THE USE OF KINETICALLY GENERATED UNSTABLE ENOLATE IONS IN THE REGIOSPECIFIC FORMATION OF CARBON–CARBON BONDS. SPECIAL APPLICATIONS TO ANNELATION PROCESSES

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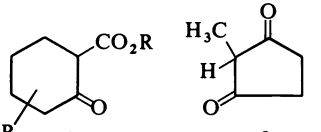
ABSTRACT

It was shown some years ago that lithium enolates of asymmetric ketones are capable of maintaining their structures in reaction with carbon dioxide and with reactive alkyl halides. This, coupled with methods for the regiospecific formation of lithium enolates, was a considerable step forward. It was not, however, until recently that we succeeded in carrying out aldol and Michael condensations with regiospecifically produced lithium enolates. We will review the development of these methods, which now permit a general solution to the problem of regiospecific formation of carbon–carbon bonds.

One of the central reactions in synthetic organic chemistry involves the formation of a new carbon–carbon bond alpha to a carbonyl group. Regiospecificity, in the important case of an unsymmetrical ketone, has been achieved in a number of classical ways.

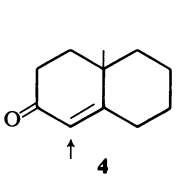
(1) By the use of intermediates in which the desired reaction site is made part of a β-dicarbonyl (e.g. **1** and **2**) or related system (**3**). In these cases the enolate involved in reaction would normally be the same whether the enolate



1 **2** **3**

is generated under kinetic or equilibrium conditions. The position at which the new carbon–carbon bond is required can also be chosen as the α-carbon of an enolizable α,β-unsaturated system. In such a situation the selectivity comes not from kinetic enolization but from choosing conditions allowing rapid equilibrium to the more stable delocalized enolate structures (e.g. **4** and **5**).

(2) By preventing enolization towards an unwanted methylene site. This is achieved in various ways, such as making the unwanted position part of a



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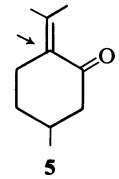

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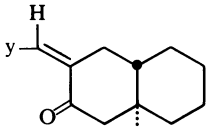
non-enolizable unsaturated system (**6**), or of a thioketal (**7**). Although this represents in a way the ultimate solution, it is obviously a fairly cumbersome process, requiring several steps for the introduction and removal of the auxiliary function.



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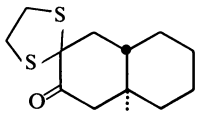

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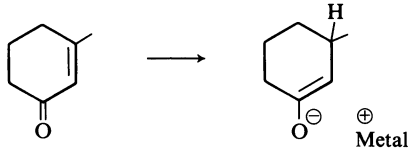
It became evident some time ago that a more general solution to the problem of regiospecific formation of carbon–carbon bonds would require the specific kinetic formation of a given enolate ion and defining conditions that would lead to its reaction with electrophilic carbon species more rapidly than the enolate would equilibrate via various proton transfers.

REGIOSPECIFIC FORMATION OF ENOLATES

The first method introduced[1] for the formation of the specific enolate of an unsymmetric ketone was based on the assumption—which proved to be correct—that the reduction of an α,β-unsaturated ketone by alkali metal in liquid ammonia should proceed with the formation of an enolate ion regiospecifically related to the starting enone. Ammonia is too weak an acid to protonate the enolate, which should therefore maintain its structural integrity (e.g. **8** → **9**). The wide availability of α,β-unsaturated ketones makes this



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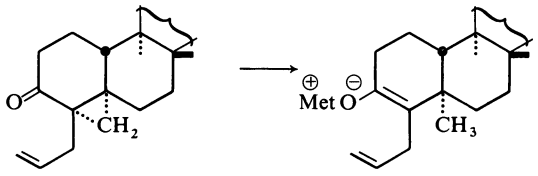
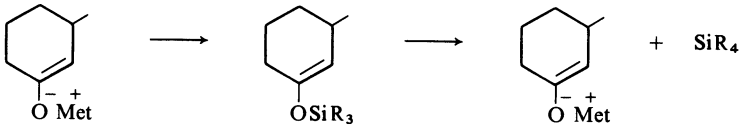
method particularly attractive. In an extension of this method, we have also used the metal–ammonia reduction of cyclopropyl ketones (**10** → **11**)[2]. The enolate ions thus produced can in some cases be used in the ammonia



