

7.01

Pyridines and their Benzo Derivatives: Structure

J. B. Harper

University of New South Wales, Sydney, NSW, Australia

© 2008 Elsevier Ltd. All rights reserved.

7.01.1	Introduction	1
7.01.2	Molecular Characteristics	2
7.01.2.1	Theoretical Methods	2
7.01.2.2	Experimental Structural Methods	4
7.01.2.3	Spectroscopic Methods	5
7.01.2.3.1	Nuclear magnetic resonance	5
7.01.2.3.2	Ultraviolet/Vis spectroscopy	6
7.01.2.3.3	Infrared spectroscopy	7
7.01.2.3.4	Mass spectrometry	7
7.01.2.3.5	Photoelectron spectroscopy	7
7.01.2.4	Thermodynamic Studies	8
7.01.2.4.1	Tautomerism	8
7.01.2.4.2	Conformation	8
7.01.2.4.3	Solvation and solvent effects	11
7.01.3	Supramolecular Characteristics	11
7.01.3.1	Extended Pyridine Derivatives	11
7.01.3.2	Interactions in Solution	16
7.01.3.2.1	Host–guest complexes	16
7.01.3.2.2	Rotaxanes and catenanes	22
7.01.3.3	Crystal Engineering: Interactions in the Solid State	27
7.01.4	Summary	35
References		35

7.01.1 Introduction

As for CHEC(1984) and CHEC-II(1996) <1984CHEC(2)99, 1996CHEC-II(5)1> this section covers the structure of pyridine, along with derivatives substituted at either nitrogen or carbon. Particularly, this will include the benzo-substituted derivatives such as quinolines and isoquinolines, along with bipyridyl systems. In addition, the saturated derivatives (such as piperidines) will also be covered. While the valence isomers of pyridine have been considered through computation (for example, see <2002JST(578)249>), the structures are not reported and, as such, these compounds will not be discussed in this section.

In general, the areas covered in this chapter will be the same as in previous editions. A change will be that studies on properties of a molecule, such as tautomerism and conformation, will be covered together in one section rather than under the experimental method used to determine them. The exception to this is the theoretical section, though when computational studies are used simply to support experimental studies they will be presented in the latter section.

Perhaps the most striking change in interest surrounding the structure of pyridines and their substituted derivatives is in terms of scale and this is reflected in the content herein. While earlier editions of this series focussed exclusively <1984CHEC(2)99> and predominantly<1996CHEC-II(5)1> on structure at the single molecule level, the trend nowadays is toward structure at the supramolecular level. This is demonstrated by the relatively reduced emphasis on what has been termed ‘bread-and-butter matters’ <1996CHEC-II(5)1> along with the dramatically increased coverage of the supramolecular structure of pyridines in this chapter. It is important to recognize that throughout this

chapter a relatively simple, though arbitrary, distinction is used to determine where the information is discussed. If the structural data relate solely to a single molecule, it will be discussed as such but when the information relates to molecules interacting with one other it will be treated in the supramolecular section, though simple dimerisation is treated with the former discussions. Note that this distinction means that some information that would not be presented in the supramolecular section of previous editions of this series will be used as introductory material to the supramolecular section in this case.

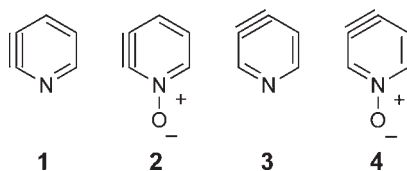
Finally, the coordinating ability of the nitrogen means that many structural studies of pyridines and their derivatives are focused on metal complexes. These are not covered in this chapter as they are amply summarized elsewhere. Further, studies in which the pyridine unit confers no particular structural differences from a benzene moiety in the same position will not be covered.

7.01.2 Molecular Characteristics

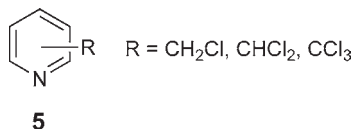
7.01.2.1 Theoretical Methods

The use of computational methods in structural chemistry has changed focus in recent years, with less emphasis on the determination of absolute structure and greater emphasis on the application of these methods to explain topics such as conformation, tautomerism, and the source of any preferences for given forms. This change dominates the section below though the computations of some simple structures have been carried out.

Among the more fundamental studies, the bond lengths in pyridine, isoquinoline, and acridine have been investigated [<1998JST\(427\)25>](#) as have the bond orders in pyridine and other heteroaromatic rings [<2002IJQ534>](#). In addition, the pyridyne and pyridyne *N*-oxide derivatives **1–4** have been compared to the parent pyridine and pyridine *N*-oxide [<2004JST\(679\)53>](#). Significant distortion of the ring in the 2,3-pyridyne **1** was observed, with a shortening of the adjacent carbon–nitrogen bond such that it is shorter than the (formally) triple bond and a corresponding bond angle of *c.* 150°. The remaining derivatives **2–4** are much more symmetrical, with the shortest bond in each case being the (formally) triple bond.



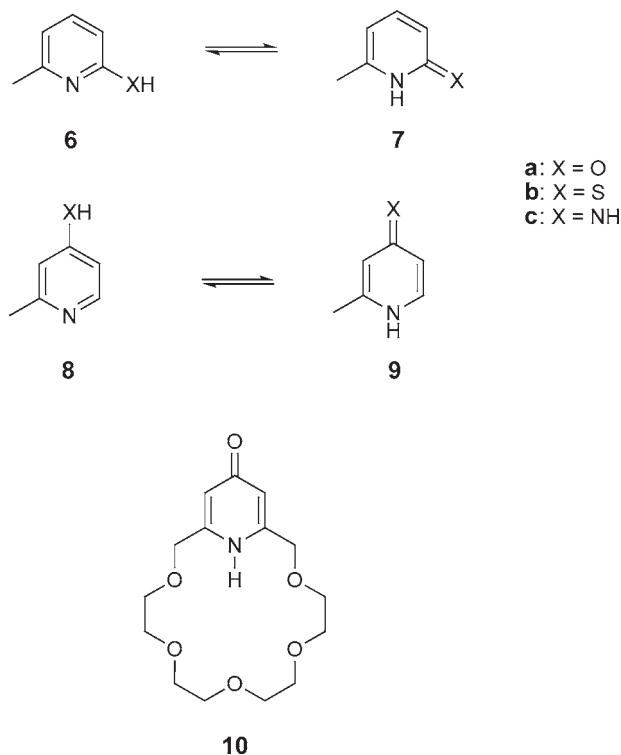
Chlorinated picoline derivatives **5** have been examined using computational methods, particularly to illustrate the differences with the analogous toluenes [<1997JST\(389\)105>](#). Particularly, the difference between the conjugative interactions in the benzene and pyridine derivatives was demonstrated with a decrease in the electron donation from the ring to the carbon–chlorine bond(s) on the substituent along with a concomitant increase in electron donation from the carbon–hydrogen bond(s) to the ring. This is consistent with the change in electronic nature of the aromatic ring, the pyridine being markedly more electron deficient and was used to explain the difference in energy barriers and computed bond lengths between the different systems.



Theoretical methods can also be used to predict the most stable geometries of alkyl-substituted pyridines. B3LYP/6-31G** calculations show that the ethyl group in 3- and 4-ethylpyridines is almost perpendicular to the plane of the aromatic ring, while the angle is lessened slightly for the 2-isomer [<2003OBC4329>](#). Similarly, the angle about the biaryl bond in phenylpyridines has been calculated to be between 28° and 46° [<2003OBC4329>](#). The effect of the pyridine nitrogen to decrease the rotational barrier in 3-arylpyridines has been investigated for a series of 4-amino-3-arylpyridines [<2003JST\(623\)263>](#).

Density functional theory (DFT) calculations have also been used to calculate the position of tautomeric equilibria of heteroatom-substituted pyridines in both the gas-phase and under solvation conditions. For the former, in the case of the oxygen and sulfur substituents, the energy difference between the tautomers is reasonably small (in the order

of 1 kcal mol^{-1}) with the -one forms **7a** and **7b** favored for the 2-substituted cases and the -ol forms **8a** and **8b** favored in the 4-substituted cases <2004JST(709)129>. When the heteroatom is nitrogen, the energy difference is much greater ($>10 \text{ kcal mol}^{-1}$) and the amino forms **6c** and **8c** dominating <2004JST(709)129>. On introduction of a dimethyl sulfoxide (DMSO) solvation model, the predominant effect is a lowering in the relative energy of the -one forms, due to introduction of dipole–dipole interactions <2004JST(709)129>. Interestingly, when the possibility of dimerization through intramolecular hydrogen bond formation is introduced, the 1H/1H dimers are favored for the oxygen- and nitrogen-substituted systems <2002JOC1515>. While gas-phase calculations predominate, computational studies incorporating models of solvation have also been considered and compared <1999J(P2)801>. For example, importance of solvent molecules in the tautomerism of hydroxy-substituted pyridines has been illustrated, <1996JPC16141, 2001JST(542)1> particularly with relevance to the observation that the pyridone tautomer of the crown ether **10** dominates <2001JHC1387>.



4-Pyridone retains a significant amount of aromatic character (*c.* 35% of that of benzene) and is planar. The effect of fluorination of these systems, particularly on the planarity and the inversion barrier at nitrogen, has been investigated using MP2/6-31G* calculations <1997JOC8063>. It was found that a single fluorine substituent at the nitrogen center was sufficient to cause significant deviation from planarity.

Calculations of conformations of 2,2'-bipyridine at the MP2/6-31G** level of theory demonstrate that stable *cis*- and *trans*-conformers exist in the gas phase, though the dihedral angle is dependent on the basis set used <1996JA10269>. For the *cis*-conformer, the dihedral angle is marked (*c.* 45°) while in the *trans*-case the lowest-energy conformer is planar. Further studies into this and isomeric bipyridines at 3-21G level indicate that the planarity of the bipyridines (and hence electron delocalization between the two pyridine rings) is maximum in the case of systems with at least one nitrogen atom in the *ortho*-position <1995JOC5291>. Further stabilization of the planar structure in this case occurs as a result of interaction of the lone pair of the nitrogen with an aromatic C–H on the adjacent ring.

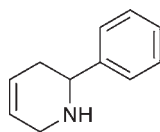
The conformation of monoprotonated 2,2'-bipyridine was examined using the MINDO/3 method (MNDO – modified neglect of diatomic overlap) <1995JST(333)275>. The monocation does not have a planar structure, rather the aromatic rings are at right angles. Perhaps most interestingly, even in the *cis*-arrangement of pyridine rings, the proton does not form a bridge between the nitrogen atoms (though different levels of theory indicate that planarity of this species may occur <1996JA10269>). This was supported by subsequent studies <2003JST(663)91> which also examined the dicationic species for which orthogonal conformation was preferred. Perhaps surprisingly given this result, a study using AM1 methodology contradicts this result showing enhanced basicity of the *syn*-form of

2,2'-bipyridine when compared to the *trans*-form; this effect was attributed to the chelating effect of the two nitrogen atoms in that conformation <1998JST(427)87>.

Computational studies at the B3LYP/6-31G** level of theory were carried out to compare the bond lengths in piperidine with those in cyclohexane to determine the effect of substituting a methylene group with nitrogen <2002JA13088>. There is significant lengthening of the axial C–H bond adjacent to the nitrogen as is consistent with significant hyperconjugative electron donation from the lone pair of the nitrogen into the antibonding C–H orbital. Importantly, the effect of donation into the equatorial antibonding orbital is shown to be much larger in azacyclohexanes than in related heterocycles <2003JA14014>.

The equatorial conformers of piperidine and its *N*-methyl derivative have been shown, using HF/6-31G* theory, to be preferred over the corresponding axial isomers by *c.* 4 and 15 kJ mol^{−1}, respectively <1996JST(365)21>, though subsequent studies demonstrated the importance of the level of theory used on the outcome; notably, AM1 and PM3 methods did give values which correlate well with experiment <1998JCC961>. Similar results were shown for a variety of 1-alkyl-*trans*-3,5-disubstituted piperidines and piperidine-1-oxides <2002JST(617)189>. Investigation of 3-substituted piperidines demonstrated that electron-withdrawing substituents favor the axial conformer, while electron-donating substituents favor the equatorial conformer <2005JST(713)245>. The number of factors contributing to the preferred conformers becomes progressively greater with the number of substituents, as demonstrated with a range of multiply substituted piperidines <1995JOC7411>.

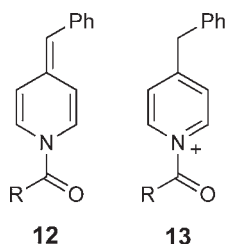
Conformational preferences have been examined computationally for phenyl substituted 3-piperidines such as the tetrahydro compound **11**. Conformations were found to be much more complicated than the corresponding cyclohexanes but a series of rules based on the substituents on the piperidine ring have been proposed to account for the conformational preferences <2001CEJ4715>. 1,2-Dihydropyridines have also been studied with planar conformations dominating for electron-withdrawing substituents, while electron-donating groups attached to the ring result in significant deviation from planar structure <2004JTC557>.

**11**

7.01.2.2 Experimental Structural Methods

While there are very many reports of crystal structures containing pyridines and their derivatives, the material covered in this section is limited to those cases where the information is either unusual or of specific interest, giving insight into an inherent structural property related to the pyridine component of the molecule.

Crystallographic studies of the dihydropyridines **12** and the corresponding protonated derivatives **13** indicated a significant (*c.* 10 pm) and 'selective' lengthening of the exocyclic carbon–nitrogen bond <1999EJO2383>. This is consistent with the structure obtained from B3LYP/6-31G* analysis, which predicts a decrease in bond order from 1.03 to 0.80. A bond shortening is observed in the crystal structures of *N*-benzyl piperidines due to an anomeric effect <2002JST(617)189>.

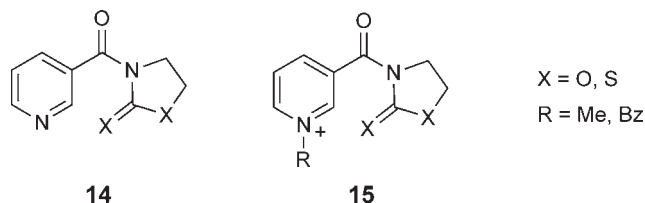


R = *t*-Bu, *trans*-PhCHCH, CH₃(CH₂)₁₀, Me,
Ph, *p*-C₆H₄-OCH₃

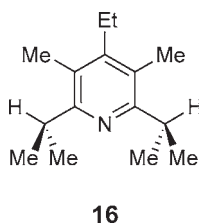
12**13**

The crystal structures of the nicotinamide derivatives **14** and **15** have been used to demonstrate the importance of interactions between the pyridinium ring and either carbonyl or thiocarbonyl moieties through intramolecular

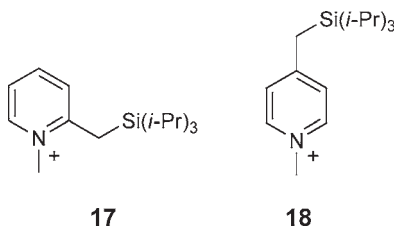
interaction [<2004JA9862>](#). Further studies, using nuclear magnetic resonance (NMR) and ultraviolet (UV) spectroscopies, showed that these interactions also exist in solution while *ab initio* calculations suggest that this interaction might be classified as a cation– π interaction.



