Forschung, Wissenschaft

The Alkylation of Enolates and Enol Derivatives: The Use of Silyl Enol Ethers *

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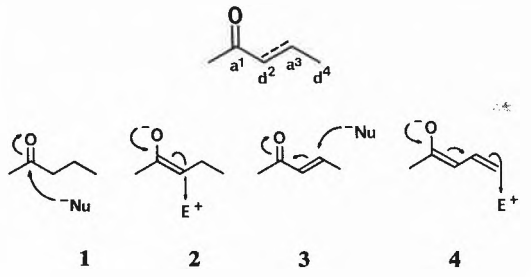
Abstract

Specific metal enolates are not always alkylated regioselectively, not is there always complete control over the degree of alkylation. These difficulties and others can sometimes be overcome using enol derivatives, of which silyl enol ethers are particularly effective. Dienolates are generally alkylated in the α-position, but their silylated analogues show some aptitude for γ-alkylation.

The Alkylation of Enolates

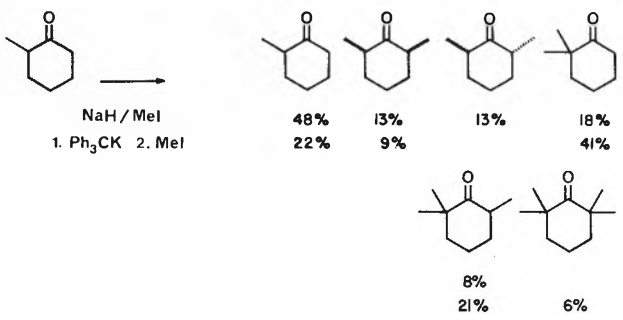
Carbonyl compounds occupy the central place in organic synthesis because they are intinsically electrophilic (**1** and **2**) and, through their enolates, potentially nucleophilic (**2** and **4**) [1].



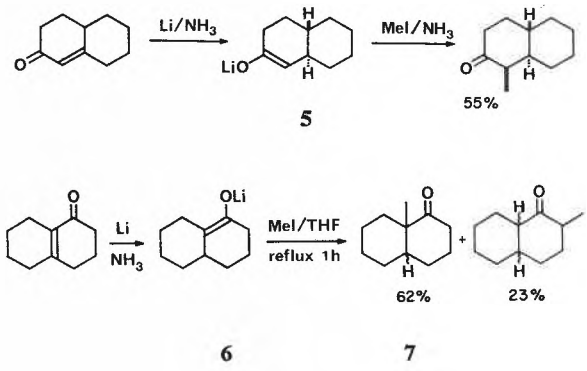
1 **2** **3** **4**

Yet there are serious problems in harnessing this potential nucleophilicity in a controlled way for alkylation. These problems include: (i) competing aldol reactions, a problem especially acute with aldehydes, (ii) *O*-alkylation in place of *C*-alkylation, (iii) polyalkylation, when the first-formed product rapidly forms a new enolate which is more reactive than the original enolate, and (iv) a specific enolate may not be alkylated regiospecifically [2]. Because of these problems, the alkylation of aldehydes, ketones and esters is rarely done by the most obvious method: treating the carbonyl compound with base and an alkyl halide. 2-Methylcyclohexanone, for example, gives all the possible methylation products (Scheme 1), even though the bases used convert the starting material completely into its sodium or potassium enolates [3].

Scheme 1:



The traditional solution to this problem is to use β-dicarbonyl compounds, which are less apt to give polyalkylation, and which alkylate specifically between the two carbonyl groups. More recently, *Stork*, having found enamines a useful but limited alternative to enolates, discovered that lithium enolates are much better behaved than sodium or potassium enolates. Thus, the specific lithium enolate (**5**) could be methylated and butylated with a high degree of control, and the enolate (**6**), a particularly testing case, could be methylated to give mainly the more substituted products (**7**) [4].



