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NEW HORIZONS IN CARBONYL CHEMISTRY: REAGENTS FOR NUCLEOPHILIC ACYLATION

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I. INTRODUCTION

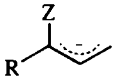
The construction of carbon–carbon bonds is the heart of organic synthesis, and is most frequently achieved through the interaction of electron-rich (nucleophilic) centers with sites which are electron-deficient (electrophilic), i.e. by polar reaction pathways. Carbon atoms which are activated by polar functionality are predisposed by their electronic environment to behave either as electrophilic or as nucleophilic centers. A fundamental approach to the development of new synthetic methods is the design of procedures which invert this characteristic reactivity mode. This has always been a powerful strategy in organic synthesis, and is illustrated by the classical example outlined in Scheme 1 (Nu^- = nucleophile; E^+ = electrophile). Thus, alkyl halides are intrinsically electrophilic reagents, but are readily transformed into nucleophilic organometallic intermediates, e.g. Grignard reagents, in which the activated carbon has suffered an inversion of polarity. Reflection on the almost ubiquitous appearance of alkyl halides and the derived organometallic reagents in synthetic schemes amply demonstrates the value of this type of latent dual role.

$$\begin{tikzcd}
{[R^+]} \arrow[r, phantom, "\Leftrightarrow"] & R\text{—}X \arrow[r, "Nu^-"] \arrow[d] & R\text{—}Nu \\
{[R^-]} \arrow[r, phantom, "\Leftrightarrow"] & R\text{—}MgX \arrow[r, "E^+"] & R\text{—}E
\end{tikzcd}$$

Scheme 1.

Although polarity inversion is not a recent conceptual development, vigorous research in this area is of comparatively recent origin. One certain stimulus has been recognition of the advantages offered by viewing synthetic transformations in terms of synthons, or functional group equivalents.[1] Corey has described these inversion operations as "symmetrization" of reactivity,[1] Evans has used the term "charge affinity inversion,"[2] and most recently Seebach has suggested the German word *umpolung* as a concise expression for this general concept.[3,4] Reversible polarity inversions offer the greatest flexibility as they permit subsequent restoration of the normal reactivity mode. These procedures frequently utilize latent or "masked" functionality.

One of the most exciting advances during the past decade has been the emergence of masked functionality from its traditional protective role into the realm of electronic and regiospecific direction of activation. The fruit of recent research in the areas of polarity inversion and latent functionality is a series of new reagents which function as synthetic equivalents of normally inaccessible intermediates. In addition to methods for inversion of carbonyl reactivity discussed herein, noteworthy examples include utilization of metalated allylic intermediates **1** ($Z = OR'$,[5] SR'[6] or NR'_2[7,8]) as equivalents of β-acyl carbanions **2**,[9] metalated N-nitroso compounds **3** as equivalents of secondary α-amino carbanions **4**[10,11] (synthons for α-hydroxy[12] and α-sulfhydryl[13] carbanions have also been reported), and several electrophilic reagents such as **5** as equivalents of α-acyl carbonium ions **6**.[14–17] Latent functionality may also appear in more subtle guise, as in the intermediates **7**[18] and **8**,[19] which, after alkylation adjacent to sulfur and [3,3] sigmatropic rearrangement, are revealed as synthons of anions **9** and **10**. Another elegantly cloaked example is that of the sulfoxide anion **11** which becomes equivalent with vinyl anion **12** upon alkylation, [2,3] sigmatropic rearrangement, and interception of the resulting sulfinate with a thiophilic reagent.[2]



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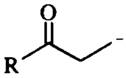

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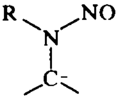

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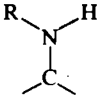

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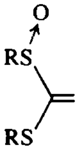

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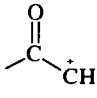

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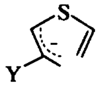
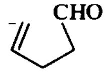


7: Y = H
8: Y = OEt



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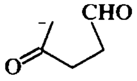

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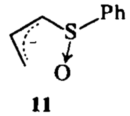

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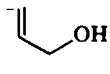

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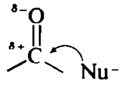
II. NUCLEOPHILIC ACYLATION

As the premier functionality in organic synthesis, the carbonyl group is intimately involved in many reactions that create new carbon–carbon bonds. A simple premise underlies the richness of traditional carbonyl chemistry: the carbonyl carbon is electrophilic, and thus (a) stabilizes an adjacent negative charge with the aid of resonance, and (b) is susceptible to attack by nucleophilic reagents (**13**). Although heterophilic carbonyl additions have been described, such occurrences are at best exceptional and remain open to mechanistic interpretation.[20] A nucleophilic acylation is any reaction in which, formally at least, the carbonyl carbon abandons its traditional role and functions as a nucleophilic center (**14**).



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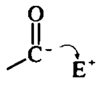

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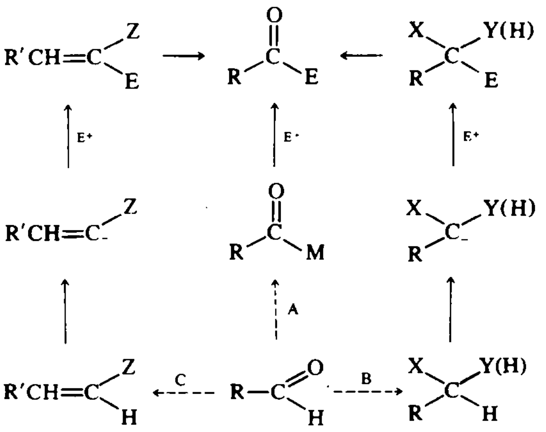
The products expected from reaction of an acyl anion (**15**) or an equivalent synthon with representative electrophiles, including carbonyl compounds of normal polarization, are depicted in Scheme 2. These reactions do not create novel functionality; the significance of nucleophilic acylation lies in the formation of familiar structural units from starting materials which are altogether different from those in conventional procedures,[21] and in the formation of certain arrangements of functionality in a more specific and direct manner than is possible with classical methods. The scope of nucleophilic acylation has been expanded beyond the boundaries of Scheme 2 by the use of more elaborately functionalized acyl anion synthons.

The area was reviewed by Seebach in 1969,[21] and major developments through early 1974 have been briefly outlined.[3] Rapid advances have continued, and an impressive variety of reagents are now available. Some methods will remain laboratory curiosities and/or mechanistic challenges, but others are taking their place beside classical carbonyl chemistry as important synthetic procedures. The perspective provided in the present Report is intended to encourage and facilitate the use of nucleophilic acylation in future synthetic work.

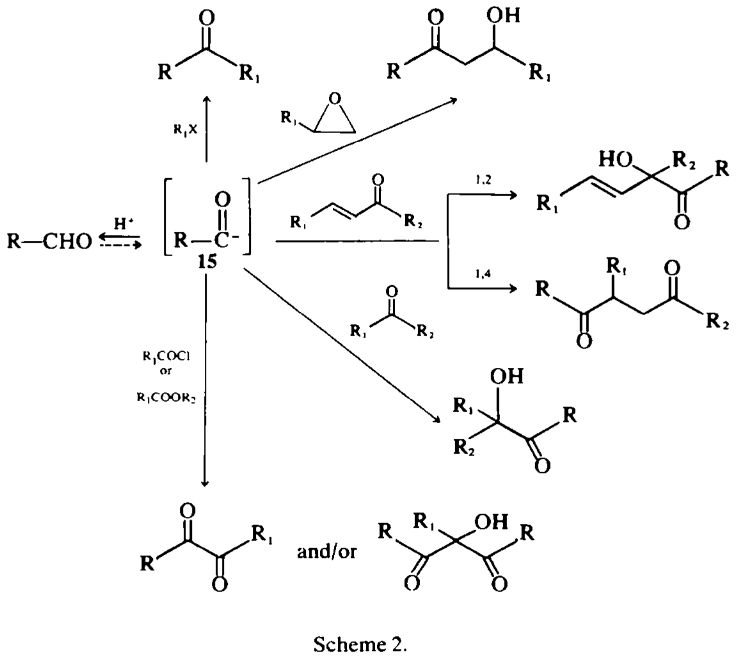
The two primary classes of nucleophilic acylating reagents are (a) acylmetallic compounds (path A, Scheme 3), and (b) reagents which use masked functionality to invert carbonyl reactivity. Examples of the latter class are metalated derivatives of enols (Path C, $Z{=}OR''$ or SR'') and other latent carbonyl functions [e.g. Path B: $X{=}OR''$, $Y{=}CN$; $X{=}Y{=}Cl$; $X{=}NO_2$, $Y{=}H$; X, $Y{=}S{-}(CH_2)_3{-}S$]. After consideration of each approach in turn, some general conclusions are drawn in the final section.



Scheme 3.

III. ACYLMETALLIC REAGENTS

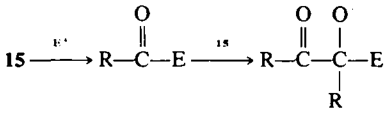
1. *Acylmetallic reagents from groups* Ia, IIa *and* IIb. Direct reaction of a carbonyl anion with an electrophile initially appears subject to experimental difficulty because the desired reaction product **16** is an unprotected electrophilic carbonyl compound and may be subject to further attack by the reagent (eqn 1). However, this potential complication is overshadowed by more serious limitations associated with the inherent instability of the carbonyl anion. The high energy of these intermediates is manifested in their propensity to undergo secondary



Scheme 2.

reactions, and is reflected in the lack of appreciable acidity exhibited by the aldehydic proton.[22]

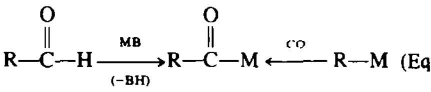
Preparation of acyl derivatives of groups Ia, IIa and IIb metal ions has been approached in two principal ways (eqn 2). The first method involves direct deprotonation of a formyl derivative to give an acylmetallic compound. This is feasible only when enolization is forbidden, but even when this requirement is satisfied, generation of carbonyl anions is not a routine accomplishment.



$$\mathbf{15} \xrightarrow{E^+} R-\overset{\overset{O}{\|}}{C}-E \xrightarrow{\mathbf{15}} R-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{\overset{O}{|}}{C}}-E$$

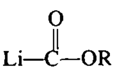
16

(Eqn. 1)



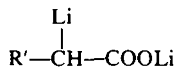
$$R-\overset{\overset{O}{\|}}{C}-H \xrightarrow[(-BH)]{MB} R-\overset{\overset{O}{\|}}{C}-M \xleftarrow{CO} R-M \quad \text{(Eqn. 2)}$$

No useful nucleophilic acylating reagents are derived from reactions of aryl or tertiary aliphatic aldehydes with base, and although formation of **17** (R=Et) appears to be competitive with acylation of α-lithiocarboxylates **18** when the latter are treated with ethyl formate,[23] the facility of generation and nucleophilic properties of formate anions **17** remain undefined.



$$Li-\overset{\overset{O}{\|}}{C}-OR$$

17



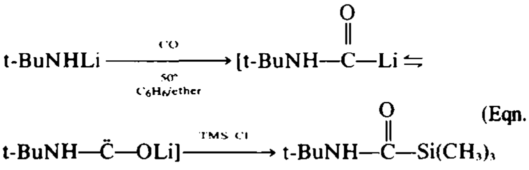
$$R'-\overset{\overset{Li}{|}}{C}H-COOLi$$

18

Reactions of formamide derivatives with base have been studied in greater detail (Scheme 4). Schollkopf and Gerhart obtained α-hydroxyamides **23a** upon treatment of bis(carbamoyl)mercury compounds **19** with n-butyllithium followed by a carbonyl compound,[24] and subsequently Banhidai and Schollkopf described the formation of a possible intermediate, **21a**, directly from the reaction of dimethylformamide with lithium diisopropylamide (LDA) at −78°.[25] Similarly, Enders and Seebach have prepared dimethylthiocarbamoyllithium (**21b**) from dimethylthioformamide and LDA at −100°.[26] Under carefully controlled conditions, intermediates **21a** and **21b** gave adducts **23a** and **23b**, respectively, with carbonyl compounds, although alkylation reactions proceeded less readily.

Experimentally, excess oxo-intermediate **21a** must be generated *in situ* in the presence of the carbonyl compound to use valuable carbonyl compounds most efficiently. In the case of thio-analog **21b**, product yields dropped dramatically when the temperature was briefly raised to −78° before introduction of the substrate. These observations attest to the lability of these intermediates, whether they are best formulated as carbamoyllithium species **21** or carbenes **22** (for the reagent formed from **19** a mercury-complexed carbene is also possible).

From the viewpoint of nucleophilic acylation, the second approach in eqn (2), carbonylation of organometallic compounds, has suffered most severely from the extraordinary reactivity of the acylmetallic intermediates. For example, Whitesides and collaborators have studied in detail the reaction of phenyllithium with carbon monoxide.[27] Benzoyllithium (Ph–CO–Li) apparently is an intermediate, but is consumed too rapidly in complex secondary reactions to elicit synthetic interest. Carbonylation reactions of other organolithium and organosodium reagents,[27-32] Grignard reagents,[33-35] and organozinc compounds[35] similarly have not provided generally applicable reagents (acyloins and complex ketones often are major products from secondary reactions of reactive intermediates), although in certain special cases acylmetallic species have indeed been trapped with external electrophiles.[29,30] For instance, the product **24** was formed by carbonylation of lithium t-butylamide and subsequent silylation (eqn 3),[30] but the reaction could not be extended to lithium dimethylamide.



$$t\text{-BuNHLi} \xrightarrow[\substack{50^\circ \\ C_6H_6/\text{ether}}]{CO} [t\text{-BuNH}-\overset{\overset{O}{\|}}{C}-Li \leftrightharpoons t\text{-BuNH}-\ddot{C}-OLi] \xrightarrow{TMS\ Cl} t\text{-BuNH}-\overset{\overset{O}{\|}}{C}-Si(CH_3)_3 \quad (55\%)$$

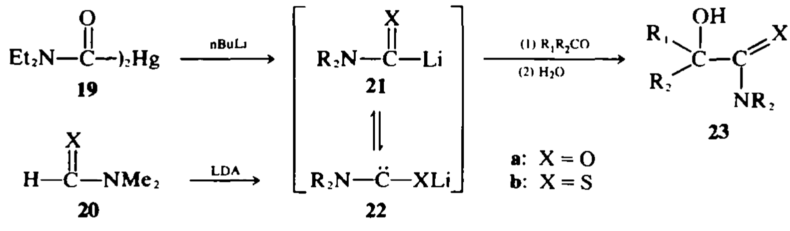
(Eqn. 3)

24

It is known that base-catalyzed reactions of alcohols and amines with carbon monoxide afford formates and formamides, respectively, and are reversible reactions.[36,37] Acylmetallic species are seemingly plausible intermediates; however, if formed, carbonyl anions are not intercepted by reactive halides, and a concerted mechanism involving nucleophile, carbon monoxide, and base has been suggested as an alternative.[37]

Transformation of acyl halides or related compounds to intermediates formally resembling acyl Grignard reagents (R–COMX) is another approach to acylmetallic reagents.[21] A decade ago, a description of the formation of acylberyllium compounds (R–CO–BeX; X = Cl, Br, I) from acid halides and beryllium metal appeared, and reactions with several electrophiles were included.[38] However, these reagents have not engendered synthetic interest in the interim, and as Seebach has noted,[21] their formation may be attended by difficulty.

Apart from the reagents shown in Scheme 4, acylmetallic intermediates in which the metal ion is not of the transition series have little preparative value. On the other

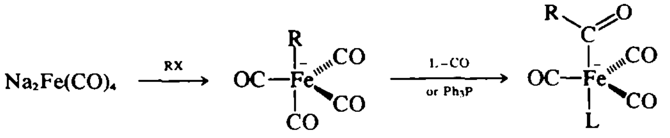


Scheme 4.

hand, coordination of carbon monoxide and/or acyl ligands with transition metal ions (notably iron and nickel) leads to compounds and reaction intermediates with more stability and greater synthetic appeal.

2. *Transition metal reagents.* Synthetic applications of transition metal reagents have been widely reviewed.[39] A reagent with particular synthetic promise in the area of nucleophilic acylation is disodium tetracarbonylferrate(–II), **25**.[40,41] During the gestation period of the present Report, Collman has summarized much of the chemistry of this dianion,[42] and the reader is referred to this work for a more detailed presentation, and particularly for mechanistic considerations.

