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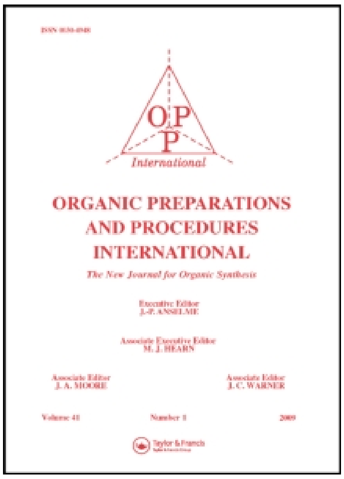

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REGIOSPECIFIC ALKYLATION OF CYCLOHEXENONES. A REVIEW

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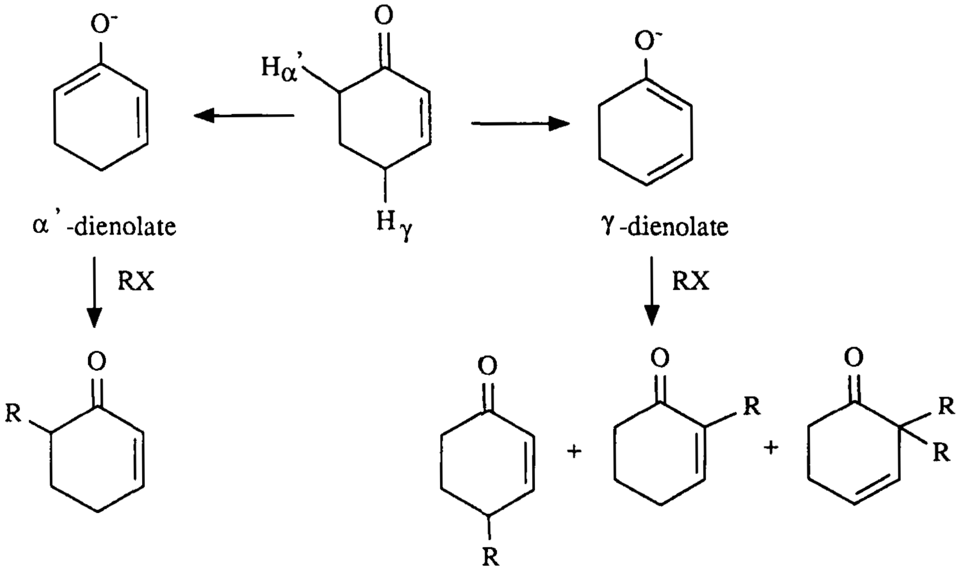
INTRODUCTION

The reaction of cyclohexenones with base can result in the formation of the α'- or the γ-dienolate which, on treatment with an electrophile, may lead to α'-, α-, or γ-alkylated product(s). While the α'-alkylated product can be readily obtained with the appropiate choice of solvent, base, and reaction temperature, in general the α- and γ-alkylated products are more difficult to generate. Attempts to prepare the α-alkylated products often lead to polyalkylation as the main path. In the case of γ-alkylation, only the 3-(disubstituted)amino-2-cyclohexen-1-ones readily undergo alkylation. The goal of this review is to describe those conditions which influence the regiospecific alkylation of cyclohexenones.



I. α'-ALKYLATIONS

The ability to regiospecifically alkylate cyclohexenones at the α'-position was reported by Stork and Danheiser in 1973.[1] They found that reaction of 3-isobutoxy-2-cyclohexen-1-one (**1**) with excess lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°, followed by the addition of allyl bromide and warming the mixture to room temperature yielded the α'-alkylated product **2** quantitatively. Since that initial study, various 3-substituted-2-cyclohexen-1-ones have been examined using similar reaction conditions. In all cases, exclusive α'-alkylated products were obtained (Table 1).

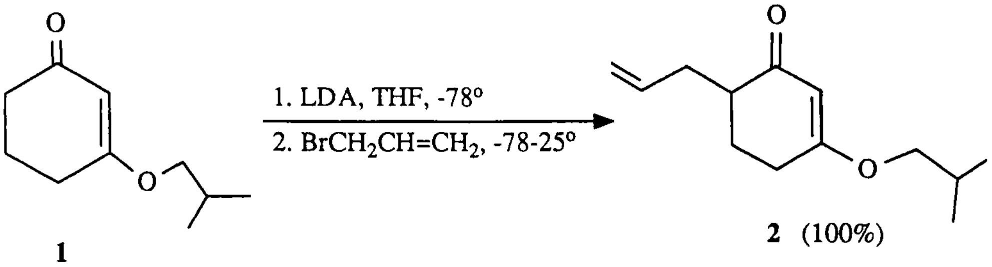
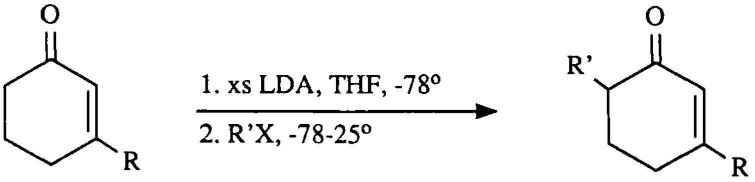


