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KETONE ENOLATES: REGIOSPECIFIC PREPARATION AND SYNTHETIC USES

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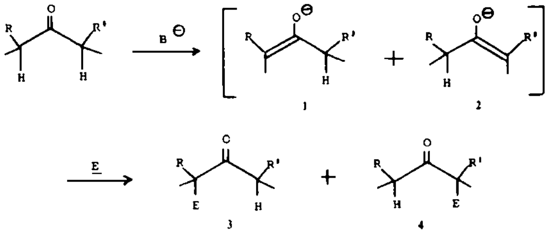
1. INTRODUCTION

Ketone enolates are useful intermediates in organic synthesis, indeed their nucleophilic properties are intensively used to form carbon–carbon bonds in a number of fundamental reactions: alkylation, aldolisation...

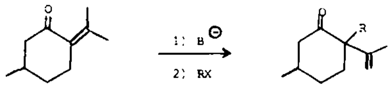
One of the main problems which limit the use of such enolates is their *regioselective formation*. Indeed an α,α'-enolisable non-symetrical ketone can lead, *a priori*, to two regioisomeric enolates (or enols) **1** and **2**. The C-reaction of such enolates with an electrophile E can give a mixture of two regioisomeric products **3** and **4**:



Consequentely, methods to make ketone enolates regiospecifically are required to avoid the formation of such mixtures.

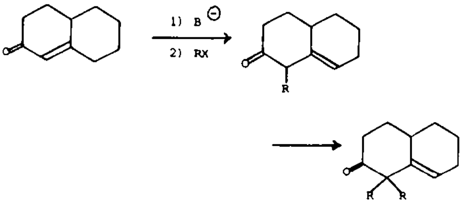
Note: protecting and activating groups are an old indirect solution to this problem.

Such a method was first used by Kon and Nutland in the regiospecific alkylation of pulegone as early as 1926:



(1)[‡]

However that method is frequently complicated by a side reaction: a competitive dialkylation, for instance:



(2)

In 1961, Stork threw light on this subject: he proposed a general method for regiospecific generation of enolates and he showed that, when such enolates are *lithium*

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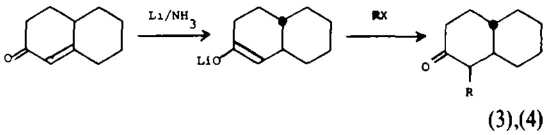
[‡] Reference numbers throughout.

enolates, they can be used without equilibriation, for instance in an alkylation reaction, even when they are *regiounstable*:

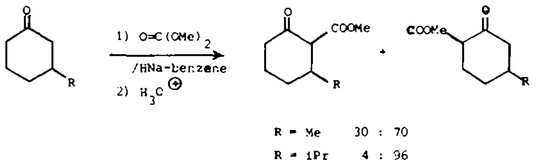


(3),(4)

Since then, enolates regiospecifically generated are more and more used in organic synthesis. The present paper relates to the control of the regioselectivity in the conversion of ketones to *enolates*, in a non-exhaustive way, until 1975 (*non*-thermodynamic enolates, which present a great synthetic utility will be more particulary developed here).

Before that, we will just recall briefly two other methods to control the regioselectivity of processes using ketones in basic media:

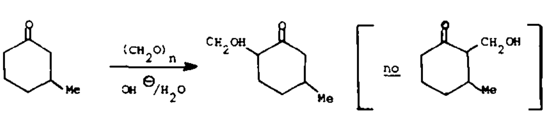
(a) a kinetic control (case of irreversible reactions), for instance in the acylation, in aprotic media, of ketones by alkyl carbonates:



(5)

In this reaction, the regioisomeric enolates (an equilibrium mixture) are generated in presence of the acylating reagent. The regio-control results from the steric hindrance between the C_3 alkyl group and the incoming group at the C_2 position (the reaction is non-reversible because the β-keto-esters [pK *ca.* 11] are generated in presence of an excess of sodium hydride which converts them into sodium salts).

(b) a thermodynamic control at the product-level (reversible reactions), for example in the aldolisation of ketones in protic media:

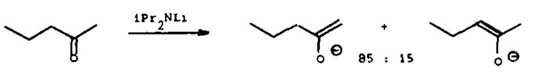


(6)

2. REGIOSPECIFIC PREPARATION OF ENOLATES (7)

2.1 *By hydrogen abstraction from a ketone*

2.1.1 *Kinetic enolates.* This kind of enolate is generated by slow addition of a ketone to an excess of a strong, hindered base at low temperature (for example −78°), in aprotic medium (THF...), therefore under non-equilibrating conditions. The less hindered proton is preferably abstracted. The regioselectivity is affected by the base (among the most common bases used, iPr$_2$NLi gives the best selectivity).



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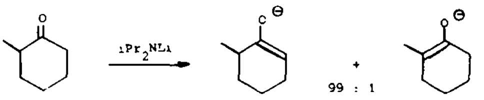

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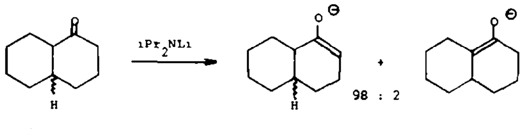
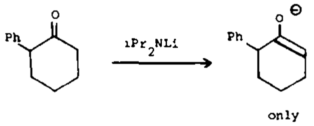


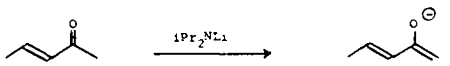
(9)

It is worth noting that despite its strong acidifying property, an α-phenyl substituent does not modify the regioselectivity:



(10),(11)

In general, with α,β-ethylenic ketones, the kinetic enolate is the less conjugated one:



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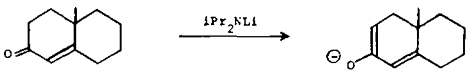

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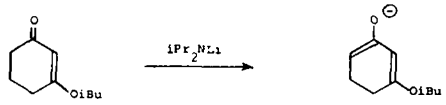

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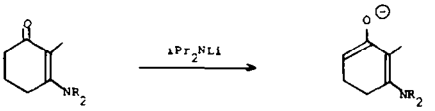

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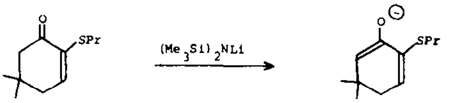
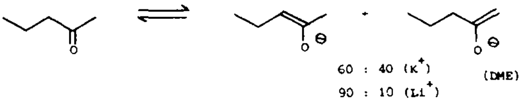


(16)

2.1.2 *Thermodynamic enolates.* These enolates are made at room temperature, or at reflux, often in a protic solvent (for example: tAmONa/tAmOH).