While structures in the solid state do not necessarily parallel those in solution, they have been used to explain solution-phase behavior where other evidence is not available. For example, the conformation of the isopropyl groups in the highly substituted pyridine **16** in the solid state is as shown, as a result of the substituents adjacent on the ring [<2004JOC536>](#). This was used to account for the greatly reduced nucleophilicity of this species.



Among the more interesting use of the X-ray-derived crystal structures of pyridinium derivatives to determine the extent of carbon–silicon hyperconjugation into the pyridinium system [<2005JOC1993>](#). The crystal structures of triflate salts of the methylpyridinium cations **17** and **18** demonstrate significant lengthening of the carbon–silicon bond, which is greater in the case of the 2-substituted **17**. This, and notable differences in the chemical shift in the ^{29}Si NMR spectra, indicate a significantly greater electron demand at the 2-position of a pyridinium cation than at the 4-position.

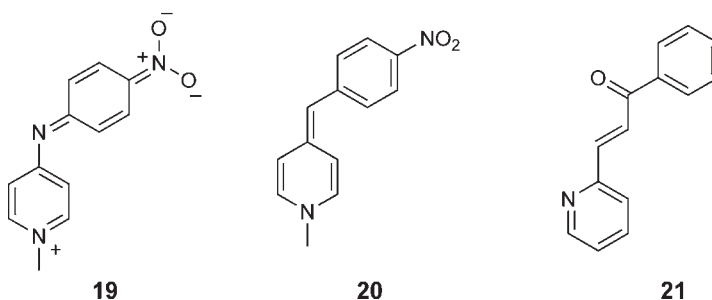


7.01.2.3 Spectroscopic Methods

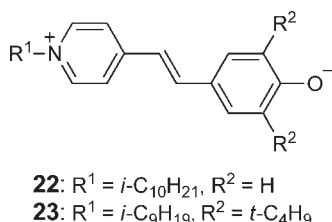
7.01.2.3.1 Nuclear magnetic resonance

The application of NMR spectroscopy to structure determination is broad; however, in this section the group of studies that allow fundamental properties of the pyridine moiety, particularly electronic distribution, will be discussed. Application to other aspects, such as conformation and tautomerism, is discussed separately in those sections below.

NMR spectroscopy has been useful in determining the extent of charge transfer in species such as the pyridoneimines and pyridonemethides. This demonstrates that the predominant canonical form of pyridoneimine is the aromatic zwitterion **19**, while the major canonical form for pyridonemethide is the quinoid **20** [<2001JOC8883>](#). In a similar vein, ^{13}C NMR spectra have been used to study polarization of the ethylene bond in pyridine chalcone derivatives such as **21** as a result of conjugation with the pyridine moiety [<1999JST\(482\)371>](#).



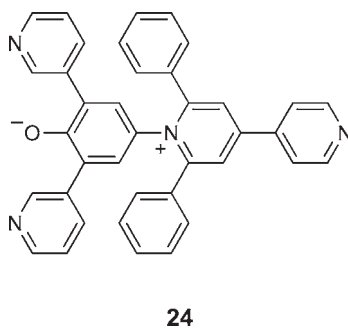
The observed chemical shifts of the resonances for the merocyanine derivatives **22** and **23** indicate that, particularly, the pyridine ring has significant aromatic character. This suggests that, even in solvents with a low dielectric constant, the predominant canonical form is the zwitterion shown [<1997JA10192>](#) supporting previous studies on the parent dye. NMR spectroscopy can also be used to provide information about the ring currents and π -electron effects in heteroaromatics, through comparison with various theoretical models [<2002J\(P2\)1081>](#).



Along with solution-state NMR spectroscopy, analysis of the solid-state spectra of nitrogen heterocycles has been carried out to evaluate the various chemical shift tensors associated with the ^{15}N nucleus [<1997JA9804>](#). Importantly, this showed the dominance of the tensor perpendicular to the plane of the aromatic system along with the key effect of protonation of the pyridine nitrogen.

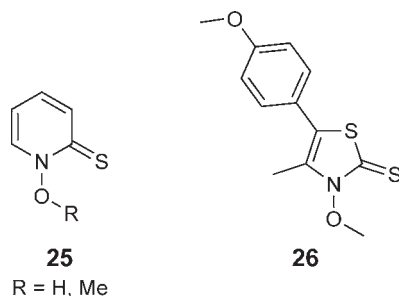
7.01.2.3.2 Ultraviolet/Vis spectroscopy

As discussed in an earlier version of these volumes [<1984CHEC\(2\)99>](#), the contribution of the various canonical forms of pyridinium *N*-phenolate betaine dyes varies dramatically with the solvent. Recently, there have been developments to increase the solubilities of such systems in various solvents [<1998CJC686, 2003JPO626, 2005JPO1013>](#), for example, through the replacement of phenyl substituents with pyridyl moieties, resulting in dyes such as the betaine **24**. Along with increasing the water solubility in this case, the result of the substitution is a hypsochromic shift of the charge transfer band due to substitution on the phenolate portion but a bathochromic shift due to substitution on the pyridinium portion; each of these effects is due to the electron-deficient nature of the pyridine [<2001EJO2343>](#).



Similar studies support the NMR spectral evidence detailed above, supporting the predominance of the zwitterionic form of the merocyanines **22** and **23** [<1997JA10192>](#) though different shifts in absorbance maxima were observed due to the ability of the *t*-butyl substituents to shield the adjacent oxygen atom.

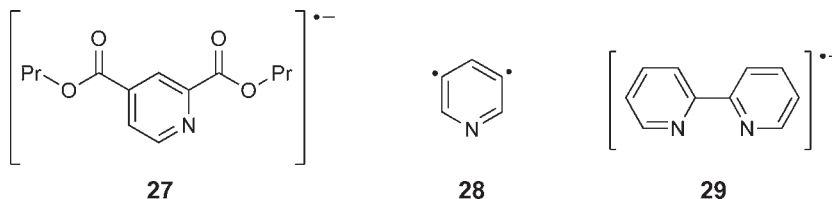
UV/Vis spectra of simple pyridines have also been used as the basis for the assignment of electronic transitions of more complex structures. This is demonstrated through the comparison of the spectra of the pyridine thiones **25** and thiazole thiones such as **26** <2005EJO869>.



7.01.2.3.3 Infrared spectroscopy

In terms of fundamental structural studies, high-resolution vibrational spectra of a series of substituted pyridines have been reported, along with detailed assignments based on theoretical models <1999JST(476)139, 2001JST(563)545>. Further, the role of the nitrogen atom in the infrared spectra of heteroaromatic species has been to increase the overall integrated intensity in the mid-IR region (*c.* 1100–1600 cm⁻¹) <2003PCA1486>. The origin of this effect is proposed to be significant C–N bond stretching and CNC out of plane bending.

In addition, infrared spectroscopy can be combined with other techniques to detect species that are otherwise difficult to observe. For example, electrochemical studies have been used to observe the pyridine radical anion **27**, where the disappearance of signals from the corresponding neutral molecules shows that no formal carbon–oxygen double bond is present <2002J(P2)1882>. Similarly, flash vacuum pyrolysis was used to generate 3,5-pyridyne **28** which was observed using infrared spectroscopy in an argon matrix <2004JA6135> while laser photolysis was used to generate the radical anion **29** which was subsequently characterized <2000PCP4682>.



7.01.2.3.4 Mass spectrometry

With the development of modern techniques, the use of mass spectrometry in elucidating the structures of pyridine and derivatives thereof continues to be used but tends to be carried out in a very case-specific fashion. Examples include the characterization of isoquinoline alkaloids <2004EJS683> and the quinolines produced by *Pseudomonas* sp. <2004JAM862>. In addition, fundamental studies have continued, including the observation that in electron-induced mass spectra of 1,2-dihydropyridine derivatives, the fragment resulting from loss of the substituent on the nitrogen atom is found in each case <1997JAM1255>.

7.01.2.3.5 Photoelectron spectroscopy

The high-resolution photoelectron spectrum of pyridine has been reported, showing the 15 main orbitals and two satellite peaks <1996CPH(207)19>. More generally, the ultraviolet photoelectron spectroscopy of pyridine and its derivatives has been reviewed with respect to understanding the geometric and electronic properties of chalcogenobispyridines <1997CCR1>. Much of the background material has been covered in previous editions of this series, but it should be noted that this review highlights the effects of changing the electronegativity of the bridging atom, such as destabilization of the pyridine antibonding molecular orbitals with increasing electron density. Photoelectron spectroscopy has also been used to determine the structures of a series of substituted quinolines <2004JOC5005>.

where the lone pair ionization energies were determined and correlated with the inductive and resonance effects of the substituents on the quinolines, and of acridine molecular anion <2004JCP11112>, indicating a relatively large intramolecular structural relaxation in the triplet states.

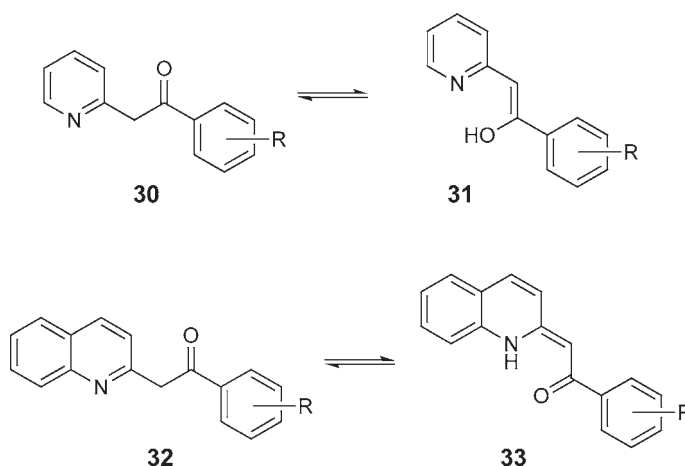
7.01.2.4 Thermodynamic Studies

7.01.2.4.1 Tautomerism

A variety of spectroscopic evidence, notably UV–Vis spectroscopy, has been used to determine the tautomeric equilibria in substituted 2-hydroxypyridines <2002ARK198>. Electron-donating substituents favor the hydroxypyridine form, while electron-withdrawing substituents favor the pyridone form; Hammett analysis of the substituent effects gives a ρ value of *c.* -4 . The effect of solvent in this case is not as marked, with polarity being of greater significance than proticity.

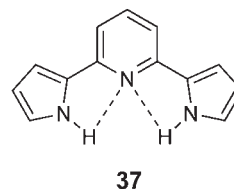
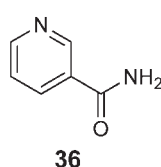
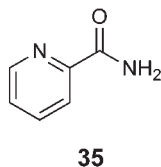
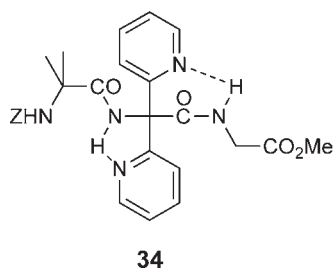
The tautomerism between 2-pyridinethione and 2-pyridine thiol has also been examined using variable temperature IR spectroscopy <2002JOC9061>. No evidence for the S–H stretch was observed in a range of solvents and this was determined computationally to be a solvent effect; the thiol form is more stable in the gas phase but the thione is more stable in solution. (The effect of phase on the tautomers of 2-hydroxy-, 2-amino-, and 2-thiopyridine has also been studied by infrared spectroscopy <2001SAA2659>.) Dimerization is also observed, with the indication that the thione dimer predominates, in contrast with the computational studies described above.

Tautomerism also arises in the case of 2-phenacylpyridines and 2-phenacylquinolines which can, in theory, exist in ketimine, enaminone, and enolimine forms and a range of NMR spectroscopic techniques can be used to determine the position of equilibrium. For the phenyl-substituted pyridines, both the ketimine **30** and enolimine **31** forms are observed and the position of the equilibrium is markedly dependent on the nature of the substituent with a Hammett ρ value of *c.* -2 <2000J(P2)2185>. Note that while two isomers of the enolimine and the ketimine are possible, only the form in which hydrogen bonding occurs is shown. (Deuterium isotope shifts in ^{13}C NMR spectra have also been used to show that only the enolimine was present in the case of other pyridines <1997J(P2)2605>.) The position of equilibrium is consistent with electron-donating substituents favoring the formation of the hydrogen bond. For the quinolines only the ketimine **32** and enaminone **33** are observed though the effect of the substituent is not as significant <2000J(P2)1259>. The proportion of the enaminone tautomer was also found to increase at low temperatures <2001JPO201>.

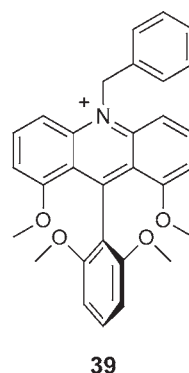
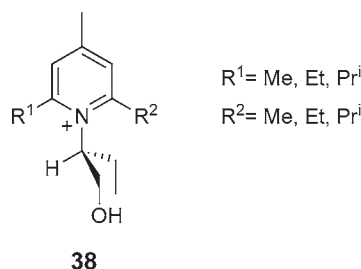


7.01.2.4.2 Conformation

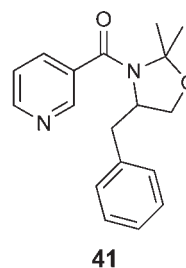
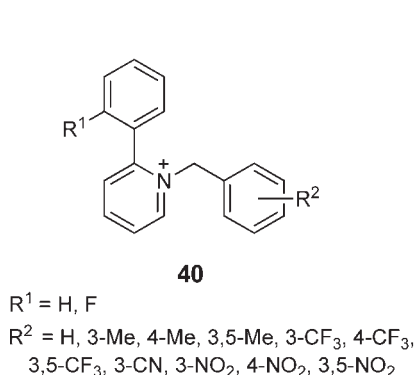
Pyridines and their derivatives have the basic nitrogen present and this can cause one conformation to be preferred. This is amply demonstrated using the α,α -dipyridylglycine derivative **34**, where interaction with the adjacent amide protons is indicated by the change in their chemical shift <2004OBC2335>. A similar interaction has been shown by dynamic NMR spectroscopic and *ab initio* methods to contribute to the increased rotational barrier in picolinamide **35** when compared to nicotinamide **36** <2003JA10125> along with leading to the preferred bifurcated double bond structure in the dipyrrole substituted pyridine **37** <2005EJO4338>. Note that in the latter case, the *cis-cis* form is the more stable.



^1H NMR spectroscopy has also been used to examine the conformational equilibria associated with rotation of the N-substituents in the pyridinium salts **38** <2004CCA391>. As might be expected, the free energy difference between the two principal conformers was found to be small, increasing with the size of the substituents. The energy barrier to rotation was found to be invariant within experimental error, irrespective of the substituents and the solvent. When additional steric interactions are introduced, such as is the case in the acridinium cation **39**, the energy barrier is significantly increased resulting in restricted rotation <2003JOC6304>.

