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XANTHATES AND VINYL ESTERS, A REMARKABLY POWERFUL ALLIANCE

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This paper is dedicated with respect, admiration, and friendship to Prof. Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – The present brief overview highlights and discusses the synthetic potential of the degenerative radical addition of xanthates to vinyl esters. The process results in the formation of masked aldehydes bearing numerous functionalities. It allows expedient and convergent syntheses of various structures, including cyclic and open-chain enones, trifluoromethyl enones, dienes, pyrroles, dithietanones, thiophenes, hydroxytetralones, naphthalenes and naphthols.

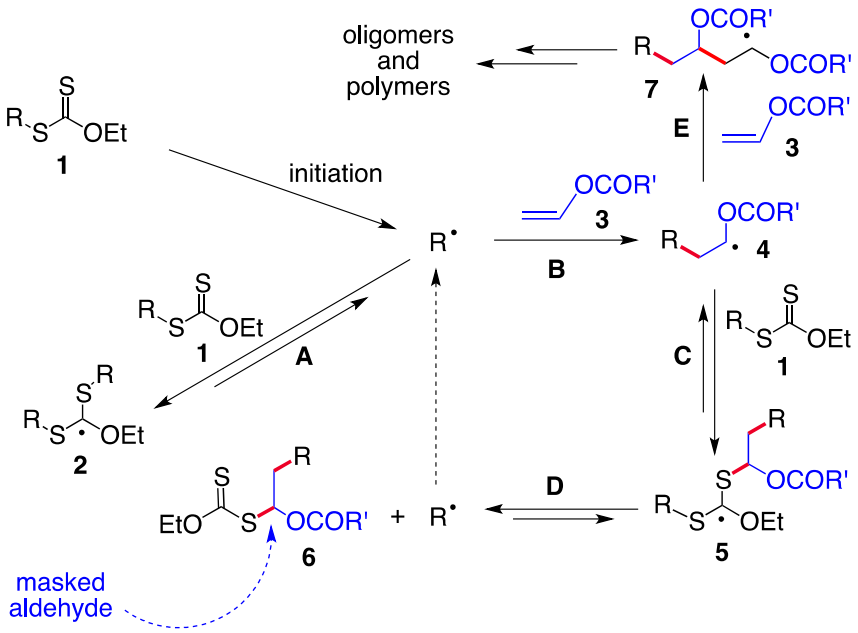
CONTENTS

1. INTRODUCTION

Vinyl esters constitute a major family of monomers for the polymer industry, but their use in the synthesis of small molecules has remained comparatively limited.[1] One notable very useful application is their participation in dipolar cycloadditions and inverse electron demand Diels-Alder cycloadditions.[2] In the present short overview, we describe how their association with the degenerative xanthate radical addition-transfer process can lead to numerous synthetically relevant transformations. These stem from

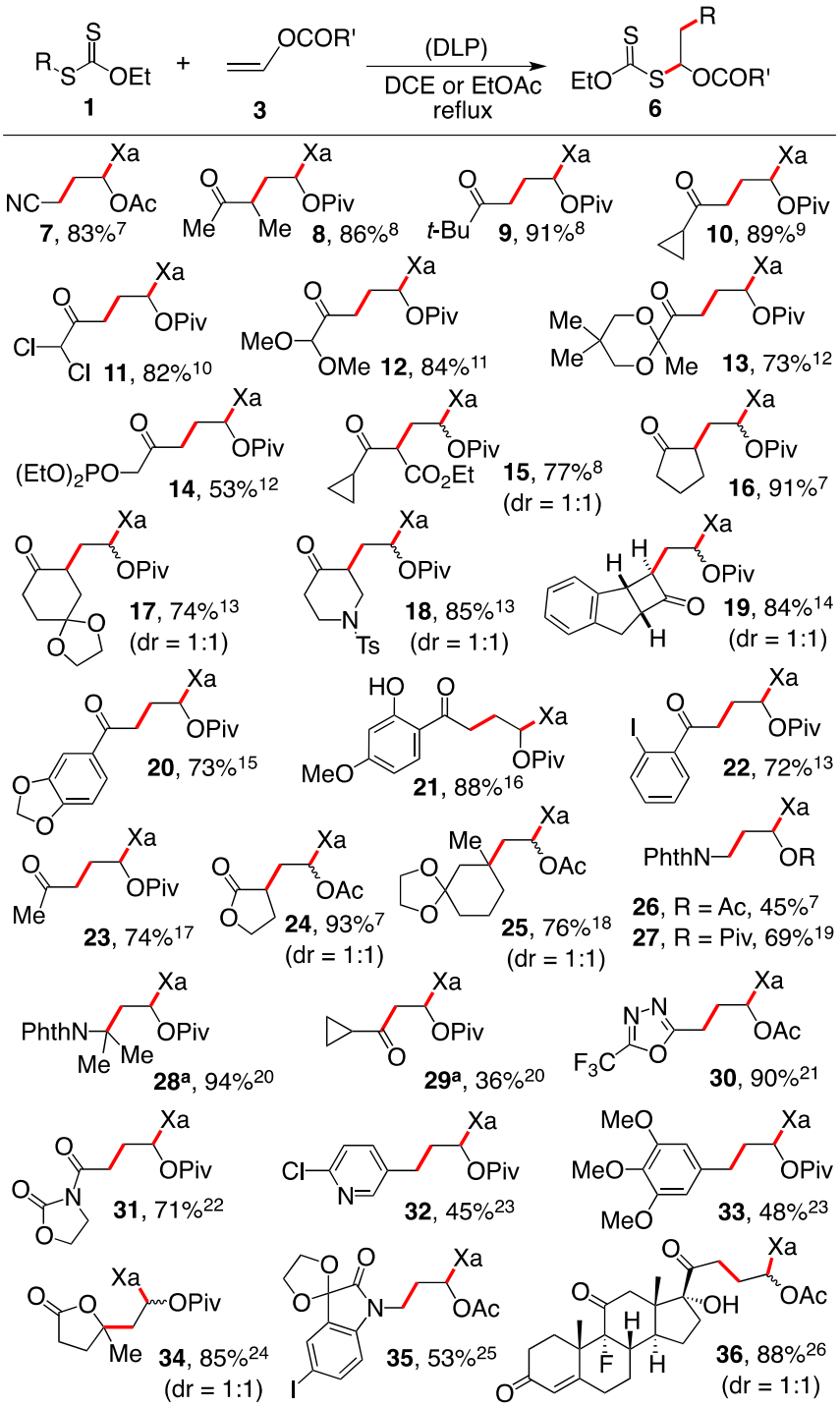
the facility with which carbon-carbon bonds can be formed at the unsubstituted extremity of the vinyl ester and the broad variety of functional group combinations that can be created.[3]

First, it is necessary to outline the basic mechanistic rationale of this unique chemistry, so that its main features can be appreciated. A simplified mechanism for the addition transfer of xanthate **1** to vinyl ester **3** is outlined in Scheme 1.[4] In an initiation step, most commonly involving the thermolysis of a peroxide, radical R• is generated from xanthate **1** and is rapidly captured by its precursor to give radical **2** (path **A**), but this step is reversible and degenerate. Radical R• is therefore not consumed and, as it is constantly regenerated, its effective lifetime increases significantly, allowing it to react with vinyl ester **3** to give finally adduct **6** via intermediates **4** and **5** (paths **B** → **C** → **D**). Stabilized adduct radicals **2** and **5** are hindered and, because they lack β-hydrogens, are unable to disproportionate. They are in fact semi-persistent species that reversibly store radicals R• and **4** in a non-reactive form, thus lowering their *absolute* concentration and curtailing unwanted radical-radical interactions. The reversibility of steps **A**, **C**, and **D** means that the *relative* concentrations of R• and **4** are also regulated. A proper selection of the reactants, *such that initial radical R• is more stable than adduct radical **4** (neglecting in a first approximation polar effects)*, ensures that the steady-state concentration of the former remains sufficiently greater than that of the latter, limiting in this manner the formation of oligomeric side-products by further additions of adduct radicals **4** to vinyl ester **3** (step **E**). Interestingly, xanthates have proven very efficient at controlling the polymerization of vinyl esters. Indeed, the unique chemistry of xanthates and related thiocarbonylthio derivatives constitute the basis of the extremely powerful RAFT/MADIX technology for the manufacture of block co-polymers from most commercial monomers.[5] At least 8000 publications and 500 patents have appeared describing work in this field.[6]



Scheme 1. Simplified Mechanism for the Radical Addition of a Xanthate to a Vinyl Ester

Much of the chemistry that will be detailed hereafter hinges on the observation that adduct **6** is at the same time a masked aldehyde and a xanthate that is capable of partaking in a second radical transformation or used as an entry into the exceptionally rich "ionic" chemistry of sulfur. The great variety of structures and functional groups that can be incorporated into the "R" group of the xanthate gives this approach an important strategic dimension. A simple glance at the examples displayed in Scheme 2 gives an idea of the broadly generality.[7-26]



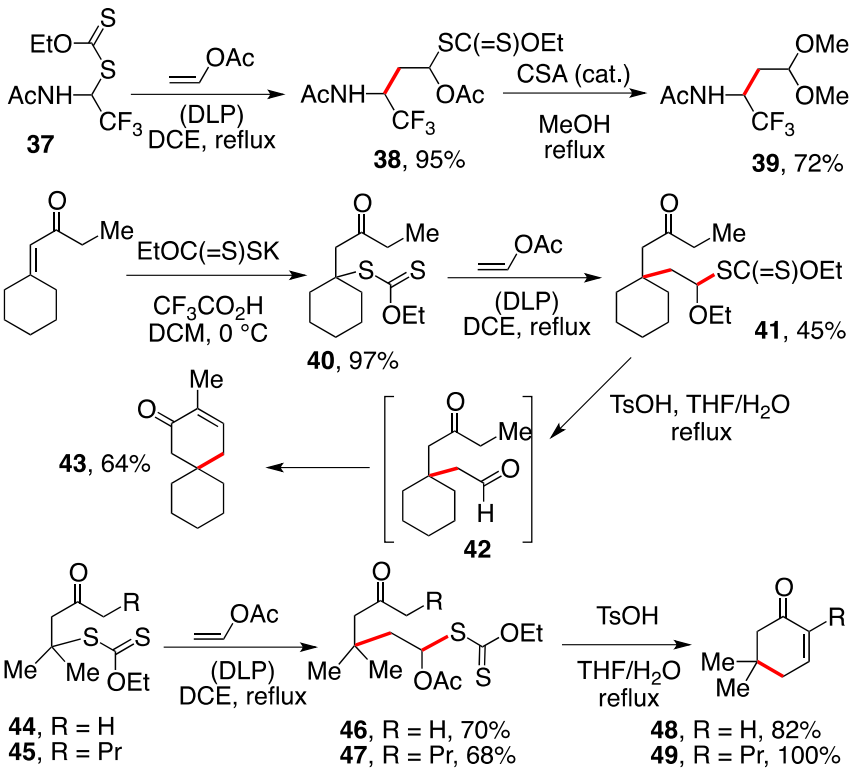
DLP = dilauroyl peroxide; Xa = -SC(=S)OEt; Piv = pivalate
a) initiated photochemically with a tungsten filament lamp.

