UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

SYNTHESIS OF NITROGEN HETEROCYCLES VIA TRANSITION METAL CATALYZED REDUCTIVE CYCLIZATIONS OF NITROAROMATICS

A Dissertation

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

degree of

DOCTOR OF PHILOSOPHY

By

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Norman, Oklahoma

2003

SYNTHESIS OF NITROGEN HETEROCYCLES VIA TRANSITION METAL CATALYZED REDUCTIVE CYCLIZATIONS OF NITROAROMATICS

A Dissertation APPROVED FOR THE

DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

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ACKNOWLEDGEMENTS

I would like to thank my wife Sijy for her unwavering support and affection. I would also like to thank my parents John O'Dell and Marlene Steele, my deceased step-parents Jim Steele and Laurie O'Dell, all for never discouraging my curiosity as a child. I owe a large debt of gratitude to all my teachers. At Wilson High School, Ronald Gunter allowed me to "mix things up" during class, and never discouraged me despite occasional exothermic reactions and the frequent disappearance of chemicals. At East Central University, Professor Daniel McInnes who provided me with my first exposure to modern organic chemistry through sweat stained shirts and chalk stained hands. At MIT Scott Virgil taught me how to do chromatography. At the University of Oklahoma the late Professor Roland Lehr, who unfortunately was unable to see me complete my studies, helped me through many difficult cume problems. Professor Nicholas for allowing me to work in his laboratory and supporting me when nothing seemed to work (I guess we didn't need the title of my initial studies: 'The chemistry of tar'). Of course I would like to thank my committee for their participation in the entire process. Susan Alguindigue for her help with NMR experiments and some of the nice figures contained herein. I appreciate the support from the OU Graduate Alumni Fellowship. I would also like to thank all the people I met while at OU, especially the Nicholas lab: Russell, Radhey, Manoj, Nick, Andrea, Masa, Jerome, Kirk, Pei, Quincai, and anyone else who helped along the way.

Wer genug gelernt hat, hat nichts gelernt.

Elias Canetti

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LIST OF ABBREVIATIONS

Å	Angstrom units
Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
Anal.	microanalysis
Ar	aryl
aq	aqueous
atm	atmosphere(s)
B-H	Baylis-Hillman
Bn	benzyl
BOC (Boc)	*tert*-butoxycarbonyl
br	broad (spectral)
Bu	butyl
t-Bu	*tert*-butyl
°C	degrees Celsius
Calcd	calculated
CAN	ceric ammonium nitrate
cat	catalyst
cm	centimeters
Cp	cyclopentadienyl
Cp*	pentamethyl cyclopentadienyl
δ	chemical shift in ppm
	downfield from TMS
d	doublet (NMR)
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylidene acetone
DBU	1,8-diazabicycloundec-7-ene
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMPI	Dess-Martin Periodinane
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EMME	ethoxymethylenemalonic ester
EDG	electron donating group
eq	chemical equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
FID	flame ionization detection
Fp_2	$[Cp(CO)_2Fe]_2$
Fp^*_2	$[Cp^*(CO)_2Fe]_2$
g	gram(s)
GC	gas chromatography
GCMS	gas chromatography mass spectroscopy
γ	gamma
h	hour(s)
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrum
Hz	hertz
IR	infrared
J	coupling constant (NMR)
L	liter(s)
LDA	lithium diisopropylamide
μ	micro
m	multiplet
M	moles per liter, metal
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
m/z	mass to charge
NMR	nuclear magnetic resonance
Ns	*p*-nitrobenezesulfonate
PCC	pyridinium chlorochromate
Ph	Phenyl

PMB	*p*-methoxybenzyl
PPA	polyphosphoric acid
ppm	parts per million (NMR)
PPN	$(PPh_3)_2N$-
Pr	propyl
i-Pr	isopropyl
q	quartet (NMR)
R_f	retention factor
rt	room temperature
s	singlet (NMR)
t	triplet (NMR)
TBAF	tetrabutyl ammonium fluoride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMB	2,4,6-trimethylbenzoate
TMPhen	3,4,7,8-tertamethyl-1,10-phenanthanthroline
TMS	trimethylsilyl, tetramethylsilane
Ts	p-toluenesulfonate
UV	ultraviolet

ABSTRACT

This research focuses on applying a catalyst system discovered in this laboratory, for the intermolecular allylic amination of alkenes with nitrobenzenes, to the synthesis of nitrogen heterocycles via an intramolecular reaction. The catalysts investigated in this study were of the general type $[Cp(CO)_2M]_2$, where M = Fe or Ru. The use of these catalysts with CO pressure (50 atm) allows for the reductive cyclization of *o*-nitro styrenes to indoles and *o*-nitroenones to 4-quinolones in moderate to good yield. The reductive cyclization of the Baylis-Hillman adducts of 2-nitro benzaldehydes and acrylates were found to produce indoles and N-formyl indolines in poor yield, in marked contrast to previously reported cyclizations of these substrates with conventional nitro reductants. Functionalization of these *o*-nitro Baylis-Hillman adducts in a variety of ways led to the discovery that the Baylis-Hillman acetates produce quinolines selectively in good yields (47-67 %) under somewhat mild conditions (7 atm CO, 150 ^{o}C, 10 mol % $[Cp^*(CO)_2Fe]_2$, .011M substrate in dioxane, where Cp* = pentamethylcyclopentadienyl). Limited mechanistic studies (crossover experiments with a mixed Cp ligand dimer) implicate the possible involvement of 17 e- radicals from dissociation of the dimeric catalyst under our reaction conditions. It has also been found that 2-nitro ketoximes cyclize to 1H-indazoles under similar conditions in poor to good yield (26-85 %).

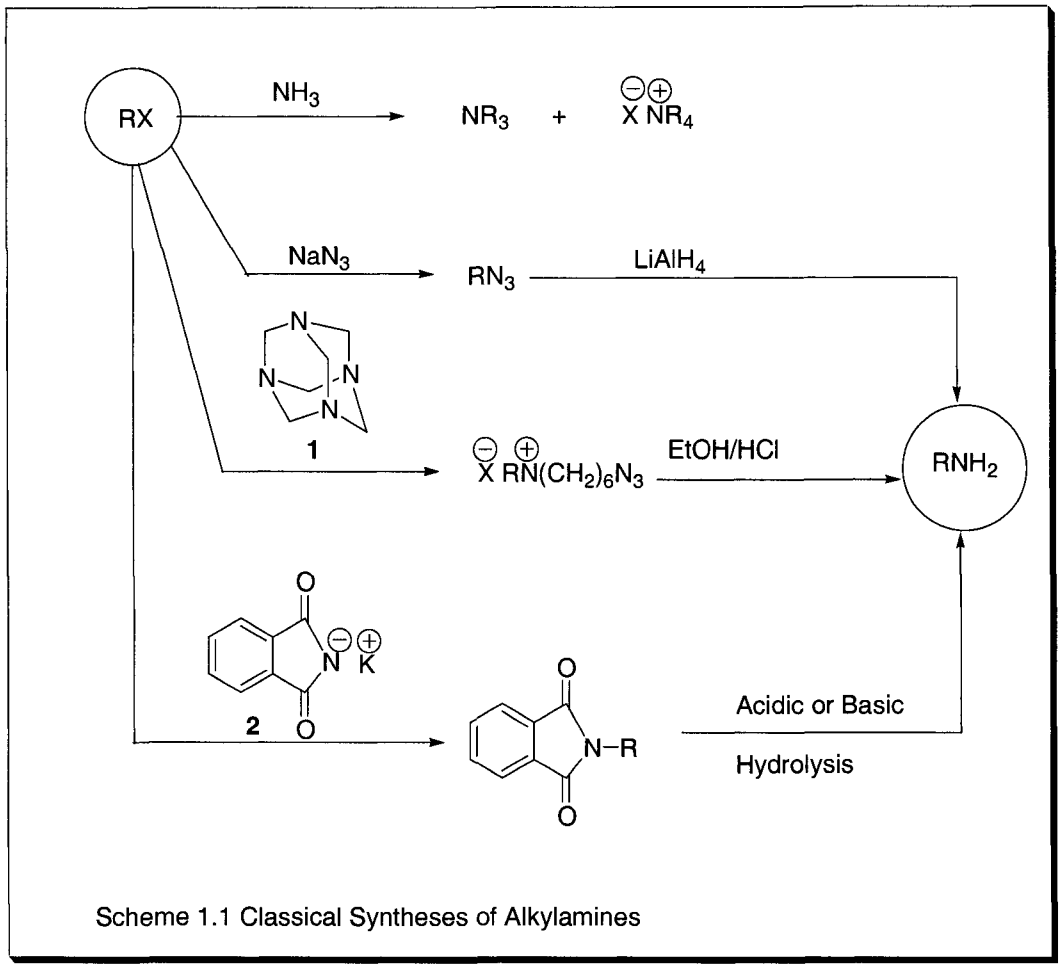
CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1: SYNTHESIS OF AMINES IN ORGANIC CHEMISTRY

1.1.1: CLASSICAL AMINATION METHODS

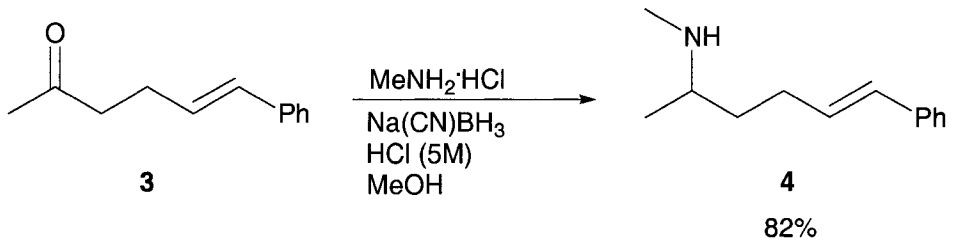
The formation of carbon-nitrogen (C-N) bonds is one of the most fundamental transformations in synthetic organic chemistry,[1] due in a large part to the prevalence of organo-nitrogen compounds in nature and their importance in medicine. While C-N bonds exist in a variety of functional groups (amides, nitriles, isonitriles, imines, etc.), one of the most important types of compounds containing C-N bonds are amines. The most straightforward method of preparing amines involves the reaction of ammonia or other amines with alkyl halides.[2] This is a convenient method for preparing tertiary amines and quaternary ammonium salts.[3] However, the propensity of amines to undergo multiple alkylations limits the use of this method for the preparation of most primary and secondary amines (Scheme 1.1).[4]



Scheme 1.1 Classical Syntheses of Alkylamines

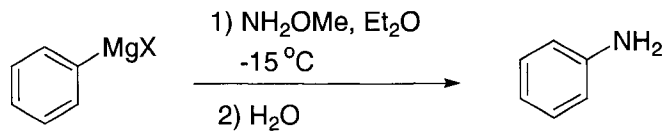
Sodium azide can react with alkyl halides to give primary azides, which when reduced, give primary amines.[5] Other indirect methods employing nucleophilic nitrogen have been developed: the Delepine reaction with hexamethylenetetramine **1**,[6] the Gabriel procedure with potassium phthalimide **2**,[7] and related methods use a bis-protected nitrogen that is alkylated and subsequently deprotected, giving primary amines (Scheme 1.1). These procedures, while sometimes quite useful, point to a fundamental limitation in the synthetic chemistry of amines, in which a protection/deprotection strategy is often required to prepare the desired amine.

Reductive amination is one of the oldest indirect methods for the synthesis of secondary and tertiary amines from ketones, by formation of a Schiff-base and subsequent reduction.[8] One pot procedures have been developed, but can give multiple alkylations, and are best conducted with a large excess of the amine under slightly acidic conditions with $NaCNBH_3$, a somewhat selective reducing agent.[9] Using this method the ketone **3** gave the secondary methyl amine **4** in 82% yield (Scheme 1.2).[10]



Scheme 1.2. A One-Pot Reductive Amination

Other researchers have used the concept of umpolung, or reversal of polarity, to prepare electrophilic aminating agents.[11] These methods have met with some success, but often require exotic aminating agents and harsh conditions (alkyl metals) to generate anions potent enough to attack the weakly electrophilic nitrogen. The Schverdina-Kotscheschow amination involves the treatment of O-methyl-hydroxylamine with Grignard reagents at low temperature and gives moderate to good yields of primary amines (Scheme 1.3).[12]



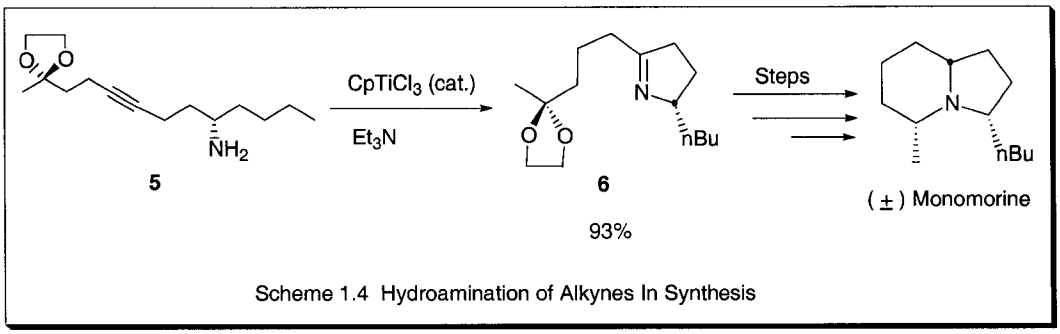
Scheme 1.3 Schverdina-Kotscheschow Amination

1.1.2: MODERN AMINATION METHODS

While the aforementioned approaches often give the desired products, the direct selective preparation of amines from readily available starting materials has long been an attractive yet unrealized goal. Ideal starting materials for amines are olefins, which are inexpensive, readily available chemical feedstocks. Many of the most recent advances in the synthesis of amines employing olefins come from developments utilizing transition metal reagents and catalysts.[13] Indeed, transition metal-mediated reactions have been responsible for some of the most remarkable transformations developed in the last 50 years. These processes often provide unique mechanistic pathways that may lead to new reactive species and subsequently new transformations that have the potential to be stereoselective. Olefins can be transformed to amines by a variety of processes including: hydroamination,[14] aziridination,[15] aminohydroxylation,[16] and allylic amination.[17]

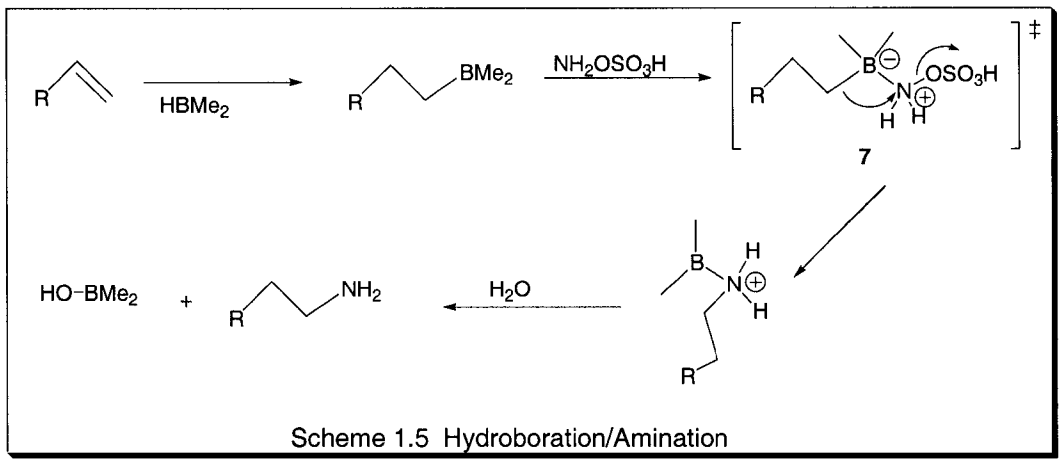
In hydroamination, an N-H bond is added across the olefinic double bond (allenes and alkynes can also be used).[14] These reactions usually require very reactive organolanthanide complexes or early transition metal complexes that are quite air and moisture sensitive, and work best when conducted intramolecularly. This type of

reaction has recently been used for the preparation of the indolizidine alkaloid Monomorine, in which the β-propargyl amine **5** was treated with $CpTiCl_3$ to give the 3,4-dihydro-2H-pyrrole **6** (Scheme 1.4).[18]



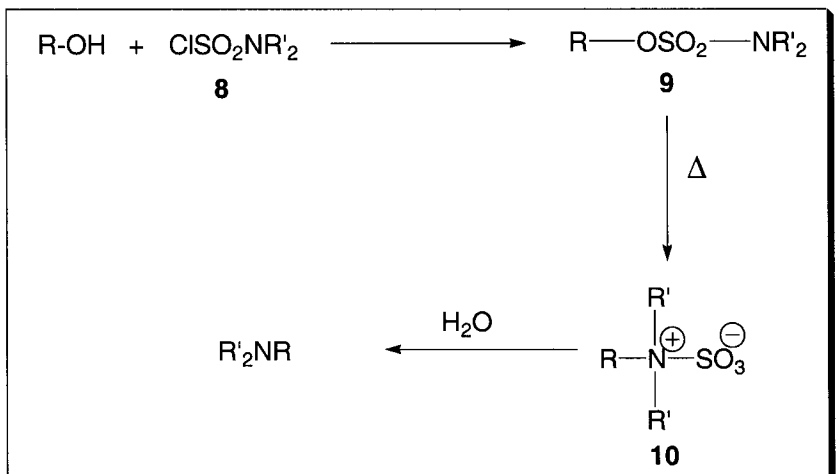
Scheme 1.4 Hydroamination of Alkynes In Synthesis

In a related more indirect approach, an olefin is subjected to hydroboration and then treatment with an aminating agent.[19] In the adduct **7** formed between the borane and amine, the alkyl group, derived from the olefin, migrates to the nitrogen, and hydrolysis of this intermediate liberates the boronic acid and amine (Scheme 1.5).



Scheme 1.5 Hydroboration/Amination

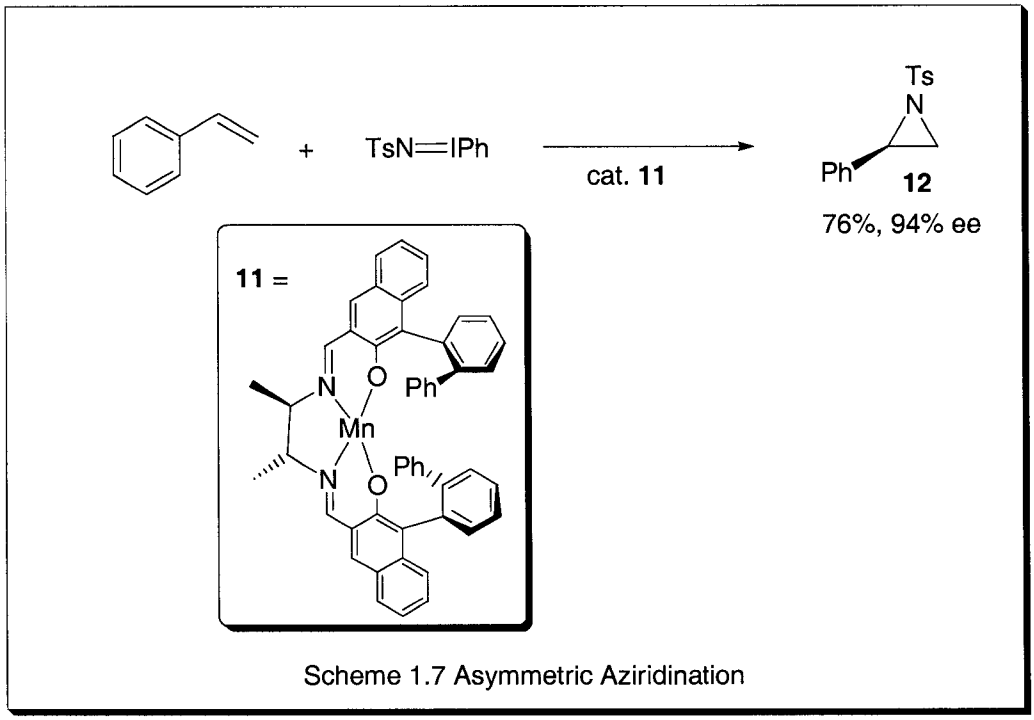
This reaction is reminiscent of a much older type of indirect amination where an alcohol (which could be derived from an olefin) is treated with sulfamoyl chloride **8** to produce the sulfamate ester **9** that rearranges when heated to give the zwitterion **10**, which when hydrolyzed gives the amine (Scheme 1.6).[20]



Scheme 1.6 Amines from Alcohols via Sulfamate Esters **8**

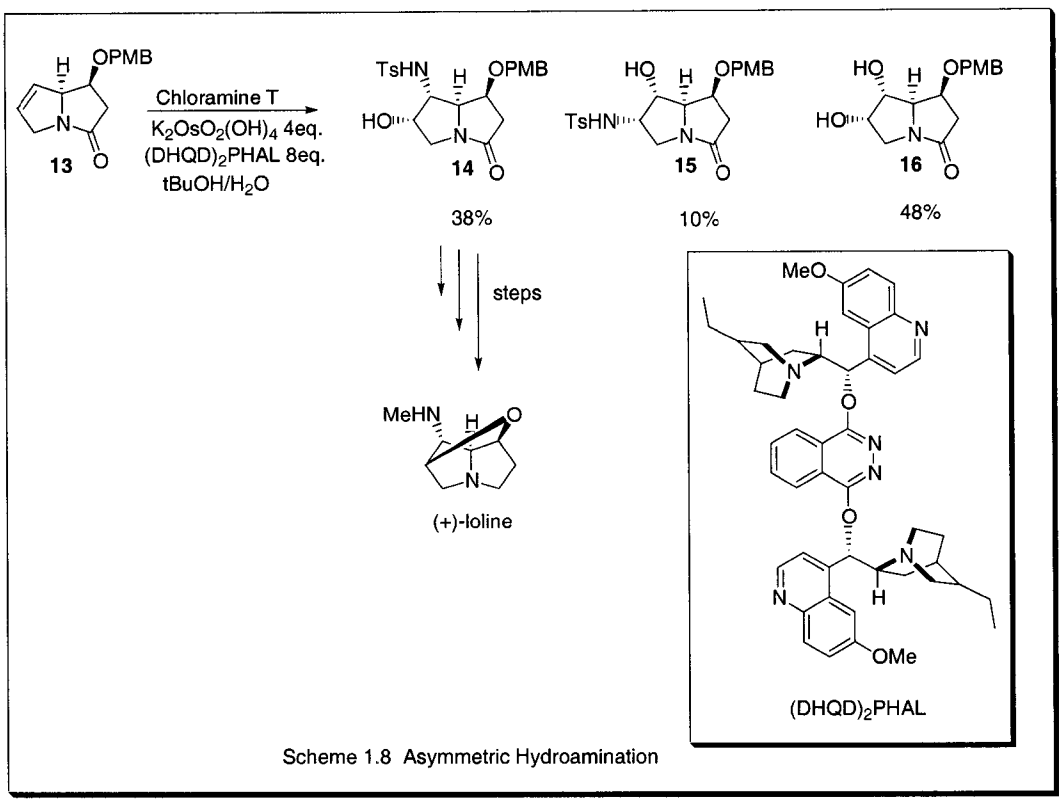
Many methods for the aziridination of alkenes have been developed,[15] and are thought to involve nitrenoid intermediates. Aziridines, important synthetic targets in themselves, are the nitrogen analogs of epoxides and can undergo further useful transformations.[21] Aziridine synthesis is a mature field and efficient asymmetric transformations have been developed. Most reactions of this type involve a nitrene precursor, tosyliminophenyliodinane for instance, and a transition metal catalyst, usually Cu, Rh, Mn, or Ru based. The metal bound nitrene can be transferred to the olefin in an asymmetric manner if an appropriate chiral ligand is employed. For example, the Mn salen complex **11** containing an extremely bulky Schiff-base ligand catalyzes the reaction

between tosyliminophenyliodinane and styrene to give the aziridine **12** in 94%ee (Scheme 1.7).[22]



Scheme 1.7 Asymmetric Aziridination

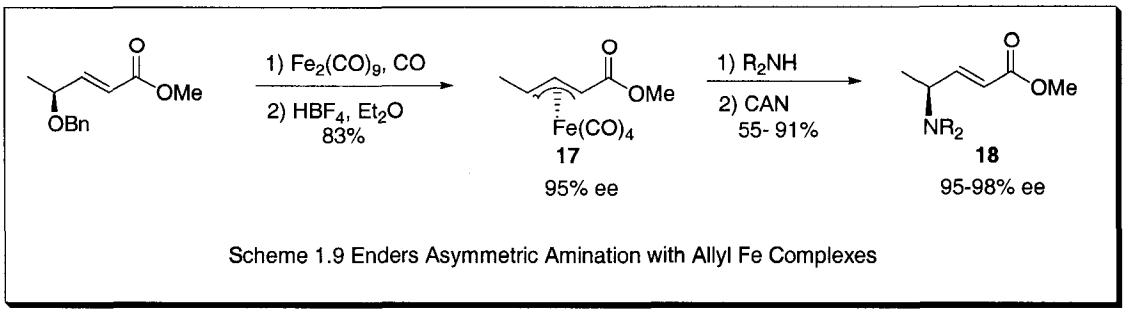
Aminohydroxylation employing osmium complexes has been used to prepare β-hydroxyamines from olefins.[16] The reaction is very similar to the Os-catalyzed dihydroxylation, also developed by Sharpless, and dihydroxylation is often a competing pathway. Like dihydroxylation the reaction always proceeds in a cis manner, with both the amino and hydroxyl groups added to the same face of the olefin. White has recently used this reaction in the asymmetric synthesis of the pyrrolizidine alkaloid (+)-loline.[23] Treatment of the olefin **13** with Chloramine T, Os complex (4eq.!), and a bulky cinchona alkaloid derived ligand (8 eq.!) gave the desired pyrolizidinone **14** along with the other regioisomer **15** and the dihydroxylation product **16** (Scheme 1.8).



Scheme 1.8 Asymmetric Hydroamination

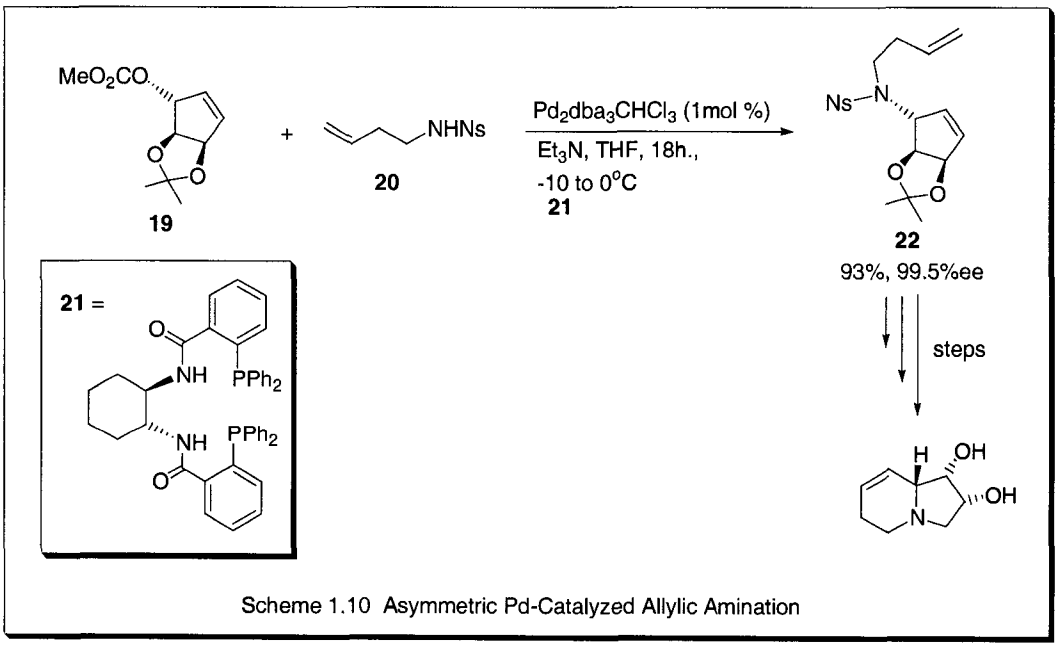
1.1.2.1: ALLYLIC AMINATION

Allylic amination is the synthesis of amines from olefins without destruction of the unsaturation, and is possibly the most attractive type of amination reaction.[17] Alkenes functionalized in the allylic position (halides, acetates, etc.) can, of course, be aminated by substitution. Conventional methods, direct alkylation or Gabriel and related procedures, give poor regioselectivity and no stereoselectivity. The ability of transition metals to form π-allyl complexes has been exploited to form allyl amines and some promising asymmetric reactions have been developed.[24] Enders has reported that cationic iron complexes **17** undergo amination with amine nucleophiles to give allyl amines **18** with excellent ee's (Scheme 1.9).[25]



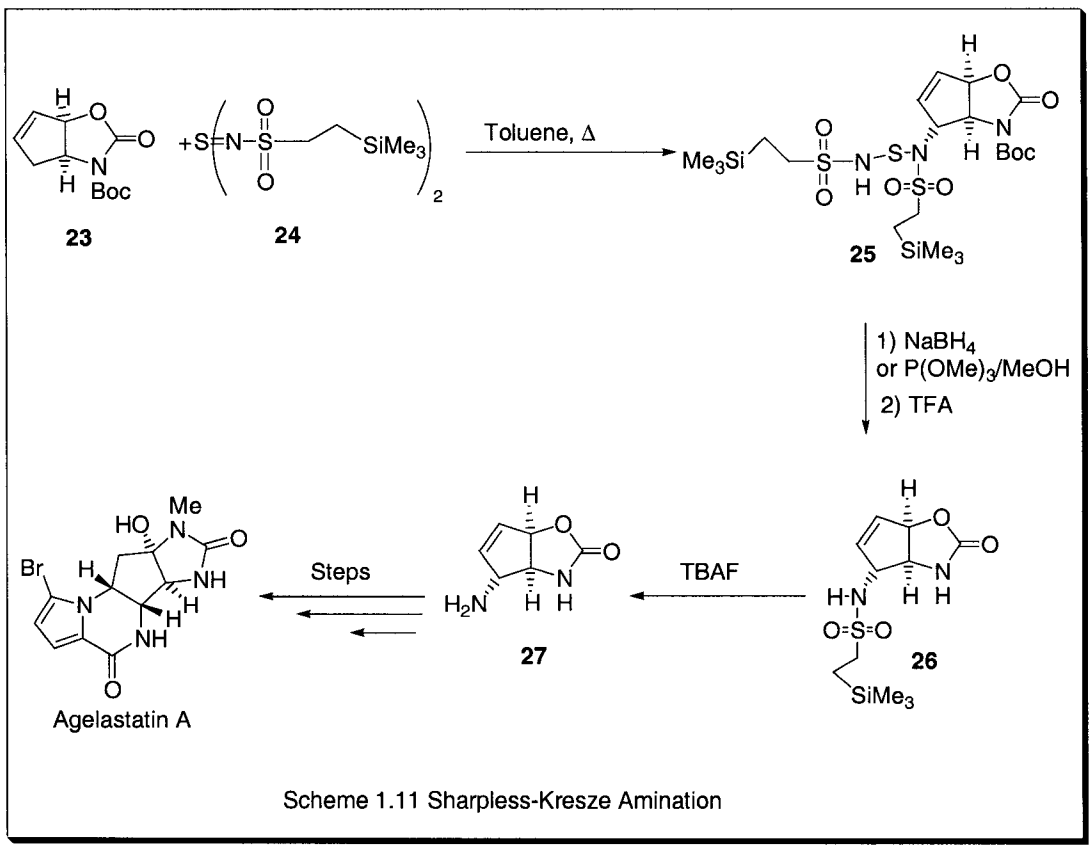
Scheme 1.9 Enders Asymmetric Amination with Allyl Fe Complexes

The Pd catalyzed amination of allyl species has also been shown to provide chiral, non-racemic allyl amines using appropriate chiral ligands. Even though the least substituted carbon of the complex is preferentially attacked, limited regioselectivity is observed at times. Blechert has used this strategy in the preparation of indolizidines, where the allyl carbonate **19** is treated with the protected amine **20**, $Pd_2dba_3{\cdot}CHCl_3$, and the bulky chiral phosphine **21**, to give the allyl amine **22** in excellent ee (Scheme 1.10).[26] Allyl amines have also been prepared by the Mitsunobu reaction,[27] the rearrangement of aziridines,[28] and the reduction of α,β-unsaturated imines,[29] hydrazones,[30] and oximes.[31]



Scheme 1.10 Asymmetric Pd-Catalyzed Allylic Amination

The direct allylic amination of unfunctionalized olefins is a somewhat rarer reaction and has the potential to be a useful industrial process. The reaction has been performed by the addition of chalcogeno-imides (X = S, Se) to alkenes, which has been called the Sharpless-Krezse amination.[32] The imide undergoes an initial ene reaction with the olefin and a subsequent [2,3]-sigmatropic rearrangement to give allyl amine. Weinreb has recently employed this kind of reaction in the synthesis of Agelastatin A (Scheme 1.11).[33]

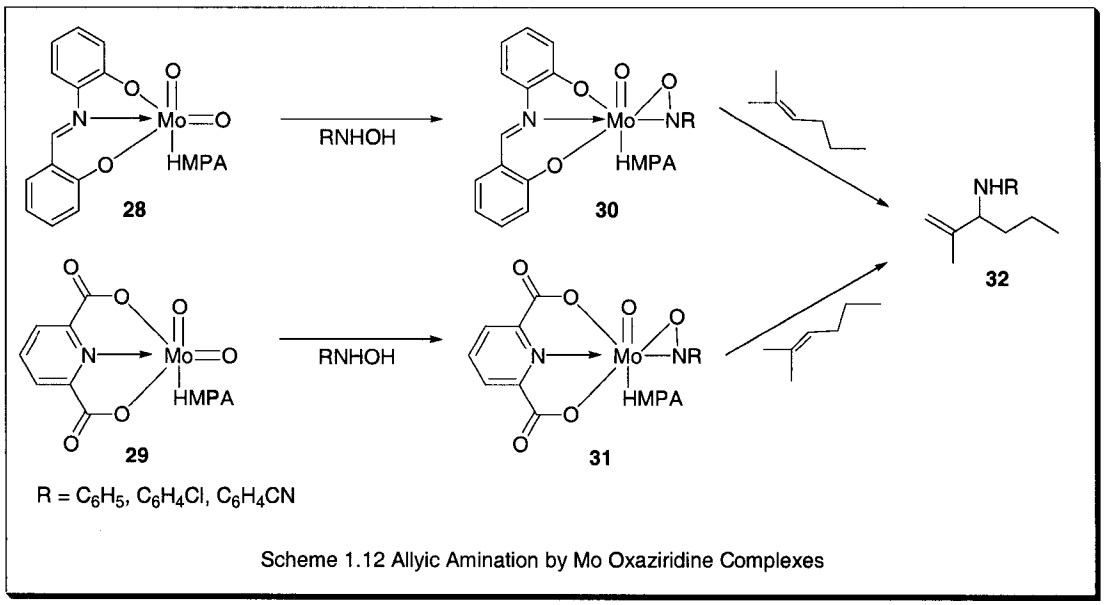


Scheme 1.11 Sharpless-Kresze Amination

The cyclic carbamate **23** was treated with the imide **24** to give the allyl amine **25,** that was deprotected to **26** and finally **27**. This sequence illustrates several drawbacks of this methodology. The reagent **24** is custom made, because of the failure of more traditional

reagents (TsN=S=NTs) to undergo deprotection after the amination. Additionally, reactions where Se imides are used are unsuitable for the synthesis of compounds meant for human consumption, due to the high toxicity of Se and Se-compounds, and even trace amounts are prohibited.

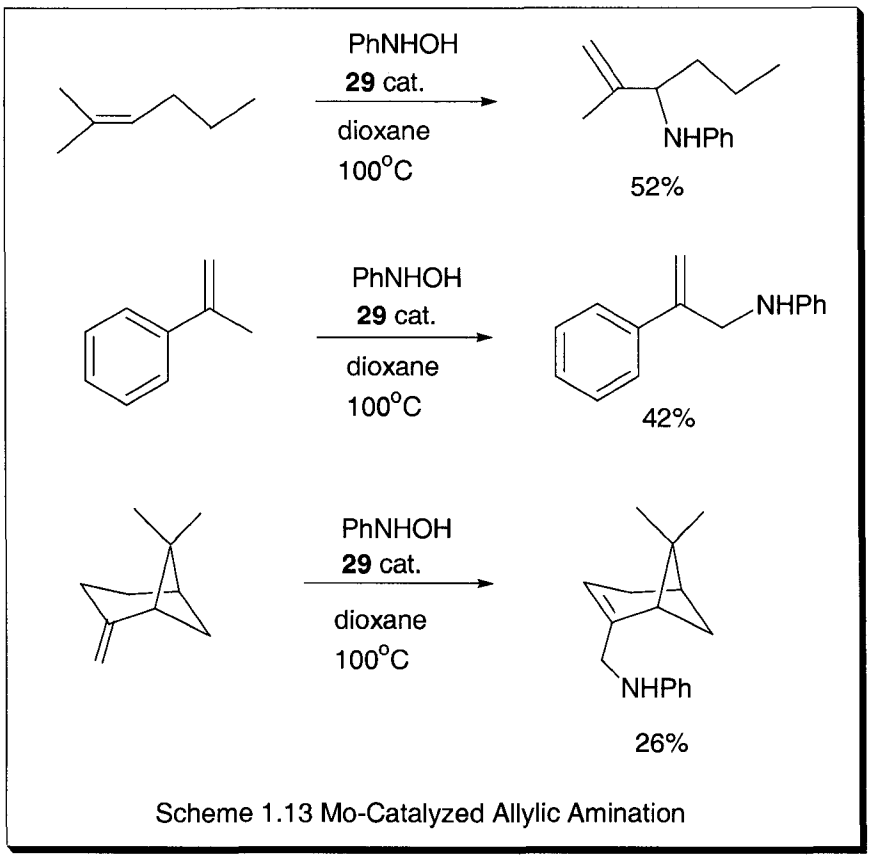
Transition metal complexes have been known to promote the allylic amination of unfunctionalized olefins. The first (stoichiometric) examples of transition metal complexes that aminate olefins were reported by Sharpless et. al.[34] These workers treated the dioxomolybdenum complexes **28** and **29** with N-aryl hydroxylamines to prepare the oxaziridine complexes **30** and **31** (Scheme 1.12).



Scheme 1.12 Allyic Amination by Mo Oxaziridine Complexes

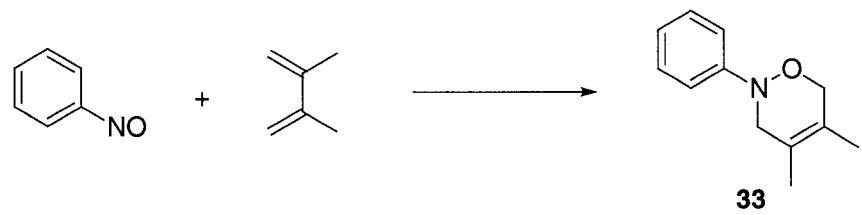
Complexes **30** and **31** reacted with olefins to give allylamine **32** with good regioselectivity, in which the N-R_2 groups is attached to the least substituted carbon that was the olefin and the double bond is transposed. This selectivity resembles that found in ene-reactions of nitroso compounds with alkenes. Nicholas et. al. were able to develop a

catalytic process based on these complexes and synthesized several allylamines (Scheme 1.13).[35]



Scheme 1.13 Mo-Catalyzed Allylic Amination

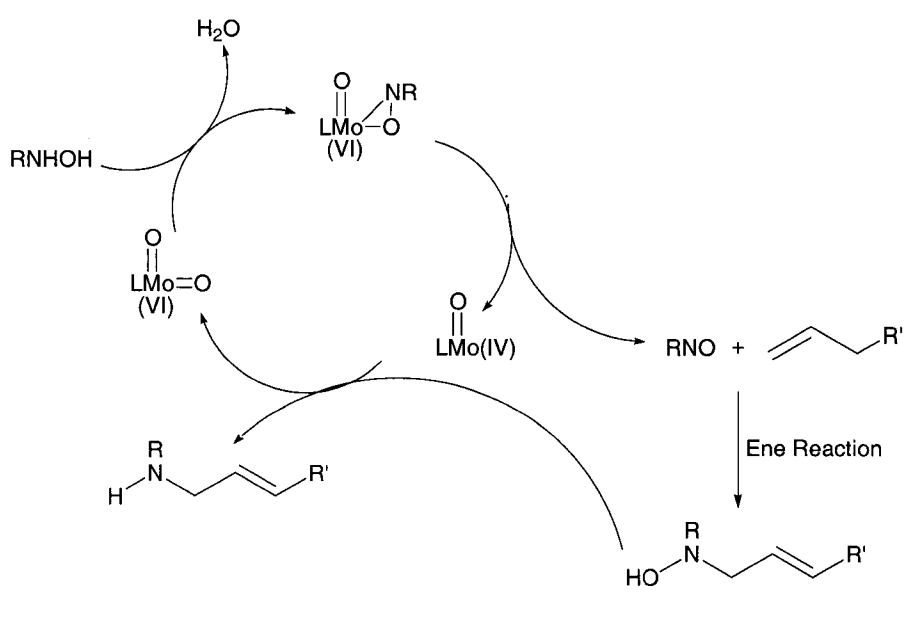
Thus N-phenyl-hydroxylamine and olefin when heated with catalytic amounts of the complex **29** gave allyl amine with high regioselectivity. However these reactions were not very efficient and substantial amounts of side products (aniline and azoxybenzene) were usually formed. Additionally, these reactions were shown to involve free nitrosobenzene, which was established by its trapping with 2,3-dimethylbutadiene. Nitrosobenzene is known to undergo a facile hetero Diels-Alder reaction with 2,3-dimethylbutadiene to give the oxazine **33** (Scheme 1.14).[36]



33

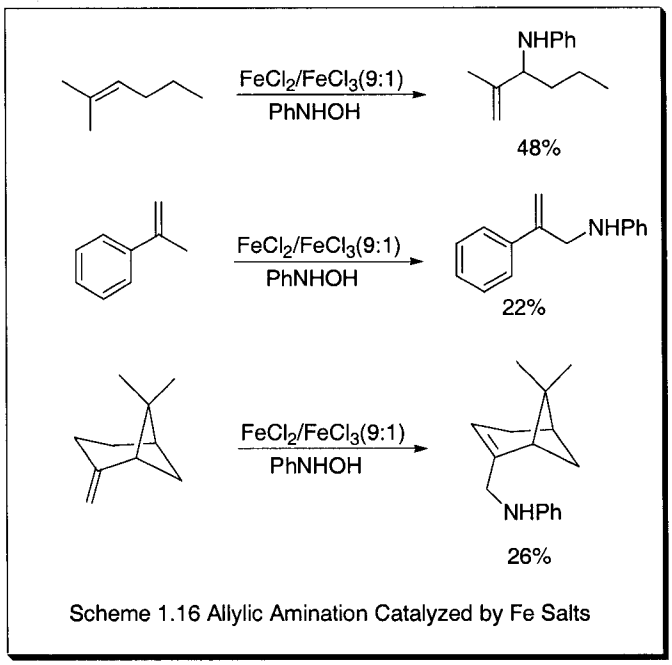
Scheme 1.14 Hetero Diels-Alder Reaction of Nitrosobenzene with 2,3-Dimethylbutadiene

This suggested that the catalytic reaction involved the generation of free nitrosobenzene (formed by oxidation of the hydroxylamine by the Mo(VI) complex) and its ene reaction with olefin to give the allylic hydroxylamine. Nicholas et. al. showed that this allyl hydroxylamine was reduced by the Mo(IV) complex to give the allyl amine and the Mo(VI) complex to complete the catalytic cycle (Scheme 1.15).[37] Other similar catalytic systems based on Fe porphyrins have also been shown to involve free nitrosobenzene.[38]



Scheme 1.15 Proposed Catalytic Cycle for Mo-Catalyzed Allylic Amination

Nicholas and Srivastava also discovered a remarkable series of amination reactions that most probably do not involve free nitrosobenzene. They found that phenylhydroxylamine would aminate olefins in the presence of $FeCl_2$ and $FeCl_3$ to produce allyl amines, again with ene-like regioselectivity (Scheme 1.16).[39]



Scheme 1.16 Allylic Amination Catalyzed by Fe Salts

The trapping experiment with 2,3 dimethylbutadiene failed to produce the hetero Diels-Alder adduct and gave only allylamine. The yields for this transformation varied widely depending on the structure of the starting olefin. During the course of this investigation, the first example of an azodioxide Fe complex was discovered and found to be an active aminating agent (Figure 1.1).[40] This complex was shown to be an active catalyst for the reaction and is likely a catalytic intermediate.[41] Similar reactions with Cu salts have also been reported.[42]

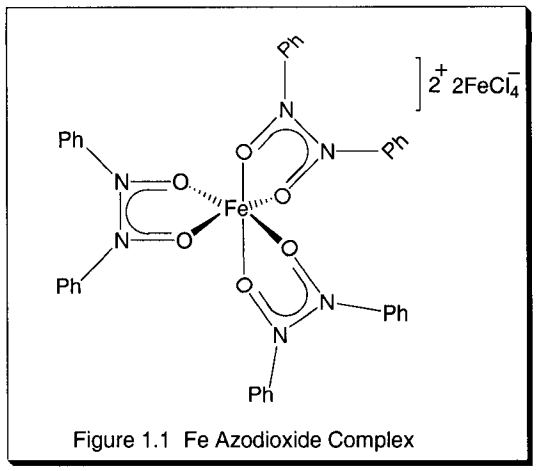
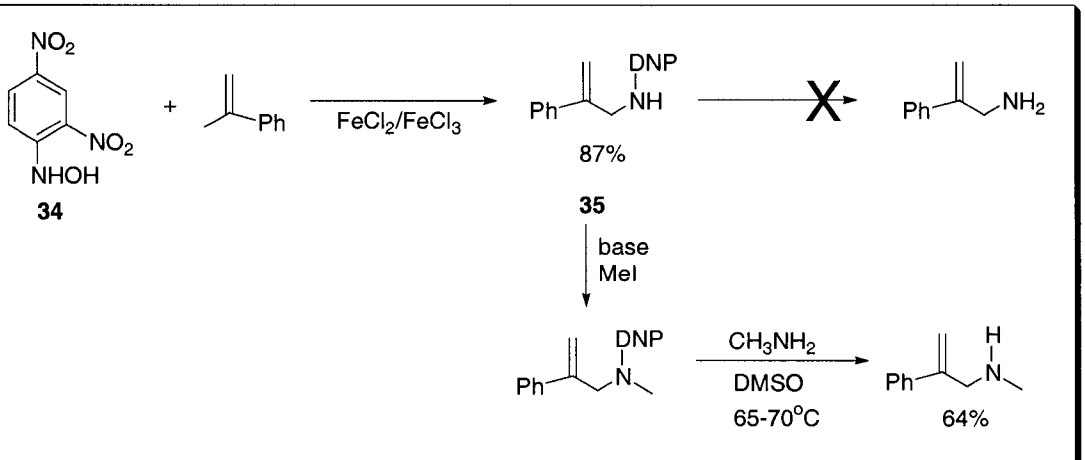


Figure 1.1 Fe Azodioxide Complex

Some improvements of the aminating agent in the iron salt-promoted reactions were made. It was found that 2,4 dinitrophenyl hydroxylamine **34** was a somewhat more effective aminating agent, giving the allyl amine **35** in 87 % yield (Scheme 1.17).[43] The usefulness of this reaction hinged upon the ability of the DNP (dinitrophenyl) protected amine to undergo deprotection, which failed to occur. However, the DNP-protected allyl amine could be alkylated and then deprotected by methyl amine, providing a route to secondary allyl amines.[44]



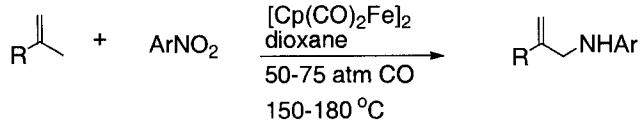
Scheme 1.17 Allylic Amination with 2,4 Dinitrophenyl Hydroxylamine

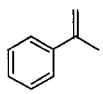
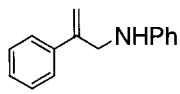
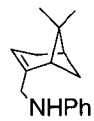
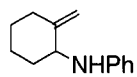
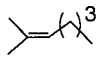
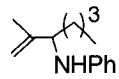
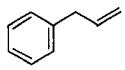
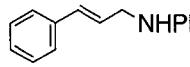
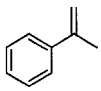
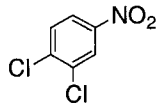
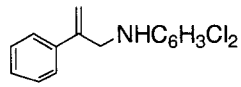
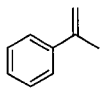
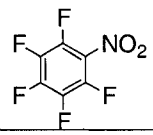
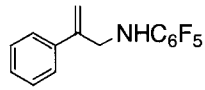
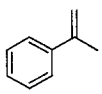
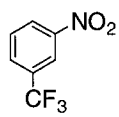
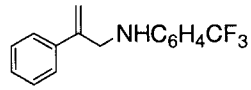
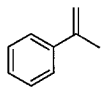
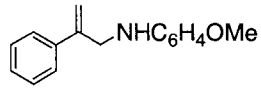
While the reactions of phenylhydroxylamine with olefins catalyzed by Fe salts are remarkable, yields vary widely. Moreover, the utility of this transformation is limited by the poor availability of hydroxylamines. An ideal starting material for allylic amination would be the aromatic nitro compounds or anilines, which are much more readily available, many commercially. Though the redox chemistry of nitrogen is extremely complex, Srivastava and Nicholas were undeterred and began investigating reactions of nitrobenzene with olefins, and discovered the allylic amination of olefins with nitrobenzenes catalyzed by the cyclopentadienyl dicarbonyl iron (II) dimer $[Cp(CO)_2Fe]_2$ under carbon monoxide pressure.[45] Thus, a series of olefins underwent allylic amination again with high ene-like regioselectivity (Table 1.1).

The intermediacy of free nitrosobenzene was also ruled out in the $[Cp(CO)_2Fe]_2$ catalyzed reactions based on the absence of oxazine **33** in reactions where 2,3-dimethylbutadiene was present. While free nitrosobenzene was ruled out, nitrenes were still a possibility, thus a probe for the intermediacy of nitrenes was needed to establish or exclude free nitrene.

Free phenyl nitrene has been observed, upon photolysis of phenylazides, by both UV-vis and IR spectroscopy.[46,47] Phenyl nitrene can also be generated thermally from azide decomposition.[48] Reactions of free nitrene include: addition to olefins to form aziridines, ring expansion, hydrogen abstraction, and insertion into single bonds and lone pairs.[49] The deoxygenation of aromatic nitro compounds by tervalent phosphorus reagents also produces products resulting from C-H insertion, ring expansion, insertion into lone pairs, and hydrogen abstraction.[50]

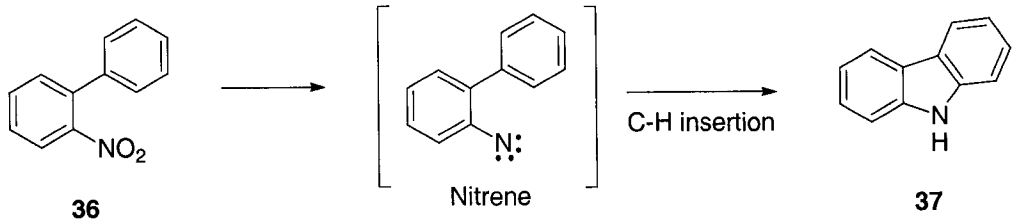
Table 1.1 Amination of Olefins with Nitrobenzenes



Entry	Alkene	Nitroarene	Allyl amine	Yield(%)
1		$PhNO_2$		92[a]
2		$PhNO_2$		64[a]
3		$PhNO_2$		27[a]
4		$PhNO_2$		10[a]
5		$PhNO_2$		13[a]
6				54
7				57
8				52
9				2

a GC Yield

While the phosphorus promoted reactions have not been shown unequivocally to involve free nitrene, the analogous chemical behavior suggests a nitrenoid intermediate.[51] The deoxygenation of 2-nitrobiphenyl **36** with tervalent phosphorous reagents gives carbazole **37** (Scheme 1.18),[50] and when 2-azidobiphenyl is heated or photolyzed carbazole **37** is also produced.[52]



36 Nitrene **37**

Scheme 1.18 Carbazole Production from 2-Nitrobiphenyl, a Probe for Nitrenes

This has been devised as a probe for the intermediacy of free nitrene when nitro groups are deoxygenated. Nicholas et. al. have shown that the $[Cp(CO)_2Fe]_2$/CO reductive system does not produce carbazole **37** from **36**, thus excluding the intermediacy of free nitrene.

Koleel-Veetil and Nicholas discovered that the pentamethylcyclopentadienyl dicarbonyl iron (II) dimer, $[Cp^*(CO)_2Fe]_2$, was a more efficient catalyst for these reactions with higher yields in some cases, but showing a strong substrate dependence.[53] After careful chromatography they also isolated an undetermined amount of the cyclic carbamoyl Fe complex and established its structure by X-ray diffraction (Figure 1.2).

