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Review

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Chemical adventures with oximes

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Affectionately dedicated to the memory of Sir Derek H. R. Barton

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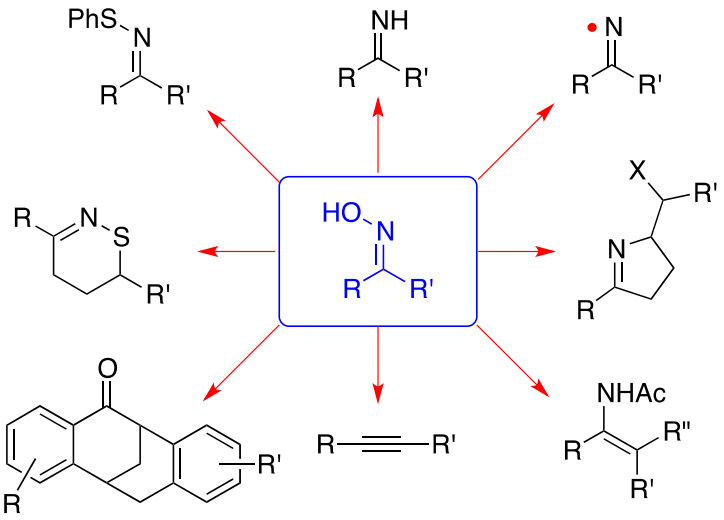
Abstract

This account is a collection of vignettes describing new reactions discovered in the author's group revolving around the chemistry of oximes. They range from ionic transformations, including reduction to unsubstituted imines and the formation of α-electrophiles, to the generation and capture of iminyl radicals, to a general synthesis of alkynes. The mechanistic reasonings and occasional serendipitous observations underlying these discoveries are discussed briefly.



Keywords: Oximes, imines, enamides, iminyls, α-electrophiles, alkynes

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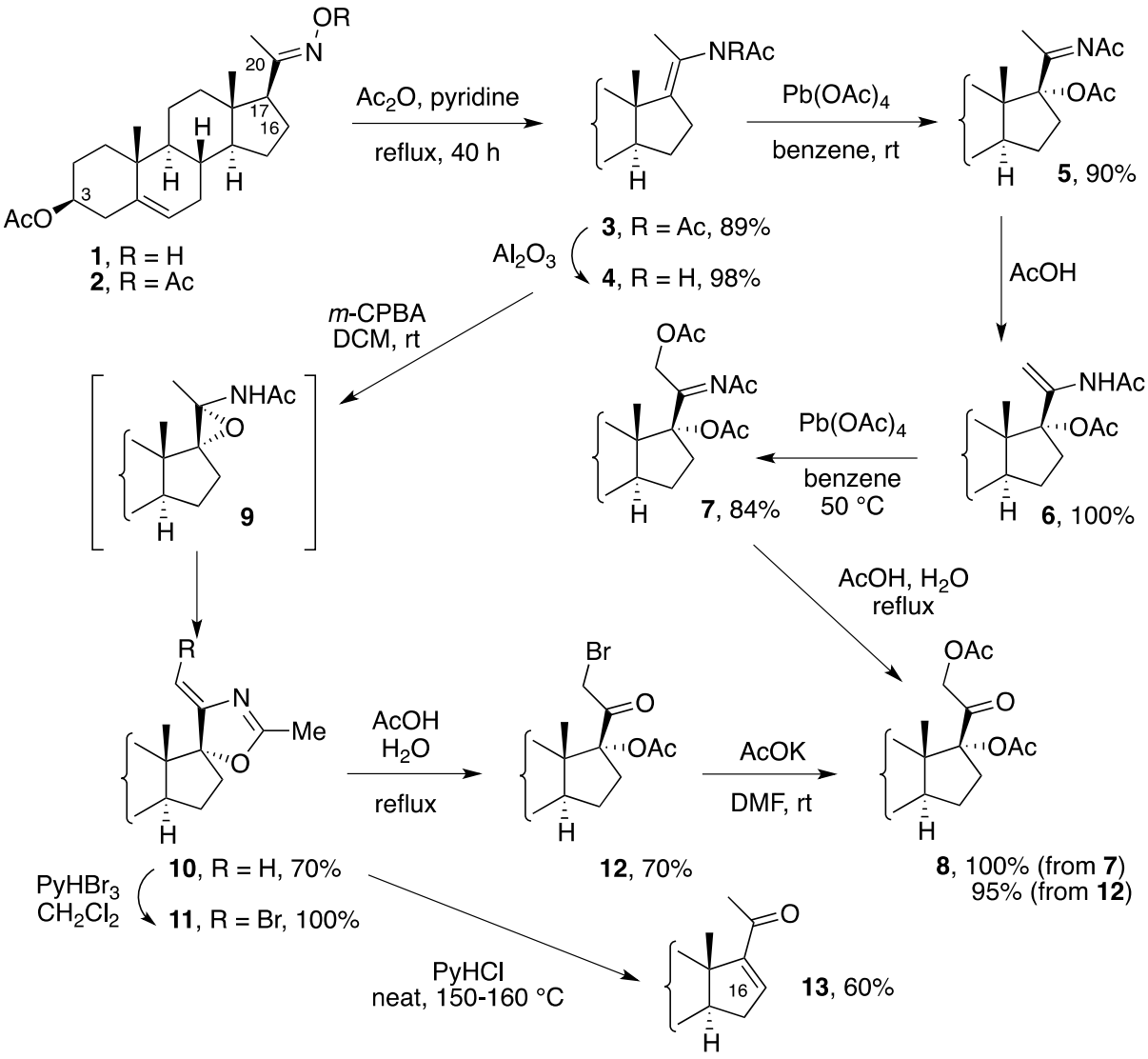
1. Introduction. An Early Encounter with Oximes

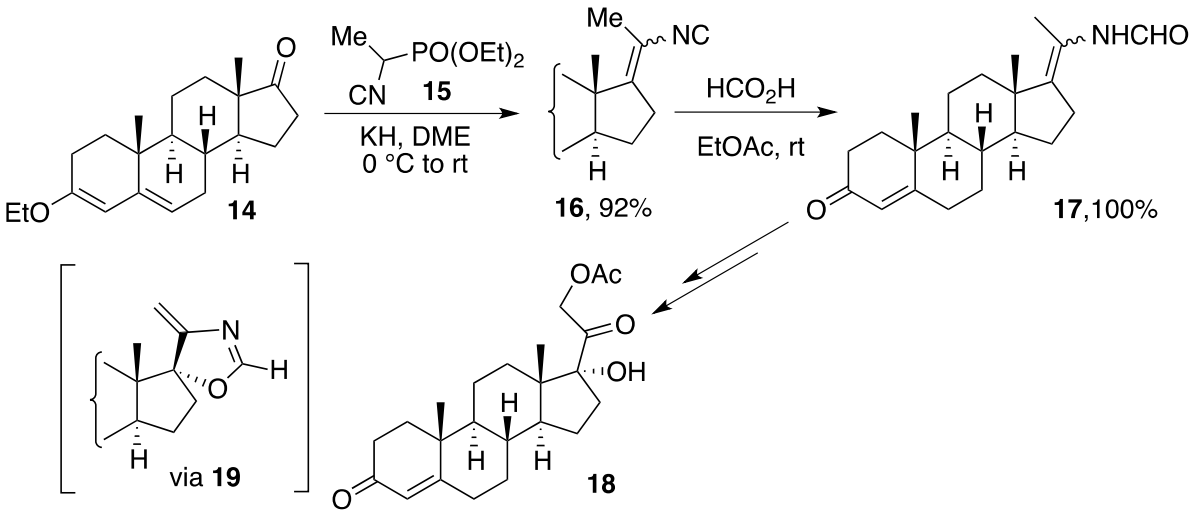
My interest in the chemistry of oximes started early. The main project of my PhD thesis under Sir Derek Barton, funded by the now defunct Roussel-Uclaf, was the construction of the corticosteroid side chain starting from 17-ketosteroids. The latter had become readily available raw materials on an industrial scale by the microbiological degradation of abundant sterols such as cholesterol and, especially, β-sitosterol and related plant sterols obtained from the waste material of the soya bean and tall oil industries.[1] The first method we devised was based on earlier observations made in a collaborative study by Professor Barton, then still at Imperial College, conducted with the team of Professor McGhie at Birkbeck College.[2] In this work, it was found that prolonged heating of 20-ketoxime **1** in a mixture of acetic anhydride and pyridine produces first enimide **3** which, upon contact with basic alumina, gives enamide **4** (Scheme 1). This strange reaction entails reduction of intermediate oxime acetate **2** by unknown species produced *in situ* by oligomerization of acetic anhydride. The reaction mixture turns completely black, but the yield of ene-imide **3** is surprisingly good. Furthermore, there is strong evidence that iminyl radicals are involved.[3] Treatment of enamide **4** with anhydrous lead tetraacetate results in a clean acetoxylation of the 17α-position to give acetylimine **5**, which is readily isomerized into enamide **6** by exposure to anhydrous acetic acid. A second acetoxylation under slightly harsher conditions then introduces an acetoxyl group at C-21. Finally, mild hydrolysis of acetylimide **7** furnishes the desired corticosteroid **8**.

This ingenious sequence is however not suitable for the large-scale production of corticosteroids. We therefore conceived of a different route based on the formation of novel dihydro-oxazole **10** via sensitive epoxide **9**.[4,5] The *m*-chlorobenzoic acid co-produced in the epoxidation step is sufficient to induce the rearrangement into key-intermediate **10**. This compound is readily converted into bromo-derivative **11**, which undergoes mild acid hydrolysis to give bromo-ketone **12**. Finally, displacement with acetate provides corticosteroid acetate **8**. Interestingly, brief heating of dihydro-oxazole **10** in neat pyridinium hydrochloride at high temperature (150-160 °C) induces ring opening, and addition of water and workup causes spontaneous hydrolysis to give enone **13**. Δ^{16}, 20-Ketosteroids are important starting materials for accessing 16-substituted corticosteroids such as dexamethasone and betamethasone.



Scheme 1. Syntheses of the corticosteroid side-chain.

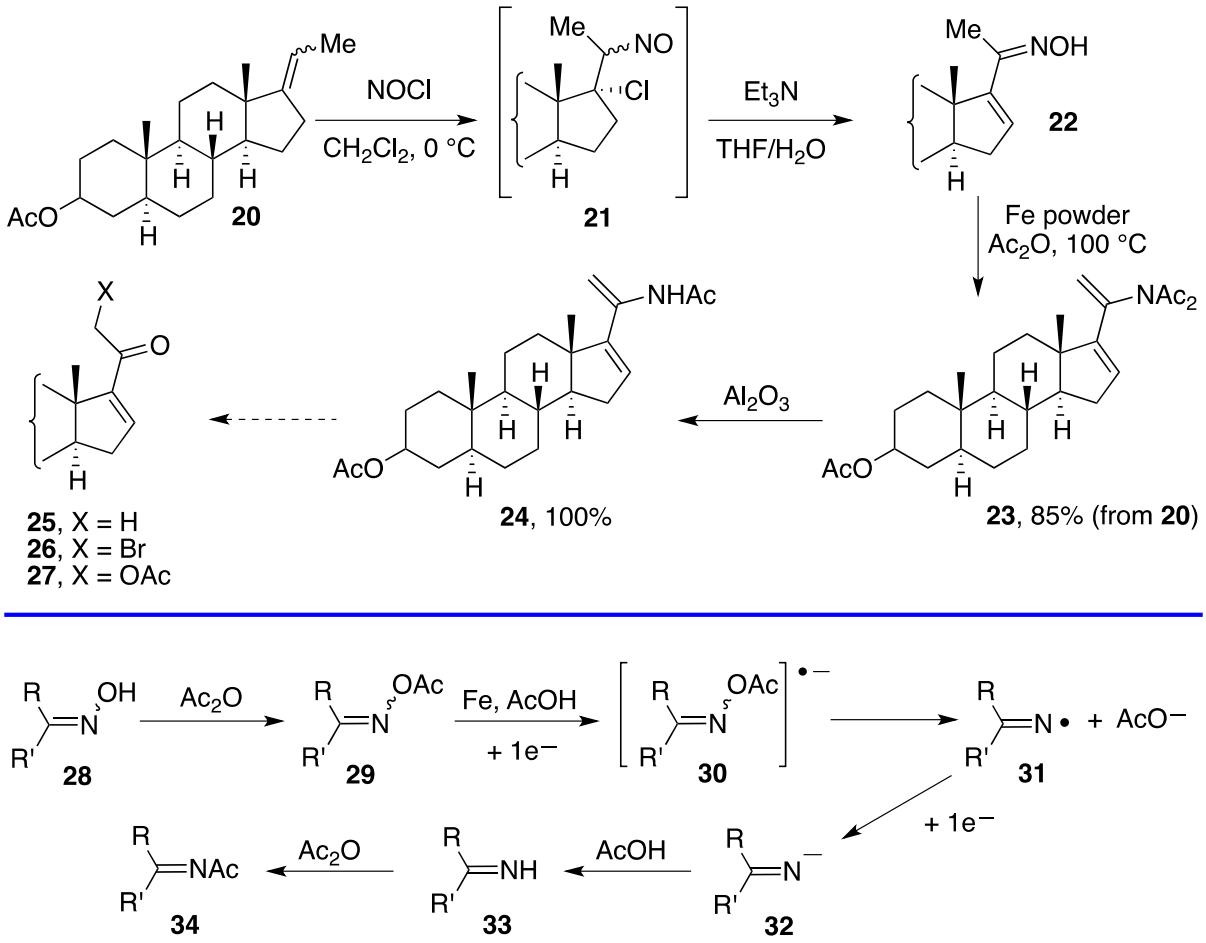
Enamide **4** derives from pregnanone oxime **1** and not from a 17-ketosteroid. To access an analogous enamide from the latter, we used the Horner-Wadsworth-Emmons (HWE) condensation of isocyanophosphonate **15** with ketone **14** to form unsaturated isonitrile **16** (Scheme 2).[4,5] Exposure to formic acid in ethyl acetate then furnishes ene-formamide **17** with concomitant unmasking of the enone in ring A. This enamide could then be converted into corticosteroid **18** using similar chemistry as above. In this case, the corresponding intermediate dihydro-oxazole **19** is somewhat fragile; it was therefore not isolated but brominated and hydrolysed *in situ.*



Scheme 2. Corticosteroids from 17-ketosteroids.