These equilibrating conditions give the more stable enolate, often the more substituted one or the more conjugated one. The regioselectivity is cation-dependent (the smaller the cation the higher the regioselectivity) and solvent-dependent.



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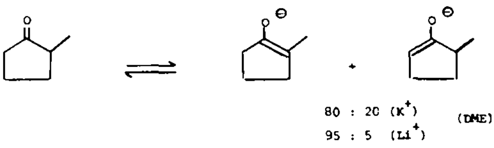
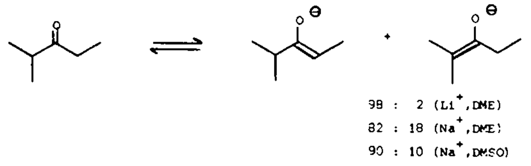


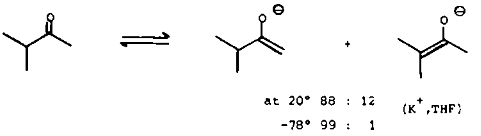
(17)

However in some cases, steric hindrance can destabilise the more substituted enolate:



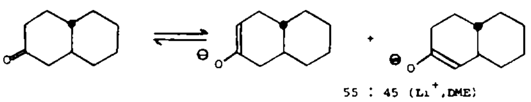
(18)

The regioselectivity is temperature-dependent too:



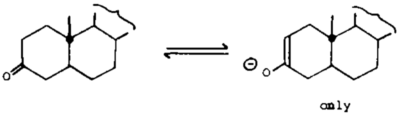
(19)

The thermodynamically controlled enolisation of the *trans* 2-decalone gives a mixture of the two possible enolates in almost the same proportions:



(17)

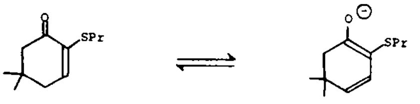
Nevertheless, if an angular methyl group is present in the decalin system, a single enolate is observed (conformational effects):



(20)

In case of α,β-ethylenic ketones or β-aryl-ketones, the thermodynamic enolate is the more conjugated one:

(21)



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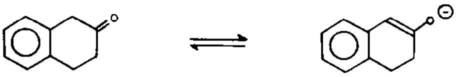
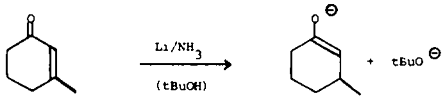
(15),(22)



(23)

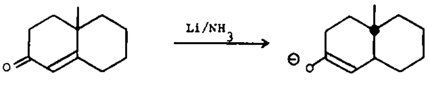
2.2 *Enolates made by action of a metal or an organometallic compound on an α-enone, a cyclopropyl ketone, or a ketone α-substituted by a leaving group*

2.2.1 *Metal-ammonia reduction of enones.* Metal-ammonia reduction of enones, generally carried out in presence of a better proton donor than ammonia (tBuOH for example), gives enolates regiospecifically, for instance:



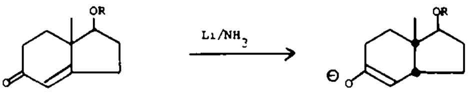
(24)

This method is especially useful in case of derivates of octalone. Indeed such a reduction affords an enolate regiospecifically which is impossible to make by direct abstraction of an hydrogen atom from the corresponding *trans* decalone (Stork):



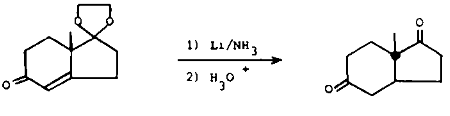
(3),(25)

Reduction of the homologous hydrindenones also gives enolates regiospecifically, but leads to a *cis* ring junction:



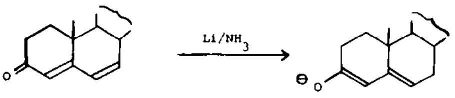
(26)

Two authors claimed that the reduction of the following ketal leads to a *trans* fused ring system,[27] but this result seems doubtful:[28]



(27)

Dienones are reduced too by lithium in ammonia:



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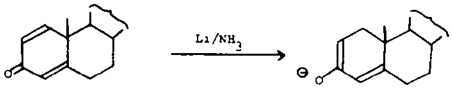
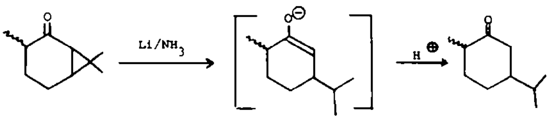


(29)

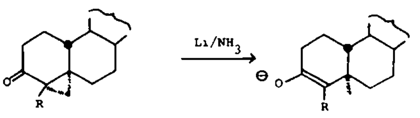
2.2.2 *Reduction of cyclopropylketones by a metal in ammonia.* The reductive cleavage of cyclopropylketones by lithium in ammonia is controlled by stereoelectronic factors (Dauben).[30]

Stork showed that such a process leads to enolates regiospecifically.[31]



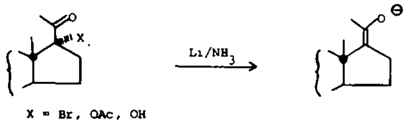
(30)

This method is especially convenient to introduce an angular methyl group stereospecifically:[30,31]



(31)

2.2.3 *Reduction of ketones α-substituted by a leaving group.* Metal-reduction of such ketones leads to enolates regiospecifically, for instance:



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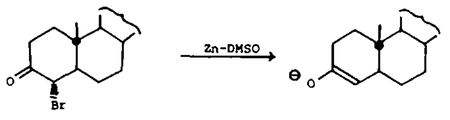
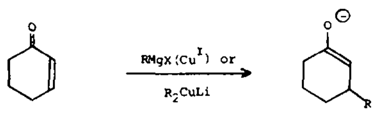


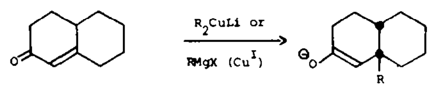
(33)

2.2.4 *Conjugate addition of organometallic compounds to α,β-ethylenic ketones.* 1,4-addition of Grignard reagents (in presence of catalytic amounts of a cuprous salt) or lithium organocopper reagents to α,β-ethylenic ketones leads to enolates regiospecifically:



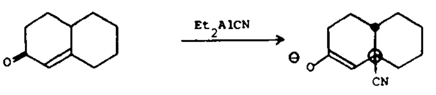
(34)