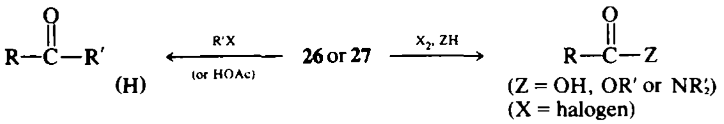
Alkylation of $Na_2Fe(CO)_4$ affords anionic alkyltetracarbonyliron(0) complexes **26**, which in the presence of triphenylphosphine or carbon monoxide are converted into anionic acyl intermediates **27** (eqn 4); complex **27a** may also be formed from reaction of **25** with acyl halides, or by addition of organolithium reagents to iron pentacarbonyl (eqn 5).[42,43]



25 **26** **27a**: L = CO **b**: L = Ph$_3$P

(Eqn. 4)

$$R{-}CO{-}Cl \xrightarrow{25} \mathbf{27a} \xleftarrow{RLi} Fe(CO)_5 \qquad \text{(Eqn. 5)}$$



$$\underset{(H)}{R{-}\overset{O}{\overset{\|}{C}}{-}R'} \xleftarrow[\text{(or HOAc)}]{R'X} \mathbf{26}\text{ or }\mathbf{27} \xrightarrow{X_2,\ ZH} R{-}\overset{O}{\overset{\|}{C}}{-}Z \qquad \text{(Eqn. 6)}$$

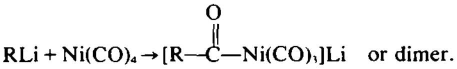
$(Z = OH, OR' \text{ or } NR'_2)$
$(X = \text{halogen})$

As outlined in eqn (6), Collman *et al.* and others have employed anions **26** and **27** in the preparation of aldehydes,[44] ketones,[44–47,51] and carboxylic acid derivatives.[48] These reactions proceed in good yield when substrate limitations are observed.[42] Thus, the initial alkylation of **25** is best conducted with primary halides and primary or secondary tosylates to avoid competitive elimination (**25** is a basic reagent); allylic halides are unsuitable as they form complexes unrelated to **26**. In the synthesis of unsymmetrical ketones, alkylation of **26** or **27** (eqn 6) requires reactive halides (primary iodides) since the nucleophilicity of the reagents decreases in the order **25** > **26** > **27b** > **27a**, and an excess of the halide is necessary to maximize the yield of ketone, particularly when **27a** is used.[45a] Ketone formation via **27a** has been shown to be stereospecific, with an overall inversion in the alkyl residue of the first substrate (R–X, eqn 4).[45a]

Most ketone, ester, and nitrile functions are unaffected under the reaction conditions. This finding precludes nucleophilic acylation of many electrophilic carbonyl substrates (see Scheme 2),[49] but allows selective reactions in complex molecules which may not be readily achieved with other acyl anion synthons. An illustrative example is shown in eqn (7).[48a]

Collman has described $Na_2Fe(CO)_4$ as a "transition metal analog of a Grignard reagent".[42] In the present context (eqns 4 and 6) it seems more appropriate to visualize this compound as in fact a *masked* synthon for the formyl ($H{-}CO^-$) and functionalized formyl ($Z{-}CO^-$) anions, as well as the formyl dianion ($O{=}C^{-2}$), and to regard intermediates **26** and **27** as distinct acylmetallic reagents as shown in Scheme 3 (Path A).

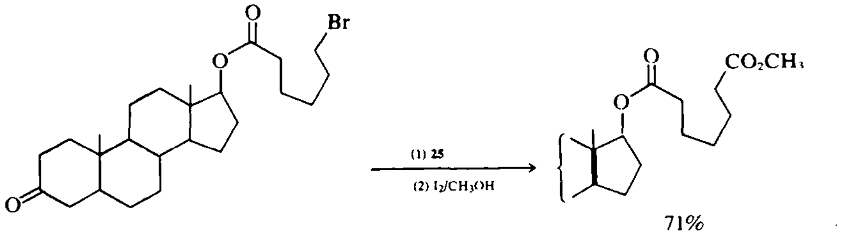
The chemistry of lithium acyltricarbonylnickelates **28**, prepared by addition of an organolithium reagent to nickel tetracarbonyl, is quite dissimilar to that of the iron complexes.[50] For example, hydrolysis of the intermediate formed from phenyllithium and $Ni(CO)_4$ gave benzoin as the major product rather than benzaldehyde, and alkylation with benzyl halides furnished α-benzylbenzoin [$PhCOC(CH_2Ph)(OH)Ph$] accompanied by only a trace amount of phenyl benzyl ketone.[51] These facts coupled with spectroscopic data prompted the suggestion that, in contrast with the mononuclear iron complexes, acylnickelates may exist in solution primarily as dimeric structures with bridging carbonyl ligands.[51]



$$RLi + Ni(CO)_4 \rightarrow [R{-}\overset{O}{\overset{\|}{C}}{-}Ni(CO)_3]Li \quad \text{or dimer.}$$

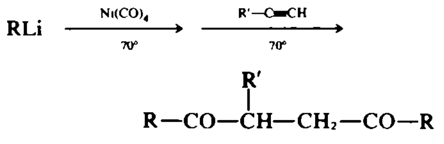
28

Two approaches to 1,4-diketones[52] involving acylnickelates have been described. In the first of these, bis-adducts **29** are formed from the reaction of terminal acetylenes with two equivalents of acyltricarbonylnickelates (eqn 8); the reaction procedes best with aroylnickelates.[54] Corey and Hegedus reported a more general process (eqn 9) in which acylnickelates form Michael adducts with unsaturated carbonyl compounds, including β,β-disubstituted substrates (e.g. mesityl oxide).[55] This insensitivity to steric



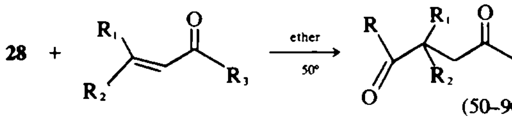
(Eqn. 7)

effects is an advantage not shared by all nucleophilic acylating reagents which undergo conjugate additions (*vide infra*).



$$\mathrm{RLi}\xrightarrow[70^\circ]{\mathrm{Ni(CO)_4}}\xrightarrow[70^\circ]{\mathrm{R'{-}C{\equiv}CH}}\mathrm{R{-}CO{-}\overset{\overset{R'}{|}}{C}H{-}CH_2{-}CO{-}R}$$

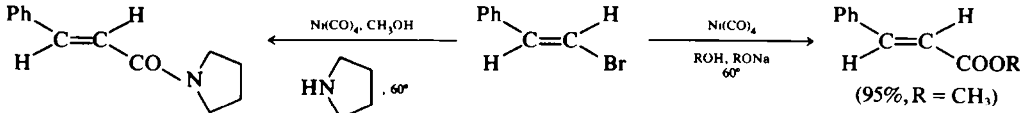
29 (24–74%) (Eqn. 8)



(50–90%)

(Eqn. 9)

The iron complexes mentioned above permit carboxylation of alkyl halides, and reagents derived from nickel carbonyl complement this by allowing the conversion of trigonal halides to carboxyl derivatives.[53] Thus, an alcoholic solution containing excess $Ni(CO)_4$ and the corresponding alcoholate affords esters from vinyl halides as shown in eqn (10) (iodobenzene gave methyl benzoate).[56] This reaction is adaptable to nucleophilic carbamoylation by replacement of the alcoholate with a nucleophilic amine, e.g. pyrrolidine (eqn 10);[56] also, nucleophilic carbamoylation of vinyl and allylic bromides may be carried out with the reagent, $Li[(CH_3)_2N{-}CO{-}Ni(CO)_3]$, obtained from addition of lithium dimethylamide to $Ni(CO)_4$.[57] In a related carboxylation procedure, aromatic acids are formed from aryl halides and $Ni(CO)_4$ in aprotic solvents in the presence of carbon monoxide and a basic promoter such as calcium hydroxide.[39f,58] Because they are generally unreactive toward these reagents and are prone to competitive elimination, alkyl halides are not usually suitable substrates.

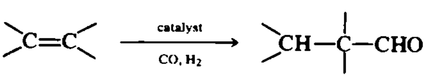


(82%)

(95%, R = CH_3)

(Eqn. 10)

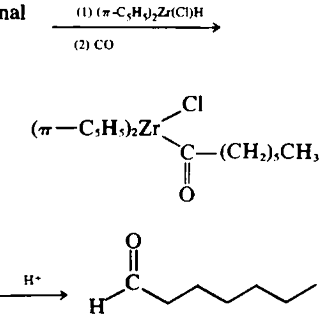
The voluminous literature on the conversion of halides and other substrates to carbonyl derivatives using transition metal reagents has been treated fully elsewhere.[39] The aspects of this work presented here were chosen for their synthetic potential as well as for a probable mechanistic relationship to nucleophilic acylation. Transition metal-catalyzed carbonylations, e.g. the hydroformylation reaction with cobalt or rhodium catalysts,[39] may bear no mechanistic relationship to nucleophilic acylation.



$$>C{=}C<\ \xrightarrow[\mathrm{CO,\,H_2}]{\text{catalyst}}\ >CH{-}\overset{|}{\underset{|}{C}}{-}CHO$$

When a carbonylation process involves the distinct reaction of an acyl complex with an electrophile, mechanistic categorization as a nucleophilic acylation is fully justified. This is often the case in reactions using stoichiometric carbonylation reagents (cf. **25–27** and aldehyde formation by protonation of the acylzirconium compound[59] shown below).

1-Hexene (or any internal hexene isomer) $\xrightarrow[(2)\ \mathrm{CO}]{(1)\ (\pi\text{-}C_5H_5)_2Zr(Cl)H}$



IV. RECENT PROGRESS IN CLASSICAL MASKED ACYL ANION EQUIVALENTS

Conceptually, nucleophilic acylation with masked acyl anions requires a carbanionic species substituted in such a fashion that, after reaction with an electrophile, the substituent(s) may be converted into a carbonyl function. The substituents should confer sufficient stability without impairing the nucleophilicity of the anion, and should simultaneously permit gentle unmasking procedures. Most masked acyl anions fall into the two general classes in Scheme 3 (paths B and C), but there are other methods which use masked functionality of a different nature, e.g. the sp-hybridized cyanide and acetylide ions.

Before embarking on a discussion of masked acyl anions of more recent vintage, it is appropriate to review several traditional approaches and their current modifications to provide the historical perspective for a full appreciation of recent developments.

1. *Cyanide ion.* Cyanide ion has been employed for decades in the conversion of halides to nitriles and thence to carboxyl derivatives upon hydrolysis (eqn 11). Displacements on alkyl halides are often carried out in aqueous alcohol or in dimethylsulfoxide, and phase transfer processes involving both liquid-liquid[60,62] and liquid-solid[61] systems have been described. The latter method (cf. eqn 12)[61] and utilization of tetraalkylammonium cyanides in methylene chloride or acetonitrile[63] are particularly suitable for reactive halides which cannot be exposed to nucleophilic solvents. Sodium dicyanocuprate $[NaCu(CN)_2]$ or cuprous cyanide convert vinyl and aryl halides to conjugated nitriles at elevated temperatures;[64] however, Corey and Hegedus have noted that tetrapotassium hexacyanodinickelate $[K_4Ni_2(CN)_6]$ gives the corresponding *trans* unsaturated nitrile (t-Ph-CH=CH-CN) from *trans*-β-bromostyrene at ambient temperature.[56]

$$(\mathrm{RCO^-\ or)HOOC^-} \Leftrightarrow \mathrm{CN}\xrightarrow{\mathrm{RX}}\mathrm{R{-}CN}\rightarrow$$

$$\mathrm{R{-}COOH\ (or\ R{-}CO{-}R')}$$

(Eqn. 11)

$$\mathrm{ArCH_2Cl}\xrightarrow[\text{18-crown-6}]{\mathrm{KCN,CH_3CN}}\mathrm{ArCH_2CN}. \quad \text{(Eqn. 12)}$$

Substitution of an acyl group for halogen is achieved when cyanide displacement is followed by reaction of the product nitrile with an organometallic reagent (e.g. R'Li or R'MgX; cf. eqn 11) and hydrolysis of the resulting imine, but this sequence is often marred by undesirable base-catalyzed reactions.[65a] A method for methyl ketone synthesis which largely avoids this problem involves treatment of the nitrile with trimethylaluminum and nickel(II) acetylacetonate in an inert solvent.[65b]

$$RCN \xrightarrow[Ni(acac)_2]{Al(CH_3)_3} \xrightarrow{H_3O^+} R—CO—CH_3.$$

Conjugate addition of cyanide to α,β-unsaturated ketones produces β-cyanoketones, which can be considered hemi-protected 1,4-dicarbonyl systems. Nagata *et al.* found that side-reactions (hydrolysis, base-catalyzed condensation) sometimes encountered in traditional procedures (e.g. KCN in aqueous alcohol) are minimized when cyanide is used in aprotic media in the presence of ammonium chloride.[66] This group has also developed organoaluminum reagents for hydrocyanation of enones.[67] The reagents employed are either an alkylaluminum cyanide (R_2AlCN) or a combination of an alkylaluminum compound and hydrogen cyanide. The scope, stereochemistry, and mechanisms of these reactions have been thoroughly investigated, with particular emphasis on steroidal enones (eqn 13).[67]

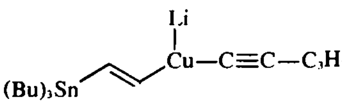
In transformations discussed in this section, the carbonyl group in the acylated product is formed directly from the nitrile function. Another important group of nucleophilic acylating agents are those in which a nitrile group stabilizes an adjacent carbanion. In these cases, it is in fact the α-carbon (the anionic center) which ultimately becomes the carbonyl carbon in the acylated product. The conceptual development of these reagents (anions of protected cyanohydrins) may be traced to a classical reaction, the benzoin condensation. This relationship and the attendant chemistry are covered in a later section (Section V.2) of this Report.

2. *Acetylide ion.* Anions of primary acetylenes are a second category of classical reagents for nucleophilic acylation. These intermediates may be alkylated and also add to carbonyl compounds, but this approach is limited by the often non-regiospecific hydration of the reaction products: both possible carbonyl compounds may be formed (eqn 14).[68] However, Stork and Borch showed that in special situations where intramolecular direction of hydration is possible, a single hydrated product is formed in good yield, as with the β- or γ-acetylenic ketones shown in eqn (15).[69]

Since diethylalkynylalanes (**30**) add 1,4- to conjugated ketones which are able to adopt a cisoid conformation,[70] and since the β-acetylenic ketones thus formed may be hydrated to 1,4-diketones as shown in eqn (15), the organoalanes are masked acyl anions of the type R—CH₂—CO which add to the β-carbon of appropriate unsaturated ketones. Furthermore, mixed cuprate **31** transfers the β-stannylvinyl group in Michael fashion to transoid cyclic α,β-enones.[71] Treatment with lead tetraacetate in acetonitrile at room temperature converts the adducts into β-ethynyl ketones, which may be hydrolyzed as in eqn (15) to the corresponding β-acetyl ketone.[71] Cuprate **31** is therefore an equivalent of the acetyl carbanion (CH_3CO^-) for conjugate additions (see **102**, **118**: Section V.5).

$$R—C{\equiv}C—Al(C_2H_5)_2$$

30



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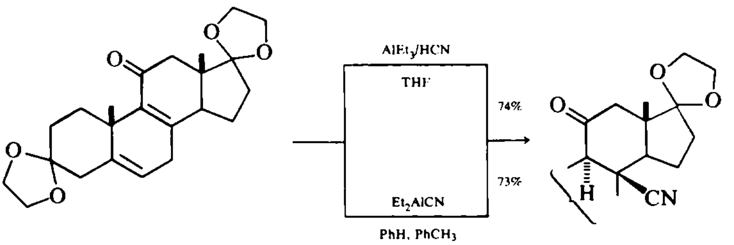
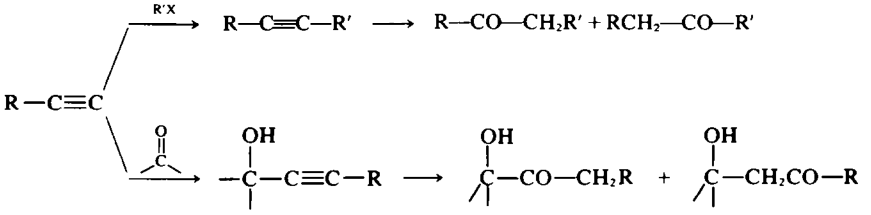
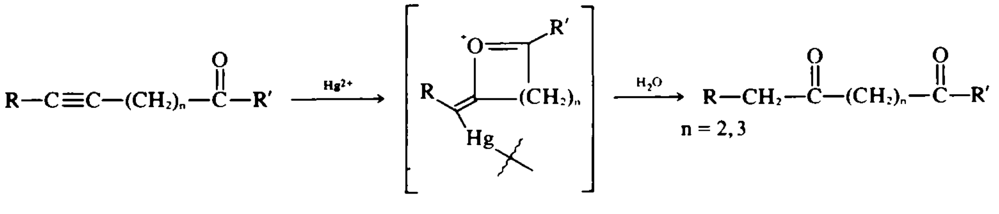


(Eqn. 13)



(Eqn. 14)



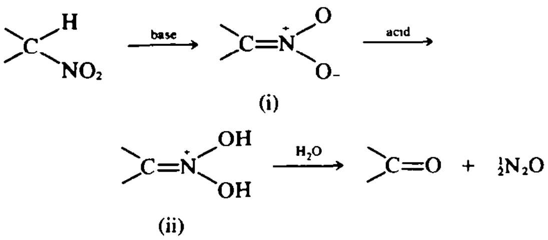
(Eqn. 15)

Another way in which regiospecific hydration can be achieved is by conjugate addition of water or a related nucleophile to an α-acetylenic ketone. Carlson and Oyler found that the propiolic acid dianion (32) is alkylated readily by terminal epoxides, and pyrones 33 are obtained in 20–30% overall yield by catalyzed addition of methanol to the intermediate acetylenic acids.[72a] This sequence is formally equivalent to epoxide opening with the α-carboxyacetyl anion (HOOC-CH$_2$-CO$^-$), followed by lactonization, as illustrated by the synthesis of (±)-pestalotin and (±)-epipestalotin (stereoisomeric 33, R = C_4H_9CHOH–) in eqn (16).[72] This basic scheme can be modified to allow the synthesis of 5,6-dihydro-2H-pyran-2-ones with varied substitution patterns.[73]

The problems associated with hydration of acetylenes are unique to this method of nucleophilic acylation. As shown in eqn (14), depending on the direction of hydration the net result is either that expected from attack by an acyl anion synthon, or is that expected from attack by an enolate anion. In other methods the carbonyl carbon of the reaction product is unambiguously the nucleophilic carbon of the acyl anion synthon (note 75→77, Section V.4).