Another route to corticosteroids from 17-ketosteroids proceeding through an enamide relied on an improved and interesting reduction of oximes.[6] This strategy, outlined in Scheme 3, started from known alkene **20** derived from the corresponding 17-ketosteroid through a Wittig olefination. Exposure to *in situ* generated nitrosyl chloride in ice-cold dichloromethane furnished nitrososteroid **21**, which was not isolated. The dichloromethane was simply evaporated and replaced with wet THF and triethylamine. This induced the elimination of HCl and formation of unsaturated oxime **22**. This compound was not purified but heated to 100 °C in acetic anhydride with addition of iron powder resulting in the smooth formation of dieneimide **23** in 85% overall yield. Adsorption on basic alumina and elution gave the corresponding acetenamide **24** quantitatively. Hydrolysis of this substance would furnish enone **25**, whereas prior bromination would give bromoketone **26** and substitution of the bromine with acetate would provide acetoxyketone **27**, all of which are useful precursors to 16-substituted corticosteroids as stated above.

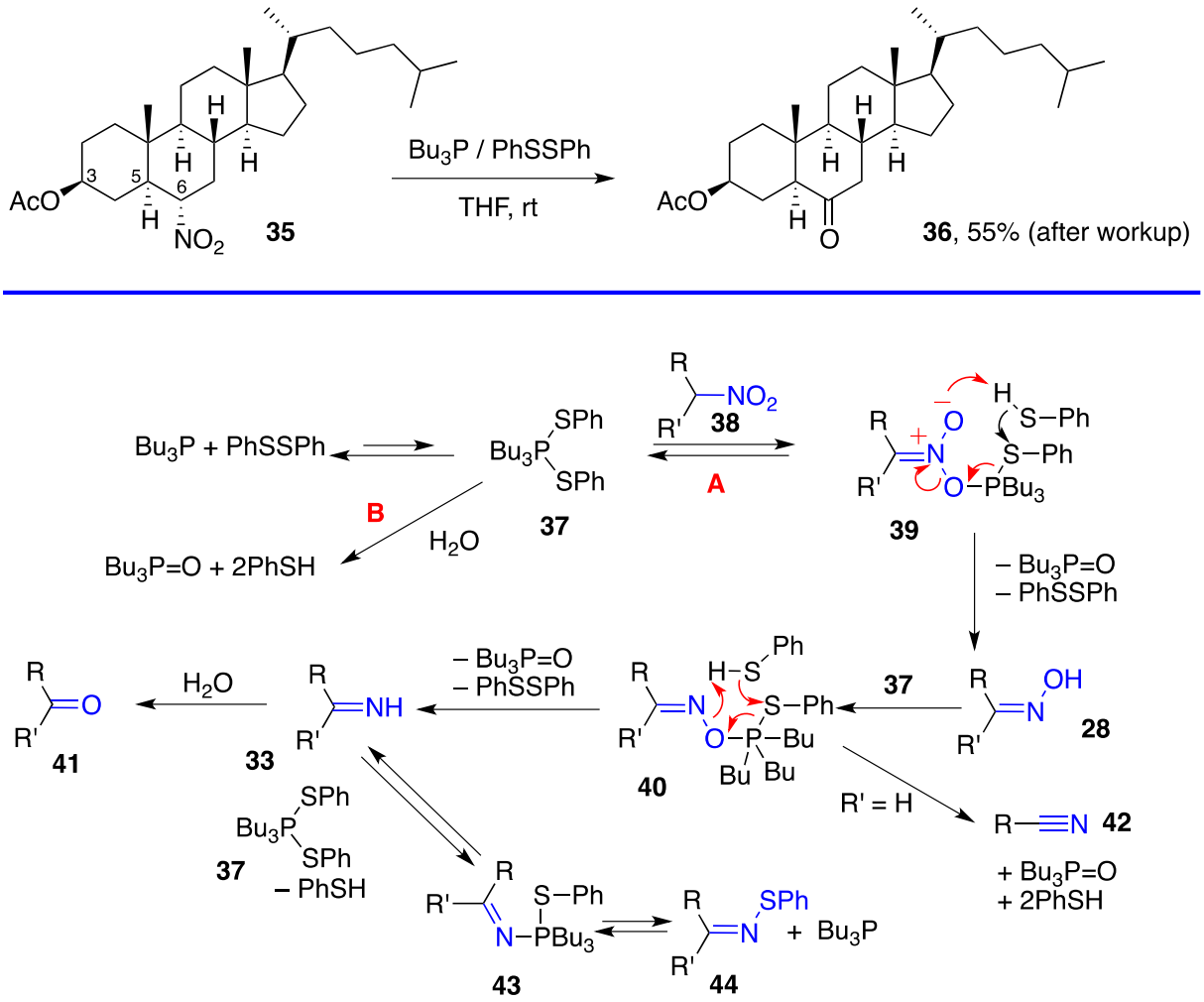
The application of the acetic anhydride / iron powder combination arose from discussions with the late Dr Jean Buendia of Roussel-Uclaf, who funded this work. It was conceived in order to replace the acetic anhydride/pyridine used above to convert oxime **1** into acetamide **4**, which is not practical for large scale work. The rationale underlying this new reduction of oximes is displayed in the lower part of Scheme 3. The acetic anhydride first converts generic ketoxime **28** into acetate **29**, which then is able to accept an electron from the iron to give radical anion. This extra electron goes into the σ* orbital of the N—O bond resulting in its rupture, with the formation of iminyl radical **31** and an acetate anion. A second electron transfer leads to iminyl anion **32** that is rapidly protonated. The protonation step may in fact precede, and indeed facilitate, the electron transfer. In any case, the resulting imine **33** is finally acetylated by the excess acetic anhydride to give *N*-acetylimine **34**, which can tautomerize into the corresponding acetenamide and further acetylated (cf., **22** → **23**).



Scheme 3. An alternative route to corticosteroids from 17-ketosteroids.

2. An Unusual Reduction of Nitroalkanes and Ketoximes

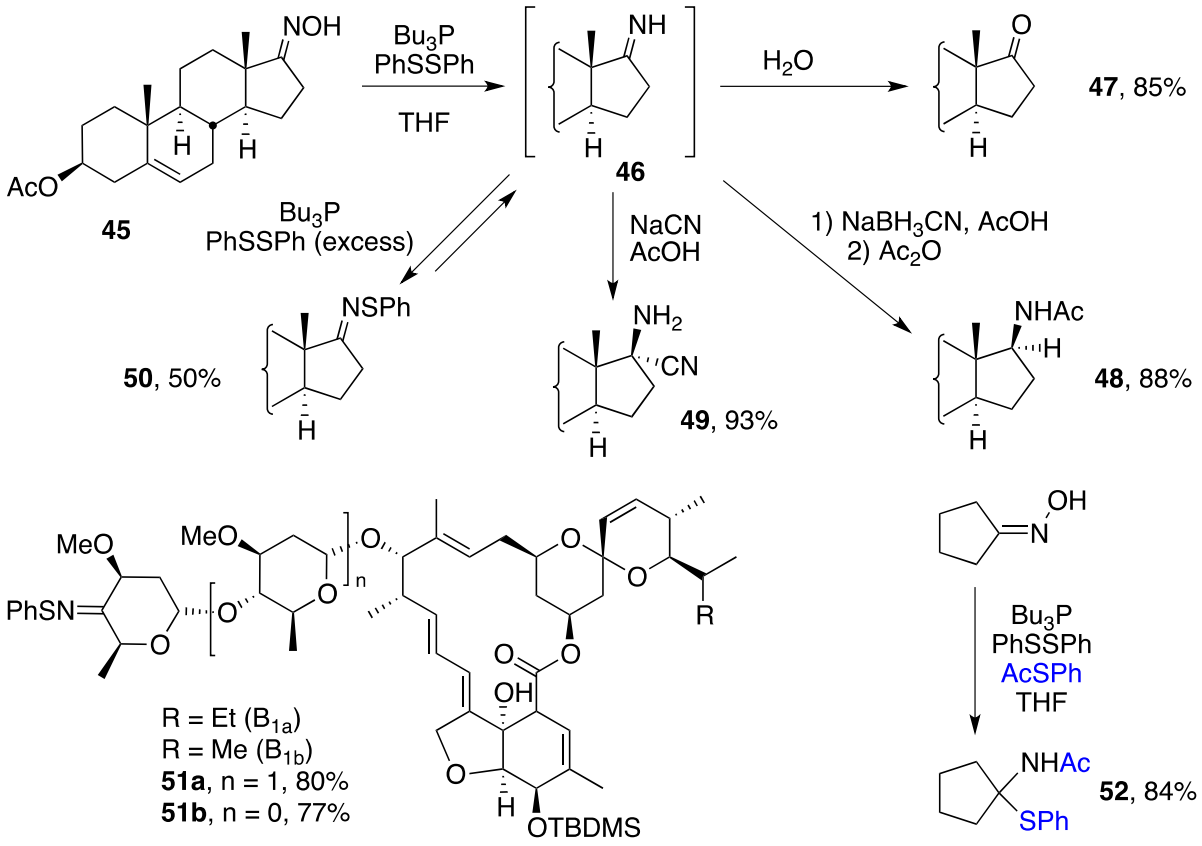
In parallel to the isocyanide and enamide routes described above, another route to corticosteroids was explored involving the condensation of nitromethane with 17-ketosteroid as the key-step.[7,8] This is a non-trivial transformation that we accomplished by using ethylenediamine and certain congeners as efficient catalysts to overcome the poor reactivity of the sterically hindered 17-ketone. I have always been fascinated by the incredibly rich chemistry of nitro compounds and, over the years, we uncovered, by accident or by design, several new reactions.[9] One such discovery arose when, in a misconceived attempt to convert a secondary nitro compound directly into a dithioketal, 6α-nitrocholestanyl acetate **35** was treated with a combination of tri-*n*-butylphosphine and diphenyl disulfide (Scheme 4). The reaction resulted in the clean formation of 6-ketosteroid **36** after an aqueous workup.[10,11]



Scheme 4. A reduction of nitroalkanes and ketoximes.

The mechanism that ultimately accounted for our experimental observations is displayed in Scheme 4. The phosphine and the disulfide react reversibly to give pentavalent phosphorus species **37** which can reduce the nitroalkane into the corresponding oxime **28** with recovery of the disulfide, as shown (Path **A**). In turn, the oxime is reduced into imine **33** which is hydrolysed to ketone **41** upon workup. The driving force is the formation of a strong P—O bond and, while the disulfide is regenerated and its action is catalytic, it is in practice best used in stoichiometric amounts, especially in small scale work, to avoid slow kinetics and because a portion of it is destroyed by any adventitious water present (path **B**). The oxime is reduced faster than the starting nitro compound and, not unexpectedly, primary nitro compounds and aldoximes (R' = H) are converted into nitriles **42**. One unexpected transformation was observed when an excess diphenyl disulfide was used. The reaction furnished phenylsulfenylimine **44**, a rare family of compounds, through an equilibrium involving intermediate **43**.

This reagent combination proved to be an excellent reductant for oximes. Vilarrasa and co-workers later reported that, in some cases, the tri-*n*-butylphosphine can be advantageously replaced by the more reactive trimethylphosphine.[12-14] Since water is removed irreversibly through path **A**, the medium is strictly anhydrous and the hydrolytically labile imines **33** are protected against premature hydrolysis. They can therefore be captured by various reagents allowing many synthetically useful transformations, in addition to simple hydrolysis to the corresponding ketone **41**. A few examples are deployed in Scheme 5.



