This is to certify that the

dissertation entitled

CHAPTER I.THE ALKYLATION OF ENOLATES AND METALLOENAMINES. CHAPTER II.REACTION OF BROMOENAMINES WITH ORGANOMETALLIC REAGENTS.THE ALPHA-ARYLATION OF KETONES.CHAPTER III.ARYLATION OF ENOLATES AND METALLOENAMINES WITH ARYL IODIDES.

presented by

Demetris Vogiazoglou

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Michael W. Rathke

Major professor

Date 18th of March 1988

CHAPTER I
THE ALKYLATION OF ENOLATES
AND METALLOENAMINES

CHAPTER II
REACTION OF BROMOENAMINES
WITH ORGANOMETALLIC REAGENTS.
THE ALPHA-ARYLATION OF KETONES

CHAPTER III
ARYLATION OF ENOLATES AND
METALLOENAMINES WITH ARYL IODIDES

By

Demetris Vogiazoglou

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1988

ABSTRACT

CHAPTER I
THE ALKYLATION OF ENOLATES
AND METALLOENAMINES

CHAPTER II
REACTION OF BROMOENAMINES
WITH ORGANOMETALLIC REAGENTS.
THE ALPHA-ARYLATION OF KETONES

CHAPTER III
ARYLATION OF ENOLATES AND METALLOENAMINES
WITH ARYL IODIDES

By

Dimitris Vogiazoglou

I. The reaction of enolates and metalloenamines of ketones and aldehydes with alkylating agents has been investigated. Imines resulting from the condensation of carbonyl compounds with 3-dimethylaminopropylamine have been deprotonated and alkylated at -78° to give, after hydrolysis, the corresponding substituted carbonyl compounds in good to excellent yields.

II. A variety of enamines have been brominated with Br_2 in the presence of triethylamine at -78° in THF. The resultant bromoenamines are found to react with diarylcuprates to give, after hydrolysis, alpha-arylketones in generally good yields.

III. Ketones have been arylated *via* their metalloenamines with aryl iodides at refluxing temperatures in cyclohexane to give, after hydrolysis, alpha-arylketones.

ACKNOWLEDGEMENTS

I wish to express my heartfelt gratitude to Dr. Michael Rathke for making my stay at MSU a most pleasant experience. I also wish to thank members of the Rathke group for making the lab a fun place to be: Michael, Rick, Paul and Ezzedine. I would also like to thank Lisa, Mark, Nick, John, Jeff, Mike Kondylis, MIke Tornaritis and Emmanuel for creating an environment in which I could feel at home.

Appreciation is also extended to Paolo, Luka, Eleni, Filippo, Sofia, Stephanos, Laura, Yiannis, Rania, Fotis and D. Dakos for making leisure time fun.

The financial assistance provided by MSU is gratefully acknowledged.

Finally, I wish to thank my family, Nikos, Athena, Lori and Vicky without whose love and support this thesis would have been impossible.

TABLE OF CONTENTS

LIST OF TABLES

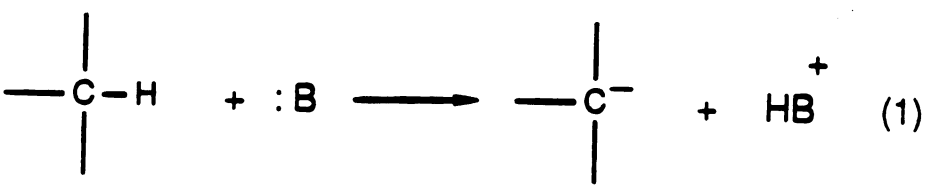
CHAPTER I

THE ALKYLATION OF ENOLATES AND METALLOENAMINES

INTRODUCTION

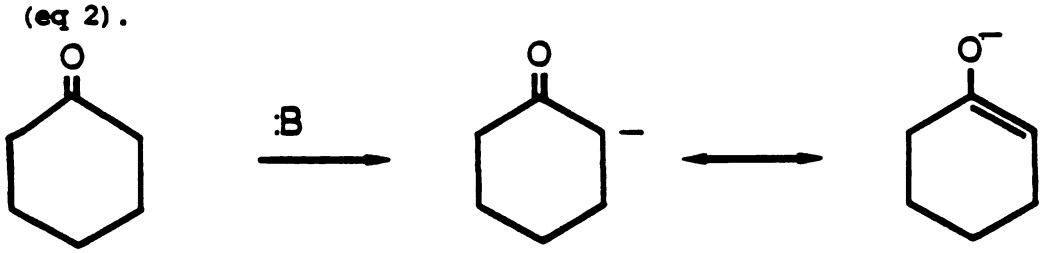
One of the most important reactions in organic synthesis is carbon-carbon bond formation, by reaction of a carbon electrophile with a carbon nucleophile:

A very useful method for generating carbon nucleophies is removal of an acidic proton by a base (eq 1).



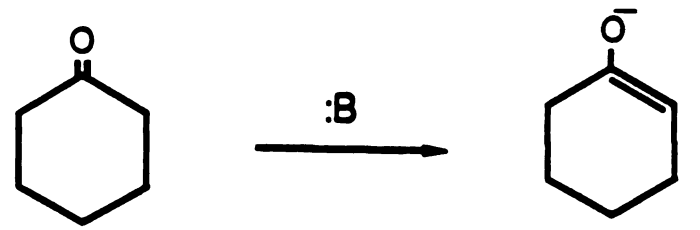
(1)

A carbonyl group bonded to the carbon nucleophile can stabilize negative charge by resonance, and hence is a key function for the formation of carbon nucleophiles. Ketones and aldehydes are examples of compounds bearing a carbonyl group from which stabilized anions can be generated. These anions, formed by deprotonation of a carbon alpha to a carbonyl group by a base, bear most of the negative charge on oxygen and are normally referred to as enolates, as illustrated for cyclohexanone, (eq 2).

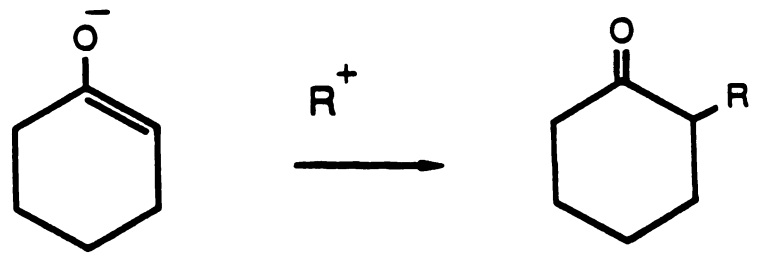


(2)

In an ideal alkylation method, the enolate is formed and alkylated rapidly, in a high yield, with no side reactions (eq 3).

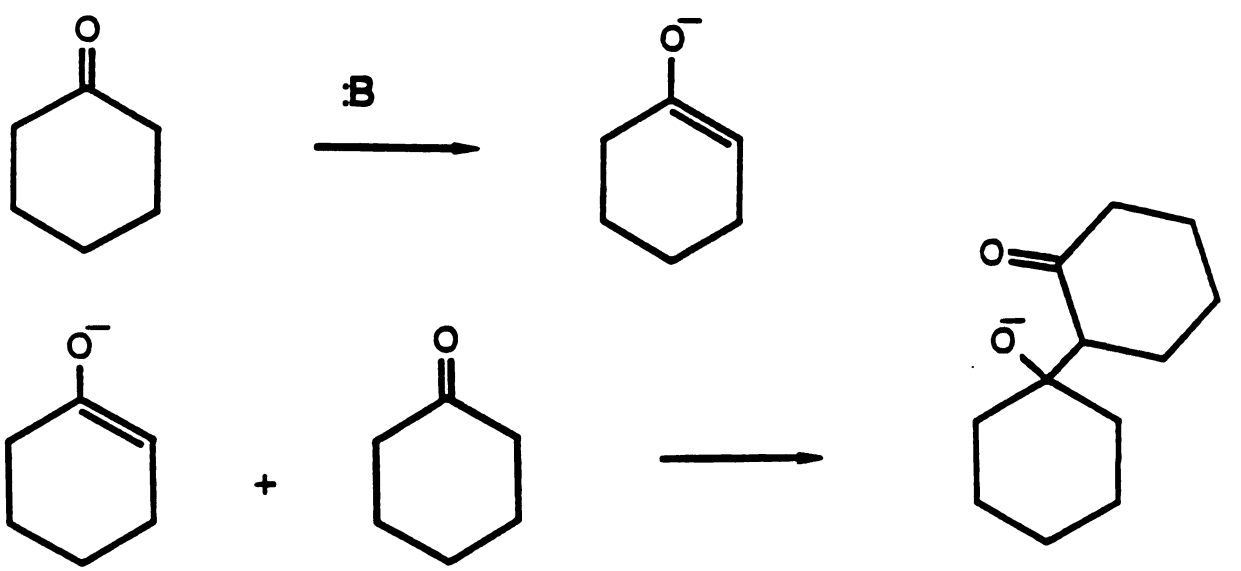


(3)

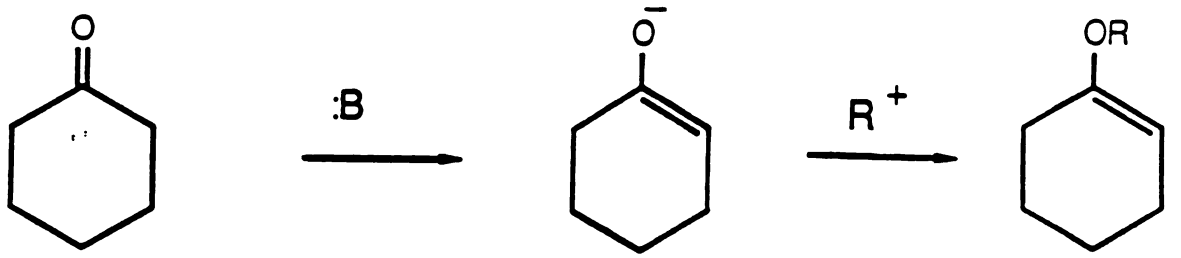


However, besides the above reaction, there are side reactions which limit the utility of enolate nucleophiles. The most common side reactions are:

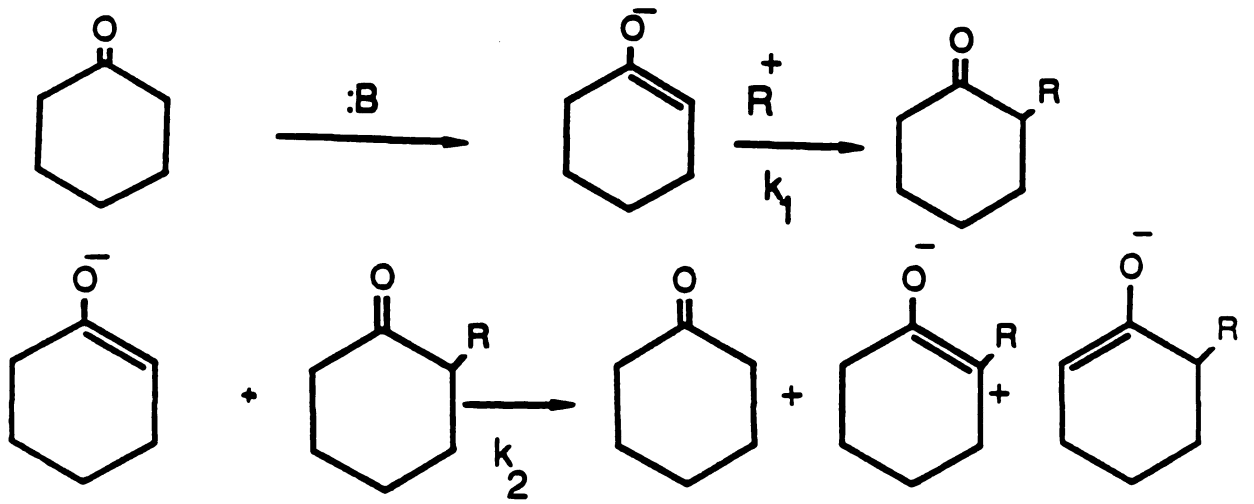
1. Condensation:

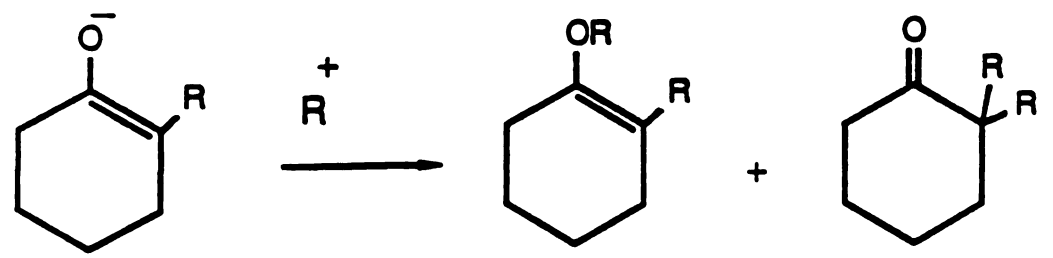


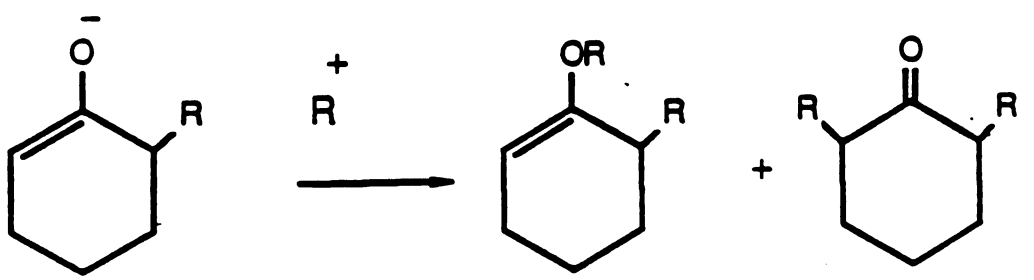
2. Alkylation at oxygen:



3. Dialkylation due to proton transfer from a monoalkylated product to enolate:

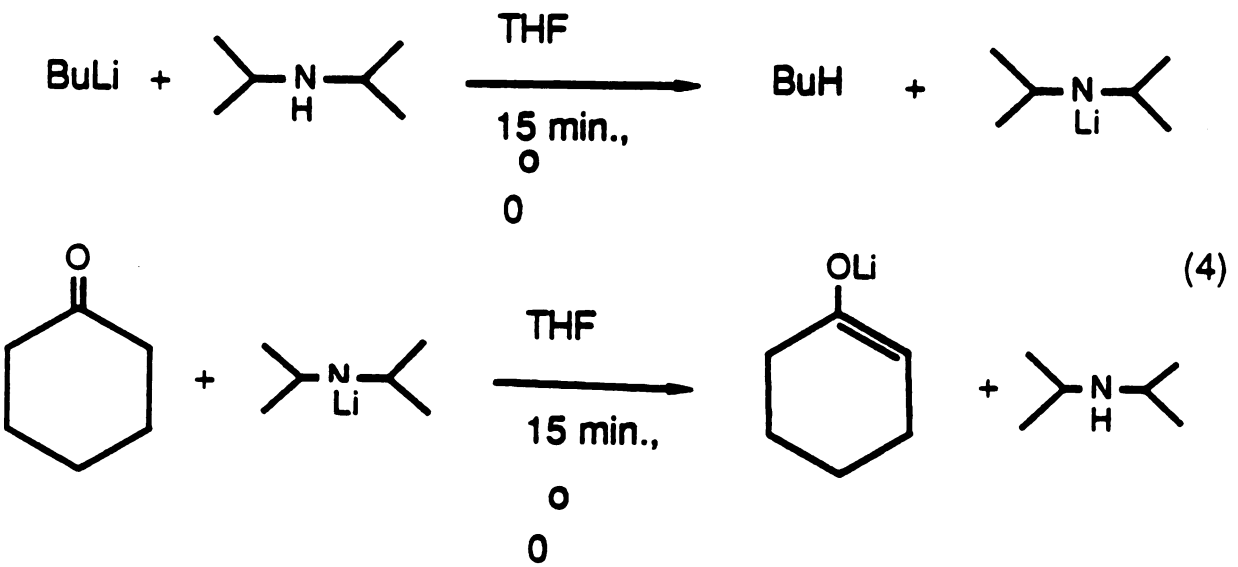






The condensation reaction to produce aldol-type products becomes a serious problem when insoluble bases such as sodium hydride, or weak bases, such as metal alkoxides, are used to generate slowly or as a state of equilibrium conditions.[1]

However, self-condensation of the enolate with starting material can be minimized by employing strong, organic soluble bases. Lithium diisopropylamide (LDA) is the most useful, since it can be easily prepared from butylithium and diisopropylamine, and moreover, is sufficiently strong to generate enolates quantitatively (eq 4).



(4)

Another advantage of LDA is its steric hindrance. Consequently, it preferentially abstracts an alpha proton from the carbonyl compound, and side products resulting from attack upon the carbonyl are usually not observed.

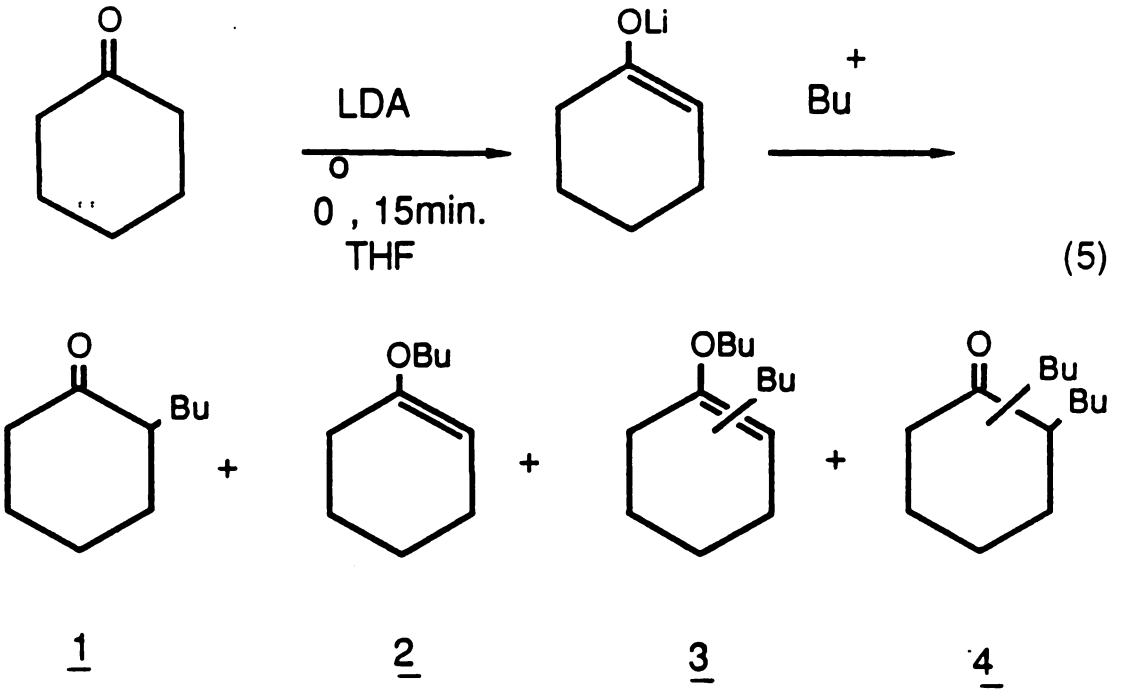
Alkylation at oxygen is another side reaction. It is known[2] that the ratio of carbon versus oxygen alkylation depends upon the alkylating agent, the leaving group, the solvent and the counter ion. For reactive alkylating agents such as MeI, $PhCH_2X$, allyl-X, oxygen alkylation is a minor side reaction especially if lithium enolates are employed.[3]

Another side reaction that can lower the yield of an alkylation reaction is dialkylation due to proton exchange. It can become a serious problem with the less reactive alkylating agents[4] such as i-PrI or BuI, due to the lower rate of alkylation vis-a-vis the higher one of hydrogen exchange ($K_1 < K_2$, page 4).

We decided to investigate the reaction between enolates and alkylating agents which, as mentioned above are not very reactive. Our goal was to increase the yield of monoalkylated product by decreasing the amount of oxygen alkylated and dialkylated compounds. We chose butyl as a representative alkyl group of relatively low reactivity. According to Conia[4], butyl bromide is 380 times less reactive than allyl bromide and 1000 times less reactive than benzyl bromide in reaction with the enolate generated from 2-methylcyclohexanone and sodium t-amyloxide.