10 11

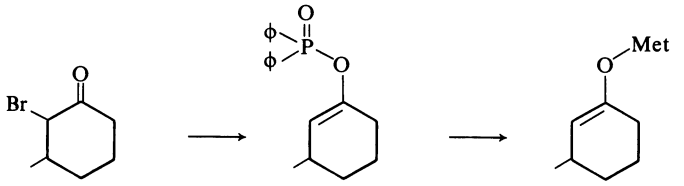
medium (e.g. with reactive alkyl halides)[1]. It is, however, desirable in many cases to isolate the species after removal of ammonia as a derivative from which the enolate can easily be regenerated.

The trimethyl silyl enol ethers, or the much more stable *tert*-butyldimethyl silyl ethers, are particularly useful for this purpose since they can be formed in excellent yields, they can often be purified by distillation, their structure can be confirmed by n.m.r. spectroscopy and, most important, regeneration of the enolate with a metal alkyl produces a tetraalkyl silane—inert under the reaction conditions—as the only byproduct. A further advantage is that when a proton source such as *tert*-butanol is used in the metal–ammonia reduction the resulting lithium *tert*-butoxide (which could lead to proton transfer) is easily converted to the easily removed volatile silyl ether (**9** → **12** → **13**).



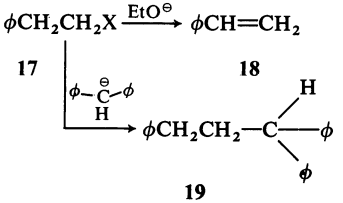
9 **12** **13**

Among other more recent methods for producing enolates regiospecifically, perhaps the most interesting involves the reduction of a bromoketone (when a method exists for its regiospecific synthesis) with various phosphorus reagents[4]. The resulting enol derivatives are again convertible to enolates with metal alkyls (**14** → **15** → **16**).



14 **15** **16**

With methods available for the regiospecific formation of enolate ions, it became crucial to determine whether they could engage in reactions with carbon electrophiles without loss of regiospecificity. Perhaps the most important contribution of our early work[1] was the demonstration that *lithium* enolates (but not sodium or potassium enolates) can in many cases meet this requirement. The unique ability of oxygen anions to remove protons (contrast **17** → **18** with **17** → **19**)[5] had led us to hope that a metal enolate of



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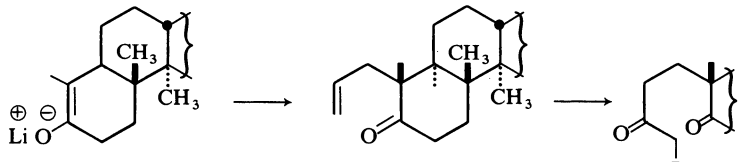
the proper degree of tightness could be found which would give a favourable ratio of carbon bond formation to proton transfer (responsible for loss of

regiospecificity). It turns out that this favourable ratio is obtained with lithium and a few other metals (such as the regiospecific enolates resulting from 1,4-addition of alkyl copper reagents).

We now turn to a consideration of the use of regiospecifically generated lithium enolates in alkylation, aldol condensation and Michael addition with special emphasis on the use of these reactions for the purpose of regiospecific annelation.

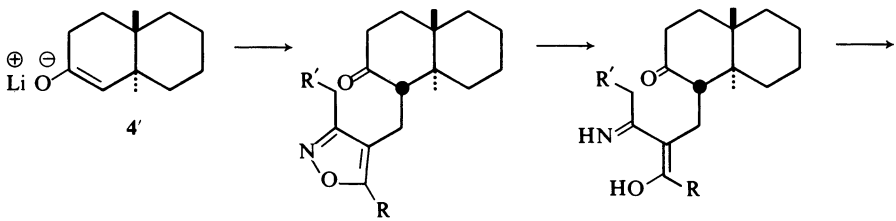
ALKYLATION

The need to maintain as favourable a ratio of alkylation rate to proton transfer as possible limits the method to reactive alkyl halides such as methyl iodide, and allylic or benzylic halides. In so far as annelation is concerned, one could use allyl bromide itself, following this by transformation, by obvious routes, to the 3-ketoalkyl structure needed to complete annelation. We used such a process (**20** → **21** → **22**) in the total synthesis of lupeol[2], but one would clearly prefer to be able to introduce directly a fragment more closely related to the required 3-ketoalkyl structure. Our first solution to



