Alkoxide-Mediated Preparation of Enolates from Silyl Enol Ethers and Enol Acetates − From Discovery to Synthetic Applications

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Dedicated to Professor Jean-Marie Poirier who passed away on May 7th, 1997

Keywords: Aldol reactions / Alkylations / Carbanions / Chirality / Terpenoids

A novel route to enolates from silyl enol ethers and enol acetates has been studied and optimized. A range of lithium, sodium and, particularly, potassium enolates were quantitatively prepared under very simple conditions. This new methodology involved an alkoxide-mediated reaction to form enolates, which were subjected to regiospecific alkylation, aldolisation, or Michael reaction. In some cases, only a catalytic amount of alkali metal alkoxides was needed. A new prenylation method, leading to polyene aldehydes belonging to the vitamin A series, has also been described. Finally, a new concept based on retroaldol reaction has been applied to asymmetric synthesis.

Introduction

Among the intermediates widely used in the construction of carbon−carbon bonds, enolates − and, in particular, regiospecifically generated enolates − have been of continuing interest. The last three decades have witnessed huge research activity in the field of enolate chemistry, made possible by the discovery of methods for the formation and use of preformed enolates, mainly lithium enolates. Classically, alkylation, aldol or Michael reactions have been investigated through the use of preformed enolates. Since the pioneering work of Stork[1−2] and House[3−5] on the formation of lithium enolates by cleavage of trimethylsilyl enol ethers with methyllithium, this method has been widely used in synthetic organic chemistry. In rare cases, enolates have been prepared from silyl enol ethers by means of alkali amides in a THF/ammonia mixture.[6−7] Other methods have required ammonium or sulfonium fluorides: for example, tetrabutylammonium fluoride (TBAF) has been used to prepare enolates from silyl enol ethers,[8−16] and tris(diethylamino)sulfonium enolates have been obtained from silyl enol ethers and tris(diethylamino)-sulfonium difluorotrimethylsiliconate.[17−20] An anhydrous TBAF equivalent − tetrabutylammonium difluorophenylstannate − has been prepared by Gingras.[21]

Dominique Cahard was born in Fecamp (Normandy) in 1968. He studied chemistry at the University of Rouen and completed his thesis in the laboratory of Prof. Pierre Duhamel and Dr. Lucette Duhamel under the guidance of Prof. Jean Marie Poirier. He then spent 19 months as a postdoctoral research associate with Prof. Christopher McGuigan at Southampton University (UK), then at the Welsh School of Pharmacy in Cardiff (Wales, UK). He also spent a short period working with Prof. Tadashi Nakata at RIKEN, Tokyo (Japan). In 1996 he joined the CNRS at the University of Rouen. His current interests are mainly in the field of enantioselective synthesis, with emphasis on electrophilic fluorination and phase transfer catalysis.

Pierre Duhamel, born in 1931 in Normandy (France) received his “Doctorat es Sciences” in 1961 from the University of Paris, under the supervision of Prof. Albert Kirrmann (Ecole Normale Supérieure, Paris). During the period from 1964−1996 he was Professor of Organic Chemistry at the University of Rouen. He has been the recipient of awards of the French Chemical Society (1962, 1989), the Society for encouraging National Industry (1986) and the French Academy of Sciences (1993). He was the co-founder of ANORCQ (Anglo Norman Organic Chemistry Colloquium) with Dr. Stuart Warren (University of Cambridge). His research interests include the development of new methodologies in synthetic and asymmetric chemistry. In collaboration with Dr. Jeanne-Marie Lecomte (Bioprojet) and Prof. Jean-Charles Schwartz (INSERM), he was involved in the design of enzyme inhibitors.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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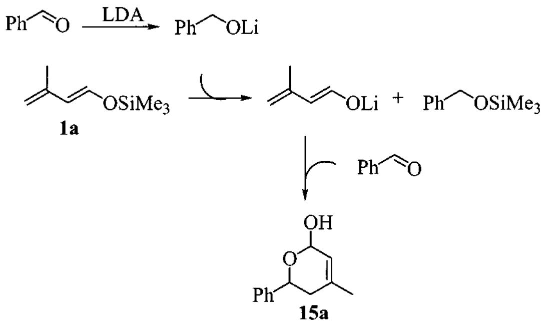
In our laboratory, the Stork method has been extended to the trimethylsilyl dienol ether of prenal, which has exhibited regioselective aldolisation at the γ-site of the dienolate.[22–23] Enol acetates have also been considered as enolate precursors, but these require two equivalents of methyllithium, giving lithium *tert*-butoxide as an undesirable by-product.[4] In this review, we summarise the current status of the alkoxide-mediated preparation of enolates from silyl enol ethers and enol acetates, as well as the scope of synthetic applications for this new methodology.