Addition of such reagents to octalone gives a *cis*-fused decalone:



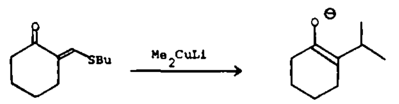
(34)

In contrast, addition of the Nagata reagent to the same enone leads to the *trans* isomer:



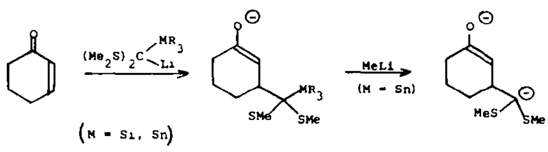
(35)

Coates reports the addition of dimethylcuprolithium to α-thiomethylene-ketones, a convenient method to introduce an isopropyl group in an indirect manner:



(36)

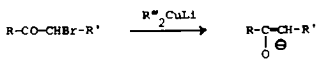
Successful conjugate addition of a "masked" acyl anion was performed by Seebach:



(37)

2.2.5 *Action of lithium organocopper reagents on* α-halogenated ketones.

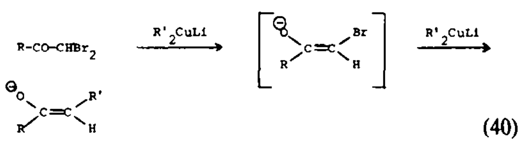
α-Monobrominated ketones:



$$\text{R-CO-CHBr-R}' \xrightarrow{\text{R}''_2\text{CuLi}} \text{R-}\underset{\text{O}^{\ominus}}{\text{C}}\text{=CH-R}'$$

(38),(39)

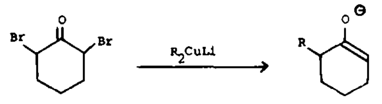
α-Dibrominated ketones (Dubois):



(40)

α,α'-Dibrominated ketones:

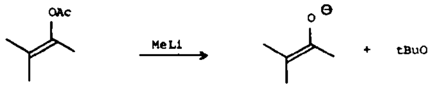
The action of a lithium organocopper reagent on an α,α'-dibrominated ketone gives an enolate regiospecifically, possibly via a cyclopropanone (Posner):



(38),(41)

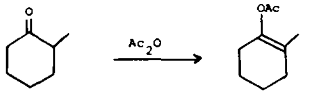
2.3 *Enolates made by cleavage of enol esters or silyl enol ethers*

Enol acetates (House). Enol acetates are cleaved by methyllithium, the by-product is lithium tertiobutylate, a strong base which can induce side-reactions.



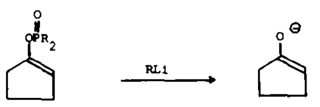
(42)

Enol acetates are made by enolate-trapping by means of acetic anhydride[18] or by direct acetylation of ketones:



(18)

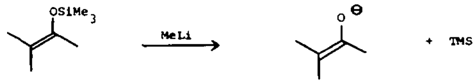
Phosphorated enol esters (Borowitz). These esters are cleaved by organolithium compounds:



(43)

Such esters are made by enolate-trapping[43] or by action of a phosphonate or a phosphite on an α-halogenated ketone.[44]

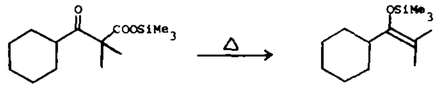
Silyl enol ethers (Stork). These ethers are cleaved by organolithium compounds, the by-product is neutral (tetralkylsilane).



(7e)

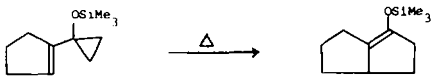
Such ethers are cleaved too by lithium amide[45,46] or by benzyltrimethylammonium fluoride.[47]

Silyl enol ethers are obtained *inter alia*: by enolate-trapping by means of trialkylchlorosilane,[48] by direct silylation of ketones using a trialkylchlorosilane in presence of a tertiary amine,[8] by silatropic rearrangement (Coates):



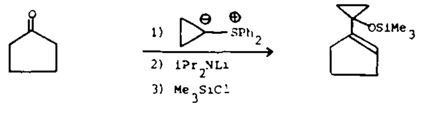
(49)

or by thermal rearrangement of vinylsiloxycyclopropanes (Trost):



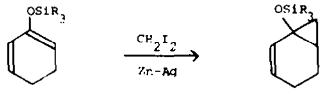
(50)

Starting vinylsiloxycyclopropanes are prepared by reaction of the Trost reagent on a ketone, followed by silylation:



(50)

or by cyclopropanation of dienol silyl ethers (Conia):



(51)

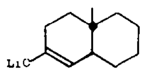
3. SYNTHETIC USES OF REGIOSPECIFICALLY GENERATED ENOLATES

3.1 *General aspects*

In general, enolates mentioned in the previous chapter, except the thermodynamic ones, are ***regiounstable.***

Nevertheless, in the absence of a sufficiently acidic proton-donating source, these enolates do not equilibrate.

Thus, the enolate **5** can be desolvated in vacuum at room temperature and then resolvated in ether without any equilibration into the thermodynamically more stable enolate **6**.[52]



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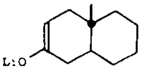


6

Equilibration of enolates results of a proton exchange. However the protonation takes place only if the pK of the proton source is near (or lower) the pK of a ketone (*ca.* 20). We have to consider three origins for a proton donor: the starting ketone itself, the protic solvent possibly used, and reaction products (ketones in general). Several factors can occur in the equilibration of a couple of enolates:

(a) *Nature of the enolate.* Certain enolates (e.g. cyclopentanone enolates) are well-known to undergo rapid equilibration.[7a,41,53] Consequently the use in synthesis of such enolates requires very mild trapping-conditions.

(b) *Temperature.* A rising of temperature assists proton-exchange, therefore the equilibriation.

