_2$ was carried out at −110 °C. Later, an equimolar amount of the α,β-unsaturated substrate was added.

More recently, Seyferth examined[33b] the carbonylation of the R(CN)CuLi. The apparent stability of these reagents decreases in the order of $R = t\text{-}C_4H_9 > sec\text{-}C_4H_9 > n\text{-}C_4H_9$.

$$R(CN)CuLi + CO \rightleftharpoons RCO(CN)CuLi$$

The synthesis of diphenylalkylcarbinols[33c] via insertion reaction was reported by Nudelman. Insertion of carbon monoxide into carbon–lithium bonds also provided a convenient one-step synthesis of 1,2-diketone diaryl derivatives[33d] where Ar = 1-naphthyl and 2,6-dimethylphenyl.

$$ArLi \xrightarrow{CO} ArC(=O)Ar + ArC(=O)C(=O)Ar$$

Thermally stable lithium bis(*N*,*N*-diethylcarbamoyl)cuprate, which is readily prepared from CO

TABLE V. Superacid-Catalyzed Formylation of Arenes with Carbon Monoxide under Pressure

substrate	superacid system	CF_3SO_3H:arene molar ratio	reaction time, h	reaction temp, °C	% yield of aldehyde
C_6H_5Me	CF_3SO_3H	1:4	24	25	8
	CF_3SO_3H	1:1	17	25	14
	CF_3SO_3H	1:1	17	65	18
	CF_3SO_3H	6:1	3.5	25	79
1,3,5-$C_6H_3Me_3$	CF_3SO_3H	6:1	3.5	25	97
C_6H_5Me	$CF_3SO_3H + TaF_5$	1:1	17	25	17
C_6H_5Me	$CF_3SO_3H + SbF_5$ (1:1)/Freon-113	1:1	2	25	71
C_6H_5Me	$CF_3SO_3H + SbF_5$ (1:1)/Freon-113	1:1	3.5	25	82
1,3,5-$C_6H_3Me_3$	$CF_3SO_3H + SbF_5$ (1:1)/Freon-113	1:1	3.5	25	72

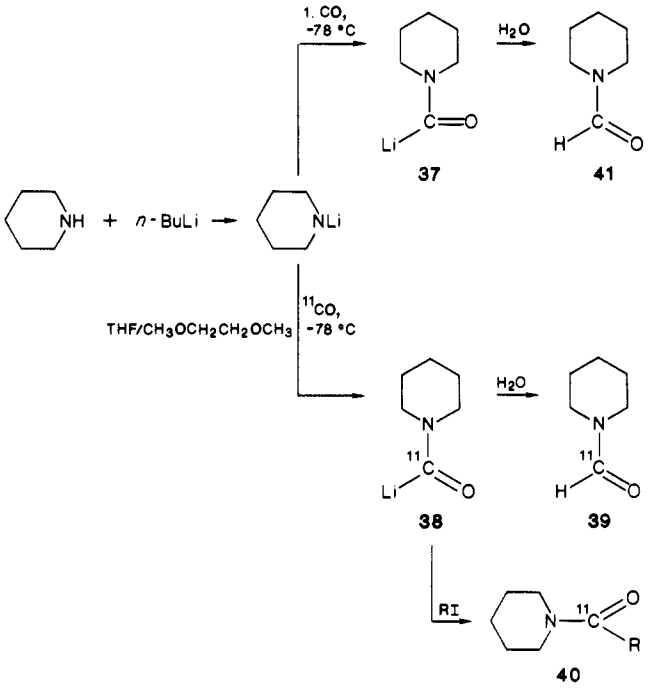
and lithium bis(*N*,*N*-diethylamino)cuprate, has been effective for direct carbamoylation.[33e]

$$CuCl + LiNEt_2 \rightarrow CuNEt_2 \xrightarrow{LiNEt_2}$$

$$(Et_2N)_2CuLi \xrightarrow{CO} (Et_2NCO)_2CuLi \xrightarrow{CH_2=CHCH_2Br} CH_2=CHCH_2CONEt_2$$

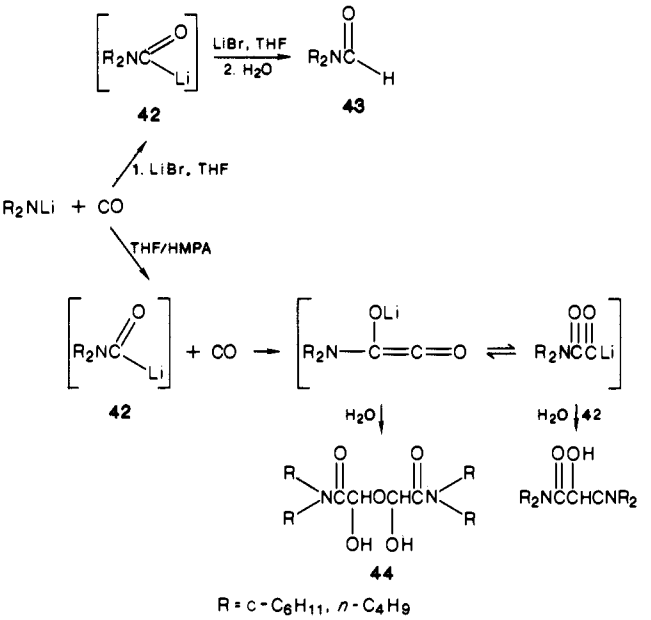
N-Alkylformamides are conveniently prepared by carbonylation of lithium dialkylamines with carbon monoxide under a variety of conditions. Solvent, temperature, and the presence of additional salts are reported to aid the carbonylation process and the stabilization of the intermediate anion.[2,33f] In these reactions excess CO is usually required. A variety of catalysts, including metallic alkoxides, cobalt-, iron-, and ruthenium-containing compounds, have been employed. The disadvantage of this method is, however, due to the secondary reactions, resulting from the reaction of the reactive acyl anion salt **37** with excess CO in the medium.