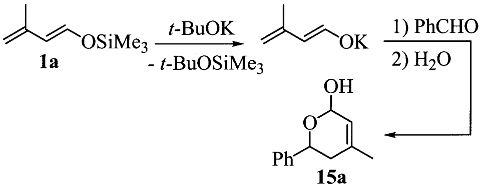
Cleavage of Silyl Enol Ethers and Enol Acetates with Alkali Alkoxides

The discovery and subsequent development of alkoxide-mediated reactions of silyl enol ethers arose from investigations concerning an unexpected by-product isolated from a crude reaction mixture. At that time we were involved in prenylation reactions with the aid of the lithium dienolate of prenal, obtained from the corresponding trimethylsilyl enol ether and methyllithium. Mechanistic considerations led us to postulate an allylic deprotonation, followed by a 1,5-shift of the trimethylsilyl group from the oxygen to the carbon atom. In fact, we found that the trimethylsilyl enol ether of prenal reacted with benzaldehyde in the presence of LDA to produce mainly the hydroxydihydropyran **15a** and benzyloxytrimethylsilane, in equal amounts (Scheme 1).



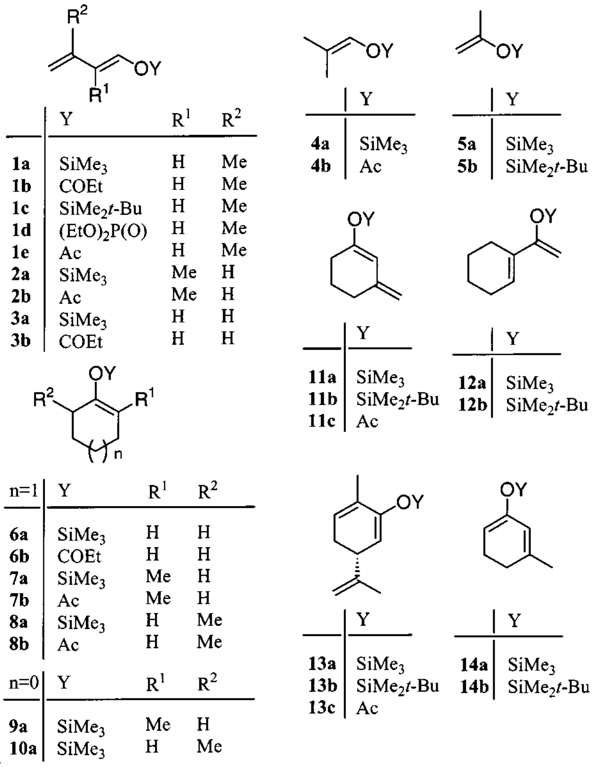
Scheme 1

We suggested a reduction of benzaldehyde by LDA[24] and a cleavage of the oxygen–silicon bond of the trimethylsilyl enol ether **1a** by the resulting phenylmethoxide, leading to benzyloxytrimethylsilane and the prenal lithium dienolate, which reacted with benzaldehyde. On this assumption, we then examined the ability of alcoholates to cleave silyl enol ethers. Potassium *tert*-butoxide was selected in the first instance. The silyl enol ether of prenal **1a** was treated with 1 equiv. of potassium *tert*-butoxide at low temperature (−78 °C) in THF. Reaction, as monitored by thin layer chromatography, was complete within 60 min. Then benzaldehyde was added to yield the dihydropyran **15a**; this being consistent with a γ-addition of the dienolate onto benzaldehyde, followed by an intramolecular attack of the alkoxide on the carbonyl group (Scheme 2).



Scheme 2

Thus, we had demonstrated for the first time the ability of an alkali metal alkoxide to generate an enolate from a silyl enol ether.[25] Furthermore, the only side product gen-



	Y	R1	R2
1a	$SiMe_3$	H	Me
1b	COEt	H	Me
1c	$SiMe_2t$-Bu	H	Me
1d	$(EtO)_2P(O)$	H	Me
1e	Ac	H	Me
2a	$SiMe_3$	Me	H
2b	Ac	Me	H
3a	$SiMe_3$	H	H
3b	COEt	H	H

	Y
4a	$SiMe_3$
4b	Ac

	Y
5a	$SiMe_3$
5b	$SiMe_2t$-Bu

n=1	Y	R1	R2
6a	$SiMe_3$	H	H
6b	COEt	H	H
7a	$SiMe_3$	Me	H
7b	Ac	Me	H
8a	$SiMe_3$	H	Me
8b	Ac	H	Me

n=0	Y	R1	R2
9a	$SiMe_3$	Me	H
10a	$SiMe_3$	H	Me

	Y
11a	$SiMe_3$
11b	$SiMe_2t$-Bu
11c	Ac

	Y
12a	$SiMe_3$
12b	$SiMe_2t$-Bu

	Y
13a	$SiMe_3$
13b	$SiMe_2t$-Bu
13c	Ac

	Y
14a	$SiMe_3$
14b	$SiMe_2t$-Bu

Scheme 3

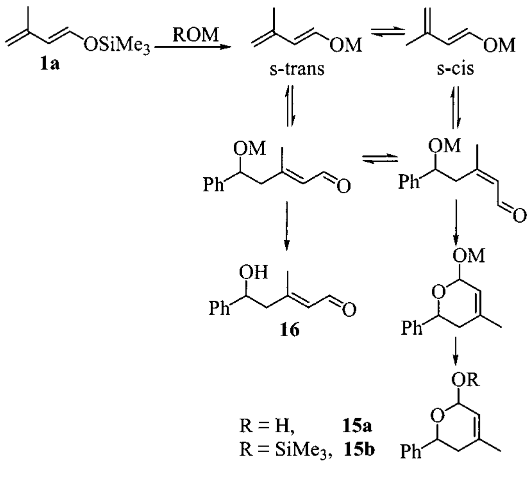
Table 1. Formation of potassium enolates from silyl enol ethers and *t*BuOK; reaction with hard electrophiles