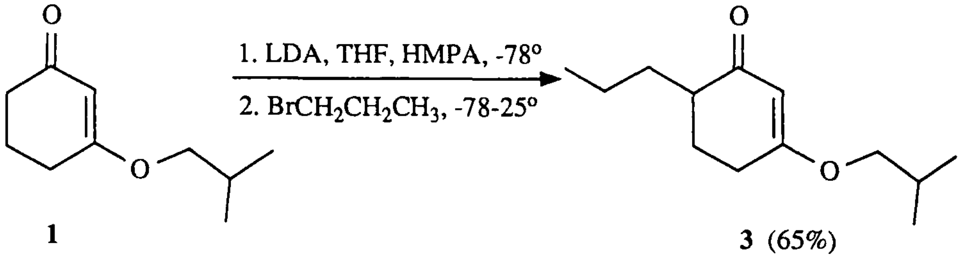
Table 1. Alkylation of Cyclohexenones



Reactant	R	R'X	Product (% Yield)	Reference
6	CH_3	$BrCH_2CO_2Et$	**7** (51)	3
8	OEt	"	**9** (50)	3
10	OEt	$BrCH_2CO_2C(CH_3)_3$	**11** (99)	4
12	$S(CH_2)_3CH_3$	CH_3I	**13** (60)	5
14	$N(CH_3)_2$	$PhCH_2Br$	**15** (76)	6

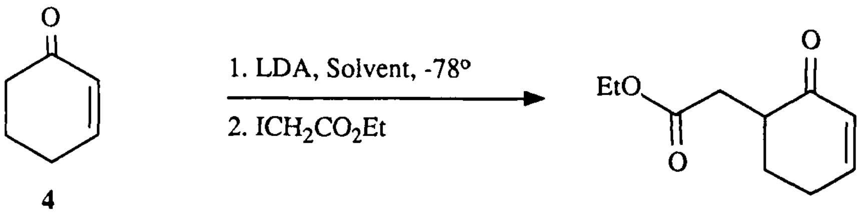
a. Effect of Solvents

Historically, the preferred solvent used in these reactions has been tetrahydrofuran. However, Stork and Danheiser found that with the less reactive electrophile, *n*-propyl bromide, 1.1 equivalents of hexamethylphosphoramide (HMPA) was required to produce 3-isobutoxy-6-propyl-2-cyclohexen-1-one (**3**) (65% yield) with the α'-dienolate of 3-isobutoxy-2-cyclohexen-1-one (**1**).[1] Typically, if the rate of alkylation is slow, HMPA is used as a co-solvent with THF to accelerate the reaction. As a substitute for the potentially carcinogenic HMPA, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) can be used.[2]



1

3 (65%)



4

5

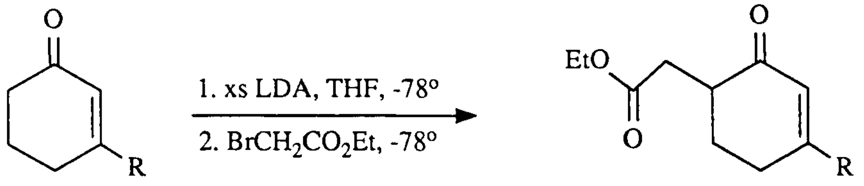
Yields: THF (65%), THF/HMPA (67%), THF/DMPU (63%), Et_2O (0%)

The use of HMPA does not automatically increase the yield of the alkylated product. In the reaction of 2-cyclohexen-1-one (**4**) with LDA at -78° followed by ethyl iodoacetate, a similar yield of the α'-alkylated product **5** was obtained regardless if THF, THF/HMPA or

THF/DMPU was employed (~65% yield).[2] Interestingly, if the latter reaction was conducted in diethyl ether, only starting material was obtained. This latter result was attributed to the physical state of the reaction, since the reaction conducted in THF was homogeneous while that conducted in diethyl ether was heterogeneous.

b. Effect of Temperature

Generally, the formation of the α'-dienolate has been carried out at a temperature between -78° to 0°, followed by addition of the electrophile at the low temperature. The reaction is then allowed to slowly warm to room temperature. Podraza and Bassfield found that the reaction of 3-substituted-2-cyclohexen-1-ones **4**, **6**, **8**, and **16** with excess LDA in THF at -78° followed by the addition of ethyl bromoacetate produced the α'-alkylated products **5**, **7**, **9**, and **17** at -78°.[2] Thus, when reactive electrophiles are used it may not be necessary to warm the reaction to room temperature to obtain a good yield of the α'-alkylated product.