Other, even less electropositive metals, like magnesium [5], zinc [6], and tin [7], have been used; they are excellent for controlled aldol reactions, as in the Reformatsky reaction, for example, but in general they are too unreactive in simple alkylations *. Thus lithium

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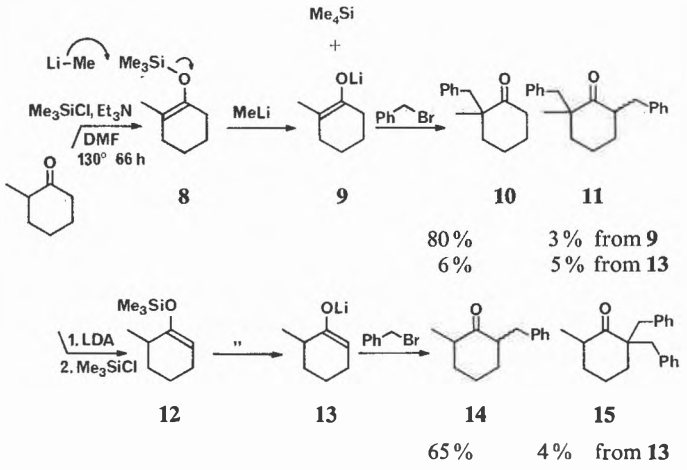
* In addition, boron enolates have very recently come to occupy a special place. Simple boron enolates promise to be very useful in stereospecific aldol reactions [8], and their "ate" salts are comparable to lithium enolates in simple alkylations [9].

appears to be the best compromise, its enolates having a high enough reactivity yet retaining a reasonable amount of control. The generation of specific lithium enolates has therefore become an important exercise. In addition to Stork's original use of enones, enol phosphates [10] and enol acetates [11] have been used, but it is now clear that the derivative of choice is the silyl enol ether. These derivatives can be made directly from aldehydes, ketones and esters, and by other methods [12]. With unsymmetrical ketones it is often possible to generate the less-substituted ether (e.g. **12**) under conditions of kinetic control and the more-substituted ether (e.g. **8**) by equilibration, giving thermodynamic control [13]. The ethers can then be converted to their lithium enolates (**8** → **9** and **12** → **13**) using methyl lithium, when the by-product is the innoccuous tetramethylsilane [14]. Alkylation of such pure enolates (**9** → **10** + **11** and **13** → **14** + **15** + **10** + **11**) is clean [13, 14], but only with the more reactive kinds of alkyl halide, like benzyl bromide, allyl bromide and methyl iodide.

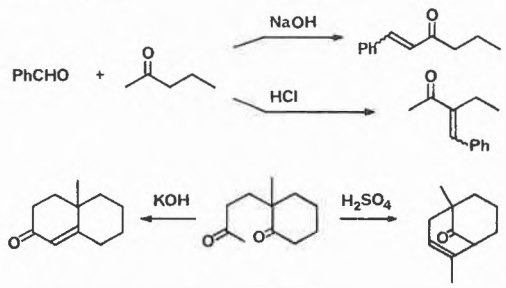


The less reactive alkyl halides, like n-butyl iodide, work occasionally, especially in the presence of HMPA, but cannot be relied upon. The alkylation of enolates with secondary or tertiary alkyl halides is usually impractical or impossible.

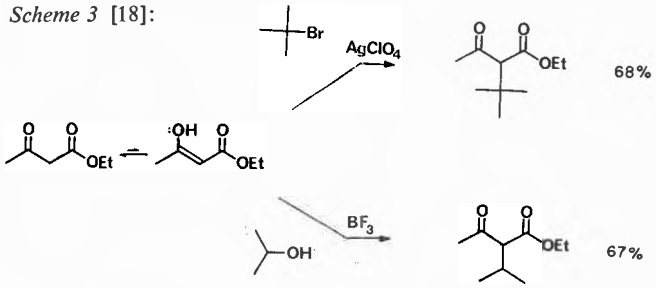
The Alkylation of Enols and their Derivatives

Instead of using enolates (**2**), it is possible to use enols. For every reaction of an enolate there is usually an equivalent reaction of the corresponding enol; all that has to change is that the electrophile must be somewhat more reactive [15]. On occasion enols have a usefully complementary regioselectivity to that of enolates, as in the examples in Scheme 2, but such selectivity is more or less accidental. As with enolates, control can be got by using the enols of β-dicarbonyl compounds; for example, these enols react with carbonium ions to give good yields of secondary and tertiary alkyl derivatives (Scheme 3) [18].

