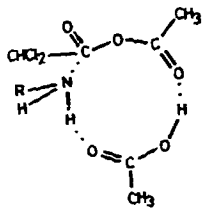

(V)

group in determining reactivity and the large autocatalytic effect of the acid product when reaction is conducted in aprotic media, this latter effect being approximately independent of the strength of the acid, which acts as a bifunctional catalyst, (V).[12] Cyclic transition states, like V, involving bifunctional catalysis by added catalyst, or by a second molecule of substrate, are proving very common, and are probably the rule, in acylations in aprotic solvents.[20] For the present reaction, in aqueous media the major product is the acetyl derivative quite simply because the haloacetyl group is the better leaving group. In benzene, where there exists no solvent H-bonding to assist leaving group departure, it would at first sight be expected that the influence of a good leaving group would be even more dominating, so that an even greater proportion of acetyl derivative would be formed. If the reaction were mainly spontaneous that would be so, but the products will usually arise principally from the autocatalytic path. In this latter route, because it is easier to place a proton on the acetyl than on the haloacetyl end of the anhydride, the former end will be lost preferentially (30b). It is difficult in this example to devise a satisfactory rationalisation involving carbonyl addition intermediates. On the whole in acylation any proposed mechanism for acid catalysis which does not incorporate important assistance of leaving group departure should be viewed with scepticism.

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Umpolung (dipole inversion) of carbonyl reactivity

Dieter Seebach and Michael Kolb

Reversal of normal reactivity of functional groups in organic chemistry has been termed symmetrisation,[1] dipole inversion[2a] or charge affinity inversion.[2b] To avoid confusion with other meanings of these words in chemistry we propose to use instead the term *umpolung*. As an example, the methods of *umpolung* of carbonyl reactivity are reviewed here, and some new results in this field obtained in Giessen are presented.

1 Irreversible *umpolung* in carbonyl additions

By nucleophiles, carbonyl groups can only be attacked at carbon as shown in Fig 1, I, III. *Umpolung* of this reactivity at first sight appears to be prevented by the position of the elements carbon and oxygen in the periodic chart, i.e. their electronegativity difference. Special electronic factors imposed by the groups attached to carbon, replacement of oxygen by less electronegative heteroatoms, and/or filling of antibonding orbitals with electrons may, however, cause electrophiles to attack carbon and nucleophiles to become bonded to the hetereoatom (Y in II, Fig 1), as exemplified by the reactions of equations (1)[3], (2)[4], and (3)[5]. For clarity, newly formed bonds are emphasised by thick lines in all equations.

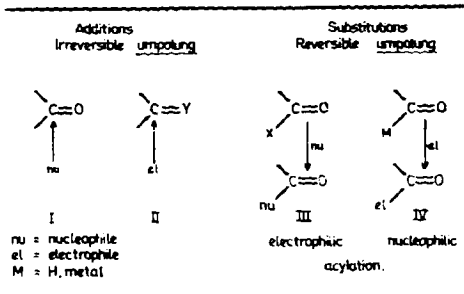
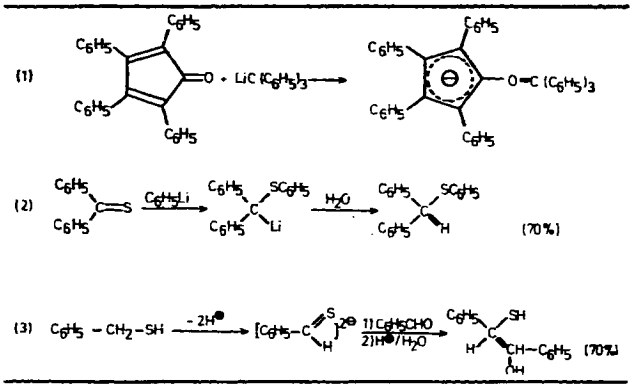


Fig 1



Reversed additions of this type lead to products which

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cannot be converted to carbonyl compounds except by oxidative processes. Therefore, this *umpolung* is called irreversible.