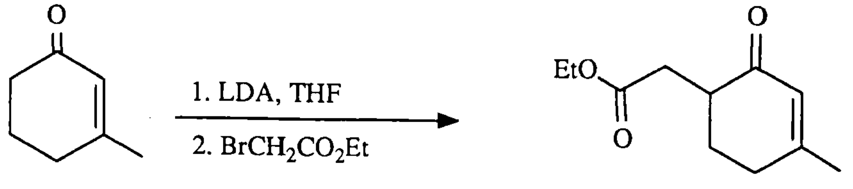


4 R = H
6 R = CH_3
8 R = OEt
16 R = Ph

5 R = H (71%)
7 R = CH_3 (88%)
9 R = OEt (56%)
17 R = Ph (87%)

The influence of temperature was investigated more thoroughly by Podraza and Bassfield.[2] The reaction of excess 3-methyl-2-cyclohexen-1-one (**6**) with LDA in THF at

-78$^{\text{O}}$ followed by the addition of ethyl bromoacetate gave an 86% yield of α'-alkylated product (**7**) while only a 30% yield of **7** was obtained when the temperature was allowed to rise to 0$^{\text{O}}$, before the electrophile was added. Thus, a high yield of the α'-alkylated product was obtained if the reaction temperature was maintained below -50$^{\text{O}}$ regardless of the stoichiometry between the base (LDA) and the 3-substituted-2-cyclohexen-1-one.



6 **7**

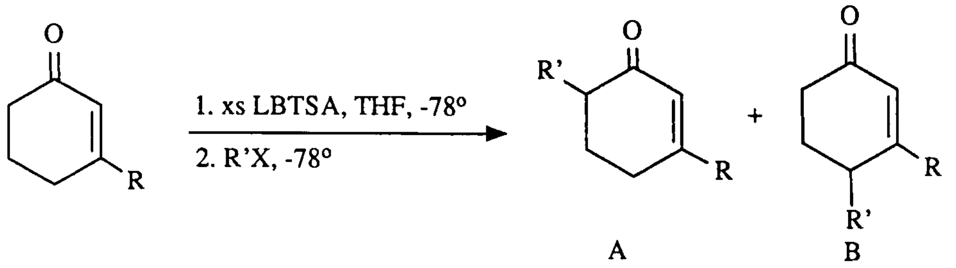
Yields: 86% (-78°), 30% (0°)

c. Effect of Base

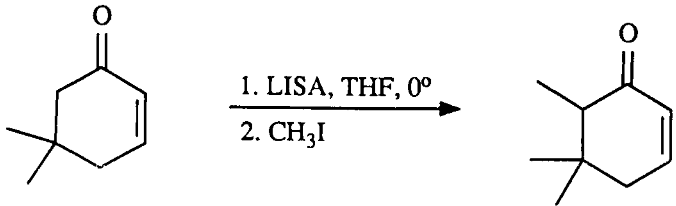
In a typical procedure, lithium diisopropylamide has been the base used to form the α'-alkylated product. Interestingly, when lithium bis(trimethylsilyl)amide (LBTSA) was substituted for LDA, the α'-alkylated product was obtained in all cases studied, except with 3-dimethylamino-2-cyclohexen-1-one **14** (Table 2). In this case, the γ-alkylated product **18** was obtained as the sole product.[6] The special case of the 3-(disubstituted)amino-2-cyclohexen-1-one derivatives will be discussed in more detail in Section III.

Reusch *et al.* found that the reaction of 5,5-dimethyl-2-cyclohexen-1-one (**19**) with lithium isopropylcyclohexylamide (LISA) in THF at 0$^{\text{O}}$, followed by treatment with methyl iodide and warming to room temperature gave an 83% yield of the α'-alkylated product **20**.[7] These results are similar to those obtained with LDA as the base. The use of alternate bases, such as potassium hydride,[8] and sodium *t*-amylate,[9,10] followed by alkylation do not generate the α'-alkylated material, only α- and γ-alkylated products (see Section II). The most common procedure for α'-alkylation proceeds by reacting the cyclohexenone with LDA in THF at -78 - 0^{o}, followed by reaction with the electrophile.