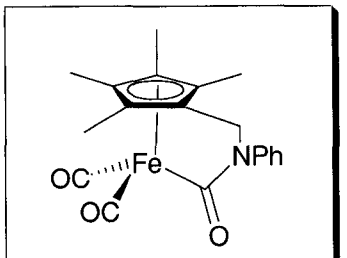
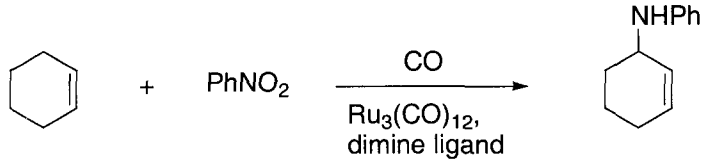


Figure 1.2 An Fe Carbomyl Complex

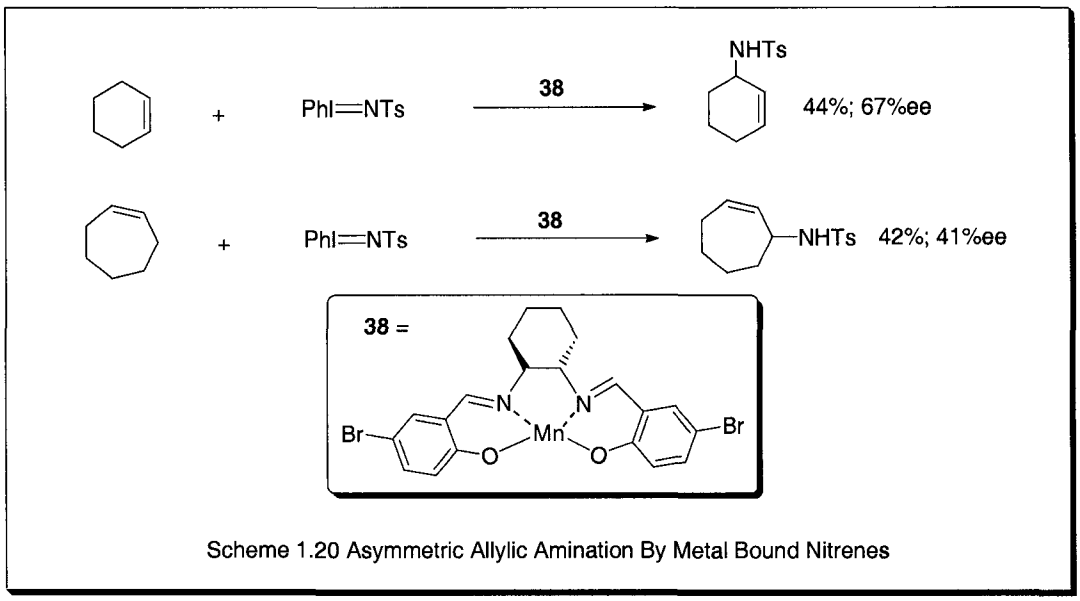
While it is not clear how the complex is formed, a mechanism might involve the intermediacy of a metal nitrene complex that inserts into a C-H bond of the Cp* ligand followed by attack on coordinated CO. This complex was found to be catalytically active, but less so than the $[Cp^*(CO)_2Fe]_2$. They deemed this complex a resting state for the active catalyst, and it was shown through labeling experiments that the NPh group was not transferred from the complex to the olefin. Srivastava and Nicholas also disclosed a photo-assisted reaction with the same catalytic system under more moderate CO pressure (T=100 °C, P = 6 atm).[54]

Cenini and co-workers, who had been working in the area of reductive carbonylation of nitro compounds for many years, discovered a similar reaction using $Ru_3(CO)_{12}$ in the amination of cyclohexene with nitrobenzene (Scheme 1.19).[55]



Scheme 1.19 Cenini's Allylic Amination of Cyclohexene

This reaction bears a striking similarity to reactions found on attempted aziridination of cyclic alkenes. In these reactions cyclohexene and cylcoheptene both gave allyl amines in moderate ee when treated with tosyliminophenyliodinane in the presence of the chiral Mn catalyst **38** (Scheme 1.20).[56] It is worth noting that Cenini's $Ru_3(CO)_{12}$ system produced some carbazole **37** from 2-nitrobiphenyl **36**, in addition to 2-aminobiphenyl, suggesting that some of the intermediates possess nitrene character. Further evidence for nitrenes in these reactions comes from the reaction phenyl azide with cyclohexene and TFA to give the same allylamine.[57]



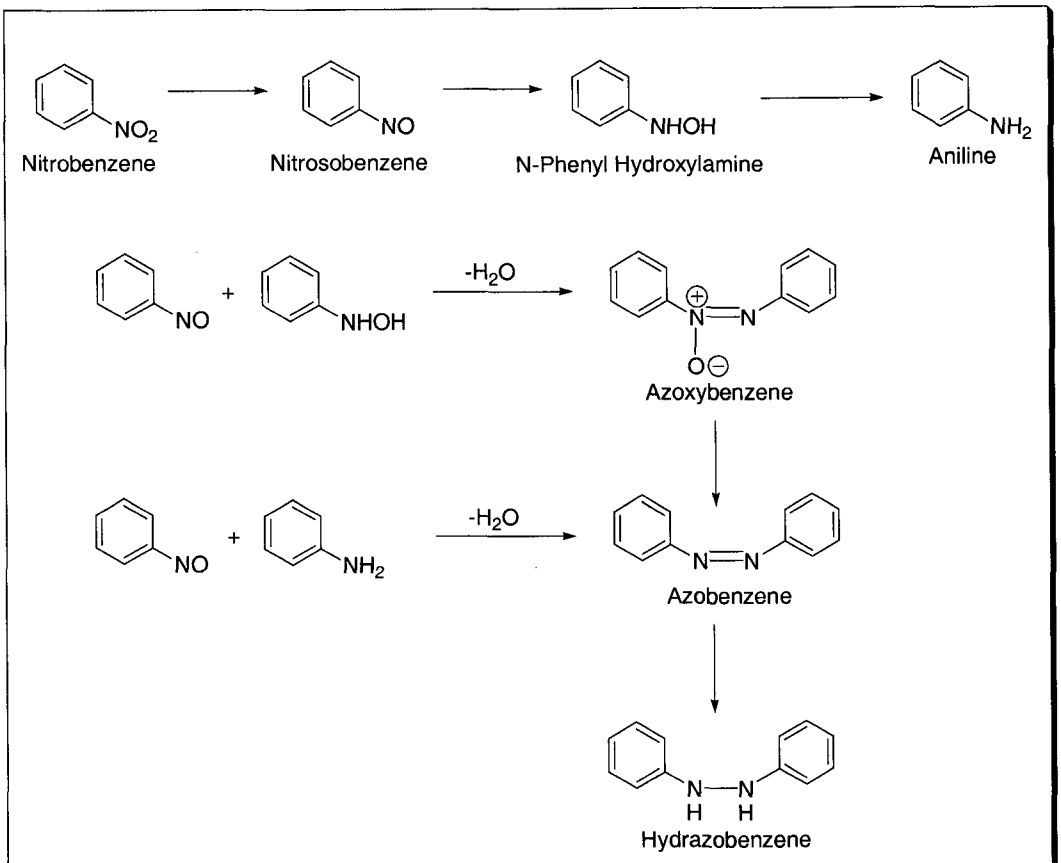
Scheme 1.20 Asymmetric Allylic Amination By Metal Bound Nitrenes

1.3: THE REDUCTION OF AROMATIC NITRO GROUPS IN ORGANIC CHEMISTRY

1.3.1: CLASSICAL METHODS

The reactions discovered by the Nicholas and Cenini groups are reductions of the aromatic nitro group, a fundamental organic transformation.[58] Many methods are available for the reduction of aromatic nitro compounds to the corresponding anilines and a few of note include: H_2/Ni,[59] H_2-Pd/C,[60] Fe/AcOH,[61] Zn/NaOH,[62] Fe/HCl,[63] Sn/HCl,[64] N_2H_4-Pd/C,[65] and sulfides/polysulfides.[66] During these reactions the nitro group likely proceeds to the nitroso, hydroxylamino, and amino oxidation states and these various reduced species often combine with one another to form azo- and azoxy-benzenes, which may also be reduced (Scheme 1.21).

It is difficult to stop the reduction at intermediate stages and nitroso compounds are rarely prepared in good yield by the reduction of nitro groups.[67] However, the hydroxylamines can often be obtained selectively. Several reductants are available for the preparation of arylhydroxylamines: Zn/NH_4Cl,[68] KBH_4/$BiCl_3$,[69] M/N_2H_4 (M = Ni, Pd),[70] and Yb.[71] These reactions are highly substrate specific and can give mixtures of products in some cases. Additionally, many reagents that will reduce nitro groups are not very chemoselective and the reactions proceed under harsh conditions (acidic/basic).

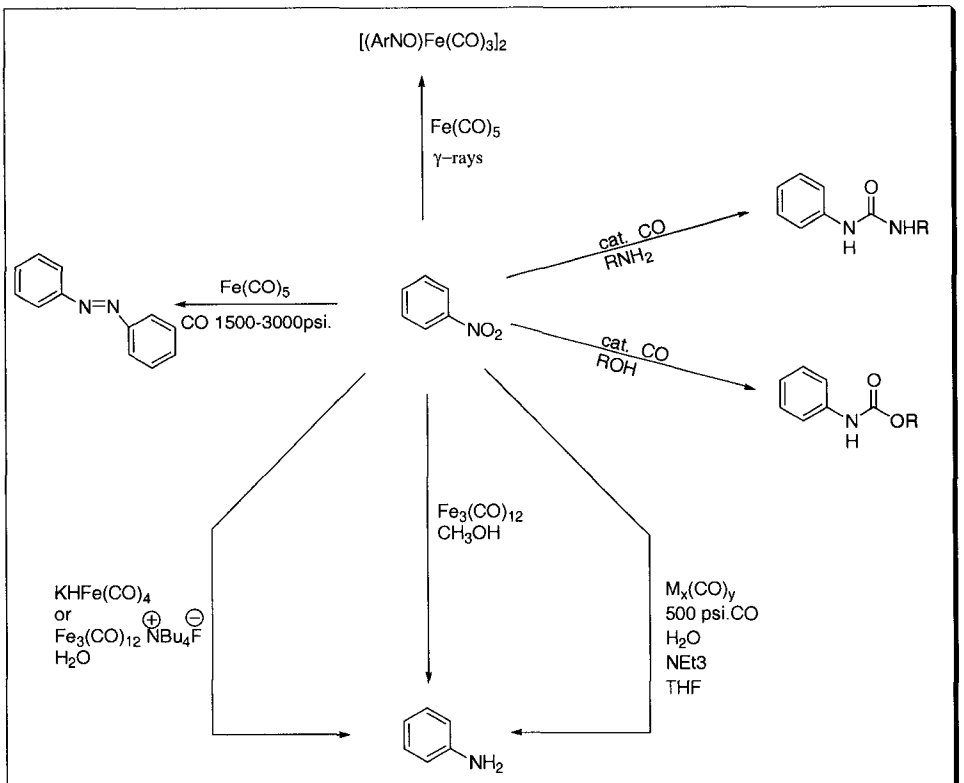


Scheme 1.21 Intermediates in the Reduction of Aromatic Nitro Compounds

1.3.2: REDUCTIVE CARBONYLATION

The behavior of metal carbonyl complexes toward aromatic nitro groups has been investigated for many years. Direct reaction of $Fe(CO)_5$ with nitrobenzene under γ-radiation has been reported to give a metal nitroso complex.[72] Metal carbonyls have also been shown to react with aromatic nitro compounds in a variety of media at various pressures to give anilines along with other reduced products (Scheme 1.22).[73] These reactions have been investigated for the preparation of ureas and carbamates industrially as an alternative to the use of phosgene. Under appropriate conditions isocyanates are

formed, and if the reaction is conducted in the presence of an amine or alcohol, the isocyanate is trapped and ureas and carbamates are formed, respectively.[74]



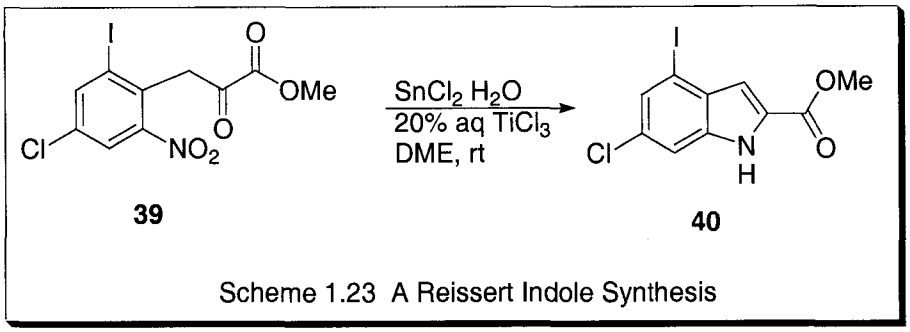
Scheme 1.22 Selected Reactions of Aromatic Nitro Groups with Metal Carbonyls

After the discovery of the aforementioned carbamate and urea syntheses it was soon realized that these reactions might provide species that could transfer the aromatic nitrogen unit to other functional groups like olefins, as Cenini and Nicholas have demonstrated. These reactions, where CO and metal complexes are used to reduce nitro compounds, have been referred to as reductive carbonylations.[60] Carbon monoxide is the stoichiometric reductant and is converted to CO_2. There is a large thermodynamic driving force for the conversion of CO to CO_2.

1.3.3: REDUCTION OF AROMATIC NITRO GROUPS IN THE SYNTHESIS OF NITROGEN HETEROCYLES

Recently, many researchers have been examining these catalytic systems for the reduction of nitro groups in an intramolecular sense, by reducing the nitro group in the presence of a reactive pendant group in an effort to prepare nitrogen heterocycles. Classical syntheses of heterocyclic nitrogen ring systems can be found in most heterocyclic chemistry textbooks,[75] and usually involve a condensation between an aromatic amine and a carbonyl component with concomitant cyclization. While these reactions are quite useful, they often require extreme conditions (acid/base/high temperature), may suffer from poor substrate availability and frequently lack regioselectivity.

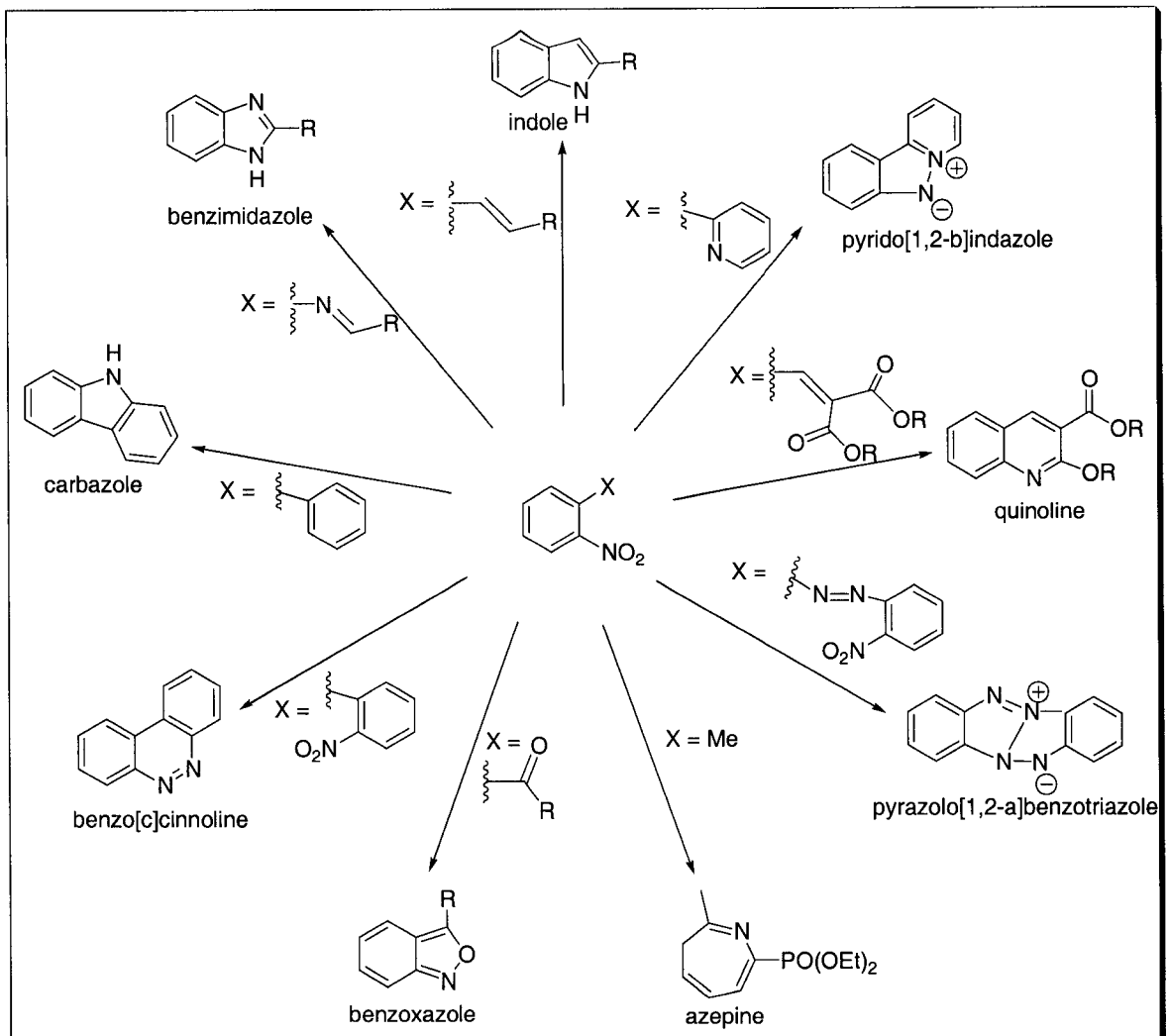
Aromatic nitro compounds are good starting materials for benzannelated nitrogen heterocycles, due to their commercial availability or ease of preparation. Early researchers used aromatic nitro groups in intramolecular reactions by doing essentially a direct reduction to the amino group and subsequent thermal cyclization (condensations). The Reissert[76] and Leimgruber-Batcho[77] indole syntheses are excellent examples of this type of reaction. Recently, for example, this type of reaction has been used in the reduction of the 2-nitroaryl pyruvate **39** with $SnCl_2/TiCl_3$ to give the indole **40** (Scheme 1.23).[78]



39 **40**

Scheme 1.23 A Reissert Indole Synthesis

After these early reactions employing classical reductants, attempts were made to deoxygenate the nitro groups and generate new reactive nitrogen species. Independently, Sundberg[79] and Cadogan[80] generated nitrenoid type intermediates (See above discussion) by the deoxygenations of aryl nitro compounds with phosphines and phosphites. These reactions have been used to synthesize a variety of heterocycles, including indoles, benzocinnolines, carbazole, and compounds resulting from apparent nitrene insertion into heteroatom lone pairs (Scheme 1.24). The conditions are somewhat extreme, usually requiring the nitro compounds to be refluxed in triethylphosphite, and frequently give low yields along with tar formation.

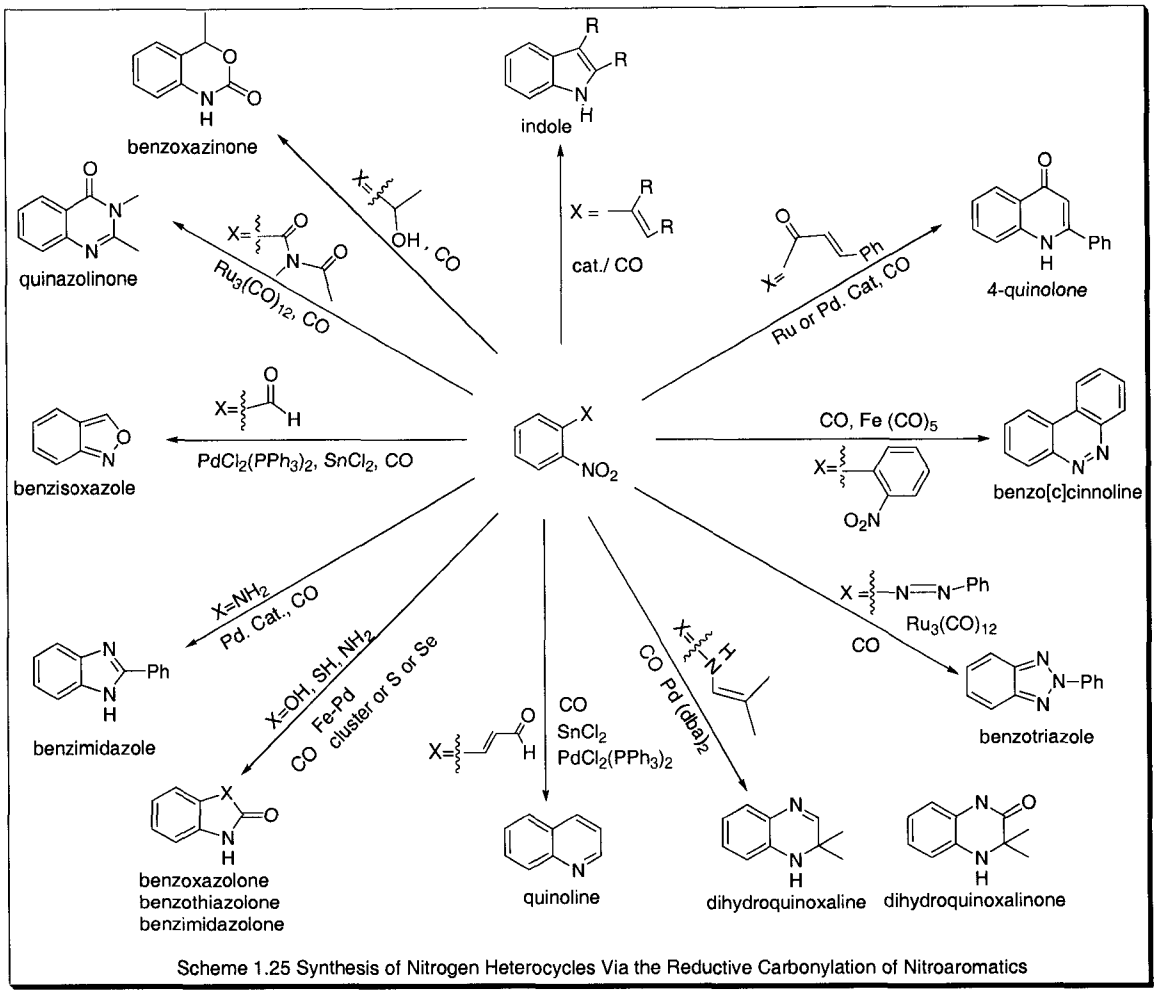


Scheme 1.24 Selected Heterocycles Synthesized by the Reductive Cyclization of Nitro Aromatics by Tervalent Phosphorous Reagents.

The reductive carbonylation of nitro groups has been used to produce active nitrogenating species for heterocyclic synthesis with catalytic amounts of complexes of Pd, Pt, Co, Mn, Rh, Se (metal), S, S/V (salts and oxides) and Group 8 transition metal carbonyl complexes.[73b, 81-110] These systems can sometimes be used at moderate CO pressures and temperatures, and usually provide a very selective reduction of the nitro group while leaving other functional groups unchanged. A variety of heterocycles have

been synthesized through these reactions including indoles,[85, 89, 93-95, 100-104, 107] benzocinnoline,[73b] benzimidazoles,[81, 82, 90, 93] 2-benzimidazolones,[84, 86, 90, 99, 108] benzotriazoles,[87] 2,1-benzisoxazoles,[95] 1,4-dihydro-3,1-benzoxazine-2-ones,[91] 2-benzoxazolinones,[83, 86, 105, 110] 2-benzothiazolones,[86] 1,2-dihydroquinoxalines,[106] 3,4-dihydroquinoxalinones,[106] 2H-indazoles,[88,95] pyrollines,[97] quinazolines,[96] 4-quinazolinones,[92] dihydroquinazolin-4-ones,[109] quinolines,[81, 95] and 4-quinolones[98, 101] (Scheme 1.25). Most of the catalytic systems studied have been shown to produce indoles. The aforementioned $Ru_3(CO)_{12}$ system of Cenini has been used with some success for the production of 4-quinolones.[98, 101] Watanabe has used $PdCl_2(PPh_3)_2$ with Lewis acids for the syntheses of 2-phenyl-indazoles, finding that $SnCl_2$ gives the best yields at only 4 atm of CO pressure. Söderberg has developed Pd systems with amine and phosphine additives that also can be used with low CO pressure (6 atm). The use of Se for reductive carbonylation, by Asian researchers,[86, 105, 108-110] requires relatively high CO pressure and is undesirable due to the high toxicity of Se.

Some of these reductive carbonylation reactions parallel the phosphine and phosphite chemistry as far as the overall transformation is concerned (indoles, benzocinnoline, benzimidazoles). However, many have very little precedent in organic chemistry, and products resulting from the incorporation of CO are sometimes isolated.



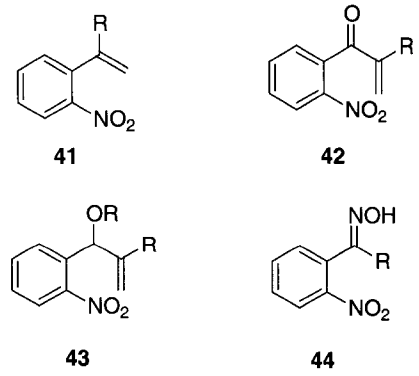
Scheme 1.25 Synthesis of Nitrogen Heterocycles Via the Reductive Carbonylation of Nitroaromatics

While these are very interesting and useful reactions the dearth of mechanistic details make them difficult to classify. Some systems provide evidence for the production of nitrenes or metal bound nitrene complexes. Workers in the field often invoke nitrene intermediates if any mechanistic comments are offered at all. The intermediacy of amines in reactions where the carbon in the C-N bond comes from a carbonyl has been supported by some mechanistic studies, making these reactions simple condensations, and the catalyst often functioning as only a nitro→amino reductant.[81, 95] In the cases where the C-N bond is formed between the nitro nitrogen and an olefin, the

active species has been shown primarily not to be free amine. The often extreme conditions, high pressure (usually above 20 atm) and temperature (typically well above 100 °C), make the elucidation of these mechanisms very difficult, and information gathered is often of an indirect nature. While in some instances organometallic species have been isolated, the relationship they have to the overall transformation is usually unclear. [111]

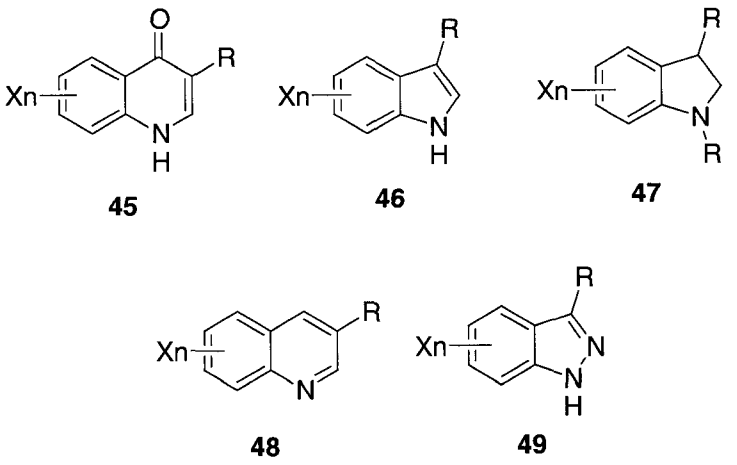
1.4: PROJECT OBJECTIVES

Given the exceptional *intermolecular* allylic amination reactions of aromatic nitro groups catalyzed by $[Cp(CO)_2Fe]_2$ and $[Cp^*(CO)_2Fe]_2$ and the syntheses of nitrogen heterocycles through the reductive cyclizations of nitro aromatics, the investigation of this system in *intramolecular* reactions was justified. We have targeted heterocycles that play important roles in medicine. Substrates were chosen initially that bore pendant unsaturation most similar to that used in the original intermolecular allylic amination, specifically the structures **41** and **42** (Scheme 1.26).



Scheme 1.26 Substrates Selected for Reductive Cyclization

A limiting factor in the potential utility of these kinds of reactions is the availability or ease of preparation of the substrate for cyclization. For this reason we turned our attention to the easily prepared Baylis-Hillman adducts **43**, and finally to *o*-nitro-ketoximes **44**. Using these substrates new synthesis of 4-quinolones **45**, indoles **46**, indolines **47**, quinolines **48**, and indazoles **49** were discovered (Scheme 1.26). In some cases mild conditions (low CO pressure) were discovered and useful high yielding syntheses of these compounds were developed.



Scheme 1.27 Heterocycles Synthesized through Reductive Cyclization of Nitroaromatics Catalyzed by Cp-M Carbonyls

CHAPTER 2

SYNTHESIS AND REDUCTIVE CYCLIZATION OF MODEL COMPOUNDS: TOWARDS THE SYNTHESIS OF 6-MEMBERED NITROGEN HETEROCYCLES

2.1: INTRODUCTION AND BACKGROUND

In order to investigate the potential of the group 8 metal carbonyl dimers as catalysts in reductive cyclizations of nitro aromatics the 4-quinolones were chosen as initial targets. Compounds possessing the 4-quinolone ring system are some of the best anti-bacterial agents in existence,[112] and a large number are available clinically (Figure 2.1).[113] While there are a few naturally occurring 4-quinolones,[114] most are entirely synthetic compounds, and due to emerging strains of drug resistant bacteria, new 4-quinolones are in high demand. According to one review over 10,000 derivatives of 4-quinolones have been reported in the literature.[115]

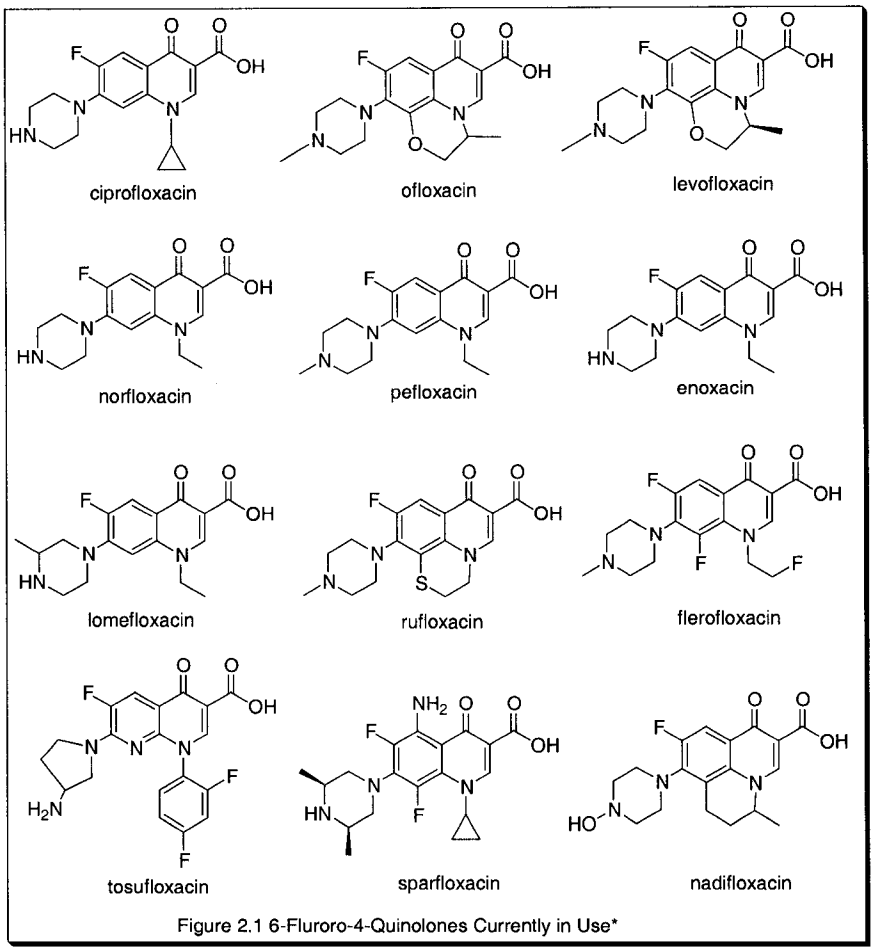


Figure 2.1 6-Fluroro-4-Quinolones Currently in Use*

*Adapted From Reference 113

2.1.1: CLASSICAL 4-QUINOLONE SYNTHESES

Classical syntheses of the 4-quinolone ring system usually involve a condensation to form the C_{4a}-C_4 bond (Figure 2.2).

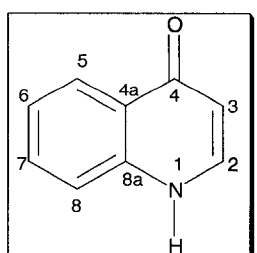
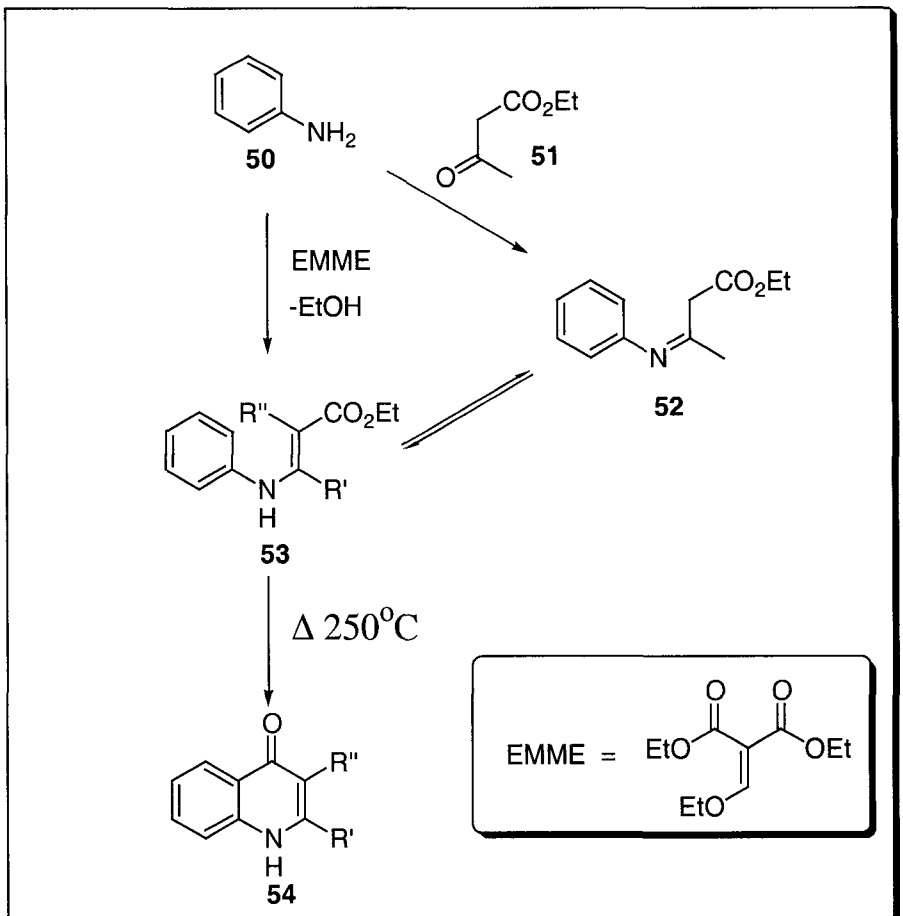


Figure 2.2 Numbering of the 4-Quinolone Ring System

The two most well known and widely used classical methods that can be found in most heterocyclic chemistry textbooks[75] are the Conrad-Limpach[116] and Gould-Jacobs[117] reactions (Scheme 2.1). In the Conrad-Limpach reaction an aromatic amine **50** is condensed with ethyl acetoacetate **51** to give the imine **52**, which is a tautomer of the aminoacrylate **53** (R'=Me; R"=H).



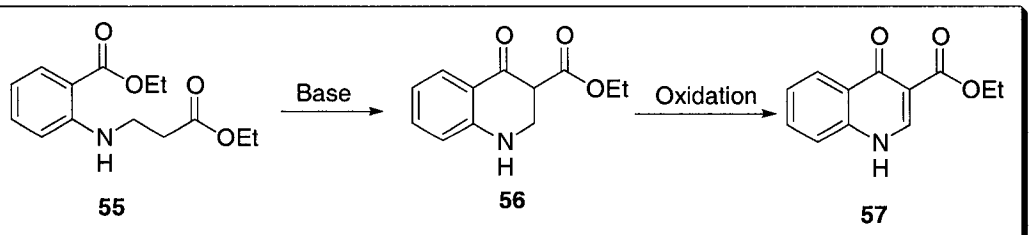
Scheme 2.1 Classical Quinolone Syntheses
Conrad-Limpach - R" = H; R' = Me
Gould-Jacobs - R" = CO_2Et; R' = H

The aminoacrylate/imine **52/53** can be heated in mineral oil, or more generally Dowtherm A, at 250 °C to give the quinolone **54** (R'=Me; R"=H). The Gould-Jacobs

reaction, which is essentially the same reaction, forms the aminoacrylate **53** from the reaction of **50** with ethoxymethylenemalonic ester (EMME). There are a variety of ways to obtain compounds of the general type **53**, and comprehensive reviews are available on the subject.[118] One drawback of these reactions is that 3-substituted anilines often give both 5 and 7 substituted quinolones. In addition to the poor regioselectivity, tar formation and production of diphenyl ureas can complicate product mixtures.[118a] At a recent meeting of the American Chemical Society, a medicinal chemistry researcher reported that scale-up of a Gould-Jacobs reaction with an aromatic amine possessing a nitro group caused a violent explosion.[119]

2.1.2: MODERN METHODS IN 4-QUINOLONE SYNTHESIS

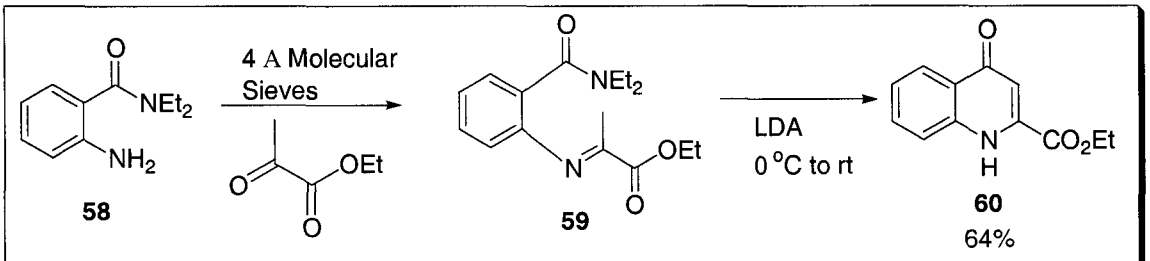
Several other strategies that avoid production of regioisomers are of some import and worth discussing. Dieckmann cyclizations in which an aryl ester **55** containing the appropriate *o*-amino alkyl ester side chain is subjected to basic conditions have been reported (Scheme 2.2).[120]



55 **56** **57**

Scheme 2.2 Dieckmann Cyclization Strategy for 4-Quinolones

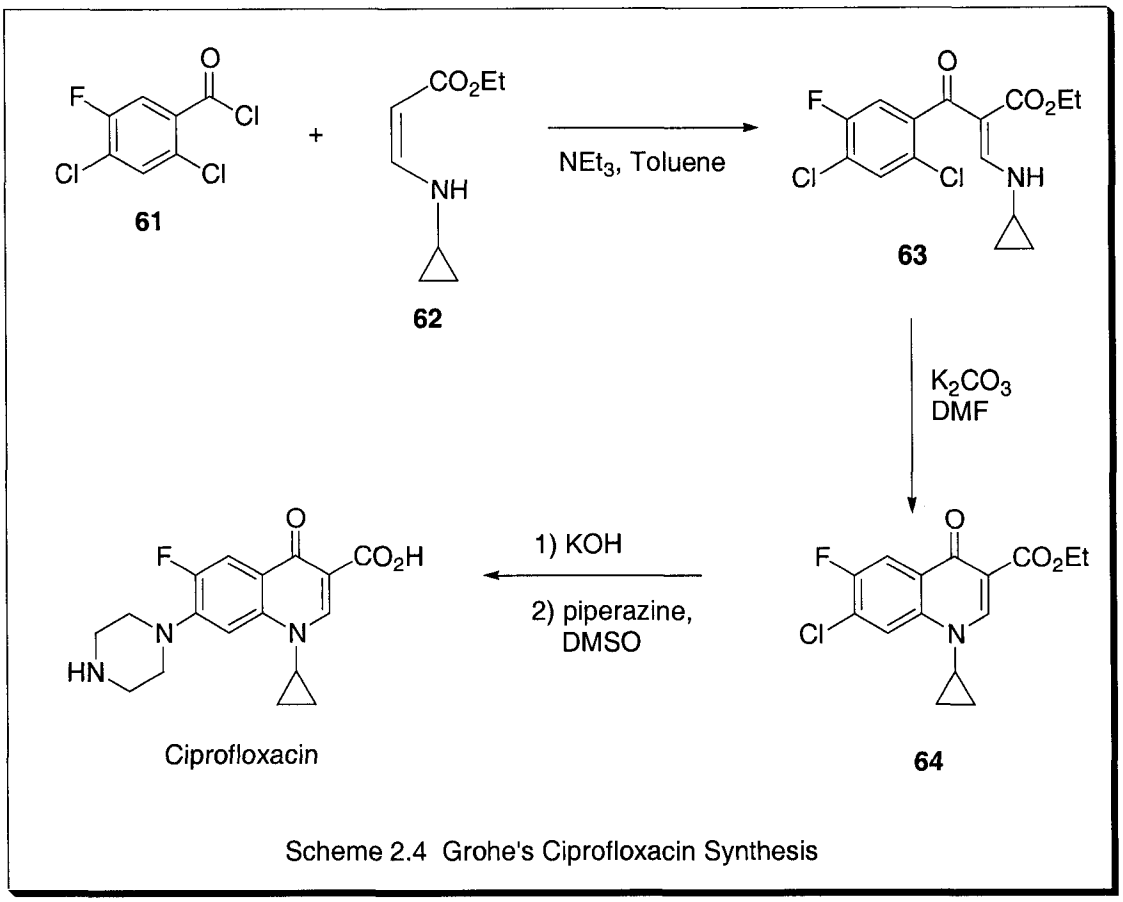
Oxidation of the dihydroquinolone **56** can afford the 4-quinolone **57**.[121] Another method relies on the addition of *o*-aminoarylcarboxylates to acetylenedicarboxylates to form aminoacrylates similar to the intermediate **53** in the Gould-Jacobs and Conrad-Limpach reactions, which can be cyclized under strongly basic conditions.[122] Snieckus has reported a modified von Niementowski reaction that gives 4-quinolones from anthranilamides.[123] In this reaction the anthranilamide **58** is condensed with an α-ketoester to give the imine **59**. Treatment of the **59** with LDA gives the 4-quinolone **60** (Scheme 2.3).



Scheme 2.3 Sneickus's Route to 4-Quinolones

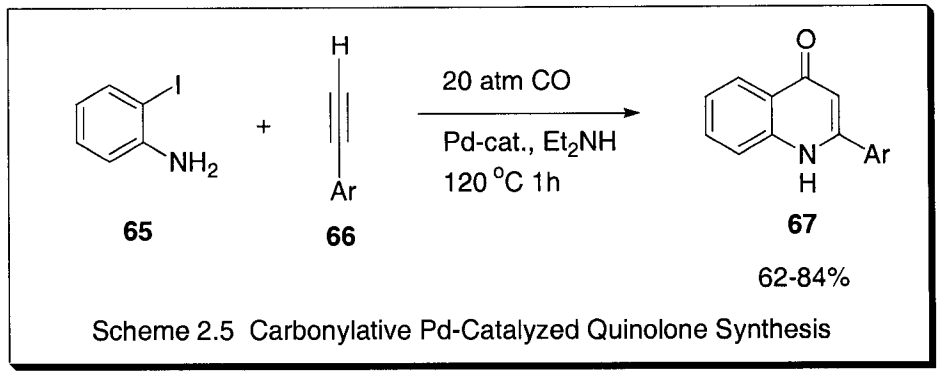
Another relatively new strategy, that was patented by Bayer for the synthesis of Ciprofloxacin, employs an intramolecular nucleophilic cyclization of a pendant cyclopropyl alkyl amino group onto the aromatic ring (Scheme 2.4).[124]

The acid chloride **61** is attacked by the enamine **62** to give the enone **63**, which under basic conditions cyclizes to form the 4-quinolone **64**. The ester **64** can be hydrolyzed under basic conditions, and then functionalized with piperazine to give Ciprofloxacin. This method relies on an aromatic ring that is sufficiently activated towards nucleophilic aromatic substitution by electron withdrawing groups.



Scheme 2.4 Grohe's Ciprofloxacin Synthesis

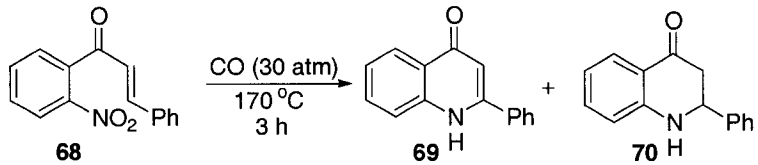
Relatively modern transition metal-mediated methods have also been applied to the synthesis of 4-quinolones with some success. The transition metal catalyzed intramolecular cyclization of anilines bearing pendant unsaturation is a well-known route to important heterocycles.[125] An elegant 2-aryl-4-quinolone synthesis has been reported starting from the *o*-iodoanilines **65**. Treating **65** with a terminal arylacetylene **66**, carbon monoxide, and a Pd catalyst along with diethyl amine gave the 2-aryl-4-quinolones **67** in moderate to good yield (Scheme 2.5).[126] However the poor availability of *o*-iodoanilines make this an impractical route to quinolones bearing substitution in positions 5 through 8. Furthermore, this method has not been shown to provide access to the 4-quinolone-3-carboxylates, the most important in the class.



Scheme 2.5 Carbonylative Pd-Catalyzed Quinolone Synthesis

Cenini and co-workers have reported a reductive carbonylation route from 2'-nitrochlacones **68**.[98a] Reduction of **68** gave the 2-phenyl-4-quinolone **69** and the dihydroquinolone **70** as the major products in varying ratios, depending on the catalyst and ligands employed (Table 2.1). Later Cenini and Penoni isolated N-hydroxy quinolones from product mixtures during these cyclizations, suggesting that they are likely intermediates on the path to the 4-quinolone.[98b]

Table 2.1 Cenini's 4-Quinolone Synthesis From o'-Nitrochalcones



Entry	Catalyst	Additive	Conversion (%)	**69** (%)	**70** (%)
1	$Ru_3(CO)_{12}$	DIAN-Me	100	38	57
2	$Pd(TMB)_2$	TMPhen	100	78	16
3	$Pd(TMB)_2$	TMPhen/TMBH	100	74	21
4	$Pd(PhCN)_2Cl_2$	-	51	26	22
5	$Pd(PhCN)_2Cl_2$	TMPhen	32	20	10

2.2: RESULTS AND DISCUSSION

2.2.1: PREPARATION AND CYCLIZATION OF 2-NITRO α-METHYL STYRENE

To investigate $[Cp(CO)_2Fe]_2$ as a catalysts for reductive heterocyclization, 2-nitroenones possessing pendant vinylic/allylic groups were prepared. The substrates closely parallel the reactants in the intermolecular reactions (Figure 2.3).

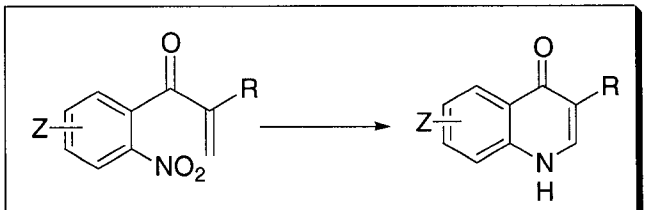
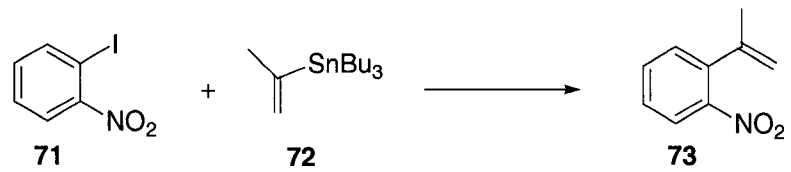


Figure 2.3 Targeted Transformation

The initial strategy for the synthesis of these compounds was a carbonylative Stille coupling,[127] starting from *o*-halonitrobenzenes. When the Stille coupling of *o*-iodonitrobenzene **71** with isopropenyltributyltin **72** was attempted under 4 atm of carbon monoxide, *o*-nitro-α-methylstyrene **73**[95] was the only coupled product (Table 2.2, Entry 1). The structure of the known oil **73** was verified by MS (EI) and ^{1}H NMR analysis. The styrene **73** has been reductively cyclized to give 3-methylindole with Pd catalysts,[95,103]and the Stille coupling represented a new preparation. After trying a few variations for the synthesis of this compound it was found that using Corey's procedure **73** could be obtained in a modest 40% yield (Table 2.2, Entry 3).[128]

Table 2.2 Synthesis of 2-Nitro-α-methylstyrene

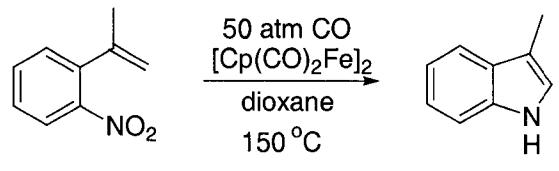


71 72 73

Entry	Solvent	CO (atm)	Catalyst	Temp. (C)	Time (h)	Yield (%)
1	THF	4	$Pd(PPh_3)_4$	60-80	15	ND
2	Toluene	0	$Pd(PPh_3)_4$	80-100	72	20
3	DMSO	0	$Pd(PPh_3)_4$ LiCl/CuCl	40-65	75	40

ND Not determined

While this compound is relatively unstable and apparently undergoes polymerization to give tarry materials when exposed to air and light, it was found that **73** could be cyclized to 3-methylindole (skatole) **74** in 40% yield (GC) with $[Cp(CO)_2Fe]_2$ as the catalyst at 200 °C under CO (Scheme 2.6). The identity of the product was confirmed by spectroscopic (^1H, ^{13}C NMR) comparison with a commercial sample.



73 **74**

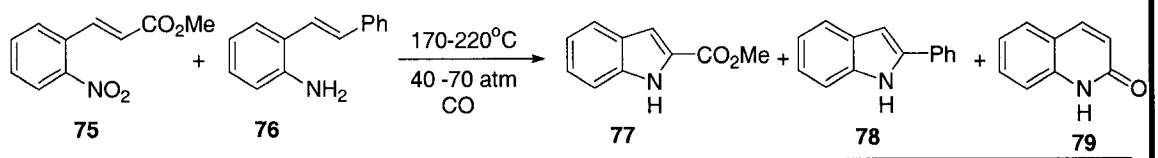
40% GC yield

Scheme 2.6 Synthesis of Skatole **74** from 2-Nitrostyrene **73**

2.2.2: IMPLICATIONS OF THE CYCLIZATION OF 2-NITRO α-METHYL STYRENE

This exact transformation (2-nitro styrene → indole) was reported by Watanabe using $PdCl_2(PPh_3)_2/SnCl_2$ and CO (20 atm) giving **74** in 41% isolated yield.[95] Similar reactions with 2-nitrostyrenes have been reported by Cenini,[85] Soderburg,[100] and others.[103] Additionally this reaction has been accomplished with tervalent phosphorous reagents.[49, 50] The Soderburg system with $Pd(OAc)_2$ catalyst, a variety of additives (PPh_3, NEt_3, DMF, MeOH) and only 4 atm of CO pressure is noteworthy for its mildness.[100] While the Fp_2 promoted cyclization was rather low yielding and required extreme conditions, it did demonstrate that this catalyst was active for these types of cyclizations.