Silyl enol ether	Cleavage *T* [°C]	Time [min]	Electrophile	Product	Yield [%]
1a	−78	60	EtCOCl	**1b**	94
1a	−78	60	$tBuMe_2SiCl$	**1c**	90
1a	−78	60	$(EtO)_2P(O)Cl$	**1d**	86
2a	−78	60	MeCOCl	**2b**	84
3a	−78	60	EtCOCl	**3b**	91
4a	−50	45	MeCOCl	**4b**	72
5a	−30	40	$tBuMe_2SiCl$	**5b**	74
6a	−20	45	EtCOCl	**6b**	79
7a	−20	45	MeCOCl	**7b**	85
8a	−20	40	MeCOCl	**8b**	84
11b	−20	90	$tBuMe_2SiOTf$	**11b**	94
12b	−20	120	$tBuMe_2SiOTf$	**12b**	70
13b	−78	90	$tBuMe_2SiOTf$	**13b**	96
14b	−78	90	$tBuMe_2SiOTf$	**14b**	83

erated during the cleavage of the oxygen−silicon bond had been the silyl ether of the alcoholate, which is inert under the reaction conditions used. Building on this discovery, we investigated the scope and limitations of this new methodology. Firstly, we examined the formation of enolates from silyl enol ethers, and also from enol acetates of various ketones and aldehydes, by trapping them with hard electrophiles (Scheme 3 and Table 1). The trimethylsilyl enol ethers were obtained in classical manner from the corresponding carbonyl compounds, by treatment with chlorotrimethylsilane and triethylamine in the presence of sodium iodide in acetonitrile.[26] When kinetically generated enolates were required to produce silyl enol ethers (e.g., compound **8a**), LDA was employed as base.[3]

The trimethylsilyl enol ethers were treated with 1 equiv. of potassium *tert*-butoxide in THF. We noticed that, for complete cleavage, silyl enol ethers of ketones needed higher reaction temperatures than those derived from aldehydes, as evidenced by yields obtained after quenching with hard electrophiles: acetyl and propionyl chloride, *tert*-butyldimethylsilyl chloride, *tert*-butyldimethylsilyl trifluoromethanesulfonate, or diethyl chlorophosphate (Table 1).

Worth noting is that the kinetic enol ether **8a**, with a regioisomer ratio of 99:1, afforded the enol acetate **8b** with the same regioisomer ratio, clearly showing that acylation proceeded with retention of the regiochemical integrity of the silyl enol ether. Other silyl enol ethers, bearing groups bulkier than trimethyl, were subjected to the alkoxide-mediated cleavage. Formation of the enolates from *tert*-butyldimethylsilyl enol ethers also occurred, but at a slower rate. Although potassium *tert*-butoxide was very efficient in enolate formation, we also examined primary and secondary alcoholates, as well as other cations (lithium and sodium), in the reaction between the silyl enol ether of prenal and benzaldehyde (Scheme 4).



Scheme 4

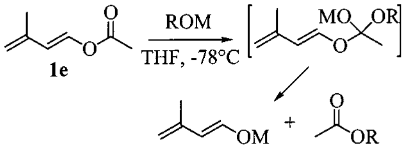
We found that all the alkali metal alkoxides examined bring about this chemical transformation (Table 2). We observed that potassium and sodium *tert*-butoxides resulted in the dihydropyran **15a**, while lithium *tert*-butoxide yielded **15a** and the hydroxy enaldehyde **16** as a single (*E*) isomer. This result may be due to the more covalent nature of the intermediate lithium alcoholate, which prevents its isomerisation and cyclisation. However, independently of the composition of the initial product mixture, acidic treatment allowed access to the corresponding polyenaldehydes.

Table 2. Cleavage of the silyl dienol ether of prenal with various alkali alkoxides; reaction with benzaldehyde

ROM	Equiv.	Time [min]	Yield [%] 15a	15b	16	Overall yield [%]
*t*BuOK	1	10	86			86
*t*BuONa	1	15	72			72
MeONa	1	15	74			74
*t*BuOLi	1	15	42		28	70
MeOLi	1	15	46		32	78
PhCH$_2$OLi	1	15	41		28	69
*t*BuOK	0.1	30	14	68		82
*t*BuOK	0.01	60	33	48		81

In some cases, the silylated dihydropyran **15b** was present after the workup. We may therefore reasonably postulate that **1a** had been cleaved by the anion of dihydropyran **15a**. As a consequence, a substoichiometric amount of alkoxide should be sufficient to initiate the reaction, with the anion of dihydropyran **15a** driving the reaction to completion. Indeed, the use of 0.01 equiv. of alkoxide resulted in the formation of dihydropyrans **15a** and **15b** in overall yields similar to those obtained using a stoichiometric amount of alkoxide (Table 2). Silylated compound **15b** was observed, but not in the expected yield, presumably due to its lability.