Table 2. Alkylation of Cyclohexenones with LBTSA as Base



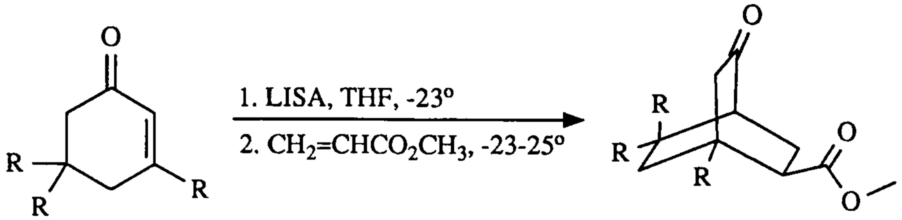
Reactant	R	R'X	Product (% Yield)		Reference
			A	B	
4	H	$BrCH_2CO_2Et$	**5** (70)	-	2
6	CH_3	"	**7** (75)	-	2
16	Ph	"	**17** (79)	-	2
14	$N(CH_3)_2$	CH_3I	-	**18** (73)	5



19 **20**

d. Michael Reaction

Lee found that α'-dienolates of cyclohexenones **4** and **24** react with Michael acceptors to form bicyclo[2,2,2]octan-2-ones **23** and **25**.[11] Since that initial discovery, many groups have investigated this reaction and obtained similar results, *generally*



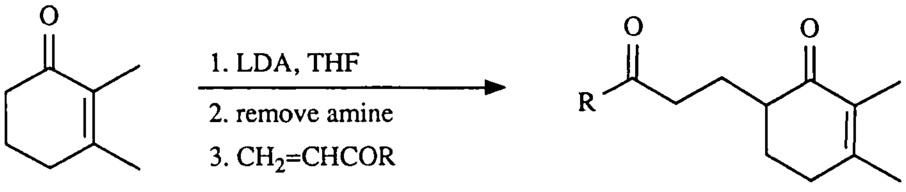
4 R = H

24 R = CH_3

23 R = H (90%)

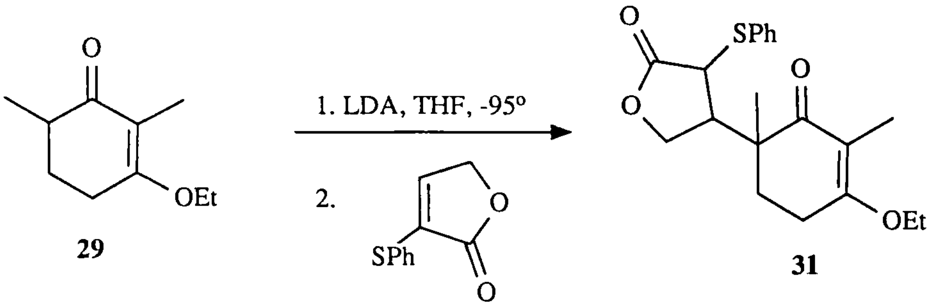
25 R = CH_3 (98%)

irrespective of the starting cyclohexenone and Michael acceptor. The excellent review of this subject makes it unneccessary to cover this topic.[12] However, several exceptions have now been disclosed. Uda *et al.* reported that the α'-dienolate of 2,3-dimethyl-2-cyclohexen-1-one (**26**) reacted with methyl or ethyl vinyl ketone to afford only the intermolecular Michael addition product **27** and **28**.[13] Holton *et al.* found that the reaction of 2,6-dimethyl-3-methoxy-2-cyclohexen-1-one (**29**) with LDA in THF followed by addition of the butenolide **30** at -95° gave the alkylation product **31**.[14]



26

27 R = CH_3 (>60%)
28 R = CH_2CH_3 (>60%)



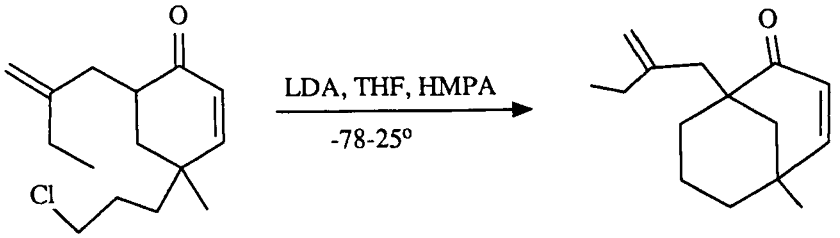
29

30

31

e. Intramolecular Reaction

Schultz and Dittami reported that an intramolecular alkylation reaction could be performed with **32** using LDA when the dienolate was generated at -78^{0} in THF/HMPA followed by warming to room temperature.[15] After chromatographic purification, an 80% yield of the α'-alkylated product **33** was obtained.