Recently Kilbourn[33f] reported the synthesis of carbon-11 (β^+ decay, $t_{1/2}$ = 20.4 min) labeled *N*-formylpiperidine and other carbonylated amines. The synthesis has the novel aspect of in situ formation of a highly reactive radiolabeled intermediate, which can be converted into numerous products. The advantage of this method over the previously reported ones is the need for only a trace amount of ^{11}CO and very short reaction times (5–7 min), which eliminates the secondary reactions.



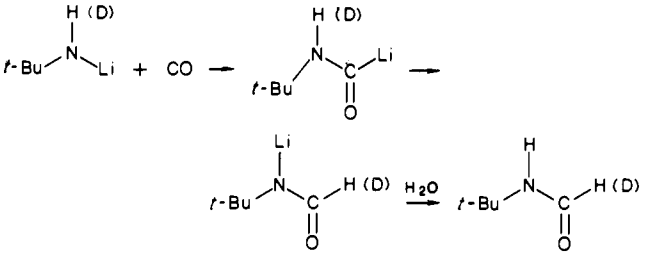
Passing a stream of ^{11}CO in helium into a cold (−78 °C) solution of lithium piperidine in tetrahydrofuran/dimethoxyethane resulted in the trapping of 10–20% of the ^{11}C activity, presumably in the form of the unstable acyl anion salt **38**. Quenching of this intermediate with water or a solution of alkyl iodide results in the formation of the formamide **39** and the amide **40**, respectively.

Nudelman[34] has reported a significant improvement for the synthesis of *N*,*N*-dialkylformamides. It was observed that added salts and low-polarity solvents affect the course of the reaction. **44** is formed as a side product by reacting **42** with excess CO. However, in

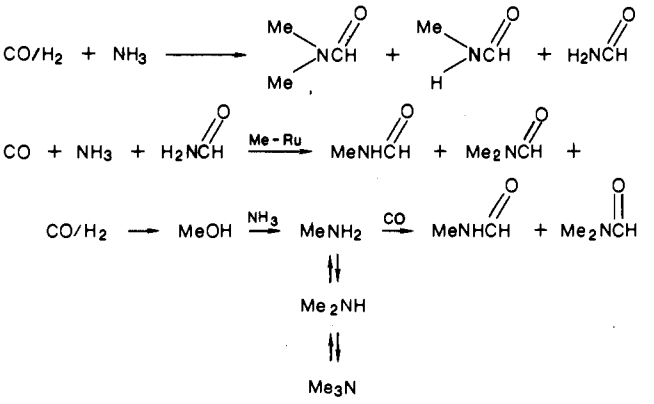


the presence of LiBr in THF this side reaction seems to be eliminated in favor of **43**, since the dialkylformamide comes from the hydrolysis of the lithium carbamoyl **42** formed by insertion of CO into the N–Li bond. Treating **42** with heavy water (i.e., D_2O) results in the formation of a deuterium-labeled N-formyl group.[35]

An interesting rearrangement has been observed with the aminocarbonyllithium reagent generated from lithium *tert*-butylamide.[36]



The preparation of *N*-methyl- and *N*,*N*-dimethylformamides has been described by Knifton,[30] using synthesis gas (CO/H_2) and ammonia. The reaction is



carried out over heterogeneous ruthenium "melt" catalysts, comprising one or more ruthenium oxide, salt, and complex species, dispersed in various phosphonium salts. This class of melt catalyst has been previously demonstrated to be particularly effective for the con-

TABLE VI. Preparation of *N*-Methylformamides from Synthesis Gas and Ammonia

catalyst precursor	Ru, mmol	NH_3, mmol	time, h	liq prod compn, wt % ΣNMR Me_2NCHO	ΣNMR MeNHCHO	ΣF H_2NCHO	liq yield, wt %	turnover freq
$Ru_3(CO)_{12}$–Bu_4PI	2.0	400	4	23.9	42.7		112	15
$Ru_3(CO)_{12}$–Bu_4PI	4.0	800	4	40.5	17.7	25.6	92	10
$Ru_3(CO)_{12}$–Bu_4PBr	2.0	400	18	59.1	12.7	10.9	83	
$Ru_3(CO)_{12}$–Bu_4PBr	2.0	400	4	13.6	21.1	59.6	105	7
$RuCl_3$–Bu_4PBr	2.0	400	4	25.0	28.5	42.5	109	12
$Ru(acac)_3$–Bu_4PBr	2.0	400	4	22.3	14.4	53.2	101	8

TABLE VII. *N*-Methylformamides from Synthesis Gas

catalyst precursor	added reactants	prod compn, mmol Me_2NCHO	MeNHCHO	H_2NCHO	reaction rate ΣNMR/mol of Ru, h	ratio ΣNMR/ΣF
$Ru_3(CO)_{12}$–Bu_4PBr	NH_3	20.3	38.9	144	7.4	0.41
$Ru_3(CO)_{12}$–Bu_4PBr	NH_3 + MeOH	41.3	152	63.8	24.2	3.0
$Ru_3(CO)_{12}$–Bu_4PBr	NH_3 + [^{13}C]MeOH	12.4	54.1	127	8.3	0.53
$Ru_3(CO)_{12}$–Bu_4PBr	NH_3 + H_2NCHO	1.8	11.8	72.6	1.7	0.19
$Ru_3(CO)_{12}$–Bu_4PBr	Me_3N	3.2	2.2			

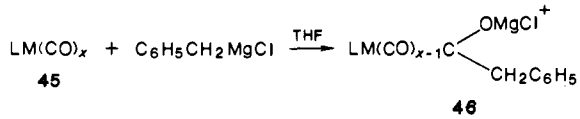
version of CO/H_2 into alkanols and diols and for the generation of carboxylic acids.[37-39]

The suggested route for the formation of the trimethylamine, a principal byproduct, is shown in the above equation. It also could result through ruthenium-catalyzed hydrogenation of the DMF fraction in the presence of syngas (Tables VI and VII).[30]

The homogeneously catalyzed activation of carbon monoxide has recently gained renewed attention based in part upon the perceived desirability of using synthesis gas (CO/H_2 mixture) as feedstock for the production of organic chemicals and fuels. A key mechanistic step proposed for such catalysis is the nucleophilic activation of coordinated CO (Scheme I).[29]