RESULTS AND DISCUSSION

We started our project by generating the enolate of cyclohexanone and examining its reaction with a variety of butylating agents. 2-Butylcyclohexanone **1** as well as the other byproducts, **2**, **3**, **4** (eq 5), were determined by Gas Liquid Chromatography (GLC).



Some representative reaction conditions are listed in Table 1.

In the case of BuCl and BuBr no reaction occurs under our standard conditions. On the contrary, BuI reacts with the enolate of cyclohexane, especially in the presence of hexamethyl phosphoramide (HMPA). However, HMPA promotes the proton exchange leading to undesirable dialkylated products. The fourth butylating agent that we studied was $(BuO)_2SO_2$. $(BuO)_2SO_2$ is more reactive than BuI. Unfortunately, it leads to increased amounts of oxygen-butylated product. The last butylating agent that we examined was BuOTs. This reagent proved to be less reactive than BuI, besides the fact that it gives low yields of oxygen and dibutylated products.

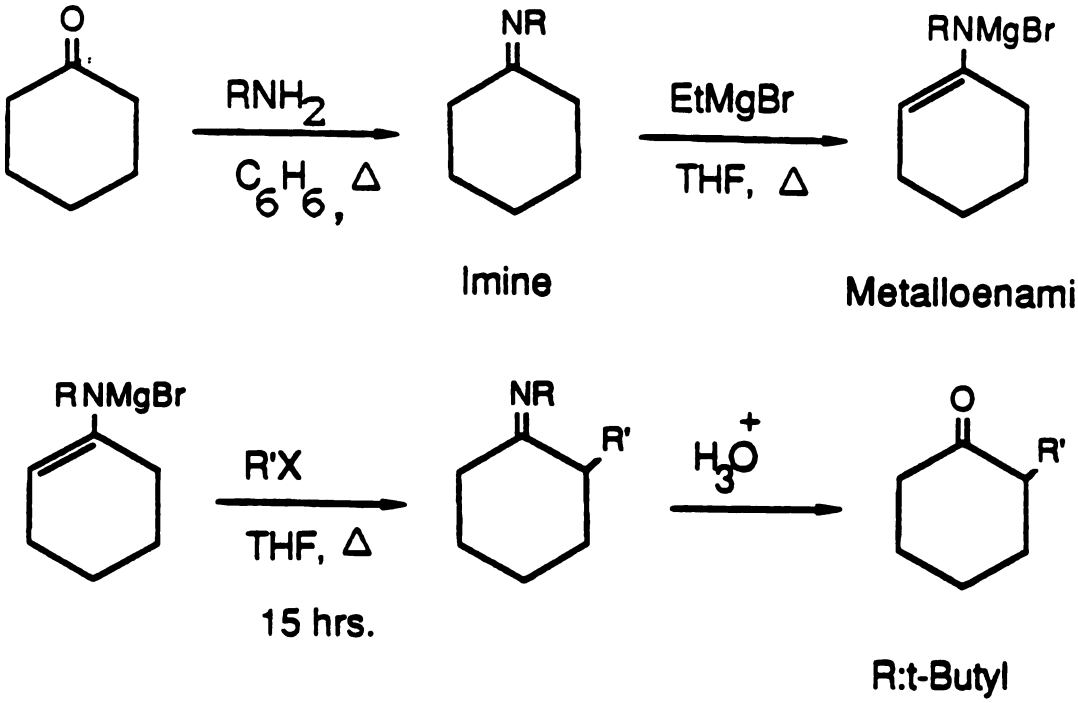
TABLE 1. Butylation of the Lithium Enolate of Cyclohexanone in THF

Butylating Agent	Temp. °C	Time hrs	HMPA 1 eq	1 Yield*%	2 Yield*%	3 Yield*%	4 Yield*%
BuCl	RT	12	Yes	0	0	0	0
BuBr	RT	12	Yes	0	0	0	0
BuI	RT	12	No	10	0	0	0
BuI	RT	12	Yes	37	Trace	Trace	4.5
BuI	Reflux	1	Yes	33	0.5	2	15
$(BuO)_2SO_2$	Reflux	1	Yes	44	13	5	7.5
BuOTs	Reflux	1	Yes	22	0.5	1	7.5

*GLC yields.

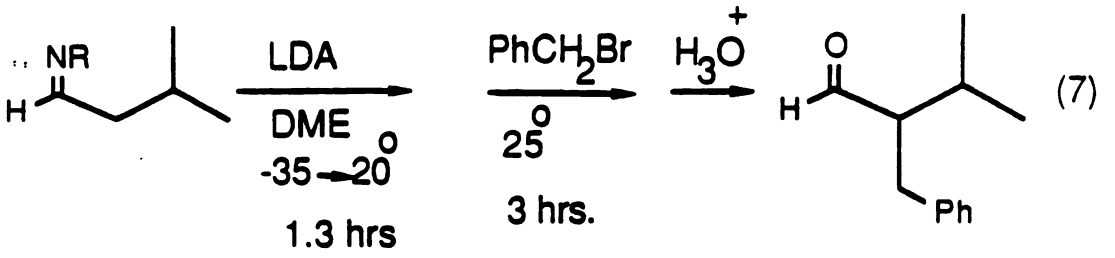
From the above study we concluded that BuI is the best butylating agent for cyclohexanone enolate. Moreover, it is commercially available at low cost, and it results in low yields of byproducts. However, this method is far from being ideal. The reaction requires hexamethylphosphoramide (HMPA) - a cancer suspected agent -, and the yield is only about 40%. The limitation of the number of leaving groups that we could use forced us to switch our attention to more suitable enolate equivalents.

A literature search revealed that the nitrogen analogs of enolates - referred as metalloenamines - can be generated from imines and alkylated with various alkylating agents of low reactivity[5] (eq 6).

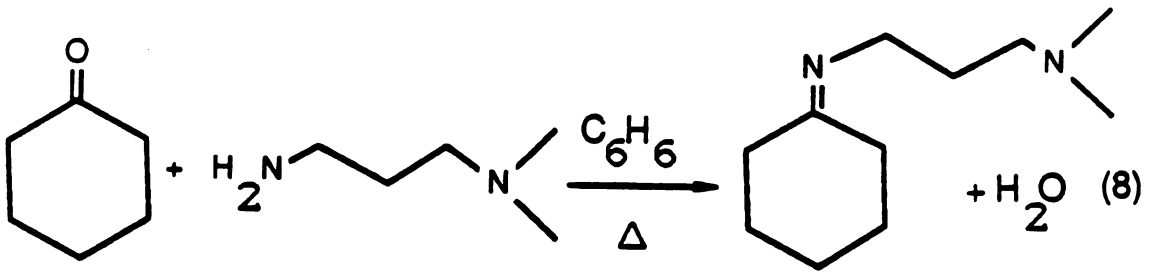


Magnesium as a counterion has little to recommend it, since formation of the metalloenamine requires elevated temperatures and long reaction times. Furthermore, the alkylation step requires vigorous conditions.

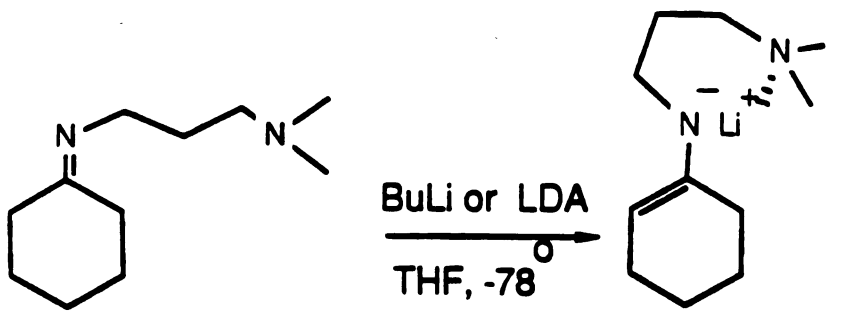
Lithiated enamines are more reactive than their magnesium analogs. They can be made by treating the imine with a strong base such as BuLi or LDA. However, the deprotonation and alkylation steps still require long reaction times[6] and temperatures above -10^0C (eq 7).



One way[7] to enhance the reactivity of lithiated enamines is to use cosolvent additives such as hexamethyl phosphoramide (HMPA) or N,N,N',N'-tetramethylethylenediamine (TMEDA). Unfortunately, most of these additives are expensive, harmful to the environment and cancer suspected agents. We thought that the rate of formation as well as the reactivity of metalloenamines might be enhanced with an imine which bears an $-N(CH_3)_2$ group as a chelating agent. These imines can be made quantitatively by refluxing ketones or aldehydes with dimethylaminopropylamine in refluxing benzene for 3-4 hours (eq 8).

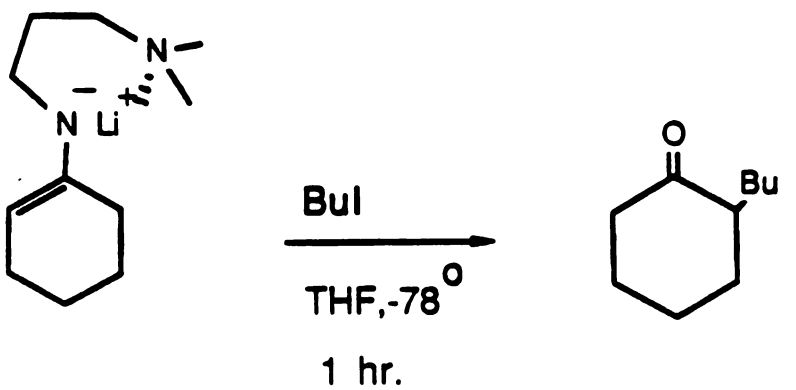


We discovered that these imines are very reactive. They can be lithiated with BuLi or LDA at -78^{0}C in one hour (eq 9).



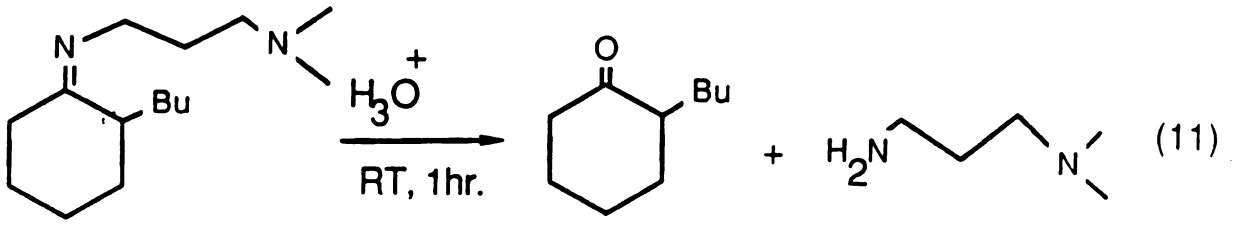
(9)

The resulted metalloenamine is also very reactive. We found that the metalloenamine of cyclohexanone can be butylated with BuI at -78°C in 15 min, (eq 10):



(10)

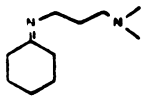
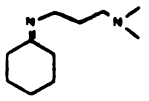
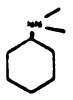
The butylated imine was hydrolyzed in slightly acidic conditions (PH~5-6) at room temperature (eq 11).



(11)

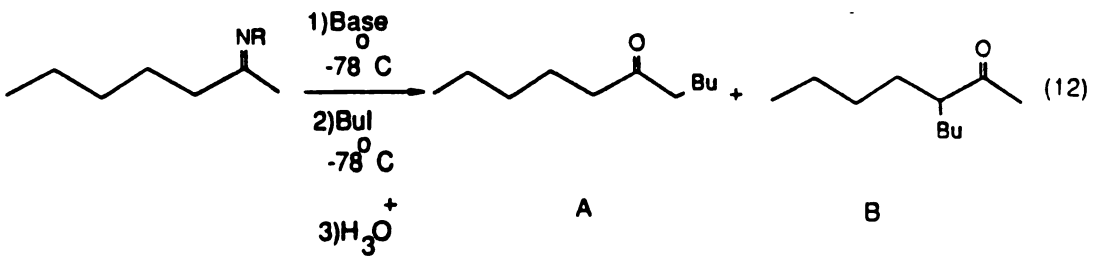
The $-N(CH_3)_2$ group accelerates lithiation probably by chelating the lithium metal and promoting the formation of monomeric reagents. The rapid butylation can be explained by presuming that the $-N(CH_3)_2$ group chelates lithium generating a more "naked" metalloenamine.[3] The parent imine was then compared with the imine of dimethylhydrazine which is considered the most reactive of conventional imines. The dimethylaminopropylamine imine of cyclohexanone is more reactive compared to dimethylhydrazine imine of cyclohexanone towards deprotonation as well as butylation. (Table 2).

Table 2. Comparison of Deprotonation and Butylation of Dimethylhydrazine and Dimethylaminopropylamine Imines of Cyclohexanone.

Imine	Temp.°C (Deprotonation Time)	Temp·°C (Butylation Time)	% yield (GLC)
	-78° (1 hr)	-78° (1 hr)	87
	0 (1 hr)	-78° (1 hr)	90
	-78° (1 hr)	-78° (1 hr)	3
	0 (1 hr)	-78° (1 hr)	31
	-78° (1 hr)	0 (1 hr)	59
	0 (1 hr)	0 (1 hr)	91

The dimethylhydrazine imine fails to react at -78°C, where the dimethylaminopropylamine imine reacts at -78°C to give very good yield of butylated cyclohexanone.

We then decided to study the reactions of: a) metalloenamines of various ketones with BuI and b) The metolloenamine of cyclohexanone with other alkylating agents. Our results are summarized in Table 3. For saturated symmetrical ketones either BuLi or LDA can be used as a base. The choice of bases is however crucial in the case of unsymmetrical ketones. 2-Heptanone, for example, upon deprotonation with BuLi and subsequent alkylation with BuI produced after hydrolysis both of possible regioisomers, where LDA employment at low temperature resulted in the nearly exclusive formation of the metalloenamine from the less hindered side (eq 12).

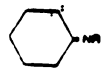
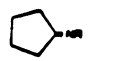
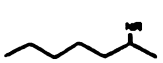
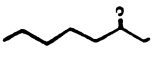
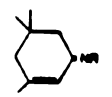
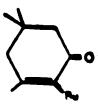
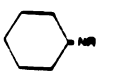
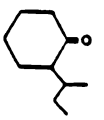
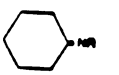
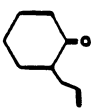


(12)

Base	A	B
BuLi	58%	11%
LDA	71%	0%

R:-$(CH_2)_3N(CH_3)_2$.

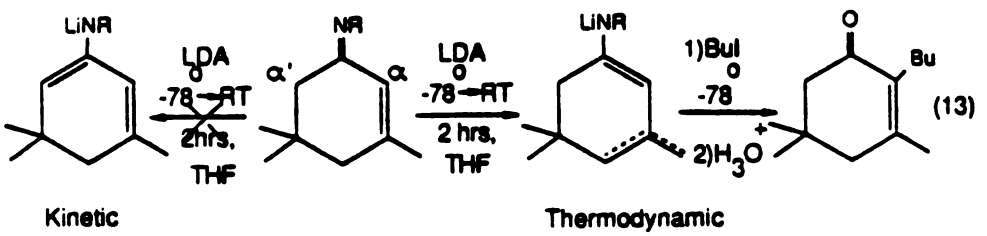
TABLE 3. Alkylation of Metalloenamines in THF

Starting material	Base	Alkylating agent	Temp. °C (Deprot. time)	Temp. °C (Alkyl time)	Hydrolysis reaction time*	Product** % Yield (Isolated)
	BuLi	BuI	-78° (1hr)	-78° (15 min)	1 hr	 80
	BuLi	BuI	-78° (1hr)	-78° (1hr)	16 hrs	 73
	LDA	BuI	-78° (1hr)	-78° (1hr)	1 hr	 71
	LDA	BuI	-78° (1hr)	-78° (1hr)	1 hr	 64
	LDA	BuI	-78° -->RT(2hrs)	-78° (2hrs)	3 days	 73
	BuLi	i-BuI	-78° (1hr)	0° (1hr)	16 hrs	 58
	BuLi		-78° (1hr)	-78° (15 min)	1 hr	 89

* The imines were hydrolyzed under slightly acidic conditions (PH~5-6) at room temperature.

** After hydrolysis. R:-$(CH_2)_3NMe_2$ in all cases.

It is surprising that the imine of isophorone gives the thermodynamic product (eq 13)



When the deprotonation and alkylation of the imine were carried out at -78°C (without warming to room temperature, to prevent equilibration) the same product was observed in lower yields. Therefore it is not likely that the initial site of deprotonation is α'. It is conceivable that the dimethyl group provides enough steric hindrance so that in the case of imines the deprotonation occurs in the α site. The only report in the literature on the imine of isophorone[5b] involves an alkylation procedure which empoloys NaH in THF containign 10% HMPA at refluxing temperatures overnight. The thermodynamic product was also isolated.

Another point worth mentioning is the alkylation step temperature. At -78°C proton exchange between alkylated imine and metalloenamine is very slow, and no dialkylated products were observed. At 0°C however, hydrogen exchange becomes a competing reaction leading to dialkylated products.

In conclusion, a method for performing alkylations using imines of dimethylaminopropylamine has been described. Unlike conventional imines these imines can be deprotonated and alkylated with primary and secondary alkyl iodides at low temperatures to give, after hydrolysis, good yields of substituted carbonyl compounds. Other advantages of these imines is their low toxicity compared to dimethylhydrazine imines as well as the inexpensiveness of the starting amine.

EXPERIMENTAL

THF was distilled from sodium benzophenone just prior to use. The carbonyl compounds were obtained from Aldrich and distilled over CaH_2. n-Butyl iodide was made from the butyl chloride and NaI in refluxing acetone. 2-Iodobutane was made from 2-butanol, phosphorous and iodide.

BuLi (1.6M in hexanes) as well as dimethylaminopropylamine were obtained from Aldrich. All the imines except the imine of propanol were made by the azeotropic method.[8] The imine of isophorone requires long reaction times (3-4 days). The imine of propanal was generated[9] at low temperatures using Na_2SO_4 as a drying agent and was used immediately, since it is unstable as a pure liquid. All reactions were carried out under an argon atmosphere. Gas chromatographic analyses were performed on a Hewlett and Packett 5880 chromatograph equipped with a 25 m x 0.25 mm column (stationary phase: fused silica, film thickness: 0.25 mm) ^1H NMR spectra were recorded on Bruker WM-250 and Varian T-60 spoectrometers with $CDCl_3$ as the solvent. Low resolution mass spectra were recorded with a Finnegan 4000 GS/MS at 70 eV.

Preparation of 2-Butylcyclohexanone

A flame-dried 50 ml round-bottom flask equipped with septum inlet and magnetic stirring was maintained under a positive argon pressure and charged with 5 ml of THF. 5 mmole (1.02 ml) of the dimethyl aminopropylimine of cyclohexanone was added. The flask was cooled to -78°C and 3.2 ml (5 mmol) of BuLi (1.6M) was added. The reaction mixture was stirred for 1 hr at -78°C and 5 mmol (0.58 mol) of BuI was added. The reaction mixture was stirred for 1 hr at -78°C and quenched with H_2O at -78°C and 3N HCl was added until the pH~5-6. The organic layer was separated and the water layer was extracted twice with 10 ml CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo, and the residue was distilled under reduced pressure (bp: 78°C/3.5mm) to give 0.62g (80%) of 2-butylcyclohexanone.