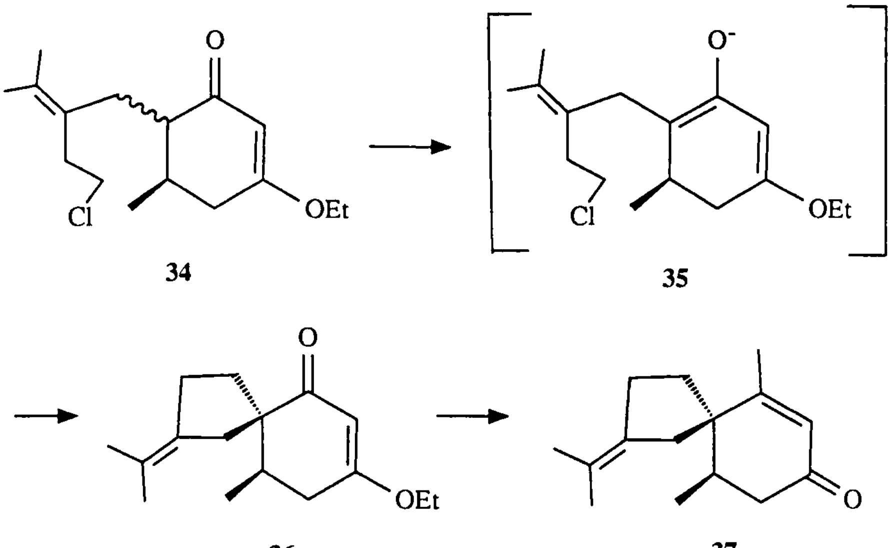


32

33 (80%)

f. 5-Substituted-2-cyclohexen-1-ones

When a 5-substituted-2-cyclohexen-1-one is used in a procedure to form an α'-alkylation product, a *trans* relationship between the 5- and 6-substituent results. This relationship was first reported by Stork *et al.* in 1973;[16] in that case, a stereospecific



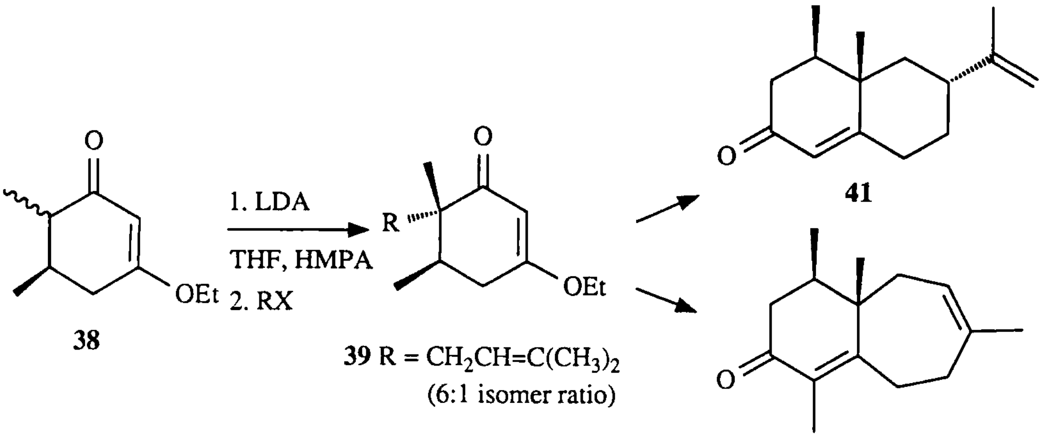
34

35

36

37

α'-alkylation of **34** occurred to form a spiroannelated cyclohexenone **36**. They verified that the cyclization step resulted in a *trans* relationship by converting **36** into (±)-β-vetivone (**37**). This basic strategy was used by Majetich *et al.* in the synthesis of nootkatone (**41**)[17] and perforenone (**42**).[18]



38

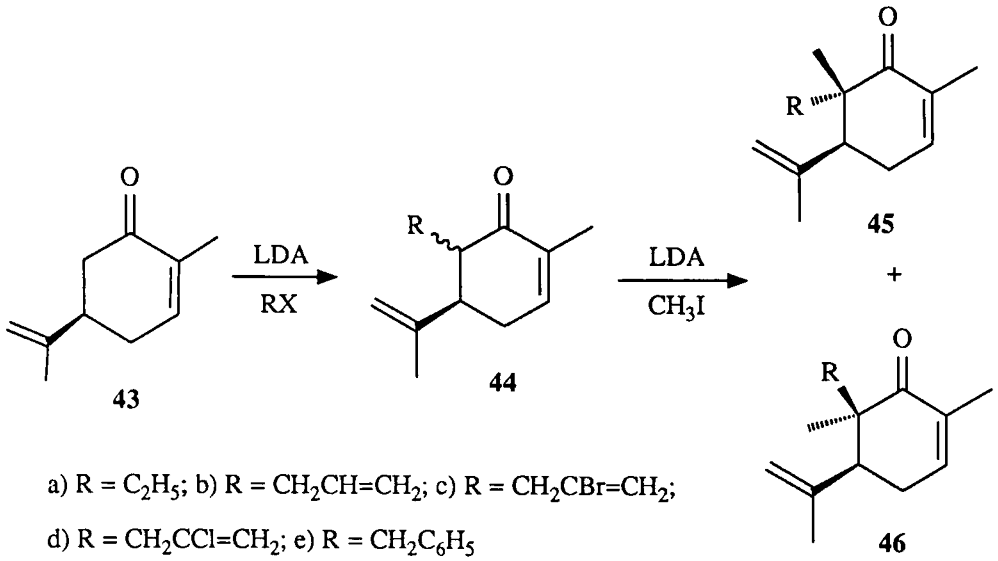
39 R = $CH_2CH{=}C(CH_3)_2$
(6:1 isomer ratio)