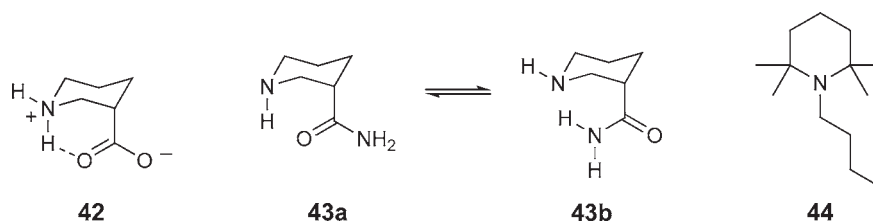


The substituted benzyl pyridinium bromides **40** have been investigated using dynamic NMR spectroscopy, to determine the importance of substitution on the aromatic edge-face interactions which determine the conformations observed in water <1999JOC7802, 2002JA1860>. The substituent effects were small (with neither changes in the quadrupole moment nor the electronic density of the interacting aromatic rings having a significant effect) but were anticipated to be important in related systems where weak interactions dominate. NMR titrations of the nicotinamide derivative **41** were used to quantify similar pyridinium-phenyl interactions, which were found to be stabilizing by 2.1 kJ mol^{-1} <2003JOC1529>.

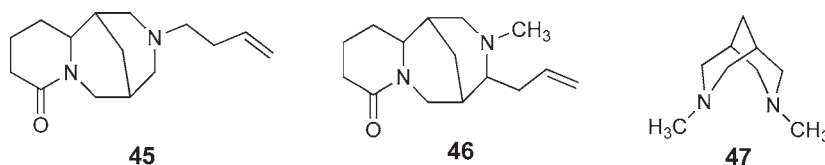


4-Aryl-1,4-dihydropyridines are of interest since related systems have application as calcium channel antagonists. The energy barrier to rotation about the aryl-dihydropyridine bond is small, with the coalescence temperatures observed by NMR spectroscopy to be well below room temperature <1996T9665>. When the aryl group at the 4-position is replaced with a biaryl group, the antiperiplanar form dominates <1997BML2519>.

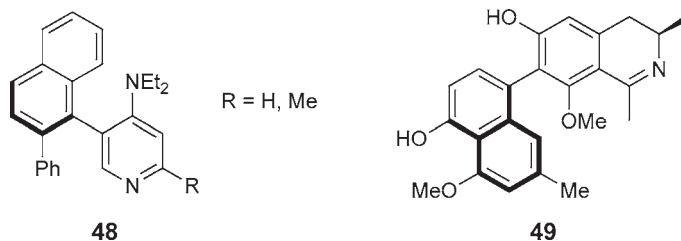
Being saturated, piperidines and related systems have a number of (potentially) readily accessible conformers. For example, piperidines can exist in two chair conformations (along with many intermediate forms) and the interaction of substituents on the ring with the heteroatom can dramatically affect the conformational preference. This may be as simple as in *N*-neopentylpyridine <1998JOC3310> but is particularly notable when intramolecular interactions stabilize a given conformation, such as in nipecotic acid **42**, where a hydrogen bond stabilizes the axial conformer. The hydrogen bond varies in strength from *c.* 4 kJ mol⁻¹ (for the cationic and anionic forms) to *c.* 8 kJ mol⁻¹ for the zwitterion shown <2000J(P2)2382>. Similar values were obtained for the *N*-methyl derivative and the cationic form of ethyl nipecotate. For the nipecotamide **43**, two intramolecular hydrogen bonds might be formed but comparison with 1-methyl nipecotamide indicates that the conformer **43b** predominates, though the strength of the hydrogen bonds was notably solvent dependent. Similar results are observed with substituted *N*-methylpiperidines where circular dichroism, along with comparison with computed NMR data, was used to confirm that the principal conformer was that with all substituents in the equatorial positions <2002JOC161>. For more complicated systems, such as the pentasubstituted piperidine **44**, intricate 'conformational schemes' based on MM3 calculations have been used to assign conformers and the rotational barriers between them <1999CEJ449>.



These arguments can be extended to systems containing multiple piperidine units, as exemplified in the quinolizidine-piperidine alkaloids <1996JST(385)23, 1999JST(474)215, 1999T14501> such as **45** and **46**. Extensive correlation NMR spectroscopy, along with use of coupling constants, allowed the conformations to be assigned through comparison with 3-methyl-3,7-diazabicyclo[3.3.1]nonane **47** and its derivatives, which exists predominantly in the chair-chair conformation shown <1998JST(446)69>. The alkaloid **45** exists exclusively in the equivalent chair-chair conformation, while its isomer **46** has *c.* 30% of the *N*-methyl-2-vinylpiperidine in the boat conformation.

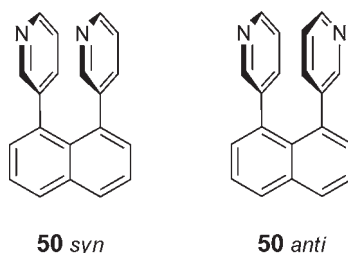


Pyridines attached to another aryl or hetaryl ring also introduce the possibility of restricted rotation about the biaryl linkage. Typically, this requires three substituents at the *ortho*-positions on the biaryl as in the case of the naphthyl derivatives **48**, where the stereochemistry is determined by NMR spectroscopy <2001J(P1)1785>. Other methods of determining conformations, such as the comparison of experimental and computed circular dichroism spectra, have been applied to the related Yaoundamine alkaloids such as the derivative **49** <1997T2817>.



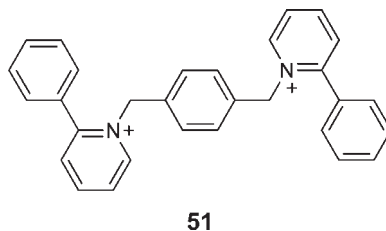
Atropisomerism has also been observed for the dipyrindyl substituted naphthalene **50**, which can exist in *syn*- and *anti*-forms, using ¹H NMR spectroscopy <1996T8703, 1996JOC7018>. While the ratio of the two forms varies with the temperature and the solvent used, each form is present in approximately equal quantities. Computational studies at the AM1 and PM3 levels were required to determine that the predominant isomer was the *anti*-form, with the

computed energy differences in agreement with the observed ratios. Subsequent two-dimensional NMR spectroscopic studies confirmed the assignment of the *anti*-form as the major one <1997T3557>. Associated crystallographic studies showed that the *anti*-form also predominates in the solid state <1997T3557>. Conversion of the dipyriddy naphthalene **50** to the corresponding *N,N*-dipyridinium salts, dipyridinium *N*-oxide, and dipyridones gave very similar ratios of *syn*- and *anti*-forms <1996JOC7018>.



7.01.2.4.3 Solvation and solvent effects

As might be anticipated, the majority of solvent effects of the structures of pyridines relate to conformational changes and, where appropriate, this has been mentioned above. It may be further exemplified by the conformational changes observed on addition of alcohols and fluorinated alcohols to solutions of the pyridinium salts such as **51** in water <2000JA738>. Helical coils are favored by the fluorinated alcohols as the co-solvent destabilizes the exposed hydrophobic side chains in other conformations along with favoring the helical conformation entropically. The former effect is less marked in nonfluorinated alcohols.

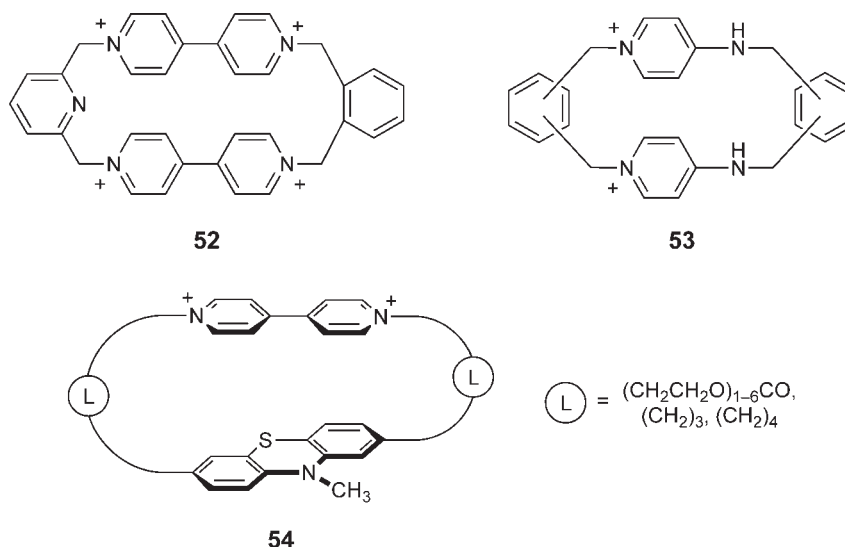


7.01.3 Supramolecular Characteristics

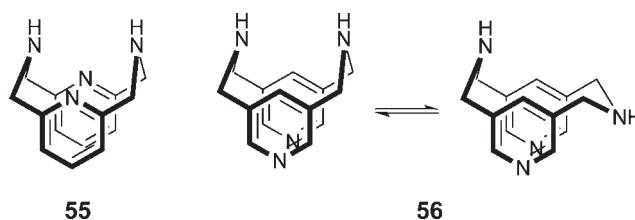
There has been a significant growth in the area of supramolecular assemblies since the publication of the last edition of this series <1996CHEC-II(5)1> and this is reflected in the much greater emphasis placed on the following section. Pyridine derivatives, particularly bipyridine and polypyridines, often play crucial roles in determining both the structure and function of these assemblies. As such, this section details the structures of such assemblies, being careful to distinguish between interactions in solution and those in the solid state. In addition, since these assemblies are often made up of large pyridine derivatives, a discussion of the structural features of these extended pyridine derivatives is also included.

7.01.3.1 Extended Pyridine Derivatives

There is a range of high molecular weight molecules containing pyridine and its derivatives, many of which have interesting application in either the biological or materials field. As a starting point for small extended pyridine derivatives, macrocycles form an important group and conformation of such is of particular interest. For example, NMR spectroscopic studies on the bipyridinium-based cyclophane **52** show that rotation about each of the pyridinium rings can be frozen <1999EJO2373>. Subsequent studies on the amino-substituted pyridinium cyclophanes **53** focused on identifying that rotation about the C–N bond is responsible for the observed coalescence of NMR spectroscopic signals <2003JOC8697>. In addition, related cyclophanes such as the phenothiazine derivatives **54** can have charge-transfer properties <2001EJO3255>. In these cases, the charge-transfer absorption is dependent on the orientation of the donor and acceptor groups, constrained by the linkers between the groups.



Conformation in such macrocycles is of most interest when there are interactions between the pyridine nitrogens and other components of the macrocyclic ring. This is demonstrated by the difference in conformational preference between the two isomeric pyridinophanes **55** and **56**. In the case of the 2,6-disubstituted pyridinophane **55**, the attractive interactions between the pyridine nitrogens and the amino protons of the macrocyclic bridge result in the boat–boat conformation shown. For the isomeric case **56**, the chair–boat and boat–boat forms have the same stability as shown by variable temperature NMR spectroscopic studies and *ab initio* calculations <2002J(P2)393>.



It is worth noting that pyridines are also often used as rigid components in cyclophanes, though they will not be discussed here since in these cases the properties of the cyclophane are not substantially effected by the presence of the pyridine nitrogen (*i.e.*, the replacement of a benzene moiety with a pyridine moiety has limited effect on the structure of the system).

Pyridine-based polymers are also of interest, particularly as they exhibit three-dimensional folding properties. For example, the extended system **57** forms two coils of a helix in both the solution and solid states through the interaction of the aromatic systems, along with the hydrogen-bonding interactions shown <1997JA10587>. Similar hydrogen bonding is observed in the complexation of dicarboxylic acids by cystinophanes <1998JA2695> and in the structure of the monodendron **58** <2000OL239>. As an extension of the latter, the amide-linked pyridine polymers **59** form both single and double helical structures, stabilized by the intramolecular hydrogen bonds shown in Figure 1 along with aromatic interactions <2000NAT720, 2001CEJ2798, 2001CEJ2810, 2002CC578, 2004T10029, 2005AGE1954, 2005CEJ6135>. The former cause the polymer to fold into a helix, the latter particularly stabilize the double helix. Interestingly, protonation of the pyridine nitrogen atoms have been shown to dramatically alter the hydrogen-bonding arrangement and cause the helix to rearrange to another form, proceeding through a linear intermediate (Scheme 1) <2003AGE2738>. The related quinoline systems **60** take up similar helical structures, as shown using NMR spectroscopy <2005CEJ6135> while the crystal structure of the related pyridine-2,6-dicarboxylic acid bisphenylamide shows the same hydrogen-bonding arrangement <1997CM2983>. Amide-linked polymers of pyridines and pyrimidines have also been shown to form helical structures based on related intramolecular hydrogen-bonding motifs <2004CC62>.

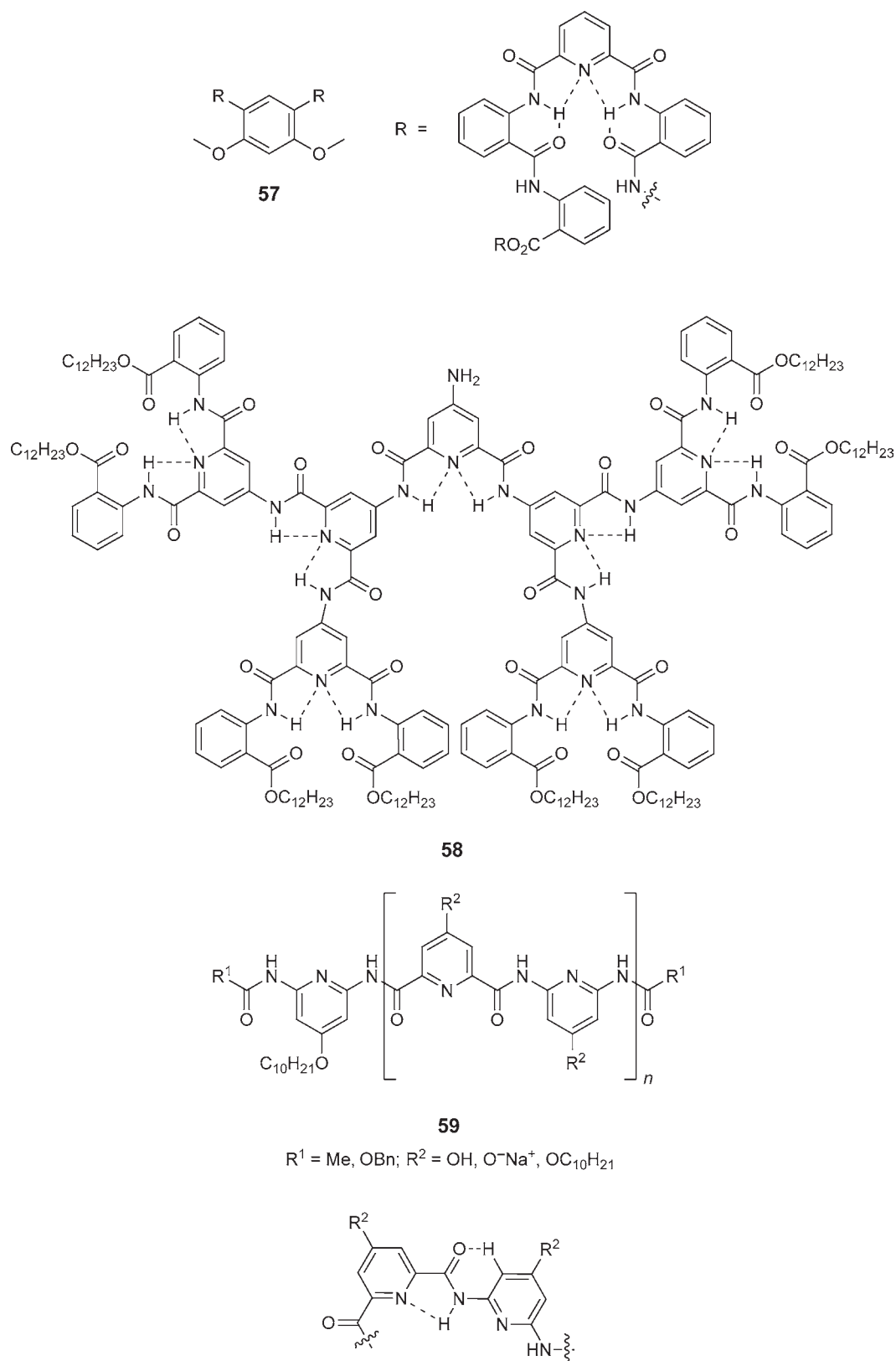
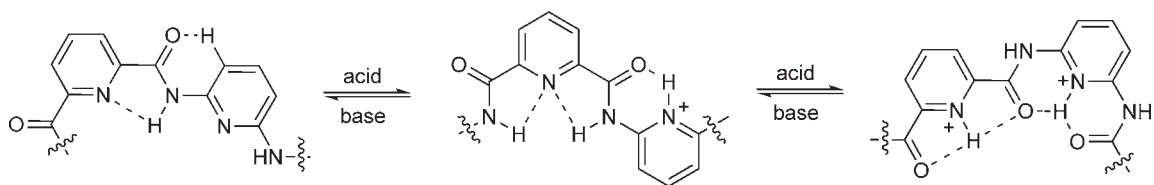
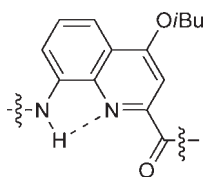


