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A Directing Effect of Neighboring Aromatic Groups on the Regiochemistry of Formation and on the Stereochemistry of Alkylation and Bromination of Ketone Lithium Enolates. Evidence for Lithium–Arene π Coordination and for a Dramatic Effect of Even Small Amounts of Copper(I) in Controlling Stereochemistry and in Limiting Polyalkylation

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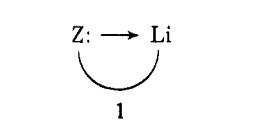
Abstract: A series of β-aryl- and β-aralkylcyclopentanones and cyclohexanones and 5-tolyl-3-hexanone was studied in the presence of lithium diisopropylamide in THF at room temperature. Enolization occurred preferentially toward the aryl group, and the magnitude of this regioselectivity paralleled the π-electron *donating* ability of the aryl group: *p*-methoxyphenyl > phenyl > *p*-nitrophenyl. A critical lithium-arene π coordination is postulated to account for these unusual results. Evidence for such π coordination came from ^{1}H and ^{13}C NMR data and from the effects of coordinating solvents. The enolate intermediates were isolated as their enol silyl ethers, or they were treated with methyl iodide, allyl bromide, methyl bromoacetate, or molecular bromine. The course of enolate reaction with these electrophiles was distinctly and reproducibly different in the absence or in the presence of copper(I). Even small amounts of copper(I) decreased the amount of polyalkylation and increased the amount of *cis*-2-alkyl-3-phenylcyclopentanone produced, even though this epimer is less stable thermodynamically then the corresponding *trans*-2-alkyl-3-phenylcyclopentanone. An explanation for this dramatic and catalytic effect of copper(I) is offered. Reaction of the more substituted enolate of 2-methyl-3-phenylcyclopentanone with methyl bromoacetate gave 2,2,3-trisubstituted cyclopentanone **25** stereospecifically; cyclopentanones like **25** should be useful precursors to AB-aromatic 19-norsteroids.

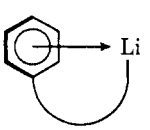
Introduction

Heteroatom-directed and -assisted lithiation reactions are well-known and useful, and they result from a strongly stabilizing Lewis base–Lewis acid coordinative interaction as represented in generalized structure **1**.[1] In analogy, it can be expected that the basic π electrons of an aromatic group might also direct and assist some lithiation reactions at nonbenzylic positions (cf. **2**). Indeed lithium complexation with the π electrons of aromatic groups has precedent. For example, an X-ray study of benzyllithium revealed lithium coordination to the π cloud of the benzyl group,[2] and this type of association has been suggested to account for the stereospecificity of the *n*-butyllithium-promoted polymerization of styrene.[3]



1

Z = OR, SR, NR_2, PR_2



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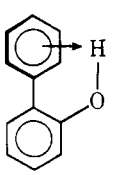
Strong spectroscopic evidence indicates the existence of hydrogen–arene π coordination in such systems as *o*-arylphenols (**3**)[4] and 2-phenylethanol (**4**).[5] Because the lithium atom in lithium enolates resembles to a significant degree the hydroxyl hydrogen atom in enols, it seemed reasonable to expect lithium–arene π coordination in lithium enolates derived from some aralkyl ketones (e.g., **5**). We reasoned that it might



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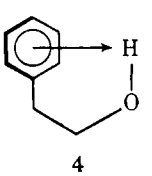

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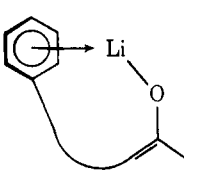

5

be possible to use the neighboring aromatic groups in some unsymmetrical aralkyl ketones to direct the lithiation of these compounds, thus providing a mild, useful, and yet unusual method for controlling the regiochemistry of ketone lithium enolate formation and possibly also for controlling the stereochemistry of alkylation and bromination of these enolates.

In 1977 we reported preliminary results dealing with regioselective formation and stereoselective alkylation of some β-aryl- and β-aralkylcyclopentanone lithium enolates;[6] we now report the full details of that work as well as its extension to aryl-substituted cyclohexanones and to acyclic 5-tolyl-3-hexanone. The effects of solvent, temperature, and lithiating agents, as well as some ^{1}H and ^{13}C NMR data, all support our original proposal of an enolate intermediate having lithium–

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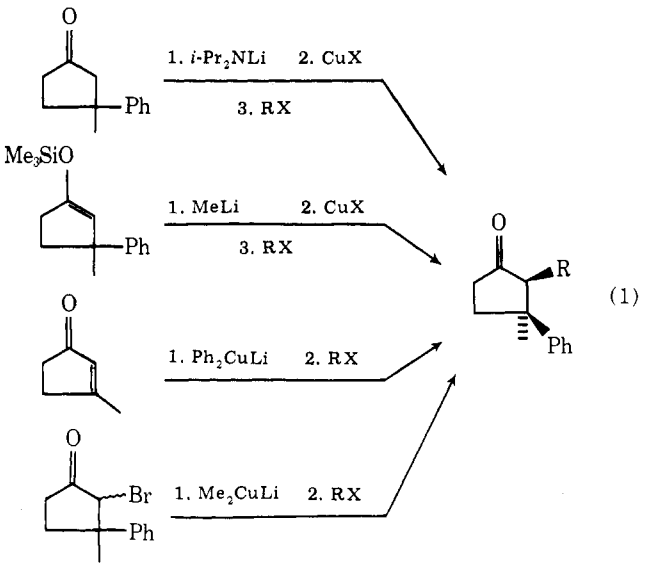
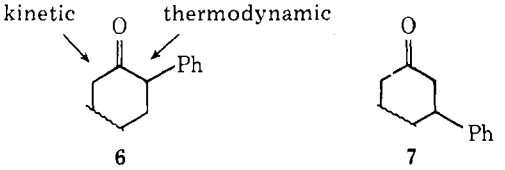
arene π coordination. The results reported here also clearly show first that the chemical outcome of enolate alkylation and bromination in most cases is distinctly and reproducibly different in the absence or in the presence of small amounts of copper(I) species and second that unsymmetrical β-phenylcyclopentanones can be regioselectively lithiated and stereoselectively monoalkylated and monobrominated at the α-carbon atom to give the less stable of two epimers in a controlled and synthetically useful fashion (eq 1).



(1)

Results and Discussion

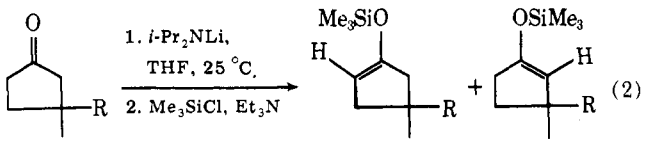
Regiochemistry of Enolate Formation. When an unsymmetrical ketone bears an adjacent substituent such as an aryl group, which can stabilize an incipient enolate ion via resonance delocalization of the negative charge, then that thermodynamic enolate is produced under equilibrating conditions. When the other (i.e., kinetic) enolate is desired, proton abstraction by a nonnucleophilic hindered base at low temperature and under nonequilibrating conditions is routinely used (e.g., **6**).[7,8] If the substituent aryl group is located on a β-carbon atom (e.g., **7**),[9] then resonance stabilization of an incipient



6 **7**

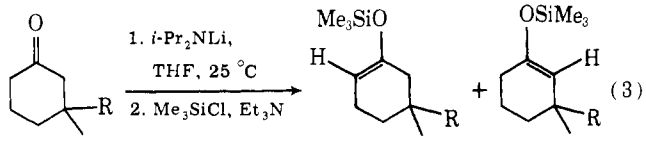
enolate ion is no longer important and inductive stabilization may play a role (e.g., $PhCH_2CO_2H$ is a slightly stronger acid than $PhCH_2CH_2CO_2H$).[10] The magnitude of such inductive stabilization should be directly related to the electron-*withdrawing* ability of para-substituted phenyl groups: *p*-nitrophenyl > phenyl > *p*-methoxyphenyl. If, however, the π electrons of the β-aryl group can coordinate with and stabilize the positive counterion of the enolate, then the magnitude of this π-coordinative stabilization should be directly related to the electron-*donating* ability of para-substituted phenyl groups (*p*-nitrophenyl < phenyl < *p*-methoxyphenyl); indeed this is what we have found.

We have allowed a series of 3-methyl-3-R-substituted cyclopentanones and cyclohexanones to react under nitrogen with 1.0 equiv of lithium diisopropylamide in tetrahydrofuran (THF) at 25 °C for 1 h, after which a mixture of trimethylsilyl chloride and triethylamine was added;[11] GLC analysis, isolation (63–91% yields), and identification of enol silyl ethers **8–11** led to the results shown in eq 2 and 3. Enol silyl ethers **8** and **10** show a characteristic NMR vinylic H multiplet centered at δ 4.4–4.6,[11] whereas enol silyl ethers **9** and **11** show a typical vinylic H triplet ($J \simeq 1$ Hz) centered at δ 4.6–4.8.



(2)

R	8	9
Ph	1.0	3.3
p-MePh	1.0	4.3
p-MeOPh	1.0	7.4
p-O_2NPh	1.0	0.9
$PhCH_2$	1.0	6.9
$PhCH_2CH_2$	1.0	2.5
$PhCH_2CH_2CH$	1.0	1.7
CH_2=CH	1.0	0.9
n-Bu	1.0	0.3



(3)

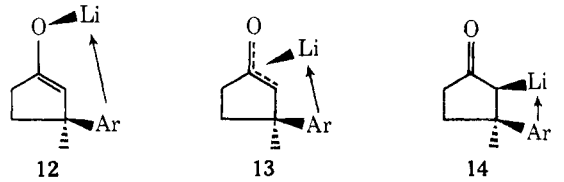
R	10	11
Ph	1.0	2.1
$PhCH_2$	1.0	13.3
n-Bu	1.0	0.1

The directing effect of a *p*-methoxyphenyl group is larger than that of a *p*-methylphenyl group, which is larger than that of phenyl itself; a *p*-nitrophenyl substituent is the least directing aryl substituent examined. This ability of a remote aryl group to direct the regiochemistry of enolate formation parallels the π-electron-*donating* ability of the aromatic group.[12] A 3-benzyl substituent, which cannot reasonably stabilize the enolate corresponding to enol ethers **9** or **11** by *inductive* forces, directs enolate formation even more effectively than a 3-phenyl group. This directing effect of a phenyl group falls off sharply as the phenyl group is removed farther and farther from the cycloalkanone ring ($PhCH_2$ > $PhCH_2CH_2$ > $PhCH_2CH_2CH_2$); this observation seems to suggest that the lithium-arene π coordination occurs between the lithium atom and the phenyl group in the same species (i.e., *intra*molecularly) rather than *inter*molecularly in which case a phenethyl group would seem to be as good a π donor as a benzyl or a phenylpropyl group. Finally, 3-methyl-3-*n*-butylcycloalkanones (which lack any aryl substituent) reacted under these conditions to give predominantly the expected enol silyl ethers **8** and **10**.

Quantitative (but not qualitative) differences exist between the five- and six-membered ring systems. The directing effect of a 3-phenyl group is more pronounced in the cyclopentanone series, whereas a 3-benzyl group exerts more of an effect in the cyclohexanone series. Undoubtedly these differences between the effect of 3-aryl and 3-aralkyl groups on five- and six-membered cycloalkanones are due mainly to conformational differences between five- and six-membered rings.[13] For example, molecular models show that the phenyl group of a 3-phenylcyclopentanone seems to be better positioned than that of a 3-phenylcyclohexanone for π bonding with the lithium atom of the corresponding lithium enolate. Although such rationalizations can be made after the fact, predictions for other systems must await more detailed information (e.g., ^{7}Li NMR[14] and IR spectroscopy[15]) on the position of the lithium atom (e.g., edge or centrosymmetric coordination with the aromatic group[16]) and on the nature of the anion (e.g., localized (**12**) or delocalized (**13**) enolate or α-lithio ketone (**14**)); more information is needed to allow distinction among the three extreme forms **12–14** possible for these arene-complexed lithium species.