(c) *Nature of the counter-ion.* The covalent character of the enolate (therefore its regiostability) increases as the associated cation becomes less electropositive, thus sodium and potassium enolates equilibrate fast, whereas magnesium, lithium, zinc, copper and aluminium enolates equilibrate much slower.[4,46]

(d) *Nature of the solvent.* Protic solvents of pK near or lower to 20 must be avoided, thus the enolate **5** mentioned bove can be changed into **6** (thermodynamically more stable) in presence of tertiobutyl alcohol (pK *ca.* 19) but not in presence of aniline (pK *ca.* 25).[52] Polar solvents are to be avoided too, because they dissociate ion-pairs, therefore they promote equilibration. Nevertheless some regiospecific alkylations take place even in presence of HMPA.[41]

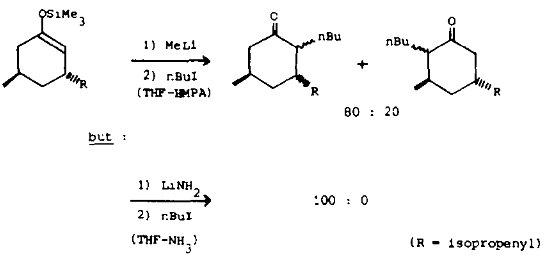
As a general rule low-energy-activation reactions (addition reactions: e.g. aldolisation) are preferred to higher energy-activation reactions (substitution reactions: e.g. alkylation).

3.2 *Carbon-carbon bond forming reactions*

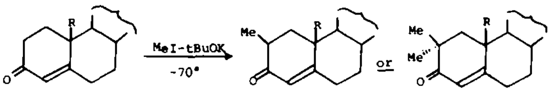
3.2.1 *Alkylation.* The first regiospecific alkylation was reported by Kon and Nutland, they alkylated the thermodynamic enolate of pulegone (*vide supra*).[1]

Fifteen years ago Stork succeeded in the alkylation of a regiounstable enolate. Such a result is due to the fact that the alkylation is faster than enolate equilibration.[3]

However partial equilibration can be observed in such reactions, especially in very polar solvents, for instance:[46]



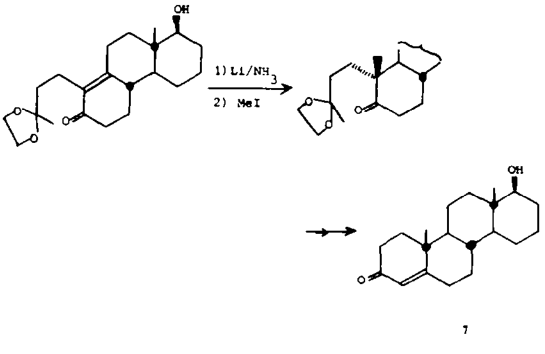
Kinetically controlled methylation of steroidal ketones takes place when the system MeI + tBuOK is used, in an aprotic solvent, at low temperature. According to the experimental conditions, the authors get a mono or a dimethyl derivate:[54]



R = H, Me

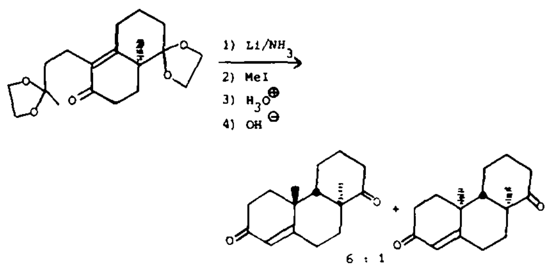
The stereochemistry of alkylation can be controlled by stereoelectronic factors, thus, with a cyclohexanone derivative the *axial* entry of the alkyl group is generally favored, except when a strong steric factor (e.g. 1,3 diaxial interaction) prevails.[55]

Such a control has been used by Stork to introduce the 19 angular methyl group, in a regiospecific and a stereospecific manner, in his synthesis of D-homotestosterone **7**.[56]

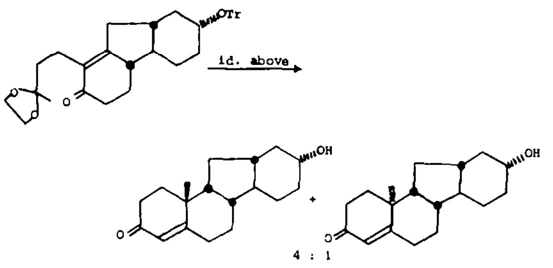


7

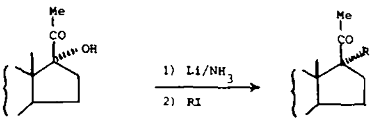
Ireland used the same sequence to prepare *trans-syn-trans* perhydrophenanthrene derivatives.[57]



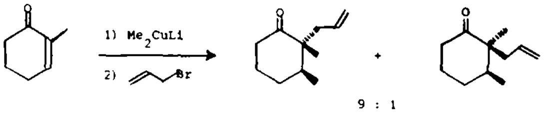
like Fried *et al.* in the synthesis of C-nor-D-homo-steroids.[58]



Several other authors observe such a stereoselectivity in regiospecific alkylations, like Weiss:[59]

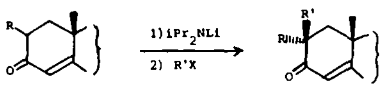


Boeckman:[60]



(Note the major *trans* relationship between the two incoming groups).

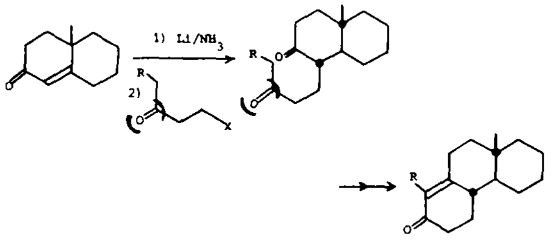
And Reusch:



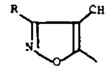
(61)

(Note the *axial* entry of the alkyl group in this last reaction.)

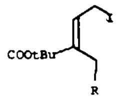
An important application of the regiospecific alkylation is the introduction of a chain bearing a "masked" carbonyl function which will be used further in an annelation reaction:[2]



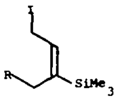
To attain this end various reagents were prepared, like 4-chloromethylisoxazoles **8**,[62] iodotiglates **9**[63] and iodomethylvinylsilanes **10**:[64]