The mechanism of these reactions has not been determined and has been described both as "obscure"[100] and a "complex situation".[101] A possible mechanism, at least in the Pd case, might involve reduction of the nitro group to the amino level and subsequent cyclization onto the olefin (free or coordinated). This type of cyclization has been shown to be a viable route to indoles by Hegedus.[125b] In order to examine the possibility of amino intermediates, Cenini and co-workers performed experiments in which methyl-2-nitrocinnamate **75** and 2-aminostilbene **76** were submitted to typical reductive cyclization conditions (Scheme 2.7).[101] The main product from the reduction of **75** was the indole **77**, and while **76** did produce indole **78** in low yield, it was not the main product. The identity of all the products was not determined and Scheme 2.7 gives only the selectivity (mol product / mol starting material converted). This experiment suffers from many problems and exactly how the experimenters hoped to glean



75 76 77 78 79

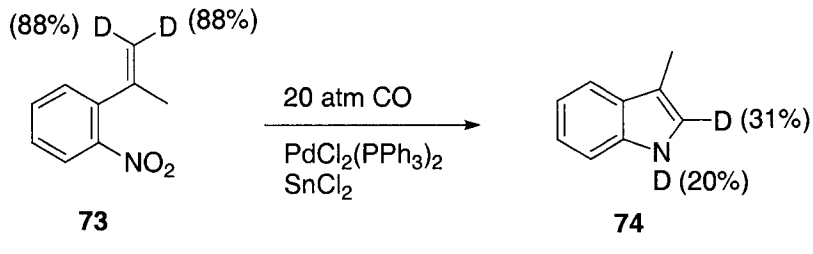
Catalyst	Conversion %		Selectivity %		
	75	76	77	78	79
Pd $(TMB)_2$ /TMPhen	100	36.8	76.4	10.2	10.1
[PPN][$Rh(CO)_4$/2-OH-pyridine	99.0	76.9	11.5	4.7	27.3
$Ru_3(CO)_{12}$	100	67.3	36.3	2.1	2.8

Scheme 2.7 Cenini's Mechanistic Probe in Reductive Cyclization of 2-Nitrostyrenes

useful information from this particular situation is unclear. Firstly, it would seem more appropriate to choose two compounds, amino and nitro, that were more similar to one another i.e. two stilbenes or two cinnamates. Since Hegedus had already reported that 2-aminostyrenes are converted to indoles with Pd catalysts,[125b] this seems to be a well-established transformation, at least for the Pd case. The case of the cinnamate is also complicated by the fact that if an aniline is produced from **75** it can cyclize to the 2-quinolone **79** via an ester aminolysis pathway. In addition, the presence of the amino compound was reported to have a deleterious effect on the selectivity of indole production from **75** for the ruthenium case. Despite the problems with these experiments, these results suggest that free amines are unlikely to be major contributors to indole formation in these reactions. Instead, Cenini et. al. postulated mechanisms involving nitrene complexes or a coordinated nitroso group. The complicity of nitroso compounds was suggested by reactions of nitrosoarenes with olefins in intermolecular reactions to give nitrones, that could be reduced to indoles. The isolation of large amounts of N-

hydroxy quinolones in the reductions of 2'-nitrochalcones,[98a] as previously discussed, also supports a mechanism that does not involve amines.

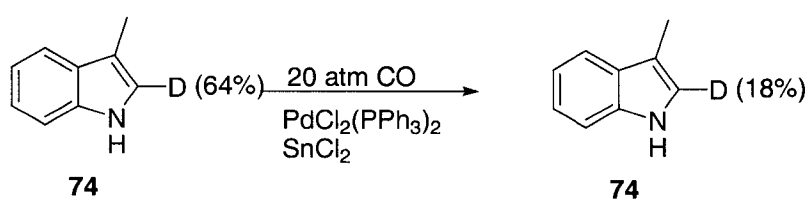
Watanabe has reported that with their catalyst system 2-aminostilbene gave no indole,[95] perhaps due to more moderate temperatures (180°C vs. 100°C). They performed labeling experiments with deuterium labeled **73** (88% in vinyl position), and upon reduction found a significant amount of deuterium incorporation (21%) in the product **74** (Scheme 2.8).



73 **74**

Scheme 2.8 Watanabe's Labeling Experiment

The 2-position contained only 31% deuterium after the reaction. In order to determine the lability of deuterium in the product, the 2-labeled indole **74** was subjected to the reaction conditions and was shown to undergo significant loss of the label (Scheme 2.9).



74 **74**

Scheme 2.9 Deterium Loss from 3-Methyl Indole Under Watanabe's Conditions

Nonetheless, the presence of the label on the indole nitrogen clearly indicates abstraction of the deuterium from the vinyl group, due to the statistical improbability of transfer of deuterium to the solvent then to the indole nitrogen. The authors postulate a nitrene intermediate inserting into the vinyl C-H bond, which is consistent with the results of the labeling experiment. Curiously, the reactive intermediate in these reactions was represented graphically by a nitrene in parenthesis adjacent to a palladium in parenthesis; no further comment on what was meant by this representation was given.

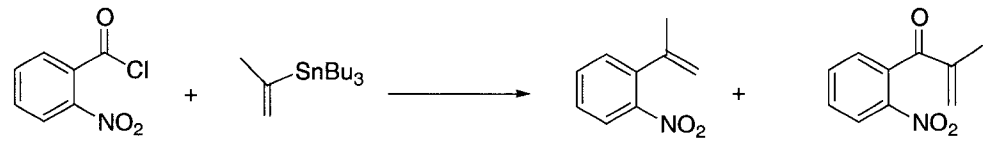
Free amines seem unlikely to be major intermediates in these reactions. The intermediacy of free nitrene has been ruled out in the case of our system and that of Watanabe by the aforementioned failure of 2-nitrobiphenyl to form carbazole. The intermediacy of imido complexes,[111] as well as nitroso compounds (presumably coordinated), as Cenini has suggested, seem like reasonable possibilities.

2.2.3: PREPARATION AND CYCLIZATION OF 2-NITRO ENONES

Undaunted by the failure of **71** to undergo a carbonylative Stille coupling to form the targeted nitroenone, the Stille coupling using the acid chloride **80** as a substrate was investigated. Under typical Stille conditions,[127b] the acid chloride **80** underwent decarbonylation (without carbon monoxide pressure) and gave only the decarbonylated styrene **73** (Table 2.3, Entries 1-2). Even with significant CO pressure the decarbonylated product was still produced (Table 2.3, Entries 3-5). A study of the literature revealed that acid chlorides are often used in place of aryl halides in the Stille coupling, when the latter are unavailable, and readily decarbonylate to give the coupled

product minus CO.[129] Despite this fact the nitroenone **81** was prepared in modest yield by using a relatively high pressure of carbon monoxide (Table 2.3, Entry 7).

Table 2.3 Stille Coupling of 2-Nitro Benzoyl Chloride with 2-Propenyl tributyltin

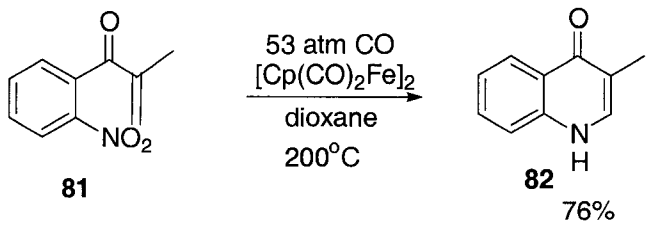


80 **72** **73** **81**

Entry	Solvent	CO (atm)	Catalyst	Temp. (C)	Time (h)	Product Ratio **73**:**81** (Yield **81**)
1	HMPA	0	$BnPdCl(PPh_3)_2$	100	72	1:0
2	HMPA	0	$BnPdBr(PPh_3)_2$	95	8	1:0
3	Toluene	1	$Pd(PPh_3)_4$	reflux	19	1:0
4	HMPA	1	$BnPdCl(PPh_3)_2$	65	3	2:1
5	HMPA	7	$BnPdCl(PPh_3)_2$	65	5	1:1.7
6	HMPA	20	$BnPdCl(PPh_3)_2$	70	5	trace:1
7	HMPA	20	$BnPdCl(PPh_3)_2$	70	10	(35)

With the nitroenone **81** in hand we were ready to attempt the reductive cyclization. The enone **81** gave 3-methylquinolone **82** in 76 % yield with $[Cp_2(CO)_2Fe]_2$ under 53 atm CO at 200 °C after chromatography (Scheme 2.10). The identity of **82**[130] was determined by modern spectroscopic methods (NMR, IR, exact mass, etc.). The compound is quite polar, and shows a strong ketone carbonyl absorption at 1630 cm^{-1}, typical of a 4-quinolone.[131] Additionally all carbons were accounted for in the ^{13}C NMR and a sharp singlet at δ 7.85 could be seen for the proton in the 2 position of the 4-quinolone in the ^{1}H NMR The mechanism of this reaction could be similar to that for

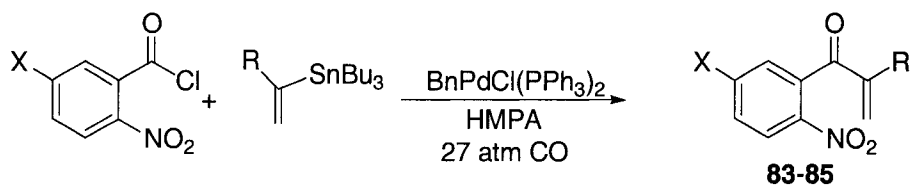
the above described indole reaction. In a closely related reaction (Table 2.1) the intermediacy of free amines has been ruled out by the failure of 2'-aminochalcones added to reaction mixtures to give any of the corresponding 4-quinolones.[101]



Scheme 2.10 Synthesis of 3-Methyl-4-Quinolone **82**

It was hoped that this strategy could be extended to prepare other quinolones. Unfortunately, the Stille coupling failed to produce the required substituted enones in adequate yield (Table 2.4).

Table 2.4 Synthesis of *o*-Nitroenones **83 - 85**

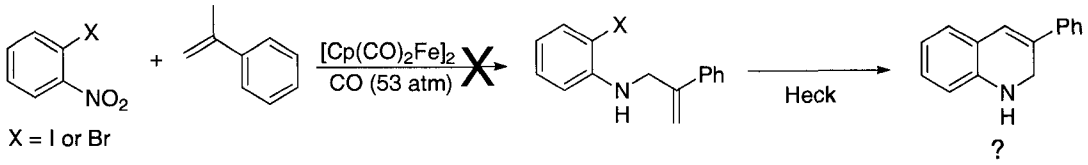


83-85

Entry	X	R	Temp. (C)	Time (h)	Product	Yield (%)
1	H	H	60	36	**83**	1
2	OMe	Me	60	40	**84**	8
3	F	Me	60	8	**85**	2

The reactions appeared to be reasonably clean by NMR of the crude mixtures, but an undetermined amount of polymeric/oligomeric material was produced along with minor side products. It is also possible that moisture from the CO could have hydrolyzed some of the acid chloride. Some of the material was undoubtedly lost upon purification, since the use of HMPA and Sn reagents required many purification steps that expose the product to multiple aqueous extractions in the air. There was no indication that the products were sensitive to air or water, and it seems unlikely that aqueous KF (a workup for the removal of Sn compounds) would affect them either. It may also be that high CO pressure inhibits an important step in the catalytic cycle, as has been suggested.[132] Regardless of the reason, these unsatisfactorily low yields prevented the application of this strategy in a more general sense. Moreover the synthesis of pharmaceuticals through this route would be unattractive due to toxicity of Sn compounds,[133] even in trace amounts.

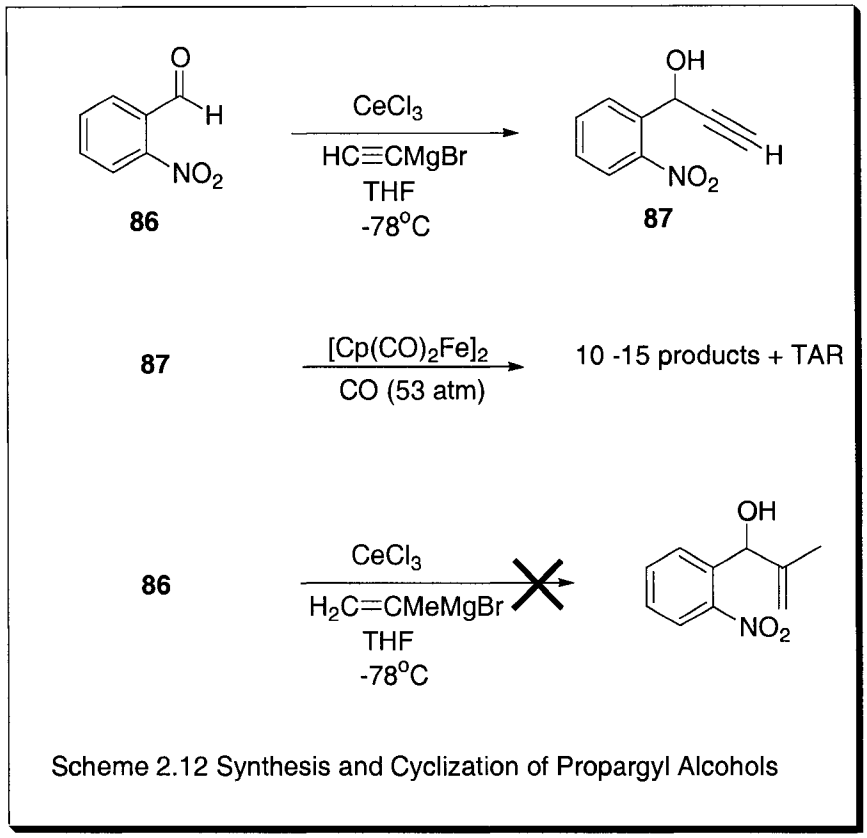
The reaction sequence for the synthesis of nitrogen heterocycles employed above could potentially be conducted in reverse order, i.e. the intermolecular amination followed by an intramolecular Heck reaction.[134] Regrettably, attempts at amination of α-methylstyrene with *o*-halonitrobenzenes failed (Scheme 2.11). Many products were detected by TLC, but GCMS of the reaction mixtures gave no indication of a product corresponding to a coupling of the two units. The halide may be to blame as metal dimers are known to participate in radical reactions with organic halides.[135]



Scheme 2.11 Attempted Intermolecular Amination / Heck Reaction Sequence

2.2.4: PREPARATION AND CYCLIZATION OF AROMATIC NITRO COMPOUNDS WITH PENDANT PROPARGYL GROUPS

Aromatic nitro compounds react with Grignard reagents to form products resulting from attack of the Grignard on the nitro group, including indoles.[136] A report by Jiminez on the reaction of ethynyl magnesium bromide with nitrobenzaldehydes in the presence of $CeCl_3$ to give propargyl alcohols was intrguing.[137] These compounds are at the same oxidation level as the nitroenones and we were interested in their behavior towards our reduction system to potentially produce quinolones. As reported, *o*-nitrobenzaldehyde **86** undergoes a facile reaction at low temperature to give the propargyl alcohol **87** in good yield (65 %) (Scheme 2.12). Lamentably, cyclization of **87** gave 10 - 15 products including quinoline (GCMS) and a large amount of tar. Interestingly, the reaction between **86** and 2-propenyl Grignard using the conditions for the synthesis of **87** also gave large amounts of tar (Scheme 2.12).



Scheme 2.12 Synthesis and Cyclization of Propargyl Alcohols

2.3: SUMMARY AND CONCLUSIONS

In these initial studies it was shown that the $[Cp(CO)_2Fe]_2/CO$ reductive system will reduce *o*-nitro-α-methylstyrene **73** to skatole **74**. Also using this system 3-methyl-4-quinolone **82** was prepared through the reduction of the nitroenone **81**. The dismal results of the Stille couplings under CO pressure prohibit any serious application of this reaction unless another route to the substrates is discovered. The intermolecular amination of α-methyl-styrene with *o*-halonitrobenzenes was unsuccessful, as was the reduction of the propargyl alcohol **87** to any reasonable amount of desired product. Despite these difficulties the catalyst system was shown to be effective for the reductive cyclizations of at least some substrates.

CHAPTER 3

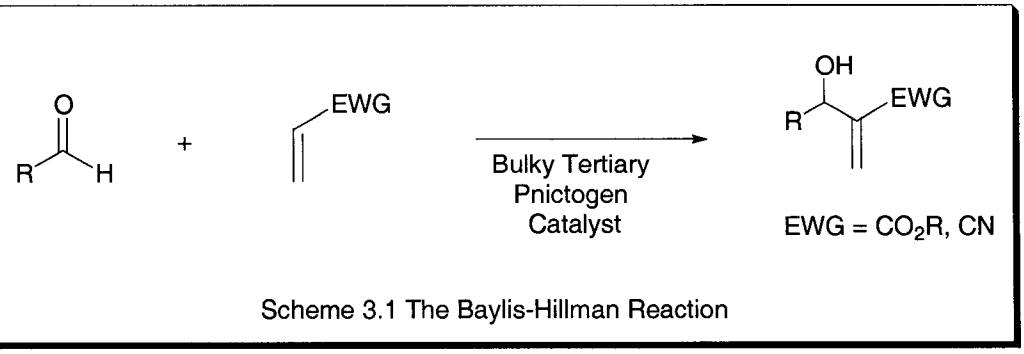
SYNTHESIS AND REDUCTIVE CYCLIZATION OF *O*-NITRO BAYLIS-HILLMAN ADDUCTS

3.1: INTRODUCTION

While the conversion of the 2-nitroenone **81** to the 4-quinolone **82** by the $[Cp(CO)_2Fe]_2$/CO reductive system was discovered, the low yielding synthesis of other substrates severely limits the utility of this transformation. Substrates for cyclization that bore pendant unsaturation that could be prepared more efficiently were desired. After some discussions with Professor Siegfried Blechert,[138] he suggested that Baylis-Hillman adducts bearing *o*-nitro groups might be interesting substrates for these reactions. Several of these compounds had been prepared by other groups and cyclized to give nitrogen heterocycles upon reduction with traditional reagents, however no reductive carbonylations of these substrates had been reported.

3.1.1: THE BAYLIS-HILLMAN REACTION

The Baylis-Hillman reaction is a powerful carbon-carbon bond forming reaction between an aldehyde and a Michael-acceptor, usually catalyzed by a tertiary amine or phosphine, giving a 2-functionalized allylic alcohol (Baylis-Hillman adduct) (Scheme 3.1).[139]



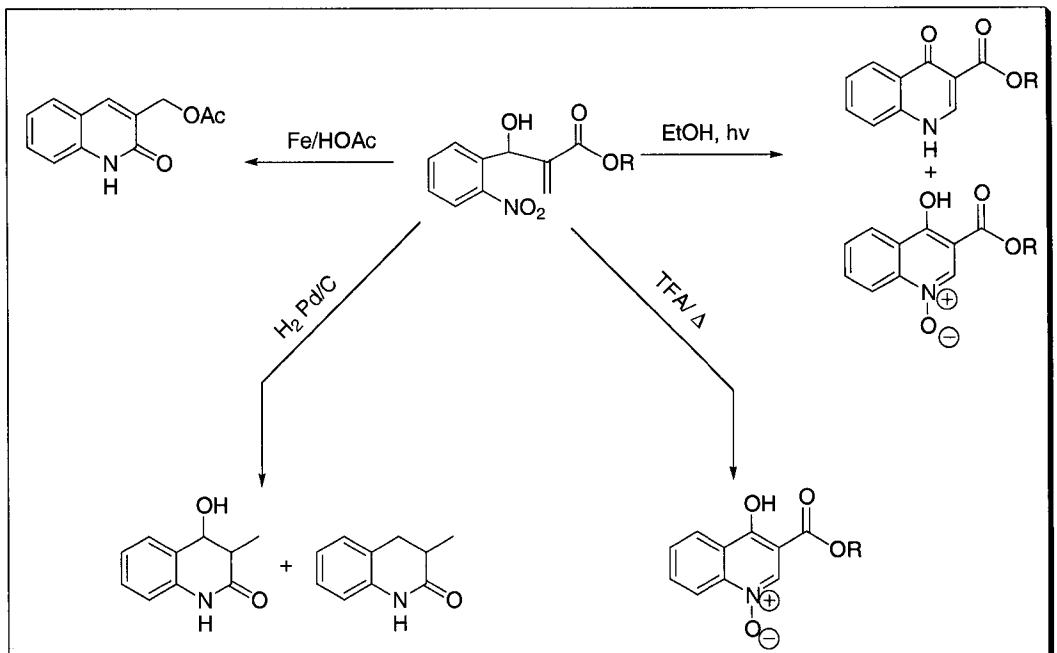
Scheme 3.1 The Baylis-Hillman Reaction

The reactions work best with aryl aldehydes and highly activated Michael-acceptors. The reactions are usually slow, but high yielding. A great many researchers have been focusing upon the synthesis and subsequent elaboration of the B-H adducts.[140]

3.1.2: *O*-NITRO BAYLIS-HILLMAN ADDUCTS IN HETEROCYCLIC CHEMISTRY

Several groups have targeted the easily prepared B-H adducts of 2-nitrobenzaldehyde as precursors to nitrogen heterocycles (Scheme 3.2). The use of electron withdrawing groups (e.g. nitro) on the aldehyde substrate increases the

electrophilicity of the carbonyl and hence the rate of the Baylis-Hillman reaction. Basavaiah has reported the synthesis of 2-quinolones by reduction of these compounds with Fe/AcOH.[141] The 2-quinoline is the result of apparent ester aminolysis and 1,3 acetate migration. Kim and coworkers were able to synthesize the 4-quinolones and 4-quinolone-N-oxides through irradiation of the B-H adducts,[142] as well as synthesis of the later by treatment with TFA.[143] Kaye et. al. have used catalytic hydrogenation of B-H adducts to produce mixtures of dihydro-2-quinolones.[144] The reactions of Kim and Kaye were generally low yielding and gave mixtures of products.



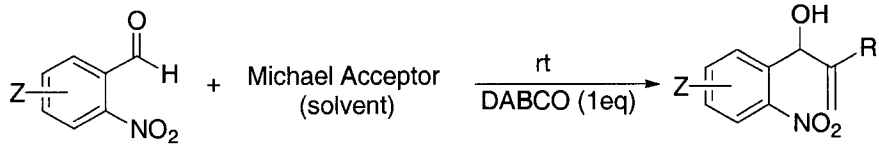
Scheme 3.2 Baylis-Hillman Adducts as Precursors to Nitrogen Heterocycles

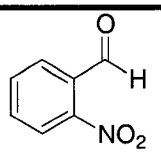
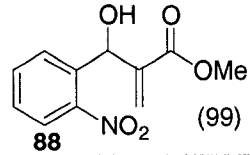
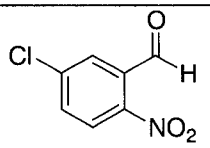
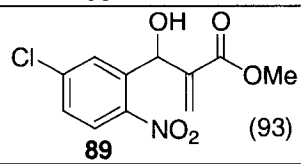
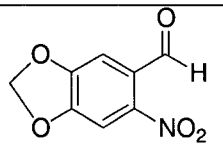
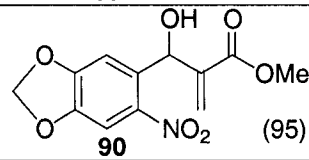
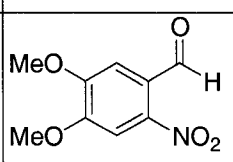
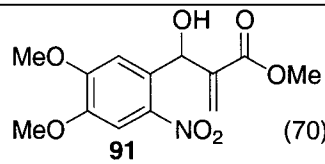
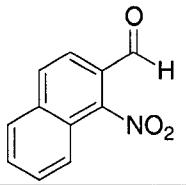
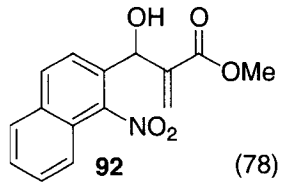
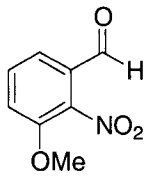
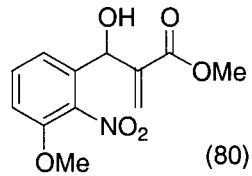
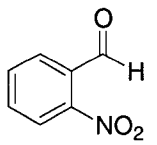
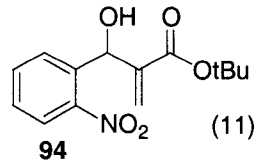
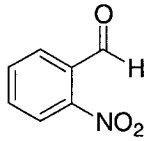
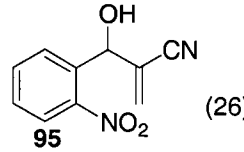
3.2: RESULTS AND DISCUSION

3.2.1: PREPARATION OF *O*-NITRO-BAYILS-HILLMAN ADDUCTS

A variety of *o*-nitro Baylis-Hillman adducts (**88-95**) bearing both EDG and EWGs were prepared (Table 3.1). By stirring the commercially available aldehydes in a neat solution of the acrylate with a stoichiometric amount of DABCO, these reactions usually proceeded in good yield, except when a bulky acrylate was employed (Entry 7). The low yield of the adduct **95** can be partially attributed to incomplete conversion of the 2-nitrobenzaldehyde (Entry 8). Isolation of these compounds usually involved column chromatography to remove small amounts of acrylate dimers. Most of these compounds have not been reported in the literature and the ones that have (**89** and **95**) had no accompanying spectroscopic data. These compounds exhibit ^{1}H NMR spectra with several salient features due to the attachment of the acrylate group: an OH signal, as well as two vinyl resonances that show a small yet distinct coupling. Additionally the IR spectrum contains a strong absorptions for the ester carbonyl (~1700-1720 cm^{-1}) and alcohol groups (~3300-3600 cm^{-1}).

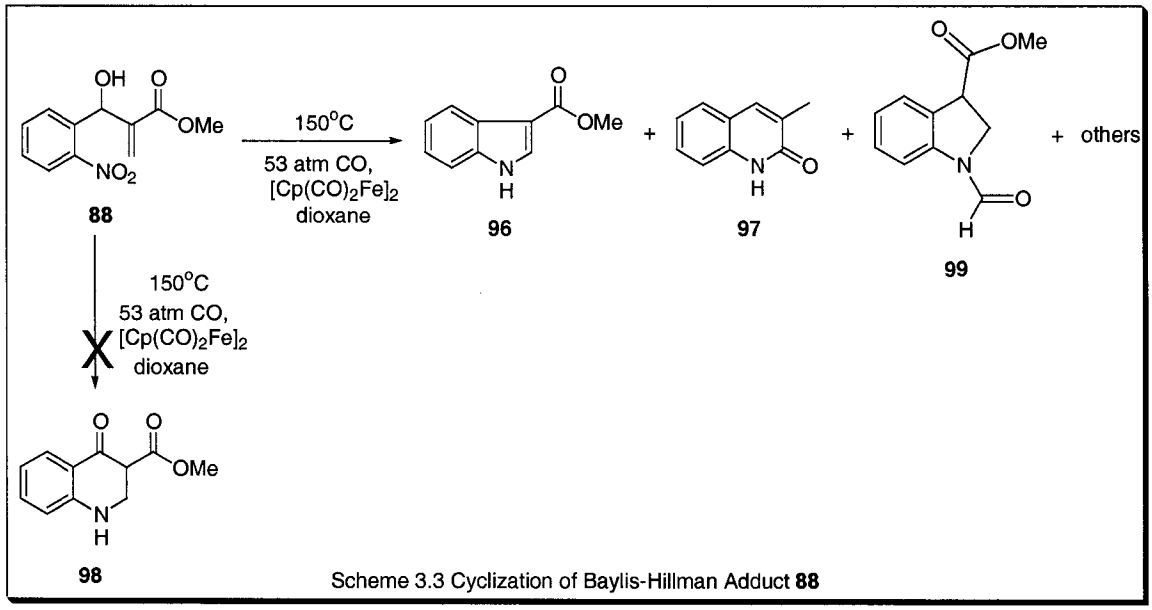
Table 3.1 Preparation of Baylis-Hillman Adducts



Entry	Aldehyde	Michael Acceptor	Time (days)	B-H Adduct (Yield)
1		Methyl Acrylate	5	 **88** (99)
2		Methyl Acrylate	3	 **89** (93)
3		Methyl Acrylate	7	 **90** (95)
4		Methyl Acrylate	7	 **91** (70)
5		Methyl Acrylate	5	 **92** (78)
6		Methyl Acrylate	7	 **93** (80)
7		t-Butyl Acrylate	7	 **94** (11)
8		Acrylonitrile	2.5	 **95** (26)

3.2.2: CYCLIZATION OF *O*-NITRO-BAYILS-HILLMAN ADDUCTS

When the Baylis-Hillman adduct **88** was heated (150 °C) in dioxane with 10 mol % of $[Cp(CO)_2Fe]_2$ under 53 atm CO a complex mixture was obtained (Scheme 3.3).

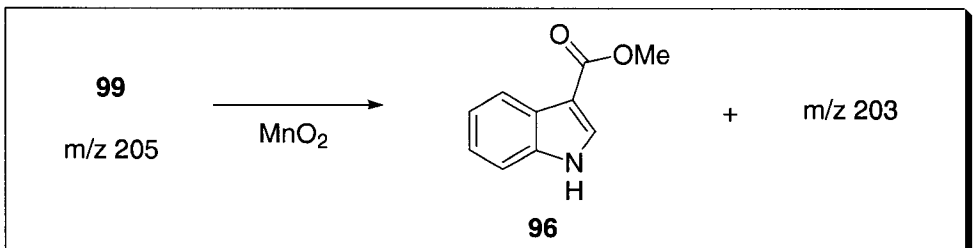


Scheme 3.3 Cyclization of Baylis-Hillman Adduct **88**

Chromatography of the product mixture gave two major products, one of apparent mass 175 and another with *m/z* 205, a few minor products, and some tar, which accounts for a poor mass balance. As Smith noted in his review of deoxygenations of nitro compounds with tervalent phosphorous reagents, "cyclizations of *o*-nitrostyrenes that take place in low yields are usually accompanied by extensive tar formation."[145] The *m/z* 175 product (17 % yield), apparently was the result of the loss of one carbon (as CO, CH_2O ?) from **88**. It was identified as methyl 3-indolecarboxylate **96** and was spectroscopically

identical to commercial material. Also detected was the known 2-quinolone **97** (4 %), arising from apparent ester aminolysis and dehydration.[146]

The other major product (20 %, *m/z* 205) corresponded formally to the removal of two oxygen atoms, consistent with the expected dihydroquinolone **98**. The ^{1}H NMR spectrum of this compound in DMSO-d_6 was temperature-dependent, the low field portion of which is shown in Figure 3.1. The two singlets at δ 8.45 and δ 9.0 (approximately 7:3 ratio at 35 °C), two doublets at δ 7.5 and δ 7.9, and some higher field resonances δ 4.0 - 4.5 coalesced at 100 °C; the original spectrum was restored upon cooling to room temperature. The NMR results suggested that two isomers of the compound were in equilibrium. Although this could be explained by the existence of a keto-enol tautomeric mixture for **98**, the sharpness of the low field resonances, the differing melting point of the compound compared to that reported for **98**,[120b] and other data (*vide infra*) pointed to an alternative structure for the *m/z* 205 product.



Scheme 3.4 Oxidation of **99** to **96**

When this compound was subjected to oxidation with MnO_2,[147] it gave a product with *m/z* 203 (loss of 2H) and a small amount of the indole **96** (Scheme 3.4). Attention was then focused upon prospective structures that could be oxidized to indoles.

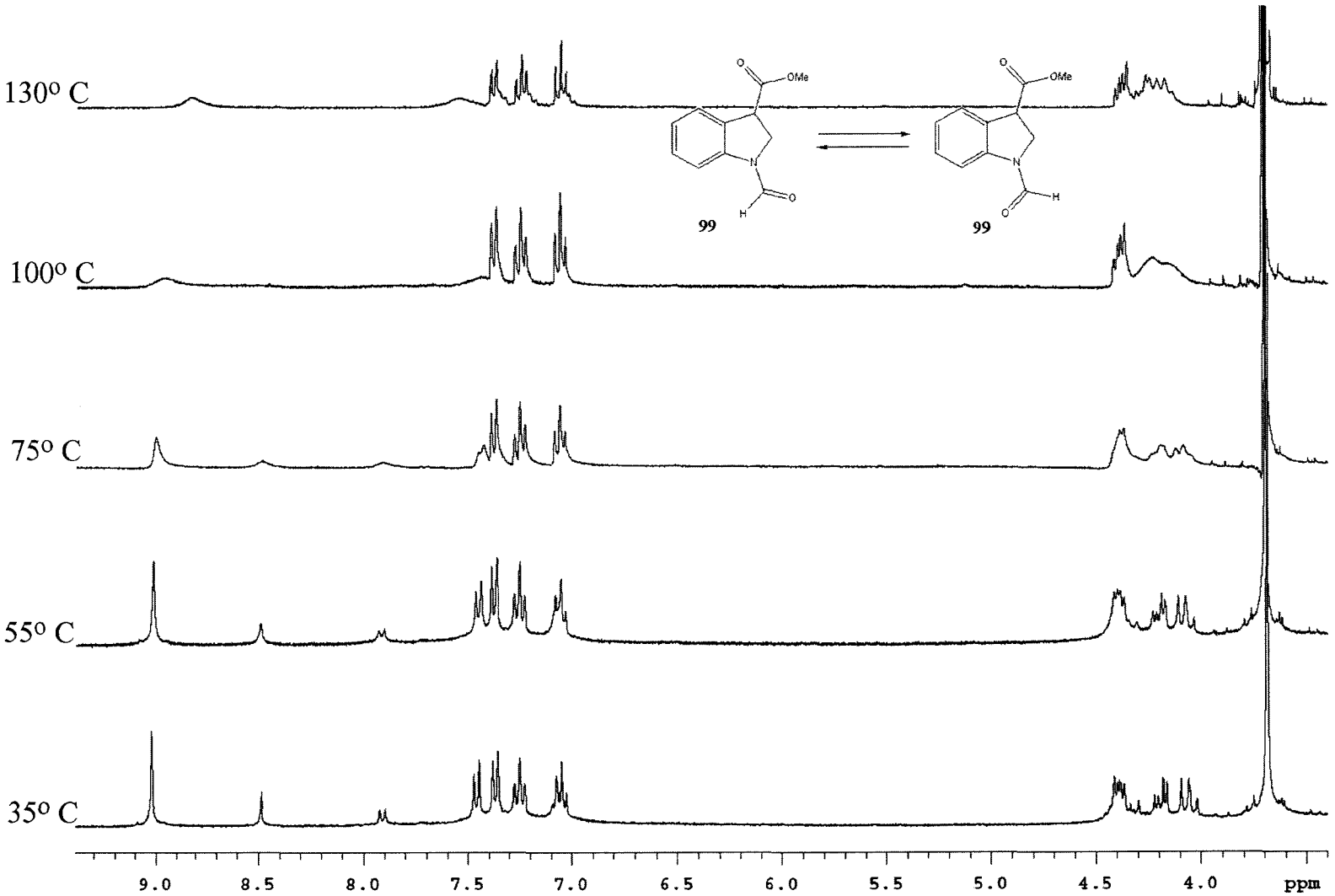
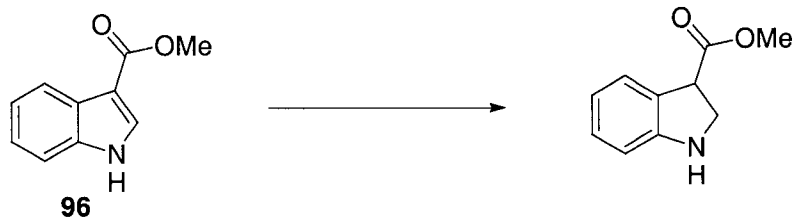


Figure 3.1 Variable Temperature 300 MHz ^{1}H NMR of **99** in DMSO-d_6

Examination of the literature of N-formylindolines, revealed ^{1}H NMR spectra strikingly similar to those obtained for the *m/z* 205 compound, with temperature-dependent spectra arising from the slowly interconverting N-formyl rotamers.[148] Indeed, when the free energy of activation is determined for the process we observed at 100 °C, from the signals at δ 9.0 and δ 8.45 using equations designed for use at the coalescence point of two differently populated species,[149] values of 19.0 and 19.7 kcal/mol are obtained (for conversion of minor to major and major to minor, respectively), which are consistent with this type of process. Using this approach the free energy of activation for rotation about the N-acetyl bond of an N-acetyl tetrahydroisoquinoline has been calculated to be 16.1 kcal/mol and 16.6 kcal/mol.[150]

Ultimately, the structure of the *m/z* 205 compound was assigned to the N-formylindoline **99**. To verify this assignment, we applied standard reaction protocols to synthesize **99** from the commercially available indole **96**. Although the direct reduction of the 2-3 C=C bond of **96** has not been reported, this transformation was attempted using reactions that have been applied to indole 2-carboxylates (Table 3.2).[151-153]

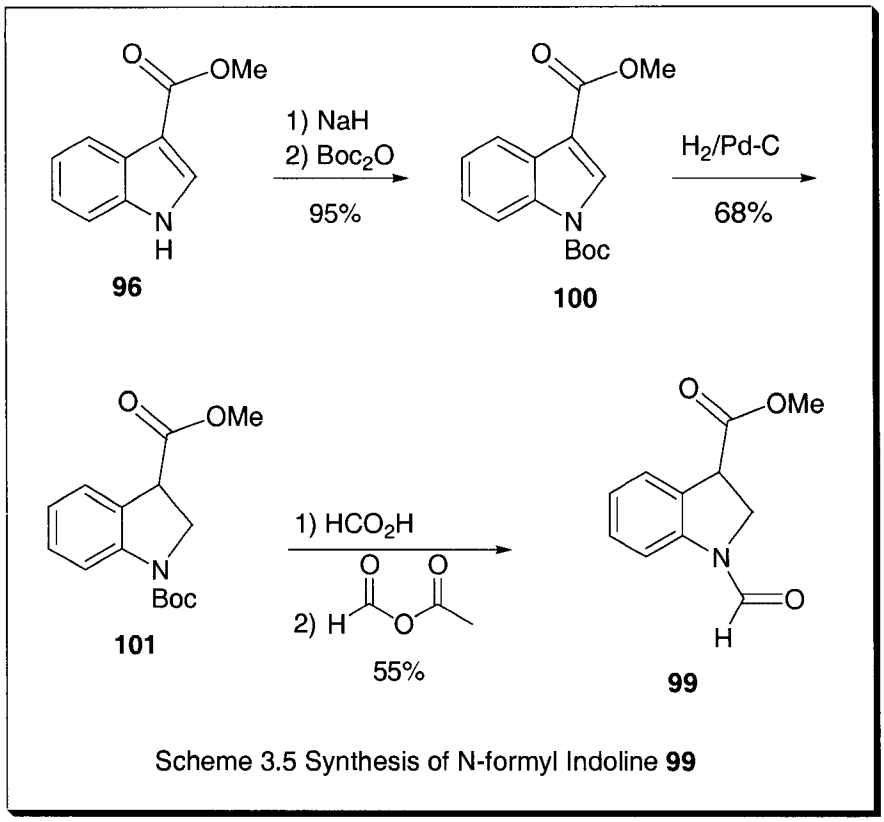
Table 3.2 Attempted Direct Reduction of **96**



96

Entry	Reference	Conditions	Result
1	-	Pd/C H_2(7 atm) benzene 100°C	N.R.
2	152	Mg/MeOH	N.R.
3	153	TFA/Et_3SiH 0°C	N.R.
4	153	TFA/Et_3SiH reflux	Complex Mixture, Tar, and trace product (GCMS)

Prolonged refluxing of **96** in Et_3SiH/TFA gave mostly tar, but a product that was most probably the indoline was detected (*m/z* 177, GCMS) along with numerous other products. In order to obtain the desired compound it was first necessary to protect the indole nitrogen. Thus **96** was protected as the N-Boc derivative **100**,[154] followed by catalytic hydrogenation to give N-Boc-indoline **101** (Scheme 3.5).[155] A one pot deprotection/formylation,[156] using formic acid followed by treatment with formic acetic anhydride, gave the N-formylindoline **99** whose ^{13}C and ^{1}H NMR was identical to that formed through the Fp_2 catalyzed cyclization of **88**.



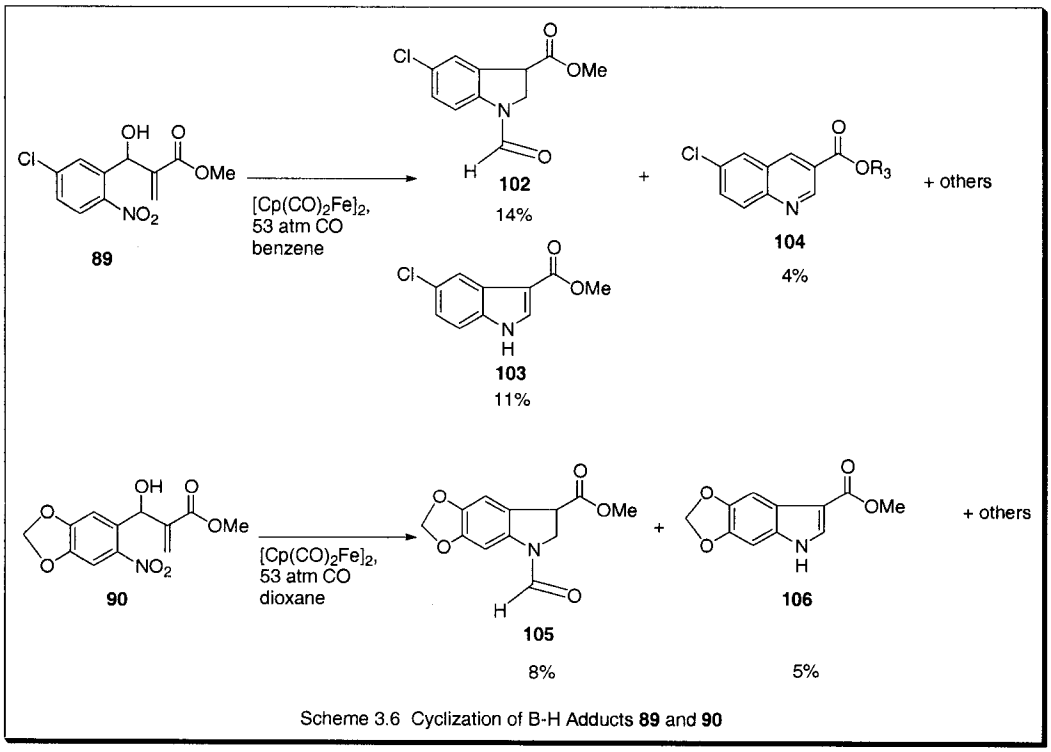
Scheme 3.5 Synthesis of N-formyl Indoline **99**

Regardless of the efficiency of this transformation, formation of the indole **96** and the N-formylindoline **99** from reaction of the B-H adduct **88** is remarkable. A control experiment reaction of **88** with $[Cp(CO)_2Fe]_2$ (35 mol %) in the absence of CO also gave the indole **96**, albeit in 7% yield, as the sole identifiable product. Additionally, when either the indole **96** or the indoline **99** were subjected to the catalytic cyclization conditions, they were recovered unchanged after several days. This result indicates that both **96** and **99** are primary products of the cyclization reaction. It is also worth noting that heating the Baylis-Hillman adduct **88** to 150 °C under 50 atm CO without Fp_2 for several days did not produce any of the products mentioned above.

The results of the Fp_2 catalyzed cyclization were compared to corresponding reactions using other CO-based reduction methods, specifically the

$PdCl_2(PPh_3)/SnCl_2/CO$ system of Watanabe[95] and the $Se/NEt_3/CO$ combination employed by Sonoda.[103] In both cases the reduction of **88** was incomplete after prolonged reaction times and the product mixtures were extremely complex (GCMS/TLC). In neither case was the N-formylindoline **99** detected; however, the indole **92** was formed in trace amounts.

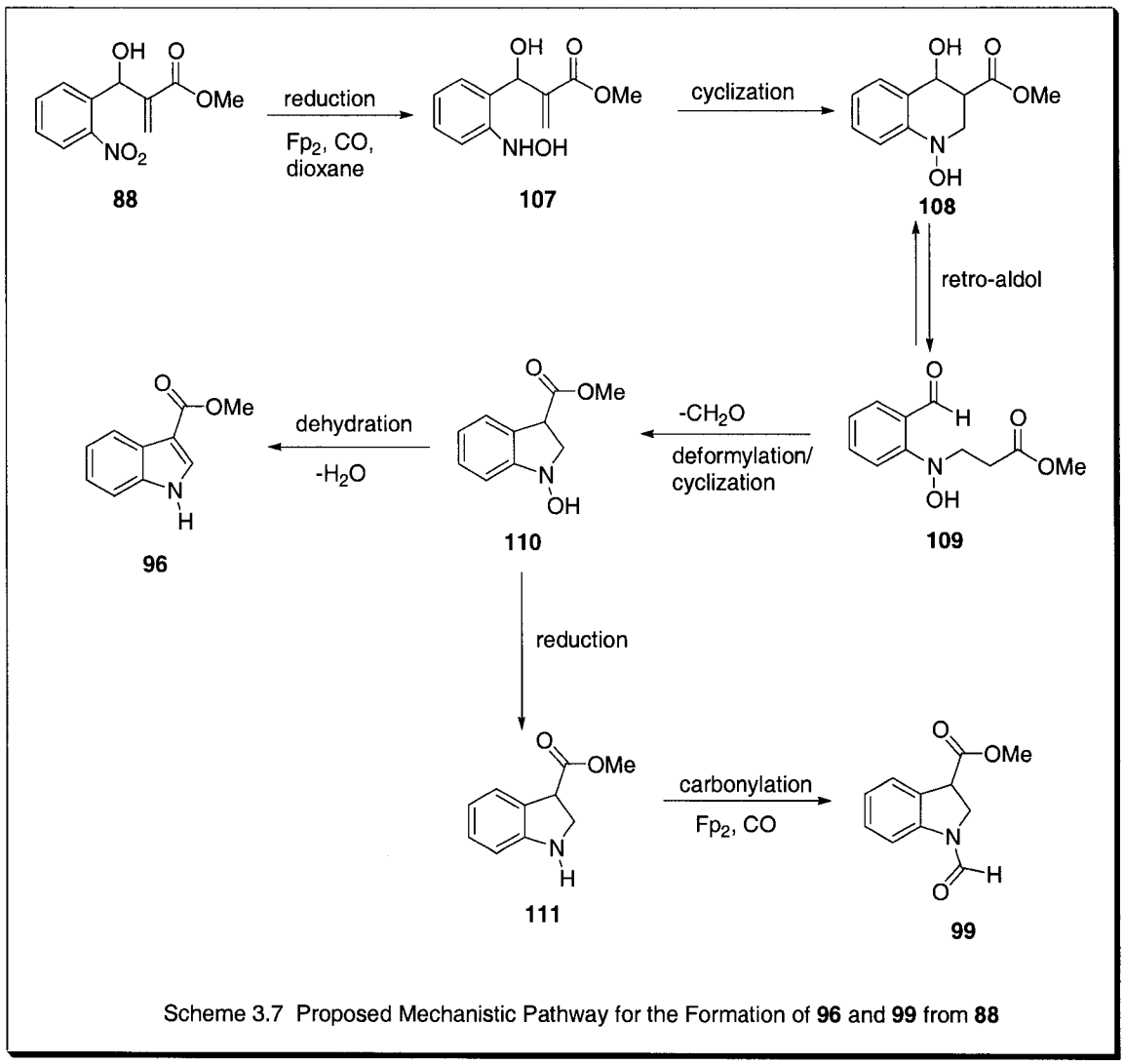
The cyclization of two other B-H adducts, **89** and **90**, gave similar results (Scheme 3.6). The 5-chloro-2-nitrobenzaldehyde adduct **89** provided a 13 % yield of N-formylindoline **102** and 8 % of the methyl 5-chloro-indole-3-carboxylate **103**; a small amount of the 6-chloroquinoline **104** was also isolated. Similarly, the adduct of the 2-nitropiperonal **90** gave the N-formylindoline **105** (8 %) and the indole **106** (5 %). Each of the N-formyl indolines apparently exists as a rotameric mixture, judging from the appearance of two formyl proton resonances in their ^1H NMR spectra as well as the presence of multiple pairs of resonances in their ^{13}C NMR spectra.



Scheme 3.6 Cyclization of B-H Adducts **89** and **90**

3.2.3: POSSIBLE MECHANISMS FOR THE FORMATION OF PRODUCTS FROM THE REDUCTIVE CYCLIZATION OF BAYLIS-HILLMAN ADDUCTS

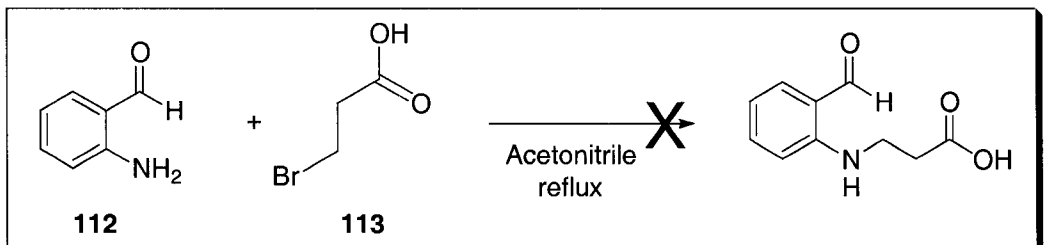
An admittedly speculative, but precedented, mechanistic outline is suggested in Scheme 3.7. Initial Fp_2-promoted reduction of the nitro group of **88** to the hydroxylamine **107** would be followed by Michael addition to the terminal olefinic carbon. The olefin may be free or coordinated. Intermediate **108** could then undergo reversible retro-aldol reaction to generate aldehyde **109**. Deformylation of **109** could be effected by seventeen electron $Cp(CO)_2Fe$,[157] either by a radical[135,158] or an organometallic pathway,[159] to generate an aryl-iron or aryl radical intermediate, which then could cyclize to indoline **110** by addition to the ester enol. The N-hydroxyindoline **110** could then dehydrate to give the indole **96** or be further reduced to the indoline **111**, which could be re-carbonylated to produce the N-formylindoline **99**. The N-carbonylation of amines to formamides by group 8 transition metal complexes and carbon monoxide is also established.[160]



Scheme 3.7 Proposed Mechanistic Pathway for the Formation of **96** and **99** from **88**

3.2.4: ATTEMPTS AT PREPARATION OF POTENTIAL INTERMEDIATES IN THE REDUCTIVE CYCLIZATION OF *O*-NITRO BAYLIS-HILLMAN ADDUCTS

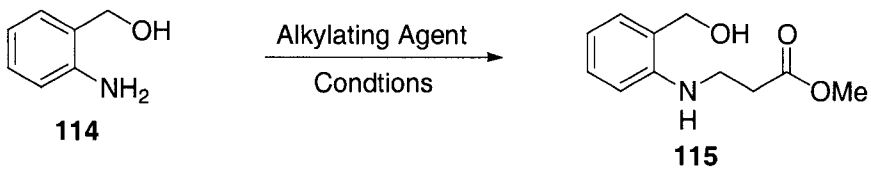
In order to corroborate the proposed mechanism, the synthesis of compounds like the intermediate **109** was attempted. Alkylation of 2-amino benzaldehyde **112** [161] with the alkyl bromide **113** did give some reaction (Scheme 3.8), however no products from the coupling of these two fragments could be detected (NMR, GCMS).



Scheme 3.8 Attempted Alkylation of 2-Amino Benzaldehyde **112**

The preparation of **112** is troublesome and **112** is prone to undergo oligmerization.[162] For these reasons, the 2-amino benzyl alcohol **114** was chosen as a more desirable starting material. It was envisioned that oxidation of the alcohol moiety in expected product **115** could be achieved after alkylation of the amino group. Unfortunately several attempts to alkylate **114** under a variety of conditions that had some precedent in the literature failed to give the desired secondary amine (Table 3.3).[163-166] A more aggressive strategy employing N- or O- protecting groups or more electron rich anilines would probably have given the desired compound, but this strategy was deemed too lengthy by one of us and the importance of obtaining compound **109** marginal at best.

Table 3.3 Attempted Alkylation of 2-Amino Benzyl Alcohol **114**



114 **115**

Entry	Ref.	Alkylating Agent	Conditions	Result
1	163a	**108**	Neat (In the Melt) wrkup. with NaOH	Intractable Tar
2	163b	Methyl Acrylate	AcOH, reflux	No desired product m/z 137, 242, 222 (GCMS)
3	163c	**108**	EtOH, NaOAc autoclave, 120°C	Intractable Tar
4	164	**108**-Methyl Ester	MeOH, NaOAc autoclave, 135°C	No desired product
5	165	**108**-Methyl Ester	MeOH,$NaHCO_3$ autoclave, 135°C	No desired product
6	166	Methyl Acrylate	AcOH, CuCl benzne, reflux	Tar, 3 major products: m/z 187, 207, 235 (GCMS)

3.3: SUMMARY AND CONCLUSIONS

During the course of this study several Baylis-Hillman adducts (**88-95**) of 2-nitro benzaldehydes were prepared, many of which had been previously unknown or undescribed. Upon reductive cyclization of these compounds it was found that indoles and N-formyl indolines were the major products. The structure of these compounds was proven through modern spectroscopic methods, comparison with known data or commercial compounds, and in the case of **99**, through an alternate synthesis. A mechanism was proposed that was consistent with observations and literature precedent. Attempts to synthesize potential organic intermediates were unsuccessful.