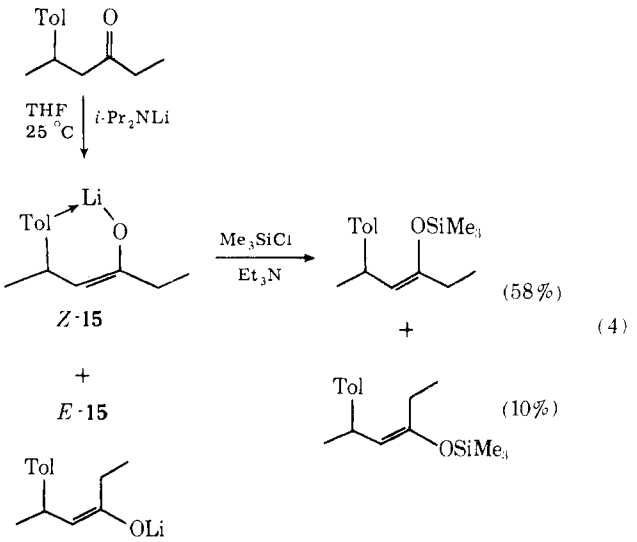
Table I. $^1H_\alpha$ Chemical Shifts for Cyclopentanone Enol Silyl Ethers **9** and the Corresponding Lithium Enolates in THF-d_8 at 32 °C

9		δ, ppm	Δδ, ppm	ratio 9/8
R = *n*-Bu		4.62	0.37	0.3
	R = *n*-Bu	4.25		
R = $PhCH_2CH_2$		4.63	0.55	2.5
	R = $PhCH_2CH_2$	4.08		
R = Ph		4.82	0.62	3.3
	R = Ph	4.20		
R = $PhCH_2$		4.74	0.76	6.9
	R = $PhCH_2$	3.98		



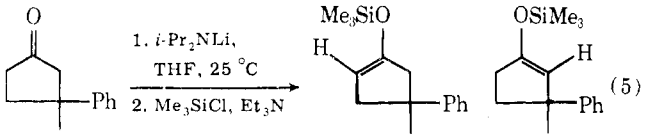
We have used ^1H and ^{13}C NMR to gather structural information on these lithium-containing intermediates.[17] ^1H NMR data for H_α are shown in Table I for various cyclopentenol silyl ethers and for the corresponding lithium enolates. The most striking feature of these data is the trend in Δδ, the difference in chemical shift between that of H_α in the enol silyl ether and that of H_α in the corresponding lithium enolate: Δδ increases as the coordinating ability of the 3-R substituent increases (i.e., as the ratio of enol silyl ethers **9**/**8** increases). The substantial upfield chemical shift of H_α in the 3-benzylcyclypentanone enolate suggests that C_α has a higher electron density than that in the 3-*n*-butylcyclopentanone enolate, for example, and that this increased electron density on C_α reflects loosening (i.e., more ionic character) of the oxygen–lithium bond of the enolate probably due to lithium–arene π coordination. The same trend was observed also in the cyclohexanone series.

The regiochemical directing effect of a neighboring aromatic group is even more dramatic in enolate formation from acyclic 5-tolyl-3-hexanone (eq 4). Lithiation with lithium diisopropylamide gave a 6:1 mixture of lithium enolates *Z*-**15** and *E*-**15**; this ratio was established by the ratio of geometric isomers observed for the product enol silyl ethers (no 2-hexen-3-ol ether was detected) and by the NMR data for these enolates. Specifically, whereas the α-carbon atom of enolate *E*-**15** appeared at a "normal" position for a lithium enolate (i.e., 102.3 ppm), the α-carbon atom of π-coordinated lithium species *Z*-**15** was shifted upfield significantly to 98.5 ppm; integration of the relative areas under the peaks at 98.5 and 102.3 ppm gave a 6:1 ratio. The upfield chemical shift of the α-carbon atom in enolate *Z*-**15** relative to that of enolate *E*-**15** apparently indicates a greater amount of electron density at C_α in π-coordinated lithium intermediate *Z*-**15**; lithium–arene π coordination seems to produce an enolate ion which resembles to a large degree a free enolate ion which can be formed by adding an external crown ether to a "normal" lithium enolate. The magnitude of this upfield shift of C_α (3.8 ppm) in *Z*-**15** is on the same order as that observed by House and by Jackman using various enolates and crown ethers.[17]



The regiospecificity observed in the lithiation of 5-tolyl-3-hexanone (eq 4) is truly remarkable. To our knowledge, this is the first example of an acyclic, unsymmetrical ketone flanked by two methylene centers bearing only hydrocarbon groups which undergoes thermodynamic enolization in only one of the two possible directions.[18] The very large magnitude of this regiocontrol is reminiscent of that observed in enolization of *cis*- and *trans*-2-decalones where strong stereoelectronic factors promote formation of one or the other enolate structural isomer, and where alkylation produces *either* 1-alkyl-*cis*-2-decalones *or* 3-alkyl-*trans*-2-decalones.[19] Thus the directing effect of a remote aryl group on the regiochemistry of enolate formation (and alkylation) has good potential for use in organic synthesis.[20]

If a lithium–arene π coordination is indeed responsible for this unusual regiochemistry of enolate formation, then the magnitude of this effect should be inversely related to the coordinating ability (e.g., DME > THF > Et_2O > pentane) of the solvent used.[21] Indeed this is the case, as shown in eq 5

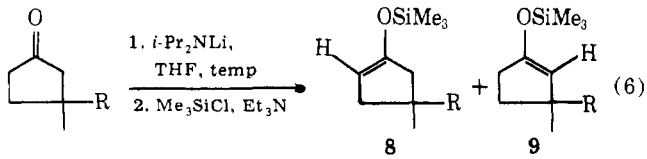


solvent			
DME	1.0	:	1.8
THF	1.0	:	3.3
Et_2O	1.0	:	5.0
pentane	1.0	:	22

and as observed also for 3-methyl-3-phenylcyclo*hex*anone. Adding 1 equiv of tetramethylethylenediamine to the lithium enolate in THF at 25 °C and then adding Me_3SiCl, however, caused an unexpected increase in the ratio of **8**:**9** to 1.0:5.6.

Control experiments established that enol silyl ethers **8**–**11** were all stable to the reaction conditions and that the enolate precursors to enol silyl ethers **8** and **9** and **10** and **11** react with trimethylsilyl chloride at the same rate.[22] For example, 1.0 equiv of a 1.4:1 mixture of enol silyl ethers **8** and **9** (R = Ph) was treated in THF with 1.0 equiv of methyllithium; after GLC analysis of a small aliquot indicated complete conversion of the enol silyl ethers to the corresponding enolates (i.e., GLC detection of only 3-methyl-3-phenylcyclopentanone), 0.5 equiv of Me_3SiCl/Et_3N was added. Workup gave 0.5 equiv of 3-methyl-3-phenylcyclopentanone and 0.5 equiv of a 1.4:1 mixture of enol silyl ethers **8** and **9** (R = Ph), indicating that the enolate precursors to enol silyl ethers **8** and **9** compete *with equal effectiveness* for the limited amount of silylating agent.

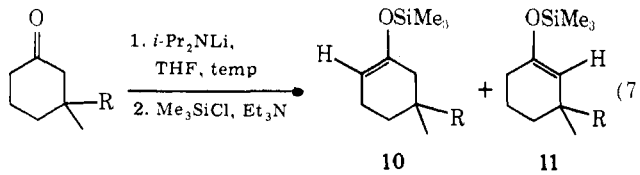
Temperature variation experiments were done to make certain that the lithium enolate precursors to enol silyl ethers **8** and **9** and **10** and **11** actually equilibrated under the "normal" reaction conditions of temperature (25 °C) and presence of secondary amine (*i*-Pr_2NH). The results are summarized in eq 6 and 7. For example, performing eq 6 in THF at 0 °C led



(6)

8 **9**

	temp, °C		
R = Ph	−78	1.0	0.7
	0	1.0	1.8
	25	1.0	3.3
	0 → 25 → 0	1.0	3.4
	reflux	1.0	4.1
	−78/HMPA	1.0	3.3
R = *n*-Bu	−78	1.0	0.22
	0	1.0	0.19
	25	1.0	0.24



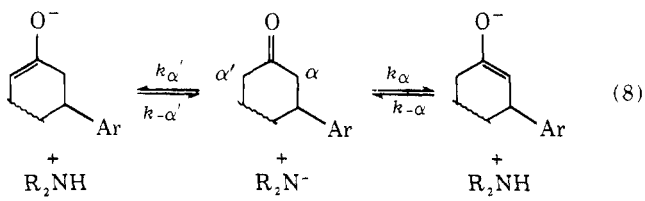
(7)

10 **11**

	temp, °C		
R = Ph	−78	1.0	0.5
	0	1.0	0.8
	25	1.0	2.1
	0 → 25 → 0	1.0	1.9
	reflux	1.0	3.2
R = *n*-Bu	−78	1.0	0.19
	0	1.0	0.15
	25	1.0	0.17
	reflux	1.0	0.20

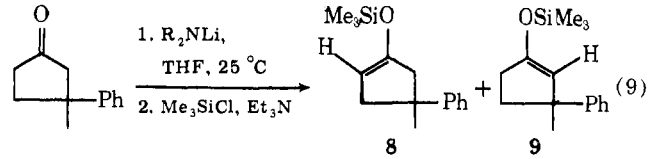
to ethers **8** and **9** in a 1.0:1.8 ratio, whereas repeating this experiment with the cycle 0 → 25 → 0 °C led to **8** and **9** in a ratio of 1.0:3.3, characteristic of the original 25 °C experiment. Furthermore, performing eq 6 at −78 °C in the absence and in the presence of hexamethylphosphoramide (which promotes proton transfer)[23] gave **8** and **9** in ratios of 1.0:0.7 and 1.0:3.3, respectively.

We envision equilibration of enolate structural isomers to occur via protonation by the secondary amine derived from the lithium amide and re-formation of the parent ketone, which subsequently suffers deprotonation from its other adjacent carbon atom (eq 8).



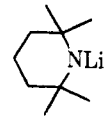
(8)

The much higher acidity of the ketone ($pK_a \simeq 20$)[12] relative to that of the amine ($pK_a \simeq 30$)[12] suggests that virtually all of the parent ketone is deprotonated and that no free parent ketone therefore is present for proton exchange to occur between it and its enolate. Enolate equilibration also occurred in the presence of *excess* lithium amide base, under which conditions certainly no free ketone was present. Furthermore, we have observed a dramatic effect on the ratio of enol silyl ethers **8** and **9** (and therefore their precursor enolates) by changing the steric environment about the amide nitrogen atom (eq 9).



(9)

8 **9**

R_2NLi		
Et_2NLi	1.0 :	1.1
i-Pr_2NLi	1.0 :	3.3
	1.0 :	8.4

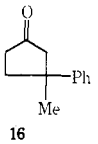
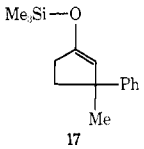
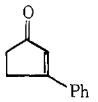
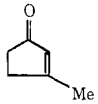
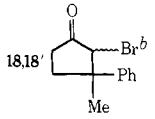
We interpret the results in eq 9 to signify that, as the amine nitrogen atom becomes more crowded, the overall equilibrium in eq 8 is shifted to the right.