3-Dimethylaminopropylimine of cyclohexanone ^1H NMR ($CDCl_3$) δ 1.7 (m, 6H), 1.8 (m, 2H), 2.2 (s, 6H), 2.4 (t, 2H), 2.5 (t, 4H), 3.4 (t, 2H) MS m/e 182 (M+), 111, 83, 72, 58($CH_2N(CH_3)_2$+), 42 IR: 2940, 2250, 1650, 1460, 900, 640 cm^{-1}

3 Dimethylaminopropyimine of cyclopentanone ^1H NMR ($CDCl_3$) δ 1.7 (m, 2H) 2 (t, 4H), 2.1 (m, 6H), 2.2 (s, 6H), 2.8 (m, 2H) MS: m/e 168(M+), 85, 72, 58, ($CH_2N(CH_3)_2$+) 48. IR: 2940, 2290, 1460, 900, 640 cm^{-1}

3 Dimethylaminopropylimine of 2-heptanone ^1H NMR ($CDCl_3$):δ.1-1.5(m, 9H), 1,8(t, 2H), 1,8(s, 3H) 2,2(5, 6H), 2,3(t, 2H), 3,2(t, 2H). MS: 198(M+), 140, 98, 84, 71, 58($CH_2N(CH_3)_2^+$), 42. IR: 2910, 2250, 1650, 1460, 900, 630 cm^{-1}

3 Dimethylaminopropylimine of isophorone ^1H NMR ($CDCl_3$) δ1 (s, 6H), 1,8(m, 5H) 2,2(m, 6H), 3,3(m, 2H), 6(d, 1H). MS: 223(M+), 151, 136, 72, 58($CH_2N(CH_3)_2$+). 42 IR: 3160, 2950, 2250, 1630, 1460, 880, cm^{-1}

2 sec-butyl cyclohexanone 'H NMR ($CDCl_3$) 0.9-1.2(m, 9H) 1,8(m, 6H), 2,2(t, 2H), 2,3(t, 1H). MS 154(M+), 125, 98, 83, 70, 55. IR 2980, 2300, 1720, 900, 660, cm^{-1}

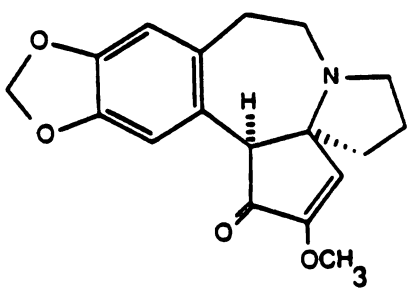
Butyl-isophorone 'H NMR ($CDCl_3$): δ0.9-1.2(m13H), 1,9(d, 3H), 2,2(m,6H) MS 194(M+), 141, 84, 55, 41. IR: 2960, 2250, 1660, 1640, 1380, 880 cm^{-1}

CHAPTER II

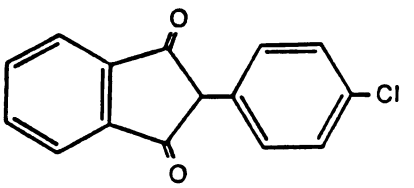
REACTION OF BROMOENAMINES WITH ORGANOMETALLIC REAGENTS. THE ALPHA-ARYLATION OF KETONES.

INTRODUCTION

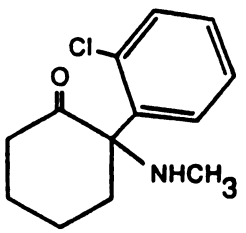
The introduction of an aryl group alpha to a carbonyl is a useful step in the synthesis of a variety of biologically and pharmacologically interesting compounds. Examples of these compounds are cephalotoxine 5, clorindione (an anticoagulant, 6), ketamine (an anesthetic, 7) and ibuprofen (an anti-inflammatory, 8)



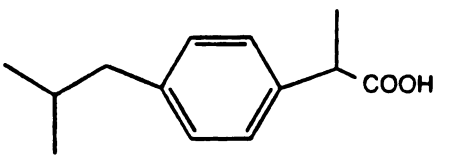
5



6

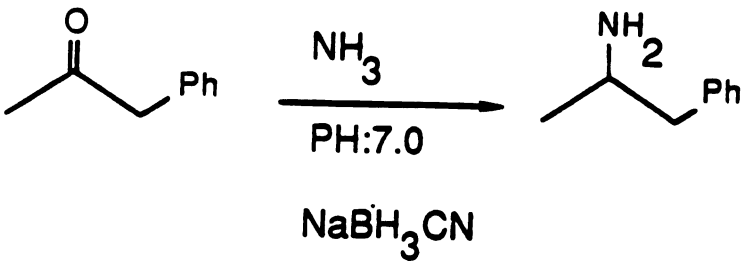


7



8

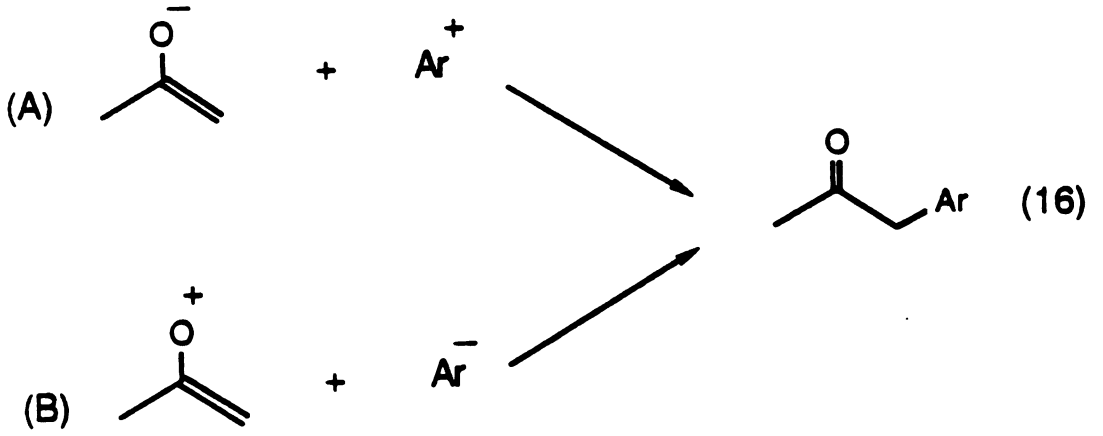
Arylated carbonyl compounds are also very useful because they provide a wide range of compounds which have other functional groups alpha to the aromatic ring. For example conversion of the carbonyl to an amine group provides amphetamine compounds.[10] (eq 15)



(15)

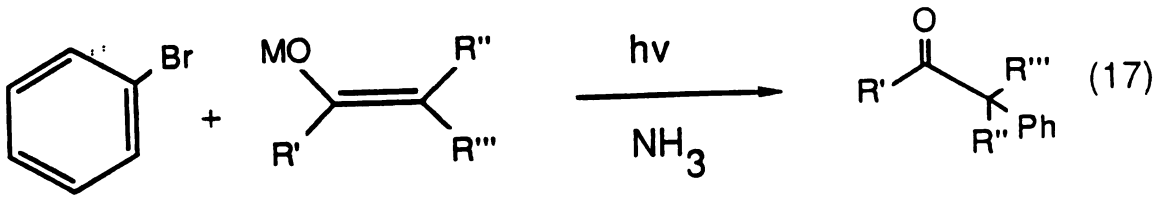
Our main goal in this project was to study the synthesis of arylated ketones.

There are two synthetic approaches toward arylated ketones: a) the reaction of an enolate or its equivalent with electron deficient aryl species, (A) and b) the connection of an "enolate cation," with an electron rich aryl species, (B), (eq 16).



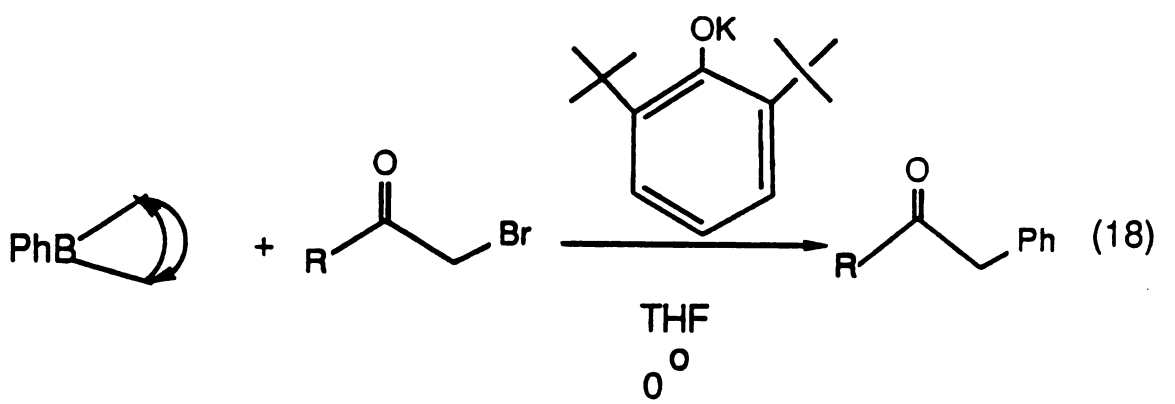
(16)

The most successful example of the first approach is the reaction of enolates with photogenerated aryl radicals[11] (eq 17).



(17)

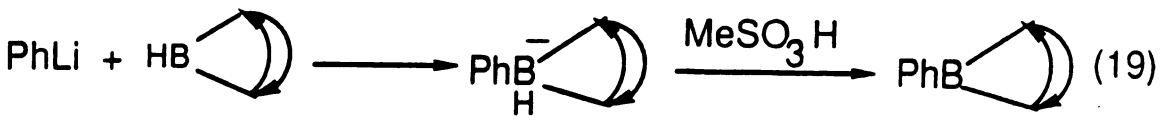
This method as well as other methods which follow disconnection (A) will be discussed extensively in the next chapter. In this chapter, disconnection (B) will be considered. One of the earliest examples of disconnection (B) is based on the reaction of arylboranes with α-bromoketones in the presence of a bulky base[12], (eq 18).



(18)

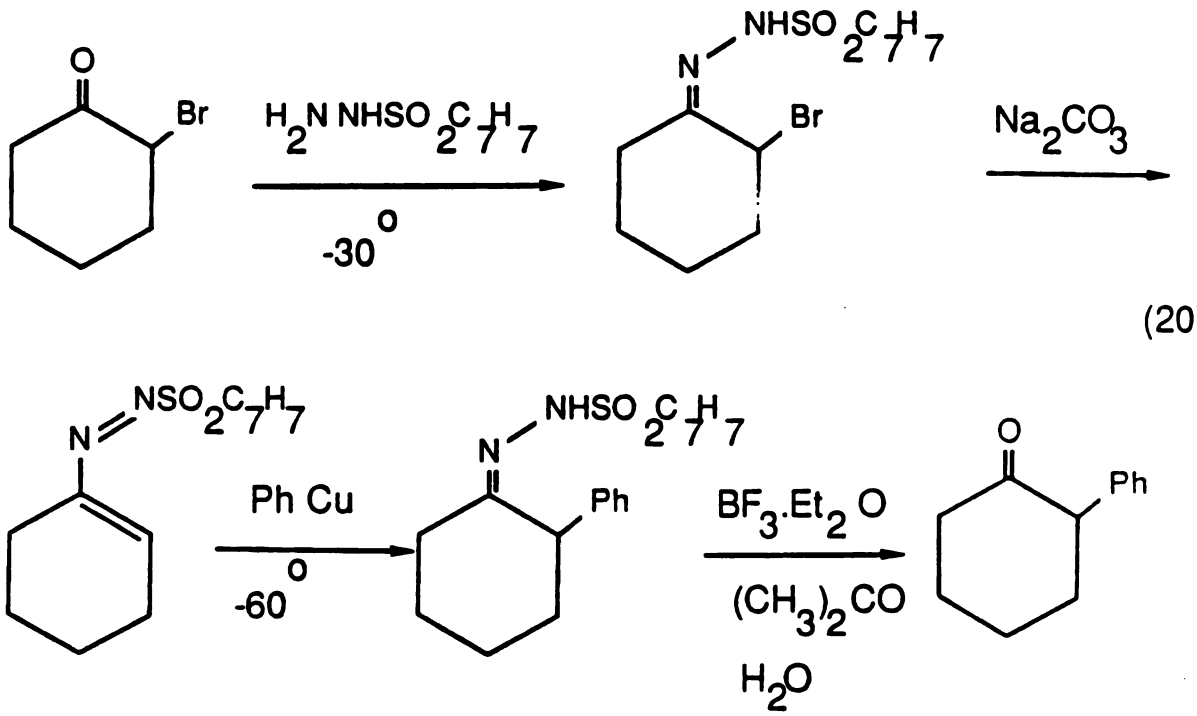
R: t-Bu	90%
R: Me	76%
R: Ph	93%

The aryl boranes can be prepared from 9-bromobicyclo[3.3.1]nonane and the appropriate aryllithium reagent, as illustrated for the case of phenyllithium, (eq 19).



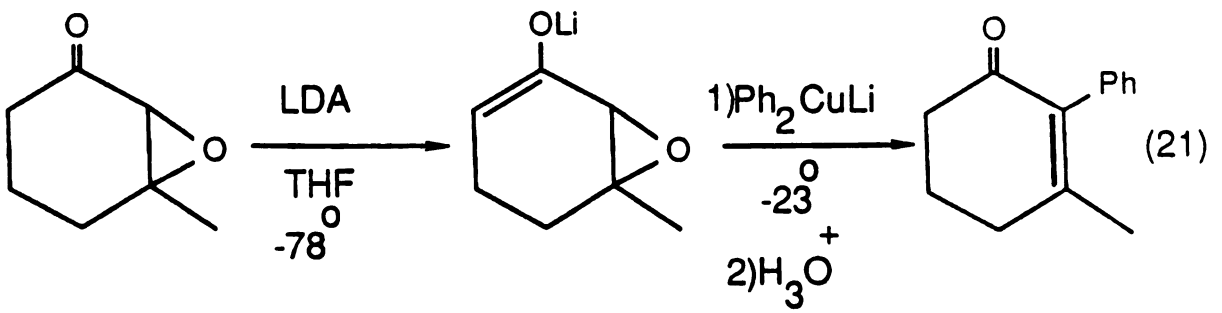
(19)

Sacks and Fuchs[13] followed a different approach. They found that toluenesulfonylazo olefins react with phenylcopper to generate after hydrolysis, a phenylated ketone. These olefins can be prepared by the reaction of an α-bromoketone with p-toluenesulfonhydrazine, followed by treatment with Na_2CO_3, (eq 20).



(20)

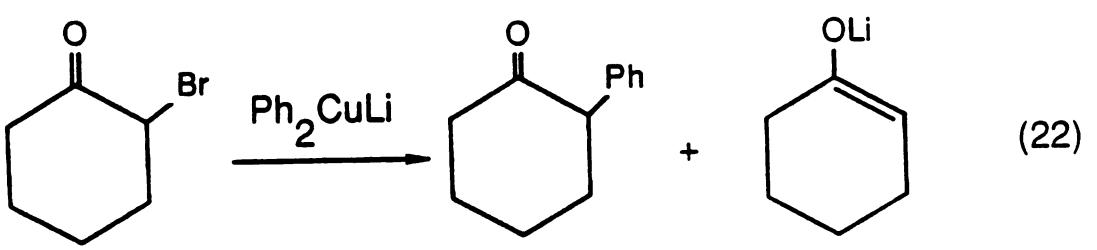
Finally, Wender[14] has developed a synthesis of α-arylketones, based on the reaction of α,β epoxyketones with lithium diphenylcuprate, (eq 21).



(21)

72%

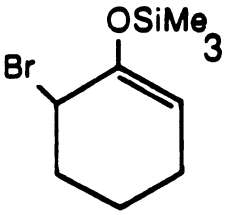
One of our first goals was to study the reaction of α-haloketones or their equivalents with electron-rich aryl species. It has been reported[15] however, that phenylcopper reagents fail to react with haloketones because of competing reduction, (eq 22).



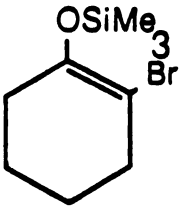
(22)

4% 80%

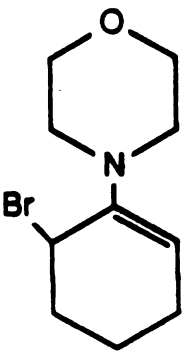
Some simple ketone derivatives which are possible candidates as haloketone equivalents are listed below for the cyclohexanone case:



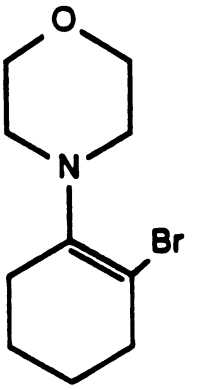
9



10

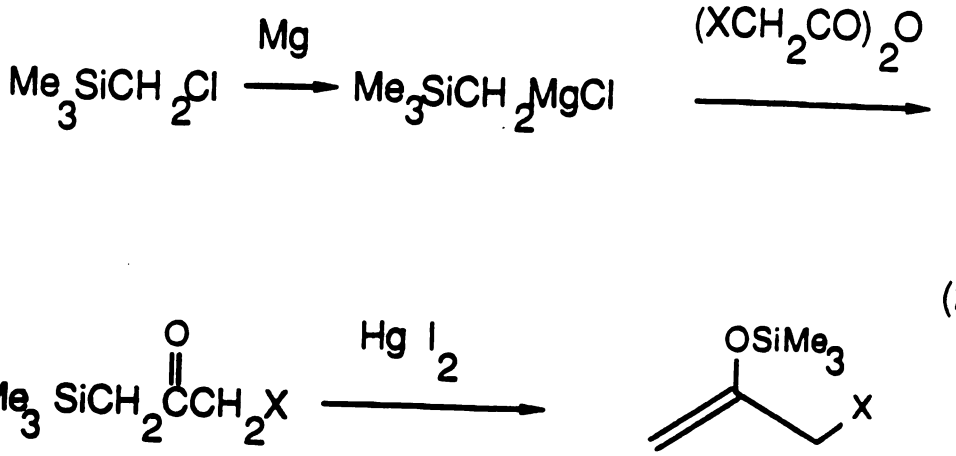


11



12

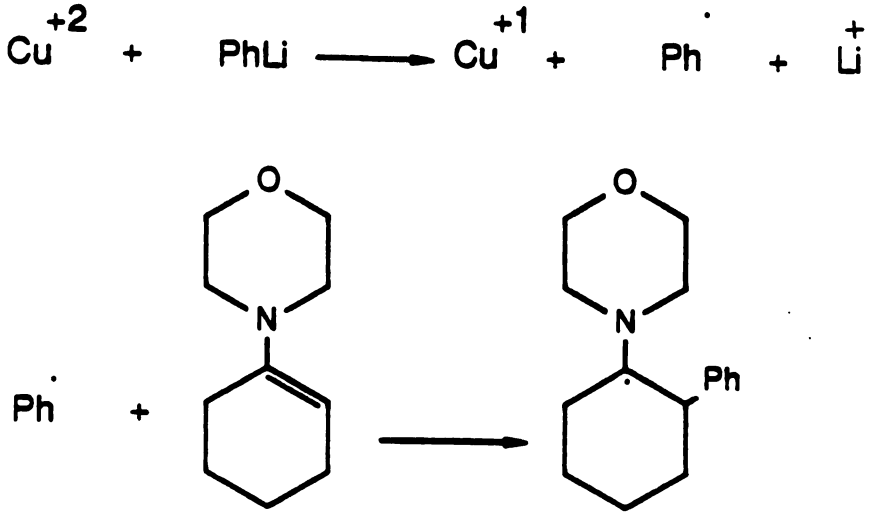
Compounds 10 and 12 possess a vinylic halogen. Therefore, one would expect them to be relatively unreactive toward nucleophilic aryl species. On the other hand, compounds 9 and 11 would be very useful to the organic chemist since they possess an allylic halogen. In fact, allylic α-halosilylenol ethers have been prepared.[16] However, the synthesis of these compounds is limited to a few simple acyclic cases and it involves a long expensive sequence (eq 23).