Figure 1

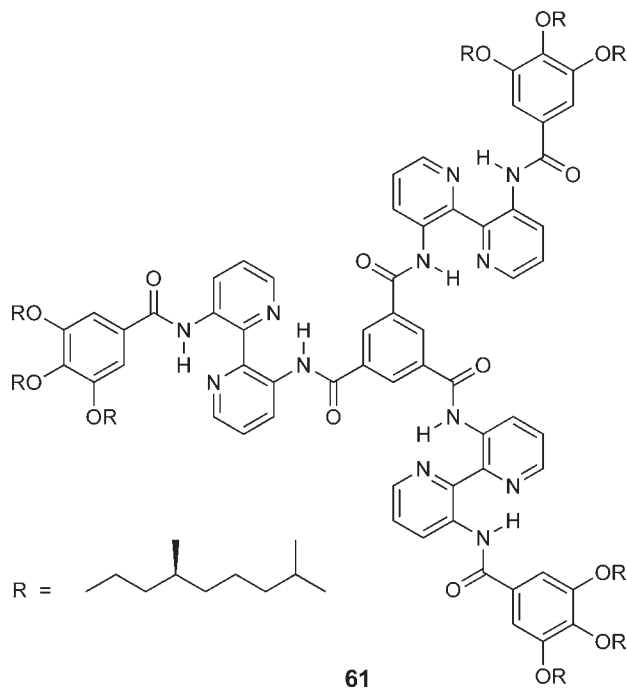


Scheme 1



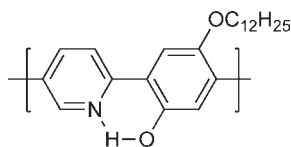
60

Similar arrangements of hydrogen bonds in diaminobipyridines result in the formation of C_3 -symmetrical discs. In the case of the systems such as the chiral **61**, aggregation into a dynamic helix in apolar solvents is observed [\[2005JA5490\]](#).



61

In addition to these helical polymers, phenylene-pyridinyls have been investigated as linear oligomers held in place by intramolecular hydrogen bonds. This is demonstrated by the oligomer **62**, and is expressed in terms of its optical properties [\[2005CEJ5889\]](#).



62

Much of the impetus for considering the pyridine systems described above and their assembly in solution is the potential to mimic biological systems. For example, the presence of heterocyclic rings in nucleic acids makes pyridines the starting points for many biomimetic models. This is exemplified by the studies of the interaction between 2-aminopyridine and 2-pyridinone (**Figure 2**) and 2-pyridinone dimers (**Figure 3**) <2002JA14486>. The former is a model for adenine–uracil interaction, while the latter is a model for uracil–uracil interactions. Both vibronic spectra and computational studies demonstrate that the latter interaction is approximately 50% stronger. Further examples are presented later.

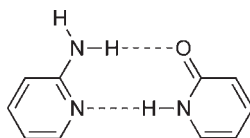


Figure 2

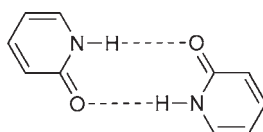
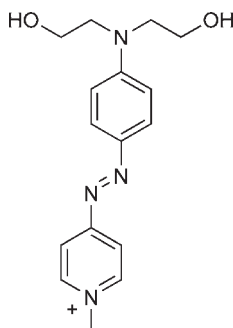


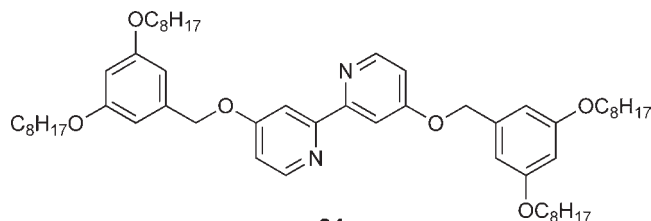
Figure 3

Extended pyridine derivatives have also been considered in the development of new materials as they present rigid systems with different electronic character than benzene. Self-assembled multilayers (SAMs) of stilbazolium derivatives, such as those based on compound **63**, have been investigated <1996JA8034> and shown to have very high structural regularity and subsequently be very smooth. These show promise for nonlinear optical materials, as they have very high second-order susceptibility.



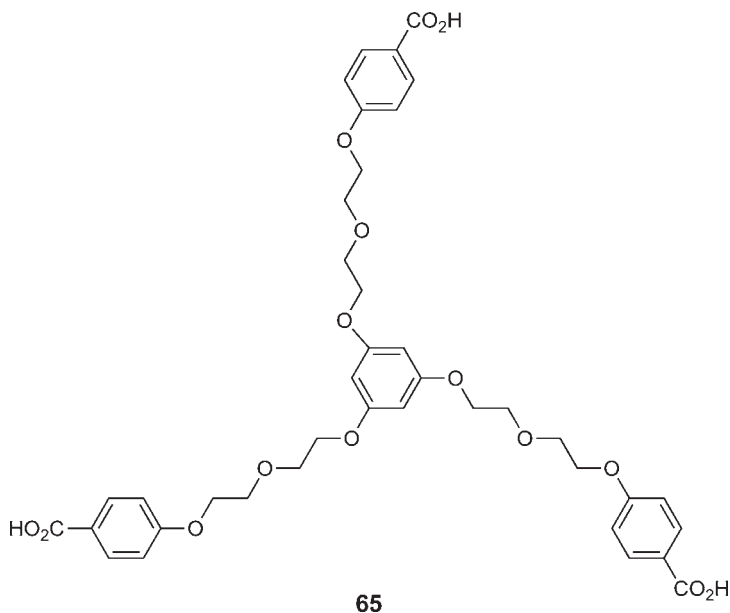
63

Bipyridine units have also formed the basis for SAMs in which conformationally pure domains are formed during self-assembly. This is demonstrated in the case of the dendritic wedge-appended series which includes the bipyridine **64**, which forms a series of homoconformational domains when deposited on a graphite surface <2005JA4033>. In this case, the *cis*- and *trans*-forms of the bipyridine define the different domains.



64

Along with monolayers on surfaces, self-assembled liquid crystals are of interest and a range of bispyridines and the tetracarboxylic acid **65** have been examined. The dynamic nature of the hydrogen-bond networks produced allows a range of phases to be realized <1996CM961>.



It is once again worth pointing out that pyridines are often used to replace benzene moieties in oligomeric systems. While in the examples above, the effect of the pyridine is marked; this is not always the case. For example, incorporation of a pyridine moiety in a *m*-phenylene ethynylene oligomer has very little effect on the resulting helical structure, though it does introduce a site of functionalization in a potential binding pocket in the folded structure <2004OL659>. Methylation at the pyridine nitrogen of this oligomer introduces stabilizing pyridinium–phenyl interactions which favor formation of a helical structure <2004CC1480>.

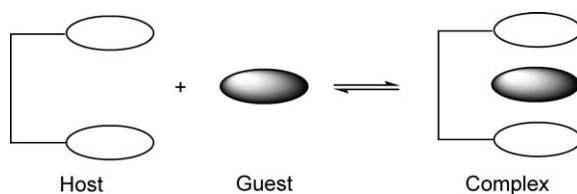
7.01.3.2 Interactions in Solution

Interactions in solution are often observed by considering the change in the spectroscopic properties of the components of the solution. Many of the species described below are characterized by considering the change in the UV and the NMR spectra, with the latter often used to determine the relative orientation of the components of a supramolecular complex. It is important to recognize that a significant amount of fundamental work on interactions in solution has also been carried out, often not considering a distinct complex. This can be used to examine interactions such as nitrogen–halogen interactions (using halogen NMR) and has application in synthons for crystal engineering (see below) <2003CGD799>.

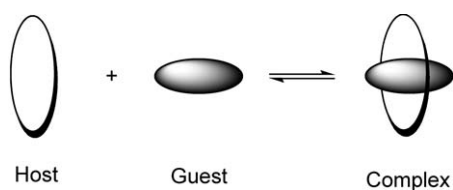
7.01.3.2.1 Host–guest complexes

A range of complexes has been reported involving pyridine and their benzo derivatives. The structure of these complexes can vary quite markedly, depending on the nature of the pyridine derivative and hence the interactions involved. It is important to make a point on nomenclature at the beginning of this section. A host–guest complex involves the noncovalent association of two (or more) species in solution <1974JA6762>. While there are a number of possible configurations, such as binding into a cleft <1990JA8902> and threading of a circular molecule about an axle (as demonstrated by complexation of a linear guest by a cyclodextrin <2004OBC337>), the key point is that, in each case, an equilibrium is established with the dissociated forms. The two examples mentioned above are shown in **Schemes 2** and **3**. This contrasts with rotaxanes (discussed in detail in the next section), which can be considered as the mechanically interlocked version of the wheel-and-axle complex; no dissociation is possible and an equilibrium is not established (**Scheme 3**). In one of the earliest reports of such molecules, it was suggested that this class of molecules be called ‘hooiplanes’ <1967JA5723>. This nomenclature was never universally adopted, with the term ‘rotaxane’ being first used in 1969 <1969LA53> and quickly supplanting the original name. Another term, pseudorotaxane, has been used in the literature since it was first introduced in 1991 <1991AGE1036>. While originally used to describe organization in the solid state, this term has subsequently been

used for host–guest complexes in solution, often with high association constants (for example, see <1999OL1001>). Similarly, ‘semirotaxane’ refers to a wheel-and-axle host–guest complex which cannot ‘dethread’ in one direction due to a bulky end group <1991MI417>; hence, it too is in equilibrium with its free components. Neither of these terms are used here as they serve only to complicate matters and provide no extra information than ‘host–guest complex’.



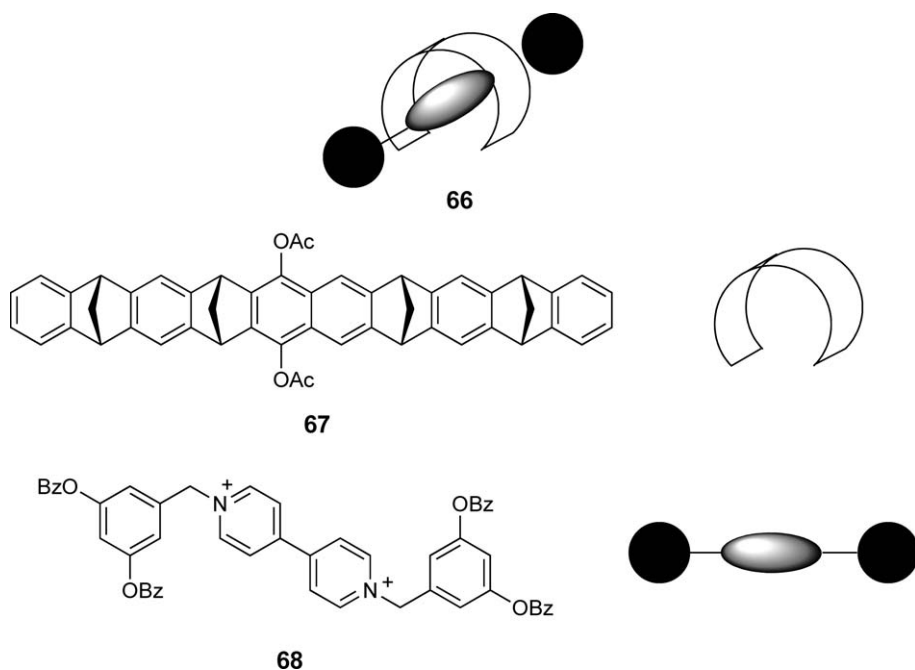
Scheme 2



Scheme 3

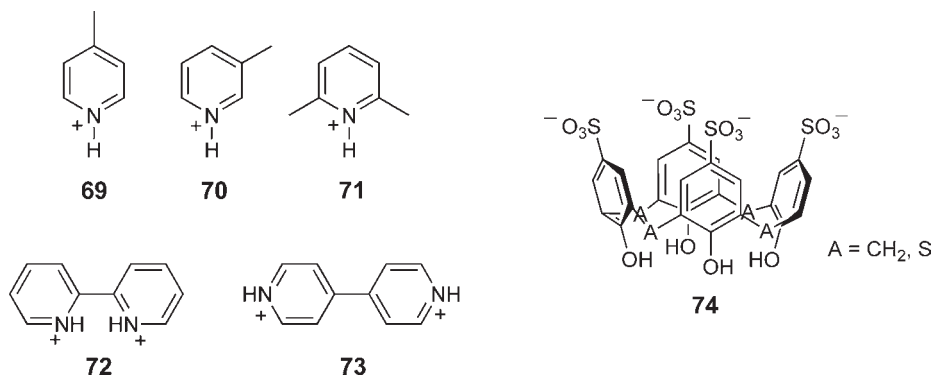
Host–guest complexes involving pyridines and their benzene derivatives can be divided into categories depending upon the interactions involved. In the largest group, pyridinium derivatives act as π -acceptors and their interaction with electron rich π -donors stabilizes the complexes. Within this group, there is still much diversity.

The simplest complexes of this group are those that involve a pyridinium guest included in a host containing electron-rich aromatics. An example of this mode of complexation is the complex **66**, formed by complexation of a tweezer-like aromatic host **67** and a dendritically appended bipyridinium dication **68** <2005AGE477, 2006JA637>.