8

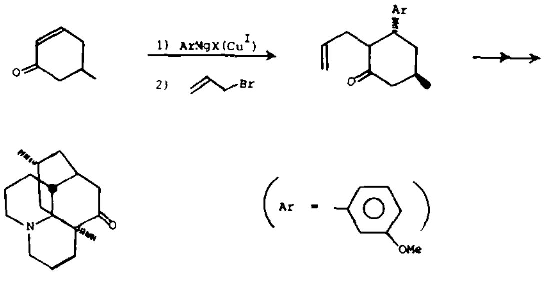


9



10

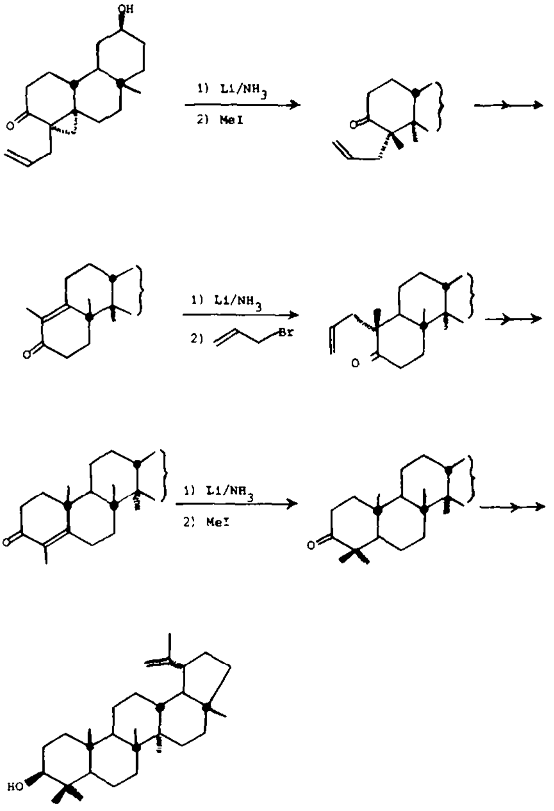
The regiospecific alkylation of enolates has been used in several total syntheses of natural compounds, like lycopodine **11**:[65]



11

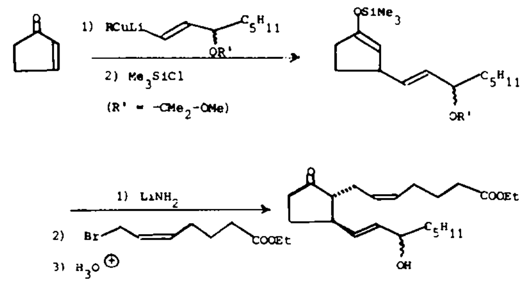
Note. This reaction is the first example of a regiospecific alkylation of an enolate generated by conjugate addition of an organometallic compound to an α-enone.

Likewise in three steps of the synthesis of lupeol **12**:[31]



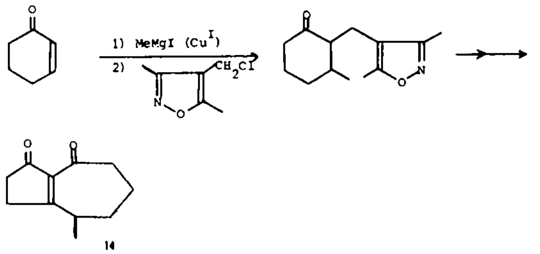
12

A regiospecific alkylation was used in the synthesis of a 11-deoxy prostaglandin **13**:[45]



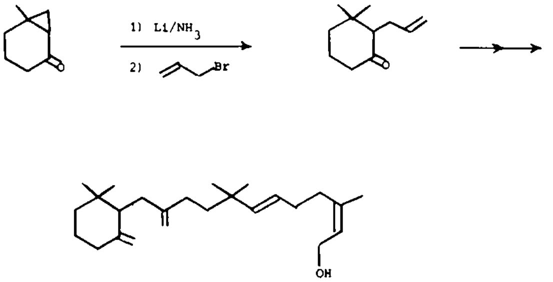
13

Also in a synthesis of substituted hydroazulenes, e.g. **14**, by Kretchmer:[66]



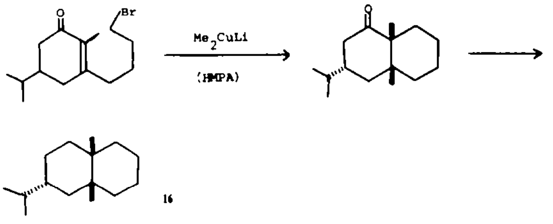
14

and by Grieco in the synthesis of diumycinol **15**:[67]



15

An intramolecular regiospecific alkylation was used by Posner in the synthesis of valerane **16**:[41]

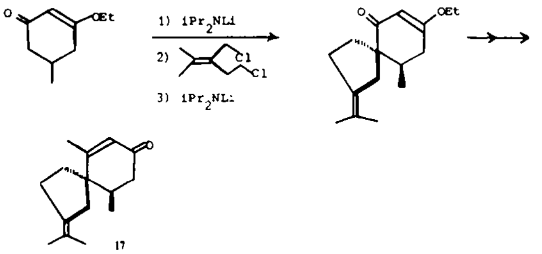


16

Several features of this conjugate addition-cycloalkylation process deserve comment.

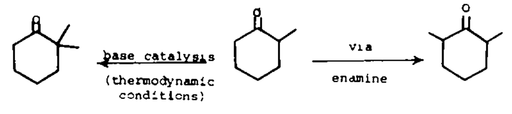
The methyl conjugate addition proceeds stereoselectively with axial introduction of the methyl group (*trans* to the isopropyl group, compare to the synthesis of lycopodine **11**). Likewise, the stereoelectronic requirements of the cycloalkylation step strongly favor a high degree of stereoselectivity in formation of a *cis*-1-decalone system, as previously reported by Conia.[7a]

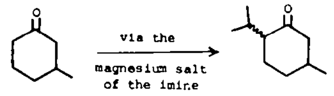
In the same way the key-step of the Stork synthesis of the β-vetivone **17** is an inter and intramolecular double regiospecific alkylation:[68]



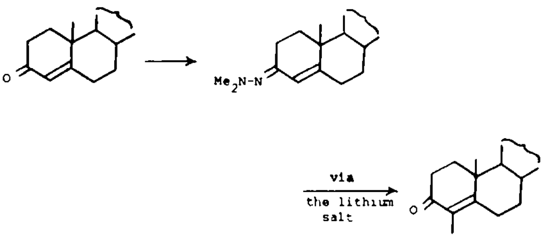
17

Note. Another method to control the regioselectivity in ketone alkylation was developed by Stork using, instead of enolates, enamines,[69] magnesium salts of imines[70] and lithium salts of N,N-dimethylhydrazones:[71]

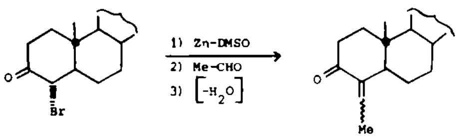




[see also (72)]

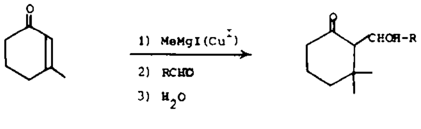


3.2.2 *Aldolisation*. One of the first examples of regiospecific aldolisation is due to Spencer:



