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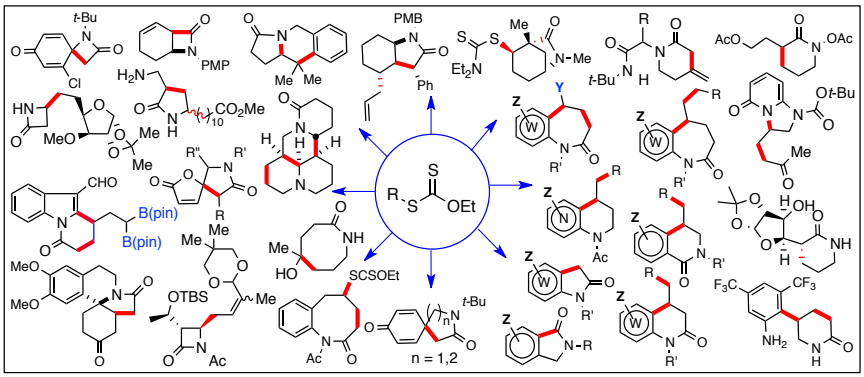
Graphical abstract



The Xanthate Route to Lactams†

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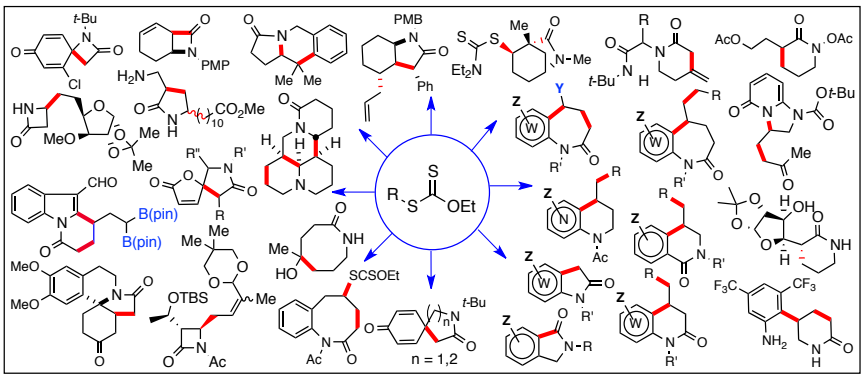
† This paper is affectionately dedicated to Professor Richard J. K. Taylor.

Graphical abstract



Abstract: Convergent routes to various classes of lactams exploiting the unique radical chemistry of xanthates are described. Emphasis is placed on reactions leading to lactams by direct radical cyclization, by intermolecular additions to alkenes followed by ring closure, and by radical additions to alkenes furnishing amino esters and aminoacids precursors that can be converted into lactams by ionic condensations. The possibility of modifying existing lactam structures is briefly discussed. Four-, five-, six-, seven- and, more rarely, eight-membered lactams can be constructed, including five-, six-, seven-membered lactams fused to aromatic and heteroaromatic rings. The latter are exemplified by oxindoles, azaoxindoles, tetrahydroquinolones, tetrahydroisoquinolones tetrahydroazaquinolones, tetrahydrobenazepinones, and tetrahydropyridoazepinones.

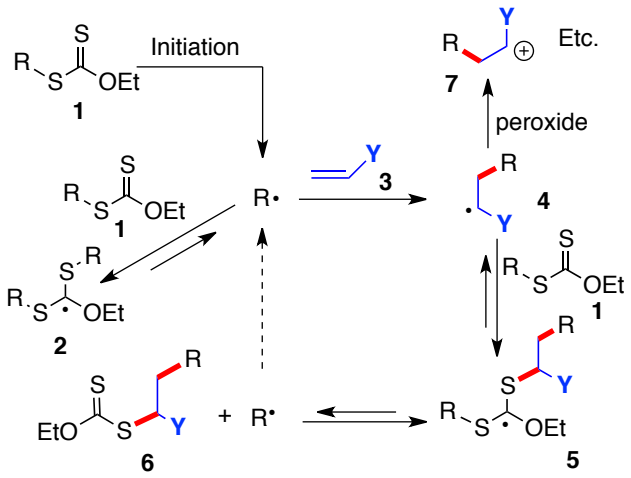
Keywords: xanthates; radical addition, lactams, pyridones; radical Smiles.

Introduction and Background

The lactam structural motif is widespread and appears in numerous natural products,[1] pharmaceuticals,[2] agrochemicals,[3] high-performance materials,[4] and in many synthetic intermediates.[5] Perhaps most notorious is the class of β-lactam antibiotics, represented chiefly by various generations of penicillins and cephalosporins.[6] These remarkable substances have saved countless millions of lives over the years and have decisively contributed to the dramatic increase in life expectancy that took place all over the planet shortly after the Second World War.[7] It is therefore of little surprise that much research effort has been devoted to the design of reactions and strategies for the synthesis and modification of lactams. The field is too vast to summarize adequately; suffice it to say that the majority of these approaches rely broadly on a few reasonably general reactions. These include intramolecular condensations of the appropriate open chain amino acids or ester precursors;[8] ring-closing metathesis (RCM) of appropriately substituted amides;[9] lactam ring formation by cycloadditions or by radical cyclizations;[10] and Schmidt and Beckmann rearrangements starting with cyclic ketones and cyclic ketoximes, respectively.[11] Modification of existing lactams is another generally applicable pathway for expanding structural diversity.[12] In the present review, the application of the unique radical chemistry of xanthates and related dithiocarbonyl derivatives, such as dithiocarbamates, to the synthesis of four-, five-, six-, seven- and even, but more rarely, eight-membered lactams is described. This technology complements traditional methods and provides a broad diversity of structures not readily accessible otherwise. However, before proceeding with the synthetic aspects, it is necessary to outline briefly the general features of the degenerative addition-transfer of xanthates, depicted in a simplified form in Scheme 1.

The reaction of xanthates **1** with alkenes **3** to give adducts **6** is a radical chain process induced by an initiator, usually a peroxide.[13] The success of this transformation derives from the special capacity of xanthates (and related dithiocarbonyl congeners) to ***store*** *active radicals*, such as R• and **4**, in the form of *rather unreactive* adducts such as **2** and **5**. These bulky radical species are stabilized by three heteroatoms. They cannot disproportionate because they bear no β-hydrogens, and their steric bulk slows down considerably their coupling to other radicals. They therefore evolve chiefly by β-scission and thereby release radicals R• and **4** back into the medium. These radicals are thus continuously regenerated and their *effective lifetime* is considerably enhanced, even in a concentrated medium. At the same time, because they are reversibly stored as adducts **2** and **5**, their *absolute concentration* is significantly lowered while their *relative concentration* is regulated through the fast equilibrium proceeding via intermediate **5** in a manner that reflects their *relative thermodynamic stabilities*. Regarding this last point, it is normally necessary to bias this equilibrium so as to favor **R•** over radical **4** and therefore drive the desired process towards product **6** and limit at the same time the formation of oligomers by further addition of radical

4 to alkene **3**. This simplified requirement, whereby the starting **R•** has to be thermodynamically more stable than adduct radical **4**, neglects possible polar effects which could be important in certain instances. Indeed, the mechanistic picture is actually highly subtle and more complex than is conveyed by the manifold in Scheme 1. The interested reader is directed to reference 14 for a more comprehensive discussion.[14]



Scheme 1. Addition of a xanthate to an alkene

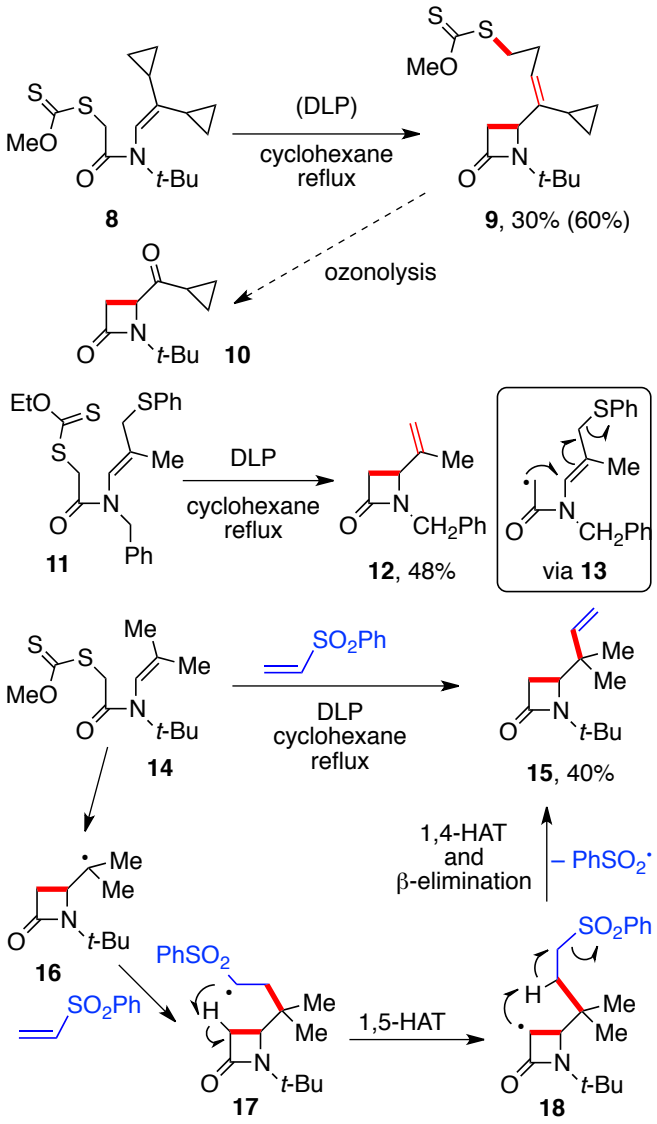
The increased lifetime and lower absolute concentration of active radicals **R•** and **4**, as well as their controlled relative concentration, translate into numerous synthetic opportunities not readily available through alternative radical processes. Radical transformations that proceed with relatively slow kinetics now become feasible. In particular, intermolecular additions to electronically unbiased alkenes, unusual cyclizations leading for example to four- and seven-membered rings, and ring-closures onto aromatic and heteroaromatic nuclei, can thus be accomplished using xanthates. The last transformation additionally exploits the ability of the peroxide to oxidize radical **4** into the corresponding cation **7** when substituent **Y** is electron-releasing. This single electron transfer (SET) crossover from the radical to the cation opens a pathway for restoring the aromaticity of the (hetero)aromatic ring following the cyclization step. From the standpoint of lactam synthesis, these unique features can be harnessed in various ways to construct lactams of almost any size. The present brief overview showcases, in sequence, applications to the synthesis of four-, five-, six-, seven- and eight-membered lactams.

Synthesis and Modification of β-Lactams

The direct synthesis of the β-lactam motif by 4-*exo* radical cyclizations is complicated by two factors, namely the relatively sluggish cyclization step and its potential reversibility.[15] The first hurdle can be overcome because of the increased lifetime imparted to radicals by the ability of xanthates to provide a reversible storage mechanism, as discussed above. As for the

complication arising from the possible reversibility, it can be circumvented by associating the cyclization step with a fast, essentially irreversible step, thus pulling the process in the desired forward direction. The first example in Scheme 2 combines the cyclization with the opening of a cyclopropane.[16] Exposure of enamide xanthate **8** to the action of sub-stoichiometric amounts of di-lauroyl peroxide (or DLP; also known as lauroyl peroxide, Laurox® or Luperox LP®) gives rise to β-lactam **9** in modest yield (throughout this review yields in parenthesis correspond to yields based on recovered starting material). The steric compression exerted by the bulky *t*-butyl group on the nitrogen further favors the process by speeding up the cyclization step. Ozonolysis of the alkene generated in the process would give the synthetically more interesting ketone **10**.

An alternative approach is to associate the cyclization with a fragmentation step. In the conversion of xanthate **11** into β-lactam **12**, the ring-closure of intermediate radical **13** is followed by the concomitant expulsion of a phenylthiyl radical.[16] In this transformation, a stoichiometric amount of DLP is required, since the phenylthiyl radical cannot propagate the chain. Throughout this review, placement of the DLP inside parentheses means that that the peroxide is used as an initiator in sub-stoichiometric amounts (as in the synthesis of β-lactam **12**). The absence of parentheses means that the DLP is used in stoichiometric amounts.

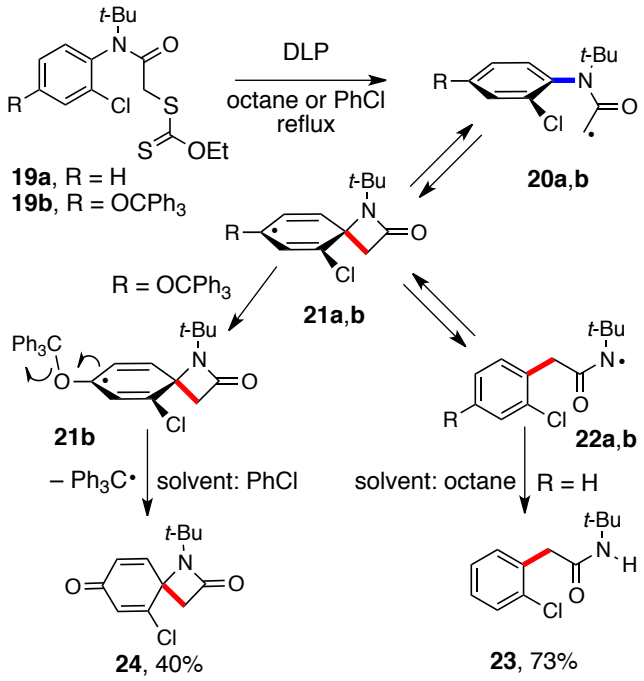


Scheme 2. Radical 4-exo cyclizations to β-lactams

A third route is to capture the cyclized radical selectively by an external olefin of matching polarity. The following example not only illustrates this strategy but also features interesting radical translocations.[16] Thus, ring-closure of xanthate **14** furnishes ultimately vinyl β-lactam **15** by rapid capture of electron-rich tertiary radical **16** with electrophilic phenyl vinyl sulfone to give first adduct **17**. This step is followed by two successive intramolecular hydrogen atom transfers (HAT), including a rare 1,4-radical translocation from intermediate radical **18**, resulting in the final expulsion of a phenylsulfonyl radical.[17]

A very unusual synthesis of a β-lactam is depicted in Scheme 3 involving the first recorded instance of a 4-*exo ipso*-cyclization on an aromatic ring.[18] It was accidentally found that xanthate **19a**, upon exposure to DLP in refluxing octane, gave rise to amide **23** in good yield.

The most reasonable reaction pathway appears to be through intermediate β-lactam **21a**, produced by cyclization of radical **20a**, and fragmentation to give amidyl radical **22a** and finally amide **23** by hydrogen atom abstraction from the solvent. The reversible cyclization step is favored by steric compression by the *t*-butyl group and by a favorable conformation due to restricted rotation around the carbon-nitrogen bond highlighted in blue in **20**.

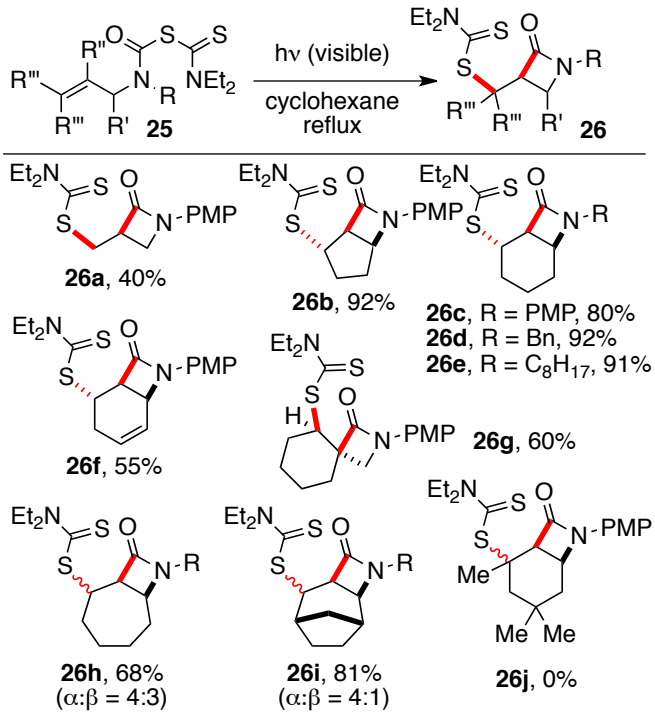


Scheme 3. Synthesis of a spiro-β-lactam

Evidence for the unprecedented 4-*exo* ring closure was adduced by starting with xanthate **19b** and using the more inert chlorobenzene as the solvent. In this case the corresponding cyclized radical **21b** can follow a different, more facile pathway, namely expulsion of a stabilized triphenylmethyl radical. This drives the equilibrium irreversibly towards the formation of the unique spirocyclic β-lactam **24**. This remarkable reaction deserves further study to delineate its scope and explore the chemistry of the unusual products, especially the photochemistry of the cross-conjugated cyclohexadienone moiety.

A different mode of 4-*exo* ring-closure leading to β-lactams is by cyclization of carbamoyl radicals. This is exemplified by the transformations in Scheme 4 reported by Grainger and co-workers.[19] They are best accomplished by using *S*-acyl dithiocarbamates **25** instead of the corresponding xanthates. In the general mechanism displayed in Scheme 1, the OEt group is just a spectator and can be replaced by other substituents based on sulfur, nitrogen, or carbon. Thus, trithiocarbonates, dithiocarbamates, and dithiocarboxylates all undergo the same general process of radical addition to alkenes. By an appropriate choice of the substituents, it is possible to fine-tune the rate of the various elementary steps and adapt the precursors to best solve the synthetic problem at hand. Indeed, the broad versatility of the reversible

addition-transfer constitutes the basis of what is now known as the RAFT/MADIX technology.[20] This technology allows the controlled polymerization of essentially every commercial monomer and the construction of block copolymers of almost every imaginable architecture. The importance of this breakthrough in polymer science is reflected in over 10000 articles published and 1000 patents filed since the appearance of the master patents in 1998.[21]

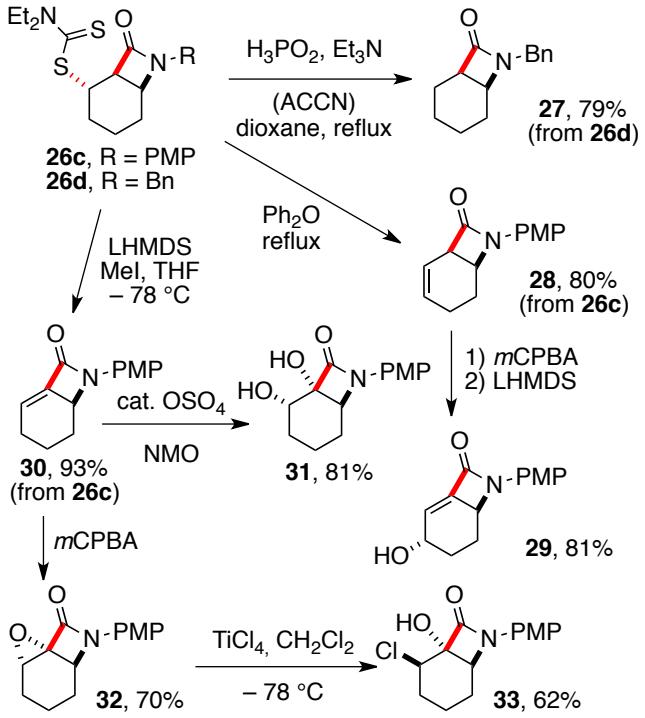


Scheme 4. β-Lactams by cyclization of carbamyl radicals (PMP = *p*-methoxyphenyl)

In the case of dithiocarbamates, it is important to increase the reactivity of the thiocarbonyl by placing an electron-withdrawing moiety on the nitrogen (even just a phenyl group) or an acyl group on the sulfur.[20] Furthermore, *S*-acyl dithiocarbonyl derivatives, such as *S*-acyl xanthates and *S*-acyl dithiocarbamates, are yellow in color and the radical chain process can be conveniently triggered by irradiation with visible light.[22] The examples collected in scheme 4 illustrate the synthesis of various β-lactams **26a-j**, including bicyclic and spirocyclic derivatives, starting from *S*-acyl dithiocarbamates **25** derived from the appropriate allylic amines.[19] In this remarkable approach, there is no need for associating the cyclization with another irreversible fast step to drive the process forward. The sluggishness of the exchange of the S-*alkyl* dithiocarbamate group in the product, as compared to the more reactive *S-acyl* dithiocarbamate of the starting material, make the whole process essentially irreversible and protects the formed β-lactam ring.

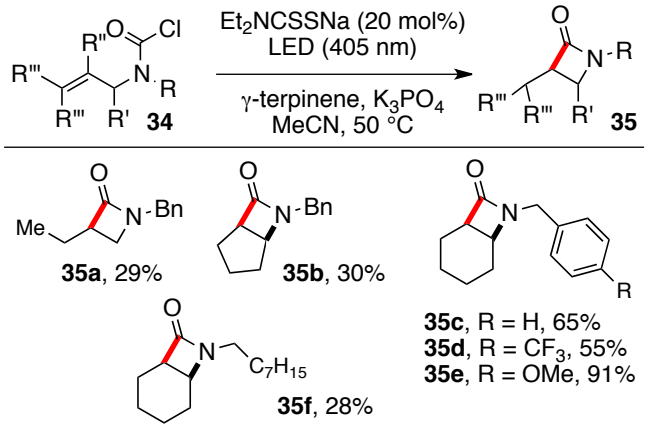
The dithiocarbamate group in the product can be reductively removed using tri-*n*-butyl stannane or Barton's hypophosphorus salts,[23] as illustrated by the synthesis of compound **27**

(Scheme 5).[19] Another, more constructive way to modify the primary cyclized products is by thermolysis, as shown by the conversion of **26c** into alkene **28**.[19b] This retro-ene, Chugaev-like elimination requires much higher temperatures than typical Chugaev reactions involving xanthates (bp of Ph_2O is 265 °C), but proceeds nevertheless in good yield. Epoxidation of alkene **28** and exposure to base furnishes allylic alcohol **29**.[19b]The dithiocarbamate in β-lactams **26** is in the β-position with respect to the carbonyl group and is readily eliminated by treatment with base and methyl iodide to give the regioisomeric alkene. This variant is exemplified by the generation of alkene **30** from adduct **26c**.[19b] The addition of methyl iodide is to scavenge irreversibly the eliminated dithiocarbamate salt. The electrophilic alkene can act as a stepping stone to more complex β-lactam derivatives. For instance, dihydroxylation leads to diol **31** and epoxidation to epoxide **32**. The latter can be further transformed into chlorohydrin **33** by the action of $TiCl_4$.[19b]



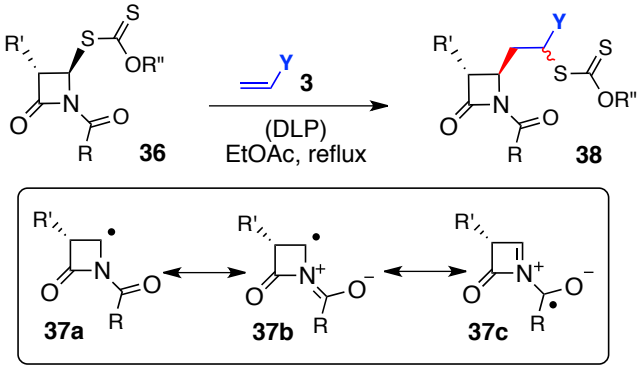
Scheme 5. Post-modifications of carbamyl radicals derived β-lactams

Melchiorre and collaborators devised experimental conditions allowing the simultaneous *in situ* generation of *S*-acyl dithiocarbamates from the carbamoyl chloride precursors **34** using catalytic amounts of dithiocarbamate salt and concomitant reduction to produce β-lactams **35** (Scheme 6).[24a] Irradiation was accomplished with blue LEDs and γ-terpinene acted as the hydrogen atom transfer agent to reduce the cyclized radical. The addition of excess potassium phosphate serves to regenerate the dithiocarbamate salt. The yields are in some cases modest due to competing premature reduction of the intermediate carbamoyl radical.