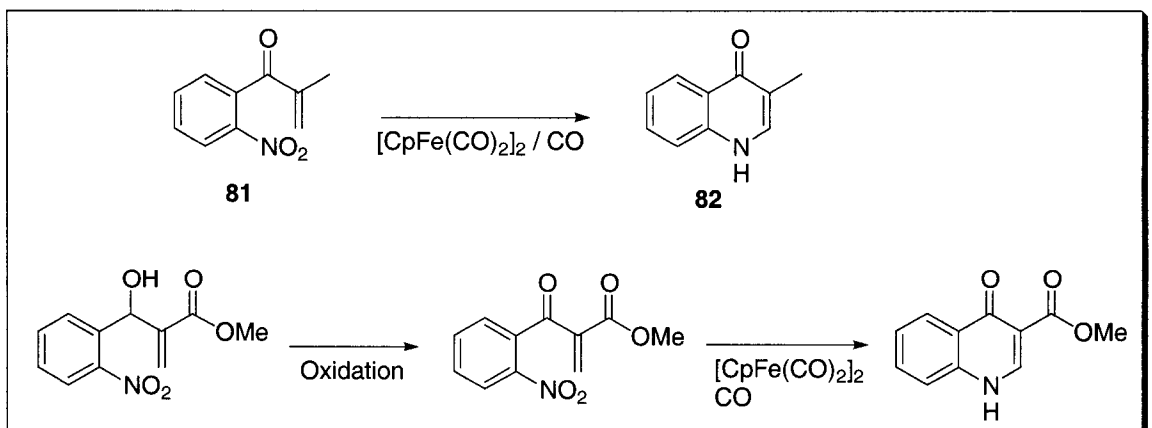
While these new cyclizations were not efficient, giving multiple products in low yield, the unusual products, as compared to those derived from reduction of the Baylis-Hillman adducts using standard reducing agents, point to unique mechanistic pathways available when using the transition metal carbonyl/CO reducing system. Given these unique results, it was thought worthwhile to seek out other substrates for these cyclizations that might provide better yields/selectivities.

CHAPTER 4

SYNTHESIS AND CYCLIZATION OF DERIVATIVES OF BAYLIS-HILLMAN ADDUCTS

4.1: INTRODUCTION

Given the surprising results obtained by the cyclization of Baylis-Hillman adducts **88-90**, which gave indoles and N-formyl indolines as major products, an investigation of the transformations of modified Baylis-Hillman adducts was in order. It was imagined that upon functionalization of the allylic alcohol the retro-aldol/decarbonylation pathway leading to the indole and N-formyl indoline might be suppressed and cyclization to our original targets, the six-membered heterocycles (quinoline and quinolone) could be achieved. Several possibilities for simple one-step modification of the B-H adducts existed including oxidation of the alcohol and O-functionalization. Oxidation of the alcohol to the ketone would provide enones analogous to the substrate **81** we had previously cyclized to the 4-quinolone **82** (Scheme 4.1).



Scheme 4.1 Proposed Route to 4-Quinolones from Baylis-Hillman Adducts

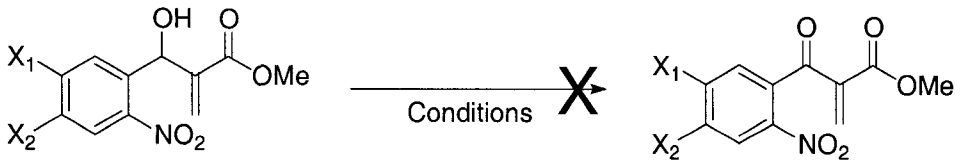
4.2: ATTEMPTED OXIDATION OF BAYLIS-HILLMAN ADDUCTS

Reports on the oxidation of Baylis-Hillman adducts of benzaldehydes to ketones are scarce. The only report dealing with this transformation claimed that Dess-Martin periodinane (DMPI) worked well in some cases;[167] however no oxidations of B-H adducts bearing *o*-nitro groups were reported. This same report also described the use of the Swern oxidation on these same substrates to give not the expected enone but rather products incorporating Cl, presumably derived from the oxalyl chloride.

With this information in mind, oxidation of the Baylis-Hillman adducts **88** - **90** was attempted (Table 4.1). DMPI did induce a reaction of **88** to give a complex mixture (TLC, NMR and GCMS). GCMS and NMR of the reaction mixtures, however, provided no evidence for the formation of the enone. Similar results were obtained with **90**. Oxidation of **88** with Jones reagent also failed, giving tar, unidentified products and recovered starting material.[168] Refluxing the adduct **90** for 14 days with PCC in CH_2Cl_2 gave mostly recovered starting material and some tar along with trace amounts of unidentified products that did not have the appropriate mass (GCMS).[169] While the Swern oxidation reportedly failed to give the desired products, it was anticipated that a variant employing SO_3·pyridine instead of oxalyl chloride might prevent the formation of the previously described Cl containing products.[170] However, after prolonged reaction times under forcing conditions no product was detected that could have been the enone, as determined by the absence of new vinylic protons in the ^1H NMR spectrum. Attempted oxidation of **89** with MnO_2[147] gave no detectable conversion of starting

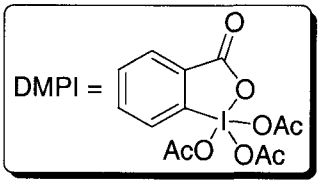
material (TLC) after refluxing in CH_2Cl_2 for 7 days. It is not readily apparent why these compounds are so difficult to oxidize, but could be due to the fact that the benzylic position can be viewed as electron deficient due to the presence of the both the o-nitro group as well as the acrylate moiety and hence less susceptible to oxidation.

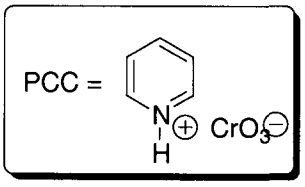
Table 4.1 Attempted Oxidation of Baylis-Hillman Adducts **88-90**



88: $X_1 = X_2 = H$
89: $X_1 = Cl$; $X_2 = H$
90: $X_1 - X_2 = OCH_2O$

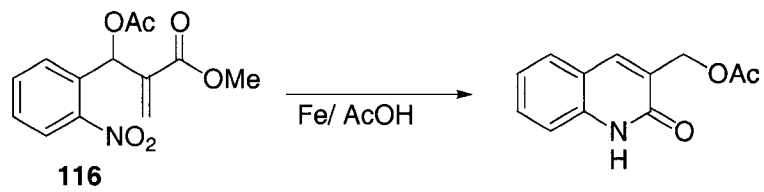
Entry	BH- Adduct	Conditions	Result
1	**89**	DMPI, CH_2Cl_2, reflux 3 days	Complex Mixture (NMR, GCMS, TLC)
2	**90**	DMPI, CH_2Cl_2, reflux 2 days	Complex Mixture (GCMS)
3	**88**	Jones Oxidation (CrO_3, H_2SO_4, Acetone) 2 additons of excess -78°C - RT	Low conversion to an unidentified product with incorrect mass (GCMS) and tar
4	**90**	PCC, CH_2Cl_2, reflux 15 days	Low conversion to multiple products with incorrect masses (GCMS) and tar.
5	**88**	Parikh-Doering Oxidation (SO_3.pyridine, DMSO, Et_3N)	No product by ^1H NMR
6	**89**	MnO_2(10eq.), CH_2Cl_2, reflux, 7days	No Reaction (TLC)





4.3: SYNTHESIS AND CYCLIZATION OF BAYLIS-HILLMAN ACETATES: A NEW SYNTHESIS OF 3-SUBSTITUTED QUINOLINES

Although it was found that oxidation of the B-H adducts failed to the desired enones, the acetylation of B-H adducts had been reported by several groups.[141, 171] This is a very simple transformation and can be accomplished most generally by treatment of the B-H adduct with acetyl chloride in pyridine. Additionally, Basavaiah had reported on the preparation of Baylis-Hillman acetates (B-H acetates) bearing *o*-nitro groups, and had shown that these were likely intermediates in the reduction of **88** to 2-quinolones with Fe/AcOH by the reduction of the acetate **116** with Fe/AcOH to give the 2-quinolone (Scheme 4.2).[141]



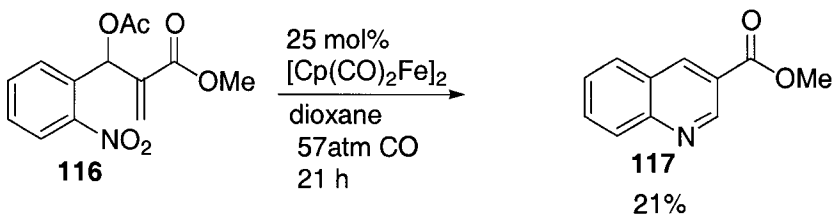
116

Scheme 4.2 Basavaiah's Synthesis of 2-Quinolones from Baylis-Hillman Acetate **116**

It is worth noting that Fe/AcOH is a typical reagent for the reduction of the nitro group to the corresponding amine/hydroxylamine and that this same reduction of the B-H adduct **88** to the 2-quinolone has also been accomplished with $SnCl_2$/AcOH (also used for the preparation of amines/hydroxylamines from nitro compounds).[172] Given the markedly different results obtained with the $[Cp(CO)_2Fe]_2$/CO system in the reduction of **88-90** we were curious to see what the products from the reductive carbonylation of B-H acetates

might be. Would the previously observed decarbonylation pathway be suppressed? Would the products be the 2-quinolones, as is the case for reduction with M/AcOH?

Upon reduction of the acetate **116** with 10 mol% of $[Cp(CO)_2Fe]_2$ and 57 atm of CO at 150°C for 21 h, the quinoline **117** was isolated in 21% yield as the major product after chromatography on silica gel along with small amounts unidentified products and starting material (Scheme 4.3).



Scheme 4.3 Initial Results of the Reduction of **116** to the Quinoline **117**

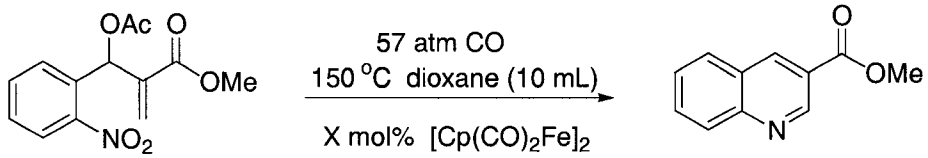
The known quinoline **117** was spectroscopically identical (^{1}H NMR) to that previously reported,[173] and gave a mp of 68-71 °C (lit.[173] mp 70-74). The ^{1}H NMR exhibited distinct doublets for the aromatic protons in the 2 and 4 positions of the heterocyclic ring, and the methyl ester showed the characteristic resonance at around δ 3.0. This reaction was very clean (low tar formation), as compared to the reduction of the Baylis-Hillman adducts, giving translucent red solutions with very little particulate material. None of the previously detected indole or N-formyl indoline were observed by NMR or GCMS of the crude material.

The quinoline **117** went cleanly through a packed GC column, had a significantly different retention time from the acetate and gave peaks with good line-shape using the FID. Because of these factors and the relative cleanness of the reaction, this

transformation was well suited for an optimization study using gas chromatographic analysis.[175] The method of internal standard was chosen to quantitatively determine the yield of the quinoline as well as conversion of the acetate. Naphthalene was chosen as the internal standard due to its inertness to the reaction conditions as well as its similarity to the product in terms of carbon and hydrogen content.

The effect of catalyst loading was studied first (Table 4.2). Increased catalyst loading had a positive effect until 35 %, after which the conversion increased and the yield decreased. This might suggest the formation of a complex derived from **116** and $[Cp(CO)_2Fe]_2$.

Table 4.2 Effect of Catalyst Loading/Concetration on the Yield of **117**



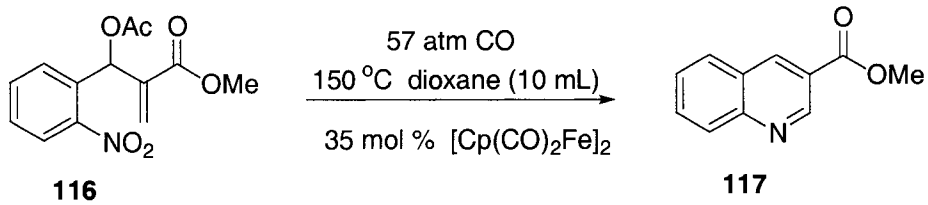
116
0.11 mmol

117

Entry	X	Conversion of **116** (%)	Yield **117** (%)
1	35	90	35
2	50	>99	36
3	75	>99	26
4	100	>99	24

It was also desirable to probe the effects of substrate concentration on the selectivity of the reaction. Intermolecular side reactions could potentially compete with quinoline formation. The use of lower substrate concentrations would decrease the number of intermolecular collisions and hence limit the possible intermolecular reactions of various reactive species generated during the course of the reaction. Reduced substrate concentration did indeed have a positive effect on quinoline formation (Table 4.3). The quinoline was formed in 69 % yield with complete conversion of the starting material after 45 h (Table 4.3: Entry 3).

Table 4.3 Effect of Substrate Concentration on the Yield of **117**

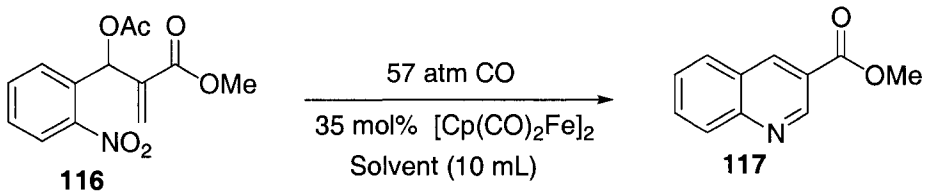


116 **117**

Entry	mmol **116**	Time (h)	Conversion of **116** (%)	Yield **117** (%)
1	1.0	21	90	35
2	0.11	22	46	21
3	0.11	45	>99	69

While the effect of solvent on the intermolecular amination reactions had been investigated, the studies were limited to benzene and dioxane (dioxane was found to be the superior solvent). It could be informative to see what the effect of more polar solvents might be. Halogenated solvents were ruled out due to the propensity of metal carbonyl dimers like $[Cp(CO)_2Fe]_2$ to react with alkyl halides.[135] A few reactions in dioxane/water and MeOH were performed (Table 4.4) .

Table 4.4 Effect of Solvent on the Conversion of **116** and Yield of **117**



116

0.11 mmol

117

Entry	Solvent	Temp. (°C)	Time (h)	Conversion of **116** (%)	Yield **117** (%)
1	dioxane	150	22	46	21
2	dioxane	150	45	>99	69
3	dioxane/H_2O (1:1)	150	22	92	29
4	MeOH	150	26	99.5	45
5	MeOH	100	23	90	26
6	MeOH	100	72	>99	37
7	dioxane/ 2.0 eq $EtN(iPr)_2$	150	24	64	25

Water had a positive effect on the rate of substrate conversion but a deleterious effect on the yield of quinoline (Table 4.4: Entry 3). MeOH exhibited similar behavior, and good conversion of the substrate could be obtained even at lower temperatures (Entries 4-6), but the quinoline was not the major product and the identity of the product(s) was not determined. The longer reaction times in MeOH gave increased amounts of quinoline even though most of the acetate had been consumed. For example, with only 10 % of the acetate remaining after 23 h the amount of quinoline detected was 26 %, however after 72 h the amount of quinoline detected was 37 %. Of course the 10% of acetate remaining could not account for an 11 % yield of the quinoline, and these percentages could be due to inherent limitations of the method of analysis. If these two considerations are put aside, it is tempting to suggest the presence of an intermediate that is converted to the quinoline. We were also concerned that acetic acid might be produced in the reaction and play some role in quinoline formation (either positively or negatively). For this reason we conducted a reaction in the presence of Hunig's base to possibly scavenge any acetic acid produced in the reaction; this medium also increased the rate of reaction but not the yield of quinoline (Entry 7). Given the outcome of these experiments it was decided that dioxane would be used as the solvent of choice for any further optimizations.

At this point yields of 69 % had been obtained and were satisfactory. However the high CO pressure employed in this cyclization would most likely preclude the general application of this reaction by most synthetic chemists. Ideally these reactions would be conducted under 1 atm of CO in regular lab glassware (bubbling CO). At pressures above ~10 atm it is necessary to use stainless steel reaction vessels which are expensive and not widely used. At intermediate pressures (1 atm to 10 atm) it is possible to use

thick-walled glass vessels that are reasonably priced and relatively safe.[175] In order to lower the CO pressure used in these reactions we chose to investigate the effect of catalyst on the outcome of the reaction.

The most critical component of most catalytic reactions is the catalyst, and while there was little rational design of this catalyst system, it did give a useful reaction. With this in mind, it was imagined that minor modifications to the catalyst might give very different results, as is often the case in transition metal catalyzed reactions. A variety of known Group 8 transition metal carbonyl dimers that had been reported in the literature were prepared including: $[Cp^*(CO)_2Fe]_2$[176] (or Fp^*_2 analogous to $[Cp(CO)_2Fe]_2$ but possessing the pentamethylcyclopentadienyl (Cp*) ligand), the analogous Ru complex $[Cp^*(CO)_2Ru]_2$,[177] the complex **118** with a dppe ligand substituted for CO,[178] and a complex reported by Angelici bearing a bridging disilyl ligand **119** (Figure 4.1).[179]

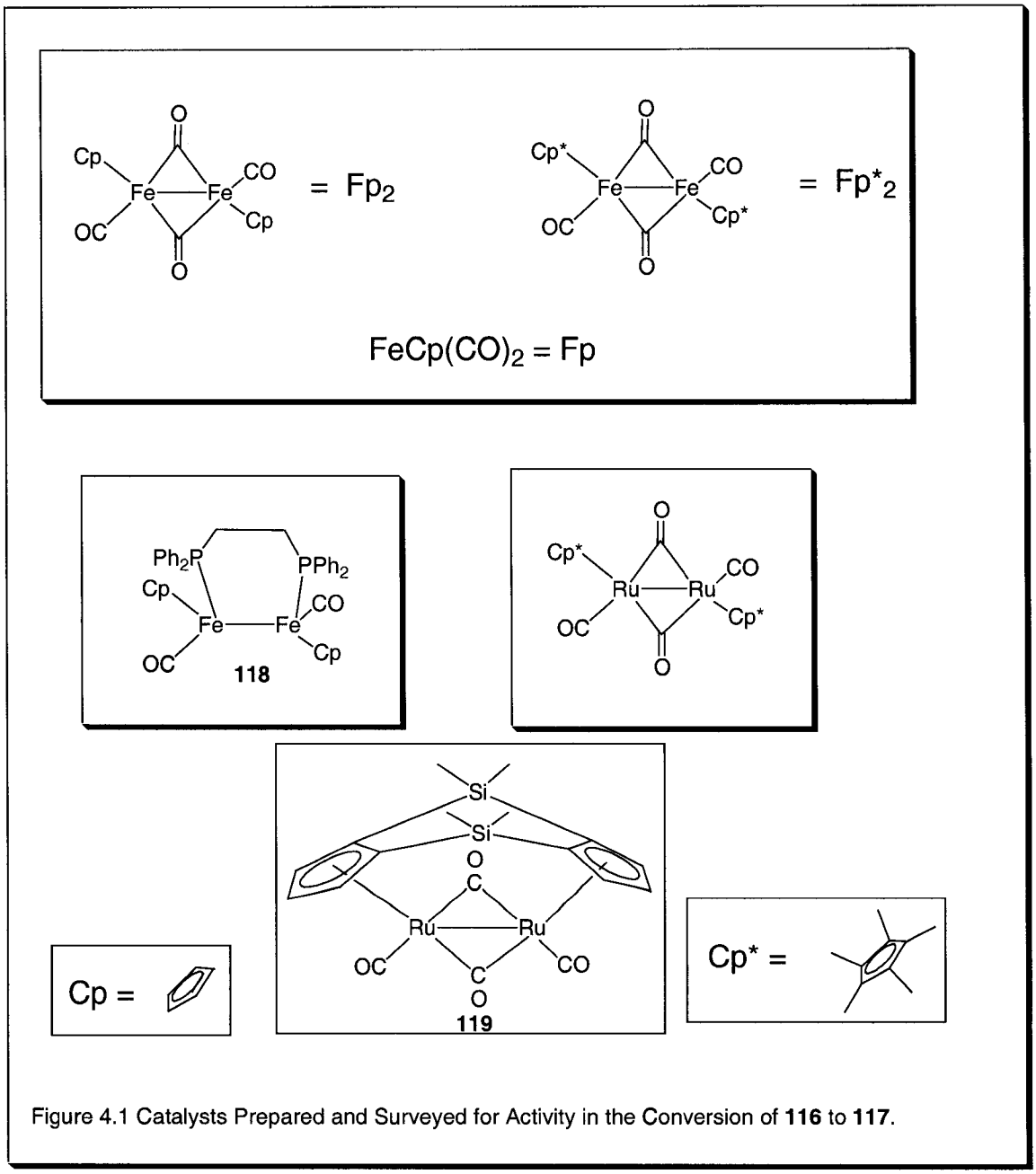
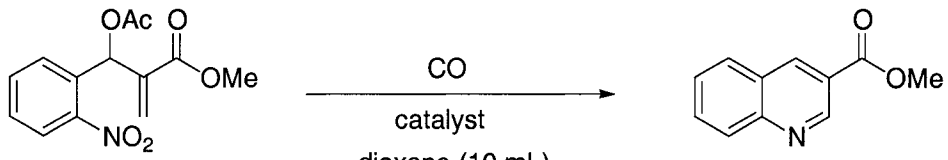


Figure 4.1 Catalysts Prepared and Surveyed for Activity in the Conversion of **116** to **117**.

Initial reactions were conducted with these catalysts at moderate to high CO pressure and it was found that all complexes were active (Table 4.5). The best yields were obtained with $[Cp^*(CO)_2Ru]_2$ and $[Cp^*(CO)_2Fe]_2$ as catalysts. The $[Cp^*(CO)_2Ru]_2$ system gave the highest yields (83%) at relatively high loading (35%) (Entry 3), and $[Cp^*(CO)_2Fe]_2$ gave a comparable yield (80%) at low loading (5%) (Entry 7).

The Si-bridged complex **119** was inferior to all catalysts surveyed (Entry 6), and the dppe complex **118** gave lower yields (24 %) than $[Cp^*(CO)_2Fe]_2$ (79 %) at 20 atm (Entries 8 and 9).

Table 4.5 Effect of Catalyst on the Conversion of **116** and Yield of **117**



116

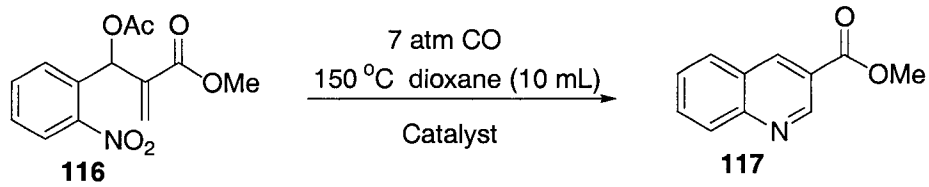
0.11 mmol

117

Entry	Catalyst (mol %)	CO (atm)	Time (h)	Conversion of **116** (%)	Yield **117** (%)
1	Fp_2 (35)	57	23	46	21
2	Fp_2 (35)	57	45	>99	69
3	$[Cp^*(CO)_2Ru]_2$ (35)	57	46	>99	83
4	$[Cp^*(CO)_2Ru]_2$ (10)	57	23	54	19
5	$[Cp^*(CO)_2Ru]_2$ (10)	57	44	>99	66
6	**119** (35)	57	46	>99	37
7	Fp^*_2 (5)	57	42	>99	80
8	Fp^*_2 (10)	20	42	>99	79
9	**118** (20)	20	44	>99	24

With these new more active catalyst the pressure was reduced drastically and the catalysts were surveyed. It was found that $[Cp^*(CO)_2Fe]_2$ gave the best results at 7 atm of CO pressure (Table 4.6: Entry 3). Unfortunately reactions at 1 atm were impractically slow, with very low conversion after several days. Using the optimized conditions ($[Cp^*(CO)_2Fe]_2$, dioxane, 150°C, 0.011 M **116** in dioxane, 7 atm CO) we were able to do a preparative scale experiment and isolate the quinoline in 67% yield after chromatography (Table 4.6: Entry 4). While these conditions might not give the highest possible yield, the aforementioned gain in synthetic convenience by using lower pressure was thought to out way a modest yield increase (~10%) at higher pressure.

Table 4.6 Active Catalysts at Lower CO Pressure (7 atm)



116 0.11 mmol

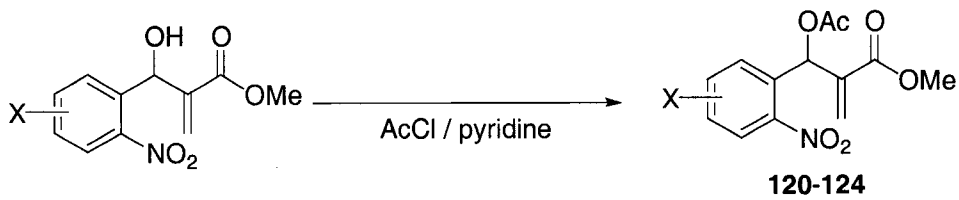
117

Entry	Catalyst (mol%)	Time (h)	Conversion of **116** (%)	Yield **117** (%)
1	Fp_2 (20)	70	ND	28
2	$[Cp^*(CO)_2Ru]_2$ (20)	70	ND	41
3	Fp^*_2 (10)	42	>99	73
4	Fp^*_2 (10)	42	>99	67[a]

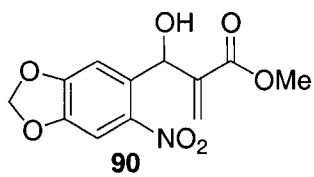
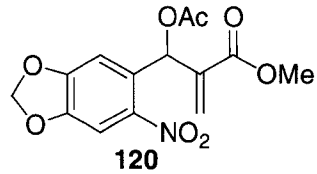
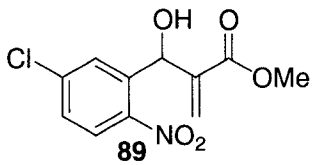
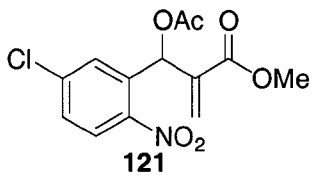
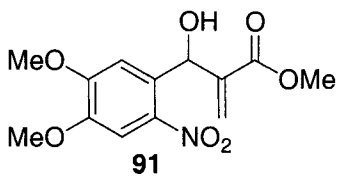
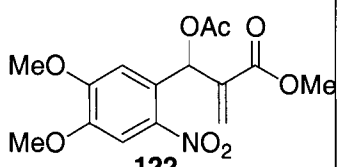
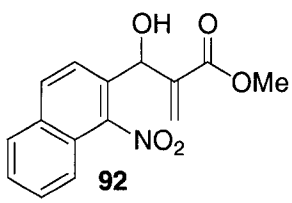
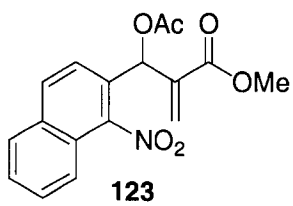
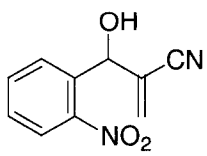
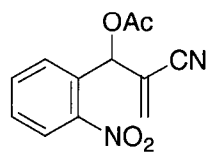
ND = Not determined; a) isolated yield after chromatography with 0.72 mmol **116**

After the initial optimization with substrate **116**, the B-H acetates **120-124** were prepared in good to excellent yield (Table 4.7). These acetates were unknown compounds and were fully characterized with modern spectroscopic methods (^{1}H NMR, ^{13}C NMR, MS, IR, combustion analysis). The ^{1}H NMR of these compounds show the distinctive resonances of the acetate methyl group at around δ 2.0 and two resonances for the vinyl group at around δ 6.0 that have characteristic geminal coupling constants. The IR spectra show strong absorptions at around ~1700 cm^{-1} and ~1750 cm^{-1} for the methyl ester and acetate functional groups. Column chromatography was performed to isolate these compounds. However, they can usually be isolated in >98% purity after workup without any purification. Moreover, crystallization of the crude material from toluene gives very pure material, although with a consequentially diminished yield (~-20%).

Table 4.7 Synthesis of B-H Acetates

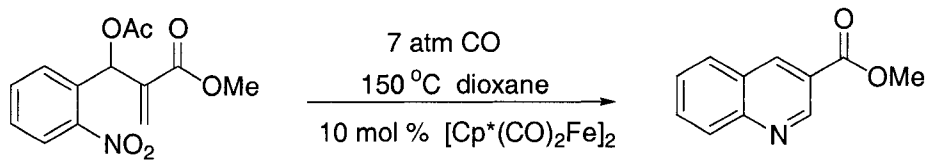


120-124

Entry	B-H Adduct	B-H Acetate	Yield (%)
1	 **90**	 **120**	94
2	 **89**	 **121**	99
3	 **91**	 **122**	96
4	 **92**	 **123**	93
5	 **95**	 **124**	71

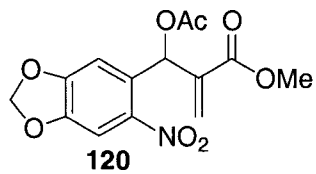
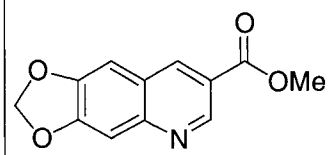
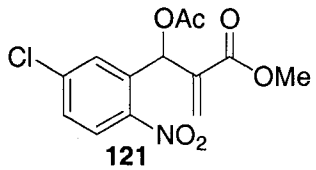
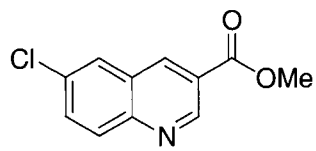
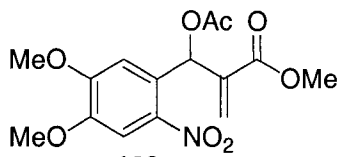
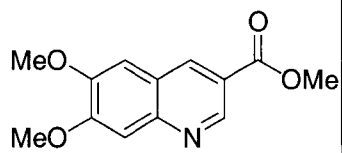
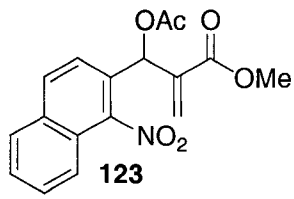
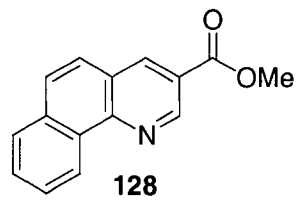
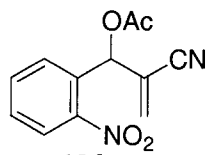
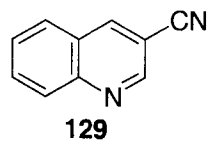
Employing the previously optimized conditions the acetates were cyclized to the appropriate quinolines **125-129** (Table 4.8). Only the quinoline **129** has been reported in the literature.[180] The identity of the unknown compounds was thoroughly verified using modern spectroscopic means (IR, ^{1}H NMR, ^{13}C NMR, MS) with purity established by combustion analysis or mp. Characteristic spectroscopic data include the aforementioned characteristic set of two doublets in the ^{1} H NMR spectra arising from the protons at the 2 and 4 position of the heterocyclic ring. The reaction is effective for substrates bearing either electron donating (entries 1 and 3) or electron withdrawing groups (entry 2), though the former react more slowly. The carbomethoxy and cyano groups are both tolerated well (entry 5). The benzo[h]quinoline **128** was also accessible (entry 4). In addition to the quinolines some minor products (inseparable) were also isolated. GCMS analysis revealed two main byproducts of 2- and 4- mass units higher than the quinoline with similar fragmentation patterns to the quinolines, suggestive of the corresponding dihydro- and tetrahydro-quinolines. The nitro B-H acetates required for this reaction are easily prepared in high yield and the reaction's tolerance for electronically diverse substituents on the aromatic ring promise to make this a general and preferred route to these quinolines. This nucleus is common to many medicinally important quinolines,[181] and it was appropriate to compare our method to other known methods for the synthesis of quinolines of this type.

Table 4.8 Synthesis of Quinolines from B-H Acetates



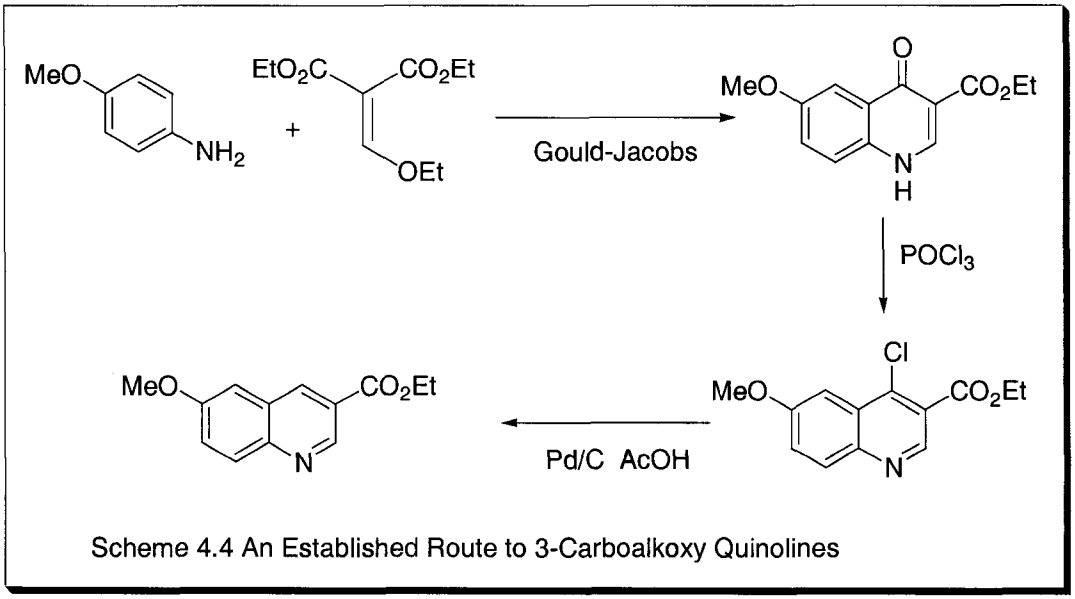
120-124
0.011M

125-129

Entry	B-H Acetate	Time (h)	Quinoline	Yield (%)
1	 **120**	81	 **125**	65
2	 **121**	52	 **126**	48
3	 **122**	89	 **127**	60
4	 **123**	40	 **128**	47
5	 **124**	39	 **129**	65

4.4: OTHER METHODS FOR PREPARING 3-CARBOALKOXY QUINOLINES

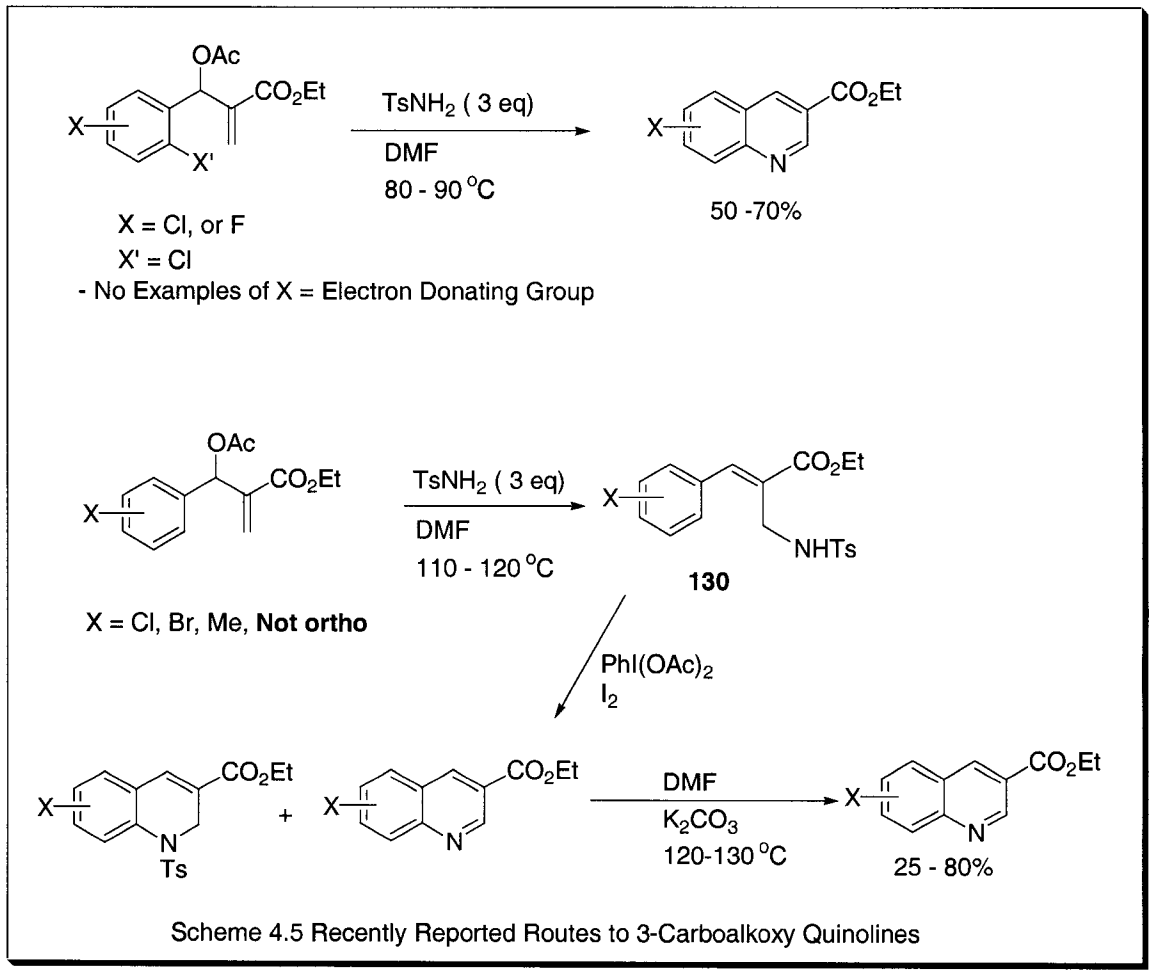
The most established route to 3-carboalkoxy quinolines, requires the preparation of 4-quinolone derivatives through a Gould-Jacobs reaction, followed by chlorination, and then catalytic reduction with H_2/Ni or Pd catalysts (Scheme 4.4).[182]



Scheme 4.4 An Established Route to 3-Carboalkoxy Quinolines

The Gould-Jacobs reaction suffers from limited regioselectivity when 3-substituted anilines are employed. More recent reports have employed sulfonamides derived from B-H acetates that undergo intramolecular aromatic substitution via the pendant amino groups (Scheme 4.5).[183] The only reported examples of this reaction employ rings with electron-withdrawing groups, which facilitates the intramolecular nucleophilic aromatic substitution. This same group has employed a rather lengthy route starting from Baylis-Hillman acetates which undergo an SN2' reaction with sulfonamides to give the tosyl amine **130**. Treatment of these amines with I_2/PhI(OAc)$_2$ promotes an oxidative

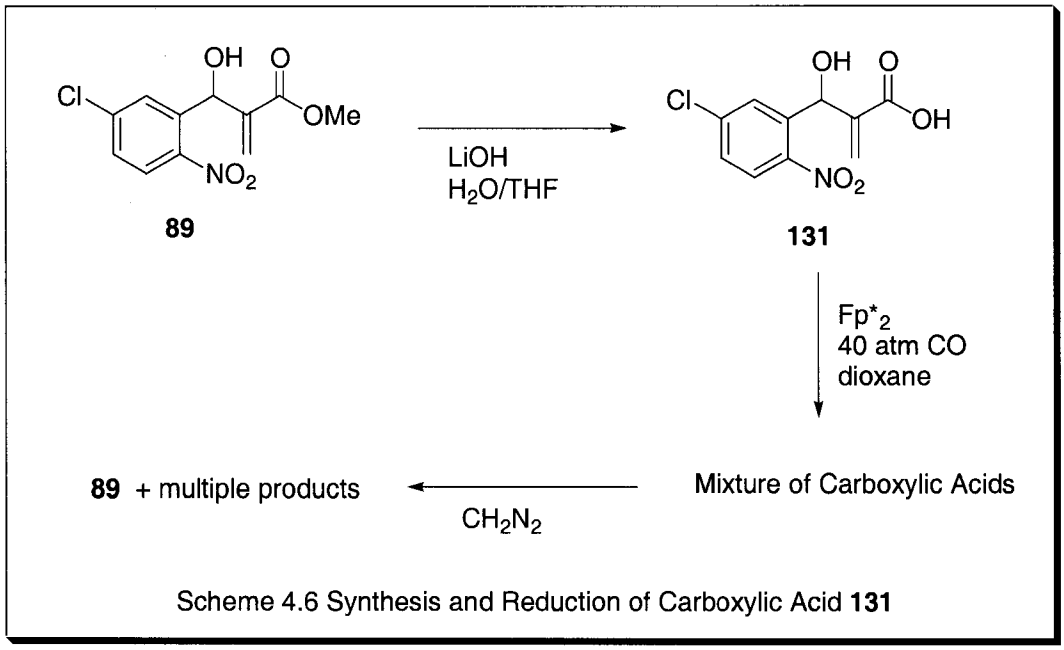
cyclization that give mixtures of products. This mixture is then treated with base to give the quinolines.[184]



Scheme 4.5 Recently Reported Routes to 3-Carboalkoxy Quinolines

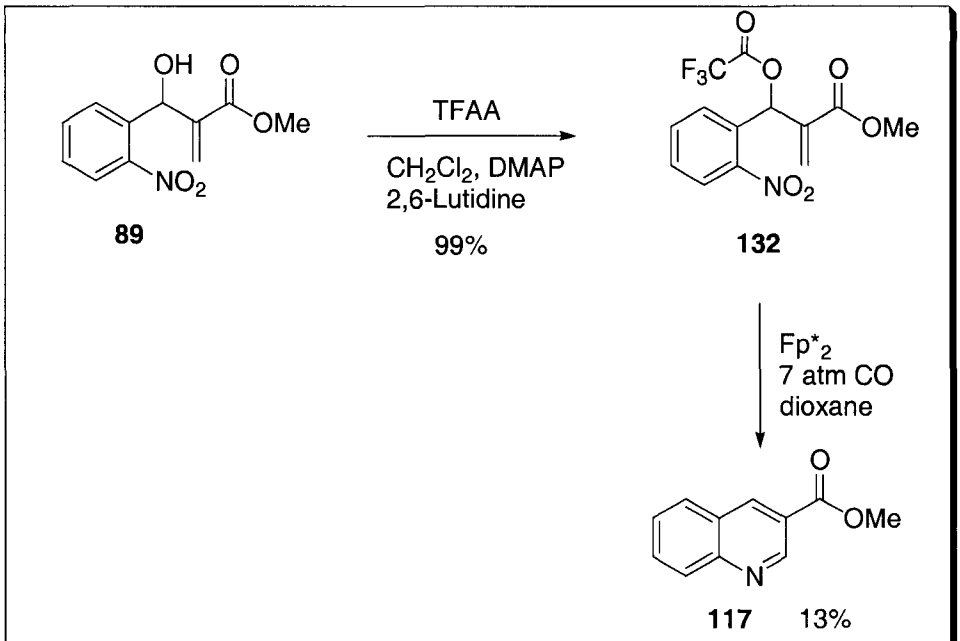
4.5: SYNTHESIS AND CYCLIZATION OF OTHER DERIVATIVES OF BAYLIS-HILLMAN ADDUCTS: CARBOXYLIC ACID, TMS ETHER AND TRIFLUOROACETATE

Given the good yields (49-67 %) of quinolines from the Baylis-Hillman acetates at moderate CO pressure (7 atm), attention was turned to the cyclization of other derivatives of the Baylis-Hillman adducts, bearing other substituents on the allylic oxygen, for example, that might undergo even more facile transformation to quinolines. The carboxyl group was also an easily modifiable functional group, and was our starting point in these modifications. The ester functionality in adduct **89** was easily cleaved with LiOH to give the carboxylic acid **131**.[185] Cyclization of this acid with $[Cp^*(CO)_2Fe]_2$ and CO (40 atm) in dioxane for 48 h gave a mixture of carboxylic acids. This mixture was esterified with diazomethane to regenerate the methyl ester (Scheme 4.6). Analysis of this mixture revealed primarily starting material along with many unidentified products. This reaction was not very selective and conversion of starting material was poor even with the high CO pressure. For these reasons this reaction was not investigated further.



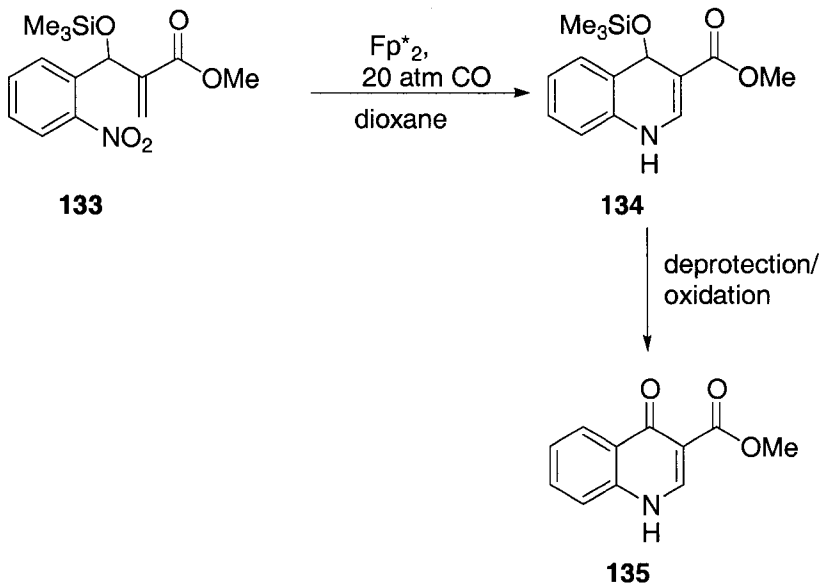
Scheme 4.6 Synthesis and Reduction of Carboxylic Acid **131**

Given the fact that the B-H acetates worked so well, it was imagined that a better leaving group might enable an even faster reaction. Trifluoroacetate is a 10^6 times better leaving group than acetate.[186] For this reason the trifluoroacetate **132** was prepared from the Baylis-Hillman adduct **88** in excellent yield (Scheme 4.7).[187] This was a new compound and was characterized by ^1H and ^{13}C NMR. It exhibits a characteristic ^{13}C NMR, with a CF_3 carbon (δ 111.5) that is split into a quartet. Unfortunately when subjected to our prior optimized cyclization conditions, the quinoline was produced in only 13% yield (GC). The other products in this reaction were not identified, but this result appears to suggest that the leaving group ability of OX in the cyclization is not the most crucial component.



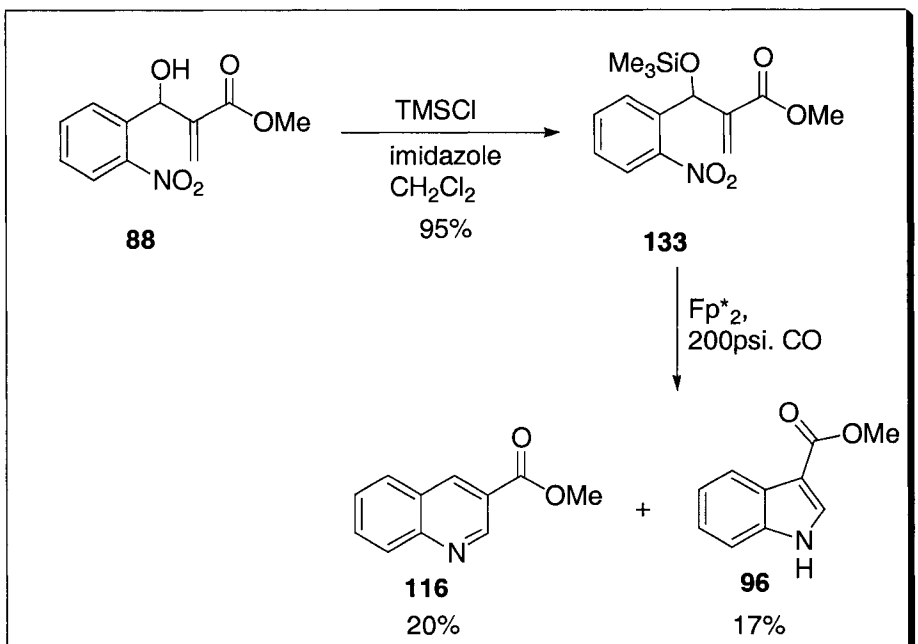
Scheme 4.7 Synthesis and Reduction of Trifluoroacetate **132**

Reactions in which the allylic oxygen could be retained in the product were also of interest, and might provide entry into heterocycles with oxygen functionality like the 4-quinolones. It was envisioned that a TMS protected BH **133** adduct that would cyclize to the TMS protected dihydroquinoline **134** that could be deprotected/oxidized to the 4-quinolone **135** (Scheme 4.8).



Scheme 4.8 Proposed Synthesis of 4-Quinolone **135** from **133**

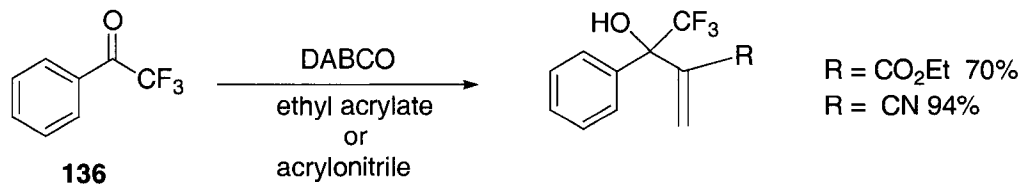
The TMS derivative **133** was prepared in 95 % yield by treatment of the Baylis-Hillman adduct **88** with TMSCl and imidazole (Scheme 4.9).[188] This was an unknown compound and was characterized by spectroscopically and had the resonance for the TMS group at δ 0.13 in the ^{1}H NMR spectrum. Unfortunately cyclization of the TMS derivative gave both the quinoline **116** and the indole **96** in almost equal amounts (GC). Quinoline formation may be accounted for by loss of TMSOH from an intermediate. The indole could arise from removal of the TMS group to generate the B-H adduct **88** under our reaction conditions.



Scheme 4.9 Synthesis and Reduction of TMS ether **133**

4.6: ATTEMPTS TO SYNTHESIZE 4-CF_3 QUINOLINES

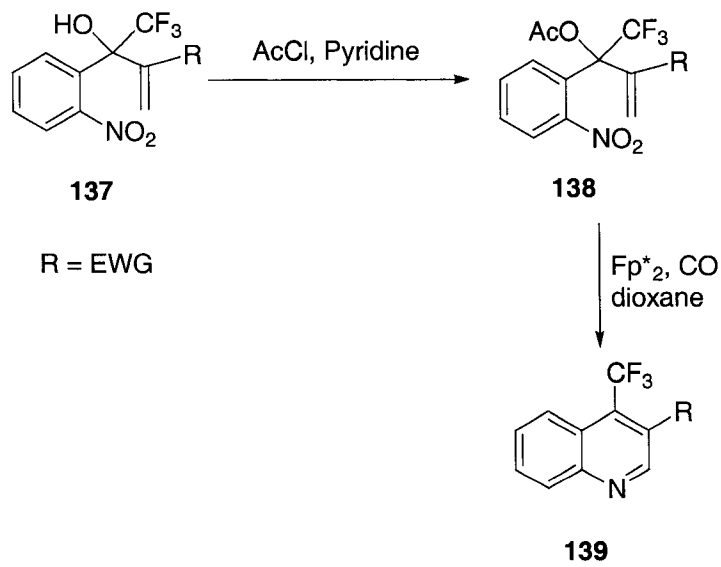
While other derivatives of the Baylis-Hillman adducts had failed to give selective/desired reactions, more complex or medicinally important quinolines might be prepared using our Baylis-Hillman acetate reductive cyclization reaction. The Baylis-Hillman reaction is generally limited to aldehydes, however Ramachandran had reported that the Baylis-Hillman reaction of trifluoro acetophenone **136** gave good yields of Baylis-Hillman adducts (Scheme 4.10).[189]



136

Scheme 4.10 Ramachandran's Report on the Baylis-Hillman Reaction of **136**

If the Baylis-Hillman adduct **137** bearing the trifluoromethyl group could be prepared it should undergo acetylation to **138** and then cyclization to form 4-trifluoromethyl quinolines **139** via our conditions (Scheme 4.11).