(33)

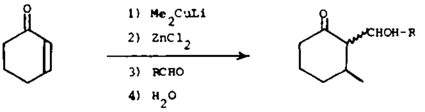
The success of such an aldolisation depends on the nature of the electrophile: aldehydes work when ketones fail.[73] The nature of the associated cation appears determinant too, thus magnesium enolates give aldols in good yields:



(74)

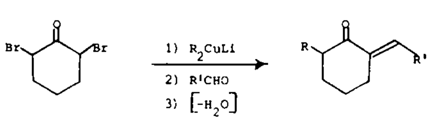
In contrast, Smith observes that copper enolates do not react with aldehydes, but after their transformation into zinc enolates (by exchange with $ZnCl_2$) the addition takes place:

(The part taken by $ZnCl_2$ in aldol condensation was first reported by House[75])



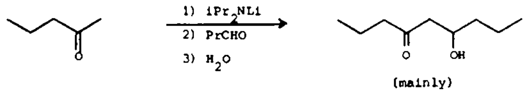
(73)

Nevertheless, in opposition to Smith, Posner relates a fruitful aldol condensation, using copper enolates:

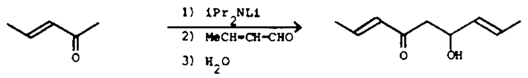


(41)

Stork[12] and Gaudemar[76] use kinetic enolates in regiospecific aldolisations:

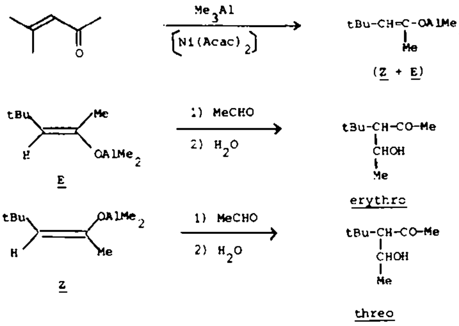


(12)



(12)

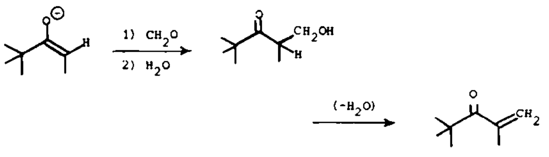
The following interesting observation was reported about the stereochemistry of aldolisation:[77]



(About the stereochemistry of the aldol condensation, see also the Ref. 75.)

Formaldehyde as an electrophile in aldol condensation leads to α-methylene-ketones **18**, which are useful intermediates in synthesis (e.g. as acceptors in Michael addition or in conjugate addition of organometallic reagents).[52]

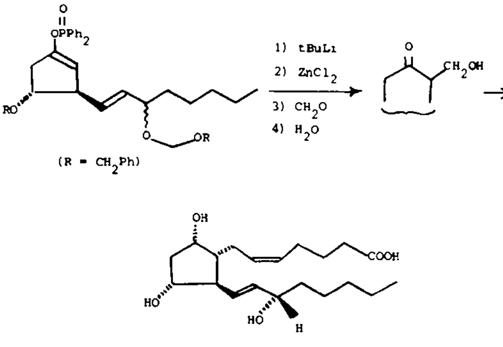
Note: Formaldehyde, a strong electrophile, can react at very low temperature with enolates, thus it can be used as trapping agent for certain enolates which undergo rapid equilibration under usual trapping conditions.



18

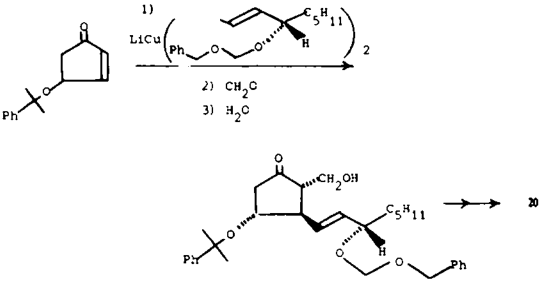
Such a formaldehyde-trapping sequence was used in the synthesis of the 19-nor D-homotestosterone, **19**:[52]

just as in two syntheses of the prostaglandin F2 α, **20**:



20

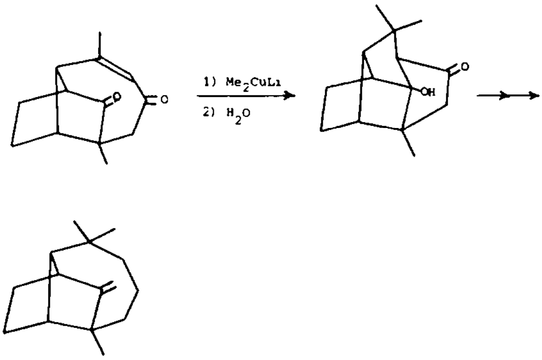
(78)



(+ mirror image of the 15-epi-isomer)

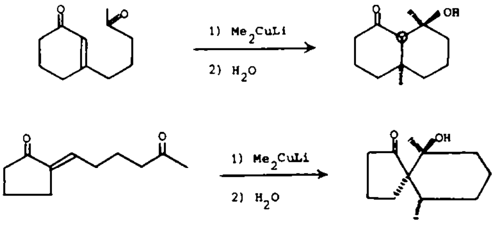
(79)

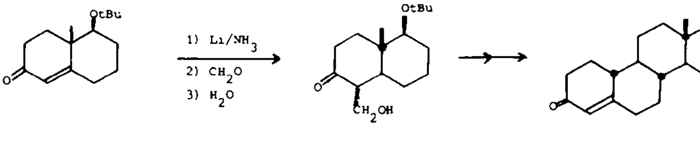
An intramolecular regiospecific aldolisation was observed by McMurry in his synthesis of longifolene **21**:[80]



21

and more recently by Näf *et al.*:[81]

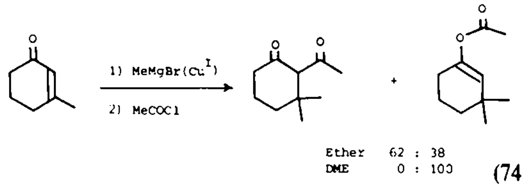




19

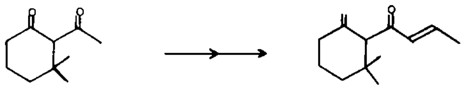
(Note the high reactivity of copper enolates in *intramolecular* aldol condensation compared to their lower reactivity in intermolecular aldolisation)