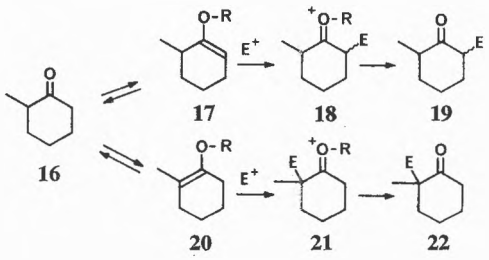
Scheme 2 [16, 17]:



Scheme 3 [18]:

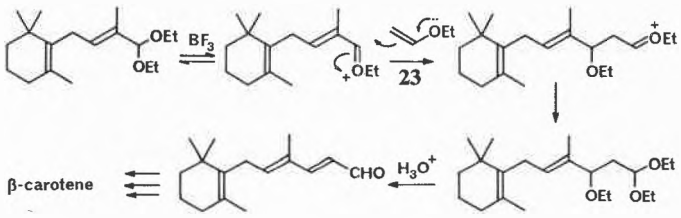


However, because of the ready interconversion (**17** ⇄ **16** ⇄ **20**) when R = H, the enols of simple unsymmetrical ketones are not generally useful; products of either type (**19** or **22**) will be found, and there is little control. To give control, R has to be something other than H, and alkyl, acyl and silyl groups have all been used.



The alkyl derivative is most useful in the case of acetaldehyde, for which ethyl vinyl ether (**23**) is a readily available substitute for the enol. It was used, for example, in the Roche synthesis of carotene (Scheme 4) [19].

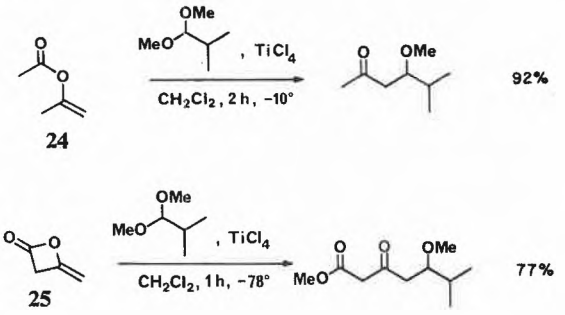
Scheme 4:



The acyl derivative is especially useful in the case of acetone, for which isopropenyl acetate (**24**) is readily available. It reacts in mixed aldol type reactions when

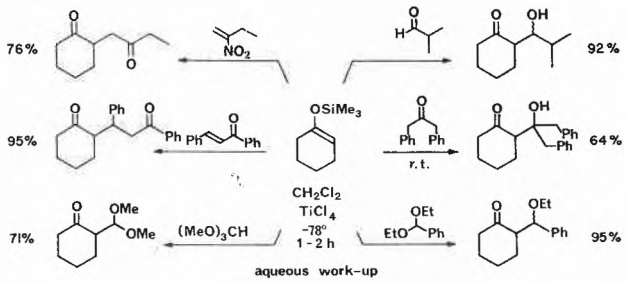
Lewis acids are present to make the electrophile reactive enough (Scheme 5) [20]. Diketene (**25**) is also a readily available acyl derivative of an enol, and reacts similarly [21].

Scheme 5:

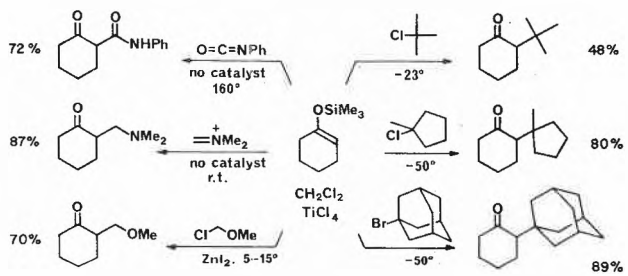


But for other aldehydes, ketones and esters, the derivative of choice is again the silyl enol ether. *Mukaiyama* and his co-workers, and others, have shown that these derivatives enter into most of the standard synthetic operations found in enolate chemistry. The electrophile, of course, has to be made more reactive, but this is easily achieved by *Lewis* acid catalysis, typically with titanium tetrachloride [22]. The reactions illustrated in Schemes 6 [23], 7 [24] and 8 [25] include mixed aldol, *Michael* and *Mannich* reactions, alkylation with tertiary alkyl, prenyl and secondary benzyl halides, and reaction with halogen, oxygen, sulphur and nitrogen electrophiles.

