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Reaction of Acyl Chlorides with Organometallic Reagents: A Banquet Table of Metals for Ketone Synthesis

R. Karl Dieter

Department of Chemistry, Howard L. Hunter Laboratory, Clemson University, Clemson, SC 29634-1905

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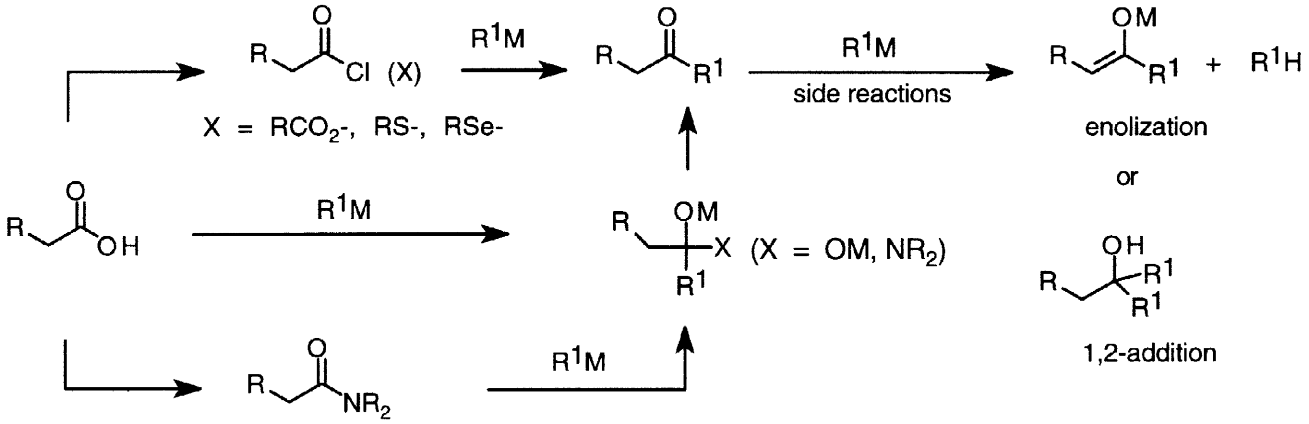
1.0 INTRODUCTION

The synthesis of ketones from carboxylic acids or their derivatives is an important synthetic operation whereby C-C bond construction and functional group interconversion is achieved. Single step conversions of carboxylic acids and their derivatives into ketones concisely illustrate the central drama of reactivity and chemical stability in organic chemistry. Two strategies have emerged which exploit the relative reactivities of the carboxylic acid derivative and product ketone toward nucleophilic attack (Scheme I). 1,2-Addition of hard organometallic reagents to carboxylic acids and amides affords tetrahedral intermediates stable to the reaction conditions. Since the ketone is unmasked by collapse of the tetrahedral intermediate during the work-up procedure, the more reactive ketone is unavailable to the attacking nucleophile. Acid chlorides, thiol esters, seleno esters, and anhydrides are more reactive toward many organometallic reagents than the product ketones and chemoselectivity can, in principle, be achieved by the influence of temperature, solvent, and modification of reagent reactivity.

Scheme I



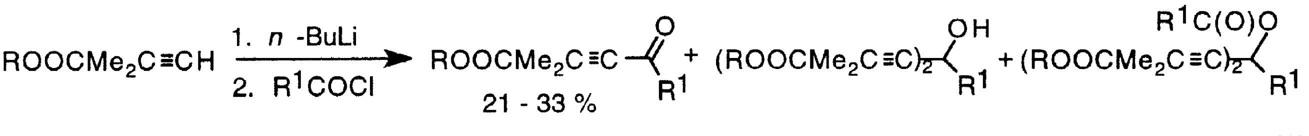
The reaction of acid chlorides with organometallic reagents provides a quick, direct, and convenient procedure for the synthesis of ketones.[1] The reaction is, however, fraught with difficulties involving the relative reactivities of the acid chloride, the ketone product, and the organometallic reagent. Investigations of this reaction have been spurred by the need to balance the reactivity of the reactants and ketone products, and by the high reactivity of acyl chlorides which makes them good probes for exploring the chemistry and reactivity of organometallic reagents. The reaction has a long history and mirrors the development of organometallic chemistry.

The first example of this reaction was reported by Freund in 1861,[2] and involved the reaction of Me_2Zn and Et_2Zn with acid chlorides. Organozinc reagents were favored for the preparation of ketones until 1936 when Gilman and Nelson[3] reported that organocadmium reagents generally gave superior results. The tendency of Grignard reagents to give tertiary alcohols by subsequent reaction with the product ketones was first circumvented in 1949 by the use of copper vessels[4] and later by Cook and Percival[5] with the use of cuprous chloride. These studies were the harbinger of ketone syntheses via transition metal chemistry. Although a wide variety of alkali and alkaline-earth, transition metal, and main group organometallic reagents react with acid chlorides to give ketones, the most useful synthetic methods generally utilize organocopper reagents and methods catalytic in palladium. The reaction of acid chlorides with organometallic reagents (i.e., of Mg, Zn, Cd) was reviewed[1a] in 1954, and new developments have been reported in a number of monographs and review articles devoted to ketone synthesis,[6] carboxylic acid derivatives,[7] or specific areas of organometallic chemistry. The latter monographs and reviews are referenced within the section for each metal. Although this review will focus on developments of the past decade, there is some overlap with the information dispersed among the organometallic reviews. This incorporation is intended to facilitate a broad historical perspective and to provide the information necessary to directly compare the various procedures using acid chlorides. A comparison of methods using acid chlorides with methods using other carboxylic acid derivatives is provided in the excellent review by O'Neill, although largely in the context of natural product syntheses.[7] When selecting a particular reaction, the reader should examine the relative amounts of acid chloride and organometallic reagent employed, the number of ligands on the reagent that are acylated, the reaction conditions, and the effort required to prepare the reagent. In this review, the direct reaction of organometallic reagents with acid chlorides will be presented in the appropriate section for each metal organized into alkali and alkaline-earth, transition, and main group metals. Those reactions involving organometallic reagents with Cu or Pd catalysis will be discussed in the sections devoted to copper and palladium chemistry as they presumably involve organocopper or organopalladium intermediates that directly lead to the observed ketones.

2.0 ALKALI AND ALKALINE-EARTH METALS

2.1 *Alkali metals (Na, Li)*

Organoalkali reagents (e.g., RNa[8] and RLi) react with acid chlorides to give ketones in low yields. The high basicity and reactivity of these reagents often results in subsequent reaction of the product ketone via either enolization or 1,2-nucleophilic addition (Scheme I). The former process protonates the organometallic reagent resulting in diminished yields of ketone and the latter affords tertiary alcohols. If the carbanionic character of the reagent is diminished by substituents or hybridization, successful acylation of organoalkali reagents can be achieved when excess acyl chloride is employed or the ketone is protected from reaction with the organometallic reagent via a non-destructive enolization event. Terminal peroxy alkynes ($pK_a \approx 25$) can be lithiated with *n*-BuLi and reacted with benzoyl chloride or caproyl chloride to give the corresponding peroxy alkynyl ketones in low yields (eq. 1).[9] The reaction failed with the simple aliphatic acid chlorides and significant amounts of alcohols and acylated

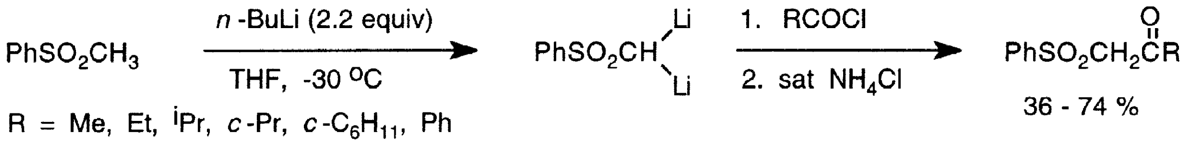


R = Me_3C-, $EtMe_2C$-, $Me(CH_2)_2Me_2C$-, $Me(CH_2)_4Me_2C$-, (1)

R_1 = $Me(CH_2)_6$-, Ph

alcohols were formed in these reactions. Lithiated perfluoro diaryl ethers (i.e., p-$CF_3C_6H_4OC_6F_4Li$) afforded tertiary alcohols upon reaction with acid chlorides, although reaction with $ClOC(CF_2)_3COCl$ gave a mixed hydroxy ketone adduct in modest yield.[10] Addition of three rather than four aryllithium reagents to the diacid chloride was attributed to solubility effects.

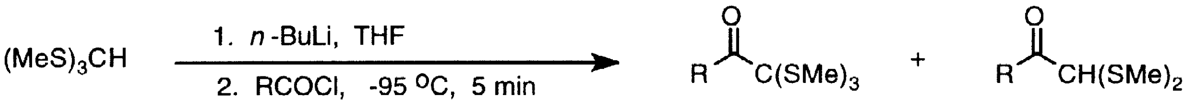
Treatment of methyl phenyl sulfone with two equivalents of *n*-BuLi affords a geminal dianion which reacts with acid chlorides to afford β-keto sulfones in modest to good yields (eq. 2).[11] The monoanion gives poor yields of ketone and the efficiency of the dianion arises from ready formation of the ketone enolate without destruction of the carbanion unit(s) needed for reaction with the acid chloride. Tris(methylthio)methyllithium (conjugate acid $pK_a \approx 27$, eq. 3) and bis(methylthio)methyllithium afford bis(dimethylthio)methylketones in good yields upon reaction with acid chlorides.[12] The former reagent gives rise to tris(methylthio)methyl ketones which react with the lithium reagent to afford the enolate anion and tetra(methylthio)methane. Quenching the enolate anion with *N*-methylthiophthalimide provides a synthesis of the tris(methylthio)methyl ketones.



$$PhSO_2CH_3 \xrightarrow[\text{THF, -30 °C}]{n\text{-BuLi (2.2 equiv)}} PhSO_2CHLi_2 \xrightarrow[\text{2. sat } NH_4Cl]{\text{1. RCOCl}} PhSO_2CH_2\overset{O}{\overset{\|}{C}}R \quad (2)$$

R = Me, Et, ^iPr, c-Pr, c-C_6H_{11}, Ph

36 - 74 %

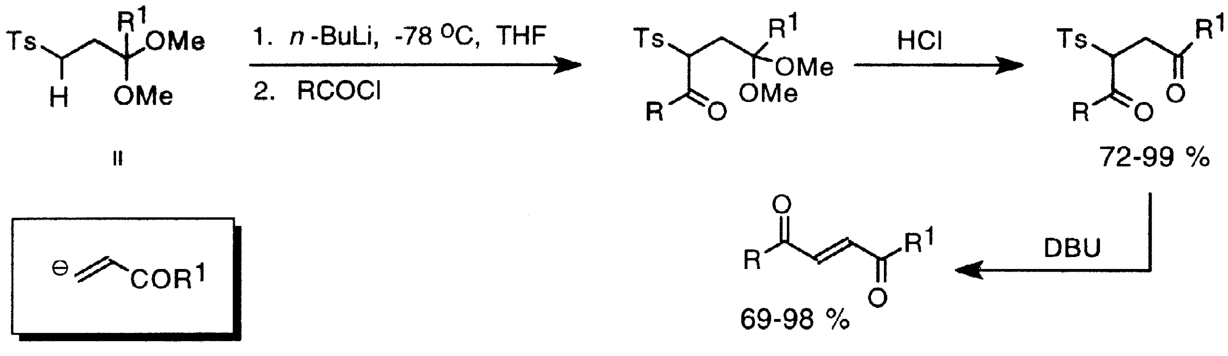


$$(MeS)_3CH \xrightarrow[\text{2. RCOCl, -95 °C, 5 min}]{\text{1. } n\text{-BuLi, THF}} R\overset{O}{\overset{\|}{C}}C(SMe)_3 + R\overset{O}{\overset{\|}{C}}CH(SMe)_2 \quad (3)$$

R	method[a]	% yield	% yield
Ph	A		36
	B		98
	C	94	
4-ClC_6H_4-	B		94
	C	92	
4-$^iBuC_6H_4$-	B		95
	C	90	
Me	B	36	33
	C	67	

[a] RCOCl + $(MeS)_3CLi$: A = 1:1.25. B = 1:2.2. C = 1:2.2 and then 1.5 equivs *N*-(methylthio)phthalimide before quenching.

Lithiated sulfones are readily acylated with acid chlorides to afford α-sulfonyl ketones (eqs. 4 and 5).[13,14] Since the conjugate bases of sulfones or terminal alkynes are quite similar in base strength, this property cannot account for their different behavior. Successful acylation of lithiated sulfones suggests that the reaction with acid chlorides is rapid, and ketone reactivity is slowed by steric factors. Lithiation of β-sulfonylacetals yields β-acylvinyl carbanion synthons while lithiation of β-sulfonyl carboxylic acids affords β-carboxyvinyl carbanion synthons; these synthons provide synthetic routes to α,β-unsaturated 1,4-diketones and γ-oxo-α,β-unsaturated carboxylic acids, respectively. The acylation of lithiated sulfones has been utilized in a synthesis of 2,5-disubstituted-3-(phenylsulfonyl)pyrrolidines via reduction of the resultant ketones, followed by alcohol dehydration and subsequent *5-endo-trig* cyclization of nitrogen onto the vinyl sulfone (eq. 6)[15]



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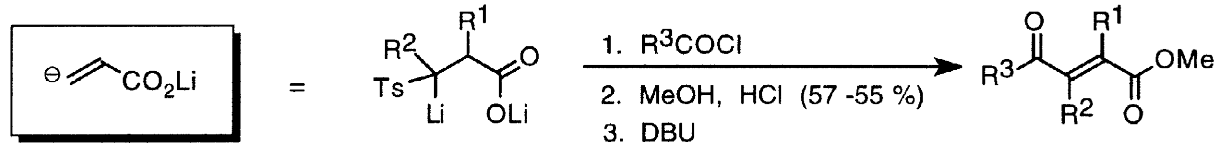

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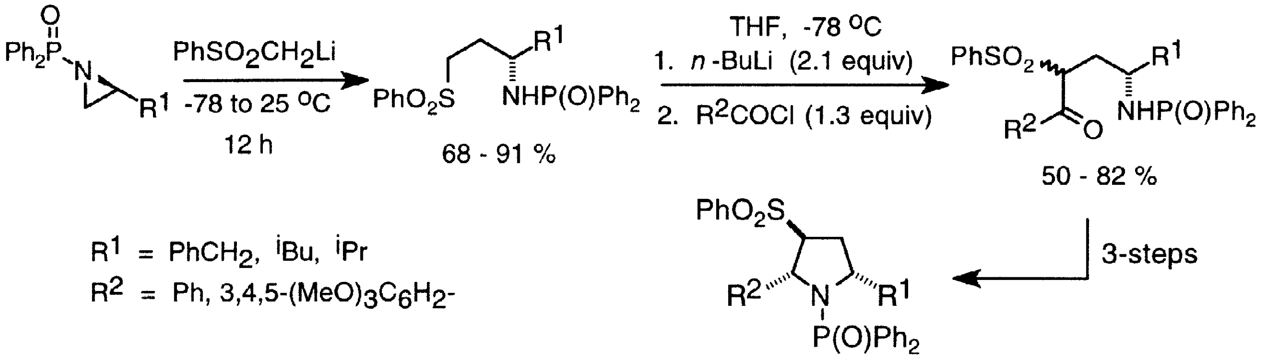
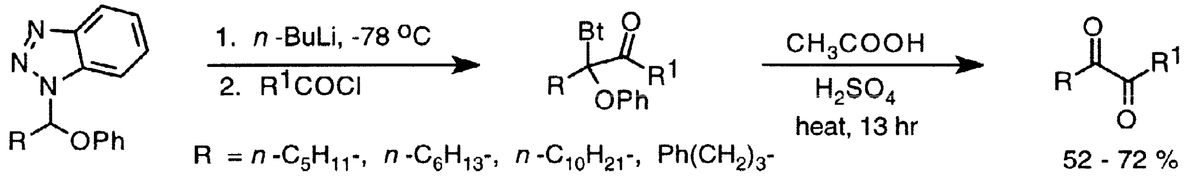


(6)

R^1 = $PhCH_2$, ${}^iBu$, ${}^iPr$
R^2 = Ph, 3,4,5-$(MeO)_3C_6H_2$-

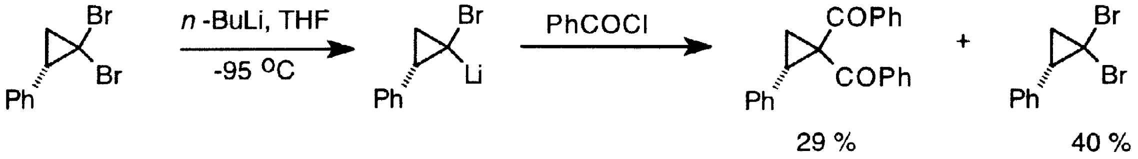
Katritzky has exploited benzotriazole chemistry in a versatile synthesis of unsymmetrical 1,2-diketones.[16] 1-(Phenoxymethyl)benzotriazole can be deprotonated with n -BuLi and the anion alkylated with a wide range of alkyl halides. Deprotonation of the alkylated 1-(phenoxymethyl)benzotriazoles and acylation with acid chlorides affords an intermediate ketone which can be hydrolyzed to the 1,2-diketone with strong acid in good overall yields (eq. 7). The rather vigorous hydrolysis conditions appear to limit the synthetic applications of the method.



(7)

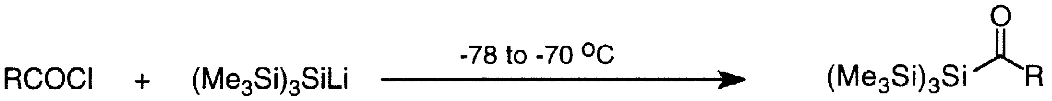
R = n-C_5H_{11}-, n-C_6H_{13}-, n-$C_{10}H_{21}$-, $Ph(CH_2)_3$-
R^1 = Ph, ${}^tBu$, Naph, 4-ClC_6H_4-, 2-MeC_6H_4-

Metal halogen exchange on 1,1-dibromocyclopropanes affords 1-lithio-1-bromocyclopropanes which react with aryl acid chlorides to afford 1,1-bisacylcyclopropanes and the starting geminal dibromide (eq. 8).[17] Halogen metal exchange between the initially formed cyclopropyl ketone and the cyclopropyllithium reagent affords an enolate anion which reacts with a second equivalent of the acid chloride. Utilization of aliphatic acid chlorides affords predominately the reduced 1-bromocyclopropane via enolization events, although cyclopropyl ketones (mono and di) can be obtained with the sterically hindered acid chloride of isobutyric acid.



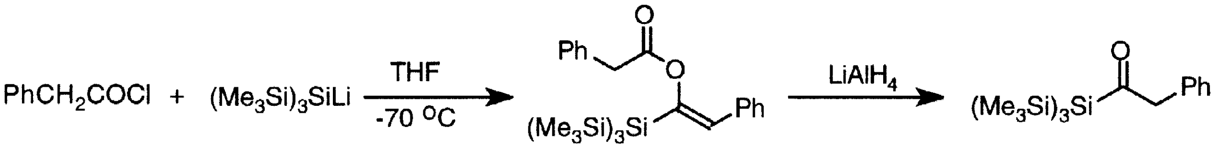
(8)

Silyl ketones (i.e., acyl silanes) have been prepared in good yields by the addition of silyllithium reagents to a three fold excess of acid chloride in THF at low temperature (eq. 9).[18-20] The reaction fails for sterically hindered aroyl chlorides (e.g., 2,6-dimethyl-, 2,6-dimethoxy-, and 2,4,6-tri-*tert*-butylbenzoyl chlorides) which give benzils (i.e., α-diketones) and tetrakis(trimethylsilyl)silane instead, presumably via SET and subsequent radical coupling.[19] Easily enolizable ketones readily result in acylation of the product ketone and $LiAlH_4$ reduction gives the desired acyl silane (eq. 10).[20] Utilization of pentane as the solvent permits use of a 1:1 ratio of acid chloride and silyllithium (eq. 9). The success of the reaction presumably revolves around the steric bulk of the $(R_3Si)_3SiLi$ anions since zinc silylcuprate reagents are used to prepare silyl ketones (vide infra).



(9)

R	RCOCl:silyllithium	solvent	% yield
Ph, Me, Me_3C	3 : 1	THF	60 - 70
Et, ^iPr	1 : 1	pentane	54 - 72



(10)

2.2 *Alkaline-Earth metals (Mg, Ca)*

For many years, it had been a tenet of organomagnesium chemistry[3,21] that the direct reaction of acid chlorides with Grignard reagents could not be used for the preparation of ketones because of the facile formation of tertiary alcohols under these reaction conditions. In 1979, Sato and co-workers demonstrated that slow addition of a Grignard reagent to a cold (-78 °C) THF solution of excess acid chloride (2.0 equiv) could afford ketones in excellent yields (eq. 11).[22] Choice of solvent was crucial as Et_2O gave tertiary alcohols as the principle products. Crude kinetic studies indicated that Grignard reagents reacted with acid chlorides at a faster rate in THF than in Et_2O. Aroyl chlorides could be converted into ketones with a 1:1 ratio of Grignard reagent and acid chloride in good yields. The procedure was extended to acid chlorides containing chloro or ester functionalities [$R(CH_2)_3COCl$, R = Cl, $-CO_2Me$; 57-81%].[23] Grignard reagents prepared from the acetals of 3-halopropanal or 4-halobutanal can be acylated in good yields with simple acid chlorides[24,25] as well as the acid chloride of proline[26] protected as the benzyloxycarbamate. Sworin[27] has suggested that intramolecular chelation of magnesium with the acetal oxygen atoms may favor formation of the dialkylmagnesium reagent in the Schlenk equilibrium and this may account for the attenuated reactivity of these reagents.

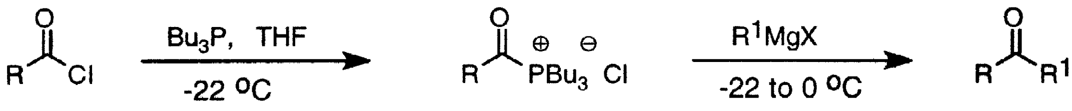
$$\underset{(1.0\ \text{equiv})}{RMgX} + \underset{(2.0\ \text{equiv})}{R^1COCl} \xrightarrow[\substack{-78\ ^oC,\ \text{THF, 30 min addition time} \\ \text{warm to room temperature}}]{\substack{\text{Inverse addition of} \\ RMgX\ \text{to}\ R^1COCl}} \underset{\substack{71-95\ \%\ \text{in THF} \\ 12-39\ \%\ \text{in}\ Et_2O}}{RCOR^1} \qquad (11)$$

Although the direct addition of Grignard reagents to acid chlorides is limited by the subsequent addition to the product ketone, the latter reaction can be suppressed by the addition of metal halides.[28,29] The use of catalytic quantities of $Fe(acac)_2$ significantly expands the synthetic utility of the reaction.[29,30,31] Three mole percent of the iron catalyst permits the reaction to be performed with a 1:1 ratio of Grignard reagent to acid chloride at room temperature (eq. 12).[30] The yields of ketones are good to excellent and the reaction can be performed in the presence of functionalities normally incompatible with Grignard reagents (e.g., aryl chlorides, aryl methyl ethers, nitriles, esters).[31] The reaction fails with nitro arenes. The reaction has been exploited in the synthesis of 2,4,6-cycloheptatrien-1-yl ketones which are rather difficult to prepare by other procedures.[32]

$$\underset{(1:1\ \text{molar ratio})}{RMgX + R^1COCl} \xrightarrow{3\ \%\ Fe(acac)_3,\ \text{THF},\ 25\ ^oC} \underset{76-90\ \%}{RCOR^1} \qquad (12)$$

R^1 = 4-ClC_6H_4-, 4-$MeOC_6H_4$-, 4-NCC_6H_4-, $MeO_2C(CH_2)_2$-, 2-furyl, 2-thienyl, $ClOC(CH_2)_3$-, $ClOC(CH_2)_4$-, (*R* & *S*)-$PhC(CF_3)OMe$-
R = Me, Ph, ^{n}Bu, Et

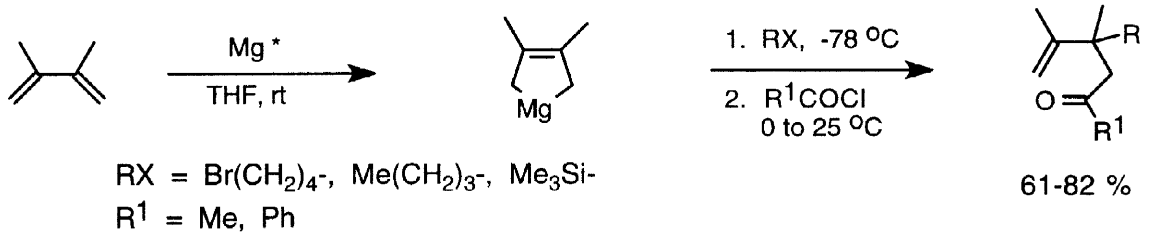
More recently, the addition of Bu_3P to acid chlorides followed by addition of Grignard reagents affords ketones in poor to excellent yields (eq. 13).[33] The reaction works well for aliphatic and aromatic acid chlorides with primary alkyl Grignard reagents, but gives modest yields with isopropylmagnesium halides. Aliphatic acid chlorides with no α-alkyl substitution give ketones in excellent yields with (*n*-R)MgX reagents and in low yields with aryl and secondary alkyl Grignard reagents. The low yields presumably result from competitive enolization of the intermediate acyl phosphonium salt depending upon the Grignard reagent. Good yields are generally obtained at -22 ° C for aliphatic acid chlorides while aromatic acid chlorides give good yields at either 0 or -22 °C. Utilization of 1.1 equivalents of Grignard reagent results in about 9% yields of tertiary alcohols.