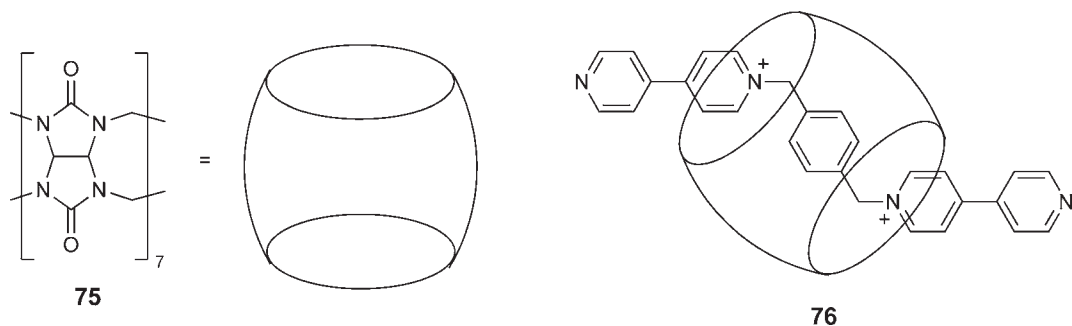


A further subgroup consists of those complexes that can be considered as a pyridinium guest included in a π -donor cavity. It is noteworthy that in all such cases, the relative size of the cavity and the guest is important in determining

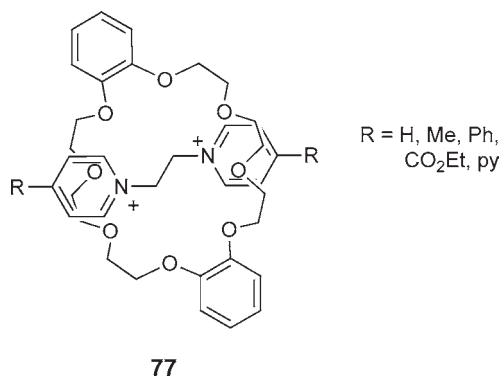
complex stability. This has been referred to, somewhat colourfully, as the ‘Goldilocks effect’ <1997CRV1325>. Calixarenes are popular as host molecules, as demonstrated by the binding of the guests **69–73** in the calixarenes **74** in aqueous solutions <2005EJO162, 2005EJO4581>. In these cases, the additional electrostatic interactions between the host and guest favor inclusion but also determine the orientation of the guest in the host. Related ‘deep-cavity’ cavitands, in which the calixarene has phenalkynyl substituents at the 4-position of the phenyl groups, have also been reported <2005EJO3801>. When a pyridinium unit is appended to the lower rim of a calixarene, it is observed to be included in another calixarene unit forming an oligomeric complex <2006TL181>.



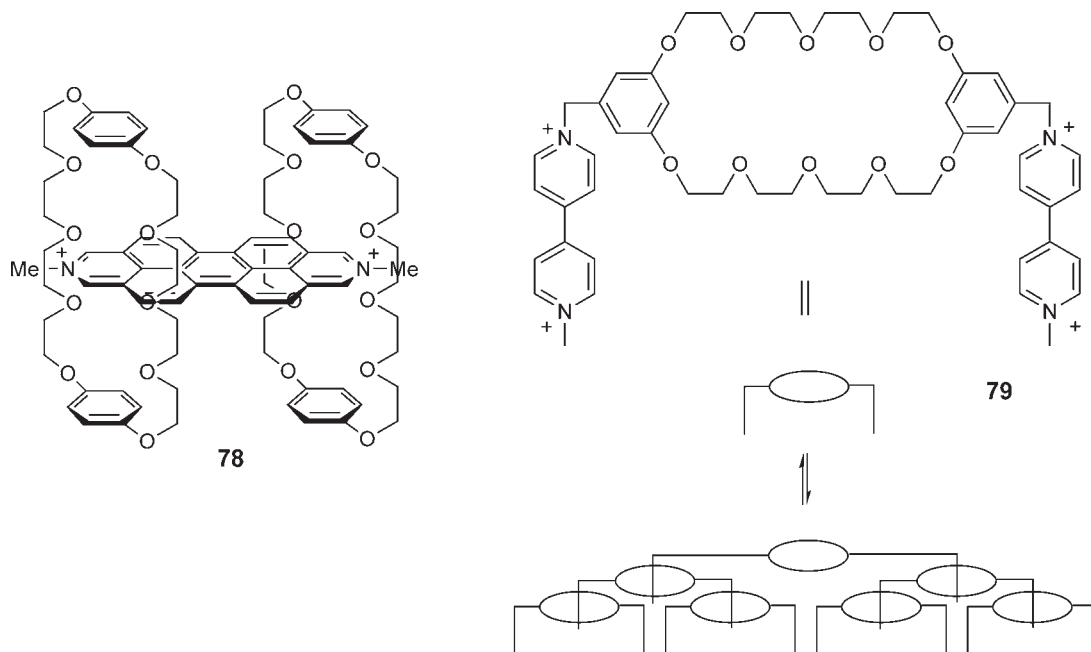
Cucurbiturils, such as cucurbit[7]uril **75**, have also been used as π -donor cavities for pyridinium derivatives, to produce complexes such as the binary dication **76** <2004OL2665> though the range of complexes reported is indeed extensive <2002OL1791, 2002PNA5007, 2004JOC1383, 2004OL185>. In these cases, the charged nitrogen heterocycles interact with the carbonyl moieties on the glycourl units. Complexes have also been noted with pyridinium salts appended to dendrimers <2003AGE2164>.



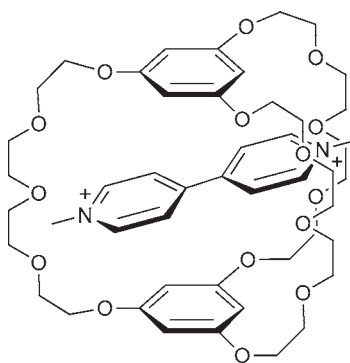
Another series of complexes is made up of pyridinium axles and crown ether wheels. The most common of these are based on 4,4'-bipyridines and the principal interactions are between the quaternary nitrogen and the oxygen atoms of the crown ether and the electron-rich aromatic moieties (where present) <1998CEJ84>. However, when the included guests are dipyridinium ethane derivatives, the important interactions are between the ethano C–H units and the oxygen atoms of the crown ether as demonstrated through the complex **77** <1998CC2757, 1998AGE2838>.



Notably, while the most common complexes contain the two components in a 1:1 ratio, other ratios are possible depending on relative concentrations of the components along with steric requirements. This is demonstrated by the 1:2 complex **78** <2003PCA4669> and the extended 'hyperbranched polymer' **79** <2004JA14738>.

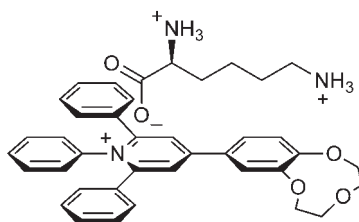


While there are very many simple complexes based on this motif, there are also some in which the inclusion is facilitated by multiple crown ether linkages between the electron-rich aromatics; this is exemplified by the complex **80** <2003JA9367, 2005JOC3231>. Similar 2:1 complexes with larger bipyridinium-based guests have also been reported <2003JA9272, 2005T10242>.



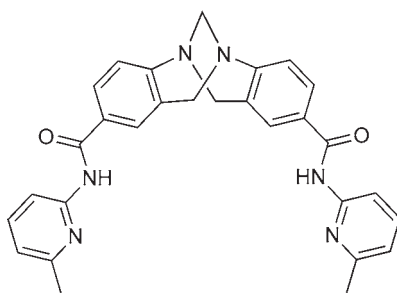
80

The key interactions in the second group are between charged pyridinium cations and anions on another molecule. These can be quite simple, such as the binding of amino acids by crown ether pyridinium compounds, demonstrated by the complex **81** <2005JST(752)68>. Equivalent systems protonated at the pyridine nitrogen atom have also been reported <2002JOC2065>. Alternatively, such interactions can be used to self-assemble much larger molecules, such as carboxylic acid and pyridine-appended resorcinarenes <2000EJO1727>. Similar interactions are also present in a range of pyridinium-based anion hosts <2003JA9699>.

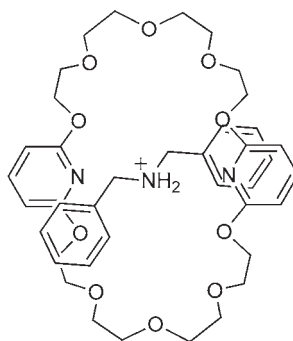


81

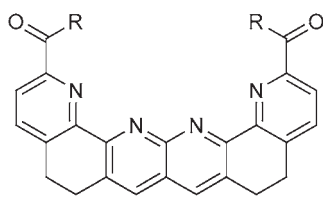
While electrostatic interactions are important in the case of pyridines and carboxylic acids, it might not be clear if proton transfer has occurred. In such cases, along with other related systems, hydrogen bonding might act as the key interaction between species containing pyridine moieties. For example, pyridine-appended Troger's base derivatives such as compound **82** form complexes with dicarboxylic acids <1997TL4503> as do related pyridine amide derivatives <1996T12223>. Pyridocrown ethers have also been shown to complex chiral ammonium perchlorates (with some enantioselectivity when the crown ether was synthesized from chiral 2,6-pyridine dimethanol) <1996JOC8391>, and dipyridocrown ether derivatives provide hydrogen-bonding opportunities for dibenzylammonium salts **83** <2000OL2947>. Bispypyridine derivatives also form complexes with 1,4-phenylenediacetic acid <2005TL7187>. Hydrogen bonding is also crucial in systems such as the clefts **84**, which have been investigated as guanidinium <1999AGE2543> and pyranoside receptors <2002PNA4972>, respectively. Related flexible systems, such as the trisubstituted benzene **85**, have also been prepared and examined as pyranoside receptors <2004JOC7448>.



82

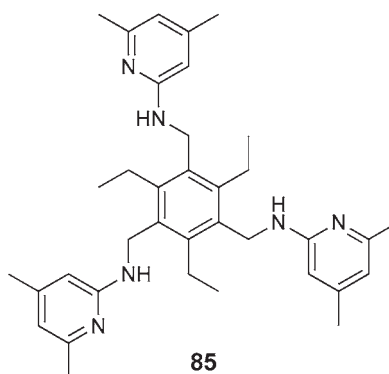


83



84

R = OH, NHC₆H₁₃



85

Hydrogen-bonded complexes have often been investigated as mimics for nucleic acid complexes. This is demonstrated in the case of pyridines such as compound **86** interacting with the thymine derivative **87** (Figure 4) <2005TL6499>. Note that in this case, there is also indication of a bifurcated C-H...O/N-H...O bond. Other studies of similar systems demonstrate that the conformation of the diaminopyridines is critical, with a *trans*-conformation and a coplanar arrangement of the carbonyl groups with the aromatic ring <1996JOC6371>. Further, complexation of the related diamidopyridine **88** was demonstrated to stabilize the *syn*-rotamer of the pyridyl carbamates **89** (Figure 5) <1998JOC7258>.

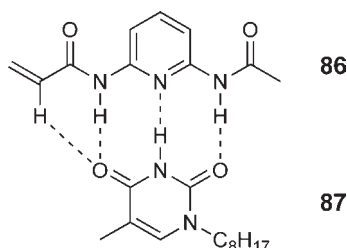


Figure 4

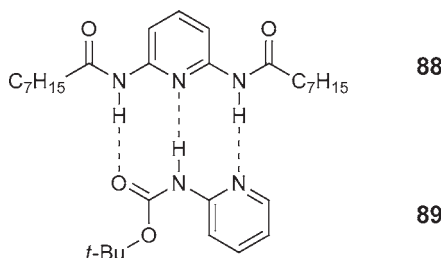
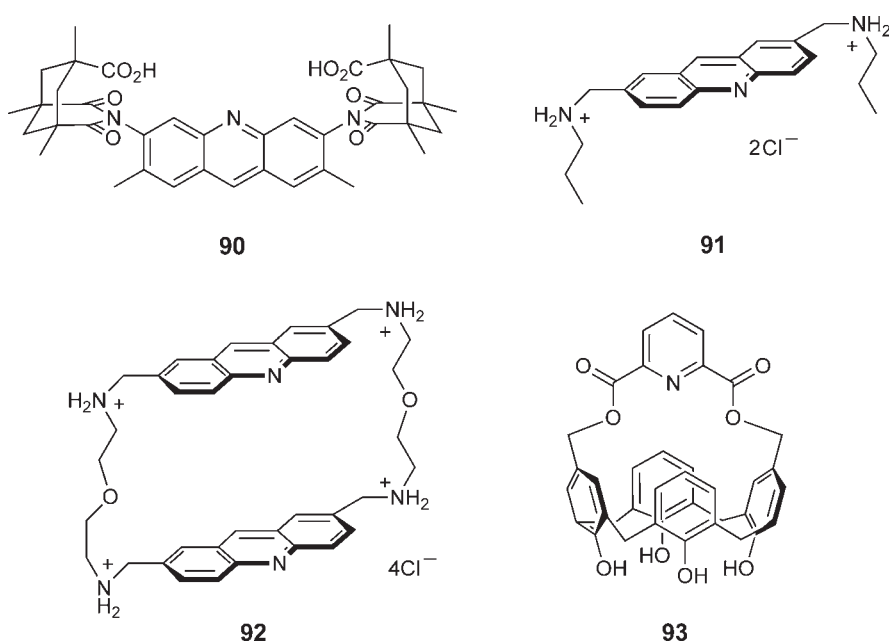


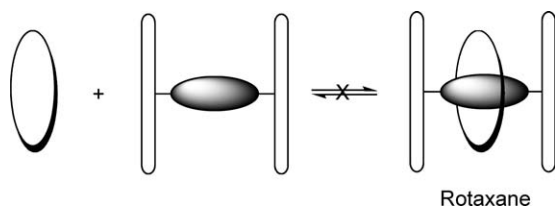
Figure 5

In addition to these interactions, pyridine and its benzo derivatives are often used as rigid frameworks in supramolecular chemistry and, in general, these will not be discussed here. However, often the properties of the pyridine portion can also be seen. For example, the acridine derivative **90** forms stable complexes with benzimidazole moieties with the principal interactions being with the carboxyl groups on the host though interaction of the aromatic moieties of the guest with the acridine portion of the host is also implied [<1996AGE1815>](#). These interactions can be in both acyclic and macrocyclic systems, as demonstrated by the receptors **91** and **92** which can both complex azobenzene dicarboxylates, with the latter having an association constant α . 100 times greater than the former [<1999EJO2479>](#). This phenomenon can be extended to the capped calixarene **93**, which complexes systems with acidic C–H bonds through the ‘soft’ aromatic portion and the ‘hard’ pyridine nitrogen [<1996JOC6881>](#); in particular, methylammonium tosylate was complexed effectively.

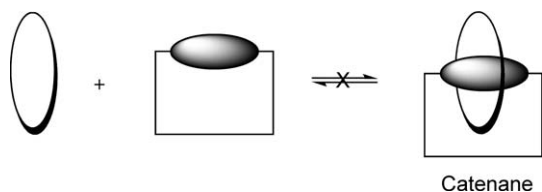


7.01.3.2.2 Rotaxanes and catenanes

As described above, a rotaxane can be considered as a mechanically interlocked wheel-and-axle complex (**Scheme 4**). The term 'rotaxane' generally refers to the simple [2]rotaxane, which involves one wheel on an axle. Higher-order rotaxanes, sometimes called polyrotaxanes, consist of an axle with two or more wheels and are named in a similar fashion; [3]rotaxanes consist of two wheels about an axle, [4]rotaxanes consist of three wheels about an axle and so forth. Related to rotaxanes are catenanes (this name was first suggested in 1960 <1960JA4433>, derived from the latin *catena* meaning chain), the simplest of which can be considered as two mechanically interlocked rings (**Scheme 5**). Nomenclature is similar to that for rotaxanes, [x]catenane refers to x interlocking rings. The simplest way of classifying rotaxanes is to relate them to the corresponding host-guest complexes described above, where 'capping' groups are added such that the complex cannot dissociate. Catenanes can also be related to an inclusion complex as they are often formed by linking two ends of an included guest <2001EJO4041> and as such catenanes can also be grouped as above.