40 R = $CH_2C(CH_2TMS){=}CHCH_3$
(6:1 isomer ratio)

41

42

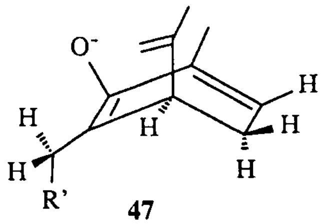
Gesson *et al.* reported that the α'-dienolate formed from carvone (**43**), on alkylation with an electrophile, yielded the α'-alkylated product **44** as a mixture of diastereomers.[19,20] Treatment of this mixture with LDA in THF, followed by methyl iodide gave product(s) **45** and **46** (Table 3). The diastereomeric ratio obtained was considered to be a result of the steric hindrance by the isopropenyl group on one side of the α'-dienolate. As illustrated in structure **47** the preferred transition state is such that the isopropenyl and the R' group are in a *trans* quasi-diaxial relationship and thus the relative bulkiness of these groups determines the diastereoselectivity.[21,22]



a) R = C_2H_5; b) R = $CH_2CH{=}CH_2$; c) R = $CH_2CBr{=}CH_2$;
d) R = $CH_2CCl{=}CH_2$; e) R = $CH_2C_6H_5$

Table 3. Alkylation of 44 with Methyl Iodide

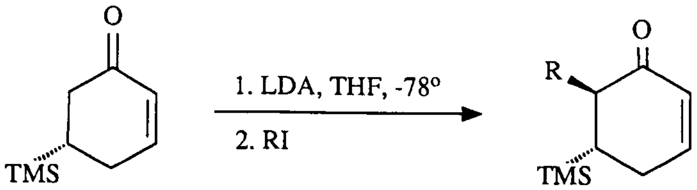
Reactant	% Yield	Product	
		45	**46**
44a	60	5	95
44b	81	0	100
44c	76	55	45
44d	65	56	44
44e	72	25	75



47

a) R' = CH_3; b) R' = $CH{=}CH_2$; c) R' = $CBr{=}CH_2$; d) R' = $CCl{=}CH_2$; e) R' = C_6H_5

Asaoka *et al.* reported that optically pure 5-trimethylsilyl-2-cyclohexen-1-one (**48**) on treatment with LDA at -78° followed by alkylation with alkyl halides gave the α'-alkylated products **49**, and **50** in good yield and in high diastereomeric purity.[23] These derivatives were converted into optically pure 2,5-disubstituted-2-cyclohexen-1-ones.

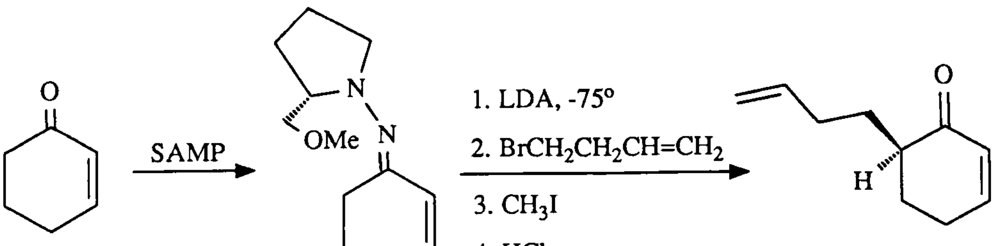


48

49 R = $CH_2CH_2C(CH_3)=CH_2$ (80%) (1 isomer)
50 R = CH_3 (67%) (10:1 isomer ratio)

g. Enantioselective Alkylation

In the absence of a 5-substituent, stereospecific alkylation can occur when a chiral auxiliary is used. This strategy, which relied on the enantioselective alkylation of hydrazone **51**, was used by Pennanen in the synthesis of (+)-eremophilenolide.[24] Hydrazone **51**, prepared by the reaction of (S)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) with cyclohexenone (**4**), was treated with LDA followed by 4-bromo-1-butene at -95° to yield α'-