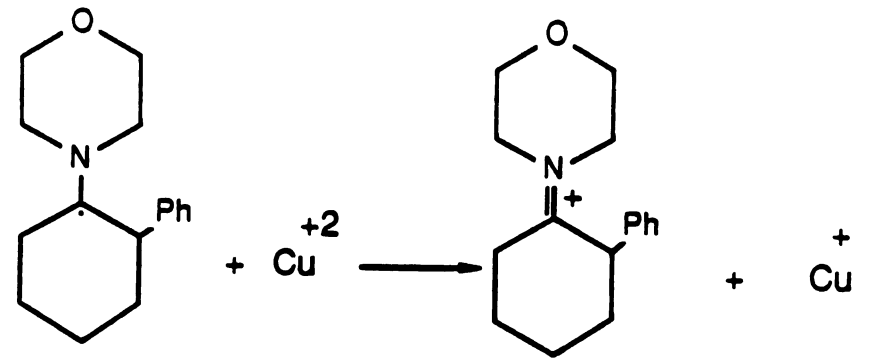


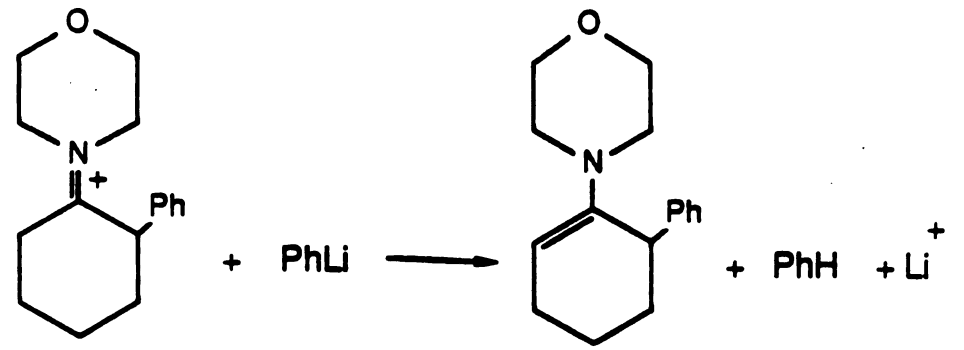
(23)

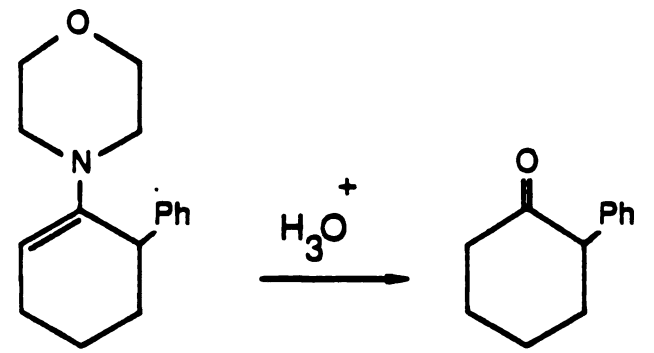
Allylic a-haloenamines 11 appeared to be interesting haloketone equivalents. Our primary aim was to develop a synthetic methodology for those compounds and then to examine their reaction with electron-rich aryl species.

Our studies began by first attempting to react the enamine of cyclohexanone with PhLi in the presence of oxidizing agents such as Cu^{+2} salts according to the mechanism:

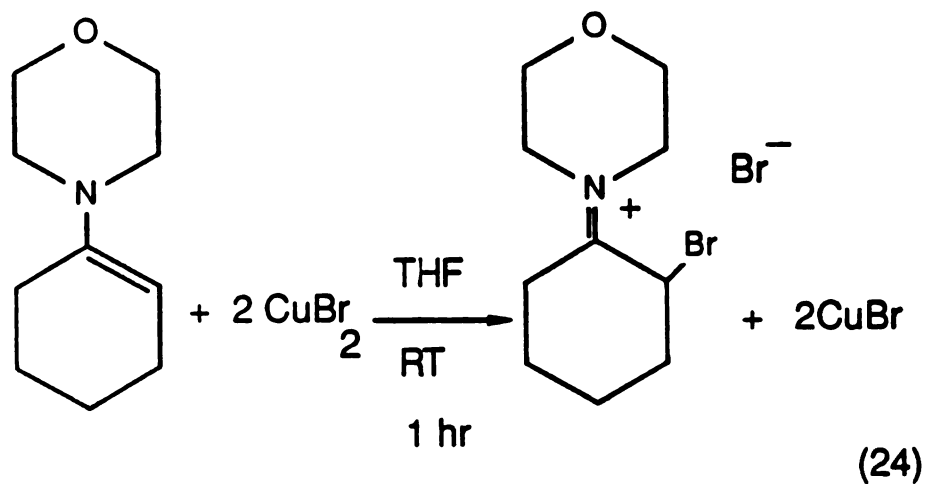



O
N
Ph
+2
Cu
+
Cu
+

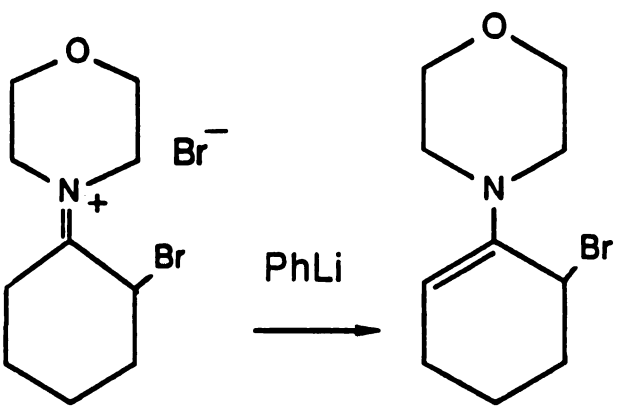

O
N
+
Ph
PhLi
PhH
Li
+

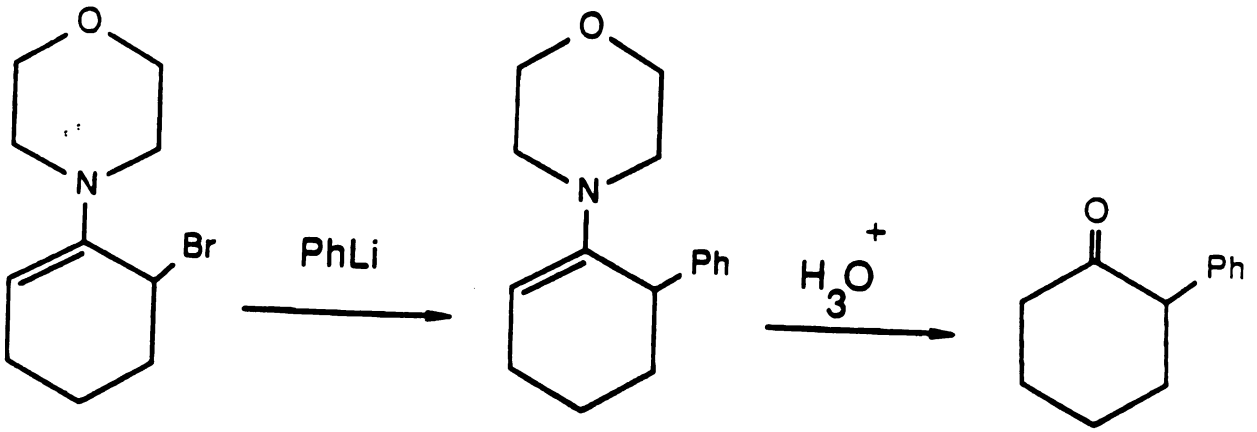

O
N
Ph
H3O
+
O
Ph

In the presence of Cu^{+2} salts such as $CuCl_2$ and $Cu(OAc)_2$ no phenylation was observed. However, in the presence of $CuBr_2$ the reaction yielded 38% of 2-phenylcyclohexanone. Most likely, the above mechanism does not operate in the presence of Cu^{+2} salts. When $CuBr_2$ was used, the reaction followed a different route: The $CuBr_2$ reacted with the enamine to give a bromoiminium salt which in the presence of PhLi gave, after hydrolysis the desired product, (eq 24). One experimental observation which supports the above statement was the formation of a white precipitate, presumably CuBr, when $CuBr_2$ was added to the enamine. The other Cu^{+2} salts gave no precipitate.

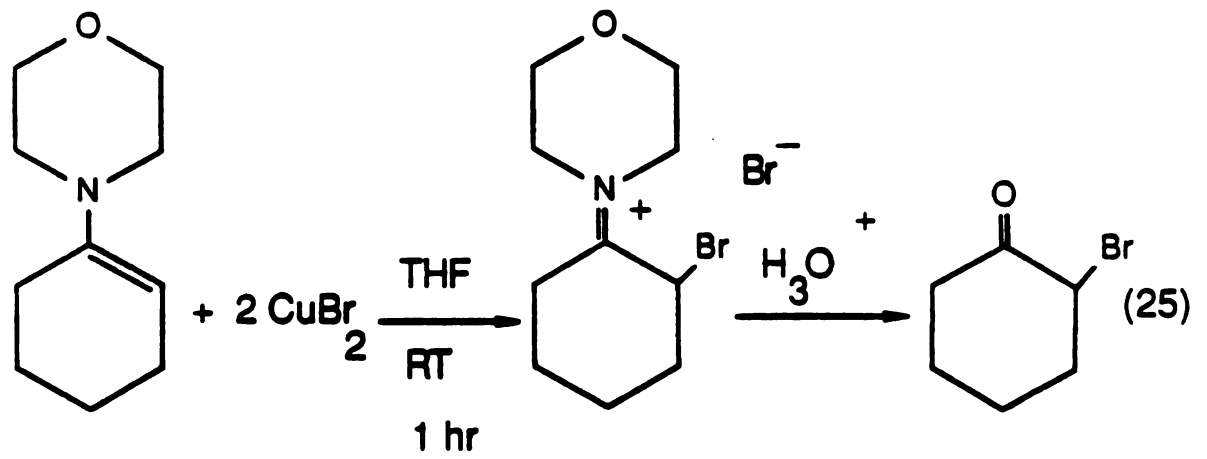


(24)

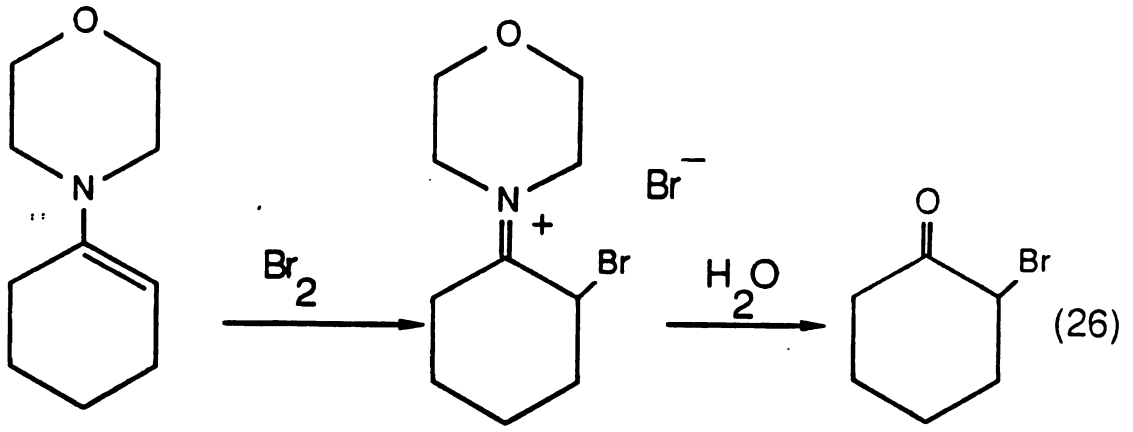




In a separate experiment, bromination of the enamine with $CuBr_2$ followed by hydrolysis of the bromoiminium salt, yielded only 40% of 2-bromocyclohexanone. The cyclohexanone recovery was 53% (eq 25).



At this point, a literature search revealed that enamines can be brominated with bromine in good yields, to form bromoiminium salts which can then be hydrolyzed to give α-bromoketones [17] (eq 26).

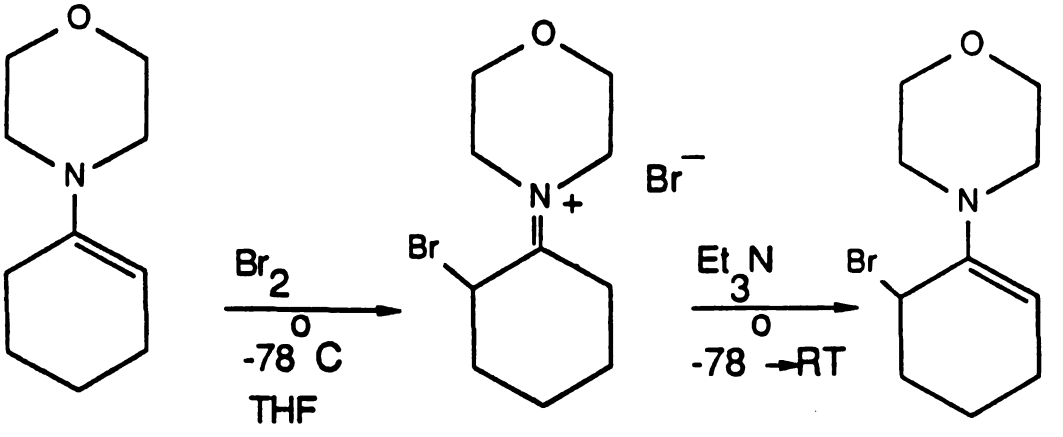


(26)

The authors proposed the above sequence as an useful methodology toward α-bromoketones.

RESULTS AND DISCUSSION

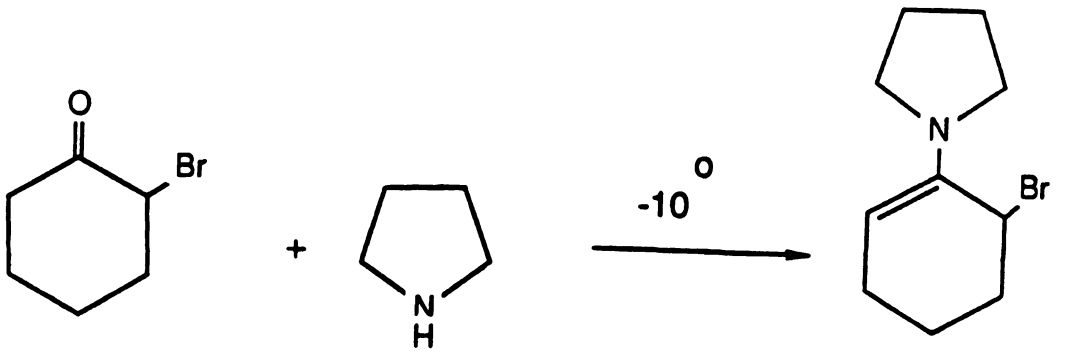
It was apparent to us that a successful synthesis of α-aryl ketones from α-bromoenamines would depend in part on the availability of the precursor α-bromoenamines themselves. Extension of the reaction between enamines and bromine, led to formation of bromoenamines in a high-yield sequence. By employing Et_3N as a base we managed to obtain bromoenamines in almost quantitative yields, (eq 27).



(27)

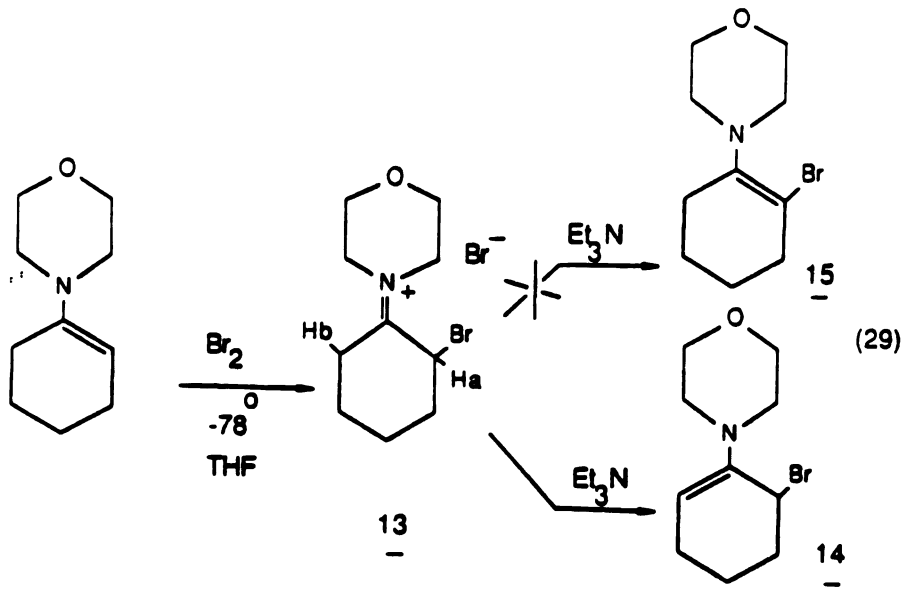
90-95 %

This is an improved method for the preparation of bromoenamine compounds. The most commonly employed method is based[18] on the reaction of bromoketones with a secondary amine (eq 28).

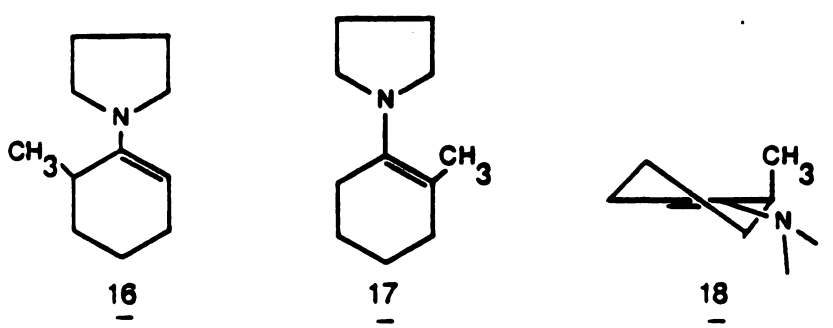


(28)

It is surprising that allylic bromide 14 are produced in this reaction. One would expect that, in the presence of triethylamine, the bromoiminium salt 13, should be converted to a vinylic bromide 15 due to the higher acidity of Ha versus Hb (eq 29). It is possible, however, that allylic strain[19] plays a more important role than hydrogen acidity. In short, the allylic strain theory suggests that pyrrolidine enamines such as that of 2-methylcyclohexanone mainly exist in the allylic form,[20] 16, because in the vinylic form 17 there are severe steric interactions between the methyl and the amine α-methylene groups. These steric interactions can be reduced by rotation about the N-C(sp^2) bond. However, this will reduce the nitrogen-lone pair interaction with the double bond. On the other hand, the enamine with an allylic methyl



group would not suffer any allylic interactions because of the quasi-axial position of the methyl 18. One can apply the same arguments in the case of the two possible bromoenamines of cyclohexanone, especially since the Van der Waals radius of bromine (1.9 Å) is about the same as the one of methyl (2.0Å).[21]

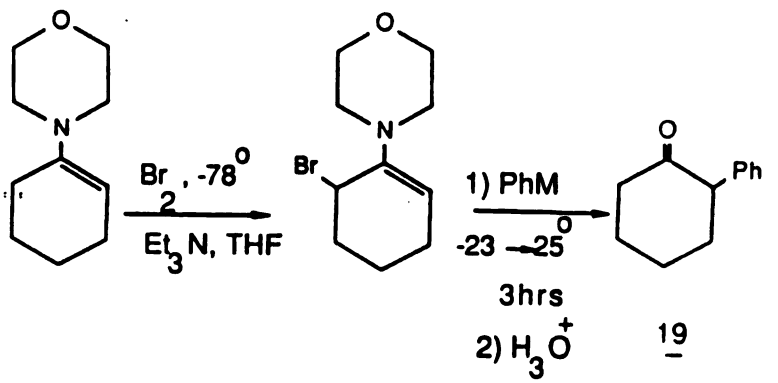


90% 10%

At any rate, NMR studies revealed exclusive formation of the allylic bromide in at least 90% yield in the cyclohexanone case.

Our next goal was to study the reaction of the bromoenamine of cyclohexanone with a variety of nucleophilic phenyl species (PhM) compounds (eq 30). Our results are summarized in Table 4.