(13)

R	R^1	% yield
$PhCH_2CH_2$	Me	85
	n -Bu	97
	i -Pr	35
	Ph	7
$EtO_2CCH_2CH_2$	*n* -Bu	89
c -C_6H_{11}	*n* -Bu	96
	Ph	86
4-$MeOC_6H_4$	Me	96
	n -Bu	78
	i -Pr	43
	Ph	100

Rieke magnesium has been used to prepare (2-butene-1,4-diyl)magnesium reagents which can be sequentially alkylated and acylated (eq. 14). Acylation of the intermediate Grignard reagent occurs in high yield without competitive 1,2-addition to the ketone product which may well reflect the "neopentyl" nature of the Grignard reagent.[34]



(14)

Organocalcium reagents prepared from alkyl halides [$Cl(CH_2)_7CH_3$, $Br(CH_2)_5OPh$, *c* -$C_6H_{11}Br$, 1-Cl-(4-CH_3)C_6H_4, and 1-Br-(4-CH_3O)C_6H_4] and Rieke calcium (via reduction of $CaBr_2$ with lithium biphenylide) react with acid chlorides to give complex reaction mixtures. Addition of CuCN·2LiBr to the organocalcium reagent affords good yields (71-84%) of ketones at -35 °C presumably via a calcium cuprate species.[35]

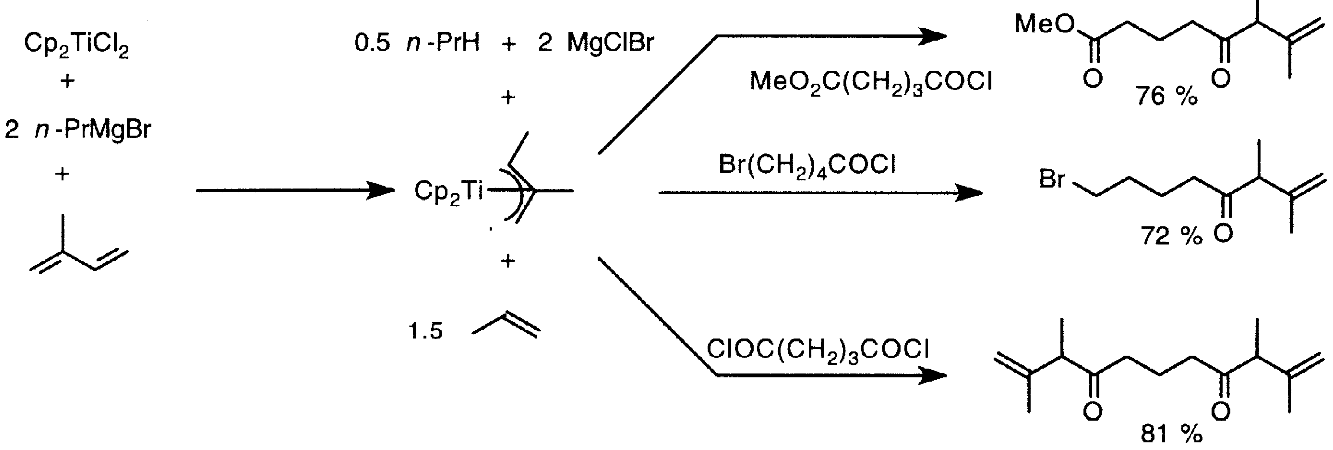
3.0 TRANSITION METALS

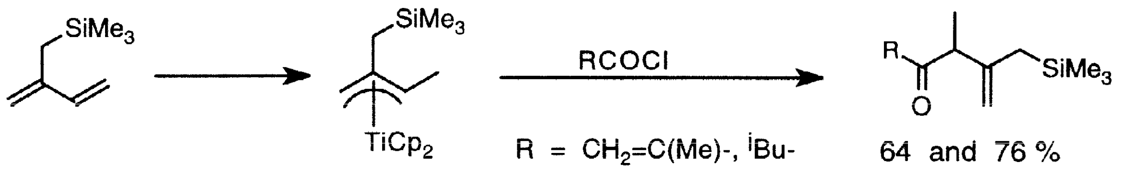
A wide range of transition metal organometallic reagents react with acid chlorides to afford ketones. The efficiency of these reactions depends on the number of ligands on the metal that can be acylated, the thermal stability of the reagent, mildness of the reaction conditions, and ease of reagent preparation. Frequently, the transition metal organometallic reagent is prepared from organolithium or Grignard reagents rendering the methods subject to all the limitations inherent in the use of strongly basic nucleophilic reagents; these include functional group compatibility, and limitations in carbanion formation. Consequently, the development of alternative methods for the preparation of transition metal reagents is an important focus of investigation. These include the use of Rieke metals[36] and transmetallation relays that begin with hydrometallation or carbometallation and often lead to organocopper[37] or organopalladium[38] species as the effective reagents.

3.1 *Group IVB (Ti, Zr) and Group VB (V)*

Organotitanium and zirconium complexes readily undergo hydrometallation of alkenes and this transformation provides a useful route to organometallic reagents not involving reductive metallation with lithium or magnesium or deprotonation with strong alkali metal bases. Organotitanium reagents such as Me_2TiCl_2 react with acid chlorides to afford per methylated alkanes (i.e., $RCMe_3$)[39] while tris(diethylamino)allyltitanium reacts with acyl imidazoles to afford β,γ-unsaturated ketones.[40] The isopropoxy analog gives only the tertiary alcohol. Alkyl titanium reagents easily undergo β-hydrogen atom elimination and synthetically useful organotitanium reagents are generally limited to allyl and vinyl reagents. Hydrotitanation of 1,3-dienes affords Ti(III) π-allyl complexes which react with acid chlorides to give β,γ-unsaturated ketones without isomerization to the α,β-regioisomers (Scheme II).[41] The more substituted end of the π-allyl complex reacts to give good regiocontrol in the formation of the β,γ-unsaturated ketones. These reaction conditions are compatible with esters, alkyl halides, and allylsilanes. Tertiary alcohols are sometimes formed as minor by-products but decrease in quantity as steric hindrance about the acid chloride carbonyl increases. The reaction of 2-trimethylsilylmethyl-1,3-butadiene with methacroyl chloride gives rise to a highly functionalized ketone containing conjugated and non-conjugated double bonds as well as an allylsilane (eq. 15). Simple aliphatic acid chlorides work equally well (eq. 15). Hydrotitanation of a triene results in isomerization of the isolated double bond, and the resultant titanium reagent gives low yields (30%) of the β,γ-enone upon acylation with benzoyl chloride (eq. 16).

Scheme II





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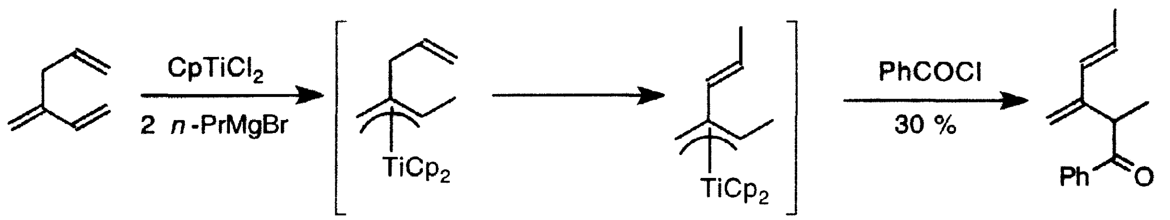
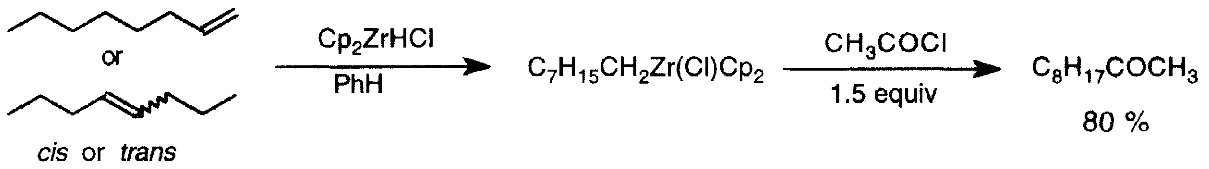


(16)

Organozirconium compounds are available from a wide variety of alkenes via hydrozirconation, but a facile rearrangement to the primary alkylzirconium reagent is generally observed (eq. 17-18). These organozirconium reagents can be directly acylated with acid chlorides,[42] although transmetallation to copper is more often cited.[37]



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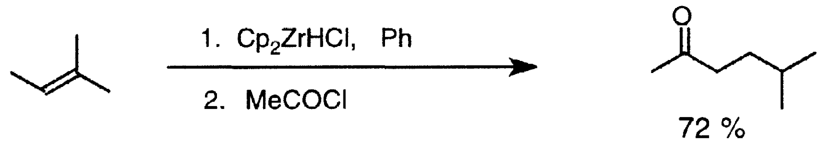


(18)

Organovanadium compounds prepared by the addition of a Grignard reagent or organolithium reagent to equimolar amounts of vandanium trichloride react with acid chlorides in CH_2Cl_2 to afford ketones in good to excellent yields (eq. 19).[43] The reaction is tolerant of a halide, nitrile, ester, or ketone functionality in the acid chloride. The high yield formation of α-halo (i.e., Cl and Br) ketones is particularly noteworthy.

$$\mathrm{RMgBr} + \mathrm{VCl_3} \xrightarrow{\mathrm{CH_2Cl_2}} \mathrm{RVCl_2} \xrightarrow{\mathrm{R^1COCl}} \underset{61 - 89\ \%}{\mathrm{RCOR^1}} \qquad (19)$$

R = Ph, *n*-Bu

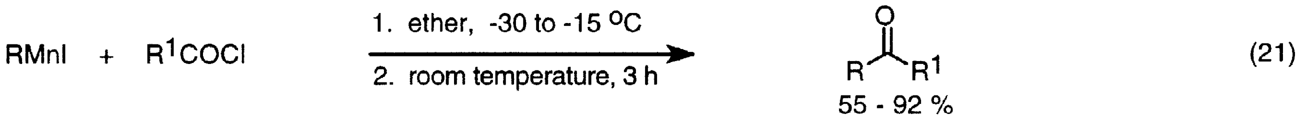
R^1 = *o*-MeC_6H_4-, *p*-NCC_6H_4-, *p*-BrC_6H_4-, Me-, $EtO_2C(CH_2)_4$-, $MeCO(CH_2)_2$-, $ClCH_2$-, EtCH(Br)-

3.2 *Group VIIB (Mn)*

The chemistry of organomanganese compounds has been reviewed.[44] In a series of studies, Normant and Cahiez explored the acylation of organomanganese compounds as a facile synthetic route to ketones.[45-48] Treatment of MnI_2 (soluble in ether) with organolithium or Grignard reagents in Et_2O can afford a series of organomanganese compounds (i.e., RMnI, R_2Mn, R_3MnLi, R_4MnLi_2) depending upon stoichiometry. They can also be prepared from $MnBr_2$ and $MnCl_2$ in slightly lower yields. Primary alkylmanganese compounds are generally prepared between -10 and +20 °C, while tertiary alkylmanganese reagents are prepared at -30 °C. These organomanganese reagents react cleanly with acid chlorides, transferring all of their alkyl ligands, to provide an efficient synthesis of ketones (eq. 20).[45] Rather similar yields are obtained with BuMnI (90%), Bu_2Mn (85%), and Bu_3MnLi (75-85%) reagents. The primary alkyl reagents, RMnI, are stable at room temperature and compatible with a variety of functional groups in the acid chloride (e.g., alkyl chlorides[46], allyl chlorides[47], esters[46,48], nitriles[49], and ketones[48,49]). The transferable ligand can be alkyl, alkenyl, alkynyl, or aryl, and the coupling reaction works well with aroyl chlorides, heteroaroyl chlorides (X = O, S)[49], and primary, secondary, or tertiary alkyl acid chlorides (eq. 21).[46] Although the chemoselective reaction of organomanganese reagents with acid chlorides in the presence of ketones (eq. 22)[49] could reasonably be expected based on the success of this method for ketone synthesis, diminished yields were observed in a 12-keto steroid.[48] The origin of this chemoselectivity is intriguing since organomanganese reagents react with ketones at -50 °C. Acylation of RMnI reagents is significantly faster at +20 °C (30 min) than at -50 °C (90-240 minutes), and the temperature has no effect on chemical yields provided sufficient reaction times are employed. Organomanganese reagents containing *tert* - or *sec*-alkyl ligands give reduced yields due to reagent instability.[46] Bis acid chlorides undergo reaction with two equivalents of the reagent to afford good yields of diketones (eq. 23).[46,49] α,β-Unsaturated acid chlorides undergo polymerization reactions unless they are β,β-dialkyl substituted. The organomanganese reagents will react with aldehydes.[46]

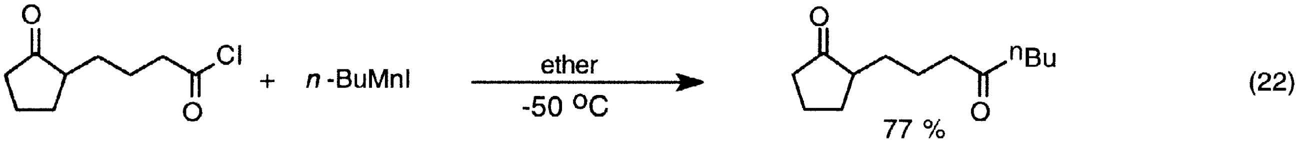
$$\text{(n equiv) }{}^{n}\text{BuM} + \text{MnX}_2 \xrightarrow{\text{Et}_2\text{O}} \text{Bu}_n\text{MnX}_{\text{I}_{2-n}\text{I}} \xrightarrow[\text{-10 to +20 }^{o}\text{C}]{\text{(n equiv) }{}^{n}\text{C}_7\text{H}_{15}\text{COCl}} \text{(n equiv) }{}^{n}\text{BuCOC}_7\text{H}_{15} \quad (20)$$

$$\text{X = I, Br, Cl} \qquad \text{(X = X or M)} \qquad \text{X = Br, Cl (73-90 \%)} \quad \text{X = I (75-90 \%)}$$



R = alkyl, alkenyl, alkynyl, aryl

R^1 = n-C_7H_{15}, i-Pr, t-Bu, $Cl(CH_2)_3$-, $MeO_2C(CH_2)_2$-, Cl_3C-, $EtOCH_2$-, Ph, n-Bu

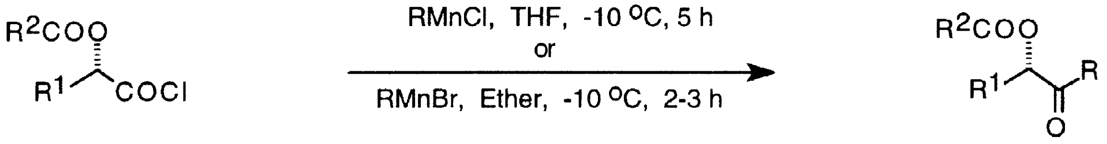


$$\underset{\text{(2.2 equiv)}}{\text{PhMnI}} + \text{ClCO(CH}_2)_4\text{COCl} \xrightarrow[\text{then rt, 3 h}]{\text{ether -30 to -10 }^{o}\text{C}} \underset{87\ \%}{\text{PhCO(CH}_2)_4\text{COPh}} \quad (23)$$

α-Heteroatom substituted ketones are difficult to prepare by alternative procedures (see organovanadium compounds and organocopper compounds) and can be readily obtained by reaction of organomanganese reagents with the α-heteroatom substituted acid chlorides (eq. 24).[47] Reagents prepared from $MnCl_2$ proved more effective with α-chloro and α,α-dichloro substituted acid chlorides. Amino substituted acid chlorides generally fail to give ketones, although a low yield (38%) of ketone was obtained from 3-pyridylcarbonyl chloride and *n* -BuMnI.[49] The organomanganese reagent, RMnI, reacts exclusively with the acid chloride when subjected to a competition experiment with allyl chloride in contrast with the organocopper reagent which reacts with both substrates.[47] The procedure has recently been extended to the preparation of scalemic α-acyloxy ketones from the corresponding α-hydroxy acids derived from α-amino acids (eq. 25).[50]

(24)

R	R^1	solvent	% yield
n-C_7H_{15}	CH_2Cl	THF / Et_2O	66
	CH_2OEt	Et_2O	84
	CCl_3	Et_2O	75
	$(CH_2)_3Cl$	Et_2O	86
n-C_4H_9	CH_2SPh	Et_2O	80
	CH_2CH_2OMe	Et_2O	84
	4-$MeOC_6H_4$	Et_2O	100
$Me_2C{=}CH$	$(CH_2)_3Cl$	Et_2O	70
n-$C_3H_7C{\equiv}C$	$(CH_2)_3Cl$	Et_2O	88



(25)

R^1 = Me, ^iPr, ^iBu, $PhCH_2$, Ph

R^2 = Me, ^tBu, Ph, H

71 - 93 %

91 - 99 % ee

R = Me, ^nBu, $^nC_6H_{13}$, $^nC_8H_{17}$, $^nC_{12}H_{25}$, ^iPr, Ph, $Me_2C{=}CH$, $^nC_5H_{11}C{\equiv}C$

A detailed study of the effect of solvent, acid chloride, and added ligands was subsequently undertaken.[51] Reaction of RMnCl with acid chlorides in THF leads predominately to ring opening of THF by the acid chloride. Nevertheless, good yields of ketones (67-88%) can be obtained by adding the acid chloride in Et_2O or hexane to the organomanganese compounds prepared from $MnCl_2$ or $MnCl_2{\cdot}2LiCl$ ($MnCl_4Li_2$) and organolithium or Grignard reagents in THF. In these mixed solvent systems, good yields of ketones were obtained when the ratio of Et_2O:THF or hexane:THF was > 3:1. Excellent yields of ketones were obtained from R^1COCl and RMnI in Et_2O when ligands such as THF (5.0 equiv), Ph_3P (2.0 equiv), and Me_2S (5 equiv) were added to stabilize the organomanganese reagents, while diminished yields (0-30%) were obtained with Et_3N and TMEDA. Dimethoxyethane promoted decomposition of RMnI at room temperature and yields of ketones obtained in the presence of HMPA were irreproducible. Utilization of THF, tetrahydropyran, tetrahydrothiophene, or dimethyl sulfide as added ligands increased the stability of secondary alkylmanganese iodides resulting in increased yields of ketones. Methylene chloride and acetonitrile could be used as co-solvents in addition to Et_2O or hexane.

The expense of MnI_2 led Cahiez to explore the use of $MnBr_2$ as a source of organomanganese compounds. Utilization of insoluble $MnBr_2$ and Grignard reagents resulted in slow reactions and subsequent decomposition of the desired organomanganese reagents.

Organomanganese reagents are readily prepared from Grignard reagents and $MnBr_2$ solubilized with an ethereal (Et_2O) solution of LiBr ($2Li + Br_2$) or alternatively by addition of $MnBr_2$ to a solution of LiBr and a Grignard reagent. The use of alkyllithium reagents poses no problems due to the insolubility of $MnBr_2$ in ether and is attributed to formation of LiBr during the transmetallation process.[52] It was also observed that the presence of lithium and magnesium halides promoted the stability of organomanganese compounds. The use of RMnBr compounds was particularly effective for transfer of an alkynyl ligand in the preparation of an alkynyl alkenyl ketone (eq. 26); the reaction failed with RMnI.

$$\mathrm{BuC{\equiv}CMnX} + \mathrm{MeCH{=}CHCOCl} \xrightarrow[20\ ^{o}\mathrm{C},\ 2\ \mathrm{h}]{\text{ether}} \mathrm{BuC{\equiv}CCOCH{=}CHMe} \qquad (26)$$

X = I 0 %
X = Br 87 %

Building on earlier work,[51] Cahiez showed that preparation of RMnCl from $MnCl_2 \cdot 2LiCl$ and RLi or RMgX in THF afforded reagents that gave good yields of ketones upon reaction with acid chlorides[53] permitting use of inexpensive $MnCl_2$. This contrasts with the ring-opening reaction noted above, and the origin of the discrepancy between the two reports is not clear. The organomanganese reagents are reported to be more stable in THF than in ether and these conditions gave modest yields of ketones with *sec*-alkylmanganese reagents, but afforded no ketones with *tert*-BuMnCl. *tert*-BuMnCl gave good yields of ketones in the presence of 1 mol % of CuCl which generally improved the yields of ketones with organomanganese reagents. Utilizing these RMnCl reagents, the first successful example of ketone preparation with an allyl manganese reagent was reported.

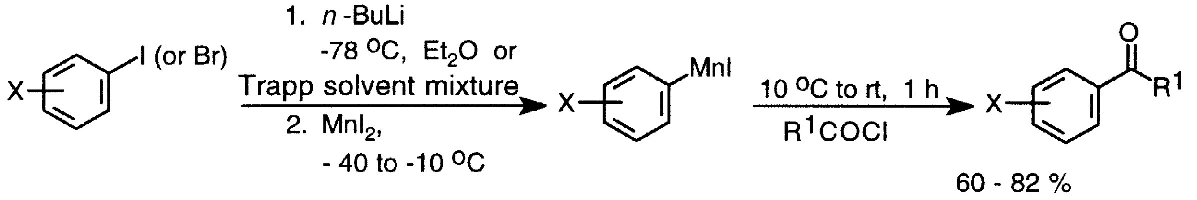
The reaction of organomanganese reagents with acid chlorides has been rendered catalytic in manganese (eq. 27).[54] This was achieved by the slow addition of the Grignard reagent to a solution of the acid chloride and 3 mol % $MnCl_4Li_2$. The success of the reaction is dependent on the relative rates of transmetallation and acylation of the various organomanganese reagents. Too rapid addition of the Grignard reagent results in excess Grignard which adds to the product ketone affording tertiary alcohols, while too slow addition results in acylation of R_2Mn and/or RMnCl. Since these latter reagents undergo transmetallation with Grignard reagents at a slower rate than R_3MnMgX, there is again an excess of Grignard reagent present to undergo 1,2-nucleophilic addition to the product ketone. The authors propose a mechanistic sequence wherein the rate of Grignard addition must be adjusted to assure a continuous supply of $R_4Mn(MgX)_2$.

$$n\text{-}\mathrm{C_7H_{15}COCl} + 3\ \%\ \mathrm{MnCl_4Li_2} \xrightarrow[\mathrm{THF},\ 0\text{-}10\ ^{o}\mathrm{C},\ 30\ \mathrm{min}]{n\text{-}\mathrm{BuMgCl}} n\text{-}\mathrm{C_4H_9COC_7H_{15}} \qquad (27)$$

87 %

mol % $MnCl_4Li_2$	Addition time (min)	% yield
1	30	70
3	30	87
3	15	61
3	60	72
5	30	82

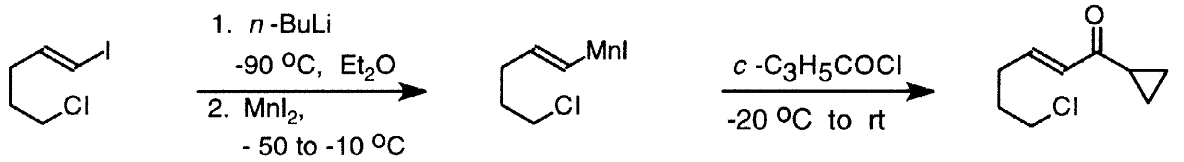
Functionalized aryl- and alkenylmanganese reagents have been prepared from the corresponding lithium reagents which in turn were prepared from the aryl or alkenyl iodides or bromides (eqs. 28-29).[55] Addition of an ethereal suspension of MnI_2 to the lithium reagent at -78 °C resulted in substantial formation of butylated material arising from coupling of the organomanganese reagent and butyl bromide generated during the halogen metal exchange. Although the $MnI_2{\cdot}2LiBr$ complex gave lower yields of ketones, satisfactory yields could be achieved by addition of the ethereal suspension of MnI_2 to the lithium reagent at -40 °C where transmetallation occurs. This procedure fails for substrates containing ester or nitrile functionalities which react with the aryllithium before transmetallation occurs. This problem can be avoided by use of the Trapp solvent mixture (THF : ether : pentane 4:4:1) which facilitates halogen metal exchange, permits transmetallation at lower temperatures (-90 to -60 °C) and stabilizes the $MnX_2{\cdot}2LiX$ (X = Br, Cl) complexes. Good yields of functionalized ketones can be obtained with these modifications. In some instances, the formation of RMnX from $MnBr_4Li_2$ and subsequent coupling with acid chlorides affords significantly higher yields than when LiBr is not employed.[56] The use of LiX salts to facilitate transition metal coupling reactions has been utilized in organopalladium and copper chemistry as well and is becoming quite common (vide infra).