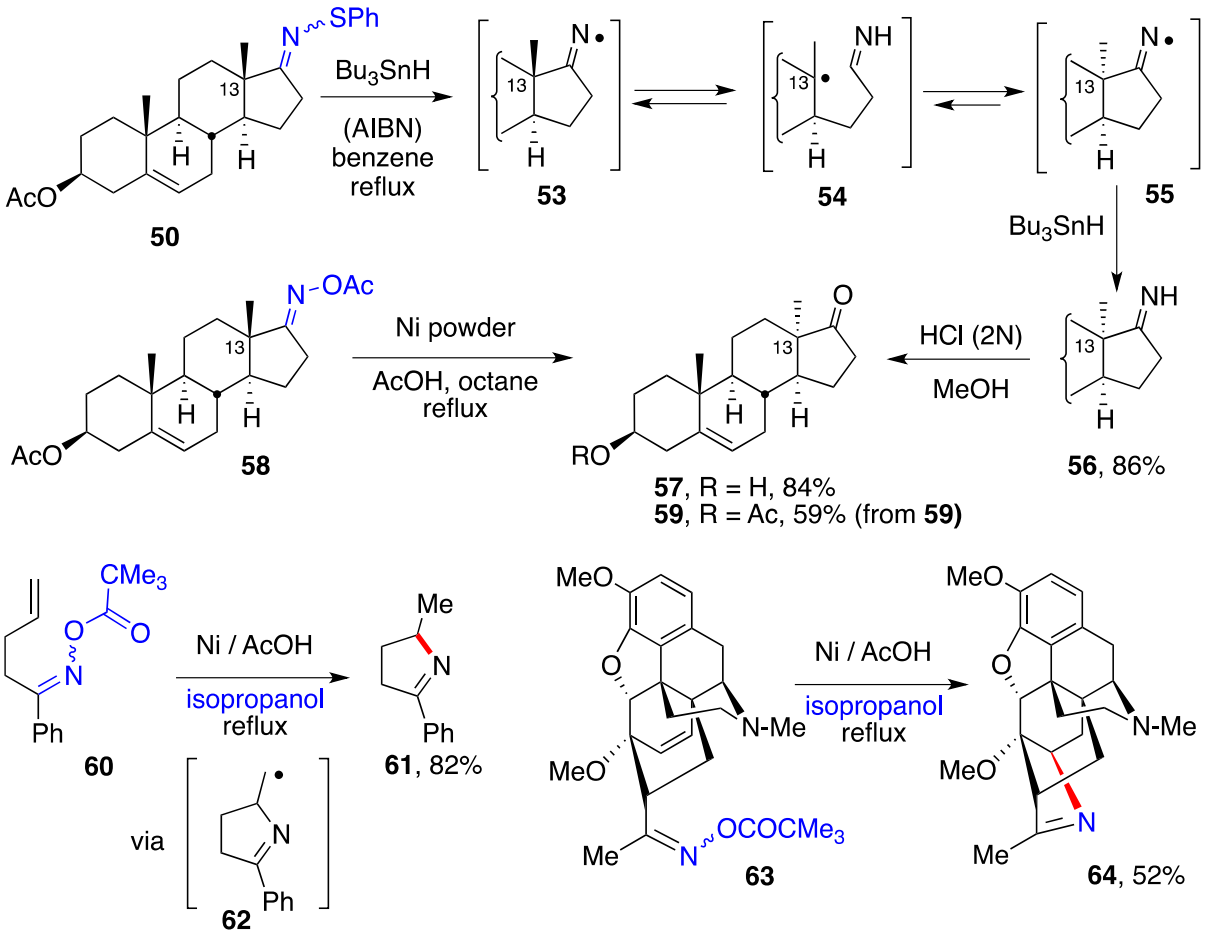
Scheme 5. Reductive transformation of ketoximes.

Steroid oxime **45** can thus be converted into ketone **47** by hydrolysis of intermediate imine **46**, whereas reduction and acetylation furnish 17-β-acetamide **48** and interception by *in situ* generated hydrogen cyanide produces aminonitrile **49**. Performing the reaction in the presence of excess disulfide generates phenylsulfenimine **50** in modest yield. More impressive examples of this last transformation were later disclosed by Jung and co-workers at Syngenta[15] and by Lukin and Narayanan at Abbott[16] and later by Vilarrasa.[13] The first group reported the synthesis of avermectin B1 (mixture of B1a and B1b) derivatives **51a**,**b** in high yield from the corresponding oximes, whereas the last two studied erythromycin analogues. Another interesting transformation is the capture of the intermediate imine with *S*-phenyl thioacetate, as illustrated by the efficient conversion of cyclopentanone oxime into acetamide **52**.[11] *S*-phenyl thioacetate is compatible with the reducing combination and can be added at the start of the reaction. It captures the imine as it is formed and avoids the unwanted trimerization often observed with simple unhindered N-unsubstituted imines.

3. Multiple Routes to Iminyls and Other Nitrogen Radicals

The unexpected formation of sulfenylimines **44**, as exemplified by compound **50**, raised the question of the possibility of using such derivatives as precursors for the little studied iminyl radicals. The affinity of stannyl radicals for sulfur and the relative weakness of the N—S bond seemed like a good driving force. Indeed, slow addition of tri-*n*-butylstannane and AIBN to a solution of 17-sulfenylimine **50** in refluxing benzene afforded 13-epi-17-iminyl-steroid **56** in high yield through the formation and ring-opening of iminyl radical **53** followed by

closure of tertiary radical **54** to give the more stable epimeric iminyl radical **55** with the less strained *cis*-CD ring junction.[17] This is a rare case where the hydrolytically labile unsubstituted imine **56** is sterically protected and can be isolated in good yield. Acid hydrolysis furnishes the corresponding ketone **57** with concomitant cleavage of the acetate at position 3.

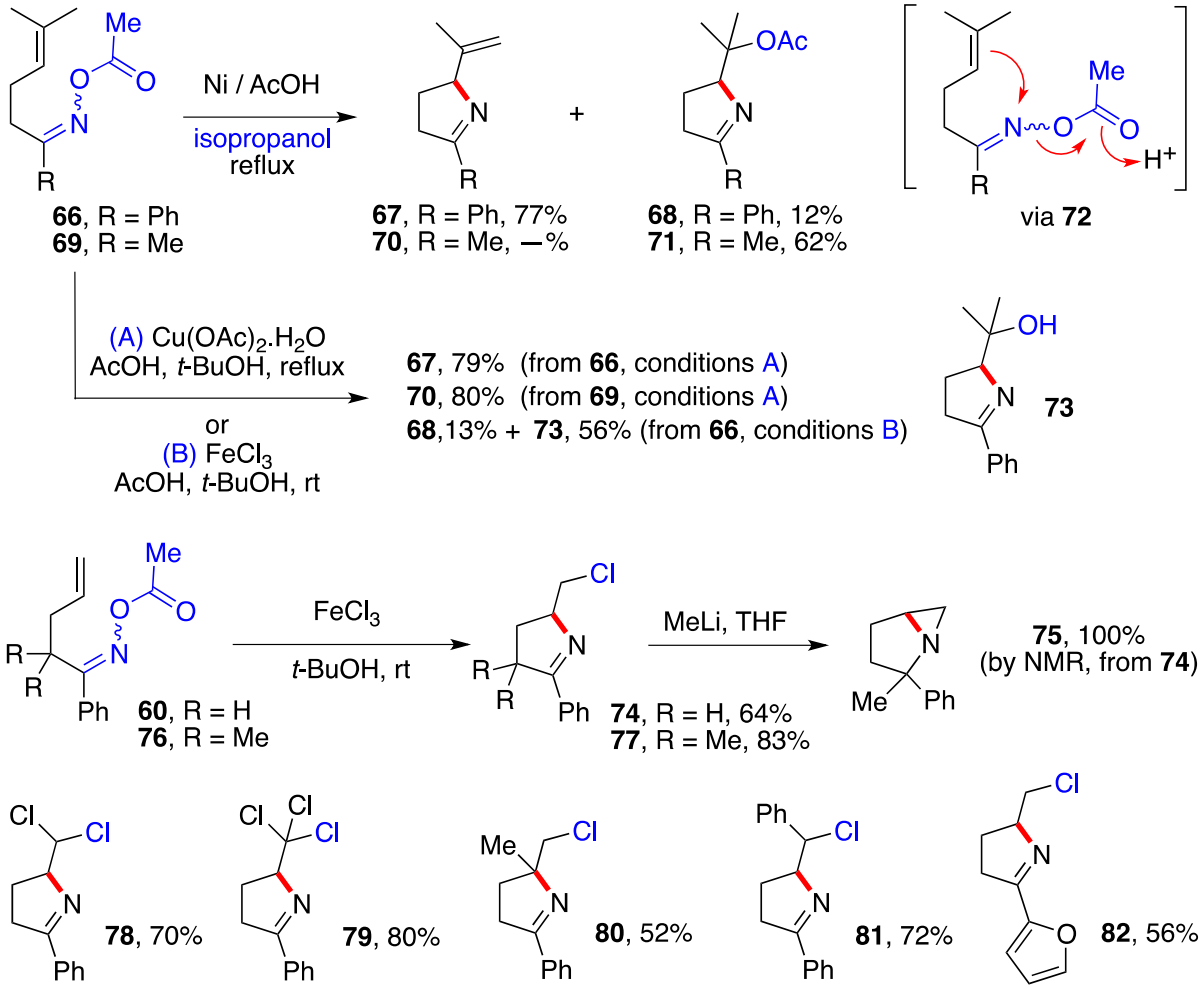


Scheme 6. Generation and capture of iminyl radicals.

Sulfenylimines proved to be excellent precursors for the generation and capture of iminyl radicals; however, their preparation is not generally straightforward, which limits the synthetic utility of this method. We therefore devised another route based on the observation pictured in Scheme 3, namely that the dissolving metal reduction of oxime acetate **29** proceeds via iminyl radical intermediate **31**. The problem that had to be addressed was the need for a reducing system where the electron transfer leading to iminyl anion **32** is sufficiently slow to allow a synthetically useful interception of iminyl radical **31**. We used the epimerisation of 17-steroid iminyl radical **53** as a convenient radical clock to gauge its lifetime and thus rapidly screen various metal/acid combinations.[18] Ultimately, we found that crude nickel powder and acetic acid in an organic solvent such as octane allowed the clean formation of 13-epi-steroid **59**, starting from 17-oxime acetate **58**. In the absence of the organic solvent or replacement of nickel by more reducing metals (such as iron) results in simple conversion of oxime acetate **58** back to the natural 17-ketone (not shown) with little, if any of the 13-epimer **59**. Under these latter conditions, the intermediate iminyl radical **53** does not live long enough to allow installation of the equilibrium leading to the more stable epimer **55**.

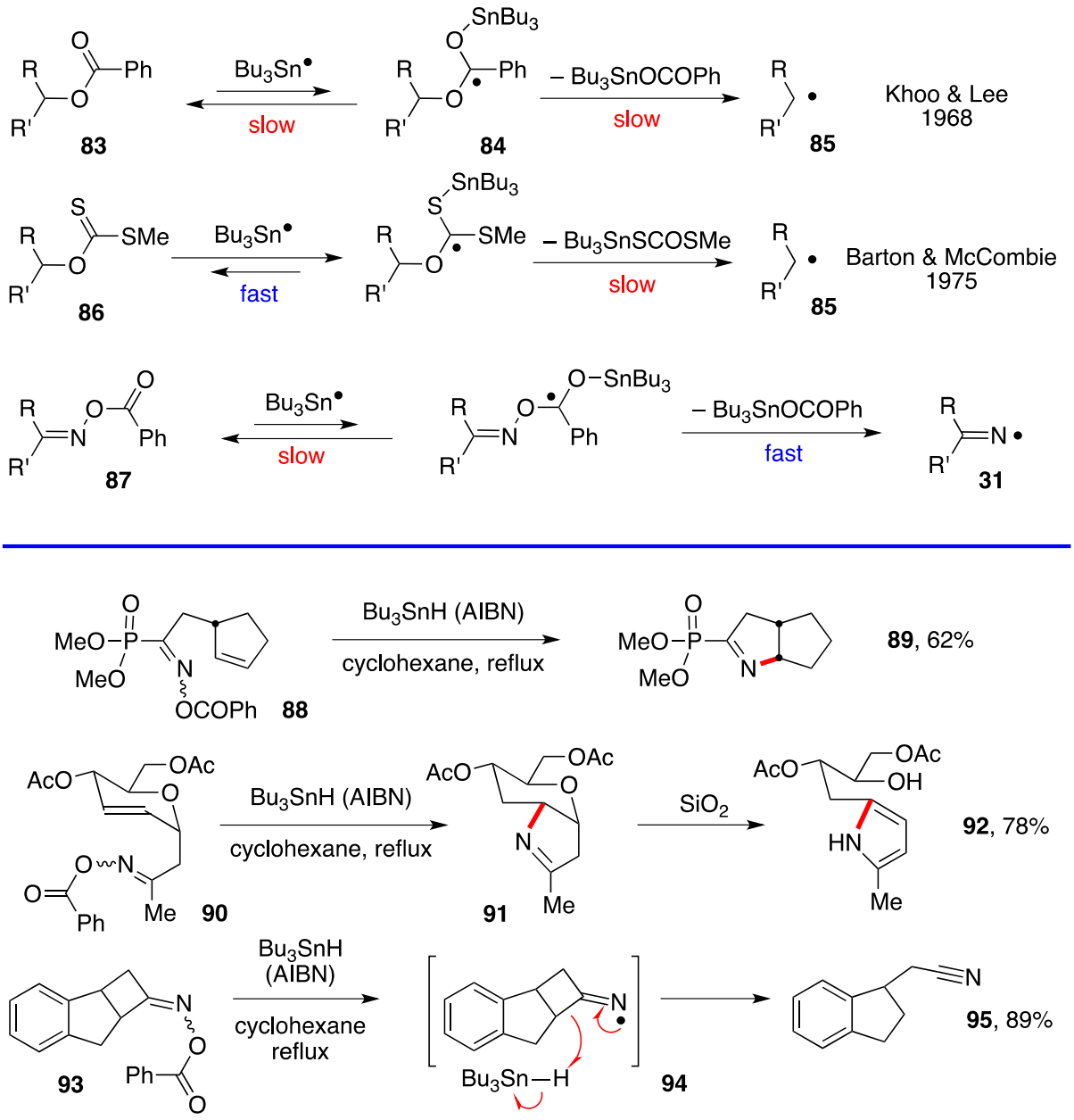
The iminyl radical can be captured by a suitably located alkene in a more generally useful synthetic transformation. This is illustrated by the formation of pyrrolenines **61** and **64**.[19] The oxime pivalate precursor **63** of the latter is derived from thevinone, the Diels-Alder adduct of thebaine with methyl vinyl ketone. In these cyclisations, isopropanol serves as the final hydrogen atom donor to quench the cyclised radical (e. g. **62**). The use of the oxime pivalates instead of the acetates is to limit unwanted hydrolysis back to the oxime, which we occasionally observed.