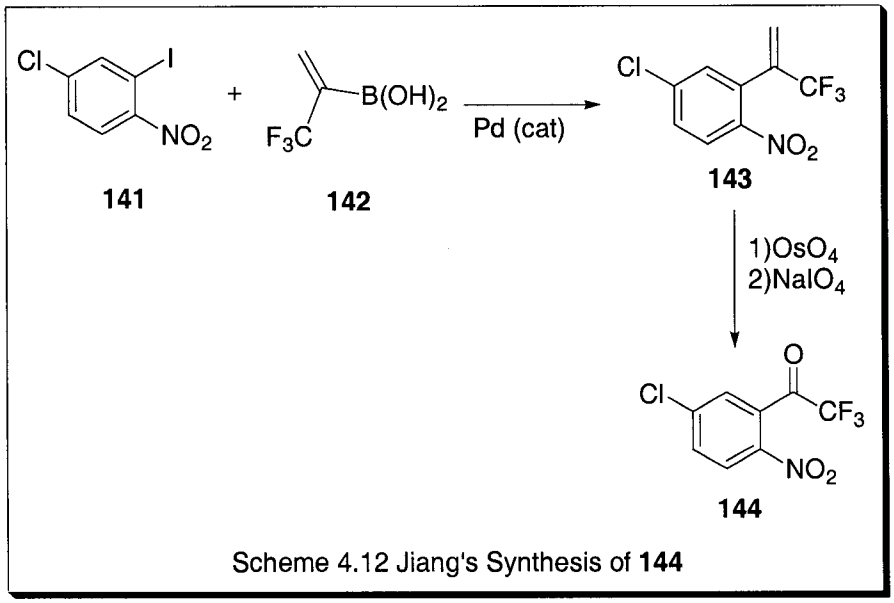


Scheme 4.11 Proposed Route to 4-Trifluoromethyl Quinolines **139**

Fluorinated organic compounds are very important medicinally due to their lipophillic behavior, which allows them to pass through biological membranes more easily than a corresponding hydrocarbon. Lipophilicity is an important factor in the efficacy of quinoline anti-malarials.[181b] While working on this project, the targeted trifluoromethyl quinolines **139** were prepared by Schlosser, through a somewhat lengthy route, that relied upon the intermediacy of a 2-quinolone prepared by a classical method.[190] The B-H acetate cyclization strategy would at least compliment this synthesis in terms of the regioselectivity of the cyclization.[191]

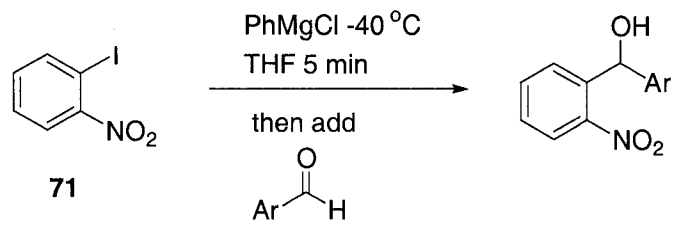
The required 2,2,2-trifluoromethyl-2'-nitroacetophenone **140** has been prepared in 2 % yield by nitration of 2,2,2-trifluoromethyl-acetophenone with fuming nitric acid,[192] and in 21 % yield by Olah with $NO_2Cl{\cdot}SbCl_5$.[193] The only other practical route to compounds of this type, to our knowledge, was a lengthy route by Jiang et. al., in which the *o*-iodo nitro benzene **141** underwent Suzuki coupling with the vinyl boronic acid **142**

to give the styrene derivative **143** (Scheme 4.12).[194] **143** was dihyroxylated with osmium tetroxide and then oxidatively cleaved with sodium periodate to give the ketone **144**. Because of the length of this route, an alternative preparation of **140** was sought.



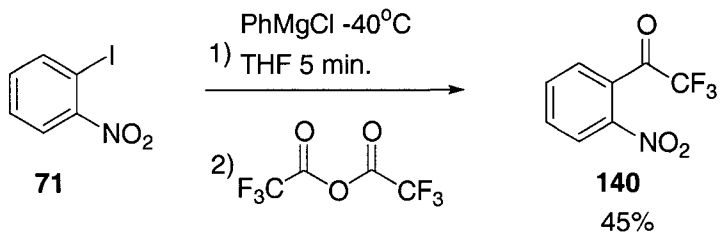
Scheme 4.12 Jiang's Synthesis of **144**

Knöchel reported on the generation of aryl Grignard reagents bearing *o*-nitro functionality at low temperature through a metal halogen exchange reaction with *o*-iodo-nitrobenzene **71** and phenyl magnesium chloride. These Grignards were reacted with aryl aldehydes to generate *o*-nitro benzhydryls (Scheme 4.13).[195]



Scheme 4.13 Knöchel's Low Temperature Generation of 2-Nitrophenyl Grignard

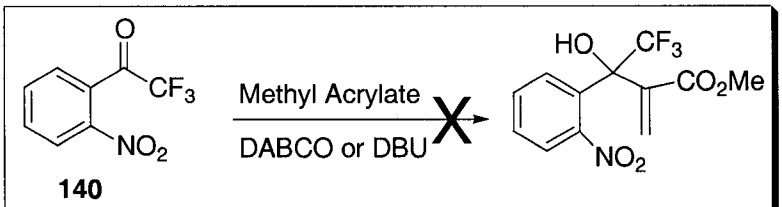
Reports on the reaction of phenyl Grignards with trifluoroacetic anhydride to give 2,2,2 trifluoromethyl acetophenone have also been made.[196] With this in mind the reaction of the *o*-nitrophenyl Grignard generated via the method of Knöchel with trifluoroacetic anhydride was attempted. Much to our delight the desired 2,2,2 trifluoromethyl-2'-nitroacetophenone **140** was produced in 45% yield (Scheme 4.14). While the compound was known, the paucity of data available made it necessary to carry out further characterization (^{1}H NMR, ^{13}C NMR).



Scheme 4.14 Synthesis of Ketone **140**

With the ketone **140** in hand its behavior under typical Baylis-Hillman reaction conditions was investigated. Unfortunately, **140** failed to undergo the desired reaction even after prolonged reaction times (up to 6 days) with either DBU or DABCO as the promoter (Scheme 4.15). The reaction with DABCO did convert a small amount of the starting material to an unidentified product that did not appear to contain the acrylate unit (^{1}H NMR). While the ketone **140** is extremely electron deficient its failure to undergo the Baylis-Hillman reaction may be attributed to steric inhibition that comes not only from the nitro group, but also from the trifluoromethyl group. While fluorine's smallness is eclipsed only by hydrogen (van der Waals radius of 147 pm for F and 120 pm for H),

the trifluoromethyl groups has been described as having an effective steric bulk comparable to isopropyl.[197] While modifications to the Baylis-Hillman reaction have been made,[198] it was felt that this chemistry was not worth further exploration.



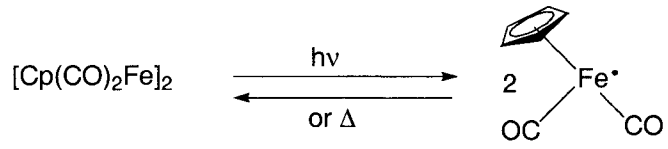
140

Scheme 4.15 Attempted Baylis-Hillman Reaction of **140**

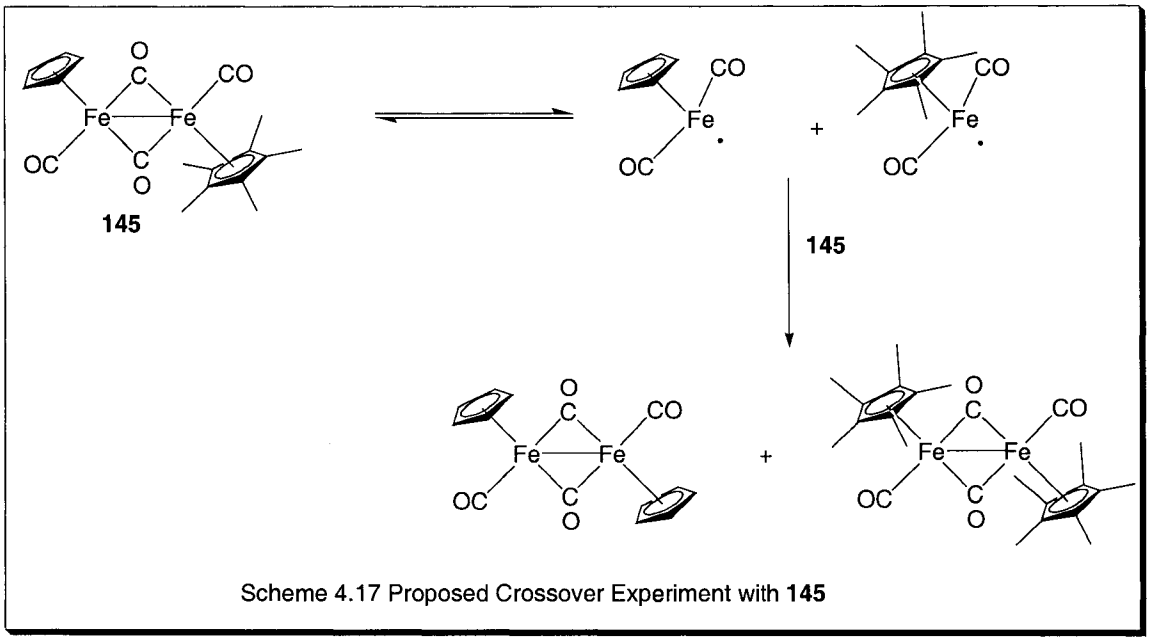
4.7: MECHANISTIC EXPERIMENTS

4.7.1: ATTEMPTS TO UNDERSTATND THE ACTIVE ORGANOMETALLIC SPECIES

It has been suggested that reductions of the aromatic nitro group by transition metal complexes and CO proceed via an initial electron transfer to the nitro group to generate a radical anion.[55,199] It is well known that $[Cp(CO)_2Fe]_2$ had been used as a promoter of radical cyclization reactions under irradiation with UV light.[135] Irradiation[200] or thermolysis[201] of the $[Cp(CO)_2Fe]_2$ dimer has been shown to cleave the dimer to give the 17 e- radical ($Fp^{\bullet}$) (Scheme 4.16). It was imagined that this radical could transfer an electron to the nitro group. However there was no evidence for the dissociation of the dimer to give the monomeric species under our reaction conditions. To determine if $[Cp(CO)_2Fe]_2$ dissociates to the monomeric radical under our reaction conditions (150° C, CO, dioxane), the mixed Cp ligand dimer $Cp(CO)_2FeFe(CO)_2Cp^*$ (**145**) was synthesized for a crossover experiment. If the dimer dissociates under our reaction conditions the crossover products $[Cp^*(CO)_2Fe]_2$ and $[Cp(CO)_2Fe]_2$ from the coupling of the radicals with other mixed Cp ligand dimers should be observed (Scheme 4.17).[202]



Scheme 4.16 Dissociation of $[Cp(CO)_2Fe]_2$



Scheme 4.17 Proposed Crossover Experiment with **145**

The desired compound **145** was prepared using a reported procedure.[203] The $Cp^*(CO)_2Fe$-I or (Fp*I) was prepared by reaction of $[Cp^*(CO)_2Fe]_2$ with I_2. The $Cp(CO)_2FeNa$ or (Fp anion) was prepared by Na/Hg amalgam reduction of $[Cp(CO)_2Fe]_2$ and was reacted immediately with Fp*I to give the mixed dimer as a dark red-brown solid that was isolated after chromatography. The mixed dimer **145** was subjected to our reaction conditions (20 atm CO, dioxane, 150 °C) for 48 h (a typical reaction time for our cyclizations), dioxane was removed *in vacuo*, and a ^1H NMR spectrum was immediately recorded of the material in benzene-d_6. Figure 4.2 shows the ^1H NMR of $[Cp(CO)_2Fe]_2$ (**A**), $[Cp^*(CO)_2Fe]_2$ (**B**), the mixed dimer **145** (**C**), and **145** after heating under 20 atm CO in dioxane (**D**). All spectra were taken in benzene-d_6. It can be clearly seen that upon heating the mixed dimer produces both $[Cp^*(CO)_2Fe]_2$ and $[Cp(CO)_2Fe]_2$. This provides strong evidence for the presence of the monomeric radical during the course of our cyclizations.

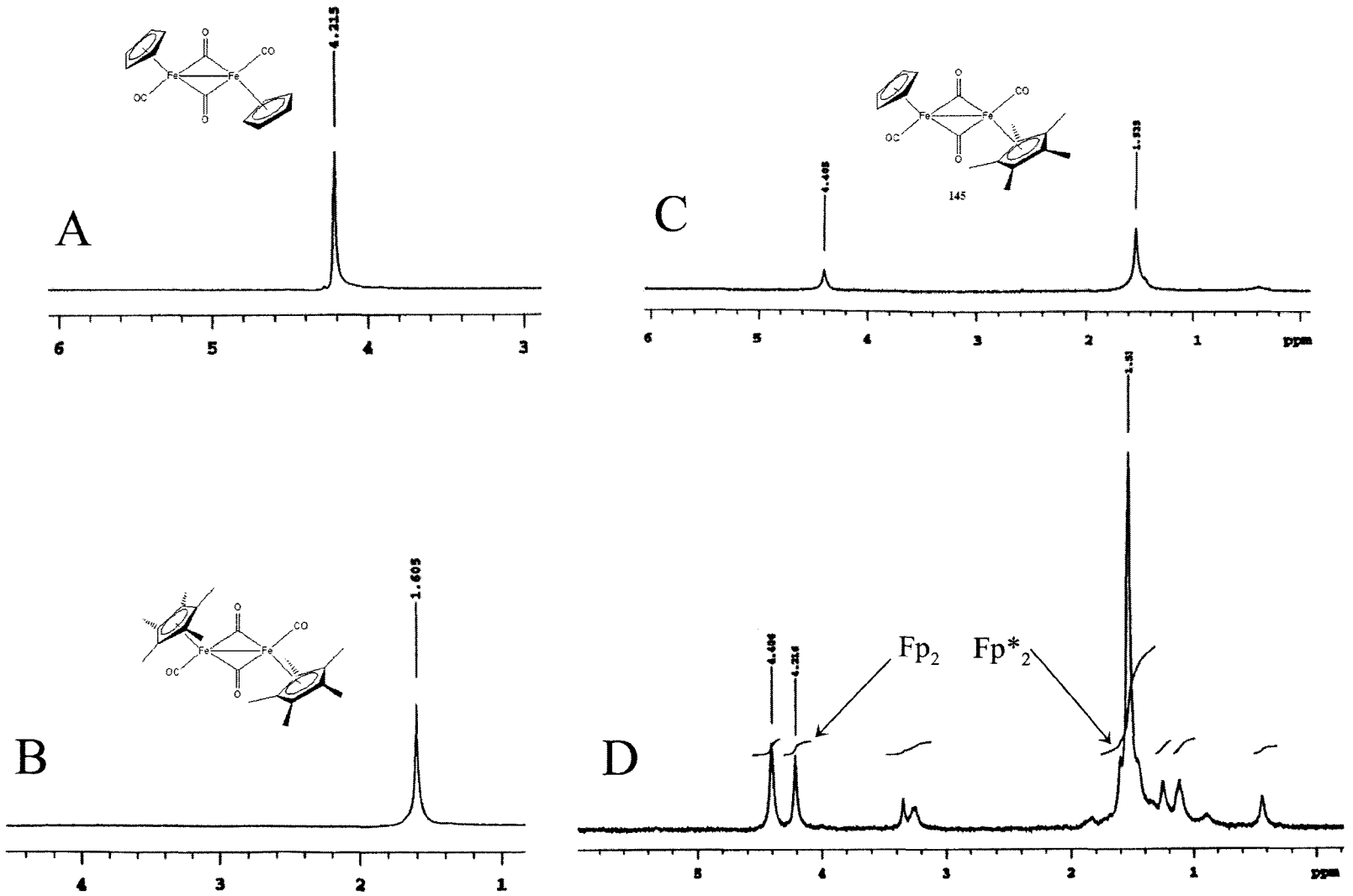


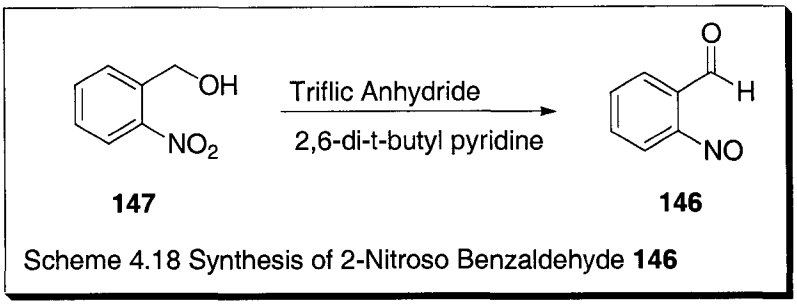
Figure 4.2 300 MHz ^{1}H NMR of $[Cp(CO)_2Fe]_2$ (**A**), $[Cp^*(CO)_2Fe]_2$ (**B**), **145** (**C**), and **145** after heating at 150 °C in dioxane under CO (**D**). (All spectra recorded in C_6D_6)

Given the relatively low CO pressure (7 atm) required for the reactions of the Baylis-Hillman acetates with the $[Cp^*(CO)_2Fe]_2$/CO as compared to previous reductions (50 atm), it was imagined that it might be possible to observe intermediates generated during the course of the reaction. While a high pressure IR cell was at our disposal, the temperature required was too great for this particular apparatus. We then turned our attention to high-pressure NMR tubes. The BH acetate **116** was placed in a high pressure NMR tube with $[Cp^*(CO)_2Fe]_2$ under 4 atm of CO pressure in benzene-d_6. At room temperature an ^1H NMR spectrum of the solution was obtained. After heating at 150°C for 3 h another ^1H NMR spectrum was collected, unfortunately the sample was nearly impossible to lock/shim and when a spectrum was recorded the lines were extremely broad and no meaningful information could be obtained. This behavior may be explained by the presence of paramagnetic Fe material in the reaction mixture. It can be seen in Figure 4.2 that the spectrum of **145** after heating under CO is slightly broadened.

4.7.2: ATTEMPTED SYNTHESIS OF POTENTIAL ORGANIC INTERMEDIATES

We were also interested in preparing Baylis-Hillman adducts/acetates that contained *ortho*-nitrogen functionality at different oxidation states. While the amino and hydroxyl amino compounds were ruled out due to the lack of available synthetic routes and their tendency to spontaneously cyclize even if they could be prepared, the nitroso oxidation state seemed like a viable target. The known 2-nitroso-benzaldehyde **146** was prepared using a recent method developed by Corrie.[204] In this reaction 2-nitrobenzyl

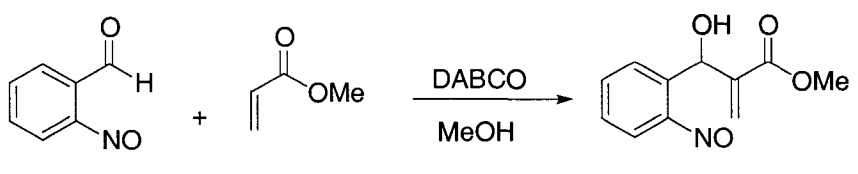
alcohol **147** was treated with triflic anhydride and 2,6-di-*t*-butyl pyridine at low temperature to give **146** (Scheme 4.18).



147 **146**

Scheme 4.18 Synthesis of 2-Nitroso Benzaldehyde **146**

The 2-nitroso benzaldehyde **146** had poor solubility in methyl acrylate, so Baylis-Hillman reactions were attempted in MeOH with this substrate. The Baylis-Hillman reaction in MeOH gave a plethora of products including the Baylis-Hillman adduct **148**, which was isolated by preparative TLC in less than a 5 % yield (12 mg) (Scheme 4.19). This low yield was disappointing, but we reasoned that if the reaction was optimized or conducted on a significantly larger scale it might be possible to isolate enough material to be useful. Even though the method used to prepare **146** was the most straightforward available,[205] the 2,6-di-*t*-butyl pyridine used was very expensive and these reactions were not studied further.

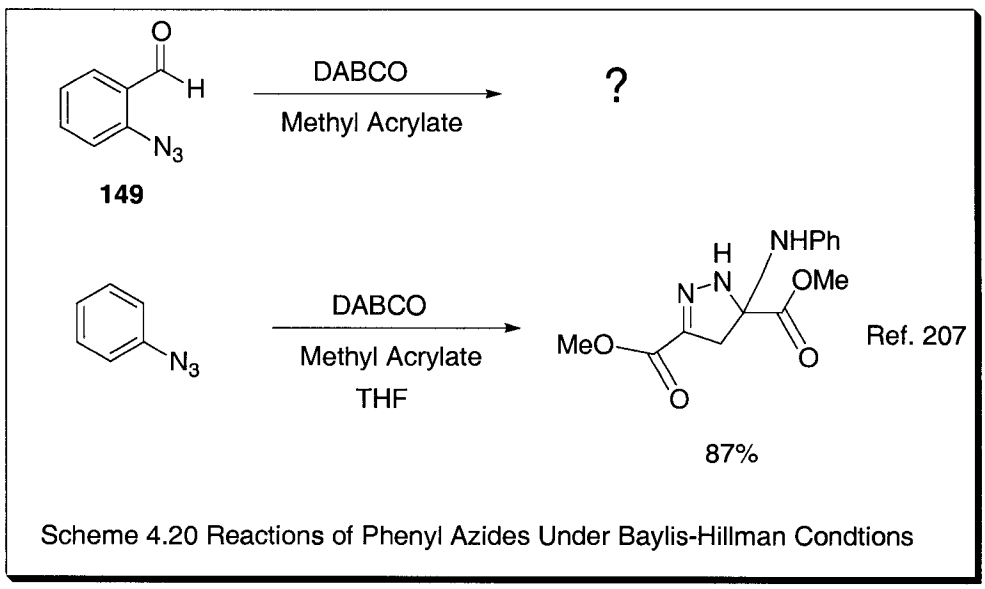


147 **148**

5%

Scheme 4.19 Baylis-Hillman Reaction of **147** in MeOH

It could also be informative to purposefully generate a nitrene in the *ortho*-position of the Baylis-Hillman adducts/acetates to see if products arising from cyclization are produced. To this end we imagined a Baylis-Hillman adduct analogous to **88** but bearing a 2-azido group instead of 2-nitro. The 2-azido benzaldehyde **149** required for the Baylis-Hillman reaction was easily prepared by reaction of 2-nitro benzaldehyde with sodium azide.[206] The Baylis-Hillman reaction with methyl acrylate did not occur, instead another reaction(s) was observed, and the products were not identified rigorously (^{1}H NMR, TLC, GCMS of crude material), but it was apparent the desired adduct was not produced. Since that time a report has been made on the reaction of phenyl azide under Baylis-Hillman conditions (methyl acrylate, DABCO, THF) to give a pyrazoline (Scheme 4.20).[207] The 1,3 dipolar cycloaddition of aryl azides to acrylates is a known reaction, and apparently the conditions of the Baylis-Hillman reaction (DABCO) accelerate a further known reaction of the cycloadducts to give the pyrolline.[208]

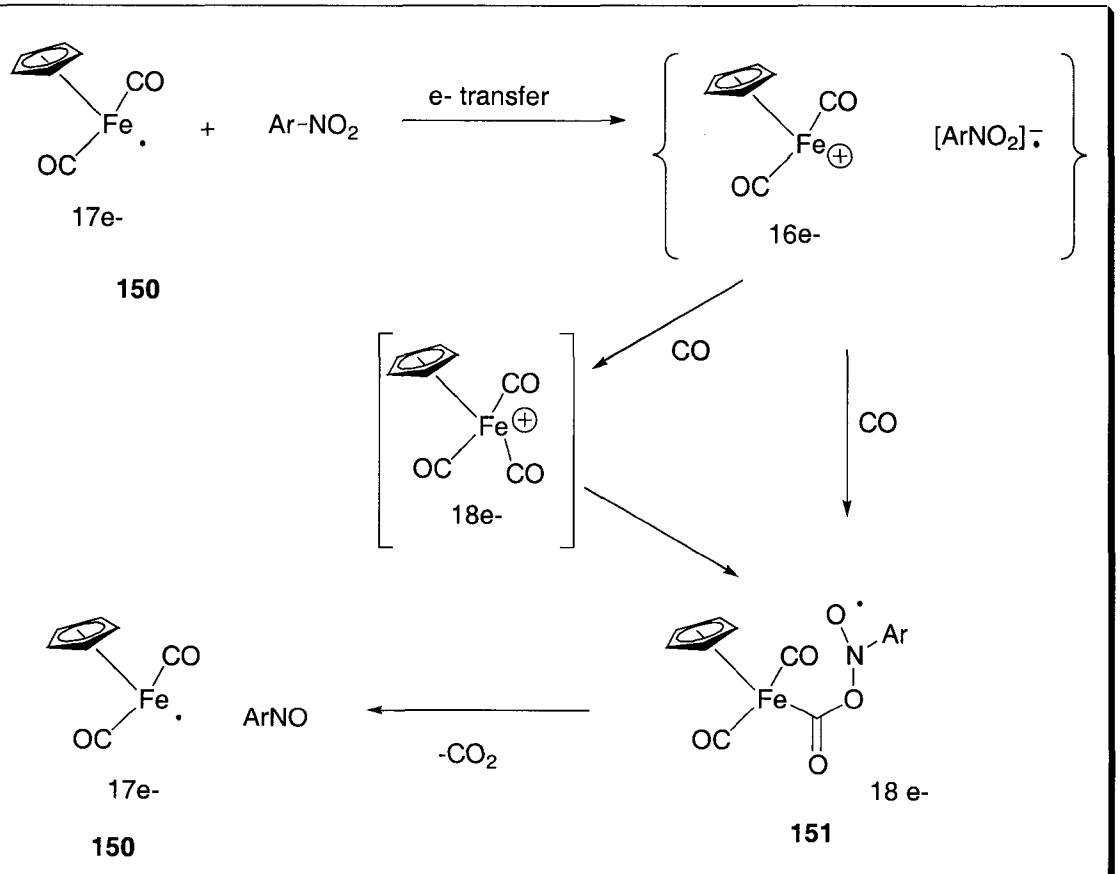


Scheme 4.20 Reactions of Phenyl Azides Under Baylis-Hillman Condtions

4.8: PROPOSED MECHANISMS

4.8.1: POTENTIAL MECHANISM FOR NITRO REDUCTION

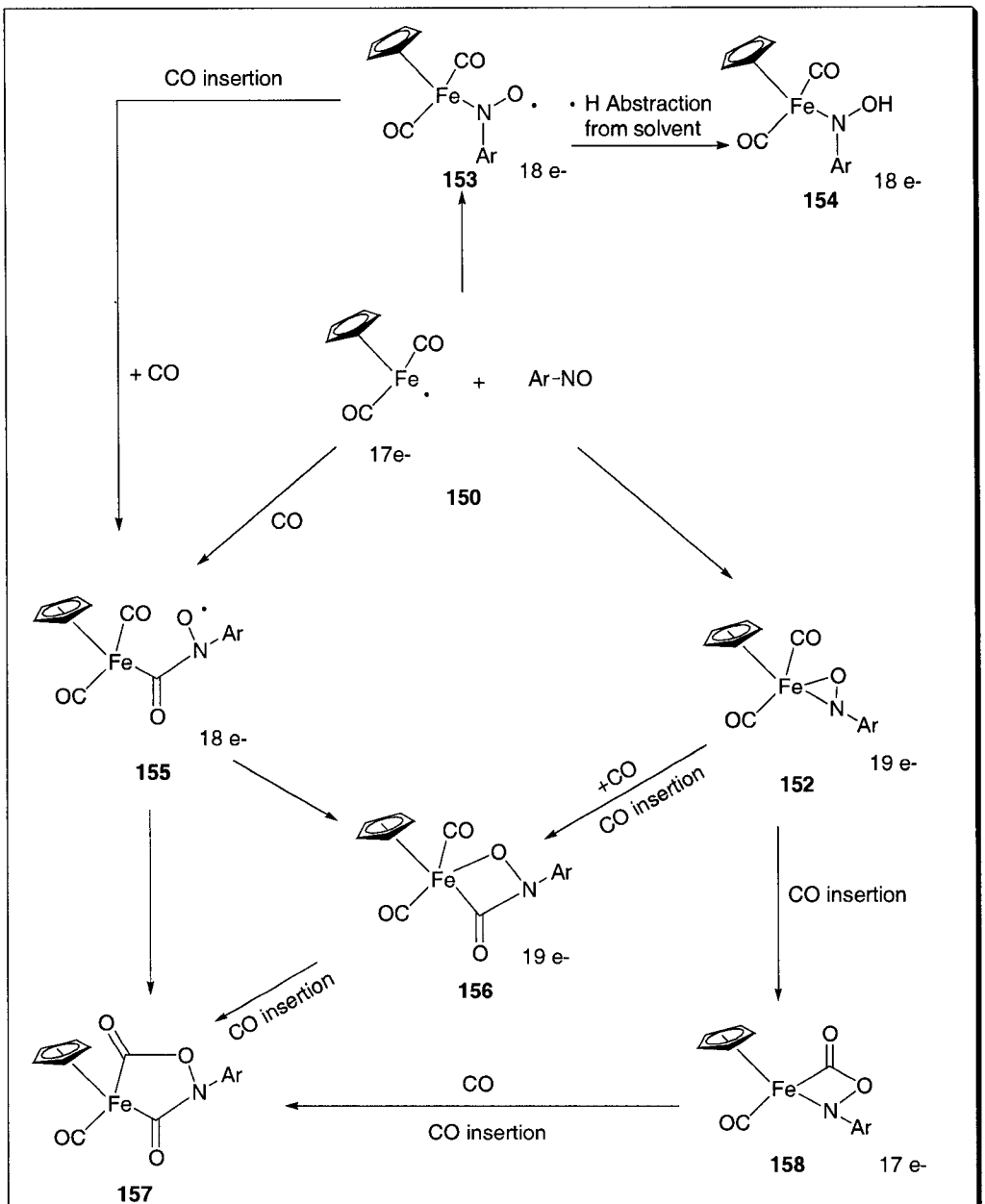
While the active catalytic intermediate(s) in the reactions of the $[Cp(CO)_2M]_2$ (M = Fe, Ru) with nitro compounds has not been established, it has been shown that the 17e- radical Fp· **150** is likely present in the reaction mixtures. It is possible to imagine this radical participating in e- transfer to the nitro group to generate the nitrobenzene radical anion, a well known species (Scheme 2.21).[209]



Scheme 4.21 Proposed Mechanism of Nitro Reduction by **150**

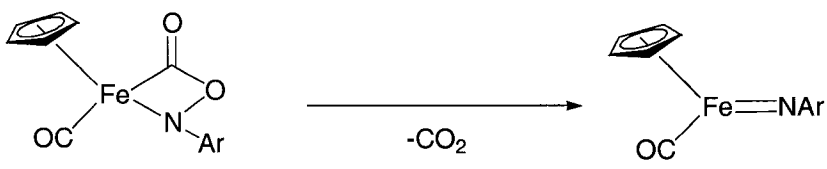
The 16e- iron complex generated from such a transfer would likely be extremely unstable and a radical ion pair would most likely be closely associated and coordinate CO rapidly. This aryl nitro radical anion could attack a coordinated CO ligand to give the 18 e- complex **151** after CO coordination. Loss of CO_2 from **151** could regenerate the 17 e- radical **150** and nitrosoarene. Nitrosoarenes are well known radical traps and nitrosobenzene has been shown to trap the radical **150** to give complexes of undetermined stucture.[210] Possibilities for the reaction of **150** with nitrosoarene include the complex **152** with a side-on bonded nitroso arene unit (Scheme 4.22). A similar Ru complex has been isolated and characterized by X-ray crystallography.[211] The reaction could also yield complexes of the type **153** resulting from generation of an iron bound nitroxide radical this radical could abstract hydrogen atom from the solvent to give **154**. It has also been suggested based on EPR studies that the adducts generated from the reaction of **150** with nitroso compounds do not have an iron bound nitrogen fragment instead they proposed (based on interpretations of EPR data) that the nitrogen fragment possessing the radical is bound to coordinated CO, as in **155**.[210b] **155** would be analogous to the intermediate **151** proposed in the reaction pathway for nitro reduction. **155** could also be generated by CO coordination and insertion into **153**. The proposed intermediate **152** could undergo CO insertion to generate complex **156**, which could also come from **155** by attack of the radical onto the Fe center. The proposed intermediate **156** has good precedent due to isolation of similar compounds in the carbonylation of nitroaromatics to isocyanates with Ru complexes.[211] The intermediates **155** and **156** could be converted to the complex **157**. While **156** has good precedent in the literature in reactions where isocyanates are produced, the Fp_2 catalyzed reactions do not to our knowledge produce

isocycanates, therefore it is plausible that CO inserts into the C-O bond of **152**, instead of the C-N bond (as in **156**), to generate **158**. The proposed species (**152-158**) would likely be very reactive and may be responsible for the observed amination reactions. On the other hand it is plausible that they undergo reactions to generate more reactive intermediates.



Scheme 4.22 Possible Reaction Pathways of **150** with Nitroso Arenes

The complex (**158**) could lose CO_2 to generate the metal nitrene complex **159** (Scheme5.23). Metal nitrene complexes have been isolated in a Ru system that generated carbazole from 2-nitrobiphenyl.[55] The complex **159** is drawn as a 17 e- species, however it could also be a 19 e- complex via CO coordination.



158 **159**

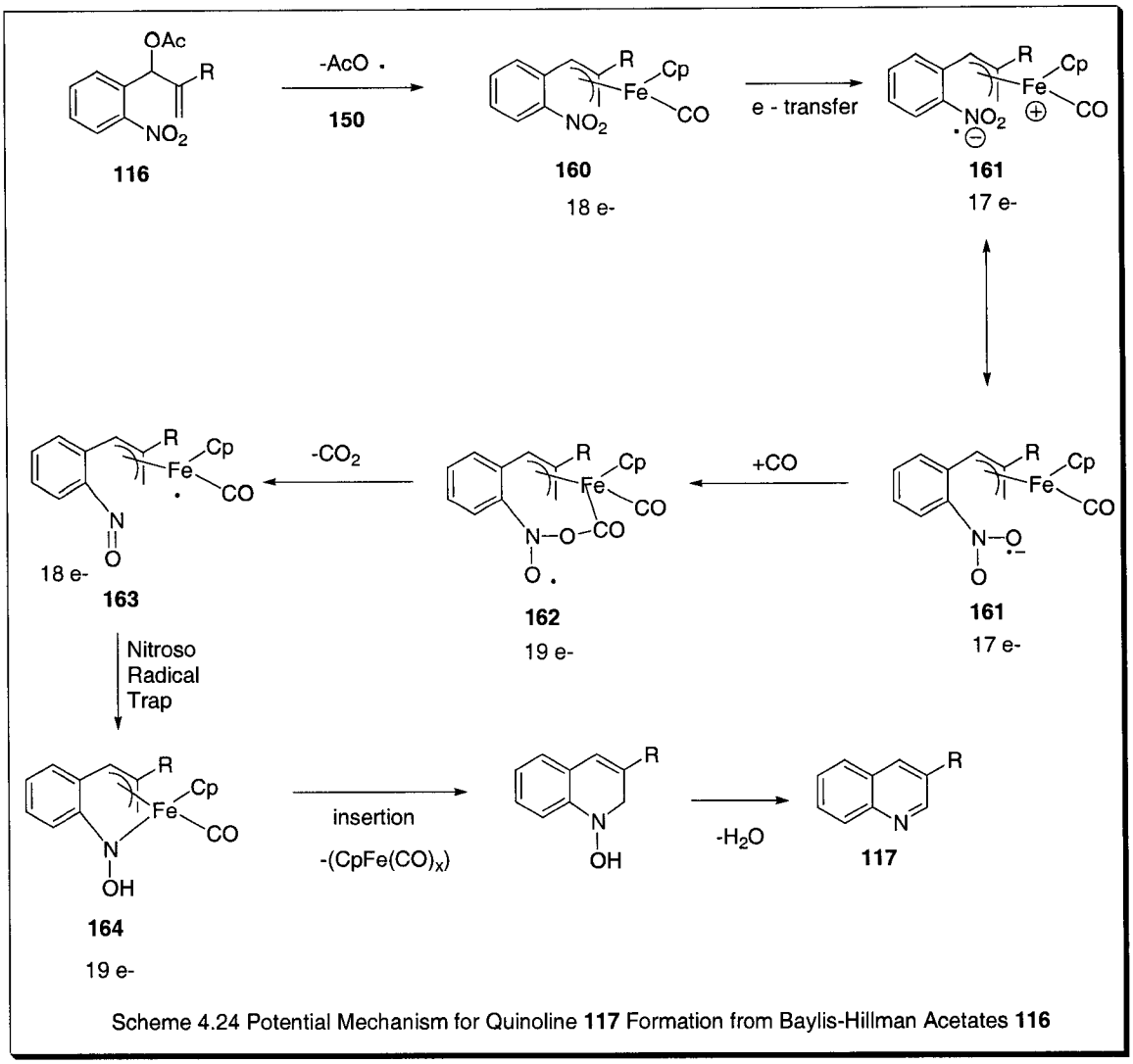
Scheme 4.23 Generation of a Nitrene Complex **159** from **158**

A weakness of these mechanisms is the reliance on the 17 e- radical **150.** The importance of this intermediate is suspect due to the fact that Angelici's complex **119** which bears a bis Cp ligand with bridging silyl groups binding the two metal centers not only through the Ru-Ru bond but also through the ligand also catalyzes the reaction of BH-acteate **116** to the quinoline **117**. Dissociation of the Ru-Ru bond seems less likely and the lifetime of a proposed diradical species is undoubtedly short. On the other hand the complex **119** is the least active of the catalysts surveyed and may be active via another pathway. This pathway may involve the generation of 19 e- radicals by coordination of reduced nitrogen species or CO to undissociated dimer molecules, causing their dissociation or forming a reduced dimeric complex. This might explain the strong dependence of the reaction rate on CO pressure. Tyler has provided kinetic evidence for the formation of 19 e- species from reaction of Fe dimers with phosphines

under irradiation.[202, 212] It has been suggested that these 19 e- species may be stabilized by a ring slippage mechanism where the radical resides on the Cp ligand.[202,213]

4.8.2: POTENTIAL MECHANISMS FOR QUINOLINE FORMATION

Since the mechanistic pathway for nitro reduction is unknown the mechanism of the Fp^*_2-catalyzed reductive cyclization to quinolines is also uncertain. The probes of the corresponding intermolecular allylic aminations have excluded free nitrosoarene and nitrene intermediates and suggested a role for coordinated organonitrogen species that may be those described above. Furthermore, the contrasting 2-quinolone products formed in reactions of B-H acetate **116** with conventional metal reductants (presumably via hydroxylamine or amine addition to the carboxylate group) appear to exclude these intermediates as well in the iron-promoted cyclizations. In addition to the intermediates previously described (**152-159**), complexes derived from reaction of the olefin with the metal species may be involved. The latter might explain the reduced CO pressure at which these reactions can be conducted, as compared to the intermolecular reactions. One such mechanism that might account for quinoline formation is given in Scheme 4.24. The acetate **116** might react with the monomeric radical **150** (with loss of ·OAc) to generate the 18 e- π-allyl complex **160**, which could transfer an electron to the nitro group to give **161**. The radical anion could attack coordinated CO to give **162**, which could lose CO_2 to generate the 18 e- radical **163**, containing the nitroso unit on the organic fragment. This radical could undergo trapping by the nitroso group to generate a nitroxide that would abstract hydrogen atom from the solvent to give **164**,



Scheme 4.24 Potential Mechanism for Quinoline **117** Formation from Baylis-Hillman Acetates **116**

analogous to the previously described **154**. The π-allyl complex **164** could insert allyl to form the N-C bond with concomitant loss of the $CpFe(CO)_x$ (via CO coordination) to give the dihydroquinoline, which could lose water to give the quinoline **117**.

The marked difference in reaction products derived from the B-H alcohols (indoles, N-formyl indolines) as compared to the B-H acetates (quinolines) is striking. While neither reaction pathway is known, it could be that formation of indole and N-

formyl indoline is suppressed due to inhibition of the proposed retro-aldol reaction of the cyclized β-hydroxy ester intermediate **108** (Section 3.2.2: Scheme 3.6).

4.9: SUMMARY AND CONCLUSIONS

A unique transformation of the Baylis-Hillman acetate **116** to quinoline **117** was discovered. After substantial optimization of reaction conditions (solvent, catalyst, CO pressure, substrate/catalyst concentration) a fairly useful reaction was developed. Using these optimized conditions a variety of quinolines **125-129** have been prepared, the majority of which are new compounds. While oxidation of the Baylis-Hillman adducts **88-90** to the desired enones was unsuccessful, several other derivatives (**131,132,133**) were prepared, but they did not undergo selective/high yielding transformation. Attempts to extend our quinoline synthesis to 4-CF_3 quinolines was unsuccessful due to the failure of **140** to undergo the Baylis-Hillman reaction; however during this investigation better route to the CF_3 ketone **140** was discovered. Mechanistic experiments were performed that show that the 17 e- radical $Cp(CO)_2Fe^{\cdot}$ **150** is probably generated under our reaction conditions. Attempts at preparation of potential organic intermediates like the nitroso Baylis-Hillman adduct were unsuccessful due to unselective/low yielding reactions.

Mechanisms for both nitro reduction and quinoline formation that have some literature precedent have also been proposed.

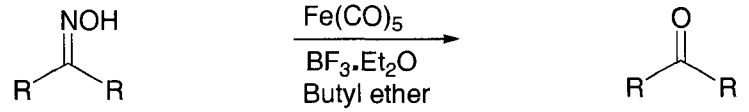
CHAPTER 5

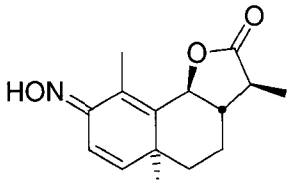
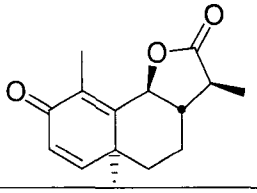
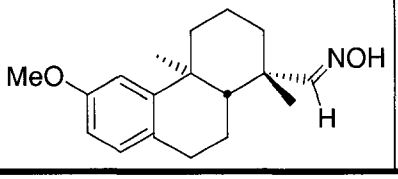
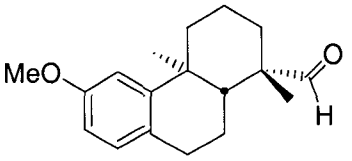
SYNTHESIS OF 1H-INDAZOLES FROM 2-NITRO KETOXIMES

5.1: INTRODUCTION

In our continuing effort to discover new amination reactions, the literature was searched for N-functional groups that might react with transition metal complexes to provide new nitrogen transfer agents. While conducting this search an early report by Alper et. al. on the reaction with $Fe(CO)_5$ with santonin oxime to give an iron complex of undetermined structure was discovered.[214] The researchers also found that if the oxime was heated with $Fe(CO)_5$ in the presence of $BF_3{\cdot}Et_2O$ the ketone was regenerated in good yield (Table 5.1). Water was excluded from these reactions, and they reasoned that the oxime oxygen was the source of the ketone oxygen. This reasoning was partly based upon the failure of fluorenone phenylhydrazone to generate fluorenone under their reaction conditions. While no clear evidence, like an ^{18}O labeling experiment, was given to support this conclusion, some interesting questions are raised: What is the identity of the nitrogen-containing product? How is the oxygen transferred from the oxime nitrogen to the oxime carbon? The most tempting explanation is the presence of adventitious moisture; however, excluding this possibility the questions remain.

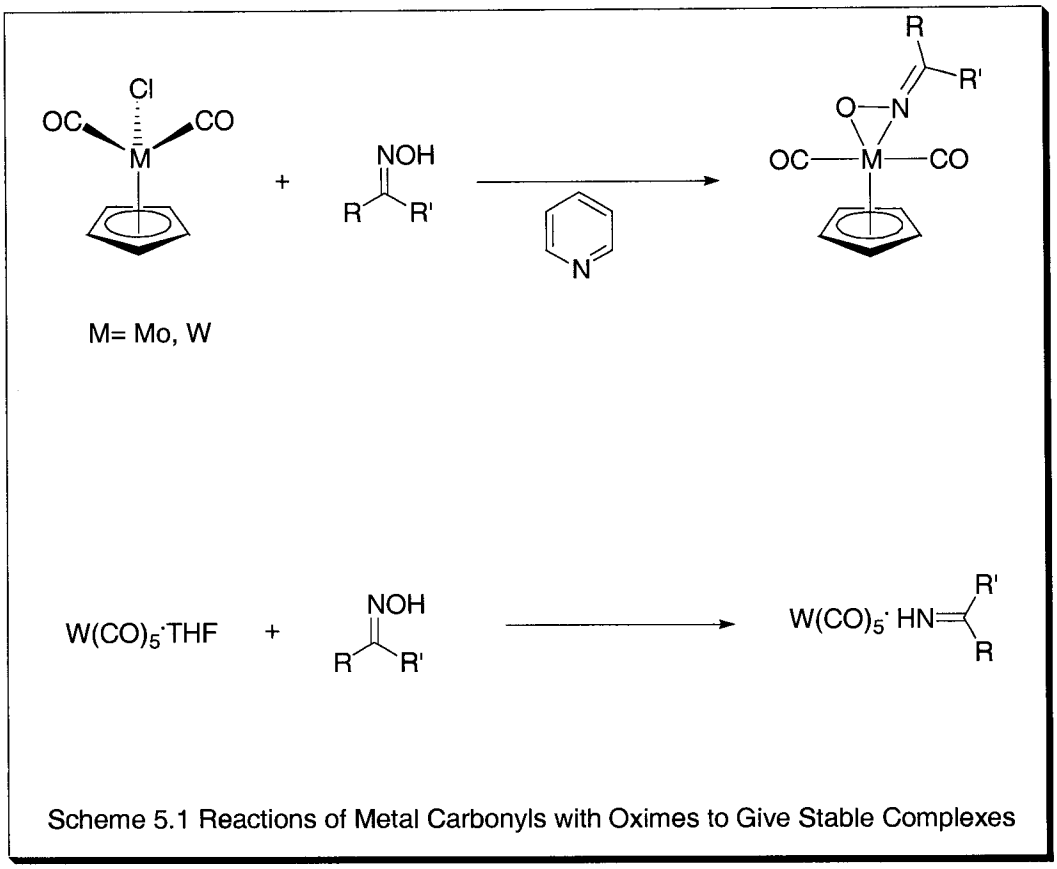
Table 5.1 Regeneration of Ketones from Oximes without H_2O*



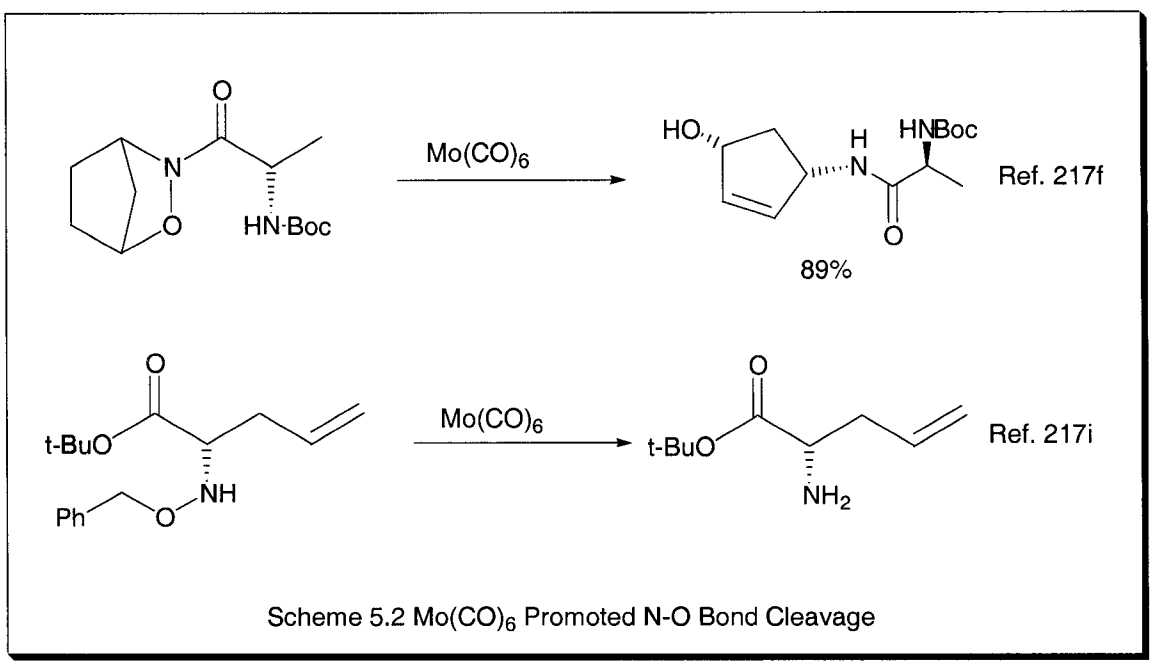
Entry	Oxime	Ketone	Yield
1			67
2			55

* Reference 214 conatins four more examples.

After considering Alper's report, it was learned that King and others had reported the reaction of metal carbonyls with oximes to give stable imine oxide [215] and imine complexes (Scheme 5.1).[216] Molybdenum hexacarbonyl is well known to promote the cleavage of N-O bonds in heterocycles[217a-h] and O-alkyl hyrdroxylamines[217i] (Scheme 5.2). Nita has reported the use of $Fe_2(CO)_9$ for this type of transformation,[217c] and also for the deoximation of ketoximes to generate ketones,[217j] which is very similar to the report by Alper.[214] Moreover, Watanabe has shown the deoxygenation of ketoximes with $Ru_3(CO)_{12}$ under CO pressure produces ketimines,[218a] and that deoxygenation of amidoximes produces amidines, under the same conditions.[218b]

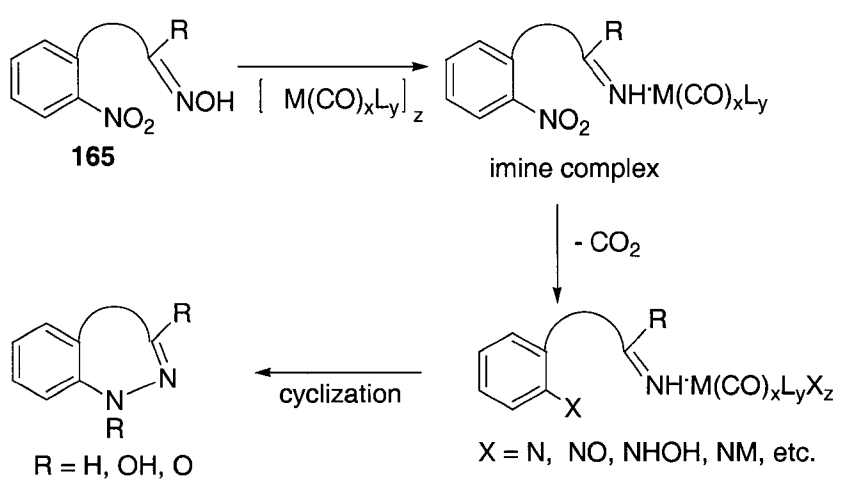


Scheme 5.1 Reactions of Metal Carbonyls with Oximes to Give Stable Complexes



Scheme 5.2 $Mo(CO)_6$ Promoted N-O Bond Cleavage

Previously it was proposed that the reductive cyclization of Baylis-Hillman acetates might proceed via an intermediate π-allyl metal complex and that this complex might facilitate the reduction of the nitro group. This type of intermediate could account for the relatively low CO pressure required to effect the reduction of the nitro group. With this idea in mind it was reasoned that an intermediate imine complex formed from the reaction of metal carbonyl dimers with oximes of the type **165** might participate in the reduction of a pendant nitro group and possibly generate an N-N bond in the process (Scheme 5.3).

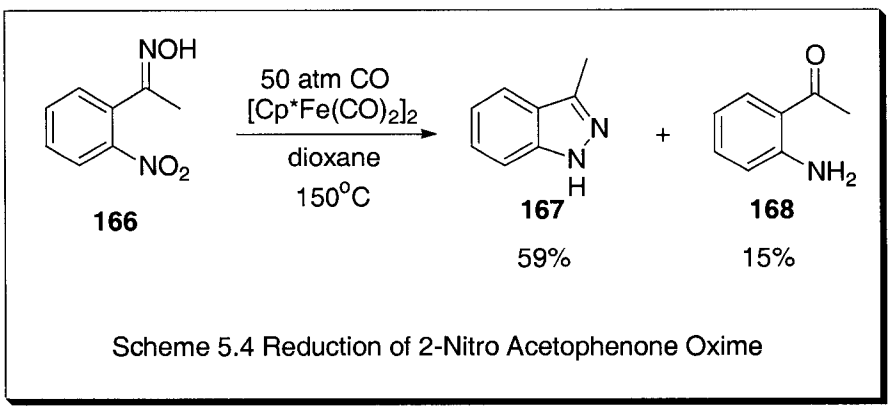


Scheme 5.3 Reaction Sequence Proposed for Reaction of Oximes with Pendant Nitro Groups

5.2: RESULTS AND DISCUSSION

5.2.1: INITAL RESULTS

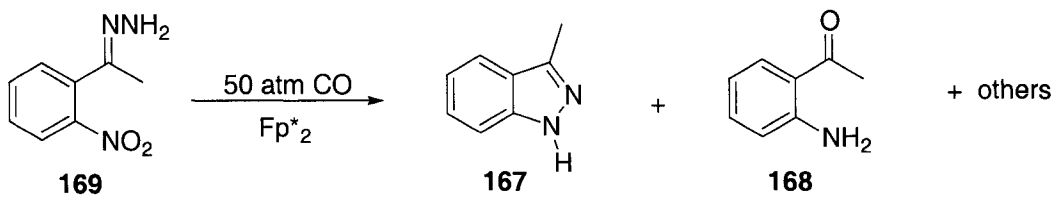
In order to test our hypothesis the oxime of commercially available 2-nitroacetophenone was prepared by a standard method using $NH_2OH{\cdot}HCl$.[219] When 2-nitro-acetophenone oxime **166** was heated with 10 mo l% of $[Cp^*Fe(CO)_2]_2$ in dioxane under 50 atm of CO, two main products were isolated: 3-methyl 1H-indazole[220] (**167**, 59 % yield) and 2-amino acetophenone (**168**, 15 %), identified spectroscopically and by comparison with authentic samples (Scheme 5.4). Small amounts of other unidentified products and some tar were also produced. Reactions conducted at lower temperatures and pressures were extremely sluggish.