(28)

X = Cl, p - CN, m - CN, o - CN, p - (menthyl-O-CO), p - $^tBuCO_2$

R^1 = $Cl(CH_2)_3$-, $Cl(CH_2)_5$-, $Br(CH_2)_{10}$-, c - C_3H_5-, EtO-, Et-

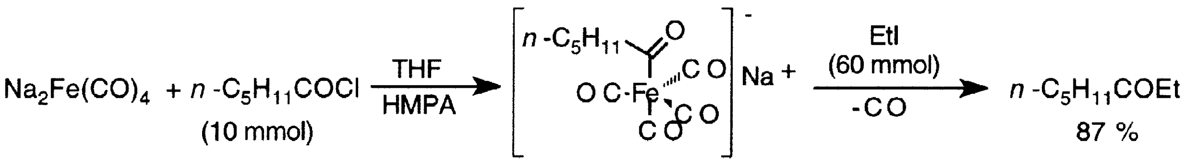


(29)

Organomanganese reagents can also be prepared from Rieke manganese [Li-naphth (cat), $MnCl_2$] and acylated with benzoyl chloride to afford ketones in modest to excellent yields (29-87%).[57] Rieke manganese is slightly soluble in THF and must be destroyed with 1,2-dibromoethane in order to minimize homocoupling of benzoyl chloride. The reaction works for primary, secondary, and tertiary alkyl halides, despite the otherwise general tendency for secondary alkylmanganese species to undergo β-hydride elimination, and the difficulty of forming tertiary alkylmanganese reagents. The reaction has been extended to thienyl halides which afford thienyl aryl ketones in low to excellent yields (34-91%).[58] The use of $MnBr_4Li_2$ gives significantly higher yields than $MnBr_2$, and *o*-substituted aroyl chlorides gave low yields of ketones illustrating a sensitivity to steric effects. 3,4-Dibromothiophenes can be sequentially alkylated (Pd, ArI) and acylated (ArCOCl). The reaction of organomanganese reagents, generated from Rieke manganese, with acid chlorides can be catalyzed by Cu(I) salts.[59] An active manganese-graphite reagent, prepared by potassium-graphite (C_8K) reduction of $MnBr_2 \cdot nLiBr$ (n = 1, 2), readily undergoes oxidative addition to allyl-, alkenyl-, aryl-, and heteroaryl halides and upon treatment with acid chlorides affords ketones in moderate yields (60-69%).[60] Utilization of other MnX_2 salts affords low yields due to solubility problems or cleavage of THF. The acylation of an aroyl chloride containing a nitro functional group proceeds in moderate yield.

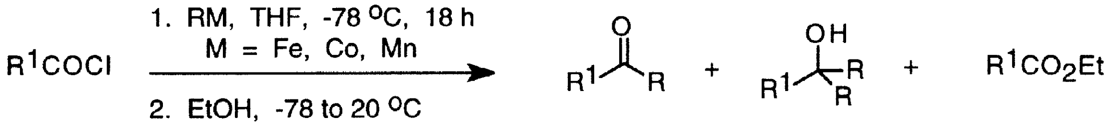
3.3 *Group VIIIB (Fe, Co, Rh)*

Ketone syntheses via intermediate organoiron species presumably involve an alkyl(acyl)iron complex which forms the ketone in a reductive elimination step. The alkyl ligand can be delivered by an electrophilic or nucleophilic reagent. Sodium tetracarbonylferrate has been touted as the transition metal analog of a Grignard reagent[61] and undergoes nucleophilic reactions with a variety of carbon electrophiles. Reaction of $Na_2Fe(CO)_4$ with acid chlorides affords an anionic acyliron complex [i.e., $RCOFe(CO)_4^- Na^+$] which can be alkylated with alkyl halides. Reductive elimination from the resultant alkyl(acyl)iron complex affords the ketones in excellent yields (eq. 30).[62] The acyliron complexes can also be prepared via carbon monoxide insertion into the corresponding alkyliron complexes obtained via alkylation of disodium tetracarbonylferrate with alkyl halides or tosylates.[62,63]



(30)

The more common procedure involves introduction of the alkyl ligand from a nucleophilic organometallic reagent. A detailed study of organoiron and cobalt reagents revealed that R_2M and R_3MLi (or MgBr) species could be acylated with acid chlorides to give ketones in good to excellent yields (eq. 31).[64] The organoiron reagents, RFeCl and R_4FeLi_2



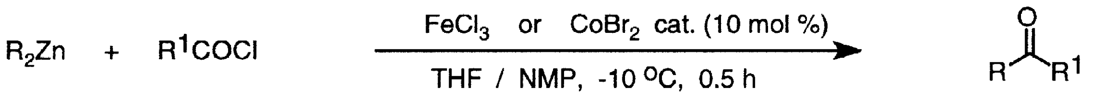
(31)

R	Reagent	Ketone	Carbinol	Ester
Ph	BuFeCl	0	0	0
	Bu_2Fe	77	0	7
	Bu_3FeLi	58	0	9
	Bu_4FeLi_2	28	0	0
	Me_2Co	94	0	0
	Me_3CoLi	96	1	0
	Me_2Mn [a]	66	28	0
	Me_2Mn [b]	90	0	0
n-C_7H_{15}	Me_2Fe	74	2	15
	Bu_2Fe	77	0	13
	Bu_3FeLi	85	0	6

[a] From $MnCl_2$. [b] From MnI_2.

were ineffective in these reactions. Preparation of the organoiron compounds required reduction of $FeCl_3$ to $FeCl_2$ followed by the requisite stoichiometry of an organolithium or Grignard reagent. The cobalt reagents gave higher yields than the iron or manganese reagents. In competition experiments between aroyl chlorides and alkanoyl chlorides, the iron, cobalt, and cuprate reagents displayed a preference for the aroyl chloride with iron and cobalt reagents displaying higher selectivity. In competition experiments between aroyl chlorides and alkenoyl chlorides, the iron and cobalt reagents showed a preference for the alkenoyl chloride while the cuprate reacted faster with the aroyl chloride; the cobalt reagent showed the greatest selectivity. Although not synthetically useful, Me_2Fe and Me_2CuLi displayed different chemoselectivities with 2-methoxyterephthaloyl dichloride and 4-methoxyisophthaloyl dichloride which raises interesting mechanistic questions.

Iron and cobalt halides have also been employed as catalysts in the acylation of diorganozinc reagents and involve organo- iron and cobalt intermediates (eq. 32).[65] Although addition of $CoBr_2$ to organolithium or Grignard reagents results in decomposition, organozinc reagents (e.g., R_2Zn or RZnX) react with $CoBr_2$ to give thermally stable (0 °C) organometallic agents. The lack of a general all purpose palladium catalyst and the necessity of using stoichiometric quantities of CuCN·2LiCl make these iron and cobalt catalyzed acylations of organozinc compounds attractive. The cobalt catalyzed reaction appears to utilize only one ligand from the dialkyzinc reagent. Previously, Fe(acac) has been utilized as an effective catalyst for the acylation of Grignard reagents (eq. 12).[28-30]



(32)

R	R^1	$CoBr_2$	$FeCl_3$
$PivO(CH_2)_5$-	Ph	84	82
	n-C_7H_{15}-	76	74
	Ph	82	
	CF_3	82	
	ClCO	83	

Rhodium complexes react with a variety of organolithium or Grignard reagents to afford alkyl or aryl Rh complexes that react with acid chlorides to afford good yields of ketones (eq. 33).[66] The reaction proceeds via a transmetallation-oxidative addition-reductive elimination sequence (see Scheme III, vide infra). The initial transmetallation reaction affords an alkyl rhodium(I) complex which then undergoes an oxidative addition to the acyl chloride to give a rhodium(III) complex. Reductive elimination from the alkyl(acyl)rhodium(III) complex generates the ketone. Utilization of rhodium complexes for ketone synthesis appears limited to the initial report. Branched alkylrhodium(I) (i.e., *sec*- and *tert*-alkyl) complexes give low yields of ketones due to β-hydrogen elimination and *s*-BuRh(I) gives *n*-Bu ketones (3:1) as the major product.

$$\mathrm{Rh^{I}Cl(CO)L_2} \xrightarrow[-78\ ^{o}\mathrm{C},\ 0.5\ \mathrm{h}]{\mathrm{RM,\ THF}} \mathrm{MCl} + [\mathrm{RRh^{I}(CO)L_2}] \xrightarrow{\mathrm{R^1COCl}} \qquad (33)$$

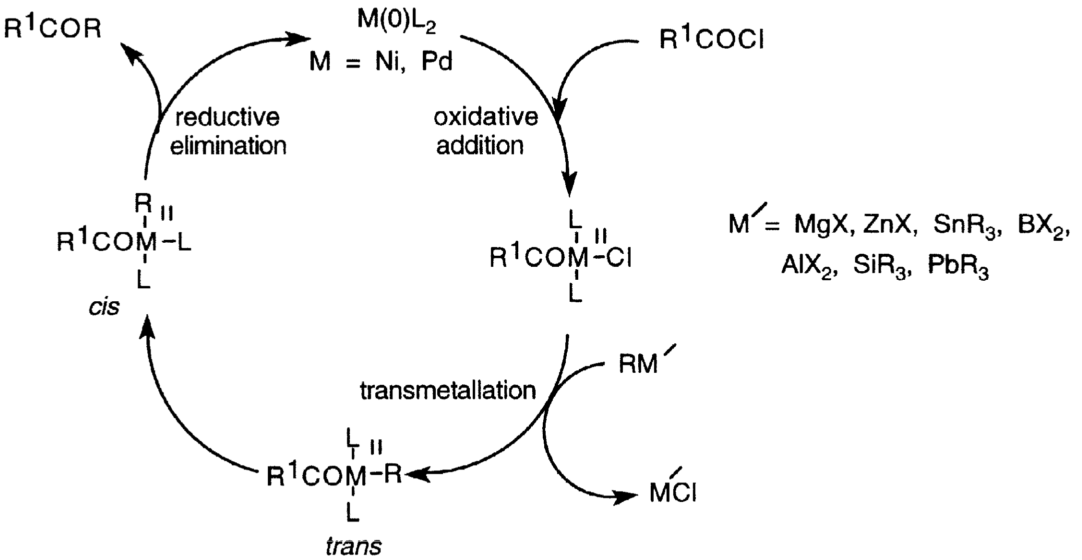
$$\mathrm{L = Ph_3P;\ M = Li,\ MgX} \qquad \mathrm{RRh^{III}(Cl)R^1CO(CO)L_2} \longrightarrow \mathrm{RCOR^1}$$

RM	R^1	% yield
MeLi	n-$C_{11}H_{23}$	77
MeMgI		58
n-BuLi		80
PhLi		96
PhMgBr		85
CH_2=$CHCH_2MgBr$		83
MeLi	Ph	82
n-BuLi		74
PhLi		94
CH_2=$CHCH_2MgBr$		71
$C_2H_5CH(Me)Li$		3
n-BuLi	$ClCH_2$	55
PhLi		80
PhLi	$C_2H_5CH(Me)$	69

3.4 *Group VIIIB (Ni, Pd)*

The extensive organic chemistry of Ni(0)[67] and Pd(0)[68] complexes can be rationalized by the general mechanistic description[69,70,71] provided in Scheme III. The zero valent metal,

Scheme III

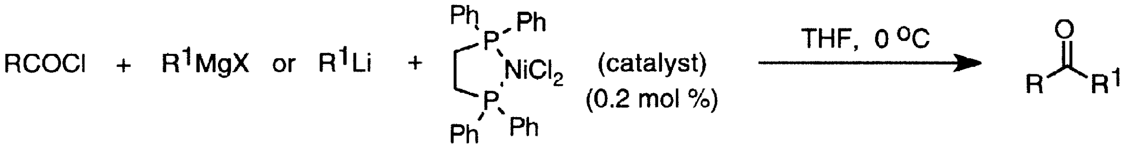


prepared separately or generated *in situ* via reduction of the M(II) species by the organometallic reagent or other reducing agents, undergoes an oxidative addition to the acid chloride. Reaction of the resultant acyl metal(II) species with a second organometallic reagent affords an acyl(alkyl)metal species via transmetallation. A wide range of metals can transfer ligands to Ni(II) or Pd(II) species. The acyl(alkyl)metal(II) species, which can exist as *cis* and *trans* stereoisomers, must assume the *cis* configuration for subsequent reductive elimination to afford the desired ketone and regenerate the zero valent metal catalyst. Those ligands and reaction conditions (e.g., added LiCl) which favor direct formation of the *cis* stereoisomer generally accelerate the overall process.[69] Although complications can arise during any of the three steps of the catalytic cycle (i.e., oxidative addition, transmetallation, and reductive elimination),[68,69] difficulties are generally encountered during the transmetallation step. A balance of the relative rates for the three steps can sometimes be crucial for the success of Pd(0) catalyzed coupling reactions.[70]

The intermediate acylpalladium complexes can sometimes undergo decarbonylation which lowers the yields of ketones in palladium catalyzed acylations of organometallic reagents. The decarbonylation event has been employed in a synthesis of aryl ketones where the aryl ligand is derived from an acid chloride. Reaction of the σ-arylpalladium complex with a ketene generated *in situ* from an acid chloride affords an α,β-unsaturated aryl ketone in modest to excellent yields (32-96%). Mechanistically, ketone formation occurs in a Heck reaction between the Pd(II) species and a ketene and does not involve the direct coupling of an organometallic reagent with an acid chloride.[72]

3.4.1 *Ni catalyzed acylation reactions*

Carboxylic acids can be converted directly into ketones with a large excess of Grignard reagent in the presence of a Ni catalyst.[73] The utilization of acyl halides was suggested by the synthesis of unsymmetrical ketones via sequential addition of Grignard reagents to *S*-phenylcarbonochloridothioate (i.e., PhSCOCl) in the presence of Ni(II) or Fe(III) catalysts.[74] Stoichiometric amounts of Ni(II) are effective in coupling benzyl, allyl, vinyl, and pentafluoroaryl halides with acid chlorides to afford the corresponding ketones. The reaction



(34)

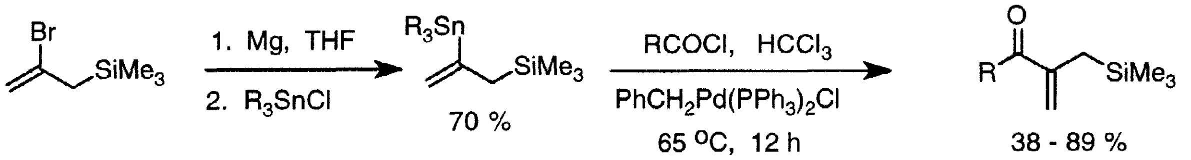
R	R^{1}MgX	R^{1}Li	% yield
Ph	Et		56
Ph	Ph		100
Ph	2-thienyl		92
Ph	*n*-C_8H_{17}		91
Ph	*i*-Bu		89
Ph	*c*-C_6H_{11}		91
PhCH(Me)CH_2	Ph		100
PhCH(Me)CH_2	2-thienyl		100
CH_2=CHC_8H_{16}	Ph		80
cis c-C_6H_{10}(2-CO_2Me)	Ph		62
ClCO	2-thienyl		80
Ph		2-(1,3-dithianyl)lithium	20
Ph		2-(2-Me-1,3-dithianyl)lithium	72

proceeds by oxidative addition of Ni(0) into both the organic halide and the acid chloride. Ligand transfer between the organonickel complex, RNiX (R = benzyl, vinyl, allyl), and the acylnickel complex affords a mixed (acyl)organonickel complex (i.e., $RNiCOR^1$), which undergoes reductive elimination at 85 °C in glyme to give the ketone.[75] An efficient synthesis of ketones has been reported which involves the reaction of acid chlorides with Grignard reagents in the presence of dichloro[1,3-bis(diphenylphosphino)ethane] nickel(II) [$Ni(dppe)Cl_2$] (eq. 34).[76] The title and table offer conflicting information as to whether acid chlorides or bromides were employed in the reaction. The latter could be intermediates if NaBr was used as an additive. The use of NaI with the acyl chlorides was noted to give by products arising from opening of the THF ring.[77]

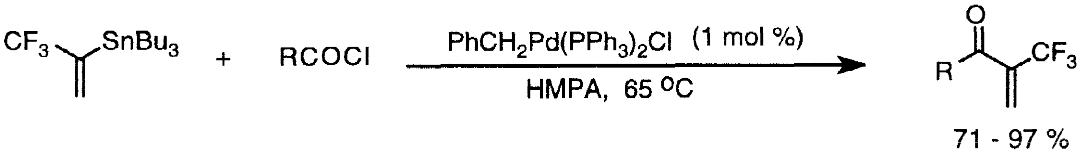
3.4.2 *Palladium catalyzed acylation of organostannanes (Pd/Sn)*

Although first reported by Migita[78] in 1977, the palladium catalyzed acylation of organostannanes was extensively developed by Stille in a reaction that has come to bear his name.[79,80] Several reviews include sections detailing various aspects and applications of the reaction,[81,82] and an extensive mechanistic discussion is provided in the review by O'Neill.[7] The reactions are generally conducted in polar solvents such as HMPA (small decreases in yield and reaction rate are observed in less polar THF or non-polar solvents such as chloroform and dichloroethane) at elevated temperatures, are accelerated by oxygen, and are sensitive to the Pd catalyst employed. The most effective palladium catalyst is $PhCH_2Pd(PPh_3)_2Cl$ employed at a concentration of 7×10^{-4} M. The success of the reaction is dependent upon the facile oxidative addition of acid chlorides to Pd(0) and is not effective with other acylating agents. The acid chloride, ketone product, and organostannane are unreactive toward each other in the absence of a Pd catalyst, and decarbonylation of an intermediate acylpalladium species (vide supra) is the only major side reaction and can be suppressed by use of a carbon monoxide atmosphere. The facility of ligand transfer from tin to the acylpalladium(II) complex is $ArC{\equiv}C\text{-} > RC{\equiv}C\text{-} > RCH{=}CH\text{-} > Ar\text{-} >$ allyl, benzyl $> MeOCH_2 > Me > Bu$, and the reaction can tolerate aldehyde, ketone, carboxylic esters, ethers, alkenes, aryl halides (sometimes problematic with ArBr), nitriles, and nitro compounds in either the acid chloride or organostannane component. Although aryl, alkynyl, alkenyl, alkyl, and α-heteroatom organostannanes can be acylated, the yields diminish for alkylstannanes larger than methyl and the method is largely used for the acylation of sp^2 hybridized carbon centers.

The procedure has been used to prepare 2-silylmethyl-α,β-enones (eq. 35) via the palladium catalyzed acylation of 3-trimethylsilyl-2-propenyl(tri-*n*-butyl)stannane.[83] Acylation of the vinyl stannane with α,β-unsaturated acid chlorides affords α,β-α',β'-dienones which can be exploited in the Nazarov cyclization to afford 4-alkyl-2-alkylidinecyclopentanones.[84] This reaction nicely illustrates the opportunities to increase the efficiency of the process based upon the acylation of organometallic reagents. The direct acylation of the magnesium cuprate, or palladium catalyzed acylation of the organozinc reagents (addition of $ZnCl_2$) would eliminate one step and could, perhaps, afford a higher yielding acylation step. A variety of α,β-enones containing perfluroroalkyl- (eq. 36)[85], arylthio- (eq. 37)[86], or alkoxyalkyl- (eq. 38)[87] substituents on the double bond are readily available by minor modifications of the procedure. Reflecting ligand migratory aptitudes, the reaction of 1-trifluoromethyl-1-tri-*n*-butylstannylethene requires heating for 3-10 hours with aroyl and alkenoyl chlorides and 22-24 hours with alkanoyl chlorides. The 2-phenylthio-α,β-enones can also be prepared via the aldol reaction of aldehydes with phenylthiomethyl ketones (limited to ArCHO and unbranched RCHO) in turn prepared via the Weinreb procedure using $PhSCH_2Li$. The acetal functionality is sensitive to the Lewis acidity of acid chlorides and the reaction must be run in DMF for good yields. The palladium catalyzed vinylation of L-*N*-protected proline acid chloride with vinyl stannanes illustrates the importance of examining a range of palladium catalysts in any given application (eq. 39).[88] The reaction fails with a number of traditional palladium catalysts and HMPA as solvent giving the enecarbamate via decarbonylation. The only catalyst to work in this application was 1,1'-bis(diphenylphosphino)ferrocene (dppf) which is known to suppress β-hydrogen elimination in palladium catalyzed coupling reactions.


(35)

R = Me, CH_2=CH-, (*E*)-MeCH=CH-, Me_2C=CH-, CH_2=CMe-, (*E*)-PhCH=CH-, MeO_2C-, MeO_2CCH_2-, $MeO_2C(CH_2)_2$-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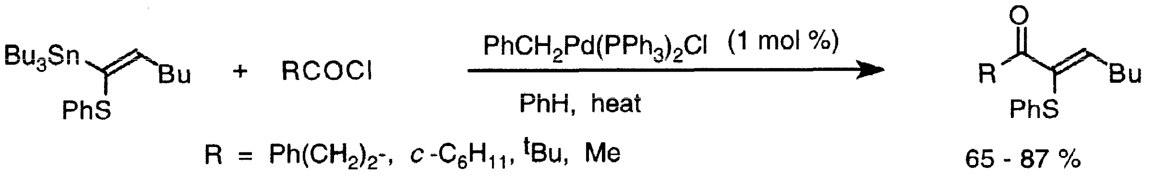
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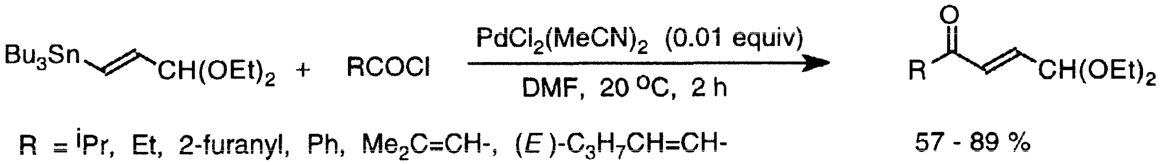
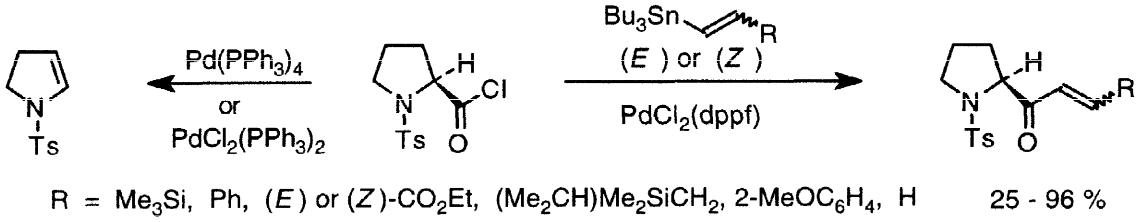
R = $Ph(CH_2)_2$-, *c*-C_6H_{11}, ${}^tBu$, Me


(38)

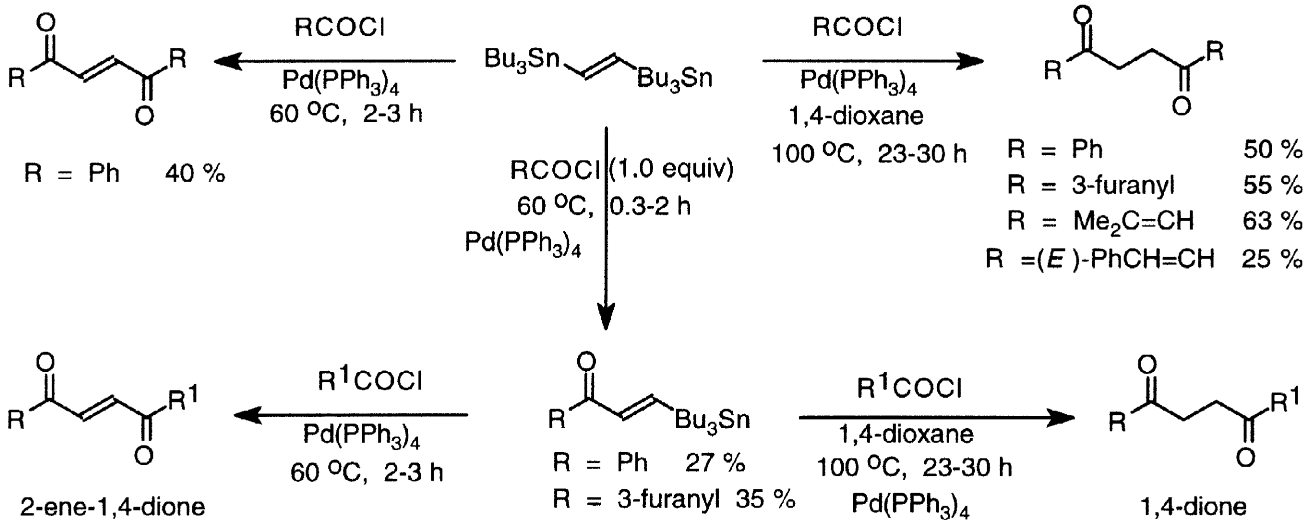
R = ${}^iPr$, Et, 2-furanyl, Ph, Me_2C=CH-, (*E*)-C_3H_7CH=CH-

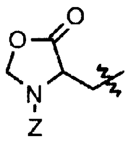

(39)

R = Me_3Si, Ph, (*E*) or (*Z*)-CO_2Et, $(Me_2CH)Me_2SiCH_2$, 2-$MeOC_6H_4$, H

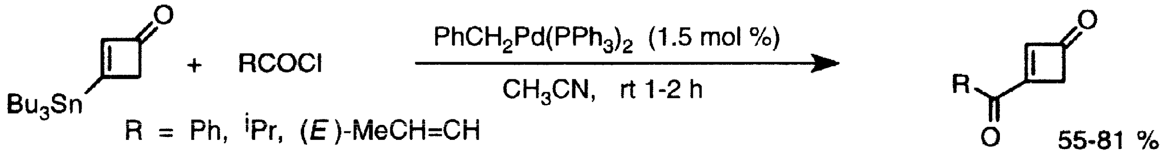
Bis-1,2-(tri-*n*-butylstannyl)ethene has been used in a general synthesis of both symmetrical and unsymmetrical 1,4-diketones and 2-ene-1,4-diones (Scheme IV).[89] Diacylation of the vinyl bis-stannane affords the symmetric diketones; lower temperatures give the enediones and the saturated 1,4-diketones form at higher temperatures via reduction of the conjugated C=C with an intermediate palladium hydride species. Mono acylation of the vinyl bis-stannane affords the β-stannylenone providing an opportunity for preparation of the unsymmetrical diketones via acylation with a different acid chloride. Again the reduction of the C=C double bond can be controlled by the temperature at which the coupling reaction is run.