2 Principle of reversible *umpolung* of carbonyl reactivity

In view of the fact that carbonyl derivatives are the 'backbone of organic synthesis',[6] another kind of carbonyl *umpolung* is of much greater importance: acylations by nucleophilic acylating reagents (Fig 1, IV), in which the carbonyl carbon atom is rendered nucleophilic only temporarily or reversibly. This is evident from the conversion V→IX by a method outlined in Fig 2 which was actually the first practical solution[7] to the synthetic problem of nucleophilic acylation: an aldehyde V is converted into its thioacetal derivative VI, in which the sulphur atoms acidify the former aldehyde proton strongly enough for replacement by lithium; the 2-lithio-1,3-dithianes VII are highly nucleophilic equivalents of acyl anions $R-C^{\ominus}=O$ because after reaction with an electrophile (→ VIII) and hydrolysis of the protecting group, which at this stage has also done its job as *umpolung* group, a carbonyl compound IX is recovered, ready for normal carbonyl reactions. Thus, VII is a nucleophilic acylating reagent, and the overall reaction[8] V → IX is an electrophilic substitution of an $H^{\oplus}$ by a $D^{\oplus}$.

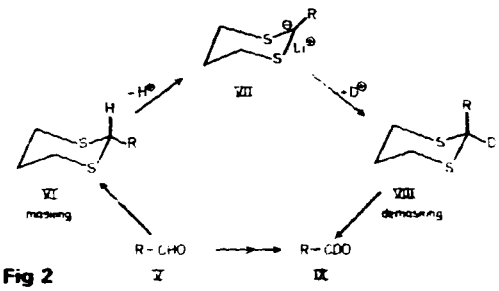


Fig 2

Classical methods of substitutive or additive nucleophilic acylations for the preparation of carboxylic acid derivatives and acyloins are reviewed in Fig 3, including the Kolbe reaction, the cyanohydrine reaction, the Strecker synthesis, the Passerini and Ugi reactions,[9] and the benzoin condensation.

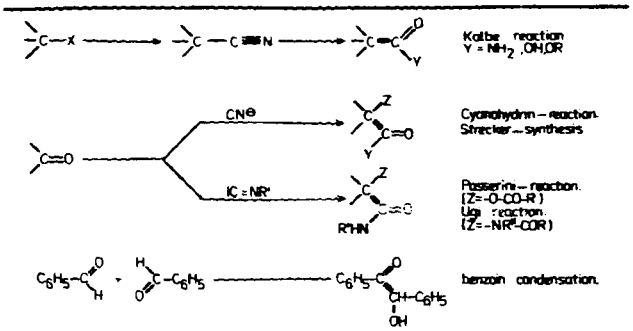
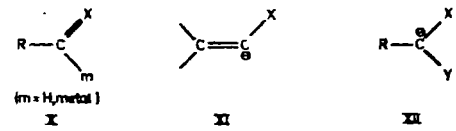


Fig 3

3 Methods of nucleophilic acylation

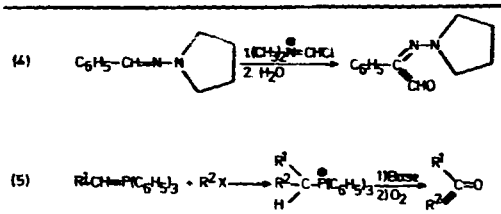
There are numerous new methods of nucleophilic acylation now available most of which evolved after the usefulness of this concept for aldehyde and ketone synthesis had been demonstrated by the dithiane method. They can be subdivided into three categories:

Unprotected acyl or acyl analogue derivatives X, vinylether type protected acyl anions XI, and acetal type protected compounds of type XII.



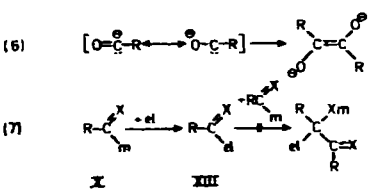
a) 'Direct' nucleophilic acylating reagents X

Reagents of this general formula with m = H are rather rare. It is, for instance, possible to attack certain aldehyde hydrazones with Vilsmeyer's reagent to do the overall transformation of equation (4).[10] A special case is reaction (5),[11] in which