Stereochemistry of Enolate Alkylation and Bromination. The enolate of 3-methyl-3-phenylcyclopentanone (**16**) was generated in four different ways: (a) via lithiation using lithium diisopropylamide; (b) via methyllithium cleavage of cyclopentenol silyl ether **17**;[24,25] (c) via diorganocopperlithium addition to 3-methyl- or 3-phenyl-2-cyclopentenone;[26] and (d) via dimethylcopperlithium–bromine exchange with α-bromocyclopentanones **18** and **18′**.[27]

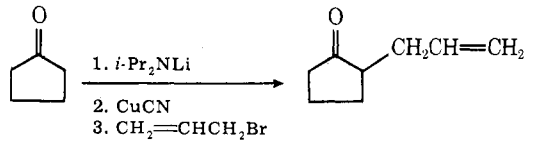
From the results for experiments 1–3 in Table II, it is clear that enolization and methylation of 3-phenylcyclopentanone **16** occurred regioselectively toward the phenyl group; only 10% of the product mixture resulted from lithiation and methylation away from the phenyl group. In the absence of copper(I), the lithium enolate produced roughly a 1:1 mixture of mono-: dimethylated products (experiment 1). Cyclopentanone lithium enolates are notoriously difficult to monoalkylate because proton transfer is much faster in five-membered cyclic ketones relative to that in cyclohexanones or in most acyclic ketones.[28] Of the two monomethylated stereoisomers **19** and **19′**, the more stable epimer **19** was produced stereoselectively.

When lithiation was followed by addition of only 10% of cuprous cyanide (experiment 2), methylation remained *regioselective* toward the phenyl group, but the reaction changed in three significant ways. First, the *extent of methylation decreased;* instead of recovering 12% of starting cyclopentanone **16**, 42% of cyclopentanone **16** was recovered. Second, the *amount of dimethylation decreased* from 47 to 10%. Third, *the less stable epimer* **19′** *was formed stereoselectively; cis*-2-methyl-3-phenylcyclopentanone (**19′**) must be the kinetic product of this reaction. Basic equilibration of **19′** led to a 95:5 mixture of isomers **19:19′**. That the 2-methyl and 3-phenyl groups of epimer **19′** are cis to each other is further shown by the ^1H NMR chemical shift of the 2-methyl doublet (δ 0.78), which is shielded relative to that of the methyl doublet (δ 0.95) of the more stable epimer **19**; this ^1H NMR methyl shielding effect of a 3-aryl group in a *cis*-2-methyl-3-arylcyclopentanone has been noted previously.[29] Experiment 3, using 1 equiv of cuprous cyanide and an extended time (14 h) for the methylation step, provides a simple, mild, convenient, regioselective, and stereoselective method for direct conversion of 3-phenylcyclopentanone **16** into the corresponding monomethylated 2-methyl-3-phenylcyclopentanone epimers **19** and **19′**. More generally, direct monosubstitution of most cyclopentanones thus appears possible if cuprous cyanide is present during reaction of the enolate intermediate with an electrophile. For example, cyclopentanone itself was lithiated and then, in the presence of copper(I), was monoallylated in 60% yield on a several-gram scale (eq 10); in the absence of copper(I), substantial diallylation occurred. This new synthetic method represents a substantial improvement on previous, usually

Table II. Methylation (MeI, HMPA, 25 °C, 6 h) of 3-Methyl-3-phenylcyclopentanone Enolate Generated in Various Ways

expt	compd	method of enolate generation	19	19′	yield, % 20	21	16
			19:19′				
1	 16	i-Pr_2NLi	90:10	34	47	10	12
2	16	1. i-Pr_2NLi 2. 10% CuCN	33:67	38	10	10	42
3	16	1. i-Pr_2NLi 2. 1 equiv CuCN	35:65	80 [a]	5	10	0
4	 17	MeLi	93:7	28	57		13
5	17	1. MeLi 2. 2% MeCu	19:81	44	19		19
6		Me_2CuLi	4:96	40			49
7		Ph_2CuLi	10:90	65			22
8	 18,18′	Me_2CuLi	4:96	74			5

[a] 14 h was allowed for the methylation step. [b] 1.25:1.0 ratio of stereoisomers.



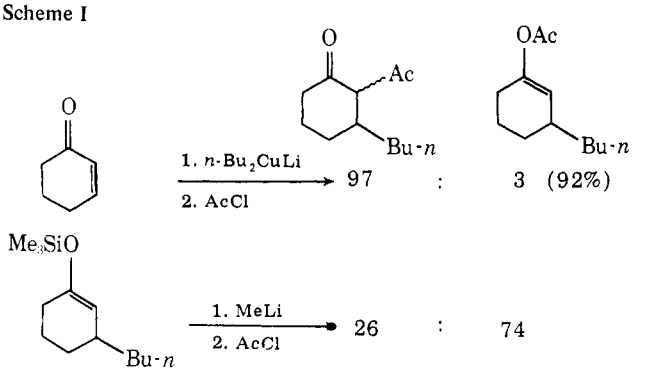
(10)

indirect procedures for monosubstitution of cyclopentanones.[30]

Methyllithium cleavage[24] of cyclopentenol silyl ether **17** (experiment 4) was expected to produce the same lithium enolate as formed in experiment 1; indeed the results of experiments 1 and 4 are very similar. Addition of only 2% methylcopper to this lithium enolate caused a dramatic *decrease in the amount of dimethylation* from 57 to 19% and a dramatic change in the ratio of epimers **19:19′** from 93:7 to 19:81: that is, *stereoselective* formation of the kinetic epimer **19′**.

The large effect of such a small amount of copper(I) on the course of this methylation reaction is especially noteworthy because House has shown that the enolate generated via dimethylcopperlithium addition to 3-methyl-2-cyclohexenone is ≥98% a *lithium* enolate.[31] Previous attempts to alter the course of reaction of an authentic lithium enolate by addition of copper(I) species have failed to produce any noticeable changes in Michael reactions,[32] and NMR spectroscopy likewise showed no change in the spectrum of a lithium enolate upon addition of copper(I).[33] Recently, however, Kurozumi and co-workers have reported that, whereas a lithium enolate undergoes O-acetylation, a "copper–lithium" enolate undergoes mainly C-acetylation upon treatment with acetyl chloride (Scheme I).[34]

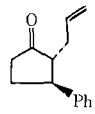
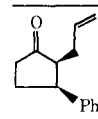
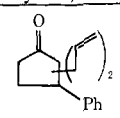
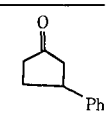
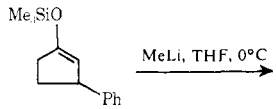
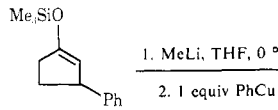
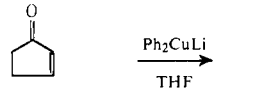
Scheme I



Likewise Berlan and co-workers have recently observed γ-deuteration of an authentic sodium dienolate but α-deuteration of the corresponding "copper" dienolate,[35] and Katzenellenbogen has reported the different chemical behavior of ester dienolates in the absence and presence of copper(I).[36] Also Rivière has reported stereochemical results which seem to support the existence of α-cuprio ketones.[37]

It seems to us that House's finding of ≤2% copper(I) in the supernatant solution generated via dimethylcopperlithium addition to 3-methyl-2-cyclohexenone at 25 °C is not incompatible with the notion that alkylation of lithium enolates often

Table III. Allylation (CH_2=$CHCH_2Br$, −78 °C, 0.5 h; 25 °C, 0.5 h) of 3-Phenylcyclopentanone Enolate Generated in Various Ways

		yield, %		
	 22	 22′	 23	
	22:22′ 70:30	(42)	(31)	(22)
	4:96	(43)		(52)
	7:93	(72)		(15)

leads to different results in the presence of even small amounts of copper(I); indeed we have shown that as little as 2% methylcopper has a dramatic effect on the course of cyclopentanone enolate alkylation. Although it is now clear that only a few percent of copper(I) can have a large effect on the course of enolate reaction with electrophiles, it is not yet clear *how* copper(I) causes this effect.

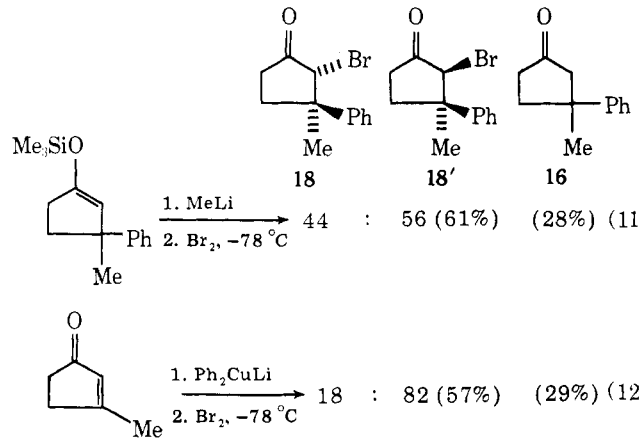
One possible explanation for the catalytic effect of copper(I) in controlling the stereochemistry and in limiting the polyalkylation of these cyclopentanone enolates demands first that alkylation of a "copper enolate" be much faster than alkylation of a lithium enolate[38] and second that once the "copper enolate" is alkylated the copper(I) is rapidly freed to react with the excess lithium enolate converting it into a "copper enolate", and this cycle is repeated many times. This explanation is probably incorrect, however, because copper(I) apparently retards rather than accelerates lithium enolate alkylation.

A second explanation is that the 3-phenylcyclopentanone lithium enolates, in the absence as well as in the presence of copper(I), are alkylated cis to the phenyl group[39] and that equilibration of this kinetic product to its thermodynamically more stable epimer occurs only in the absence of any copper(I). Somehow, even a small amount of copper(I) diminishes the reactivity of a lithium enolate and also retards proton transfer from neutral ketone to the enolate, thereby preventing epimerization. At this time, we favor this explanation, even though it is not clear by what mechanism copper(I) is exerting its extraordinary effect.

The complementary pair of experiments 6 and 7 showed that, whether the β-phenyl group was present in the reactant or was introduced via diphenylcuprate β-addition, the major product of α-methylation was *cis*-α-methyl-β-phenylcyclopentanone (**19′**); note the complete absence of any polymethylated products! We have used this cis-vicinal dialkylation procedure recently in a simple formal total synthesis of the sesquiterpene hydrocarbon (±)-laurene.[40]

Experiment 8 showed that a β-phenylcyclopentanone enolate intermediate generated via organocuprate–halogen *exchange*[27] (and not organocuprate *addition*) also underwent α-methylation leading stereoselectively to cis isomer **19′**. Note that cis isomer **19′** was produced from *both* epimeric bromides **18** and **18′** and that this is a clean, good-yield reaction.[41]

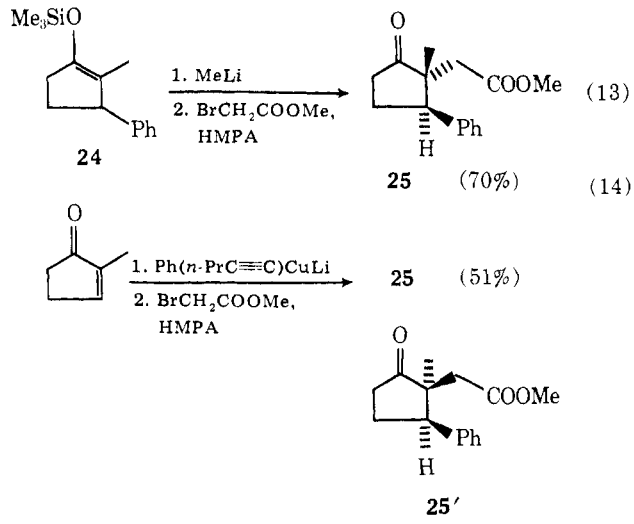
Besides mono*alkylation*, we have found that mono*bromination* of cyclopentanone enolates can be achieved at −78 °C and that the presence of copper(I) directs production of mainly the more hindered *cis*-2-bromo-3-phenylcyclopentanone **18′** (eq 11 and 12).[42] Equilibration of **18′** forms a mixture rich in *trans*-2-bromo-3-phenylcyclopentanone **18.** Epimers **18** and



18′ are characterized also by the chemical shift of the singlet for the methine H: δ 4.3 and 4.7 for **18** and **18′**, respectively.