3.2.3 *Acylation.* The main limitation in the acylation of enolates is the competitive O-acylation, which becomes especially important (if not exclusive) when polar solvents are used:



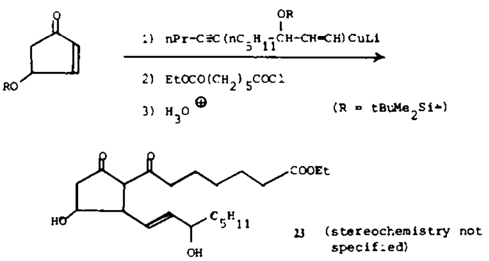
(74)

The previous C-acylated compound is used by Näf in the synthesis of the γ-damascone **22**:[74]



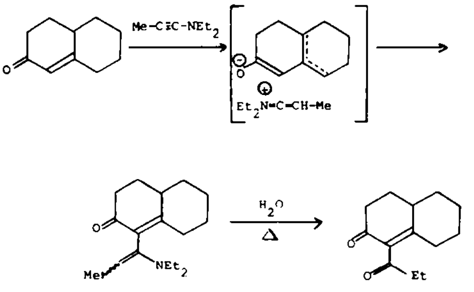
22

The same sequence was applied by Tanaka in the synthesis of a 7-oxo prostaglandin **23**:[82]

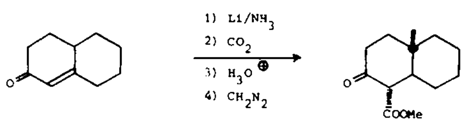


23 (stereochemistry not specified)

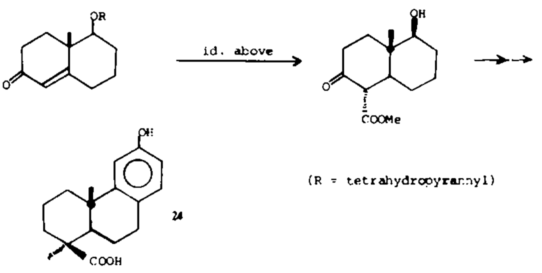
Note. Ynamines as acylating reagents. Ynamines can react with certain hindered transoïd enones, like octalone. They work as base and at the same time as enamination agent, allowing the indirect regiospecific introduction of an acyl group:[83]



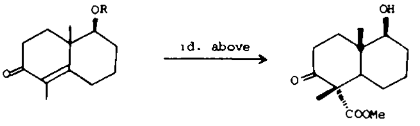
3.2.4 *Carboxylation.* The first example of a regiospecific carboxylation is due to Stork:[3,4]



Spencer used the former sequence in his synthesis of podocarpic acid **24**:[84,85]

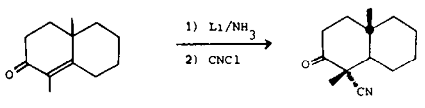


In a similar reaction the same author observes that the carboxyl group is introduced in equatorial position (*trans* to the angular methyl group):

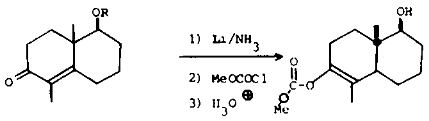


(84)

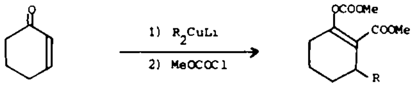
A similar stereochemical observation was reported by Kuehne, in the cyanation of such enolates, by means of cyanogen chloride:[86]



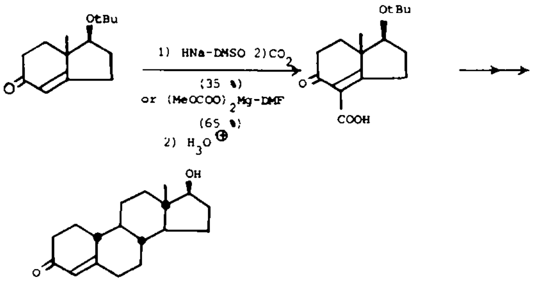
Spencer observes only O-carbomethoxylation in an enolate-trapping by methyl chlorocarbonate:[84]



In contrast, using the same reagent, Salomon got the enol carbonates corresponding to C-carbomethoxylation:[87]



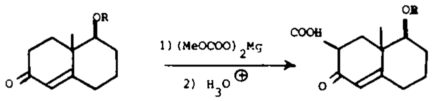
In their synthesis of the 19-nortestosterone **25**, Hajos *et al.* carbonate the thermodynamic enolate of an hydrindenone. They report that yields are improved, when they use magnesium methylcarbonate instead of carbon dioxide:[88]



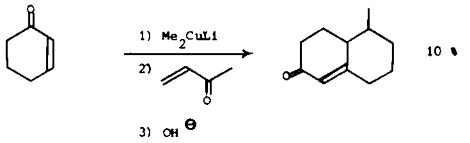
25

Note like most of the other reactions with this kind of enolate, the carbonation of the intermediary thermodynamic dienolate anion takes place at the α-position.[89]

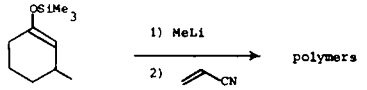
In contrast the carbonation of the homologous octalone, using magnesium methylcarbonate, takes place at the "kinetic" position:[88]



3.2.5 *Michael addition.* The action of an enolate, in *aprotic* media on an α,β-ethylenic ketone or an α,β-ethylenic nitrile gives the desired adducts in poor yields (if not polymers only), because of the important polymerization of these Michael acceptors:

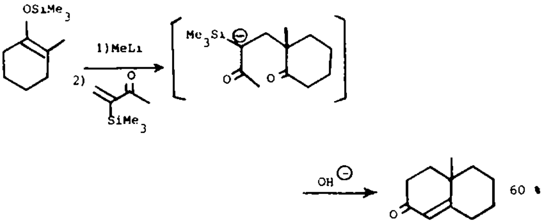


(90)



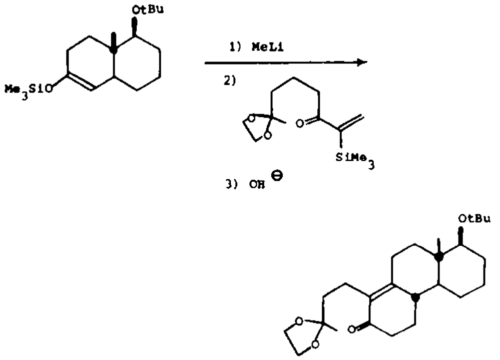
(46)