Scheme 5.4 Reduction of 2-Nitro Acetophenone Oxime

Attempts to suppress the formation of ketone **168** by the addition of drying agents (4Å molecular sieves, MgO, BaO) to the reactions were unsuccessful; no change in the **167/168** ratio was found. This suggests that the ketone byproduct is not the result of oxime hydrolysis but may derive from O-transfer from the oxime or nitro functions. The

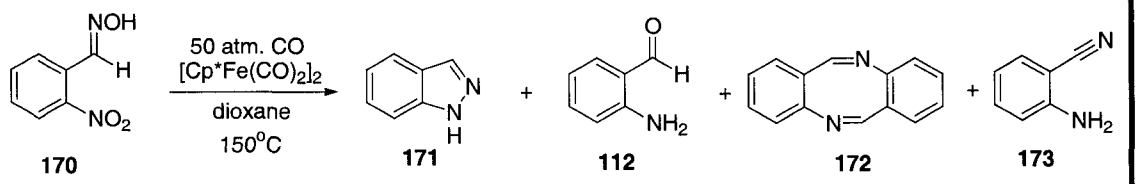
latter seems more likely due to the fact that the hydrazone of 2-nitro acetophenone [221] (**169**) was reductively cyclized to give 3-methyl-indazole, 2-amino acetophenone, and other products (GCMS) (Scheme 5.5). The indazole might come from an intramolecular nucleophilic aromatic substitution of the nitro group.[222] The reaction is not as clean as the oxime cyclization and gives many other products. Regardless, this experiment does suggest that the oxygen of amino acetophenone **167** generated in these cyclizations is derived from the nitro group.



169 **167** **168**

Scheme 5.5 Reductive Cyclization of the Hydrazone **169**

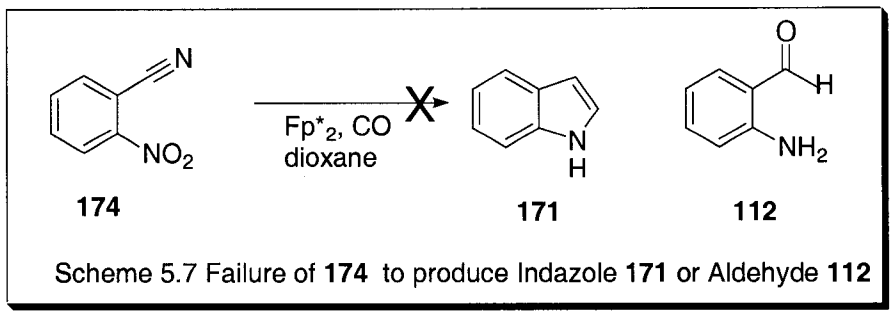
While the formation **168** was unavoidable, this novel transformation had never been reported in the literature. It was hoped that the reaction could be extended to 2-nitro benzaldoximes, due to their commercial availability/ease of preparation. The commercial 2-nitro benzaldoxime **170** was reduced with the $[Cp^*Fe(CO)_2]_2$/CO system. Unfortunately, in addition to 1H-indazole **171**, 2-amino benzaldehyde **112**, and what was most probably the diazocine **172** (from the dimerization of 2-amino benzaldehydes, GCMS),[162] the reaction also produced a large amount of 2-amino benzonitrile **173** from apparent dehydration of the oxime (Scheme 5.6).



170 171 112 172 173

Scheme 5.6 Reduction of 2-Nitro Benzaldoxime **170**

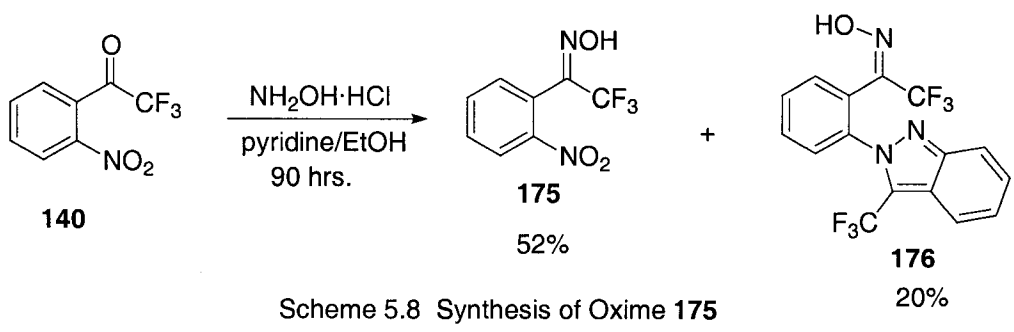
The indazole **170** was identified by ^{1}H NMR spectroscopy and gave spectra identical to that described in the literature.[223] The identity of **112** was proven by comparison to an authentic sample. The benzonitrile **173** was identified on the basis of its mass spectrum (GCMS, same mass as indazole, but differing retention time and fragmentation pattern) and ^{1}H NMR spectrum. The ^{1}H NMR spectrum of **173** gave the characteristic ortho aromatic signals as well as a broad singlet that integrated to 2 protons. The dehydration of aldoximes to nitriles is a well-known reaction that can be accomplished by many reagents.[224] In order to determine the intermediacy of a nitrile in these reactions, the commercial 2-cyano nitrobenzene **174** was subjected to our reaction conditions (Scheme 5.7). None of the products from the reaction of **174** were produced from the reaction of **169**, and while not rigorously identified they appear to be azo- and azoxy- benzenes based on GCMS of the crude material.[225] This rules out dehydration of the benzaldoxime as an initial reaction step, pointing instead toward dehydration at a later stage of nitro reduction.



Scheme 5.7 Failure of **174** to produce Indazole **171** or Aldehyde **112**

5.2.2: SYNTHESIS OF 2-NITRO KETOXIMES

Although benzaldoximes appeared to be inefficient substrates for this reaction, we wanted to have some sense of the generality of the reaction by changing substituents on the aromatic ring and by using 2-nitrobenzophenone oximes. Unfortunately, no other *o*-nitro ketones were available commercially, but they were fairly easy to prepare. The previously synthesized trifluoromethyl ketone **140** was used to prepare the oxime **175**. While the oxime was produced as a single isomer in 52 % by refluxing **140** in EtOH/pyridine with $NH_2OH{\cdot}HCl$, the oximation also gave an unusual side product the 2-aryl indazole **176** in 20 % yield (Scheme 5.8).



Scheme 5.8 Synthesis of Oxime **175**

The identity of **176** was determined by X-ray crystallography, NMR (^{1}H, ^{13}C, ^{19}F), and HRMS; an ORTEP diagram of the crystal structure is shown in Figure 5.1. This is an interesting product in itself, and results from obvious removal/reduction of two nitro groups, and formation of an N-N bond. When considering possible mechanisms for the formation of **176**, the prospect of nitro reduction by hydroxylamine/pyridine is unprecedented. The hydroxylamine could displace the nitro group via a nucleophilic aromatic substitution reaction to give an aryl hydroxylamine.[222] A highly speculative mechanism that includes this feature is presented in Scheme 5.9. The mechanism relies on the generation of the benzylic carbene **177** from the oxime **175** via loss of NO, and while the generation of carbenes from oximes is an unknown reaction, carbenes bearing an α-CF_3 can be very stable.[225]

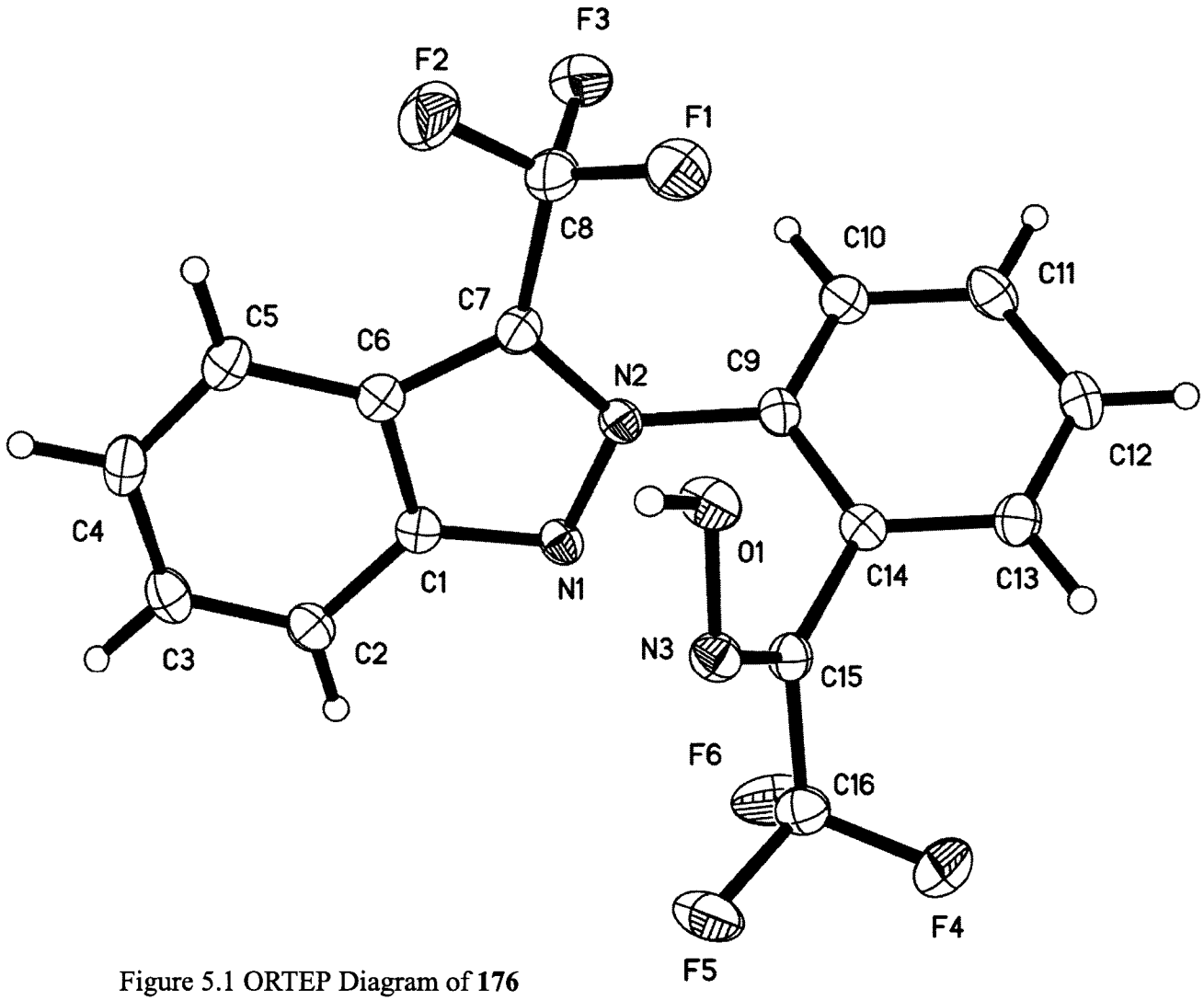
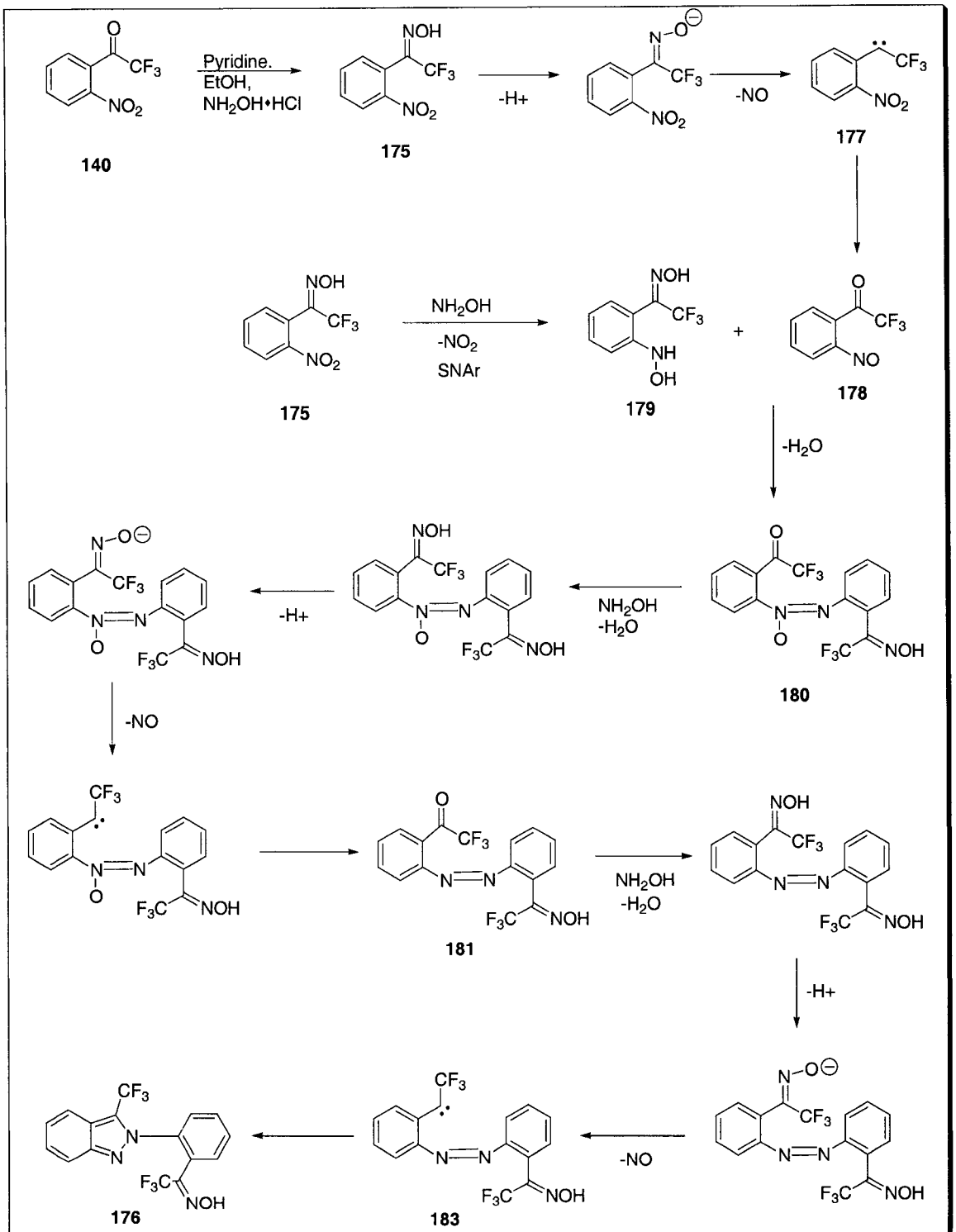


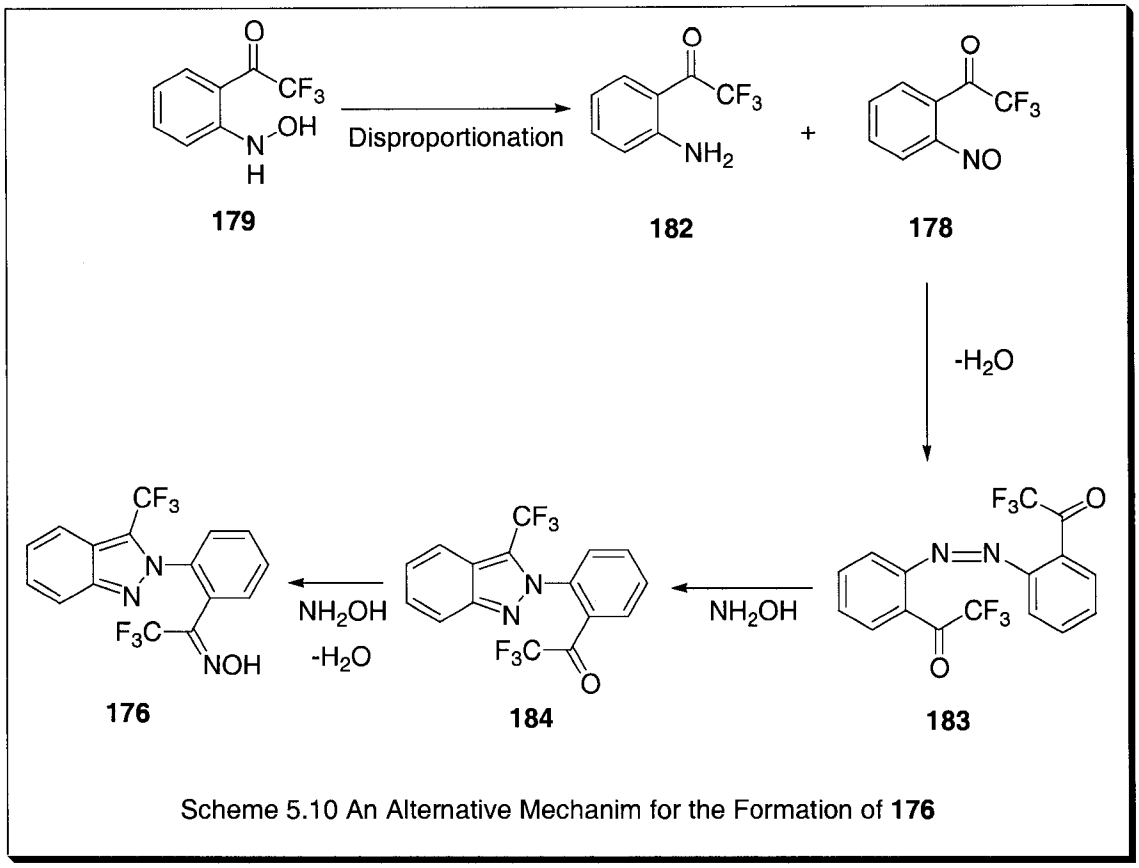
Figure 5.1 ORTEP Diagram of **176**



Scheme 5.9 Proposed Mechanistic Pathway for the Formation of **176** from **140**

The intramolecular deoxygenation of a nitro group by the carbene generated from photolysis of (2-nitrophenyl)diazomethane to give nitroso benzaldehyde has been reported.[226] In this same manner the carbene **177** could give the nitroso compound **178**. Condensation of **178** with the aryl hydroxylamine **179** (generated from the nucleophilic aromatic substitution of the nitro group by hydroxylamine) would give the azoxybenzene **180**. Reduction of **180** could occur via another oximation/carbene formation/deoxygenation pathway to give the azo compound **181**. **181** could generate the carbene **182** after oximation. Attack of the carbene on the lone pair of the azo nitrogen would give the indazole **176**.[227] It would be interesting to do experiments to see if this type of carbene can really be generated from α-trifluoromethyl oximes, by using different conditions (stronger base, trapping, etc.) and other oximes.

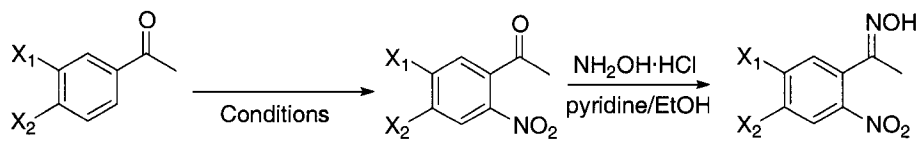
Another mechanism that does not involve the generation of carbenes is presented in Scheme 5.10. The hydroxylamine **179** could disproportionate to give the amine **182** and the nitroso compound **178**. Condensation of **182** with **178** would give the azo-compound **183**. Azo-*o*-benzophenone is known to cyclize to 2-(*o*-benzoylphenyl)-3-phenyl indazole when heated with ammonium sulfide.[228] In the same manner, but deoxygenated by hydroxylamine, **183** would give the ketone **184**, followed by oximation to **176**.



Scheme 5.10 An Alternative Mechanim for the Formation of **176**

Attempts to use other methods for the oximation of **140** were unsuccessful. The use of hydroxylamine *O*-sulfonic acid, which has been reported for the synthesis of trifluoromethyl ketoximes,[229] was unsuccessful and gave tarry materials and recovered starting material after prolonged reaction times. The reaction of **140** with NH_2OH·HCl in aqueous KOH [230] gave gross degradation of the ketone to multiple unidentified products that appear to have lost significant fragments (CF_3, NO_2), based on GCMS. It was hoped that by slightly modifying the base the side reaction could be suppressed, and to this end DMAP was used with NH_2OH·HCl. Surprisingly the use of DMAP gave a different reaction with products that were not identified.

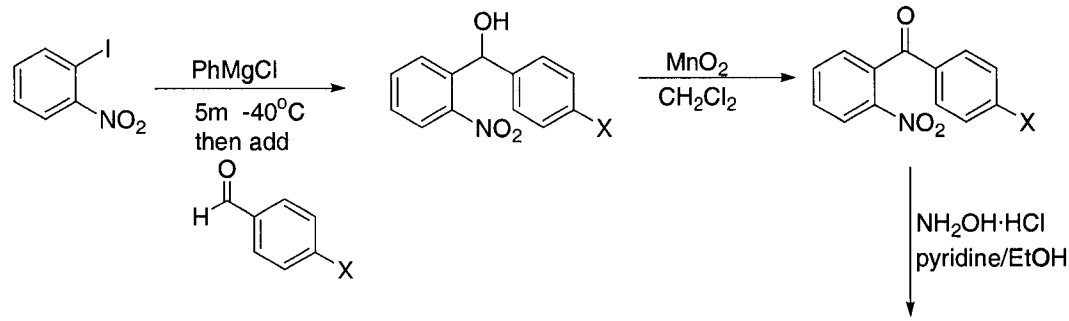
The preparation of other oximes was less problematic. Using known methods both 3,4-dimethoxy acetophenone and 3-bromo acetophenone were effectively nitrated to give the known ketones **185**[231] and **186**[232] respectively. Their conversion to the previously unknown oximes **187** and **188** was also very straightforward (Scheme 5.11). These oximes were characterized by: ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and purity was established by combustion analysis. The isomeric ratios (*E*:*Z*) were determined by ^{1}H NMR.



X_1	X_2	Conditions	Ketone	Yield (%)	Oxime	Yield (%)	E/Z
OMe	OMe	HNO_3/AcOH	**185**	65	**187**	98	72/28
Br	H	90% HNO_3	**186**	61	**188**	96	67/33

Scheme 5.11 Synthesis of Substituted 2-Nitro Acetophenone Oximes

For the preparation of the 2-nitro benzophenone oximes, Knöchel's low temperature PhMgCl exchange method was used to generate the 2-nitrophenyl Grignard.[195] Reaction of these Grignard reagents with the appropriate aldehydes produced the requisite benzhydryls **189**[195] and **190**[233] in good yield. Oxidation of the alcohols with MnO_2 in CH_2Cl_2 gave the benzophenones **191**[234] and **192**[235] in excellent yield. The oximation also proceeded as planned to give the oximes **193**[236] and **194** (Scheme 5.12).



X	Grignard	Oxidation	Oximation	
	Product (%)	Product (%)	Product (%)	E:Z
H	**189** (79)	**191** (93)	**193** (73)	ND
OMe	**190** (79)	**192** (87)	**194** (95)	5:1

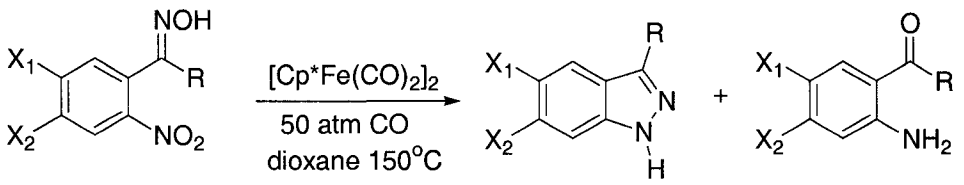
Scheme 5.12 Synthesis of 2-Nitro Benzophenone Oximes

5.2.3: SYNTHESIS OF 1H-INDAZOLES

Cyclization of the oximes (**165**, **175**, **187**,**188**, **193**, **194**) with the appropriate conditions (10 mol% Fp^*_2, dioxane, 150 °C, CO) gave low to good yields of the desired indazoles **167**, **195-199** along with the 2-amino ketones, which were isolated in some cases (**168**, **200**) (Table 5.2). The 4',5'-dimethoxy-2'-nitroacetophenone oxime **187** gave the highest yield (**196**, 85%), and the bromo oxime **188** gave the poorest (**197**, 26 %). While substitution of the R group of the oxime had little effect for alkyl or aryl groups, trifluoromethyl substitution gave a poorer yield (**195**, 40%). The higher yield with the substrate bearing ED groups is somewhat surprising given that more electron rich species

should be harder to reduce. The geometry of the oxime has little or no effect on the outcome of the cyclization, as evidenced by the fact that the reactions of *E*-**187** and *E/Z*-**187** gave nearly identical product mixtures after the same reaction time under identical conditions.

Table 5.2 Synthesis of 1H-Indazoles



Entry	Oxime	R	X_1	X_2	Indazole (%)	Amine (%)[a]	Time (h)
1	**166**	Me	H	H	**167** (59)	**168** (15)	46
2	**175**	CF_3	H	H	**195** (40)[b]	-	72
3	**187**	Me	OMe	OMe	**196** (85)	-	68
4	**188**	Me	Br	H	**197** (26)	-	80
5	**193**	Ph	H	H	**198** (52)	**200** (17)	75
6	**194**	*p*-MeO-Ph	H	H	**199** (56)	-	75

a) The amine was detected (GCMS) in all cases, but not always isolated.
b) Yield based on recovered starting material

5.3: THE SIGNIFICANCE OF THE SYNTHESIS OF 1H-INDAZOLES FROM NITRO KETOXIMES

Indazoles are important compounds as evidenced by their preponderance in the chemical patent literature as kinase inhibitors.[237] In addition, the indazole Lonidamine (Figure 5.2) is under investigation as both an anti-cancer drug[238] and an anti-spermatogenic agent.[239]

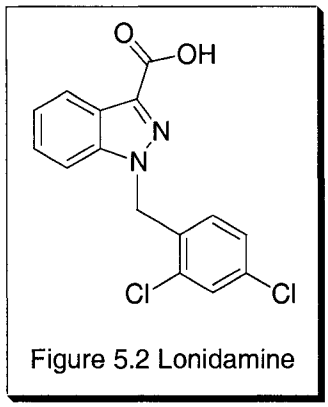
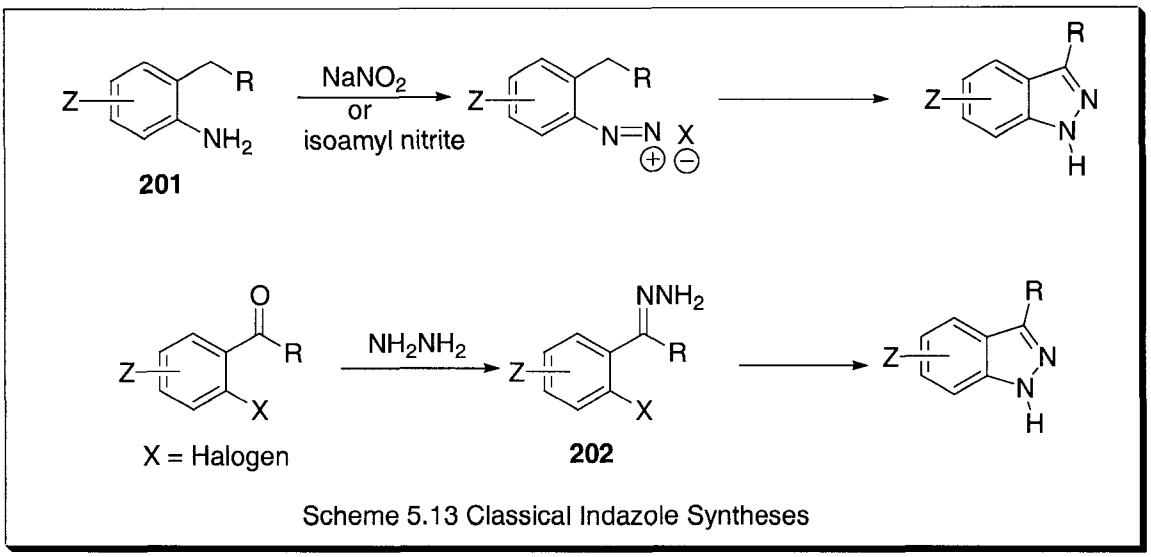


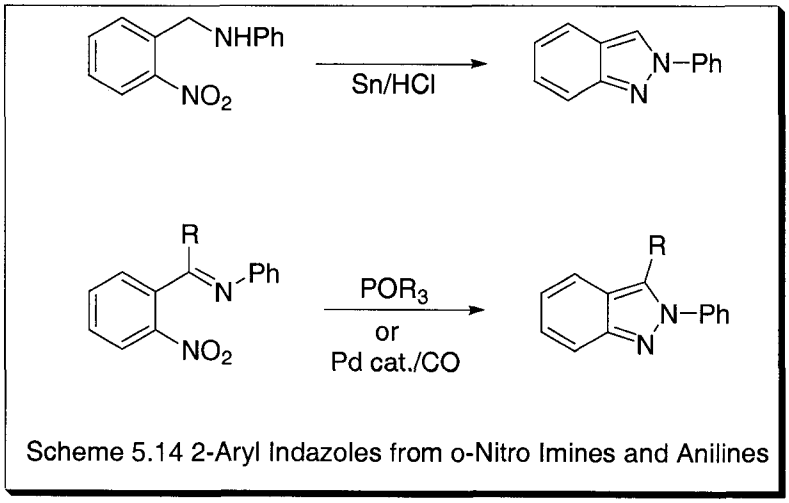
Figure 5.2 Lonidamine

Indazoles were originally prepared by Fischer,[240] and many syntheses have since been reported.[241] Two commonly used methods involve the diazotization of 2-alkylanilines **201** and the cyclization of *ortho*-substituted hydrazones **202** (Scheme 5.13). The former usually requires acidic conditions and works best with electron deficient aromatic substrates while the later employs hydrazine, a basic reducing agent, and has a similar electronic character.



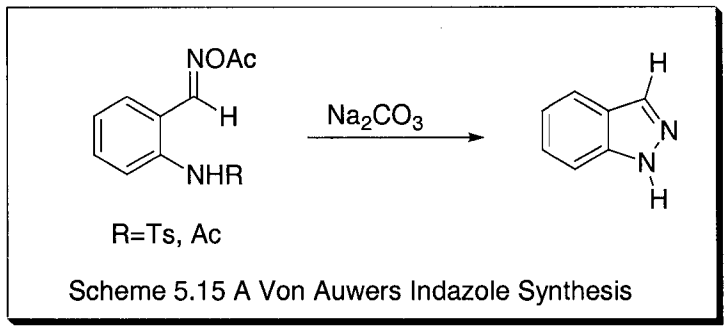
Scheme 5.13 Classical Indazole Syntheses

The reductions of *o*-nitrobenzylanilines **201**[242] and *o*-nitroimines **202**[95, 243] provide a route to 2-arylindazoles, but to our knowledge the conversion of o-nitroketoximes to 1H-indazoles had not been reported (Scheme 5.14).



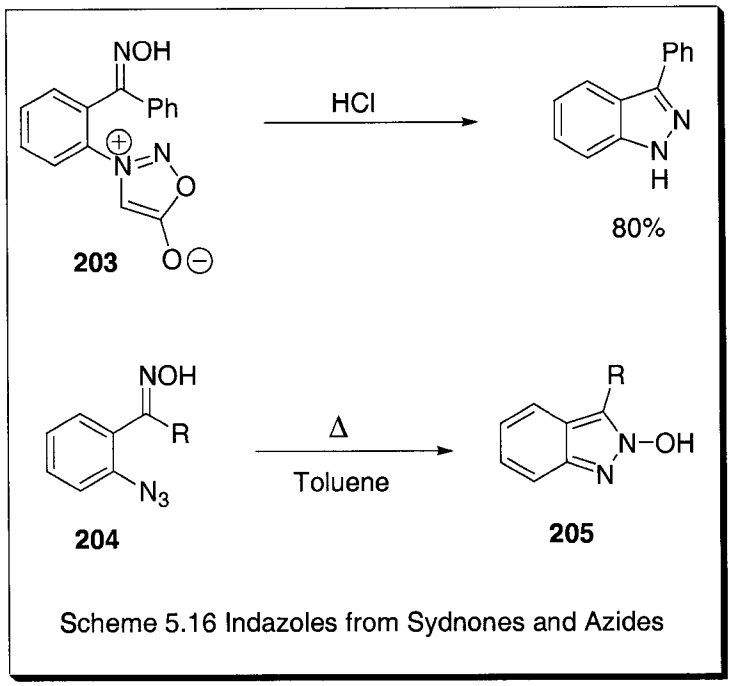
Scheme 5.14 2-Aryl Indazoles from o-Nitro Imines and Anilines

Von Auwers described a synthesis of 1-acylindazoles by treatment of 2-aminoketoximes with acetic anhydride;[244] however, the identity of the product was subsequently called into question.[245] The same investigator was able to prepare indazoles from benzaldoxime acetates bearing *o*-tosyl- or *o*-acyl-amino groups (Scheme 5.15).[246]



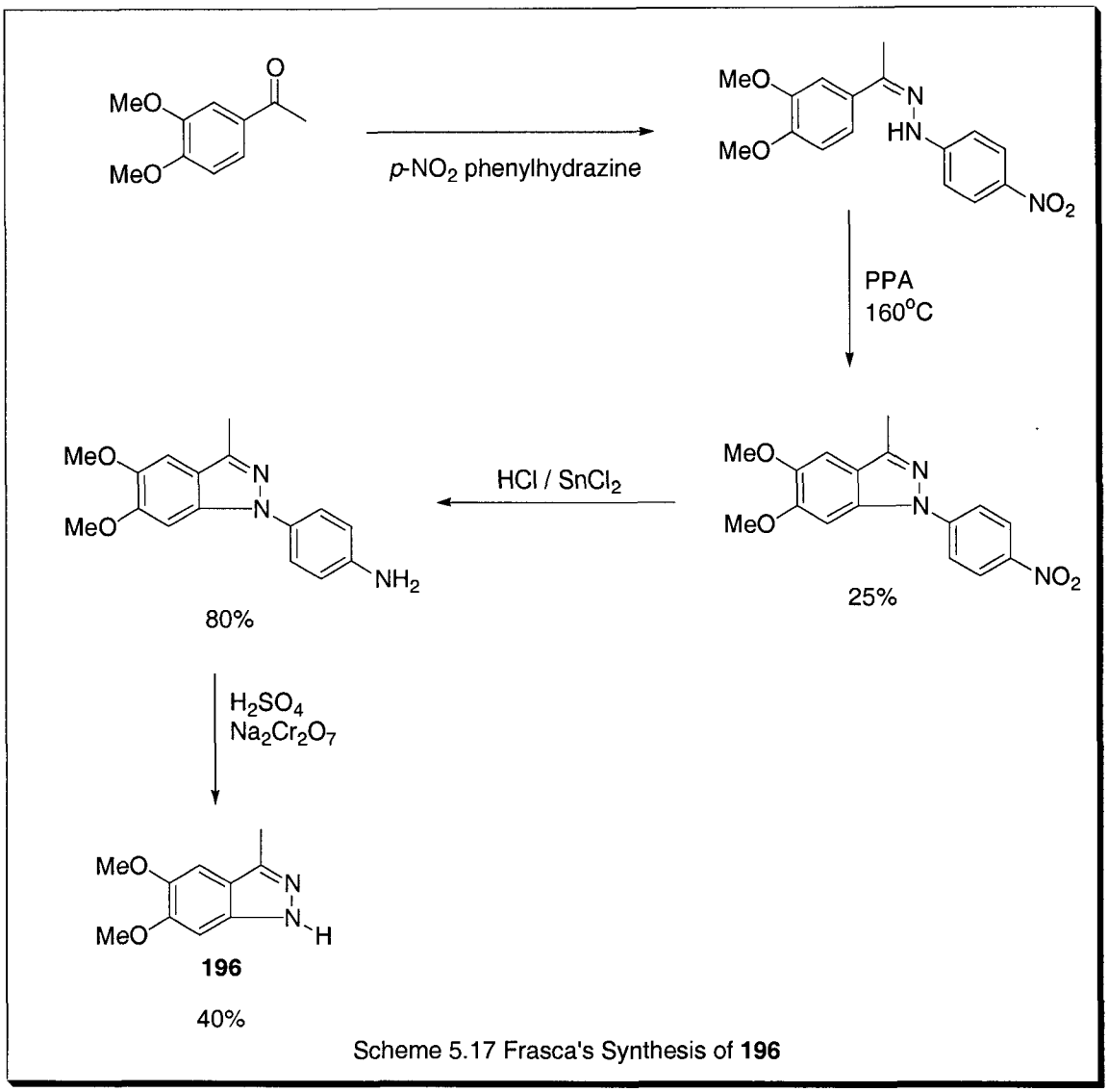
Scheme 5.15 A Von Auwers Indazole Synthesis

Others have shown that sydnones **203** with pendant oxime units cyclize under acidic conditions to give 1H-indazoles,[247] and that *o*-azidobenzaldoximes **204** give 2-hydroxy-indazoles **205** upon boiling in alkali (Scheme 5.16).[248] These conditions are not suitable for substrates bearing acid/base sensitive groups.



Scheme 5.16 Indazoles from Sydnones and Azides

The yields for our cyclization are quite variable and substrate dependent, and thus it is unlikely to be a preferred route for indazoles that have been prepared in high yields through other methods. The most remarkable aspect of the reaction is the good yield of indazole **196** obtained with the dimethoxy-substituted oxime **187**. This compound has been prepared only once in a 40% yield, through a lengthy route (Scheme 5.17).[249] Obviously our route provides a more efficient route to this indazole. The electronic character (high yields with EDG's) of our reaction compliments that of existing methods, and holds some promise for the preparation of electron rich indazoles.

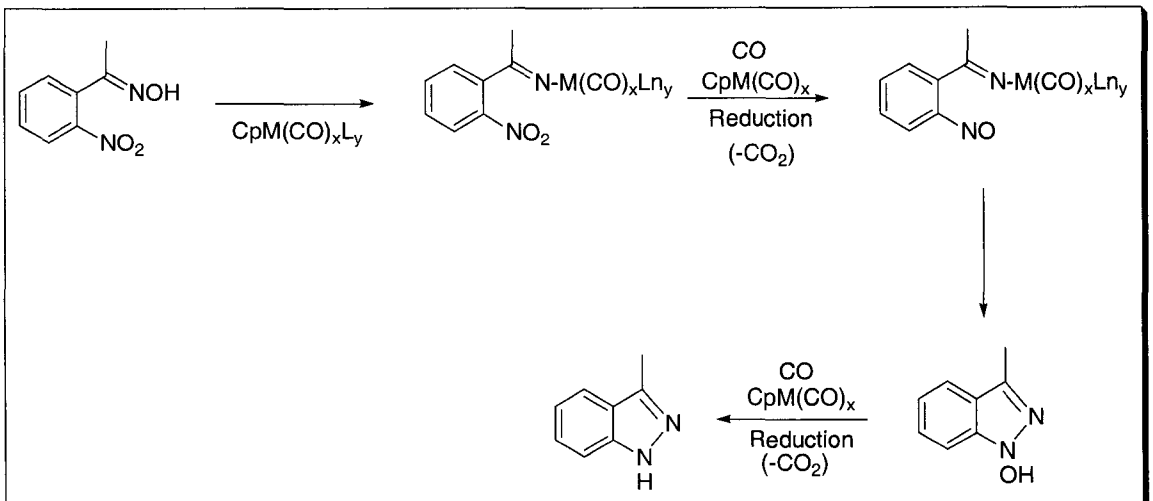


Scheme 5.17 Frasca's Synthesis of **196**

5.4: POTENTIAL MECHANISMS FOR 1H-INDAZOLE FORMATION

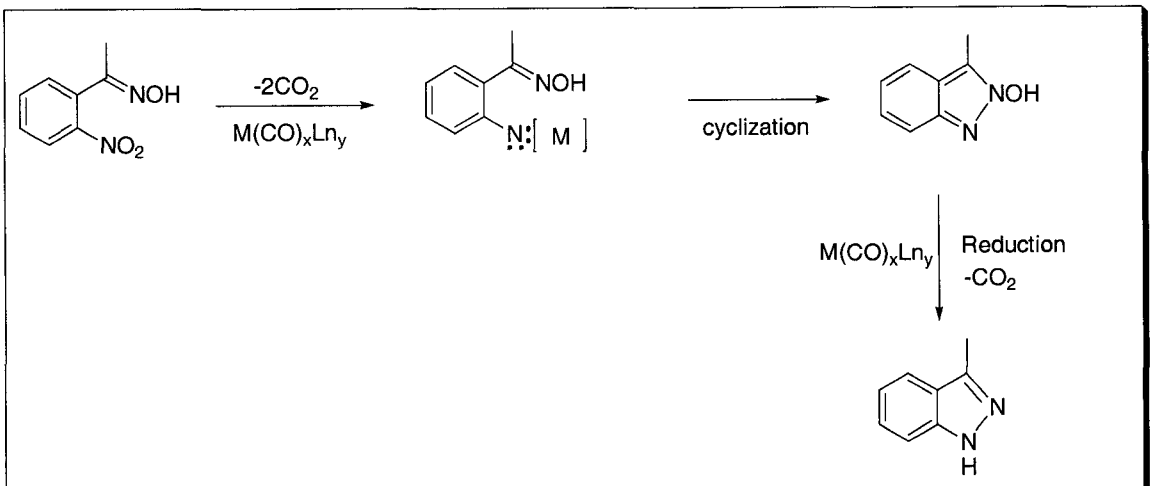
Although the mechanism of this transformation is not yet known, it formally involves the removal of three oxygen atoms from the *o*-nitro-ketoxime. Although both the nitro- and oxime-functions are deoxygenated, presumably by O-transfer to coordinated CO (→ CO_2), the order of these steps and the nature of the intermediate, which undergoes N-N bond formation, are uncertain. As previously suggested,

transition metal carbonyls are known to react with oximes to form imine complexes,[214, 216] which might be intermediates. The imine (free or coordinated) or a derived iminyl radical[250] could then N-couple with the nearby nitroso group[251] (free or coordinated) to form the nitrogen-nitrogen bond (with subsequent deoxygenation) (Scheme 5.18).



Scheme 5.18 Mechanism for Indazole Formation through a Nitroso Intermediate

It is also possible that the reaction proceeds through a nitrene complex that attacks the oxime-nitrogen lone pair to give 2-hydroxy indazole (Scheme 5.19). Deoxygenation of the 2-hydroxyindazole by M/CO could then give the indazole. This would be analogous to the reaction observed with 2-azido ketoximes,[248] which probably proceeds through free nitrene. It is also possible that the oxime is converted to the imine, which undergoes the reaction analogous to the known 2-aryl indazole synthesis.[75, 243]



Scheme 5.19 Mechanism for Indazole Formation through a Nitrene Intermediate

5.5: SUMMARY

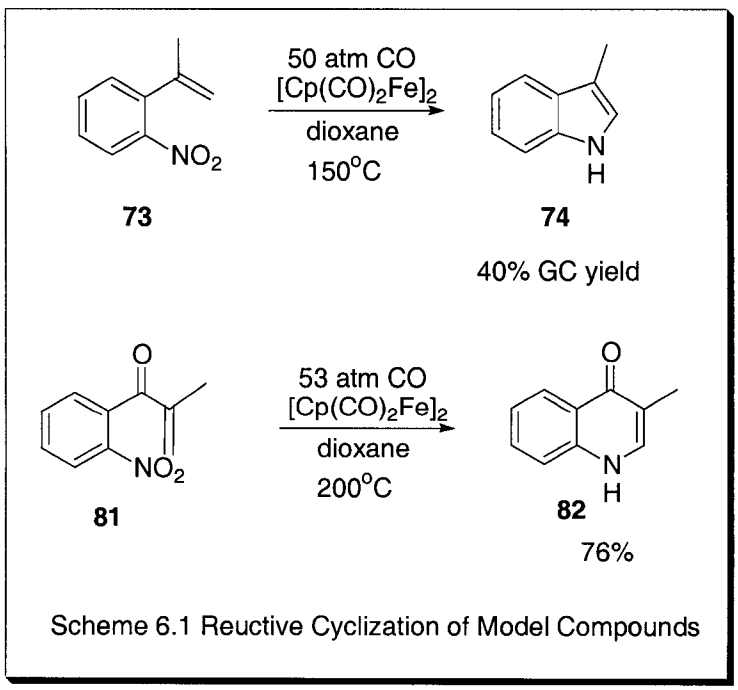
The novel transformation of o-nitro ketoximes into 1H-indazoles was discovered. These reactions work well for substrates bearing electron donating groups. While the mechanism of these reactions is not known, it may involve imine complexes or metal nitrene complexes. During the preparation of the oxime **175** the unusual 2-phenyl indazole **176** was isolated, and a mechanism for its formation was proposed.

CHAPTER 6

PROJECT SUMMARY AND FUTURE DIRECTIONS

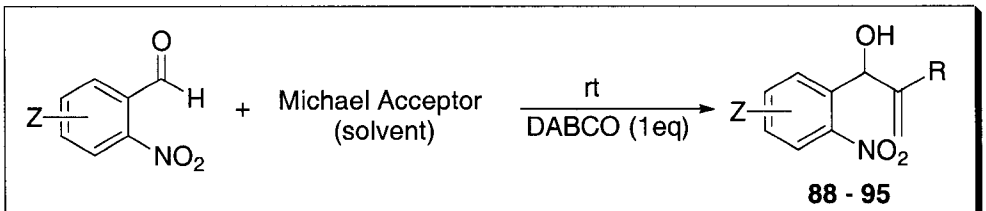
6.1: PROJECT SUMMARY

Our initial goal during these investigations was to see if $[Cp(CO)_2Fe]_2$ would catalyze the intramolecular reductive carbonylative cyclizations of nitro-aromatics bearing unsaturation. We prepared the previously described *o*-nitro styrene **73** through Stille coupling methodology, and found that upon reductive carbonylation **73** produced 3-methyl indole (Scheme 6.1). We also prepared the nitroenone **81** through a Stille coupling, and found that it cyclized to give the 4-quinolone **82** in 76 %. We synthesized other compounds (**83 - 85**) analogous to **81**, but bearing other substituents, however these compounds were obtained in very low yield (1 - 8 %).



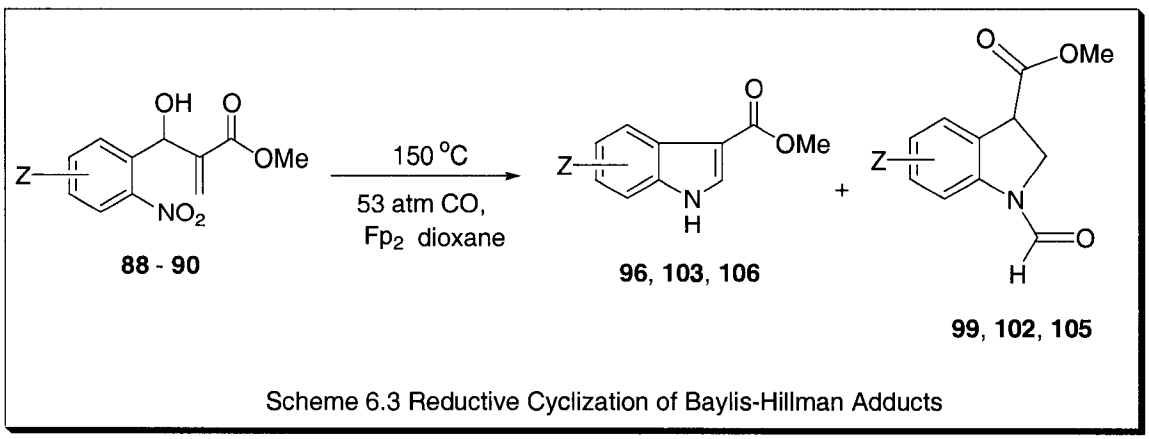
Scheme 6.1 Reuctive Cyclization of Model Compounds

After successfully cyclizing the initial model compounds (**73**, **81**) we focused upon substrates that were easier to prepare. This led us to investigate the Baylis-Hillman adducts of 2-nitro benzaldehydes as precursors to nitrogen heterocycles. We prepared the Baylis-Hillman adducts (**88** - **95**) (Scheme 6.2). Many of these were new compounds and were fully characterized.



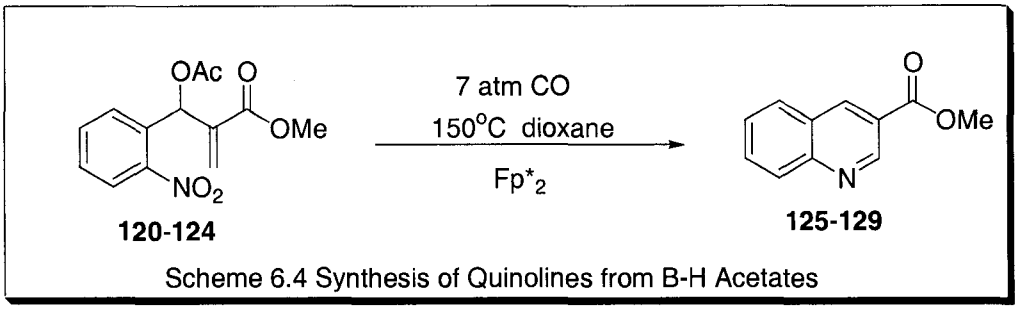
Scheme 6.2 Synthesis of Baylis-Hillman Adducts

Cyclization of the Baylis-Hillman adducts (**88** - **90**) using $[Cp(CO)_2Fe]_2$ and CO gave many products, the major ones being the indoles (**96**, **103**, **106**) and N-formyl indolines (**99**, **102**, **105**; Scheme 6.3).[252] These reactions are quite unusual and unprecedented. While mechanistically fascinating, these transformations are of little practical value.



Scheme 6.3 Reductive Cyclization of Baylis-Hillman Adducts

We imagined that derivatization of the Baylis-Hillman adducts might provide substrates that would undergo reactions that were not only novel, but also efficient. For these reasons we prepared the known Baylis Hillman acetate **116**, which gave the quinoline **117** as the major product upon reductive carbonylation with $[Cp(CO)_2Fe]_2$. After optimization of this reaction with respect to catalyst concentration, substrate concentration, solvent, catalyst, and CO pressure, we found that good yields of **117** could be achieved at relatively low CO pressure (7 atm) by using 10 mol % $[Cp^*(CO)_2Fe]_2$ with a .011M substrate concentration in dioxane at 150 °C. With these optimized conditions we prepared the quinolines **125** - **129**, by cyclization of the Baylis-Hillman acetates **120** - **124** in good yield (Scheme 6.4).[253] Other derivatives (**131**, **132**, **133**) were prepared that gave unselective/low yielding cyclizations. Attempts to prepare potentially medicinally important 4-CF_3 quinolines were unsuccessful due to the failure of ketone **140** to undergo the Baylis-Hillman reaction.

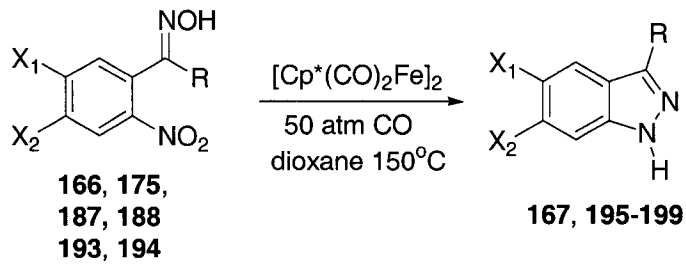


120-124 **125-129**

Scheme 6.4 Synthesis of Quinolines from B-H Acetates

With a reasonably good reaction (**116** → **117**), we wanted to probe the mechanism of the reaction. Since electron transfer had been proposed to be a likely first step in aromatic nitro reductions by CO/metal complexes, and the existence of the 17 e- radicals (Fp· **150**) well-established from the dissociation of the dimer $[Cp(CO)_2Fe]_2$, we devised a mechanistic probe for the intermediacy of **150** under our reaction conditions. We prepared the mixed Cp ligand dimer **145** and observed the crossover products $[Cp(CO)_2Fe]_2$and $[Cp^*(CO)_2Fe]_2$ after heating in dioxane under CO. While this does not unequivocally prove the existence of **150** under our reaction conditions it does provide strong evidence for it. A mechanism for nitro reduction and quinoline formation based upon the presence of the **150**, was proposed and may involve metal bound nitroso groups or metal nitrene complexes.

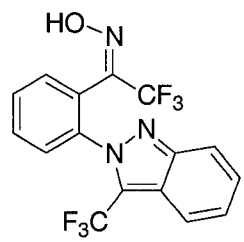
We became aware of reports on the reaction of metal carbonyls with ketoximes to yield ketones, ketimines, and stable complexes. We imagined that these complexes might participate in the reduction of pendant nitro groups. To our surprise and delight the reductive carbonylation of 2-nitro ketoximes (**165**, **175**, **187**, **188**, **193**, **194**) gave the 1H-indazoles (**166**, **195** - **199**) as major products (Scheme 6.5).[254] The reaction works best with oximes bearing electron-donating groups ($X_1 = X_2 = OMe$) and compliments existing methods. During the preparation of the ketoxime **175** we isolated the unusual 2-phenyl indazole **176** (Figure 6.1).