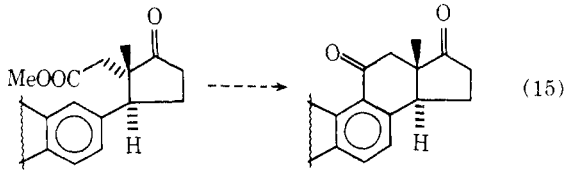
To extend even further the scope of this copper(I) effect on enolate alkylation, we have examined *allylation* of an authentic lithium enolate in the absence and presence of copper(I) (Table III). Note that no HMPA was used in these allylation reactions. The authentic lithium enolate produced much diallylated product, and monoallylated stereoisomers **22** and **22′** were isolated in 70:30 ratio in which the more stable epimer **22** predominated. The same reaction in the presence of 1 equiv of phenylcopper led to *no diallylated products* and to formation mainly of the less stable monoallylated epimer **22′** in which the 2-allyl and 3-phenyl groups are cis. Likewise diphenylcopperlithium addition to 2-cyclopentenone and then reaction with allyl bromide led mainly to *cis*-2-allyl-3-phenylcyclopentanone in good yield.

Finally, when the more highly substituted lithium enolate of 2-methyl-3-phenylcyclopentanone is generated and trapped with methyl 2-bromoacetate, attachment of the electrophilic acetate group occurred exclusively trans to the 3-phenyl group, both *in the presence as well as in the absence of copper(I)* (eq 13 and 14). The remarkable stereochemical purity of 2,2,3-trisubstituted cyclopentanone **25** was established by ^1H NMR spectroscopy as has been done before for similar systems. For example, the quaternary methyl singlet of cyclopentanone **25** appeared at δ 0.7, whereas that of its epimer (**25′**) is documented to appear at δ 1.3.[43] In the NMR spectrum of cyclopentanone **25,** there was no singlet whatsoever discernible in the range δ 1.2–1.4; by expanded NMR integration we placed an upper limit of <1.0% on the amount of epimeric **25′** that could have been present.



Although there is a β-phenyl group in the enolate precursor to 2,2,3-trisubstituted **25**, the β-phenyl group is obviously not directing α-alkylation cis to itself, nor is the product **25** subject to epimerization. Apparently, the relatively weak metal–arene π coordination which we have observed in enolates of 3-aryl-2-*H*-2-cyclopentenones is not present in enolates of 3-aryl-2-*alkyl*-2-cyclopentenones; the additional 2-alkyl substituent apparently disfavors buildup of electron density on carbon 2 and thus favors the more usual, highly covalent, lithium–oxygen bonded enolate.[44] Such a covalent enolate could then be alkylated from the side opposite the 3-phenyl group (steric approach control) leading to 2,2,3-trisubstituted cyclopentanone **25** in which the bulky phenyl and methoxycarbonylmethyl groups are trans to each other (product development control).[45] Presumably the synergistic effect of both of these factors, operating in the same direction, may be the basis for the observed stereospecificity in eq 13 and 14. There is literature precedent for organocopper-generated *tertiary* enolates to be subject to these factors and to give *either* cis or trans α,β-dialkylation products.[46,47] Clearly, the factors governing the structure and dynamics of lithium enolates in the presence of copper(I) are very delicately balanced.

The results reported here have broad implications generally for the chemistry of metal-containing unsaturated organic compounds and specifically for formation and reaction of other unsaturated metal enolates and enamides.[48] We are currently exploring use of the stereospecific trans α,β-dialkylation sequence shown in eq 14 in a short, simple, stereocontrolled total synthesis of 9,11-secosteroids[43,49] and ultimately of A,B-aromatic 11-keto 19-norsteroids (e.g., eq 15).[50,51]



(15)

Experimental Section

General. Microanalyses were performed by Galbraith Laboratory, Inc., Knoxville, Tenn., or by Chemalytics Inc., Tempe, Ariz. Infrared absorption bands are expressed in reciprocal centimeters (cm^{-1}) using polystyrene calibration; only peaks yielding structural information are reported. Nuclear magnetic resonance peak positions are expressed as downfield shifts in parts per million (δ) from tetramethylsilane internal standard. Resonances are characterized as multiplet (m), quartet (q), triplet (t), doublet (d), or singlet (s). Quantitative GLC analysis involved addition of a weighed amount of internal standard to a measured aliquot from a reaction mixture and comparison of peak areas of product and standard. Appropriate response factors for pairs of compounds (standard and product) were determined independently by analysis of known mixtures of the standard and a particular product.

Reagents and Solvents. The following solvents and reagents were distilled from CaH_2 and stored over 4 Å molecular sieves: diethyl ether, benzene, toluene, 1,2-dimethoxyethane (DME), hexamethylphosphoric triamide (HMPA), tetramethylethylenediamine (TMEDA), diethylamine, triethylamine, diisopropylamine, and 2,2,6,6-tetramethylpiperidine. Tetrahydrofuran was distilled from benzophenone sodium ketyl and stored over 4 Å molecular sieves. Triphenylmethane was recrystallized from benzene/petroleum ether prior to use. All other commercial solvents, reagents, or authentic samples of reaction products were purchased from Aldrich Chemical Co., J. T. Baker, or Eastman Organic.

Alkyllithium reagents were obtained from Aldrich Chemical Co. or Ventron (Alfa Inorganics) as 1.0–2.0 M solutions in the solvents indicated: methyllithium (ether), *n*-butyllithium (hexane), and vinyllithium (THF). The concentration of organolithium reagents was determined by a double titration procedure.[52] Lithium diisopropylamide (LDA) solutions were standardized by a variation of the method of Watson and Eastman.[53] Thus, commercial menthol (2 mmol) was dissolved in dry THF (5 mL) under nitrogen at −70 °C and a few crystals of phenanthroline were added. The LDA was added dropwise by syringe until the pale yellow color of lithium methoxide phenanthroline changed to the characteristic rust color of lithium diisopropylamide phenanthroline. The end point comes with little warning but is easily detected within ±1 drop from a typical syringe needle. At temperatures above −22 °C the end point is more difficult to detect.

Cuprous iodide and cuprous bromide (Fisher Chemical Co.) were continuously extracted with THF in a Soxhlet extractor for 12 h and dried in vacuo at 25 °C; the cuprous iodide and bromide thus purified remained pure for several months and aliquots were used for reactions with organolithium reagents to generate cuprates(I). Dimethyl sulfide complexed cuprous bromide was prepared by the method of House and Whitesides.[54]

Preparation of Organocuprate Reagents. All reactions involving organocuprate reagents were carried out in an inert atmosphere of prepurified nitrogen or argon with careful exclusion of oxygen and water. This was accomplished by a system that included a three-neck round-bottom flask with a Teflon-coated magnetic stirring bar, a nitrogen- or argon-filled balloon attached to a T-joint, and two serum stoppers on the flask. The appropriate amount of cuprous salt was placed in the round-bottom flask which was then evacuated and purged with nitrogen or argon three times. The balloon joint allowed the flask to be maintained under an inert atmosphere throughout the reactions.

General Procedure for Preparation of 3-Methyl-3-R-cycloalkanones (Tables IV and V). Method A. Copper-Catalyzed Grignard Addition. This method is represented by the preparation of 3-methyl-3-*p*-methoxyphenylcyclopentanone. To a mixture of 0.41 g (2.0 mmol) of dimethyl sulfide complexed cuprous bromide[55] and 0.980 g (10.0 mmol) of 3-methylcyclopent-2-en-1-one in 10 mL of anhydrous THF at 0 °C under an inert atmosphere was added dropwise 20 mmol of *p*-methoxyphenylmagnesium bromide[56] during 1 h with vigorous stirring.[57] After the addition was complete the resulting dark gray mixture was stirred at 0 °C for 1.5 h. The reaction mixture was then poured into 50 mL of saturated aqueous ammonium chloride and diluted with diethyl ether. The layers were separated and the aqueous phase extracted with two 30-mL portions of diethyl ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the remaining oil evacuated at 2.5 mm until a constant weight was obtained. The crude product was purified by column chromatography (silica gel, petroleum ether/CH_2Cl_2 gradient) to afford 1.099 g (54%) of 3-methyl-3-*p*-methoxyphenylcyclopentanone as a colorless oil: NMR ($CDCl_3$) δ 7.22 (d, J = 8 Hz, 2 H), 6.92 (d, J = 9 Hz, 2 H), 3.74 (s, 3 H), 2.05–2.65 (m, 6 H), 1.30 (s, 3 H); ^{13}C NMR (THF-d_8) 218.43, 157.98, 127.14, 126.44, 113.89, 55.14, 52.44, 43.17, 36.72, 36.98, 29.45 ppm; mass spectrum (70 eV) *m/e* (rel intensity) 204 (M^+, 50), 189 (65), 175 (100), 161 (30), 133 (85); high-resolution mass spectrum *m/e* 204.117 (calcd for $C_{13}H_{16}O_2$, 204.115).

Method B. Stoichiometric Cuprate Addition. This method is represented by the preparation of 3-methyl-3-benzylcyclopentanone. To 8.15 mmol of dibenzylcuprate at −40 °C was added 0.576 g (6.0 mmol) of 3-methylcyclopentenone in 2 mL of THF. The resulting dark mixture was allowed to stir for 1 h at −40 °C and then warmed to 0

Table IV. Preparation of 3-Methyl-3-R-cyclopentanones

R	method of prepn	isolated % yield	high-resolution mass spectrum exact *m/e* of parent ion (best empirical formula)	miscellaneous
Ph	b	85		see ref *a*
p-MePh	a	82		see ref *b*
p-MeOPh	a	54	204.117 ($C_{13}H_{16}O_2$)	R_f 0.65 (CH_2Cl_2, silica gel); see detailed exptl
p-O_2NPh		66	219.243 ($C_{12}H_{13}NO_3$)	mp 115–116 °C
$PhCH_2$	b	56	188.120	R_f 0.60 (CH_2Cl_2, silica gel); see detailed exptl
$PhCH_2CH_2$	a	75	202.298 ($C_{14}H_{18}O$)	R_f 0.70 (CH_2Cl_2, silica gel)
$PhCH_2CH_2CH_2$	a	83	216.299 ($C_{15}H_{20}O$)	R_f 0.72 (CH_2Cl_2, silica gel)
CH_2=CH	a	70		R_f 0.60 (15% Et_2O/pet ether, silica gel)
n-Bu	b	85		bp 82 °C (2.2 mm), ref *c*

[a] J. R. Bantick and E. Rothstein, *J. Chem. Soc. C*, 2512 (1971). [b] A. Casares and L. A. Maldonado, *Synth. Commun.*, 11 (1976). [c] D. J. Brunelle, Ph.D. Thesis, The Johns Hopkins University, 1974.

Table V. Preparation of 3-Methyl-3-R-cyclohexanones

R	method of prepn	isolated % yield	high-resolution mass spectrum exact *m/e* of parent ion (best empirical formula)	miscellaneous
Ph	b	88		n^{25}_D 1.5397, bp 85 °C (0.20 mm), see ref *a*
$PhCH_2$	b	86	202.297 ($C_{14}H_{18}O$)	R_f 0.65 (CH_2Cl_2, silica gel)
n-Bu	b	85		bp 82 °C (2.2 mm), see ref *b*

[a] J. R. Bantick and E. Rothstein, *J. Chem. Soc. C*, 2512 (1971). [b] D. J. Brunelle, Ph.D. Thesis, The Johns Hopkins University, 1974.