3. *Nitronate anions in* 1,4-*diketone synthesis*. Conjugate addition of nitronate anions to enones (eqn 17) has been an established reaction for many years,[74] but has captivated relatively little interest as a method for nucleophilic acylation because of the conditions which are encountered in the Nef reaction,[75] the traditional procedure for conversion of an aliphatic nitro group to a carbonyl.

The classical Nef reaction involves conversion of the nitroalkane to the corresponding nitronate anion (i) with base, and treatment of (i) with sufficiently strong acid to yield the protonated nitronic acid (ii),[75c] which ultimately leads to carbonyl compound and nitrous oxide. Many types of functionality are incompatible with these conditions, and a number of alternative methods have been examined in recent years.[76–81]



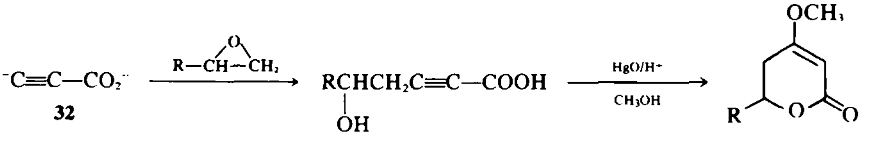
These methods have included oxidation of nitronate anions with permanganate[76] or persulfate[77] ion, reductive procedures with titanium(III) salts,[78] ozonolysis of nitronate anions,[79] the use of alkyl nitrite esters in combination with sodium nitrite[80] and modifications of the Nef procedure.[81]

McMurry and his group have extensively investigated the reductive method, and a detailed account of this work has been provided.[78a] The modification which seems most compatible with other functional groups entails treatment of the nitronate salt in methanol with buffered (pH ca. 6) aqueous titanium(III) chloride (eqn 18).[78a,b]

In some cases, a problem with the classical Nef procedure may be a lack of solubility of the nitronate ion in aqueous base. Good yields of 1,4-diketones have been obtained from γ-nitro ketones when the conversion was carried out with ethanolic sodium hydroxide followed by aqueous hydrochloric acid (3N).[81a] A second modification, which is of particular value in aldehyde formation from primary nitroalkanes, consists of addition of the nitronate anion in methanol to cold methanolic sulfuric acid to furnish the aldehyde dimethylacetal (78–99% yield, eqn 19).[81b]

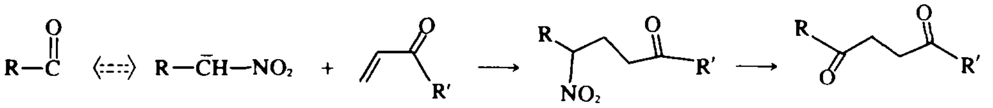
V. RECENTLY DEVELOPED MASKED ACYL ANION EQUIVALENTS

Recently there have emerged a new series of reagents with masked carbonyl groups which promise to supplant

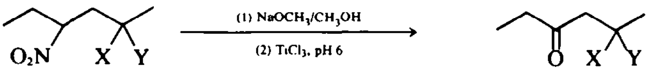


33

(Eqn. 16)

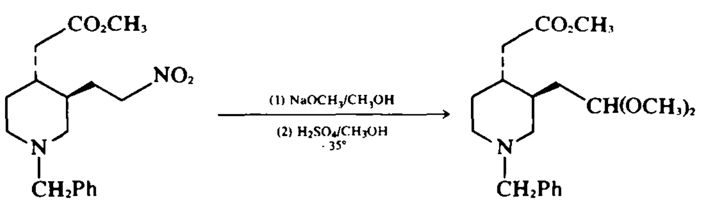


(Eqn. 17)



(Eqn. 18)

X,Y = =O(90%)
X,Y = —OCH$_2$CH$_2$O— (70%)



(Eqn. 19)

in large measure the more traditional masked acyl anions. As was previously mentioned, these reagents with few exceptions follow the general directions of paths B and C in Scheme 3. Most masked acyl anions are metallic salts of carbon acids and as such they share a common characteristic, i.e. their carbanionic nature. Aldehyde hydrazones, although not broadly useful reagents, are a special class of masked acyl anion as they are neutral molecules with functionality incorporating simultaneously a nucleophilic center (the aza-enamine moiety) and a protected carbonyl group. Reactions of certain of these compounds with electrophiles such as Vilsmeier's reagent [$(CH_3)_2{}^+N{=}CHCl$] and sulfonylisocyanates (eqn 20) have been reported.[82]

1. *Metallo aldimines*. Although properly considered as masked acyl anions, metallo aldimines **34**[83] defy classification within paths B and C of Scheme 3, and are reminiscent of the acylmetallic reagents (Path A). Walborsky *et al.*[83a-c] have used metallo aldimines as masked acyl anions in the preparation of aldehydes, ketones (from primary halides), α-keto acids and esters, and α- and β-hydroxyketones (cf. Scheme 2). After reaction of **34** with the appropriate electrophile and hydrolysis of the intermediate imine, the carbonyl products are obtained (eqn 21).

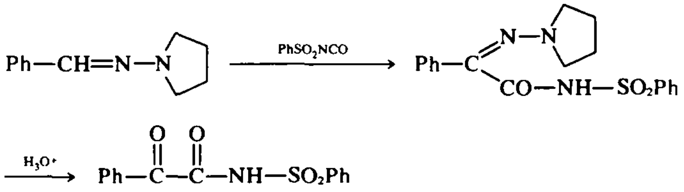
The reagents are prepared *in situ* by the addition of aliphatic organolithium compounds to tertiary isonitriles. The formation of **34** is less efficient with aryllithium or Grignard reagents, and fails altogether with less basic anions such as lithium phenylacetylide; vinyllithium and propenyllithium undergo complicated side reactions.[83a] An interesting ring enlargement (believed to occur via the expected metalated aldimine) to give a cyclobutanone was observed when a cyclopropyllithium reagent was treated with 1,1,3,3-tetramethylbutyl isocyanide **35** (eqn 22).[84] Suitable isonitriles are **35** and t-butyl isocyanide; in certain cases, *e.g.* triphenylmethyl isocyanide, dissociation of **34** to a new combination of organolithium compound (R'Li) and nitrile (RCN) becomes the major process.[85]

As shown in eqn (23), an α-amino acid is obtained when the α-amino carboxylate resulting from reaction of a metallo aldimine with carbon dioxide is reduced rather than directly hydrolyzed.[86] Amino acids of moderate optical purity were formed when a chiral isonitrile, (R)-(+)-2-phenyl-2-butylisonitrile, was used.[86]

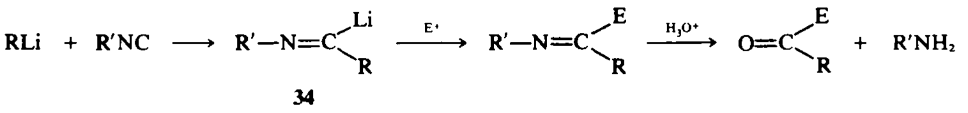
A novel but circuitous route to ketones via metallo aldimines is suitable for synthesis of ketones containing two secondary residues (eqn 24).[87] In this method, a dialkylchloroborane is added to **34** (R = t-Bu), and migration[88] of an alkyl group from boron to carbon is induced by trifluoroacetic anhydride, or by thioglycolic acid when the migrating group is secondary; ketones are produced upon subsequent oxidation with alkaline hydrogen peroxide (e.g. cyclopentyl iso-propyl ketone in 91% yield by GLC).[87]

2. *Protected cyanohydrin anions and related reagents for ketone synthesis*. The mechanism of the benzoin condensation[89] has now been firmly established[90] as that proposed by Lapworth[91] just after the turn of the century. As depicted in Scheme 5, cyanide serves a catalytic role in generation of carbanion **36** which is synthetically equivalent with the benzoyl anion ($PhCO^-$). This relationship suggested that anions derived from protected aldehyde cyanohydrins could function as nucleophilic acylating reagents, and subsequent works exemplify superbly how mechanistic understanding may foster new synthetic methods: protected cyanohydrin anions are indeed efficient precursors to a wide variety of ketones (see Table 1).

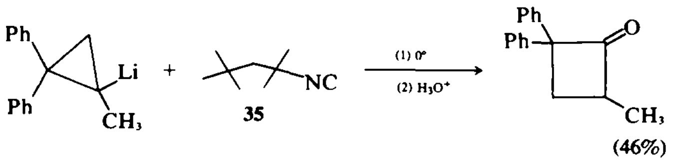
In an approach to tetracycline synthesis, Barton *et al.* successfully cyclized the protected cyanohydrin **37**, and after regeneration of the carbonyl function obtained compound **38b** (eqn 25).[92] Almost simultaneously, Stork



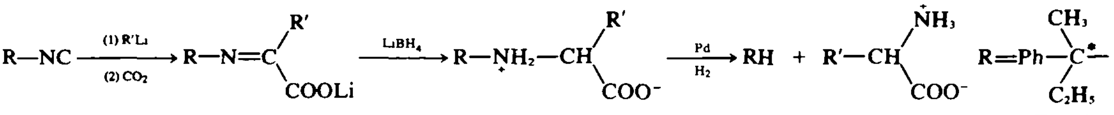
(Eqn. 20)



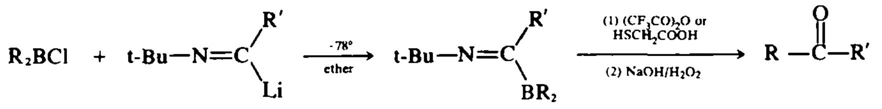
(Eqn. 21)



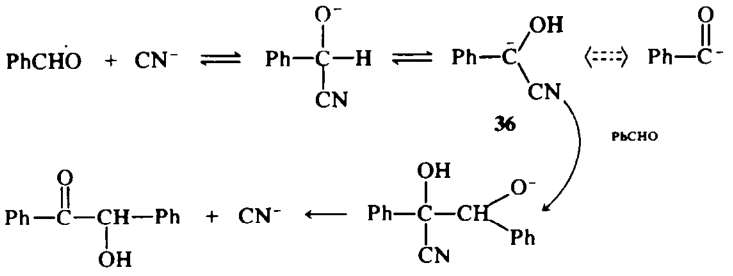
(Eqn. 22)



(Eqn. 23)

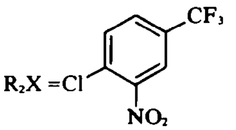
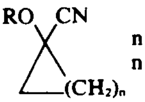


(Eqn. 24)



Scheme 5.

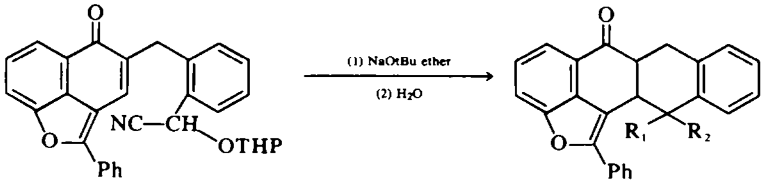
Table 1. Examples of ketones and cyanohydrins prepared by reaction of electrophiles with anions of protected cyanohydrins

	Reagent	Electrophile	Product (% yield)	Ref.
i	**39** (R=CH$_3$)^a, LDA	R$_2$X = *i*-PrBr	**41** (85)	93
ii	**39** (R = vinyl)^a, LDA	R$_2$X = *n*-C$_6$H$_{13}$Br	**41** (75)	93
iii	**39** (R = Ph)^b, NaH	R$_2$X = 	**42** (42)	95
iv	**39** (R=Ph)^c, LDA	R$_2$X = *t*-BuI	**42** (85)	99
v	**39** (R=2-furyl)^c, LDA	R$_2$X = *i*-PrI	**42** (80)	99
vi	**39**^{a} = $R_1O\text{–}\underset{\displaystyle CN}{CH}\text{–}(CH_2)_n\text{–}CH_2Cl$, [(CH$_3$)$_3$Si]$_2$NNa		 n = 1 (62) n = 2 (61)	94
vii	**39** (R=Ph)^c, LDA	$CH_3\text{–}\overset{\displaystyle O}{\overset{\|}{C}}\text{–}CH_3$	$Ph\text{–}CO\text{–}\overset{\displaystyle OH}{\overset{\vert}{C}}(CH_3)_2$ (78)	101
viii	**39** (R=Ph)^c, LDA	CH$_3$CHO	Ph–CO–CH(OH)–CH$_3$ (84)	101
ix	**39** (R=Ph)^d, K$_2$CO$_3$	CH$_3$CHO	$Ph\text{–}CO\text{–}\overset{\displaystyle OB_z}{\overset{\vert}{CH}}\text{–}CH_3$ (59)	102
x	**39** (R=*p*-O$_2$N–C$_6$H$_4$–)^d, Ac$_2$O	quinoline-1-oxide	2-aroylquinoline (58)	104

^{a}R$_1$ = 1-ethoxyethyl; ^{b}R$_1$ = THP; ^{c}R$_1$ = TMS; ^{d}R$_1$ = benzoyl.

and Maldonado[93] described a general method for ketone synthesis by alkylation of protected (as the adducts with ethyl vinyl ether) cyanohydrin anions **40** followed by removal of the protective group [eqn (26); R′ = –CH(OC$_2$H$_5$)CH$_3$]. Anions **40** are generated from aromatic or aliphatic aldehyde derivatives **39** with lithium diisopropylamide (LDA); the alkylation step proceeds smoothly with primary iodides and bromides, most secondary bromides, and with allylic and homoallylic bromides.[93] Conjugated aldehydes provide synthons for the unsaturated acyl anion **43**.

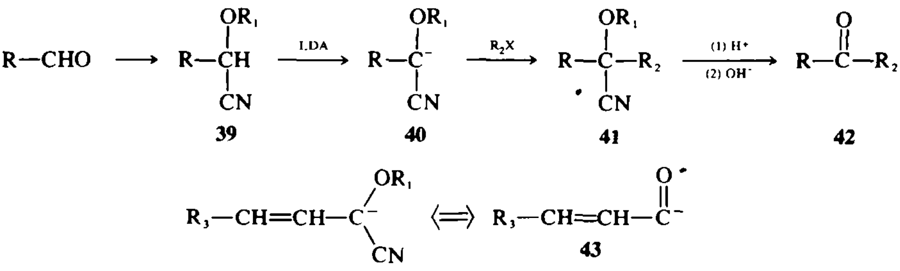
Adaptions of this general scheme have included the synthesis of cyclopropanone and cyclobutanone cyanohydrins by intramolecular displacement (vi: Table 1),[94] and the use of strongly activated aryl halides as electrophiles (iii: Table 1).[95] The protective function R$_1$ has been varied to include tetrahydropyranyl (cf. eqn 25),[92-95] benzoyl[102,104] and trimethylsilyl groups.[96-101] The latter modification stems from the work of Evans and others who have recently demonstrated that protected cyanohydrins, e.g. **39** (R$_1$ = TMS) are formed efficiently from carbonyl compounds and trimethylsilyl cyanide (TMSCN), particularly in the presence of catalysts such as zinc iodide or a cyanide-crown ether complex.[96,98] The carbonyl can be liberated by treatment with acid, silver fluoride,[96c] or triethylammonium hydrofluoride, followed by base.[100] Anions **40** (R$_1$ = TMS) from aryl and heterocyclic aldehydes have been used by Hunig *et al.* for



37

38a: R$_1$ = CN, R$_2$ = OTHP
38b: R$_1$,R$_2$ = =O

(Eqn. 25)



$$R{-}CHO \longrightarrow \underset{\mathbf{39}}{R{-}CH(OR_1)(CN)} \xrightarrow{LDA} \underset{\mathbf{40}}{R{-}C^-(OR_1)(CN)} \xrightarrow{R_2X} \underset{\mathbf{41}}{R{-}C(OR_1)(R_2)(CN)} \xrightarrow[(2)\ OH^-]{(1)\ H^+} \underset{\mathbf{42}}{R{-}C(=O){-}R_2}$$

(Eqn. 26)

$$R_3{-}CH{=}CH{-}C^-(OR_1)(CN) \Longleftrightarrow \underset{\mathbf{43}}{R_3{-}CH{=}CH{-}\overset{O}{\overset{\|}{C}}{}^-}$$