Scheme IV



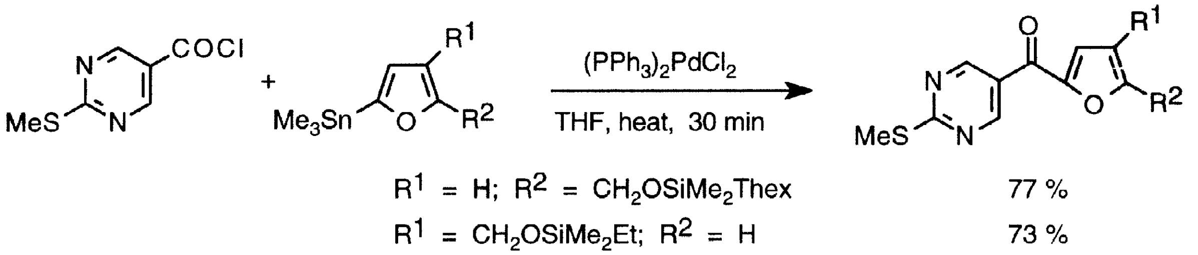
R	R^1	% yield 1,4-diketone	% yield ene-1,4-dione
Ph	Me	47	86
2-furanyl		100	93
Ph	*t*-Bu	87	
Me	Ph	70	
n-Bu		65	56
Me	3-furanyl	70	
Ph		64	
Me	Me_2C=CH	86	
Ph		97	
Me	(*E*)-PhCH=CH	52	36
Me	MeCH(NHBz)$(CH_2)_3$	37	
n-Bu		38	50
Ph		38	
Me		45	

Cyclobutenones with electron withdrawing functional groups in the 3-position have been prepared via acylation of the 3-stannylcyclobutenones in moderate to excellent yields with minor amounts (10-15%) of the by-product arising from self coupling of the organostannane. The coupling is, in some instances, facilitated by CuI and must be conducted under anhydrous conditions (eq. 40).[90]



(40)

Aryl- and heteroarylstannanes are also effectively coupled with acid chlorides (eqs. 41-42).[91-92] The latter reaction has been used in the synthesis of the aromatic amino acid, L-kunurenine.[92] A solid phase synthesis of 1,4-benzodiazepine derivatives utilizes the coupling of a Boc protected ortho amino aryltrimethylstannane with aroyl or alkanoyl chlorides.[93] The ligandless catalyst $Pd_2dba_3\cdot CHCl_3$ must be employed in the presence of an acid scavenger (e.g., K_2CO_3 or ${}^iPr_2EtN$) to prevent protodestannylation and carbamate deprotection.



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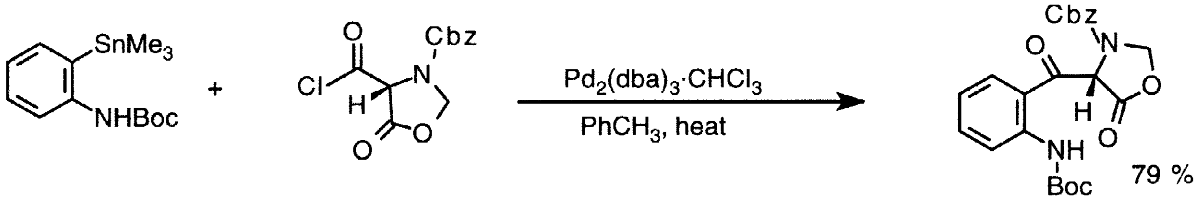

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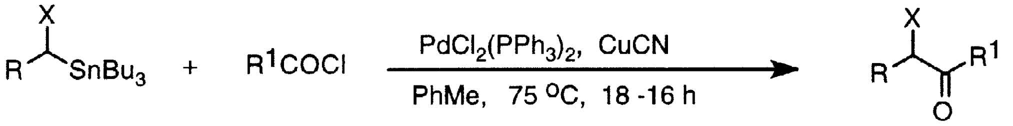


(43)

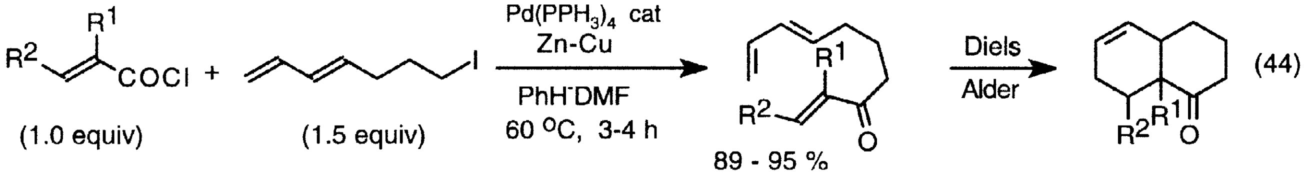
R	X	R^1	% yield
$Me(CH_2)_6$	OAc	Ph	74
	OBz		70
	OBz	$4\text{-}NO_2C_6H_4$	40
		Me	<5
		$MeO_2C(CH_2)_2$	40
	N-phth	Ph	45[a]
	$O_2CC_6H_4\text{-}4\text{-}NO_2$		50
Ph	OAc		78
		$Me(CH_2)_3$	68
	OMOM	Ph	80
(*E*)-$Me(CH_2)_2CH=CH$	OAc		57
t-Bu			50
$Ph(CH_2)_2$	OMOM		30
	OMe		0

[a] R^1COBu formed in 28% yield.

α-Heteroatom substituted alkylstannanes preferentially transfer the heteroatom functionalized ligand in reactions with acid chlorides in the presence of palladium catalysts (eq. 43).[94] The reaction works well for easily transferable benzylic or allylic ligand systems containing ether or ester substituents while non-conjugated aliphatic systems require an ester heteroatom substituent. Coupling of α-oxygenated aliphatic stannanes and alkanoyl chlorides proceeds in poor yields. The yields of coupled products are reduced in the presence of air and a carbon monoxide atmosphere results in preferential transfer of the butyl group.

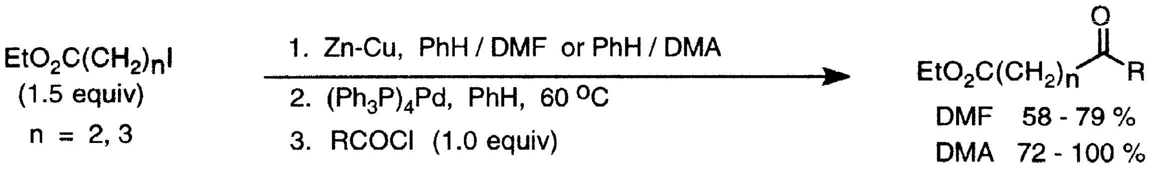
3.4.3 Palladium catalyzed acylation of organozinc and copper reagents (Pd/Zn and Cu)

Stille's development of palladium catalyzed coupling of organostannanes with acyl chlorides prompted a series of studies with organozinc reagents. The first study by Fujisawa examined the preparation of benzyl ketones (55-88% yields) by the reductive coupling of benzyl bromide and acyl halides (1:1 ratio respectively) in the presence of zinc powder (2.0 equivalents) and 2-10 mol % of $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$. These proved superior to other Pd or Ni catalysts which gave substantial amounts of dibenzyl.[95] Good yields of benzyl ketones were achieved under mild conditions (DME, rt, 20 min.) in THF, acetonitrile, dioxane, and DME while poor yields were obtained in HMPA or DMF. Excellent yields of ketones were achieved with aroyl chlorides (> 80%) and linear alkanoyl chlorides (> 78%), while yields decreased with branching in the benzyl halide or acyl halide. Ester, α,β-alkenyl, and haloarene functional groups were tolerated in the acid chloride, although diminished yields were observed. No ketone was formed with pivaloyl chloride and low yields of ketone were obtained with *p* -$NO_2C_6H_4CH_2Br$. The palladium catalyzed acylation of organozinc reagents was concurrently extended to RZnI[96] (R = alkyl, alkenyl, 1-alkynyl, aryl: 25 °C, < 6 h, 71-89% isolated yields) and R_2Zn[97] (R = alkyl, aryl: THF/Et_2O, 0-23 °C, 82-98%) reagents prepared from organolithium or Grignard reagents and $ZnCl_2$. The alkenyl group was transferred from RZnX reagents with 98% stereospecificity and more efficiently with a Pd-catalyst generated from $PdCl_2(PPh_3)_2$ and $^iBu_2AlH$.[96] The reactions with RZnX were sluggish in Et_2O or THF/Et_2O solvent systems and required THF. By contrast, reactions with R_2Zn were conducted in THF/Et_2O, and use of aroyl chlorides required pure Et_2O in order to minimize formation of ArCHO via β-hydrogen elimination events. Catalyst effectiveness was in the order: $Pd(PPh)_4$ < $BnPdCl(PPh_3)_2$ < (dppf)$PdCl_2$. The organozinc reagents could also be prepared from alkyl iodides and Zn-Cu although the resulting organozinc reagents were acylated at elevated temperatures (60 °C).[98,99] This procedure avoids the use of cuprates which tend to undergo conjugate addition to the product α,β-unsaturated ketones (eq. 44).[98]



(44)

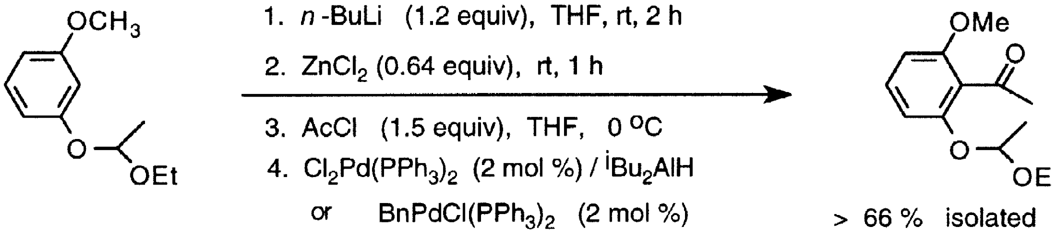
The acylation of organozinc reagents derived from iodo esters $EtO_2C(CH_2)_nI$ (n = 1, 2) gave significantly higher yields in dimethylacetamide (DMA, 72-100%) than in DMF (58-79%) employing a 50% excess of iodo ester (eq. 45).[99] This procedure has been extended to the corresponding iodo ketones (i.e., $RCO(CH_2)_nI$ using 1.3-1.8 equivs of halide) which affords diketones in moderate to excellent yields (53-91%) in the presence of $Pd(PPh_3)_4$ at mildly elevated temperatures (40 °C).[100]



(45)

R = Et, n-C_7H_{15}-, Ph, 4-$MeOC_6H_4$-, 4-ClC_6H_4-, 2-$MeOC_6H_4$-, PhCH=CH-, CH_2=C(Me)-, $MeO_2C(CH_2)_4$-, $MeO_2C(CH_2)_7$-, $EtO_2C(CH_2)_8$-

Ortho lithiation of appropriately substituted aromatic rings followed by treatment with $ZnCl_2$ affords functionalized R_2Zn (eq. 46)[101] or RZnCl (eq. 47)[102] reagents that are acylated with acid chlorides in the presence of palladium catalysts in good to excellent yields. The RZnCl reagents must be used in 50% excess (1.5 equivalents) perhaps because of chelation with the Directing Metallation Groups (DMG). DMG such as aminals, imines, and sulfonamides failed to function effectively because of chelation problems or formation of multiple products. Utilization of TMEDA in the deprotonation step retards the cross coupling reaction.



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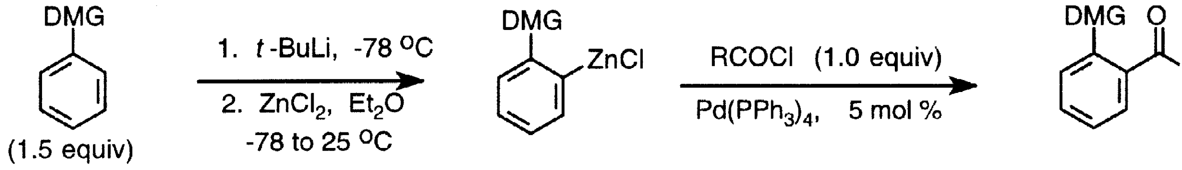
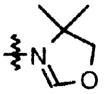


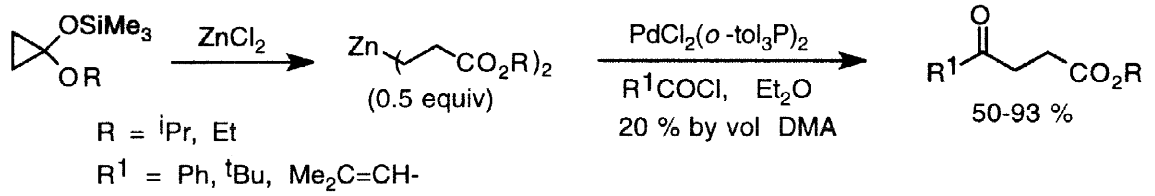
(47)

DMG = Directing Metallation Group

R \ DMG		-CON(i-Pr)2	-OMOM	CH_2NEt_2
Ph	92	95[a]	97	69[b]
c-C_5H_9-	86	94[a]	93	55[b]
(E)-EtCH=C(Me)-	83	76[a]	75	57[b]

[a] Et_2O:THF (10:1) to stabilize the aryl amide. [b] Et_2O:THF (1:1) to elevate the reflux temperature.

A zinc homoenolate generated from cyclopropanone ketals afforded both C- and O-acylated products; the ratio of C:O-acylation was dependent upon stoichiometry, additives, and solvents (Eq. 48)[103]. O-Acylation can be suppressed by adding 20% by volume of dimethylacetamide (DMA). Conversion of serine into the iodo α-amino acid provides a convenient route to the corresponding organozinc reagent which can be acylated with palladium catalysis to afford a wide variety of α-amino acid derivatives (eq. 49).[104-106] Acylation with the acid chloride of acrylic acid followed by acid promoted cyclization provides a convenient route to scalemic 4-oxopipecolic acid derivatives (eq. 50).[105] Acylation with ethyl oxalyl chloride gives modest yields of the mono acylated product and the bis acylated product via decarbonylation of the intermediate acyl palladium complex followed by addition of the zinc reagent to the carbon monoxide ligand (eq. 51). In this case the zinc cuprate reagent proved superior.[106] Chelation controlled acylation of 2-(alkoxycarbonyl)cyclopentylzinc iodides with Pd catalysis occurs with *cis*-selectivity.[107] A review by Knochel lists 43 examples involving the acylation of functionalized organozinc reagents aided by palladium catalysis. The reaction tolerates ester (50-100%), ketone (53-91%), and Boc-protected α-amino ester (41-90%) functionalities.[108]



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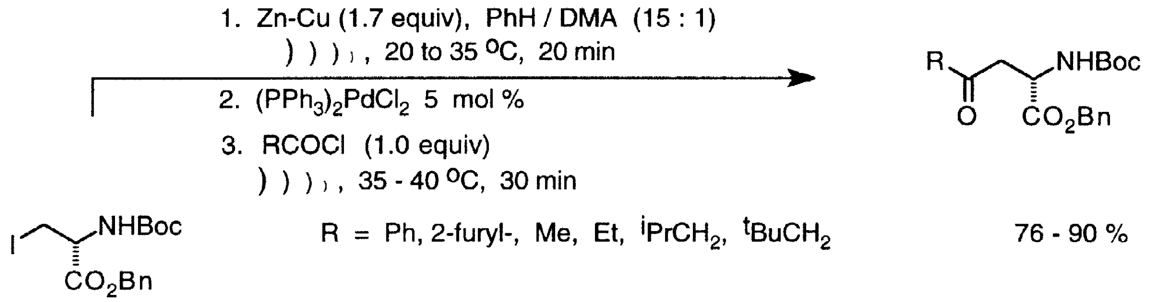

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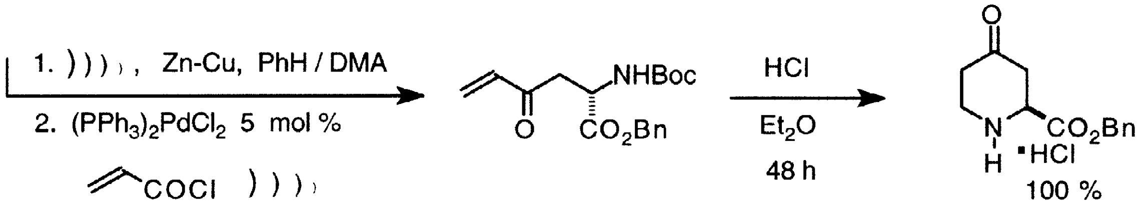

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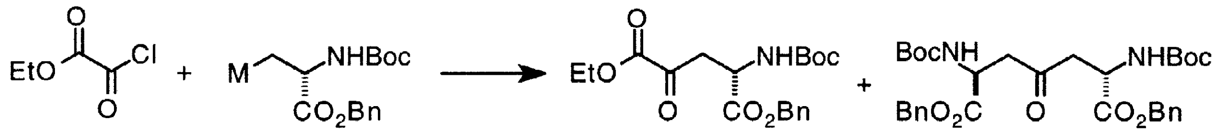
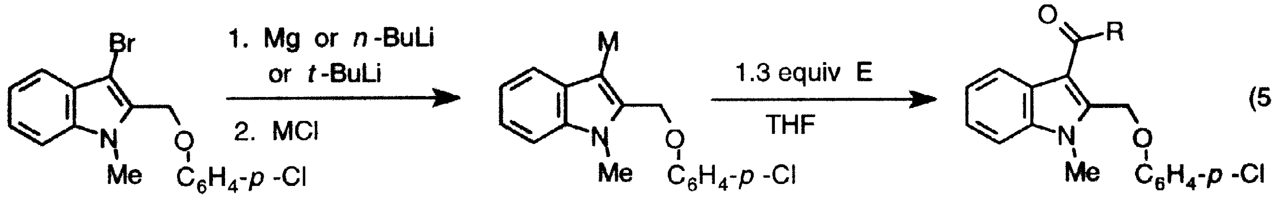


(51)

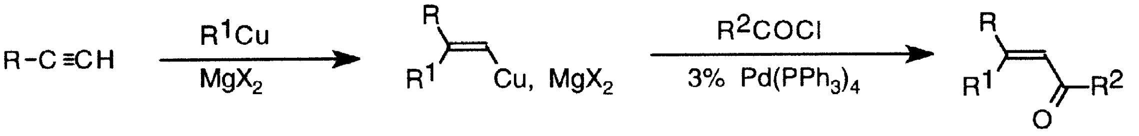
The acylation of 3-metallo-2-phenoxymethylindoles (M = Li, Mg, Cu, Zn) was examined for several organometallic systems. Only the organozinc reagents in the presence of a Pd catalyst gave good yields of the 3-indolyl ketones (eq. 52).[109] The lithium and Grignard reagents gave largely the reduction product while the copper reagent and the Weinreb procedure failed. The yields were obtained with excess (1-3 equiv.) of acid chloride, although too much AcCl/$ZnCl_2$ resulted in zinc mediated cleavage of THF.



(52)

M	catalysts	E	Temp (°C)	% yield
Li		$MeCOCl$	-78	4
MgBr		$MeCOCl$		0
Li		$MeCONMe(OMe)$		43
ZnCl	CuI	$MeCOCl$	+25	0
ZnCl	$Pd(PPh_3)_2Cl_2$	$MeCOCl$	-35	74
ZnCl	$Pd(PPh_3)_2Cl_2$	$BnCOCl$	-35	61
ZnCl	$Pd(PPh_3)_2Cl_2$	$PhCOCl$	-35	66
ZnCl	$Pd(PPh_3)_2Cl_2$	$CH_3(CH_2)_2COCl$	-35	70
ZnCl	$Pd(PPh_3)_2Cl_2$	$ClCH_2COCl$	-35	33

α,β-Alkenyl- and α,β-α',β'-dialkenyl ketones are readily prepared by efficient acylation of vinyl copper derivatives (1.1-1.2 equivs.) in the presence of a palladium catalyst (eq. 53).[110a] In the absence of a palladium catalyst, the alkenyl copper reagents gave low yields of ketones, while the cuprates gave mainly products arising from subsequent conjugate addition to the product enone in THF or Et_2O. Improved yields (31% for MeCOCl and 44-61% for MeCOBr based on both alkenyl ligands) were achieved with an Et_2O/THF/HMPA (70:30:4 equiv) solvent system which slows the conjugate addition reaction and accelerates the acylation reaction. Higher yields could be obtained in tetrahydropyran (THP) which undergoes ring cleavage slower than THF in the presence of the acid chlorides. The vinyl copper reagents are



(53)

R	R^1	R^2	additive[a]	% yield
H	n-C_7H_{15}-	Me	$ZnBr_2$	80
H	Et	n-C_7H_{15}-	$ZnBr_2$	85
H	^nBu	^nBu	2 $MgBr_2$ + 1 CuBr	76
Me	^iPr	^tBu		84
Me	n-C_7H_{15}-	Me		70
Me	Et	Ph		73
EtO	^nBu	Me		74
Me	^nBu	(E)-MeCH=CH-		85 (100)[b]
Bu	^iPr	Me_2C=CH-		58 (93)[b]
H	Et	(E)-n-C_6H_{13}CH=CH-	$ZnBr_2$	87
H	Et	(E)-n-C_6H_{13}CH=CH-	$ZnBr_2$	88
H	^iPr	3-furanyl		85

[a] Added to the lithium dialkenylcuprate reagent. [b] GLC yield.

directly available via carbocupration of alkynes (RMgX + CuI)[111] which provides for stereo defined reagents. Treatment of vinylcuprates with $ZnCl_2$ affords a mixture of vinyl copper and vinyl zinc species both of which undergo Pd catalyzed acylation. Alternatively, treatment of $(alkenyl)_2CuLi$ reagents with MgX_2 and CuX also affords the vinyl copper reagents obtained via carbocupration. The effectiveness of this palladium catalyzed acylation of vinyl copper reagents reflects the facility of alkenyl ligand transfer in transmetallation sequences and, although unexplored, the method may not fare as well for alkylcopper reagents. A $CuI/(Ph_3P)_2PdCl_2$ catalyst system converts terminal alkynes and acyl chlorides into alkynyl ketones in modest to excellent yields (61-96%).[110b] Simple alkanoyl chlorides react with the triethylamine employed in the reaction resulting in low yields of ketone.

3.4.4 *Palladium catalyzed acylation of main group organometallics (Pd/B, Al, Si, Pb)*

Palladium catalyzed acylation of Group IIIA metals is rather limited. Although Negishi showed that alkyl- and arylborates can be acylated in the absence of palladium catalysts, both alkenylboranes and alkenylborates failed to undergo acylation even with Pd catalysts.[96] Sodium tetraphenylborate affords phenyl ketones (51-100%) in the presence of $Pd(PPh_3)_4$[71], and the method has been extended to a silicon supported Pd(0) complex[112] which affords approximately a 6% diminution in yield upon each recycling of the column. The $Pd(PPh_3)_4$ reaction works well with both aroyl and alkanoyl chlorides while the silicon supported catalyst gives only trace amounts of product with alkanoyl chlorides.