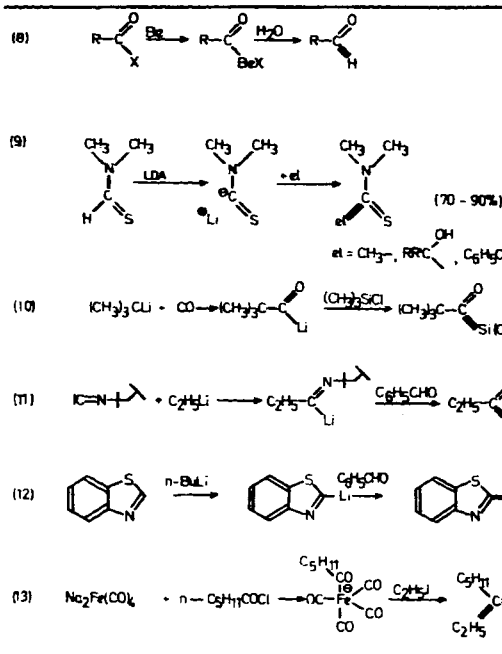


the electrophile R^2X is acylated using a phosphorous ylid as nucleophile.

Acylmetal derivatives X, m = metal, are difficult to generate and/or, once obtained, are either unstable, undergoing dimerisation as oxo-carbene anions, equation (6),[12] or are reactive only towards certain electrophiles. Thus, a reagent X, equation (7), is useful for acylation only if it does

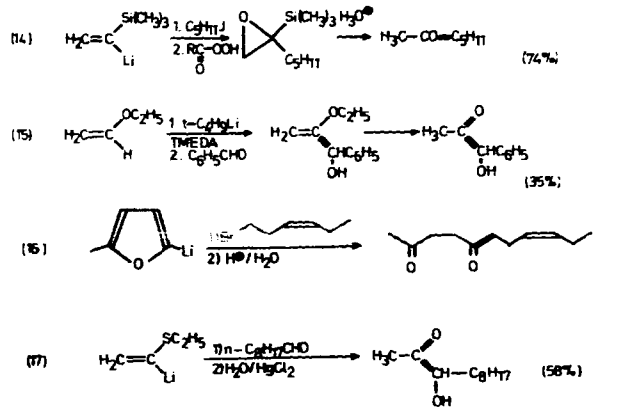


not attack its unprotected product XIII; the relative reactivities of X as a nucleophile and XIII as an electrophile can be delicately controlled by the choice of R (steric and electronic effects), X (electronegativity, bulk), m (electropositivity), and el (reactivity *versus* reactivity of XIII). Examples are given in equations (8),[13] (9),[14] (10),[15] (11),[16] (12),[17] and (13).[18,19]



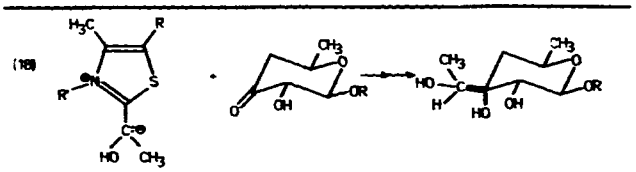
b) Vinylether type protected acyl anions XI

Until now, the heteroatoms X = silicon, oxygen, or sulphur in XI, have been used to achieve nucleophilic acylation. The products are protected against attack by their precursors. It is often difficult to prepare solutions of α-heterosubstituted vinyl alkali metal derivatives. Some recent carbonyl syntheses using this kind of nucleophilic acylation are outlined in equations (14),[20] (15),[21] (16),[22] and (17).[23]

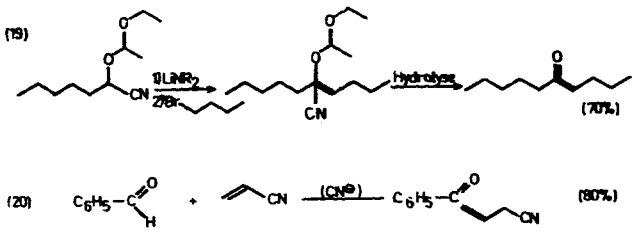


c) Acetal type protected reagents XII

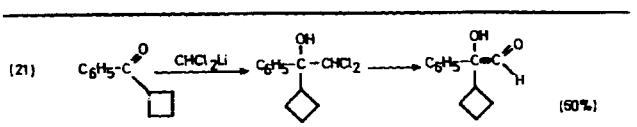
A reagent of this type is obviously used by nature. A thiamine-pyrophosphate derivative has been shown to be the responsible 'active aldehyde' in the formation of branched sugars[24] equation (18). Closely related[25] is the use of cyanohydrins or their derivatives. As in the benzoin condensation,[26] Fig 3,