Scheme 2. Examples of Xanthate Additions to Vinyl Acetate and Vinyl Pivalate

Each of these compounds contains a newly formed carbon-carbon bond (in red) and harbors a latent aldehyde. Dilauroyl peroxide (DLP) is used to initiate the process with the exception of two examples, **28** and **29**, where the precursors are the yellow, light sensitive *S*-acyl xanthates [R-C(=O)S-C(=S)OEt]. The initiation is simply accomplished by irradiation with visible light (a decarbonylation step, R-C•=O → R• + C=O, is involved in the case of **28**).[20] Furthermore, it was found in many instances that the yield of the radical additions was slightly higher with vinyl pivalate than with vinyl acetate (cf. **26** and **27**). The more robust pivalate group offered moreover some advantages when further transformations were considered, as will be discussed later.

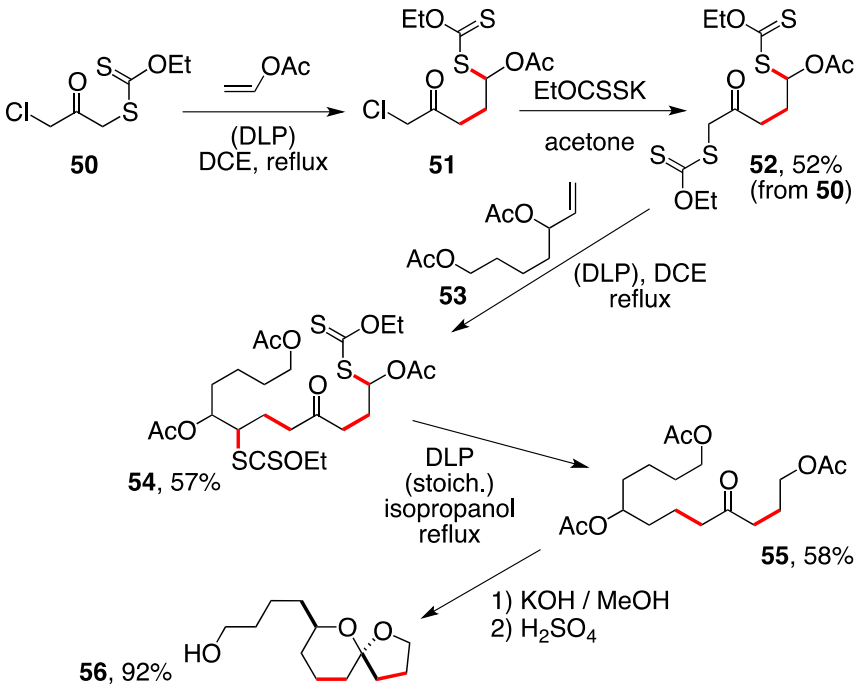
2. SYNTHESIS OF ALDEHYDES, CYCLOHEXENONES AND RELATED DERIVATIVES

The latent aldehyde group in the adducts can be revealed by simple hydrolysis. Aldehydes are best converted into more conveniently stored acetals or captured *in situ* when possible. An example of the former is shown in Scheme 3, where geminal (trifluoromethyl)acetamido adduct **38** derived from xanthate **37** is transformed directly into crystalline acetal **39** by treatment with camphorsulfonic acid (CSA) in methanol.[27] Two examples of the latter are depicted in the same Scheme. Thus, exposure of addition product **41** of xanthate **40** to vinyl acetate to aqueous acid furnishes directly cyclohexenone **43**.[18] This transformation, which proceeds by way of intermediate aldehyde **42**, is a variation on the classical Robinson annulation. Cyclohexenones **48** and **49** were prepared by a similar sequence. In all cases, a quaternary center is created very easily.



Scheme 3. Aldehydes and Cyclohexenones

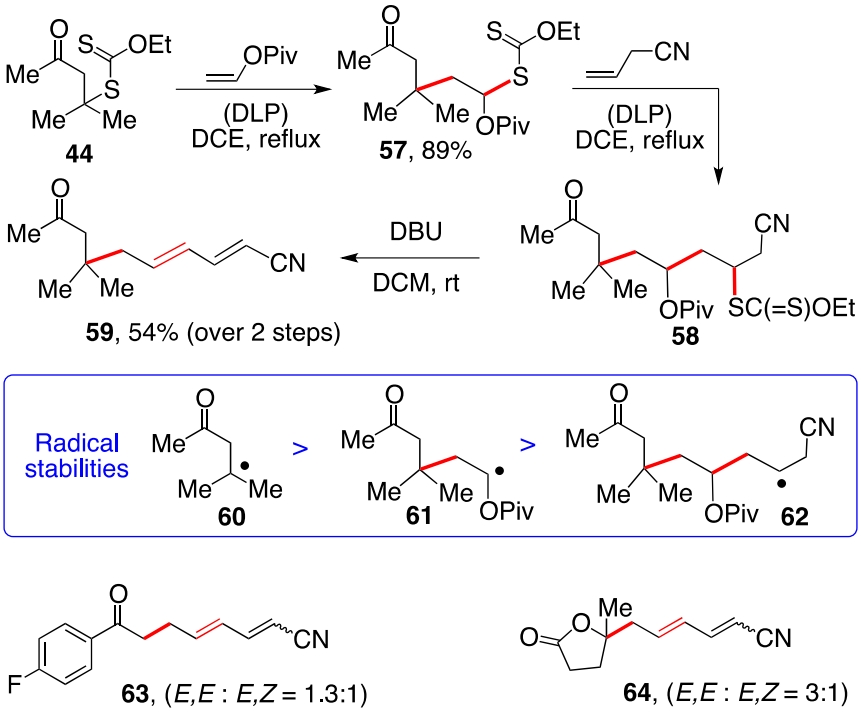
Advantage can be taken from the presence of the xanthate group in adducts **6** to effectuate a second radical operation. The simplest is a radical based reductive dexanthylation, a transformation that can be accomplished by numerous reagents such as tributylstannane,[28] tris(trimethylsilyl)silane,[29] hypophosphorus salts,[30] or with a combination of DLP and 2-propanol.[31] The last method allies cheapness and lack of obnoxious smell upon workup, and it use is illustrated by the sequence in Scheme 4 leading to the formation of spiroketal **56**.[32] In this synthesis, the addition of xanthate **50** to vinyl acetate serves to introduce the two carbons needed to form the tetrahydrofuranyl subunit. Remarkably, the reactive α-chloroketonyl motif remains intact, and adduct **51** can be readily converted into a new xanthate **52**. A regioselective second radical addition to allylic acetate **53** gives compound **54**, where both xanthates are easily removed with DLP/2-propanol to furnish triacetate **55**. Finally, saponification and acidification complete the formation of the desired spiroketal **56**. In this route to spiroketals, two carbon-carbon bonds have been sequentially introduced on either side of the ketone initially present in chloroacetonyl xanthate **50**. Indeed, the formation of intermediate **55** represents an overall unsymmetrical dialkylation of acetone where the radical addition to two alkenes, in this case vinyl acetate and allylic acetate **53**, replaces the ubiquitous ionic alkylation of enolates. This approach complements nicely traditional enolate chemistry and opens up numerous synthetic opportunities.[33]



Scheme 4. Synthesis of Spiroketals

Instead of simply reductively removing the xanthate end-group from adducts **6**, it would be more productive to use it to create another carbon-carbon bond, as depicted in Scheme 5.[25] Thus, addition of

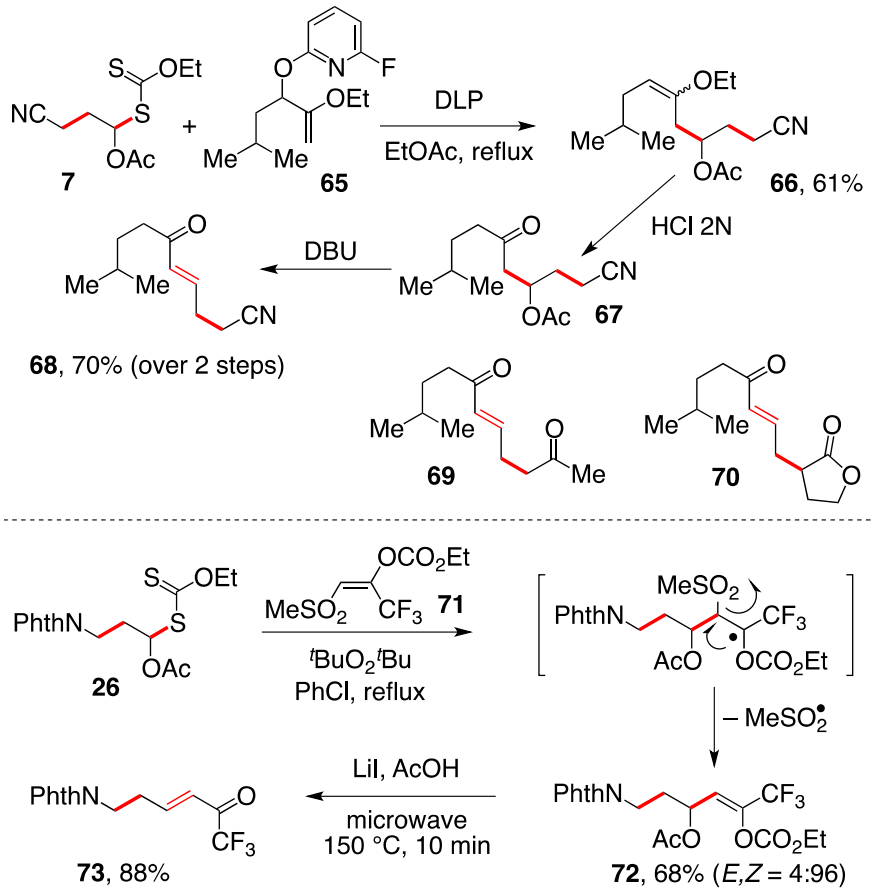
xanthate **44** to vinyl pivalate furnishes adduct **57**. Note again the better yield as compared to the acetate analogue **46**. A second addition to allyl cyanide gives rise to a new adduct **58**, where the xanthate is located β to the cyano group. Treatment with base (DBU) causes therefore its elimination, and this is followed by elimination of the pivalate to give finally dienenitrile **59** as the *E,E* geometrical isomer. The success of this sequence hinges on the observation that tertiary radical **60** derived from the first xanthate **44** is more stable than radical **61**, which in turn is more stable than radical **62** corresponding to the final adduct **58**. This is in keeping with the condition stated in the introduction that initial radical R• must be more stable than adduct radical **4** (Scheme 1). The small stabilization of **61**, provided by the lone pair of the pivaloyloxy oxygen, is therefore what makes this second addition possible and allows a considerable and rapid increase in complexity. Two additional examples of diene formation, **63** and **64**, are given in the lower part of Scheme 5. The latter is prepared from adduct **34** in Scheme 2, itself derived from levulinic acid.[25]