Although (*E*)- and (*Z*)-alkenylalanes react with acid chlorides, the reaction shows poor stereoselectivity (*E* :*Z* , 2-13:1).[96] Excellent yields (>90%) and stereoselectivity can be achieved in the palladium $[Cl_2Pd(PPh_3)_2 + {}^iBu_2AlH]$ catalyzed reactions of acetyl chloride with (*E*)-(2-methyl-1-octenyl)dimethylalane (92% diastereomeric ratio) and its *n*-butylalanate (96% dr) obtained via addition of *n* -BuLi.[96] An independent examination of the reaction also revealed the ability of acid chlorides to acylate R_3Al and R_2R^1Al reagents in the presence of

$$\underset{(1\text{-}2\ \text{equiv})}{R^1R_2Al} + \underset{(1\ \text{equiv})}{R^2COCl} \xrightarrow[0\ -\ 25\ ^\circ C]{Pd(PPh_3)_4\ (0.05\ \text{equiv}),\ THF} R^1COR^2 \qquad (54)$$

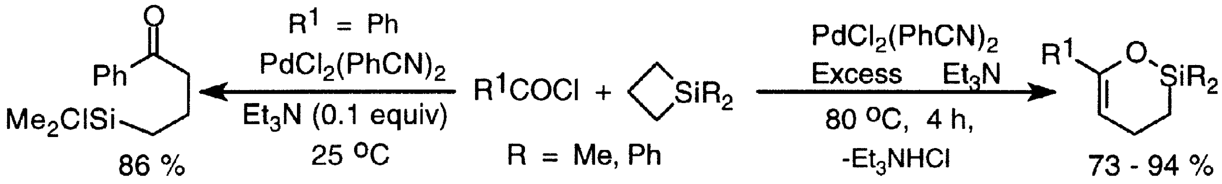
R	R^1	R^2	% yield
Et	Et	Ph	70
Me	Me	Ph	74[a]
Et	Et	PhCH=CH	68
Et	Et	$CH_2=C(CH_2)_8$	71
Me	Me	$CH_2=C(CH_2)_8$	59
Et	$C_4H_9C{\equiv}C$	Ph	67
Et	$C_4H_9C{\equiv}C$	C_7H_{15}	65
Et	$C_4H_9C{\equiv}C$	PhCH=CH	74
Et	$PhC{\equiv}C$	C_7H_{15}	61
Et	$C_6H_{13}C{\equiv}C$	$CH_2=C(CH_2)_8$	55
Et	$Me_3SiC{\equiv}C$	$CH_2=C(CH_2)_8$	51
${}^iBu$	(*E*)-$C_4H_9CH=CSiMe_3$	Ph	51
${}^iBu$	(*E*)-$C_6H_{13}CH=CSiMe_3$	$CH_2=C(CH_2)_8$	53

[a] GLC determined yield.

Pd catalysts such as $Pd(PPh_3)_4$ (eq. 54).[113] Other Pd catalysts generated from $Pd(OAc)_2$ + Ph_3P (1:2) and $PdCl_2(PPh_3)_2$ were also effective, but the organoaluminum compounds could not be effectively acylated in the presence of other transition metal catalysts such as $RuCl_2(PPh_3)_2$, $NiCl_2(PPh_3)_2$, and $RhCl(PPh_3)_3$.[113]

Silacyclobutanes undergo reactions with acid chlorides in the presence of a palladium catalyst to form either 3-(chlorosilyl)butyl ketones or cyclic silyl enol ethers depending upon the reaction conditions (Scheme V).[114] Control experiments suggest that the reaction proceeds by oxidative addition of the acid chloride with a Pd(0) species, followed by transmetallation of the silacyclobutane and subsequent reductive elimination to afford the 3-(chlorosilyl)butyl ketone. The latter species in the presence of excess amine and at higher temperatures undergoes intramolecular silylation to afford the cyclic silyl enol ether. The reaction only proceeds in the presence of small amounts of amine necessary to promote regeneration of the Pd(0) catalyst. Straight chain aliphatic acid chlorides gave low yields of products with Et_3N due to ketene formation via base catalyzed elimination of HCl, but high yields can be obtained by using sterically hindered amines (e.g., $^iPr_2NEt$). The reaction can also be catalyzed with a Pt complex, $Pt(CH_2{=}CH_2)(PPh_3)_2$ [87%, 10 h at 80-100 °C], but was less efficient than with the Pd catalysts.

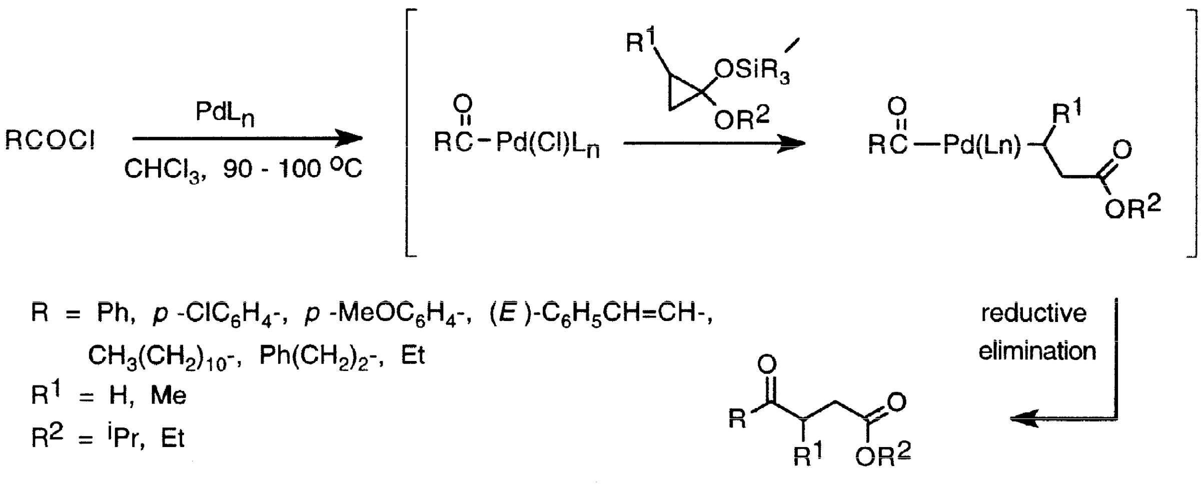
Scheme V



R^1 = Ph, p-MeC_6H_4-, p-$MeOC_6H_4$-, p-FC_6H_4-, 2-furanyl, c-C_6H_{11}-, (E)-PhCH=CH-, $Ph(CH_2)_2$-, $CH_2{=}CH(CH_2)_8$-, n-C_6H_{13}-,

Although the nucleophile is generally delivered to the acyl palladium complex via an organometallic reagent, other nucleophiles may be employed in palladium catalyzed ketone synthesis. The reaction of acid chlorides with siloxycyclopropanes and catalytic quantities of a

Scheme VI



R = Ph, p-ClC_6H_4-, p-$MeOC_6H_4$-, (E)-$C_6H_5CH{=}CH$-, $CH_3(CH_2)_{10}$-, $Ph(CH_2)_2$-, Et
R^1 = H, Me
R^2 = ^iPr, Et

palladium/phosphine complex affords moderate to excellent yields of 1,4-dicarbonyl compounds.[115] 1-Alkoxy-1-(trialkylsiloxy)-cyclopropanes afford 4-ketoesters (Scheme VI), while 1-alkyl- or 1-aryl-1-siloxycyclopropanes afford 1,4-diketones in moderate to good yields (42-22%). In these reactions the siloxycyclopropanes function as homoenolate synthons to afford the alkyl(acyl) palladium complex which releases the ketone product upon reductive elimination.

Tetra-alkyllead compounds can be acylated in the presence of palladium catalysts under relatively mild conditions (eq. 55).[116] They are more reactive than the corresponding tetra-alkylstannanes. Good yields of ketones can be achieved with 0.6 equivalents of the R_4Pb reagent suggesting that two of the four ligands can be utilized in the reaction. This is a result of the disproportionation of two molecules of the initially formed R_3PbCl to a molecule of R_4Pb and R_2PbCl. Utilizing 1.3 equivalents of R_4Pb gives nearly a quantitative yield of ketone. The reaction can tolerate α,β-unsaturated acid chlorides.

$$R^1COCl \quad + \quad R_4Pb \quad \xrightarrow[\substack{\text{THF, 65 °C} \\ \text{or PhH, reflux}}]{Pd(PPh_3)_4 \text{ (1 mol \%)}} \quad \underset{60 - 78\ \%}{R^1COR} \quad + \quad R_3PbCl \qquad (55)$$

R = *n*-Bu, Et

R^1 = Ph, $Me(CH_2)_6$-, $Me(CH_2)_3CH(Et)$-, PhCH=CH-

3.5 *Group IB (Cu)*

The first reported example of an organocopper reagent was phenylcopper prepared by Reich.[117] Henry Gilman prepared ethylcopper in 1936[118] and methylcopper and lithium dimethylcuprate in 1952.[119] Kharasch's report[120] of the copper catalyzed conjugate addition of Grignard reagents to enones in 1941 followed by House's (1966)[121a] and by Corey and Posner's (1967-68)[121b] utilization of stoichiometric lithium dialkylcuprates unleashed an explosive development of organocopper chemistry. Organocopper and organopalladium reagents are the two most widely used organometallic reagents in organic synthesis, although wider industrial use of copper reagents in synthesis (several pheromones are industrially produced using copper chemistry)[121c] awaits further developments in catalytic methods. Despite their wide versatility, the capriciousness of organocopper reagents is problematic and arises from their air, moisture, and thermal instability along with the plethora of effects arising from Cu(I) precursor salt, non-transferable ligands, solvents, and additives employed.[111]

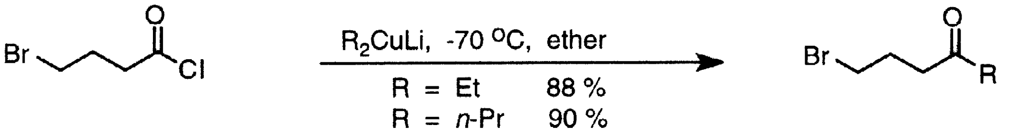
3.5.1 *Copper species from alkyllithium reagents*

The reaction of acid chlorides with organocopper(I) reagents (RCu) was first reported[118] by Gilman in 1936 and the use of lithium dimethylcuprate was reported by Whitesides in 1967.[122] Shortly, thereafter, Posner[123,124] and Riviere[125] explored the reactions of lithium dialkylcuprates for the preparation of ketones (eq. 56). Cuprates prepared from CuI and alkyllithium reagents in Et_2O gave good yields of ketones with aromatic, and straight chain α-alkyl, and α,α-dialkyl substituted aliphatic acid chlorides. The reaction is compatible with ketones, nitriles, esters, alkyl halides (eq. 57)[126], and aryl iodides but incompatible with, α-chloro acid chlorides, and α,β-unsaturated acid chlorides. Chemoselective acylation of cuprates with α,β-unsaturated acid chlorides can be achieved by employing an ether:THF:HMPA solvent combination that slows down the 1,4-conjugate addition reaction of the product relative to the acylation reactions (eq. 58).[127] 4-Nitrobenzoyl chloride reacted with lithium dimethylcuprate to give the methyl ketone, but the reaction failed with lithium di-*n*-butylcuprate. Excellent yields were obtained when three equivalents of cuprate were used but modest to good yields could be obtained with a 1:1 molar ratio of cuprate to acid chloride. The reaction did not go to completion with acyl fluorides.

$$R^1COCl \; + \; R_2CuLi \xrightarrow[15\ \text{min.}]{Et_2O,\ -78\ ^{o}C} R^1COR \qquad (56)$$

R^1	R_2CuLi^a			Ref
	Me	Bu	Ph^b	
n-C_5H_{11}	81	79		123
c-C_6H_{11}	86	80		123
Ph_2CH	93, $(65)^b$	90	88	123, (125)
t-Bu	84	90		123
$3,5$-$(CF_3)_2C_6H_3$	92	75-80		123
4-$NO_2C_6H_4$	50			123
CH_3	-		55	125
Ph	58^b		59	125
Me_2CH	45^b		67	125
CH_3CHCl	traces		15	125
PhCH=CH	polymer			125
$NC(CH_2)_{10}$	80	95		124
n-$BuCO(CH_2)_4$	95	83		124
$MeO_2C(CH_2)_4$	<20	85		124
n-$BuO_2C(CH_2)_4$	83	93		124
$ClOC(CH_2)_4$	92	90		124
$I(CH_2)_{10}$	91	93		124
4-IC_6H_4	98	85		124
$C_6H_4^c$	72	87		124

[a] Equivalents of cuprate added (3.0). [b] Equivalents of cuprate added (1.0). [c] Acyl fluoride employed.



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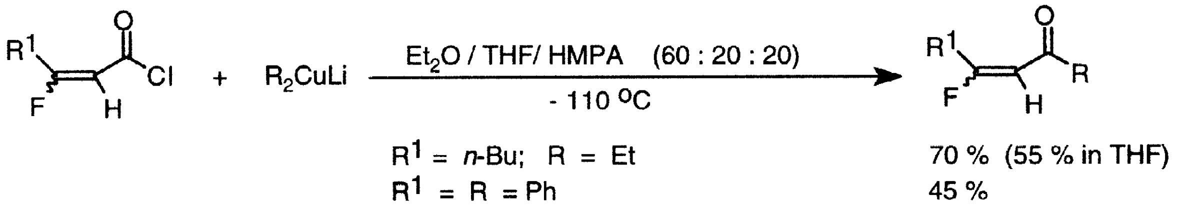

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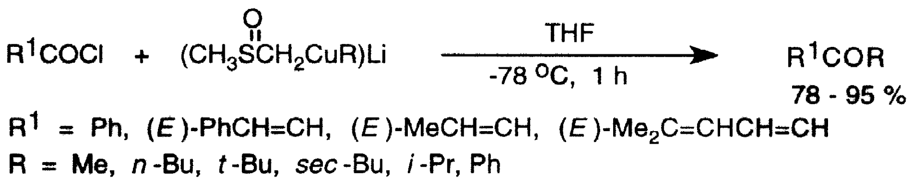
Reaction of the moderately reactive and relatively stable (0 °C) lithium dimethylcuprate with acid chlorides is a very reliable reaction for the preparation of methyl ketones[128-131] and has been used in synthetic routes to cyclooctatetraene[129], polyunsaturated [4.4.4]propellanes,[130] and monobromobenz[a]anthracenes.[131] Methyl or ethyl ketones utilized in the synthesis of vellaral[132], manicone[133], erythronolide B[134], monensin A[135], and (+)-phyllanthocin[136] have been prepared by the reaction of lithium dimethyl or diethyl cuprate with acid chlorides in yields of 75-100%. The chemoselective reaction of lithium di(trimethylsilyl)cuprate or lithium diethylcuprate with an acid chloride in the presence of a *tert*-butylthiol ester was employed in a synthesis of narbonolide,[137] and erythronolide B.[134]

The necessity of employing three equivalents of cuprate reagent in order to obtain high yields of ketones, prompted a search for mixed heteroatom cuprates containing a non-transferable ligand.[138-140] These lithium heteroatom(*tert*-butyl)cuprates displayed the following thermal stability order: PhS (0 °C) > PhO (-30 °C) > t-BuO (-50 °C) > Et_2N, *t* -BuS (<-78 °C). The combination of cuprate reactivity and thermal stability resulted in the *t* -BuOCuRLi, PhOCuRLi, and PhSCuRLi reagents giving the highest yields of ketones with only 1.1 equivalents of cuprate reagent being employed (eq. 59). These mixed cuprates gave significantly higher yields of ketones with fewer equivalents than the corresponding lithium dialkylcuprates. Low yields of ketones were obtained with Grignard reagents under copper catalysis.

$$\mathrm{PhCOCl} + ({}^{t}\mathrm{BuCuX})\mathrm{Li} \xrightarrow{-78\ ^{\circ}\mathrm{C},\ \mathrm{THF}} \mathrm{PhCO}^{t}\mathrm{Bu} + \mathrm{PhCOX} \qquad (59)$$

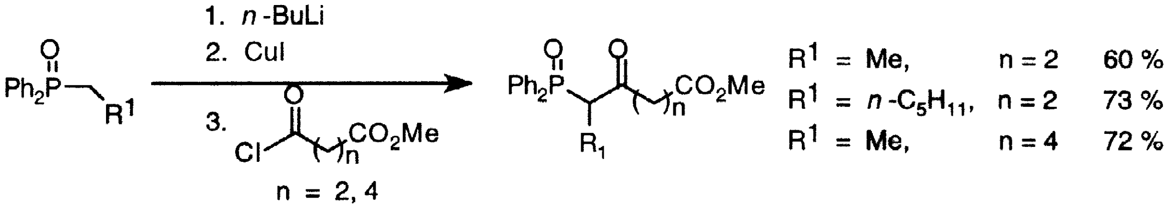
RM + CuI	X	equiv	% yield PhCO^{t}Bu	 PhCOX
	NEt_2	1.1	50	20
	t -BuS	1.1	75	25
	t BuO	1.1	98	
	PhO	1.1	87	
	PhS	1.1	99	
	t -Bu	2.0	76	
	Me	3.0	72	
	-	3.0	37	
t -BuMgCl + CuI (100 mol %)		1.1	34	
t-BuMgCl + CuI (10 mol %)		1.1	33	
t-BuLi + CuI (10 mol %)		1.1	5	

Mixed homo cuprates (i.e., RR^1CuLi) containing a non-transferable ligand derived from DMSO have also been examined and found to give good to excellent yields of ketones upon reaction with acid chlorides.[141] This reagent gives no competing 1,4-conjugate addition when α,β-unsaturated chlorides are employed and provides a convenient synthesis of α,β-enones (eq. 60). Although α-phosphinylalkylcopper reagents are significantly less reactive than the corresponding alkylcopper reagents, they have successfully been acylated with acid chlorides to give the corresponding β-keto phosphine oxides (eq. 61).[142] From the communication, however, it is unclear whether the organocopper(I) reagent or an organocuprate reagent was employed.



$$\mathrm{R^1COCl} + \mathrm{(CH_3\overset{O}{\overset{\|}{S}}CH_2CuR)Li} \xrightarrow[-78\ ^{o}\mathrm{C},\ 1\ \mathrm{h}]{\mathrm{THF}} \mathrm{R^1COR}\quad 78 - 95\ \% \qquad (60)$$

R^1 = Ph, (*E*)-PhCH=CH, (*E*)-MeCH=CH, (*E*)-Me_2C=CHCH=CH
R = Me, *n*-Bu, *t*-Bu, *sec*-Bu, *i*-Pr, Ph



(61)

In introducing new mixed amido- and phosphido- heteroatom cuprates, Bertz examined the thermal stability of a wide range of cuprate reagents by aging them at various temperatues for 30 minutes and then adding excess benzoyl chloride to the cuprate solution (eq. 62).[143-144] This study also provides some clues as to the relative reactivity of these mixed cuprates. The reagents Li(*c*-C_6H_{11})$_2$NCuBu, Li(Et_2N)Cu^tBu, and Li(PhS)Cu^tBu give lower yields of ketone at -50 °C than at 0 °C indicating that the actual yield reflects both reactivity of the cuprate and its thermal stability as measured in this protocol. The amidocuprate, Li(Et_2N)CuBu, is not formed at -78 °C and the solution must be warmed to -50 °C for cuprate formation to occur.

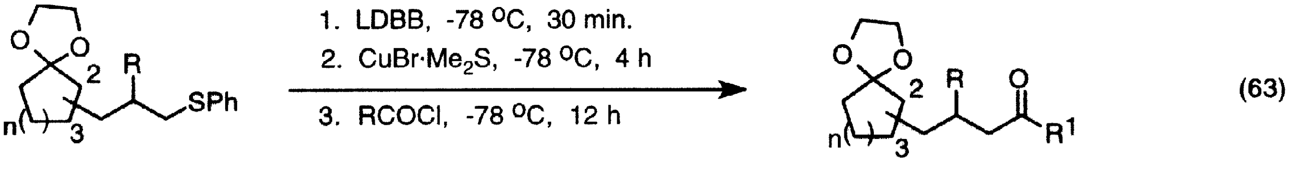
$$\mathrm{PhCOCl} + (\mathrm{RCuX})\mathrm{Li} \xrightarrow[\substack{\text{at -78, -50 or 0 }^{o}\mathrm{C}\\ \mathrm{Et_2O}\text{ or THF}}]{\text{cuprate aged, 30 min}} \mathrm{PhCOR} + \mathrm{PhCOX} \qquad (62)$$

R = *n*-Bu, *t*-Bu

	temperature (°C) at which cuprate is aged		
organocopper reagent[a]	-50	0	25
Li(Ph_2P)CuBu	90	99	95
Li(*c*-C_6H_{11})$_2$PCuBu	100	97	89
Li(Ph_2N)CuBu	100	25	1
Li(*c*-C_6H_{11})$_2$NCuBu	75	98	89
Li(Et_2N)CuBu	100	98	73
Li(Et_2N)Cu^tBu	20	90	81
Li(PhS)CuBu	100	19	0
Li(PhS)Cu^tBu	18	97	80
CuBu	94	5	0
(Bu_2P)CuBu	100	92	0
(cod)CuBu[b]	100	4	0
$LiCuBu_2$	96	89	82
Li($^tBuC{\equiv}C$)CuBu	100	92	89
Li(CN)CuBu	97	92	60
$Li_2(CN)CuBu_2$	99	95	84
Li($PhSO_2CH_2$)CuBu	96	86	38
Li($PhSO_2CH_2$)CuBu[c]	99	99	91

[a] Solvent inferred to be Et_2O unless noted. [b] COD = cyclo-octa-1,5-diene. [c] THF

The use of lithium dialkylcuprates containing additional functionality in the alkyl ligand is more problematic when the cuprate reagents are prepared from the corresponding organolithium or magnesium reagents. Organolithium reagents prepared by reductive metallation of phenyl sulfides with lithium di-*tert*-butylbiphenyl (LDBB) have been converted into cuprates which react with acid chlorides to afford ketones in moderate to good yields (eq. 63).[145]

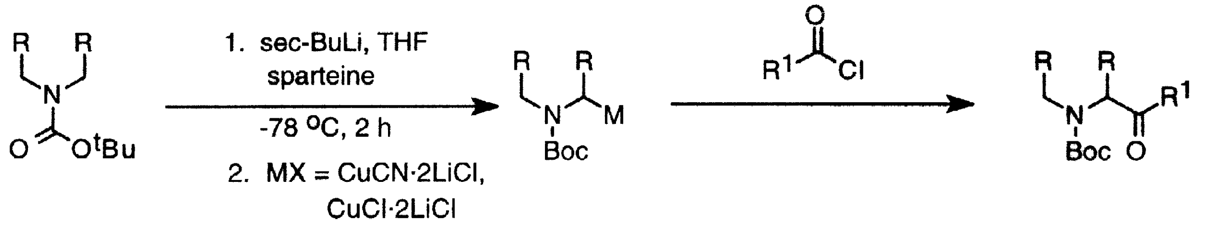


position	R	n	R^1	% yield
3	H	1	Me	55
2	H	1	Me	70
2	H	1	Ph	59
2	H	1	^{i}Pr	73
2	H	1	^{t}Bu	52
2	H	1	Et	71
2	Me	1	Me	70[a]
2	Me	1	^{t}Bu	52[a]
2	H	2	Me	68
2	H	2	^{t}Bu	66
2	H	2	Ph	70
3	H	2	Me	67

[a] A (1:1) mixture of diastereomers was formed.

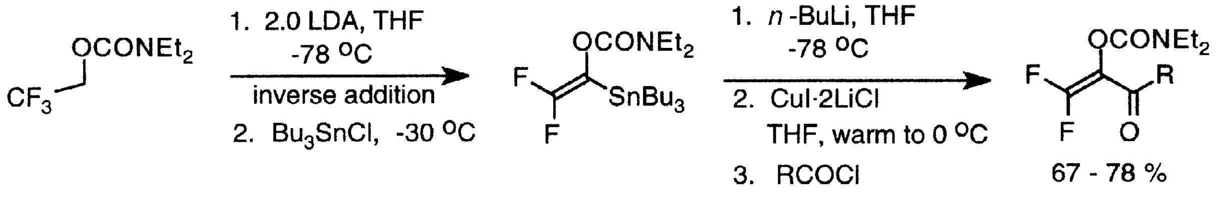
The utilization of functionalized ligands is an important focus of development in organocopper chemistry, and α-heteroatom alkylcopper reagents represent one class of functionalized ligand systems. Dieter and co-workers have extensively developed the chemistry of α-aminoalkylcuprate reagents and found that good to excellent yields of α-amino ketones can be obtained via acylation when the reagents are prepared from Cu(I) salts solubilized by LiCl (eq. 64).[146] Excellent yields of ketones are obtained with the reagent prepared from 2 RLi + CuCN·2LiCl while modest yields are achieved with RCuCNLi. Interestingly, good yields are obtained with an organocopper reagent prepared from one equivalent of the α-lithioamine and one equivalent of CuCl·2LiCl and represents an efficient process both in terms of ligand utilization and stoichiometry (i.e., RCOCl : RCu, 1:1).