This type of activation of CO via such reactions with H_2O or base has importance not only for the water gas shift reaction adjustment of CO/H_2 ratios in synthesis gas feedstocks but also as a methodology for using carbon monoxide/water mixtures for the catalytic reduction and hydroformylation/hydroxymethylation of various organic substrates.[40-42] Quantitative studies of the reactions of the nucleophiles CH_3O^- and HO^- with the pentacarbonyl complexes, $M(CO)_5$, show that they follow the reactivity order Os > Ru > Fe, forming the methoxy carbonyl adduct. This was attributed to electronic factors, the respective abilities of the various $M(CO)_4$ fragments to accommodate negative charge, and the metal–ligand bonding changes in going from a strongly π-accepting CO to a stronger σ-donor but weaker π-acceptor ($CO_2CH_3^-$) ligand. The very low reactivity of $Ru(CO)_4$ ($P[OCH_3]_3$) confirms the importance of such electronic effects.[29]

The reactivities of nucleophiles such as benzylmagnesium chloride with metal carbonyl complexes **45**

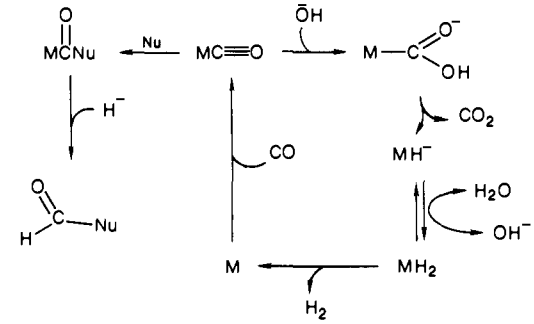


45 **46**

L = phosphine, phosphite, CO
M = Cr, Mo, W; x = 5
M = Fe; x = 4

was tested according to their geometric, steric, and nucleophilic properties. The chromium triad shows a similar pattern, i.e., W > Mo > Cr. These observations have been rationalized in terms of lesser steric constraints as well as the somewhat higher CO force constants for the heavier metal center.[43a]

SCHEME I

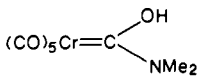


Marks et al. reported[43b] the synthesis and characterization of chlorobis(pentamethylcyclopentadienyl)-thorium and -uranium dialkylamides and bis(dialkylamides). It was shown that the amide compounds undergo facile migratory insertion of carbon monoxide to produce the corresponding η^2-carbamoyl complexes.

Recently, various aryl halides were catalytically converted into α-keto amides and amides on treatment with secondary amines and carbon monoxide.[43c] Palladium complexes containing phosphine ligands showed the highest reactivity among other transition-metal complexes. It was also shown that the reactivity of phenyl halide decreases in the order PhI > PhBr ≫ PhCl.

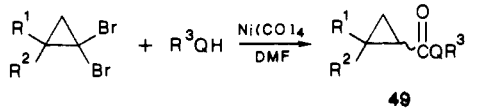
The hydrogenation of a 1:1 mixture of chromium hexacarbonyl and lithium dimethylamide ($LiNMe_2$) known to produce **47** in THF (35 psi H_2, 130 °C, 18–24 h) yielded several organic products, including methanol (10%) and dimethylformamide (DMF, 30% yield). When HMPA (hexamethylphosphoric triamide) was used as solvent, the yields of DMF and MeOH were lower (DMF, 15%) but the yield of DMF was improved (40%) by running the reaction at 70 °C instead of 130 °C. A probable mechanism for DMF formation was suggested as shown in Scheme II.[40] Protonation of the anionic complex **47** with trifluoroacetic acid in acetone-d_6 at 25 and 130 °C does not give rise to DMF,

ruling out formation of 48 followed by its thermal decomposition to give DMF.



48

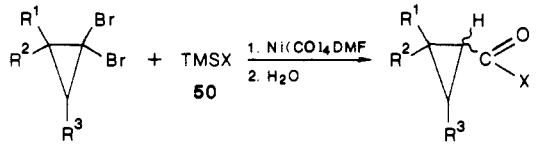
Nickel enolates have been utilized in a number of related reactions. $Ni(CO)_4$-induced reductive carbonylation reactions of *gem*-dibromocyclopropanes with amines or alcohols have been examined (Table VIII).[44]



49

Q = O, NH, NR^4

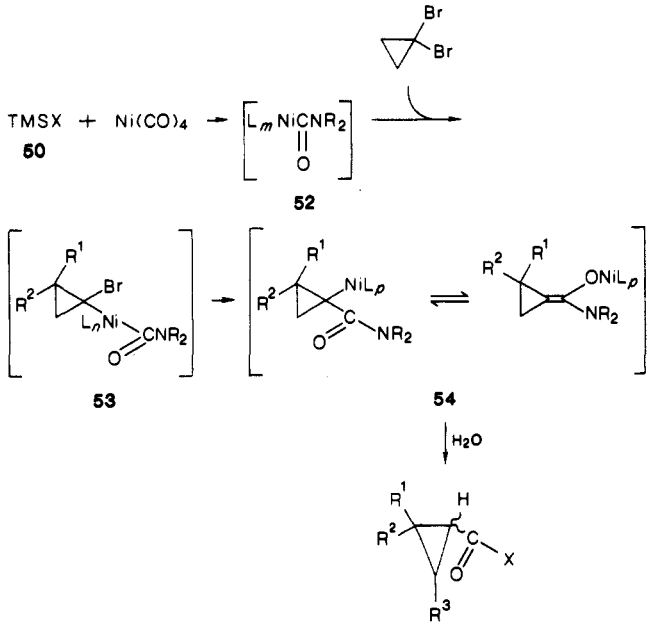
The potential importance of such reactions is to overcome the difficulty involved in introducing carbonyl functionalities into a cyclopropane ring. Recently[45] silylamines and silyl sulfides **50** have been used with $Ni(CO)_4$ to give the corresponding cyclopropyl derivatives **51**. The mechanism of this reaction is quite



50 **51**

X =  , NMe_2, NEt_2, SR

different from that involving chromium enolate **47** discussed previously. First $Ni(CO)_4$ is assumed to form a complex with TMSX **50** to generate **52**. The reaction