Finally, we have extended our methodology to enol acetates (Scheme 5). We have shown that alkoxides reacted with enol acetates under standard conditions (THF, −78 °C), resulting in the formation of the enolate and of an alkyl acetate.



Scheme 5

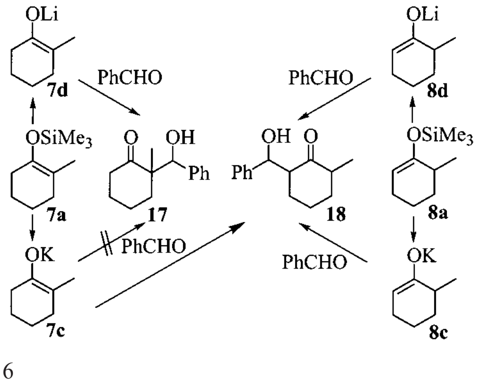
House's reaction traditionally requires 2 equiv. of MeLi, one for the preparation of the enolate and a second to react with the acetone produced, yielding lithium *tert*-butoxide.[5] In the light of our results, we reconsidered this well-documented reaction, arguing that the second equivalent of MeLi should not be necessary, since *t*BuOLi generated in situ should also be able to cleave the enol acetate. Indeed, 1 equiv. of MeLi on enol acetate **1e** resulted in an overall yield of 86% for the reaction with benzaldehyde (69% of **15a** and 17% of **16**, in agreement with previous results for lithium alkoxides).

Thus, we have demonstrated that enolates can be efficiently generated from silyl enol ethers or enol acetates in a very simple manner, by treatment with an alkali metal alkoxide. Enol derivatives of aldehydes, ketones, enaldehydes, or enones[25,27] have been used to illustrate the process. In aldolisation reactions, only a catalytic amount of alkoxide was needed, since we have shown that the aldol anion is able to cleave the silyl enol ether. Finally, an alkyl trimethylsilyl ether was produced, as a nonbasic by-product, during the reaction.

Regioselective Aldol Reaction and Alkylation of Unsymmetrical Ketones

Regioselective reactions of enolates are vitally important in synthetic organic chemistry. Kinetic deprotonation of unsymmetrical ketones classically leads to a single enolate − i.e., the less substituted one − while thermodynamically obtained enolates usually consist of a mixture of the two regioisomers. Because of this lack of convenient methods for regioselective and stereoselective preparation of potassium enolates, while lithium enolates have been widely studied, few publications concern their potassium counterparts. Having mastered the preparation of both lithium and potassium enolates, we undertook a set of experiments on silyl enol ethers of unsymmetrical ketones.

In the first instance, the aldol reaction was targeted. For this purpose, we prepared tri- and tetrasubstituted trimethylsilyl enol ethers (**8a** and **7a**) of 2-methylcyclohexanone. Potassium enolates **7c** and **8c** were prepared from **7a** and **8a**, respectively, with the aid of *t*BuOK (Scheme 6). Lithium enolates were obtained in only modest yields using *t*BuOLi, because of incomplete cleavage of the silyl enol ethers. We circumvented this drawback by first performing the cleavage with *t*BuOK, followed by metal exchange with lithium bromide.[28] Initially, enolates thus formed were trapped with acetyl chloride to ensure that their formation proceeded with retention of the regiochemical integrity of the silyl enol ethers. Then, certain of this retention, we examined the aldolisation with benzaldehyde. Results are reported in Table 3. As expected, trisubstituted lithium and potassium enolates **8d** and **8c** resulted in the aldol **18** (Scheme 6) as a mixture of the four diastereomers, which were isolated as pure products by flash chromatography.



Scheme 6

In the same manner, tetrasubstituted lithium enolate **7d** resulted in the aldol **17**. Starting from the potassium enolate **7c**, we obtained an unprecedented result; none of the expected aldol **17** was observed, but exclusive formation of the aldol **18** had taken place. A test experiment was conducted on a 1:1 mixture of silyl enol ethers **7a/8a**. Cleavage with *t*BuOK and treatment with benzaldehyde furnished **18** as the sole product, thus demonstrating that a mixture of silyl enol ethers, such as is often obtained in their preparation, may be used directly in this highly regioselective aldol reaction. We also wish to emphasise that starting from the same silyl enol ether and using its lithium or potassium enolate provided a regioselective route to either aldol **17** or **18**.

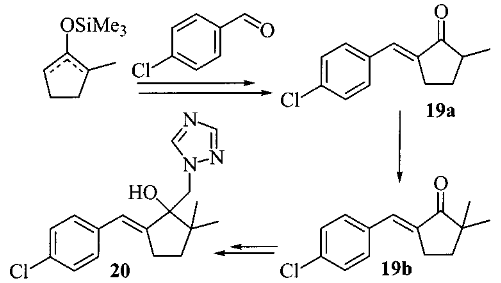
From a mechanistic point of view, the formation of the less constrained aldol **18** from potassium enolate **7c** is the result of the retroaldol reaction. Since potassium enolates **7c** and **8c** cannot equilibrate before the addition of the benzaldehyde, as proved by acetyl chloride trapping, only a cation effect can account for the formation of a single regioisomer. Indeed, in the case of potassium enolates, a retroaldolisation has been established. The primary product of reaction between enolate **7c** and benzaldehyde gave the aldolate of **17**, which equilibrated with the more stable aldolate regioisomer of **18** by a retroaldolisation. In order to provide more evidence of this mechanism, we treated aldol **17** with potassium hydride, and we recovered exclusively all four diastereomers of the aldol **18**, in the same ratio as when starting from **8a**. On the other hand, the same aldol **17** remained unchanged in the presence of methyllithium after 2 h at −78 °C. These experiments on regio- and stereoselectivity led us to conclude that the aldol reaction is under thermodynamic control with potassium enolates and under kinetic control with lithium enolates. Identical results were observed with trimethylsilyl enol ethers (**9a** and **10a**) of 2-methylcyclopentanone, as well as with the two regioisomeric trimethylsilyl enol ethers of the acyclic isobutyl methyl ketone.[28] Reactions with substituted benzaldehydes bearing electron-donating or electron-withdrawing groups, as well as with aliphatic aldehydes, were similar.[28]