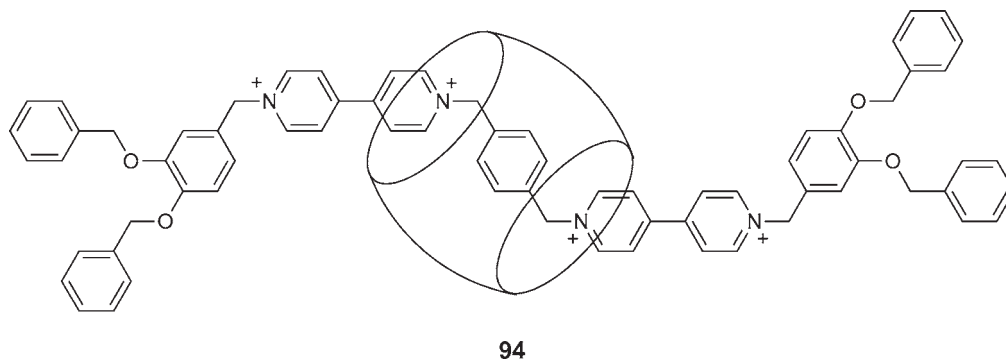


Scheme 4



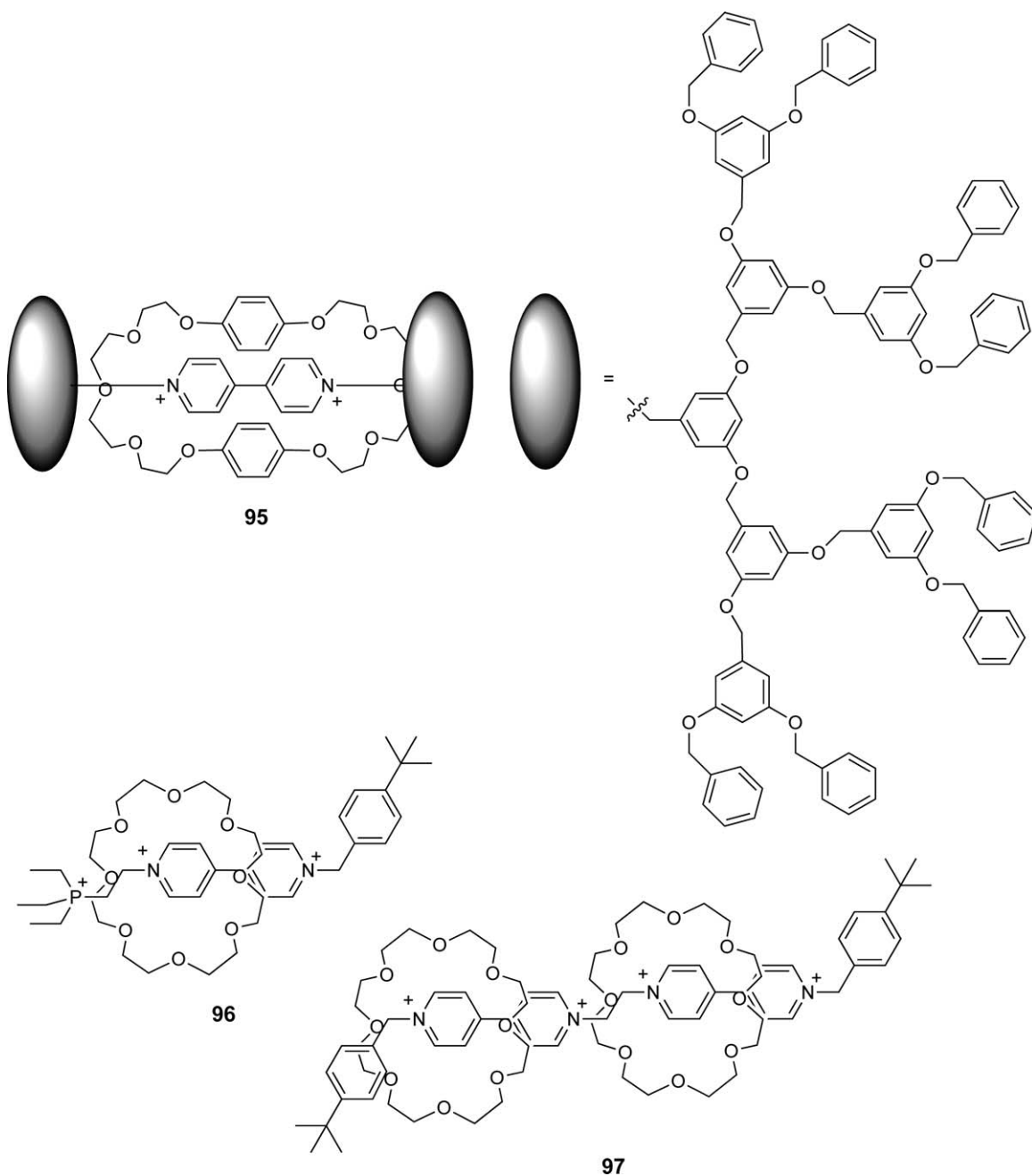
Scheme 5

A large range of rotaxanes are based on the inclusion complexes of a pyridinium guest in a flexible host containing electron-rich π -systems. In the case of the cucurbituril derivatives, the complex **76** can be 'capped' to give the rotaxane **94** <2004OL2665>.

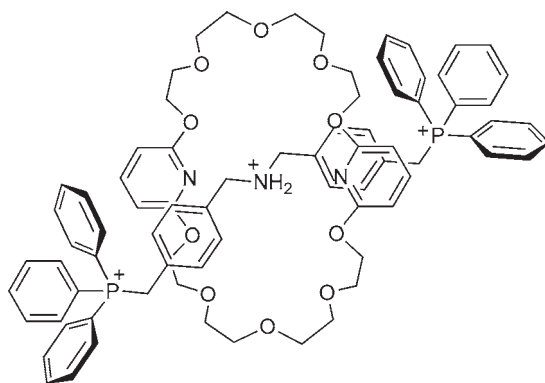


Polyethers, either involving aromatic groups or not, have shown wide application in the formation of this class of rotaxanes. In the case of the former type, the interaction of the electron-rich aromatic groups with the bipyridinium units is the most often used as the means to form the precursor and is demonstrated by rotaxane **95** in which dendritic stoppers are used <1996JA12012>. In the case of the latter type, the interaction of the ether oxygen atoms in the ring

with the bipyridinium host (often referred to as a C–H···O interaction) acts to stabilize the initial complex and the rotaxane products are exemplified by structures **96** and **97**, which can have a variety of end groups, including *tert*-butyl benzyl <1998CC2757, 2000CC845> and phosphonium <2004OBC2751> groups, to prevent dethreading. Note that the addition of other functionalities, such as amides, on the pyridinium units can allow other templating features (such as coordination to an anion) to facilitate rotaxane formation <2002JA12469>.

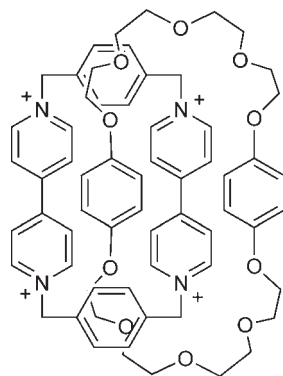


Complexes based on hydrogen bonding to pyridine moieties have also been capped by phosphonium groups to yield rotaxanes, such as structure **98** which is related to the inclusion complex **83** described previously, although not synthesized from it <2000OL2947>.



98

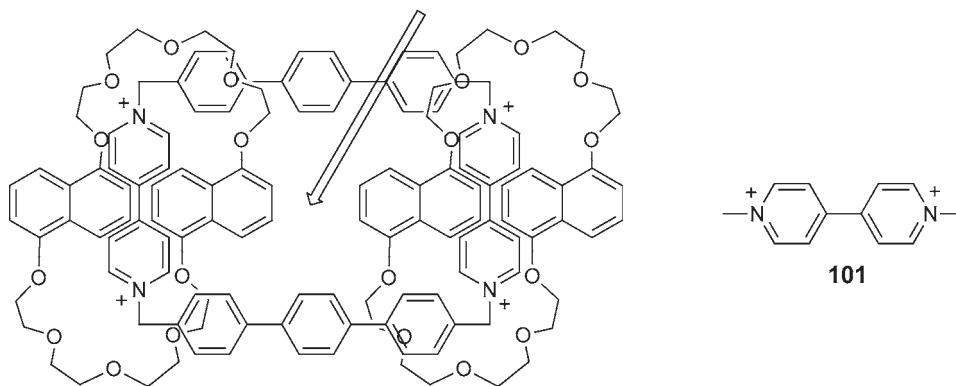
Catenanes based on the inclusion complexes of macrocyclic polyethers containing electron-rich aromatic units and bipyridinium guests form a large group. These are exemplified by the catenane **99** <2001ACR433>; higher-order homologues have also been produced <2000CEJ2262>. Replacement of one of the 1,4-dibenzyl units in the quaternary cation of the catenane **99** with a calixarene produces a related catenane (assembled using the same interactions) with a potential binding site <1999JOC3572>. Simple polyethers may also act as one component of the catenane <2004CC138>.



99

A study of particular note uses the related [3]catenane **100** to demonstrate the relative importance of the aromatic and C–H···O interactions <1999JA1479>. This structure might be thought to have a geometrically ideal binding site for a guest such as the bipyridinium cation **101** but was found by various spectroscopic techniques not to form a complex. Computational studies indicate that the aromatic interactions are comparable to those in the catenane formation, indicating the relative importance of C–H···O interactions in forming these interlocked structures <1999JA1479, 2001JA9264>.

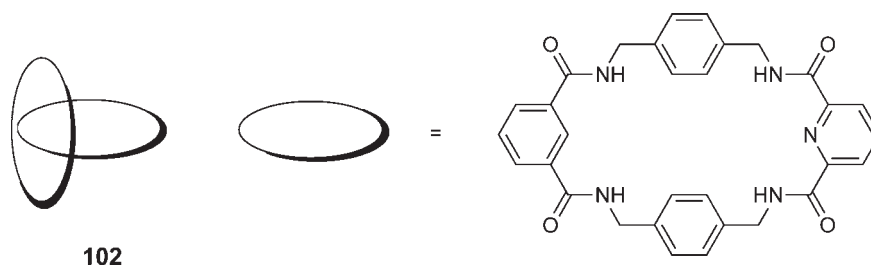
Potential binding site



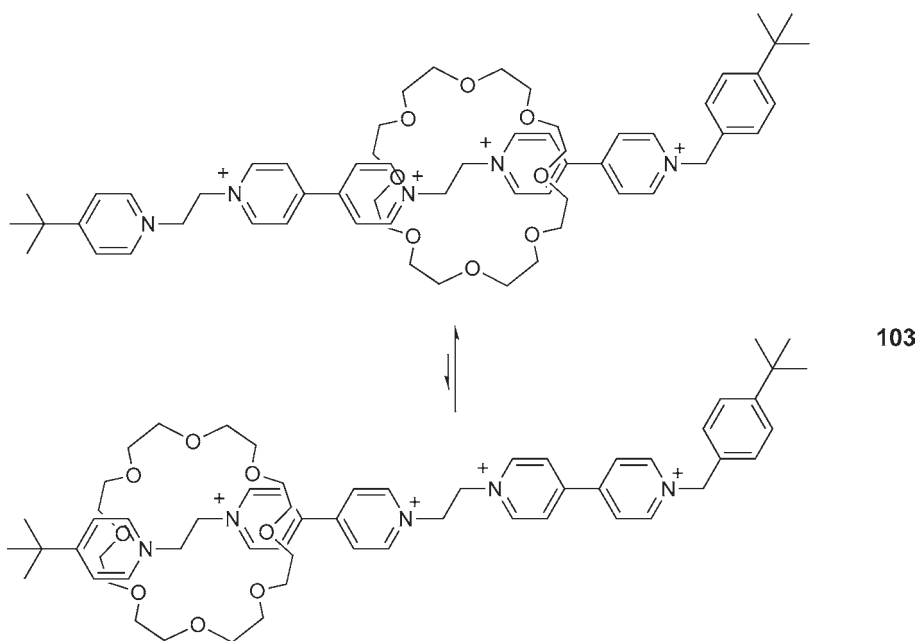
100

101

Once again, pyridines are often used as simply rigid structural components in catenanes. Hydrogen bonding may limit the extent of rotation in such systems, as is demonstrated in the homocircuit catenane **102** <1998JA6458>.



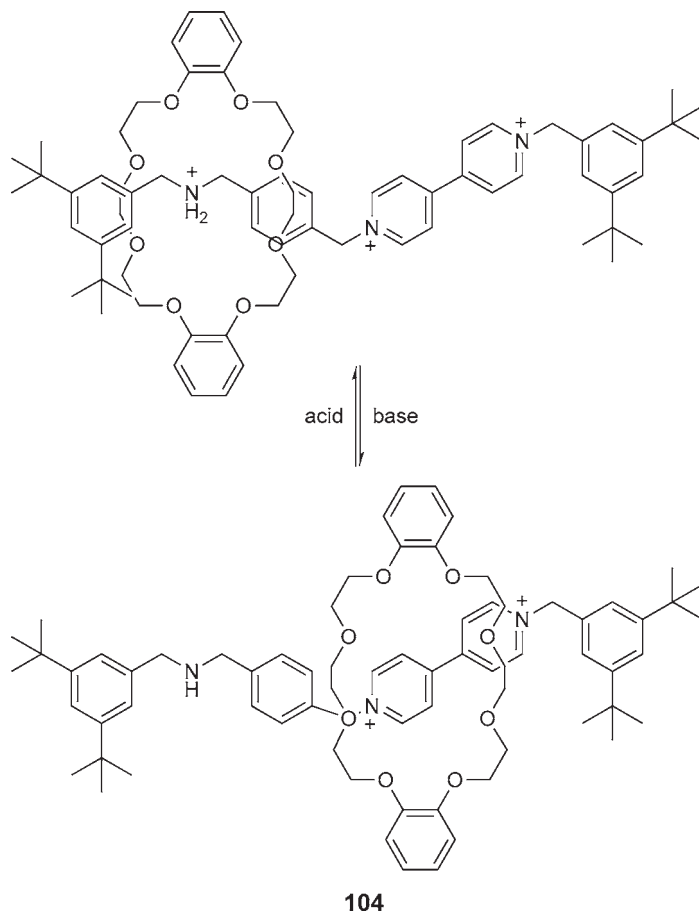
One of the driving forces for the design and synthesis of rotaxanes and catenanes, including those based on pyridine and its derivatives, is the development of nanoscale devices. Since both these supramolecular motifs have mobility, as the components are mechanically rather than covalently linked, they have been much studied with this in mind (for example, see <2001ACR433>). In particular, the rotaxanes and catenanes in which there are two or more sites of interaction (often referred to as 'stations') are of interest as switches. In the simplest form of this concept, there are two or more sites of interaction between which the other component of the supermolecule 'shuttles'. These sites may be identical, as is the case for [3] and [4]rotaxanes based on the [2]rotaxane **95** above <1996JA12012>, but the more interesting case is when they are different and a distinct preference for a given site may be observed, as is the case for rotaxane **103**, where there is a distinct preference for the bispyridinium ethane site (Scheme 6) <2000CC1939>.