Scheme 5. Synthesis of Dienenitriles

Two alternative routes to unsaturated structures starting with adducts to vinyl esters are pictured in Scheme 6. The first consists in the addition-fragmentation of xanthate **7** to 2-fluoropyridyl-6-oxy derivative **65** to give enol ether **66**.[17] Homolytic cleavage of the normally strong carbon-oxygen is seldom observed in radical reactions. Indeed, the inertness of such bonds towards homolytic β-eliminations is one of the reasons why radical processes are so useful for the synthesis and modification of oxygen rich substrates such as carbohydrates, terpenes, and sundry other natural products. Placing a fluoropyridine on the oxygen weakens the C—O bond sufficiently to permit its homolytic rupture under mild conditions.

Allylic alcohols thus become very attractive radical allylating agents.[34] In the case of enol ether **66**, hydrolysis furnishes ketone **67**, which is directly treated with DBU base to induce the β-elimination of the acetate and generate enone **68**. Enones **69** and **70** were similarly prepared from adducts **23** and **24**, respectively.[17]



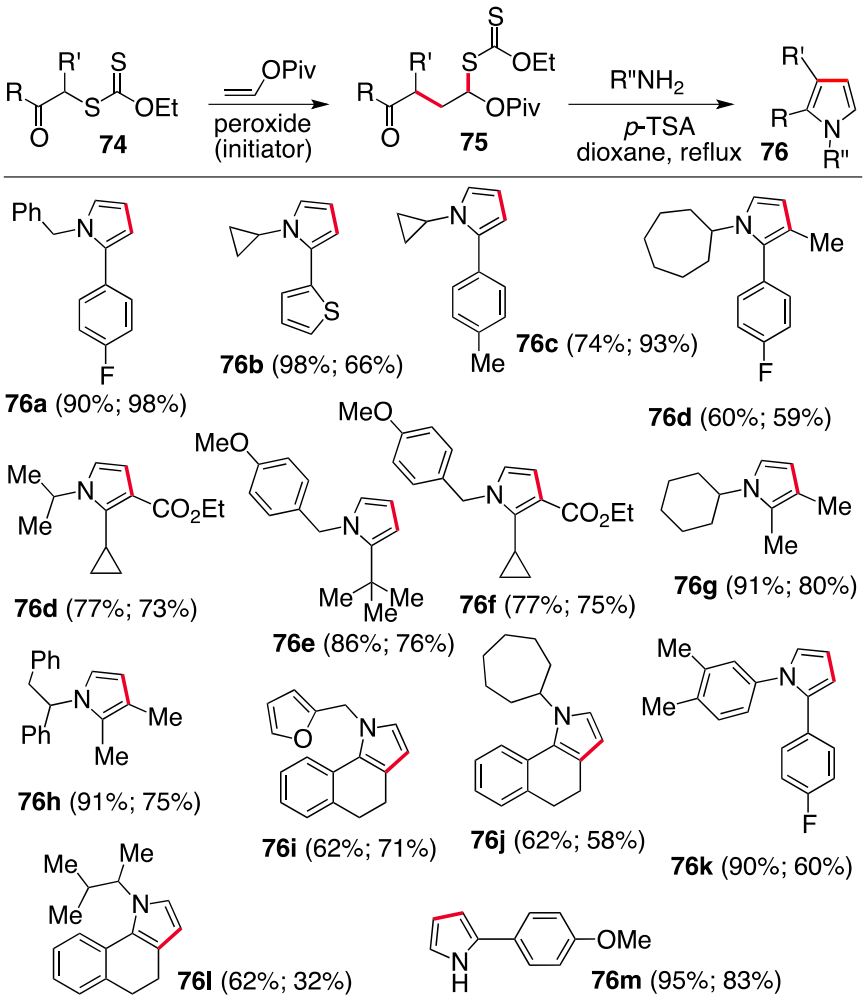
Scheme 6. Synthesis of Enones

The second approach exploits the ready homolytic fragmentation of the carbon-sulfur bond, as shown in the lower part of Scheme 6 for the reaction of adduct **26** to vinyl sulfone **71**. Addition-fragmentation with expulsion of a methanesulfonyl radical results in the formation of enol carbonate **72**.[7] This compound undergoes conversion into trifluoromethyl enone **73** upon brief heating with lithium iodide in acetic acid in a microwave oven.

3. SYNTHESIS OF PYRROLES

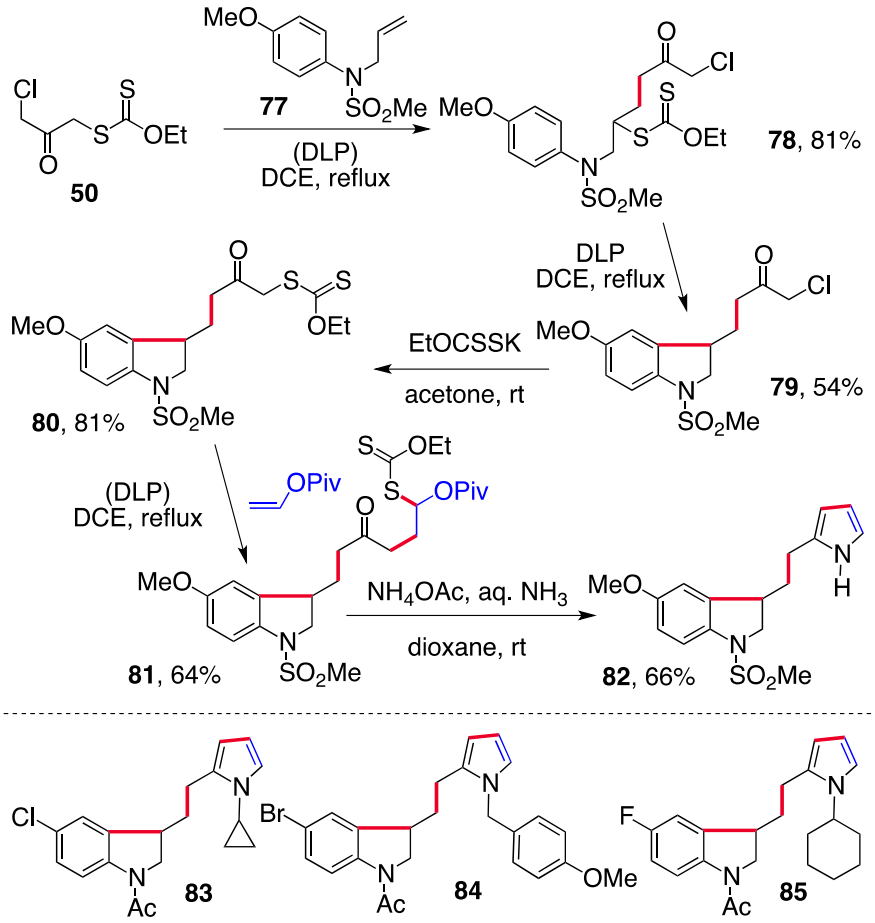
Inspection of the adducts to vinyl esters displayed in Scheme 2 shows that many are derived from α-ketonyl xanthates **74** and have general structure **75** (Scheme 7). They are therefore latent 1,4-ketoaldehydes and should react with ammonia or primary amines and anilines to give pyrroles **76** by what may be viewed as a variant of the venerable Paal-Knorr synthesis.[35] This indeed the case, as

indicated by the variegated examples in Scheme 7.[8,36] Two yields are given under each structure. The first corresponds to the radical addition to vinyl pivalate and the second to the condensation with the amine.



Scheme 7. Synthesis of Pyrroles

Most of the examples concern aliphatic primary amines, but condensation with ammonia to give an *N*-unsubstituted pyrrole (**76m**) or with an aniline to give an *N*-aryl-pyrrole (**76k**) is also possible. Both open chain and cyclic ketones derived xanthates can be used and the yield for both steps, which can be telescoped in principle, is generally good. This approach overcomes the main limitation of the Paal-Knorr synthesis, namely the access to 1,4-dicarbonyl precursors, and allows the construction of a very diverse library of pyrroles by simply modifying the xanthate and amine partners.