Scheme 6. β-Lactams by reductive cyclization of carbamyl radicals

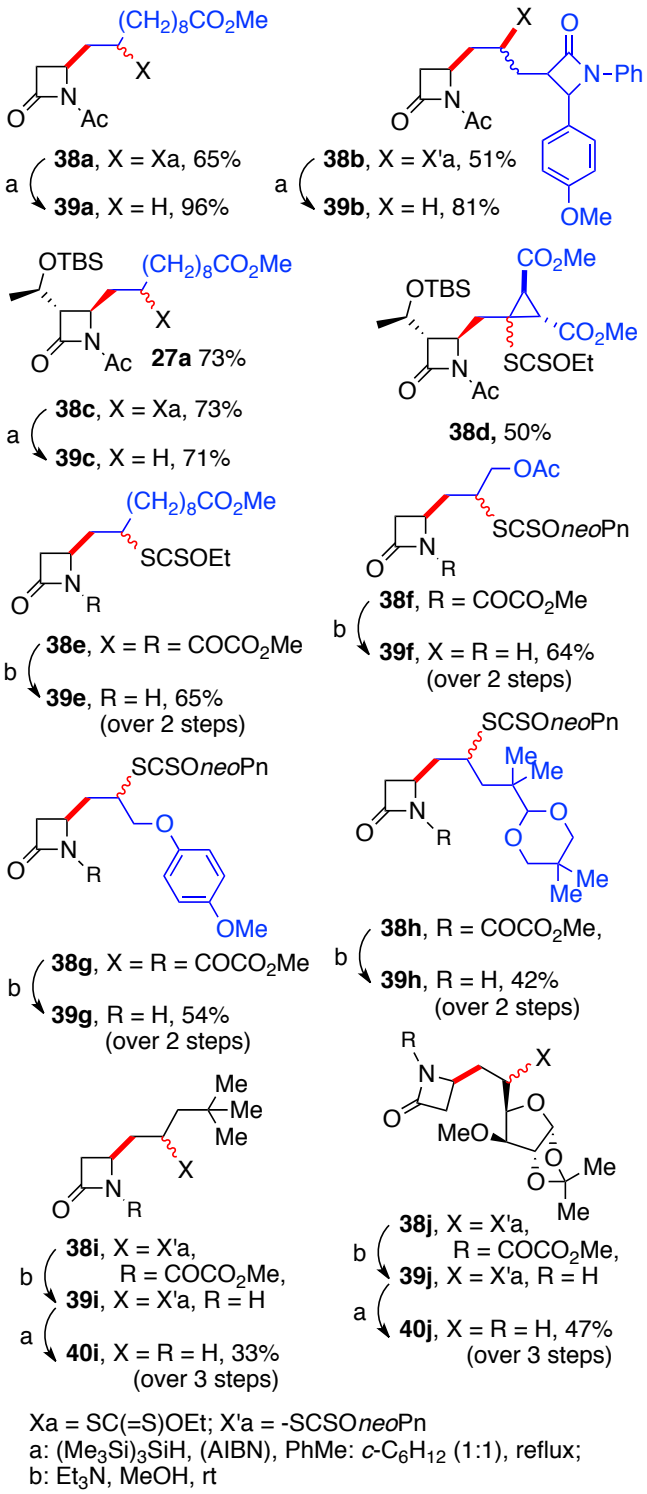
The metal-free radical chemistry of xanthates allows modification of existing β-lactam rings through the generation of radicals stabilized by an adjacent imide motif.[25] This strategy is outlined in Scheme 7.[26] In the addition of xanthates **36** to alkene **3** leading to adduct **38**, the intermediate radical **37** has some allylic character (**37b** and **37c**) and thus acquires sufficient stability to conform to the requirement stated in the introduction, namely that the starting radical (**37** here) must be more stable than the adduct radical (not shown). Indeed, no clean additions are observed in the absence of the *N*-acetyl group.



Scheme 7. Modification of β-lactams

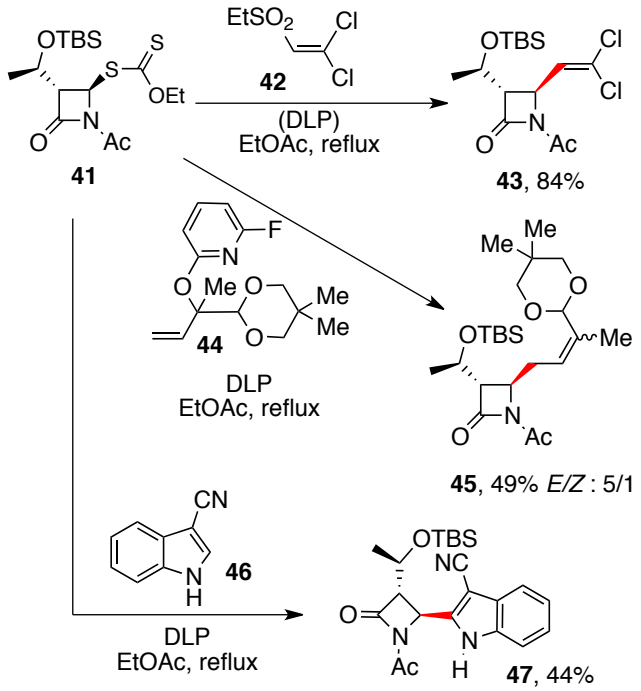
The examples pictured in Scheme 8 give an idea of the possibilities.[26] To simplify the structures, the xanthate groups in many cases were reductively removed using tris(trimethylsilyl)silane, a particularly mild reducing agent.[27] Examples **38b**, **38d** and **38j** are especially noteworthy, for such complex β-lactams would be quite tedious to obtain by other routes. Replacing the acetyl by an oxalyl group, as in adducts **38g-j**, opens access to *N*-

unsubstituted derivatives. The oxalyl group can be readily cleaved by simple exposure to a solution of triethylamine in methanol without harm to the fragile 4-membered ring.[28]



Scheme 8. Examples of β-lactam modification

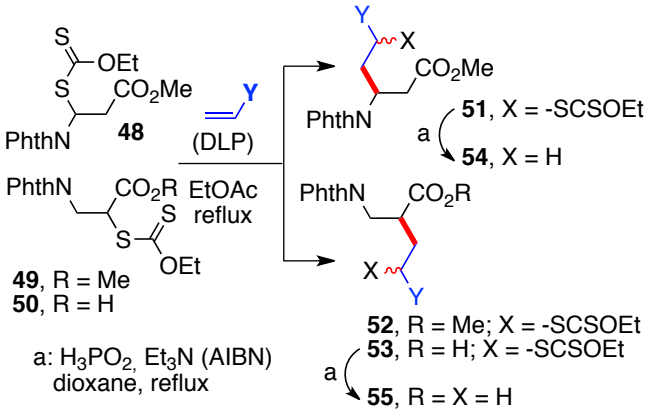
Further variations are depicted in Scheme 9.[26] Compound **43** derives from reaction of xanthate **41** with dichlorovinyl ethyl sulfone **42** through an addition-elimination process. An ethylsulfonyl radical is eliminated which extrudes sulfur dioxide to give a reactive ethyl radical that propagates the chain.[29] The formation of β-lactam **45** results from addition-elimination to alkene **44**. This time a fluoropyridoxyl radical is eliminated through the homolytic rupture of a carbon-oxygen bond.[26] This strategy for transforming allylic alcohols into radical allylating agents is remarkably versatile and powerful.[30] Finally, direct addition of xanthate **41** to 3-indolecarboxaldehyde **46** furnishes adduct **47** in reasonable yield. The last two transformations require stoichiometric amounts of peroxide. In the case of the indole, the peroxide oxidizes the intermediate radical to the corresponding cation and thus allows rearomatization to take place (see Scheme 25).



Scheme 9. Further examples of β-lactam modification

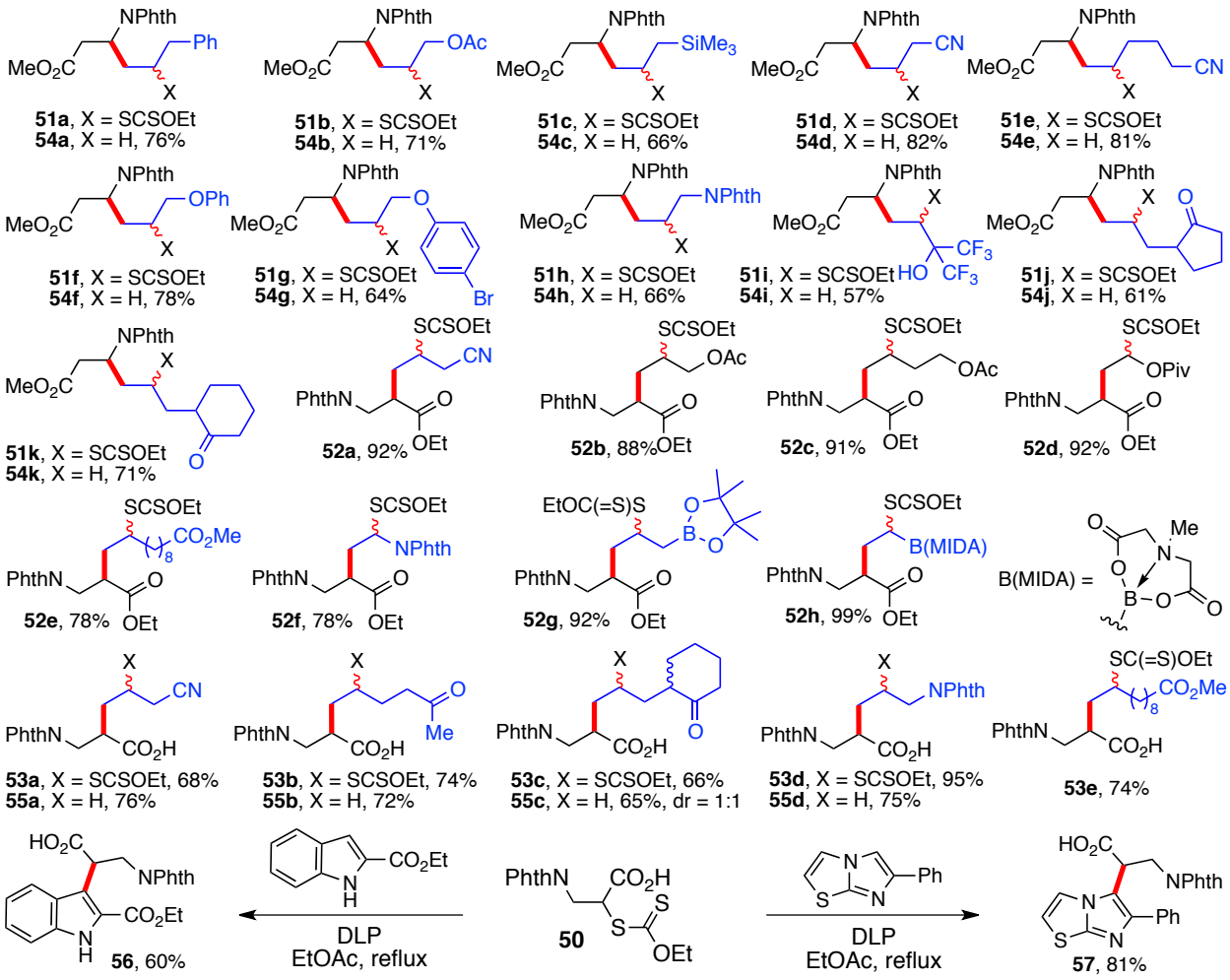
One of the traditional routes to β-lactams is by cyclo-condensation of β-aminoacids and, conversely, β-lactams can serve as convenient precursors to β-aminoacids.[12] The ability of xanthates to mediate intermolecular radical additions to both activated and unactivated alkenes can be easily harnessed to access protected β-aminoacids decorated with a broad variety of substituents. Both β^2- and β^3-aminoacids, according to the nomenclature introduced by Seebach,[31] can be obtained starting with xanthates **48**-**50** (Scheme 10).[32] Note that in the case of **48**, the corresponding radical is adjacent to the phthalimide group and has a partial allylic character, in the same manner as for the *N*-acetyl β-lactam radical **37** discussed above

(Scheme 7). In the majority of cases, the structures were simplified by reductively removing the xanthate group from adducts **51**-**53** using Barton's hypophosphorous salt method.



Scheme 10. Synthesis of protected β-amino acids

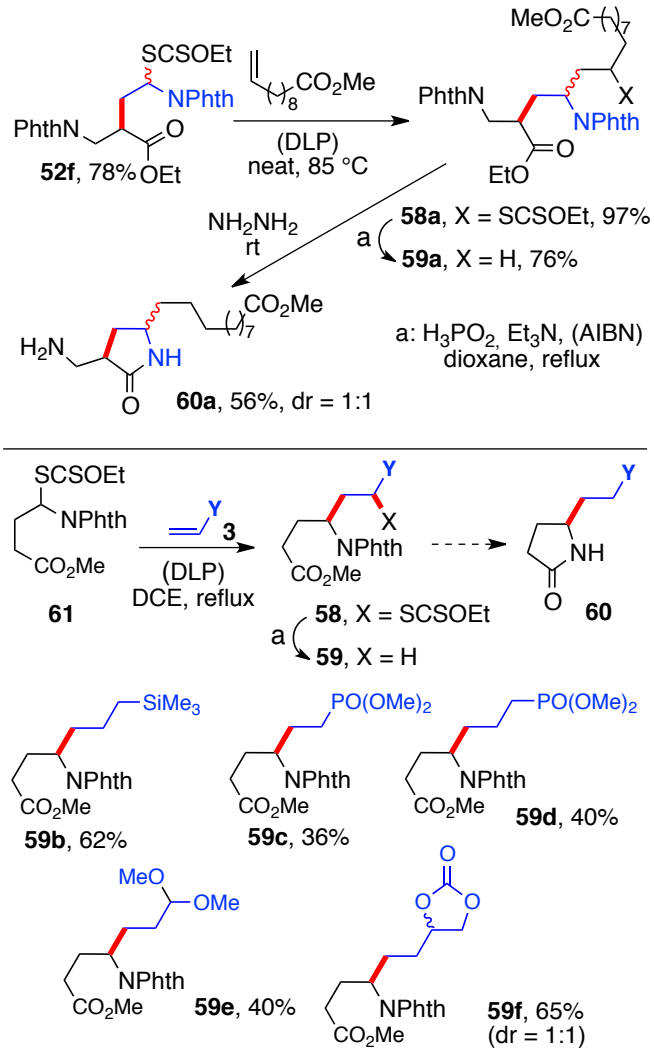
Numerous examples are pictured in Scheme 11. Compounds **51a-k** are protected β^3-aminoacids derived by addition of xanthate **48**.[32a]The yields given are for the combined addition and reduction steps. Adducts **52a-h** arise from xanthate **49** and correspond to protected β^2-aminoacids.[32b] Finally, *N*-protected β^2-aminoacids **53a-e** were prepared from xanthate **50**. *N*-Protected β^2-aminoacids **56** and **57** derive by direct addition of xanthate **50** to the corresponding heteroaromatic precursor.[32b] It is noteworthy that carbon-carbon bonds are readily created despite the presence of a free carboxylic acid. This tolerance for polar groups is one of the hallmarks of radical chemistry that is little appreciated by synthetic chemists trained mostly in ionic and organometallic chemistry.



Scheme 11. Synthesis of protected β-amino acids

Synthesis of γ-Lactams

The faster rate of ring-closure leading to five membered lactams as compared to β-lactams, as well as their greater thermodynamic stability translates into a broader range of methods for their synthesis. Protected γ-amino acid precursors are readily available by a variety of intermolecular radical additions of xanthates. Examples of this convergent strategy are presented in Scheme 12. For instance, xanthate **52f**, obtained as shown in the previous Scheme by addition of xanthate **48** to *N*-vinyl phthalimide, can in turn be made to react with an alkene such as methyl 10-unecylenate to give the corresponding adduct **58a**.[32b] Reductive dexanthylation and unmasking of both amines with hydrazine results in spontaneous ring-closure leading to γ-lactam **60a**. Precursor **59a** contains *two* protected amino groups but only one cyclization mode is observed upon liberation of the amines, reflecting as expected the more ready formation of a 5-membered as compared to a 4-membered ring.

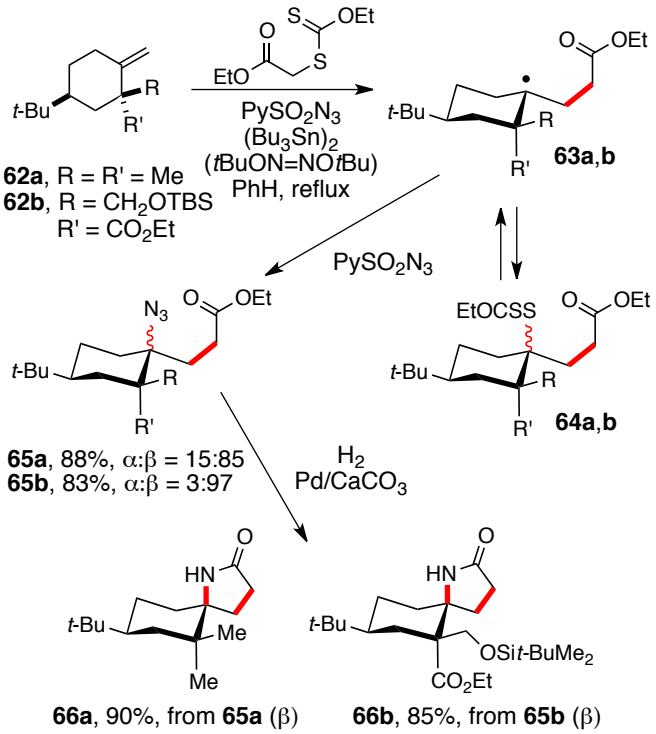


Scheme 12. Synthesis of functional γ-lactams

It is interesting to note that in the sequence from xanthate **48** to γ-lactam **60a**, two carbon-carbon bonds have been created by two successive intermolecular radical additions. This synthesis is a more elaborate version of the prototypical transformation starting with xanthate **61**. This reagent is easily available from glutamic acid and contains the elements necessary to build the basic γ-lactam motif.[33] Its addition to alkene **3** furnishes adduct **58** and protected amino ester **59** upon removal of the xanthate group. Cleavage of the phthalimide would result in closure to γ-lactams **60**. Precursors **59b-f** have been thus prepared but not converted into the corresponding γ-lactams; they give nonetheless an idea of the possibilities of this approach.

In most of the above transformations, the xanthate group was reductively removed for convenience to simplify the structures. The presence of this remarkable group in the initial adducts is in fact a formidable asset. While it can obviously be used for mediating another

radical based transformation, it constitutes an entry into essentially every other sulfur functionality: thiol, sulfide, disulfide, sulfoxide, sulfone, sulfonic acid, sulfonyl chloride, sulfonamide, sulfur ylid etc.;[34] it can be converted into a bromide,[35] an alcohol,[36] a ketone,[19c] or an azide[37] and so on. Its transformation into an azide was developed by Renaud and co-workers and exploited as a powerful, elegant route to γ-lactams (Scheme 13).[38]

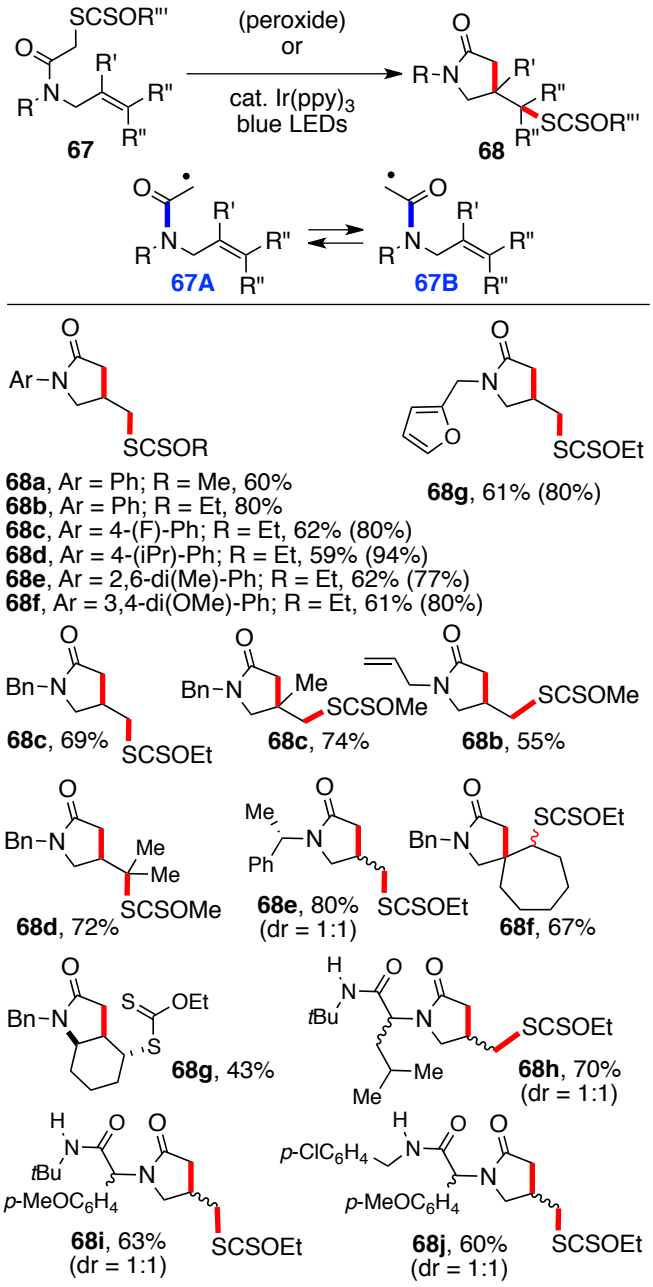


Scheme 13. Synthesis of γ-lactams via azide transfer

In an illustration of this variant, addition of ethyl α-xanthyl acetate was reacted with alkenes **62a,b** in the presence of pyridylsulfonyl azide to give compounds **65a,b**.[38] These arise by capture of intermediate radical **63a,b** by the sulfonyl azide in an addition-fragmentation process with elimination of a pyridylsulfonyl radical. The fact that the intermediate radicals **63a,b** are in equilibrium with xanthates **64a,b** is of no consequence. Indeed, the reversibility of the xanthate exchange is a tremendous advantage attached to this chemistry. Mild reduction of the azide group to the amine results in the spontaneous closure to lactams **66a,b**. This approach opens a route to countless γ-lactams since both the alkene and xanthate partners can be varied extensively.

A complementary, equally powerful approach to γ-lactams is by a 5-exo cyclization starting from xanthates of general structure **67** (Scheme 14).[39] γ-Lactams **68** with almost any substitution pattern can be constructed. Indeed, every carbon on structures **67** and **68** can be substituted but, for the sake of clarity, only partially substituted drawings are shown. Numerous examples are presented in Scheme 14 with further variations in the following

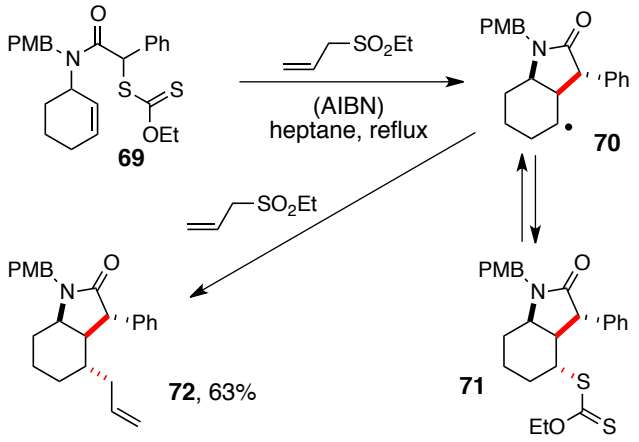
schemes. The precursors are trivial to make from allylic amines by substituting the halogen in the corresponding α-haloamides with a xanthate salt. The precursors for the last three examples, **68h-j**, arise from an Ugi multicomponent transformation (see Scheme17 below).[40] Lactams **68b-f** were obtained by using catalytic amounts of iridium complex and irradiation with blue LEDs as the initiating system.[41] Such redox catalysts have become fashionable in recent times.[42]



Scheme 14. Synthesis of γ-lactams by 5-*exo* ring-closure

One of the issues concerns the slow rotation around the amide bond (in blue) and the existence of two main rotamers **67A** and **67B**, with only the former being capable of cyclizing.[43] The rotamer radical **67B** that does not evolve into product **68** is recycled by exchanging a xanthate group with the starting material **67** and ultimately complete conversion can be achieved. This is a key advantage of this chemistry that overcomes problems encountered with other methods, where rotamers with the wrong geometry for cyclization are irreversibly destroyed, for example by hydrogen atom transfer as in the case of stannane based processes.