We were surprised to find that in the case of oxime acetate **66**, the reaction did not furnish the expected pyrrolenine but gave instead alkene **67** as the major product in addition to a small amount of tertiary acetate **68** (Scheme 7).[19] In the case of the methyl analogue **69**, it is tertiary acetate **71** that dominated, with little or no alkene **70**. Initially, with our mind fixated on radical chemistry, we assumed that the tertiary radical arising from the cyclisation of the iminyl was not abstracting a hydrogen atom from the isopropanol rapidly enough and was finally either reacting with adventitious oxygen or being oxidized to the corresponding cation by electron transfer, perhaps to the starting oxime acetate. Nevertheless, we later returned to this reaction and performed a blank experiment on compound **66** in the absence of the nickel powder.[20] Pyrrolenines **67** and **68** were indeed produced, albeit in different ratios. Obviously, in the case of electron rich internal alkene traps, an ionic substitution involving nucleophilic attack on the oxime nitrogen, as shown in structure **72**, overtakes the radical process.



Scheme 7. Unusual ionic reactions of oxime esters.

Two other experiments we performed were replacing the isopropanol with *t*-butanol, a solvent that lacks easily abstractable hydrogen atoms, and using cupric acetate (conditions **A**) or ferric chloride (conditions **B**) in place of the nickel powder.[20] Under the former conditions, oxime acetates **66** and **69** furnished alkenes **68** and **70** respectively in good yield. Under the latter, oxime acetate **66** was converted mostly into tertiary alcohol **73**. We later also found that with ferric chloride, and in the absence of acetic acid, even substrates with unsubstituted terminal alkenes reacted to give chlorine-substituted pyrrolenines. Thus, oxime actate **60**, which under the Ni/AcOH/isopropanol conditions produces reduced pyrrolenine **61** (Scheme 6), now reacts with ferric chloride to give chloride **74**. The reaction of this compound with methyllithium leads to bicyclic aziridine **75** in quantitative yield (by NMR). Pyrrolenines **77**-**82** are further examples of this ferric chloride mediated transformation.

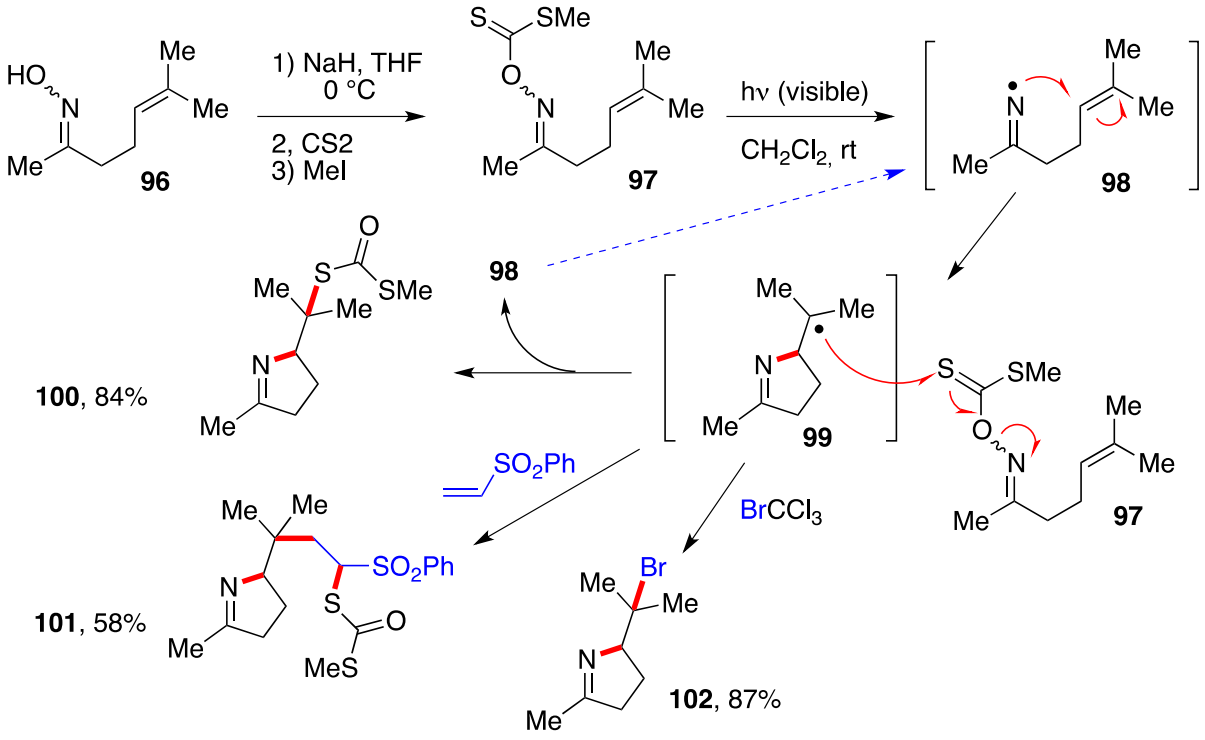


Scheme 8. Iminyl radicals from oxime benzoates.

In parallel, we developed a more traditional route to iminyl radicals, based this time on oxime benzoates **87**. A few years before the publication of the famous Barton-McCombie deoxygenation,[21] Khoo and Lee reported a deoxygenation process for alcohols based on reacting the corresponding benzoates **83** with tri-n-butyltin hydride (Scheme 8).[22] This older method did not attract much attention because it is limited to cases where the carbon-centered radical **85** generated is particularly stabilized (e. g., benzylic or allylic). The attack of a benzoate by stannyl radicals is relatively slow and strongly reversible. If the subsequent fragmentation of adduct **84** is also slow because the carbon radical **85** produced is unstabilized, then the whole sequence becomes inefficient. In contrast, the Barton-McCombie deoxygenation employs xanthates **86** and other related thiocarbonyl derivatives. The reaction of stannyl radicals with a thiocarbonyl group, while still reversible, is much faster as compared to a carbonyl and compensates for the relative sluggishness of the subsequent irreversible rupture of the C—O bond. This gives the Barton-McCombie deoxygenation a much broader scope and raises it to a genuine landmark in radical chemistry.

In view of these considerations, we surmised that, in the case of oxime benzoates **87**, the first reversible but sluggish addition of the stannyl radicals to the carbonyl of the benzoate will now be compensated by a fast irreversible scission of the relatively weak N—O bond to give iminyl radicals **31**. Indeed, this simple approach proved effective for generating not only iminyls but most other synthetically useful nitrogen centered radicals such as amidyls, carbamyls, ureidyl, and amidinyls.[23-26] Three examples are presented in the lower part of Scheme 8 illustrating generation and capture of iminyls. In the case of deoxyglucose derived oxime **90**, the resulting pyrrolenine **91** did not survive chromatographic purification on silica and underwent elimination into pyrrole **92**. Cyclobutyliminyl radical **94** cleaves regioselectively to give ultimately nitrile **95** in high yield.

The logical question that next arose was how would oxime xanthates behave? Both the radical addition to the thiocarbonyl and the subsequent fragmentation steps are now so fast and efficient that radical chains can be initiated and propagated under organotin-free conditions by simple heating and/or irradiation with visible light (Scheme 9).[27]



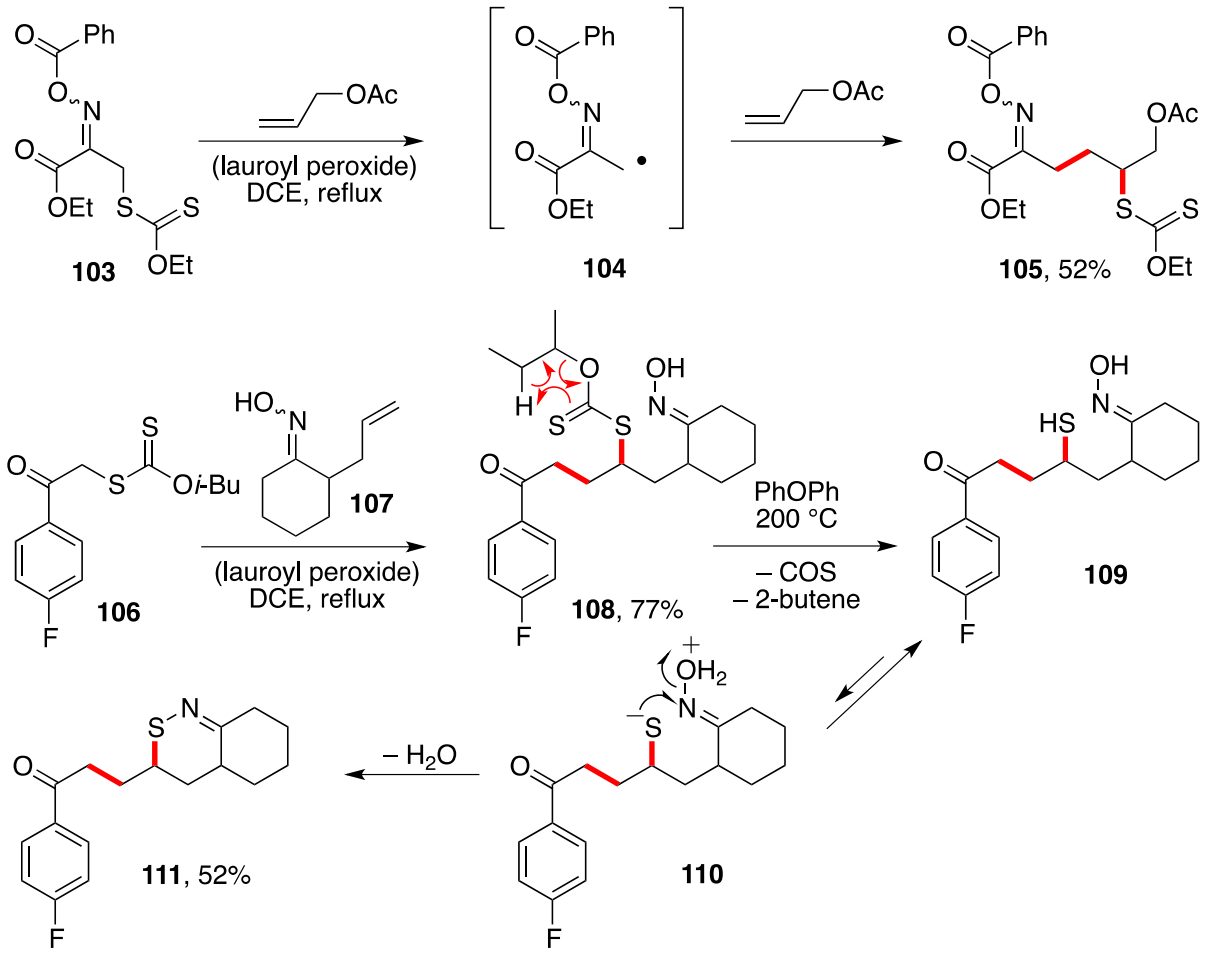
Scheme 9. Iminyl radicals from oxime xanthates.

We found that oxime xanthates such as **97** can be prepared in the usual way, by treating the anion of the oxime with carbon disulfide and methyl iodide in one pot. These substances proved to be relatively fragile, being sensitive to heat and light, but could be quickly purified by chromatography on silica and used directly in the desired radical transformation. Thus, irradiation of xanthate **97** with visible light at room temperature generates iminyl radical **98** which rapidly cyclizes, and the resulting tertiary carbon radical **99** reacts with starting xanthate **97** to give dithiocarbonate **100** and iminyl **98** that propagates the chain. The intermediate carbon radical **99** can be captured by an electrophilic alkene, such as phenyl vinylsulfone, to give more complex pyrrolenine **101**. It is also possible to accomplish a bromine atom transfer to give bromide **102** by irradiating in bromotrichloromethane as the solvent.