°C. After stirring for 30 min at 0 °C the resulting mixture was poured into 50 mL of saturated aqueous ammonium chloride, diluted with 20 mL of diethyl ether. The organic layer was separated and the aqueous phase extracted with two 30-mL portions of diethyl ether; the ether extracts were combined and dried over anhydrous sodium sulfate and the solvent was removed in vacuo to provide a yellow, viscous oil. The crude product was purified by column chromatography (silica gel, gradient hexane/CH_2Cl_2) to provide 742 mg (56%) of a slightly yellow, viscous oil: NMR ($CDCl_3$) δ 7.04–7.38 (m, 5 H), 2.61 (s, 2 H), 1.64–2.40 (m, 4 H), 1.02 (s, 3 H); IR (thin film) cm^{-1} 3025, 2950, 2932, 1742, 1600, 750, 724, 700; ^{13}C NMR (THF-d_8) 219.13, 138.13, 130.22, 128.12, 126.41, 51.62, 47.22, 40.59, 36.59, 34.50, 25.60 ppm; mass spectrum (70 eV) *m/e* 188 (M^+); high-resolution mass spectrum *m/e* 188.120 (calcd for $C_{13}H_{16}O$, 188.120).

Preparation of 3-Methyl-3-*p*-nitrophenylcyclopentanone. To a dry three-neck round-bottom flask under argon was added 0.454 g (2.84 mmol) of 3-methyl-3-phenylcyclopentanone in 10 mL of dry acetonitrile and the mixture was cooled to 5 °C. To this was added dropwise over a 15-min period 6.0 mL (3.0 mmol, 0.5 M) of nitronium tetrafluoroborate in sulfolane. The ice bath was removed and the reaction mixture was stirred for 12 h at room temperature. After this time the resulting solution was poured into 50 mL of water and diluted with 30 mL of diethyl ether. The layers were separated and the aqueous phase extracted with 30 mL of diethyl ether. The ether extracts were combined and washed with two 10-mL portions of water and then dried over anhydrous sodium sulfate. The crude product was column chromatographed (silica gel, CH_2Cl_2) to provide 0.435 mg (66%) of a yellow solid, mp 95–98 °C which was recrystallized from cyclohexane (3% $CHCl_3$): mp 115–116 °C; NMR ($CDCl_3$) δ 8.20 (d, J = 10 Hz, 2 H), 7.50 (d, J = 10 Hz, 2 H), 2.25–2.80 (m, 5 H), 1.40 (s, 3 H); IR (thin film) cm^{-1} 1742, 1520, 1600, 1350; mass spectrum (70 eV) *m/e* 219 (M^+); high-resolution mass spectrum *m/e* 219.243 (calcd for $C_{12}H_{13}NO_3$, 219.242).

General Procedure for Formation of Enol Silyl Ethers 8–11. To 1.0 mmol of lithium diisopropylamide solution[58] was added over a 20-min period 1.0 mmol of the 3-methyl-3-R-cycloalkanone as a solution in 5.0 mL of the designated solvent. The reaction mixture was allowed to stir for 40 min and then 10.0 mmol of chlorotrimethysilane and 10.0 mmol of triethylamine were added together rapidly and the resulting mixture was stirred for 3 h at the desired temperature. The isomeric enol silyl ethers were isolated by pouring the crude reaction mixture into cold (0–5 °C) saturated aqueous sodium bicarbonate, diluting with ether, and extracting the aqueous phase with diethyl ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the resulting residue evacuated at 0.5 mm until a constant weight was obtained. The resulting reaction mixtures were analyzed by analytical GLC (10 ft × 1/8 in. SE-30, 20 mL/min) and by ^1H NMR.

General Procedure for the Preparation of Authentic Enol Silyl Ethers 9 and 11. The procedure employed is exemplified by the preparation of 1-trimethylsiloxy-3-methyl-3-phenylcyclopentene. Thus, to 11.0 mmol of lithium diphenylcuprate at 0 °C in 20 mL of diethyl ether was added 3.5 mmol (0.29 g) of 3-methylcyclopentenone in 2 mL of diethyl ether. After 2 h at 0 °C a mixture of freshly distilled (3.50 mL, 25 mmol) triethylamine and 3.17 mL (25 mmol) of chlorotrimethylsilane was rapidly added via a pressure equilibrating addition funnel and stirred at room temperature for 2.5 h. After this period the resulting dark mixture was poured into an ice-cold mixture of 5 mL of concentrated ammonium hydroxide and 50 mL of saturated aqueous sodium bicarbonate and diluted with ether. The layers were rapidly

separated and the aqueous phase extracted with two 30-mL portions of diethyl ether. The extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the resulting oil evacuated at 0.25 mm until a constant weight was obtained. The crude product was purified by Florisil column chromatography (50 g of Florisil, 2.5% CH_2Cl_2/hexane) to obtain 0.68 g (80%) of a colorless oil: NMR ($CDCl_3$) δ 7.12–7.50 (m, 5 H), 4.81 (t, J = 1 Hz, 1 H), 1.92–2.70 (m, 4 H), 1.40 (s, 3 H), 0.20 (s, 9 H); ^{13}C NMR ($CDCl_3$) 154.62, 133.65, 133.14, 131.40, 130.78, 130.51, 117.06 ppm; mass spectrum (70 eV) m/e (rel intensity) 246 (M^+, 20), 148 (100).

Supplementary Tables VIII and IX contain physical and spectral properties of enol silyl ethers **9** and **11**, and supplementary Tables X and XI contain GLC and ^1H chemical shift data for enol silyl ethers **8** and **10** (see paragraph at end of paper).

Preparation of 5-*p*-Tolyl-3-hexanone. To 20 mmol of lithium dimethylcuprate at 0 °C in 50 mL of diethyl ether was added 1.55 g (8.9 mmol) of 1-*p*-tolyl-1-penten-3-one in 15 mL of diethyl ether over a 15-min period. The resulting mixture was allowed to stir for 4 h at 0 °C and then was poured into 100 mL of saturated aqueous ammonium chloride and diluted with 100 mL of diethyl ether. The layers were separated and the aqueous phase extracted with two 50-mL portions of diethyl ether. The ether extracts were combined and dried over sodium sulfate. The solvent was removed in vacuo and the resulting oil was purified by column chromatography ($CHCl_3$, silica gel, R_f 0.60) to afford 1.32 g (84%) of colorless oil: NMR ($CDCl_3$) δ 7.08 (s, 4 H), 3.30 (m, 1 H), 2.30 (s, 3 H), 2.24 (q, J = 8 Hz, 3 H) 2.65 (d, J = 9 Hz, 2 H), 1.30 (d, J = 10 Hz, 3 H), 1.00 (t, J = 8 Hz, 3 H); IR (thin film) cm^{-1} 3015, 2985, 2940, 1715, 1605, 815, 720; ^{13}C NMR (THF-d_8) 210.0, 143.4, 135.6, 129.2, 126.7, 50.9, 36.6, 35.2, 22.0, 20.9, 7.6 ppm; mass spectrum (70 eV) m/e 178 (M^+, 60), 163 (100).

Preparation of (*Z*)- and (*E*)-2-*p*-Tolyl-4-trimethylsiloxy-3-hexene. To 10 mmol of lithium dimethylcuprate at 0 °C in 25 mL of diethyl ether was added 0.87 g (5.0 mmol) of 1-*p*-tolyl-1-penten-3-one in 7 mL of diethyl ether over a 10-min period. The resulting mixture was allowed to stir for 4 h at 0 °C and then 6.32 mL (40 mmol) of chlorotrimethylsilane and 7.0 mL (40 mmol) of triethylamine were added together and the mixture was allowed to stir at room temperature for 3 h. After this time the reaction mixture was poured into a mixture of 50 mL of cold saturated aqueous sodium bicarbonate and 2 mL of concentrated ammonium hydroxide. The layers were quickly separated and aqueous phase was extracted with 30 mL of diethyl ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the crude product was purified by Florisil column chromatography (10% CH_2Cl_2/petroleum ether) to yield 0.71 g (57%) of a colorless oil: NMR ($CDCl_3$) δ 7.05 (q, 4 H), 4.63 (d, J = 10 Hz), 3.61–3.8; 2 (m, 1 H), 2.32 (s, 3 H), 2.02 (q, J = 8 Hz, 2 H), 1.25 (d, J = 8 Hz, 3 H), 0.95 (t, 3 H), 0.22 (s, 9 H); ^{13}C NMR (THF-d_8) 150.12, 144.0, 134.12, 128.21, 126.09, 112.12, 111.96 ppm absorptions (α carbons for E and Z isomers) integrate 1:4, respectively; mass spectrum (70 eV) m/e (rel intensity) 262 (M^+, 65), 247 (100).

Reaction of 5-*p*-Tolyl-3-hexanone with Lithium Diisopropylamide Followed by Addition of Chlorotrimethylsilane/Triethylamine. The procedure and product isolation were as previously described in the general Experimental Section except that enolate formation was allowed to proceed for 6 h. The crude product was analyzed by GLC (10 ft × 1/8 in. SE-30, 150 °C), which indicated that three products were present. Product A (10.5 min, 12%) was shown by comparison of its retention time to be 5-*p*-tolyl-3-hexanone. Products B and C (14.8 and 15.7 min) were isolated by Florisil column chromatography (10% CH_2Cl_2/petroleum ether) (68%) as a colorless liquid and were identified as (*Z*)- and (*E*)-2-*p*-tolyl-4-trimethylsiloxy-3-hexene by comparison of GLC retention time with that of material prepared by the route previously described. The *Z*:*E* ratio was determined to be 6:1 by integration of the vinyl absorption in the NMR[59] and by integration of the GLC trace.

Study of the Effect of Temperature on the Regiochemistry of Enol Silyl Ether Formation from 3-Methyl-3-phenylcyclopentanone. The general procedure was used except that the temperature of enolate formation was varied. After 1 h at this temperature chlorotrimethylsilane/triethylamine was added and the reaction mixture was maintained at this temperature for 1 h and then was allowed to warm to room temperature. The product ratios and yields were determined by analytical GLC (SE-30, 20 mL/min, 165 °C, hexadecane as internal standard) to be 1-trimethylsiloxy-4-methyl-4-phenylcyclopentene (retention time of 10.3 min) and 1-trimethylsiloxy-3-methyl-3-phenylcyclopentene (retention time 9.4 min).

Study of the Effect of Solvent on the Regiochemistry of Enol Silyl Ether Formation from 3-Methyl-3-phenylcyclopentanone. The general procedure was employed but the solvent for enolate formation was varied. When pentane was employed, 6 h at 25 °C was used for enolate formation. The yields and ratios were determined by GLC analysis with a calibrated internal standard (see eq 5).

Reaction of 3-Methyl-3-phenylcyclopentanone with Diethylamide Followed by Addition of Chrlorotrimethylsilane/Triethylamine. The procedure was analogous to that used when lithium diisopropylamide was employed. Diethylamide was generated at room temperature in THF by the addition of 1.0 equiv of *n*-butyllithium to 1.0 equiv of diethylamine. After the normal workup, analytical GLC (10 ft SE-30, 170 °C) showed 48% of 1-trimethylsiloxy-3-methyl-3- phenylcyclopentene and 42% of 1-trimethylsiloxy-4-methyl-4-phenylcyclopentene with 9% of starting ketone.