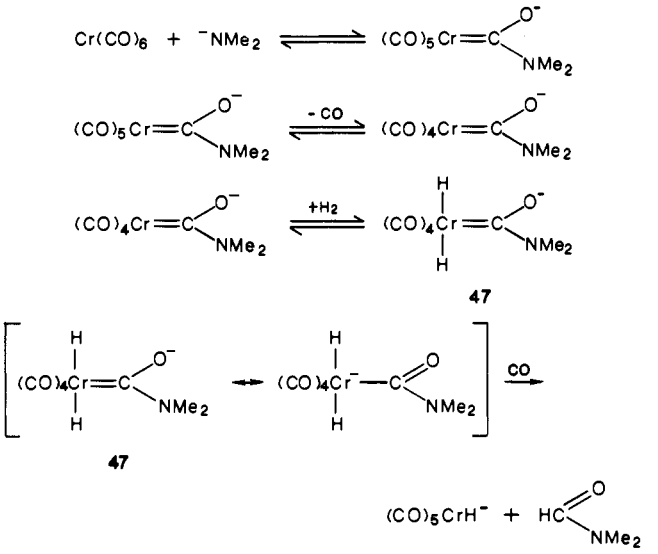


53 **54**

of **52** with *gem*-dibromocyclopropane forms the nickel carbenoid complex **53**. The migration of the carbamoyl group gives the enolate **54**, protonation (upon workup) of which completes the reaction.

Recently, the palladium-catalyzed formylation of a variety of organic substrates (aryl iodides, benzyl halides, vinyl iodides, vinyl triflates, and allylic halides) with tin hydride and carbon monoxide was reported.[46] In general, electron-donating or -withdrawing substituents on the aryl halides have no effect on the formylation reaction; however, the *p*-nitro substituent causes significant reduction in the yield of aldehyde. Also, steric hindrance about the electrophile will provide a diminished yield.

SCHEME II



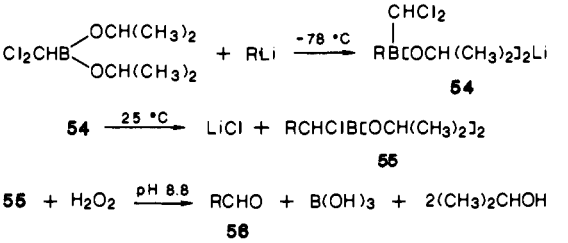
V. Formylation of Organometallic Reagents

After reviewing reagents developed for electrophilic formylations and some aspects of the carbonylations of organometallics, we will now discuss recent development of methods for nucleophilic type reactions of organometallic reagents such as Grignard or organolithium reagents with formylating agents, primarily *N*-formylamines.

On the subject of the nucleophilic type reactions, the readers are recommended to refer to the reviews by Lever[47a] on reagents for nucleophilic acylation and Reich et al.[47b] for the preparation of silyl ketones.

A. Boron Ester Derivatives as Formylating Agents

Carbonylation of organoboranes has been reviewed.[3b] Boron esters have been used as indirect formylating agents, involving several steps. This makes these



54 **55** **56**

formylating methods less attractive and practical. Rathke and co-workers[47c] in 1976 reported the reaction of dichloromethane boronate with organolithium or organomagnesium reagents, which upon oxidation by hydrogen peroxide yielded aldehydes.

Organolithium reagents react at low temperature, but Grignard reagents must be used, however, at higher temperature. Different α-chloro boronic esters and a variety of nucleophiles have been studied (Table IX).[48]

TABLE VIII. Preparation of Cyclopropanecarboxylic Acid Derivatives

R^1	R^2	R^3QH (molar equiv)	$Ni(CO)_4$, molar equiv	yield, % (trans:cis)
Ph	H	*n*-PrOH (2.5)	6	62 (34:66)
Ph	H	PhOH (2.5)	6	57
Ph	H	*m*-ClC_6H_4OH (2.5)	6	56
Me	CO_2Me	*n*-PrOH (2.5)	6	75
Me	CN	*n*-PrOH (2.5)	6	51
Ph	H	*n*-$PrNH_2$ (2.5)	6	78 (45:55)
Ph	H	*n*-$PrNH_2$ (2.5)	1	52
Ph	H	*n*-$PrNH_2$ (1)	1	52
Ph	H	*n*-$PrNH_2$ (1)	1	0
Ph	H	$PhNH_2$ (2.5)	6	63 (50:50)
Ph	H		6	66
Ph	H	CH_2=$CHNH_2$ (2.5)	6	56
Me	CO_2Me		6	44

TABLE IX. Reactions of α-Chloroboronic Esters with Nucleophiles

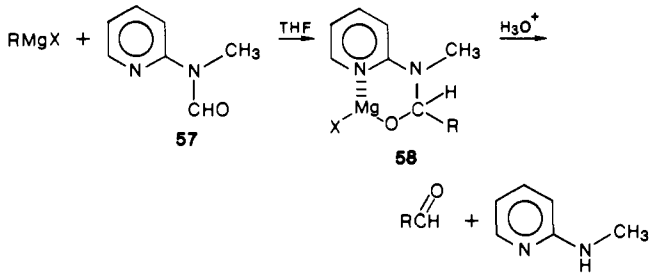
$R^1CHClBO_2C_2R_4^2$			product		
R	R′	nucleophile	structure	bp, °C/Torr	yield, %
c-C_5H_9	H	NaSPh	$C_5H_9CH(SPh)BO_2C_2H_4$	120–124/0.2	91
$(CH_3)_3C$	H	NaSPh	$(CH_3)_3CCH(SPh)BO_2C_2H_4$	105–110/0.15	88
c-C_5H_9	H	PhMgBr	$C_5H_9CH(Ph)BO_2C_2H_4$	90–93/0.1	90
c-C_5H_9	H	*n*-C_4H_9Li	$C_5H_9CH(C_4H_9)BO_2C_2H_4$	85–89/2.8	92
c-C_5H_9	H	c-$C_6H_{11}MgCl$	$C_5H_9CH(C_6H_{11})BO_2C_2H_4$	85–88/0.1	94