Vinylcopper reagents are available by the carbocupration of alkynes employing alkylcopper(I) reagents derived from Grignard reagents.[147] The acylation reactions afford modest yields with polar additives such as HMPA[127] and conjugate addition to the product α,β-enone can occur when the vinyl copper reagent is not β,β-dialkyl substituted.[148] Although simple lithium dialkenylcuprates react with the product α,β-enone, success can be achieved using the more reactive acyl bromides.[148] Still, the most useful procedure involves the palladium catalyzed acylation of the vinylcopper reagents (vide supra, eq. 53).[110a] Recently, several highly functionalized vinyl cuprates have been employed for the preparation of α,β-enones (eqs. 65-66). The preparation of the cuprate from CuI·2LiCl proved to be more effective than when the cuprate was prepared from CuBr·Me_2S.[149] The vinyl copper reagents can also be generated by cuprate reduction of α-carboalkoxy ketene dithioacetals and are acylated in good yields (eq. 66).[150]



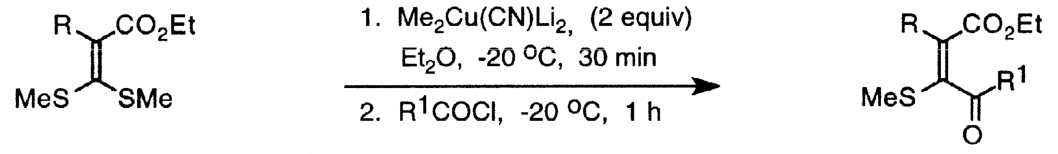
(64)

R	R^1	% yield CuCN·2LiCl 0.5 equiv	CuCN·2LiCl 1.0 equiv	CuCl·2LiCl 0.5 equiv	CuCl·2LiCl 1.0 equiv
$-(CH_2)_2-$	Et	100	55		70
	Me_3C				88
	$Cl(CH_2)_2$				62
	Ph	100		89-93	62-65
	(*E*)-MeCH=CH			84	60
	Me_2CH=CH	99			50-57
Me	Et	98	55		85
	Me_3C				96
	$Cl(CH_2)_2$				63
	Ph	100			73
	(*E*)-MeCH=CH				55
	Me_2CH=CH				46-53



(65)

R = Et, *i*-Pr, *i*-Bu, *t*-Bu, Ph



(66)

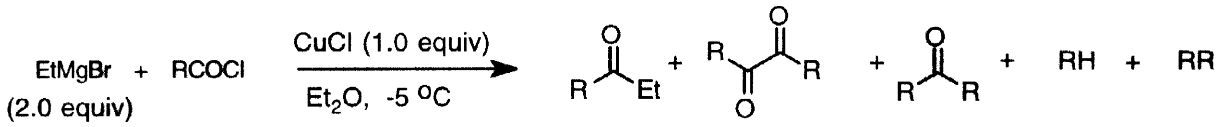
R = CH_2=$CHCH_2$-, Et, Ph

71-93 % (*E* : *Z* 86:14 to 89:11)

R^1 = *n*-Pr, *c*-C_6H_{11}, *t*-Bu, (*E*)-MeCH=CH-, Ph, 2-furanyl, *p*-MeC_6H_4-

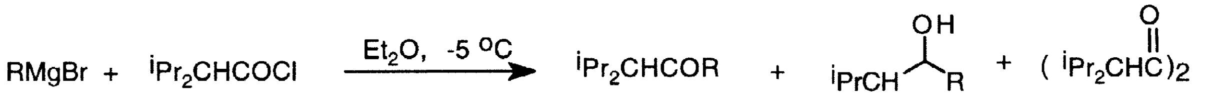
3.5.2 *Copper species from Grignard reagents*

Magnesium dialkylcuprates prepared from Grignard reagents and CuCl react with sterically hindered acid chlorides to give good to excellent yields (69-91%) of ketones.[151a] Low yields (31-39%) were obtained with ${}^{t}BuMgCl$ and α,α-dialkyl-substituted alkanoyl chlorides. A detailed study of the reactions of sterically hindered alkanoyl chlorides with Grignard reagents in the presence of CuCl revealed a multitude of reaction products which were attributed, in part, to radical decomposition of alkylcopper(I) species (eq. 67).[151b-c] Consistent with this view, yields of ketone increased upon addition of α-methylstyrene (eq. 68). Interpretation of these results is problematic since the stoichiometry described in the general experimental procedure suggests the formation of R_2CuMgX and not RCu·MgXX'. Given the ease of CuCl oxidation to $CuCl_2$, the presence of trace amounts of cupric chloride could conceivably provide an alternative explanation.



(67)

R		% selectivity			
${}^{t}BuCH_2$	100	-	-	-	-
${}^{t}BuCH(Me)$	99	1	-	-	-
${}^{i}Pr_2CH$	77	19	4	-	-
${}^{t}Bu_2CH$	67	7	26	-	-
$Me_2{}^{i}PrC$	77	-	2	17	4
$Me_2{}^{t}BuC$	62	-	1	37	-
${}^{i}Pr_3C$	53	-	-	47	-

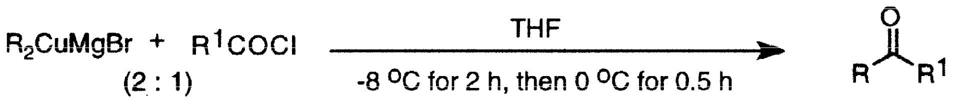


(68)

	% yield					
additive	R = Et,	R = ^{t}Bu	R = Et,	R = ^{t}Bu	R = Et,	R = ^{t}Bu
no additive	92	20	8	0	0	0
CuCl	48	80	22	0	21	12
CuCl + α-(Me)Styrene	91	93	3	7	3	0

Halomagnesium dialkylcuprates are readily prepared from Grignard reagents and Cu(I) salts at -10 to -15 °C over 5-6 hours in diethyl ether. Formation of a cuprate reagent is indicated by the lack of a positive Gilman test[152a] and failure of the organometallic reagent to react with ethyl acetate.[152b] The magnesium dialkylcuprates are less stable than the corresponding lithium dialkylcuprates, but are reported to give 13-15% (using a 2:1 ratio of cuprate to acid chloride) higher yields of ketone than the corresponding lithium dialkylcuprates (eq. 69). Reagent stability is solvent dependent: THF > THF-Et_2O > Et_2O-PhMe ≥ Et_2O-PhH > Et_2O. The disparity in ketone yields obtained with $Me_2CuMgBr$ or

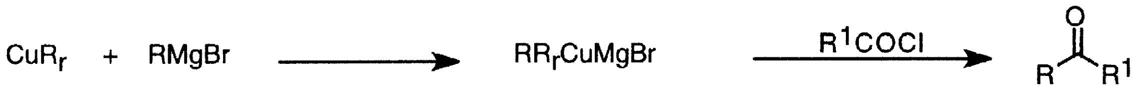
$Ph_2CuMgBr$ and nitrobenzene reflects the greater susceptibility of $Me_2CuMgBr$ to oxidative coupling with nitro compounds. Mild conditions for ketone formation (34-81% yields) employing organocopper magnesium reagents have been reported.[153]



(69)

R	R^1	% yield
Ph	Me	68
	Ph	72
	p - $NO_2C_6H_4$ (1:1)	76
Me	Ph	65
	p - $NO_2C_6H_4$	18

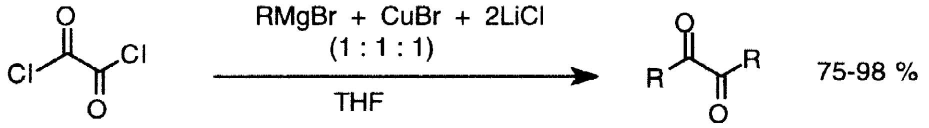
Although standard non-transferable ligands (R_r = residual ligand) proved ineffective for mixed magnesium cuprates, the mixed halomagnesium methyl(alkyl)cuprates prepared from MeCu (MeLi + CuI) and Grignard reagents gave excellent yields of ketones upon acylation with acid chlorides (eq. 70).[154] Small amounts of methyl ketones (< 10%) were obtained as by-products from competitive transfer of the methyl group in the mixed cuprate. In contrast to R_2CuLi reagents, these cuprate species formed suspensions at -78 °C. The generally diminished reactivity of magnesium cuprates in comparison to lithium cuprates is illustrated by the respective ketone yields obtained with the alkynyl and heteroatom mixed cuprates.



(70)

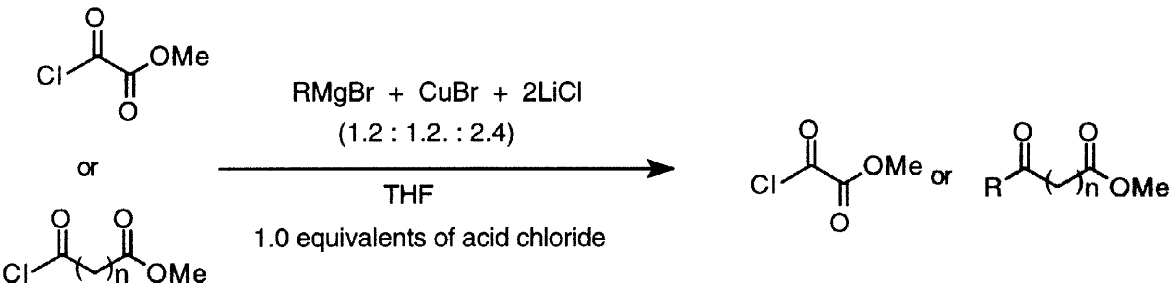
			% yield	
LR_r	R	R^1	$RR_rCuMgBr$	RR_rCuLi
t -BuCC≡C	*n* -Bu	Ph	28	74
t -BuO			0	94
PhS			0	79
I			46	
Me			85	
	$Me(CH_2)_{15}$	Me	75	
	$Me(CH_2)_3$	Ph	85	
	$Me(CH_2)CHMe$	Me	90	
	t -Bu	Ph	93	
		t -Bu	90	
	p -MeC_6H_4	Ph	79	
	Ph	*t* -Bu	100	
		Me	84	
		Ph	96	

Transition metal catalyzed acylation of Grignard reagents with oxalyl chloride failed with Ni, Pd, and Fe catalysts, and with lithium dialkylcuprate reagents. Low yields of ketones could be obtained with RCu reagents, and the addition of LiBr was essential for the high yield formation of ketones (eq. 71).[155] 2-Thienylmagnesium bromide/CuI gave 12% and 98% yields of the α-diketone without and with added LiBr, respectively.[155] This methodology could be extended to methyl oxalyl chloride and monoesters of dicarboxylic acid chlorides (eq. 72).[156] The reactions with methyl oxalyl chloride give homocoupling products at room temperature and were conducted at -78 °C, while the monoesters of dicarboxylic acid chlorides were reacted at room temperature. These reactions efficiently utilize one equivalent of the acid chloride and of the Grignard reagent. The reaction fails for β-diester acid chlorides. Dialkynyl-1,2-diones have been prepared in low to excellent yields from oxalyl chloride and alkynylcopper (RC≡CCu, R = Ph, Si^iPr_3, $C(OMEM)Me_2$, 60%, 85%, and 37% respectively) compounds prepared from alkynyllithium reagents and CuBr· 2LiCl.[157] 2,5-Dibromoterephthaloyl dichloride[158] and 3,6-dibromo-2,5-pyridinedi(carboxylic acid dichloride)[159] have been converted into the corresponding diketones with RCuCNLi and $RCu{\cdot}SMe_2$ reagents for the preparation of planar polymers.[160]



(71)

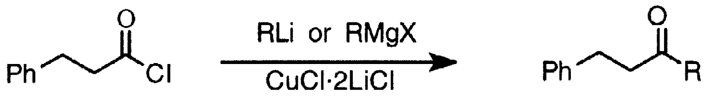
R = *n* -C_8H_{17}-, *n* -$C_{10}H_{21}$-, 3-pentyl, *c* -C_6H_{11}-, Ph, *o* -MeC_6H_4-, *m* -MeC_6H_4-, *p* -MeC_6H_4-
p -$MeOC_6H_4$-, 2 -*m*-xylyl



(72)

R	% yield α-ketoester	% yield ω-ketoester		
		n = 2	n = 3	n = 7
n -$C_{10}H_{21}$	89	80	80	76
c -C_6H_{11}	75	87	89	91
2-(1,3-dioxane-2-yl)ethyl	71	95	82	95
Ph	86	91	97	94
p -MeC_6H_4	93	91	98	97
2,6-$Me_2C_6H_3$	89	90	88	96
p -$MeOC_6H_4$	68	82	79	74
2-thienyl	87	93	91	98

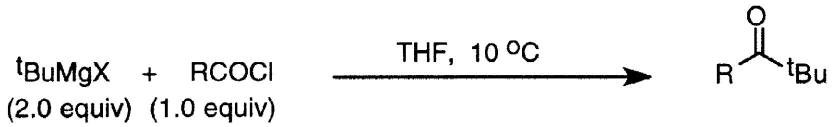
Independently, Dieter and co-workers discovered that treatment of alkyllithium or Grignard reagents with stoichiometric amounts of CuCl·2LiCl gave good to excellent yields of ketones upon reaction with the acid chloride of 2-phenylpropanoic acid (eq. 73).[146] This protocol gave higher yields of ketones than existing organocuprate procedures and appears to be operationally simpler than the organomanaganese procedures. Nevertheless, CuCl is both light and moisture sensitive in contrast to other Cu(I) salts and appropriate precautions must be taken.



(73)

R	% yield Li	Mg
n-Bu	90	96
t-Bu	72	
s-Bu	82	89
Ph	39	87

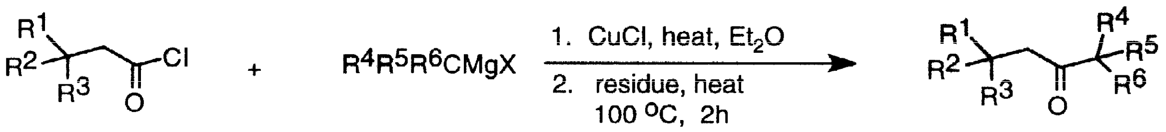
Percival first reported the successful formation of ketones from acid chlorides and Grignard reagents in the presence of inorganic salts (i.e., CuCl, $CoCl_2$, $FeCl_3$, $AlCl_3$, $MnCl_2$, $ZnCl_2$) and achieved moderate yields of ketones with CuCl (48%) and $FeCl_3$ (72%) at -65 °C.[28] The coupling of Grignard reagents with acid chlorides has been catalyzed by Li_2CuCl_4 and gave an 80% yield of 6-undecanone from the reaction of hexanoyl chloride with pentylmagnesium bromide.[161] The relative merits of Li_2CuCl_4 and Li_2MnCl_2 catalysts has been presented in a German patent (eq. 74).[162] Higher yields are obtained with the copper catalyst and yields fall off when the catalyst concentration falls below 0.01 mole %.



(74)

catalyst	R	mol-%:	10	1	0.1	% yield 0.01	0.001	0.0001
Li_2CuCl_4	Ph		90	96	93	95	77	77
Li_2MnCl_4	Ph		88	81	83	82	81	77
Li_2CuCl_4	Me	60	concentration of Li_2CuCl_4 not specified product yields without catalyst range between < 2 to 41%					
	$^tBuCO(CH_2)_4$	71						
	n-decyl	82						
	^iPr	34						
	EtO_2CCH_2	61						
	p-ClC_6H_4	81						
	3-pyridyl	47						

Sterically hindered 1,2-di-*tert*-alkylethylenes have been prepared from the corresponding ketones via reduction and dehydration. The requisite ketones were prepared by acylation of Grignard reagents in the presence of CuCl (0.74 equivalents) at elevated temperatures (100 °C, eq. 75).[163] A limitation of this procedure involves the difficulty in making Grignard reagents bulkier than Et_3CMgX.



(75)

R^1	R^2	R^3	R^4	R^5	R^6	% yield
Et	Et	Et	Me	Me	Et	89
			Et	Et	Et	80
n-C_3H_7-	*n*-C_3H_7-	*n*-C_3H_7-	Et	Et	*n*-Bu	65

3.5.3. *Copper species from transition metals: organozinc, manganese, & zirconium reagents (Cu / Zn, Mn, Zr)*

Organocopper complexes are available by transmetallation of a wide range of organometallic reagents (e.g., from Ti, Mn, Zr, Sm, Zn, Hg, B, Al, Sn, Pb, Te compounds).[164] Procedures involving the preparation of organocopper reagents from organozinc reagents have been developed.[108] Knochel has exploited the use of CuCN·2LiCl in the reactions of organozinc reagents with acid chlorides to form ketones. The reaction presumably involves the intermediacy of a zinc cyano(alkyl)cuprate reagent and proceeds at 0 °C in THF (eq. 76).[165] Knochel's review of organozinc reagents tabulates 68 examples in 23 references involving the acylation of functionalized zinc cuprates [i.e., FG-RCu(CN)ZnX or FG-RCuZn(R-FG)] occurring in moderate to excellent yields (32-86%).[108] Groups compatible with organozinc formation and with the resultant zinc cuprates include ether, acetate, esters, thio ethers, nitrile, borate esters, imide, alkyne, phosphate, halides, nitro, $N(TMS)_2$, and ketone functional groups. The reaction can be performed with stoichiometric or catalytic (10 mol %) amounts of CuCN·LiX. Knochel later showed that cuprate reagents prepared from dialkyl zinc reagents were more reactive, and that both ligands from R_2Zn were ultimately utilized in the acylation reaction (eq. 77).[166a] This is in marked contrast with organozinc reagents in the absence of Cu(I) salts, which react slowly with acid chlorides and competitively promote opening of the THF ring by Zn(II) catalysis. Oxazol-2-ylzinc chloride reagents react with acid chlorides in the presence of CuI (5 mol% to 1 equiv) to afford 2-acyl-acyloxazoles in modest yields (54-80%).[166b] Utilization of organozinc precursors extends

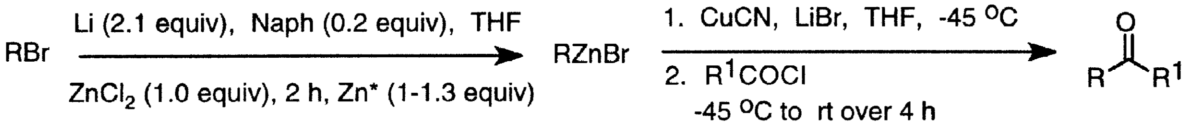
$$\mathrm{RI} \xrightarrow[\text{2. CuCN·2LiX, 0 °C, 10 min}]{\text{1. activated Zn, THF, 25-40 °C}} \mathrm{RCu(CN)ZnI} \xrightarrow[\text{0 °C, 3 h}]{\mathrm{R^1COCl}} \underset{\text{81 - 94 \%}}{\mathrm{RCOR^1}} \qquad (76)$$

R = *n*-Bu, *i*-Pr, *s*-Bu, *c*-C_6H_{11}, $EtO_2C(CH_2)_3$, *t*-$BuO_2CCH(Me)(CH_2)_3$, $NC(CH_2)_3$

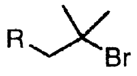
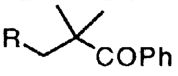
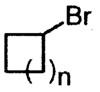
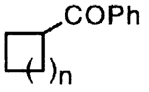
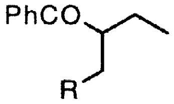
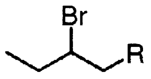
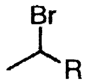
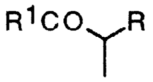
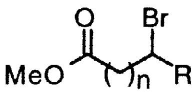
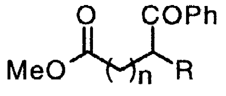
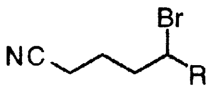
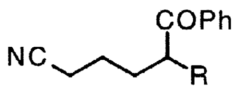
$$\mathrm{Et_2Zn + AcO(CH_2)_5I} \xrightarrow[\text{1-12 h}]{\text{45-55 °C}} \mathrm{[AcO(CH_2)_5]_2Zn} \xrightarrow[\text{2. PhCOCl}]{\text{1. CuCN·2LiCl}} \underset{\text{87 \%}}{\mathrm{PhCO(CH_2)_5OAc}} \qquad (77)$$

organocopper chemistry to a wide range of functionalized alkyl halides.

Primary alkyl or aryl organozinc reagents can be prepared by the use of Rieke zinc generated by reduction of $ZnCl_2$ with lithium naphthalide. They afford good to excellent yields of ketones upon treatment with stoichiometric amounts of CuCN·2LiCl and an acid chloride.[167] Using Rieke zinc, organozinc reagents RZnBr can be prepared at room temperature or at reflux for sterically hindered alkyl bromides (e.g., 1-bromoadamantane). There is no formation of R_2Zn reagents or simple reduction of the alkyl halide (i.e., no RH formation). The resultant tertiary alkyl cuprates generated *in situ* with catalytic amounts of CuCN·2LiBr are more reactive than the corresponding primary alkyl reagents (eq. 78).[168] The reaction fails for cyclopropylzinc bromide.[168a] The procedure has been utilized in the preparation of chloromethyl ketones (eq. 79).[169] In this study, organozinc formation and the zinc cuprates were found to be compatible with nitrile, amine, ester, and ketone functionalities. Organozinc reagents generated from ω-halo-α-amino acids have been extensively employed by Jackson and co-workers (eqs. 80-81).[170-171] The reactivity of the resultant zinc cuprates [i.e., RCu(CN)ZnBr by stoichiometry] was less than that of cuprates prepared via Rieke Cu*.[171] Zinc silylcuprate reagents have been used for the preparation of silyl ketones.[172]

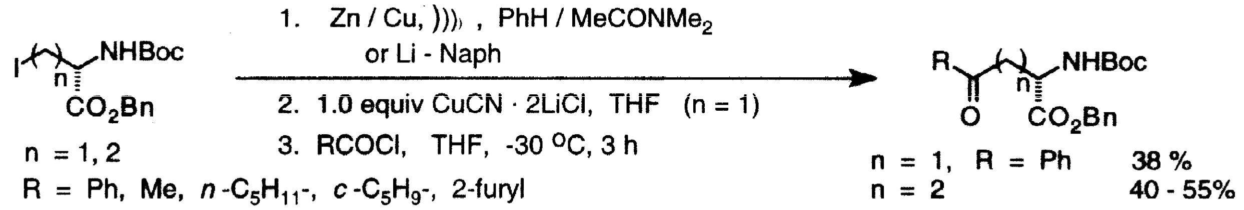


(78)

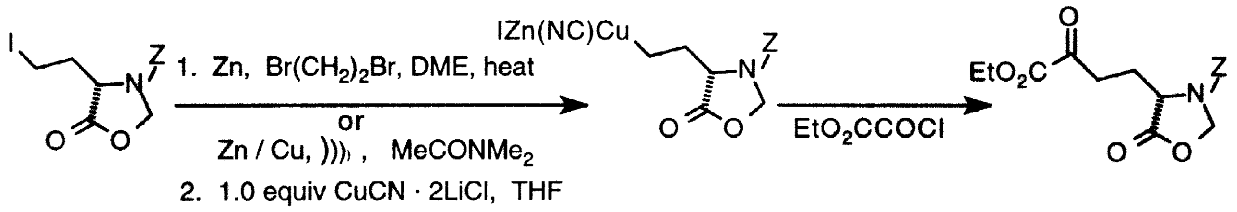
alkyl halide	R(n)	R^1	product	% yield
	H	Ph		75
	Me	Ph		86
	(1)	Ph		75
	(2)	Ph		84
	(3)	Ph		99
	H	Ph		95
	Me	Ph		87
	Me	$Cl(CH_2)_4$-		62
	$Me(CH_2)_5$-	Ph		88
	Me, (1)	Ph		75
	n-Bu, (3)	Ph		54
	Bu	Ph		60

$$\mathrm{RBr} \xrightarrow{\text{Zn*, THF, 30 min}} \mathrm{RZnBr} \xrightarrow[\text{2. } ClCH_2COCl]{\text{1. CuCN·1.3LiBr}} \underset{52-87\ \%}{RCOCH_2Cl} \qquad (79)$$

R = $Me(CH_2)_5$-, $Me(CH_2)_7$-, $Me(CH_2)_9$-, $NC(CH_2)$-, $NC(CH_2)_3$-, $NC(CH_2)_4$-, $EtO_2C(CH_2)_2$-, $MeCO(CH_2)_4$-, 2-NCC_6H_4-

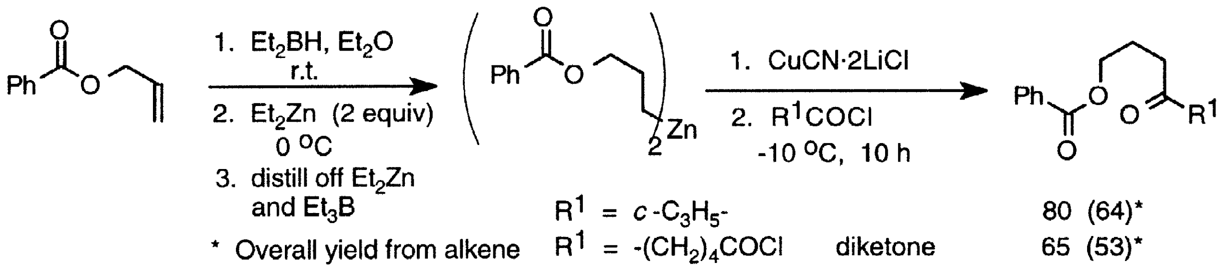


(80)

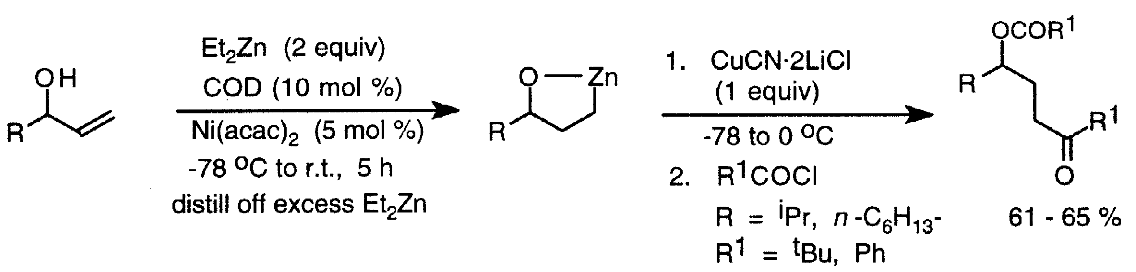


(81)

Transmetallation relays provide opportunities to convert alkenes into organometallic reagents that can be acylated. Dialkylzinc reagents can be prepared by hydroboration of alkenes followed by transmetallation with diethylzinc (eq. 82),[173] while alkoxy(alkyl)zinc reagents (eq. 83)[174] can be prepared from allylic alcohols via a hydrozincation reaction promoted by Ni(acac)$_2$ and 1,5-cyclooctadiene (COD). Treatment of the organozinc reagents with CuCN·2LiCl affords the zinc cuprates which react with acid chlorides to afford the ketones in modest yields. The procedures are complicated by the need to remove the Et$_3$B and Et$_2$Zn by vacuum distillation in order to drive the transmetallation sequences to completion and to eliminate formation of ethylcuprates which would be competitively acylated.