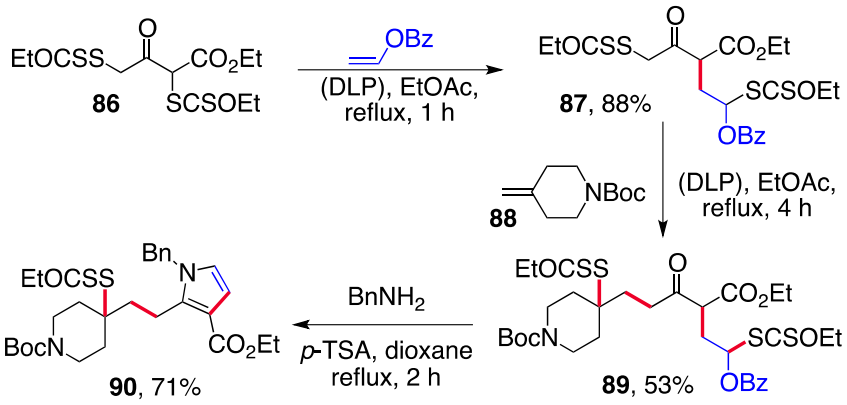


Scheme 8. Synthesis of Complex Pyrroles

More complex pyrroles can be swiftly assembled by taking advantage of the ability of xanthates to mediate the formation of more than one carbon-carbon bond. This is illustrated by the sequence in Scheme 8 starting with the same chloroacetonyl xanthate **50** used previously in the synthesis of spiroketal **56**.[37] Addition to *N*-allylsulfanilide **77** affords the usual adduct **78** in high yield. Further exposure to the peroxide causes ring closure onto the aromatic ring to give indoline **79**. The chloroketone, which survived both carbon-carbon forming steps, is converted into xanthate **80** and then made to react with vinyl pivalate in a third carbon-carbon forming reaction. The resulting adduct **81** is finally condensed with ammonia to provide pyrrole **82**. Three other pyrroles **83-85** were prepared by a similar sequence.

A conceptually related approach is based on the observation that an unsymmetrical bis(xanthyl) ketone such as **86** reacts regioselectively from the most substituted end, reflecting the relative stability of the corresponding radicals (Scheme 9).[38] In the case of compound **86**, it is easier to generate the radical that is stabilized by both the ketone and the ester groups and, in the presence of limiting amounts of vinyl benzoate, the addition takes place to give only product **87**. Opposed to a second alkene such as **88**, this bis-xanthate will react at the position adjacent to the ketone, as this now corresponds to the more stable radical. Condensation with benzylamine under acidic conditions then provides pyrrole **88** without the

remaining xanthate being affected. The complex pyrroles presented in Schemes 8 and 9 would be difficult to prepare by more conventional approaches.

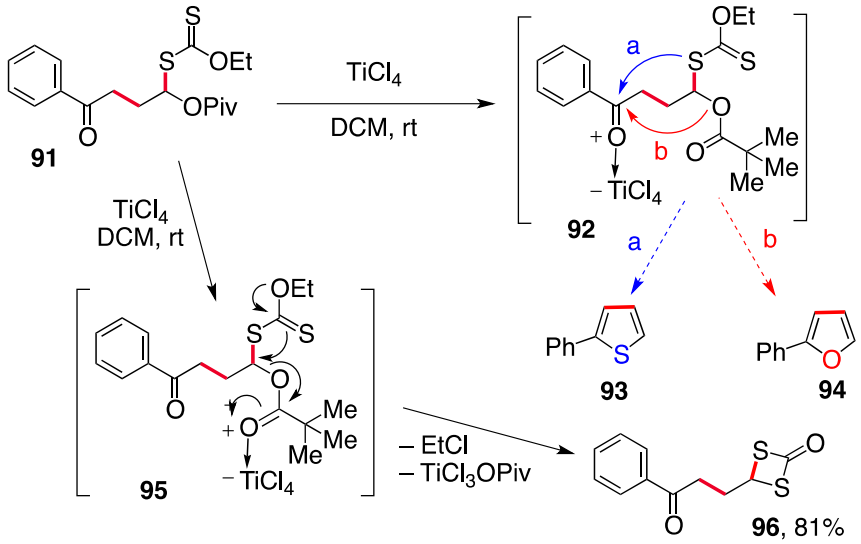


Scheme 9. Further Complex Pyrroles

4. SYNTHESIS OF DITHIETANONES AND THIOPHENES

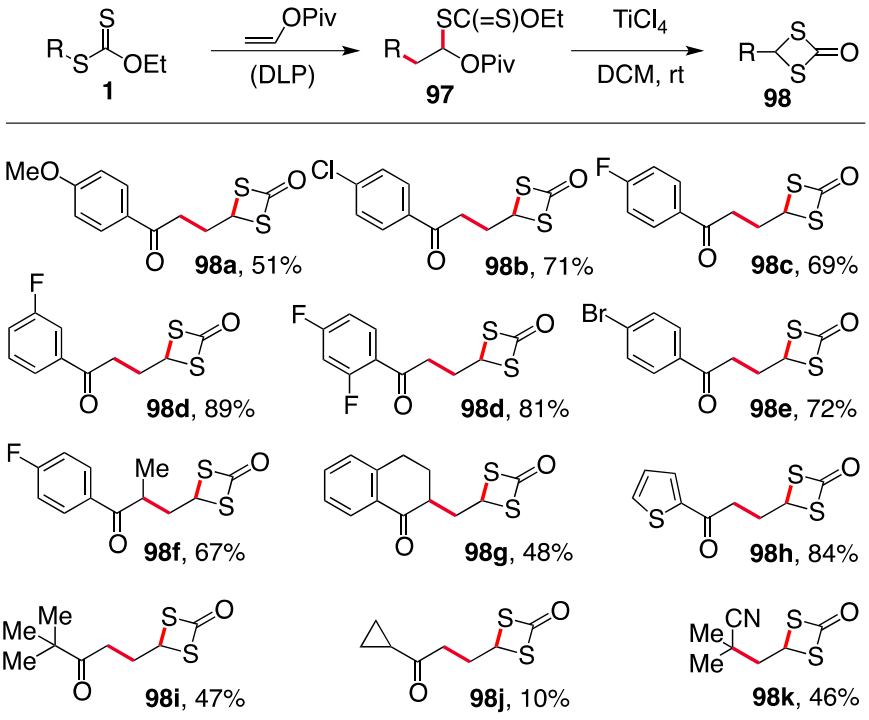
Thiophenes constitute a fundamental class of five-membered heteroaromatics.[39] Their aromaticity, polarizability, and relative chemical stability have found important applications in the fields of electroluminescence, non-linear optics, photochromic materials, liquid crystals, and organic semiconductors.[40] The thiophene motif is also present in a number of natural products and biologically active synthetic substances, one example of the latter is Plavix, a non-peptide fibrinogen receptor antagonist which has been in clinical use for many years.[41]

The Paal synthesis of thiophenes parallels the Paal-Knorr synthesis of pyrroles mentioned above in that it also relies on 1,4-dicarbonyl precursors.[39] In this case, the dicarbonyl derivative is reacted with phosphorus pentasulfide or, in more modern versions, with Lawesson's reagent as the source of the thiophene sulfur. In our case, the sulfur is already present in the guise of the xanthate group in adducts to vinyl pivalate of general structure **75**. We therefore envisaged that the addition of a Lewis acid would activate the ketone carbonyl towards attack by the sulfide sulfur of the xanthate. This is illustrated for adduct **91** proceeding to thiophene **93** via structure **92** in Scheme 10 (path a). Attack by the oxygen of the ester would furnish the corresponding furan **94** via path b. In the event, exposure of xanthate **91** to $TiCl_4$ in dichloromethane (DCM) did give both thiophene **93** and furan **94**, but only as very minor components. By far the dominant product was the unexpected 1,3-dithietanone **96**.[42] Clearly, the Lewis acid activated the pivalate ester much more than the ketone and triggered its substitution by the thiono sulfur of the xanthate to give the observed dithietanone by way of intermediate **95**.



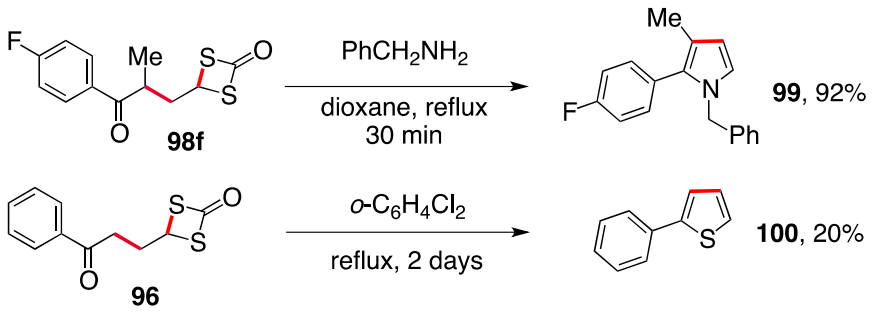
Scheme 10. Unexpected Formation of a 1,3-Dithietanone

The examples collected in Scheme 11 further illustrate this expedient synthesis of 1,3-dithietanones we accidentally discovered.[13,42] Substrates possessing a ketone appear to be better precursors, even if generalization at this stage is certainly premature and more work is needed to delineate more precisely the scope and limitations of this transformation. Nevertheless, the yields are moderate to good and synthetically useful, except for dithietanone **98j**, where the reaction was likely complicated by the concomitant opening of the cyclopropane ring induced by the Lewis acid.