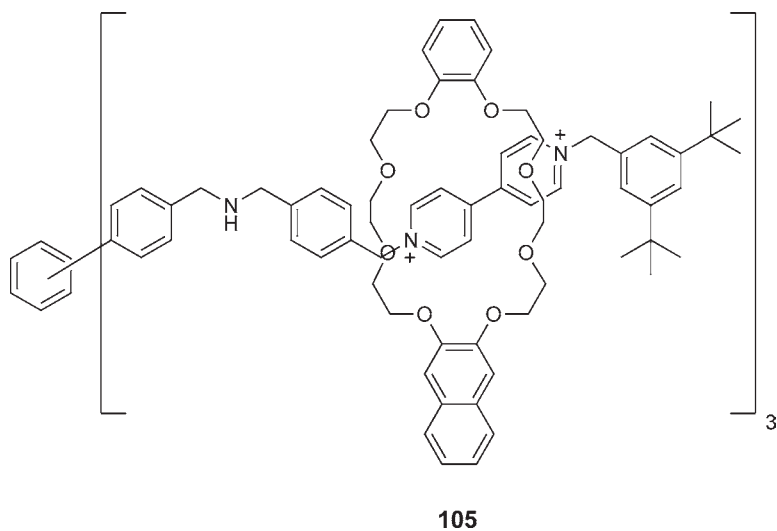
Scheme 6

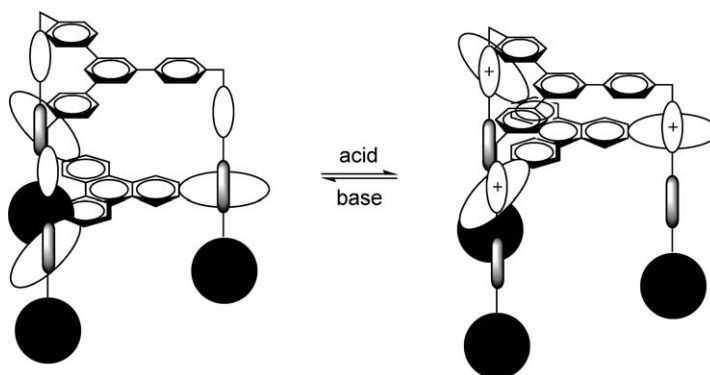
The alternative might be considered a 'molecular switch' where the nature of the interactions at one of these sites is changed by external stimuli. This changes the preference for occupancy of the different binding sites, resulting in the molecule 'switching'. A further stimulus can then be used to reset the switch to its original state. An example is the acid–base switchable rotaxane **104** in which the polyether ring occupies the binding site around the protonated amine in acidic solution but around the bispyridinium unit in basic solution (Scheme 7) <1997AGE1904, 1998JA11932>. Closely related systems, such as those which differ only subtly in the nature of the stoppers on the rotaxane, have also been reported <2002JOC9175>. The switchable nature can be taken further to the trifurcated

system **105**, which can be considered a [4]rotaxane or, alternatively, a ‘molecular elevator’ in which the addition of acid causes the elevator car (the polyether component) to move to the newly protonated amine binding site (**Scheme 8**) <2004SCI1845>.



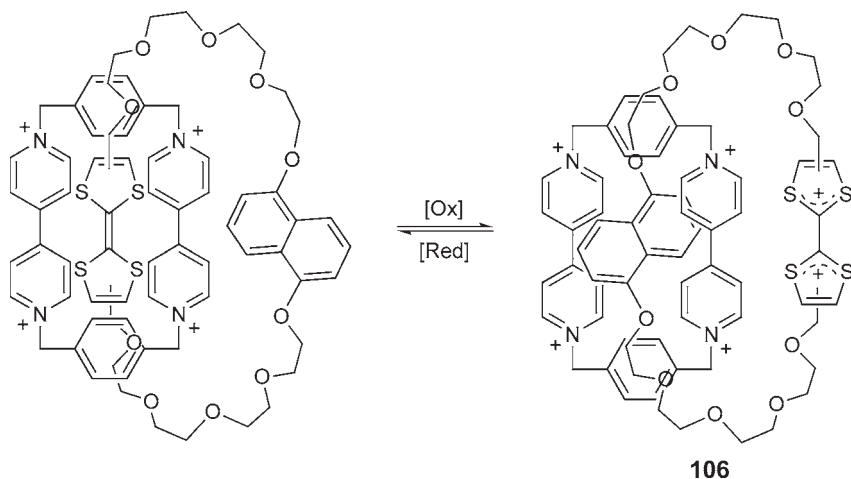
Scheme 7





Scheme 8

Other stimuli have also been used and this is demonstrated by the redox switchable catenane **106** <2000JOC1924>; interaction of the bipyridinium cation with the tetrathiafulvalene unit is preferred to the naphthoxy portion of the polyether but oxidation leads to rotation of the ether ring and an alternate state; reduction leads to a reversion to the original state (Scheme 9). It is worth noting that switching of the corresponding simple association complex (termed in the publication ‘pseudorotaxane’) occurs under redox conditions. Similar switching is observed in related rotaxane systems <2003CEJ2982>. Oxidation and reduction can also be carried out on the bipyridinium portion of the catenane **107** resulting in rotation to give an alternate state (Scheme 10) <2001CEJ3482>. Similar results have been demonstrated with a related [3]catenane.

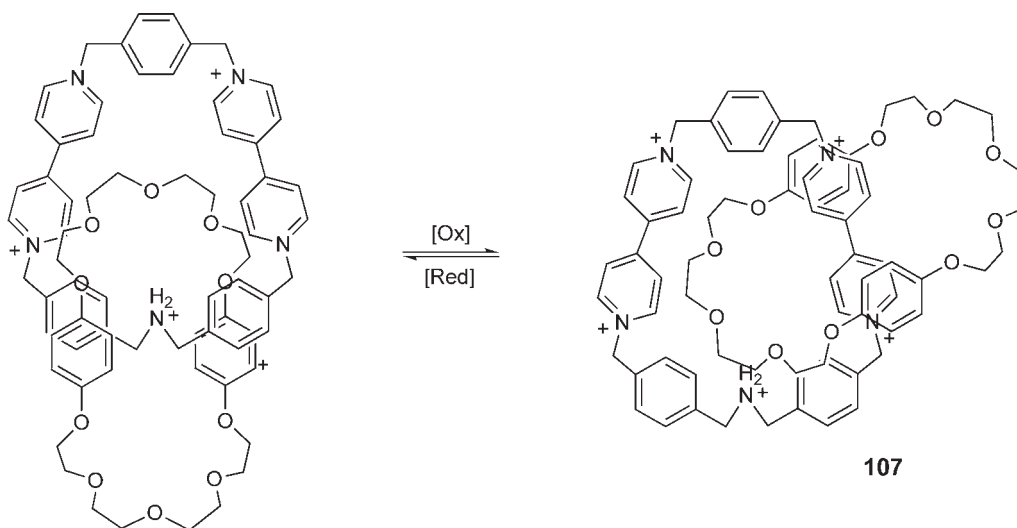


Scheme 9

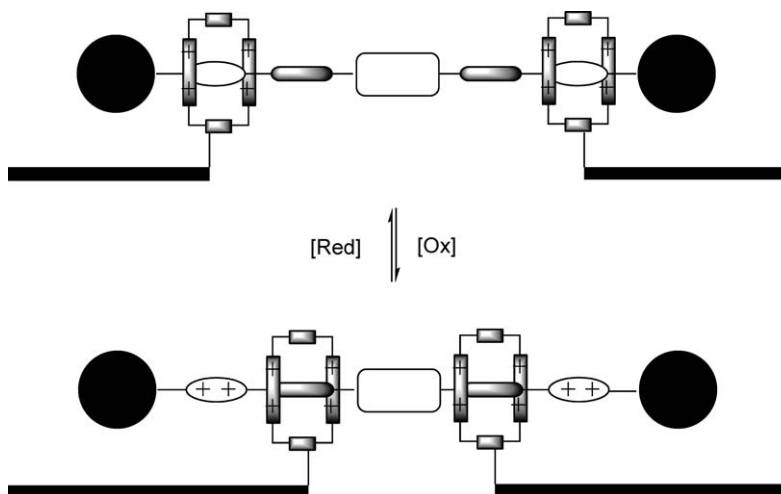
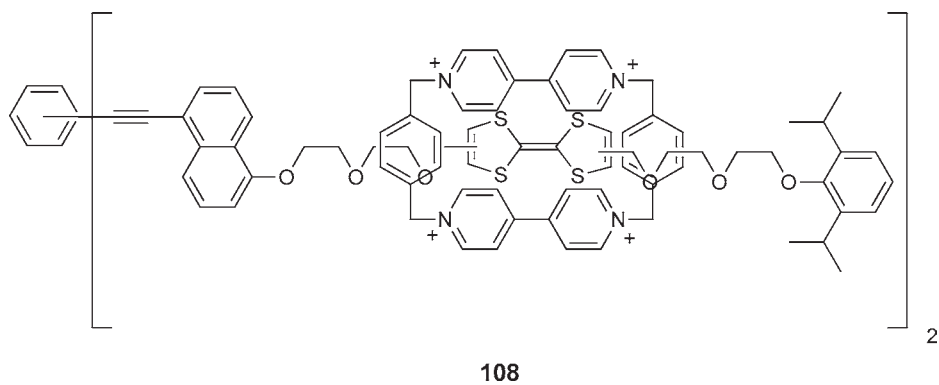
Such oxidation-controlled molecular motion has also been used to produce ‘molecular muscles’ out of [3]rotaxanes such as **108** (the ‘wheel’ portion of which has been attached to a surface) which either expand or contract depending on the oxidation state (Scheme 11) <2005JA9745>.

7.01.3.3 Crystal Engineering: Interactions in the Solid State

Some of the most significant recent advances in the structural studies of pyridine and its benzo derivatives have been in the area of crystal engineering, a working description of which “might see modern crystal engineering as the bottom-up construction of functional materials from molecular or ionic building blocks” <2003CC2751>. A range of different structures can be found within crystals; however, it is the interactions that exist between the molecules present which will be focused on here. While aryl face–face, aryl face–edge, and halogen–halogen interactions present in crystals made up of pyridine derivatives are present in other structures, the nitrogen atom present means that other interactions, such as C–H···N and nitrogen–halogen interactions, can be introduced to further organize the crystal structure. Examples of the structures resulting from these synthons are numerous and many allow the inclusion of a range of organic guests within the lattice structure.



Scheme 10



Scheme 11

There are many examples of crystal engineering where the pyridine portion of the molecule is simply a rigid scaffold about which the elements that ultimately define the crystal structure are arranged. These will not be covered in this review as the principal origins of the crystal structure are not related to the presence of the pyridine ring. In addition, pyridine may be included in a crystal structure as occluded solvent (for example, see <2004CEO484>). Unless a particular structural motif is illustrated by this, such examples will also not be included. Crystal engineering can involve crystals of a single compound, either with or without an included guest, or two or more compounds. No distinction is made here, as the synthons involved are the same; however, generally it is commented on in the text.

The work of Bishop *et al.*, using a series of closely related diquinoline derivatives, has highlighted the importance of a series of crystallographic synthons associated with the presence of a pyridine moiety. Particularly, the C–H···N synthon that often results in a dimeric interaction (Figure 6), which was first shown in the case of the quinolines **109** <1997J(P2)2099>, is highlighted along with the fact that the various interactions compete with one another to determine which final structure predominates. Modifying the bicyclononane portion of the structure to give the oxygen **110** and sulfur **111** analogues, demonstrates the fine balance of interactions of synthons as, perhaps surprisingly, the supramolecular structures are significantly different. The oxygen derivatives **110** show, along with C–H···N interactions, a significant interaction between the ether oxygen and the *peri*-hydrogens <2001CEO107> while the equivalent interactions are not present in the sulfur derivatives **111** <2001CEO265>. In the sulfur cases **111**, these two interactions are replaced by an interaction between the *peri*-hydrogens and the quinoline nitrogen on an adjacent molecule.

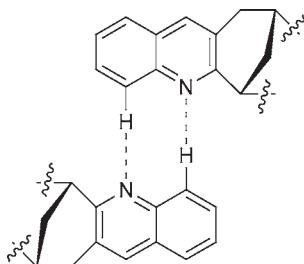
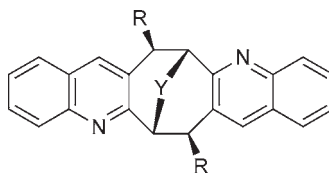


Figure 6

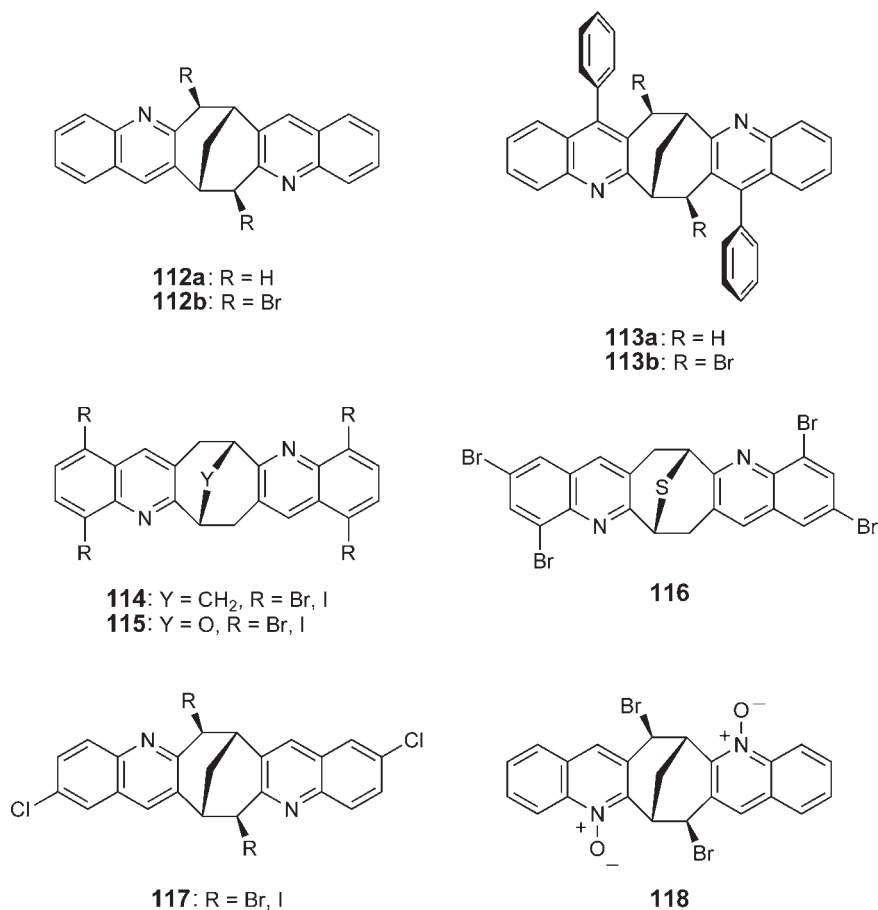


109: Y = CH₂, **a** R = H **b** R = Br

110: Y = O, **a** R = H **b** R = Br

111: Y = S, **a** R = H **b** R = Br

Other modifications of the parent **109** result in changes to the observed crystal structure. While the crystal structure of the regioisomer **112a** has not been reported, the corresponding bromide **112b** shows equivalent dimerization to the isomer **109b** though in this case the dimerization is *syn* to the bromine atom <2001CEO225, 2004CGD837>. The presence of substituents typically introduces additional packing interactions, such as edge–face aromatic interactions in the phenyl derivative **113** <2004CEO618> and (further) halogen–halogen, halogen–aromatic and nitrogen–halogen interactions in the halo derivatives **114–117** <2002CEO194, 2002CGD421, 2003CEO417, 2003CEO422, 2005CEO139>. In the cases of the halides **114** and **115**, the structure differs from nonring brominated **109b** and **110a** with the halogen–halogen interactions driving the crystal into a staircase structure in which no C–H···N interactions are observed <2002CGD421, 2003CEO417, 2003CEO422>. Alternatively, modification of the pyridine nitrogen atom will disrupt the C–H···N dimers, as is the case for the quinoline *N*-oxide species **118**, though even here related bifurcated C–H···O(–N)···H–C interactions are observed <1999AJC1047>.