Scheme 6 [23]:

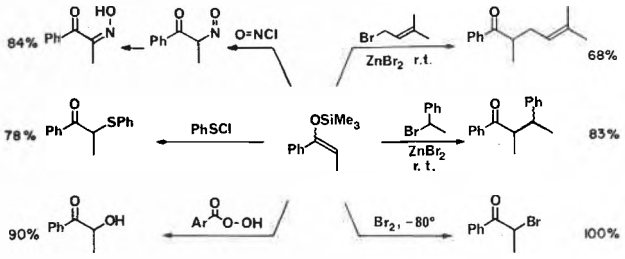


Scheme 7 [24]:

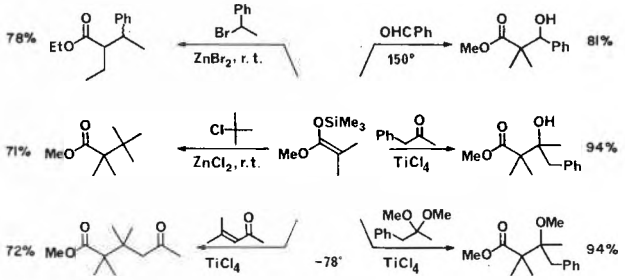


The reactions in Scheme 9 [26] show that the silyl enol ethers of esters can also be used in these reactions.

Scheme 8 [25]:

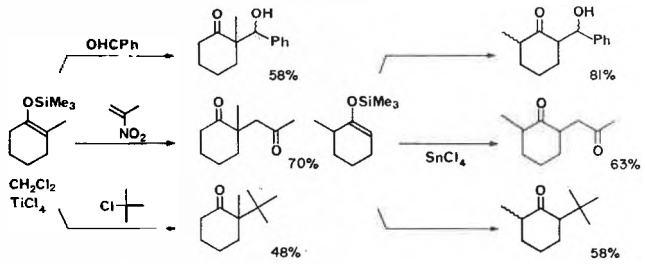


Scheme 9 [26]:

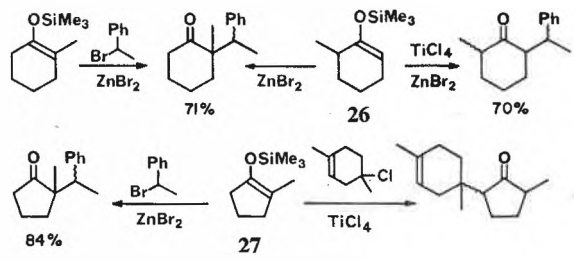


Where tested, the reactions are regioselective, as shown by those illustrated in Scheme 10 [27].

Scheme 10 [27]:



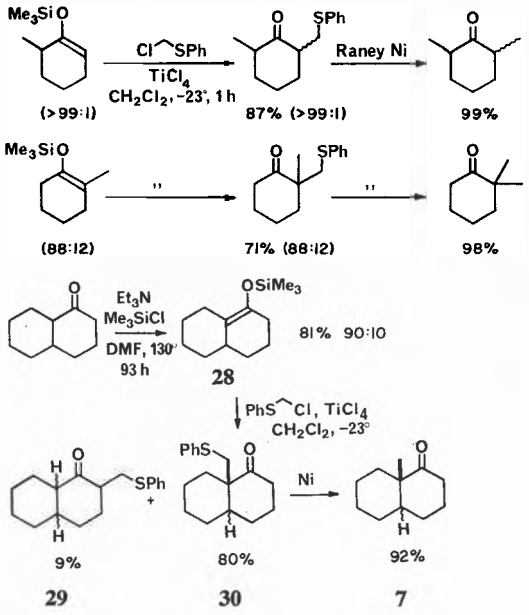
But in one case (**26** with 2-phenylethyl bromide and zinc bromide), we found loss of regioselectivity in a secondary benzylation at the *less* substituted side of a ketone. In another (**27** with a tertiary alkyl halide and titanium tetrachloride), we found loss of regioselectivity on the *more* substituted side of a ketone, a result which stopped an extraordinarily short synthesis of trichodiene and bazzanene [28]. However, failures of this kind appear to be rare.



To extend the usefulness of silyl enol ethers to the area of alkylation with primary and secondary alkyl halides in general, we have recently introduced the method of

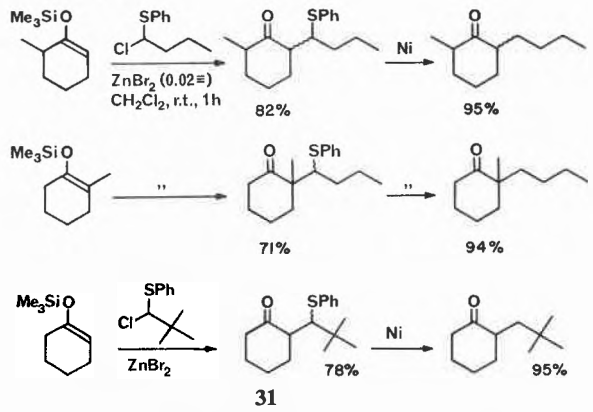
phenylthioalkylation followed by desulphurisation with Raney nickel. This works for methylation (Scheme 11) even in the testing case (**28** → **30** → **7**), where the reaction is completely regioselective: the proportion of **29** in the product merely reflects the proportion of the corresponding silyl enol ether contaminating **28** [29].