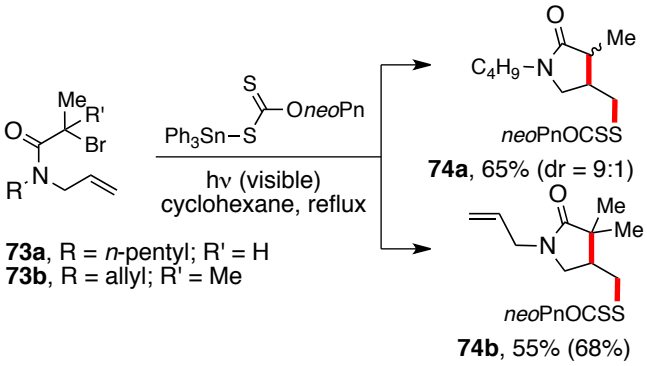
The cyclization leading to the lactam can be combined with another radical transformation. such as an allylation. This synthetically interesting variant is illustrated in Scheme 15, whereby xanthate **69** is directly converted into bicyclic lactam **72** bearing a pendent allyl group with complete control of the relative stereochemistry.[44] In this process, the intermediate cyclized radical is in equilibrium with xanthate **71** but is ultimately captured by ethyl allyl sulfone to give the desired product.



Scheme 15. Synthesis of a γ-lactam by cyclization-allylation

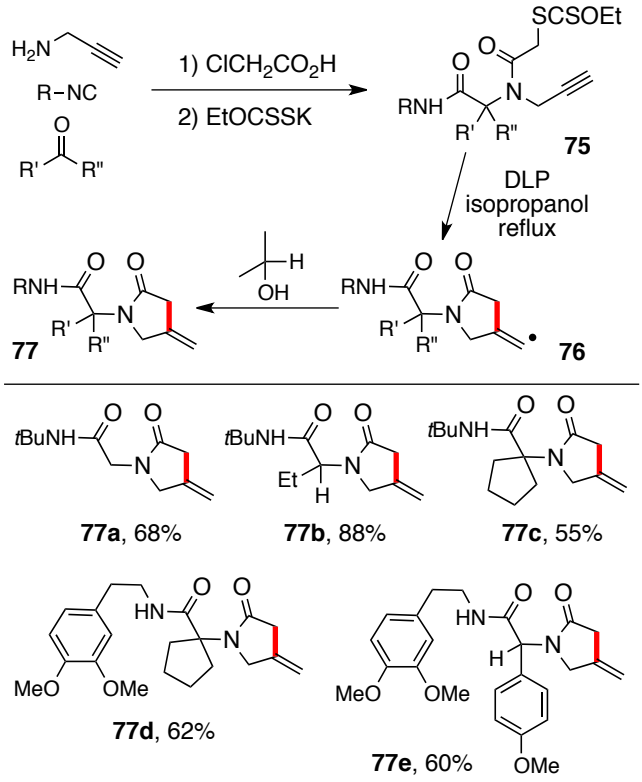
Most starting xanthates are prepared by substitution of a good nucleofuge with a xanthate salt, typically potassium *O*-ethyl xanthate. Like all nucleophilic substitutions, these reactions are sensitive to steric hindrance and the synthesis of tertiary xanthates by such routes often proceeds poorly.[45] One solution to this difficulty is to generate the requisite xanthate by a radical process. This is exemplified in Scheme 16 by irradiation with visible light of bromides **73a,b** with *O*-neopentyl *S*-triphenyltin xanthate (*neo*Pn = neopentyl), which leads directly to lactams **74a,b** possessing the correct xanthate attachment.[46] The triphenytin radicals produced upon irradiation of the tin xanthate react with the starting bromide to produce the corresponding carbon radical. Cyclization and xanthate transfer furnish the observed products and concomitantly regenerate the triphenytin radicals to propagate the chain. In this manner, even tertiary bromide **73b**, which is not easily substituted by a xanthate

salt under ionic conditions, can be converted into lactam **74b** with the pendant xanthate bearing side-chain.



Scheme 16. Synthesis of γ-lactams from bromides

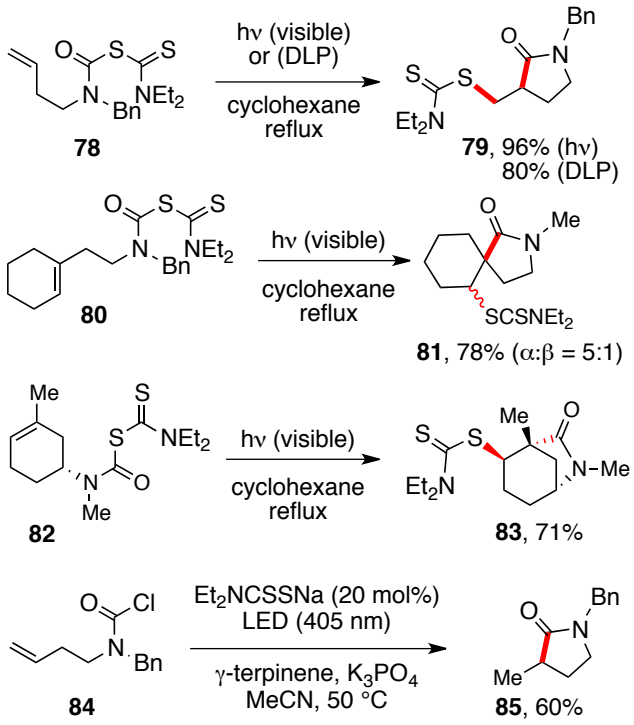
Radical additions to alkynes are generally slower than corresponding additions to alkenes. Additions of xanthates to alkynes are further complicated by the tendency of the resulting vinyl xanthate adducts to undergo further reactions under the usual experimental conditions. Such additions have thus remained limited in scope. Intramolecular additions to alkynes, by contrast, can be very useful when conducted in isopropanol, a solvent with reasonable hydrogen atom donor properties.[47] In the context of γ-lactams, such cyclizations were combined with the Ugi multicomponent process to prepare the requisite precursors, as pictured in Scheme 17.



Scheme 17. Synthesis of methylene γ-lactams

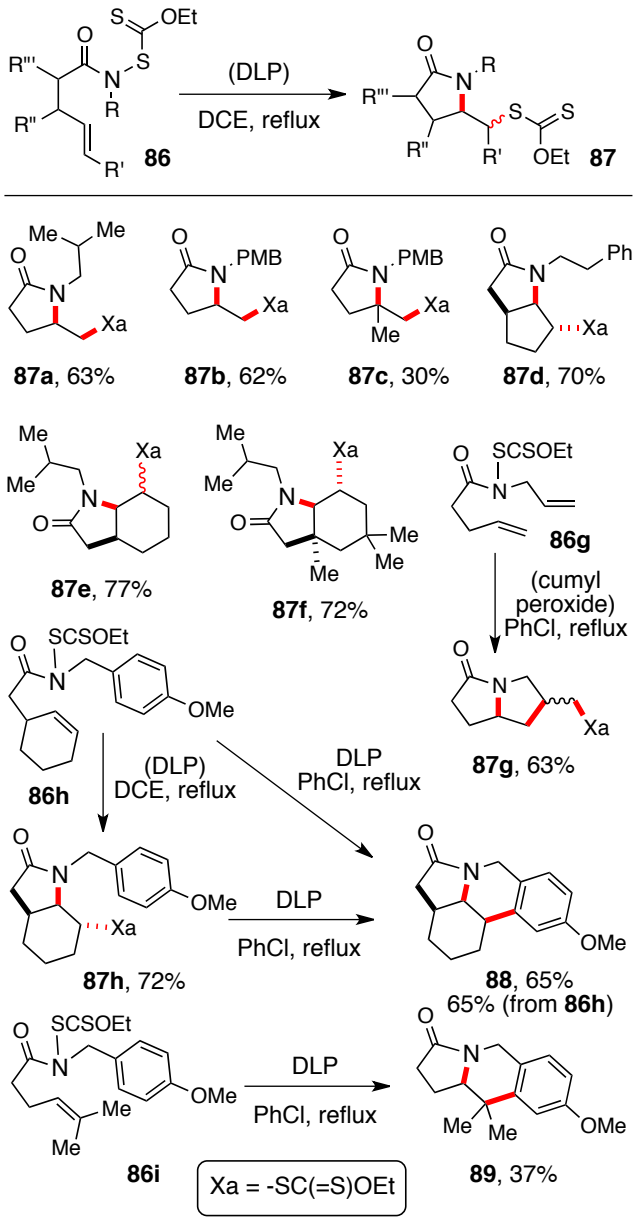
Combining propargylamine with an isonitrile, an aldehyde or a ketone, and chloroacetic acid followed by displacement of the chlorine with potassium *O*-ethyl xanthate results in the formation of compounds **75**. Treatment with stoichiometric amounts of DLP leads to exo-methylene γ-lactams **77** via hydrogen atom abstraction from isopropanol by intermediate vinyl radical **76**. Five examples **77a-e** are displayed in Scheme 17.[48] The *exo* methylene could in principle isomerized with base or acid to give the *endo* isomer or used as a springboard for further more elaborate transformations.

The 5-*exo* ring-closure of carbamoyl radicals constitutes another convenient route to γ-lactams, as depicted in Scheme 18. The same conditions used for the synthesis of β-lactams discussed earlier (Schemes 4 and 6) were applied in the present case. Examples **79**, **81**, and **83**, taken from the work of Grainger,[19] involve irradiation of the corresponding *S*-acyl dithiocarbamate precursors **78**, **80**, and **82** with visible light. DLP was also used with comparable efficiency in the case of dithiocarbamate **78**. Lactam **83** could be processed efficiently into (–)-apanorphine through a sequence that featured conversion of the dithiocarbamate into a ketone.[19c]The last example, **85**, relies on the procedure developed in the group of Melchiorre, also discussed above (Scheme 6), starting from carbamaoyl chloride **84** and using γ-terpinene as the final reducing agent for the cyclized radical.[24a]



Scheme 18. γ-Lactams by cyclization of carbamyl radicals

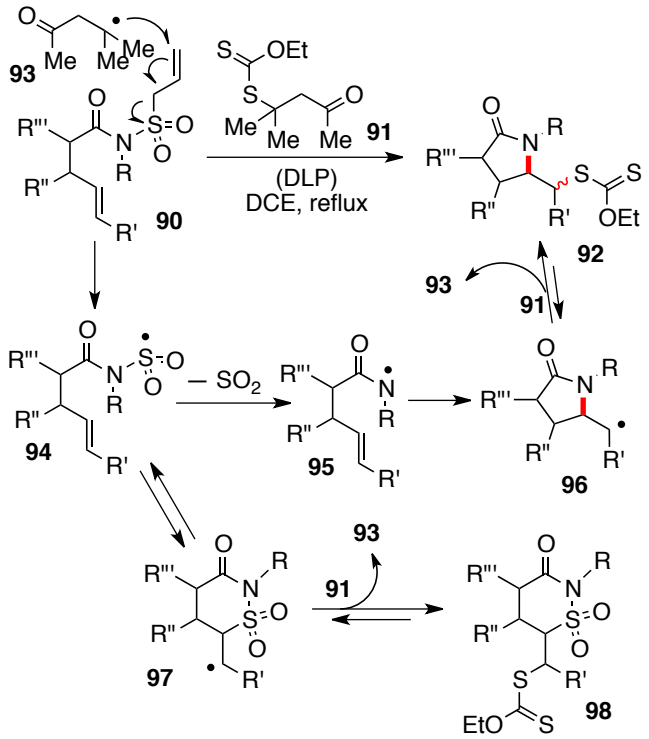
Yet another approach to building γ-lactams involves 5-*exo* ring-closures of amidyl radicals. Xanthates have been used in two different manners for generating nitrogen centered radicals. The first hinges on *N*-xanthyl amides **86** which, upon initiation with DLP, evolve into γ-lactams **87**.[49] Various examples are assembled in Scheme 19. The first six, **87a-f**, correspond to simple cyclizations, while example **87g** illustrates an instance of double cyclization to internal alkenes. In the case of *N*-xanthyl amides **86h**, initiation with DLP in refluxing DCE furnishes bicyclic lactam **87h**. Further treatment with stoichiometric amounts of DLP in refluxing chlorobenzene induces ring-closure on the benzene ring to give tetracyclic lactam **88**. This compound can be obtained directly from precursor **86h** by performing the reaction in refluxing chlorobenzene from the start. Finally, tricyclic lactam **89** was produced directly from its precursor **86i**.



Scheme 19. γ-Lactams by cyclization of amidyl radicals

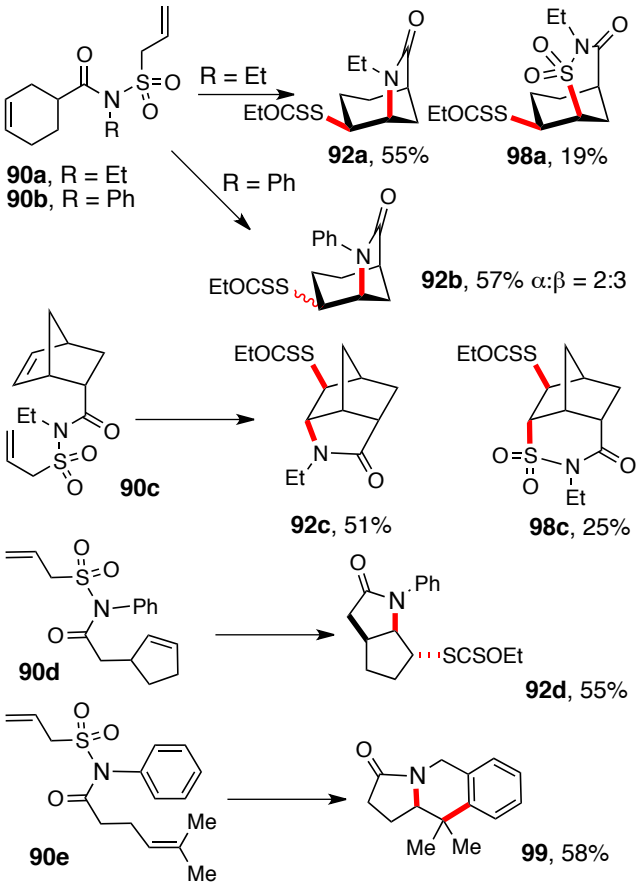
The second route to amidyl radicals, outlined in Scheme 20, is more complex.[50] It starts with allylsulfonamides **90** and a xanthate such as **91**, and leads to lactams of generic structure **92**. Addition of DLP as the initiator generates tertiary radical **93**, which undergoes addition-elimination to allylsulfonamide **90** to produce sulfonyl radical **94**. This species can evolve in two different ways. It can extrude sulfur dioxide and the resulting amidyl radical **95** closes into lactam **96** in the usual manner to give the final product after reversible transfer of the xanthate from tertiary xanthate **91**. This last step regenerates radical **93** to propagate the

chain. Intermediate sulfonyl radical **94** can also cyclize reversibly onto the internal alkene to furnish sultam **98** after xanthate transfer onto radical **97**.



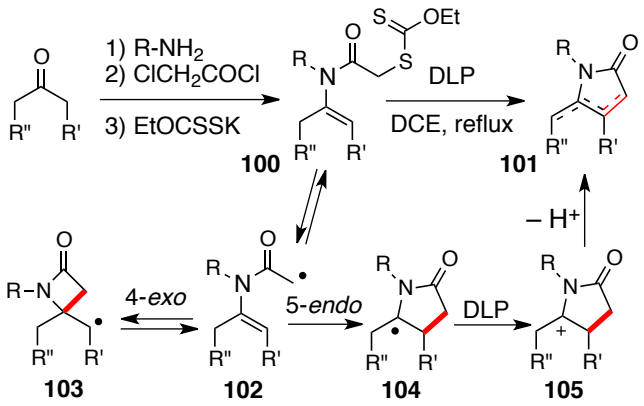
Scheme 20. γ-Lactams by cyclization of amidyl radicals from allysulfonamides

Which of the two pathways dominates depends on the structure, the substituents and the reaction parameters, especially the temperature and the concentration. In the case of *N*-ethyl derivative **90a**, both lactam **92a** and sultam **98a** are obtained in an approximately 3:1 ratio (Scheme 21).[50] Placing a phenyl group on the nitrogen, as in **90b**, accelerates the loss of sulfur dioxide by stabilizing the resulting amidyl radical and favors in consequence the formation of lactam **92b**, which now becomes the exclusive cyclized product. The competing formation of sultam **98c** alongside lactam **92c** is again observed starting with *N*-ethyl precursor **90c**, but not with *N*-phenyl derivatives **90d** and **90e**, which give only lactams **92d** and **99**. In the latter case a second cyclization to the phenyl ring takes place.



Scheme 21. Examples of γ-Lactams from allysulfonamides

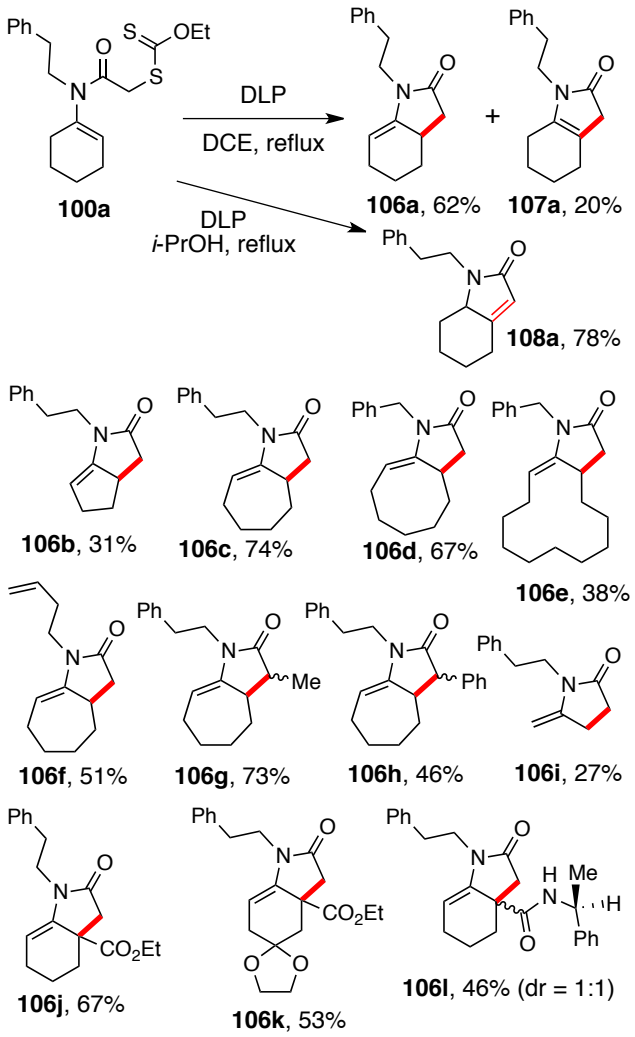
One mode of cyclization that has a tremendous potential for synthesis, but which has not attracted the attention it deserves, is the 5-*endo-trig* mode pictured in Scheme 22.[51] Radical **102** generated from enamide **100** can undergo a 4-*exo* ring-closure to give radical **103**, but this step is reversible. As discussed above, this equilibrium can be pulled towards the β-lactam by combining this step with a fast, irreversible step. The 5-*endo* closure by contrast is relatively slow but irreversible. The resulting radical **104** is tertiary, stabilized, and therefore incapable of propagating the chain process. However, being electron rich, it is easily oxidized into cation **105** by electron transfer to the peroxide; and loss of a proton furnishes unsaturated γ-lactam **101**.



Scheme 22. γ-Lactams by 5-*endo* cyclization

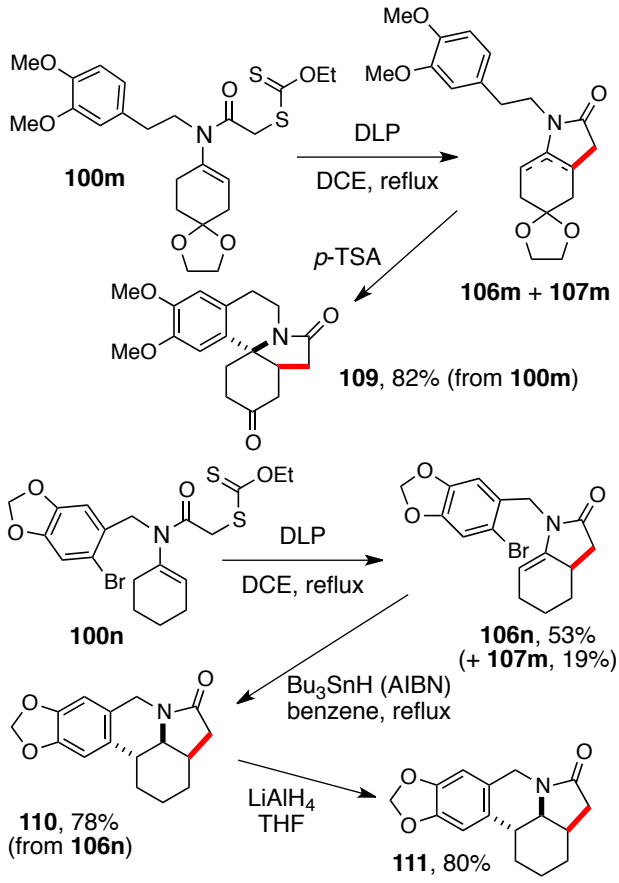
The synthetic utility of this unusual mode of ring formation derives from the broad accessibility of the requisite enamides **100** and the presence of an alkene in the final lactam **101**. The synthesis of the starting material consists in simply heating a ketone with a primary amine to form the corresponding imine, reaction with chloroacetyl chloride to form the chloroacetamide and substitution of the chlorine with a xanthate salt. The first two steps are usually conducted in the same flask, without isolation of the hydrolytically labile imine. The radical chemistry of xanthates is particularly adapted to exploiting the sluggish 5-*endo* cyclization mode. The relative long life of radical **102**, which is continuously regenerated from its xanthate precursor **100**, allows it to overcome the kinetic barrier of the cyclization step.

Several examples of unsaturated γ-lactams obtained by a 5-*endo* ring closure are collected in Scheme 23.[51] In refluxing DCE, enamide **100a** is converted into two isomeric lactams **106a** and **107a** in good combined yield, whereas in refluxing isopropanol, where proton transfers are faster, the most stable regioisomer **108a** is formed. Lactams **106b-l** are other examples featuring different ring combinations and substituents. Example **106f** is interesting in that it shows that the 5-*endo* cyclization, even though relatively slow, is still faster than the 6-*exo* cyclization on the terminal alkene present on the nitrogen substituent. The last example, **106l**, represents a failed attempt to control the absolute stereochemistry at the quaternary carbon center.[51b] Further effort is clearly needed to find an effective chiral auxiliary that solves this problem. For cyclizations on rings other than six-membered, it seems that γ-lactam isomers of type **106** dominate. In the case of compounds **106j-l**, the presence of a substituent at the site of radical attack obviously prevents the formation of the other regioisomers.