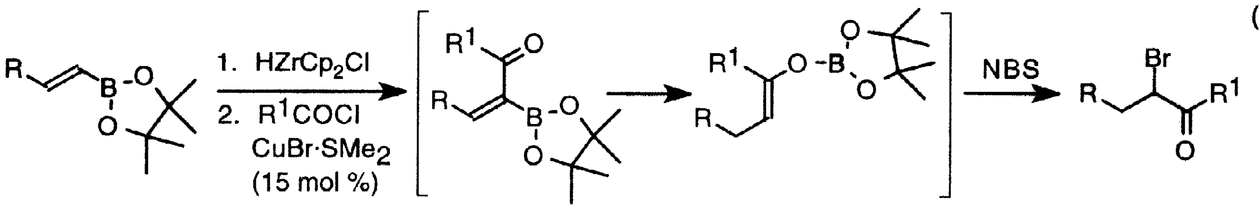


(82)



(83)

Although organomanganese reagents can be acylated directly to afford ketones, the use of catalytic amounts of CuCl affords higher yields for some RMnCl complexes in THF (i.e., R = Me, Ar, *sec*-R, *tert*-R).[53,54,164] Added CuCl has little effect in Et$_2$O. 1,8-Disubstituted naphthalenes have been prepared in low yields (6-32%) by directed lithiation of 1-dimethylaminonaphthalene followed by transmetallation with MnCl$_2$ and subsequent acylation with CuCl catalysis.[175] Hydrozirconation of alkenes results in migration of the zirconium atom to the least hindered position in the chain or ring, and transmetallation with catalytic amounts of CuBr·SMe$_2$ (5-10 mol %) followed by treatment with an acid chloride affords good yields of ketones (52-90%).[164,176] Acylation of *gem*-borazirconocenes, prepared via hydrozirconation of vinyl(dialkoxy)boranes, in the presence of 15 mol % CuBr·SMe$_2$ affords α-bora ketones which rearrange to enol borates. Trapping the enol borates with *N*-bromosuccinimide affords α-bromo ketones regioselectively (eq. 84).[177]



(84)

3.5.4 Copper species from main group organometallic reagents (Al, Sn)

Although the acylation of tetraorganotin (and occasionally organosilicon) compounds have frequently employed Pd or Pd/Cu catalysts (i.e., the Stille reaction with acid chlorides as the electrophile), the reaction can be effected by Cu(I) salts alone.[178-179] The reaction of [α-(acyloxy)alkyl]tributylstannanes with CuCN (8 mol %) in non-polar aromatic solvents gave low yields of ketones with either benzoyl chloride (22%) or alkanoyl chlorides (<10%).[178a] Tin to copper transmetallation explains the failure of the coupling reaction in the absence of Cu(I) salts, and trapping of the intermediate with 2-cyclohexenone in a conjugate addition reaction provides experimental evidence for an intermediate organocopper species.[178a] Investigations by Linderman revealed that the reaction afforded a mixture of ketone, acyloxyalkyl dimer, and ketones arising from competitive transfer of the butyl group.[179] The reaction fails for stannanes containing α–oxygenated ether derivatives consistent with the earlier report.[178a,179] α-[(Acyloxy)alkyl]tricyclohexylstannanes couple with aroyl and alkanoyl chlorides in good to excellent yields (employing two to four equivalents of the acid chloride) in the presence of CuCN. Under these conditions, both the dimerization reaction, and transfer of the simple alkyl ligand on tin (i.e., cyclohexyl) are non-competitive with ketone formation and these properties may result from the difficulty of a cyclohexyl ligand on tin occupying "an apical position in a trigonal bipyramidal Sn intermediate".[179]

Alkynyl silanes react with acid chlorides at elevated temperatures (80 °C) in the presence of stoichiometric or catalytic quantities of CuCl to give alkynyl ketones in good yields (69-91%).[178b] CuCl is far superior to other Cu(I) salts and DMF or 1,3-dimethyl-2-imidazolidinone (DMI) must be utilized to promote alkynyl transfer from silicon to copper, of which this is the first reported example.

Reaction of trialkylaluminum compounds (R$_3$Al, R = Me, Et, ^{i}Bu) with acid chlorides [R^{1}COCl, R^1 = Ph, CH$_2$=CH(CH$_2$)$_8$-] in the presence of Cu(acac)$_2$/PPh$_3$ affords ketones in modest to excellent yields (55-95%).[180] The procedure involves formation of alkylcopper(I) reagents[181] and is inefficient in alkyl ligand since it requires two moles of R$_3$Al/mole of R^{1}COCl. Acyltrimethylgermanes can be prepared in excellent yields (82-92%) by acylation of Me$_3$GeCu·SMe$_2$ obtained by deprotonation of Me$_3$GeH with *t* -BuLi followed by treatment with CuBr·SMe$_2$ complex.[182]

3.5.5 Copper species from Rieke Cu

The preparation of organocopper reagents from organolithium or Grignard precursors seriously limits the functionality that can be present in the organocopper reagent. Rieke[36] has examined the direct formation of organocopper compounds via oxidative addition of zero valent copper prepared from various combinations of Cu(I) salts and reducing agents [CuI/K/naphthalene (10 mol %)[183], CuCl/ Li-naphthalide,[184a] $\mathrm{CuCl{\cdot}SMe_2}$/Li-naphthalide[184a], $\mathrm{CuI{\cdot}P(Et)_3}$/Li-naphthalide[184], CuCN·nLiX/Li-naphthalide[36]]. The reactivity of the copper metal is inversely related to particle size and is best achieved by rapid reduction of $\mathrm{CuI{\cdot}P(Et)_3}$ with stoichiometric amounts of Li-naphthalide. Increasing electron donation by the ligand increases the reactivity of the zero valent Cu* (i.e., $\mathrm{R_3P > Ar_3P > SMe_2 \gg R_3N}$), and the reactivity of the resulting organocopper reagent in coupling reactions.[185] Use of $\mathrm{PPh_3}$ minimizes homo coupling by-products which can be troublesome with alkyl bromides and iodides. Alkyl- (-78 °C), aryl- (0 to 25 °C), vinyl- (0 to 25 °C) and alkynylcopper (0 to 25 °C) reagents can be readily prepared from the bromides and iodides and react with acid chlorides to afford ketones in modest to good yields.[184,185] Aryl copper reagents couple with acid chlorides between 0 °C (e.g., PhCu and $\mathrm{NCC_6H_5Cu}$) and 185 °C ($\mathrm{C_6F_5Cu}$) reflecting the stability of the organocopper reagent (eq. 85, Table 1.). Alkylcopper reagents couple with acid chlorides between -35 and 25 °C and require excess acid chloride (2.65-6.65 equivalents) since the electrophile reacts with the excess active copper (5 equivalents /equiv. of RBr).[185] The yield of ketone also reflects the temperature at which the Cu(I) salt is reduced with lower temperatures (-110 °C) favoring both the reductive formation of the zero valent copper species and the subsequent oxidative addition (eq. 85, Table 2).[36,186] The order of active copper reactivity prepared from various Cu(I) precursors is: (2-thienylCuCN)Li[187] > $\mathrm{CuI{\cdot}PR_3}$ > CuCN·nLiX[186]. Product isolation is greatly facilitated by the absence of phosphines in the crude reaction mixture and both (2-thienylCuCN)Li and CuCN·nLiX offer advantages in this regard. Organocopper reagents can be prepared from alkyl halides containing ester,[188] nitrile, alkyl chloride, alkyl fluoride, nitro, oxiranes, and ketones,[189] although the latter two functionalities can undergo intramolecular cyclizations depending on the chain length between the functionality and C-Cu bond.[36,185,186,187] The procedure has also been employed in the acylation of (haloaryl)copper reagents prepared from haloiodobenzenes and active copper (Table 1.).[190] 2-Thienyl cuprates prepared from Rieke copper are the most effective reagents for preparing ^{11}C-methyl ketones.[191]

$$\mathrm{CuI{\cdot}PEt_3}\ \text{ or }\ \mathrm{CuCN{\cdot}2LiCl}\ \text{ or }\ \text{2-thienylCu(CN)Li} \xrightarrow[\text{0 to -100 }^{o}\text{C, see Table 2.}]{\text{Li-naphthalide, THF, 10 min}} \mathrm{Cu^*}$$

$$\mathrm{Cu^*} + \mathrm{RX} \xrightarrow[\text{-35 }^{o}\text{C, 1 h}]{} \text{organocopper reagent} \xrightarrow[\text{-35 to 25 }^{o}\text{C or -35 }^{o}\text{C}]{\text{1. }\mathrm{R^1COCl}} \mathrm{RCOR^1} \qquad (85)$$

Low temperature generation of active copper via reductions of CuCN·nLiX[186,192] or (2-thienylCuCN)Li[187a,193] was used in the preparation of allylic cuprates which undergo acylation at the more substituted carbon atom of the allylic system (eqs. 86-87).[192,193]

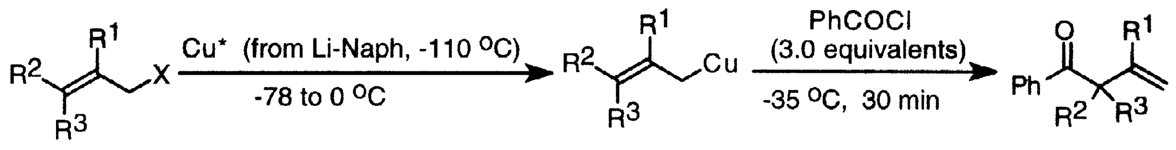
Table 1. Acylation of organocopper reagents generated from Rieke copper (eq. 85).

RBr or (RI)	R^1	% yield^{a,b} CuI·PEt_3	% yield^{c,d} CuCN·2LiCl	% yield^{d,e} 2-thienylCuCNLi	Ref.
C_6F_5	Ph	25 (165 °C)^f			184
Ph	Ph	60-70(85 °C)^f	87		184, 186
p-MeC_6H_4	Ph			86	187
p-$MeOC_6H_4$	Ph			87	187
p-$MeOC_6H_4$	*n*-Bu			63	187
p-$Me_2NC_6H_4$	Ph			81	187
o-BrC_6H_4	Ph	10^g			190
m-BrC_6H_4	Me	71^g			190
	Ph	64^g			190
p-BrC_6H_4	Ph	34^g			190
	Me	28^g			190
o-ClC_6H_4	Ph	60^g			190
	Me	65^g			190
	2,4,6-$Me_3C_6H_2$	56^g			190
	2-MeO-5-ClC_6H_3	70^g			190
m-ClC_6H_4	Me	74^g			190
	Ph	72^g			190
p-ClC_6H_4	Ph	55^g	83	90	187, 190
	Me	13^g			190
o-FC_6H_5	Ph	73^g			190
	Me	57^g			190
	2-thienyl	53^g			190
m-FC_6H_4	Me	50^g			190
p-FC_6H_4	Ph	61^g		93	187, 190
	Me	10^g			190
p-$PhCOC_6H_4$	Ph	85		44	187, 189
o-NCC_6H_4	Ph	71-95 (0 °C)^f			184, 186
	Me	41-46 (0 °C)^f	74		184
m-NCC_6H_4	Ph			62	187
p-NCC_6H_4	Ph		60	75	186,187
$Me(CH_2)_7$	Ph	83	82	73	185-187
$NC(CH_2)_3$	$Me(CH_2)_2$	79	86	61	185-187
	Ph	61			185
$Cl(CH_2)_6$	Ph	83	80	42	185-187
8-bromo-1,2-epoxyoctane	Ph	59		65	185,187
p-$EtO_2CC_6H_4$	Ph	85			185
	Me	66-69^g			185, 188
	Ph	67^g			188
o-$RO_2CC_6H_4$	Ph	73^g	51		186, 188
	Me	41^g			188
$EtO_2C(CH_2)_2$	Ph	79	43		185, 186
$EtO_2C(CH_2)_3$	$MeO_2C(CH_2)_2$	93	81	47	185-187
	Ph	49			185
$EtO_2C(CH_2)_4$	Ph	54^g			188
$MeCO(CH_2)_4$	Ph	19^c			185b

[a] 2.65-6.65 Equivalents of RCOCl were used per equivalent RX. [b] Acylation was performed at -35 to 25 °C unless otherwise noted. [c] 3.0 Equivalents of PhCOCl were used per equivalent of RX. [d] Acylation was performed at -35 °C [e] 2.46 Equivalents of ROCl were used per equivalent of RX. [f] Temperature at which acylation was performed. [g] Overall yield (organocopper formation and acylation).

Table 2. Ketone yields as a function of Cu(I) salt and temperature at which it is reduced to activated Cu*.

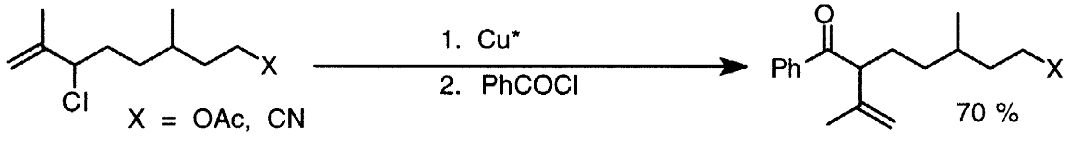
Cu(I)	red. temp. (°C)	RX	%yield RCOPh
CuI·PPh_3	0	*c* -hexyl bromide	25
	-78		62
	-100		82
CuCN·2LiBr	-100		57
	-78		40
CuCN·2LiCl	-100		42
	-78		43
	0	PhCl	2
	-60		44
	-100		61



X = Cl, OAc

(86)

R^1	R^2	R^3	% yield Ref. 192 CuCN·2LiBr	Ref. 193 2-thienylCuCNLi
H	H	H	63	-
Me	H	H	75	78
H	Me	Me	74	56



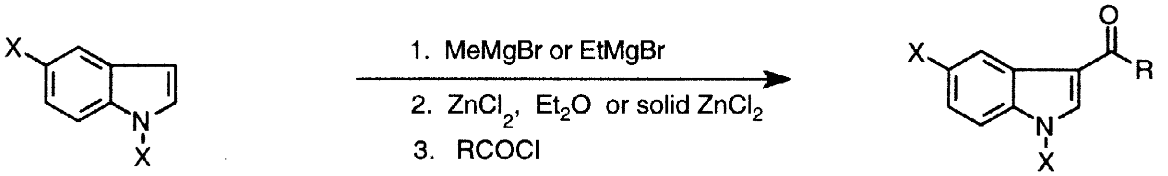
(87)

Copper mono-anions can be prepared by reduction of Cu(I) salts with two equivalents of lithium naphthalide at -110 °C to produce a two electron reducing agent. This anionic copper species readily reduces aryl and alkyl chlorides as well as the corresponding bromides and iodides.[194] Acylation of the resultant organocopper species with acid chlorides gave poor (i.e., for 2-bromo-octane and PhF) to excellent yields (33-99% GLC, 28-89% isolated) of ketones.

3.6 *Group IIB organometallics (Zn, Cd, Hg)*

Organometallic reagents derived from Group IIB metals are generally unreactive toward acid chlorides and require forcing conditions for direct acylation.[1a] Successful ketone synthesis generally requires either transmetallation to a more reactive organometallic reagent (e.g., Cu[164] or Pd), or activation of the acyl chloride with Lewis acids. Although not frequently competitive with other methods of ketone synthesis, the organometallic reagents of Group IIB have found use for the preparation of allyl, alkenyl, and propargyl ketones.

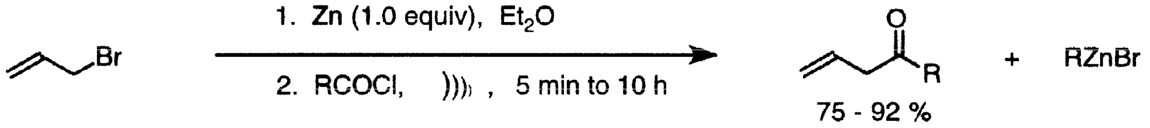
Although organozinc reagents were the first organometallic reagents employed in the conversion of acid chlorides into ketones, they quickly fell out of favor due to extremely limited reactivity. Organozinc reagents are rarely employed in this reaction today in the absence of copper, palladium, or other transition metal catalysis. Nevertheless, zinc salts of indole or its derivatives (eq. 88),[195,196] and allylic organozinc reagents (eq. 89)[197] are sufficiently reactive to afford ketones from acid chlorides under activating conditions. The more basic Grignard reagents give low yields of indoyl ketones due to competing 1,3-diacylation and subsequent enolization of the product ketones.[198,199] These side reactions can be minimized by use of non-polar solvents or by using the less reactive organozinc reagents. In the absence of Lewis Acids, modest yields of ketones are obtained.[196] The highest yields of indolyl ketones are obtained when the organozinc reagent is generated with a Grignard reagent or BuZnCl and two equivalents of $ZnCl_2$ followed by addition of one equivalent of a stronger Lewis acid such as $AlCl_3$.[195] This suggests that the indoylzinc reactions are, perhaps, best viewed as Friedel-Crafts acylations of a double bond enhanced in electron density via nitrogen metallation.



(88)

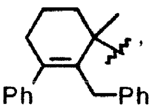
X	R	Lewis Acid	% yield	Ref
H	p-FC$_6$H$_4$-	AlCl$_3$	80	195
H	Ph	-	47	196
H		AlCl$_3$	77	195
H		SnCl$_4$	76	195
H		TiCl$_4$	63	195
H		BF$_3$	76	195
H	^{t}Bu	AlCl$_3$	92	195
H	^{i}Bu	AlCl$_3$	81	195
H	Me	AlCl$_3$	70	195
H		-	55	196
H	ClCH$_2$-	-	36	196
H	Cl(CH$_2$)$_2$-	-	42	196
H	(E)-MeCH=CH-	-	37	196
H	Me$_2$C=CH-	-	70	196
H	(E)-Me$_2$CH=CH-	-	60	196
H	MeCH=CMe	-	52	196
H	1-cyclohexenyl	-	65	196
H	c-C$_6$H$_{10}$=CH-	-	70	196
H	3-indolyl-CO-	-	65	196
Br	Ph	AlCl$_3$	82	195
EtO$_2$C-	Ph	AlCl$_3$	82	195

The acylation of allylzinc is sufficiently mild to afford the β,γ-enones with no isomerization to the α,β-isomers (eq. 89).[197] The reaction works well for alkanoyl, aroyl, and alkenoyl chlorides under ultrasonic irradiation, although 1.5 equivalents of the allylzinc reagent must be employed for α-alkyl substituted (both mono and di) acid chlorides.

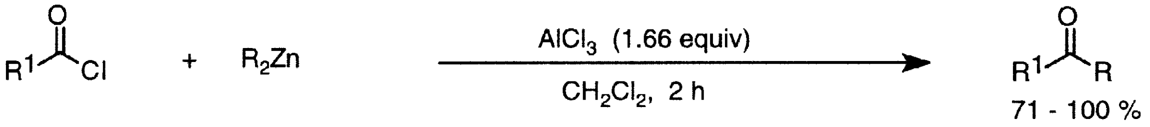


(89)

R = *n* -Pr, *i* -Pr, $PhCH_2$-, $CH_3(CH_2)_6$-, $Ph(CH_2)_2$-, $Me(CH_2)_7CH{=}CH(CH_2)_7$-, $PhCH_2CH(COCl)(CH_2)_3$-, Ph, *c* -C_6H_{11}-,



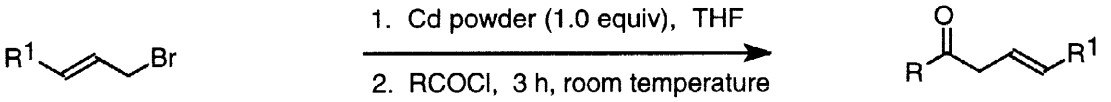
Dialkylzinc reagents are acylated in good yields with acid chlorides in the presence of $AlCl_3$, although 1.66 equivalents of the acid chloride were employed (eq. 90)[200]. This reaction is likely to go through an acylium ion or acyl halide-$AlCl_3$ complex illustrating the general reluctance of organozinc reagents to form ate complexes with Lewis acids in contrast to the more reactive organometallic derivatives (e.g., organolithium and magnesium reagents).