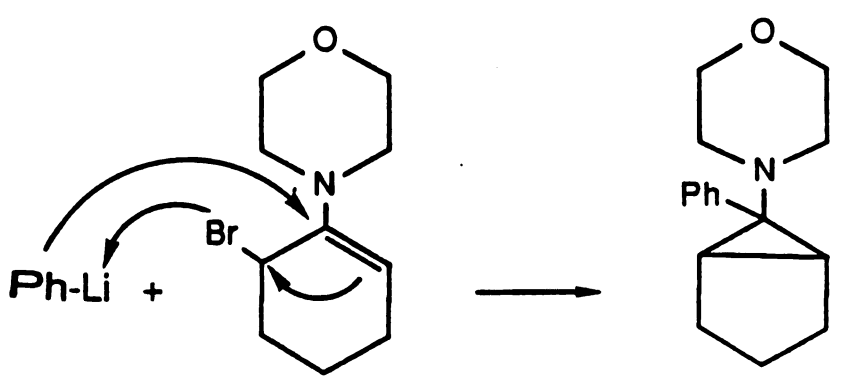
TABLE 4. Reaction of Bromoenamine of Cyclohexanone with PhM



(30)

PhM	19, Yield % (GLC)
PhLi	19
$PhCuS(CH_3)_2$	68
PhCu	78
Ph_2CuLi	94

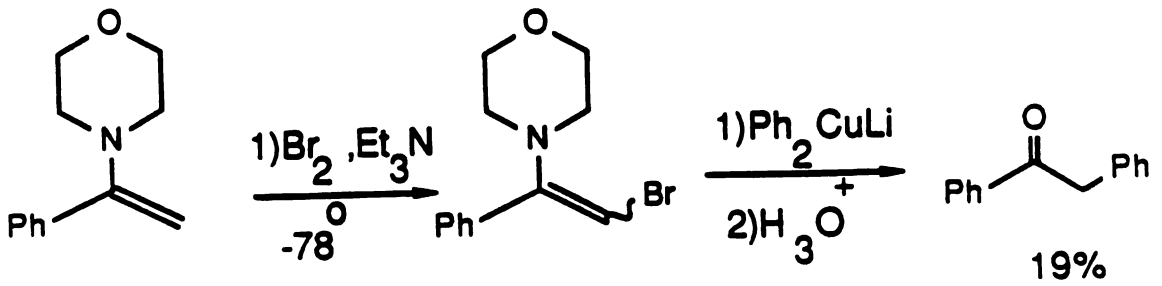
It appears that Ph_2CuLi is a superior phenylating agent for the bromoenamine of cyclohexanone. PhLi gave only 19% of the product. This low yield could be attributed to a competing Favorski-type product (eq 31). That product has been isolated from the reaction of haloenamines with bases.[22]



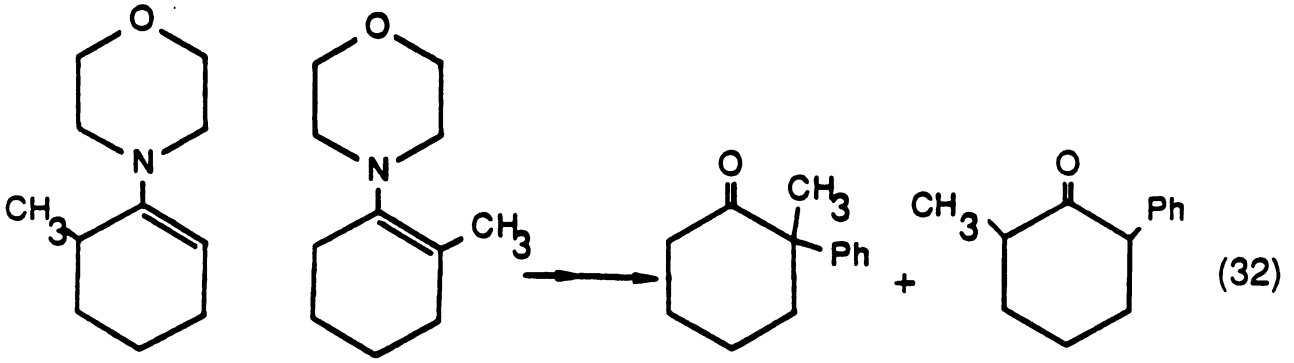
(31)

Since the superiority of Ph_2CuLi as a phenylating agent was obvious, we focused our attention on the reaction of Ph_2CuLi with various ketones. These results are listed in Table 5.

Enamines which exist only in the vinylic form such as that of acetophenone were phenylated in poor yields:

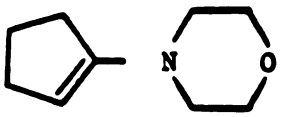
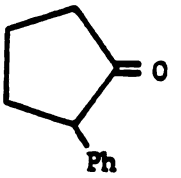
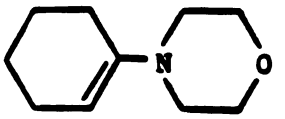
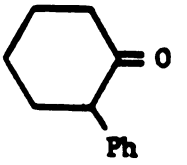
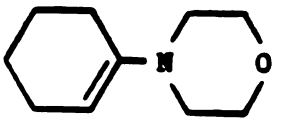
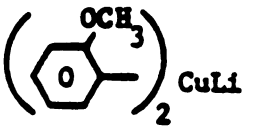
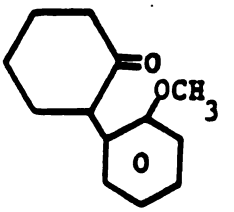
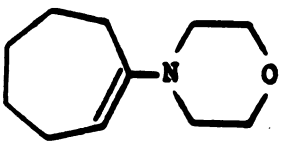
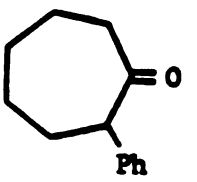
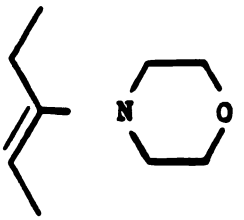
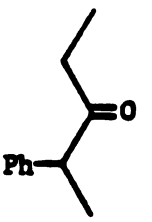
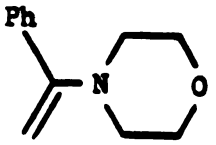
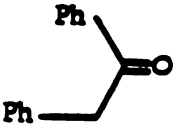


The regioselectivity of the phenylation was briefly examined using the equilibrium mixture of morpholine enamines of 2-methylcyclohexanone 20 and 21 (eq. 32). Interestingly, Ph_2CuLi and PhCu gave different regioisomer major product:

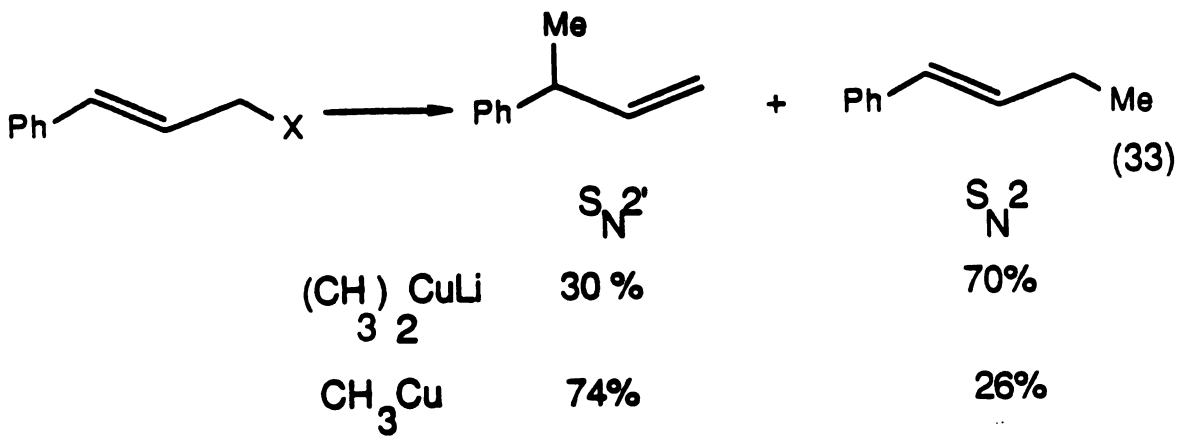


20	21		
48 %	52%	17%	68% Ph_2CuLi
		54%	18% PhCu

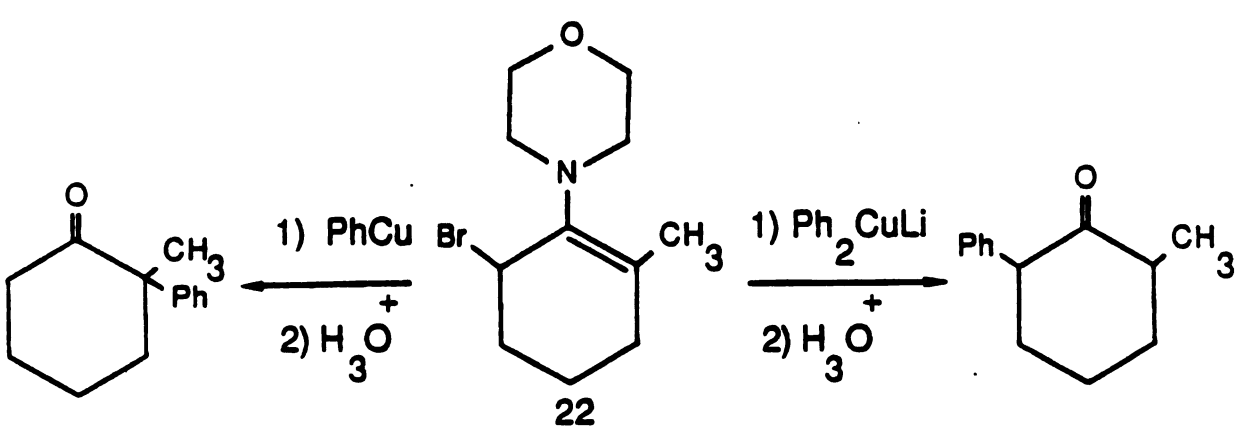
TABLE 5. Bromination-Phenylation of Examines with Ph_2CuLi

Enamine	Organocuprate	Product (isolated yield, %)	
	Ph_2CuLi		(65)
	Ph_2CuLi		(87)
			(69)
	Ph_2CuLi		(81)
	Ph_2CuLi		(72)
	Ph_2CuLi		(19)

In neither case, however, is the ratio of the products related simply to the ratio of starting materials. Presumably, this is the result of the known ability of organocuprates to react with allylic substrates both with and without allylic rearrangement [23], (eq 33).



We were unable to identify the major bromoenamine produced in the case of the enamine of 2-methyl cyclohexanone. It is likely that the major isomer is 22 which then couples with Ph_2CuLi by an S_N2 reaction and with PhCu by an S_N2' reaction:



In this chapter, a new synthesis of α-phenyl ketones from enamines and phenyl copper reagents in two high-yield steps was described. The sequence appeared to provide a simple method for the phenylation of symmetrical ketones in good yield.

EXPERIMENTAL

THF was distilled from sodium benzophenone still. Ether was taken from a freshly opened can. Triethylamine was distilled from calcium hydride before use and stored under argon. Phenyllithium was purchased from Aldrich. Copper (I) iodide was purchased from E. M. Industries and was used without purification. All the enamines except that of acetophenone were prepared by the azeotropic method.[24] The enamine of acetophenone was prepared using $TiCl_4$ as a water scavenger.[24] All reactions were carried out under an argon atmosphere. Gas chromatographic analyses were performed on a Hewlett and Packett 5880 chromatograph equipped with a 25m x 0.25 mm column (stationary phase: fused silica, film thickness 0.25 mm). ^1H NMR spectra were recorded on Bruker WM-250 and Varian T-60 spectrometers with $CDCl_3$ as the solvent and are reported as part per million in the δ scale relative to internal Me_4Si. Low resolution electron impact mass spectra were obtained with a Finnegan 4000 GS/MS at 70 ev.

Preparation of 2-Phenylcyclohexanone

Bromine (5 mmol, 0.8 g) was added dropwise to a solution of the morpholine enamine of cyclohexanone (5 mmol, 0.84 ml) and triethylamine (5.5 mmol, 0.77 ml) in THF (5 ml) at -78°C. After 10 minutes the cold bath was removed, and the reaction mixture was stirred for 10 additional minutes. 10 ml of ether was added to the flask, and the ammonium salt was removed by filtration. The solution of bromoenamine was injected into a flask containing 5 mmol of Ph_2CuLi in 5 ml of THF.

Diphenylcopperlithium was prepared by the addition of 5 ml of PhLi (2M, 10 mmol) to a suspension of CuI (5 mmol, 0.95 g) in THF (5 ml) at -23°C. The reaction mixture was stirred for 2 hrs at -23°C and for 1 hr at room temperature. Cold hydrochloric acid was added (10 mmol, 5 ml) and after 6 hrs the organic layer was separated. The water layer was extracted twice with 10 ml ether, the combined organic layers were dried with K_2CO_3, and the ether was removed. Silica-gel chromatography [hexane-ether (60:40)] gave 2-phenylcyclohexanone as a white solid, mp 55-56° (0.76 g, 87% yield). ^1H NMR ($CDCl_3$) δ 1.5-2.6 (m, 8 H), 3.4-3.8 (m, 1 H), 7.2-7.4 (m, 5 H). MS M/e 174 (M+, 3), 120(25), 105(100), 91 (8), 77(64). In a separate experiment, solvent was removed from the bromoenamine solution and the residue (14, eq 29) was examined: ^1H NMR (CD_3CN) δ1.6-3.1 (m, 10 H), 3.7 (t, 4 H), 4.9 (m, 2 H).

Using a similar procedure, the following compounds were prepared.

2-Phenylcyclopentanone. ^1H NMR ($CDCl_3$) δ 1.76-2.6 (m, 6 H), 3.1-3.5 (m, 1H), 7.2-7.4 (m, 5 H). MS M/e 161 (M+ +1, 12) 160 (27), 104 (100), 91 (17), 78 (19), 77 (15).

2-Phenylcycloheptanone. ^1H NMR ($CDCl_3$) δ1.2-2.8 (m, 10 H), 3.5-3.8 (m, 1 H), 7.2-7.4 (m, 5 H). MS M/e 188 (M+, 25) 117 (78), 104 (90), 91 (100), 84 (47), 78 (33), 77 (32), 51 (37).

2-Phenyl-3-pentanone. ^1H NMR ($CDCl_3$) δ 0.8 (t, 3 H), 1.3 (d, 3 H), 2.2 (q, 2 H), 3.6 (q, 1 H), 7.2 (S, 5 H). MS M/e 163 (M+ +1, 70), 154 (25), 105 (89), 104 (50), 91 (18), 77 (39), 57 (100).

2-Phenylacetophenone. ^1H NMR ($CDCl_3$) δ 4.2 (S, 2 H), 7.2 (S, 5 H), 7.4-8.2 (m, 5 H), MS M/e 196 (M+, 1), 105 (100), 91 (8), 77 (51), 65 (10).

2-methyl-6-phenylcyclohexanone. ^1H NMR ($CDCl_3$) δ 0.9-2.8 (m, 10 H), 3.5-3.9 (m, 1 H), 7.1-7.5 (m, 5 H). MS M/e 188 (M+, 53), 130 (78), 117 (81), 115 (33), 104 (74), 91 (100), 78 (23), 77 (27).

2-Methyl-2-phenylcyclohexanone. ^1H NMR ($CDCl_3$) δ1.1-2.8 (m, 11 H), 7.2-7.4 (m, 5 H). MS M/e 188 (M+, 63), 145 (80), 144 (97), 131 (97), 129 (48), 118 (80), 117 (71), 91 (100), 77 (40).

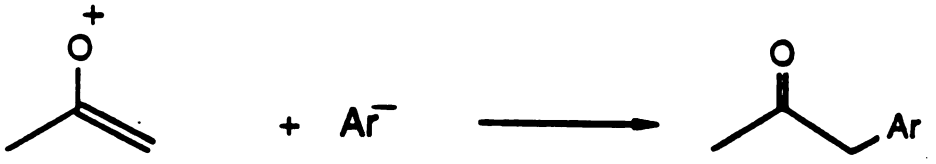
2-(2-Methoxyphenyl)cyclohexanone. ^1H NMR ($CDCl_3$) δ 1.6-2.8 (m, 8 H), 3.8 (s, 3H), 3.7-4.1 (m, 1H), 6.8-7.5 (m, 4H). MS M/e 204 (M+, 79), 160 (49), 147 (100), 121 (44) 119 (30), 91 (75), 77 (22), 65 (23).

CHAPTER III

ARYLATION OF ENOLATES AND METALLOENAMINES WITH ARYL IODIDES

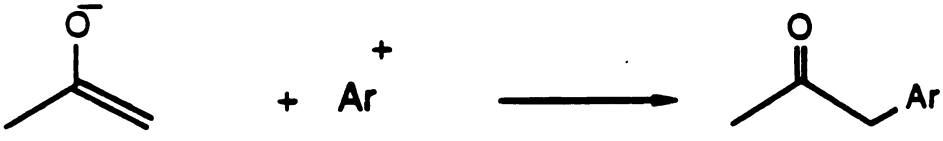
INTRODUCTION

In the second chapter we focused our attention on arylation procedures which follow the general scheme, (eq 34).



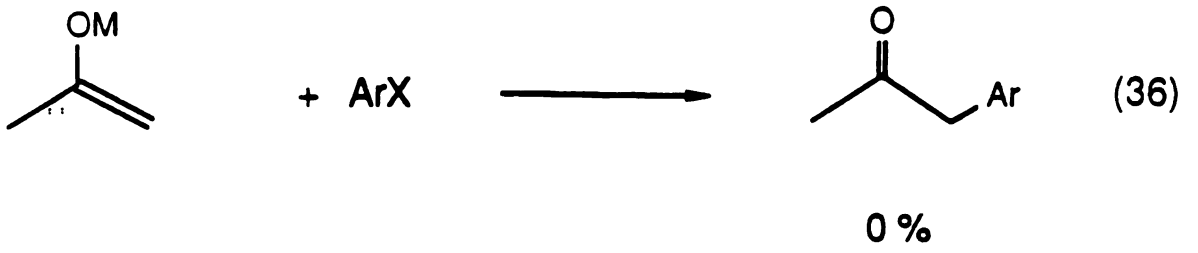
(34)

Another approach towards arylated ketones is the combination of an enolate (or its equivalent) with electron-deficient aryl species, (eq 35).

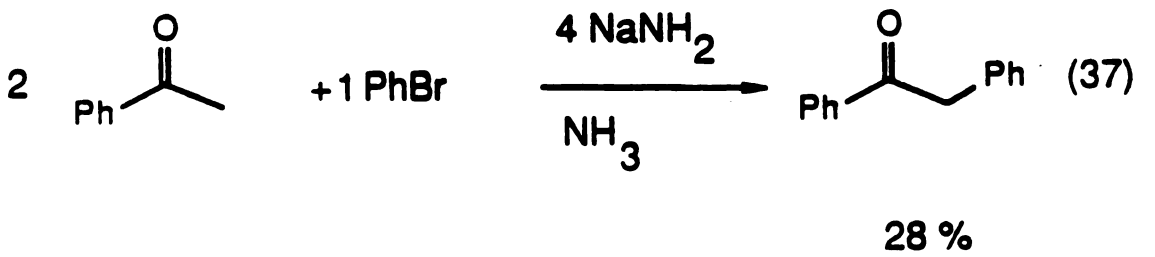


(35)

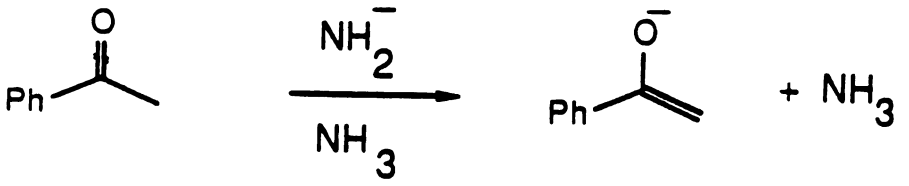
Unfortunately, reaction between an enolate and aryl halides does not take place (eq 36).

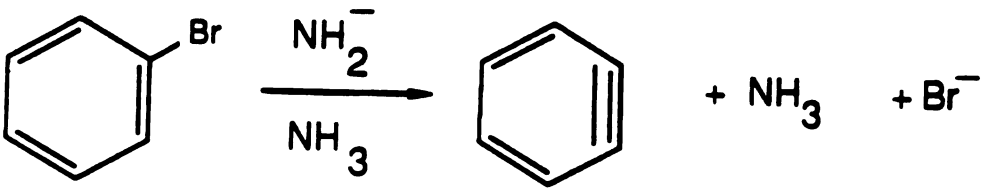


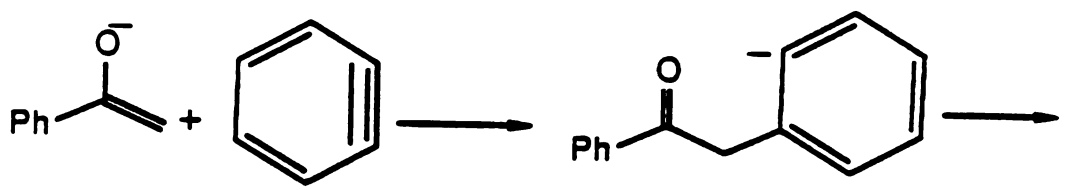
However, in the presence of certain bases such as $NaNH_2$ in NH_3, phenylation is observed in moderate yields [26] as illustrated for acetophenone, (eq 37).