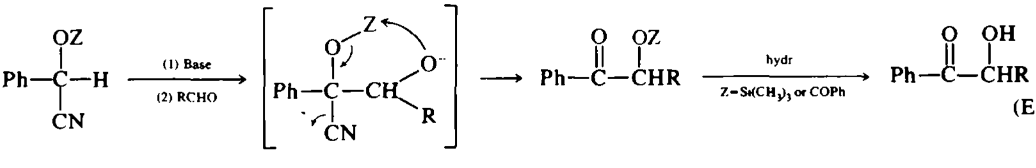
the preparation of a large number of ketones in which one residue is aromatic or heterocyclic (iv, v: Table 1).[99,100] In view of the competition between displacement and elimination so frequently encountered in reactions of nucleophiles with secondary halides, it is striking that alkylation of **40** (R = Ph; R_1 = TMS) proceeded well even with a tertiary iodide (iv: Table 1).[99]

The nature of the electrophile has also been varied. Thus, anions of trimethylsilyl-protected[101] and O-benzoyl[102] aromatic aldehyde cyanohydrins react with aldehydes (the former reagents also add to ketones: Table 1, example vii) to give the expected α-hydroxyketones after hydrolysis, but in each case an interesting intramolecular deprotective silylation or benzoylation, respectively, occurs as shown in eqn (27) (see Table 1, examples viii and ix).[101,102]

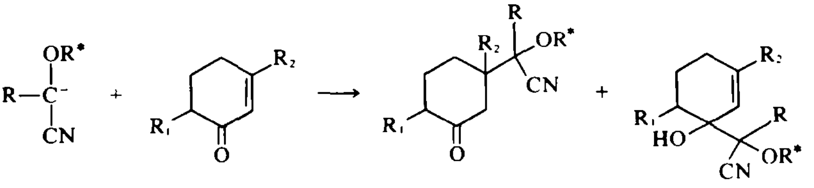
Stork and Maldonado explored the reaction course of aliphatic protected cyanohydrin anions with unsaturated carbonyl substrates (eqn (28); R^* = α-ethoxyethyl).[103a] Mixtures of 1,2- and 1,4-addition products (**44** and **45**) are formed when the anion is from a saturated aldehyde; the conjugate addition product predominates when a bulky anion (eqn 28b) or hindered carbonyl function (eqn 28c) is a reaction partner. These trends were interpreted mechanistically in terms of the steric requirement for transfer of the lithium ion from the reagent to the enone carbonyl. In contrast, when the reagent is derived from an unsaturated aldehyde, 1,2-addition may be reversible, and in this case the product of conjugate addition **44** is indeed formed in good yield (eqn 28d), even from β,β-disubstituted enones; the more heavily β-substituted enones gave almost entirely carbonyl addition products (eqn 28e) when the reagent was a saturated anion. Conjugate addition of unsaturated aliphatic reagents has been applied to construction of 13-oxi prostanoids,[103c] and conjugate addition of an aryl cyanohydrin anion has been used in a recent β-cuparenone synthesis.[103b]

Another type of electrophile which has been used are heterocyclic N-oxides (cf. example X, Table 1).[104] Certain of these compounds are aroylated in the position adjacent to the nitrogen atom, with concomitant deoxygenation of the N-oxide, when they are heated in acetic anhydride with a sufficiently acidic O-benzoyl aromatic aldehyde cyanohydrin. Initially isolated products are the benzoylated cyanohydrins of the acylated heterocycle, from which the free ketones are obtained on alkaline hydrolysis.[104]

Anions adjacent to primary nitriles can be alkylated, and efficient methods for the oxidative decyanation[105] of secondary nitriles ($R_2CH{-}CN \rightarrow R_2C{=}O$) then allow one to consider the anions $R\bar{C}HCN$ as potential synthons for the acyl anion RCO^-. In this sense, the nitrile group serves as an operator functionality and not as a source of the carbonyl carbon in the final ketonic product (cf. Section IV.1). Conversion of a secondary nitrile to the corresponding decyanated ketone can be carried out in several ways, e.g. by way of the α-halo nitrile,[105b] but the most appealing approach is direct introduction of an α-hydroxyl substituent to give a cyanohydrin, from which the carbonyl can be freed readily. Selikson and Watt[105a] have recently shown that the transformation can be effected in good yield by reaction of the anion of a secondary nitrile[105d] with molecular oxygen at low temperature to provide the α-hydroperoxynitrile, which is converted to the cyanohydrin and thence to the ketone, without isolation of intermediates (eqn 29).



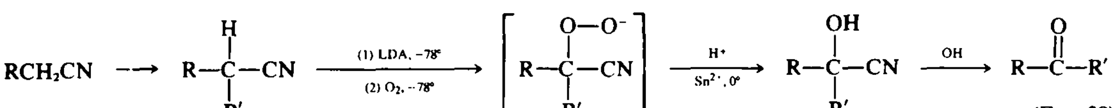
(Eqn. 27)



44 **45**

(Eqn. 28)

R	R_1	R_2	44		45	
CH_3	H	H	3	:	2	(Eqn. 28a)
n-pentyl	H	H	2.7	:	1	(Eqn. 28b)
CH_3	CH_3	H	6	:	1	(Eqn. 28c)
$CH_3\underset{H}{C}{=}\underset{H}{C}{-}$	H	CH_3	70%		—	(Eqn. 28d)
CH_3	H	CH_3	—		90%	(Eqn. 28e)



$$\mathrm{RCH_2CN} \longrightarrow \mathrm{R{-}\overset{H}{\underset{R'}{C}}{-}CN} \xrightarrow[(2)\ O_2,\ -78^\circ]{(1)\ LDA,\ -78^\circ} \left[\mathrm{R{-}\overset{O-O^-}{\underset{R'}{C}}{-}CN}\right] \xrightarrow[Sn^{2+},\ 0^\circ]{H^+} \mathrm{R{-}\overset{OH}{\underset{R'}{C}}{-}CN} \xrightarrow{OH} \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}R'}$$

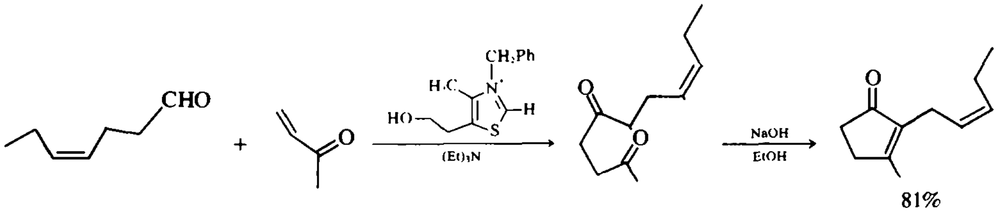
(Eqn. 29)

In formal analogy with the benzoin condensation (Scheme 5), aromatic and heterocyclic aldehydes add conjugatively as the corresponding acyl anion equivalents to α,β-unsaturated nitriles, esters, and ketones in the presence of catalytic amounts of cyanide ion or the conjugate base of a thiazolium salt.[106–108] Stetter and Kuhlmann have found that aliphatic aldehydes can also be used with the latter catalyst, e.g. in the *cis*-jasmone synthesis[108] in eqn (30), while cyanide is too basic to be employed with these substrates.[107,108] The crucial intermediate is the anion of an unprotected cyanohydrin in the case of cyanide catalysis (see **36**, Scheme 5), or the anion **46**, which is formally derived from an α-hydroxy acid.

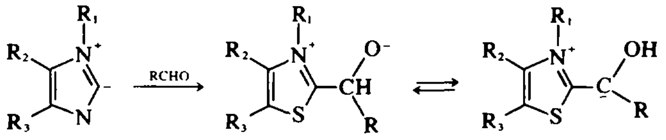
More subtly linked to the benzoin condensation, the anion from an unprotected α-hydroxyketone has also been used as an acyl anion equivalent for preparation of aryl ketones. As shown in eqn (31), alkylation of benzoin[93b] followed by reduction to the vicinal diol and oxidative cleavage leads to aryl benzyl (or allyl) ketones.[109] A more general sequence is shown in eqn (32).[110,111] In this route the acyl anion equivalent is the enediolate of an acyloin, and thus the acyl anion $R\text{-}CO^-$ is originally contained in an ester (RCO_2R_1) [see the following Section (V.3) for related cases]. It should be noted that both procedures (eqns 31 and 32) involve production of equivalent amounts of aldehyde in the final step, and furthermore, the theoretical yield (based on ester) of ketone in the acyloin route (eqn 32) is 50%, since half of the starting ester is consumed in aldehyde production.

A number of examples of nucleophilic acylation with anions of protected α-aminonitriles have also been reported,[112,113] but in general these reagents have received much less attention than anions of the more readily accessible, and more readily deprotected, cyanohydrins. Two examples are provided in eqns (33) and (34). The first is a cyanoethylation of a pyridine derivative; the product **47** was used to prepare myosmine and nornicotine, constituents of tobacco smoke.[112] In the second example, preparation of deoxybenzoin derivatives, which were desired as starting materials for alkaloid synthesis, was achieved by alkylation and subsequent deprotection of α-aminonitriles.[113]

3. *The carboxyl function in nucleophilic acylation.* As a



(Eqn. 30)



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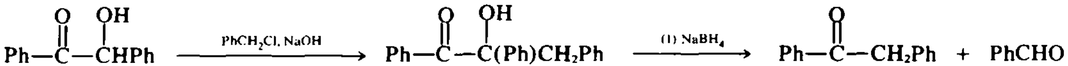
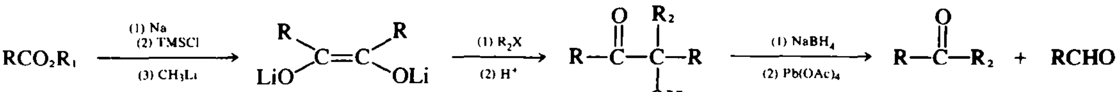
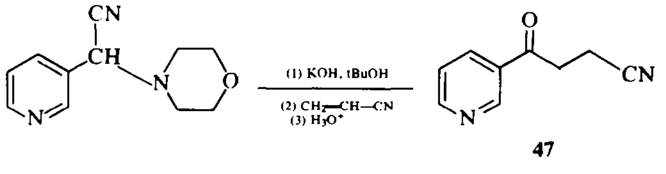


$$\mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}\overset{OH}{\overset{|}{C}}HPh} \xrightarrow[DMSO]{PhCH_2Cl,\ NaOH} \mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}\overset{OH}{\overset{|}{C}}(Ph)CH_2Ph} \xrightarrow[(2)\ NaIO_4]{(1)\ NaBH_4} \mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}CH_2Ph} + \mathrm{PhCHO}$$

(Eqn. 31)

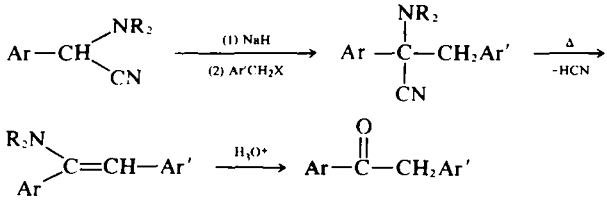


(Eqn. 32)

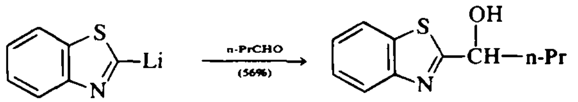


47

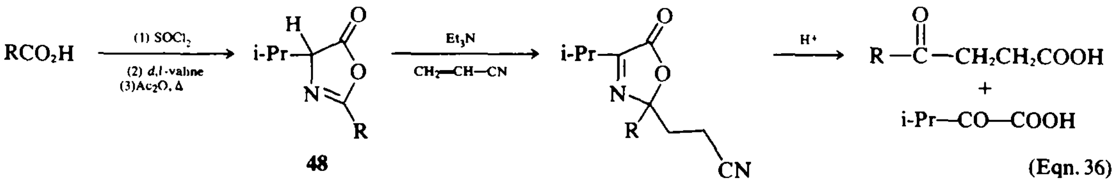
(Eqn. 33)



(Eqn. 34)



(Eqn. 35)



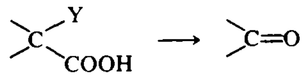
48

(Eqn. 36)

source of acyl anion equivalents, the carboxyl carbon may be used either as the nucleophilic center ($RCOOH \Rightarrow R'CO^-$) or, alternatively, as an operator function to activate the adjacent carbon ($R'CH_2COOH \Rightarrow R'CO^-$) [compare Sections IV.1 and V.2].

One example of the former process in which an ester is the source of the nucleophilic acyl equivalent has already been mentioned (eqn 32).[110,111] Certain metalated heterocyclic rings[114] are formally masked nucleophilic carboxyl functions (see eqn 35),[114a] and an interesting sequence for conjugate additions utilizes anions of oxazol-5-ones (**48**), prepared in several steps from the acid. With acrylonitrile these anions react at C-2 as shown in eqn (36), although C-4, or mixtures of C-2 and C-4 oxazolone adducts are formed with other electrophilic olefins such as acrolein and methyl vinyl ketone.[115a] The reaction products with acrylonitrile can be hydrolyzed with alkali to yield γ-keto nitriles, or with acid to give γ-keto carboxylic acids (eqn 36).[115b]

For the carboxyl group to be used in the second way, i.e. as an activating function, suitable methods akin to the unmasking of other acyl anion equivalents are required for the transformation of an acid (or a readily accessible derivative) to the corresponding carbonyl compound containing one less carbon atom (**iii**→**iv**). This has been accomplished with multi-step routes,[116,117] but convenient methods for oxidative decarboxylation of α-sulfenylated acids (**iii**, Y = SR) recently reported by Trost and Tamaru[117,118] lend practical value to this approach, and form the basis for new aldehyde and ketone syntheses (Scheme 6).

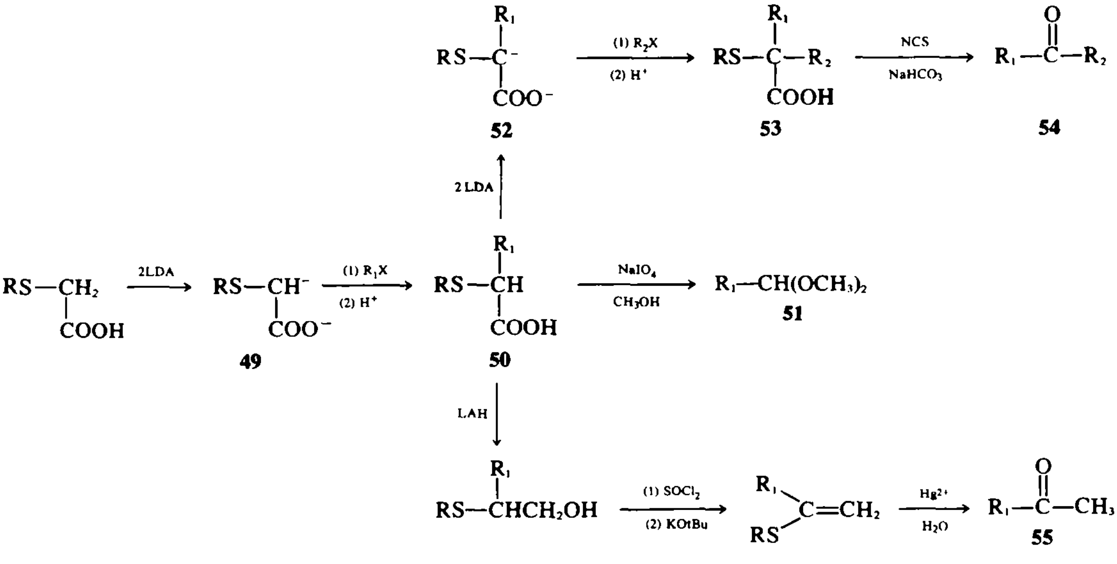


(iii) (iv)

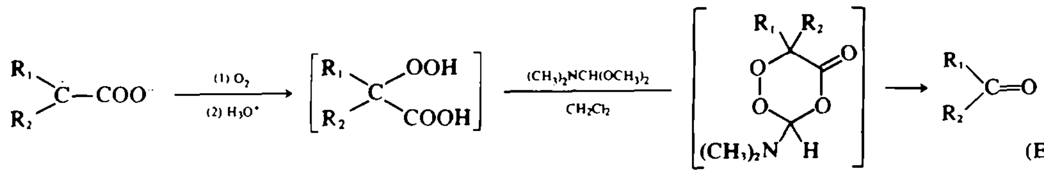
The nucleophilic acyl synthons are dianions (**49**, **52**) of α-sulfenylated acids (which are reminiscent[119] of anions of protected cyanohydrins, eqn 26), formed from the corresponding acids with two equivalents of lithium diisopropylamide.[118] Reaction of the dianion of methylthioacetic acid (**49**, $R=CH_3$) with primary or secondary halides furnishes the alkylated product **50**, which can be elaborated by a second alkylation (e.g. with primary halides) to provide the fully substituted acid **53**. Oxidative decarboxylation of the aldehyde precursor **50** with sodium periodate in methanol gives the aldehyde dimethylacetal **51**, while ketones **54** are liberated from the dialkylated acids **53** with N-chlorosuccinimide/sodium bicarbonate in an alcoholic medium, or with sodium periodate.[117,118]

Thus the readily available dianion **49** ($R=CH_3$) is a formyl anion (HCO^-) synthon, and substituted dianions **52** are acyl anion (R_1CO^-) equivalents. The reduction-elimination-hydrolysis sequence[120a,121] shown in Scheme 6 utilizes dianion **49** as an acetyl carbanion (CH_3CO^-) in methyl ketone (**55**) synthesis.[122] Furthermore, since the dianion of an aliphatic carboxylic acid may be sulfenylated in good yield to form the α-carboxy sulfide **50**,[120] in principle any carboxylic acid R_1CH_2COOH can be employed as an acyl anion (R_1CO^-) synthon.