Reaction of 3-Methyl-3-phenylcyclopentanone with 2,2,6,6-Tetramethylpiperidide Followed by Addition of Chlorotrimethylsilane/Triethylamine. The procedure was as previously described except that lithium 2,2,6,6-tetramethylpiperidide was employed as the base. Lithium tetramethylpiperidide was generated by the method of Olofson,[60] where 1.0 mmol of *n*-butyllithium was added to a THF solution of 1.0 mmol of 2,2,6,6-tetramethylpiperidine. To the resulting solution was added 0.188 g (1.0 mmol) of 3-methyl-3-phenylcyclopentanone and the solution was allowed to stir for 5 h at room temperature. After this time 1.58 mL (10.0 mmol) of chlorotrimethylsilane and 1.76 mL (10.0 mmol) of triethylamine were added together and rapidly. After 6 h at room temperature the reaction products were isolated in the normal manner. The crude product mixture was analyzed by analytical GLC (10 ft × 1/8 in. SE-30, 170 °C, hexadecane internal standard) to contain 71% of 1-trimethylsiloxy-3-methyl-3-phenylcyclopentene and 8% of 1-trimethylsiloxy-4-methyl-4-phenylcyclopentene with 21% starting ketone by comparison of the GLC retention times with those of authentic samples.

Control Experiment. Rates of Enolate O-Silylation. To 54 mg (0.23 mmol) of a 1.36/1.0 mixture of trimethylsiloxy-3-methyl-3-phenylcyclopentene and trimethylsiloxy-4-methyl-4-phenylcyclopentene in 5 mL of THF at room temperature was added 0.13 mL of 1.8 M (0.23 mmol) methyllithium and the mixture was stirred for 2.5 h after which time a mixture of 0.115 mmol of chlorotrimethylsilane and 0.022 mL (0.115 mmol) of triethylamine was added and stirred for 3 h. After normal workup the product was found by GLC (10 ft × 1/8 in. SE-30, 165 °C) to be a 1.35/1.0 ratio of trimethylsiloxy-3-methyl-3-phenylcyclopentene and trimethylsiloxy-4-methyl-4-phenylcyclopentene (41%) along with ≈45% of 3-methyl-3-phenylcyclopentanone (hexadecane as internal standard).

Representative Procedure for Lithium Enolate Sample Preparation for ^1H and ^{13}C NMR Analysis. To 1.2 mmol of trimethylsiloxy-3-methyl-3-*p*-methoxyphenylcyclopentene under an inert atmosphere in 1.0 mL of THF was added 1.2 mmol of methyllithium dropwise and the mixture was allowed to stir for 1 h at 25 °C. After this time the resulting enolate solution was injected by syringe into a dry NMR tube fitted with a serum cap and under an inert atmosphere.

Preparation of 3-Methyl-3-phenylcyclopentanone (16). To 1.43 g (10.0 mmol) of cuprous bromide in 20 mL of diethyl ether at 0 °C was added dropwise 9.52 mL of 2.1 M (20.0 mmol) phenyllithium and the solution was allowed to stir for 15 min. To the resulting dark green diphenylcuprate solution was added dropwise 0.475 g (5.0 mmol) of 3-methyl-2-cyclopentenone as a solution in 5 mL of diethyl ether. The resulting dark green mixture was stirred for 3 h at 0 °C and poured into 100 mL of saturated aqueous ammonium bicarbonate. The ether phase was diluted with 100 mL of diethyl ether, the layers were separated, and the aqueous phase was extracted with three 50-mL portions of diethyl ether. The ether extracts were combined and dried over anhydrous sodium sulfate to afford a viscous oil which was purified by column chromatography (silica gel, CH_2Cl_2) to afford 0.74 g (85%) of a colorless oil: NMR ($CDCl_3$) δ 7.15 (s, 5 H), 2.20–2.45 (m, 6 H), 1.25 (s, 3 H); IR (thin film) cm^{-1} 1740, 1605; mass spectrum (70 eV) m/e 174 (M^+). These spectral data are in good agreement with those in the literature.

Reaction of 3-Methyl-3-phenylcyclopentanone with Lithium Diisopropylamide and then with A–C. A. Methyl Iodide. To a solution of 2.0 mmol of lithium diisopropylamide at 25 °C was added dropwise 0.374 g (2.0 mmol) of 3-methyl-3-phenylcyclopentanone in 5 mL of

THF over a 20-min period. The resulting solution was allowed to stir for 1 h at 25 °C and then a mixture of 1.42 g (10 mmol) of methyl iodide in 1.0 mL of HMPA was added and then stirred for 6 h at 25 °C. After this time the reaction mixture was poured into 50 mL of water and diluted with ether. The layers were separated and the aqueous phase was extracted with two 30-mL portions of diethyl ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford a viscous oil which was analyzed by GLC (10 ft × ⅛ in., SE-30, 160 °C) and shown to consist of five products: A, 11.0 min; B, 13.0 min; C, 15.5 min; D, 17.5 min; E, 21.0 min. The crude product mixture was separated by preparative GLC (10 ft × ¼ in., SE-30, 170 °C) where five products were isolated. Product A (22 mg, 12%) was identified as 3-methyl-3-phenylcyclopentanone (**16**) by comparison of its GLC retention time and spectral data with those of a sample previously prepared. Product B (58 mg, 31%) was identified as *cis*-2,3-dimethyl-3-phenylcyclopentanone (**19**): NMR ($CDCl_3$) δ 7.15–7.28 (m, 5 H), 2.52–2.80 (m, 5 H), 1.25 (s, 3 H), 1.02 (d, J = 7 Hz, 3 H); IR (thin film) cm^{-1} 1745, 1601, 765, 710; mass spectrum (70 eV) *m/e* (rel intensity) 188 (M^+, 90), 173 (50), 139 (100); high-resolution mass spectrum 188.273 (calcd for $C_{14}H_{18}O$, 188.272). Product C (3.6 mg, 13%) was identified as *trans*-2,3-dimethyl-3-phenylcyclopentanone (**19′**): NMR ($CDCl_3$) δ 7.19 (broad s, 5 H), 2.50–2.21 (m, 5 H), 1.26 (s, 3 H), 0.178 (d, J = 7 Hz, 3 H); IR (thin film) cm^{-1} 1742, 1605, 770, 842; mass spectrum (70 eV) *m/e* 188 (M^+); high-resolution mass spectrum 188.271 (calcd for $C_{13}H_{16}O$, 188.272). The cis relationship between the α-methyl and β-phenyl groups is based on the unusually high field α-methyl doublet[29,61] and on the fact that **19′** when treated with a catalytic amount of sodium acetate in refluxing ethanol equilibrated to a 96/4 mixture of **19**/**19′**. Product E (107 mg, 60%) was identified as 2,2,3-trimethyl-3-phenylcyclopentanone (**20**): NMR ($CDCl_3$) δ 7.20 (s, 5 H) 1.75–2.80 (m, 4 H), 1.20 (s, 3 H), 1.10 (s, 3 H), 0.57 (s, 3 H); IR (thin film) cm^{-1} 1740, 1562, 1440, 770; mass spectrum (70 eV) *m/e* (rel intensity) 202 (M^+, 25), 187 (60), 159 (75), 145 (95), 131 (80), 117 (100). These spectral data are consistent with those in the literature.[62] Product D (18 mg, 10%) was identified as 3,5-dimethyl-3-phenylcyclopentanone (**21**): NMR ($CDCl_3$) δ 7.20 (broad s, 5 H) 2.05–2.74 (m, 3 H), 2.42 (s, 2 H), 1.20 (s, 3 H), 1.08 (d, J = 7 Hz, 3 H); IR (thin film) cm^{-1} 1742, 1602, 775; mass spectrum (70 eV) *m/e* (rel intensity) 188 (M^+, 60), 173 (35), 144 (30), 119 (100). **21** did not equilibrate to **19** or **19′** upon treatment with sodium acetate in refluxing ethanol.

B. 0.1 Equiv of Cuprous Cyanide and Then Methyl Iodide. The procedure was as previously described except that to the cyclopentanone lithium enolate at 25 °C was added via a cannula 0.2 mmol of cuprous cyanide. The resulting solution was allowed to stir for 1 h at 25 °C and was then treated as previously described. The crude product was analyzed by GLC (10 ft × ⅛ in., SE-30, 160 °C) and was shown to consist of five products: A, 11.0 min; B, 13.0 min; C, 15.5 min; D, 17.5 min; and E, 21.0 min. Product A (42%) was identified as 3-methyl-3-phenylcyclopentanone (**16**) by a mixed injection with an authentic sample previously isolated. Product B (13%) was identified as *cis*-2,3-dimethyl-3-phenylcyclopentanone (**19**) by comparison of its GLC retention time with that of an authentic sample previously isolated. Product C (26%) was identified as *trans*-2,3-dimethyl-3-phenylcyclopentanone (**19′**) by comparison of its GLC retention time and mixed injection with an authentic sample. Product D (10%) was identified as 3,5-dimethyl-3-phenylcyclopentanone (**21**) by comparison of its GLC retention time with that of an authentic sample previously isolated. Product E (10%) was identified as 2,2,3-trimethyl-3-phenylcyclopentanone (**20**) by comparison of its GLC retention time and mixed injection with an authentic sample. When 40 mg of the crude product mixture was treated with a catalytic amount of sodium acetate in refluxing ethanol, product C equilibrated to product B, where the ratio of B to C after equilibration was 95:5.

C. 1.0 Equiv of Cuprous Cyanide and Then with Methyl Iodide. The procedure was as previously described except that 2.0 mmol of cuprous cyanide was employed. The crude product mixture was analyzed by GLC (10 ft × ⅛ in., SE-30, 160 °C) and shown to consist of four products: **19** (13.0 min, 28%), **19′** (15.5 min, 52%), **21** (17.5 min, 10%), and **20** (21.0 min, 5%).

Preparation of Authentic 1-Trimethylsiloxy-3-methyl-3-phenylcyclopentene (17). To 10 mmol of lithium diphenylcuprate in 10 mL of diethyl ether at 0 °C was added 0.29 g (3.5 mmol) of 3-methyl-2-cyclopentone. After 2 h at 0 °C a mixture of freshly distilled 3.5 mL (0.25 mmol) of triethylamine and 3.17 mL (0.25 mmol) of chlorotrimethylsilane was rapidly added via an addition funnel and stirred at room temperature for 2.5 h. After this period the resulting dark mixture was poured into saturated aqueous sodium bicarbonate, the layers were rapidly separated, the aqueous phase was extracted with diethyl ether, and the ether extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the resulting oil was evacuated at 0.25 mm until a constant weight was obtained. The crude product was purified by Florisil column chromatography (50 g of Florisil, 2.5% CH_2Cl_2/hexane) to obtain 0.68 g (80%) of a colorless oil: NMR ($CDCl_3$) δ 7.12–7.50 (m, 5 H), 4.81 (t, J = 1 Hz, 1 H), 1.92–2.70 (m, 4 H), 1.40 (s, 3 H), 0.20 (s, 9 H); IR (cm^{-1}) 1665, 1605, 1290, 825, 695; ^{13}C NMR ($CDCl_3$) 154.5, 133.65, 133.14, 131.40, 130.78, 130.51, 117.06 ppm; mass spectrum (70 eV) *m/e* 246 (M^+).