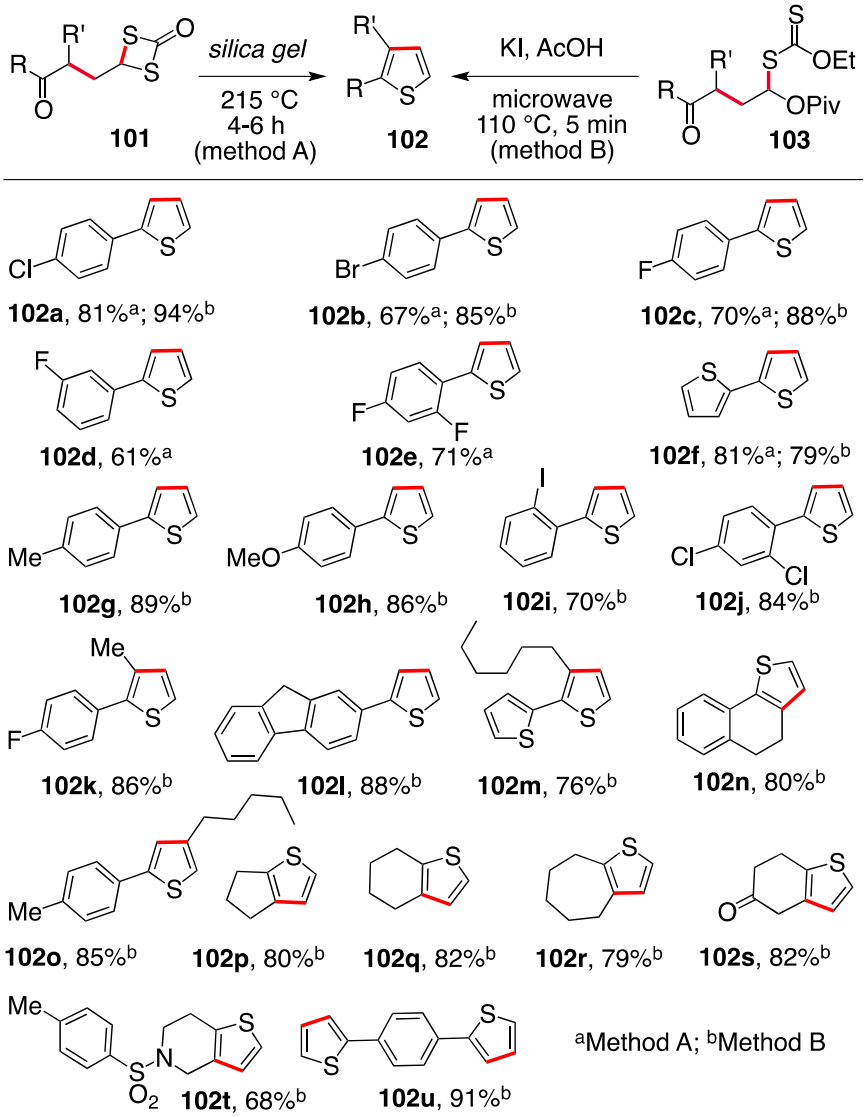
Scheme 11. Examples of Dithietanones

The 1,3-dithietanone motif can be viewed as a masked aldehyde and preliminary studies indicate it to be also a convenient latent thioaldehyde.[13,43] Thus, heating dithietanone **98f** with benzylamine in refluxing dioxane gives rise to pyrrole **99** in high yield (Scheme 12). In contrast, an initial attempt to thermolyze the dithietanone in compound **96** and capture the incipient thioaldehyde by the ketone were disappointing. The 1,3-dithietanone structure proved to be surprisingly stable to heat and, after refluxing for two days in *o*-dichlorobenzene (bp 178-180 °C), the yield of the expected thiophene **100** was only 20%.



Scheme 12. Pyrroles and Thiophenes from 1,3-Dithietanones

After some experimentation, better conditions were found to convert 1,3-dithietanones of general structure **101** into the corresponding thiophenes **102**.[13] Adsorbing the substrate on silica and heating neat to 215 °C for 4 hours afforded the desired thiophenes in fair to good yields, as underscored by the six examples **102a-f** in Scheme 13. An even more convenient and superior route to thiophenes was developed in parallel; it circumvented the need to prepare the diethanones by using directly their xanthate precursors **103** (method B). Simply heating a mixture of adducts **103** and KI in acetic acid at 110 °C for 5 minutes in a microwave oven furnished the corresponding thiophenes good yield. The numerous examples arrayed in Scheme 13 testify to the broad variety of thiophenes accessible by this second approach.[13]

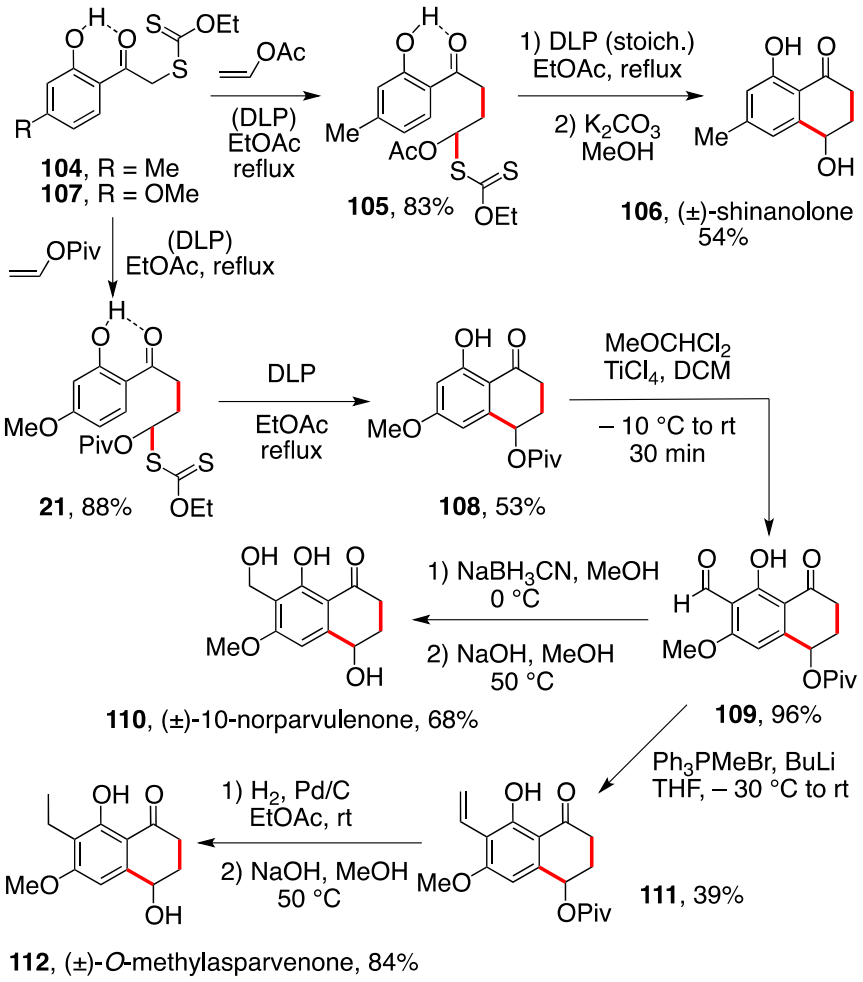


Scheme 13. Syntheses of Thiophenes

5. SYNTHESIS OF TETRALONES AND NAPHTHALENES

The ability to engage the xanthates adducts to vinyl esters in a second radical process provides an expedient route to the 4-hydroxytetralone family of natural products. Thus, (±)-shinanolone, one of the simpler members of the group, can be obtained in only two steps from xanthate **104** (Scheme 14).[16] The radical addition to vinyl acetate proceeds smoothly to give the normal adduct **105** in high yield. Further exposure to the peroxide regenerates the intermediate carbon centered radical which adds to the aromatic ring to give the target tetralone **106**, after saponification without prior purification of the intermediate acetate. The cyclization step requires stoichiometric amounts of the peroxide, as it is needed to oxidize the resulting cyclized cyclohexadienyl radical to the level of the cation and thus restore the aromaticity through loss of a proton. Such cyclizations can be viewed as the radical analogues of the intramolecular Friedel-Crafts reaction. One remarkable feature of this sequence is the successful creation of two new carbon-carbon bonds in the presence of an unprotected phenol. Phenols are well-known inhibitors of

radical chains and several phenols are industrial additives used as polymerization inhibitors for the preservation of various monomers.[43] In the present case, the hydrogen bonding of the phenol hydrogen with the oxygen of the ketone slows down considerably the hydrogen abstraction step[44] and allows the desired radical additions to take place unhindered. This hydrogen bonding plays a second beneficial role by freezing the conformation in a manner propitious for cyclization. Replacing this phenolic hydroxy group by a methoxy substituent results in a significant decrease in the efficacy of the cyclization step.[16]

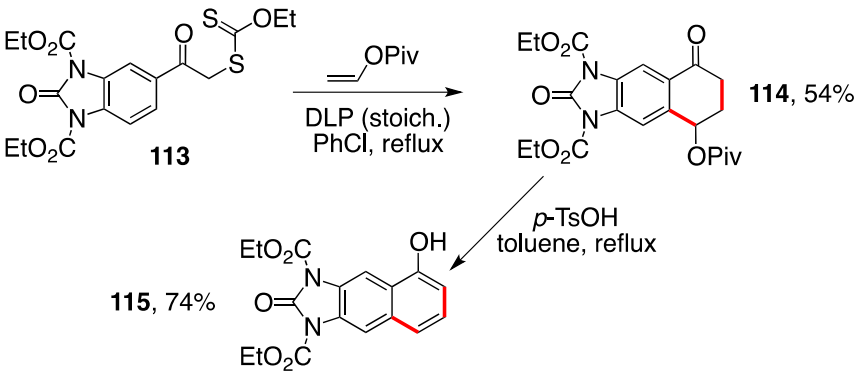


Scheme 14. Syntheses of 4-Hydroxytetralone Natural Products

The synthesis of the more complex 4-hydroxytetralone natural products, (±)-10-norparvuleneone **110** and (±)-*O*-methylasparvenone **112**, starts with xanthate **107** (Scheme 14).[45] Its addition to vinyl pivalate furnishes the expected adduct **21**,[16] first pictured in Scheme 2 in the introductory section. Further exposure to stoichiometric amounts of DLP induces ring closure to tetralone **108**. To complete the synthesis of (±)-10-norparvulenone **110**, it only remains to introduce a hydroxymethyl group and saponify the pivalate. This was accomplished by applying first a more recent variant of the Reimer-Tiemann reaction using dichloromethyl methyl ether and $TiCl_4$ to give aldehyde **109** in high yield, followed by

reduction with borohydride and treatment with methanolic sodium hydroxide. To access (±)-*O*-methylasparvenone **112**, aldehyde **109** was first converted into vinyl tetralone **111**, which was reduced catalytically and saponified. It is worth mentioning that (±)-*O*-methylasparvenone **112** is a rare nitrogen-free serotonin antagonist, with potential use in combatting neurological disorders.[46]