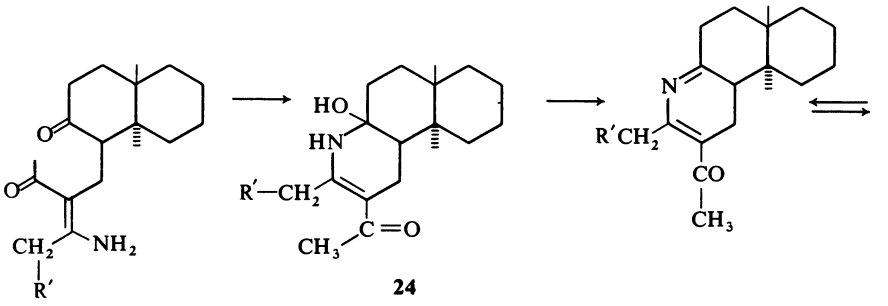
20 **21** **22**

this problem was to use a particular benzyl-type halide, a 4-halomethylisoxazole. We had previously shown that such a system can be thought of as a



4' **23**

protected 3-ketoalkyl group by virtue of the transformations illustrated below[7]. The sequence is not as forbidding as it appears since **24** is formed directly from **23** on Raney nickel reduction at atmospheric pressure and **24** is converted directly into **25** upon the proper base treatment. Nevertheless the route to **23** via alkylation of the enolate **4** is only moderately successful because 4-halomethylisoxazoles are considerably less reactive than benzyl



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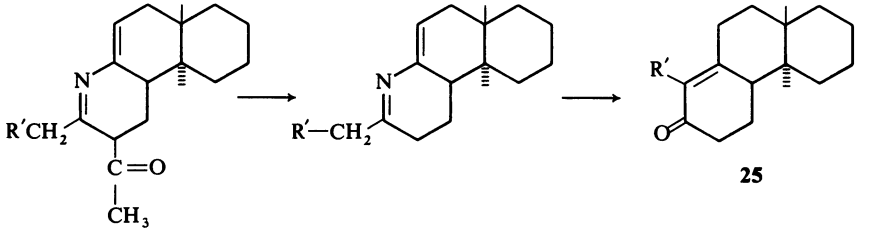
halides, and indeed the alternative sequence involving direct alkylation of **4** followed by catalytic hydrogenation over palladium to **23** was more satisfactory.



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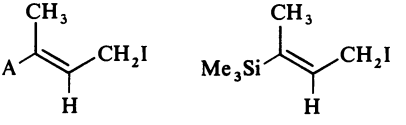
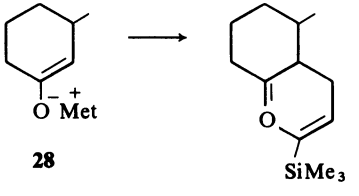
The use of an allylic iodide of type **26** would be very attractive if a function A compatible with stable, reactive allylic halides and permitting simple transformation to a 3-ketoalkyl system could be found. We have recently shown that these requirements are fulfilled when A is a trimethylsilyl group, as in **27**[8]. For instance, addition of **27** to the enolate **28** (regiospecifically formed



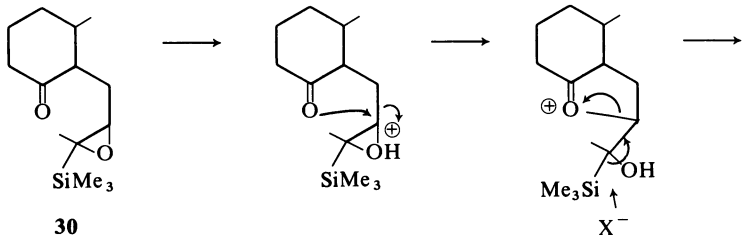
26 **27**

via $(CH_3)_2LiCu$ addition to cyclohexenone) in a 2:1 tetrahydrofuran–ether mixture led to **29** in 75 per cent yield. The value of the vinyltrimethylsilyl