166, 175, 187, 188 193, 194

167, 195-199

Scheme 6.5 A New Synthesis of 1-H Indazoles



176

Figure 6.1

6.2: FUTURE DIRECTIONS

6.2.1:ORGANOMETALLIC/INORGANIC CHEMISTRY

Although some interesting and useful reactions were discovered, the use of CO pressure hampers the general application of this strategy by synthetic chemists. If reactions could be conducted at atmospheric pressure they might be adopted more readily. Therefore catalysts that are active at atmospheric pressure (bubbling CO) are needed. We have seen a marked improvement on these reactions by the use of $[Cp^*(CO)_2Fe]_2$ as opposed to $[Cp\ (CO)_2Fe]_2$ in the quinoline synthesis. This fact may point to the proclivity of dimers possessing more hindered Cp ligands to undergo homolysis more readily to generate the monomeric radicals of type **150**.[255] Metal dimers possessing pentaryl Cp rings ($[(\eta^5\text{–}C_5Ar_5)(CO)_2Fe]_2$) are known to produce radicals thermally.[255] It would be interesting to prepare these types of compounds and test them for catalytic activity in the reductive carbonylation of nitro groups.

While the NMR experiments we performed were conducted with solvents that were deoxygenated by bubbling N_2 through solutions, further high pressure NMR experiments could be attempted with more thoroughly deoxygenated solvents (freeze thaw). Attempts to isolate organometallic species could also be made by doing stoichiometric preparative scale reactions and careful chromatography, possibly with jacketed columns under argon.

The search for more active deoxygenating agents/catalysts could be a main thrust of research efforts related to this project. While the transfer of oxygen from the nitro

group to many groups (CO, PR_3, SR_2, etc.) is thermodynamically favorable[256] ($PhNO_2$ + $PMe_3 \rightarrow$ PhNO + $OPMe_3$; ΔG = -40 kcal/mol),[257] there seems to be a large kinetic barrier to these processes. The prevalence of Mo-containing enzymes that catalyze oxo-transfer processes in nature has spurred a great deal of research in inorganic/bioinorganic chemistry directed toward a mechanistic understanding oxo-transfer.[258] Most of these studies have been directed towards the transfer of oxygen from sulfoxides to phosphines. Very little work has been directed toward the application of these Mo systems for the deoxygenation of nitroaromatics, and the systems that have been studied focused upon the conversion of nitro→amino in protic media.[259] While perhaps mechanistically interesting, the production of primary aromatic amines in protic media is not likely to produce active nitrogenating species for reactions of the type described in this work (i.e. amination of olefins).

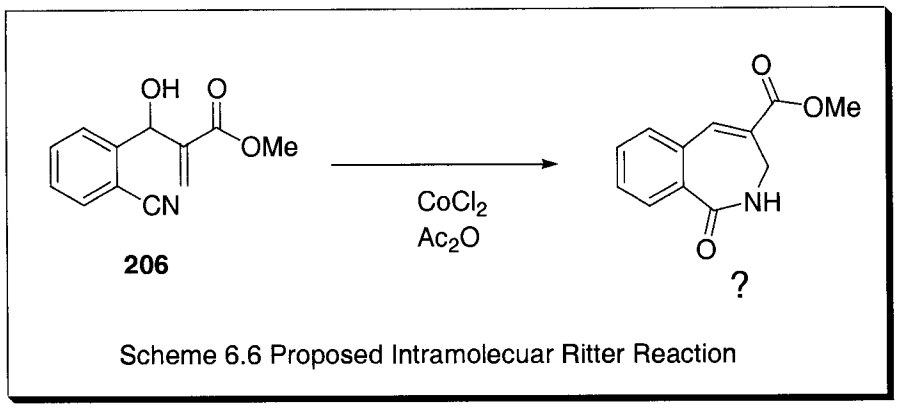
We have studied several systems for transfer including $Mo(O)_2(acac)_2/P(OEt)_3$, $Mo(O)_2$(dipic)HMPA/PPh_3, and $Mo(O)_2$(dipic)HMPA/$P(OEt)_3$; all of which failed to reduce the nitro group. These reactions rely on the transfer of oxygen from the Mo(VI) species to the phosphine to generate Mo(IV) species and PPh_3O.[260] These systems have been shown to deoxygenate DMSO and other sulfoxides to give sulfides. These systems are complicated by the fact that reduced molybdenum species (Mo(IV)) can comproportionate with Mo(VI) species to form Mo(V) species that are often very stable and inactive to oxo-transfer to phosphines. We became aware of a report detailing the use of $[PPh_4]_2[Mo^{VI}(O)_2(NCS)_4]$ for the deoxygenation of DMSO with PPh_3 that claimed that a stable Mo^{IV} complex was produced ($[PPh_4]_2[Mo^{IV}O(NCS)_4]$) upon reaction with PPh_3.[261] They "presumed" that they correctly identified the complex based on IR

spectroscopy (956 cm-1 attributed to an oxo group) and UV spectroscopy (456 nm). Based on this report we prepared $[PPh_4]_2[Mo^{VI}(O)_2(NCS)_4]$ and stirred it at room temperature with PPh_3 and nitrobenzene. No reduction of the nitrobenzene occurred, however a bright red precipitate was produced exhibiting a strong IR absorption at $960cm^{-1}$. A crystal structure of this species revealed a Mo^V complex.[262] While the Mo systems seem inappropriate for nitro reduction, many other metal oxo complexes exist that could in principal deoxygenate nitrogroups in an analogous PR_3/MO_2Ln system. Complexes of Re,[263] W,[264] Nb,[265] and V[266] are possibilities.

6.2.2: ORGANIC CHEMISTRY

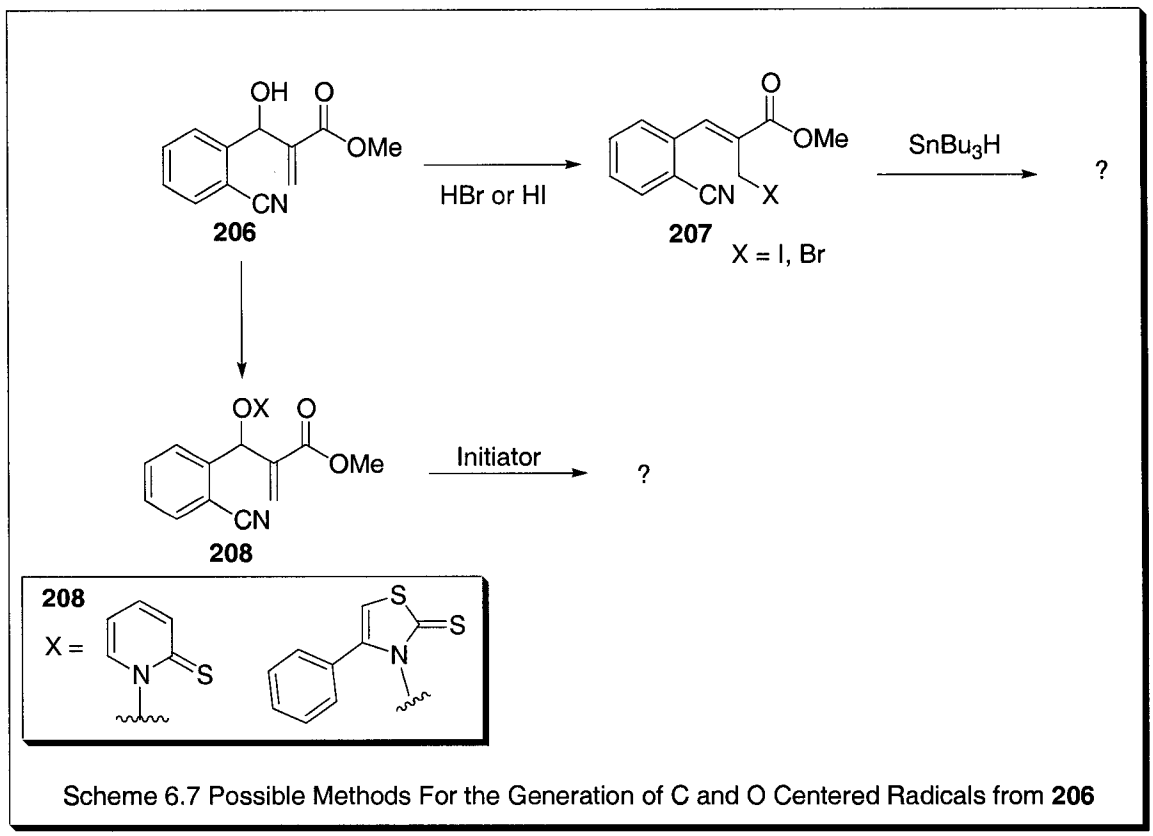
The chemistry of Baylis-Hillman adducts is perhaps more fascinating. While we have prepared the nitroso Baylis-Hillman adduct, it was not obtained in a reasonable quantity; further optimization of the reaction conditions are necessary. This compound is interesting in its own right, apart from the potential intermediacy in the reductive carbonylation reactions. It would be interesting to fully investigate products formed by a variety of conditions (photolysis, reduction by standard reagents).

Baylis-Hillman reactions possessing an *o*-CN group have, to our knowledge, not been prepared. These adducts **206** should be accessible, however, and they may also undergo intermolecular reactions like the Ritter reaction,[267] which has been performed under neutral conditions [268] (Scheme 6.6). Intramolecular Ritter reactions are relatively rare,[267] but are receiving increased attention.[269]



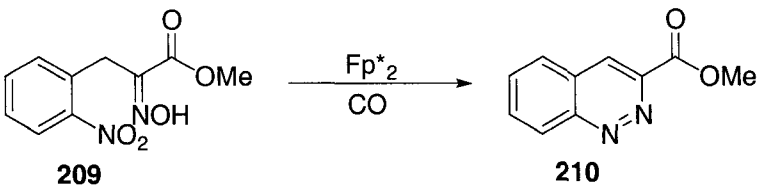
Scheme 6.6 Proposed Intramolecuar Ritter Reaction

The adduct **206** could also be converted to the bromide or iodide **207**, by known reactions (Scheme 6.7).[270] This substrate (**207**) would be an interesting case for a potential radical cyclization onto a nitrile, addition of radicals to nitriles is a relatively unexplored field.[271] Alternatively generation of alkoxy radicals in the benzylic position by a known method[272] via **208** might also provide some interesting chemistry.



Scheme 6.7 Possible Methods For the Generation of C and O Centered Radicals from **206**

The oxime chemistry also deserves further exploration. The oxime of 2-nitrophenyl methyl pyruvate (**209**) is a known compound,[273] and might cyclize upon reductive carbonylation to cinnoline **210** (Scheme 6.9). Cinnolines have medicinal properties much akin to the quinolines.[124] The chemistry of the CF_3 ketone **140** also deserves further study, due to its unusual behavior in rather standard reactions (formation of **176**).



209 **210**

Scheme 6.8 Proposed Synthesis of Cinnolines **210**

CHAPTER 7

EXPERIMENTAL SECTION

7.1: GENERAL CONSIDERATIONS

Unless specified otherwise all reactions were carried out under an atmosphere of nitrogen with magnetic stirring, using dried, freshly distilled solvents and oven dried glassware. High pressure reactions were carried out in Parr stainless steel reaction vessels (Parr Company, PA) equipped with glass-liners. All reagents and $[Cp(CO)_2Fe]_2$ were purchased from U.S. suppliers. The following compounds were prepared according to standard literature procedures and gave satisfactory spectroscopic data: **72**,[274] $(PPh_3)_2Pd(CH_2Ph)Cl$,[275] **87**,[137] **112**,[161] **116**,[171] $[Cp^*(CO)_2Fe]_2$,[176] $[Cp^*(CO)_2Ru]_2$,[177] $Cp_2Fe_2(CO)_2(dppe)$ (**118**),[178] $[(C_5H_3)_2(SiMe_2)_2]Ru_2(CO)_4$ (**119**),[179] **146**,[204] **149**,[206] **166**,[236] **169**,[221] **185**,[231] **186**,[232] **189**,[195] MnO_2.[147] TLC was performed using either ANALTECH HPTLC with fluorescent indicator, or plates from SorbTech. Flash chromatography was performed using Kieselgel 230-400 mesh (Merck). Infra-red (IR) spectra were obtained on a Bio-Rad FTS-7 FT-IR instrument. Nominal masses were obtained by electron impact (EI) using a Thermoquest GCQ system (ThermoFinnigan, San Jose, CA) equipped with a capillary gas chromatograph (for GCMS) and direct insertion probe for solid samples. Exact mass data were obtained with a micromass Q-TOF electrospray ionization (ESI) instrument (Waters, UK) and processed using the MassLynx 3.5 software package. ^1H, ^{13}C, ^{19}F NMR spectra were recorded on Varian Mercury 300 or

Varian Unity Inova-400 spectrometers, and were referenced with an internal standard of TMS, residual solvent protons, or $CFCl_3$ for ^{19}F spectra. Melting points were obtained with a Mel-Temp apparatus and are uncorrected. Elemental analysis was performed by Midwest Microlabs (Indianapolis, IN). The configuration of the oximes was determined by comparison of the ^{13}C NMR resonances of the methyl groups of the two isomers.[276]

7.2: STILLE COUPLINGS

1-Isopropenyl-2-nitrobenzene (73)[95]

In a 250 mL round bottom flask equipped with a magnetic stirrer 2-iodo nitrobenzene (3.01 g, 12.0 mmol) was combined with $Pd(PPh_3)_4$ (1.39g, 1.2 mmol), CuCl (6.00 g, 60.0 mmol), LiCl (3.04 g, 72.0 mmol), isopropenyltributyl tin **72**,[274] and DMSO (90 mL). The solution was heated to 65 °C and monitored for the disappearance of 2-iodo nitrobenzene by TLC. After 70 h the reaction was stopped and the solution was diluted with Et_2O and washed with brine (3 x 30mL). The brine was back extracted with Et_2O (10mL) and combined with the previous extract. The ether extraction was stirred with saturated aqueous KF (40mL) for several hours. The ether extract was washed with water (2 x 30mL), dried with $MgSO_4$, and concentrated on a rotary evaporator. The oily residue was chromatographed on SiO_2 with a gradient elution of Et_2O/Hexanes (1:9 to 1:4) to give the known **73** (786 mg, 40%) as a straw colored oil: ^1H NMR (400 MHz, acetone-d_6) δ 2.07 (s, 3 H), 4.91 (s, 1H), 5.12 (s, 1 H), 7.42 (d, 2 H), 7.57 (t, 1 H), 7.69 (t, 1 H), 7.90 (d, 1 H).

2-Methyl-1-(2-nitrophenyl)prop-2-en-1-one (81)

$(PPh_3)_2Pd(CH_2Ph)Cl$ [275] (64 mg, 0.09 mmol) was sealed in a glass vial which was scored to ensure breakage. This vial along with 2-nitrobenzoyl chloride (1.67 g, 9.00 mmol), isopropenyltributyltin **72**[274] (3.40 g, 10.3 mmol), and HMPA (4 mL) were added to a 120 mL glass-lined Parr reaction vessel equipped with a large magnetic stirring bar. The vessel was flushed three times with CO (fume hood) and finally charged to 20 atm. The vessel was manually shaken until the vial containing the catalyst was broken, after which the reaction was heated to 70°C for 10 h. After cooling and venting of CO (fume hood), the reaction mixture was diluted with ether and stirred with saturated aqueous KF (30 mL) for 1 day. The ether layer was separated and filtered to remove a white precipitate (Bu_3SnCl), and washed with brine (3 x 20mL). Solvent was removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/hexanes, 1:4) to give the product slightly contaminated with Bu_3SnCl. Recrystallization from Et_2O/hexanes gave pale yellow prisms of the nitroenone **81** (0. 600 g, 35%): $R_f = 0.5$ (Et_2O/hexanes, 1:1); mp 61.5-63 °C; IR (KBr) 3321, 3097, 3027, 2957, 1660, 1521, 1436, 1343, 1189 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.96 (dd, J = 1.2Hz, J= 0.3 Hz, 3 H), 5.35 (d, J = 0.9 Hz, 1 H), 5.99 (q, J = 1.2 Hz, 1 H), 7.57 (ddd, J = 7.1 Hz, J = 1.2 Hz, J = 0.3 Hz, 1 H), 7.77 (tdd, J = 8.1 Hz, J = 1.2 Hz, J = 0.6 Hz, 1 H), 7.88 (td, J = 7.5 Hz, J = 1.2 Hz, 1 H), 8.20 (dd, J = 8.3 Hz, J= 1.2 Hz, 1 H); ^{13}C NMR (75.45 MHz, DMSO-d_6) δ 17.8, 125.1, 129.5, 129.6, 131.9, 135.4, 134.8, 143.7, 146.1, 194.5; MS (ESI) 192 (M+H, 30), 214 (M+Na, 100), 405 (M_2+Na, 11.4); Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.52; H, 4.79; N, 7.27.

1-(2-Nitrophenyl)prop-2-en-1-one (83)

$(PPh_3)_2Pd(CH_2Ph)Cl$[275] (69 mg, 0.10 mmol) was sealed in a glass vial which was scored to ensure breakage. This vial along with 2-nitrobenzoyl chloride (1.80 g, 9.70 mmol), vinyltributyltin (3.10 g, 9.80 mmol), and HMPA (4 mL) were added to a 120 mL glass-lined Parr reaction vessel equipped with a large magnetic stirring bar. The vessel was flushed three times with CO (fume hood) and finally charged to 27 atm. The vessel was manually shaken until the vial containing the catalyst was broken, after which the reaction was heated to 60 °C for 36 h. After cooling and venting of CO (fume hood), the reaction mixture was diluted with ether and stirred with saturated aqueous KF (30 mL) for 24 h. The ether layer was separated and filtered to remove a white precipitate (Bu_3SnCl), and washed with brine (3 x 20mL). Solvent was removed *in vacuo* and the residue was dissolved in CH_3CN and filtered to remove insoluble Sn material. Solvent was removed *in vacuo* and the residue was purified by flash chromatography (EtOAc/hexanes, 7:13) to give **83** as a yellow gum (20 mg, 1%): $R_f = 0.3$; IR (neat) 3104, 2929, 1698, 1530, 1348 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 5.92 (dd, J = 17.6 Hz, J = 0.4 Hz, 1 H), 6.13 (dd, J = 10.8 Hz, J = 0.4 Hz, 1 H), 6.68 (dd, J = 17.6 Hz, J = 10.8 Hz, 1 H), 7.60 (dd, J = 7.6 Hz, J = 1.6 Hz, 1 H), 7.81 (dt, J = 8.0 Hz, J = 1.6 Hz, 1 H), 7.91 (dt, J = 7.6 Hz, J= 1.2 Hz, 1 H), 8.20 (dd, J = 8.0 Hz, J = 1.2 Hz, 1 H); MS (EI) 177 (10), 150 (50), 134 (100), 104 (30), 91 (15).

1-(5-Methoxy-2-nitrophenyl)-2-methylprop-2-en-1-one (84)

In the manner described for compounds **83** and **81**, 5-methoxy-2-nitrobenzoyl chloride (1.50 g, 6.96 mmol), **72**[274] (1.10 g, 3.30 mmol), and $(PPh_3)_2Pd(CH_2Ph)Cl$[275] (30 mg, 0.04 mmol) were combined in a stainless steel autoclave with HMPA (4mL) under 27 atm CO. After heating at 60°C for 24 h the above described workups were performed to give an Et_2O solution that was dried with $MgSO_4$ and concentrated. The residue was chromatographed on SiO_2 with Et_2O/hexanes to give the ketone **84** as a white gum (60mg, 8%): ^1H NMR (300 MHz, acetone-d_6) δ 2.02 (dd, J = 1.2 Hz, J = 0.3 Hz, 3 H), 4.00 (s, 3 H), 5.41 (m, 1 H), 5.90 (m, 1 H), 7.00 (d, J =3.0 Hz, 1 H), 7.24 (dd, J = 9.0Hz, J =3.0 Hz, 1 H), 8.21 (d, J = 9.0 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 16.5, 56.2, 113.2, 114.0, 115.0, 115.8, 139.1, 143.1, 162.4, 194.2.

1-(5-Fluoro-2-nitrophenyl)-2-methylprop-2-en-1-one (85)

In the manner described for compounds **83** and **81**, 5-fluoro-2-nitrobenzoyl chloride (1.09 g, 5.40 mmol), **72** (1.80 g, 5.44 mmol), and $(PPh_3)_2Pd(CH_2Ph)Cl$ (39 mg, 0.06 mmol) were combined in a stainless steel autoclave with HMPA (4 mL) under 27 atm CO. After heating at 60 °C for 8 h the above described workups were performed to give an ethereal that was dried with $MgSO_4$ and concentrated. The residue was chromatographed on SiO_2 with Et_2O/Hexanes (gradient elution, 1:3 to 2:3) to give the ketone **85** as a yellow oil which fluoresced blue under UV light on TLC plates with fluorescent indicator (26 mg, 2%): R_f = 0.66 (Et_2O/hexanes, 2:3); ^1H NMR (300 MHz, acetone-d_6) δ 2.03 (dd, J = 0.9 Hz, J = 0.6 Hz, 3 H), 5.50 (q, J = 0.9 Hz, 1 H), 6.00 (q, J = 1.5 Hz, 1 H), 7.40 (dd, J = 8.0 Hz, J = 3.0 Hz, 1 H), 7.53 - 7.60 (m, 1 H), 8.35 (dd, J = 9.0 Hz, J = 4.8 Hz, 1 H).

7.3: SYNTHESIS OF 4-QUINOLONE 82

3-Methylquinolin-4(1H)-one (82)[130]

In a glass-lined 15 mL Parr reaction vessel the nitroenone **81** (75 mg, 0.39 mmol) and Fp_2 (7 mg, 0.02 mmol) were combined in dioxane (10 mL). The vessel was purged thrice with CO (fume hood) and charged to 53 atm. The vessel was then heated to 200 °C for 8.5 h. After cooling and venting of the CO (fume hood), the reaction mixture was filtered to remove insoluble material and concentrated. Preparative TLC, eluting with EtOAc/hexanes (1:1), gave the quinolone **82** (48 mg, 76%): R_f = 0.1; IR (KBr) 3460, 2865, 1630 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.95 (s, 3 H), 7.23 (td, J = 7.5 Hz, J = 1.2 Hz, 1 H), 7.46 (dd, J = 6.6 Hz, J = 0.6 Hz, 1 H), 7.55 (td, J = 7.7 Hz, J = 1.5 Hz, 1 H), 7.85 (s, 1 H), 8.07 (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H), 8.29 (s, 1 H); ^{13}C NMR (75.45 MHz, DMSO-d_6) δ 13.6, 116.2, 117.8, 122.3, 123.8, 124.7, 130.8, 136.5, 139.5, 176.4; MS (EI) 159 (83), 130 (100), 104 (10), 92 (5), 77 (18), 63 (8), 51(8); HRMS (ESI) *m/z* calcd for $C_{10}H_9NONa$ (M+Na) 182.0582, found 182.0591.

7.4: ORGANOCERIUM MEDIATED ADDITON OF GRIGANRDS TO 2-NITRO BENZALDEHYDE

1-(2-Nitrophenyl)prop-2-yn-1-ol (87)[137]

Anhydrous $CeCl_3$ (8.13 g, 33.0 mmol) was stirred in THF (40 mL) at 0°C for 1.5 h. Ethynyl magnesium bromide (66 mL, 0.5M in THF) was added drop-wise via syringe over 5 min. The reaction mixture was stirred for an additional 2 h, followed by addition of 2-nitro benzaldehyde (1.00 g, 6.60 mmol). The reaction was complete after 2 h (TLC). The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and stirred. The mixture was filtered and extracted with Et_2O (4 x 30 mL). The ethereal solution was dried over $MgSO_4$ and solvent removed *in vacuo*. The residue was chromatographed on SiO_2 with Et_2O/hexanes (1:1) to give 765 mg of a light brown solid that was the alcohol **87** (4.32 mmol, 65 %): R_f = 0.26 (Et_2O/hexanes, 2:3); mp 56-59 °C (previously reported as an oil);[137] ^1H NMR (300 MHz, acetone-d_6) δ 3.08 (d, J = 2.4 Hz, 1 H), 5.49 (s, 1 H), 6.12 (s, 1 H), 7.58 (dt, J = 7.5 Hz, J = 1.2 Hz, 1 H), 7.75 (dt, J = 7.8 Hz, J = 1.2Hz, 1 H), 7.95 (dd, J = 7.8 Hz, J = 1.2 Hz, 1 H), 8.04 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 59.8, 75.0, 83.3, 124.9, 128.5, 129.4, 133.7, 136.3, 148.3.

7.5: SYNTHESIS OF BAYLIS-HILLMAN ADDUCTS

Methyl 2-[hydroxy(2-nitrophenyl)methyl]acrylate (88)

2-Nitrobenzaldehyde (2.00 g, 13.2 mmol) was dissolved in methyl acrylate (20 mL), DABCO (1.48 g, 13.2 mmol) was added slowly over 5 min upon which the solution became a dark orange-red. The solution was stirred at room temperature for 5 days. The methyl acrylate was removed *in vacuo*, and the residue was dissolved in Et_2O, washed with 1M HCl (3 x 20 mL), and then with water (2 x 10 mL). The ether extract was concentrated on a rotary evaporator and then chromatographed over silica gel (Et_2O/hexanes, 1:1) to give **88** (R_f = 0.28) as a straw colored oil (3.10 g, 99%), which crystallized from cold ether as white needles: mp 28-29 °C; IR (film) 3445, 2946, 1699, 1537 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.64 (s, 3 H), 5.1 (br s, 1 H), 5.81 (d, J = 1.2 Hz, 1 H), 6.26 (m, 2 H), 7.52 (td, J= 8.1 Hz, 1.8 Hz, 1 H), 7.69 (td, J = 7.8 Hz, J = 1.2 Hz, 1 H), 7.76 (dd, J = 7.8 Hz, 1.8 Hz, 1 H), 7.9 (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 51.7, 66.4, 124.4, 124.6, 128.9, 129.2, 133.2, 137.3, 143.1, 148.8, 165.8; MS (EI) 220 (M+ -OH, 10), 191 (M+ -NO_2, 100), 160 (40), 132 (146), 117 (38), 117 (38), 104 (40), 77 (42), 51 (28); HRMS (ESI) *m/z* calcd for $C_{11}H_{11}NO_5Na$ (M+Na) 260.0535, found 260.0463.

Methyl 2-[(5-chloro-2-nitrophenyl)(hydroxy)methyl]acrylate (89)

5-Chloro-2-nitrobenzaldehyde (1.00 g, 5.30 mmol), sold as a mixture from Aldrich of at least 77% purity, was dissolved in 15 mL of methyl acrylate. DABCO (0.60 g, 5.4 mmol) was then added over 5 min after which the solution darkened. The reaction mixture was stirred at room temperature for 4 days, followed by the workup described for compound **88**. Chromatography on silica gel with Et_2O/hexanes (gradient elution: 1:5 to 1:1) gave 1.07 g of the Baylis-Hillman adduct **89** as a yellow solid: (93 %, based upon the purity of the starting material) R_f = 0.40 (Et_2O/hexanes, 1:1); mp 63-65°C; IR (KBr) 3475, 1722, 1529, 1367, 1297 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.69 (s, 3 H), 5.38 (d, J = 5.1Hz, 1 H), 5.81 (d, J = 0.9 Hz, 1 H), 6.29 (m, 2 H), 7.59 (dd, J = 8.7 Hz, J = 2.4 Hz, 1 H), 7.79 (d, J = 2.4 Hz, 1 H), 8.0 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 52.2, 66.8, 125.7, 127.0, 129.3, 129.6, 139.5, 140.5, 143.2, 147.5, 166.1; MS (EI) 254 (M+ -OH, 1), 227 (30), 225 (M+ -NO_2, 100), 194 (20), 166 (15), 138 (6); HRMS (ESI) m/z calcd for $C_{11}H_{10}NO_5Na$ (M+ Na) 294.0145, found 294.0103.

Methyl 2-[hydroxy(6-nitro-1,3-benzodioxol-5-yl)methyl]acrylate (90)

2-Nitropiperonal (3.00 g, 15.4 mmol) was dissolved in methyl acrylate (20 mL), DABCO (1.72 g, 15.4 mmol) was added slowly over 5 min upon which the solution became a dark orange-red. The reaction mixture was stirred at room temperature for 7 days; after one day a yellow precipitate formed. After the above described workup, chromatography on silica gel using a gradient elution with Et_2O/hexanes (20% to 50% Et_2O) gave 4.10 g (95 %) of **90**: R_f = 0.2 (Et_2O/hexanes, 1:1); mp 122-123.5 °C; IR (KBr) 3494, 1712, 1637, 1531, 1482, 1343, 1256, 1030, 879, 822 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 3.71 (s, 3

H), 4.02 (br s, 1 H), 5.67 (d, J = 0.9 Hz, 1 H), 6.15 (m, 3 H), 7.17 (s, 1 H), 7.49 (s, 1 H); ^{13}C NMR (75.45 MHz, CD_3CN) δ 52.6, 67.3, 104.5, 105.7, 108.2, 125.5, 135.2, 142.2, 143.4, 148.2, 153.0, 166.8; MS (EI) 235 (M+ -NO_2, 20), 221 (32), 204 (76), 188 (64), 176 (100), 160 (26), 148 (18), 135 (9), 120 (7), 104 (4), 77 (3), 53 (8); HRMS (ESI) *m/z* calcd for $C_{12}H_{11}NO_7Na$ (M+Na) 304.0433, found 304.0412; Anal. Calcd for $C_{12}H_{11}NO_7$: C, 51.25; H, 3.94; N, 4.98. Found: C, 51.25; H, 3.99; N, 4.86.

Methyl 2-[hydroxymethyl-(4,5-dimethoxy-2-nitrophenyl)]acrylate (91)

DABCO (1.78 g, 11.8 mmol) was added to a solution of technical grade (80%) 6-nitro veratraldehyde (2.50 g, 11.8 mmol) in methyl acrylate (15 mL). After stirring for 10 days at room temperature, methyl acrylate was removed *in vacuo* and the straw colored oil taken up in Et_2O (40 mL). The ethereal solution was washed sequentially with 1M HCl (3 x 20 mL) and water (2 x 10 mL). The ether extract was dried with $MgSO_4$ and concentrated. The residue was dissolved in a minimal amount of hot toluene and allowed to stand at –10°C over night. The solution containing a white solid was filtered and washed with cold hexanes to give (1.85 g, 66%) of the Baylis-Hillman adduct **91**: mp 80-81 °C; IR (KBr) 3336 (br), 1720 (s), 1521, 1267, 1066 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 3.69 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 5.09 (br s, 1 H), 5.58 (s, 1 H), 6.15 (s, 1 H), 6.34 (s, 1 H), 7.35 (s, 1 H), 7.58 (s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 52.0, 56.4, 67.1, 108.4, 110.9, 124.5, 133.0, 140.7, 144.0, 148.7, 153.9, 166.4; MS (EI) 297 (M+, 10), 280 (98), 270 (40), 220 (45), 192 (100), 176 (60), 164 (42), 136 (36); Anal. Calcd for $C_{13}N_{15}NO_7$: C, 52.53; H, 5.09; N, 4.71. Found: C, 52.77; H, 5.10; N, 4.64.

Methyl 2-[hydroxymethyl-(1-nitro-2-naphthyl)]acrylate (92)

1-Nitro-2-naphthaldehyde (1.23 g, 6.10 mmol) was dissolved in methyl acrylate (15 mL), DABCO (523 mg, 4.97 mmol) was added and the solution was stirred for 5 days at room temperature. The methyl acrylate was removed *in vacuo*, and the residue was taken up in Et_2O (35 mL) and washed with 1M HCl (3 x 20 mL) and water (2 x 10 mL). The ethereal solution was dried with $MgSO_4$ concentrated and the residue was redissolved in a minimal amount of hot Et_2O and placed in a –10 °C freezer overnight. The beige crystals were filtered to give (1.38 g, 78 %) of the Baylis Hillman adduct **92**: mp 135-137 °C; IR (KBr) 3475, 1707, 1529, 1297 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 3.59 (s, 3 H), 4.20 (d, J = 4.5 Hz, 1 H), 5.78 (d, J = 3.9 Hz, 1 H), 6.05 (dd, J = 1.5 Hz, J = 0.9 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 1 H), 7.61-7.77 (m, 3 H), 7.99 (dd, J = 7.2 Hz, J = 2.1 Hz, 1 H), 8.06 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (75.45 MHz, CD_3CN) δ 52.5, 67.9, 122.3, 124.8, 125.2, 126.7, 128.6, 129.0, 129.8, 131.9, 132.0, 134.1, 142.3, 166.3; MS (EI) 270 (M^+-OH, 35), 241 (100), 209 (20), 181 (18), 152 (10); HRMS (ESI) *m/z* calcd for $C_{15}H_{13}NO_5Na$ (M+Na) 310.0691, found 310.0637.

Methyl 2-[hydroxy(3-methoxy-2-nitrophenyl)methyl]acrylate (93)

3-Methoxy-2-nitrobenzaldehyde (1.00 g, 13.2 mmol) was dissolved in methyl acrylate (15 mL), DABCO (619 mg, 5.52 mmol) was added slowly over 5 min upon which the solution became a dark orange-red. The solution was stirred at room temperature for 7 days. The methyl acrylate was removed *in vacuo*, and the residue was dissolved in Et_2O, washed with 1M HCl (3 x 20 mL), and then with water (2 x 10 mL). The ether extract was concentrated on a rotary evaporator and then chromatographed over silica gel

(Et_2O/hexanes, 1:1) to give **93** as a green oil (1.21 g, 82%); celadon crystals could be obtained from Et_2O: mp 102-104°C. IR (KBr) 3506, 2950, 1722, 1529, 1297 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 3.62 (s, 3 H), 3.87 (s, 3 H), 3.96 (br s, 1 H), 5.56 (s, 1 H), 5.93 (t, J = 1.2 Hz, 1 H), 6.34 (t, J = 0.9 Hz, 1 H), 7.01 (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H), 7.13 (dd, J = 8.7 Hz, J = 1.2 Hz, 1 H), 7.46 (t, J = 7.8 Hz, 1 H); ^{13}C NMR (75.45 MHz, CD_3CN) δ 52.3, 57.2, 67.7, 113.2, 118.0, 120.0, 126.5, 132.0, 135.3, 142.0, 151.2, 166.2; MS (EI) 268 (M+1, 20), 250 (90), 221 (100), 188 (8), 161 (25); HRMS (ESI) *m/z* calcd for $C_{12}H_{13}NO_6Na$ (M + Na) 290.0641, found 290.0570.

_t_-Butyl 2-[hydroxy(2-nitrophenyl)methyl]acrylate (94)

2-Nitrobenzaldehyde (2.00 g, 13.2 mmol) was dissolved in *t*-butyl acrylate (15 mL), DABCO (1.48 g, 13.2 mmol) was added slowly over 5 min upon which the solution became a dark orange-red. The reaction mixture was stirred at room temperature for 7 days. The methyl acrylate was removed *in vacuo*, and the residue was dissolved in Et_2O, washed with 1M HCl (3 x 20 mL), and then with water (2 x 10 mL). The ether extract was concentrated on a rotary evaporator and then chromatographed over silica gel (Et_2O/hexanes, 1:1) to give **94** as a straw colored oil (420 mg, 11%): ^1H NMR (300 MHz, acetone-d_6) δ 1.35 (s, 9 H), 5.06 (br s, 1 H), 5.78 (s, 1 H), 6.19 (s, 1 H), 6.23 (s, 1 H), 7.55 (m, 1 H), 7.93 (d, J = 7.8 Hz, 1 H).

2-[Hydroxymethyl-(2-nitrophenyl)]acrylonitrile (95)

2-Nitrobenzaldehyde (2.00 g, 13.2 mmol) was dissolved in acrylonitrile (15 mL) and DABCO (1.48 g, 13.2 mmol) was added. After stirring at room temperature for 3 days,

the acrylonitrile was removed *in vacuo*. The dark residue was dissolved in Et_2O (40 mL) and washed with 1M HCl (3 x 20 mL) and water (2 x 10 mL). The Et_2O extract was concentrated and chromatographed on SiO_2 with Et_2O/Hexanes (2:3) to give one main product of R_f = 0.20 as a yellow oil (693 mg, 26%) which was the Baylis-Hillman adduct **95**: IR (CH_2Cl_2) 3054, 2986, 2306, 1530, 1422, 1263 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 5.8 (br s, 1 H), 6.07 (s, 1 H), 6.09 (d, J = 0.9 Hz, 1 H), 6.15 (d, J = 0.9 Hz, 1 H), 7.61 – 7.68 (m, 1 H), 7.84 (m, 1 H), 7.98 (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H), 8.03 (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 69.2, 117.4, 125.1, 126.3, 129.4, 130.1, 131.8, 134.3, 135.7, 148.7; HRMS (ESI) *m/z* calcd for $C_{10}H_8N_2O_3Na$ (M+Na) 227.0433, found 227.0456.

7.6: CYCLIZATION OF BAYLIS-HILLMAN ADDUCTS

Cyclization of Baylis-Hillman adduct **88**

Compound **88** (0.20 g, 0.84 mmol) and Fp_2 (30 mg, 0.09 mmol) were placed in a glass-lined, stainless steel Parr reaction vessel with dioxane (10 mL). The vessel was flushed three times with CO (fume hood) and charged to 53 atm. The reaction vessel was the heated to 150°C for 14 h. After cooling and venting of CO (fume hood), the resulting brown reaction mixture was filtered to remove insoluble material, concentrated and then chromatographed on silica gel with a gradient elution of Et_2O/hexanes (1:5 to 9:1) to give the following compounds:

Methyl 1H-indole-3-carboxylate (96)

25 mg (17%); R_f = 0.25 (Et_2O/hexanes, 1:1); spectroscopically identical to material purchased from Aldrich.

3-Methylquinolin-2(1H)-one (97)[146]

6 mg (4%); R_f = 0.26 (Et_2O/hexanes, 3:1); spectroscopically identical to literature compound.[146]

Methyl 1-formylindoline-3-carboxylate (99)

34 mg (20 %); R_f = 0.20 (Et_2O/hexanes, 3:1); mp 84-85.5 °C; IR (KBr) 1732, 1665, 1594, 1497, 1367, 1283, 1220, 1174 cm^{-1}; ^1H NMR (300 MHz, DMSO -d_6) δ 3.69 (s, 3 H), 4.0-4.5 (m, 3 H), 7.09 (m, 1 H), 7.26 (m, 1 H), 7.37 (d, J = 7.8 Hz, 1 H), 7.48 (d, J = 8.1 Hz, 0.7 H, major isomer), 7.91 (d, J = 7.8 Hz, 0.3 H, minor), 8.50 (s, 0.3 H, minor), 9.04 (s, 0.7 H, major); ^{13}C NMR (75.45 MHz, DMSO-d_6) δ 44.0, 44.5, 46.9, 48.9, 52.5, 110.2, 115.6, 123.7, 124.1, 125.3, 125.9, 128.5, 128.6, 128.8, 129.4, 140.8, 158.3, 160.0, 171.2, 171.3; MS (EI) 205 (M^+, 60), 177 (8),145 (35), 118 (100), 91 (17); Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.45; H, 5.47; N, 6.74.

Cyclization of Baylis-Hillman adduct **89**

The Baylis-Hillman adduct **89** (240 mg, 0.89 mmol) and Fp_2 (35 mg, 0.10 mmol) were placed in a glass-lined, stainless steel 15 mL Parr reaction vessel with benzene (10 mL). The vessel was flushed thrice with CO (fume hood) and charged to 53 atm. The reaction vessel was heated to 150 °C while stirring for 18 h. After cooling and venting the CO

(fume hood), the resulting dark brown solution was filtered to remove insoluble material, the filtrate concentrated, and then chromatographed on silica gel with a gradient elution of Et_2O/hexanes (1:5 to 9:1) giving the following compounds:

Methyl 5-chloro-1-formylindoline-3-carboxylate (102)

30 mg (13 %); R_f = 0.13 (Et_2O/hexanes, 3:1); IR (KBr) 3452, 2975, 1738, 1684, 1491, 1367, 1321, 819 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 3.72 (s, 3 H), 4.05-4.15 (m, 1 H), 4.24 – 4.47 (m, 2 H), 7.26 (m, 2 H), 7.41 (m, 0.7 H, major isomer), 7.93 (d, J = 8.7 Hz, 0.3 H, minor isomer), 8.42 (s, 0.3 H, minor), 8.86 (s, 0.7 H, major); ^{13}C NMR (75.45 MHz, CD_3CN) δ 45.1, 45.6, 48.1, 50.2, 53.2, 111.8, 117.6, 126.0, 126.3, 127.1, 128.8, 129.3, 131.7, 158.5, 160.5, 171.7; MS (EI) 241 (M^+, 15), 239 (50), 211 (16), 180 (31), 154 (32), 152 (100), 117 (78), 89 (14); Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 54.91; H, 4.33; N, 5.54.

Methyl 5-chloro-1H-indole-3-carboxylate (103)

23 mg (11%); mp 110-112 °C; R_f = 0.18 (Et_2O/hexanes, 1:1); IR (KBr) 3250, 1680, 1524, 1443cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 3.87 (s, 3 H), 7.23 (dd, J = 8.8 Hz, J = 2.1 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1 H), 7.97 (s, 1H), 8.07 (d, J = 2.1 Hz, 1 H), 10.06 (br s, 1 H); ^{13}C NMR (75.45 MHz, CD_3CN) δ 51.4, 114.3, 120.8, 123.6, 133.8, 165.4; MS (EI) 211 (15), 209 (50), 178 (100), 150 (24), 123 (8); HRMS (ESI) *m/z* calcd for $C_{10}H_8ClNO_2Na$ (M+ Na) 232.0141, found 232.0080.

Methyl 6-chloroquinoline-3-carboxylate (104)

8 mg (4%); R_f = 0.2 (Et_2O/hexanes, 1:3); mp 170-172 °C; IR (KBr) 3066, 2950, 1722, 1491, 1436, 1336, 1267, 1097, 819 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6) δ 4.00 (s, 3 H), 7.89 (dd, J = 9.0 Hz, J = 2.4 Hz, 1 H), 8.12 (d, J = 9.0 Hz, 1 H), 8.24 (d, J = 2.1 Hz, 1 H), 8.93 (d, J = 1.5 Hz, 1 H), 9.35 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 52.7, 132.7, 127.5, 130.9, 132.7, 133.3, 137.7, 148.0, 150.0, 165.3; MS (EI) 221 (M^+, 100), 190 (95), 162 (70), 127 (27), 99 (16), 74 (5); HRMS (ESI) *m/z* calcd for $C_{11}H_8NO_2ClNa$ (M+ Na) 244.0141, found 244.0092.

Cyclization of Baylis-Hillman Adduct **90**

The Baylis-Hillman adduct **90** (200 mg, 0.71 mmol) and Fp_2 (27 mg, 0.08 mmol) were placed in a glass-lined, 15 mL stainless steel Parr reaction vessel with dioxane (10 mL). The vessel was flushed thrice with CO (fume hood) and charged to 53 atm. The reaction vessel was heated to 150 °C while stirring for 24 h. After cooling and venting of CO (fume hood) the resulting dark brown solution was filtered to remove insoluble material, concentrated, and then chromatographed on silica gel with a gradient elution of Et_2O/hexanes (1:5 to 9:1) giving the following compounds:

Methyl 5-formyl-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indole-7-carboxylate (105):[277] 14 mg (8%); R_f = 0.25 (Et_2O/hexanes, 3:1); IR (KBr) 2973, 2919, 1730, 1669, 1483, 1297, 1220, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3 H), 4.10-4.24 (m, 2 H), 4.40-4.58 (m, 1 H), 5.95 (m, 2 H), 6.69 (s, 0.7 H, major isomer), 6.86 (s, 0.3 H, minor isomer), 6.88 (s, 0.7 H, major), 7.69 (s, 0.3 H), 8.41 (s, 0.3 H, minor), 8.74 (s, 0.7 H, major); ^{13}C

NMR (75.45 MHz, $CDCl_3$) δ 44.5, 44.9, 47.9, 49.7, 52.8, 92.2, 99.3, 101.6, 105.4, 106.4, 120.5, 130.7, 156.5, 158.2, 171.1; MS (EI) 249 (M^+,65), 190 (100), 160 (40), 132 (60), 104 (40), 77 (10); HRMS (ESI) *m/z* calcd for $C_{12}H_{11}ClNO_5Na$ (M+ Na) 272.0535, found 272.0551.

Methyl 5H-[1,3]dioxolo[4,5-f]indole-7-carboxylate (106)

8 mg (5%); R_f = 0.20 (Et_2O/hexanes, 1:1); IR (KBr) 3351, 2950, 1676, 1545, 1467, 1297, 1197, 1081, 1027, 942, 819 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6) δ 3.7 (s, 3 H), 5.96 (s, 2 H), 6.98 (s, 3 H), 7.45 (s, 1 H), 7.85 (s, 1 H), 10.81 (br s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 50.3, 92.8, 99.6, 101.1, 108.0, 120.7, 130.1, 131.6, 144.5, 145.5, 165.0; MS (EI) 219 (100), 188 (80), 160 (27), 130 (5), 103 (6), 74 (10); HRMS (ESI) *m/z* calcd for $C_{11}H_9NO_4Na$ (M+Na) 242.0429, found 242.0483.

7.7: ALTERNATIVE PREPARATION OF 99

Methyl 1-(2,2-dimethylpropanoyl)-1H-indole-3-carboxylate (100).

The commercial indole **96** (3.00 g, 17.1 mmol) was placed in a 50 mL round bottom flask with NaH (0.54 g, 22.3 mmol) and cooled with an ice bath. THF (20 mL) was added with stirring, and gas evolution was observed. After 5 min Boc_2O (4.86 g, 22.2 mmol) was added and a solid precipitated. The solution was stirred overnight. The reaction mixture was then quenched with sat. NH_4Cl (20 mL), diluted with ether and washed with water (3 x 20 mL). The ethereal solution was then dried with $MgSO_4$ concentrated under vacuum, and chromatographed with Et_2O/hexanes (1:10) to give a 4.50 g (95%) of **100** as

a white solid: mp 125-127 °C; R_f = 0.25 (1:20, Et_2O/hexanes); IR (KBr) 3166, 2981, 1745, 1714, 1560, 1451, 1374, 1150, 726 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 1.71 (s, 9 H), 3.89 (s, 3 H), 7.32 – 7.44 (m, 2 H), 8.12 – 8.21 (m, 2 H), 8.23 (s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 28.1, 51.5, 85.8, 112.4, 115.8, 122.0, 124.4, 125.7, 128.1, 132.3, 136.1, 149.3, 164.3; MS (EI) 275 (M^+, 11), 175 (100), 144 (63), 116 (10); HRMS (ESI) *m/z* calcd for $C_{15}H_{17}NO_4Na$ (M+ Na) 298.1055, found 298.1144.

Methyl 1-(2,2-dimethylpropanoyl)indoline-3-carboxylate (101)

The N-Boc indole **100** (2.25 g, 8.20 mmol) was placed in Fischer-Porter bottle[175] with 5 % Pd/C (500 mg), MeOH (10 mL) and EtOAc (30 mL). The bottle was purged thrice with H_2 (fume hood) and charged to 7 atm. After stirring for 3 days at room temperature the vessel was recharged with H_2 to 7 atm and an additional 300 mg of 5% Pd/C was added. After another two days of stirring the reaction was stopped and the reaction mixture was filtered through Celite and concentrated. Chromatography on silica gel with Et_2O/hexanes (gradient elution 1:20 to 1:10) gave 1.54 g (68%) of **101** as a white solid with R_f = 0.1 (Et_2O/hexanes, 1:20) and an undetermined amount of recovered starting material: mp 53-54 °C; IR (KBr) 2981, 1745, 1699, 1491, 1398, 1004, 741 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 1.58 (s, 9 H), 3.75 (s, 3 H), 4.12 (m, 3 H), 4.31 (m, 2 H), 6.96 (td, J = 7.4 Hz, J = 1.2 Hz, 1 H), 7.23 (tdd, J = 7.7 Hz, J = 1.5 Hz, J = 0.6 Hz, 1 H), (ddd, J = 8.0 Hz, J = 1.5 Hz, J = 0.6 Hz, 1 H), 7.84 (br s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 29.5, 50.5, 52.6, 65.9, 115.1, 122.6, 125.5, 129.1, 152.1, 172.0; MS (EI) 277 (M+, 20), 221 (80), 177 (100), 118 (58), 89 (8); HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NO_4Na$ (M+ Na) 300.1212, found 300.1252.

Methyl 1-formylindoline-3-carboxylate (99)

The N-Boc indoline **101** (0.730 g, 2.64 mmol) was stirred in formic acid (8 mL) for one hour at rt. Acetic formic anhydride, preformed by the addition of acetic acid (0.5 mL) to formic acid (1.0 mL) with stirring for one hour, was then added. The solution was stirred at rt for 4 h. Formic acid was removed *in vacuo*, the residue was dissolved in ether (20 mL) and then extracted with aqueous saturated $NaHCO_3$ (3x15 mL). The ether extract was dried with $MgSO_4$, concentrated, and chromatographed using Et_2O/hexanes (gradient elution 1:1 to 9:1) to give 0.295 g (55%) of the previously described N-formyl-indoline **99**.

7.8: PREPARATION OF BAYLIS-HILLMAN ACETATES

The following procedure is representative for the preparation of acetates **120-124**:

The Baylis Hillman adduct **90** (500 mg, 1.78 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled with an ice bath. Pyridine (0.290 mL, 3.56 mmol) was added followed by acetyl chloride (0.260 mL, 3.56 mmol) and the solution stirred for 1 h. The reaction mixture was diluted with ether and washed with 2M HCl (2 x 20 mL), saturated $NaHCO_3$ (2 x 20 mL), and H_2O (1 x 10 mL). The organic layer was dried with $MgSO_4$ and concentrated to give the acetates generally as white solids that were obtained in pure form by recrystallization from toluene or by silica gel chromatography with 1:1 hexane/ether.

Methyl 2-[acetyloxymethyl-(6-nitro-1,3-benzodioxol-5-yl)]-acrylate (120)

94% yield; mp 123-125 °C; IR (KBr) 1753, 1714, 1521, 1220, 1035 cm^{-1}; ^1H NMR (CD_3CN) δ 2.07 (s, 3 H), 3.72 (s, 3 H), 5.58 (d, J = 1.2 Hz, 1 H), 6.14 (d, J = 0.9 Hz, 1 H), 6.15 (d, J = 0.9 Hz, 1 H), 7.04 (s, 1 H), 7.12 (d, J = 1.2 Hz, 1 H), 7.55 (s, 1 H); ^{13}C NMR (CD_3CN) δ 21.2, 52.9, 69.5, 104.9, 106.2, 108.1, 123.1, 128.5, 130.6, 139.5, 153.5, 166.0, 170.2; MS (ESI) 346.1 (M + Na, 63); Anal. Calcd for $C_{14}H_{13}NO_8$: C, 52.02; H, 4.05; N, 4.33. Found: C, 51.92; H, 4.07; N, 4.30.

Methyl 2-[acetyloxymethyl-(5-chloro-2-nitrophenyl)]-acrylate (121)

99% yield; mp 103-104 °C; IR (KBr) 1753, 1706, 1521, 1204, 1027 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 2.14 (s, 3 H), 3.74 (s, 3 H), 3.74 (s, 3 H), 5.74 (d, J = 1.2 Hz, 1 H), 6.43 (d, J = 0.3 Hz, 1 H), 7.21 (d, J = 0.3 Hz, 1 H), 7.67-7.71 (m, 2 H), 8.12 (td, J = 9.0 Hz, J = 1.5 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 20.6, 52.5, 68.7, 127.5, 128.5, 129.4, 130.3, 135.7, 138.8, 140.0, 165.2, 169.4; MS (ESI) 336 (M + Na, 100); Anal. Calcd for $C_{13}H_{12}NO_6Cl$: C, 49.78; H, 3.86; N, 4.47. Found: C, 49.85; H 3.89; N 4.46.

Methyl 2-[acetyloxymethyl-(4,5-dimethoxy-2-nitrophenyl)]-acrylate (122) 96% yield; mp 145-147 °C; IR (KBr) 1753, 1719, 1523 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 2.10 (s, 3 H), 3.75 (s, 3 H), 3.95 (s, 3 H), 3.96 (s, 3 H), 5.58 (d, J = 1.2 Hz, 1 H), 6.35 (s, 1 H), 7.10 (s, 1H), 7.27 (d, J =1.2 Hz, 1 H), 7.68 (s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 21.0, 52.7, 56.8, 56.9, 69.6, 109.1, 110.9, 128.4, 128.6, 140.1, 149.7, 154.7, 165.9, 169.7; HRMS (ESI) *m/z* calcd for $C_{15}H_{17}NO_8Na$ (M+Na) 362.0852, found 362.0816.

Methyl 2-[acetyloxymethyl-(1-nitro-2-naphthyl)]-acrylate (123)

93% yield; mp 105-107 °C; IR (KBr) 1753, 1707, 1529 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 2.12 (s, 3 H), 3.72 (s, 3 H), 5.89 (d, J = 1.5 Hz, 1 H); 6.50 (d, J = 0.9 Hz, 1 H); 6.90 (s, 1 H), 7.68 (d, J = 9.0 Hz, 1 H), 7.71 – 7.81 (m, 3 H), 8.13 (m, 1 H), 8.23 (d, J = 9.0 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 21.4, 53.3, 70.3, 123.1, 125.6, 126.1, 128.6, 129.4, 129.7, 129.9, 130.8, 132.9, 135.3, 139.6, 166.1, 170.1; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}NO_6Na$ (M + Na) 352.0797, found 352.0558.