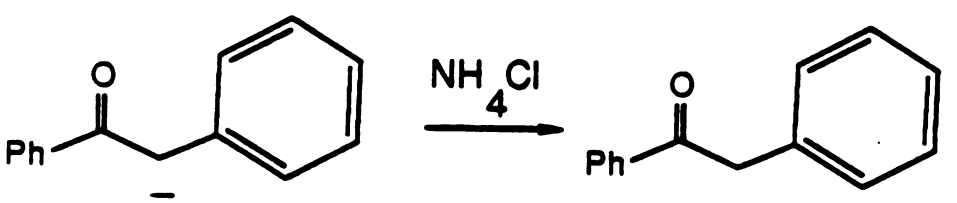


The mechanism for the above reaction is believed to be addition of the ketone enolate to benzyne, the dehydrohalogenated derivative of bromobenzene:


O
Ph
NH2−
NH3
O−
Ph
+ NH3

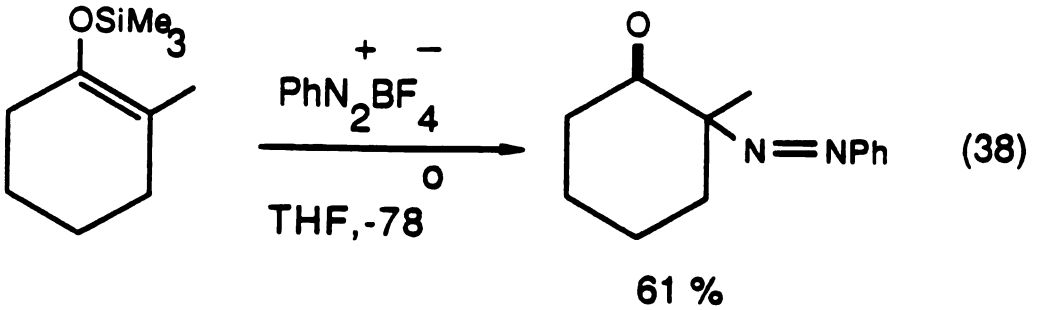

Br
NH2−
NH3
+ NH3
+ Br−


O−
Ph
+
O
−
Ph


O
Ph
−
NH4Cl
O
Ph

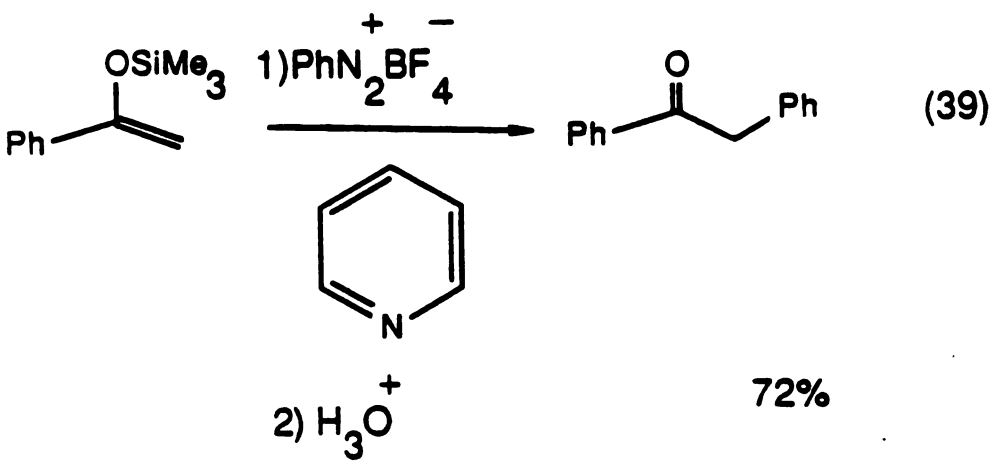
Besides the moderate yields, other disadvantages of the benzyne mechanism are the requirement of a large excess of base and the lack of regioselectivity in cases of mono and polysubstituted aryl halides.

Another source of electron deficient aryl species are arenediazonium salts. These species are known to react with silyl enol ethers to produce diazenes,[27] (eq 38).



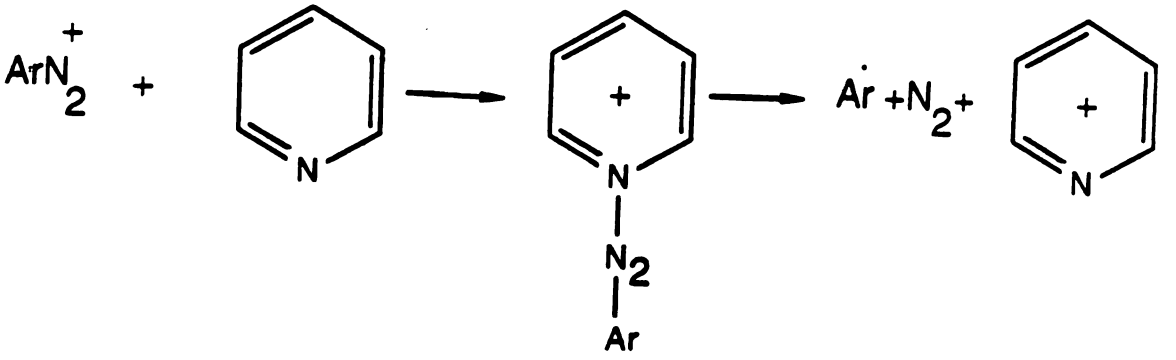
(38)

However, when pyridine is employed as a solvent,[28] the desired α-arylated ketones can be obtained, (eq 39).



(39)

The authors proposed that the key step in the above reaction is formation of aryl radicals via decomposition of azo-type adducts:

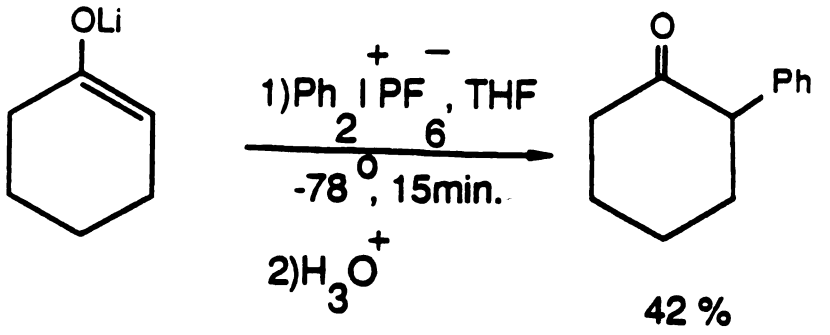


23

24

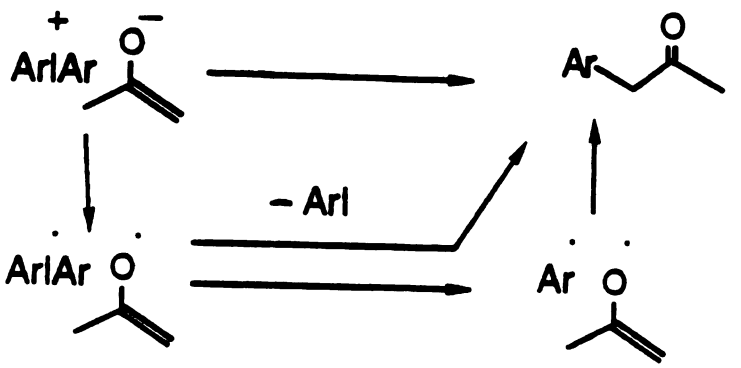
The yield varies according to the nature of R group in the silyl enol ether 23. When R is aliphatic the yield is quite low (31%), as illustrated for the silyl enol ether of 2 nonanone . On the other hand, when R is an aryl group the yield, depending upon the diazonium salt used, is between 58-72%. The authors suggested that the resulting radical intermediate, 24, can be stabilized if R is an aryl group (benzylic-type radical). In the aliphatic case, the phenyl radical generated will not be so readily captured, and is eventually trapped by pyridine with the formation of a substantial amount of phenylpyridines.

A second arylation procedure which is believed to proceed via a radical mechanism is the reaction of diphenyl iodonium salts with ketone enolates[29] (eq 40).

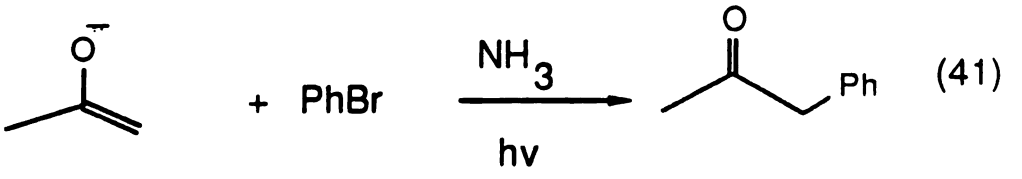


(40)

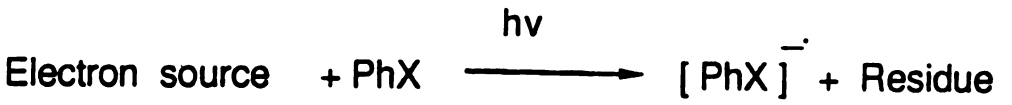
It was proposed[30] that electron transfer from the enolate to the iodonium ion gives radical pairs, which then can react either by radical displacement of the enolate on diphenyliodine or by coupling of the enolate and phenyl radicals:

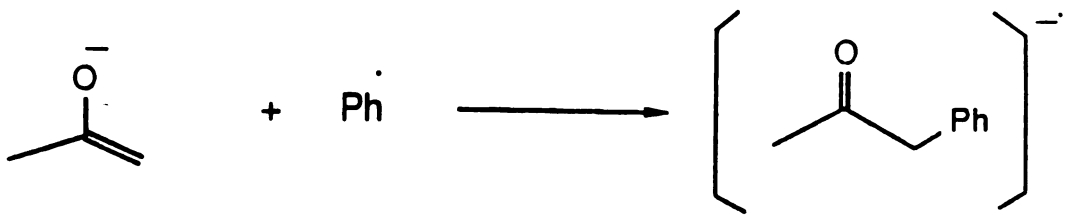


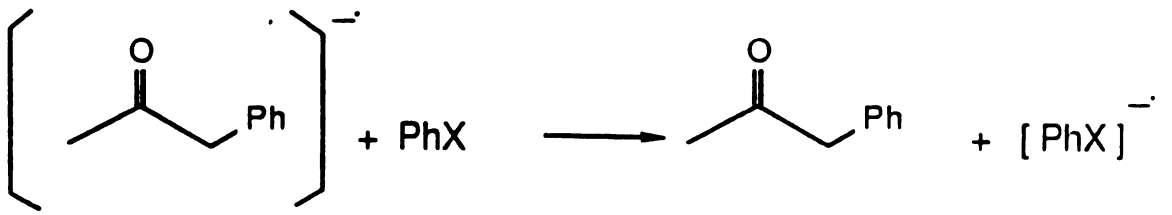
One of the most useful arylation procedures was discovered by Bunnett[31] He found that aryl halides undergo a light induced reaction with ketone enolates in liquid ammonia or DMSO (eq 41).



The proposed radical chain mechanism was termed as the $S_{RN}1$ reaction, The four following steps are involved:







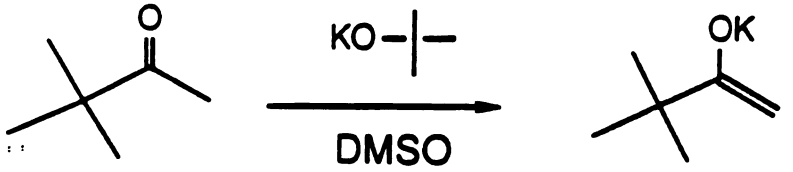
The process is a chain reaction. The mechanism of photoionization is not known but an attractive possibility is that a charge transfer complex of nucleophile with substrate undergoes electron transfer from one moiety to the other upon interaction with a photon [32] (eq 42).

$$PhX.Nu^{-} \xrightarrow{h\nu} [PhX]^{-\cdot} + Nu^{\cdot} \qquad (42)$$

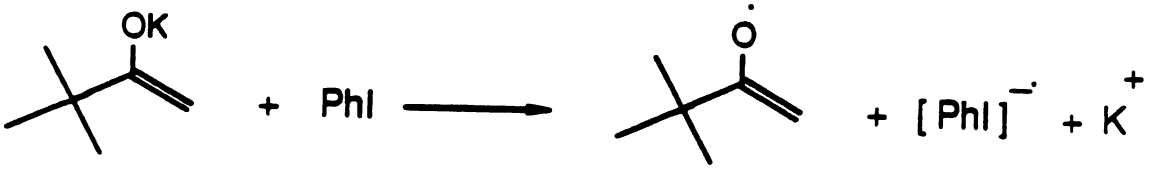
There are other ways to initiate the SRN_1 mechanism. Alkali metals,[33] Fe^{+2} salts[34] can serve as initiators in liquid ammonia. Alkali metals such as potassium dissolve in ammonia to furnish primarily potassium cations and solvated electron anions. Combination of solvated electrons with aryl halides produces phenyl halide radical anions (eq 43) which enter the catalytic cycle. The function of the

$$e^{-}_{NH_3} + PhX \longrightarrow [PhX]^{-\cdot} \qquad (43)$$

Fe^{+2} salts is unclear. Possibly there is an electron transfer from Fe^{+2} to PhX, or an iron-mediated electron transfer from nucleophile to PhX to generate the radical anion of phenyl halide. There are also cases,[35] such the reaction of pinacolone enolate with iodobenzene in DMSO, where neither light nor reducing agent is required. A reasonable possibility[36] is thermally activated electron transfer from the enolate to iodobenzene (eq 44).

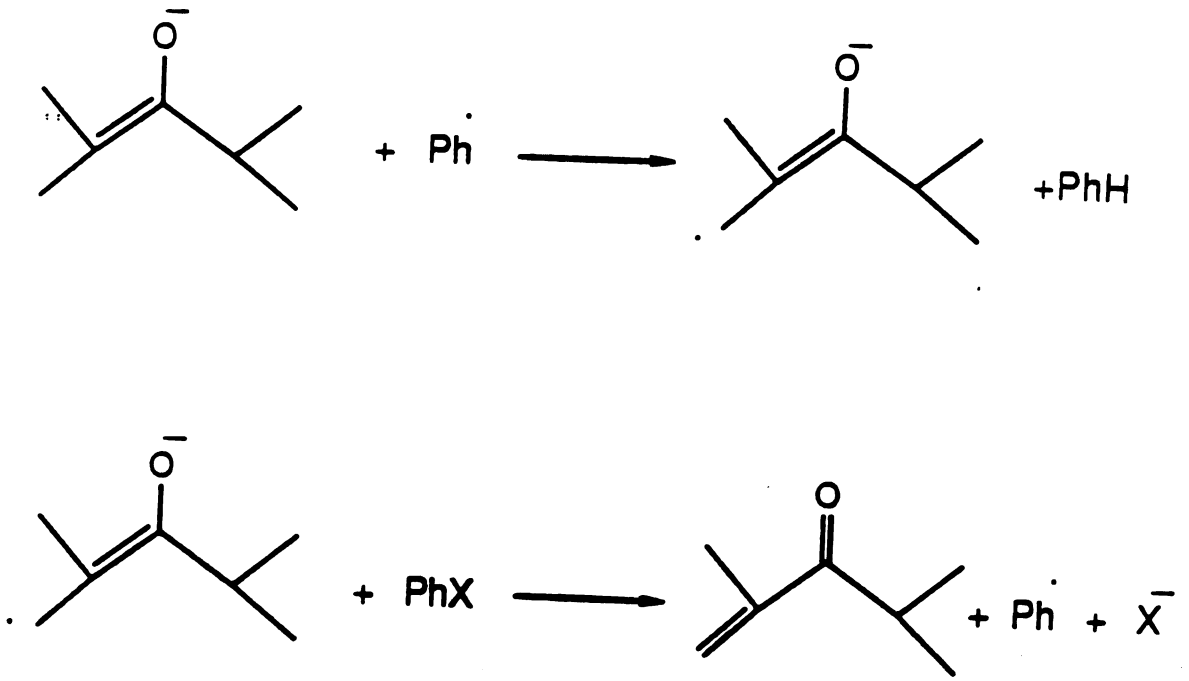


(44)



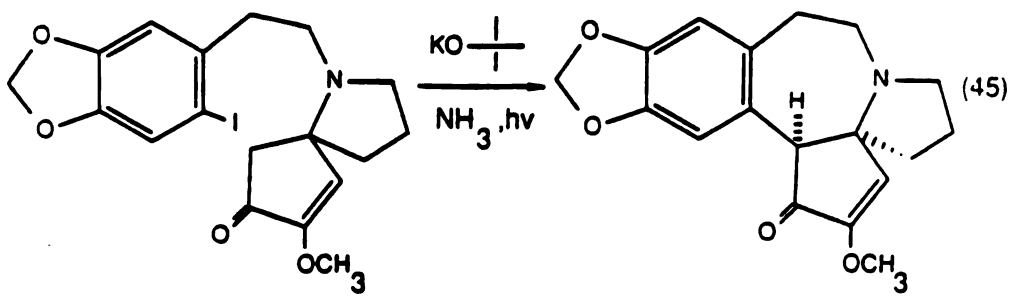
By means of competition experiments, the relative reactivities of pairs of halobenzenes have been measured.[31] Invariably the order of reactivity is: PhI>PhBr>PhCl>PhF.

Even though Bunnett was the first to study the $S_{RN}1$ reaction, he never developed general synthetic procedures based on his results. Semmelhack applied the photo-$S_{RN}1$ reaction to the arylation of various ketone enolates.[37] He found that the $S_{RN}1$ reaction operates efficiently with enolate anions derived from simple ketones, but dialkylsubstituted ketones, such as diisopropylketone give low yields. He attributed this to hydrogen atom transfer from the β-carbon to the phenyl radicals:



He also compared various solvents for the photo-$S_{RN}1$ reaction of pinacolone enolate with bromobenzene. He found that solvent can slow the reaction by donating hydrogen atoms to chain-carrying radicals, producing benzene as a byproduct. THF almost completely inhibited the photo-$S_{RN}1$ process, leading slowly to benzene as the major product. On the other hand no benzene was formed in liquid ammonia

Semmelhack applied the $S_{RN}1$ reaction to the synthesis of a natural product. In his successful cephalotaxine synthesis he employed an intramolecular photo-$S_{RN}1$ reaction[38] (eq 45).