To avoid such a polymerization, Stork introduced the α-silyl-vinylketones, a new class of reagents in which the atom of silicon, due to its vacant *d* orbitals, can stabilize an adjacent negative charge:



(91)

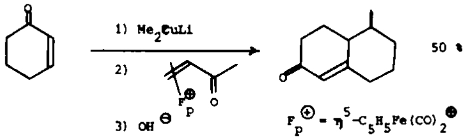
These new annelating agents were used to trap regiounstable enolates[92–94] for instance:



(92)

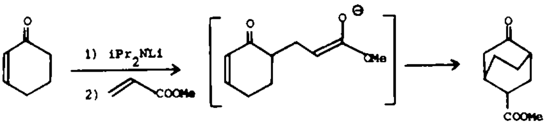
(Note the double utilization of silicon derivatives in these last reactions)

The above mentioned polymerization can be avoided also, using, instead of α,β-ethylenic ketones, certain of their metallic complexes:

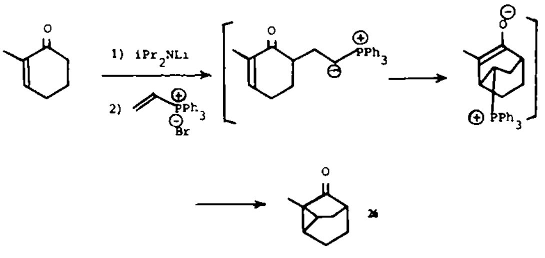


(95)

Lee reports a case of an intermolecular Michael addition followed by an *intramolecular* addition:[96]

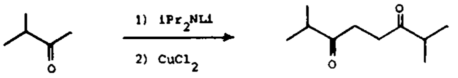


Such a sequence was used in an efficient synthesis of the tricyclic ketone **26**, in a single step, from a cyclohexenone:[97]

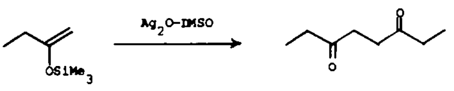


26

3.2.6 *Coupling reactions.* Saegusa prepares several 1,4-diketones by coupling of regiospecifically generated enolates, by means of copper salts or silver oxide:



(98)

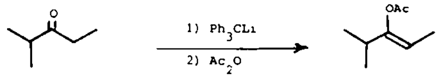


(99)

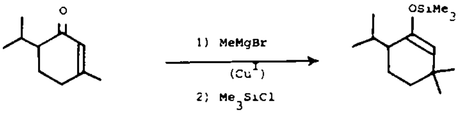
Such a method is convenient to prepare symetric diketones (from a single enolate), but the cross-coupling of two enolates generally leads to a mixture of several diketones.

3.3 *Miscellaneous reactions*

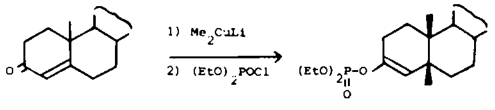
(a) *O-Esterification and O-silylation.* The regiospecifically generated enolates can be trapped by anhydrides, trialkylchlorosilanes, or phosphochloridates to lead to the corresponding O-derivatives.



(42)



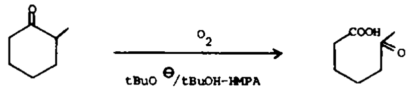
(48)



(44)

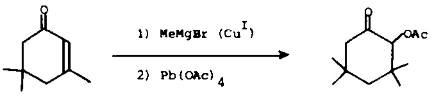
In general, such derivatives are easily purified and can be used, for instance, to regenerate the starting enolates.

(b) *Oxidation, hydroxylation.* The enolates can be oxidized directly by means of molecular oxygen:



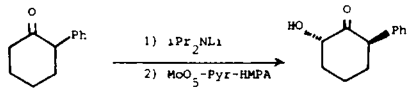
(100)

by lead tetracetate:



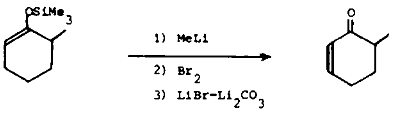
(101)

or by a metal peroxide:



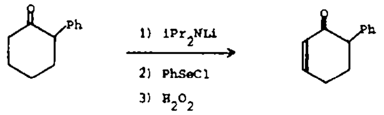
(11)

The indirect oxidation can be performed by bromination of the enolate, followed by elimination of HBr (Stotter):

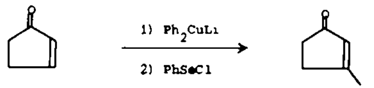


(102)

or by seleniation, followed by oxidative elimination (Reich):

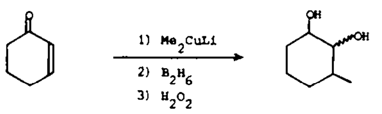


(10)



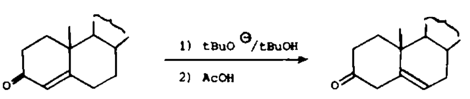
(10)

One can realize the hydroxylation of enolates by hydroboration, followed by hydrogen-peroxide oxidation:



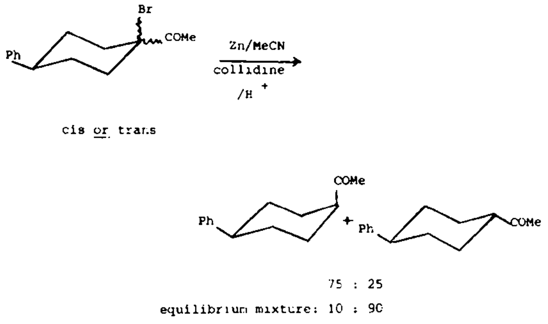
(103)

(c) *Protonation (deuteriation).* The protonation of an enolate allows introduction of an atom of hydrogen (deuterium) regiospecifically, for example:



(104)

The last process, called "deconjugation", allows to prepare β,γ-ethylenic ketones from the corresponding α,β-isomers. The protonation of an enolate is kinetically controlled, thus one can observe a certain stereoselectivity in such a process:



(105)

4. CONCLUSION

An important part of the considerable successes registered these last few years in organic synthesis originates from the introduction of new regioselective and stereoselective processes. We have seen that, despite their relative novelty, enolates formed regiospecifically from ketones already are the key-intermediates in a number of syntheses of sometimes very complicated compounds.

They are new, sophisticated weapons in the armory of the Chemists.

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