Scheme 11 [29]:

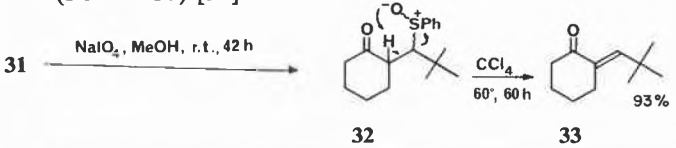


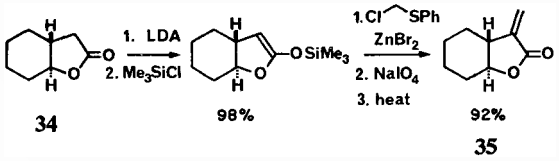
It also works for other primary alkyl halides such as butyl and even neopentyl (Scheme 12) [30].

Scheme 12 [30]:

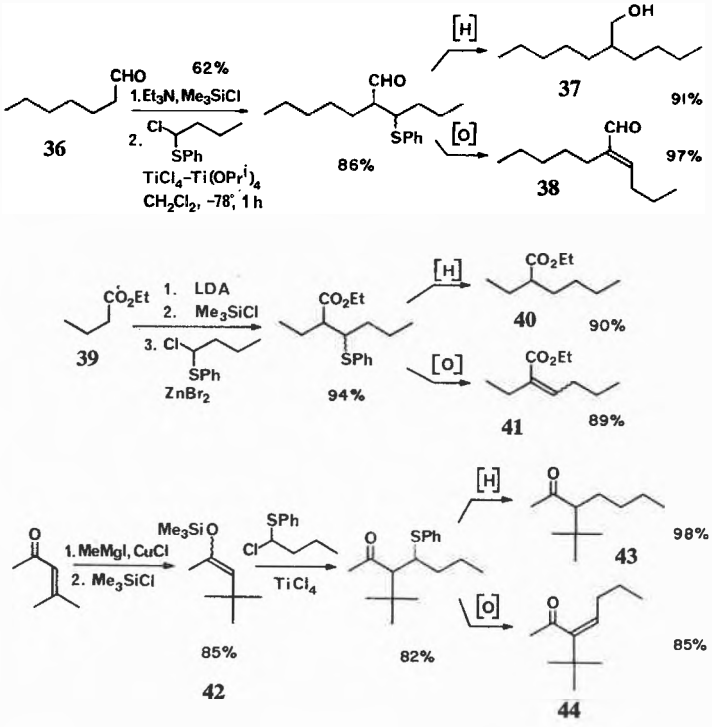


Furthermore, an oxidative work-up (**31** → **32** → **33**) makes the phenylthioalkylation into an alkylidenation [30]. This is probably the best method now available for introducing an exomethylene group into lactones (**34** →→ **35**) [31].



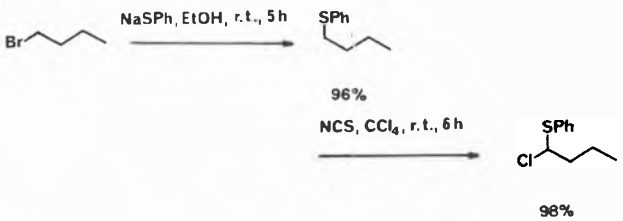


Both the alkylation and the alkylidenation sequences work well for aldehydes (**36** → **37** or **38**), esters (**39** → **40** or **41**) and hindered ketones (**42** → **43** or **44**) [30].



The α-phenylthioalkyl chlorides used in all these reactions are available in high yield from the corresponding alkyl bromide, as illustrated in Scheme 13.