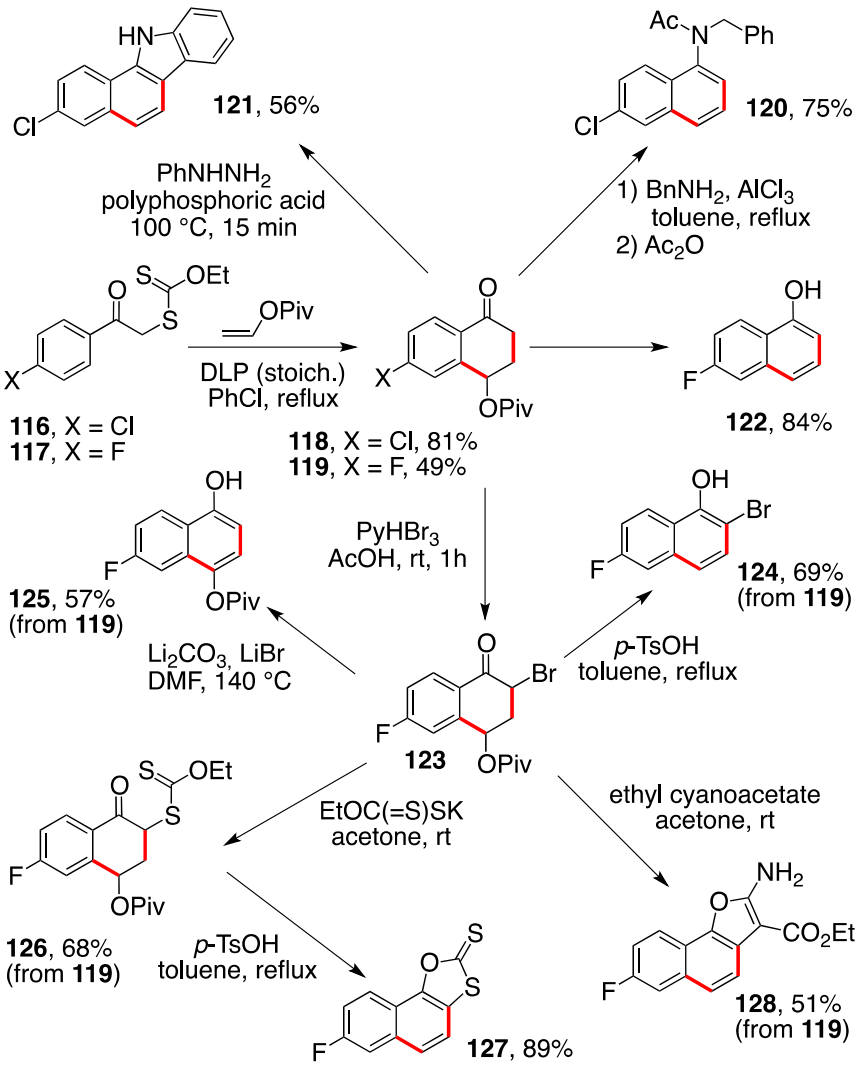
This ready access to hydroxytetralones, coupled with the robustness of the pivaloyloxy group towards broad range of reagents and reaction conditions, provides a practical, versatile synthesis of another family of important aromatic compounds, namely naphthalenes.[47] The example in Scheme 15 illustrates the underlying concept. The DLP mediated reaction of xanthate **113** with vinyl pivalate in refluxing chlorobenzene furnishes tetralone **114** directly in 54% yield. Heating this compound with *p*-toluenesulfonic acid in toluene causes elimination of pivalic acid and the formation of protected 6,7-diamino-1-naphthol **115**. In principle, both steps could be telescoped, allowing a one-pot synthesis of naphthol **115** directly from xanthate **113**.



Scheme 15. Synthesis of a Substituted 1-Naphthol

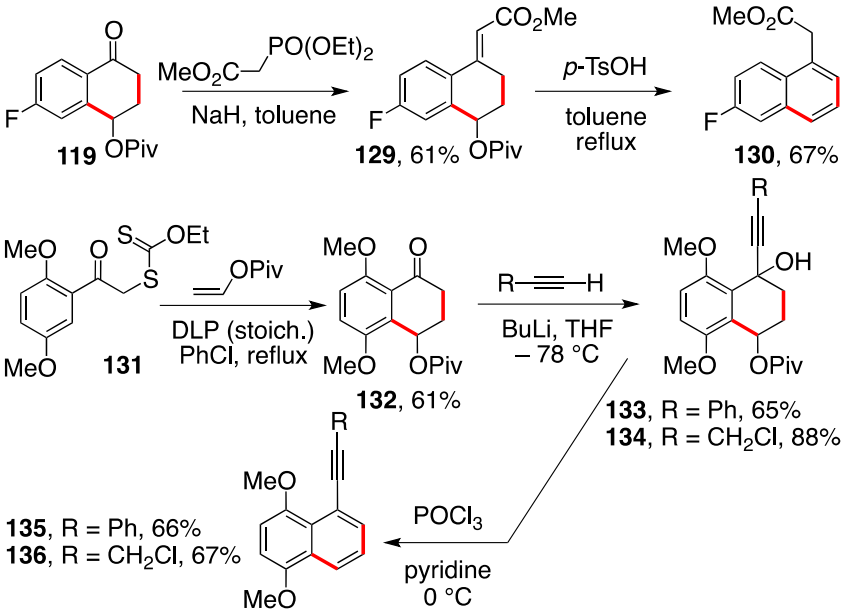
The flexibility and versatility of this approach to naphthalene derivatives can be appreciated by examining the transformations in Scheme 16.[47] In the same way as for xanthate **113**, xanthates **116** and **117** were annulated into tetralones **118** and **119** by reaction with vinyl pivalate and stoichiometric DLP. Heating the former with benzylamine and aluminum trichloride furnished directly the corresponding *N*-benzyl-1-aminonaphthalene, which was more conveniently isolated as acetamide **120**. Alternatively, heating with phenylhydrazine and polyphosphoric acid resulted in a Fischer indole type transformation to give benzocarbazole **121**. Treatment with acid in refluxing toluene converted fluorotetralone **119** into fluoronaphthol **122** in high yield. More interesting, however, is the finding that bromination to give bromoketone **123** could be accomplished without affecting the pivalate. Exposure to acid now furnishes 2-bromo-6-fluoro-1-naphthol **124** in 69% overall yield. Elimination of the bromine under basic conditions results in aromatization into naphthol **125**, without loss of the pivalate group. This compound corresponds to a *regioselectively monoprotected* 1,4-napthathalenediol. The bromine can be substituted by a xanthate

to give compound **126**, which could in principle act as the starting point for another radical addition, but which in this case was simply transformed by acid into tricyclic dithiocarbonate **127**. Finally, substitution with ethyl cyanoacetate afforded directly naphthofuran **128**.



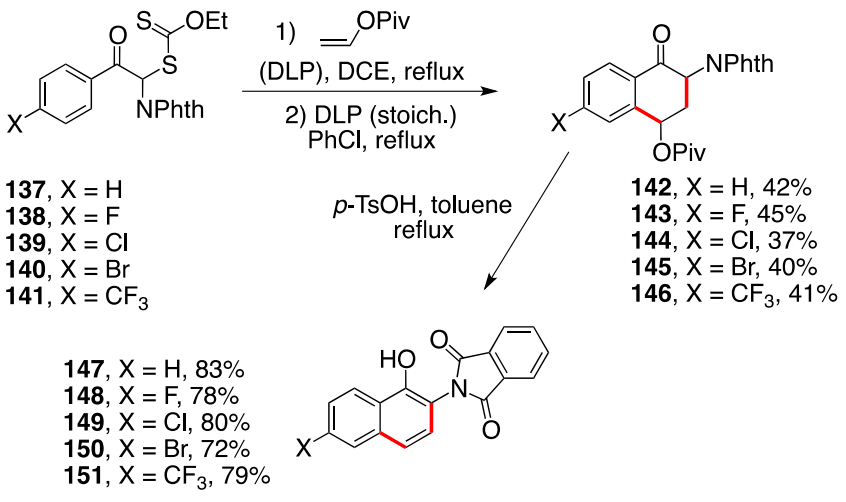
Scheme 16. Syntheses of Naphthalene Derivatives

This broad diversity of accessible naphthalenes could be further expanded by noting that various nucleophilic agents can be added to the ketone group prior to the acid induced aromatization step, as illustrated by the transformations in Scheme 17.[47] Thus, Horner-Wadsworth-Emmons condensation to give unsaturated ester **129** proceeded normally and exposure to acid furnished methyl 6-fluoro-1-naphthylacetate **130**. The addition of lithium phenylacetylide and lithium 3-chloropropynylide to dimethoxytetralone **132** also proceeded normally and afforded the corresponding carbinols **133** and **134**, again without harm to the pivalate group. Aromatization required only mild conditions to give naphthalenes **135** and **136**.



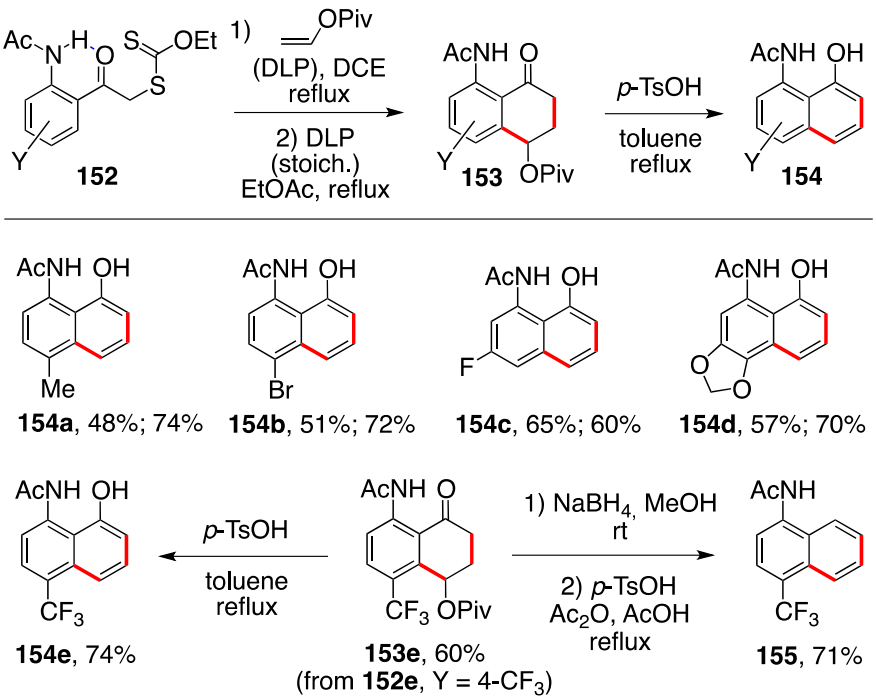
Scheme 17. Further Examples of Substituted Naphthalenes

All the naphthalene syntheses presented above started from xanthate precursors unsubstituted on the carbon bearing the xanthate group. Including a substituent at this position provides access to naphthalenes with different substitution patterns. From a medicinal perspective, the introduction of an amino group is particularly relevant. A series of phthalimido substituted xanthates **137**-**141** were therefore prepared and converted into the corresponding tetralones **142**-**146**. No effort was expended to develop a one-step procedure in this case and the addition to vinyl pivalate and ring-closure were performed separately. Aromatization by treatment with *p*-toluenesulfonic acid proceeded uneventfully to furnish phthalimido protected 2-amino-1-naphthols **147**-**151** in good yield. The ability to access aminonaphthols possessing electron-withdrawing groups such as the trifluoromethyl group in compound **151** is worthy of note. These groups deactivate the aromatic ring vis-à-vis traditional electrophilic substitutions of the Friedel-Crafts type.