28 **29**

group in this connection is based on the fulfilled anticipation that the corresponding epoxide **30** would undergo very facile opening, assisted by the carbonyl group, as shown:



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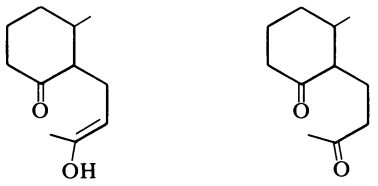
Indeed, the transformation is partially effected by the *m*-chlorobenzoic acid formed during epoxidation and is completed by treatment with formic acid for less than a minute. The diketone **31** is thus obtained from **29** in over



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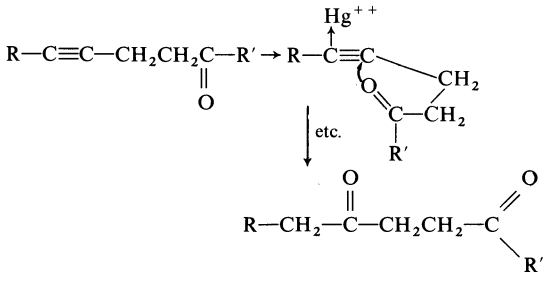
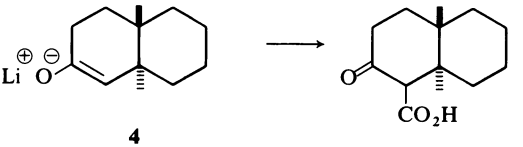
80 per cent yield. This ketone participation is reminiscent of the similar assistance we had demonstrated in the specific hydration of 3-ethynyl ketones to 1,4 diketones[9].



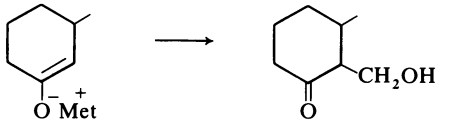
ALDOL CONDENSATIONS

One of the first reactions we had studied with regiospecifically generated unstable lithium enolates, trapping with carbon dioxide as in **4** → **32**[1] is mechanistically related to the aldol condensation. It was not, however, until very recently that we learned how to carry out the potentially most versatile



4 32

of these reactions, that with formaldehyde. We first showed[10] that addition of gaseous formaldehyde, at $-10°$ to the ether solution from the 1,4-addition of methylmagnesium bromide in the presence of one per cent of $CuI \cdot Bu_3P$ resulted in 70 per cent yield of regiospecific hydroxymethylation to **33**.



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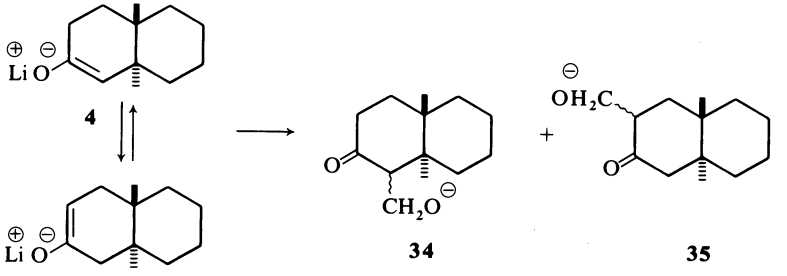
When, however, we attempted trapping of the lithium enolate produced by addition of a mixture of **4** and 1 equiv. of *tert*-butanol (to ensure complete reduction of **4**) to lithium in liquid ammonia followed by removal of ammonia and replacement with anhydrous tetrahydrofuran, mixtures of the two possible regioisomers **34** and **35** were produced. This showed that the relatively slow reaction with formaldehyde (which has to be introduced as a gas) allowed equilibrium between **4** and **4′**. This equilibrium took place

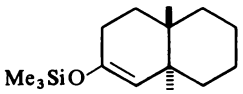


4 **4′**. **34** **35**

only during the addition of formaldehyde because (*vide infra*) trapping at this stage with trimethylchlorosilane gave the silyl ether corresponding to **4** in almost quantitative yield. We believe that **34** reacts with the lithium *tert*-butoxide in the mixture to give a small amount of *tert*-butanol which allows rapid equilibration of **4** to the more stable **4′**.