4. An Alliance with Xanthates

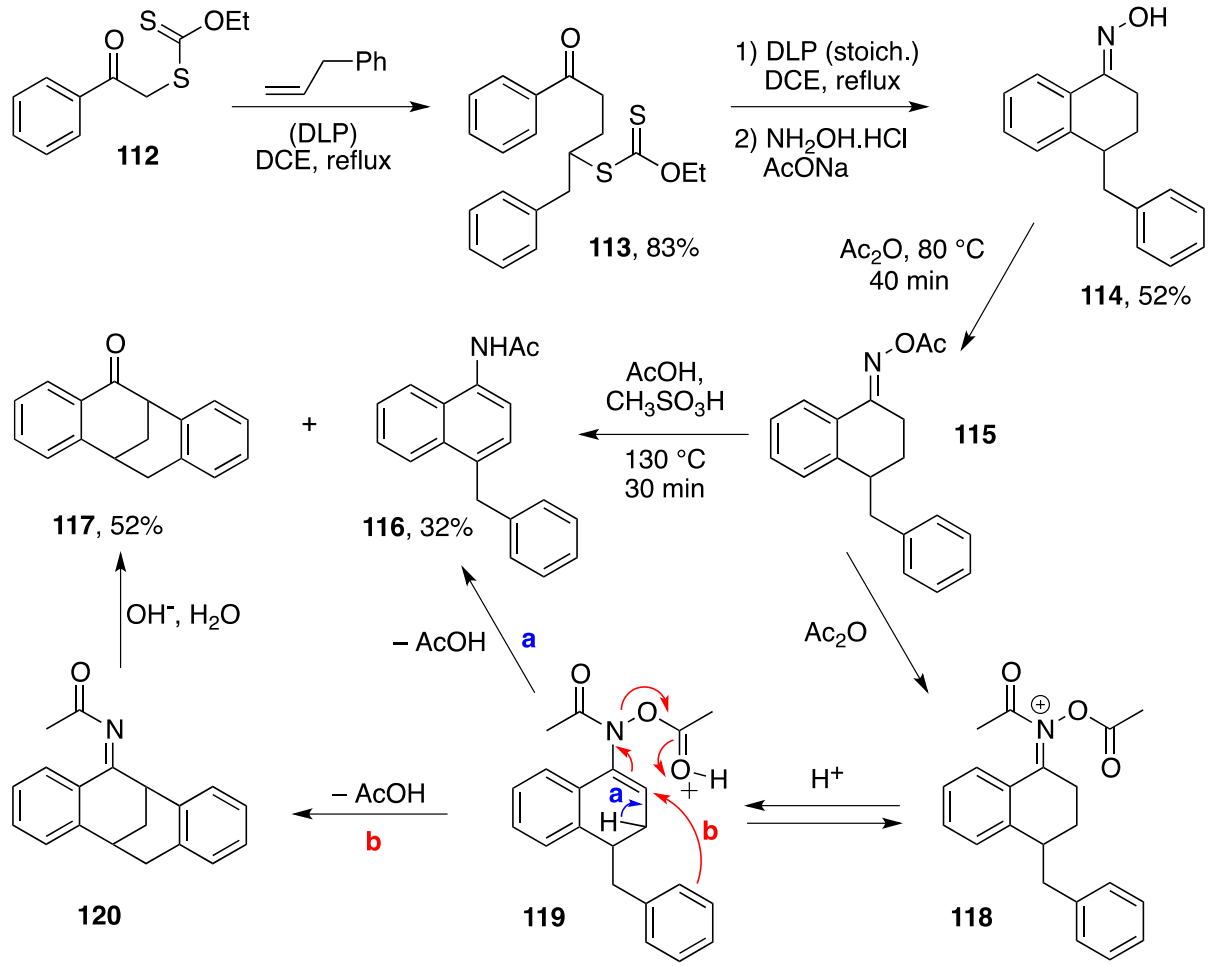
Much of our research efforts have revolved around the chemistry of xanthates. Nearly 40 years ago, we uncovered an unusually powerful process whereby, under appropriate conditions, a xanthate can be made to add to an alkene by a radical chain mechanism.[28-30] A new carbon-carbon bond and a new carbon-sulfur bond are formed in the process and the method exhibits numerous interesting aspects that will not be discussed here. With respect to oximes, this xanthate chemistry can be applied in many ways to rapidly construct various interesting oxime derived structures. In the example displayed at the top of Scheme 10, pyruvate xanthate **103** adds to allyl acetate to give adduct **105**, where the new bonds formed are colored in red.[31] The reaction proceeds via radical **104** and is initiated by substoichiometric amounts of DLP (di-lauroyl peroxide, also sold under lauroyl peroxide). Many other alkenes can be used and the oxime benzoate can in principle be subjected to a variety of transformations, including reduction into the corresponding amine, thus opening a simple access to numerous novel amino acids.

Alternatively, the oxime motif can be placed on the alkene partner, as shown in the second example where *p*-fluoroacetophenyl xanthate **106** smoothly adds to the terminal alkene of xanthate **107** to give adduct **108**.[32] Because of the presence of the secondary butyl group on the xanthate, this compound undergoes a Chugaev elimination upon heating to 200 °C in diphenyl ether to form thiol **109** which, under these rather harsh thermal conditions, reacts further through intermediate **110** to produce dihydrothiazine **111** in a useful yield. Dihydrothiazines were a virtually unknown class of heterocycles before the present route was developed.



Scheme 10. The xanthate route to pyruvyloximes and dihydrothiazines.

The xanthate group in the addition products of phenacyl xanthates can be further exploited to mediate a second carbon-carbon formation through ring-closure onto the aromatic ring. This constitutes a practical, convergent route to α-tetralones.[33] It can be accomplished by treating the adduct with stoichiometric amounts of peroxide, as shown by the conversion of adduct **113** derived from xanthate **112** and allylbenzene into oxime **114**, obtained by treatment of the intermediate tetralone (not shown) with hydroxylamine under the usual conditions (Scheme 11). The initial purpose of this synthesis was to establish a general approach to naphthylamines by application of the little used Schroeter reaction. This is an extension of the earlier Semmler-Wolff reaction and allows the conversion of oximes of α-tetralones into *N*-acetyl-naphthylamines. Thus, oxime **114** was first acetylated into acetate **115** by heating gently in neat acetic anhydride followed by addition of acetic and methanesulfonic acids and a more vigorous heating to 130 °C.[34] The expected *N*-acetyl-naphthylamine **116** was indeed isolated; it was, however, the minor component. The major product turned out to be tetracyclic ketone **117**, produced after a hydrolytic workup. We had in fact unwittingly captured an intermediate in the Schroeter reaction and diverted it from its normal pathway.



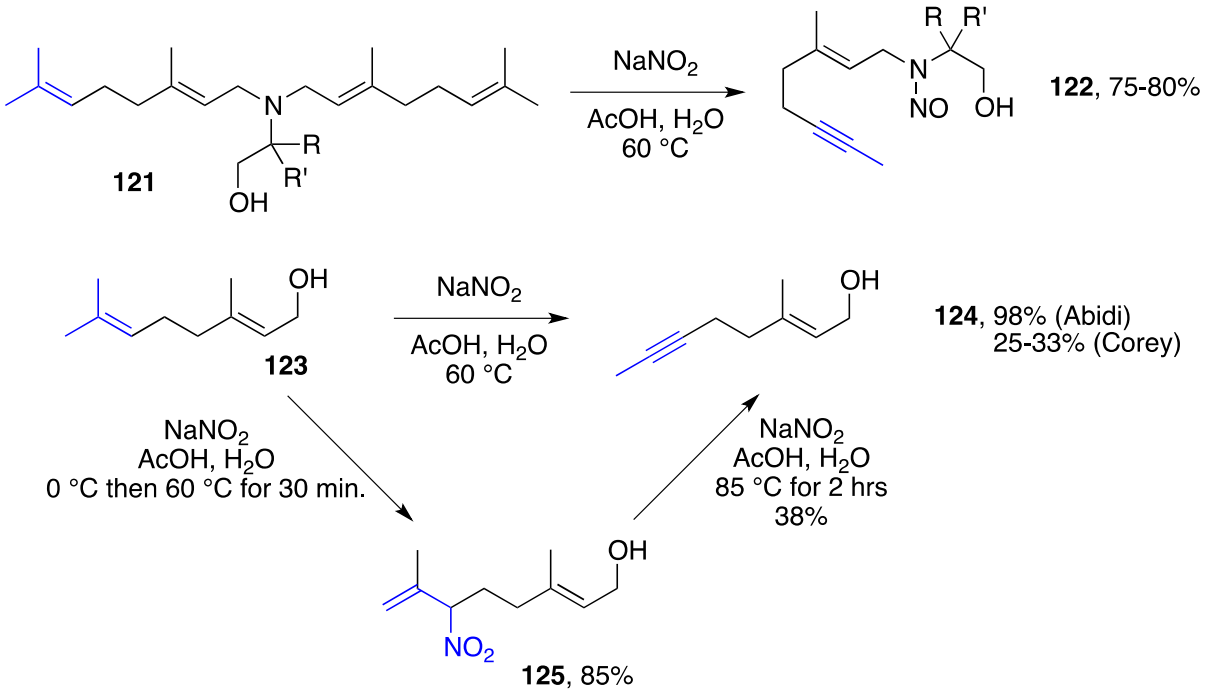
Scheme 11. Oximes as α-electrophiles.

The normal Schroeter sequence leading to the naphthylamide **116** starts by acetylation of oxime acetate **115** to give intermediate **118** which, under the strongly acidic medium, is in equilibrium with protonated species **119**. Loss of a proton and cleavage of the relatively weak N—O bond (path **a**) gives naphthylamide **116** after tautomerization of the intermediate *N*-acetylimine (not shown). Because of the presence of a suitably located pendant phenyl ring, a competing intramolecular Friedel-Crafts reaction can take place leading to *N*-acetylimine **120**, according to path **b**. This compound cannot tautomerize to the corresponding *N*-acetylenamide and is simply hydrolyzed into ketone **117** upon aqueous basic workup. This serendipitous finding opens a simple, flexible, and modular pathway to rare tetracyclic bridged ketones such as **117**.[34] Furthermore, the intermediate acetylimides (e. g. **120**) can be isolated by modifying the workup procedure and serve, in principle as a springboard to access a variety of nitrogen derivatives (amines, aminonitriles, amino acids, etc.).

5. Syntheses of Alkynes

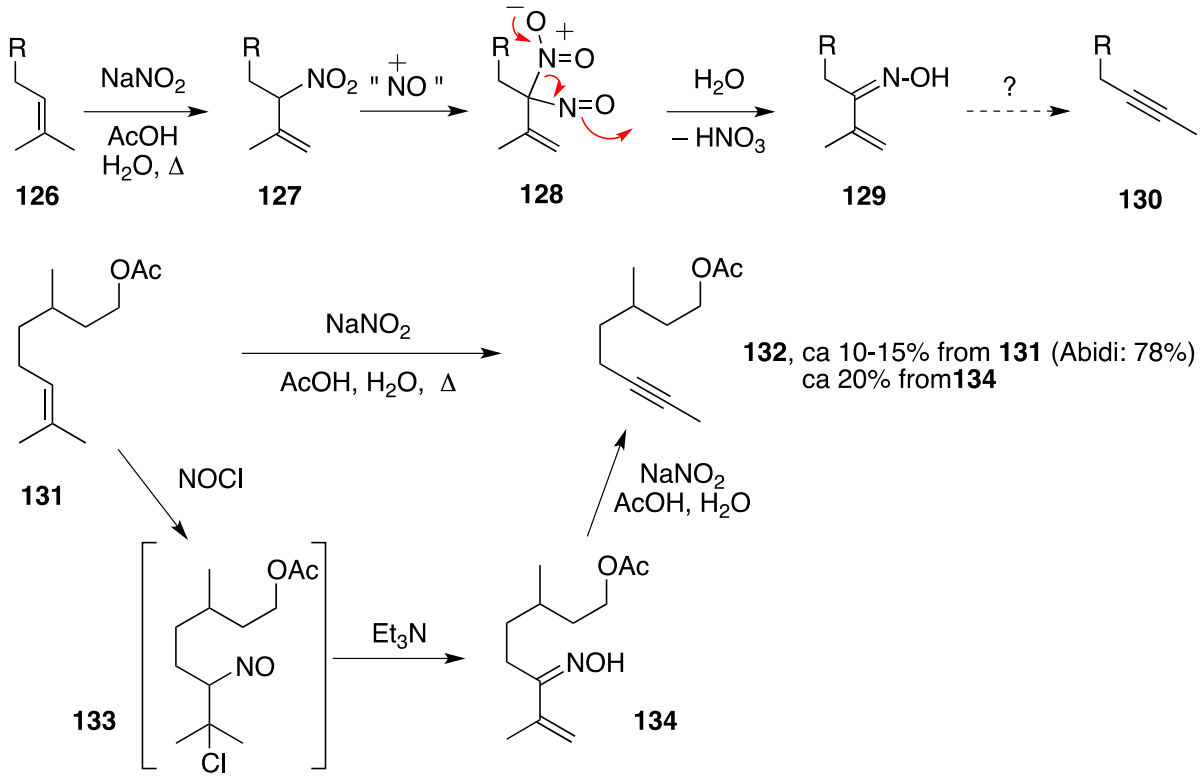
Serendipity is a wonderful ally in chemical research and in science, more generally. One remarkable accidental discovery was made many years ago by Sharon L. Abidi, a chemist working at the National Fishery Research Laboratory in the US. She was interested in the effects of nitrite on the environment and, in one study, reacted

tertiary terpenylethanolamines **121** with an excess of sodium nitrite in acetic acid at 60°C. The major products from these reactions turned out to be, unexpectedly, *N*-nitrosoalkynylamines **122** (Scheme 12).[35-37] In this incredible transformation, the isopropylidene group in the geraniol chain is somehow converted into an alkyne by the formal loss of the elements of methane. These observations were first described in 1985 and then in two subsequent papers in 1986, but no mechanism was provided. Shortly thereafter, Corey and co-workers reported the results of their mechanistic study.[38] While they could reproduce the reaction, they could not reproduce the yields (nor could we). For instance, Abidi claimed a nearly quantitative yield for acetylene **124** from geraniol **123**, but the Harvard group could only secure 25-33%, certainly after much hard work. However, they made a key finding, namely that allylic nitro derivative **125** is an intermediate that can be isolated in good yield by working under somewhat gentler conditions and a shorter reaction time.



Scheme 12. A remarkable synthesis of alkynes.