Wasserman and Lipshutz recently provided another new method for oxidative decarboxylation whereby an acid dianion is oxygenated at low temperature and the resulting α-hydroperoxy acid (see eqn 29) is converted to



Scheme 6.



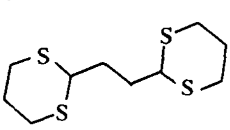
(Eqn. 37)

a carbonyl compound on reaction with dimethylformamide dimethylacetal.[123] The decarboxylation step may involve the cyclic fragmentation of an intermediate peroxy lactone as in eqn (37).

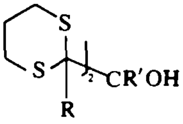
4. *Nucleophilic acylation with anions of 1,3-dithianes, dithioacetals, and derivatives.* In the decade since the initial communication by Corey and Seebach describing the use of 2-lithio-1,3-dithianes as masked acyl anions,[124] the chemistry of these versatile reagents has been explored without abate and often with extraordinary success. The field was reviewed by Seebach in 1969,[125] and in a recent article Seebach and Corey concisely summarized reactions of lithiodithianes and supplied many experimental details.[126] Although a complete description of the multi-faceted chemistry of these intermediates lies beyond the scope of this Report, the most salient features of their utility as acyl anion equivalents are presented herein.

Metalation of 1,3-dithiane (**56**, R=H) or an alkyl relative **56** typically is effected with one equivalent of n-butyllithium in tetrahydrofuran at ca. −20°.[126] Metalation of dithianes and other organic molecules containing sulfur is accomplished with relative ease in comparison with the oxygen analogs. Stabilization of an adjacent carbanion by sulfur generally has been attributed to overlap of the carbanion orbital with vacant *d*-orbitals on sulfur, a conjugative resonance effect which is not possible with oxygen. However, recent physical data[127a] and theoretical calculations[127b,c] indicate that the carbanion is highly localized on carbon, and Streitwieser and Wolfe have each concluded that the principal factor in stabilization is a polarization effect rather than electron delocalization.[127]

Lithiodithianes add to the β-carbon of nitroolefins[16] and several related dithioacetal-type reagents do give Michael adducts with enones (*vide infra*). Also, alternative approaches to cyclic and acyclic 1,4-diketones have been described using bis-dithiane **60**,[128,132] and dithianes are instrumental in certain routes to functionalized cyclopentenones.[52,133,134,232] Acylation of anion **57** with carbon dioxide gives the expected 2-carboxy dithiane **58c**; acylation with esters or acid halides usually leads to significant formation of bis-adducts **61** unless the acylating agent is used in large excess, or unless the lithiodithiane is the metalated parent (**57**, R=H) and is used in equimolar excess to compensate for product enolization.[126]

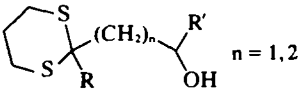


60

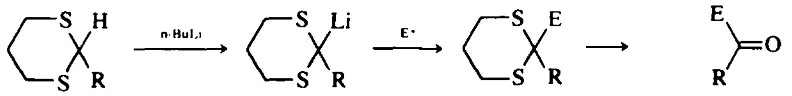


61

Since many masked acyl anions are not alkylated by such weak electrophiles as epoxides, one point of particular interest is that lithiodithianes react effectively, albeit at moderate rate, with oxiranes and certain oxetanes to give thioketals **62** of β- and γ-hydroxy ketones.[125,126,135] These reactions must be carried out in the cold to ensure stability of the reagent during the prolonged reaction periods.



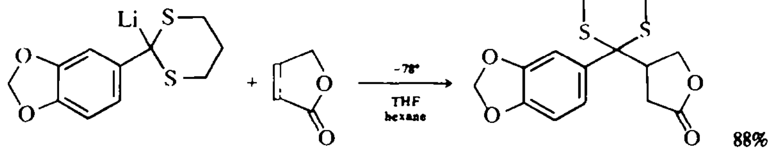
62



56 **57** **58**

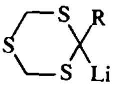
59a: E = R′
b: E = C(OH)R$_1$R$_2$
c: E = COOH
d: E = COR

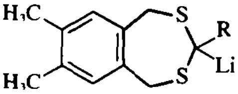
Lithiodithianes react efficiently with most halides (e.g. primary or acyclic secondary iodides and bromides)[126,128,129] and carbonyl compounds[126] (cf. **58a**, **58b**). Although aliphatic reagents (**57**, R = alkyl) normally add exclusively in a 1,2 manner to α,β-unsaturated carbonyl compounds,[124,130] an efficient Michael addition of a 2-aryl-2-lithio-1,3-dithiane to 2-butenolide has been observed.[131]



Apart from limited conjugate addition reactions, lithiodithianes participate in all of the reactions in Scheme 2, but mild and specific methods for carbonyl liberation are essential for a masked acyl anion to be utilized to full effectiveness. Dithioketals are notably resistant to acidic or basic hydrolysis, and along with the firm establishment of the reactions of lithiodithianes with electrophiles, there has been a vigorous search for alternative methods for dithioketal hydrolysis. Procedures now available include treatment of the dithioketal (or dithioacetal) in a hydrolytic medium with metallic ions [Hg(II),[130,136–138] Cu(II),[139] Ag(I)[138] or Tl(III)[140]], or with alkylating agents (methyl iodide,[141,142] methyl fluorosulfonate,[142,143] Meerwein salts[144]), aminating agents (chloramine-T,[145] *O*-mesitylenesulfonylhydroxylamine[146]), or oxidizing agents (N-halosuccinimides,[136] peracids,[147] 1-chlorobenzotriazole,[147a] ceric ammonium nitrate,[148] concentrated sulfuric acid[149]). Thioacetal monosulfonium salts (prepared with methyl fluorosulfonate) may be converted to the corresponding hemithioacetals or acetals directly by treatment with methanol, ethylene glycol, or mercaptoethanol in dichloromethane;[150] this procedure circumvents isolation of the aldehyde in an unprotected form. These methods are quite effective in uncomplicated situations, but in addition to dithioketals, there are other functionalities which may be altered by these reagents. Thus, in complex molecules the choice of hydrolytic conditions must be made with care. The most commonly employed methods are those which use mercuric salts and N-halosuccinimides.[136] Selective hydrolysis of dithioketals in the presence of ketals is possible,[125,133a] and selectivity between non-equivalent dithioketal functions has been achieved under precisely controlled conditions.[151]

The success of the dithiane method has stimulated exploration of related systems, and a number of metalated cyclic and acyclic dithioacetal derivatives have been used as masked acyl anions, including lithiotrithianes **63**,[125,152] and the seven-membered cyclic intermediates **64**.[153] Although the latter anions are sufficiently stable to survive conditions for epoxide opening (seven days, 0°),[153b] metalated 1,3-dithiolanes **65** are too labile to be useful in nucleophilic acylation; these compounds suffer facile cyclic elimination to olefin and lithium dithiocarboxylate.[126]


63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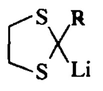
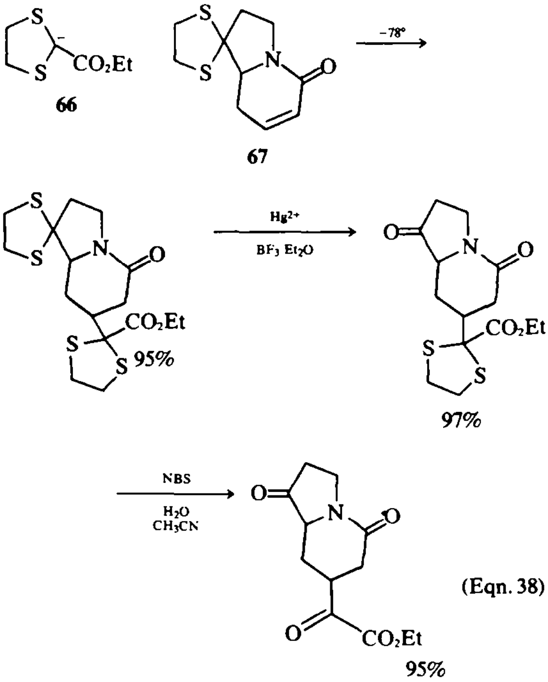
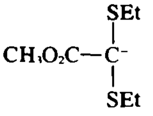

65

On the other hand, conjugate additions of the more stabilized anion **66** occur readily, and an example illustrating selective hydrolysis of dithioketals is presented in eqn (38).[154]

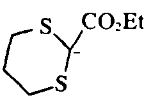


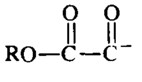
(Eqn. 38)

The related acyclic anion **68** also adds 1,4 to many unsaturated carbonyl compounds, but appears to be less reactive than cyclic analog **66**, as no conjugate addition occurred with enone **67** (see eqn 38) under a variety of conditions.[154,155] Anions **66**, **68**, and **69** (which has been used in α-keto ester synthesis)[156] are each the synthetic equivalent of the carbonyl anion **70**, formally derived from an alkyl glyoxalate.[†]


$CH_3O_2C-\overset{SEt}{\underset{SEt}{C^-}}$

68


69


$RO-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}^-$

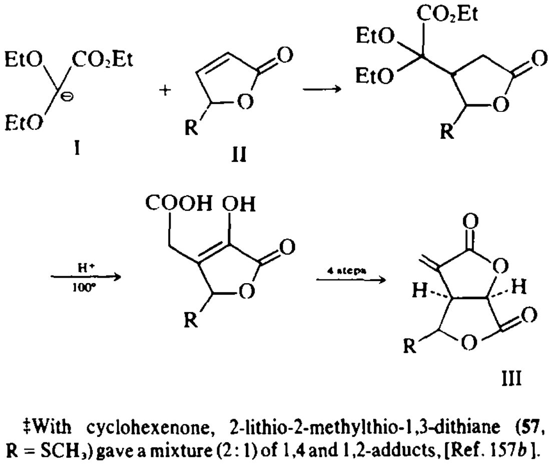
70

As with **66** and **68**, dithioacetal anions which are more strongly stabilized (see eqn 28, Section V.2) than lithiodithianes generally add 1,4 and not 1,2 to unsaturated carbonyl compounds. Conjugate additions have also been described with tris(phenylthio)methyllithium **71** [an alkoxycarbonyl (RO–CO⁻) synthon][157a],[‡] and lithiated bis(methylthio)silylmethanes [$(MeS)_2CLi(SiMe_3)$],[158] with lithium cuprates **72** derived from bis(phenylthio)acetal anions (which can also serve as ketone precursors[159]),[139] and with anions of dithioacetal monosulfoxides (**73**).[160] More specifically, conjugate addition of **73** (R′=H or alkyl) occurs with unsaturated esters; with enones, **73** (R′=alkyl) gave Michael products whereas **73** (R′=H) gave carbonyl adducts.[160]

Anions (**73**, R=CH_3 or C_2H_5) of alkyl alkylthiomethyl sulfoxides play a broad role as acyl anion equivalents. Reactions of **73** with electrophiles[160–169] have been studied principally by Schlessinger and his group and by Ogura, Tsuchihashi *et al.* Catalytic amounts of aqueous perchloric acid or mineral acids suffice to liberate the

---

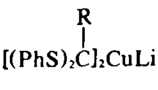
[†] The first conjugate addition of a fully oxygenated equivalent of acyl anion **70** has been accomplished [R. E. Damon and R. H. Schlessinger, *Tetrahedron Letters* 4551 (1975)] whereby the anion (I) of ethyl diethoxyacetate was added in Michael fashion to butenolide II (R = n-C_8H_{17}) in a synthesis of the antifungal bis-lactone *d,l*-4-isoavenaciolide (III; 51% overall from II).



[‡] With cyclohexenone, 2-lithio-2-methylthio-1,3-dithiane (**57**, R = SCH_3) gave a mixture (2 : 1) of 1,4 and 1,2-adducts, [Ref. 157*b*].

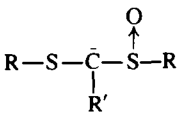
$(PhS)_3CLi$

71



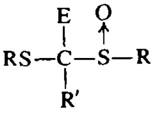
$[(PhS)_2\overset{R}{C}]_2CuLi$

72



$R{-}S{-}\overset{-}{\underset{R'}{C}}{-}\overset{O}{\overset{\uparrow}{S}}{-}R$

73

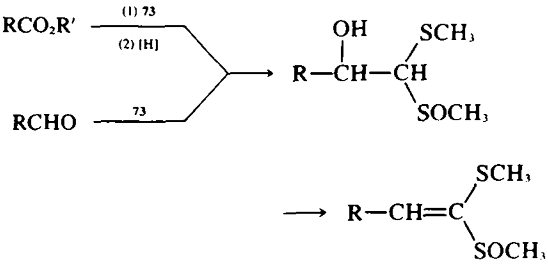


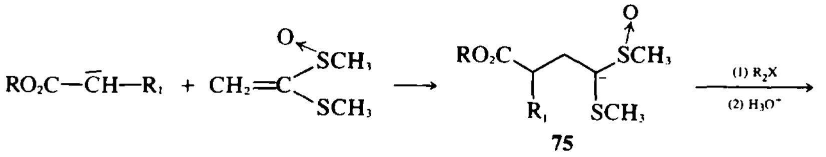
$RS{-}\overset{E}{\underset{R'}{C}}{-}\overset{O}{\overset{\uparrow}{S}}{-}R$

74

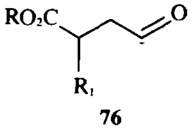
carbonyl from adducts **74**, but mercury ion-assisted hydrolysis may also be used.[162,166] Alkylation, acylation, and reactions of **73** with carbonyl compounds each lead to the expected products, and have been utilized in synthesis of aldehydes,[161–163] acyclic[162,164] and cyclic ketones,[165] α-dicarbonyl compounds,[166] and α-ketols;[166,167] an α-amino acid synthesis is achieved by addition of **73** to nitriles.[168]

Ketene thioacetal monosulfoxides can be prepared from the reaction products of anions **73** with esters or aldehydes (an alternative route[14a] may be more suitable for large scale preparation).[160,169] These compounds are Michael receptors for enamines, sodium enolates of β-dicarbonyl compounds, and lithium enolates of esters, and have already been mentioned in the Introduction (see **5**) as synthetic equivalents of α-acyl carbonium ions (R-CO-CH_2^+).[14] A simultaneous function as a ketene dipole ($^+CH_2CO$) can also be achieved by alkylation of the Michael intermediate **75** followed by hydrolysis (eqn 39).[146] Anion **75** as written is a γ-carbalkoxyacyl anion (**76**) synthon, but when the enolate **77** is a more stable anion than **75** (e.g. when R_1=CO_2R or vinyl), conversion of **75** to **77** occurs, and alkylation and hydrolysis then lead to β-formyl ester derivatives.[146]





(Eqn. 39)



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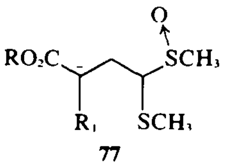
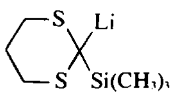


77

Ketene thioacetals **80** have also proven to be versatile intermediates. These compounds are most conveniently prepared from aldehydes and ketones with metalated silyldithiane **78** or related acyclic reagents,[170–173] or from methyl esters and bis(dimethylaluminum)1,3-propanedithiolate **79**.[174] As shown in eqn (40), ketene thioacetals can be metalated (n-BuLi/HMPA or LDA) to form the allylic anions **81**, which alkylate almost exclusively at the 2-position of the dithiane moiety.[174,175] Thus anions **81** are masked, α,β-unsaturated acyl anion synthons.