This difficulty could be avoided by using aniline instead of *tert*-butanol as the proton donor in the lithium reduction. Under otherwise identical conditions, the correct hydroxymethyl compound **37** was obtained in 60 per cent yield. Even better results were obtained by trapping the enolate by

addition of trimethylchlorosilane, after removal of ammonia. The trimethylsilyl enol ether **36**, which was obtained in over 90 per cent yield (distilled), was reconverted to the lithium enolate **4'** with methyl lithium in tetrahydrofuran. Addition of formaldehyde then gave the crystalline hydroxymethyl compound **37** in 90 per cent yield.



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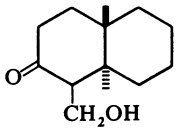

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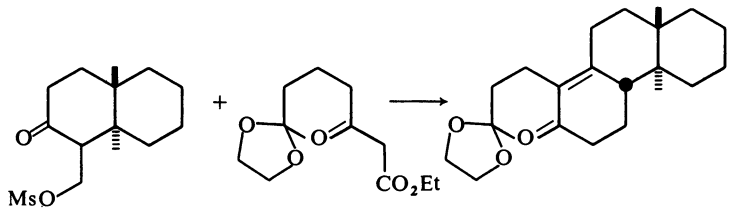
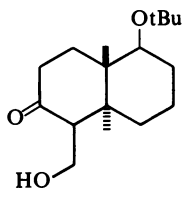
We have referred to the versatility of hydroxymethyl ketones. They are, for instance, equivalent to α-methylene ketones which can lead to a wide variety of products via 1,4-addition. We illustrate their use in an annelation sequence. Reaction of the crude mesylate from **37** with the β-keto ester **38** in the presence of sodium *tert*-amylate in *tert*-amyl alcohol, followed by heating with aqueous base, gave an 80 per cent yield of the annelation product



38 **39**

39. The same sequence of steps was used for the conversion of **40** to the annelation product **41** (m.pt, 121–122°), which was then transformed by standard procedures to the known (±) 19-nor-D-homotestosterone (**42**) identical with an authentic sample[7].



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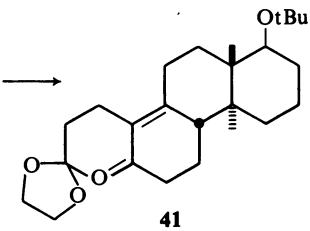

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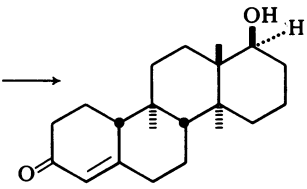

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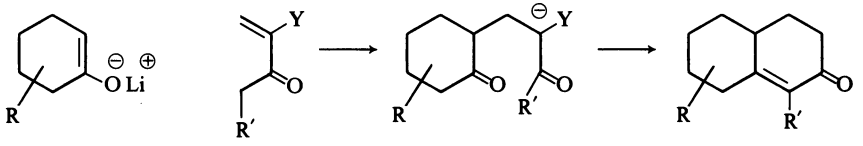
MICHAEL ADDITIONS

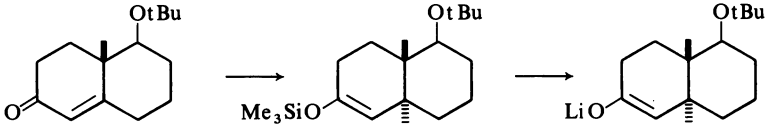
Aside from the intrinsic interest of being able to do Michael additions

(necessarily under aprotic conditions) with unstable kinetic anions, the successful use of the reaction under these conditions would be a particularly simple solution to the annelation problem. We were, of course, aware that the use of a substance such as methyl vinyl ketone, under aprotic conditions, leads largely to the polymerization of the substance.