TABLE X. Conversion of Grignard Reagents to Aldehydes with 2-(*N*-Methyl-*N*-formylamino)pyridine

RMgX	yield of RCHO, %	bp, °C/Torr
C_6H_5MgBr	72	62–66/10
1-naphthyl-MgBr	76	84–89/0.05
$C_6H_5CH_2CH_2MgBr$	75	58–61/1
$C_6H_5CH_2Cl$	80	75–80/10
$C_6H_5CH_2CH(CH_3)MgBr$	81	51–54/0.05
C_6H_5C≡$CMgI$	75	69–70/1.5
C_6H_5CH=$CHMgBr$	70	73–77/1

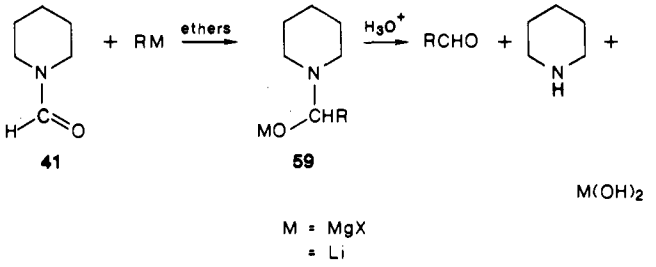
B. Formylation with *N*-Formylalkylamines

Comins and Meyers[49] reported the use of 2-(*N*-methyl-*N*-formylamino)pyridine (**57**) as a formylating agent for Grignard reagents in 70–80% yield (Table X).



2-(*N*-methyl-*N*-formylamino)pyridine is not commercially available. It is prepared by the reaction of 2-aminopyridine with phenyl formate at room temperature, followed by methylation of 2-(*N*-formylamino)-pyridine with methyl iodide. The presence of the additional ligand (pyridyl nitrogen) and the ready formation of a six-membered chelate ring **58** was considered to prohibit the release of the aldehyde under the reaction conditions, thus protecting it from further reaction with the organometallic reagents.

Olah and Arvanaghi subsequently developed[50] the use of the readily available *N*-formylpiperidine as an efficient general formylating agent. In ether or hydrocarbon solution at room temperature *N*-formylpiperidine (**41**) reacts with aryl-, alkyl-, vinyl-, and



ethynyllithium or Grignard compounds and results in formation, upon acidic workup, of the corresponding pure aldehydes in excellent yields (Table XI). Piperidine can, if necessary, be easily recovered and recycled after carbonylation with CO (see section IV). The results with *N*-formylpiperidine demonstrate that chelate ring formation is not crucial for the success of the reaction.

N-formylmorpholine (**60**) can also be used as an efficient formylating agent for Grignard and organolithium reagents.[51] Treatment of this reagent in ether at 0 °C with a wide variety of organolithium or Grignard reagents results in formation, upon acidic workup, of

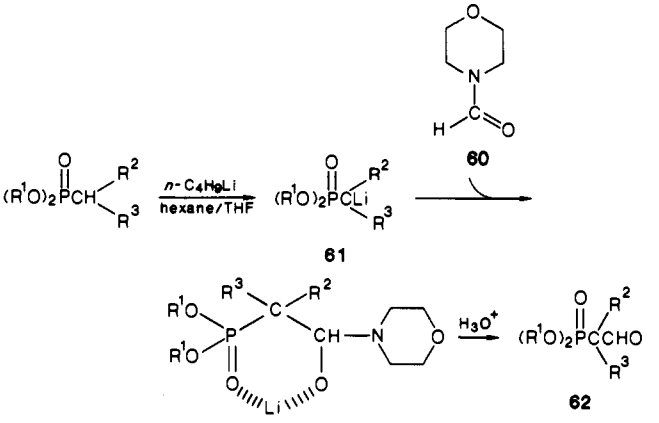
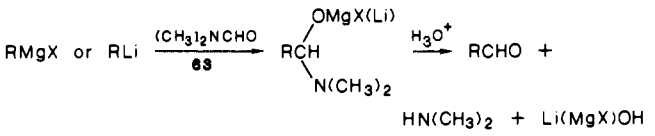


TABLE XI. Aldehydes by Reaction of Grignard and Organolithium Reagents with *N*-Formylpiperidine or *N*-Formylmorpholine

RMgX or RLi	yield, %		solvent	mp, °C, or bp, °C/mmHg
	N-formylpiperidine	*N*-formylmorpholine		
C_6H_5MgBr	96	89	ether	63–64/10
$C_6H_5CH_2MgCl$	89	84	ether	76–78/10
1-naphthyl-MgBr	94	92	ether	142/6
9-phenanthryl-MgBr	97		ether	108.4
$C_6H_5{\equiv}CMgI$	85		THF/ether	65/0.1
$C_6H_5CH{=}CHMgBr$	86	81	ether	85/2
$C_6H_5CH_2CH_2MgCl$	78	70	ether	87/1
c-C_3H_5MgBr	80		ether	101–102/760
c-C_6H_9MgBr	72	69	ether	73–76/100
2-norbornyl-MgBr	76	74	ether	52/7
sec-butyl-Li	77		*n*-hexane	91–94/760
n-butyl-Li	83	78	*n*-hexane	101/760
c-C_3H_5Li	75		ether	96–98/740
C_6H_5Li	94	90	benzene	63–64/10
$C_6H_5C{\equiv}CLi$	94		*n*-hexane	65/0.1
	93	80	ether	

the corresponding pure aldehyde (Table XI). α-Lithioalkanephosphonates **61** are also formylated by *N*-formylmorpholine as well as *N*-formylpiperidine in THF at −78 °C to furnish, upon acidic workup, the corresponding aldehydes **62** (Table XII).[51]

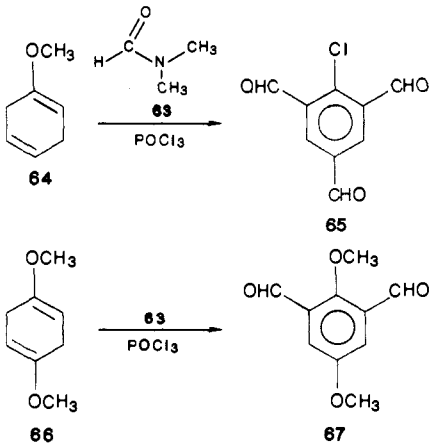
Contrary to earlier reports,[52,53] Grignard reagents as first described by Bouveault[6] react with *N,N*-dimethylformamide (**63**) in usual etheral solvents to give



upon acidic workup the corresponding aldehydes in good yields.[54] The reaction, however, must be carried out under mild conditions (0–20 °C) and with avoidance of excess Grignard reagent. Otherwise secondary reactions, particularly reduction and electron-transfer reactions, take place (Table XIII).