Reaction of 1-Trimethylsiloxy-3-methyl-3-phenylcyclopentene (17) with Methyllithium and Then with A and B. A. Methyl Iodide. To a THF solution of 0.370 g (1.05 mmol) of enol silyl ether **17** at 0 °C was added dropwise 1.0 mmol of methyllithium; after 1.5 h 1.02 mL (20 mmol) of methyl iodide mixed with 1.0 mL of HMPA was added. The resulting solution was stirred for 0.5 h at 0 °C and 6 h at room temperature. The products were isolated by pouring into water, separating the layers, extracting the aqueous phase with three 30-mL portions of diethyl ether, and drying the combined ether extracts with anhydrous sodium sulfate. After solvent removal 0.285 g of crude material was obtained which by analytical GLC (10 ft × ⅛ in., SE-30, 160 °C) consisted of four products: **16** (11.0 min, 13%), **13** (13.0 min, 28%), **19′** (15.5 min, 1%), and **20** (17.5 min, 60%). 2,2,3-Trimethyl-3-phenylcyclopentanone (**20**): NMR (CCl_4) δ 7.20 (s, 5 H), 1.75–2.80 (m, 4 H), 1.20 (s, 3 H), 1.10 (s, 3 H), 0.57 (s, 3 H); IR (thin film) cm^{-1} 1740, 1562, 1440, 770; mass spectrum (70 eV) *m/e* (rel intensity) 202 (M^+, 25), 187 (60), 154 (75), 145 (95), 131 (80), 117 (100).

B. 0.02 Equiv of Methylcopper and Then with Methyl Iodide. The lithium enolate solution (10.0 mmol) generated from 1-trimethylsiloxy-3-phenylcyclopentene prepared as previously described was added via syringe dropwise with stirring to a cold (0–10 °C) slurry of 0.20 mmol of methylcopper.[63] After the addition was complete the resulting solution was allowed to warm to 10–15 °C and stirred for 30 min at 10–15 °C. After this time 10.2 mL (100 mmol) of methyl iodide mixed with 10 mL of HMPA was added and the resulting solution was stirred for 6 h at 25 °C. Product isolation was as previously described. After solvent removal 2.89 g of crude product was obtained which by analytical GLC (10 ft × ⅛ in., SE-30, 160 °C) was shown to contain four products, as indicated in Table II.

Reaction of 3-Methyl-2-cyclopentenone with Lithium Diphenylcuprate and Then with Methyl Iodide. To an ethereal slurry (15 mL) of 1.43 g (19 mmol) of cuprous bromide at 0 °C was added dropwise 9.52 mL (20 mmol) of 2.1 M phenyllithium and the solution was allowed to stir at 0 °C for 5 min. To the resulting dark green cuprate solution was added 0.475 g (5.0 mmol) of 3-methyl-2-cyclopentenone as a solution in 2 mL of diethyl ether. The reaction mixture was allowed to stir for 2 h at 0 °C and then 4.62 mL (40.0 mmol) of methyl iodide mixed with 1.0 mL of HMPA was added via syringe and stirred for 6 h at 25 °C. After this time the resulting mixture was poured into saturated aqueous ammonium chloride and diluted with diethyl ether. Typical workup gave 1.68 g of crude product. Analytical GLC (10 ft × ⅛ in., SE-30, 170 °C) indicated that three products were present: **16** (12.8 min, 22%), **19** (14.4 min, 7%), and **19′** (15.9 min, 58%).

Preparation of 2-Allyl-1-cyclopentanone. To 10.0 mL (71.5 mmol) of diisopropylamine in 15 mL of dry THF under N_2 at −78 °C was added 45.0 mL of 1.6 M *n*-butyllithium (72.0 mmol). Cyclopentanone (5.0 g, 59.5 mmol) in 35 mL of THF was added to the lithium diisopropylamide dropwise over 1 h. The solution was allowed to stir for another 2 h, at which time CuCN (540 mg, 6.04 mmol) and 10.3 mL of HMPA (59.3 mmol) in 5 mL of THF was added. After 1 h, 10.8 mL (131 mmol) of allyl bromide in 2 mL of THF was added. The reaction mixture was allowed to stir at −78 °C for 5 h, then quenched with solid ammonium chloride, and allowed to warm slowly to 25 °C and left to stir overnight. The reaction mixture was filtered and rinsed with ether. The ether and THF were removed with an aspirator. The product was distilled at 69 °C at 15 mm pressure (lit.[64] bp 78–85 °C (20 mm)) to give 5.2 mL (4.36 g, 59%) of 2-allylcyclopentanone: NMR (CCl_4) δ 5.4–6.1 (1 H) (m), 5.1 (1 H) (m), 4.85 (1 H) (m), 1.1–3.0 (9 H) (m).

Reaction of 1-Trimethylsiloxy-3-methyl-3-phenylcyclopentene with Methyllithium and Then with Bromine (Preparation of α-Bromocy-

clopentanones 18 and 18′). To 0.268 g (1.1 mmol) of 1-trimethylsiloxy-3-methyl-3-phenylcyclopentene at 0 °C in 10 mL of THF was added dropwise 0.90 mL (1.1 mmol) of methyllithium. The resulting solution was stirred for 30 min at 0 °C and then cooled to −78 °C. After stirring at −78 °C for 5 min, 0.176 g (1.1 mmol) of bromine in 5 mL of chloroform was added and stirred for 1.0 min. After this time aqueous saturated sodium bicarbonate was added and the resulting mixture was warmed to room temperature. The crude mixture was extracted with three 30-mL portions of pentane, and the pentane extracts were combined and dried over anhydrous sodium sulfate to afford a reddish oil after solvent removal. The crude product was purified by preparative TLC to afford 0.170 g (61%) of the bromo ketones **18** and **18′** as a colorless oil: NMR (CCl_4) δ 7.42–7.26 (m, 5 H), 4.70 (s, 0.56 H), 4.26 (s, 0.44 H), 2.05–2.65 (m, 4 H), 1.32 (s), and 1.30 (s, 3 H). The 4.26 and 4.70 peaks are the epimeric protons on the carbon bearing bromine, where the δ 4.26 peak is for methyl and bromine cis (i.e., **18**) and the δ 4.70 peak for methyl and bromine trans (**18′**): IR (thin film) cm^{-1} 3030, 3015, 1145, 1408, 760, 1380, 692; mass spectrum (70 eV) *m/e* (rel intensity) 254 (M^+, 50), 252 (55), 183 (30), 175 (100); high-resolution mass spectrum 253.056 (calcd for $C_{12}H_{13}OBr$: 235.053). Equilibration using sodium acetate in refluxing ethanol gave **18:18′** in a ratio of 4:1.

Reaction of 3-Methyl-2-cyclopentenone with Diphenylcopperlithium and Then with Bromine (Preparation of α-Bromocyclopentanones 18 and 18′). To 8.0 mmol of lithium diphenylcuprate in 10 mL of diethyl ether at 0 °C was added 0.384 g (4.0 mmol) of 3-methyl-2-cyclopentenone in 2 mL of diethyl ether and the mixture was stirred at 0 °C for 1.5 h, after which time the reaction mixture was cooled to −78 °C. After stirring at −78 °C for 15 min a solution of 0.80 mL (25 mmol) of bromine in 5 mL of diethyl ether was added and the resulting dark mixture was allowed to stir for 15 min at −78 °C. The crude mixture, still at −78 °C, was poured directly into saturated aqueous ammonium chloride. The crude product was diluted with pentane, the layers were separated, and the aqueous phase was extracted with pentane. The pentane extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford 1.8 g of crude product. This material was purified by column chromatography (10% Et_2O/CH_2Cl_2) to afford 0.53 g (57%) of a colorless oil: NMR ($CDCl_3$) was as previously reported except that the ratio of the δ 4.3 (**18**) to the δ 4.7 (**18′**) peaks equaled 1.0:4.3; IR (thin film) as previously reported except for the intensities of the 1380- and 1408-cm^{-1} bands.

Reaction of 2-Bromo-3-methyl-3-phenylcyclopentanone with Lithium Dimethylcuprate and Then with Methyl Iodide/HMPA. To a solution of 2.0 mmol of lithium dimethylcuprate in 8 mL of diethyl ether at 0 °C was added 0.252 g (1.0 mmol) of 2-bromo-3-methyl-3-phenylcyclopentanone in 2.0 mL of diethyl ether. The addition was accompanied by the formation of a bright yellow color. After 1 h at 0 °C a mixture of 10.0 mmol of methyl iodide and 1.0 mL of HMPA was added. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature, stirred for 2 h, and quenched. The products were isolated in the usual manner. Analytical GLC (10 ft × ⅛ in., SE-30, 175 °C, 20 mL/min) indicated several products: **16** (8.5 min, 5%); **19** (10.5 min, 4%); **19′** (11.7 min, 70%).

Reaction of 2-Cyclopentenone with Lithium Diphenylcuprate and Then with Allyl Bromide. To 8 mmol of lithium diphenylcuprate in 10 mL of diethyl ether at 0 °C was added 0.328 g (4.0 mmol) of cyclopentenone and the mixture was allowed to stir for 1.5 h at 0 °C. After this time the resulting mixture was cooled to −78 °C and 25 mmol (1.79 mL) of allyl bromide was added; the resulting dark mixture was allowed to warm to room temperature and then worked up in the normal manner. Analytical GLC (10 ft × ⅛ in., SE-30, 170 °C, 20 mL/min) indicated one major product (12.9 min) and two minor products (11.7 and 9.5 min); 40 mg of the crude product was treated with a catalytic amount of sodium acetate in refluxing ethanol for 1 h. After this equilibration the 9.5-min peak did not change but the ratio of the 12.9-min to the 11.7-min peak had changed to 0.04. The remaining crude product was chromatographed on 80 g of silica gel, eluted with $CHCl_3$, to afford 0.47 g of a colorless oil. This material was further purified by preparative GLC (10 ft × ¼ in., SE-30, 65 mL/min, 180 °C) where three products were isolated. Product A, 8% (analytical GLC yield 14% by internal standard), was identified as 3-phenylcyclopentanone: NMR (CCl_4) δ 2.18–2.65 (m, 7 H), 7.30 (s, 5 H); IR (CCl_4) cm^{-1} 1744. This material had analytical GLC retention time and spectral data identical with those of authentic material.[65] Product B (67%) was identified as *cis*-3-phenyl-2-allylcyclopentanone: NMR (CCl_4) δ 7.0 (s, 5 H), 5.10–5.48 (m, 1 H), 4.70 (d, J = 12 Hz, 2 H), 1.58–2.60 (m, 7 H), 2.82–3.02 (m, 1 H); IR (thin film) cm^{-1} 1740, 1610, 1600, 910, 880; mass spectrum (70 eV) *m/e* 200 (M^+, rel intensity 80), 182 (10), 171 (15), 158 (100), 143 (25), 129 (80), 117 (90); high-resolution mass spectrum 200.285 (calcd for $C_{14}H_{16}O$: 200.283). Product C (5%) was identified as *trans*-3-phenyl-2-allylcyclopentanone: NMR (CCl_4) δ 6.98 (5 H, s), 5.20–5.59 (m, 1 H), 4.52–4.90 (m, 2 H), 3.2 (m, 1 H), 1.8–2.6 (m, 7 H); mass spectrum (70 eV) *m/e* 200 (M^+). *cis*-3-Phenyl-2-allylcyclopentanone equilibrated to a 95:5 mixture of *trans*- to *cis*-3-phenyl-2-allylcyclopentanone upon refluxing with a catalytic amount of NaOAc in ethanol for 4 h.