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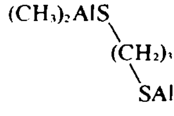

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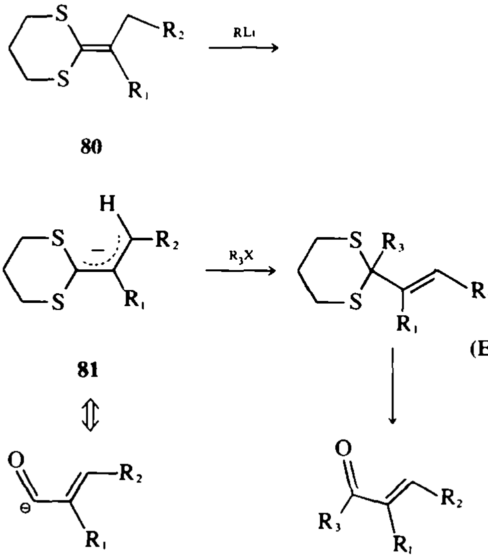
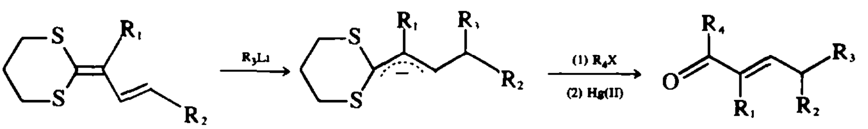


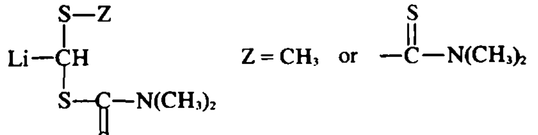
(Eqn.40)

Ketene thioacetals (**82**) from α,β-unsaturated carbonyl compounds provide access to another interesting hypothetical intermediate, a vinylogous ketene dipole: $^+CH_2CH{=}CH{-}CO^-$. In this system the vinyl anion can be generated by nucleophilic attack of an organolithium reagent at the terminus, and alkylation again occurs next to sulfur as shown in eqn (41).[176] Ketene thioacetals have been employed in other reactions of synthetic interest.[171,177] For example, the reductive nucleophilic acylation of carbonyl compounds to the homologous aldehyde ($R_2CO \rightarrow R_2CHCHO$) is discussed in Section VIII.

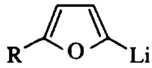
New acetal-like reagents for nucleophilic acylation continue to surface (cf. the metalated dithiocarbamate reagents **83**[178,179] for aldehyde synthesis), and this area will

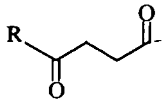

(Eqn. 41)

certainly continue to expand in method and in scope. Perhaps equally important is the stimulus for research in the general area of nucleophilic acylation which was provided by the pioneering studies of Corey and Seebach[124] on lithiodithianes a decade ago.

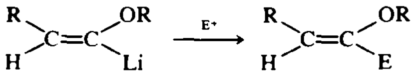

83

5. *Metalated enol derivatives as masked acyl anions.* As was shown in Scheme 3, metalation of a protected enol, e.g. an enol ether, followed by reaction with an electrophile and hydrolysis is a general approach to nucleophilic acylation. First obtained by Gilman and Breuer over forty years ago,[180] the oldest reagents of this type are metalated furan derivatives **84**, which are now most conveniently formed by reaction of the furan with n-butyllithium.[181-183] Ramanathan and Levine demonstrated in 1962 that 2-furyllithium (**84**, R=H) reacted with a variety of electrophiles,[181] and synthetic applications of metalated furans has continued,[184] although rarely as a method for nucleophilic acylation. However, furans are converted to 1,4-dicarbonyl compounds upon hydrolysis; thus metalated intermediates **84** are masked γ-keto acyl anions **85**. This property was utilized by Büchi and Wüest in an efficient (40-45% overall yield) conversion of 2-methylfuran to *cis*-jasmone (eqn 42).[185]


84

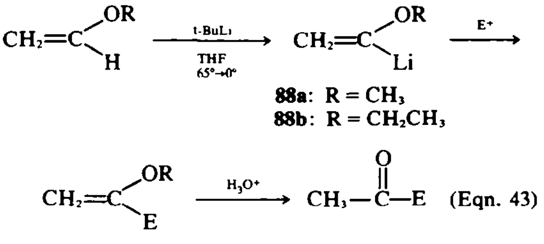

85

Until quite recently the formation and reactivity of metalated acyclic enol ethers had not been explored in detail. There are two particularly attractive features in this approach. First, enol ethers are hydrolyzed to carbonyl compounds under extremely mild acidic conditions. This is an advantage not shared by dithioacetal reagents and could offer a new approach to synthesis of sensitive materials. Secondly, in contrast with most of the masked acyl anions, metalated enol ethers **86** provide adducts with electrophiles (**87**) in which the latent carbonyl is protected with a type of functionality (enol ether) that could be transformed in ways other than simple hydrolysis. Thus, this approach could lead not only to products of nucleophilic acylation but also to more elaborate structural modifications.

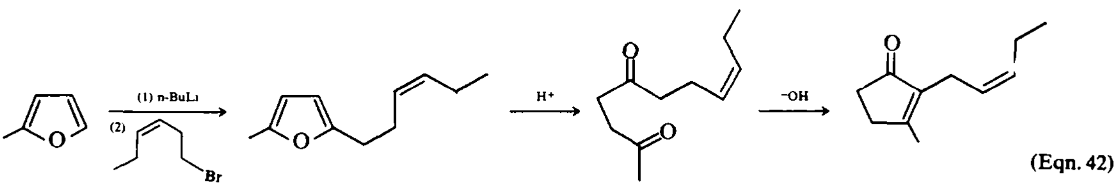

86 **87**

It has been shown in Baldwin's laboratory that methyl vinyl ether is metalated quantitatively in the α-position by addition of t-butyllithium in pentane to a cold (−65°) solution of the enol ether in tetrahydrofuran (THF) and subsequent warming to ca. 0°.[186] A brilliant yellow precipitate present at low temperature forms even when the enol ether is absent and is apparently a solid complex of t-butyllithium and THF (stoichiometry 2:1) which has been described previously.[187] As the solution is allowed to warm the precipitate dissolves (ca. −45°) and between −5° and 0° the yellow color fades sharply; the solution remains colorless and homogeneous when recooled to −65°, and this indicates complete formation of α-methoxyvinyllithium (MVL) **88a**, the synthetic equivalent of the acetyl carbanion (CH_3CO^-). Metalation of ethyl vinyl ether proceeds similarly to **88b** (EVL).

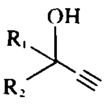
Solutions of MVL or EVL prepared in the above manner react smoothly at low temperature with a broad array of electrophiles to furnish adducts **89** which may be isolated (75–95% yield) and characterized or may be converted directly to carbonyl compounds **90** upon gentle acidic hydrolysis (e.g. aqueous methanolic 0.02 N HCl, 25°).[186] By-products produced in the lithiation step (isobutane, excess vinyl ether) are volatile and since **88a** and **88b** exhibit excellent nucleophilic properties, the crude reaction products normally are sufficiently pure to be carried on in a synthetic scheme without further manipulation.


88a: $R = CH_3$
88b: $R = CH_2CH_3$
89 **90**
(Eqn. 43)

Schöllkopf and Hänssle[188] have described the metalation of ethyl vinyl ether in THF at −30° in the presence of N,N,N′,N′-tetramethylethylenediamine (TMEDA), but the product yield in the only reported reaction suggests that this procedure is less efficient than that described above.[186] Büchi and Wüest found that ethyl vinyl ether could be metalated at ambient temperature with n-butyllithium in THF-hexane,[189] and although two-thirds of


(Eqn. 42)

the vinyl ether is lost in this method, it may be of utility in large-scale work with inexpensive vinyl ethers. When the reaction is run in hexane, the desired products are accompanied by ethynyl carbinols (**91**) resulting from the addition of lithium acetylide to the carbonyl compound, and thus β-metalation, and subsequent decomposition of the β-lithio vinyl ether to acetylide ion, may be the secondary reaction consuming the reagent at room temperature. However, ethynyl carbinols are not observed when the metalation is carried out in the presence of THF, and adducts (**92**) with carbonyl compounds are formed in excellent yields when the carbonyl substrate is the limiting reagent (ca. 0.3 equiv).[189]



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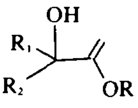
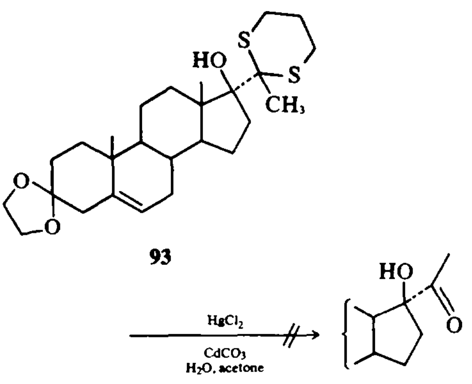


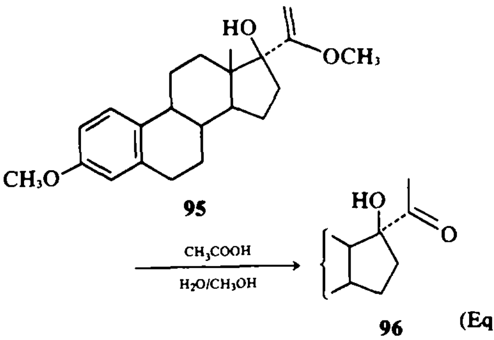
92

Masked acyl anions of the type RCH_2CO^- are obtained when enol ethers bearing alkyl β-substituents are metalated with t-butyllithium in the presence of TMEDA by allowing the cold (−70°) mixture to warm slowly to ambient temperature.[186] The solution should be returned to low temperature prior to addition of an electrophile (eqn 44). Schlosser found that metalation could be effected at −78° with a combination of sec-butyllithium and potassium t-butoxide when the enol was protected as a tetrahydropyranyl ether (eqn 45).[190] Attempts to prepare and utilize α-lithio-β,β-disubstituted enol ethers have been without success, presumably because of the added inductive effect of the second alkyl β-substituent.[186,191]



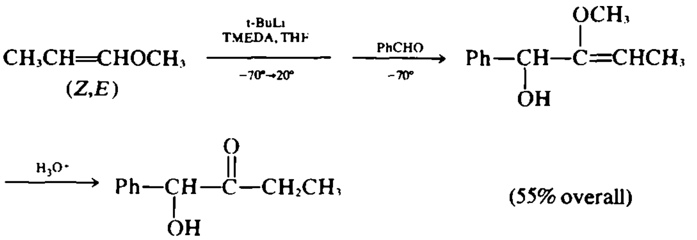
93

94 (Eqn. 46)



95

96 (Eqn. 47)

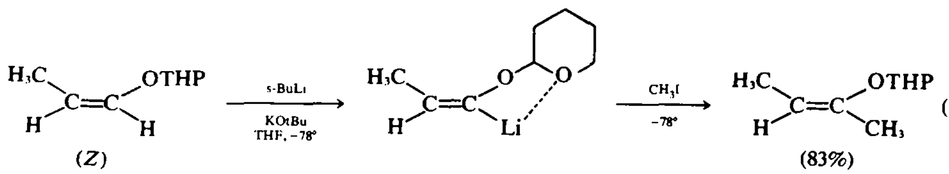


$$\underset{(Z,E)}{\mathrm{CH_3CH{=}CHOCH_3}} \xrightarrow[-70^\circ\to 20^\circ]{\text{t-BuLi, TMEDA, THF}} \xrightarrow[-70^\circ]{\text{PhCHO}} \mathrm{Ph{-}\underset{OH}{\underset{|}{C}H}{-}\overset{OCH_3}{\overset{|}{C}}{=}CHCH_3}$$

$$\xrightarrow{H_3O^+} \mathrm{Ph{-}\underset{OH}{\underset{|}{C}H}{-}\overset{O}{\overset{\|}{C}}{-}CH_2CH_3}$$

(Eqn. 44)

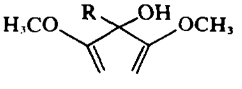
(55% overall)



(Eqn. 45)

Reactions of metalated enol ethers with aldehydes and ketones proceed readily to form hydroxy enol ethers (cf. **92**) and thence the α-ketols upon hydrolysis. The advantage offered by facile hydrolytic procedures is illustrated with the examples in eqns (46) and (47). Attempted mercury(II)-assisted hydrolysis of dithiane **93** (formed in 59% yield from reaction of the corresponding 17-keto steroid and 2-lithio-2-methyl-1,3-dithiane) led to complicated reaction mixtures in which none of the expected ketol **94** could be detected.[117c] In contrast, adduct **95** was obtained from MVL and estrone methyl ether in 74% yield and was hydrolyzed smoothly (76%) with methanolic aqueous acetic acid to ketol **96**.[186]

Lithio vinyl ethers are alkylated† by primary iodides or allylic halides and are acylated by aromatic acids (0.5 equiv) or nitriles. Aliphatic or aromatic esters add two equivalents of reagent to give bis-adducts. For example, the interesting bis-enol ethers **97** are formed from esters and MVL and upon hydrolysis give α-hydroxy-β-dicarbonyl compounds **98**;[186] these compounds are not readily accessible by procedures other than nucleophilic acylation.[192]



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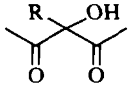

98

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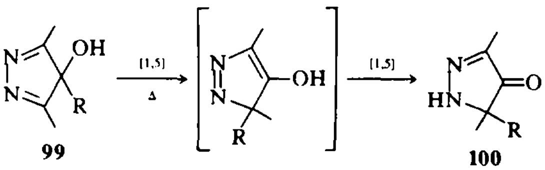
†For the preparation of acyl silanes via EVL and halosilanes see E. M. Dexheimer and L. Spialter, *J. Organometal. Chem.* **107**, 229 (1976).

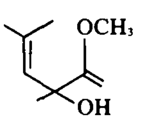
Hydroxy diones **98** condense readily with hydrazine hydrate to furnish 4-hydroxy-4-substituted pyrazoles **99**, which upon being heated briefly in the melt undergo a facile thermal reorganization to 2-pyrazolin-4-ones (**100**).[193] Isopyrazoles with two alkyl or aryl substituents in the 4-position are known,[194a] but isopyrazoles **99** appear to be the first examples where one of the substituents is hydroxyl. Also, although several 2-pyrazolin-4-ones have been described,[194b] the present rearrangement is a novel and direct synthetic approach to these compounds. The rearrangement undoubtedly occurs via two sequential [1,5] shifts (eqn 48) and is related to the Van Alphen–Hüttel rearrangement of geminally disubstituted pyrazolenines.[195] This overall sequence, $RCO_2R_1 \rightarrow$ **100**, is an example of nucleophilic acylation in which extensive elaboration of the original electrophilic center has been achieved (Section VIII).



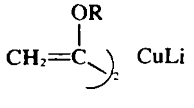
99 **100**

(Eqn. 48)

With unsaturated carbonyl compounds, metalated enol ethers give exclusively the products of carbonyl addition (e.g. **101** from mesityl oxide and MVL); this mode of reactivity is complemented by conjugate additions of the copper "ate" complexes **102** of MVL and EVL.



101

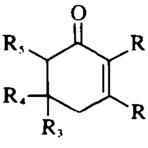


a: $R = CH_3$
b: $R = C_2H_5$

102

Cuprate **102b** has been formed by addition of an EVL solution to cuprous iodide suspended in THF at −78°, and subsequent warming to ca. −30° to complete the reaction;[196] cuprate **102a** has been prepared from MVL and a THF solution of cuprous iodide and dimethyl sulfide at −40°.[197] Mixed cuprates (e.g. with 1-pentynylcopper) can be formed from which only the vinyl ether ligand is transferred to the enone,[196] and this permits efficient utilization of more valuable enol ethers.

Examples of Michael additions of cuprates **102** to cyclohexenones **103** are given in Table 2. These data show that, while the yield of 1,4-adduct **104** is not markedly affected by substitution at C-2, C-5 or C-6, these reagents are acutely sensitive to additional substitution in the β-position;[196,197] a similar effect was found with acyclic enones.[196]



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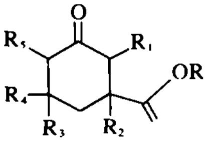


104

Enol ethers **104** give 1,4-diketones under mild hydrolytic conditions. When the diketone is very sensitive to traces of acid, contact of **104** with wet silica gel suspended in benzene is a particularly gentle hydrolytic procedure.[196] Chavdarian and Heathcock demonstrated that adducts **104** were converted efficiently to γ-keto esters upon ozonolysis (eqn 49).[197] This observation establishes a synthetic equivalency between cuprate **102** and the alkoxycarbonyl anion ($ROCO^-$) in conjugate additions, and is an alternative to the use of trithiocarbanion **71**[157] in γ-keto ester synthesis.