We approached the problem by postulating that there might be a substituent Y that could be placed on the α-position of the α,β-unsaturated ketone which could fulfil the following requirements: (a) the function Y should stabilize the anion resulting from 1,4-addition, which would then be less reactive than the initial anion undergoing Michael addition; (b) Y should offer some steric hindrance to further reaction with the vinyl ketone; and (c) Y should be easily removed after addition, ideally in the process of cyclization itself.

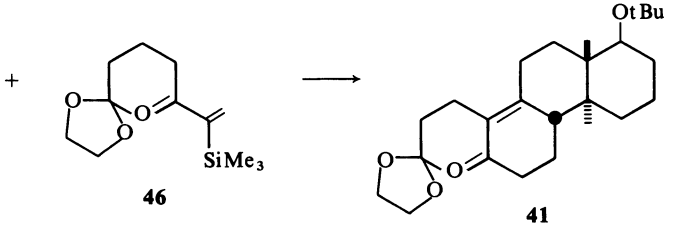


We thought that a trialkylsilyl group (again!) might fulfil all of these requirements and this has indeed proved to be the case[12], as we now illustrate[13]: The trimethylsilyl enol ether **44** (88 per cent yield, distilled) derived, as usual, from the lithium–ammonia reduction of **43** was reconverted to the lithium enolate **45** with methyl lithium in *dry* glyme. Addition of the α-trimethylsilyl



43 **44** **45**

vinyl ketone **46** at −78° and allowing to warm for 30 min, followed by refluxing with 5 per cent methanolic sodium methoxide for 3 h gave in 74 per cent yield the already mentioned tricyclic enone **41** (m.pt, 122°).



46 **41**

CONCLUSION

We have illustrated the growing importance of kinetically generated lithium enolates which were first introduced some thirteen years ago. It is now possible to carry out not only certain alkylations, but also aldol and even Michael additions completely regiospecifically.

ACKNOWLEDGEMENT

In closing, I would like to express my heartfelt thanks to my many collaborators past and present, most of whom are mentioned in the references and my appreciation to the National Institutes of Health, the National Science Foundation and the Petroleum Research Fund who supported most of this work.

REFERENCES

[1] G. Stork, P. Rosen and N. L. Goldman, *J. Amer. Chem. Soc.* **83**, 2965 (1961);
G. Stork, P. Rosen, N. L. Goldman, R. V. Coombs and J. Tsuji, *J. Amer. Chem. Soc.* **87**, 275 (1965).
[2] G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco and J. Labovitz, *J. Amer. Chem. Soc.* **93**, 4945 (1971).
[3] G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.* **90**, 4462 (1968).
[4] I. J. Borowitz, E. W. R. Casper, R. K. Crouch and K. C. Yee, *J. Org. Chem.* **37**, 3873 (1972).
[5] E. Bergmann, *J. Chem. Soc.* 412 (1936).
[6] G. Stork, *Pure Appl. Chem.* **17**, 383 (1968);
R. M. Coates and L. Ofenshain Sandefur, *J. Org. Chem.* **39**, 274 (1974).
[7] G. Stork, S. Danishefsky and M. Ohashi, *J. Amer. Chem. Soc.* **89**, 5459 (1967);
G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.* **89**, 5463, 5464 (1967).
[8] G. Stork and M. Jung, *J. Amer. Chem. Soc.* **96**, 3682 (1974).
[9] G. Stork and R. Borch, *J. Amer. Chem. Soc.* **86**, 935 (1964).
[10] G. Stork and J. D'Angelo, *J. Amer. Chem. Soc.* **96**, 7114 (1974).
[11] Compare Z. G. Hajos and D. R. Parrish, *J. Org. Chem.* **38**, 3244 (1973).
[12] G. Stork and B. Ganem, *J. Amer. Chem. Soc.* **95**, 6152 (1973).
Cf. R. K. Boeckmann, Jr, *J. Amer. Chem. Soc.* **95**, 6867 (1973).
[13] G. Stork and J. Singh, *J. Amer. Chem. Soc.*, **96**, 6181 (1974).