Scheme 13:



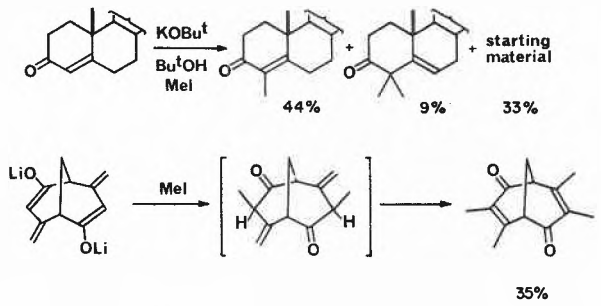
Recently *Reetz* has reported the first example of the introduction of a secondary alkyl group by this type of procedure: the silyl enol ether of pinacolone reacts with the diethylthio acetal of acetone in the presence of ferric chloride, and desulphurisation then gives isobutyl t-butyl ketone in 63% overall yield [32].

The γ-Alkylation of Silylated Dienolates

Another problem with enolates is the difficulty of

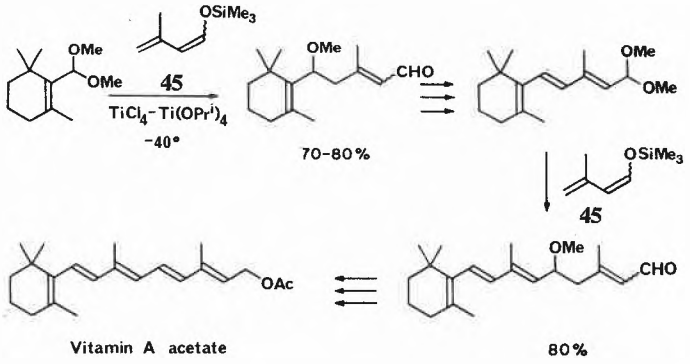
getting reactivity of type (**4**); although the γ-alkylation of dienolates (**4**) is formally possible, it is rarely observed. Dienolates usually react faster at the α-position, as shown by the two examples in Scheme 14 [33].

Scheme 14 [33]:

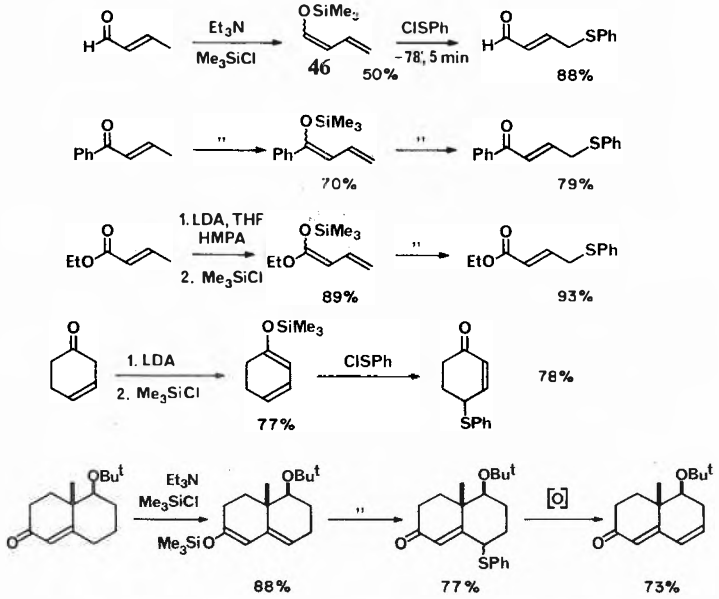


Mukaiyama and *Ishida* have found that the silylated dienolates of crotonaldehyde (**46**) and of its 3-methyl derivative (**45**) react at the γ-position in *Lewis* acid-catalysed, mixed aldol types of reactions, and they used this selectivity, in the latter case, in their synthesis of vitamin A acetate (Scheme 15) [34].

Scheme 15 [34]:



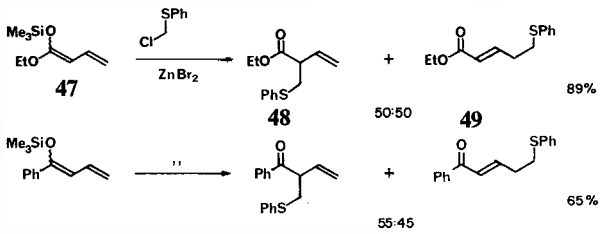
Scheme 16 [35]:



We have taken up this hint, and have begun to look at how general attack at the γ-position is in silylated dienolates. We find that sulphenylation (Scheme 16) is highly γ-selective [35].