Scheme 18. Syntheses of Protected 2-Amino-1-naphthols

A yet different substitution arrangement around the naphthalene ring can be assembled by starting with xanthates derived from *o*-acetamidoacetophenones **152** (Scheme 19).[48] In the same manner as for phenol analogues **104** and **107** in Scheme 14, the hydrogen bonding between the amide hydrogen and the ketone oxygen freezes the pendent side-chain in a conformation that is favorable for cyclization onto the aromatic ring and improves its efficacy. Subjecting the resulting tetralones **153** to acid treatment then provides the expected acetamidonaphthols, as shown by examples **154a-e**. The first of the two yields indicated in Scheme 19 corresponds to the addition-cyclization leading to tetralones **153 a-e**, whereas the second is for the aromatization step. In the case of tetralone **153e**, reduction of the ketone prior to treatment with acid allows the synthesis of 4-trifluoromethyl-1-acetamidonaphthalene **155**. A mixture of acetic anhydride and acetic acid was used in this instance instead of toluene in order to prevent partial hydrolysis of the acetamido group (the reduction of the ketone generates an alcohol in close proximity to the acetamido group and N- to O- exchange of the acetyl group becomes possible).



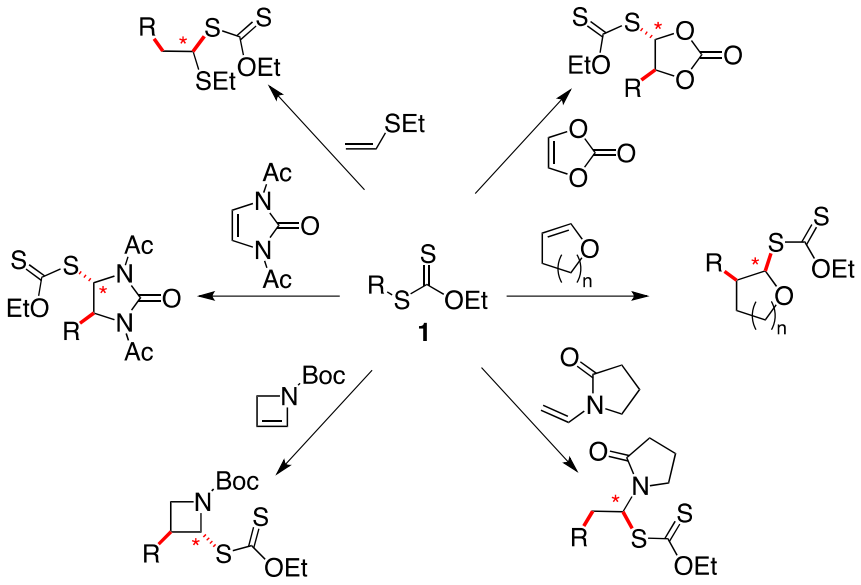
Scheme 19. Syntheses of Acetamidonaphthalenes

6. CONCLUSION AND PERSPECTIVES

Aldehydes, like ketones, are fundamental building blocks that can be modified in an infinite number of ways. The radical addition of xanthates to vinyl esters generates masked aldehydes bearing numerous other functionalities derived from the xanthate partner. This is a powerful alliance for synthesis. The present brief overview has highlighted applications to the synthesis of cyclic and open chain enones, trifluoromethyl enones, dienes, pyrroles, dithietanones, thiophenes, hydroxytetralones, naphthalenes and

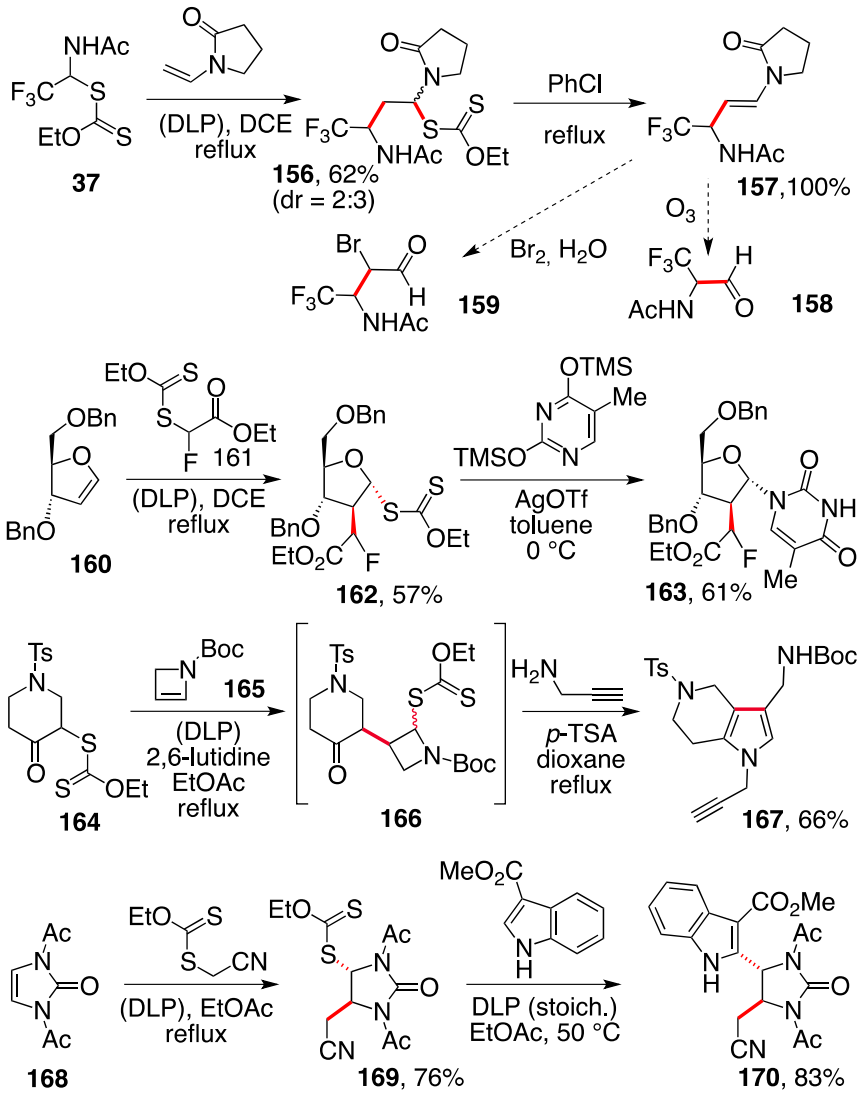
naphthols, many of which would not be easily accessible otherwise. Numerous other transformations and variations can be conceived exploiting the presence of a latent aldehyde or a xanthate in the addition products. From a practical standpoint, it is worth noting that the reagents involved are very inexpensive, the experimental conditions are mild and compatible with a large variety of functional groups, and scale-up is often straightforward.

There are other readily available alkenes that also lead to adducts bearing masked aldehydes that can then be further transformed in a similar or in some cases different manner. These include vinylidene carbonate, dihydrofurans,[49] *N*-vinyl pyrrolidone,[27] azetines,[50] imidazolones,[51] vinyl sulfides,[52] as shown in the generic manifold in Scheme 20. The masked aldehyde carbon is starred.



Scheme 20. Additions Leading to Masked Aldehydes

Illustrative examples of transformations involving these more elaborate alkenes that harbor a latent aldehyde function are depicted in Scheme 21. In the first, *N*-vinylpyrrolidone, a cheap industrial monomer, is used as the radical trap in conjunction with xanthate **37**. The resulting adduct **156** is thermally unstable because of the more effective weakening of the C—S bond by the lone pair of the nitrogen. Heating in refluxing chlorobenzene is thus sufficient to induce elimination of the xanthate to give quantitatively enamide **157**.[27] While this compound could be hydrolysed into the corresponding aldehyde, it could also in principle be cleaved by ozonolysis into aldehyde **158** possessing one less carbon. Overall, this would be a very useful one carbon homologation of the starting xanthate. Bromination (or chlorination) in the presence of water would furnish α-bromo- (or α-chloro-) aldehyde **159**. α-Halo-aldehydes have emerged as exceedingly useful synthetic building blocks.[53]



Scheme 21. Further Transformations of Masked Aldehyde Adducts

The second example, taken from the study by Lequeux and collaborators,[49] concerns the synthesis of a deoxynucleotide analogue **163** by addition of a fluoroacetate xanthate onto dihydrofuran **160** and exploiting the presence of the anomeric xanthate in intermediate **162** to introduce the thymine subunit. The third illustration is the preparation of bicyclic pyrrole **167** containing a valuable protected aminomethyl substituent in the 3-position by reaction of xanthate **164** with *N*-Boc-azetine **165**, followed by aminolysis of adduct **166** with propargylamine.[50] Finally, adduct **169** was obtained from addition to imidazolone **168** and the xanthate group used to mediate a second intermolecular addition to methyl 3-indolecarboxylate to give the highly decorated structure **170**.[51]

In summary, it is hoped that these varied examples, spanning numerous structural types, will encourage synthetic chemists to apply the manifold possibilities offered by this unusually powerful chemistry of xanthates. Indeed, the ability to create carbon-carbon bonds in a manner not hitherto feasible by ionic or

organometallic reactions allows the design and implementation of retrosynthetic disconnections that could simplify considerably synthetic planning.