We applied our new methodology to the synthesis of 2-[(4-chlorophenyl)methylidene]-5,5-dimethylcyclopentanone (**19b**), a key intermediate in the synthesis of the potent fungicide **20**, prepared until now from 2,2-dimethylcyclopentanone.[29] A mixture of regioisomeric trimethylsilyl enol ethers of 2-methylcyclopentanone was treated with *t*BuOK and *p*-chlorobenzaldehyde and the resulting aldolate was

Table 3. Aldolisation of enolates of 2-methylcyclohexanone with benzaldehyde

Silyl enol ether	Conditions	Enolate	Product (yield [%])	*threo*/*erythro*	*cis*/*trans*
8a	*t*BuOK + LiBr	**8d**	**18** (66)	1.3:1	1.1:1
8a	*t*BuOK	**8c**	**18** (80)	5.7:1	2:1
7a	*t*BuOK + LiBr	**7d**	**17** (72)	2.2:1	
7a	*t*BuOK	**7c**	**18** (78)	5.7:1	1.8:1

then treated with an excess of *t*BuOK for crotonisation, to yield the enone **19a**. Further enolisation and alkylation with methyl iodide gave the desired compound **19b** (Scheme 7). This expeditious transformation of 2-methylcyclopentanone trimethylsilyl enol ethers into enone **19b** occurs in a one-pot fashion with an overall yield of 80%, and avoids the laborious preparation of 2,2-dimethylcyclopentanone.[30]

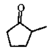
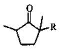


Scheme 7

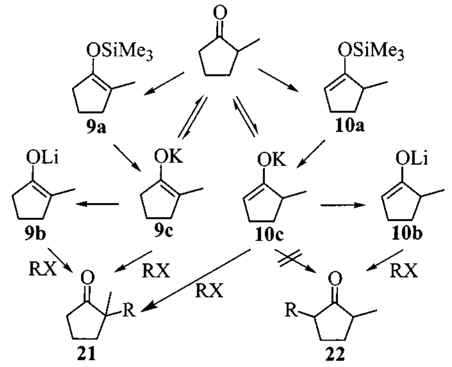
We have demonstrated that, with unsymmetrical ketones, a suitable choice of enolate counter-cation permits highly regioselective aldolisations. The synthetic advantage of this method is that any mixture of regioisomeric silyl enol ethers can be used to generate a single aldol product selectively. Thus, when the regiocontrolled preparation of silyl enol ethers of unsymmetrical ketones is difficult, our method may be of great utility. Our results are strikingly different from those of Kuwajima (ammonium enolates)[8–14] and Noyori (sulfonium enolates)[17–20] since, in spite of the use of naked enolates, retroaldolisation was prevented due to the formation of a trimethylsilyloxy aldol when a large excess of TMSCl was present in the reaction mixture[19] or when a catalytic amount of TBAF was used.[14]

Alkylation of enolates is a very important reaction for the construction of carbon–carbon bonds.[31] The literature reports intensive studies on lithium enolates but very few articles concerning potassium enolates. We carried out an in-depth comparative study on alkylation of regio- and stereocontrolled potassium and lithium enolates of unsymmetrical ketones obtained from their silyl enol ethers.[32] Results for the alkylation of 2-methylcyclopentanone are summarized in Table 4. Alkylating agents used were methyl iodide, allyl bromide, and benzyl bromide (−78 °C for potassium enolates; −15 °C for lithium enolates). As previously noted, lithium enolates were prepared by cleavage of the trimethylsilyl enol ethers by *t*BuOK and subsequent metal exchange with LiBr. We observed that lithium enolates **9b** and **10b** resulted predominantly in the expected monoalkylated ketones **21** and **22**. In contrast, both potassium enolates **9c** and **10c** surprisingly led to the most substituted alkylated ketone **21** (Scheme 8). The regioisomeric 2,5-disubstituted ketone **22** was detected along with a dialkylated product, both as very minor by-products.