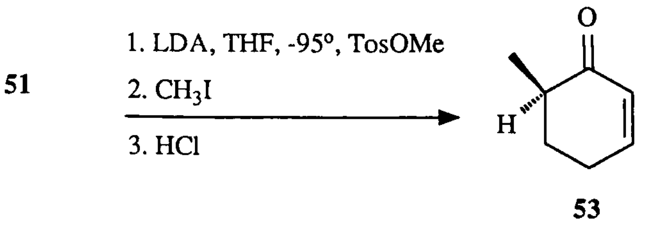


4

51

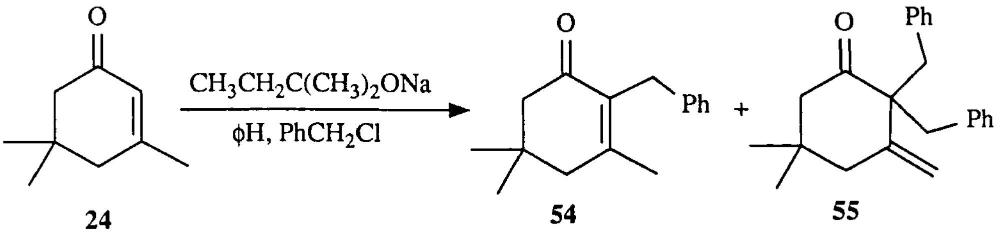
52 (26%)

alkylated product **52** (26%), after regeneration of the keto group. The same hydrazone **51** was used by Tokoroyama *et al.* to form 6-methyl-2-cyclohexen-1-one (**53**) as a single enantiomer.[25]



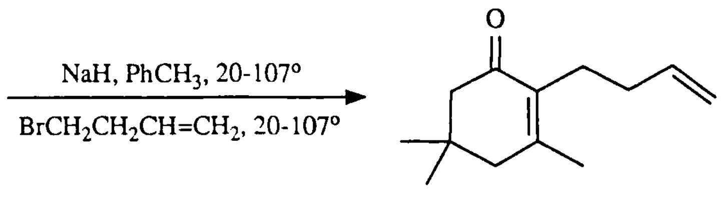
II. α-ALKYLATION

Typically, thermodynamic conditions (excess proton source and elevated temperature) produce an α-substituted-β,γ-unsaturated product which reacts further to form either an α-substituted-α,β-unsaturated compound by isomerization of the β,γ-double bond or undergoes further alkylation to form the dialkylated product.[26] In 1962, Conia and Craz reported that reaction of 3,5,5-trimethyl-2-cyclohexen-1-one (**24**) with sodium *t*-amylate in benzene followed by benzyl chloride gave a mixture of the α-alkylated product **54** and the α,α-dialkylated product **55**.[27]



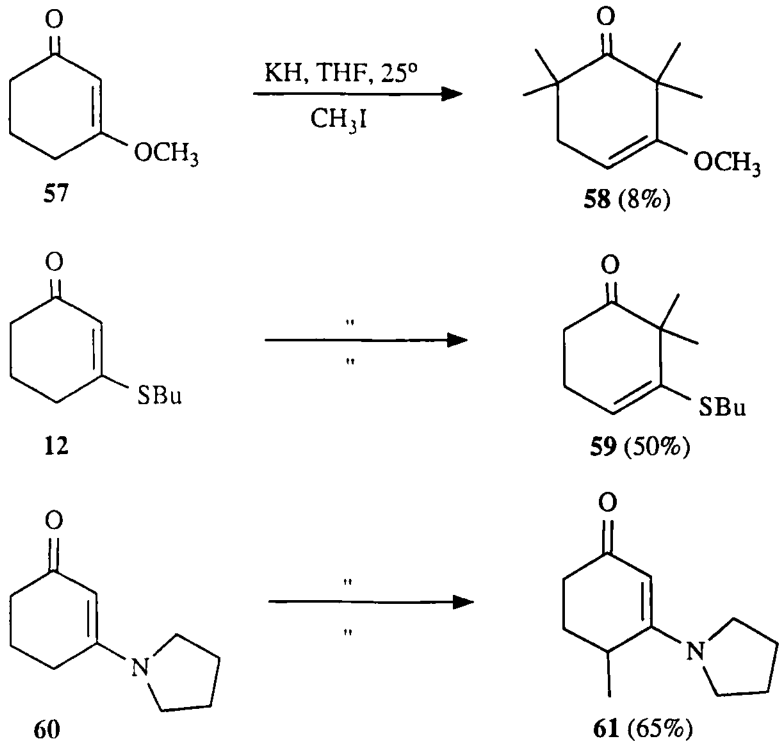
Monoalkylation of **24** was achieved by Naf *et al.* in 1989,[28] by reaction of **24** with sodium hydride in toluene followed by 4-bromobut-1-ene to yield **56** (54%). Gammill and

24



56 (54%)

Bryson found that the reaction of cyclohexenones **57** and **12** with excess potassium hydride in THF at room temperature followed by addition of methyl iodide generated polyalkylated cyclohexenones **58** and **59**, while 3-pyrrolidinyl-2-cyclohexen-1-one (**60**) gave only the γ-alkylated product **61**.[8] Schultz and Kashdan observed that if the α-position of a 2-