Scheme 23. Examples of γ-lactams by 5-*endo* cyclization

The ability to accomplish 5-*endo* cyclizations and access richly decorated structures such as those deployed in Scheme 23 opens many opportunities for the synthesis of natural products, especially alkaloids. Two examples are offered in Scheme 24.[51a]In the first, a one pot synthesis of the functional erythrina skeleton **109** is shown, starting from enamide **100m**. Treatment with DLP and exposing the resulting mixture of **106m** and **107m** to the action of *p*-toluenesulfonic acid causes a Friedel-Crafts type ring-closure onto the electron rich aromatic nucleus to give tetracyclic compound **109** in high yield. The second example is the short, three-step synthesis of α-lycorane **111** from enamide **106n**.[51a] Reaction with DLP gives a separable mixture of **106n** and **107n** in a good combined yield, with the former dominating nearly 3:1. A second, tributylstannane mediated 6-*endo* cyclization affords pentacyclic lactam **110** with the correct relative stereochemistry. Finally, reduction with $LiAlH_4$ provides the desired α-lycorane **111**.

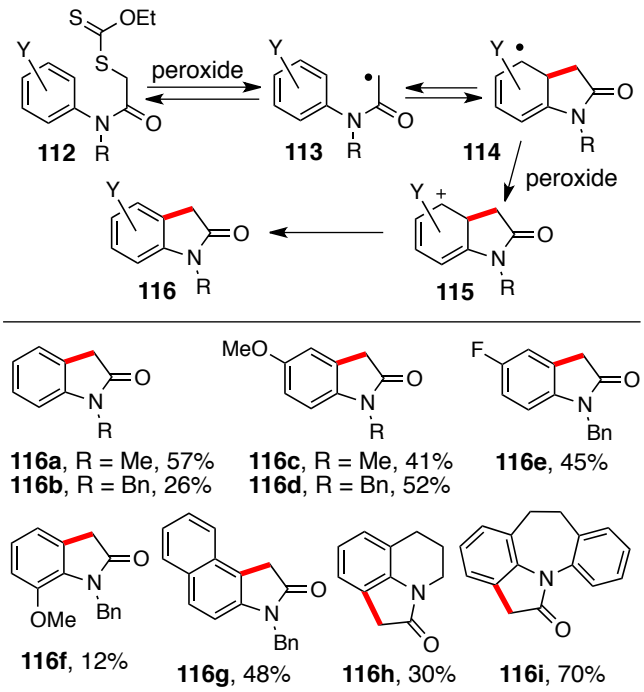


Scheme 24. Further examples of γ-lactams by 5-*endo* cyclization

Synthesis of Oxindoles and Azaspirocyclic Cyclohexadienones

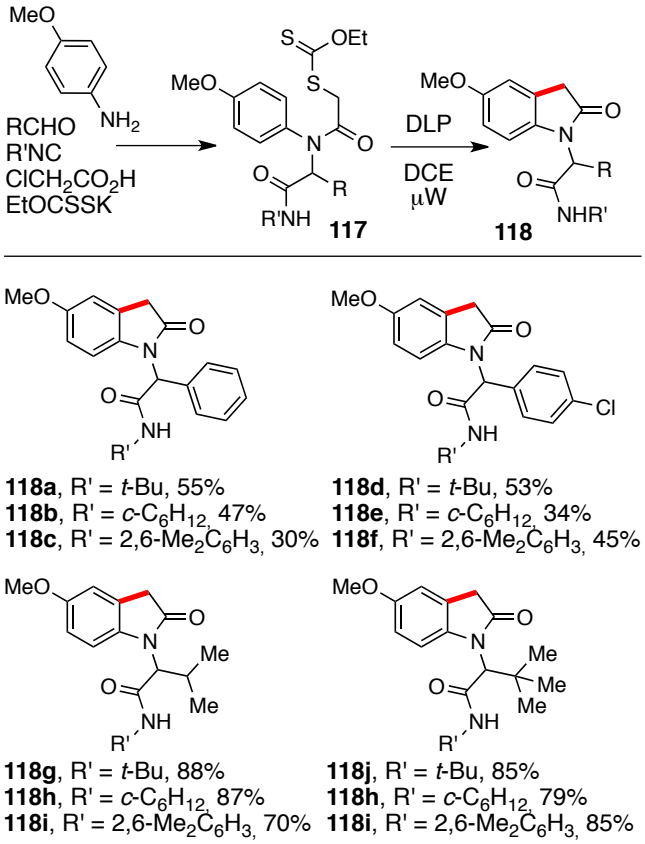
The 5-*endo* cyclization is related conceptually to another important ring-closure mode, namely the formation of oxindoles by radical addition to aromatic nuclei. This strategy is outlined at the top of Scheme 25.[39b] Radical **113**, generated reversibly from its xanthate precursor **112**, can cyclize onto the aromatic ring to give cyclohexadienyl radical **114**. This step is also reversible and reflects the strong driving force of restoring the aromaticity. Cyclohexadienyl radical **114** is too stabilized to propagate efficiently the radical chain but can be oxidized by electron transfer to the peroxide to give cation **115**, which readily loses a proton to give finally oxindole **116**. Interestingly, cation **115** is the same as the classical Wehland intermediate produced in Friedel-Crafts and other electrophilic aromatic substitutions. This cation, however, is produced under exceedingly mild conditions that are compatible with a broad range of substituents. In addition, the radical cyclization is favored by both electron-donating and electron-withdrawing groups on the aromatic ring, even though the oxidation step leading to cation **115** is slowed down in the latter case and could result in lower yields. Nevertheless, the ambiphilic character of the radicals expands quite

considerably the range of substrates to electron-poor aromatic and, indeed, heteroaromatic, ring systems, such as pyridines, that are recalcitrant partners in electrophilic substitutions.



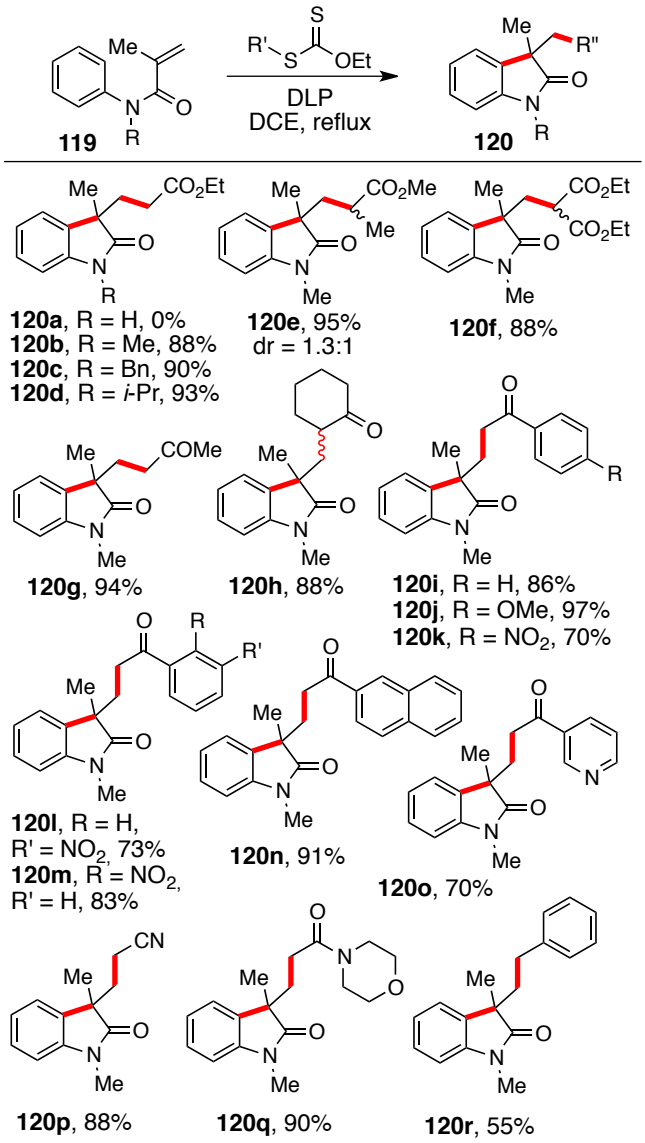
Scheme 25. A radical route to oxindoles

Examples **116a-i** in Scheme 25 are taken from an early study.[39b] The unoptimized yields are variable but give nevertheless an idea of the possibilities. In the case of **116f**, the steric repulsion between the benzyl and the *o*-methyl substituents is probably the cause of the low yield. The cyclization in oxindole **116g** takes place exclusively at position 1 of the naphthalene ring. Further examples, **118a-i** are assembled in Scheme 26.[52] These oxindoles derive from xanthate precursors **117a-i** prepared by an alliance with the formidable Ugi reaction.



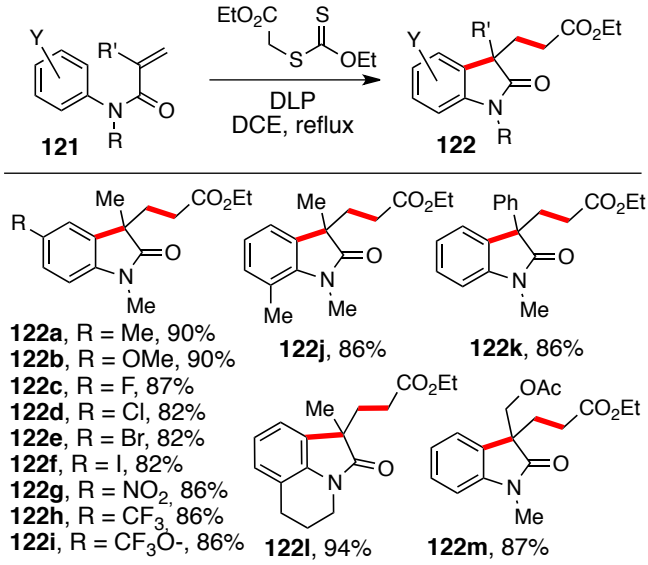
Scheme 26. Further examples of oxindoles

A convergent variant of this route to indoles is to generate the requisite radical adjacent to the carbonyl group of the anilide by addition of a xanthate to an *N*-methacrylanilide **119** (Scheme 27). Oxindoles **120b-r** were thus prepared.[53] It is important to place a substituent on the aniline nitrogen, even a simple methyl group, for otherwise no corresponding oxindole is formed (e.g. **120a**). This observation applies to *all* such cyclizations leading to oxindoles. In this set of examples, little variety has been introduced in the methacrylanilide partner **119**. The diversity derives from the xanthate component.



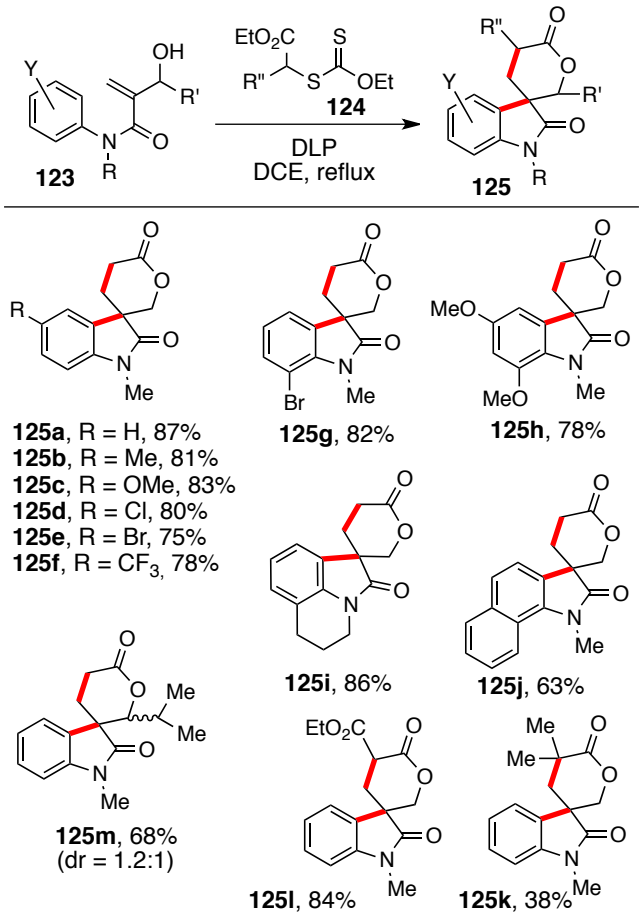
Scheme 27. A convergent route to oxindoles

In the second set of examples collected in Scheme 28 and extracted from the same study,[53] it is anilides **121** that have been modified and reacted with the same xanthate to give oxindole **122a-m** possessing a propionate side chain. Two observations are worth underlining. The first is that it is necessary for R'≠ H. The reason is that this hydrogen in the corresponding oxindole **122** is very easily abstracted and the resulting radical leads to unwanted side-products such as dimers. The second is the ability to produce oxindoles substituted by electron-withdrawing groups such as nitro (**122f**) and trifluoromethyl (**122g**) which are not readily accessible by traditional ionic methods. A similar set of oxindoles was prepared by Melchiorre and co-workers starting from dithiocarbamates generated *in situ* instead of the xanthates. [24b]



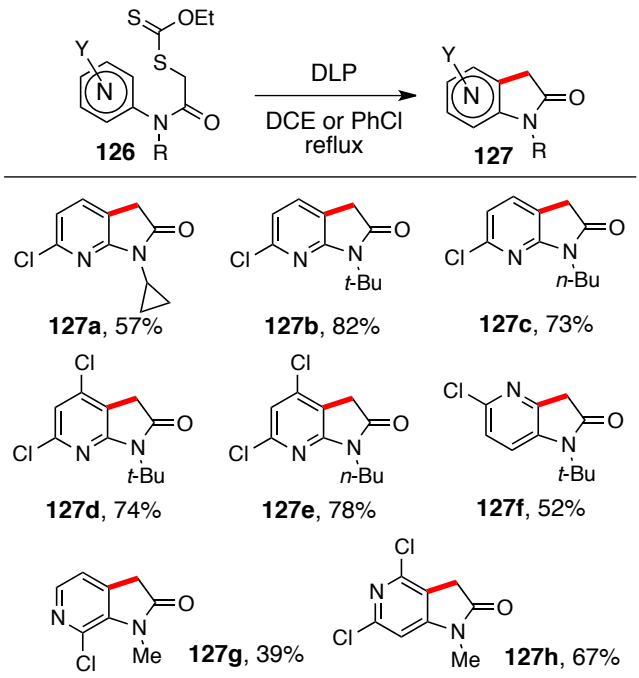
Scheme 28. Further examples of oxindoles by addition-cyclization

A further extension of this approach is presented in Scheme 29, whereby addition of a series of α-xanthyl substituted xanthates **124** to α-hydroxyalkyl acrylanilides **123** furnishes oxindoles **125** featuring a spirolactone motif arising from the spontaneous intramolecular transesterification.[54] The starting acrylanilides **123** result from a Morita-Baylis-Hillman reaction. Overall, this constitutes an effective route to a library of diverse polycyclic structures.



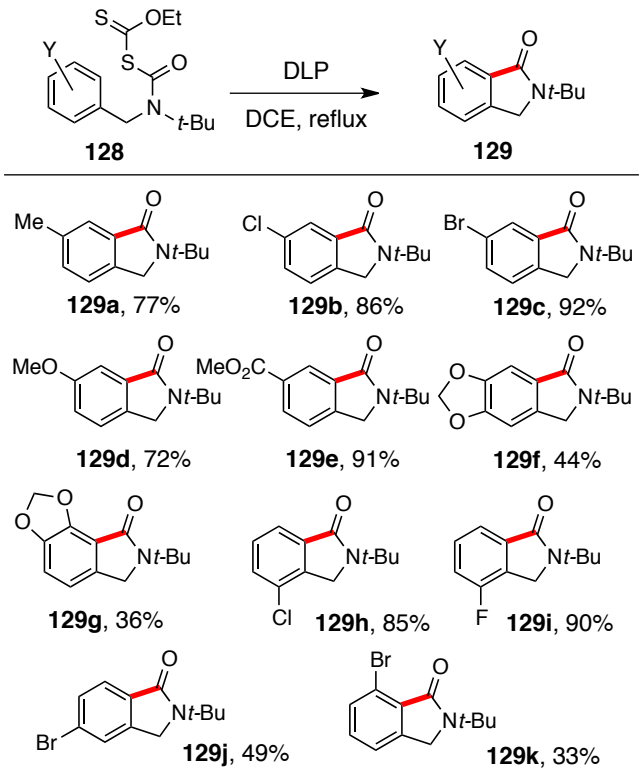
Scheme 29. Spiro-oxindoles by addition-cyclization

In contrast to oxindoles, which are available through a variety of classical and more modern reactions, azaoxindoles are much less accessible. Pyridines are poor substrates in typical electrophilic aromatic substitutions; and aminopyridines bearing an additional vicinal substituent that allows construction of the lactam motif through ionic or organometallic reactions are rarely offered commercially. Constructing azaoxindoles by the radical cyclization of xanthates **126**, pictured in Scheme 30, has many advantages.[55] The starting aminopyridines are simpler and more widely available since they do not need the presence of an extra adjacent functionality. Moreover, pyridines are usually more reactive towards radicals as compared to benzene rings. This translates into azaoxindoles with a broad variety of substitution patterns becoming accessible. The eight examples in Scheme 30, **127a-h**, are illustrative. The extranuclear nitrogen can be placed on all positions on the pyridine rings and the presence of the chlorine atoms represents a useful handle for post-modification. Derivatives **127b**,**d**,**f** are particularly interesting because exposure to trifluoroacetic acid cleaves the *N*-*t*-butyl group and provides access to the *N*-unsubstituted derivatives, which are perhaps more significant from a medicinal chemistry point of view.



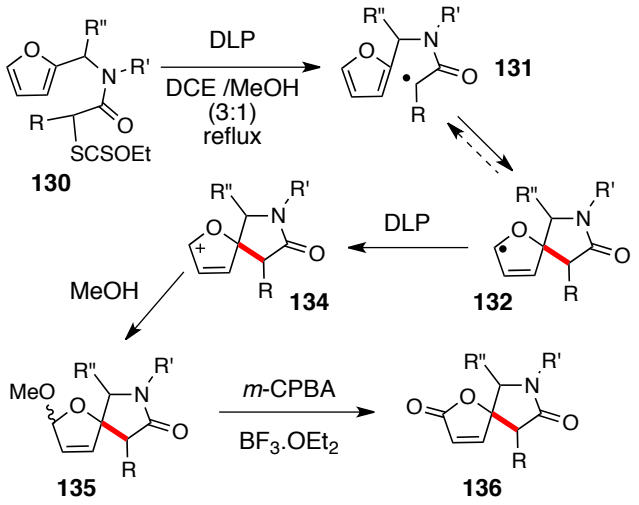
Scheme 30. Synthesis of azaoxindoles

Another family of relatively inaccessible compounds are the isoindolin-1-ones. Using xanthate chemistry, these become available from *N*-*t*-butyl benzylamines via the corresponding *S*-carbamoyl xanthates **128** (Scheme 31).[56] Mere exposure to DLP in refluxing DCE causes ring closure to the aromatic ring, as exemplified by isoindolinones **129a-k**. Both electron-donating and electron-accepting groups on the aromatic ring are tolerated (e.g., MeO- in **129d** and -CO_2Me in **129e**). The latter is particularly interesting because it augurs well for the possibility of extending this strategy to the synthesis of the even less accessible aza-isoindolines by starting with pyridine-based substrates. Removal of the *t*-butyl group in compounds **129** can be accomplished in nearly quantitative yield by heating in refluxing trifluoroacetic acid.[56]



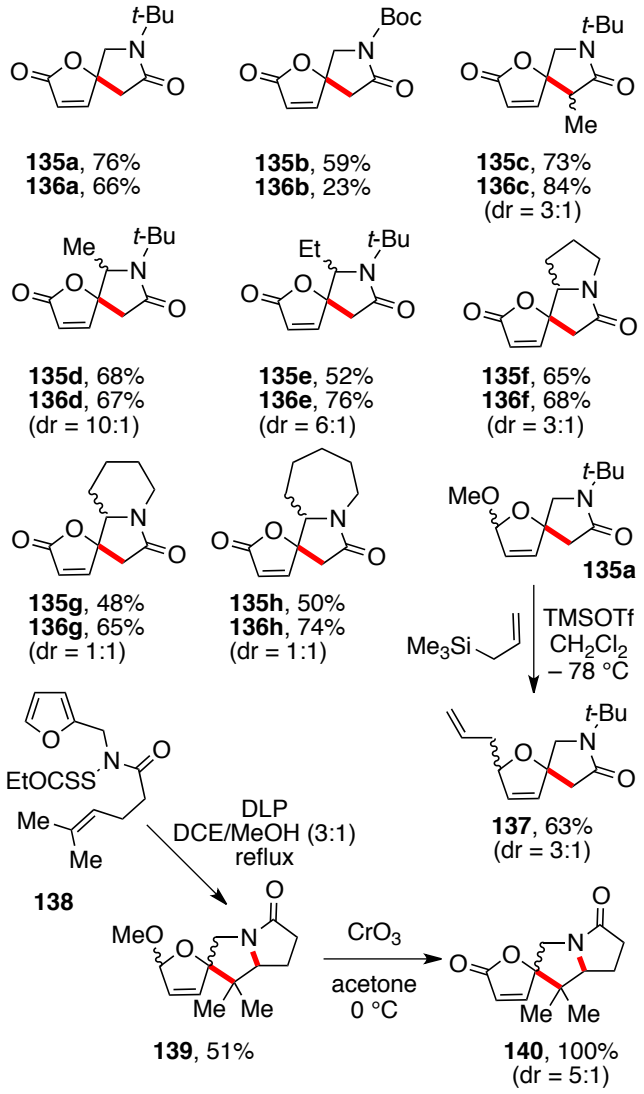
Scheme 31. Synthesis of isoindolin-1-ones

An alternative mode of cyclization on the aromatic ring provides a convenient access to an interesting family of spirolactams. This is illustrated by the behavior of xanthate **130** upon exposure to DLP in a mixture of DCE and methanol (Scheme 32).[57] The corresponding radical **131** attacks the neighboring furan ring at the *ipso* position to give allylic radical **132**. This step is in principle reversible, but probably only to a small extent or even not at all because of the much weaker aromatic character of the furan ring. Electron transfer from electron-rich adduct radical **132** to the peroxide furnishes stabilized cation **133**, which is rapidly quenched by methanol to give acetal **135**. This hydrolytically labile product is best converted into the more robust lactone **136** using for example *m*-chloroperbenzoic acid (*m*-CPBA). This operation concomitantly removes a chiral center and simplifies spectroscopic characterization.