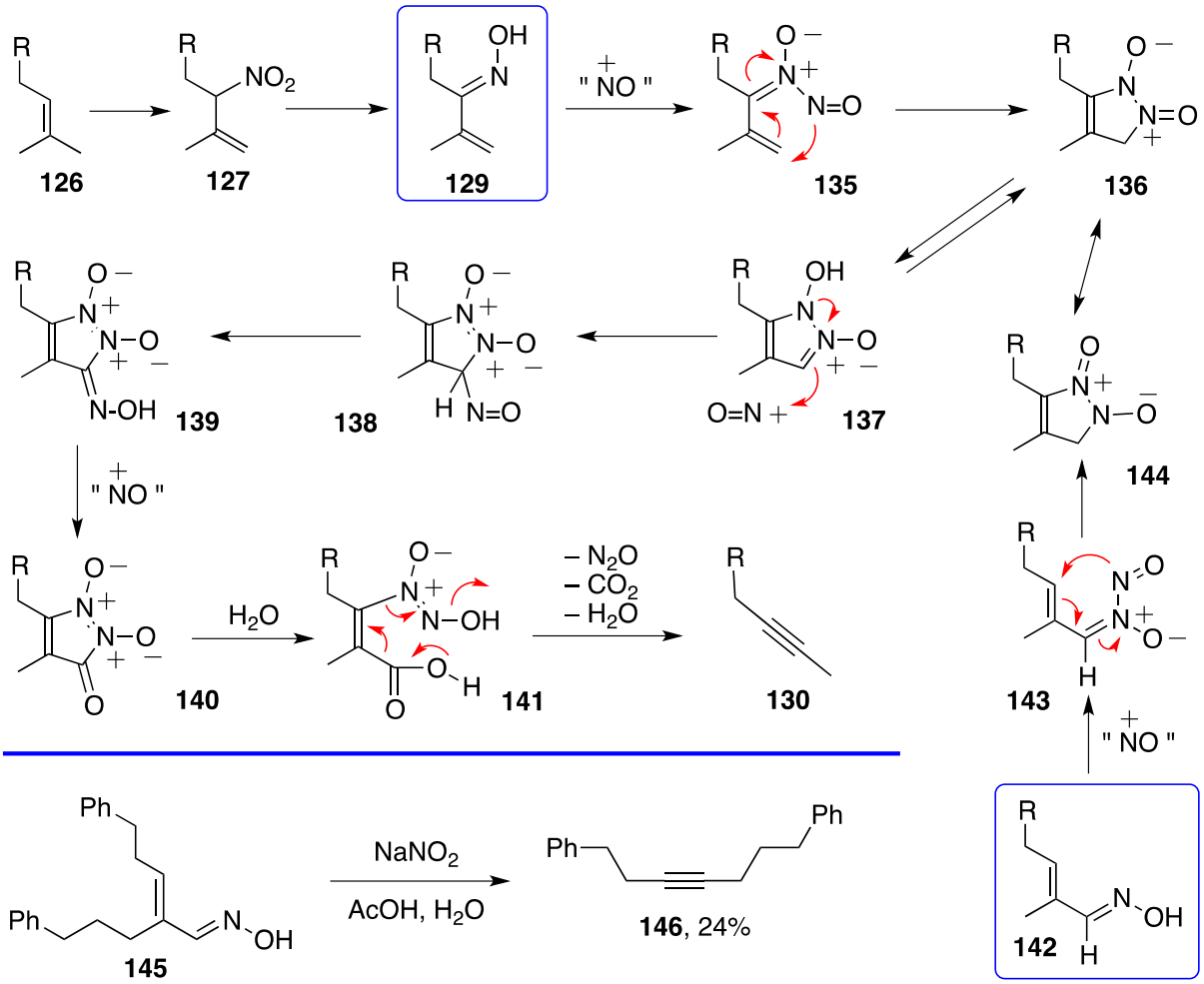
This key information allowed us to formulate an alternative mechanism where we postulated that unsaturated oxime **129** could be a later intermediate, as shown in the generic sequence outlined at the top of in Scheme 13.[39,40] This substance would derive from pseudo nitrole **128**, formed by nitrosation of Corey's allylic nitro intermediate **127**. Pseudo nitroles are well-known derivatives, even if they have attracted little attention in recent times. So now the question is whether an unsaturated oxime such as **129** could indeed furnish alkyne **130** under the Abidi conditions.



Scheme 13. Unsaturated oxime as a possible intermediate.

To test the plausibility of this mechanistic hypothesis, we prepared oxime **134** from citronellyl acetate **131** by treatment with nitrosyl chloride and elimination of HCl with mild base in a manner similar to the one we used earlier to obtain steroid oxime **22** (Scheme 3). In the event, exposure to sodium nitrite in hot aqueous acetic acid indeed gave rise to the expected alkyne **132** in around 20% yield. In our hands, the direct conversion of citronellyl acetate **131** into alkyne **132** proceeded in only 10-15%, in stark variance with Abidi's claim of a 78% yield for this transformation. Thus, despite the poor yield, unsaturated oxime **134** could nevertheless be an intermediate in the Abidi reaction.

Saturated oximes react with nitrous acid to give back the parent aldehyde or ketone. This reaction is one of the lesser known Claisen reactions.[41] In contrast, work by the late Jeremiah Freeman showed that α,β-*unsaturated oximes* give unusual heterocyclic structures when exposed to nitrous acid. However, α,β-*unsaturated oximes* where the alkene moiety is terminal and unsubstituted, as in generic structure **129**, were not examined in these studies.[42] Nevertheless, in strict analogy with Freeman's findings, we postulated that oxime **129** reacts with nitrous acid to give *N*-nitroso intermediate **135**, which then undergoes an electrocyclic ring closure into heterocycle **136**, as pictured in Scheme 14; but, unlike the more substituted examples studied by Freeman, heterocycle **136** can proceed further by a series of tautomerizations and nitrosations to furnish ultimately intermediate **141** which finally collapses into the desired alkyne **130**. The driving force is the loss of carbon dioxide, nitrous oxide, and water.

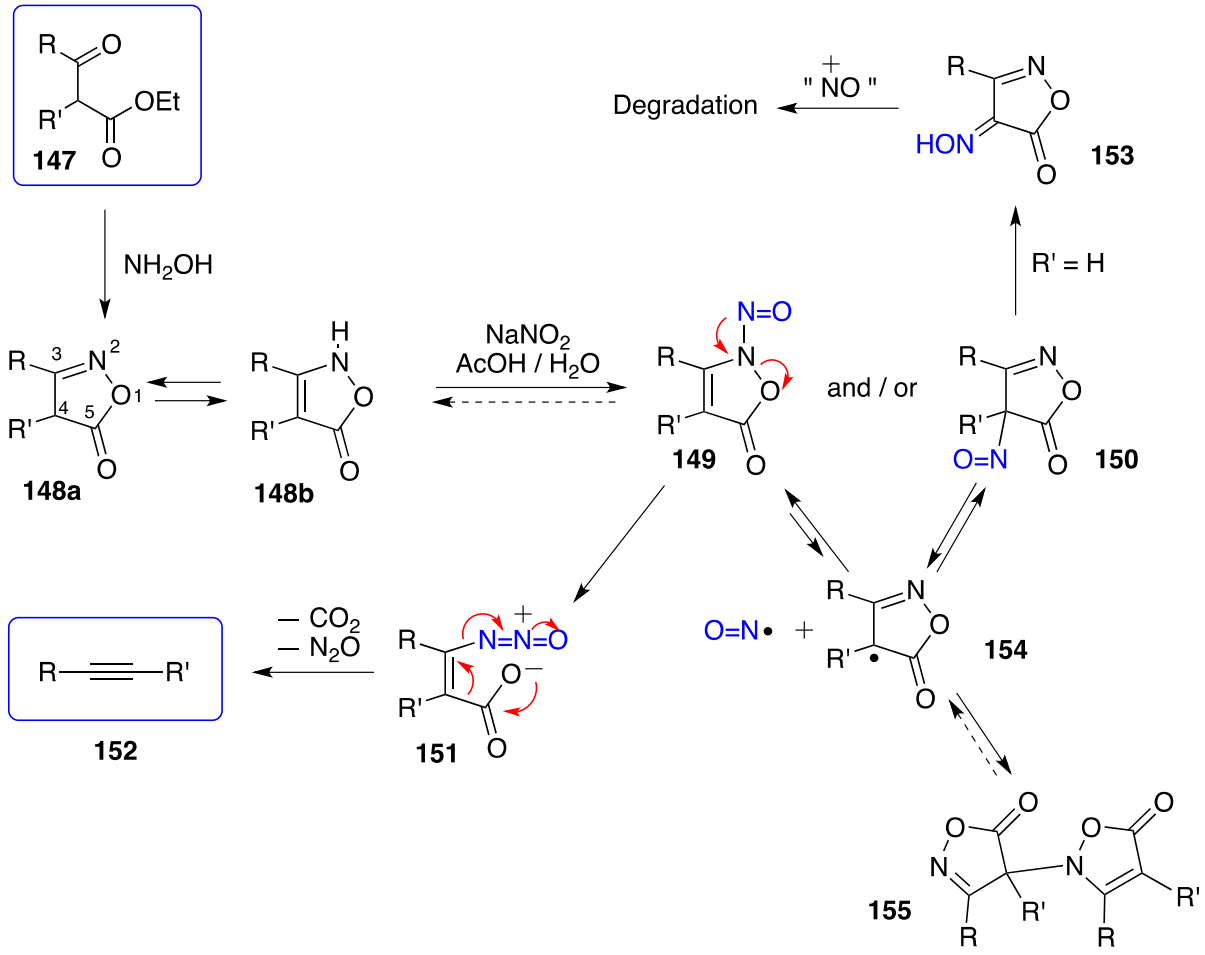


Scheme 14. A plausible mechanism for alkyne formation.

While this mechanism is mostly speculative, we did obtain some evidence for the first steps. If heterocycle **136** is indeed a possible intermediate, then isomeric oxime **142** should also produce acetylene **130** under the same nitrosative conditions. This is because its nitrosation would give derivative **143** and electrocyclic ring closure would lead *to the same postulated heterocyclic intermediate* **136**. Indeed, when we subjected oxime **145** to the action of sodium nitrite in aqueous acetic acid, we were pleased to find that the expected alkyne **146** was formed in a yield comparable to the one observed for the conversion of citronellol derived oxime **134** into alkyne **132**.

In attempting to understand the mechanism of the remarkable reaction discovered by Abidi, we thus discovered a hitherto unknown transformation of α,β-unsaturated oximes of type **129** and **142** into alkynes **130**. However, even if the poor yields could be improved, this finding would remain of modest synthetic utility because of the quite limited availability of such oxime substrates. Nevertheless, this study guided us to another possibility, which ultimately proved vastly more interesting. By reflecting upon the structure of late intermediate **141**, it occurred to us that an analogous unstable species **151** could in fact be obtained directly by nitrosating an isoxazolinone **148** (Scheme 15).[43] This nitrosation could occur at positions 2 and/or 4 of the isoxazolone to give *N*-nitroso- and/or *C*-nitroso isoxazolones **149** and/or **150** respectively. Only the former can collapse into unstable species **151**, which would then lose carbon dioxide and nitrous oxide to furnish the desired alkyne **152**. We surmised that the unreacted *C*-nitroso isomer **150** could in principle revert back to starting material **148a**,**b** by an ionic "retro-nitrosation" through attack by water on the nitroso group, and this

would hence ensure that all the substrate would eventually be transformed into alkyne **152**. We also realized from the outset that C-4 had to be substituted (i. e., R' ≠ H); for otherwise the nitroso group will rapidly tautomerize into the more stable oxime **153** which would then lead to decomposition products upon nitrosation. At any rate, this hypothesis was easily tested, since isoxazolones **148**, which can be viewed superficially as cyclic oxime esters, were well-known and accessible in one step from readily available β-ketoesters **147**.

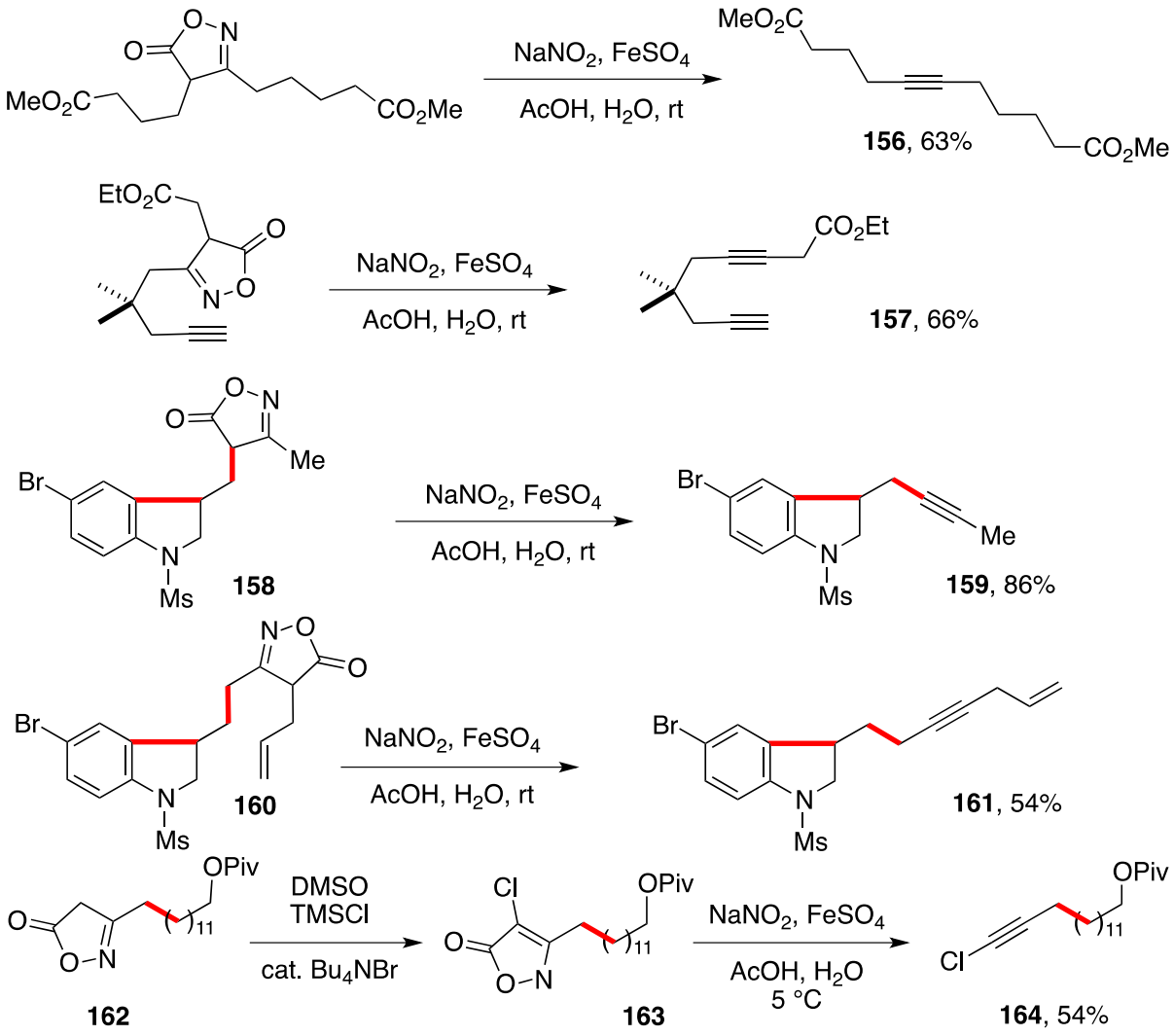


Scheme 15. An alternative route to alkynes.