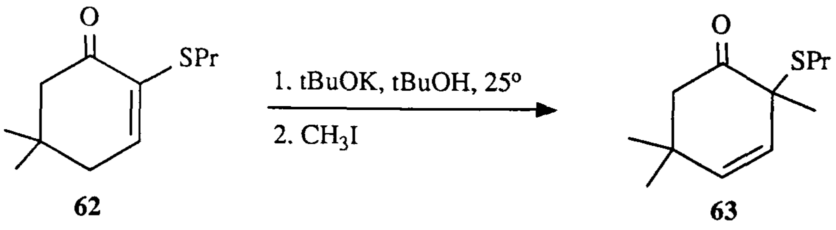


57 **58** (8%)

12 **59** (50%)

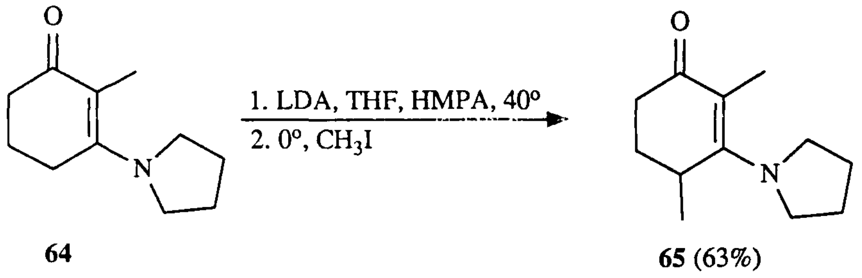
60 **61** (65%)

cyclohexen-1-one derivative was substituted, an α-alkylated-β,γ-unsaturated product could be easily synthesized.[29] For example, 2-thio-*n*-propyl-5,5-dimethyl-2-cyclohexen-1-one (**62**) gave predominately the α-alkylated-β,γ-unsaturated product **63** on reaction with potassium *t*-butoxide in dry tert-butyl alcohol followed by treatment with methyl iodide.



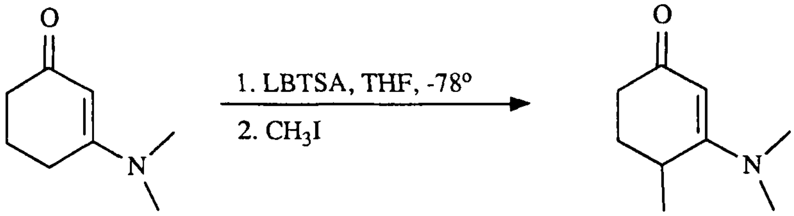
III. γ-ALKYLATION

The γ-alkylation of cyclohexenones can presently only be generated by indirect routes with one exception. That exception is when the starting cyclohexenone is a 3-(disubstituted)amino-2-cyclohexen-1-one. In the case of 2-methyl-3-pyrrolidinyl-2-cyclohexen-1-one (**64**), Telschow and Reusch found that the γ-alkylated product **65** was obtained when an excess of **64** was used and the dienolate, formed with LDA in THF, was heated to 40° before reaction with the electrophile.[30]



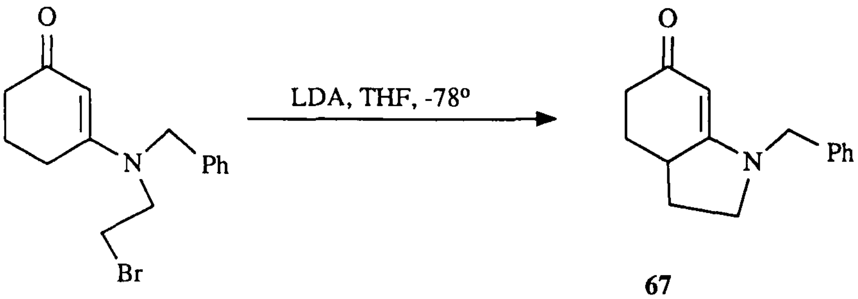
Mariano *et al.* found that the reaction of 3-dimethylamino-2-cyclohexen-1-one (**14**) with excess lithium bis(trimethylsilyl)amide at -78° in THF initially formed the α'-

dienolate which rapidly equilibrated to the γ-dienolate at low temperature and formed 4-methyl-3-dimethylamino-2-cyclohexen-1-one (**18**) when treated with methyl iodide.[6] Interestingly, this equilibrium was found to be very slow if diethyl ether was used as the solvent. In 1974, Bryson and Gammill reported on the intramolecular alkylation of halide **66**, using LDA in THF at -78°, to form the γ-alkylated product N-benzyl-2,3,3a,4-tetrahydro-6(5H)-oxoindole (**67**).[31] Two indirect methods to form the γ-alkylated products use the ketal of Hagemann's ester[32] and γ-sulfonylcyclohexenone ketal[33] which will not be reviewed here.



14

18 (73%)



66

67

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