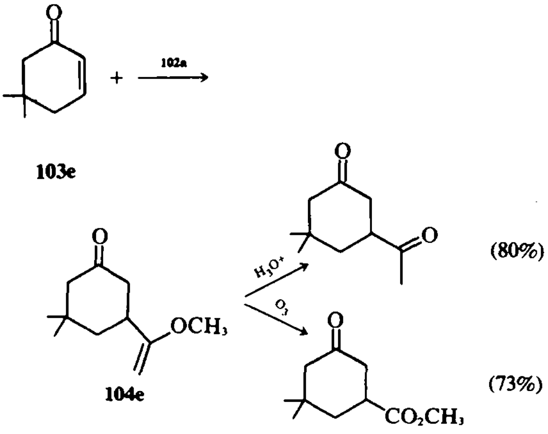
Table 2. Yield of Michael adducts from cuprates **102** and enones **103**

Reagent	Enone	R_1	R_2	R_3	R_4	R_5	Yield (%) of **104**
102a	**103a**	H	H	H	H	H	66
102b	**103a**	H	H	H	H	H	84
102b	**103b**	H	H	H	H	CH_3	90
102b	**103c**	H	H	H	H	*i*Pr	78
102b	**103d**	CH_3	H	H	H	H	80
102a	**103e**	H	H	CH_3	CH_3	H	67
102a	**103f**	H	CH_3	CH_3	CH_3	H	< 20
102b	**103g**	H	CH_3	H	H	H	< 10

Cuprates **102** couple efficiently with allylic and benzylic bromides (MVL itself gave halogen-metal exchange with benzyl bromide), but are unreactive toward alkyl halides.[196,197] Attempts to open cyclohexene oxide failed with cuprate **102b**[196] as well as with uncomplexed MVL.[191]

Metalated vinyl thioethers **105**, formed from the corresponding vinyl sulfide[198] and sec-butyllithium at −78°, have also been used as nucleophilic acyl equivalents.[199] These reagents react at −78° with halides, aldehydes, and with terminal epoxides; hydrolysis can be carried out with mercuric ion in aqueous acetonitrile (see eqn 50).[199–201]

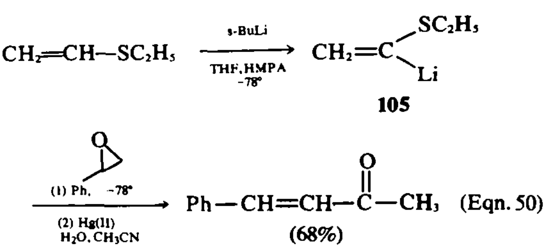
Metalation of 2-alkoxy-1-alkyl (or aryl) thioethylenes occurs essentially quantitatively adjacent to sulfur to form **106**.[199b] At −70°, these anions form adducts with



103e

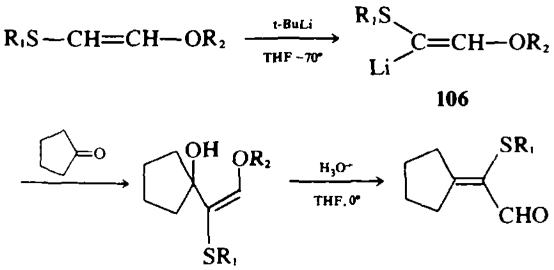
104e

(Eqn. 49)



105

carbonyl compounds, and also with halides and epoxides in the presence of HMPA.

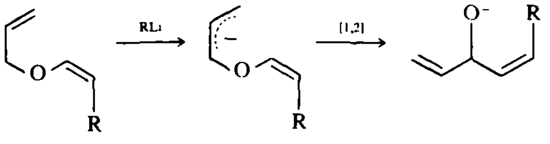


106

Certain metalated enol derivatives are synthetic equivalents of α,β-unsaturated acyl anions. The metalated methoxybutadiene **107** is a crotonyl anion synthon,[186] and carbanions formed from allenic ethers undergo alkyation and carbonyl addition to furnish allenes **108**, which are converted into unsaturated carbonyl compounds upon mild hydrolysis (eqn 51).[204,205]

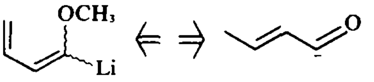
Carlson[206,207] has devised synthetic equivalents of the β-acyl carbonyl anions **111** by appropriate substitution in the allenic anion, which in these cases is formed by deprotonation of the corresponding substituted acetylene.

When vinyl and allylic (or benzylic) sites are both available in a single ether, it was recently shown that metalation usually occurs at the allylic (or benzylic) position, and the resulting anion (**112**) undergoes a facile anionic [1,2] migration of the vinyl group from oxygen to carbon.[208] The products thus obtained are alcoholates of divinylcarbinols (or benzylvinylcarbinols) **113**, and the geometry of the migrating group is preserved; rearrangement normally occurs too rapidly to permit alkylation at carbon.



112 **113**

Steric effects suppress allylic lithiation in the allyl vinyl ether **114**, and metalation occurs in approximately equal degree at the α- and β-positions of the vinyl group. The β-lithio derivative fragments to acetylene and alcoholate, while the α-lithio compound undergoes another type of [1,2] shift (eqn 52).[208]



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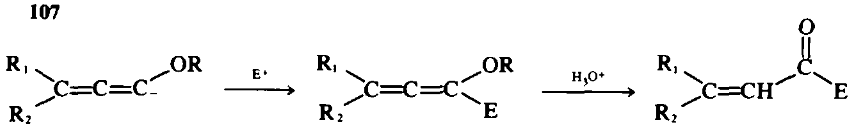
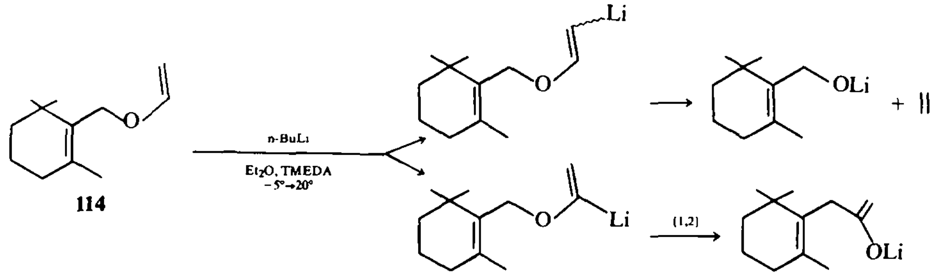


108

(Eqn. 51)



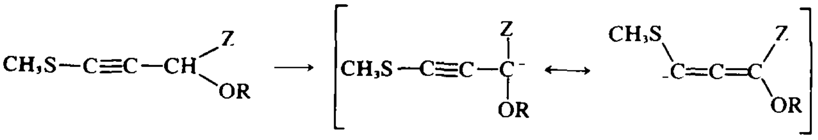
114

(Eqn. 52)

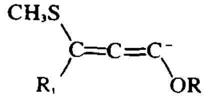
Thus, anions **109a** and **109b** react in the allenic form, and are synthons for carbonyl anions **111a** and **111b**. Furthermore, alkylation of anion **109a** followed by deprotonation leads to allenic anion **110** which is a synthon for carbonyl anion **111c**.[207]

Metalated allyl alkyl ethers and thioethers were cited earlier (cf. **1**) as β-acyl carbanion (RCOCH$_2$CH$_2^-$) equivalents.[5,6] On the other hand, metalated vinyl ethers and thioethers are carbonyl anion (RCO$^-$) synthons.

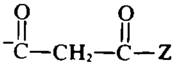
Metalated enol ethers and related intermediates are now firmly established as useful masked acyl anion equivalents. Several advantages to this method were pointed out in the foregoing discussion, and there are many unexplored facets of the chemistry of the reaction products of these reagents with electrophiles. The latter concept is illustrated briefly by the spiroannelation sequence shown below, whereby the adduct **115** from MVL and cyclohexanone is converted under Simmons–



109a: Z = H
b: Z = OR

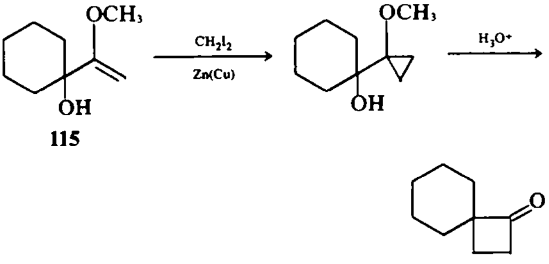


110



111a: Z = H
b: Z = OR
c: Z = R$_1$

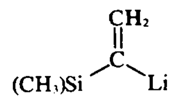
Smith conditions to the corresponding methoxycyclopropyl carbinol,[209] which rearranges smoothly to the versatile synthetic intermediate **116**[210] during hydrolytic workup.



115

116

Lithiated vinyl silane **117**[211] and cuprate **118**[212] are conceptually and structurally linked to metalated enols. These reagents are masked acyl anions since vinyl silanes are converted to carbonyl compounds by β-elimination of the corresponding epoxysilanes under acidic conditions.[213]



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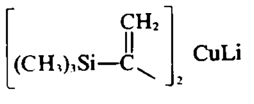
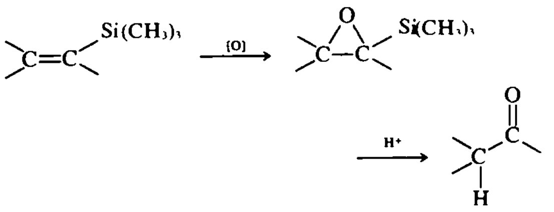
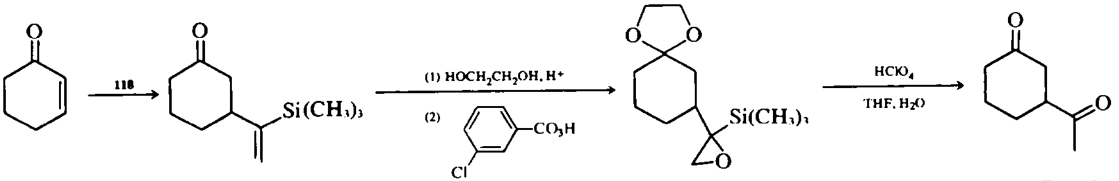


118



Gröbel and Seebach prepared lithio compound **117** in three steps from tris(trimethylsilyl)methyllithium and obtained the expected products from reactions of the reagent with several electrophiles.[211] Although this method is unlikely to be used routinely because of complicated reagent preparation and unmasking procedures, the derived cuprate **118** has been demonstrated by Boeckman and Bruza to add efficiently in Michael fashion to transoid cyclic α,β-unsaturated ketones.[212] In contrast with copper complexes **102** of MVL and EVL,[196,197] conjugate additions of cuprate **118** proceed readily with β,β-disubstituted enones (see eqn 9, Section III.2[55] and 31,[71] Section IV.2). However, conversion of the Michael adducts to γ-diketones may entail an additional carbonyl protection step prior to epoxidation in order to circumvent Baeyer–Villiger oxidation with peracid. After ketalization and epoxidation, 3-acetylcyclohexanone was obtained in moderate yield by hydrolysis of epoxysilane **119** (eqn 53).[212]



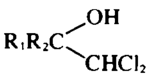
119

(Eqn. 53)

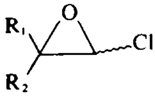
6. *Dihaloalkyllithium reagents.* Dichloromethyllithium (**120**), first prepared by Köbrich,[214] is a formyl anion (HCO^-) synthon. This compound is formed by metalation of dichloromethane at low temperature[214b] and adds to carbonyl compounds (R_1R_2CO) to give, depending upon the experimental conditions, dichloromethyl carbinol **121**, chloroepoxide **122**, or α-chloroaldehyde **123**.[214a] Epoxide **122** is a precursor to aldehyde **123**,[215] and α-hydroxyaldehydes can be obtained by hydrolysis of either **121**[216] or **123**.[215]

$LiCHCl_2$

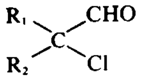
120



121

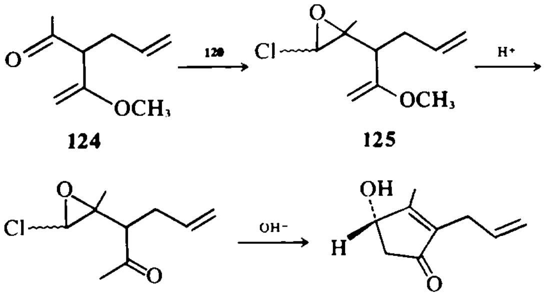


122



123

In Büchi's group, dichloromethyllithium has been used in the key step of a synthesis of allethrolone as shown in eqn (54).[217] Chloroepoxide **125** gives allethrolone (**126**: 72% yield based on enol ether **124**) when treated with dilute aqueous methanolic barium hydroxide at room temperature.

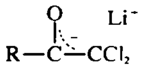


124 **125**

126 (Eqn. 54)

Dibromomethyllithium [$LiCHBr_2$] formerly was best obtained by metalation of dibromomethane with dichloromethyllithium,[214a] but a recently described metalation using lithium diisopropylamide appears more convenient.[218] Also recently described are the preparation and reactions with electrophiles of the functionalized dihaloalkyllithiums **127**,[219] **128**[220] and **129**.[221] The site of bond formation in reaction of ambident nucleophile **129** is determined by the structure of the carbonyl substrate.[221]

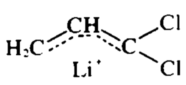
7. *Other nucleophilic formylating reagents.* In addition



127

$LiCCl_2—CO_2R$

128



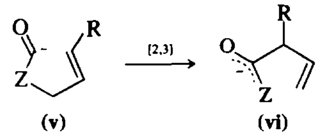
129

to 2-lithio-1,3-dithiane (**56**, R=H) and the other formyl anion equivalents already discussed (cf. **25**, **49**, **73** (R′=H), **83** and Section VIII), there are other reagents which transfer a nucleophilic formyl group. For instance, tosylmethylisocyanide **130** reacts with carbonyl compounds in the presence of equivalent amounts of thallium(I) ethoxide to give 4-ethoxy-2-oxazolines (**131**) which yield monomeric α-hydroxyaldehydes upon hydrolysis (eqn 55).[222-224]

Carbenes which are flanked by two heteroatoms are stabilized by contribution from resonance forms which render the divalent carbon potentially nucleophilic $(\mathrm{X{-}\bar{C}{=}\overset{+}{Y}} \leftrightarrow \mathrm{X{-}\ddot{C}{-}Y} \leftrightarrow \mathrm{\overset{+}{X}{=}\bar{C}{-}Y})$. Nucleophilic transfer of the masked acyl function can be achieved,[225,226] and an example of aldehyde synthesis from halides using a nucleophilic triazole carbene is shown in eqn (56).[226] Alkylation of carbene **132** with primary iodides gives the triazolium iodide **133**; reduction and hydrolysis lead to the formylated product (see eqn (57), following section).

VI. INTRAMOLECULAR NUCLEOPHILIC ACYLATION BY [2,3] SIGMATROPIC REARRANGEMENTS

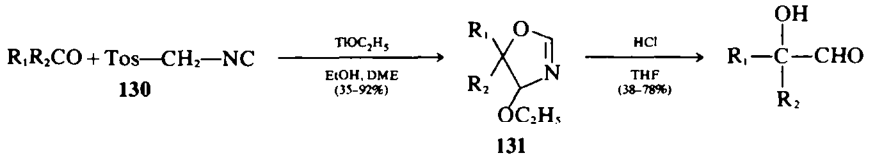
As seen in previous sections, cyclic ketones may be prepared from masked acyl anions and α,ω-difunctional electrophiles such as 1,n-dihalides.[47,94,128,165] An example of intramolecular conjugate addition of an acyl anion synthon was also given in eqn (25).[92] There is another group of intramolecular nucleophilic acylations which proceed via [2,3] sigmatropic rearrangements[227,228] schematically represented below (v → vi). These reactions simultaneously invert and homologate allylic systems.



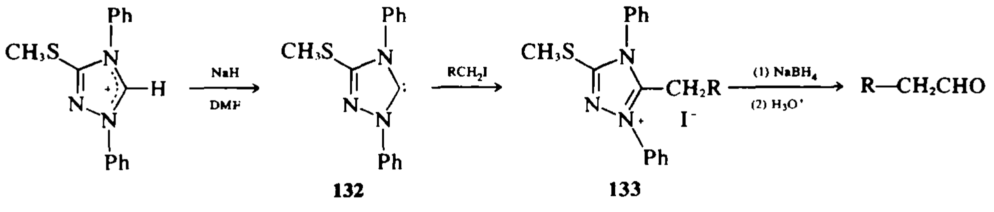
The first example of [2,3] rearrangement of a nucleophilic carbene (cf. eqn 56) was described by Baldwin and Walker, who found that carbene **134** (obtained from the tosylhydrazone) rearranges quantitatively to dithioester **135** (eqn 57).[229] Nucleophilic carbenes may also be involved in the conversion of certain allylic alcohols to rearranged homologous amides by thermolysis of the corresponding mixed amide acetals (eqn 58), as discovered in Büchi's laboratory.[230] The transformation can be carried out simply by heating an appropriate allylic alcohol with an N,N-dimethylformamide acetal.

Sequences using other masked acyl anions are given in eqns (59)–(61). Thus, [2,3] rearrangements of allylic dithianyl ylides (cf. **136**),[231,232] dichloro sulfonium ylide **137**,[233] and anions (**138**) of protected cyanohydrins[234] have each been reported. The methods recently developed in Gassman's group for ortho substitution of aromatic amines[235] and phenols[236] and for benzofuran synthesis[237] from phenols involve an aromatic ring in the [2,3] process (cf. eqn 62).