Table 4. Alkylation of enolates of 2-methylcyclopentanone

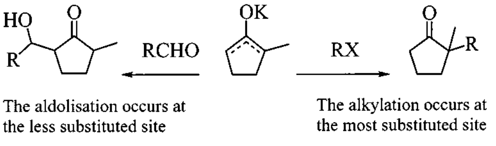
Silyl enol ethers	Enolates	RX	Alkylation products [%][a]			
				**21**	**22**	
9a	**9b**	$CH_2{=}CHCH_2Br$	8	88	<2	<2
		$PhCH_2Br$	21	75	<2	<2
10a	**10b**	$CH_2{=}CHCH_2Br$	18	17	63	<2
		$PhCH_2Br$	30	15	53	<2
9a	**9c**	$CH_2{=}CHCH_2Br$	10	86	<2	<2
		$PhCH_2Br$	10	86	<2	<2
10a	**10c**	$CH_2{=}CHCH_2Br$	14	82	<2	<2
		$PhCH_2Br$	13	79	6	<2
9a	**9c**	MeI	16	67	2	13
10a	**10c**	MeI	16	68	1	13
9a/10a : 1/1	**9c/10c** : 1/1	MeI	15	69	1	13

[a] Conversion determined by ^1H NMR for R = allyl or benzyl and by GC for R = methyl.



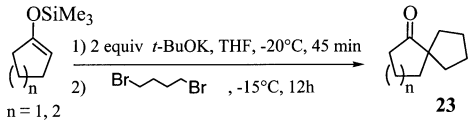
Scheme 8

Identical results were obtained on alkylation of 2-methylcyclohexanone, starting from **7a** and **8a**. We have interpreted these results as representing an equilibration of the two potassium regioisomeric enolates via the parent 2-methylcyclopentanone, initiated by a catalytic amount of a ketonic species (**21** or **22**). The alkylation reaction then takes place on the most nucleophilic tetrasubstituted potassium enolate **9c**. In the case of lithium enolates, the strength of the oxygen–metal bond prevents the equilibration. With onium enolates obtained from silyl enol ethers, alkylation is reported to proceed with retention of the structure of the starting silyl enol ether, due to the enhanced nucleophilicity of these naked enolates. The experimental conditions should be noted: the onium enolates are not preformed but obtained in the presence of the alkylating agent. Thus, they are trapped as soon as they are generated, preventing proton transfer and their equilibration before alkylation.[8,20] Unlike the aldolisation reaction, which occurs exclusively on the less substituted site of unsymmetrical ketones, the alkylation occurs on the most substituted site, whatever the potassium enolate. The aldolisation product thus reflects the relative stability of the potassium aldolates, whilst the alkylation product relies on equilibration of potassium enolates and reaction at the most nucleophilic tetrasubstituted enolate (Scheme 9).



Scheme 9

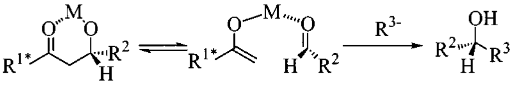
We applied this alkylation to the one-pot synthesis of spiroketones **23** from silyl enol ethers and dibromo alkanes (Scheme 10). The spiroketones **23** were obtained in good yields (76−78%) and the method compares favourably with those reported in the literature.[33−34]



Scheme 10

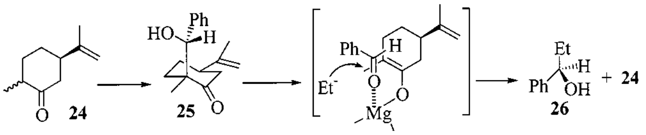
Application of the Retroaldol Reaction to Asymmetric Synthesis

Retroaldol cleavage of an enantiomerically pure aldol results in an enolate and a carbonyl compound. Immediately after the cleavage of the C−C bond, these two products are retained in close proximity, as they are both coordinated to the same metal cation. Thus, the enolate masks one face of the carbonyl compound and a nucleophilic addition will occur stereoselectively on the unmasked face (Scheme 11).[35]



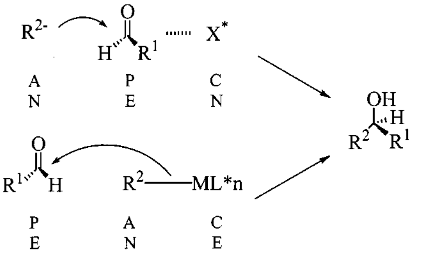
Scheme 11

Using the above methodology, we prepared aldols from benzaldehyde and trimethylsilyl enol ethers of chiral carbonyl compounds such as (+)-citronellal, (+)-dihydrocarvone, and (+)-pulegone.[35,36] With (+)-dihydrocarvone **24** as starting material, only one pure stereoisomer **25** was obtained after one crystallisation. Treatment of aldol **25** with ethylmagnesium bromide did not result in an addition reaction on the carbonyl group of **25**, but in addition onto that of benzaldehyde resulting from the retroaldolisation, affording alcohol **26** with the expected (*R*) configuration (*ee*: 35%). Aldol **25** can thus be considered as benzaldehyde with a carbonyl-masked *Si* face. Furthermore, the recovered ketone **24** can be reused (Scheme 12).[35]



Scheme 12

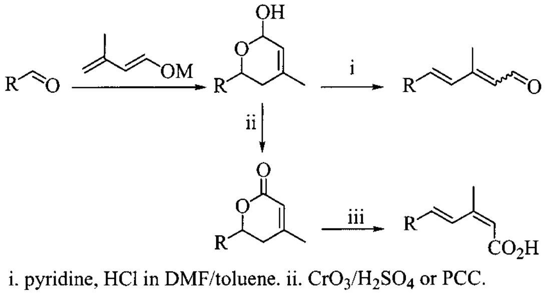
To the best of our knowledge, this result is the first reported retroaldolisation of an APC/NEN reaction in which the three species involved in the asymmetric step are achiral (A), chiral (C), prochiral (P) and either nucleophilic (N) or electrophilic (E).[37] Alcohols such as **26** have classically been obtained by reactions of the PAC/ENE type (Scheme 13).