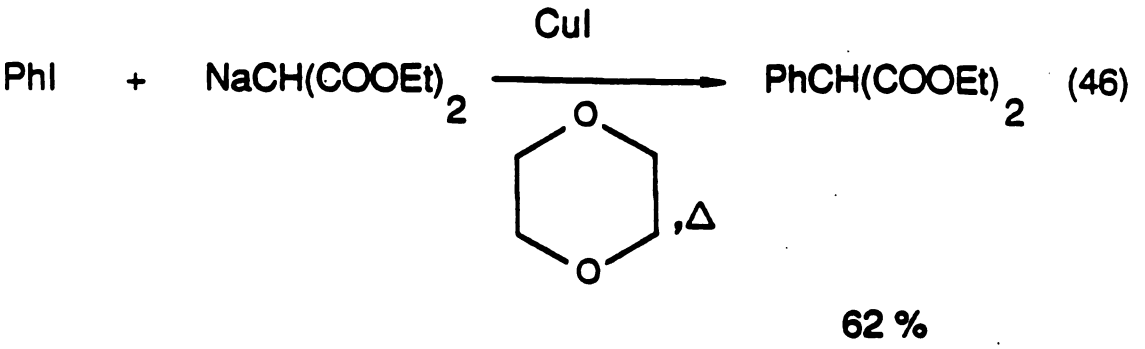
(45)

94 %

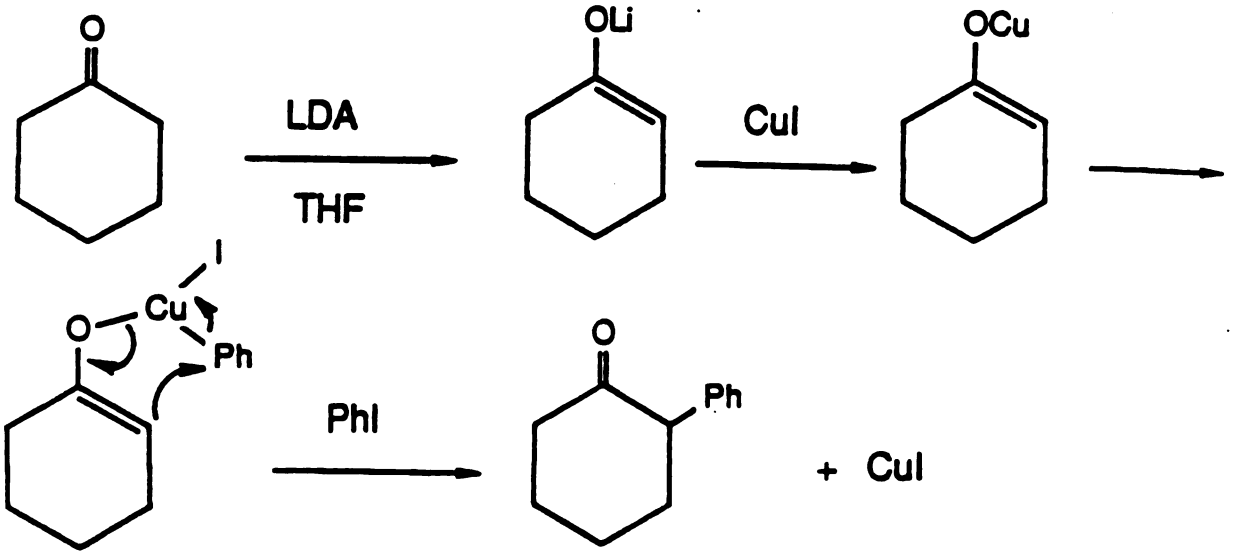
Other methods gave successful ring closure including addition to a transient aryne (15% yield) and coupling via a σ-aryl nickel complex (30%). The photo $S_{RN}1$ reaction gave superior results (94%).

The photoinduced $S_{RN}1$ reaction has other advantages to offer. It does not require activation by other substitutents (contrary to aromatic nucleophilic substitution (S_NAr) reactions). Therefore $S_{RN}1$ reactions occur satisfactorily with simple phenyl halides. The nucleophile invariably occupies the position vacated by the halogen. This contrasts with substitution by the aryne mechanism in which cine substitution often occurs.[39] It is not sensitive to steric effects of ortho substituents. Even the photostimulated reaction of 1-iodo-2,4,6-triisopropylbenzene with acetone enolate gives a significant amount of substitution product.[40] On the other hand $S_{RN}1$ reaction does have some disadvantages. It requires [37] a three-fold excess of enolate in order to obtain satisfactory yields. Moreover, it requires expensive photochemical apparatus.

Our intention was to develop a new arylation method based on the reaction of an enolate or its equivalents with a phenyl halide. It has been known for many years[41] that copper (I) salts of heteroatom nucleophiles react under relatively mild conditions with unactivated aryl halides to give substitution. It is also known[42] that copper-promoted nucleophilic substitution is successful using stable carbanions such as that of sodium diethylmalonate (eq 46).

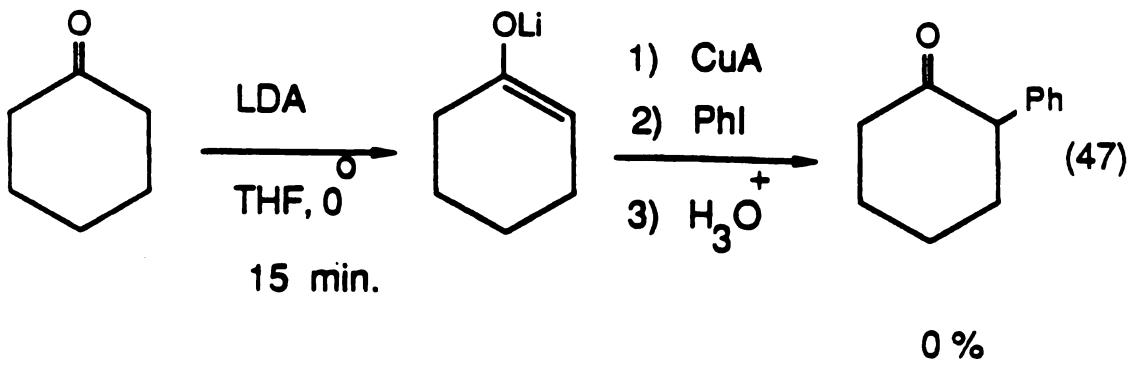


The above results encouraged us to examine the reaction of ketone enolates with phenyliodide in the presence of various copper (I) salts. Our assumption was that an oxidative addition followed by a reductive elimination would yield the desired product:



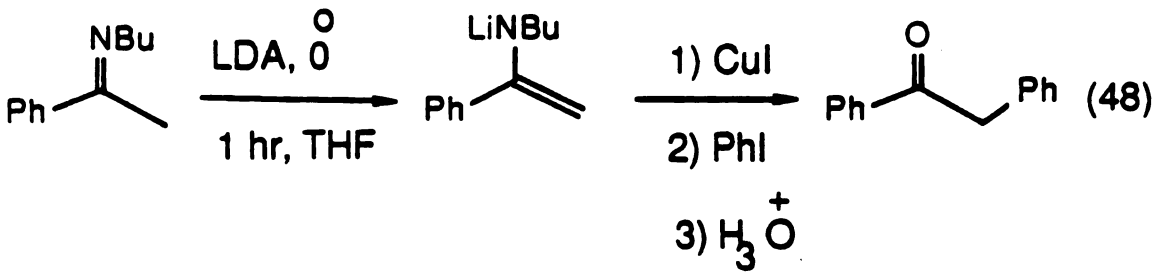
RESULTS AND DISCUSSION

The enolate of cyclohexanone was prepared and reacted with phenyl iodide in the presence of various copper (I) salts ($CuBr.Me_2S$, CuI, $Cu(CH_3CN)_4 PF_6$, (eq 47).



No trace of 2-phenylcyclohexanone was formed at various amounts of copper salts and at temperatures ranging from -78°C to 66°C. The recovery of PhI was almost quantitative in all cases, even when the amount of copper (I) salts and the reaction temperature varied.

Our unsuccessful experiments with various copper (I) salts led us to use other enolate equivalents. The metalloenamines - the nitrogen equivalent of enolates - were our first target. We were hoping that in the presence of copper (I) salts the metalloenamines would react with phenyl iodide, (eq 48).

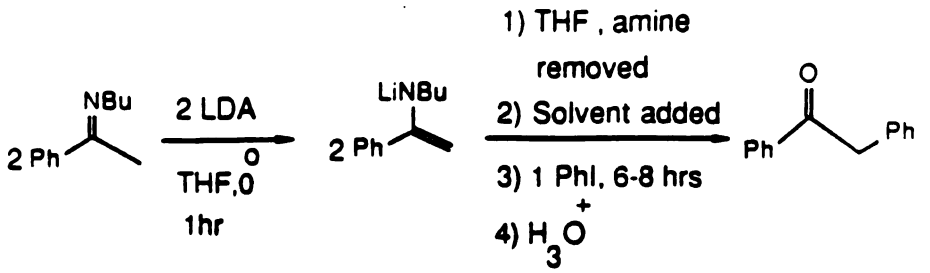


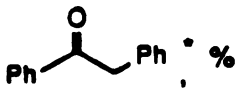
(48)

The yield for the above reaction was 66%. To our surprise, a control experiment without copper (I) yielded 64% of phenylated acetophenone. Therefore, copper (I) was not required for the above reaction.

The synthetic aspect of the arylation of metalloenamines was our first goal. Our hope was to develop a method for the arylation of ketones. An ideal method should: a) give high yield of products with minimum side reactions b) employ a 1:1 ratio of the two reagents c) use materials and solvents which are inexpensive. We decided to use acetophenone and phenyl iodide as our model compounds. One of our first goals was to maximize the yield using different solvents. One difficulty was that in the presence of THF a lot of PhI was converted to PhH, presumably by hydrogen abstraction from the methylene units of THF which are next to the oxygen. Therefore we decided to make the metalloenamine in THF, then remove the THF by applying high vacuum and then introduce various other solvents. Our results for the reaction below are listed in Table 6.

TABLE 6 Reaction of the Metalloenamine of Acetophenone (2 eq) with PhI (1 eq) Under a Variety of Solvents



Solvent	Temperature	 * %	PhI,** %
THF	RT	64	0
THF	Reflux	66	0
Pentane	RT	18	82
Pentane	Reflux	66	33
Ether	Reflux	40	60
Hexane	Reflux	84	16
Cyclohexane	Reflux	83	17
DMF	RT	0	96
Benzene	RT	40	40

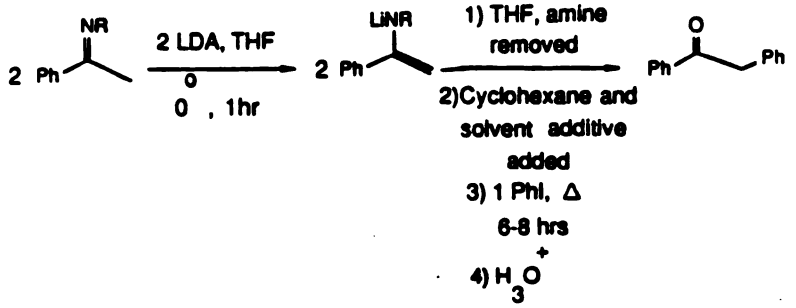
*Yield determined by GLC.

**Recovered PhI determined by GLC.

From the above table one can see that the solvents that give the best results are hexane and cyclohexane at refluxing temperatures.

Our next change was the group attached to the nitrogen on the imine. We examined the reaction of a variety of metalloenamines of acetophenone with PhI. Our results are listed in Table 7.

TABLE 7 Arylation of various Metalloenamines of Acetophenone (2 eq) with PhI (1 eq)



R	Solvent Additives	Ph(C=O)CH2Ph * %	** PhI, %
n-Bu-	None	84	16
$(CH_3)_2N(CH_2)_3$-	None	80	16
t-Bu-	None	45	20
$(CH_3)_2N$-	None	0	100
n-Bu-	TMEDA (2eq)	24	17
n-Bu-	HMPA (2 eq)	55	0
$(CH_3)_2N(CH_2)_3$-	TMEDA (2 eq)	33	4
$(CH_3)_2N(CH_2)_3$-	HMPA (2 eq)	45	0
n-Bu-	12-Crown-4	16	0

*Yield determined by GLC.
** Recovered PhI determined by GLC.

The n-butyl imine together with the dimethylamino propyl imine work the best. It is surprising that the dimethylhydrazine imine gave no product.

We were hoping that the addition of cosolvents such as hexamethyl phosphoramide (HMPA) or N,N,N',N'-tatramethylenediamine (TMEDA) as well as 12-crown-4 ether would improve the yields by solvating the lithium.

However, as it can be seen from Table 7 none of the possible additives increased the yield of the phenylated product.

The mass balance of phenyl iodide and product are low. Presumably, all of the above solvent additives donate a hydrogen to the phenyl radical.as shown on page 64.

The effect of different initiators on the reaction yield was our next goal. As it can be seen for Table 8 none of them was successful for the reactions.

We were hoping that Na and $CrCl_2$ would improve the yield by generating phenyl radicals:

$$Na + PhI \longrightarrow Na^{+} + [PhI]^{-\cdot}$$

$$[PhI]^{-\cdot} \longrightarrow Ph^{\cdot} + I^{-}$$

These phenyl radicals would then enter the catalytic cycle.

The diphenyliodonium salts could also generate a radical chain mechanism:

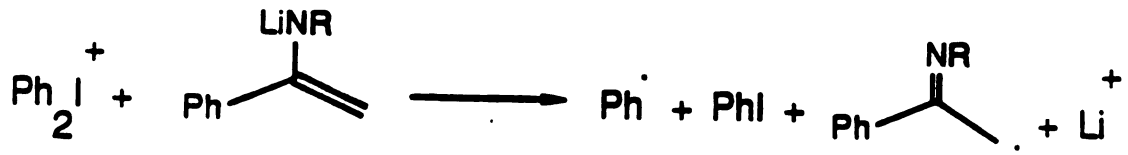
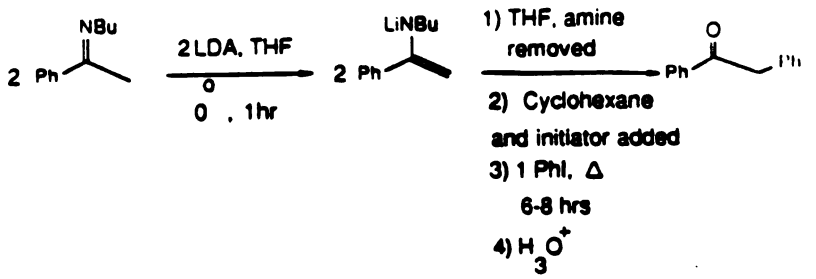


TABLE 8 The Effect of Various Initiators on the Reaction of the nButylimine of Acetophenone (2 eq) with PhI (1 eq)



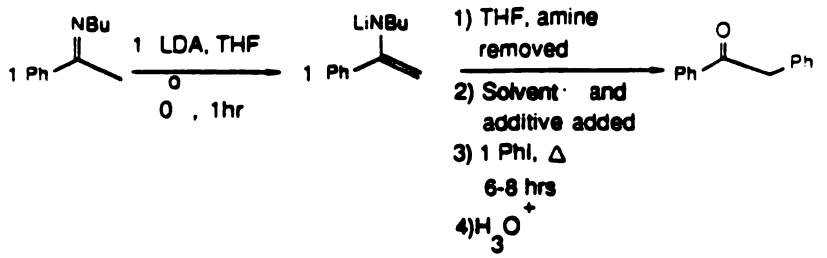
Iniatiator	O, Ph, Ph * %	PhI,** %
Na (0.15 ep)	67	12
CrCl2 (0.1 ep)	76	0
Ph_2IPF_6 (0.1 eq)	15	77
Ph_2IBF_4 (0.1 eq)	44	38

*Yield determined by GLC.
**Recovered PhI.determined by GLC.

Presumably none of the above reagents was able to initiate phenyl radicals more efficiently than the metalloenamine itself.

Our last point of investigation was the ratio between the metalloenamine and PhI. In all of the above experiments we use one extra equivalent of the metalloenamine. A series of experiments using equivalent amounts of the metalloenamine and the PhI was completed. The results listed in Table 9 are disappointing.

TABLE 9 Reaction between 1 eq of Imine and 1 eq PhI.GLC Yields.

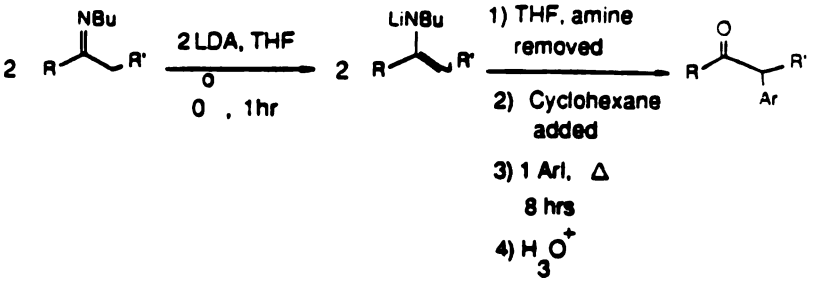


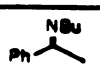
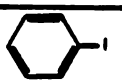
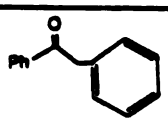
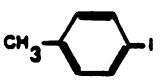
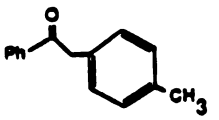
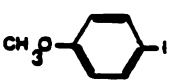
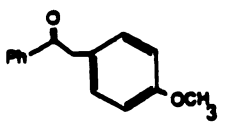
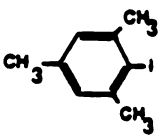
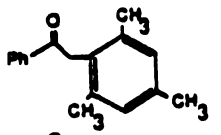
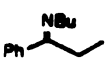
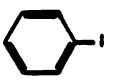
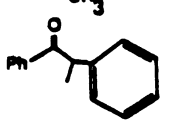
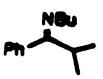
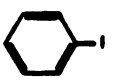
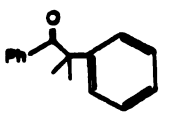
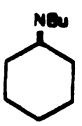
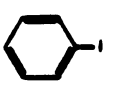
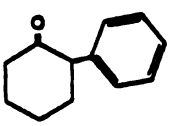
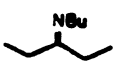
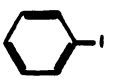
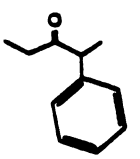
R	Concentration	Solvent	Additive	*%	PhI** %
n-Bu-	0.5	Hexane	None	23	63
n-Bu-	1	Hexane	None	26	53
n-Bu-	5	Cyclohexane	None	25	38
n-Bu-	1	Cyclohexane	None	40	31
$(CH_3)_2N(CH_2)_3$-	0.5	Hexane	None	14	56
$(CH_3)_2N(CH_2)_3$-	1	Hexane	None	15	68
n-Bu-	1	Hexane	0.1eqCuI	13	25
n-Bu-	1	Hexane	0.1eqCrCl2	34	22

*Yield determined by GLC.
** Recovered PhI determined by GLC.

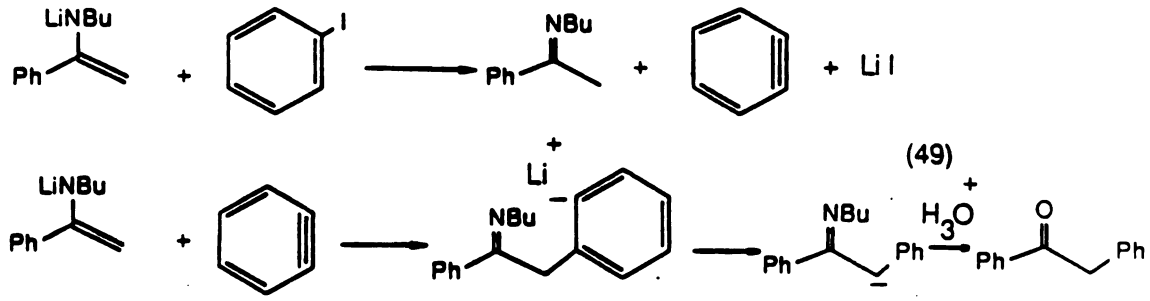
We examined the phenylation of a variety of metalloenamines using 2 eq of metalloenamines and 1 eq of ArI. Our results are listed in Table 10.

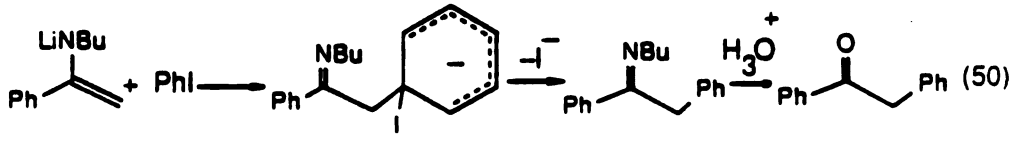
TABLE 10 Reaction of Metalloenamines with Aryl Iodides. Isolated Yields

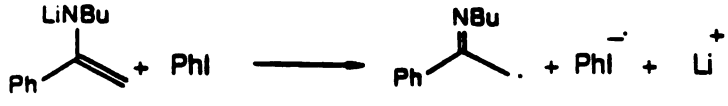


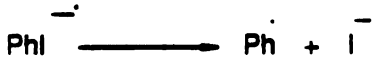
Imine	Aryl iodide	Product	Yield %
			73
			46
			42
			41
			75
			39
			38
			72

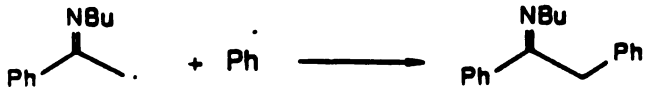
Regarding the mechanism of this reaction, one can say that the most likely pathways are: a) benzyne mechanism (eq 49) b) direct nucleophilic substitution (eq 50) c) an aromatic substitution by an $S_{RN}1$ mechanism (eq 51) d) Metal-halogen exchange followed by coupling (eq 52).