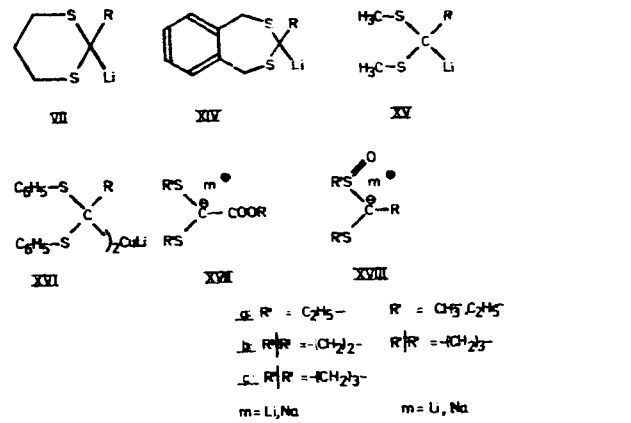
the acidifying effect of the nitrile group and the reversibility of cyanohydrin formation are used to convert an aldehyde into a masked acyl anion. Two new applications are shown in equations (19)[27] and (20).[28]



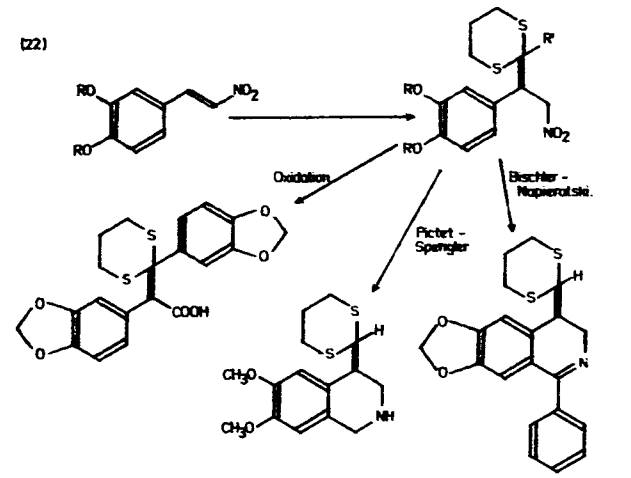
Although known[29] for many years, α-halo-alkyllithiums have only recently been recognised as potentially useful precursors for the preparation of aldehydes,[30] see equation (21).



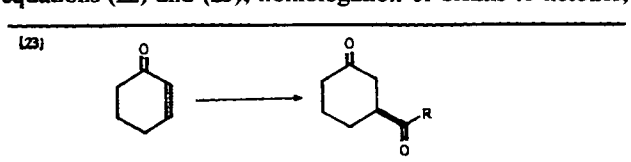
The now most widely applied method of nucleophilic acylation is the use of carbanions derived from thioacetals. Much recent work in this area has been devoted to the improvement of hydrolysis methods[31] (see step VIII → IX of Fig 2). Alkylative[31a] and oxidative[31b] hydrolyses became available as alternatives to the classical methods which employ heavy metals such as mercury.[32] Besides that, new electrophilic substrates and almost all conceivable variations of the metallated thioacetal system VII have been checked.



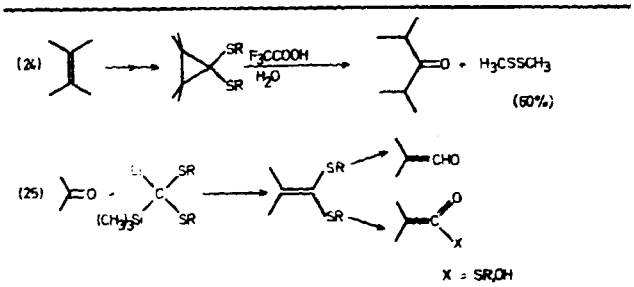
Thus, the dithiane ring was 'contracted', to us dithiolanes in XVIIb,[33] 'enlarged', to use a seven membered ring in XIV,[34] 'opened up', to use alkyl and aryl derivatives XV,[35,36] XVI,[37] XVIIa,[38] and XVIII,[39,40] one of the sulphurs was oxidised to the sulphoxide stage, XVIII, the substituent R was made anion stabilising as in XVIIa, b, and c,[41,42] and the metal Li was replaced by Cu in XVI and Na in XVII and XVIII. It is not possible to go into details about the results of all these investigations here.[43] They have brought about an appreciable expansion of the scope of nucleophilic acylation.