Reaction of 1-Trimethylsiloxy-3-phenylcyclopentene with Methyllithium and Then with A and B. A. Allyl Bromide. To 10 mmol of 1-trimethylsiloxy-3-phenylcyclopentene in 10 mL of tetrahydrofuran at 0 °C was added 8.9 mL (10 mmol) of methyllithium and the mixture was allowed to stir at 0 °C for 1 h. After this time the reaction mixture was cooled to −78 °C and 0.88 mL (20 mmol) of allyl bromide was added. The resulting solution was allowed to warm to room temperature and stirred at room temperature for 30 min. After product isolation as previously described the crude product was analyzed by analytical GLC (10 ft × ⅛ in., SE-30, 170 °C, 20 mL/min), which indicated four products. Product A (8.0 min) was identified as 3-phenylcyclopentanone (22%) by comparison of its GLC retention time with that of previously identified material (*p*-cymene as internal standard). Product B (13.5 min, 30%) has been identified as *trans*-2-allyl-3-phenylcyclopentanone (**22**) by comparison of its GLC retention time with that of an authentic sample previously prepared. Product C (15.0 min, 12%) was identified as *cis*-2-allyl-3-phenylcyclopentone (**22′**) by retention time and by the fact that under equilibrating conditions the ratio of the 13.5- and the 15.0-min peaks, which was originally 2.0/1.2, changed to 10/1. Product D (19.5 min, 31%) was isolated by thin layer chromatography (silica gel, 5% Et_2O/petroleum ether, double development) and identified as a diallylated product: NMR (CCl_4) δ 7.22 (s, 5 H), 5.26–5.98 (m, 2 H), 4.80–5.30 (m, 4 H), 2.80–1.9 (m, 5 H), 3.02 (m, 2 H); mass spectrum (70 eV) *m/e* 229 (M^+).

B. 1.0 Equiv of Phenylcopper and Then with Allyl Bromide. To 10 mmol of the enol ether in 10 mL of THF at 0 °C was added 8.9 mL (10 mmol) of methyllithium and the mixture was allowed to stir at 0 °C for 1 h. After this time the resulting enolate solution was added dropwise to a slurry of 10 mmol of phenylcopper in 10 mL of THF at 0 °C. The resulting mixture was allowed to stir for 1 h at 0 °C and then cooled to −78 °C and 0.88 mL (20 mmol) of allyl bromide was added. The resulting solution was allowed to warm to room temperature and stirred at room temperature for 30 min. After product isolation as previously described the crude product was analyzed by analytical GLC (10 ft × ⅛ in., SE-30, 170 °C, 20 mL/min), which indicated that three products were present: 3-phenylcyclopentanone (8.0 min, 52%), **22** (13.5 min, 1%), and **22′** (15.0 min, 42%). Product **22′** was isolated by thin layer chromatography (silica gel, 5% Et_2O/petroleum ether) to afford 0.64 g (38%) of a colorless oil: NMR (CCl_4) δ 7.0 (s, 5 H), 5.10–5.48 (m, 1 H), 4.70 (d, J = 12 Hz, 2 H), 1.58–2.60 (m, 7 H), 2.82–3.02 (m, 1 H); IR (thin film) cm^{-1} 1740, 1610, 1600, 910; mass spectrum (70 eV) *m/e* 200 (M^+, rel intensity 80), 182 (10), 158 (100). Equilibration of **22** led to a 10:1 ratio of **22:22′**.

Preparation of Lithium (*n*-Pentynyl)phenylcuprate. To 0.258 g (2.0 mmol) of cuprous *n*-propylacetylide[66] under an inert atmosphere was added 5.0 mL of dry diethyl ether. The resulting slurry was cooled to 5 °C and 1.14 mL (2.0 mmol) of phenyllithum was added dropwise. After the addition was complete the resulting dark green solution was stirred for 15 min at 0 °C.

Preparation of Methyl *t*-2-Phenyl-1-methyl-5-oxocyclopentane-1-*r*-acetate (25) via the Reaction of 2-Methyl-2-cyclopentenone with Lithium Phenyl(*n*-pentynyl)cuprate and Then with Methyl Bromoacetate. To 2.0 mmol of lithium (*n*-pentynyl)phenylcuprate in 5.0 mL of Et_2O under argon at 0 °C was added 1.0 mmol (96 mg) of 2-methylcyclopentenone via syringe in 1.0 mL of diethyl ether. The addition was accompanied by the immediate formation of yellow-green precipitate. The reaction mixture was allowed to stir for 2.5 h at 0 °C and the resulting mixture was added via a syringe to a solution of 0.89 mL (10.0 mmol) of methyl bromoacetate and 5.0 mL of HMPA at 0 °C. The resulting yellow mixture was allowed to warm to room temperature and stirred at room temperature for 24 h. The crude product was poured into 50 mL of aqueous saturated ammo-

nium chloride and diluted with 30 mL of diethyl ether. The layers were separated and the aqueous phase was extracted with diethyl ether. The ether extracts were combined and dried over anhydrous sodium sulfate. After solvent removal the crude product was purified by preparative TLC ($CHCl_3$, silica gel, R_f 0.35), 118 mg (51%) of colorless, viscous oil **25:** NMR ($CDCl_3$) δ 7.0–7.5 (m, 3 H), 3.62 (s, 3 H), 1.95–2.90 (m, 7 H), 0.72 (s, 3 H); IR (thin film) cm^{-1} 1747, 1730, 1605, 1220, 890, 840; mass spectrum (70 eV) *m/e* 248 (M^+); high-resolution mass spectrum 248.423 (calcd for $C_{15}H_{18}O_3$, 248.421). GLC analysis (10 ft × ⅛ in., SE-30, 195 °C) indicates one peak (22 min).

Preparation of 1-Trimethylsiloxy-3-phenyl-2-methylcyclopentene (24). To an ethereal solution of 3.0 mmol of lithium diphenylcuprate at 0 °C was added via syringe 0.144 g (1.5 mmol) of 2-methyl-2-cyclopentenone and the mixture was stirred for 1.5 h at 0 °C. After this time a mixture of 1.58 mL (10.0 mmol) of chlorotrimethylsilane and 1.75 mL (10.0 mmol) of triethylamine was added and stirred for 8 h at room temperature. The crude product was poured into an ice-cold mixture of 5 mL of ammonium hydroxide in 50 mL of saturated aqueous sodium bicarbonate and diluted with diethyl ether. The layers were quickly separated and the aqueous phase was extracted with diethyl ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the crude product was purified by column chromatography (Florisil, 40% CH_2Cl_2/petroleum ether) to afford 300 mg of colorless oil **24** (65%): NMR ($CDCl_3$) δ 7.45–7.05 (m, 5 H), 1.65–2.24 (m, 4 H), 1.45 (s, broad, 3 H), 0.20 (s, 9 H); IR (thin film) cm^{-1} 1665, 1250, 840, 890; mass spectrum (70 eV) *m/e* 245 (M^+).

Reaction of 1-Trimethylsiloxy-3-phenyl-2-methylcyclopentene (24) with Methyllithium Followed by Methyl Bromoacetate. Preparation of Methyl *t*-2-Phenyl-1-methyl-5-oxocyclopentane-1-*r*-acetate (25). To 160 mg (0.65 mmol) of 1-trimethylsiloxy-2-methyl-3-phenylcyclopentene under an inert atmosphere in 5 mL of THF at 0 °C was added 0.38 mL (0.75 mmol) of methyllithium and the mixture was stirred for 1 h at 0 °C. To the resulting solution were added 0.45 mL (5.0 mmol) of methyl bromoacetate and 1.0 mL of HMPA and the mixture was stirred at room temperature for 10 h. The crude product was poured into aqueous ammonium chloride and diluted with ether. The layers were separated and the aqueous phase was extracted with 30 mL of ether. The ether extracts were combined and dried over sodium sulfate. The solvent was removed and the crude product was purified by preparative TLC (silica gel, $CHCl_3$) to afford 92 mg (64%) of a colorless oil **25** whose spectra and GLC retention time were identical with those of methyl *t*-2-phenyl-1-methyl-5-oxocyclopentane-1-*r*-acetate previously described.

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Supplementary Material Available: Tables VI and VII containing spectral data for the 3-methyl-3-R-cycloalkanones; Tables VII and IX containing physical and spectral data for enol silyl ethers **9** and **11;** Tables X and XI containing GLC retention times and vinylic H chemical shift data for enol silyl ethers **8** and **10** (3 pages). Ordering information is given on any current masthead page.

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Hydrogen Bonding in N-Substituted Amino Acids. Crystal Structure of the *N,N*-Diethyl-β-alanine–Benzene Inclusion Compound

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Abstract: Supersaturated solutions of *N,N*-diethyl-β-alanine (NNDEBA) in benzene deposit orthorhombic crystals, space group *Pbcm*, having four molecules of NNDEBA and four molecules of benzene in a unit cell with dimensions (160 K) a = 5.491 (1), b = 13.426 (3), c = 17.766 (6) Å. The amino acid molecules form hydrogen-bonded chains of zwitterions parallel to the b axis of the crystal. The molecules are situated on a crystallographic mirror plane, but the hydrogen-bonded oxygen appears to undergo large amplitude motion, so that the oxygen is ±0.46 Å out of the mirror plane most of the time. This motion leads to a mean N–O distance of 2.66 (2) Å. The in-plane N–O distance is computed to be 2.594 (5) Å. The zwitterion chains stack to form sheets parallel to the *ab* plane, with the ethyl groups nearly perpendicular to the sheets. Such a packing forms channels in which the benzene molecules are found. Electrostatic calculations in the point dipole approximation show that dipole–dipole interactions greatly stabilize an *ab* plane, but do not contribute significantly to the binding between adjacent *ab* planes.

Previous studies[1,2] have established that in aprotic solvents the equilibrium constant for the tautomeric equilibrium between the classical and zwitterionic forms of N,N-dialkylated amino acids is solvent dependent. Current work in our laboratory is concerned with the observation that some of these compounds also exhibit proton transfer in the solid state,[3] whereas others do not.

N,N-Disubstituted amino acids have only a single functional proton, so one might anticipate that the crystal of each such compound would contain only one kind of N–H–O hydrogen bonding configuration. If this expectation is realized in practice, structural, spectroscopic, and thermodynamic studies of this class of compounds could provide experimental results that would bear on the nature of the hydrogen-bond potential function.

The present paper reports the crystal structure of the benzene inclusion compound of *N,N*-diethyl-β-alanine (NNDEBA), $(C_2H_5)_2N(CH_2)_2COOH$, in which there occurs a single kind of very short NH–O hydrogen bond.

Experimental Section

Single-Crystal X-ray Investigation. NNDEBA was synthesized by the general procedure previously described.[1] A single crystal of NNDEBA–benzene was cut from a large, polycrystalline mass that formed when a sealed vial that originally contained a supersaturated solution of NNDEBA in benzene stood undisturbed for several years. The crystal, with dimensions 0.3 × 0.3 × 0.3 mm, was covered with the resin portion of an epoxy cement to prevent it from disintegrating. It was mounted onto a Syntex $P2_1$ four-circle diffractometer system fitted with a copper-target X-ray tube and a graphite monochromator. A stream of cold nitrogen gas maintained the crystal temperature at about 160 K. Information derived from a rotation photograph taken about a randomly oriented axis was used in the Syntex autoindexing and least-squares programs to determine the cell dimensions. Axial photographs indicated that the cell was orthorhombic. Seventeen reflections in the range $17° \leq 2\theta \leq 70°$ were used in the determination of cell and orientation parameters. The cell dimensions (160 K), obtained using λ Cu Kα = 1.54178 Å, are a = 5.491 (1), b = 13.426 (3), and c = 17.766 (6) Å. The structure is described in space group *Pbcm* (vide infra).

The crystal density, measured by flotation at room temperature, is 1.10 g cm^{-3}, whereas the density of a crystal having just four NNDEBA molecules in the unit cell would be 0.736 g cm^{-3}. The higher observed density suggests that the crystal also contains benzene. A unit cell with the cited dimensions containing four molecules of the amino acid and four molecules of benzene would have a density of 1.13 g cm^{-3}.

A set of intensity data was obtained using θ–2θ scan with scan speeds varying between 2 and 60 deg min^{-1} for $2\theta < 130°$. The $P2_1$ diffractometer scans in steps of about 0.01°. Stationary background intensities were measured at each end of the scan. The peaks were scanned from $[2\theta(\alpha_1) - 1.1]°$ to $[2\theta(\alpha_2) + 1.1]°$ employing a total background counting time equal to half the counting time for the scan.

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