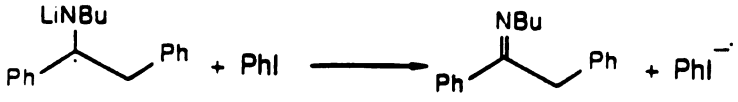


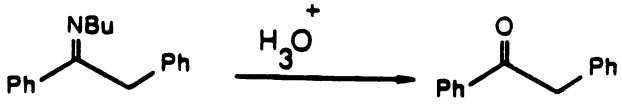


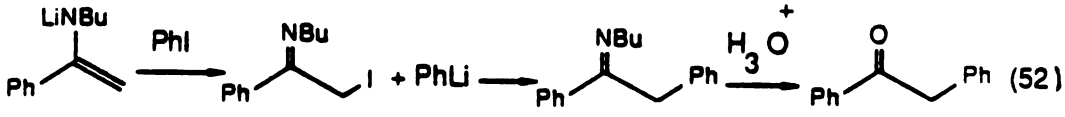




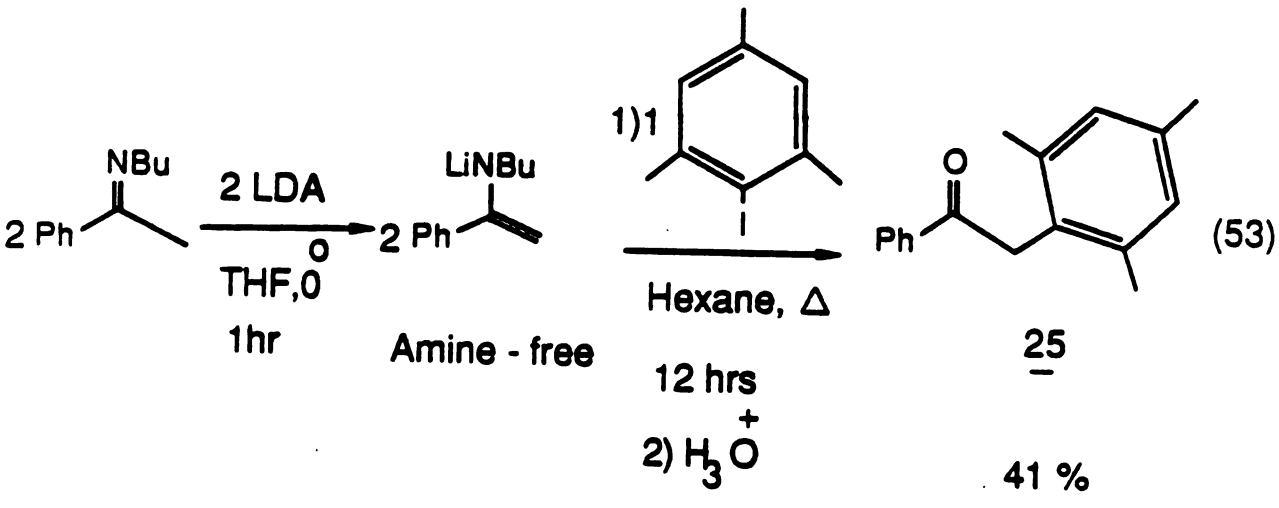






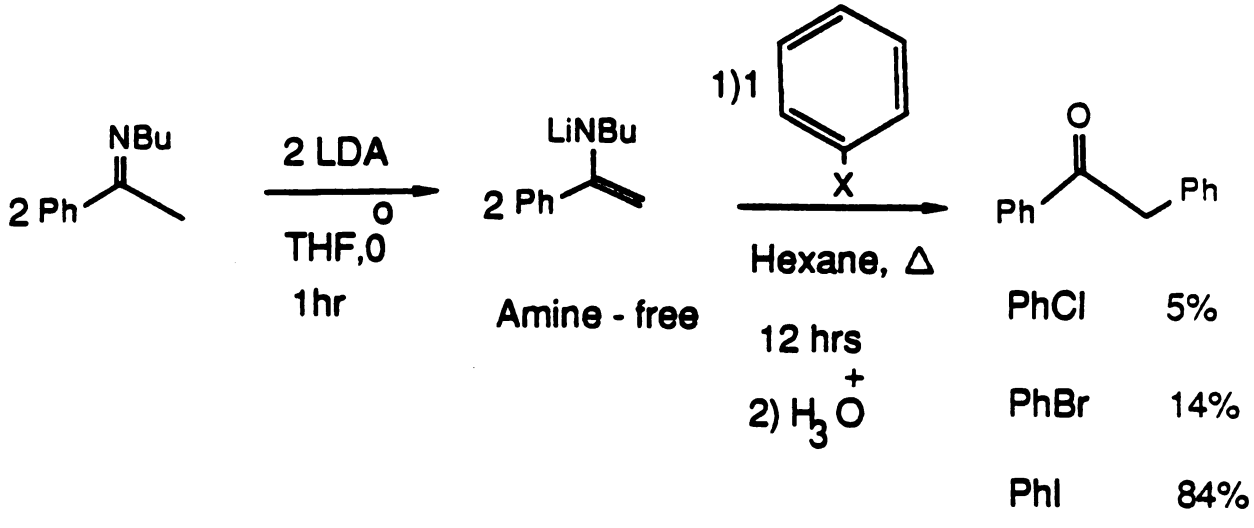


One way to exclude the benzyne mechanism was to achieve arylation in a case where no benzyne intermediate can be formed. 2-Iodomesitylene cannot form benzyne. The desired product 25 was obtained in 41% yield (eq 53).

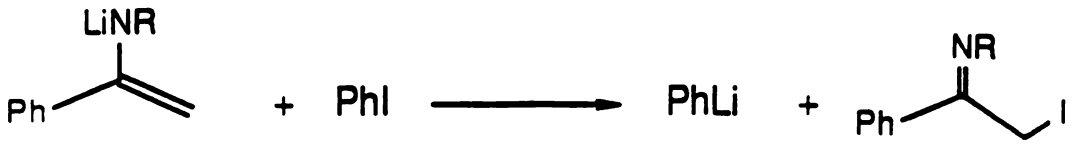


Therefore, benzyne mechanism is not operative, at least in this case.

For determining which mechanism prevails in an aromatic nucleophilic substitution, the halogen mobility order is a criterion of some value. In most direct aromatic nucleophilic substitution reactions,[43] it is ArF>>ArCl~ArBr~ArI. In our studies the reactivity order for the following reaction was ArI> ArBr>ArCl. Therefore one can say that unless the expulsion of the halogen is rate-limiting an addition-elimination mechanism (S_NAr) does not operate in this case.

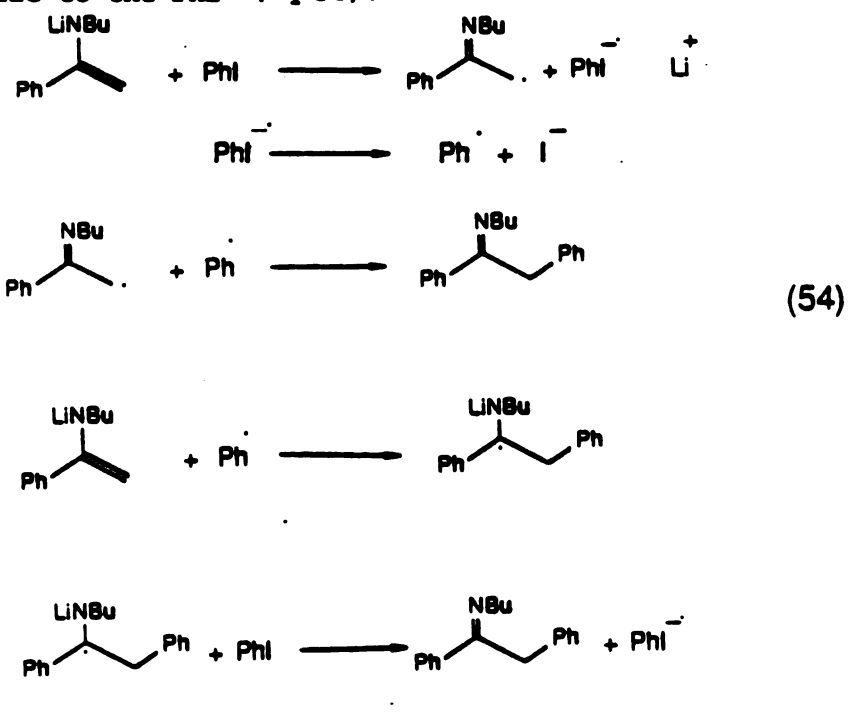


One can argue also about the last mechanism (metal-halogen exchange followed by coupling) in the following points: One would expect to see some 1,4-diketone producted from metalloenamine-iodoimine coupling. However, we were unable to observe any 1,4-diketone or pyrrole derivative. We found that benzophenone inhibits the reaction. If metal-halogen exchange mechanism was operating, benzophenone would have no effect. On the other hand, if a radical mechanism operates the yields are lower because benzophenone quenches the radical anions to produce a relatively stable ketyl which terminates the chain process. Another point is that the equilibrium for the reaction:



lies on the side of the weaker base.[44] Although there are no accurate pk values for the metalloenamine and PhLi, one would expect that the basicity of PhLi should be at least five pK units higher than that of metalloenamines. The low yield of the phenylation when no excess of metalloenamine was used (Table 9) also supports the radical chain mechanism: The phenyl radical is trapped more efficiently by the use of excess metalloenamine.

From the above observations one can presume that the most likely mechanism that operates is an $S_{RN}1$ mechanism. Light is not required since the yields are the same under light and in the dark. One can explain the fact that the reaction occurs spontaneously in the dark by proposing that the $PhI^{-\cdot}$ is thermally produced by electron transfer from the nucleophile to the PhI (eq 54).



(54)

The phenyl radicals generated in the second step react with the matalloenamine to generate a phenylated nitrogen analog of a ketyl which then can generate more phenyl radicals by an electron-transfer process.

In summary, a new phenylation method for ketones was developed. It is based on the reaction of metalloenamines with aryliodides in hydrocarbon solvents and refluxing temperatures. This method has the advantage that it requires neither special apparatus nor exotic reagents, and it is suitable for large scale reactions. On the other hand it has certain disadvantages: a) one equivalent of imine is wasted. It gives good yields for some compounds but it fails to react with others. In spite of these limits, this method probably ranks among the best at present, for the α-arylation of ketones.

EXPERIMENTAL SECTION

All the imines were prepared by the azeotropic method.[8] All amines and ketones were purchased from Aldrich and used without further purification. BuLi was purchased from Aldrich as 1.6 M solution in hexanes. All the aryl halides were purchased from Aldrich and used without purification. Diisopropylamine and THF were distilled from CaH_2. 2-Iodomesitylene was synthesized from 2-bromomesitylene by lithiation[45] followed by quenching the organolithium reagent with iodine.[46] Mass, NMR and IR spectra were recorded with the same instruments as in the previous chapters.

Preparation of deoxybenzoin. BuLi (12.8 ml, 20 mmol was slowly added to a solution of diisopropylamine (2.8 ml, 20 mmol) in THF (10 ml) at 0°. After 15 min 20 mmol (3.8 ml) of the n-butylimine of acetophenone was added dropwise and the reaction mixture was stirred for 1 hour. THF and diisopropylamine were removed by vacuum distillation to 40°. High

vacuum was applied for 30 min and a warm bath (~40°C) was applied to the flask for 10 additional minutes to remove traces of the solvent and diisopropylamine. Argon was introduced
and 10 ml of cyclohexane was added. The flask contents were heated slowly with a heating mantle to reflux. Iodobenzene (1.12 ml, 10 mmol) was then added dropwise. The initially light yellow solution became dark red-brown. After 8 hours of reflux, the reflux was immersed in an ice-water bath and 5 ml of water was added followed by 15 ml of 3N acetic acid. Shortly the light yellow solution turned dark red-brown. After 8 hours of reflux an ice-cold bath was applied to the flask and 5 ml of water was added followed by 15 ml of 3N acetic acid.

After 4 hours stirring to complete the hydrolysis of the imine, the organic layer was separated and the water layer was extracted twice with 25 ml of ether. The combined organic layers were dried with magnesium sulfate, filtered and the solvents were evaporated. Distillation at low temperature (58°/5 mm) removed the acetophenone and the phenyl iodide. Kugelrohr distillation at 115°/0.5 mm gave a light yellow oil which was crystallized from hexane to afford 1.43 g of 2-phenylacetophenone (73%), mp 54-56°.

^{1}H NMR (CD_3CN) δ 4.2 (s,2H), 7.2 (s,5H), 7.4-8.2(m,5H) MS m/e relative intensity 196 (M+,1), 105 (100), 91(8), 77 (51), 65(10).

With a similar procedure, the following compounds were prepared.

<u>2-(4 Methylphenyl)acetophenone:</u> ^{1}H NMR ($CDCl_3$) δ 2.2 (s,3H), 4.2 (s,2H), 7.1(s,4H), 7.3-7.6(m,3H) 7.8-8.2(m,2H); MS, m/e(relative intensity) 210(M+.1), 105(100), 104(45), 77(51).

2-(4-Methoxyphenyl)acetophenone: ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 4.1 (s,2H), 6.7-8.1 (m, 9H); MS m/e (relative intensity) 226 (M+,9), 135(11), 121(90), 120(31), 105(100), 77(87).

2-(1,3,5-Trimethylphenyl)acetophenone: ^{1}H NMR ($CDCl_3$) δ 2.1 (s,6H), 2.2 (s,3H), 4.2(s,2H), 6.8(s,2H), 7.1-7.6 (m,3H) 7.7-8.1(m,2H); MS m/e (relative intensity) 238(11), 133(39), 105(100), 77(33).

2-Phenylpropiophenone: ^{1}H NMR ($CDCl_3$) δ 1.5 (d,3H), 4.7(q,1H), 7.1-7.6(m,8H), 7.9-8.2(m,2H); MS m/e (relative intensity) 210(3), 105(100) 104(29), 88(11).

2-Phenylisobutyrophenone: ^{1}H NMR ($CDCl_3$) δ1.5(s,6H), 6.4-6.7(m,2H) 7.0-7.6(m,8H); MS m/e (relative intensity) 224(M+,1), 160(34), 105(48), 104(100), 91(24), 77(29).

2-Phenylcyclohexanone: ^{1}H NMR ($CDCl_3$) δ1.6-2.8(m,8H), 3.4-3.8(m,1H), 7.1-7.5(m,5H) ms, m/e (relative intensity) 174 (M+,3), 120(25), 105(100), 91(8), 77(64).

2-Phenyl-3-pentanone: ^{1}H NMR ($CDCl_3$) δ0.8(t,3H), 1.3 (d,3H), 2.3(q,2H), 3.7(q,1H), 7.2(s,5H); MS, m/e (relative intensity) 163(M+1, 70) 154(25), 105(89), 104(50), 91(18),77(39),57(100).

BIBLIOGRAPHY

Bibliography

1. H.O. House, "Modern Synthetic Reactions." 2nd Edition, W.A. Benjamin Inc., New York, 1972, chapter 9.
2. O.A. Reutov and A.L. Kurts, Rus. Chem. Rev, 46, 1040, (1977).
3. R.L. Augustine, "Carbon-Carbon bond formation," Marcel Dekkar, New York, 1979.
4. J. Conia, Rec. Chem. Prog., 24, 43, (1963).
5. a) G. Stork and S.R. Dowd, J. Am. Chem. Soc., 85, 2178, (1963).
   b) G. Stork and J. Benaim, J. Am. Chem. Soc., 93, 5938, (1971).
6. H.O. House, W.C. Liang, and P.D. Weeks, J. Org. Chem., 39, 3102.
7. P.F. Hudrlik and C. N. Wan, J. Org. Chem., 40, 2963, (1975).
8. J. K. Whitesell and M. A. Whitesell, Synthesis, 517, (1983).
9. A. I. Meyers, G. S. Poindexter and Z. Brich, J. Am. Chem. Soc., 43, 892, (1978).
10. R. F. Borch, M.D. Bernstein and H. D. Durst, J. Am. Chem. Soc., 93, 2897, (1971).
11. R. A. Rossi and J. F. Bunnett, J. Org. Chem., 38, 3020, (1973).
12. H. C. Brown, H. Nambu and M. M. Rogic, J. Am. CHem. Soc., 91, 6852, (1969).
13. C. E. Sacis and P. L. Fucks, J. Am. Chem. Soc., 97, 7372, (1975).
14. P. A. Wender, J. M. Erhardt and L. J. Letendre, J. Am. Chem. Soc., 103, 2114, (1982).

15. a) C. E. Sacks and P. L. Fucks, J. Am. Chem. Soc., 97, 7372, (1975).
b) G. H. Posner and J. J. Sterling, J. Am. Chem. Soc., 95, 3076, (1973).

16. A. Hosomi, A. Shirahata, Y. Araki and H. Sakurai, J. Org. Chem., 46, 4631, (1981).

17. W. Seufert and F. Effenberger, Chem. Ber. 112.1670, (1979).

18. D. Cantacuzene and M. Tordeux, Tet. Lett., 50, 4807, (1979)

19. P. W. Hickmott, Tetrahedron, 38. 1975, (1982).

20. W. D. Gurowitz and M. A. Joseph, J. Org. Chem., 32, 3289 (1967).

21. L. Pauling, "The Nature of the Chemical bond," Third Edition, Cornell University Press, Ithaca, N.Y., 1960.

22. J. Szmuszkovicz, M. F. Grostic and J.F.Zieserl. Tet..Lett., 3969 (1967).

23. K. Maruyama and Y. Yamamoto, J. Am. Chem. Soc., 99, 8068.

24. a) P. Y. Sollenberger and R. B. Martin, "Chemistry of the Amino Group," S. Patai, Interscience, New York, 1968.
b) J. K. Whitesell and M. A. Whitesell, Synthesis, 517, (1983).

25. W. A. White and H. Weingarten, J. Am. Chem., 32, 213, (1967).

26. W. W. Leake and R. Levine, J. Am .Chem. Soc., 81, 1169, (1959).

27. M. E. Garst and D. Lukton, Syn. Comm. 10, 155, (1980).

28. T. Sakakura, M. Hara and M. Tanaka, J. Chem. Soc., Chem. Comm. 1545, (1985).

29. a) P. A. Manis, DOctoral Thesis, Michigan State University, 1982, p. 49.
b) F. M. Beringer, W. J. Daniel, S.A. Galton and G. Rubin, J. Org. Chem., 31, 4315 (1966).

30. F. M. Beringer, S. A. Galton and S. J. Huang, J. Am. Chem. Soc., 84, 2819, (1962).

31. J. F. Bunnett, Acc. Chem. Res., 11, 413, (1978).

32. S. Hoz and J. F. Bunnett, J. Am. Chem. Soc., 99, 7463, (1977).

33. H, J, Jun abd H, F, Bunnett, J. Am. Chem. Soc., 92, 7463, (1977).

34. C. Galli and J. F Bunnett, J. Org. Chem., 49, 3041, (1984).

35. R. G. Scamehorn and J. F. Bunnett, J. Org. Chem., 38, 1407, (1973).

36. N. Kornblum, R. E. Michel and R. C. Kerber, . Am. Chem. Soc., 88, 5662, (1966).

37. M. F. Semmelhack and T. Bergar, J. Am. Chem. Soc., 102, 7765, (1980).

38. M. F. Semmelhack, B. F. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong and L. D. Jones, J. Am. Chem. Soc., 97, 2507, (1975).

39. J. K. Kim, Ph.D. Dissertaion, University of California, Santa Cruz, 1970.

40. J. F. Bunnett and B. F Gloor, J. Org. Chem., 39, 382, (1974).

41. J. Lindley, Tetrahedron 40, 1433, (1984).

42. J. Tsutsune, K. Mantuvala, H. Wakemoto, and T. Kitao, Chem. Lett., 367, (1980).

43. G. P. Briner, J. Miller, M. Liveris and P. G. Lutz, J. Chem. Soc., 1265, (1954).

44. D. J. Cram, "Fundamentals of Carbonion Chemistry," Academic Press, New York, 1965.

45. H. Gilman and J. W. Morton, Org. React. 8, 286 (1954).

46. Organic Synthesis, 65, 108 (1987).