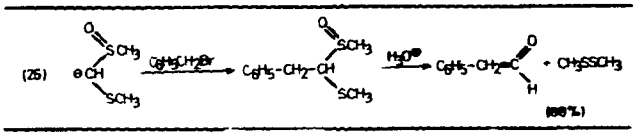
Some examples are: Michael-additions of the reagents VII,[41] XV, R = $(CH_3)_3Si$ and $(CH_3)_3Sn$,[44] XVI,[37] XVII[33,38,41] and XVIII, R′ = C_2H_5,[40] to unsaturated carbonyl compounds and to nitroolefins to give 1,3- and 1,4-dicarbonyl and 4-acyl-dihydro- and -tetrahydro-isoquinoline derivatives, equations (22) and (23); homologation of olefins to ketones,



equation (24), which can also be used as ring enlargement;[35] dithioolefination using silyl substituted metallated thioacetals, equation (25),[36,45,46] the product ketene thioacetals can be reduced and hydrolysed to aldehydes[45] or hydrolysed directly to thioesters[44] or acids,[47-49] (other uses of ketene thioacetals see section 4). Furthermore, some of the new thio-



acetal reagents XV–XVIII are less expensive to prepare (CH_3SH, C_2H_5SH are cheaper than propane-1.3-dithiol, cf. also $Na^{\oplus}$ instead of $Li^{\oplus}$ as counterion) and their products are less expensively (see above, hydrolysis methods without mercury) and more readily hydrolysed to free carbonyl derivatives, example see equation (26).[39b]



This lability to hydrolysis is however not always desirable as demonstrated in the synthesis[50] of pestalotin[51] XIX, Fig 4, where the protecting thioacetal group *must* survive before hydrolysis several synthetic steps carried out under a variety of conditions.

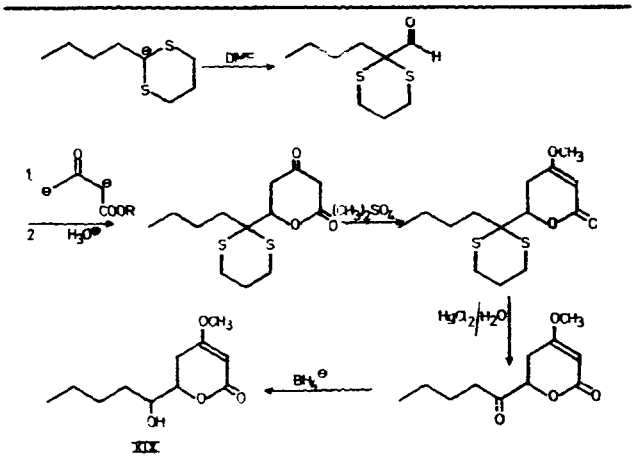


Fig 4

4 Vinylogous *umpolung* of carbonyl reactivity with ketene thioacetals

The versatility of carbonyl groups in synthetic operations is caused by the fact that the reactivity towards nucleophiles is transferred in conjugated systems XX, Fig 5, from the origin, C^1, to the other odd numbered carbons of the chain, for instance C^3 (Michael-addition); similiarly, $H^{\oplus}$-abstraction