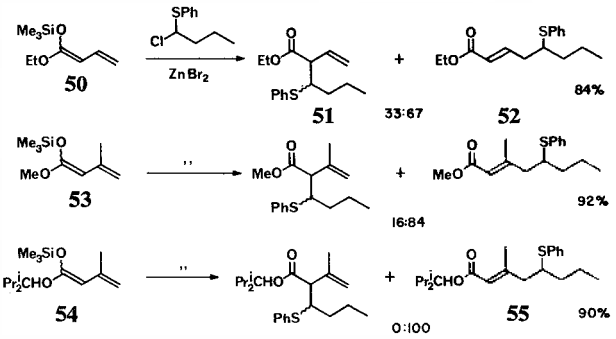
Phenylthiomethylation, however, was not as selective; it gave nearly equal amounts of the α- and γ-products with the silylated dienolates in Scheme 17 [36].

Scheme 17 [36]:



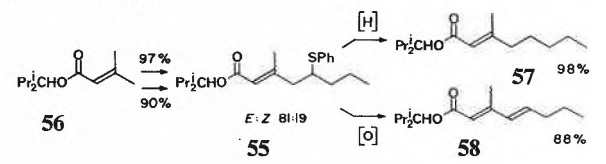
Quite small changes improved the selectivity: changing from phenylthiomethylation (**47** → **48** + **49**) to phenylthiobutylation (**50** → **51** + **52** in Scheme 18) raised the γ- to α-ratio to 67:33, and the presence of an extra methyl group in the dienolate (**53**) raised it again to 84:16. Finally, enlarging the ester group from the methoxy group of **53** to the diisopropylmethyl group of **54** achieved our goal of essentially complete γ-selectivity.

Scheme 18 [36]:



The product (**55**) in this last case can be worked up reductively (**55** → **57**) or oxidatively (**55** → **58**) in the usual way, to give what amounts overall to the γ-alkylation or alkylidenation of an $\alpha\beta$-unsaturated ester (**56**) (Scheme 19).

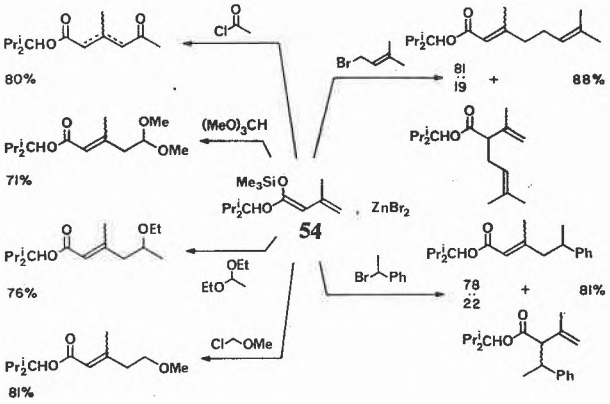
Scheme 19 [36]:



Other electrophiles also shown high, though not always complete γ-selectivity with this silylated dienolate

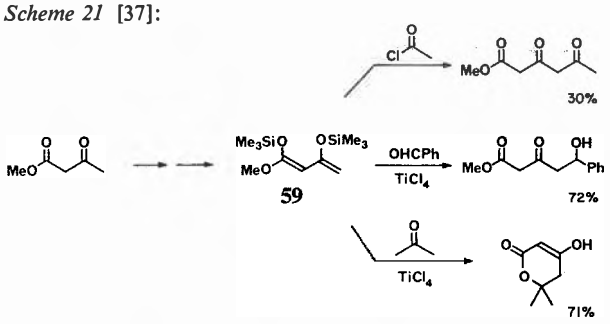
(**54**), as shown by the reactions in Scheme 20 [36].

Scheme 20 [36]:



In related work, *Chan* has shown that the silylated dienolate (**59**), having the advantage of a second silyloxy substituent, is also highly γ-selective, as shown by the selection of reactions in Scheme 21 [37].

Scheme 21 [37]:



Currently, we are pursuing the goal of general, controlled γ-selectivity without having to resort to the variations of structure which limit the examples above. We have already found that changing the silyl group has a substantial effect [38], and we have therefore every hope of finding the answer to this long-standing problem.

A modified version of this lecture was given to the Basel Chemical Society on the 8th November 1979. I should like to thank Dr. *Fuerst* for inviting me to give the lecture, Professor *Chan* for leading us into this field [24], and my two collaborators *Ian Paterson* and *Jon Goldhill*, both for the work that they did and for their initiative in taking up this challenge.

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