Scheme 32. An unusual route to furan derived spirolactams

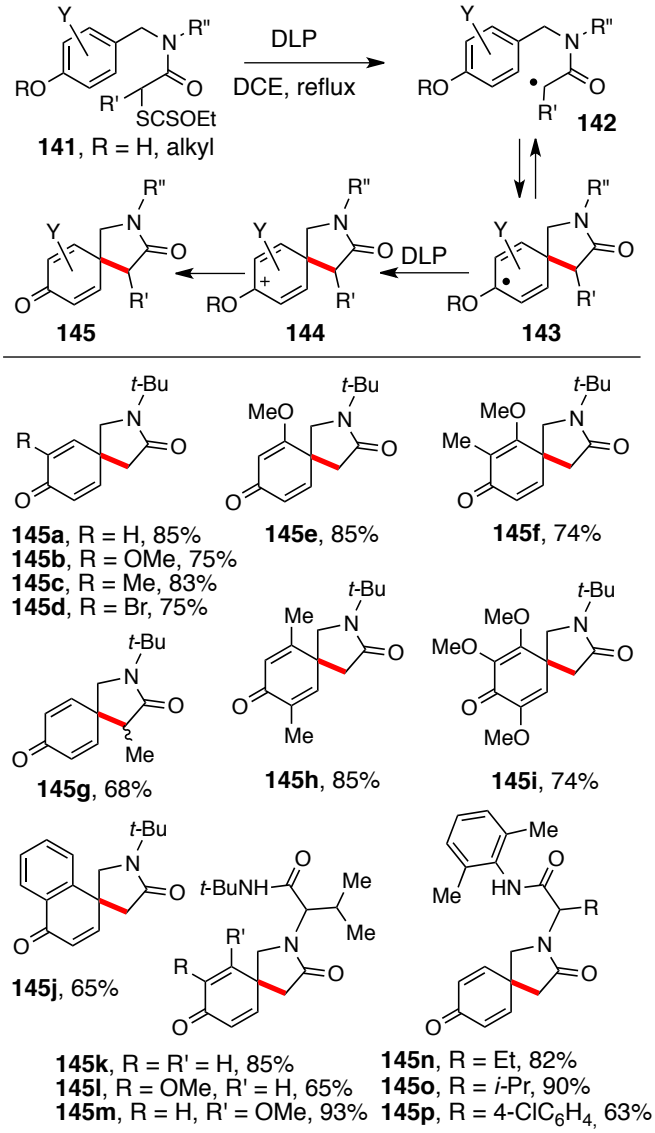
A number of examples are displayed in Scheme 33.[57] Only lactones **136 a-h** are pictured, but the yields for the respective acetal precursors **135 a-h** are also given so that an idea of the efficiency of the radical *ipso* addition can be obtained. In addition to oxidation into spirolactone **136a**, acetal **135a** could be converted into allyldihydrofuran **137** by treatment with trimethylsilyl triflate (TMSOTF) and allyl trimethylsilane.[57] The last example illustrates a radical cascade starting from xanthate **138** and features an initial amidyl radical cyclization followed by the *ipso* addition to the furan ring to give tricyclic compound **139**.[49] Oxidation of the acetal with chromium trioxide finally produces lactone **140** quantitatively.



Scheme 33. Examples of furan derived spirolactams

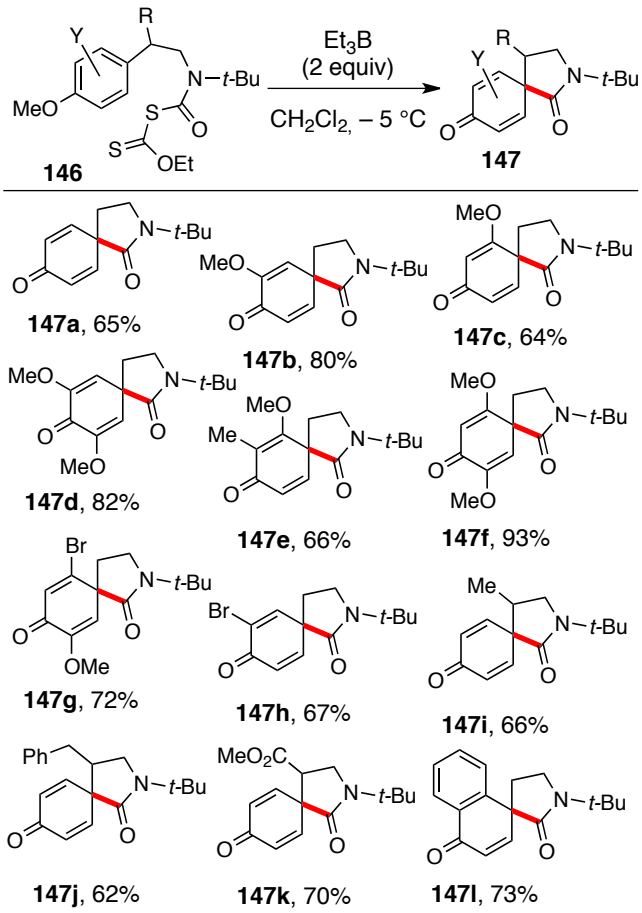
This strategy for creating spirolactams was extended by Miranda to aryl derivatives possessing a substituent that facilitates the oxidation step by stabilizing the resulting cation.[58] This requirement is shown in xanthate **141**, where a free hydroxy or, more conveniently, an alkoxy group is placed in the *para* position with respect to site of radical attack (Scheme 34). Thus, radical **142** cyclizes reversibly to give electron-rich spirocyclohexadienyl radical **143**. Irreversible oxidation of the latter by the peroxide drives the equilibrium towards cation **144**, which finally collapses into dienone **145**. The examples arrayed in the same Scheme are representative. In spirolactams **145a-j**, the *t*-butyl group improves the cyclization step through a steric compression effect; however, while this group could in principle be removed by treatment with trifluoroacetic acid, these conditions could cause the Wagner-Meerwein 1,2-migration of one of the arms of the spirolactam to give ultimately a phenol. Such

rearrangements are well known with crossed cyclohexadienones.[59] The precursors for the last six examples **145k-p** were prepared using the Ugi reaction.[60]



Scheme 34. Spirolactams by radical *ipso* addition

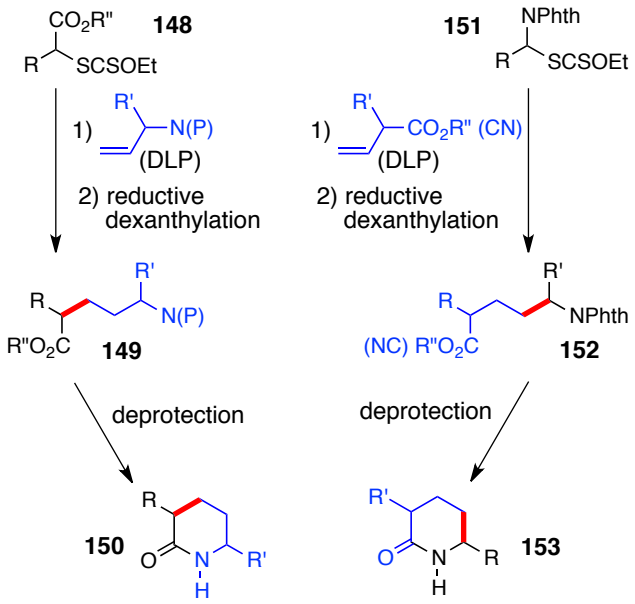
Miranda further extended this *ipso* dearomatizing cyclization to carbamyl radicals.[61] This leads to the isomeric spirolactam skeleton **147** starting from the *S*-carbamoyl xanthate **146**, as shown in Scheme 35. It appears that in this case initiation with a combination of triethylborane and oxygen is the most efficient. Capture of the cyclized cyclohexadienyl radicals (analogous to **143** in the previous Scheme) by triplet oxygen is the most likely pathway leading to cyclohexadienones **147**. These spiro derivatives are relatively rare and the present approach, illustrated by examples **147a-l**, constitutes by far the best synthetic route.



Scheme 35. Spirolactams by *ipso* addition of carbamyl radicals

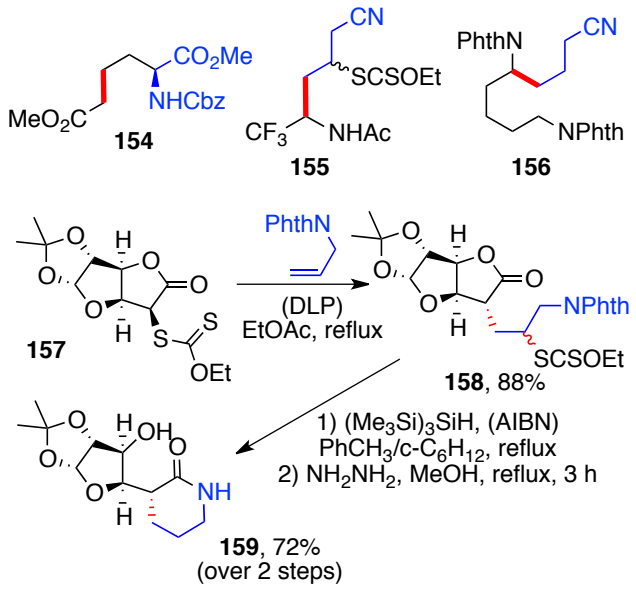
Synthesis of Six-Membered Ring Lactams

As for γ-lactams, xanthate chemistry offers a variety of paths to δ-lactams. Many are similar in concept, but the larger ring size of the δ-lactams permits a number of different approaches. One the basic route common to all lactams is to access amino acid derivatives with the correct number of carbon atoms between the amino and acid groups (Scheme 36). In the intermolecular addition to alkenes, the amino group can be on the alkene and the carboxylic acid or ester function on the xanthate, or vice-versa. The former corresponds to the addition of xanthate **148** to a protected allylamine or the addition of an α-phthalimido xanthate **151** to a 3-butenoate ester (or nitrile). After reductive dexanthylation, the former furnishes aminoester **149** and the latter **152**, and, upon deprotection of the amine, δ-lactams **150** and **153** respectively. In these compounds, the carbon-carbon bond generated through the radical addition and colored in red is in a different position of the lactam ring. This flexibility provides access to numerous combinations of substituents. Nearly all the positions around the ring can be substituted, even though for clarity only two substituents are shown.



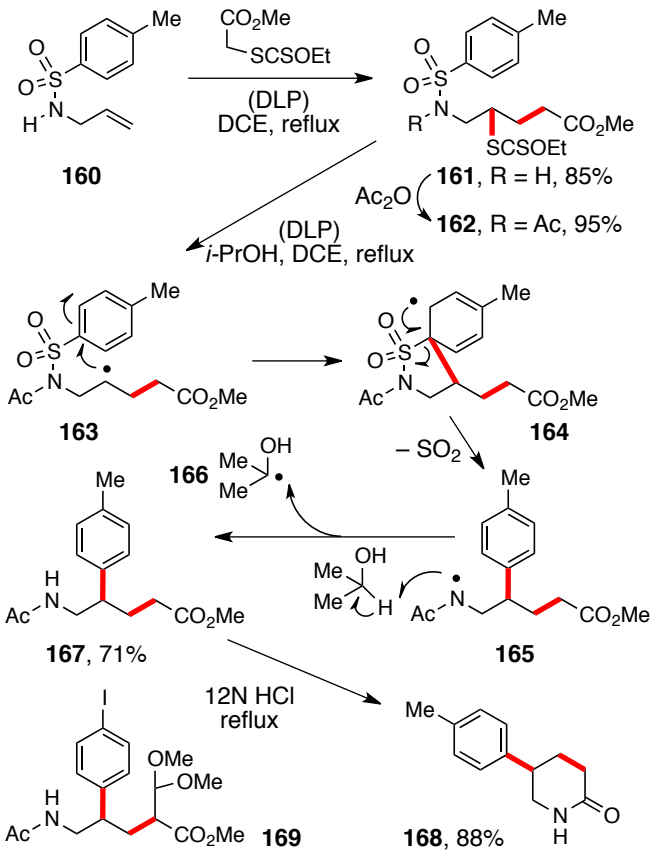
Scheme 36. Two convergent routes to δ-lactams

Homoglutamic derivative **154**,[62] α-trifluoromethyl acetamidonitrile **155**,[63] and phthalimide protected diaminonitrile **156**[33] pictured in Scheme 37 can all be converted in principle to the corresponding δ-lactams. In the case of the nitriles, the cyclization to lactams proceeds via hydrolysis of the intermediate amidine, which could be isolated if desired.[64] Amidines are of medicinal chemistry interest in their own right and are useful precursors to imidazoles.[65] Reductive dexanthylation and deprotection of adduct **158** from the addition of glucuronolactone derived xanthate **157** to *N*-allyl phthalimide results in spontaneous cyclization to lactam **159** in good overall yield.[66] This sequence is a testimony to the power of this convergent approach, since lactam **159** would indeed be quite difficult to obtain by classical routes.



Scheme 37. Examples of δ-lactams and δ-lactam precursors

An interesting variation of the above approach allows access to 5-arylpiperidones through an alliance with a radical Smiles rearrangement.[67] This possibility is illustrated by the sequence in Scheme 38. Addition of an α-xanthyl acetate to *N*-allyl *p*-toluenesulfonamide **160** gives the usual adduct **161** in high yield. This step is followed by acetylation under standard conditions to provide xanthate **162**. All the elements are now set for the key Smiles rearrangement. This is accomplished by heating with stoichiometric amounts of DLP in refluxing isopropanol. This treatment generates radical **163** which undergoes the desired *ipso* addition to give intermediate **164**. Fragmentation and loss of sulfur dioxide leads to amidyl radical **165**, an electrophilic species that rapidly abstracts a hydrogen atom from the solvent to afford compound **167**. The ketyl radical **166** coproduced is oxidized into acetone by electron transfer to the peroxide. Hydrolysis of the acetamide results in ring closure to piperidone **168**, in which the tolyl moiety of the initial sulfonamide now occupies the position originally held by the xanthate. All three components in this convergent pathway to 5-aryl piperidones can be modified to introduce diversity: the allylamine and the arylsulfonyl chloride used to make the *N*-allyl arylsulfonamide partner, and the xanthate. Compound **169** is another acetamido ester reported in the same study but not converted into the corresponding piperidone.

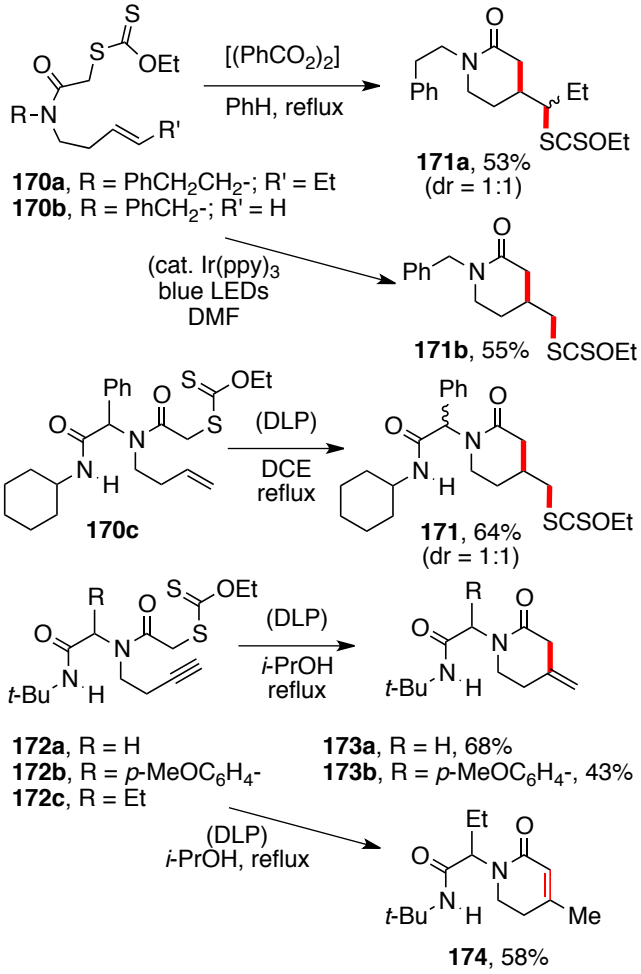


Scheme 38. δ-Lactams by a radical Smiles rearrangement

Direct radical cyclization could constitute another important route to δ-lactams. However, the 6-*exo* is generally significantly slower than the 5-*exo* ring-closure and has been relatively rarely employed hitherto, because the cyclization step does not compete effectively against other pathways open to the uncyclized radical. The existence of two slowly (on the radical timescale) interconverting rotamers in the case of amides complicates matters further (see **67A** and **67B** in Scheme 14). Indeed, many years ago, Stork and Mah had to use the uncommon tri-*n*-butylgermanium hydride to secure a good yield of δ-lactams by cyclization of bromoacetamides derived from homoallylic amines.[68] The more common tri-*n*-butyltin hydride proved to be too fast a reducing agent and premature reduction prevailed over ring-closure, even under high dilution conditions. The comparative long life of radicals produced through the chemistry of xanthates overcomes most of these hurdles and allows efficient 6-*exo* closures to afford δ-lactams without the need for high dilution techniques.

Examples of 6-*exo* cyclizations are displayed in Scheme 39.[39b,40,41] Peroxide or irradiation in the presence of an iridium based redox catalyst initiates effectively the radical process. Precursor **170c** derives through application of the Ugi reaction.[40] Cyclization to alkynes is also feasible and, as with γ-lactams, isopropanol is used as the solvent and the source of the final hydrogen atom transfer.[48] Xanthates **172a,b** gave the expected *exo*-methylene lactams

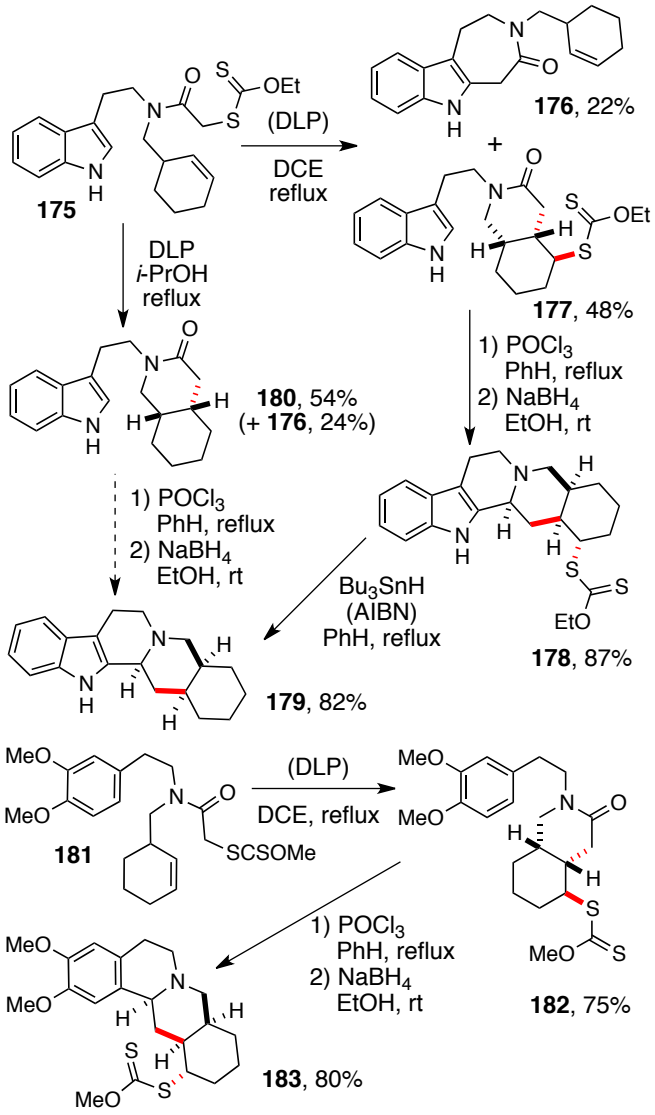
173a,b, whereas xanthate **172c** furnished the *endo* derivative **174**. This unexpected outcome is probably due to the presence of adventitious traces of acid which caused the isomerization of the kinetic *exo* methylene product into its more thermodynamically stable *endo* isomer.



Scheme 39.

Six-membered nitrogen heterocycles are very common motifs in alkaloids,[69] and the radical cyclization of xanthates opens up interesting, and in many cases unusual, routes to natural substances containing not just piperidone, but also piperidine and pyridine subunits. The application of this chemistry to the synthesis of allyohimbane and berbane derivatives is outlined in Scheme 40.[70a] Treatment of easily prepared xanthate **175** with DLP in refluxing DCE gives rise to the desired cyclized xanthate **177** as the major product. The intermediate radical also attacks the indole to give 7-membered ring lactone **176** as the minor product (more on such lactams in the next section). In another context, a similar unwanted cyclization could be blocked by placing a bulky TBS on the indole nitrogen.[70b] In the present case, not similar attempt was made. Piperidone **177** was simply subjected to the action of phosphorus

oxychloride followed by sodium borohydride reduction of the intermediate cyclic iminium chloride to furnish pentacyclic compound **178** in high yield. Reductive removal of the xanthate completed the synthesis of (±)-alloyohimbane **179**.

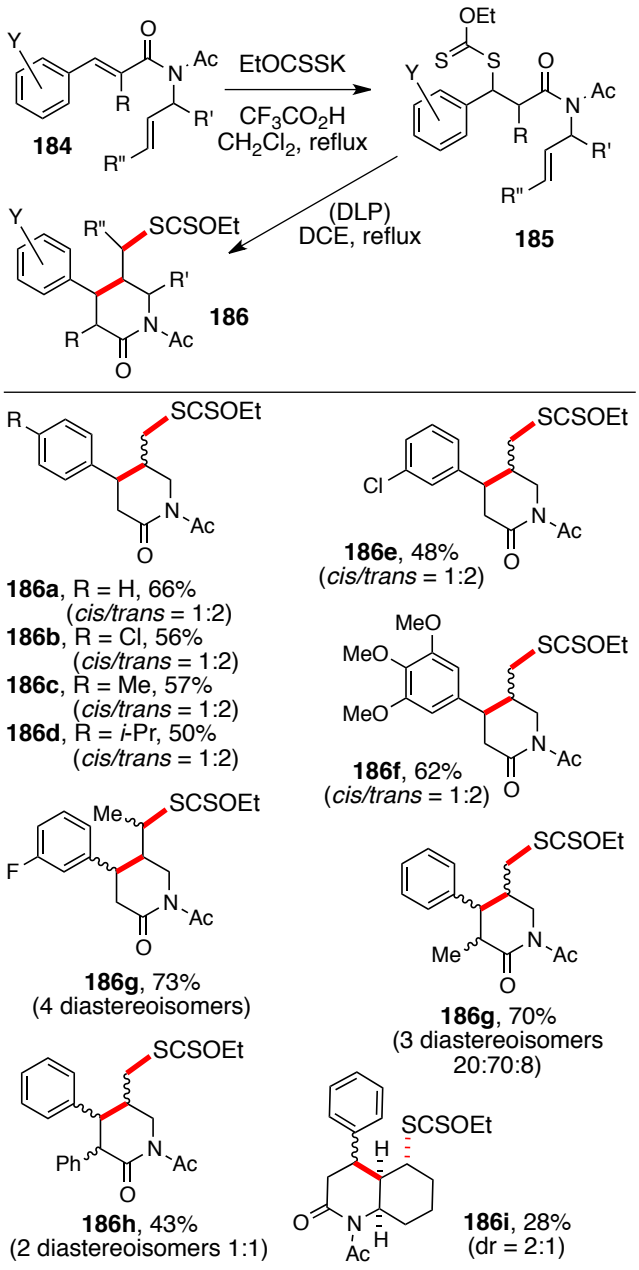


Scheme 40. Synthesis of alloyohimbane and berbane derivatives

A shorter route to alloyohimbane is to perform the radical cyclization in isopropanol as both the solvent and reducing agent for the final cyclized radical. This leads directly to sulfur-free lactam **180**, alongside smaller amounts of the same side-product **176** observed previously. Compound **180** had been converted earlier into alloyohimbane **179** under the same Bischler-Napieralski conditions. Xanthate **181** was converted in the same manner into berbane derivative **183**.[70] In this case, no seven-membered ring lactam side product is formed, reflecting the lower propensity of the benzene ring toward radical attack as compared to an

indole. Interestingly, in both series, the xanthate group survives the relatively harshly acidic conditions of the Bischler-Napieralski cyclization and its presence in compounds **178** and **183** allows numerous further transformations.