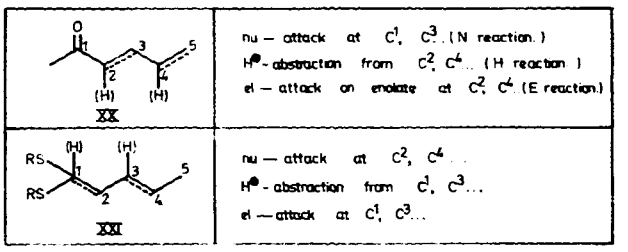
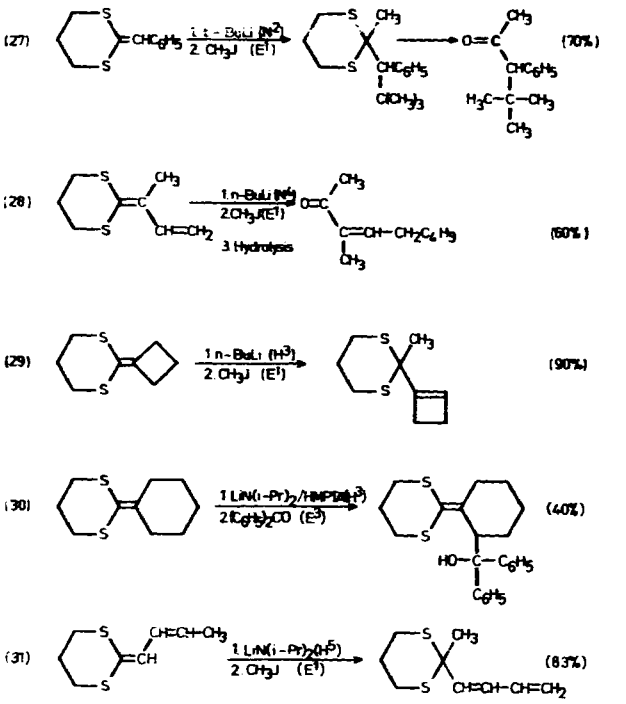
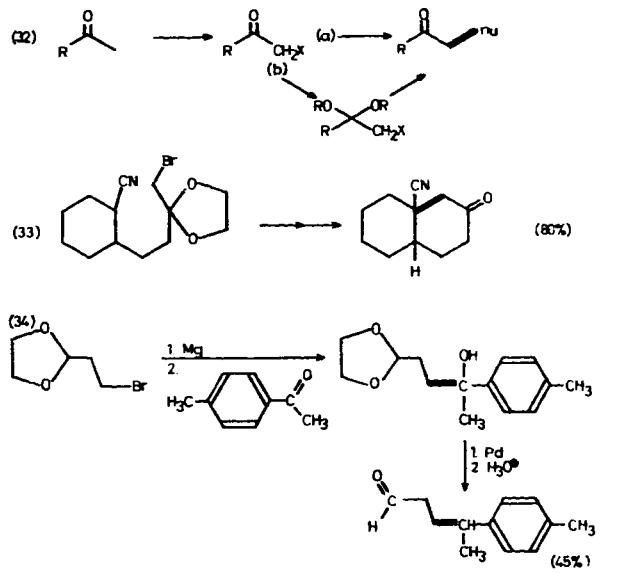


Fig 5

to form an enolate is possible not only from C^2 of an aldehyde, ketone, or ester but also from C^4 of an α,β-unsaturated carbonyl system. The sites of the various reactivities are indicated in the upper part of Fig 5. In the previous sections we have discussed the means of *umpolung* of C^1; using the terminology of Fig 5, the reactions mentioned above are, with respect to the acylating reagent, H^1- and/or E^1-reactions. As shown in the lower part of Fig 5, it should be feasible to reverse the reactivities of other carbons as well. In appropriate ketene thioacetals XXI, the carbons which cannot be reached by a reagent of a certain reactivity ('philicity') in normal carbonyl derivatives ought to be attacked. With

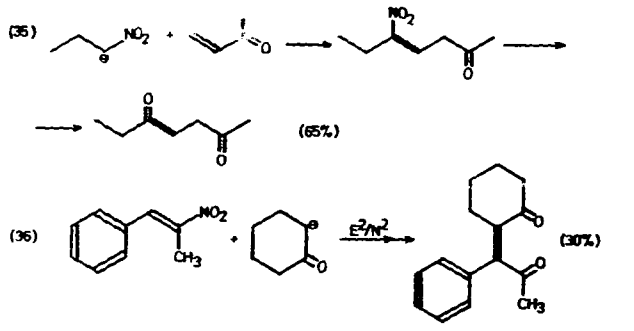


ketene thioacetals being readily available[36,45,46] by the process of equation (25), we were able to test this and actually found examples of N^2-, N^4-, H^3-, H^5-, and E^3-reactions as evident from the transformations described in equation (27)[52] (N^2-addition only occurs in the absence of allylic hydrogens), and (28) – (31)[53] (note the pronounced E^1-reactivity of conjugated dithiane anions).