(90)

R^1 = MeCH=CH-, PhCH=CH-, C_7H_{15}-, Ph, $PhCH_2$-
R = Me, Et

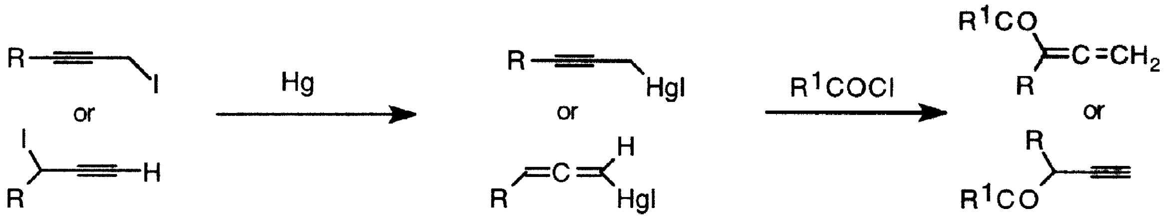
Organocadmium reagents have been largely supplanted by more reactive organometallic species, although they have proved useful for the preparation of β,γ-unsaturated ketones (eq. 91).[198] They react with oxalyl chloride to afford symmetrical diketones in low to modest yields.[199]



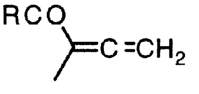
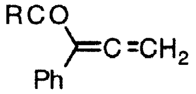
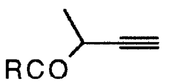
(91)

R^1 = H, (*E*)-Me
R = Ph, *p*-$NO_2C_6H_4$-, *p*-BrC_6H_4-, $PhCH_2$-, ^{n}Pr

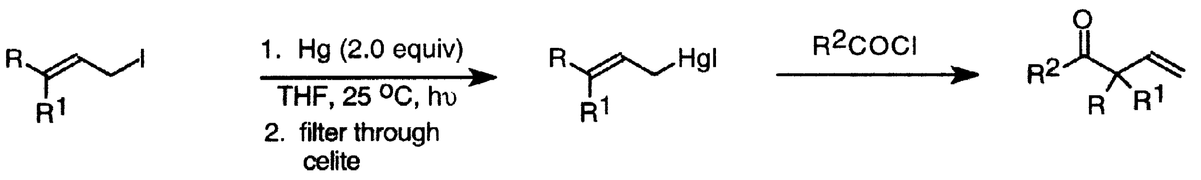
The acylation of organomercurials (i.e., R_2Hg and RHgX) has been reviewed and is briefly summarized.[203] Some organomercurials can be acylated directly with acid chlorides, although useful yields generally require addition of AlX_3[204] or palladium catalysts.[205,206] The reaction of dialkylmercury compounds (R = Et, *n* -Bu, *n* -C_6H_{13}) with alkanoyl or aroyl chlorides in the presence of $AlBr_3$ occurs in yields of 75-100% in methylene chloride, although the stoichiometry of alkyl transfer was not established.[204] The palladium catalyzed reaction fails with RHgCl and gives lower yields with the acid bromides.[205] Vinyl mercury halides, RHgCl, require the use of $AlCl_3$ and give excellent yields (72-100%) upon reaction with alkanoyl, alkenoyl, or aroyl chlorides.[207] The reaction may occur by electrophilic addition to the alkene followed by elimination of mercuric chloride. Aryl mercury compounds [i.e., Ar_2Hg and ArHgX] afford excellent yields of ketones upon treatment with acid chlorides in the presence of $AlBr_3$ (R_2Hg, 72-100%)[204] or palladium catalysts[205,206], although the latter reaction fails with RHgCl. The more reactive dialkynylmercurials transfer both groups under thermal conditions in hexane (40-70%).[208] Propargyl and allenyl mercurials undergo clean acylation with acid chlorides in the presence of $AlCl_3$ to afford allenyl and propargyl ketones in excellent yields. The reaction occurs regioselectively with allylic rearrangement so that propargylmercurials lead to allenyl ketones and allenylmercurials lead to propargyl ketones (eq. 92).[209]



(92)

organomercurial	R^1	product	% yield
$MeC{\equiv}CCH_2HgI$	$Me(CH_2)_2$		85
	$Cl(CH_2)_3$		90
$PhC{\equiv}CHgI$	$Me(CH_2)_2$		92
$MeCH{=}C{=}CHHgI$	$Me(CH_2)_2$		82
	(E) MeCH=CH		87
	(E) PhCH=CH		92

The thermal acylation of allylmercuric halides affords either α,β-unsaturated ketones or enol ethers within a 1,4-diene framework. The former arise via isomerization of the initially formed β,γ-enone under the reaction conditions, while the enol ethers result from acylation of an intermediate α-mercurated ketone.[210] These problems have recently been resolved by reacting allylic mercuric iodides with acid chlorides in the presence of an equimolar amount of $AlCl_3$ (eq. 93)[211], although the reaction proceeds with complete allylic rearrangement. The allylic mercuric iodides can be prepared directly from the allylic iodides in a single step or from allylic chlorides or bromides in two steps. Although excellent yields are obtained with alkanoyl, alkenoyl, and aroyl chlorides, the reaction fails with acid chlorides containing an electron withdrawing group or chlorine substituent [e.g., R = 3,5-$(NO_2)_2C_6H_3$-, *o* -ClC_6H_4-, $ClCH_2$-, $Cl(CH_2)_3$-, Cl_2CH-, EtO_2CCH_2-, $EtO_2C(CH_2)_2$- in RCOCl]. The method is limited by the fact that allylic systems that can give rise to a tertiary carbocation undergo addition of HCl and by the inability to prepare allylic mercurials containing a secondary carbon center bound to mercury.



(93)

R	R^1	% yield R'HgI	R^2	% yield
H	H	98	*n* -Pr	82
H	H		Ph	87
H	H		(*E*)-MeCH=CH	97
H	H		Me_2CH	84
H	H		*p* -$MeOC_6H_4$	90
Me	H	78	*n* -Pr	70
Me	Me	44	*n* -Pr	86
Me	Me		Me_2CH	93
Me	Me		(*E*)-MeCH=CH	96
Ph	H	38	Me	82
Ph	H		*n* -Pr	69
EtO_2C	H	43	*n* -Pr	89

4.0 MAIN GROUP METALS

4.1 Group IIIA (B, Al, Ga, In, Tl)

Although organoboranes do not undergo acylation reactions with or without transition metal catalysts, both alkyl[212] and aryl lithium[213] organoborates can be directly acylated without catalysts (eq. 94).[212] The tetra-alkyl borates can be generated by addition of alkyl- or

$$BR_3 \xrightarrow{LiR^1} LiBR^1R_3 \xrightarrow[25\ ^{\circ}C]{R^2COCl} RCOR^2 \text{ or } R^1COR^2 + BR_3 \qquad (94)$$

R^1	R	R^2	% yield[a]
n -Bu	*n* -Bu	Ph	80
s -Bu	*n* -Bu	Ph	57
c-C_5H_9	*n* -Bu	Ph	89
n -Bu	*n* -Bu	*n* -Bu	53
n -Bu	*n* -Bu	$CH_2=CH(CH_2)_3$	69
c-C_5H_9	*n* -Bu	$MeO_2C(CH_2)_2$	76
$PhCH_2$	*n* -Bu	Ph	88[b]
$PhCH_2$	*n* -Bu	*p* -IC_6H_4	(72)[b,c]
CH_3SOCH_2	*n* -Bu	Ph	(51)[b,c]
CH_3SOCH_2	*n* -Bu	$MeO_2C(CH_2)_2$	(61)[b,c]
CH_3SOCH_2	*n* -Bu	*p* -$NO_2C_6H_4$	(55)[b,c]

[a] By GLC. [b] R^1COR^2 is formed. [c] Isolated yields.

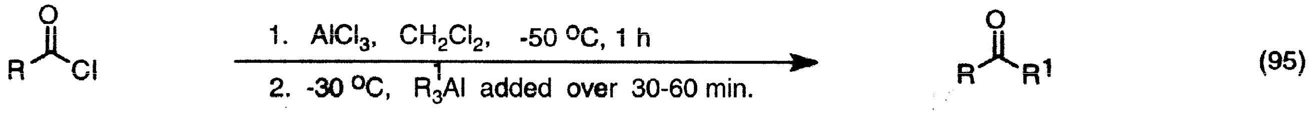
aryllithium reagents to trialkylboranes and the facility of ligand transfer is inversely proportional to the basicity of the corresponding lithium reagent (i.e., benzyl, methylsulfinylmethyl > primary alkyl > secondary alkyl).[213] Borate anions containing alkynyl or thioalkoxymethyl ligands undergo an intramolecular alkyl transfer reaction.

The acylation of organoaluminum reagents has been briefly reviewed in a monograph which covers the literature up to 1972.[214] The reagents of choice are $RAlCl_2$ because of efficient ligand utilization and because they do not react with the ketone products. Trialkylaluminum and dialkylaluminum chlorides can be used but only transfer one alkyl ligand, while the R_3Al reagents react with ketones to give quaternary centers via the carbinols. Although straight chain alkylaluminum compounds are not particularly sensitive to β-hydrogen elimination under these acylation conditions, this side reaction forming olefins and alkylaluminum hydrides becomes problematic in branched alkylaluminum reagents.[215] Reaction of ω-phenylcarboxylic acid chlorides with alkylaluminum sesquichlorides (i.e., $R_3Al + AlCl_3 \rightarrow R_2AlCl + RAlCl_2$ for an average stoichiometry $R_{1.5}AlCl_{1.5}$) afforded high yields of ketones (91-98%) with the exception of 4-phenylbutyric acid chloride which gave a mixture of ketone and 1-tetralone via a Friedel-Crafts acylation reaction.[216] The alkylaluminum sesquichlorides also react with dicarboxylic acid chlorides of five or more carbons in length to give the diketones in good yields (70-90%). Succinic and phthalic acid chlorides give keto acids via an intermediate chlorolactone.[214] Keto acid chlorides [$R^1CO(CH_2)_nCOCl$, n > 2) give diketones (10 - 60%) upon reaction with two equivalents of $RAlCl_2$ illustrating the need for additional amounts of $RAlCl_2$ or $AlCl_3$ when oxygenated functional groups are present in the acid chloride.

R_3Al reagents have been shown to be effective when combined with two equivalents of $AlCl_3$ which has the effect of generating $RAlCl_2$ *in situ*.[216] Under these conditions, alkyl ketones can be prepared in moderate yields (40-72%) which can be improved (65-90%) by adding R_3Al to a complex of $RCOCl{\cdot}AlCl_3$ at low temperature (-10 to -20 °C).[215] The procedure was extended to the synthesis of unsaturated ketones from the corresponding unsaturated acid chlorides.[217,218] Adding one equivalent of $(R^1)_3Al$ to the $RCOCl{\cdot}AlCl_3$ complex of methacroyl chloride gave α,β-enones in moderate yields (37-40%) while reaction with β-alkyl substituted alkenoyl chlorides gave ketones in good yields (65-88%).[217] Optimization of the conditions involved slow addition of 0.4 equivalents of R_3Al to the $RCOCl{\cdot}AlCl_3$ complex at low temperature (-30 °C) (eq. 95).[200,218] Addition of Me_3Al to a mixture of 3-phenylpropanoyl chloride and $AlCl_3$ gave 1-indanone, suggesting that an acylium ion is not an intermediate in these acylation reactions.[200]

Organoaluminum reagents can be prepared from olefins via hydrozirconation followed by transmetallation with $AlCl_3$. They give excellent yields (64-98%) of ketones upon treatment with acid chlorides at -30 °C in methylene chloride.[219] Hydrozirconation of alkynes followed by transmetallation affords vinylalanes which give excellent yields (97-98%) of α,β-unsaturated ketones. Carbozirconation of 1-pentynyldimethylalane afforded a 1,1-bismetalloalkene which reacted with acetyl chloride to give the α,β-enone as a 98:2 *Z* : *E* mixture of stereoisomers.[220a] Assuming the carbozirconation proceeds with *syn* addition, the observed stereoselectivity implies acylation of the C-Al bond.[220b] The use of vinylalanes in the synthesis of α,β-enones does not appear to be a frequently used procedure.

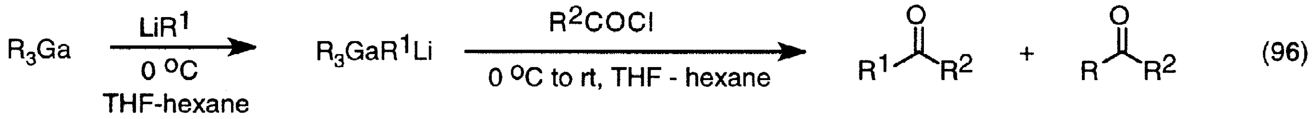
Deprotonation of 2-picoline, 4-picoline, or 2,6-lutidine followed by treatment with Et_2AlCl affords trialkylaluminums that can selectively transfer the picolyl and lutidyl ligands


(95)

R	R^1	% yield	Ref.
MeCH=CH	Me	100	200
Me_2C=CH		73	218
	n-C_8H_{17}	88	200
PhCH=CH	Me	95	218
Ph		93	218
$PhCH_2CH_2$		91	218
$PhCH_2$		75	218
n-C_7H_{15}		98	218
MeCH=CH	Et	96	218
n-C_8H_{17}	n-C_8H_{17}	100	200

forming α-pyridyl ketones in good to excellent yields.[221] The procedure has been exploited in the preparation of α-pyridyl ketones from peracetylated aldonic acid chlorides.

Trialkylgallium compounds, first prepared in 1932, display low reactivity toward organic electrophiles and are sensitive to air and moisture. Gallium ate complexes, R_3GaR^1M (M = Li, MgX), prepared *in situ* by addition of R^1Li or R^1MgX to R_3Ga species are effectively acylated with acid chlorides to afford ketones in very good yields (eq. 96).[222] The

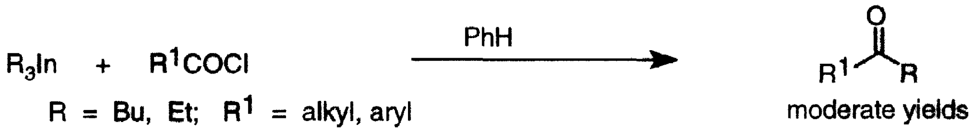

(96)

R	R^1	R^2	% yield R^1COR^2	% yield $RCOR^2$
Ph	n-Bu	Me		88
Ph	Me	Me		84
Ph	n-Bu	$PhCH_2$		82
n-Bu	n-Bu	Ph	83	
Ph	n-Bu	Ph		90
$PhCH_2$	n-Bu	Ph		58
$PhCH_2$	Ph	Ph		69
Et	Ph	Ph	79	
n-Bu	n-Bu	p-$NO_2C_6H_4$	75	
n-Bu	n-Bu	2-furyl	78	
Ph	n-Bu	(E)-PhCH=CH		90
Et	Ph	m-$MeOC_6H_4$	34[a]	46[a]
Et	Ph	Ph	46[a]	37[a]
Et	PhC≡C	Ph	63	19
c-C_5H_9	n-Bu	Ph	74	0

[a] Prepared from PhMgBr and Et_3Ga.

efficacy of ligand transfer is $PhCH_2 > Ph > PhC{\equiv}C > Bu, Et > c$ - cyclopentyl. The selectivity of ligand transfer is generally high for the lithium ate complexes and low for the magnesium ate complexes. Alkynyl ligands are not as selectively transferred as in the corresponding thallium reagents.

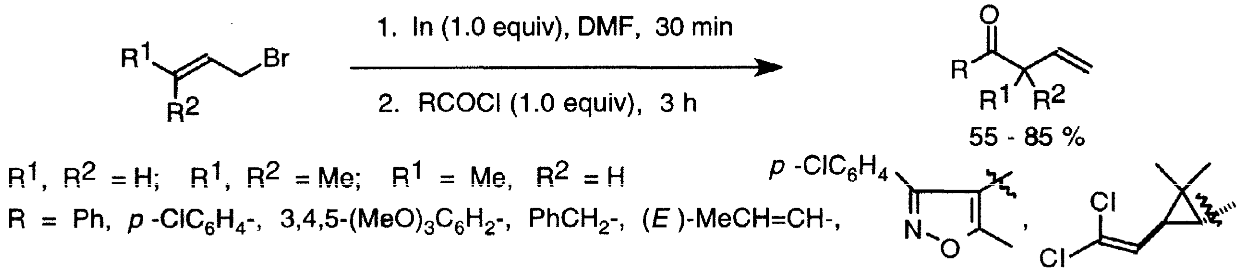
Trimethylindium has been reported to transfer all three of its ligands to afford methyl ketones in high yields.[223] Trialkylindium reagents afford moderate yields of ketones upon reaction with acid chlorides in benzene (eq. 97).[224]



R = Bu, Et; R^1 = alkyl, aryl

(97)

Reaction of allyl halides with indium metal (1.0 equiv.) forms an intermediate organoindium species that can be acylated with acid chlorides to afford β,γ-unsaturated ketones under mild conditions and in high yields.[225] The reaction proceeds with allylic rearrangement (eq. 98).



R^1, R^2 = H; R^1, R^2 = Me; R^1 = Me, R^2 = H

R = Ph, p-ClC_6H_4-, 3,4,5-$(MeO)_3C_6H_2$-, $PhCH_2$-, (E)-MeCH=CH-,

(98)

Triorganothallium compounds are prepared by the addition of organolithium (in Et_2O) or Grignard (in THF) reagents to dialkylthallium chloride. The latter reagents, R_2TlCl, are stable to light, air, moisture, oxygen, acids and are insoluble in water and organic solvents. Trialkylthallium reagents react with acid chlorides within seconds or a few minutes to cleanly afford ketones in high yields (eq. 99).[223] The R_2TlCl by-product precipitates from solution and can be filtered, dried and reused. The reaction tolerates ether, olefin, ester, and nitro functionality in the acid chloride. Dimethyl(phenylethynyl)thallium selectively transfers the ethynyl ligand to decanoyl chloride and acetyl chloride affording the ketones in 77% and 73% yields, respectively. Dimethylphenylthallium, however, reacts with decanoyl chloride to afford 2-undecanone and phenyl nonanyl ketone as a 2:3 mixture. The clean formation of products, the lack of over reaction, mild reaction conditions, and ability to recycle the R_2TlCl precursor are compromised by the need to use organolithium or Grignard precursors, a potential problem of ligand selectivity in the acylation reaction, and by the toxicity of the Tl

$$R_2TlCl \xrightarrow[\text{RMgX, THF}]{\text{RLi, Et}_2\text{O} \atop \text{or}} R_3Tl + R^1COCl \xrightarrow[25\ ^{\circ}C]{Et_2O\ \text{or}\ THF} \underset{73-97\ \%}{R^1COR} \qquad (99)$$

R = Me, Et, Ph

R^1 = C_9H_{19}-, $CH_2{=}CH(CH_2)_8$-, c-C_5H_9-, $MeO_2C(CH_2)_8$-, Ph, 4-$MeOC_6H_4$-, Me compounds. The procedure seems to be an excellent method for preparing alkynyl ketones.

4.2 *Group IVA (Ge, Sn, Pb)*

Organostannanes generally require transition metal catalysis (e.g., Cu or Pd) for reaction with organic electrophiles. Nevertheless, there are a few examples where the organostannane undergoes direct acylation with acid chlorides without transition metal catalysis. Reduction of trichloronitromethane affords a nitro tin enolate that is readily acylated with acid chlorides.[226] Cyclopropyl- and alkenylstannanes containing a sulfonyl functionality on the same carbon as the stannyl group react with acid chlorides to afford the ketones in modest to good yields.[227] A few examples of heteroaroylstannanes are capable of undergoing acylation without transition metal catalysis.[228] (*N,N*-Dialkylaminomethyl)tri-*n*-butylstannanes afford good yields of *N,N*-dialkylaminomethyl ketones (64-81%) upon reaction with acid chlorides under mild conditions (0-60 °C).[229]

Although Group IVA tetraalkyl organometallic reagents are generally quite sluggish in their reactions with organic electrophiles, the alkynyl ligand displays excellent reactivity. Triethylalkynyllead compounds, $Et_3PbC{\equiv}CR$, react with acid chlorides at room temperature in minutes to afford alkynyl ketones in excellent yields (R = Ph, 96%; R= C_4H_9, 84%).[230] The reaction failed with bis(trimethylplumbyl)acetylene which gave intractable tars upon reaction with acetyl chloride.

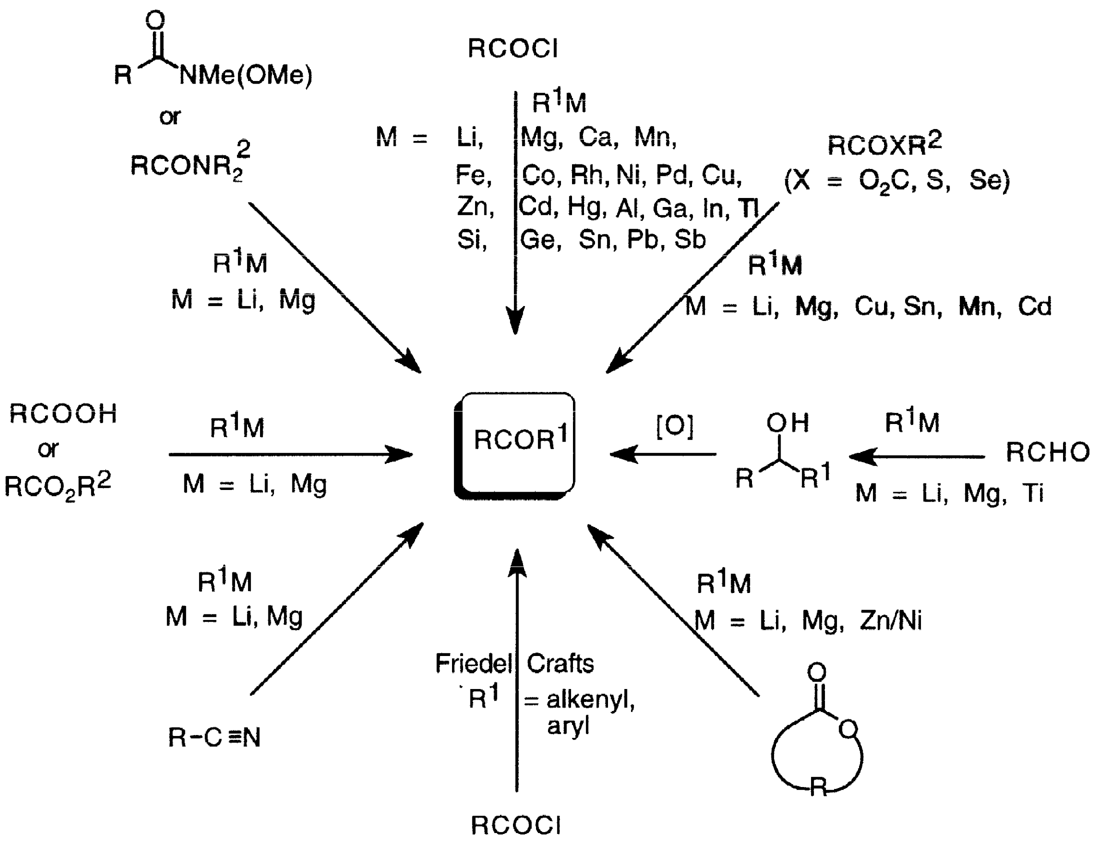
4.3 *Group VA (Sb)*

The acylation of pentaphenylantimony occurs with a wide range of acid chlorides to afford phenyl ketones.[231] Excellent yields of ketones are obtained with aroyl chlorides (77-87%) and ethyl oxalyl chloride (100%). Modest yields are obtained with alkenoyl chlorides (64%) which gave significant amounts of biphenyl and low yields are obtained with alkanoyl chlorides (13%). Modest yields can be achieved with the alkanoyl chlorides in the presence of $Pd(PPh_3)_4$ (50%).

5.0 SUMMARY

The principal synthetic routes to ketones from carbonyl compounds involve reaction of carboxylic acids[232] and their derivatives with organometallic reagents via nucleophilic acyl substitution, Friedel-Crafts acylation of alkenes and arenes[233], and 1,2-nucleophilic addition to aldehydes followed by oxidation.[234] Nitriles can serve as a carboxylic acid equivalent since 1,2-nucleophilic addition of organometallic reagents followed by hydrolysis affords ketones (Scheme VII). Nucleophilic addition to amides (e.g., the Weinreb procedure[235]), lactones, carboxylic acids, aldehydes, and nitriles is generally limited to potent nucleophilic reagents that are also strongly basic, although the enhanced reactivity of aldehydes permits utilization of less basic allylic metal derivatives. Friedel-Crafts acylation requires the use of Brönsted or Lewis acids. In contrast, the acylation of organometallic reagents permits the widest range of reaction conditions and opportunities to moderate reagent reactivity and basicity. The utilization of transmetallation relays allows for synthetic pathways that avoid the use of strongly basic reagents and extends the range of functional groups that can be converted into the organometallic reagent. In short, the reaction of acid chlorides with organometallic reagents remains the most versatile ketone synthesis.

Scheme VII



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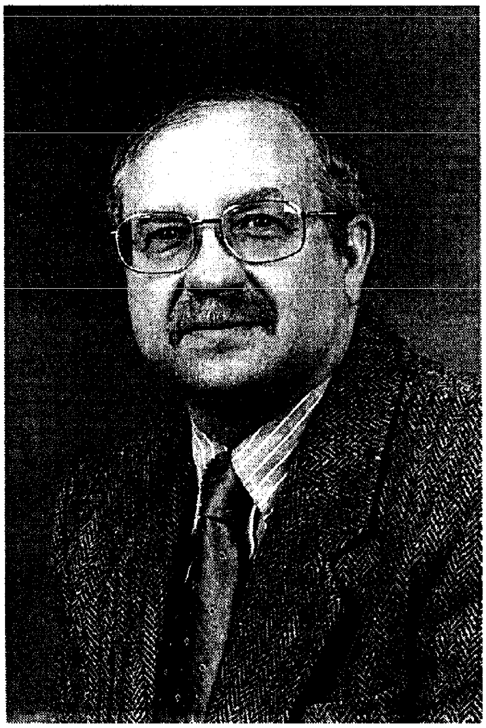
Biographical sketch



R. Karl Dieter

R. Karl Dieter was born in Philadelphia, Pennsylvania, in 1951. He received a B.A. degree in chemistry from Lehigh University in Bethlehem, Pa. in 1973 and went on to pursue doctoral work at the University of Pensylvania in Philadelphia under the supervision of Professor Amos B. Smith, III. After receiving the Ph.D. degree in organic chemistry in 1978, he conducted postdoctoral studies on marine natural products in Professor Jerrold Meinwald's group at Cornell University with the aid of an American Cancer Society Postdoctoral Fellowship. In 1979 he joined the faculty of Boston University, where he established programs on α-oxoketene dithioacetal and organocopper chemistry before moving to Clemson University in 1985. His recent work in organocopper chemistry has led to the development of α-aminoalkylcuprate reagents. Although centered on organocopper chemistry, his research interests include organometallic chemistry, organosulfur chemistry, synthetic methodology, asymmetric synthesis, and natural products.