Our first experiment was only partially successful. The reaction was quite clean but the expected alkyne was formed as the minor component in modest yield. The major product turned out to be an unsymmetrical dimer of structure **155**. Clearly, such a compound almost certainly arose from the nitrogen to carbon coupling of radical **154**. This key observation indicated that nitroso intermediates **149** and (especially) **150** were undergoing a spontaneous *reversible homolysis at room temperature*. The gaseous nitric oxide released escapes from the medium leaving radicals **154** behind which ultimately couple to give dimer **155**. To curtail the formation of this unwanted side-product, we modified our experimental procedure. First, now that we knew that radicals were involved, we operated under an inert atmosphere and thoroughly degassed the solutions, in contrast to the preliminary experiments performed in an open flask. Second, we added ferrous sulfate and allowed it to react with part of the sodium nitrite and acetic acid (used in excess) before the addition of the substrate and the remainder of the reagents. The combination of ferrous sulfate with sodium nitrite and acetic

acid generates nitric oxide *in situ* and, since this is a persistent radical, its presence prevents the formation of unwanted dimers **155** by selectively capturing radical **154** through what is called the persistent radical effect (PRE). PRE, also known as the Fischer-Ingold effect, is an extremely important principle that is unfortunately not widely appreciated.[44,45] Thus, in our system, isomeric nitroso intermediates **149** and **150** were not interconverting by an ionic "retro-nitrosation" as we initially anticipated, but rather via homolysis to radical **154** which reversibly recombines with nitric oxide.

With this key experimental modification in place, the transformation of isoxazolinones **148** into alkynes **152** becomes a quite powerful synthetic tool. Five examples are displayed in Scheme 16. Only one tautomer for the isoxazolinone precursors is shown for clarity. Diyne **157** is taken from a very recent study by Tavakoli and Dudley and represents a valuable precursor for the synthesis of polycyclic compounds.[46] The skipped arrangement between the alkyne and the ester is quite sensitive to base induced isomerization to the allene but survives under the mildly acidic experimental conditions of our procedure. The skipped enyne in example **161** is also a rather fragile arrangement vis-à-vis base and oxidation.[47]

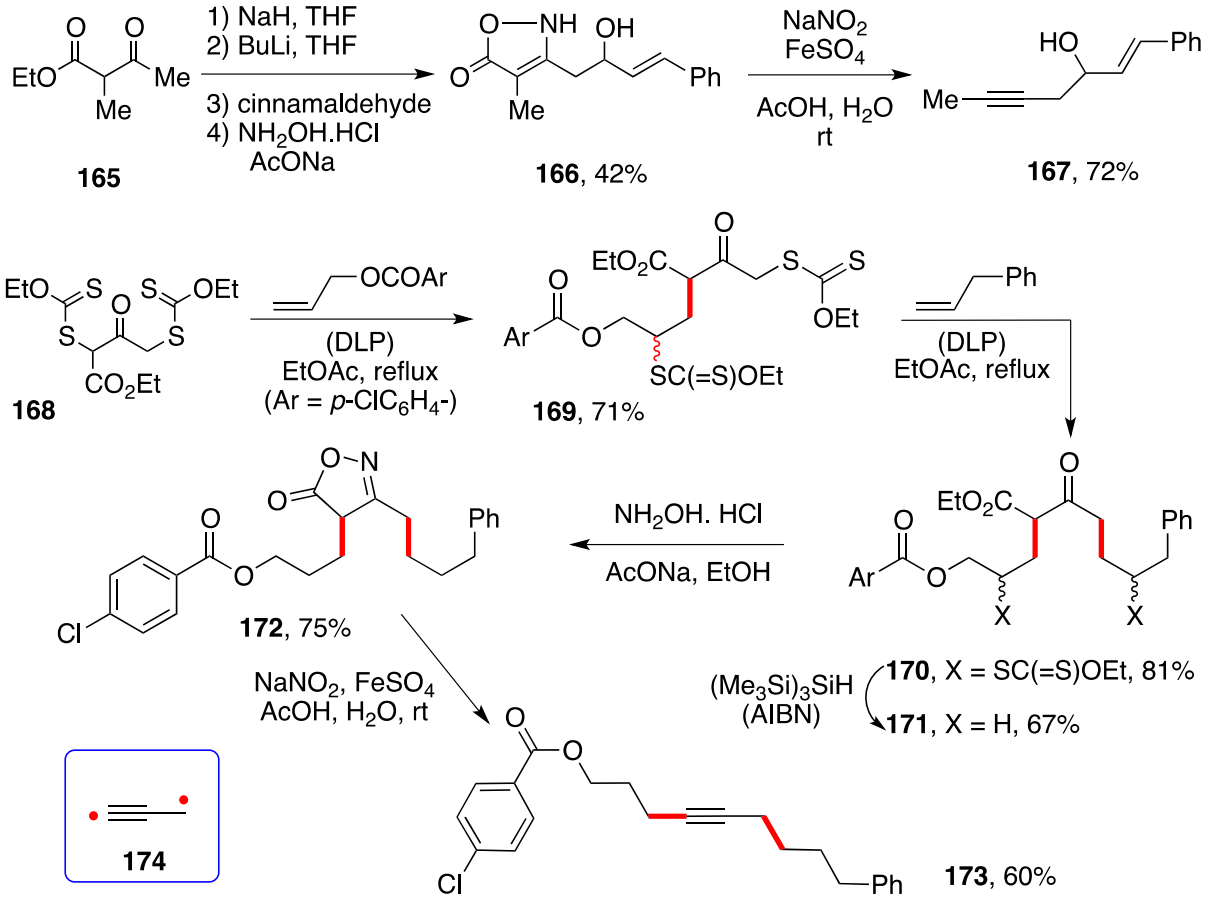


Scheme 16. Examples of alkynes.

As stated above, oxazolidinones **148** with R' = H are not suitable for the synthesis of terminal alkynes because the corresponding *C*-nitroso intermediate **150** rapidly isomerizes into oxime **153**. It is however

possible to prepare terminal chloroalkynes such as **164** by starting with 4-chloro-oxazolidinone precursor **163**.[48] Chloroalkynes can be reduced to the parent terminal alkynes or used in a number of transition metal catalyzed transformations. The β-ketoesters used to prepare oxazolidinones **158**, **160**, and **162** were all three obtained using the xanthate radical addition briefly described above, applied twice for the first two.[47,48] The carbon-carbon bonds created through this procedure are colored in red. A further example of this alliance is outlined in Scheme 17.

This transformation connects β-ketoesters with alkynes. Any method that furnishes β-ketoesters can be used in principle to obtain the corresponding alkynes via the intermediate isoxazolinone. For instance, the generation and capture of the dianions of β-ketoesters, and especially acetoacetates, is a powerful, well-established synthetic tool.[49] Thus, the dianion of ethyl 2-methyl-acetoacetate **165** reacts with cinnamaldehyde at the least acidic terminus and condensation with hydroxylamine provides isoxazolinone **166**. Nitrosative cleavage then furnishes the expected corresponding alkyne **167**.[50]

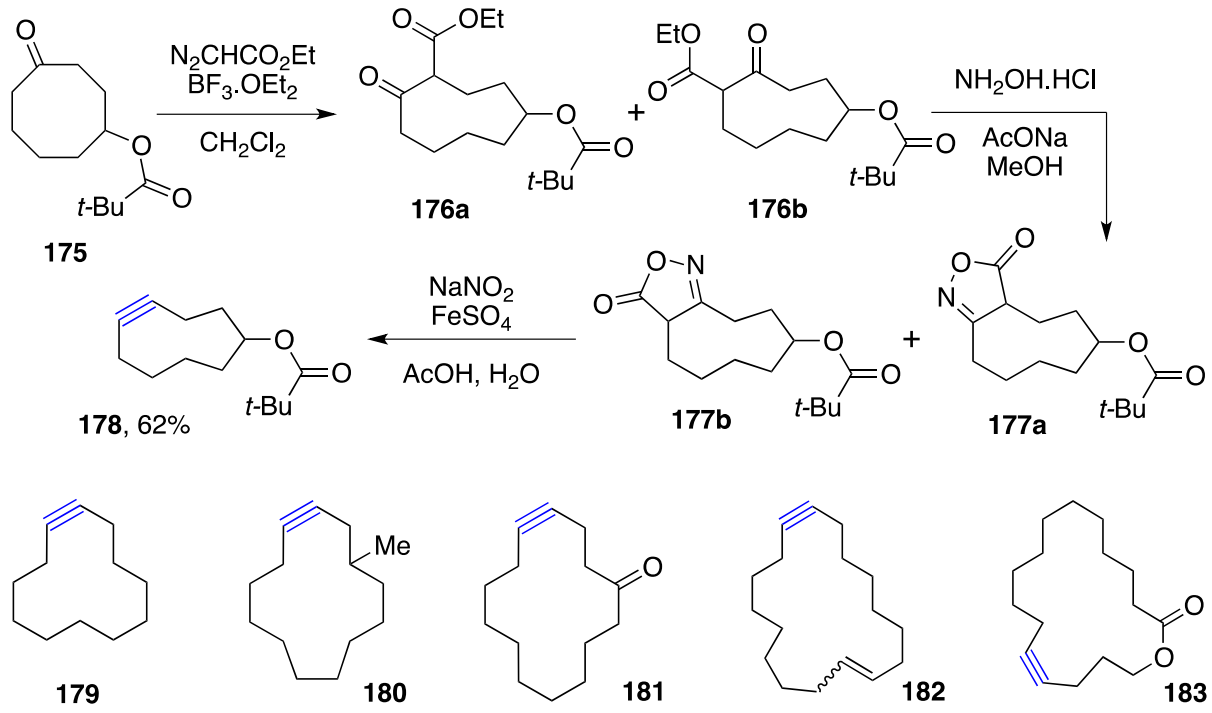


Scheme 17. Further examples of alkynes.

An alternative approach to produce more complex β-ketoesters starts with di-xanthate **168**.[51] This substance undergoes regioselective radical addition to allyl *p*-chlorobenzoate to give adduct **169**. The high regioselectivity is the result of the greater radical stabilization of the radical in-between the ester and the ketone. Again, the difference in radical stabilities allows a second regioselective radical addition of adduct **169** to allylbenzene to produce compound **170**, from which both xanthate groups can be reduced off with tris(trimethylsilyl)silane. Condensation of the resulting ketoester **171** with hydroxylamine and nitrosative cleavage affords alkyne **173**. Numerous other alkene partners could in principle be used in this sequence to

provide a broad variety of alkynes. In a sense, di-xanthate **168** is the synthetic equivalent of hypothetical diradical **174**.

A further important route to β-ketoesters consists in the Lewis acid promoted reaction of ketones with diazoacetates.[52] In the case of 4-pivaloxy-cyclooctanone **175**, this leads to two regioisomeric ketoesters **176a** and **176b** containing one extra carbon in the ring (Scheme 18).[53] Interestingly, the corresponding isoxazolinones **177a** and **177b** produce *the same alkyne* **178** upon nitrosative cleavage. Overall, this transformation can be viewed as the insertion of a two-carbon acetylene motif in place of the ketone, with a corresponding increase in the size of the ring by one carbon atom. An analogous sequence was used to prepare cycloalkynes **179**-**183**. Indeed, the association of the ring expansion of cycloalkanones with diazoacetates with the nitrosative cleavage of the derived isoxazolinones represents a particularly convenient route to cycloalkynes. It tolerates a variety of substituents and does not suffer from the formation of the difficult to remove allene isomers often observed with methods relying on base-induced eliminations.