Scheme 13

Reactivity and Synthetic Applications of the Prenal Potassium Dienolate

γ-Regiospecific reaction of dienolates of α,β-unsaturated aldehydes is a longstanding challenge. Serious problems include the facts that enolates of unsaturated carbonyl compounds can react at either the α- or γ-position, and that self-condensation of the dienolate with the starting carbonyl compound can occur. These have been partially alleviated by using ambident anions, such as anions of imines, hydrazones, phosphorus ylides, or phosphonates.[22] Nevertheless, there is no general procedure producing a highly γ-regioselective reaction. In our laboratory, Guillemont et al. reported a new prenylation method using the lithium enolate of prenal in reactions with aldehydes and α,β-unsaturated aldehydes.[23] We focused on prenylation using the potassium dienolate of prenal, generated by our method from the corresponding silyl enol ether. As mentioned in the first part of this review, the potassium dienolate of prenal reacted with benzaldehyde to yield the dihydropyran **15a** in a manner consistent with a γ-addition of the dienolate onto benzaldehyde, followed by an intramolecular attack of the alkoxide onto the carbonyl group. Worth stressing is that, in all cases, only γ-products were observed. From a mechanistic point of view, a kinetic α-coupling followed by a retroaldolisation, giving the observed γ-coupling, cannot be ruled out, as reported in the cases of the enolate of 3-substituted crotonate esters[38] and metallated senecioamides.[39] Dihydropyrans were easily transformed into the corresponding dienals in DMF/toluene in the presence of a catalytic amount of pyridinium chloride.[40] This two-step prenylation procedure is very attractive from a synthetic point of view (Scheme 14). Also facile was the synthesis of dienic acids of controlled regio- and stereochemistry by oxidation

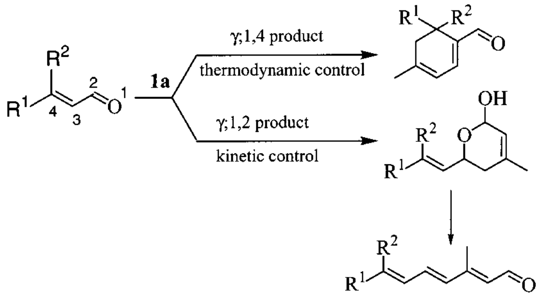


i. pyridine, HCl in DMF/toluene. ii. CrO_3/H_2SO_4 or PCC.
iii. 1. *t*-BuOK, THF then HCl 3N

Scheme 14

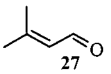
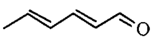
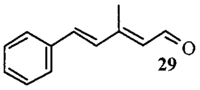
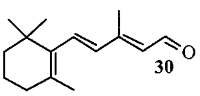
of dihydropyrans followed by ring-opening of the resulting dihydropyrones (Scheme 14). The oxidation was conducted using either Jones' reagent (CrO_3 in acidic medium) or Corey's method (PCC) to give the (2*Z*,4*E*)-dienic acids exclusively. The method gives good yields and requires only cheap reagents and mild conditions.[41]

When treated with α,β-unsaturated aldehydes, we were able to achieve selectivity for either γ;1,2 addition or γ;1,4 addition by means of manipulation of the reaction conditions (Scheme 15).[42] An excellent kinetically regiocontrolled γ;1,2 addition gave dihydropyrans as direct precursors of polyunsaturated aldehydes, whereas the γ;1,4 product was obtained under thermodynamic conditions. Both low temperatures (−78 °C) and short reaction times promote regioselective γ;1,2 addition. Raising the temperature or the reaction time favours the γ; 1,4 addition (Table 5).

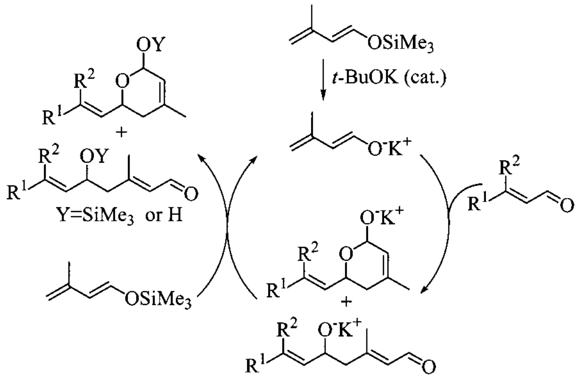


Scheme 15

Table 5. Reaction of the potassium dienolate of prenal with α,β-unsaturated aldehydes