In contrast, reactions of alkyl- and aryllithium with *N,N*-dimethylformamide, in some cases, did not give satisfactory results. This can be attributed to competing one-electron-transfer processes.[54]

Recently[55] some 1-methoxy-1,4-cyclohexadienes (**64** and **66**) were reacted with dimethylformamide (**63**) in



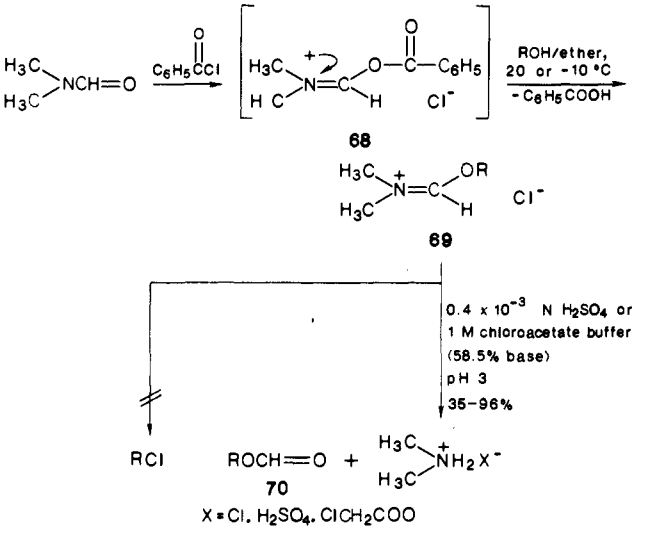
the presence of phosphoryl chloride (Vilsmeier reaction). This interesting reaction is a convenient way to

TABLE XII. Preparation of Dialkyl (1-Formylalkyl)phosphonates Using *N*-Formylpiperidine and *N*-Formylmorpholine

$(R^1O)_2P(O)$-CR^2R^3CHO			yield, %		bp, °C/mmHg
R^1	R^2	R^3	*N*-formyl-morpholine	*N*-formyl-piperidine	
C_2H_5	H	H	85	87	72–6/0.25
i-C_3H_7	H	H	83	83	72–8/0.5
C_2H_5	CH_3	H	94	95	93–5/2
i-C_3H_7	CH_3	H	91	93	80–5/1
C_2H_5	CH_3	CH_3	83	87	98–100/4
C_2H_5	C_2H_5	H	80	82	98–102/2.8

polyformylate aromatic compounds (**65** and **67**).

An interesting extention to the Vilsmeier–Haack reaction has been reported. The reaction of the adduct benzoyl chloride–dimethylformamide **68**, generated in



situ, with the stoichiometric amount of a wide variety of alcohols in ether solution at room temperature, gives rise to the formation of the corresponding imidate ester chlorides **69** in good yields. Hydrolysis of **69** under acidic conditions [0.4×10^{-3} N sulfuric acid, or 1 M chloro acetate buffer (58.5% base) at 0–5 °C] provides formic acid esters **70** derived from primary, secondary, allylic, and benzylic alcohols.[56]

TABLE XIII. Formylation of Grignard Reagents with *N,N*-Dimethylformamide

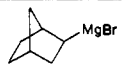
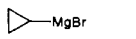
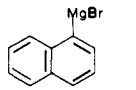
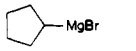
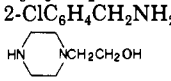
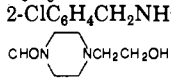
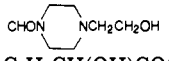
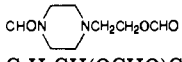
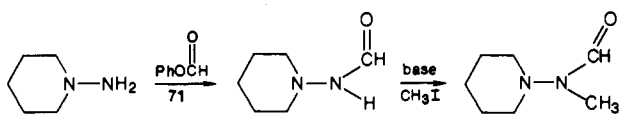
Grignard reagent	solvent	yield, %	bp, °C/mmHg
	ether	71	47–8/5
$C_6H_5CH_2CH_2MgBr$	ether	81	87/1
	THF	59	100/760
	ether	87	115–6/0.2
$C_6H_5CH{=}CHMgBr$	ether	68	85/2
n-$C_5H_{11}MgBr$	ether	63	131–3/760
n-C_4H_9MgBr	ether	56	103–4/760
C_6H_5MgBr	ether	88	57/13
	ether	71	58–60/20

TABLE XIV. Formylation with 2-Formyl-2-methyl-1,3,4-thiadiazoline-5-thione

R^1R^2NH, ROH	solvent	product	yield, %
$C_6H_5NH_2$	acetone	C_6H_5NHCHO	87
2-$ClC_6H_4CH_2NH_2$	acetone	2-$ClC_6H_4CH_2NHCHO$	85
	acetone		93
$C_6H_5HNCH_3$	acetone	$C_6H_5N(CHO)CH_3$	84
$C_6H_4(CO)_2NH$	DMF	$C_6H_4(CO)_2NCHO$	83
4-$NO_2C_6H_4CH_2OH$	acetone	4-$NO_2C_6H_4CH_2OCHO$	89
	acetone		78
$C_6H_5CH(OH)COOH$	acetone	$C_6H_5CH(OCHO)COOK$	84

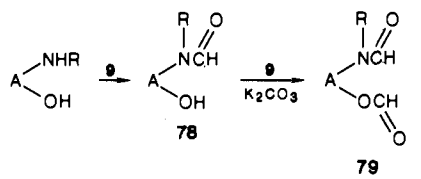
Fréchet and Amaratunga[57] have reexamined different *N*-formylalkylamines as formylating agents under comparable conditions. Their findings suggest the importance of an additional ligand for the success of the reaction. However, most reagents are not readily available. **72** is prepared by the reaction of *N*-amino-



72

piperidine with a 10% excess of phenyl formate (**71**) followed by methylation. **73**, **74**, **75**, and **76** (Chart I) were prepared by the same procedure, however, **77** was prepared by the reaction of piperazine and phenyl formate (**71**) in 2:1 ratio (see Chart I).