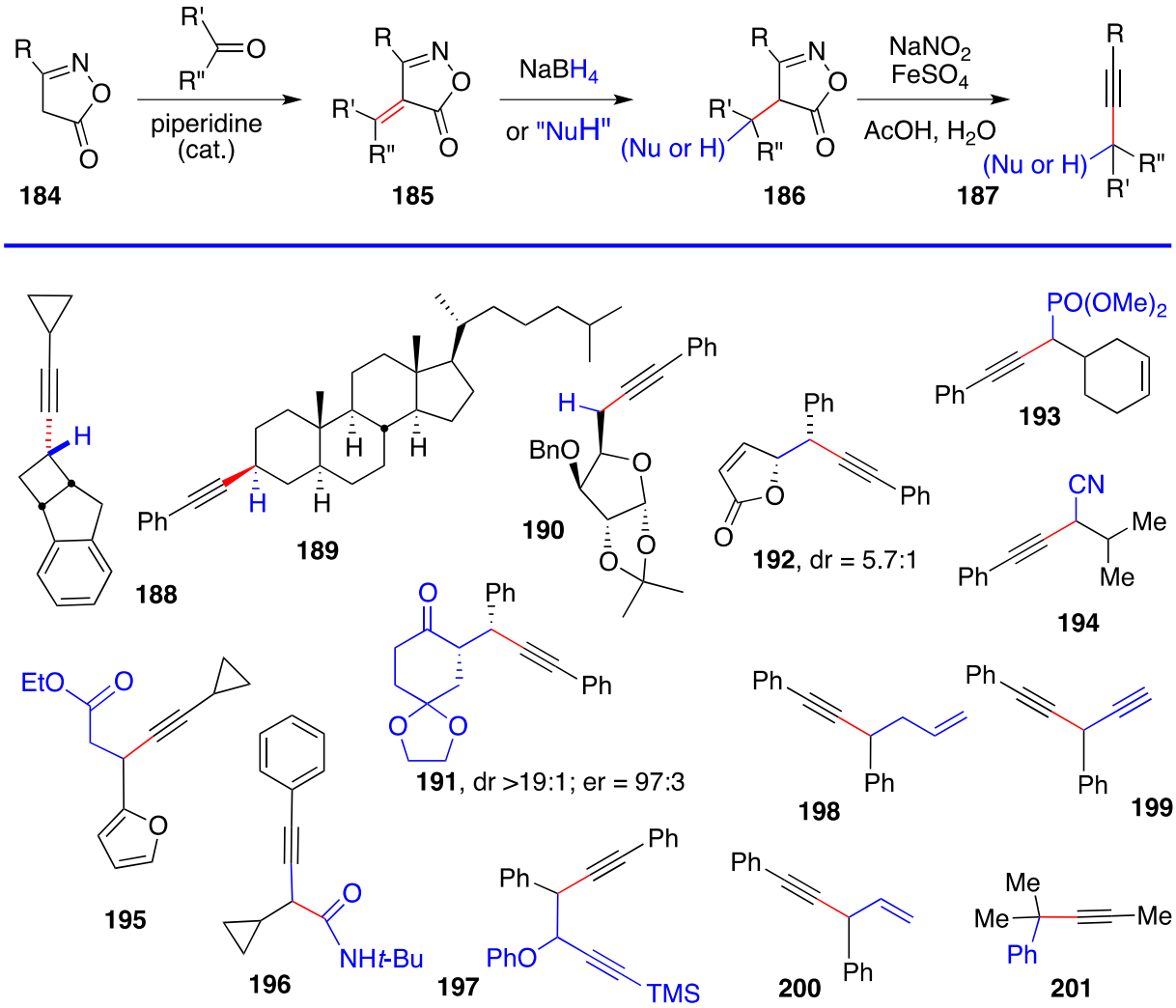


Scheme 18. Examples of cycloalkynes.

Finally, further alkyne diversity can be secured by exploiting the specific reactivity of the isoxazolinone moiety itself. For example, 4-unsubstituted isoxazolinones **184** participate readily in Knoevenagel-type condensations with aldehydes and ketones to give strongly electrophilic alkylidene derivatives **185**. These can be reduced with borohydride or subjected to conjugate additions by numerous nucleophiles (Scheme 19),[54-58] leading to functional isoxazolinones **186** and then to alkynes **187**.

The examples assembled in Scheme 19 illustrate some of the possibilities. Alkynes **188**, **189**, and **190** were obtained through reduction of the 4-alkylidene isoxazolidinone precursors with sodium borohydride.[54] In the first two, the hydride attacks stereoselectively from the least hindered face of the molecules. Alkynes **191** and **192**, both reported by Jurberg and co-workers,[55,56] were derived by a chiral amine mediated addition of monoprotected 1,4-cyclohexanedione, for the first, and a Lewis acid catalyzed Mukaiyama-type addition of an enol silyl ether, for the second. The high levels of diastereo- and enantio-selectivities in the case of alkyne **191**

are impressive. In examples **193** and **194**, the nucleophiles are dimethyl phosphite and hydrogen cyanide,[54] respectively, whereas for alkynes **195** and **196**, a Reformatsky reagent[57] and *t*-butyl isocyanide[58] were used as the nucleophilic partners. Alkynes **197**, **198**, **199**, and **200** all arise from reaction of the same 4-benzylidene isoxazolinone with an allenylzinc derivative for the first and with three different Grignard reagents for the others.[57] Alkyne **197** was obtained as one diastereoisomer, but its configuration was not determined.[57] The last example, **201**, results from the conjugate addition of phenylcopper to 3-methyl-4-isopropylidene-isoxazolidinone.[57]



Scheme 19. Alkynes from further modifications of isoxazolinones.

Conclusions

Working with oximes over the years has been a constant source of wonder and pleasant surprises. That a moiety as small as an oxime could have such a rich and varied chemistry is indeed something to behold. Our adventures in this area have been a mix of conceptions and serendipitous observations. They have nevertheless resulted in a number of synthetically useful findings. Perhaps the most general and enduring in the long run are the reduction to unsubstituted imines, the various methods for the generation of iminyls and

their extension to other nitrogen centered radicals, and, finally, the powerful synthesis of alkynes, which provides a concise access to numerous structures not readily available by other routes. Hopefully, the present brief account will inspire younger chemists to carry the torch and expand further the chemistry of this remarkable functional group.

Acknowledgements

No chemistry laboratory can function without dedicated and talented younger colleagues. I therefore wish to express my heartfelt thanks to my students and post-doctoral collaborators for making this chemistry possible. I also wish to record my sincere gratitude to my long-time associate, Dr Béatrice Sire, who has now retired and who, over a period of 25 years, contributed so much and so decisively to many of our research projects. Last, but not least, I wish to thank all the institutions, agencies, and industries that have funded us over the years.

References

1. Batth, R.; Nicolle, C.; Cuciurean, I. S.; Simonsen, H. T. *Plants* **2020**, *9*, 1144. https://doi.org/10.3390/plants9091144
2. Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1242-1244. https://doi.org/10.1039/P19750001242
3. Boar, R. B.; Jetuah, F. K.; McGhie, J. F.; Robinson, M. S.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2163-2165. https://doi.org/10.1039/p19770002163
4. Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1981**, 774-775. https://doi.org/10.1039/c39810000774
5. Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Nouv. J. Chim.* **1982**, *6*, 295-300.
6. Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. I* **1985**, 2191-2192. https://doi.org/10.1039/p19850002191
7. Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1982**, 551-552. https://doi.org/10.1039/c39820000551
8. Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Bull. Soc. Chim. Fr. (II)* **1983**, 61-65.
9. Zard, S. Z. *Helv. Chim. Acta* **2012**, *95*, 1730-1757. https://doi.org/10.1002/hlca.201200324
10. Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1984**, 337-338. https://doi.org/10.1039/c39840000337
11. Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. I* **1986**, 2243-2252. https://doi.org/10.1039/p19860002243
12. Burés, J.; Vilarrasa, J. *Tetrahedron Lett.* **2008**, *49,* 441-444. https://doi.org/10.1016/j.tetlet.2007.11.110
13. Esteban, J.; Costa, A. M.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.*, **2004**, 45, 5563-5567. https://doi.org/10.1016/j.tetlet.2004.06.002
14. Burés, J.; Isart, C.; Vilarrasa, J. *Org. Lett.* **2007**, *9*, 4635-4638. https://doi.org/10.1021/ol702212n

15. Lamy, E.; Lüthi, P.; Paturel, C.; Winkler, T.; Jung, P. M. J. *Tetrahedron Lett.* **2006**, *47*, 5657-5660. https://doi.org/10.1016/j.tetlet.2006.06.019
16. Lukin, K. A.; Narayanan, B. A. *Tetrahedron* **2002**, *58*, 215-219. https://doi.org/10.1016/S0040-4020(01)01154-1
17. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron **1994**, 50, 1757-1768*. https://doi.org/10.1016/S0040-4020(01)80850-4
18. Boivin, J.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron Lett. **1992**, 33, 7849-7852*. https://doi.org/10.1016/S0040-4039(00)74760-5
19. Boivin, J.; Schiano, A.-M.; Zard, S. Z.; Zhang, H. *Tetrahedron Lett.* **1999**, *40*, 4531-4534. https://doi.org/10.1016/S0040-4039(99)00720-0
20. Bingham, M.; Moutrille, C.; Zard, S. Z. *Heterocycles* **2014**, *88*, 953-960. https://doi.org/10.3987/COM-13-S(S)94
21. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. I* **1975**,1574- 1585. https://doi.org/10.1039/p19750001574
22. Khoo, L. E.; Lee, H. H. *Tetrahedron Lett*. **1964**, *8*, 4351-4354.
23. Boivin, J.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 249-252. https://doi.org/10.1016/S0040-4039(00)76523-3
24. Callier, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 6109-6112. https://doi.org/10.1016/0040-4039(94)88089-1
25. Gennet, D.; Zard, S. Z.; Zhang, H. *Chem. Commun.* **2003**, 1870-1871. https://doi.org/10.1039/b304545e
26. Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603-1618. https://doi.org/10.1039/b613443m
27. Gagosz, F.; Zard, S. Z. *Synlett* **1999**, 1978-1980. https://doi.org/10.1055/s-1999-2971
28. Quiclet-Sire, B.; Zard, S. Z. *Pure & Appl. Chem.* **2011**, *83*, 519-551. https://doi.org/10.1351/PAC-CON-10-08-07
29. Quiclet-Sire, B.; Zard, S. Z. *Isr. J. Chem.* **2017**, *57*, 202-217. https://doi.org/10.1002/ijch.201600094
30. Zard, S. Z.*Helv. Chim. Acta* **2019**, *102*, e1900134. https://doi.org/10.1002/hlca.201900134
31. Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2023**, *21*, 910-924. https://doi.org/10.1039/D2OB02159E
32. Zard, S. Z. *Chimia*, **2020**, *74*, 9-17. https://doi.org/10.2533/chimia.2020.9
33. Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2013**, *15*, 5886-5889. https://doi.org/10.1021/ol402973q
34. Quiclet-Sire, B.; Tölle, N.; Zafar, S. N.; Zard, S. Z. *Org. Lett.* **2011**, *13*, 3266-3269. https://doi.org/10.1021/ol2012204
35. Abidi, S. L. *J. Chem. Soc. Chem. Comm.* **1985**, 1222-1223. https://doi.org/10.1039/c39850001222
36. Abidi, S. L. *Tetrahedron Lett.* **1986**, *27*, 267-270. https://doi.org/10.1016/S0040-4039(00)83993-3
37. Abidi, S. L. *J. Org. Chem.* **1986**, *51*, 2687-2694.

https://doi.org/10.1021/jo00364a013
38. Corey, E. J.; Seibel, W. L.; Kappos, J. C. *Tetrahedron Lett.* **1987**, *28*, 4921-4924. https://doi.org/10.1016/S0040-4039(00)96659-0
39. Boivin, J.; Pillot, E.; Roger, W.; Williams, A.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 3333-3336. https://doi.org/10.1016/0040-4039(95)00522-E
40. Zard, S. Z. *Chem. Commun.* **2002**, 1555-1563. https://doi.org/10.1039/b203383f
41. Claisen, L.; Manasse, O. *Chem. Ber.* **1889**, *22*, 526-530. https://doi.org/10.1002/cber.188902201119
42. Freeman, J. P. *Chem. Rev.* **1973**, *73*, 283-292. https://doi.org/10.1021/cr60284a001
43. Boivin, J.; Elkaim, L.; Ferro, P. G.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 5321-5324. https://doi.org/10.1016/S0040-4039(00)92375-X
44. Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925-3927. Sadly, Professor Keith U. Ingold, who suggested the explanation to the late Prof. Hanns Fischer, passed away on September 8th, 2023, when the present manuscript was being completed. https://doi.org/10.1021/ja00274a012
45. Leifert, D.; Studer, A. *Angew. Chem. Int. Ed.* **2020**, *59*, 74-108. https://doi.org/10.1002/anie.201903726
46. Tavakoli, A.; Dudley, G. B. *J. Org. Chem.* **2022**, *87*, 5773−5784. https://doi.org/10.1021/acs.joc.2c00110
47. Boutillier, P.; Zard, S. Z. *Chem. Commun.* **2001**, 1304-1305. https://doi.org/10.1039/b101751i
48. Huppé, S.; Rezaei, H.; Zard, S. Z. *Chem. Commun.* **2001**, 1894-1895. https://doi.org/10.1039/b106657a
49. Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065-1114. https://doi.org/10.1021/cr00036a007
50. Huppé, S. PhD thesis, University of Paris XI, Orsay, 1997.
51. Anthore-Dalion, L.; Liu, Q.; Zard, S. Z. *J. Am. Chem. Soc.* **2016**, *138*, 8404-8407. https://doi.org/10.1021/jacs.6b05344
52. Wovkulich, P. M. in *Comprehensive Organic Synthesis*, B. M. Trost, B. M. and I. Fleming, Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 843-861. https://doi.org/10.1016/B978-0-08-052349-1.00022-6
53. Boivin, J.; Huppé, S.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 5737-5740. https://doi.org/10.1016/00404-0399(50)11469-
54. Boivin, J.; Huppé, S.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 8735-8738. https://doi.org/10.1016/S0040-4039(96)02015-1
55. Jurberg, I. D. *Chem. Eur. J.* **2017**, *23*, 9716-9720. https://doi.org/10.1002/chem.201701433
56. Capreti, N. M. R.; Jurberg, I. D. *Org. Lett.* **2015**, *17*, 2490−2493. https://doi.org/10.1021/acs.orglett.5b01004
57. Renard, D.; Rezaei, H.; Zard, S. Z. *Synlett* **2002**, 1257-1260. https://doi.org/10.1055/s-2002-32956
58. Dias-Jurberg, I.; Gagosz, F.; Zard, S. Z. *Org. Lett.* **2010**, *12*, 416-419.

https://doi.org/10.1021/ol902472r

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Samir Z. Zard was born in 1955 in Ife, Nigeria. His training as a chemist started at the American University of Beirut, then at Imperial College, London, and finally at the Université Paris-Sud, Orsay, France, where he received his doctorate under the supervision of Professor Sir Derek Barton in 1983. His main research concerns the study and development of new reactions and processes, with a special interest in radicals, organosulfur derivatives, alkynes, and nitro compounds. In addition to a number of academic awards, he received in 2007 the Croix de Chevalier de la Légion d'Honneur. He is currently an emeritus professor at Ecole Polytechnique and an emeritus Director of Research Exceptional Class in the CNRS