2-[Acetyloxymethyl-(2-nitrophenyl)-acrylonitrile (124)

71% yield; yellow oil, R_f = 0.25; IR (KBr) 2228, 1750, 1528 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 2.18 (s, 3 H), 6.24 (d, J = 0.9 Hz, 1 H), 6.36 (s, 1 H), 6.98 (s, 1 H), 7.65 – 7.72 (m, 1 H), 7.82 – 7.89 (m, 2 H), 8.11 (d, J = 7.8 Hz); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 20.5, 70.2, 116.6, 121.5, 125.5, 129.1, 130.7, 131,8, 134.7, 135.3, 148.5, 169.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{10}N_2O_4Na$ (M+Na) 269.0538, found 269.0490.

7.9: CYCLIZATION OF BAYLIS-HILLMAN ACETATES: SYNTHESIS OF 3-SUBSTITUTED QUINOLINES

The following procedure is representative for the preparation of quinoline **117** is representative of that used for quinolines **125** -**129**.

Methyl quinoline-3-carboxylate (117)

In a glass-lined, stainless steel Parr reactor or a thick-walled glass vessel (e.g. Fischer-Porter bottle[175]) the acetate **116** (200 mg, 0.72 mmol) was combined with $[Cp^*(CO)_2Fe]_2$ (35 mg, 0.07 mmol) and dioxane (70 mL). The vessel was flushed thrice with CO (FUME HOOD!), charged to 7 atm (15 eq) with CO, and heated to 150 °C with an oil bath for 41 h. After cooling, the vessel was vented (FUME HOOD!) and the ruby colored solution was concentrated on a rotary evaporator. The solid red-brown residue was chromatographed on SiO_2 with Et_2O / hexanes (2:3) to give (134 mg, 67 %) of a white solid which was the quinoline **117**:[173] R_f= 0.35 (1:1, Et_2O/hexanes), spectroscopically identical to that reported previously. mp 68-71°C; lit.[173] 70-74°C. A portion of the catalyst $[Cp^*(CO)_2Fe]_2$ was also recovered (13 mg, 0.03 mmol).

Methyl [1,3]dioxolo[4,5-g]quinoline-7-carboxylate (125)

80 h reaction time; chromatography with $CHCl_3$ / MeOH (30:1, R_f = 0.44); 65% yield; white needles, mp 210-213 °C; IR (KBr) 1709, 1470, 1203 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.95 (s, 3 H), 6.27 (s, 1 H), 7.36 (s, 1 H), 7.42 (s, 1 H), 8.71 (d, J = 2.1 Hz, 1 H), 9.12 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 53.3, 104.3, 105.2,

106.9, 138.1, 149.1, 167.1; MS (EI) 231 (M+, 100), 200 (95), 172 (65), 142 (15), 114 (20); Anal. Calcd for $C_{12}H_9NO_4$: C, 62.33; H, 3.92; N, 6.05. Found: C, 62.42; H, 3.94; N, 6.08.

Methyl 6-chloroquinoline-3-carboxylate (126)

24.5 h reaction time; chromatography with $CHCl_3$ / MeOH (30:1; $R_f = 0.78$); 48% yield; mp 174-176 °C; IR (KBr) 3066, 2950, 1722, 1491, 1436, 1336, 1267, 1097, 819 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 4.00 (s, 3 H), 7.89 (dd, J = 9.0 Hz, J = 2.4 Hz, 1 H), 8.12 (d, J = 9.0 Hz, 1 H), 8.24 (d, J = 2.1 Hz, 1 H), 8.93 (d, J = 1.5 Hz, 1 H), 9.35 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 52.7, 132.7, 127.5, 130.9, 132.7, 133.3, 137.7, 148.0, 150.0, 165.3; MS (EI) 221 (M^+, 100), 190 (95), 162 (70), 127 (27), 99 (16), 74 (5); HRMS (ESI) *m/z* calcd for $C_{11}H_8ClNO_2Na$ (M+ Na) 244.0141, found 244.0092.

Methyl 6,7-dimethoxyquinoline-3-carboxylate (127)

89 h reaction time; chromatography with $CHCl_3$ / MeOH (30:1; $R_f = 0.44$); 60% yield; mp 161-163 °C; IR (KBr) 1722, 1618, 1599, 1505, 1432 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.95 (s, 3 H), 4.0 (s, 3 H), 4.04 (s, 3 H), 7.43 (s, 1 H), 7.45 (s, 1 H), 8.70 (s, 1 H), 9.14 (s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 51.9, 55.7, 55.8, 106.5, 107.9, 121.3, 122.7, 136.1, 147.5, 147.8, 150.9, 154.9, 165.9; HRMS (ESI) m/z calcd for $C_{13}H_{14}NO_4$ (M + H) 248.0923, found 248.0795 (100); m/z calcd for $C_{13}H_{13}NO_4Na$ (M + Na) 270.0742, found 270.0569 (44).

Methyl benzo[h]quinoline-3-carboxylate (128)

40 h reaction time; chromatography with Et_2O/hexanes (3:7; $R_f = 0.32$); 47 % yield; mp 125-127 °C; IR (KBr) 3066, 2949, 1706, 1610, 1323, 1267, 1214 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 4.01 (s, 3 H), 7.76 – 7.86 (m, 2 H), 7.93 – 8.1 (m, 3 H), 8.90 (d, J = 2.1 Hz, 1 H), 9.26 – 9.34 (m, 1 H), 9.45 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 53.5, 125.4, 126.4, 126.8, 127.3, 128.9, 129.6, 130.1, 130.9, 132.4, 136.2, 138.0, 150.0, 150.1, 166.8; MS (EI) 237 (M+, 100), 206 (60), 178 (65), 151 (25); Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.20; H, 4.75; N, 5.95.

Quinoline-3-carbonitrile (129)[180]

39 h reaction time; chromatography with Et_2O/hexanes (4:7; $R_f = 0.32$); 65 % yield; mp 104-106°C; lit.[180] 107-108 °C; IR (KBr) 2228, 1619, 1489 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.77 (t, J = 7.5 Hz, 1 H), 7.97 (t, J = 7.5 Hz, 1 H), 8.08 - 8.15 (m, 2 H), 8.90 (d, J = 1.5 Hz, 1 H), 9.10 (d, J = 1.5 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 107.2, 117.7, 126.9, 129.0, 129.3, 130.1, 133.3, 142.5, 149.3, 150.5; MS (EI) 154 (M+, 100), 127 (20), 100 (5).

7.10: PREPARATION OF OTHER DERVIATES OF BAYLIS-HILLMAN ADDUCTS: ACID (131), TRIFLUOROACETATE (132), AND TMS ETHER (133)

2-[(5-Chloro-2-nitrophenyl)(hydroxy)methyl]acrylic acid (131)

To a of the Baylis-Hillman Adduct **89** (500 mg, 1.95 mmol) in THF/H_2O (1:1/ 25mL) was added LiOH (234 mg, 9.75 mmol). Upon addition the solution turned pink and eventually yellow. After 3 h all starting material was consumed (TLC), and the reaction mixture was acidified to pH 6-7 with 6M HCl. The solution was extracted with Et_2O (3x 20 mL) and the ether extract dried with $MgSO_4$. Solvent removal *in vacuo* gave **131** as yellow solid (421mg, 1.74 mmol): ^{1}H NMR (300 MHz, acetone-d_6) δ 5.33 (br s, 1 H), 5.82 (s, 1 H), 6.32 (s , 1 H), 6.35 (s, 1 H), 7.60 (d, 1 H), 7.80 (s, 1 H), 8.00 (d, 1 H), 11.10 (br s, 1 H).

Methyl 2-{(2-nitrophenyl)[(trifluoroacetyl)oxy]methyl}acrylate (132)

The Baylis Hillman adduct **88** (200 mg, 0.84 mmol), 2,6-lutidine (110 μL, 0.90 mmol), and DMAP (12 mg, 0.10 mmol) were dissolved in CH_2Cl_2 (15 mL) and stirred at 0°C. Trifluoroacetic anhydride (177 μL, 1.26 mmol) was added dropwise via syringe. After stirring for 2 h the solution was diluted with Et_2O (50 mL) and washed consecutively with 2M HCl (2 x 20mL), saturated aqueous $NaHCO_3$ (2 x 20mL), and H_2O (2 x 10 mL). The organic portion dried with $MgSO_4$ and solvent was removed *in vacuo* to give **132** as a yellow oil (278 mg, 99%), that was greater than 98% pure by ^{13}C NMR: IR (neat) 2953, 1792, 1722, 1527, 1443, 1350 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 3.78 (s, 3 H), 5.77

(d, J = 1.2 Hz, 1 H), 6.57 (s, 1 H), 7.50 (s, 1 H), 7.76 (m, 2 H), 7.89 (dt, 1 H), (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 52.7, 73.2, 111.5 (q, $^{1}J_{CF}$ = 284 Hz), 126.1, 129.5, 130.1, 130.8, 131.4, 135.1, 137.4, 148.6, 156.3 (q, $^{2}J_{CF}$ = 42 Hz), 165.0.

Methyl 2-{(2-nitrophenyl)[(trimethylsilyl)oxy]methyl}acrylate (133)

The Baylis Hillman adduct **88** (900 mg, 3.80 mmol) and imidazole (517 mg, 7.59 mmol) were dissolved in CH_2Cl_2 (15 mL) and stirred at 0 °C. TMSCl (1.00 mL, 7.88 mmol) was added dropwise via syringe, upon which a white precipitate formed and the mixture was allowed to warm to room temperature. After stirring for 2 h the reaction mixture was poured into distilled H_2O. The solution was diluted with EtOAc (100 mL) and the organic phase collected. The organic portion was washed with saturated aqueous $NaHCO_3$ (3 x 20 mL) and dried with $MgSO_4$. Solvent was removed *in vacuo* to give **133** as a yellow oil (1.12 g, 95 %), that was greater than 99% pure by ^{13}C NMR: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.13 (s, 9 H), 3.65 (s, 3 H), 5.85 (t, J = 1.2 Hz, 1 H), 6.27 (m, 1 H), 6.37 (s, 1 H) 7.54 (m, 1 H), 7.72 (m, 2 H), 7.92 (dd, J = 8.1 Hz, J = 0.9 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 0.01, 52.0, 67.7, 124.6, 125.1, 129.3, 130.0, 133.6, 137.5, 143.7, 148.9, 165.8; HRMS (ESI) m/z calcd for $C_{14}H_{19}NO_5SiNa$ (M+Na) 332.0930, found 332.0813.

7.11: PREPARATION OF KETONE 140

2,2,2-Trifluoromethyl-2'-nitroacetophenone (140)[192,193]

Phenylmagnesium chloride (13.2 mL, 2.0M in THF) was added to a solution of 1-iodo-2-nitrobenzene (6.0 g, 24.0 mmol) in THF (40 mL) at –40°C. After 5 min trifluoroacetic anhydride (4.23 mL, 30.0 mmol) was added dropwise. The reaction mixture was stirred for 1h at –40°C, quenched with saturated NH_4Cl (60 mL), and extracted with ether (4 x 30 mL). The ether extracts were combined and dried over $MgSO_4$, concentrated and then chromatographed on SiO_2 (Et_2O/hexane:1:4), giving 2.34 g (10.7 mmol, 45%) of 2,2,2-trifluoro-2'-nitroacetophenone **140**: (R_f = 0.3); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.83 (d, J = 6.6 Hz, 1 H), 8.05- 8.12 (m, 2 H), 8.45 (d, J = 7.2 Hz, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 116.0 (q, $^1J_{CF}$ = 302 Hz), 125.0, 129.8, 129.9, 133.9, 136.2, 184.3 (q, $^2J_{CF}$ = 39 Hz).

7.12: PREPARATION OF 2-NITRO KETOXIMES

2,2,2-Trifluoro-2'-nitro-acetophenone oxime (175)

2,2,2-trifluoro-2'-nitro-acetophenone **140** (800 mg, 3.65 mmol) was refluxed in ethanol (10 mL) and pyridine (20 mL) with hydroxylamine hydrochloride (650 mg, 9.0 mmol) for 91 h. Solvent was removed *in vacuo* and the residue chromatographed on SiO_2 (Et_2O/hexanes, 1:5) to give 445 mg (1.9 mmol, 52%) of **175** as a single isomer of undetermined stereochemistry: R_f = 0.35; mp 83-90 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.59 (d, J = 7.2 Hz, 1 H), 7.85 (dt, J = 7.65 Hz, J = 1.5 Hz, 1 H), 7.95 (dt, J = 7.5 Hz, J

= 1.5 Hz, 1 H), 8.29 (dd, J = 8.4 Hz, J = 0.9 Hz, 1 H), 12.02 (br s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 121.3 (q, $^{1}J_{CF}$ = 272 Hz), 125.5, 130.7, 132.4, 135.1, 144.9 (q, $^{2}J_{CF}$ = 34 Hz), 148.7; ^{19}F NMR (282.35 MHz, $CDCl_3$) δ -67.24 (s, 3F); MS(EI) 186 (100), 167 (8), 138 (21), 63 (4). HRMS (ESI) *m/z* calcd for $C_8H_5N_2O_3F_3Na$ (M+ Na) 257.0151, found 257.0157. Also isolated was:

(1Z)-2,2,2-Trifluoro-1-{2-[3-(trifluoromethyl)-2H-indazol-2-yl]phenyl} ethanone oxime (176)

(125 mg, 20%) which was crystallized from ether and gave crystals suitable for X-ray analysis (Figure 5.1) (See Section **7.14** for a full description of X-ray data). The material could be recrystallized from CCl_4 to give a white powder (>99% pure by ^{13}C NMR): mp 199-200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 8.4 Hz, 1 H); 7.4 (dt, J = 7.5 Hz, J = 0.9 Hz, 1 H), 7.50 (m, 1 H), 7.56 - 7.68 (m, 3 H), 7.79 (dd, J = 8.4 Hz, J = 1.2 Hz, 1 H), 7.86 (d, J = 9.0 Hz, 1 H); 9.90 (br s, 1 H); ^{13}C NMR (100.57 MHz, acetone-d_6) δ 118.7, 119.3, 121.1 (q, $^{1}J_{CF}$ = 274 Hz), 121.2 (q, $^{1}J_{CF}$ = 268 Hz), 125.6, 127.2, 127.6, 129.9, 130.4, 131.1, 138.9, 144.5 (q, $^{2}J_{CF}$ = 34 Hz), 148.4. ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 118.7, 119.2, 120.1 (q, $^{1}J_{CF}$ = 274 Hz), 120.6 (q, $^{1}J_{CF}$ = 270 Hz), 121.3, 125.4, 125.5, 127.3, 127.8, 130.3, 130.5, 130.7, 137.5, 145.1 (q, $^{2}J_{CF}$ = 34 Hz), 148.3; ^{19}F NMR (282.35 MHz, $CDCl_3$) δ -55.22 (s, 3 F), -67.01 (s, 3 F); HRMS (ESI) *m/z* calcd for $C_{16}H_9N_3OF_6Na$ (M + Na) 396.0548, found 396.0601.

4',5'-Dimethoxy-2'-nitroacetophenone oxime (187)

To a of 4',5'-dimethoxy-2'-nitroacetophenone **185**[231] (600 mg, 2.67 mmol) in pyridine (5 mL) and ethanol (10 mL) was added hydroxylamine hydrochloride (1.00 g, excess). The solution was refluxed for 7 h and solvent was removed *in vacuo*. The residue was dissolved in $CHCl_3$ (30 mL) and washed with 2M HCl (3 x 20 mL). $CHCl_3$ was removed *in vacuo* to give **187** as a light yellow solid. Recrystallization from a minimal amount of hot ethanol gave 150 mg of yellow crystals that were the pure *E* isomer: mp 171-172 °C; The supernatant liquid gave 470 mg of a mixture of isomers whose ratio was determined to be 5:3 (*E*:*Z*) by ^{1}H NMR, for a total yield of 620 mg (2.58 mmol, 98%, 72% *E*, 28% *Z*); MS(EI) 241 (18), 209 (100), 194 (25), 180 (10), 164 (24), 150 (46); *E* isomer: IR (KBr) 3448, 2965, 2556, 1524, 1319 cm $^{-1}$; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.12 (s, 3 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 6.99 (s, 1 H), 7.57 (s, 1 H), 10.30 (s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 15.4, 56.5, 56.7, 108.2, 112.9, 128.6, 141.3, 149.6, 153.7, 154.2; Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.03; N, 11.66. Found: C, 49.72; H, 5.01; N, 11.39. *Z* isomer: ^{1}H NMR (300 MHz, acetone-d_6) δ 2.18 (s, 3H), 3.97 (s, 3 H), 3.98 (s, 3 H), 6.89 (s, 1 H), 7.63 (s, 1 H), 9.69 (s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 21.0, 56.5, 56.7, 107.8, 110.8, 126.4, 140.4, 149.2, 151.9, 154.4.

5'-Bromo-2'-nitroacetophenone oxime (188)

To a solution of 5-bromo-2-nitro-acetophenone **186**[232] (500 mg, 2.05 mmol) in EtOH/Pyridine (20 mL 1:1) was added hydroxylamine hydrochloride (900 mg). The solution was refluxed for 27 h and solvent was removed *in vacuo*. The residue was dissolved in Et_2O (20 mL) and washed with 2M HCl (3x 15mL) and H_2O (2x 15mL).

The ether layer was dried with $MgSO_4$ to give 509 mg (1.97 mmol, 96%) of **188** as a white solid as a mixture of isomers (67% *E*: 33% *Z*, by ^1H NMR): mp 167–171° C. A portion of this mixture was subjected to column chromatography to separate the two isomers for spectroscopic purposes. Thus chromatography with 30% Et_2O in hexanes gave two compounds, the least polar of which was the *E* isomer ($R_f = 0.35$) and the more polar the *Z* isomer ($R_f = 0.30$). *E* isomer: IR (KBr) 1341, 1523, 3239 cm^{-1}, ^1H NMR (300 MHz, acetone-d_6) δ 2.18 (s, 3 H), 7.79 (d, J = 2.1 Hz, 1 H), 7.83 (dd, J = 8.7 Hz, J = 2.1 Hz, 1 H), 7.92 (d, J = 8.7 Hz, 1 H), 10.73 (s, 1 H). *Z* isomer: ^1H NMR (300 MHz, acetone-d_6) δ 2.25 (s, 3 H), 7.67 (d, J = 1.8 Hz, 1 H), 7.82 (dd, J = 9.0 Hz, J = 2.4 Hz, 1 H), 8.25 (d, J = 8.7 Hz, 1 H), 10.07 (s, 1 H),; Anal. Calcd for $C_8H_7N_2O_3Br$: C, 37.09; H, 2.72; N, 10.81. Found: C, 37.21; H, 2.81; N, 10.63.

2-Nitrobenzophenone oxime (193)[236]

A solution of 2-nitrobenzhydryl **189**[195] (723 mg, 3.20 mmol) in CH_2Cl_2 (15 mL) was refluxed with 1.6 g of MnO_2[147] for 20 h. The reaction mixture was filtered through Celite to give 674 mg (2.97 mmol, 93%) of 2-nitrobenzophenone **191**[234] as yellow solid: mp 104-106 °C, lit.[234] mp 105-106 °C. The 2-nitrobenzophenone **191** (650 mg, 2.86 mmol) was refluxed in pyridine/ethanol (1:2 / 20 mL) for 30 h. Solvent was removed *in vacuo* and the residue was dissolved in ether and washed with 2M HCl (2 x 20 mL). The ether extract was concentrated and chromatographed on SiO_2 with $CHCl_3$/MeOH (35:1) to give 510 mg (2.10 mmol, 73%) of **193**[236] as a white solid along with 140 mg of recovered starting material. mp 117-121°C, lit.[236] mp 122-123°C.

(4-Methoxyphenyl)(2-nitrophenyl)methanone oxime (194)

Applying the method of Knochel,[195] phenylmagnesium chloride (4.4 mL, 2.0M in THF) was added to a of 1-iodo-2-nitrobenzene (2.00 g, 8.0 mmol) in THF (40 mL) at –40°C. After 5 min *p*-anisaldehyde (1.2 mL, 10.0 mmol) was added dropwise over 5 min. The reaction mixture was stirred for 1 h at –40°C, quenched with saturated NH_4Cl (60 mL), and extracted with ether (4 x 30 mL). The ether extracts were combined and dried over $MgSO_4$, concentrated, and then chromatographed on SiO_2 (35% ether/ 65% hexane), giving 1.64 g (6.33 mmol, 79%) of (4-methoxyphenyl)(2-nitrophenyl)methanol **190**[233] as a yellow oil; $R_f = 0.28$; ^1H NMR (400 MHz, acetone-d_6) δ 3.75 (s, 3H), 5.14 (s, 1 H), 6.41 (s, 1 H), 6.86 (d, J = 6.6 Hz, 2 H), 7.24 (d, J = 6.6 Hz, 2 H), 7.51 (t, J = 6.3 Hz, 1 H), 7.73 (t, J = 5.7 Hz, 1 H), 7.87 (dd, J = 6.0 Hz, J = 0.9 Hz, 1 H), 7.95 (d, J = 6.0 Hz, 1 H). ^{13}C NMR (100.57 MHz, acetone-d_6) δ 55.5, 70.7, 114.4, 124.9, 129.0, 129.3, 129.6, 133.8, 136.2, 140.4, 149.4, 160.0. The (4-methoxyphenyl)(2-nitrophenyl)methanol **190** (1.64 g, 6.33 mmol) and 1.23 g of MnO_2[147] were heated to reflux in CH_2Cl_2 (35 mL). After 23 h the reaction was only 40% complete (^1H NMR) so the mixture was then refluxed for 24 h more with an additional 3.0 g of MnO_2.[147] The reaction mixture was filtered through Celite and evaporated to give an orange solid that was dissolved in a minimal amount of hot Et_2O and recrystallized at 0 °C to give 1.41 g (5.49 mmol, 87 %) of (4-methoxyphenyl)(2-nitrophenyl)methanone **192**[234] as rose-colored crystals: mp 106-107°C, lit.[235] mp 86-90°C; ^1H NMR (300 MHz, CD_3OD) δ 3.87 (s, 3 H), 7.01 (d, J = 9.0 Hz, 2 H), 7.51 (dd, J = 7.5 Hz, J = 1.5 Hz, 1 H), 7.72 (d, J = 9.0 Hz, 2 H), 7.76 (dd, J = 8.1 Hz, J = 1.5 Hz, 1 H), 7.85 (dt, J = 7.5 Hz, J = 1.2 Hz, 1 H), 8.24 (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H); ^{13}C NMR (100.57 MHz, CD_3OD) δ 56.3, 115.3, 125.8, 130.2, 130.3, 132.0,

133.1, 135.5, 137.6, 148.4, 166.1, 194.4. To a solution of (4-methoxyphenyl)(2-nitrophenyl)methanone **192** (1.31 g, 5.06 mmol) in pyridine/ethanol (20 mL 1:1) was added 2.00 g of hydroxylamine hydrochloride. The solution was refluxed for 40 h. Solvent was removed *in vacuo* and the residue was dissolved in ether and washed with 2M HCl (2 x 20 mL). The ether extract was dried with $MgSO_4$ to give 1.31 g (4.82 mmol, 95%) of a yellow solid that was the oxime **194**, mp 142-148°C. The ratio of *E/Z* isomers was determined by ^{1}H NMR to be 5:1. Recrystallization from ethanol gave the pure *E*-isomer: IR (KBr) 3228, 1607, 1529, 1262 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 3.82 (s, 3 H), 6.92 (d, J = 9.0 Hz, 2 H), 7.36 (dd, J = 7.5 Hz, J = 1.5 Hz, 1 H), 7.44 (d, J = 9.0 Hz, 2 H), 7.74 (dt, J = 7.5 Hz, J = 1.5 Hz, 1 H), 7.86 (dt, J = 7.5 Hz, J = 1.2 Hz, 1 H), 10.43 (s, 1 H), 8.20 (dd, J = 8.1 Hz, J = 1.2 Hz, 1 H); ^{13}C NMR (100.57 MHz, acetone-d_6) δ 55.0, 114.0, 124.2, 128.1, 128.4, 129.8, 130.0, 130.7, 133.9, 148.8, 153.2, 161.0; MS (EI) 272 (M+, 53), 242 (8), 225 (27), 211 (15), 196 (22), 182 (100), 167 (53), 154 (85), 139 (19), 77 (24), 63 (21); Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.74; H, 4.46; N, 10.12. *Z*-isomer: ^{1}H NMR (300 MHz, acetone-d_6) δ 3.90 (s, 3H), 10.83 (s, 1H).

7.13: SYNTHESIS OF 1-H INDAZOLES

3-Methyl-1H-indazole (167)[278]

In a glass-lined, stainless steel Parr reaction vessel 2-nitro-acetophenone oxime (**166**, 200 mg, 1.11 mmol) and $[Cp^*(CO)_2Fe]_2$ (54 mg, 0.11 mmol) were combined with dioxane (40 mL). The vessel was flushed three times with CO and charged to 50 atm (Caution: FUME HOOD!). The reaction vessel was heated at 150 °C for 46 h. The vessel was cooled to room temperature and the pressure was discharged (FUME HOOD!). The resulting brown solution was concentrated by rotary evaporation and then chromatographed on silica gel with a gradient elution of ether/hexanes (1:1 to 4:1) giving 86 mg of **167** (0.65 mmol, 59 %) as a light brown solid: R_f = 0.29 (1:1 Ether/hexanes); mp.110-114 °C, lit.[278] 110-112 °C;. Also isolated was 2-amino-acetophenone **168** mg (0.16 mmol, 15 %) which was spectroscopically identical to a commercial sample.

3-Trifluoromethyl-1H-indazole (195)[279]

In the manner described for **167**, 300 mg (1.28 mmol) of the oxime **175** was combined with $[Cp^*(CO)_2Fe]_2$ (60 mg, 0.13 mmol) in dioxane (60 mL) and charged to 50 atm with CO. After heating at 150 °C for 72 h, cooling, and solvent evaporation, the residue was purified by preparative TLC with (30% EtOAc/hexanes) to give the indazole **195** that was slightly contaminated with a product of the same R_f, along with 72 mg (0.31 mmol) of recovered **175**. Indazole **195** was purified by preparative TLC, eluting with $CHCl_3$/MeOH (30:1) to give 72 mg (0.39 mmol, 30 %): R_f = 0.54 ; mp 73-78 °C, lit.[279] mp 104 °C; Sublimation of this material at 100 °C (0.1 mm) gave a white powder, mp

94-97 °C: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.35 (t, J = 7.2 Hz, 1 H), 7.52 (t, J = 6.0 Hz, 1 H), 7.75 (d, J = 8.4 H, 1 H), 7.85 (d, J= 8.0 Hz, 1 H), 13.2 (br s, 1 H); ^{13}C NMR (75.45 MHz, acetone-d_6) δ 111.9, 119.9, 120.2, 123.4 (q, $^{1}J_{CF}$ = 268 Hz), 123.7, 128.3, 135.2 (q, $^{2}J_{CF}$ = 38 Hz), 142.1; ^{19}F NMR (282.35 MHz, $CDCl_3$) δ -61.67 (s, 3 F); MS (EI) 186 (100), 167 (8), 138 (20), 63 (4).

5,6-Dimethoxy-3-methyl-1H-indazole (196)[249]

As above, 240 mg (1.00 mmol) of the oxime **187** and 49 mg (0.10 mmol) of $[Cp^*(CO)_2Fe]_2$ in dioxane (60 mL) was heated at 150 °C for 68 h under 50 atm. CO. After cooling and solvent evaporation chromatography of the residue on silica gel with ethyl acetate/hexanes (4:1) gave 163 mg (0.85 mmol, 85%) of **196** as a yellow solid that could be recrystallized from cold ether to give light brown crystals. R_f = 0.30; mp 163-167 °C, lit.[249] mp 164 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 2.45 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3H), 6.96 (s, 1 H), 7.10 (s, 1H), 11.54 (br s, 1 H); ^{13}C NMR (100.57 MHz, acetone-d_6) δ 12.1, 56.1, 56.4, 92.5, 101.1, 116.5, 138.0, 141.8, 146.8, 152.0; MS(EI) 192 (100), 177 (64), 149 (24), 134 (17), 108 (22), 80 (13).

5-Bromo-3-methyl-1H-indazole (197)

As above, 260 mg (1.00 mmol) of the oxime **188** and $[Cp^*(CO)_2Fe]_2$ (49 mg, 0.10 mmol) of in dioxane (70 mL) was heated at 150 °C for 80 h under 50 atm. CO. After cooling and solvent evaporation the tarry residue was refluxed in H_2O (150 mL) for 1 h and filtered hot. The H_2O was cooled and extracted with Et_2O (3 x 30 mL). Solvent was removed *in vacuo* to give a brown residue that was purified by preparative TLC eluting

with ethyl acetate/hexanes (2:1), gave 54 mg (0.26 mmol, 26%) of **197** as a yellow gum. ^{1}H NMR (400 MHz, acetone-d_6) δ 2.51 (s, 3 H), 7.42 (dd, J = 8.8 Hz, J = 2.0 Hz, 1 H), 7.47 (dd, J = 8.8 Hz, J = 0.4 Hz, 1 H), 7.88 (dd, J = 2.0 Hz, J = 0.4 Hz, 1 H); GCMS (EI) 212 (82), 210 (100), 209 (58), 182 (12), 130 (12).

3-Phenyl-1H-indazole (198) [280,281]

The oxime **193** (294 mg, 1.21 mmol) with $[Cp^*(CO)_2Fe]_2$ (60 mg, 0.12 mmol) was heated to 150 °C under 50 atm CO in dioxane (70 mL) for 75 h. After concentration, chromatography of the residue on silica gel with 30% ethyl acetate/hexanes gave 123 mg of 3-phenyl-indazole **198** (0.63 mmol, 52 %): R_f = 0.30; mp 102-108 °C lit.[280] mp. 107-108 °C; the ^{13}C NMR spectrum was identical to that described in the literature.[281] Also recovered was 2-amino-benzophenone **200**, 40 mg (0.20 mmol, 17%), that was spectroscopically identical to an authentic sample.

3-(4-Methoxyphenyl)-1H-indazole (199) [280]

The oxime **194** (305 mg, 1.12 mmol) with $[Cp^*(CO)_2Fe]_2$ (55 mg, 0.11 mmol) was heated at 150 °C under 50 atm CO in dioxane (70 mL) for 75 h. After concentration, chromatography of the residue on silica gel with $CHCl_3$/methanol (30:1) gave **199** that was slightly impure. Preparative TLC of this mixture with CH_2Cl_2/acetone (95:5) gave 140 mg of **199** (0.63 mmol, 56 %) as a yellow gum. R_f = 0.43 (CH_2Cl_2/acetone); ^{1}H NMR (300 MHz, CD_3CN) δ 3.92 (s, 3 H), 7.16 (d, J = 9.0 Hz, 2 H), 7.30 (dt, J = 6.5 Hz, J = 0.9 Hz, 1 H), 7.50 (dt, J = 7.8 Hz, J = 1.2 Hz, 1 H), 7.66 (d, J = 9.0 Hz, 1H), 8.02 (d, J =

9.0 Hz, 2 H), 8.10 (d, J = 8.1 Hz, 1 H), 11.62 (br s, 1 H); MS (EI) 224 (100), 209 (62), 181 (30), 152 (20).

7.14: DETAILS OF X-RAY DATA FOR 176

The data were collected at 100 (2) K on a Bruker Apex diffractometer[282] using MoKα (λ =0.71073 A) radiation. Intensity data, which approximately covered the full sphere of the reciprocal space, were measured as a series of ω oscillation frames each 0.3° for 35 sec / frame. The detector was operated in 512 x 512 mode and was positioned 5.99 cm from the crystal. Coverage of unique data was 99.6% complete to 52.0°(2θ). Cell parameters were determined from a non-linear least squares fit of 4324 reflections in the range of $4.9 < \theta < 25.2°$.The data were corrected for absorption by multi-scan method form equivalent reflections[282] giving minimum and maximum transmission of 0.962 and 0.973. A total of 11771 reflections were measured and merged to 3061 unique reflections (R(int) = 0.024). The structure was solved by the direct method using SHELXTL system,[283] and refined by full-matrix least squares on F^2 using all reflections. All the non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were included with idealized parameters. Final R1 = 0.054 is based on 2785 "observed reflections" [$I>2\sigma(I)$], and $wR^2 = 0.146$ is based on all reflections (3061 unique reflections). Details of the crystal data are given in Table 7.1.

Table 7.1 Crystal data and structure refinement for **176**

Empirical formula	$C_{16} H_9 F_6 N_3 O$	
Formula weight	373.26	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.3516(17) Å	α= 90°.
	b = 15.767(3) Å	β= 98.371(2)°.
	c = 10.6976(19) Å	γ = 90°.
Volume	1560.5(5) $Å^3$	
Z	4	
Density (calculated)	1.589 Mg/m^3	
Absorption coefficient	0.151 mm^{-1}	
F(000)	752	
Crystal size	0.26 x 0.22 x 0.18 mm^3	
Theta range for data collection	2.20 to 26.00°.	
Index ranges	-11<=h<=11, -18<=k<=19, -13<=l<=13	
Reflections collected	11771	
Independent reflections	3061 [R(int) = 0.0235]	
Completeness to theta = 26.00°	99.7 %	
Absorption correction	None	
Max. and min. transmission	0.9733 and 0.9617	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3061 / 36 / 245	
Goodness-of-fit on F^2	1.069	
Final R indices [I>2sigma(I)]	R1 = 0.0537, wR2 = 0.1432	
R indices (all data)	R1 = 0.0571, wR2 = 0.1461	
Extinction coefficient	0.021(2)	
Largest diff. peak and hole	1.289 and -0.645 $e.Å^{-3}$	

Table 7.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **176**. *

	x	y	z	U(eq)
F(1)	8320(1)	802(1)	6281(1)	31(1)
F(2)	10206(1)	1547(1)	7002(1)	44(1)
F(3)	9917(1)	1075(1)	5108(1)	37(1)
F(1')	8284(2)	749(1)	5908(3)	31(1)
F(2')	9659(3)	1467(2)	7281(2)	44(1)
F(3')	10302(2)	1216(2)	5484(3)	37(1)
O(1)	5749(1)	1718(1)	6958(1)	22(1)
F(4)	1874(1)	2499(1)	4549(1)	37(1)
F(5)	3013(1)	3510(1)	5594(1)	32(1)
F(6)	3431(1)	3225(1)	3727(1)	36(1)
N(1)	6777(1)	3066(1)	4495(1)	17(1)
N(2)	7214(1)	2257(1)	4754(1)	17(1)
N(3)	4727(1)	2322(1)	6522(1)	19(1)
C(1)	7777(2)	3550(1)	5193(1)	17(1)
C(2)	7809(2)	4447(1)	5269(1)	20(1)
C(3)	8923(2)	4805(1)	6061(2)	23(1)
C(4)	10014(2)	4304(1)	6771(2)	24(1)
C(5)	10015(2)	3440(1)	6712(1)	22(1)
C(6)	8867(2)	3046(1)	5900(1)	18(1)
C(7)	8448(1)	2216(1)	5573(1)	19(1)
C(8)	9211(1)	1404(1)	6015(1)	29(1)
C(9)	6255(2)	1594(1)	4231(1)	17(1)
C(10)	6739(2)	981(1)	3468(2)	21(1)
C(11)	5792(2)	350(1)	2963(2)	24(1)
C(12)	4375(2)	348(1)	3197(2)	23(1)
C(13)	3890(2)	979(1)	3943(1)	20(1)
C(14)	4825(2)	1608(1)	4477(1)	17(1)
C(15)	4327(2)	2255(1)	5333(1)	17(1)
C(16)	3169(2)	2879(1)	4806(1)	21(1)

*U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Table 7.3 Bond lengths [Å] and angles [°] for **176**

F(1)-C(8)	1.3209(16)
F(2)-C(8)	1.3208(15)
F(3)-C(8)	1.3537(15)
F(1')-C(8)	1.3424(19)
F(2')-C(8)	1.3621(18)
F(3')-C(8)	1.273(3)
O(1)-N(3)	1.3812(16)
F(4)-C(16)	1.3435(19)
F(5)-C(16)	1.3249(19)
F(6)-C(16)	1.3309(19)
N(1)-C(1)	1.3460(19)
N(1)-N(2)	1.3551(17)
N(2)-C(7)	1.3445(17)
N(2)-C(9)	1.4374(18)
N(3)-C(15)	1.2766(19)
C(1)-C(2)	1.416(2)
C(1)-C(6)	1.420(2)
C(2)-C(3)	1.366(2)
C(3)-C(4)	1.420(2)
C(4)-C(5)	1.364(2)
C(5)-C(6)	1.421(2)
C(6)-C(7)	1.3965(19)
C(7)-C(8)	1.5079(17)
C(9)-C(10)	1.383(2)
C(9)-C(14)	1.400(2)
C(10)-C(11)	1.388(2)
C(11)-C(12)	1.383(2)
C(12)-C(13)	1.392(2)
C(13)-C(14)	1.389(2)
C(14)-C(15)	1.490(2)
C(15)-C(16)	1.511(2)
C(1)-N(1)-N(2)	104.79(11)
C(7)-N(2)-N(1)	112.55(11)

C(7)-N(2)-C(9)	130.27(12)
N(1)-N(2)-C(9)	116.87(11)
C(15)-N(3)-O(1)	111.53(12)
N(1)-C(1)-C(2)	127.24(13)
N(1)-C(1)-C(6)	111.43(13)
C(2)-C(1)-C(6)	121.33(13)
C(3)-C(2)-C(1)	117.14(14)
C(2)-C(3)-C(4)	121.70(15)
C(5)-C(4)-C(3)	122.46(14)
C(4)-C(5)-C(6)	117.30(14)
C(7)-C(6)-C(1)	103.69(12)
C(7)-C(6)-C(5)	136.23(14)
C(1)-C(6)-C(5)	120.08(14)
N(2)-C(7)-C(6)	107.53(11)
N(2)-C(7)-C(8)	124.56(11)
C(6)-C(7)-C(8)	127.90(11)
F(3')-C(8)-F(2)	83.03(16)
F(3')-C(8)-F(1)	120.03(18)
F(2)-C(8)-F(1)	110.12(12)
F(3')-C(8)-F(1')	109.44(19)
F(2)-C(8)-F(1')	124.80(17)
F(1)-C(8)-F(1')	17.41(16)
F(3')-C(8)-F(3)	23.75(14)
F(2)-C(8)-F(3)	106.09(12)
F(1)-C(8)-F(3)	105.54(11)
F(1')-C(8)-F(3)	91.20(16)
F(3')-C(8)-F(2')	108.06(18)
F(2)-C(8)-F(2')	27.63(15)
F(1)-C(8)-F(2')	87.17(17)
F(1')-C(8)-F(2')	104.01(19)
F(3)-C(8)-F(2')	128.96(18)
F(3')-C(8)-C(7)	115.53(17)
F(2)-C(8)-C(7)	110.62(11)
F(1)-C(8)-C(7)	113.14(11)
F(1')-C(8)-C(7)	110.85(14)
F(3)-C(8)-C(7)	110.99(11)

F(2')-C(8)-C(7)	108.28(16)
C(10)-C(9)-C(14)	121.72(13)
C(10)-C(9)-N(2)	119.91(13)
C(14)-C(9)-N(2)	118.33(13)
C(9)-C(10)-C(11)	119.03(14)
C(12)-C(11)-C(10)	120.31(15)
C(11)-C(12)-C(13)	120.20(14)
C(14)-C(13)-C(12)	120.52(14)
C(13)-C(14)-C(9)	118.20(13)
C(13)-C(14)-C(15)	120.46(13)
C(9)-C(14)-C(15)	121.28(13)
N(3)-C(15)-C(14)	126.63(13)
N(3)-C(15)-C(16)	114.07(13)
C(14)-C(15)-C(16)	119.21(12)
F(5)-C(16)-F(6)	107.21(13)
F(5)-C(16)-F(4)	106.61(13)
F(6)-C(16)-F(4)	106.23(12)
F(5)-C(16)-C(15)	113.04(12)
F(6)-C(16)-C(15)	112.21(13)
F(4)-C(16)-C(15)	111.14(13)

Symmetry transformations used to generate equivalent atoms:

Table 7.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **176***

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	31(1)	23(1)	39(1)	14(1)	1(1)	-1(1)
F(2)	37(1)	31(1)	57(1)	10(1)	-23(1)	-2(1)
F(3)	25(1)	28(1)	57(1)	-2(1)	6(1)	4(1)
F(1')	31(1)	23(1)	39(1)	14(1)	1(1)	-1(1)
F(2')	37(1)	31(1)	57(1)	10(1)	-23(1)	-2(1)
F(3')	25(1)	28(1)	57(1)	-2(1)	6(1)	4(1)
O(1)	29(1)	21(1)	15(1)	-1(1)	-1(1)	6(1)
F(4)	20(1)	36(1)	53(1)	-3(1)	-4(1)	1(1)
F(5)	37(1)	28(1)	30(1)	-7(1)	1(1)	13(1)
F(6)	38(1)	46(1)	27(1)	16(1)	12(1)	20(1)
N(1)	21(1)	15(1)	16(1)	1(1)	2(1)	0(1)
N(2)	19(1)	15(1)	17(1)	1(1)	3(1)	0(1)
N(3)	20(1)	17(1)	19(1)	1(1)	3(1)	0(1)
C(1)	18(1)	19(1)	13(1)	0(1)	4(1)	-1(1)
C(2)	24(1)	18(1)	19(1)	1(1)	5(1)	-1(1)
C(3)	28(1)	19(1)	24(1)	-3(1)	8(1)	-5(1)
C(4)	21(1)	28(1)	22(1)	-5(1)	3(1)	-8(1)
C(5)	19(1)	27(1)	20(1)	-1(1)	0(1)	-1(1)
C(6)	18(1)	20(1)	16(1)	1(1)	4(1)	-1(1)
C(7)	17(1)	21(1)	20(1)	1(1)	2(1)	-1(1)
C(8)	23(1)	21(1)	40(1)	5(1)	-6(1)	0(1)
C(9)	20(1)	15(1)	15(1)	2(1)	0(1)	-2(1)
C(10)	23(1)	20(1)	21(1)	1(1)	7(1)	0(1)
C(11)	32(1)	18(1)	22(1)	-5(1)	8(1)	-1(1)
C(12)	29(1)	18(1)	21(1)	-3(1)	1(1)	-6(1)
C(13)	21(1)	21(1)	19(1)	1(1)	2(1)	-3(1)
C(14)	20(1)	16(1)	13(1)	2(1)	2(1)	1(1)
C(15)	17(1)	17(1)	17(1)	0(1)	3(1)	-2(1)
C(16)	22(1)	24(1)	18(1)	-1(1)	3(1)	2(1)

*The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + .. + 2\ h\ k\ a^*\ b^*U^{12}]$

Table 7.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **176**

	x	y	z	U(eq)
H(1A)	6039	1801	7728	33
H(2A)	7087	4784	4789	24
H(3A)	8968	5405	6140	27
H(4A)	10771	4581	7306	29
H(5A)	10753	3114	7194	27
H(10A)	7705	992	3291	25
H(11A)	6118	-83	2455	29
H(12A)	3732	-84	2846	27
H(13A)	2912	978	4089	24

Table 7.6 Torsion angles [°] for **176**

C(1)-N(1)-N(2)-C(7)	-0.55(16)
C(1)-N(1)-N(2)-C(9)	173.69(12)
N(2)-N(1)-C(1)-C(2)	-179.37(14)
N(2)-N(1)-C(1)-C(6)	0.26(16)
N(1)-C(1)-C(2)-C(3)	178.88(15)
C(6)-C(1)-C(2)-C(3)	-0.7(2)
C(1)-C(2)-C(3)-C(4)	0.7(2)
C(2)-C(3)-C(4)-C(5)	-0.4(3)
C(3)-C(4)-C(5)-C(6)	0.1(2)
N(1)-C(1)-C(6)-C(7)	0.10(16)
C(2)-C(1)-C(6)-C(7)	179.75(13)
N(1)-C(1)-C(6)-C(5)	-179.19(13)
C(2)-C(1)-C(6)-C(5)	0.5(2)
C(4)-C(5)-C(6)-C(7)	-179.14(17)
C(4)-C(5)-C(6)-C(1)	-0.1(2)
N(1)-N(2)-C(7)-C(6)	0.63(16)
C(9)-N(2)-C(7)-C(6)	-172.64(14)
N(1)-N(2)-C(7)-C(8)	-178.61(12)
C(9)-N(2)-C(7)-C(8)	8.1(2)
C(1)-C(6)-C(7)-N(2)	-0.43(15)
C(5)-C(6)-C(7)-N(2)	178.69(17)
C(1)-C(6)-C(7)-C(8)	178.78(13)
C(5)-C(6)-C(7)-C(8)	-2.1(3)
N(2)-C(7)-C(8)-F(3')	101.1(2)
C(6)-C(7)-C(8)-F(3')	-78.0(2)
N(2)-C(7)-C(8)-F(2)	-166.80(13)
C(6)-C(7)-C(8)-F(2)	14.1(2)
N(2)-C(7)-C(8)-F(1)	-42.71(18)
C(6)-C(7)-C(8)-F(1)	138.21(15)
N(2)-C(7)-C(8)-F(1')	-24.1(2)
C(6)-C(7)-C(8)-F(1')	156.8(2)
N(2)-C(7)-C(8)-F(3)	75.72(16)
C(6)-C(7)-C(8)-F(3)	-103.37(16)
N(2)-C(7)-C(8)-F(2')	-137.56(19)

C(6)-C(7)-C(8)-F(2')	43.4(2)
C(7)-N(2)-C(9)-C(10)	-63.5(2)
N(1)-N(2)-C(9)-C(10)	123.43(15)
C(7)-N(2)-C(9)-C(14)	118.84(17)
N(1)-N(2)-C(9)-C(14)	-54.19(17)
C(14)-C(9)-C(10)-C(11)	-1.9(2)
N(2)-C(9)-C(10)-C(11)	-179.46(13)
C(9)-C(10)-C(11)-C(12)	1.6(2)
C(10)-C(11)-C(12)-C(13)	-0.2(2)
C(11)-C(12)-C(13)-C(14)	-0.9(2)
C(12)-C(13)-C(14)-C(9)	0.6(2)
C(12)-C(13)-C(14)-C(15)	-176.62(13)
C(10)-C(9)-C(14)-C(13)	0.8(2)
N(2)-C(9)-C(14)-C(13)	178.38(13)
C(10)-C(9)-C(14)-C(15)	178.04(13)
N(2)-C(9)-C(14)-C(15)	-4.4(2)
O(1)-N(3)-C(15)-C(14)	1.5(2)
O(1)-N(3)-C(15)-C(16)	177.95(12)
C(13)-C(14)-C(15)-N(3)	110.47(18)
C(9)-C(14)-C(15)-N(3)	-66.7(2)
C(13)-C(14)-C(15)-C(16)	-65.79(19)
C(9)-C(14)-C(15)-C(16)	117.03(15)
N(3)-C(15)-C(16)-F(5)	14.92(19)
C(14)-C(15)-C(16)-F(5)	-168.37(13)
N(3)-C(15)-C(16)-F(6)	136.32(14)
C(14)-C(15)-C(16)-F(6)	-46.98(19)
N(3)-C(15)-C(16)-F(4)	-104.90(15)
C(14)-C(15)-C(16)-F(4)	71.80(17)

Symmetry transformations used to generate equivalent atoms:

Table 7.7 Hydrogen bonds for **176** [Å and °]

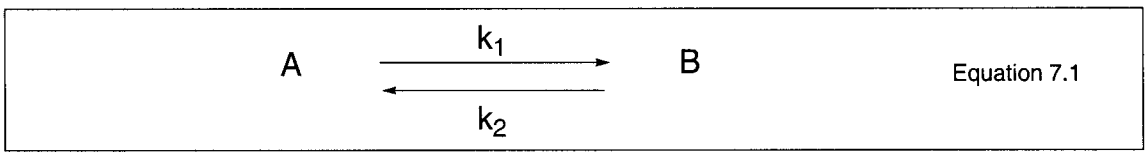
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1A)...N(1)#1	0.84	1.93	2.7654(16)	176.7

Symmetry transformations used to generate equivalent atoms:

#1 x,-y+1/2,z+1/2

7.15: ΔG CALCULATION FOR ROTAMERS OF 99 AT 100 ^{o}C

The presence of conformers in solution is a very common occurrence in chemistry. When two species (A and B) exist in solution their interconversion can be expressed by Equation 7.1.



Equation 7.1

If the rate(s) of this process (k_1 and k_2) are slow enough (close to the NMR time scale usually s or ms), it is possible to observe the two species by NMR (the two species have separate resonances). At a certain temperature the process becomes too fast for distinction of the two species by NMR, and the resonances merge into one set. This temperature is referred to as the coalescence temperature. While magnetic phenomenon are not always easily related to chemical transformations/dynamics, and highly mechanism dependent, the dynamics of many systems can be assumed to be related to a single rate limiting process for the conversion of A to B (B to A).[284] For the simplest case for the conversion of A to B and B to A, $k_1 = k_2 = k$, and the rate of conversion at coalescence can be determined by the simple Equation 7.2:

$$k = \frac{\pi (\delta v)}{(2)^{1/2}}$$

Equation 7.2

Where δv is the chemical shift difference of the two species in Hz before coalescence. This rate can be substituted into the Eyring equation and the following expression for ΔG

for the process at that temperature can be determined (Equation 7.3).

$$\Delta G = -RT_c [\ln (k/T_c) + \ln (h/K)] \qquad \text{Equation 7.3}$$

Where R is the gas constant, Tc is the coalescence temperature, h is Planck's constant, and K is Boltzmann's constant.

However, when the two species A and B are unequally populated i.e. $k_1 \neq k_2$, the Equation 7.2 is invalid. The equations have been derived to directly calculate ΔG at coalescence for two unequally populated species from T_c, δν, and ΔP, where ΔP is the difference of the fractional population of the two species A and B i.e. $P_A + P_B = 1$ (Equations 7.4 and 7.5).[149]

$$\Delta G_A = 4.57\ T_c \left[10.62 + \log \frac{X}{2\pi (1 - \Delta P)} + \log \frac{T_c}{\delta \nu} \right] \qquad \text{Equation 7.4}$$

$$\Delta G_B = 4.57\ T_c \left[10.62 + \log \frac{X}{2\pi (1 + \Delta P)} + \log \frac{T_c}{\delta \nu} \right] \qquad \text{Equation 7.5}$$

Where $X = 2\pi\delta\nu\tau$, where $\tau^{-1} = \tau_A^{-1} + \tau_B^{-1}$; and τ_A and τ_B are the lifetimes of the two species A and B respectively. The value calculated with this equation is in cal/mol. It is not necessary to measure $\tau_A + \tau_B$. Instead Shanan-Atidi and Bar-Eli have calculated all possible values for the expressions log {X/[2π(1-ΔP)]} and log {X/[2π(1+ΔP)]}and given a table of these values plotted against ΔP.

Since ΔP = 0.7 - 0.3 = 0.4 the values 0.21 and 0.60 are obtained for log {X/[2π(1-ΔP)]} and log {X/[2π(1+ΔP)]} respectively with said tables. Using equations

7.4 and 7.5 the calculation can be made (Scheme 7.1).

$$\Delta G_A = 4.57\ (373.15)\left[10.62 + 0.21 + \log\frac{373.15}{162.5}\right] = 19{,}000\ \text{cal/mol}$$

$$\Delta G_B = 4.57\ (373.15)\left[10.62 + 0.60 + \log\frac{373.15}{162.5}\right] = 19{,}700\ \text{cal/mol}$$

Scheme 7.1 Calculation of ΔG for **99**

Assuming that T_c was measured accurately to the nearest degree, and δv to the nearest .1 Hz, the values are ΔG_A = 19.0 kcal/mol and ΔG_B = 19.7 kcal/mol, using the formyl proton resonances. Of course this value is only good for 100°C and more accurate results can be obtained with line-shape analysis, however this method is extremely simple.

7.16: METHOD OF INTERNAL STANDARD

The following equations were used to obtain quantitative data by GC with FID detection with naphthalene as an internal standard:

$$RRF_A = \frac{Q_A}{Q_{\text{naphthalene}}} \times \frac{M_{\text{naphthalene}}}{M_A} \times \frac{MW_A}{MW_{\text{naphthalene}}}$$

$$M_A = \frac{Q_A}{Q_{\text{naphthalene}}} \times \frac{M_{\text{naphthalene}}}{RRF_A}$$

Where: Q_A = Integration of Analyte Peak

$Q_{\text{naphthalene}}$ = Integration of Naphthalene Peak

MW_A = Molecular Weight of Analyte

$MW_{\text{naphthalene}}$ = Molecular Weight of Naphthalene

M_A = amount (g) of Analyte

$M_{\text{naphthalene}}$ = amount (g) of Naphtahlene

RRF_A = Response Factor of Analyte

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