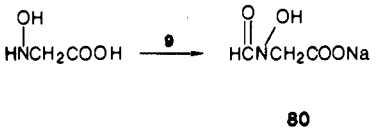
The N-formyl derivative of 2-methyl-1,3,4-thiadiazoline-5-thione (**9**) (section III.A) has been used as a formylating agent for amines and alcohols. Primary and secondary amines are formylated at room temperature or below to give the corresponding N-formyl compounds **78**. The formylation of polyhydroxy compounds gen-



78 **79**

erally requires the presence of a weak base such as potassium carbonate.[58] Both selective N-formylation **78** and N,O-diformylation **79** of amino alcohols, however, were achieved in the absence as well as the presence of potassium carbonate (Table XIV).[15]

N-Formyl-*N*-hydroxyglycine (**80**) (hadacidin) and



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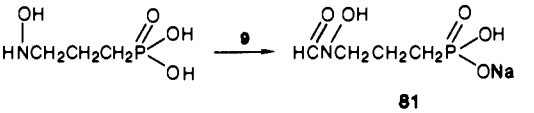
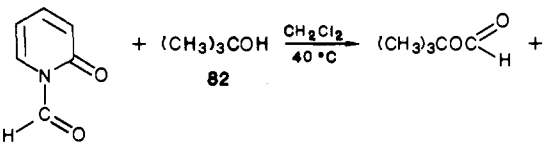


81

3-(*N*-formyl-*N*-hydroxyamino)propylphosphonic acid (**81**) were prepared by this reagent.

N-formylpyridone (**36**) is utilized to formylate amines, alcohols, and thiols.[7] In a series of amines, primary



36 **82**

amines react best and tertiary the worst. Tertiary alcohols can be also formylated despite their steric requirement.

C. Formylation with Formic Acid or Its Derivatives

Reaction of Grignard reagents with formic acid itself was reported to afford aldehydes only in very low yields.[59,60] However, Sato has illustrated[61] that the reaction is solvent dependent. Best results are obtained in THF. Grignard reagents react with formic acid in THF to produce the expected adduct **83**. Another

$$HCOOH + C_2H_5MgBr \rightarrow \underset{\mathbf{83}}{HC(=O)OMgBr} + C_2H_6 \underset{\mathbf{83}}{HC(=O)OMgBr} +$$

$$RMgBr \rightarrow \underset{\mathbf{84}}{HC(R)(OMgBr)_2} \xrightarrow{H_2O} RC(=O)H$$

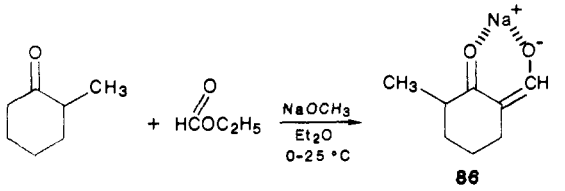
equivalent of Grignard reagent produces the bis adduct **84**, which on hydrolysis gives the aldehyde. Various alkyl, aryl, allyl, benzyl, and vinyl Grignard reagents give the corresponding aldehydes. The reaction with vinyl Grignard reagents proceeds with retention of configuration (Table XV).

A more convenient use of formic acid is in the form of its salts as formylating agents. Grignard reagents react with lithium (sodium) formate (**85**) in boiling

$$RMgX + HCOOLi(Na) \rightarrow \underset{\mathbf{85}}{RC(=O)H}$$

THF, giving the corresponding aldehydes in good yields. Alkyl, aryl, and vinyl Grignards can be used (Table XVI).[62]

Although ethyl formate is known to react with enolates to provide α-protection, **86**, albeit in low yield, harder anions (Grignards and organolithiums) do not react.[63a]



86

The reaction of alkyl formate with organolithium reagents was also attempted; however, the obtained product was only the alcohol.[27]

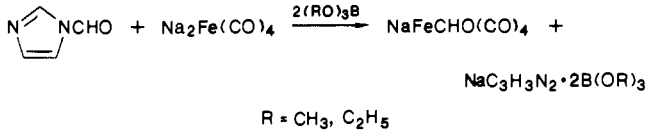
D. Formylation of Transition-Metal Complexes

In 1973, Collman and Winter reported[63b] the preparation and characterization of the kinetically stable formyl complex of $(CO)_4Fe(CHO)N(PPh_3)_2$. This salt

$$Na_2Fe(CO)_4 + HC(=O)OC(=O)CH_3 \xrightarrow[25\ °C]{THF} HC(=O)Fe(CO)_4^-\ N(PPh_3)_2^+$$

was isolated from the treatment of $Na_2Fe(CO)_4$ with acetic formic anhydride in tetrahydrofuran.

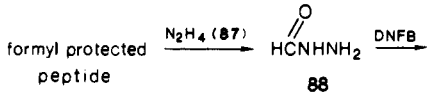
Later, Miller et al. reported[63c] the successful production of a formyliron complex via the reaction be-



tween $Na_2Fe(CO)_4$ and *N*-formylimidazole. This reaction was facilitated by the use of trialkylboron in HMPA and THF.