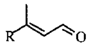
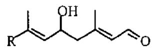
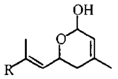
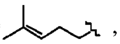
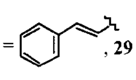
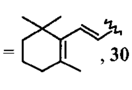
α,β-enaldehydes	Conditions	γ ; 1,2 : γ; 1,4 (yield [%])
 **27**	-78°C, 5 min	9 : 1 (nd)
	-78°C, 3hrs	2.8 : 1 (53)
	0°C, 3 hrs	1 : >99 (45)
 **28**	-78°C, 5 min	19 : 1 (nd)
	-78°C, 3hrs	2.2 : 1 (55)
 **29**	-78°C, 3hrs	>99 : 1 (66)
	-40°C, 3hrs	2.6 : 1 (65)
 **30**	-78°C, 3hrs	>99 : 1 (68)
	-40°C, 3hrs	4.6 : 1 (67)
	-10°C, 3 hrs	1 : >99 (59)

We further studied the outcome of the prenylation reaction with α,β-enaldehydes, using catalytically generated potassium prenal dienolate (Scheme 16). All experiments were run at −78 °C with 1−10 mol-% *t*BuOK. Two compounds, both resulting from a γ;1,2-addition, were obtained: a hydroxydihydropyran and a hydroxy enaldehyde, which has never been observed in experiments performed using 1 equiv. of *t*BuOK. The significant advantage of the catalytic use of the alkali metal alkoxide is the formation of an *O*-silylated intermediate, which prevents retroaldolisation, thus inhibiting the formation of the γ;1,4-coupled product (Table 6).[43]



Scheme 16

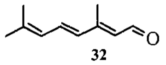
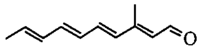
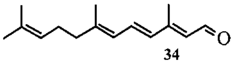
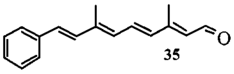
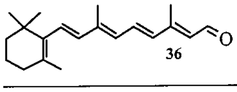
Table 6. Reaction of the catalytically generated potassium dienolate of prenal with α,β-unsaturated aldehydes

α,β-enaldehydes 	*t*-BuOK [equiv]	Hydroxy enaldehydes 	Hydroxy dihydropyrans 	Overall yield [%]
R = Me, **27**	1	0	56	56
	0,05	44	33	77
	0,01	43	33	76
R =  , **31**	0,05	38	24	62
R =  , **29**	1	0	66	66
	0,05	21	59	80
R =  , **30**	1	0	66	66
	0,1	0	55	55
	0,05	0	47	47

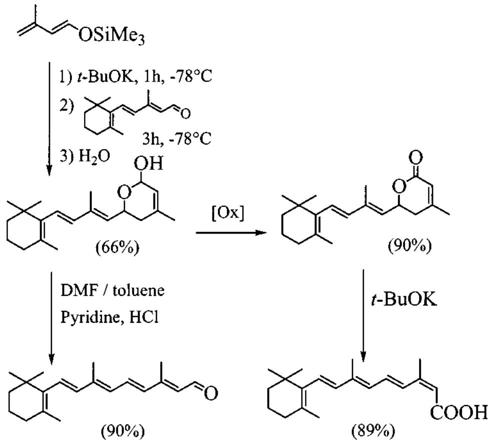
We mainly recovered the (2*E*) isomers of the hydroxy enaldehydes, since the (2*Z*) isomers cyclised to the dihydropyrans. Products of the reaction were converted into polyenaldehydes with the aid of pyridinium hydrochloride in DMF and toluene[40] or 10% HCl in 1,2-dichloroethane.[44] In this transformation, it is possible to observe by thin layer chromatography that the dihydropyran is the intermediate in the conversion of the hydroxyenaldehyde into the polyenaldehyde (Table 7).

Finally, we have illustrated our methodology nicely in the synthesis of polyene compounds belonging to the vitamin A series, carrying out an efficient two-step synthesis of retinal from β-ionylideneacetaldehyde and prenal potassium dienolate.[43] The oxidation of the dihydropyranol into the dihydropyrone permitted direct access to 13-*cis*-retinoic acid (Scheme 17).[41]

Table 7. Conversion of hydroxy enaldehydes and hydroxydihydropyrans into polyenaldehydes

Polyenaldehydes	From hydroxy enaldehydes		From hydroxy dihydropyrans	
	Yield [%] (Method)	2E / 2Z	Yield [%] (Method)	2E / 2Z
 **32**	74 (B)	38/62	89 (A)	70/30
			89 (B)	15/85
 **33**			72 (A)	65/35
 **34**	95 (A)	67/33	72 (A)	68/32
			84 (B)	74/26
 **35**	81 (B)	70/30	88 (A)	74/26
 **36**			90 (A)	4 isomers: 54/28/16/2

[a] Method A: Pyr, HCl; DMF/toluene (1:1), reflux, 10 min; Method B: 10% HCl/1,2-dichloroethane (1:1), 25 °C, 10 min to 4 h.



Scheme 17

Conclusion

This unique preparative method is of great value for the production of potassium enolates, which have thus been made as easily available as lithium enolates. The mild conditions and the use of easy-to-handle reagents, as well as the high selectivity, make this method very attractive for further synthetic applications. The catalytic use of alkali metal alkoxides in aldol or Michael reactions is obviously of great interest. We believe our methodology will be of general value to chemists involved in enolate chemistry.

Acknowledgments

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