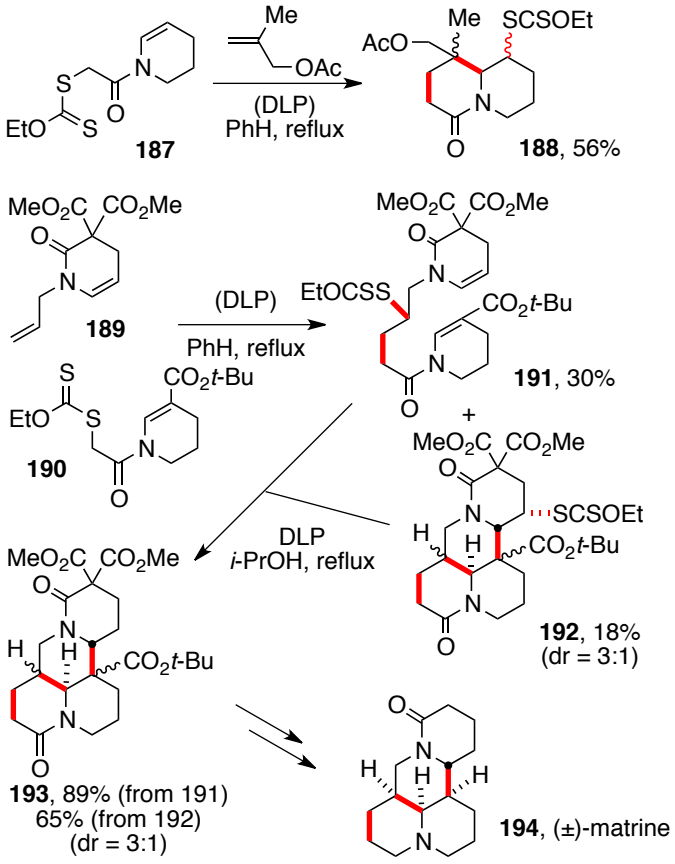
An alternative strategy exploiting the 6-*exo* cyclization hinges on the ability to accomplish a Michael addition to unsaturated imides **184** of *in situ* generated xanthic acid (Scheme 41).[71] The resulting adducts **185** are now set for the usual addition-transfer reaction triggered by DLP to furnish 4-aryl-2-piperidones **186**. A number of typical examples **186a-i** are collected in Scheme 41. This approach complements the one based on the radical Smiles rearrangement leading to 5-aryl-2-piperidones **168** in Scheme 38. It is also convergent and modular, since precursors **185** are derived simply from cinnamic acids and allylamines. These substrates are readily available with very diverse substitution patterns.



Scheme 41. δ-Lactams by 6-*exo* cyclization benzylic radicals

The ability to perform intermolecular addition to both activated and electronically unbiased alkenes allows the construction of δ-lactams by a formal 4+2 process. This convergent approach can rapidly provide quite complex molecular scaffolds. One example is shown at the top of Scheme 42, whereby enamide xanthate **187** is reacted with methallyl acetate to afford bicyclic lactam **188**.[72] Another, far more interesting application, is the total synthesis of (±)-matrine **194** depicted in the same Scheme.[73] The sequence starts with the reaction of enamide xanthate **190** with *N*-allyl lactam **189** which furnishes two major products, the

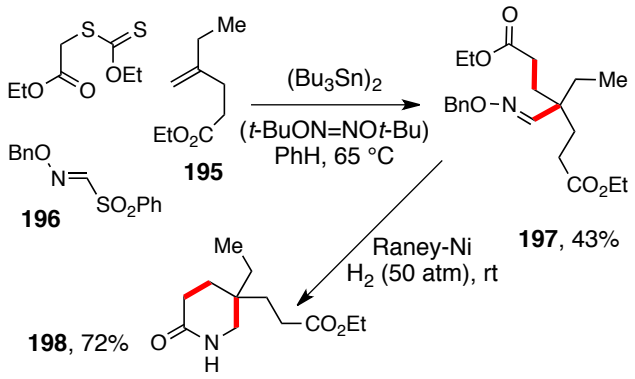
simple adduct **191** and tetracyclic derivative **192**, with the former dominating. The transfer of the xanthate is sufficiently fast that it is able to capture the intermediate adduct radical before it has cyclized onto the *t*-butyl ester activated alkene. This is however of no consequence for the synthesis of matrine, since both products can be converted into advanced intermediate **193** by further treatment with DLP in isopropanol which, as noted above, also acts the final hydrogen atom donor. Three carbon-carbon bonds are formed in this process with an acceptable control of the stereochemistry (the minor diastereomer has the relative stereochemistry of allomatrine). Conversion of intermediate **193** into matrine **194** require only very few steps: reductive decarboxylation of the *t*-butyl ester via a Barton thiohydroxamate ester, reduction of the less hindered lactam with diborane, and double acid hydrolysis/ spontaneous decarboxylation of the geminal dimethyl carboxylates. The last two steps can be done in one pot.



Scheme 42. δ-Lactams by addition-cyclization

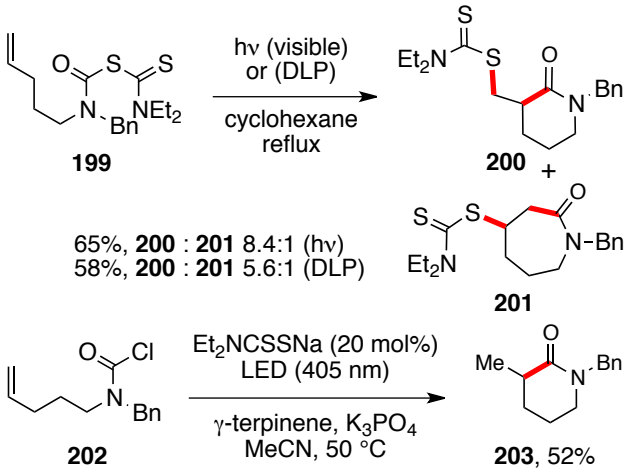
A conceptually different three-component route to δ-lactams was devised by Landais.[74] In the one example involving a xanthate displayed in Scheme 43, ethyl α-xanthylacetate was made to react with alkene **195** and phenylsulfonyloxime **196** using a combination of hexabutylditin and di-*t*-butyl hyponitrite as initiator. The electrophilic radical derived from the ester adds

preferentially to alkene **195** to give a nucleophilic tertiary carbon radical, which in turn reacts with electrophilic oxime **196** to afford finally compound **197**. Two carbon-carbon bonds are created in this process, as well as a quaternary center. Catalytic reduction of the oxime to the amine is followed by concomitant internal aminolysis of either of the two equivalent ester groups to give lactam **198**.



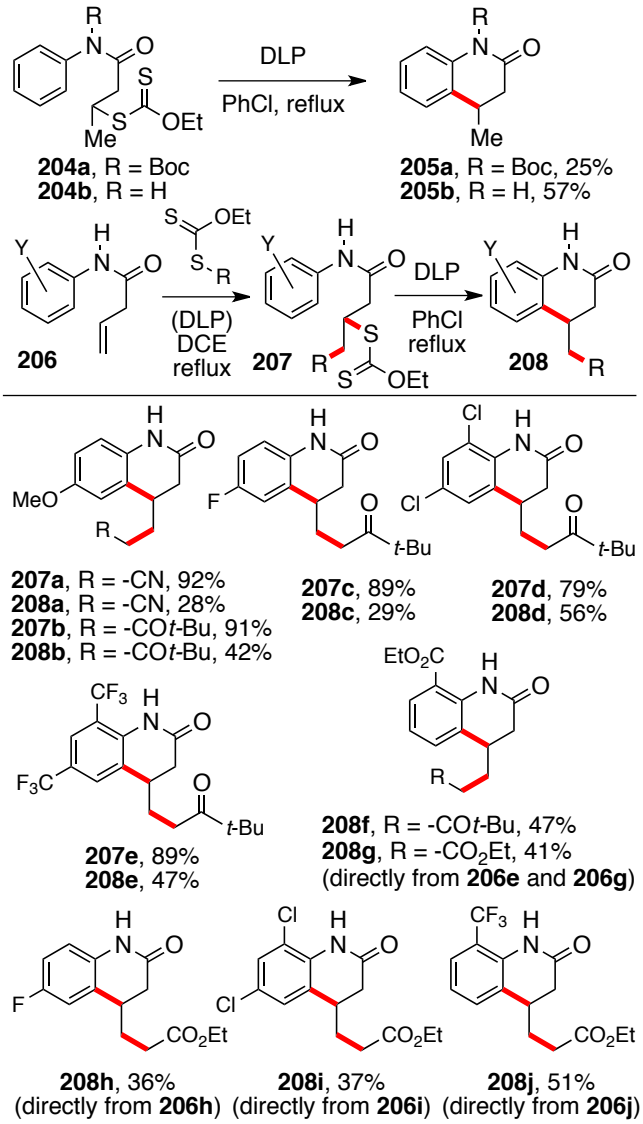
Scheme 43. A three-component route to a δ-lactam

The cyclization of carbamyl radicals has also been used to prepare δ-lactams (Scheme 44). Two examples have been reported. The first, described by Grainger,[19a] starts from *S*-carbamyl dithiocarbamate **199**. This compound can be cyclized into lactam **200** either by initiation with light or with DLP in comparable yield. Under both conditions a small amount of seven-membered ring lactam **201** is formed, resulting from a 7-*endo* cyclization. The second is taken from the study by Melchiorre.[24b] It starts from carbamyl chloride **202** and furnishes sulfur-free lactam **203**.



Scheme 44. δ-Lactams by cyclization of carbamyl radicals

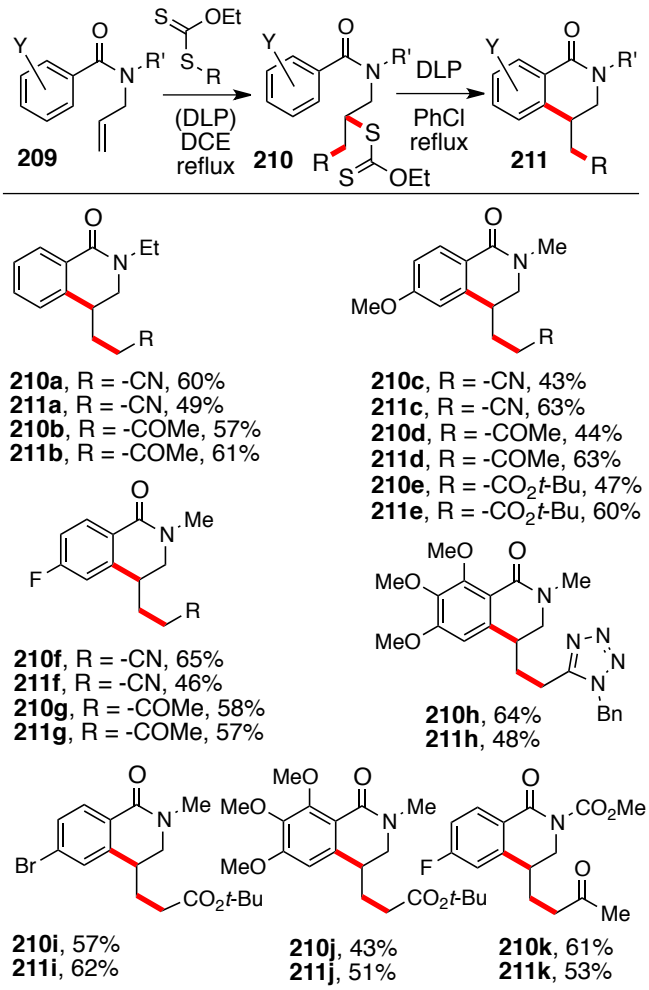
Ring-closure onto (hetero)aromatic rings leading to the formation of a fused six-membered ring is expected to be one notch more difficult than the related 6-*exo* cyclization in the aliphatic series and has not been widely exploited in synthesis. When the xanthate chemistry was applied to the synthesis dihydroquinolones by cyclization of xanthate **204a,b**, a surprising observation was made, namely that the *N*-unsubstitued substrate **204b** gave the corresponding dihydroquinolone **205c** more effectively than *N*-Boc xanthate **204a** (Scheme 45).[75] Remember that in the synthesis of oxindoles, the *N*-unsubstituted precursor did not produce any oxindole under the usual conditions (cf. **120a** in Scheme 27). The reason for this divergent behavior is not clear and further experiments are needed to clarify this point, especially that it is well known that acetanilide, for example, exists solely as the Z-rotamer[76] which, when transposed to the corresponding radical, is not propitious for cyclization (cf **67B** in Scheme 14).



Scheme 45. Dihydroquinolones by addition-cyclization

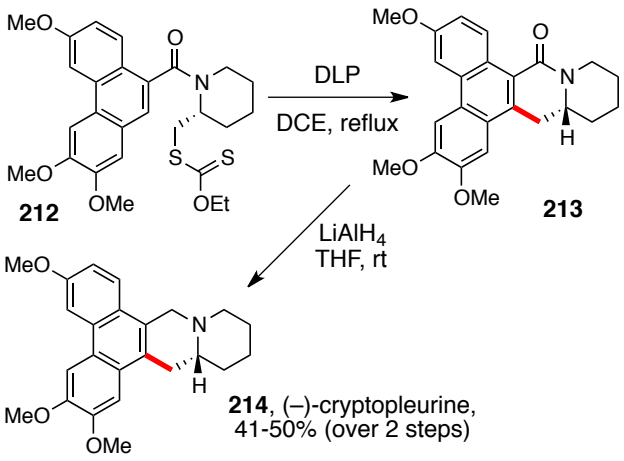
More complex dihydroquinolones can be assembled by a convergent route combining the intermolecular addition of a xanthate to 3-butenalides **206** with the cyclization of the resulting adducts **207**.[75] In this manner two carbon-carbon bonds are created to generate dihydroquinolones **208**. In examples **208a-e** pictured in Scheme 45, the yield of intermediates **207a-e** is given, even though the structures are not shown. In the case of examples **208f-j**, the addition and cyclization were conducted in the same pot. This is a convenient, modular synthesis of a broad diversity of dihydroquinolones, many accessible only with difficulty by other chemistries. Fluorinated compounds **208e** and **208j** are particularly noteworthy from a medicinal chemistry standpoint.

The isomeric dihydroisoquinolones **211** can be obtained by the same strategy of xanthate addition to *N*-allylbenzamides **209** and cyclization of the resulting adducts **210** (Scheme 46).[77] This approach benefits from the same modularity and opens access to numerous combinations of substituents, as illustrated by compounds **211a-k**. As for the dihydroquinolones in the previous Scheme, the yield for the intermediate adducts is given but the structures are not shown for the sake of space and clarity. Hydrolytic cleavage of the carbamate in compound **211k** would furnish the *N*-unsubstituted derivative, if so desired. It would nevertheless be interesting to examine the behavior of *N*-unsubstitued intermediates (**210**, R' = H) to see if they cyclize with the same ease as isomeric adducts **207**.



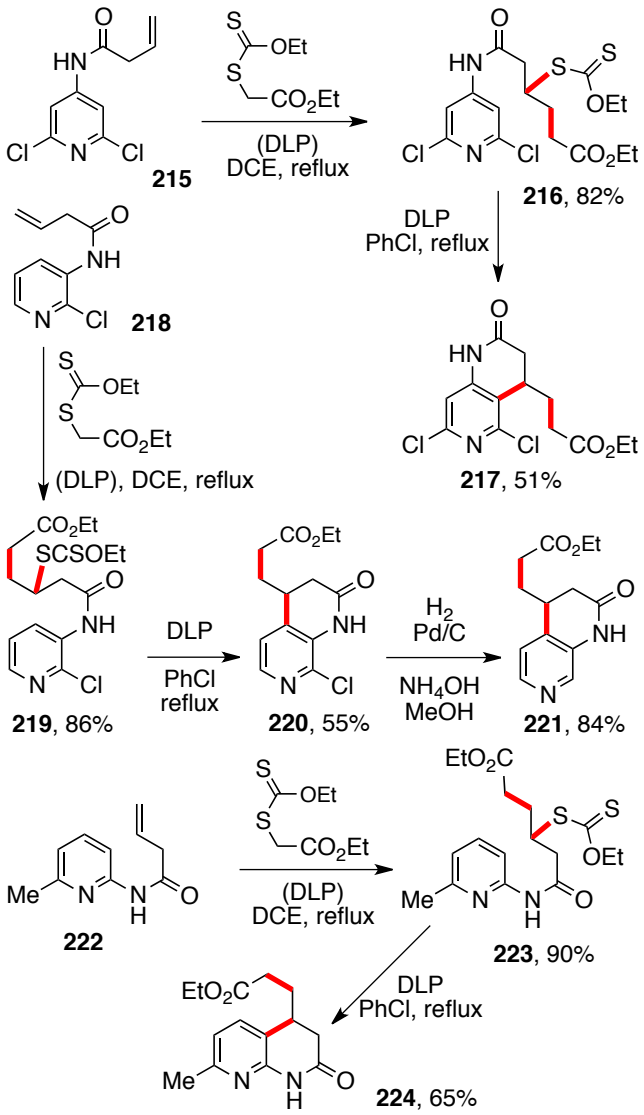
Scheme 46. Dihydroisoquinolones by addition-cyclization

This route to dihydroisoquinolones was exploited by Opatz in a short synthesis of (–)-cryptopleurine **214**, the last steps of which are outlined in Scheme 47.[78] Thus, treatment of xanthate **212** with DLP induces cyclization into lactam **213** and reduction with lithium aluminum hydride provides the target molecule **214**.



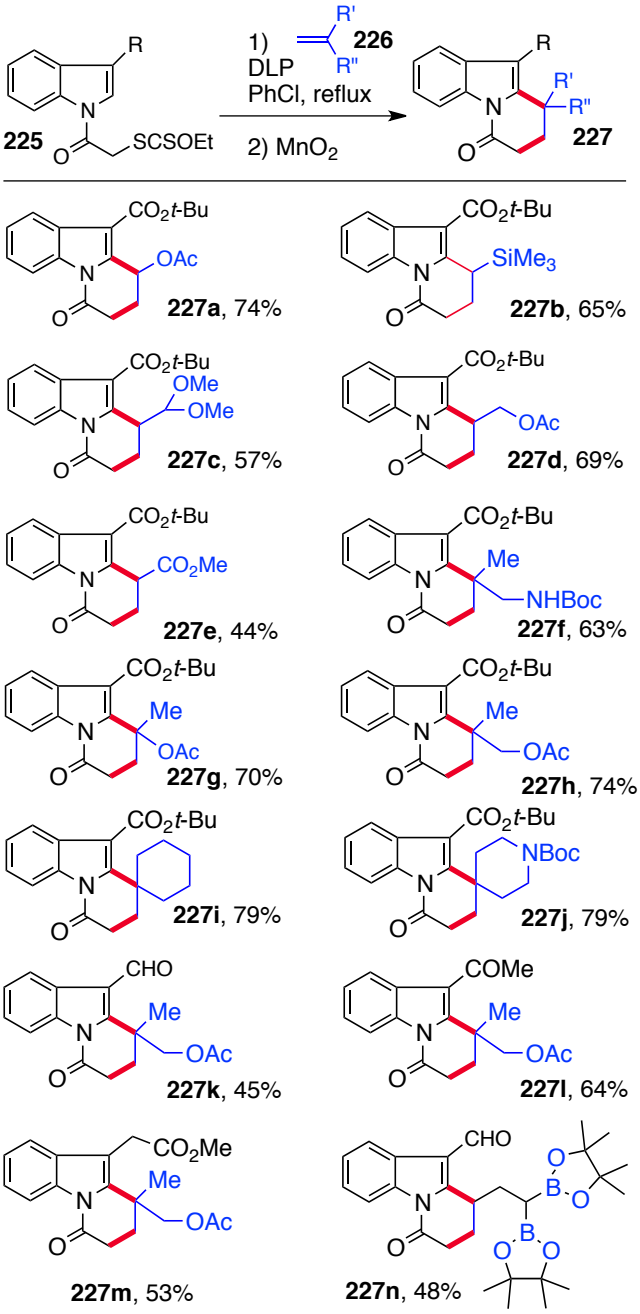
Scheme 47. Last steps in the synthesis of (–)-cryptopleurine

Dihydroazaquinolones also succumb to the same approach.[55] This represents an important expansion of the scope, since this family of heterocycles is only tediously accessible by other routes. Three examples are deployed in Scheme 48 covering different arrangements. The first starts from 3-butenamide **215**, which is converted into adduct **216** and cyclized to give lactam **217**. The same sequence beginning with amide **218** furnishes lactam **220** via intermediate **219**. In this case, it was demonstrated that the chlorine can be removed by catalytic hydrogenation to produce less functionalized congener **221**. The presence of the chlorine in this case is to block the more favorable cyclization on position-2 of the pyridine ring. Finally, amide **222** affords the corresponding dihydroazaquinolone **224** via adduct **223**.



Scheme 48. Synthesis of dihydroazaquinolones

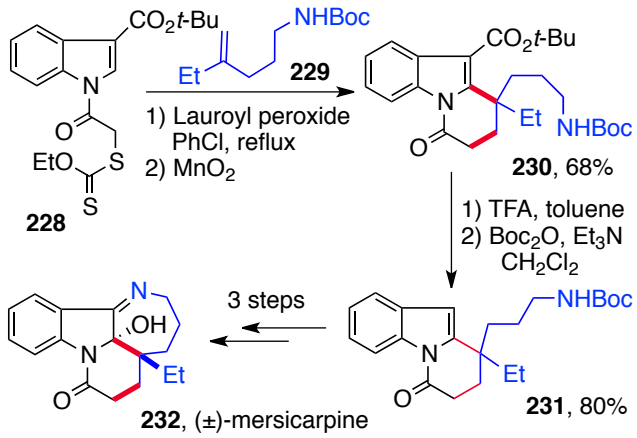
A formal 4+2 process can be used to annulate a δ-lactam on an indole ring, as shown by the generic conversion of xanthate **225** into tricyclic indole derivative **227** by addition to alkene **226** and concomitant cyclization on position-2 of the indole.[79] Examples **227a-n** illustrate the scope of this method for the concise construction of complex polycyclic structures. Best results are obtained when the indole moiety is substituted on position-3 (**225**, R ≠ H), in order to speed up the cyclization and stabilize the cyclized radical. Furthermore, in many cases it was necessary to complete the aromatization process by treating the crude product with manganese dioxide. The ability to access spiro derivatives, **227i** and **227j**, and bis(boronate) **227n** are worthy of note.[80]



Scheme 49. Synthesis of δ-lactams fused to an indole ring

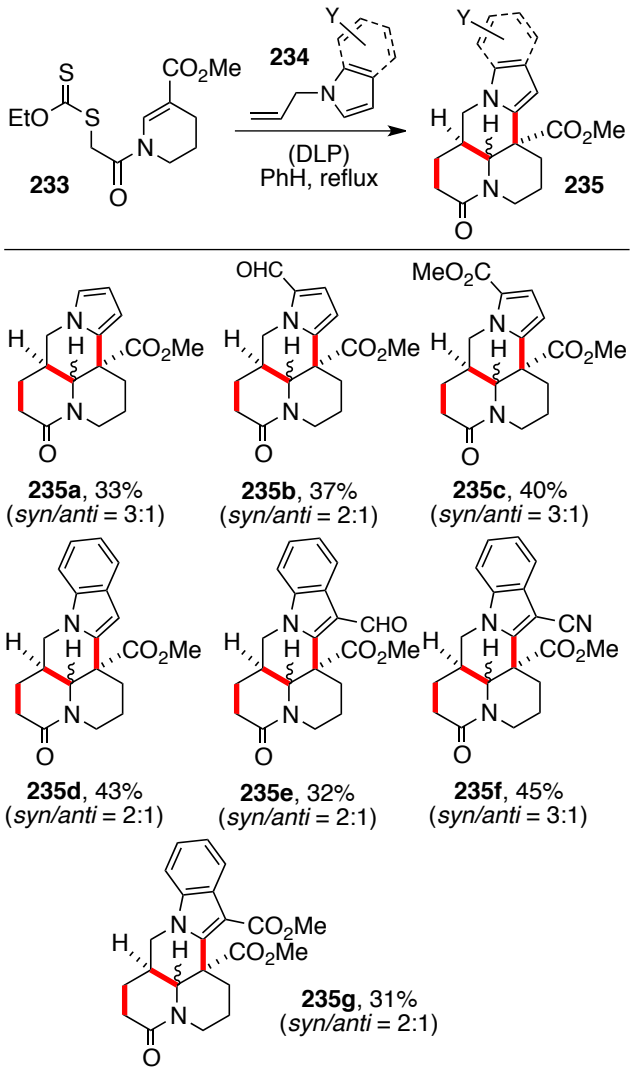
Many of the examples displayed in Scheme 49 feature the creation of a quaternary center attached to position 2 of the indole. Similar quaternary centers are present in numerous indole alkaloids, with one prominent example being mersicarpine **232** (Scheme 50).[81] Indeed, this molecule is an obvious choice for illustrating the power of xanthate chemistry.[79] Applying the addition-cyclization to xanthate **228** and alkene **229** furnishes tricycle **230** in 68% yield. Treatment with trifluoroacetic acid cleaves the *t*-butyl ester and induces the decarboxylation

of the resulting free carboxylic acid. It also deprotects the amine, which has to be re-protected to give intermediate **231**, a compound that had already been transformed into mersicarpine by Kerr and co-workers.[82] The sequence in Scheme 50 thus constitutes a short formal total synthesis of the target alkaloid.