REFERENCES AND NOTES

1. G. Roscher, "*Vinyl Esters. Ullmann's Encyclopedia of Chemical Technology*", Weinheim: Wiley-VCH, 2007.
2. "*Cycloaddition* Reactions in Organic Synthesis", ed. by S. Kobayashi and K. A. Jorgensen, Wiley-VCH Verlag GmbH, 2001; "The Chemistry of Heterocyclic Compounds, Volume 59: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products", ed. by A. Padwa and W. H. Pearson, John Wiley & Sons, Inc., New York, 2002; "Methods and Applications of Cycloaddition Reactions in Organic Syntheses", ed. by N. Nishiwaki, John Wiley & Sons, Inc., Hoboken, New Jersey, 2014.
3. For reviews of the xanthate transfer, see: S. Z. Zard, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 672; B. Quiclet-Sire and S. Z. Zard, *Top. Cur. Chem.*, 2006, **264**, 201; B. Quiclet-Sire and S. Z. Zard, *Chem. Eur. J.*, 2006, **12**, 6002; S. Z. Zard, *Aust. J. Chem.*, 2006, **59**, 663; B. Quiclet-Sire and S. Z. Zard, *Pure Appl. Chem.*, 2011, **83**, 519; B. Quiclet-Sire and S. Z. Zard, *Chimia*, 2012, **66**, 404; B. Quiclet-Sire and S. Z. Zard, *Isr. J. Chem.*, 2017, **57**, 202.
4. For a more detailed mechanistic discussion, see: S. Z. Zard, *J. Phys. Org. Chem.*, 2012, **25**, 953.
5. "Handbook *of RAFT Polymerization*", ed. by C. Barner-Kowollik, Wiley-VCH, Weinheim, 2008.
6. For a very recent review, see: S. Perrier, *Macromolecules*, 2017, **50**, 7433.
7. L. Anthore and S. Z. Zard, *Org. Lett.*, 2015, **17**, 3058.
8. B. Quiclet-Sire, L. Quintero, G. Sanchez-Jimenez, and S. Z. Zard, *Synlett*, 2003, 75.
9. N. Charrier and S. Z. Zard, *Angew. Chem. Int. Ed.*, 2008, **47**, 9443.
10. L. Anthore, S. Li, L. V. White, and S. Z. Zard, *Org. Lett.*, 2015, **17**, 5320.
11. C. Mougin, J. Sançon, and S. Z. Zard, *Heterocycles*, 2007, **74**, 211.
12. M. Corbet, M. de Greef, and S. Z. Zard, *Org. Lett.*, 2008, **10**, 253.
13. H. Jullien, B. Quiclet-Sire, T. Tétart, and S. Z. Zard, *Org. Lett.*, 2014, **16**, 302.
14. G. Binot and S. Z. Zard, *Tetrahedron Lett.*, 2003, **44**, 7703.
15. J. V. Suarez-Meneses, E. Bonilla-Reyes, E. A. Ble-Gonzalez, M. C. Ortega-Alfaro, R. A. Toscano, A. Cordero-Vargas, and J. G. Lopez-Cortes, *Tetrahedron*, 2014, **70**, 1422.
16. L. Petit and S. Z. Zard, *Chem. Commun.*, 2010, **46**, 5148.
17. L. Debien, B. Quiclet-Sire, and S. Z. Zard, *Org. Lett.*, 2011, **13**, 5676.
18. G. Binot, B. Quiclet-Sire, T. Saleh, and S. Z. Zard, *Synlett*, 2003, 382.
19. B. Quiclet-Sire and S. Z. Zard, *Org. Lett.*, 2008, **10**, 3279.

20. M. Heinrich and S. Z. Zard, *Org. Lett.*, 2004, **6**, 4969.
21. L. Qin and S. Z. Zard, *Org. Lett.*, 2015, **17**, 1577.
22. N. Charrier, B. Quiclet-Sire, and S. Z. Zard, *J. Am. Chem. Soc.*, 2008, **130**, 8898.
23. Z. Ferjancic, B. Quiclet-Sire, and S. Z. Zard, *Synthesis*, 2008, 2996.
24. F. Lebreux, B. Quiclet-Sire, and S. Z. Zard, *Org. Lett.*, 2009, **11**, 2844.
25. S. K. Bagal, L. Tournier, and S. Z. Zard, *Synlett*, 2006, 1485.
26. L. Debien, B. Quiclet-Sire, and S. Z. Zard, *Org. Lett.*, 2012, **14**, 5118.
27. F. Gagosz and S. Z. Zard, *Org. Lett.*, 2003, **5**, 2655.
28. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574; For a review, see: S. W. McCombie, W. B. Motherwell, and M. J. Tozer, *Org. React.*, 2012, **77**, 161.
29. C. Chatgilialoglu, C. Ferreri, Y. Landais, and V. I. Timokhin, *Chem. Rev.*, 2018, **118**, 6516; C. Chatgilialoglu, *Chem. Rev.*, 1995, **95**, 1229.
30. D. H. R. Barton, D. O. Jang, and J. Cs. Jaszberenyi, *Tetrahedron Lett.*, 1992, **33**, 5709; J. Boivin, R. Jrad, S. Juge, and V. T. Nguyen, *Org. Lett.*, 2003, **5**, 1645; C. McMaster, R. N. Bream, and R. S. Grainger, *Org. Biomol. Chem.*, 2012, **10**, 4752.
31. A. Liard, B. Quiclet-Sire, and S. Z. Zard, *Tetrahedron Lett.*, 1996, **37**, 5877.
32. M. de Greef and S. Z. Zard, *Org. Lett.*, 2007, **9**, 1773.
33. S. Z. Zard, *Acc. Chem. Res.*, 2018, **51**, 1722.
34. L. Debien, B. Quiclet-Sire, and S. Z. Zard, *Acc. Chem. Res.*, 2015, **48**, 1237.
35. For selected monographs and reviews on pyrroles, see: (a) A. Jones and G. P. Bean, "*The Chemistry of Pyrroles*", Academic Press: London, 1977; (b) A. Jones, *Pyrroles*, Wiley, New York, 1990; (c) L. N. Sobenina, A. I. Mikhaleva, and B. A. Trofimov, *Russ. Chem. Rev.* (*Engl. Transl.*), 1989, **58**, 163; (d) V. Estévez, M. Villacampa, and J. C. Menéndez, *Chem. Soc. Rev.*, 2010, **39**, 4402.
36. For a review, see: B. Quiclet-Sire and S. Z. Zard, *Synlett*, 2017, **28**, 2685.
37. O. Bergeot, C. Corsi, M. El Qacemi, and S. Z. Zard, *Org. Biomol. Chem.*, 2006, **4**, 278.
38. L. Anthore-Dalion, Q. Liu, and S. Z. Zard, *J. Am. Chem. Soc.*, 2016, **138**, 8404.
39. "The *Chemistry of Heterocyclic Compounds, Vol 44: Thiophene and Its Derivatives*", ed. by S. Gronowitz, Wiley, New-York, 1991; J. A. Joule and K. Mills, *Heterocyclic Chemistry*, 5th edn., Wiley-VCH, Weinheim, 2010.
40. S. Allard, M. Forster, M. B. Souharce, H. Thiem, and U. Scherf, *Angew. Chem. Int. Ed.*, 2008, **47**, 4070; J. M. Tour, *Acc. Chem. Res.*, 2000, **33**, 701; S. J. Higgins, *Chem. Soc. Rev.*, 1997, **26**, 247; C. Wang, H. Dong, W. Hu, Y. Liu, and D. Zhu, *Chem. Rev.*, 2012, **4**, 2208; Y. Lin, Y. Lia, and X. Zhan, *Chem. Soc. Rev.*, 2012, **41**, 4245; C. Li, M. Liu, N. G. Pschirer, M. Baumgarten, and K. Müllen, *Chem. Rev.*, 2010, **110**, 6817; "*Handbook of Oligo- and Polythiophenes*", ed. by D. Fichou,

Wiley-VCH, Weinheim, Germany, 1999; A. Mishra, C.-Q. Ma, and P. Bäuerle, *Chem. Rev.*, 2009, **109**, 1141; I. F. Perepichka, D. F. Perepichka, H. Meng, and F. Wudl, *Adv. Mater.*, 2005, **17**, 2281.

41. H. Sugihara, H. Fukushi, T. Miyawaki, Y. Imai, Z. Terashita, M. Kawamura, Y. Fujisawa, and S. Kita, *J. Med. Chem.*, 1998, **41**, 489.
42. B. Quiclet-Sire, G. Sanchez-Jimenez, and S. Z. Zard, *Chem. Commun.*, 2003, 1408.
43. H. Zweifel, "*Stabilization of Polymeric Materials*", Springer, Berlin, 1997.
44. D. V. Avila, K. U. Ingold, J. Lusztyk, W. H. Green, and D. R. Procopio, *J. Am. Chem. Soc.*, 1995, **117**, 2929.
45. A. Cordero Vargas, B. Quiclet-Sire, and S. Z. Zard, *Org. Lett.*, 2003, **5**, 3717.
46. M. Bös, R. Canesso, N. Inoue-Ohga, A. Nakano, Y. Takehana, and A. J. Sleight, *Bioorg. Med. Chem.*, 1997, **5**, 2165.
47. A. Cordero-Vargas, I. Pérez-Martin, B. Quiclet-Sire, and S. Z. Zard, *Org. Biomol. Chem.*, 2004, **2**, 3018.
48. N. D. M. Tran and S. Z. Zard, *Org. Biomol. Chem.*, 2014, **12**, 3251.
49. L. Jean-Baptiste, S. Yemets, R. Legay, and T. Lequeux, *J. Org. Chem.*, 2006, **71**, 2352.
50. S. Han and S. Z. Zard, *Org. Lett.*, 2014, **16**, 1992; S. Han and S. Z. Zard, *Tetrahedron*, 2015, **71**, 3680.
51. S. Han and S. Z. Zard, *Org. Lett.*, 2014, **16**, 5386.
52. M.-G. Braun and S. Z. Zard, *Org. Lett.*, 2011, **13**, 776.
53. R. Britton and B. Kang, *Nat. Prod. Rep.*, 2013, **30**, 227.

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