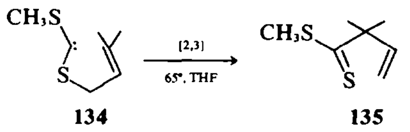
Despite the considerable attention devoted to reactions of masked acyl anions with external electrophiles, the



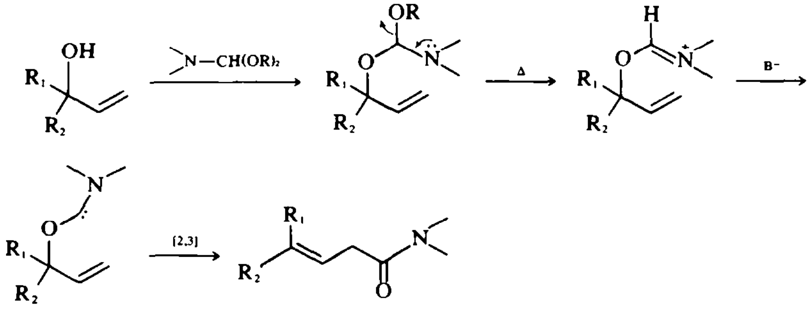
(Eqn. 55)



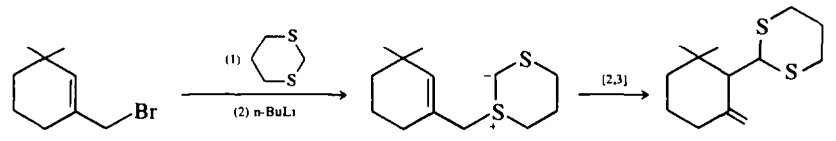
(Eqn. 56)



(Eqn. 57)

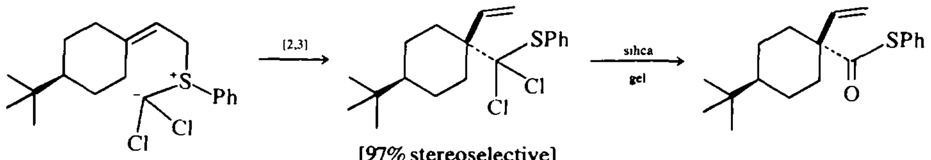


(Eqn. 58)



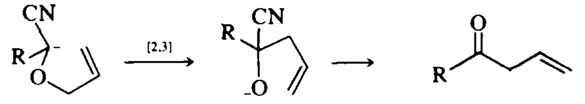
136 80%

(Eqn. 59)



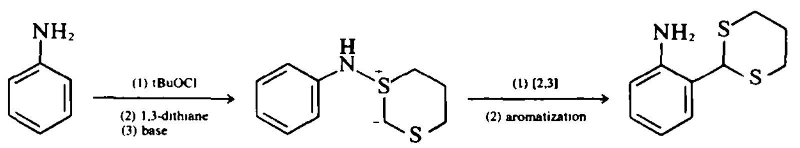
137 [97% stereoselective]

(Eqn. 60)



138 76%, R = $CH_2CH(CH_3)_2$

(Eqn. 61)



(Eqn. 62)

possibilities for intramolecular nucleophilic acylation have yet to be fully realized. One reason may be that these reactions have not heretofore been gathered together as examples of the general process v→vi. It is hoped that this brief survey will stimulate further work in this synthetically significant area.

VII. MASKED VINYLOGOUS ACYL ANIONS†

There are several methods which formally transfer a vinylogous acyl anion (**139**) to an electrophilic center. These processes reverse the polarity of the normally electrophilic β-carbon in an α,β-unsaturated carbonyl compound.

Corey has used 1,3-bis(methylthio)allyllithium **140** as a β-formylvinyl anion (**139**, R=H) synthon in reactions with halides, carbonyl compounds, and epoxides; the resulting vinyl sulfides **141** are converted to β-substituted-α,β-unsaturated aldehydes by mercury ion promoted hydrolysis.[238] Reaction of anion **140** with an epoxycyclopentane was instrumental in a total synthesis of prostaglandin $F_{2\alpha}$.[239]

The lithiated 2-allylthiothiazoline **142** is also a β-formylvinyl anion synthon. After an alkylation step, the unsaturated aldehyde is unmasked by sequential treatment with methyl iodide, then dimethylsulfoxide-sodium bicarbonate (eqn 63).[240]

More elaborately substituted α,β-unsaturated carbonyl compounds can be prepared with anions of γ-oxosulfone acetals (cf. **143**).[241a,b] The product structure varies with the initial substitution pattern in the anion and/or subsequent alkylations. Unmasking consists of carbonyl deprotection followed by elimination of benzenesulfinic acid at room temperature in basic media [e.g. $(C_2H_5)_3N$/THF or dilute aqueous NaOH]. The sequence is illustrated with the (±)-nuciferal synthesis outlined in eqn (64).[241a]

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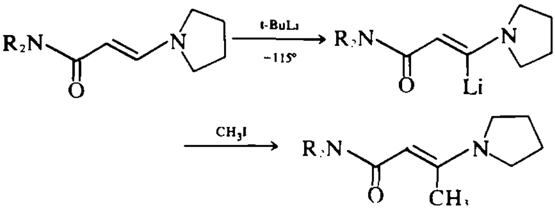
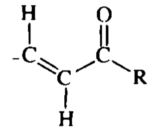
†An unmasked vinylogous carbamoyl anion has recently been reported [R. R. Schmidt and J. Talbiersky, *Angew. Chem.* Internat. Ed. Engl. 15, 171 (1976)]. Metalation of β-acylenamines with t-BuLi at −115° (at higher temperature addition reactions compete) occurs in the β-position. The anion once formed is stable at higher temperatures.





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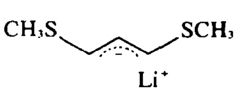

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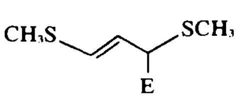

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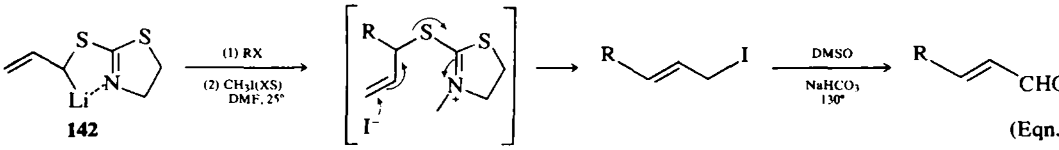
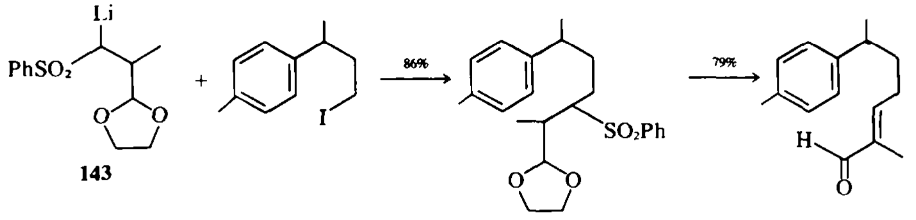


142

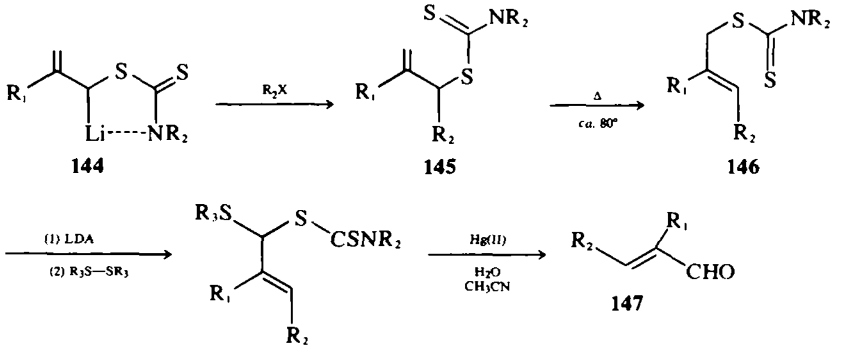
(Eqn. 63)



143

(Eqn. 64)

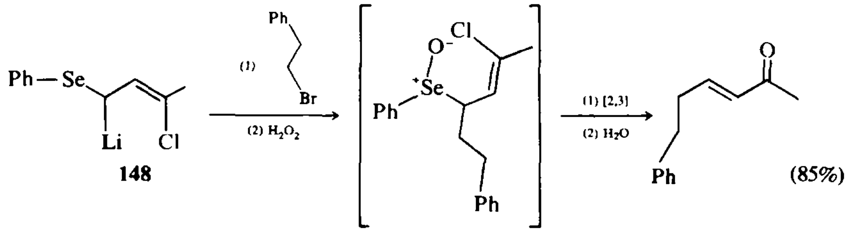
An interesting route to α,β-disubstituted-α,β-unsaturated aldehydes takes advantage of the facile [3,3] rearrangement of S-allyl dithiocarbamate **145**, obtained by regiospecific alkylation of the α-lithioallyl compound **144**, to the more stable isomer **146** (eqn 65).[242-244] Sulfenylation and hydrolysis in the presence of mercuric ion liberate the enal **147**.



144 **145** **146** (Eqn. 65)

147

Reich has recently shown that the metalated allylic selenide **148** is a synthon for the β-anion of methyl vinyl ketone [i.e. $CH_3CO{-}CH{=}CH^-$] in reactions with primary halides (eqn 66) and terminal epoxides.[245] Adducts were converted to the enones by [2,3] sigmatropic rearrangement of the corresponding selenoxides.[246]

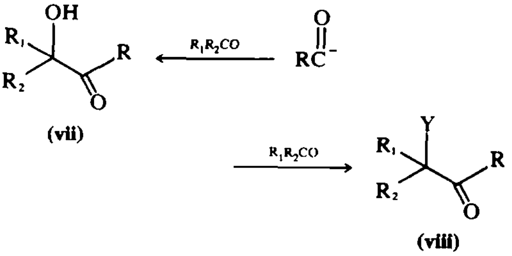


148

(Eqn. 66)

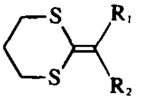
VIII. NUCLEOPHILIC ACYLATION WITH ELABORATION AT THE ELECTROPHILIC CENTER

The product normally obtained from nucleophilic acylation of a carbonyl compound is an α-ketol (**vii**). There are also reactions involving nucleophilic transfer of masked acyl functions which lead not to α-ketols, but to products (**viii**) in which the electrophilic center has been elaborated in some different way.



(vii) **(viii)**

Conversion of carbonyl compounds (R_1R_2CO) to the homologous aldehydes or ketones [$R_1R_2CH{-}CO{-}R(H)$] is an example in which an additional reduction at the electrophilic carbon has occurred. This transformation can be achieved in a variety of ways,[252] including (a) reduction and hydrolysis of ketene thioacetals **149** (cf. Section V.4);[171-173,247] (b) hydrolysis of vinyl ethers **151**[248] and vinyl thioethers[200,249] **153** prepared from carbonyl compounds and the Wittig reagent **150** or metalated phosphonate **152**, respectively; (c) oxidation of vinylboranes **155** obtained from carbonyl compounds and reagent **154**;[250] and (d) pyrolysis of the glycidic esters **156**,



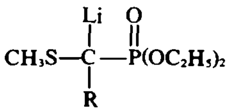
149

$Ph_3P{=}CHOCH_3$

150

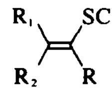
$R_1R_2C{=}CHOCH_3$

151

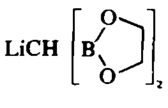


$CH_3S{-}C(Li)(R){-}P(O)(OC_2H_5)_2$

152



153



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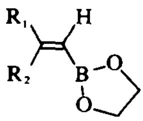

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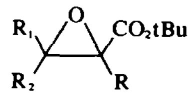
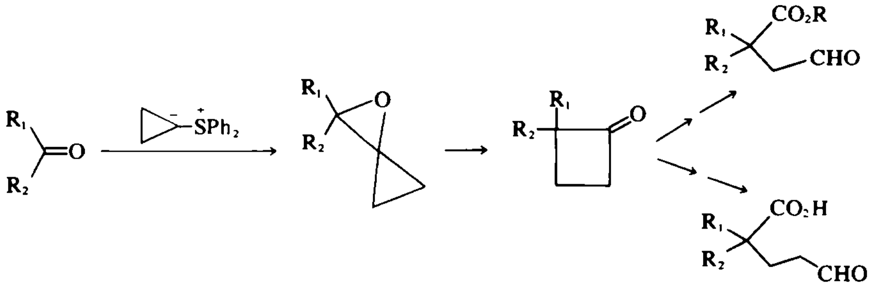


156

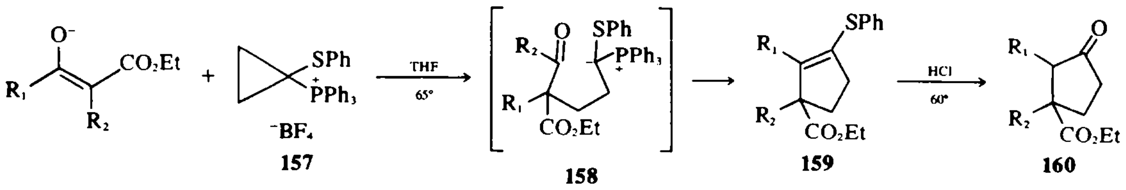
formed in the usual way.[251] Methods for reductive nucleophilic carboxylation ($R_1R_2CO \rightarrow R_1R_2CHCO_2R$)[169,173,177h,253,254,255b,c] and reductive cyanation ($R_1R_2CO \rightarrow R_1R_2CHCN$)[222,255a,256,257] are also available.

Moreover, the secoalkylation procedures[121,210,258,259] developed in Trost's group may be viewed as nucleophilic acylations in which the electrophilic carbon has been alkylated (e.g. eqn (67); cf. also **115**→**116** and eqn (48), Section V.5).

A recent cyclopentenone synthesis[260] is another example of elaborative nucleophilic acylation. The masked acyl anion is the ylide **158**, formed by treatment of the enolate of a β-keto ester with phosphonium salt **157** (eqn 68). The annelation sequence involves intramolecular Wittig condensation to form vinyl sulfide **159** followed by hydrolysis to keto acid **160**. From the net transformation, phosphonium salt **157** is the equivalent of the acyl zwitterion, $+CH_2$-CH_2-CO^-.[260]



(Eqn. 67)

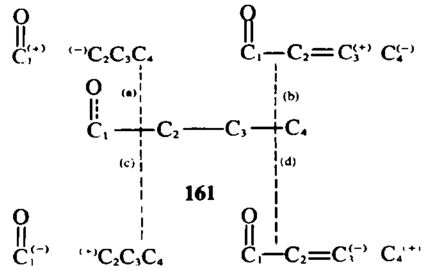


(Eqn. 68)

IX. CONCLUSION

Though the carbonyl anion *per se* remains for the most part an untamed and elusive chemical creature, there clearly are a number of more readily harnessed intermediates which may be used in its stead for the price of one or more additional manipulations. Moreover, the efficiency of many of these methods parallels that of classical carbonyl chemistry, and therefore practical alternative synthetic strategies are in hand.

Thus, when possible approaches to construction of the molecular unit **161** (Scheme 7)[261] are under examination, in addition to the classical procedures (a) and (b), methods utilizing synthons for acyl [cf. (c)] or vinylogous acyl [cf. (d)] anions also bear consideration. The best approach may be dictated by the nature of the most accessible fragments of the desired unit **161**. When a nucleophilic acylation sequence is most appropriate, reagent selection may be determined by the available "$O{=}C_1^-$" unit (e.g. halide or aldehyde, etc.) as well as by the compatibility of other functionality present with the unmasking procedures for the applicable reagents. Limitations on the electrophilic reaction partner have been mentioned in discussion of individual reagents, and the Report is concluded with several observations on methodology.



Scheme 7.

The substituent (R) in the acyl anion (RCO^-) synthon can be derived from a variety of functional types. When an organolithium reagent is the source (cf. **28**, **34**), an additional synthetic step is required if it is not among the commercially available reagents. Although aliphatic nitro compounds and carboxylic acids will likely receive increasing attention as more specific methods for carbonyl generation are available (Sections IV.3, V.3), the most widely useful reagents at present are formed from halides or aldehydes. Halides are homologated in conversion to acyl anion equivalents ($RX \rightarrow RCO^-$; e.g. dithianes and related reagents, Section V.4), while aldehydes provide synthons with unaltered carbon chains $RCHO \rightarrow RCO^-$; e.g. protected cyanohydrins and metalated enolic compounds, Sections V.2, V.5); methods using oxidative decarboxylation or decyanation (Sections IV.1, V.3) truncate the carbon chain by one unit.

Currently the most versatile and accessible reagents are metalated dithioacetal derivatives (Section V.4), metalated enolic compounds (Section V.5), and protected cyanohydrin anions (V.2). However, other methods, though more limited in overall scope, may provide the reagent of choice as a result of their particular selectivity (e.g. eqn 7) or reactivity (e.g. **28**, **31** and **118** in conjugate additions to β,β-disubstituted enones), or when a particular structural unit (e.g. carboxylic acids, cf. Section V.3) is most readily available as a precursor for the acyl anion equivalent.

The high level of current interest in nucleophilic acylation promises that new methodology will continue to unfold and to reveal new horizons in carbonyl chemistry.

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[261] In structure 161, the C_2–C_3 bond, traditionally formed by alkylation of the enolate $O{=}C_1{-}\bar{C}_2$ with an electrophilic $^+C_3C_4$ unit, in principle can be derived from a nucleophilic C_3C_4 unit and an α-acyl cation synthon ($O{=}C_1{-}C_2^+$): cf. **5**< = >**6**; Refs. 14–17.