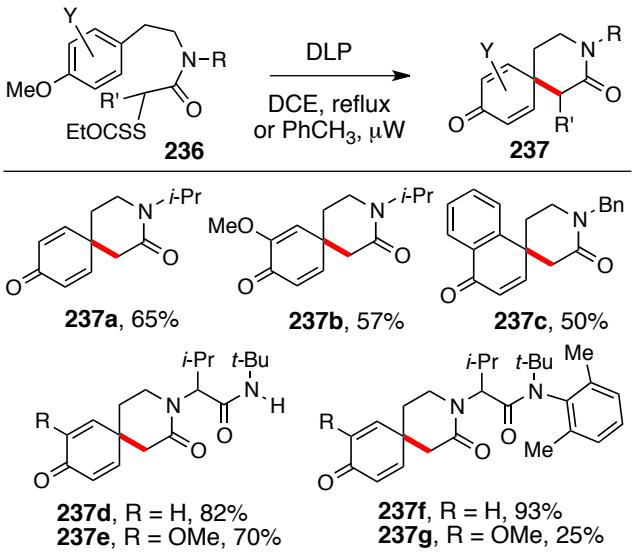
Scheme 50. Formal synthesis of (±)-mersicarpine

Miranda and co-workers combined the formal 4+2 strategy used earlier in the synthesis of matrine (Scheme 42) with the cyclization onto pyrrole and indole rings to prepare a library of alkaloid-like molecules of medicinal interest.[83] To this end, xanthate **233** was made to react with *N*-allyl-pyrrole or *N*-allyl-indole **234** to give tetracyclic or pentacyclic structures **235** by a similar cascade to the one used for the synthesis of matrine (Scheme 51). Stoichiometric amounts of peroxide are needed to oxidize the final radical in the sequence and restore the aromaticity of the heteroaromatic ring. The yield of compounds **235a-g** is moderate but three carbon-carbon bonds are zipped up in one simple operation.



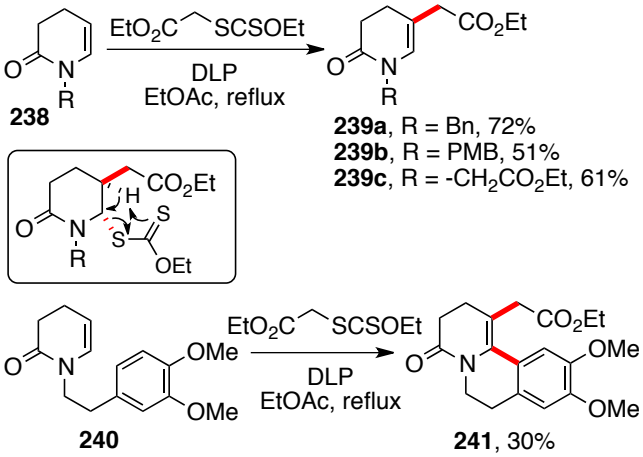
Scheme 51. Expedient syntheses of matrine analogues

The group of Miranda was also able to extend their synthesis of spiro-γ-lactams to the higher homologues by *ipso* ring-closure of xanthates of general structure **236** to give spiropiperidones **237** with various substitution patterns, as exemplified by compounds **237a-g** (Scheme 52).[58] The precursors for the last four examples were obtained through the Ugi reaction.[60]



Scheme 52. Spiro-δ-lactams by radical *ipso* addition

To complete this section, mention must be made of a recent synthesis of δ-lactams reported by Gillaizeau consisting of the reaction of a xanthate with a cyclic enamide such as **238**.[84] The addition takes place on the most nucleophilic and accessible terminus of the alkene to give modified lactam **239a-c** (Scheme 53). As with the 5-endo-cyclization discussed earlier (cf. Scheme 22), the adduct radical is oxidized by the peroxide into the cation followed by loss of a proton to regenerate the enamide. Another pathway to the same enamides is by thermal, Chugaev-like elimination of the xanthate from the normal adduct (see box in Scheme 53), which occurs at moderate temperatures in the case of adducts to enamides.[63]

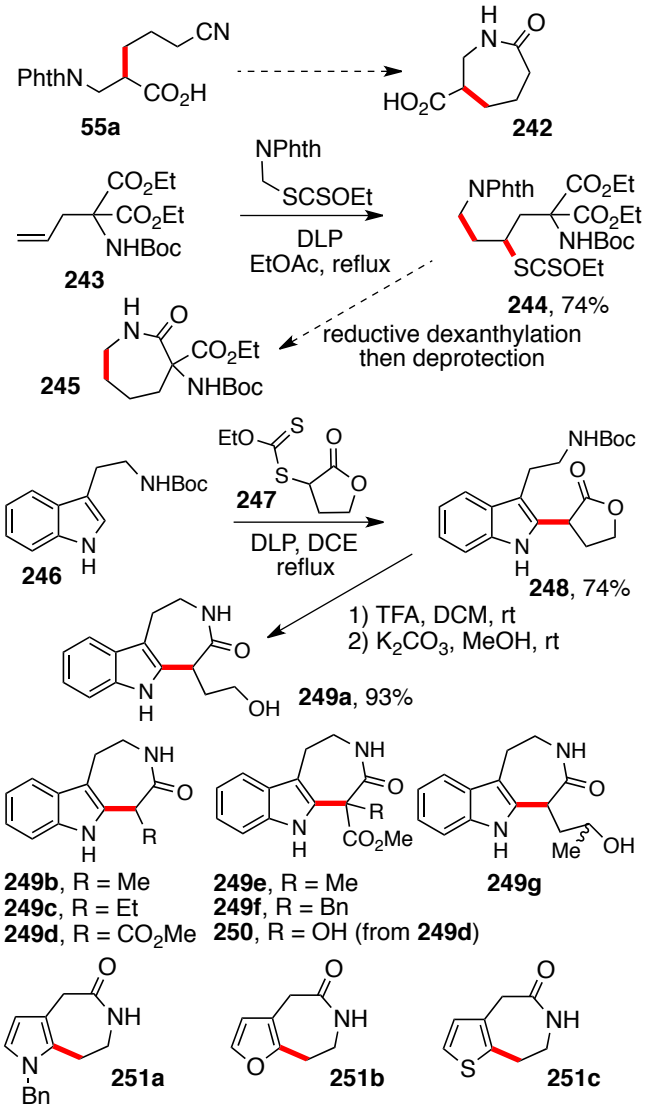


Scheme 53. δ-Lactams by direct modification of cyclic enamides

Whatever the pathway leading to products **239a-c**, and the two are not mutually exclusive, this approach represents a simple method for the modification of existing lactams which could be of more general impact. In principle, cyclic enamides of various sizes should undergo the same transformation using a multitude of functional xanthates as the reacting partner. A more complex variant is also presented in Scheme 53, involving the addition-cyclization on enamide **240** to give unsaturated tricyclic lactam **241**.[84] The alkene in compound **241** is presumably the result of further oxidation by the peroxide of the saturated primary product (not shown).

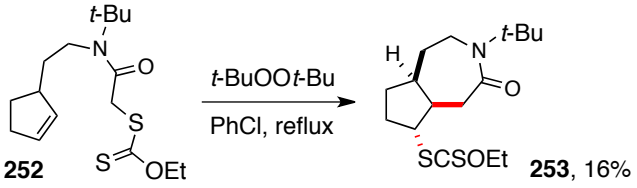
Synthesis of Seven-Membered Ring Lactams

The routes leading to seven-membered ring lactams parallel those for δ-lactams. For the synthesis of protected open chain amino acids or esters, it is sufficient to select the correct combination of xanthate and alkene, with the possibility of placing the protected amine or carboxylate on either component. The carboxylate group can be replaced by a nitrile surrogate, as shown in Scheme 54 by compound **55a** which, in principle, could be easily converted into ε-lactam **242**. Precursor **55a** is the result of addition of xanthate **48** to allylcyanide, as discussed in Schemes 10 and 11 above.[32b]In the case of adduct **244**, which could be a precursor to lactam **245** bearing a protected amino acid motif, the amine masked as a phthalimide is on the xanthate and the ester is on the alkene partner **243**.[85]
Examples for actual cyclizations of aminoesters into ε-lactams have been reported by Martinez.[86] Thus, addition of xanthate **247** to protected tryptamine **246** furnishes lactone **248** in good yield. Removal of the Boc group with TFA followed by neutralization causes spontaneous closure into lactam **249a**. Lactams **249b-g** were prepared in the same manner by simply modifying the xanthate partner. Hydroxy analogue **250** was isolated when the reaction leading to lactam **249d** was left running for a long time without protection from air. This is obviously the result in this case of areal oxidation of the easily formed enolate. Lactams **251a-c** attached to a pyrrole, a furan, and a thiophene, were prepared by a related route where the amino group was produced by reduction of a nitrile.



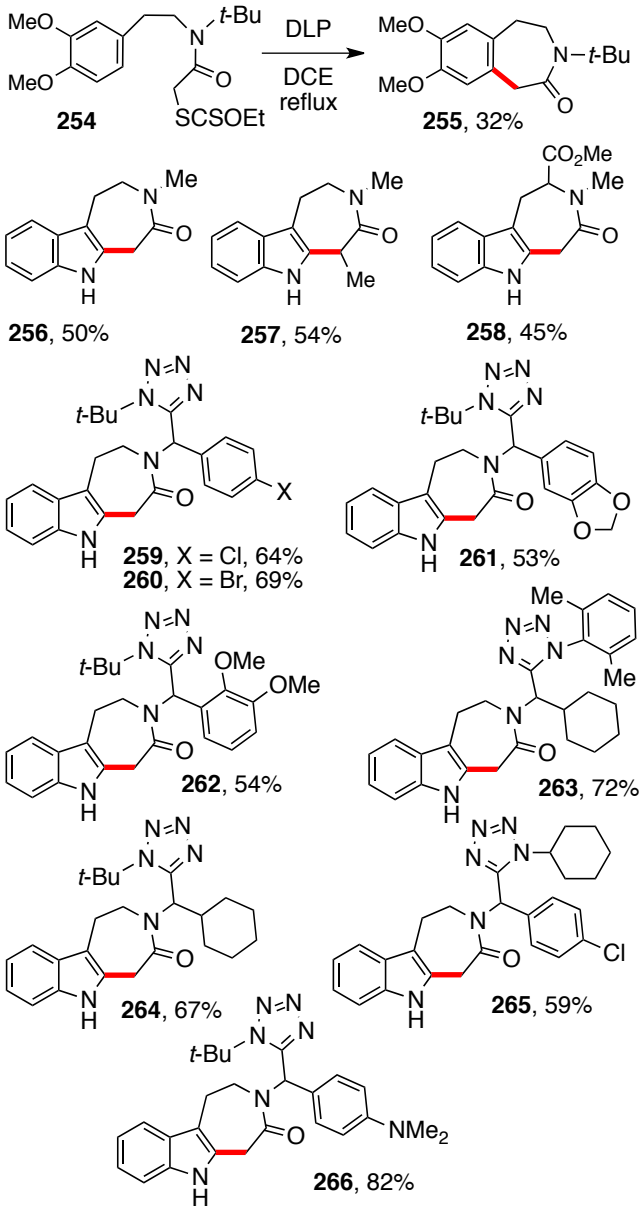
Scheme 54. ε-Lactams by cyclization of ε-aminoesters

Few seven-membered lactams have been prepared by direct radical cyclization onto alkenes. Compound **253** obtained from xanthate **252** is an early example (Scheme 55).[39b]The yield is poor but could certainly be increased by using more recent improved conditions. ε-Lactam **201**, isolated as a minor side-product (see Scheme 44), represents an instance of a 7-*endo* closure.



Scheme 55. Synthesis of ε-lactams by 7-*exo* ring-closure

The formation of lactam **176**, an unwanted side product in the synthesis of alloyohimbane depicted in Scheme 40, is an example of formation of an ε-lactam by direct radical cyclization onto a heteroaromatic ring. This uncommon mode of ring closure can be generalized thanks to the unique features of xanthates and their ability to mediate radical reactions with relatively high energy barriers. Thus, formation of benzazepinone **255** from xanthate **254** by radical cyclization onto a benzene ring is possible, albeit in modest yield (Scheme 56).[87] A similar transformation on an indole ring is more efficient, as shown by examples **256**-**258**[87] and the more elaborate examples **259**-**266** reported by Robles and Gámez-Montaño.[88] The tetrazole precursors for the latter were obtained by the azide variation of the Ugi reaction .

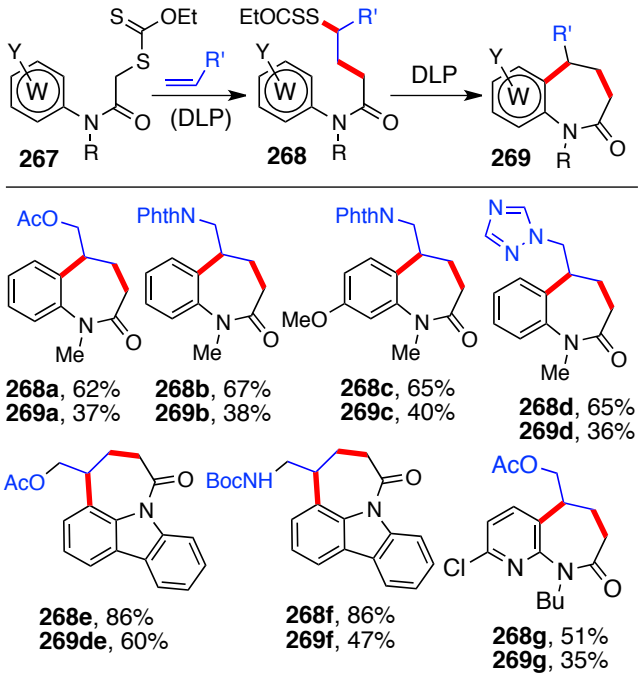


Scheme 56. Synthesis of ε-lactams by ring-closure onto (hetero)aromatic

A more interesting synthesis of benzazepinones revolves around an addition-cyclization process starting from xanthates **267** (Scheme 5). Addition to the alkene furnishes adduct **268** and exposure to further amounts of peroxide induces closure onto the aromatic ring to give benzazepinone **269**. The advantages of this approach are modularity, convergence, readily accessible starting materials, and access to a broad range of building blocks for medicinal chemistry. The benzazepinone motif is one of the most important pharmacophores and methods expanding the diversity of available structures are in high demand.

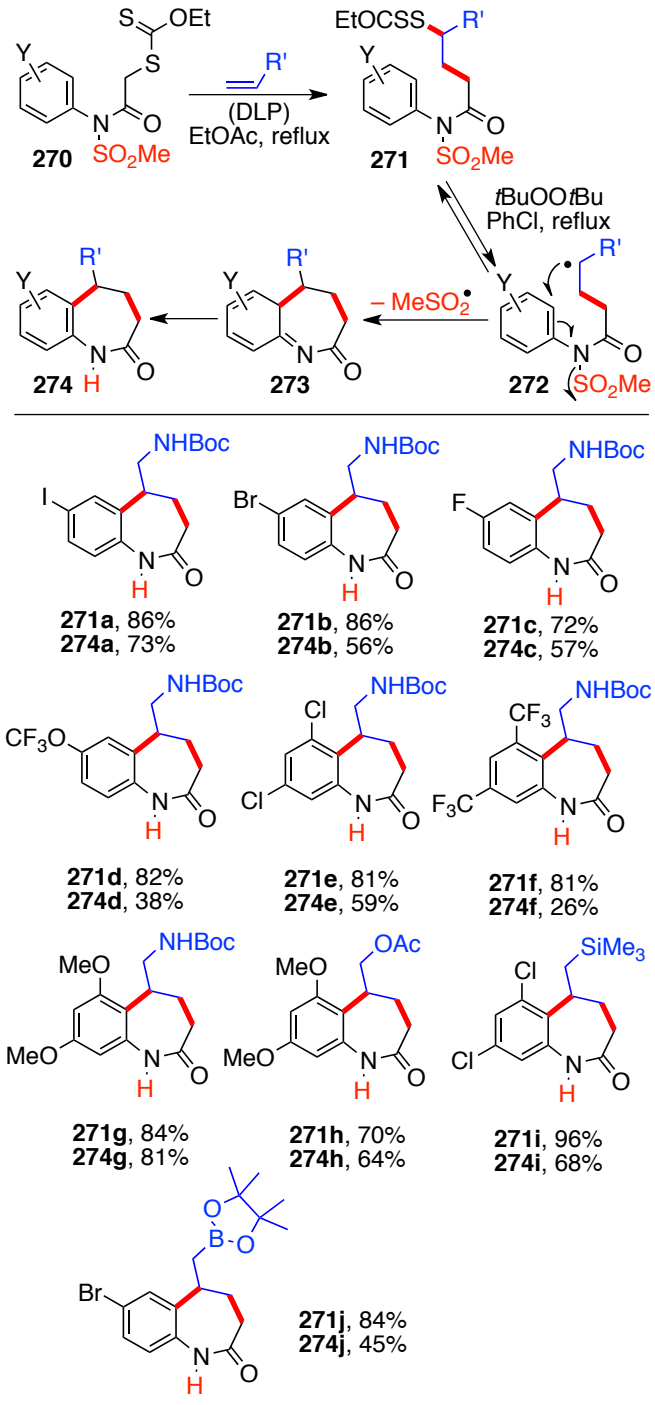
The examples collected in Scheme 57 (and the following Schemes) are representative. For the sake of clarity, the yields for the intermediate adducts, **268a-g**, are shown, but not the

structures. Note, furthermore, that the yields for the intermolecular addition to the unactivated alkenes are significantly higher than those for the cyclization step, reflecting the inherent difficulty of the latter process. Aryl,[87] carbazole,[87] and pyridine[55] scaffolds can be employed and additional heteroaromatic rings can be introduced, such as the triazole moiety in **269d**.[89]



Scheme 57. Benzazepinones by addition and ring-closure onto (hetero)aromatic

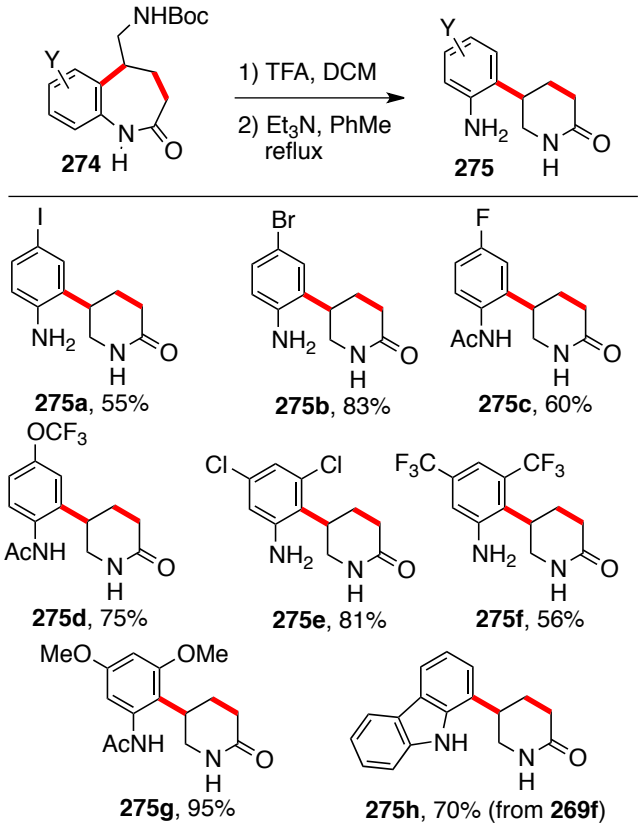
For the cyclization step to succeed, it is necessary for the nitrogen atom in the amide precursors to be substituted, i.e., R ≠ H in structure **267**. This requirement parallels the case of the oxindoles, but contrasts with that of the dihydro-2-quinolones discussed in the preceding section. It is of course possible to introduce a temporary blocking group that could be later removed. A simpler and more appealing solution is to start with methanesulfonylanilide **270** (Scheme 58).[90] Addition to the alkene affords the usual adduct **271** and heating with di-*t*-butyl peroxide at the higher temperature of refluxing chlorobenzene regenerates intermediate radical **272**, which undergoes cyclization and concomitant expulsion of a methanesulfonyl radical. Prototropic isomerization the resulting acylimine **273** finally gives the desired *N*-unsubstituted benzazepinone **275**. Elimination of the sulfonyl radical not only frees the amide nitrogen but allows simultaneous rearomatization without the need to oxidize the cyclized cyclohexadienyl radical into the corresponding cation, as in almost all the previously discussed radical additions to (hetero)aromatics. This strategy is illustrated by examples **274a-j** displayed in Scheme 58.[90] Here again, the yields of intermediates **271a-j** are given without the structures. Note the presence of halides on the aromatic ring, especially iodine and fluorinated groups, and a boronate on the side chain of benzazepinone **24j**.