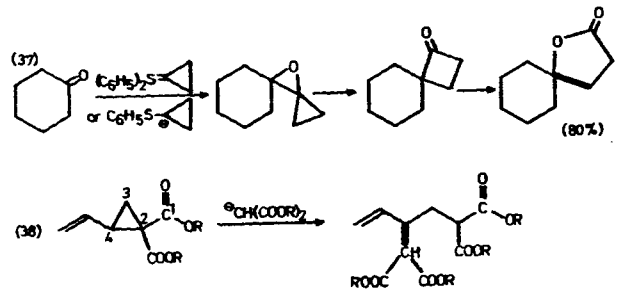


5 Miscellaneous cases of *umpolung* of reactivity in the carbon chain of carbonyl compounds

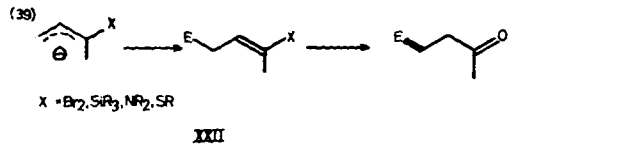
There are various other methods of attacking carbonyl derivatives with *umpolung* of their normal reactivity. A classical N^2-process involves halogenation in the α-position[54] and SN_2-type substitution, equation (32a); to prevent competitive nucleophilic addition, acetal protection is a common method, equation (32b). This has been used recently in a new annelation procedure, equation (33)[55]. An E^3-reaction of an aldehyde using the same protection is exemplified by equation (34)[56]. The ready conversion of a secondary nitroalkane to a ketone allows E^1-reactions with an α-nitroanion, equation (35),[57] and N^2-additions starting from nitroolefins, equation (36).[58]



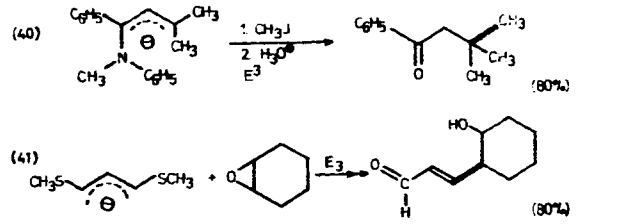
More tricky are the spiro-annelation method of equation (37),[59] an E^3/N^1-process, and the use of a three membered ring to steer nucleophilic attack to C^4 as shown in equation (38).[60]



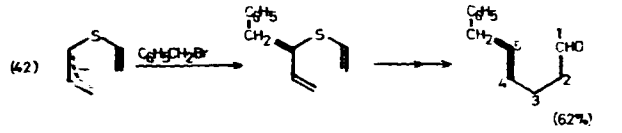
Finally, there is a large group of reagents consisting of heterosubstituted allylic anions XXII to which electrophiles add at the carbon remote from the heteroatom. Hydrolysis of the intermediate vinylic products furnishes carbonyl



derivates in an overall E^3-reaction, equation (39). X may be boron,[61] silicon,[62] nitrogen,[63–65] or sulphur.[66,67] For this principle to work, it is of course important to have high nucleophilicity at the γ-position of XXII. With $X = NR_2$, on one side of the scale, this appears to be the case, see equation (40),[63] with divalent sulphur on the other hand, the α-position



is found to be always more nucleophilic (cf. section 4), therefore, thioallylanions can only be used applying special structural precautions as evident from the reaction in equation (41).[66] The vinylthioallyllithium reagent of equation (42)[67] rests upon a thio-Claisen rearrangement to accomplish an E^5-coupling.



In the case of silicon, the regiospecificity appears to be controlled by the steric requirements of the groups attached to silicon, while not enough data are available to judge the general behaviour of boron substituted anions XXII.

6 Conclusion

The brief survey given here shows that the methods of *umpolung* of carbonyl reactivity have come along with intensive research in the field of organometallic chemistry. Including these new possibilities in the planning of synthetic sequences shows that unexpected short cuts are available which justify their application even on industrial scales. It is obvious from the literature that use is made of many of the highly reactive organolithium reagents mentioned *at early stages of syntheses*. Once the advantages will be fully recognised, chemists will develop modifications which can be carried out under milder and more specific conditions required for polyfunctional substrates *in the final steps* of natural product and pharmaceutical syntheses. *Umpolung* of the reactivity of other ubiquitous functional groups in organic molecules is being investigated in many laboratories. Thus, we have succeeded in preparing nitrosamine anions $R\text{-}N(NO)\overset{\ominus}{C}R_2$ which synthetically are equivalents of nucleophilic secondary aminoalkylating reagents,[68] $R\text{-}NH\text{-}\overset{\ominus}{C}R_2$. This represents an *umpolung* of aminoalkylation which is normally only possible with electrophilic species $R_2N\text{-}\overset{\oplus}{C}R_2$.

Acknowledgements

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