VI. Formylation of Polymers and Formylated Peptides

There are several enzymatic reactions of one carbon fragment metabolism where the formate group is a participant. The formyl group is also found in at least two naturally occurring polypeptides, masking the amino group at the end of the chain. Limited information exists only on the formate and formyl content of various tissues. An interesting reaction is the method of deformylation of these peptides or amino acids. Hydrazine (**87**) is used as a deformylating agent to measure



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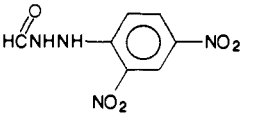


89

the formyl content of these tissues. The formyl groups are measured as *N*-formyl-*N'*-2,4-dinitrophenylhydrazine (**89**).[64]

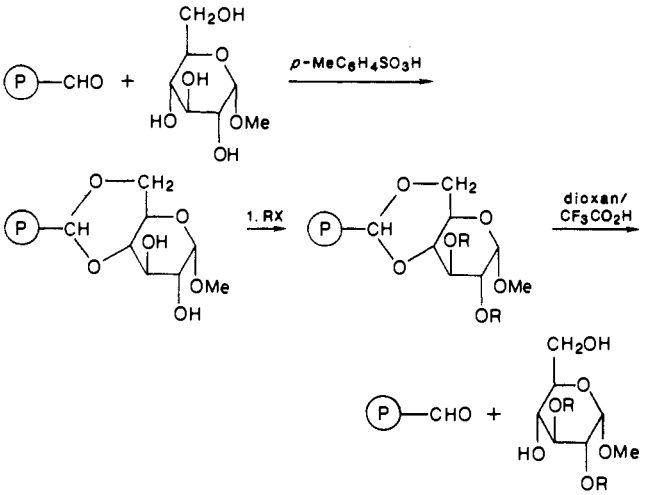
Functionalized resins have found numerous applications recently as supports in solid-phase synthesis, reagents or protecting groups in organic synthesis, and supports for chromatography or catalysis. Fréchet has reviewed[65] the preparation of different functional polystyrene resins and their use. Formylated polystyrene resins are mainly used as protecting groups for saccharides and polysaccharides.[66] These formylated polystyrenes are prepared by standard methods. For example, lithiated polystyrene resins when treated with DMF or *N*-formylpiperidine upon acidic workup produce the corresponding formylated resin **90**.[67]

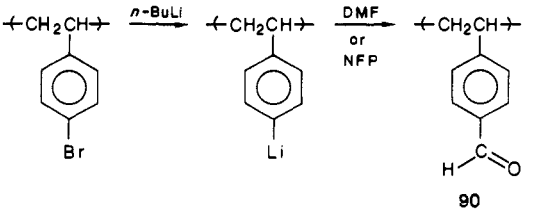
TABLE XV. Formylation of Grignard Reagents with Formic Acid

RMgBr	RCHO	yield, %
$C_6H_{13}MgBr$	$C_6H_{13}CHO$	75
$C_8H_{17}MgBr$	$C_8H_{17}CHO$	70
$C_3H_7CH(CH_3)MgBr$	$C_3H_7CH(CH_3)CHO$	38
$BrMg(CH_2)_4MgBr$	$OHC(CH_2)_4CHO$	55
C_6H_5MgBr	C_6H_5CHO	81
$C_6H_5CH_2MgBr$	$_6H_5CH_2CHO$	61
$C_3HCH{=}CHCH_2MgBr$	$C_3H_7CH(CHO)CH{=}CH_2$	50
$C_4H_9CH{=}CHMgBr$	$C_4H_9CH{=}CHCHO$	
E/Z = 15/85	E/Z = 16/84	60
E/Z = 65/35	E/Z = 65/35	58
$C_6H_5CH{=}CHMgBr$	$C_6H_5CH{=}CHCHO$	
E/Z = 89/11	E/Z = 87/13	67

TABLE XVI. Formylation of Grignard Reagents with Lithium (Sodium) Formate

		yield, %	
RMgBr(Cl)	RCHO	HCOOLi	HCOONa
C_6H_5MgBr	C_6H_5CHO	85	79
C_6H_5MgCl	C_6H_5CHO	80	72
o-$CH_3OC_6H_4MgBr$	o-$CH_3OC_6H_4CHO$	85	76
$(CH_3)_2CHMgCl$	$(CH_3)_2CHCHO$	80	75
p-BrC_6H_4MgBr	p-BrC_6H_4CHO	83	69
$C_6H_5CH_2MgCl$	$C_6H_5CH_2CHO$	79	
1-naphthyl-MgBr	1-naphthaldehyde	78	
$C_6H_5CH{=}CHMgBr$	$C_6H_5CH{=}CHCHO$	72	



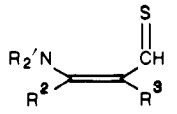


90

VII. Thioformylation

Thioketones are well-known stable compounds. Reports on the synthesis of thioaldehydes, however, are scarce. Early attempts to prepare thioaldehydes in-

variably led to the isolation of oligomeric and polymeric species.[68] Woodward reported the first stable monomeric compound containing the thioformyl group.[69a] Vedejs et al.[69b] recently described the preparation and characterization of monomeric thiopivaldehyde, the first aliphatic thioaldehyde under ordinary laboratory conditions (the preparation was achieved by photolysis of the corresponding phenacyl sulfide). Reid and his coworkers[70] have utilized the Vilsmeier–Haack reaction to synthesize a number of heterocyclic thioaldehydes. Enamines also react with dimethylformamide in the presence of phosphoryl chloride to give the corresponding Vilsmeier salt, which on in situ solvolysis with alcoholic NaHS produces the thioaldehyde **91**.[71] Much further work is needed to extend the scope of synthetic methods for the preparation of thioaldehydes.



91

$R_2'N$ = morpholino, $R^2 = R^3$ = Ph

$R_2'N$ = pyrrolidino, $R^2 = R^3$ = Ph

$R_2'N$ = morpholino, R^2 = Ph, R^3 = H

$R_2'N$ = morpholino, R^2, $R^3 = (CH_2)_3$

VIII. Conclusions

Their ready accessibility coupled with versatile chemical properties makes aldehydes an important class of organic compounds.

Recent research has established the synthetic utility of a series of useful formylating agents, both in electrophilic and nucleophilic reactions. In this article a general overview of these formylating agents is given, which involves a single-step reaction. The preparative advantages and applicability of the reagents are discussed. The most attractive formylating reagents are those readily obtained or inexpensive and commercially available. Only brief relevant discussion of two-step aldehyde syntheses via carbonylation of organolithium and Grignard reagents with carbon monoxide and formylation with boron esters has been included, as these reactions were reviewed elsewhere.

Acknowledgments. Support for our studies over the years on formylation reactions and methods by the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

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