Scheme 58. Synthesis of *N*-unsubstituted benzazepinones

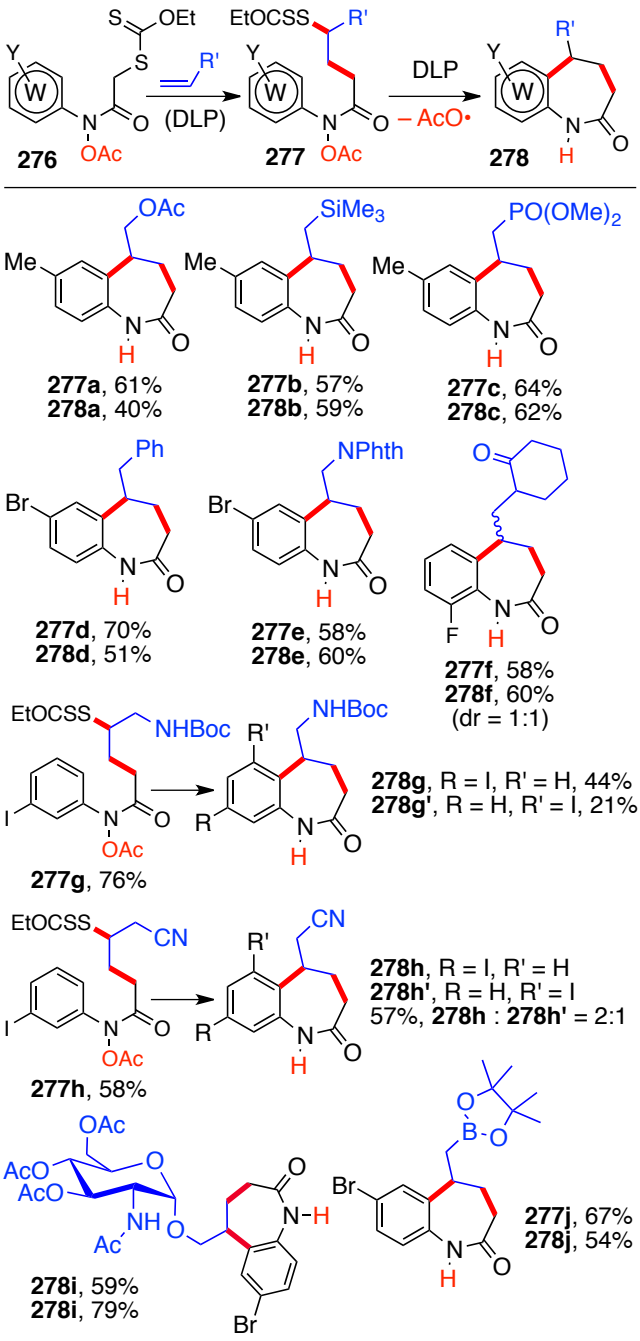
Inspection of the examples in Scheme 58 reveals that the majority contain a protected amine in the side chain. This is not fortuitous. Removal of the Boc group and heating with triethylamine in refluxing toluene triggers a trans-amidation process converting **274'** into 5-

arylpiperidones **275** (Scheme 59). This isomerization, illustrated by examples **275a-h**, constitutes an unusual and counterintuitive, yet short synthesis of this family of medicinally relevant molecules.[90]



Scheme 59. 2-Piperidones by rearrangement of aminomethyl-benzazepinones

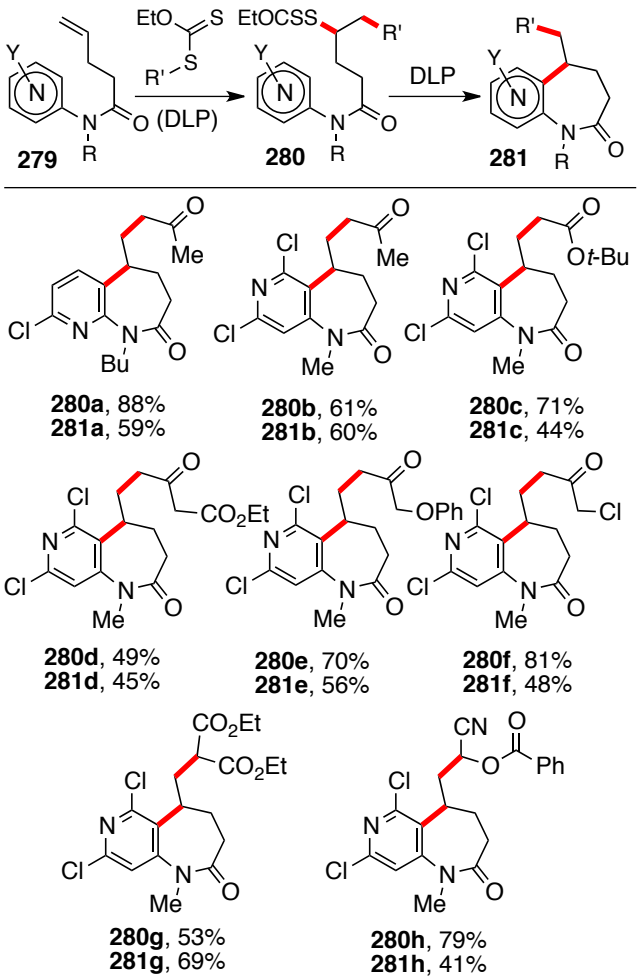
A conceptually related approach to *N*-unsubstituted benzazepinones is to start with hydroxamic esters **276** (Scheme 60).[91] Exposure of the corresponding adducts **277** to further amounts of peroxide induces cyclization of the intermediate radical and subsequent fragmentation to give benzazepinones **278**. The nitrogen-oxygen bond is weak and is cleaved under milder conditions than those used for the sulfonamides in the previous route. An assortment of benzazepinones **278a-j** prepared by this variant are collected in Scheme 60, along with the yield of the respective precursors **277a-j**. A range of substituents can be present on both the aromatic ring and on the appended side chain, including phosphonate (**278c**), carbohydrate (**278i**), and boronate (**278j**). When the substituent on the aromatic ring in the starting material is in the meta position, as in iodides **277g** and **227h**, two regioisomeric benzazepinones **278g,g'** and **277h,h'** are obtained with a 2:1 selectivity.



Scheme 60. Synthesis of *N*-unsubstituted benzazepinones from hydroxamates

An alternative strategy for constructing seven-membered rings fused to aromatics is presented in Scheme 61 as it applies to the case of pyridines but should be easily extended to other (hetero)aromatics.[55,92] In this approach, 4-pentenylamides **279** are made to react with various xanthates and the resulting adducts **280** closed into azabenzazepinones **281** by further treatment with peroxide. Examples **281a-h** are illustrative and provide an idea of the diversity of functional groups that can be introduced into the structures. Of particular note are

chloroketone **281f** and cyanohydrine benzoate **281h**.[92] In the former, the fact that a reactive electrophilic α-chloroketone moiety can partake in two carbon-carbon bond forming processes and remain intact is quite remarkable and constitutes a testimony to the mildness of the method. As for the latter, the cyanohydrin benzoate is a latent aldehyde and can act therefore as a springboard for myriad transformations hinging on such a useful functional group.

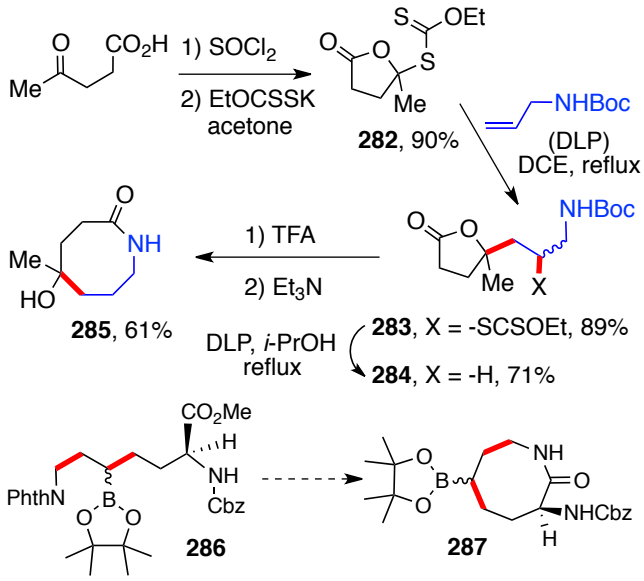


Scheme 61. Benzazepinones by addition and ring-closure onto pyridines

Synthesis of Eight-Membered Ring Lactams

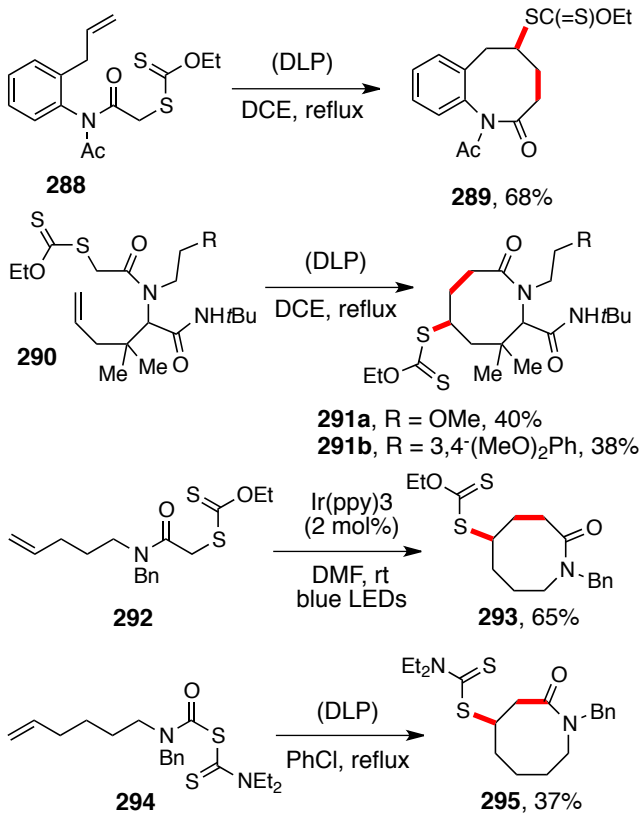
The formation of medium sized rings is generally difficult to accomplish with most methods, radical or otherwise, because of unfavorable entropic factors and repulsive intracyclic interactions. Fewer routes have therefore emerged for the synthesis of 8-membered ring lactams. Two will be discussed in this section. The first relies on the ease of synthesis of aminoacids with the correct number of atoms between the amine and carboxylic acid groups.

The first example in Scheme 62 involves xanthate **282**, a reagent readily prepared from levulinic acid.[93] Its addition to *N*-Boc allylamine produces adduct **283**, which is readily dexanthylated by treatment with stoichiometric amounts of DLP in isopropanol.[47] Unmasking of the amine with TFA and neutralization with triethylamine gives azocan-2-one **285** by aminolysis of the lactone. The second concerns boronate **286**, which was obtained by two successive radical additions and which could in principle be converted into lactam **287**, even though this might not be a trivial operation given the other functional groups present.[94]



Scheme 62. Synthesis of eight-membered ring lactams

The second route to 8-membered lactams hinges on an 8-*endo* cyclization,[95] a rare ring closure mode that is in fact quite easy to implement when an amide link is present in the main chain. The amide group diminishes the intracyclic repulsion, and the rigidity imparted by the restricted rotation around the amide bond decreases the degrees of freedom of the system. Four examples are portrayed in Scheme 63. In the first, xanthate **288** is converted into benzazocanone **289** in 68% yield.[96] A small amount (27%) of the isomeric 7-membered ring lactam (not shown), formed by a 7-*exo* cyclisation, is also produced. In a similar fashion, lactams **291a,b** were obtained from the corresponding xanthate precursor **290**, albeit in moderate yield.[40] Xanthate **292** is cyclized into lactam **293** by irradiating in the presence of an iridium complex acting as a redox catalyst.[41] Finally, dithiocarbamate **294** furnishes lactam **295** by closure of the intermediate carbamoyl radical.[19a]

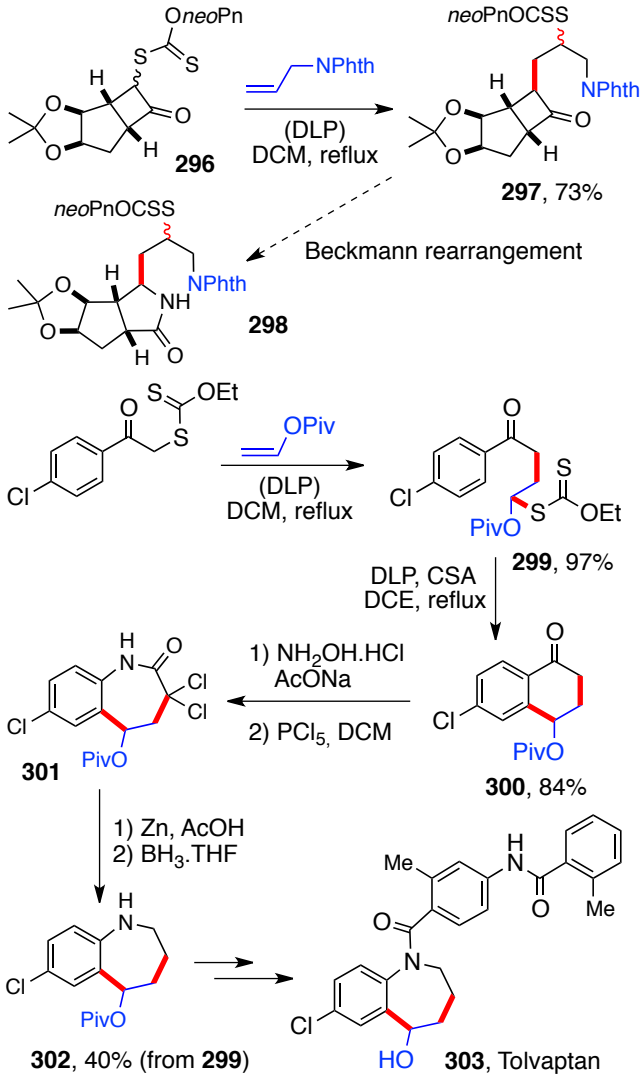


Scheme 63. Eight-membered ring lactams by 8-*endo* cyclization

Concluding Remarks

The transformations described so far constitute only a small fraction of the synthetic opportunities offered by the xanthate addition-transfer technology. The ability to mediate intermolecular additions to both activated and electronically unbiased alkenes; to accomplish cyclizations on aromatics and heteroaromatics and, in the latter case, even intermolecular additions; to allow the formation of 4,5,6,7, and sometimes even 8 membered rings; to tolerate numerous functionalities, especially polar groups, represent considerable synthetic advantages. A few further possibilities and perspectives for the synthesis of lactams will be discussed to conclude this review.

The chemistry of xanthates is very effective for the synthesis of ketones.[97] In alliance with the Beckmann and related rearrangements, it constitutes a powerful tool for accessing lactams of almost every size. For instance, substituted cyclobutanones are readily available by the usual addition process, as shown by the conversion of xanthate **296** into adduct **297**.[98] Ring expansion of cyclobutanone **297** by a Beckmann rearrangement on the oxime would lead to γ-lactam **298**. It is worth pointing out that, unlike higher cycloalkanones, alkylation of cyclobutanone enolates is generally problematic.[99] This contrasts starkly with the facile additions of the corresponding radicals.



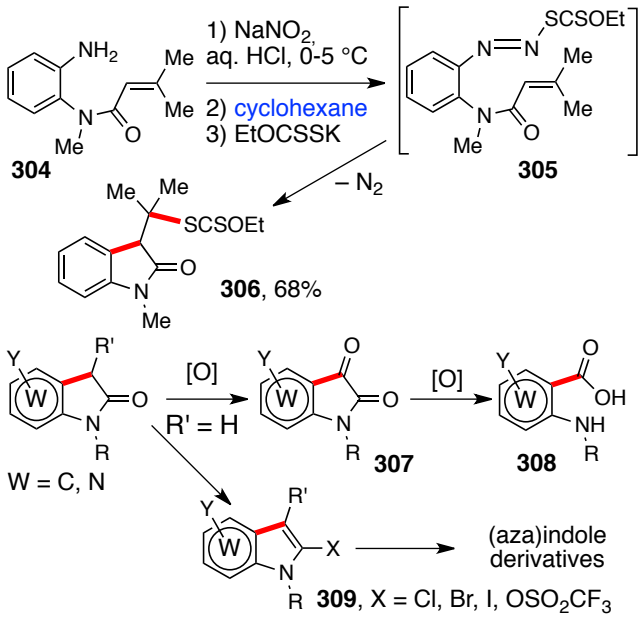
Scheme 64. Lactams by the Beckmann rearrangement

One actual application is the synthesis of Tolvaptan **303**, a vasopressin V_2 receptor antagonist (Scheme 64). [100] Starting from *S*-*p*-chlorophenacyl xanthate, addition to vinyl pivalate produces adduct **299** and ring-closure by further treatment with DLP in the presence of camphorsulfonic acid (CSA) leads to tetralone **300**. Beckmann rearrangement on the corresponding oxime mediated by phosphorus pentachloride affords dichlorolactam **301**. Interestingly, the benzylic pivalate group remains intact under the strongly acidic medium of the rearrangement. Dechlorination and reduction of the amide gives benzazepine **302** which can be processed into Tolvaptan.

Another is a modification of the lesser known Leuckart reaction, originally employed to prepare thiophenols from anilines by treatment of the corresponding diazonium salt with a xanthate salt.[101] If an alkene is suitably positioned, as in aniline **304** (Scheme 65), the

intermediate aryl radical can be intercepted to give, in this case, oxindole **306**.[102] This transformation proceeds via diazene **305**, which evolves into oxindole **306** by a radical chain mechanism. All the reactions of xanthates discussed so far are not exothermic and do not pose any safety hazard, even upon scale up. In this case, however, owing the fast loss of molecular nitrogen and the high reactivity of the ensuing aryl radical, the decomposition of diazene **305 is exothermic** and initiated by laboratory lighting or even by traces of impurities. Suitable precautions must therefore be taken and the classical procedure must be modified as described hereafter.

Diazenes such as **305** are generally insoluble in water and precipitate from the medium as soon as they are formed upon addition of the xanthate to the diazonium salt. If the diazene happens to be a liquid, the exothermic chain process taking place in the neat material can become uncontrollable. It is therefore important to add a layer of cyclohexane (or another suitable non water miscible solvent) before portion-wise incorporation of the xanthate salt with stirring.[102] Under these conditions, the diazene dissolves in the organic layer as it is formed and its decomposition remains under control. This is a minor but key experimental modification that makes the process safe.

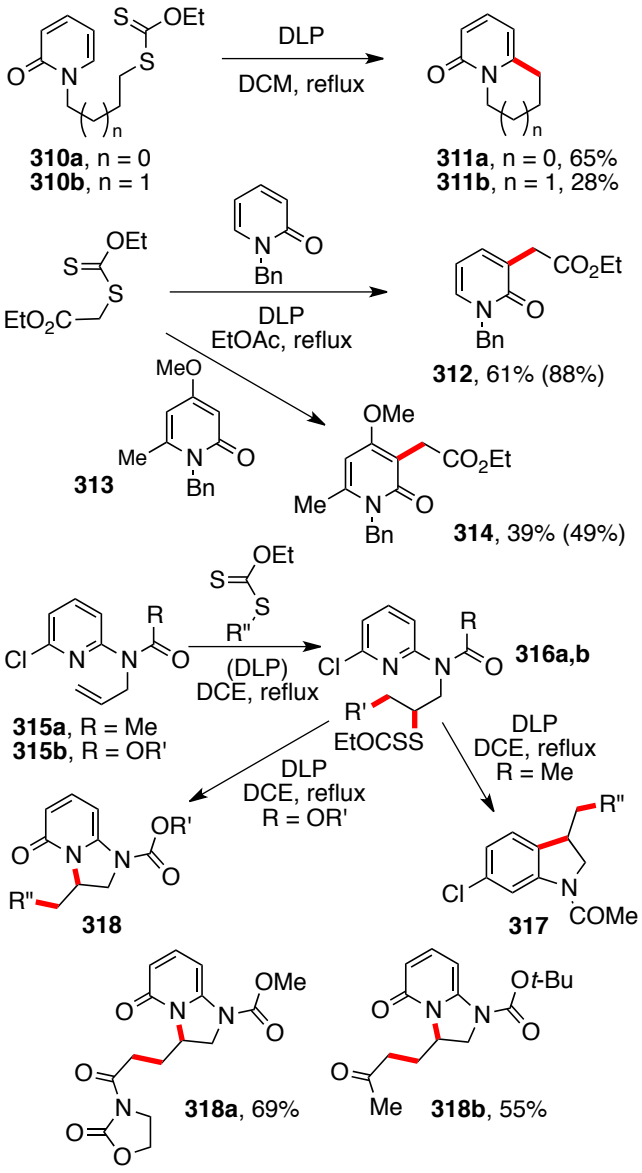


Scheme 65. Alternative route to oxindoles and further transformations

The main limitation of the diazonium route to (aza)oxindoles is the accessibility of the 1,2-diamino (hetero)arenes. It provides nevertheless oxindoles with substituents not necessarily easy to obtain by the approaches described earlier. In any case, a facile access to (aza)oxindoles with almost any substitution pattern translates into a entry to other important building blocks. Two are shown in Scheme 65. The first is oxidation into isatins **307** and oxidative cleavage to give anthranilic acids **308**.[103] The second is conversion into 2-

haloindoles or 2-indole triflates **309**, which are stepping stones to numerous transition metal-based coupling reactions.[104]

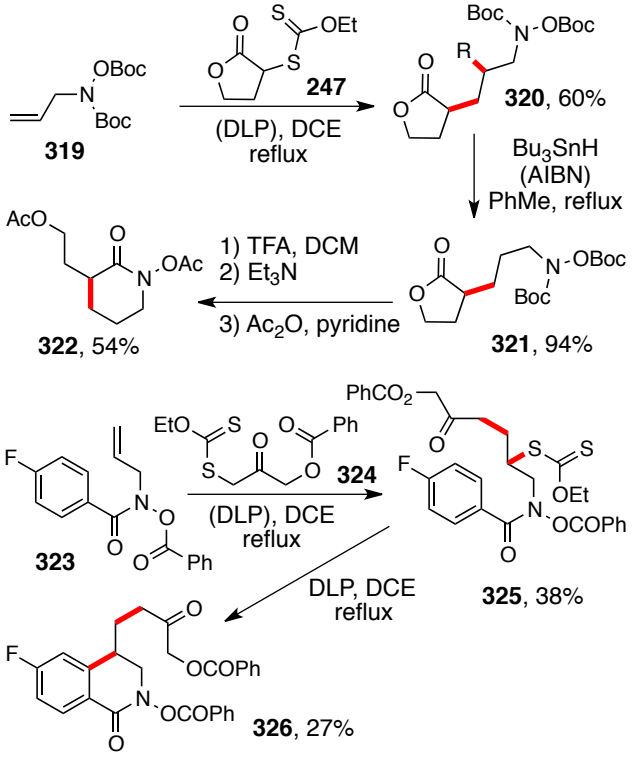
2-Pyridones constitute an important subfamily of δ-lactams. They can be converted into pyridines or reduced to piperidones. Xanthate chemistry can indeed be applied to prepare a diversity of these compounds. Some examples are displayed in Scheme 66. The construction of bicyclic pyridones such as **311a,b** can be accomplished by cyclization of the respective precursors **310a,b**.[105] Bimolecular additions are also possible, as illustrated by the synthesis of simple pyridone **312** and the more substituted pyridone **314** from precursor **313**.[84]



Scheme 66. Various routes to 2-pyridones

An unexpected path to pyridones was uncovered when examining a convergent synthesis of azaindolines by addition to protected *N*-allyl aminopyridines.[106] In the case of acetamides **315a**, the addition and cyclization furnished indeed the expected indolines **317**. However, when carbamate protected substrates **315b** were examined, exposure of the corresponding adducts **316b** to the same conditions resulted in the surprising formation of pyridones **318** through, at the time, an unprecedented radical attack on the pyridine nitrogen. It is remarkable that a seemingly trivial modification of the protecting group has such a profound influence on the course of the reaction. Further work is still required to unravel the factors undergirding this behavior. From a preparative point of view, this unexpected observation opens access to unusual pyridone derivatives that may be of medicinal interest, as illustrated by compounds **318a** and **318b**. The yields shown are for the cyclization step.

N-Hydroxy lactam derivatives constitute another interesting class of lactams that can equally be accessed by the radical chemistry of xanthates. Two examples are presented in Scheme 67 to conclude this review. The first concerns the addition of xanthate **247** to protected *N*-allylhydroxylamine to give compound **321** after reduction of the initial adduct **320**.[107] Deprotection of the hydroxylamine moiety with TFA and neutralization with triethylamine induces spontaneous ring closure to afford *N*-acetoxypiperidone **322** after acetylation. The second example involves the addition of xanthate **324** to compound **323**.[108] Further treatment of the resulting adduct **325** with DLP causes ring-closure into *N*-benzoyloxy dihydroxisoquinolone **326**. The yield of the cyclization step is still modest but should be improvable by further work.



Scheme 67. Synthesis of cyclic hydroxamates

The present review on the application of the reversible addition transfer of xanthates to the synthesis of lactams reflects the multifaceted and unique properties of this chemistry. Lactams of all kinds and substitution patterns are accessible and many more possibilities have not yet been explored or implemented. Non-negligible practical advantages include inexpensive reagents, mild experimental conditions, tolerance to numerous polar and non-polar functional groups, and, not least, safety and scalability.

Acknowledgements

I am greatly indebted to my co-workers, whose names appear in the references, and who made this chemistry possible by their enthusiasm, skill, and dedication. I am in particular most grateful to *Dr Béatrice Sire*, who has contributed decisively to many of the projects and was instrumental to their success. I also thank the following organisations and companies who have provided financial support over the years: Ecole Polytechnique, CNRS, DGA, MNRT, the Royal Society; the Royal Commission for the Exhibition of 1851, the China Science Council, Aventis (now Sanofi), Rhodia (now part of Solvay), Laboratoires Servier, and Syngenta.

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