Modification of the linker unit alters the relative geometry of the aromatic rings and hence the packing in the crystal, as is the case for the bicyclo[2,2,2]octane derivative **119** <2002CEO585> in which the C–H···N interactions are weaker and not in a dimeric structure. A series of bicyclo[3,3,0]octane-based diquinolines has also been studied, including the nonring-substituted systems **120** <1999CC2389, 2003EJO72>, which undergo self-resolution into enantiomeric crystals for the unsubstituted **120a**, while the bromo derivative **120b** introduces a new bifurcated C–H···N···H–CBr–Ar interaction. The effect of ring halogenation in these derivatives is again shown by the significant differences in these structures to the chlorinated derivatives **121**, with the C–H···N interaction being dominated by the introduced π -halogen interactions <2002JSU409>. In the tetrahalo **122** the C–H···N interactions are weak <2002CEO585> and the bromides **123** and **124** (like species **114** and **115**) cannot form C–H···N dimers <2003OBC1435, 2004OBC175, 2002CEO510>. Modification of the pyridine nitrogen to give, for example, the oxide **125** gives similar results to that observed for the bicyclononane system **118** <1999AJC1047>.

Perhaps the most important finding from these studies is that there is a very subtle interplay of forces occurring in the crystallization of these compounds and an array of different structures is possible. However, it is important to realize that there are also more gross effects. Hydrogen bonds between the pyridine nitrogen and a hydrogen attached to an electronegative element also form a key synthon in crystal engineering. For crystals of a single compound, the functional group appended can be an oxime <2000CEO145, 2001CGD47, 2005JOC9115> or an alcohol <1997JST(404)33, 2003CEO414>. In some cases, as observed with pyridyl-substituted α,β -unsaturated ketoximes **126**, subtle changes in the structure of the oxime result in changes from a discrete tetrameric structure (as in the case **126a** <1999T7835, 2000CEJ2865>) to strands of molecules which subsequently interact in a helical fashion (as in the case of **126b** <2005JOC9115>). In addition, intermolecular interactions are observed between the diol **127** and pyridines (in which the host **127** acts to selectively include given pyridines when steric factors are taken into account) <2000CEG251>, between diphenols and bipyridines <2005CGD1041>, between tetraphenols and bipyridines <2005CGD1575>, and between bipyridines and complex bisphenols such as spirobichromane **128** <2005CGD1889>. Note that in many of these cases aromatic C–H···O interactions are also present. Further, these can involve simple pyridines or extended structures such as calixarenes **129** which may subsequently also encapsulate other species (Figure 7) <2004JA9669>.

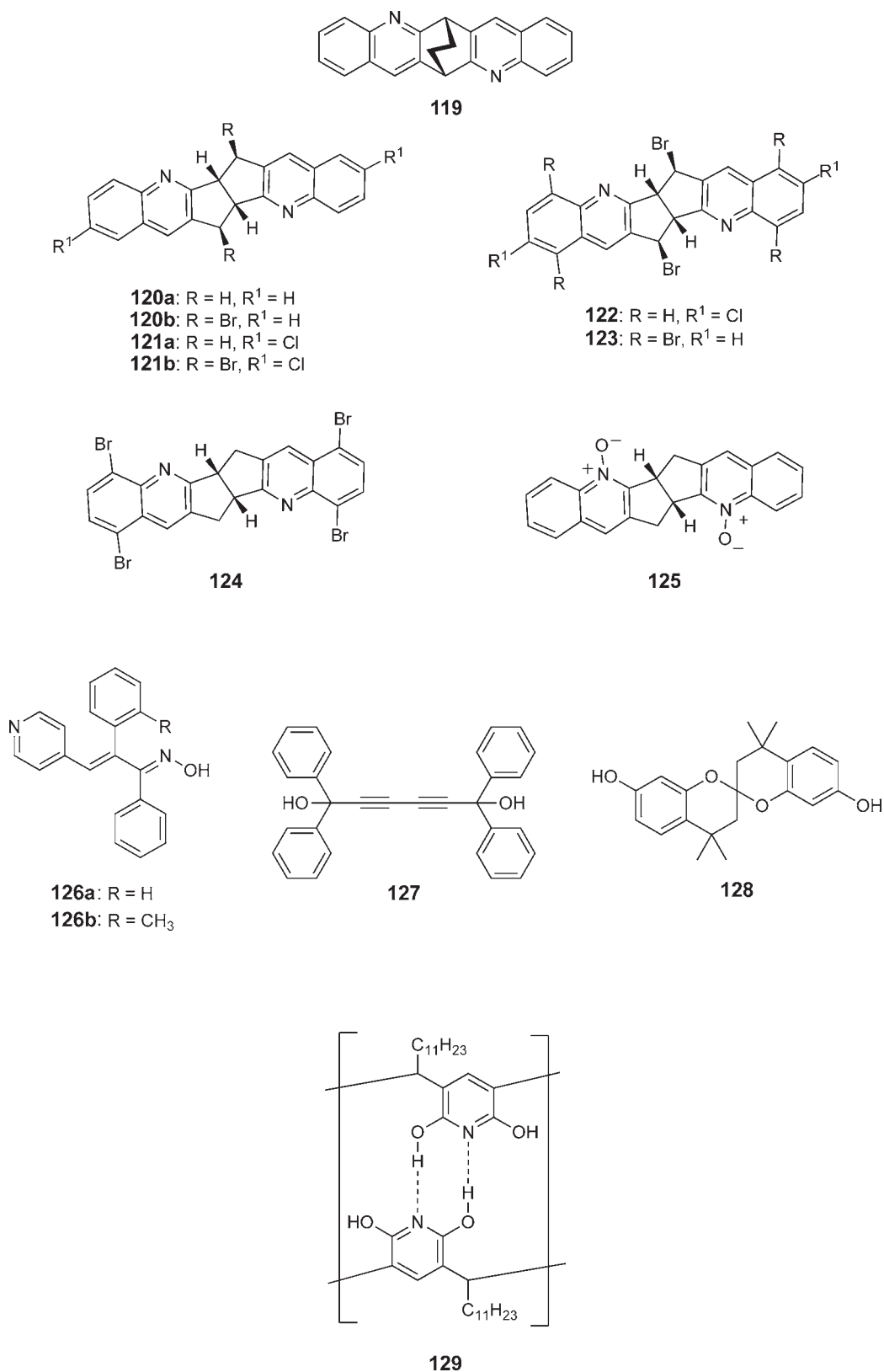


Figure 7

This hydrogen-bonding motif can readily be extended to co-crystals and this has been used to produce what is arguably one of the more interesting examples of ‘supramolecular’ crystal engineering. The resorcinarene **130** crystallizes with bipyridine in such a way that hydrogen bonds between the resorcinarene hydroxyl groups and bipyridine form a supramolecular capsule in which aromatic moieties, such as nitrobenzene <2000CC359> and benzophenone <2001CGD271>, can be included albeit in a disordered fashion (Figure 8). It is worth noting that the other inclusion modes of benzophenone are based on an alternative conformation of the resorcinarene, in crystals prepared through alternative methods <2001CEO78>. When the co-crystallization occurs with a larger potential guest, such as ferrocene or its acetylated derivatives, the host becomes the equivalent of a deep cavity calixarene (Figure 9) <2000CC517>. The formation of such extended cavities in the solid state has also been demonstrated through co-crystallization of resorcinarenes and substituted pyridines <1999CC181>.

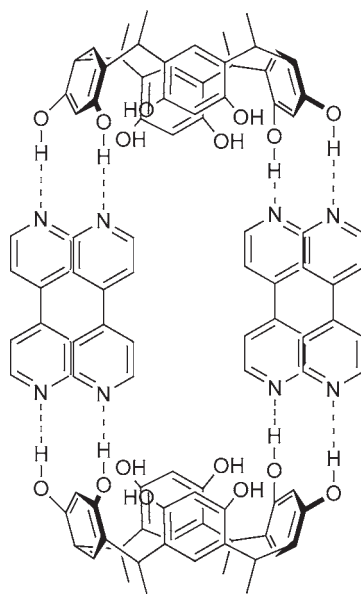
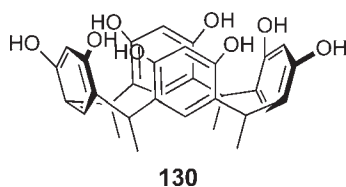


Figure 8

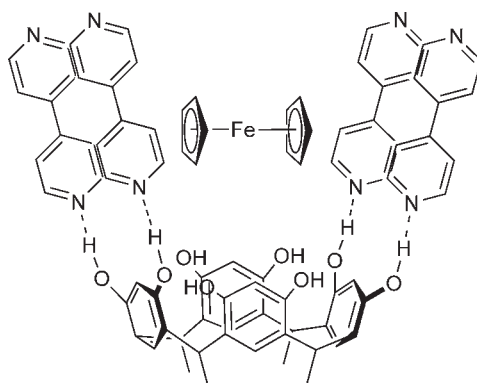
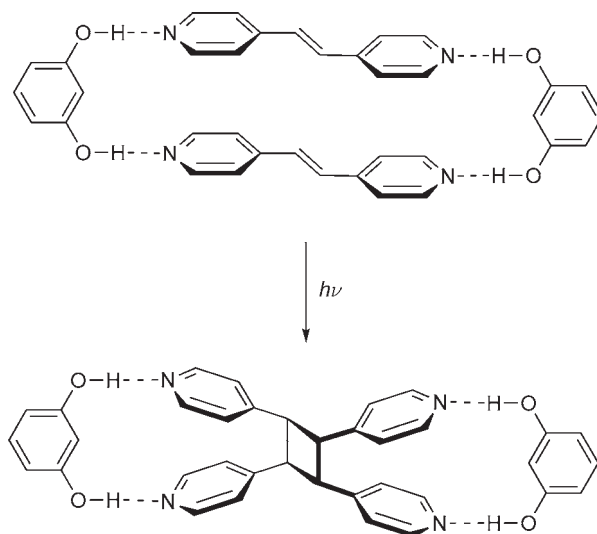


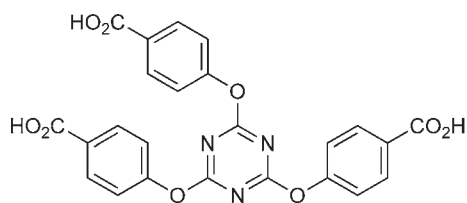
Figure 9

Hydrogen bonding can be used to orient systems in co-crystals such that subsequent reaction can occur. This is demonstrated in the co-crystals of resorcinol and bipyridyl systems, which are oriented such that irradiation of the sample produces a cyclobutane (**Scheme 12**) <2000JA7817>.

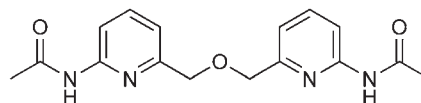


Scheme 12

In some cases, it is not clear whether a hydrogen bond exists or whether transfer of the proton occurs and an electrostatic interaction is the principal synthon. The extent of this proton transfer has recently been evaluated in terms of the difference in the pK_a values for the acid and base <2005CEO551>. Irrespective of the extent of proton transfer the interaction between a pyridine and an acid has been shown to be the principal interaction in a myriad of co-crystals of pyridines and (predominantly carboxylic) acids, which may also include aromatic solvents. These include examples in which crystals form between pyridines and benzoic acids <1999AJC71, 2000JST(552)233>, bipyridines and a range of mono-, di-, and tricarboxylic acids <1999CEG137, 2002CEG9, 2002CGD325, 2005CEO108, 2005CEO551, 2005CGD727, 2005CGD1683>, *iso*-nicotinamides and a series of mono- and dicarboxylic acids <2001AGE3240, 2002JA14425>, dimethylaminopyridine and picric acid <2003AXEo913>, bispyridines and tricarboxylic acids <2003CGD547>, bispyridines and phenanthrolines with 1,2,4,5-benzenetetracarboxylic acid <1996AXC2538, 2003JOC9177>, bipyridine and quinoline sulfonic acids <2004AXCo284>, pyridine and the various phthalic acids <2004CEO207>, aminopyridine and aminobenzoic acids <2004CGD545>, bipyridine and the triazine derivative **131** <2005CEO193>, bipyridine and 1,3,5-benzenetri(phosphonic acid) <2005CGD1767>, 3,5-dinitro-4-methylbenzoic acid and *trans*-1,2-bis(4-pyridyl)ethene <2005TL2411>, and the bispyridine derivative **132** 1,4-phenylenediacetic acid <2005TL7187>. While not strictly a carboxylic acid, crystal structures involving anilic acids and dipyrindyl systems are clearly related to the above discussed systems <2001JOC5987>. The crystal structures of pyridinecarboxylic acids also show the same motifs <2002JOC556>. In all of the above examples, aromatic C-H...O interactions are also present and the interactions of π -systems are also often present; the former are discussed below.



131



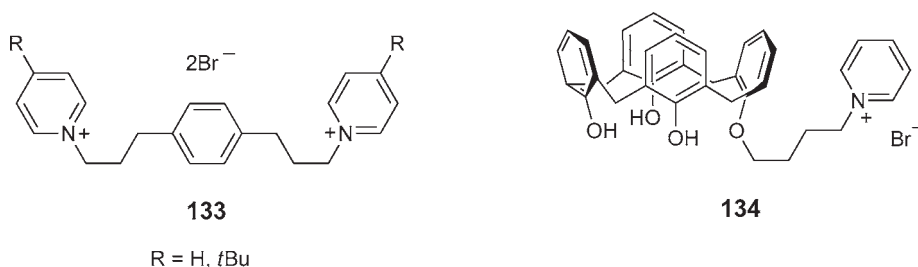
132

Hydrogen-bonding motifs have also been observed with verdazyl radical-substituted pyridines, which co-crystallize with hydroquinone <2001JA7154>, and with *N*-oxide derivatives of pyridine, such as found in co-crystals of 4,4'-bipyridine-*N*-oxide and cyclohexanetricarboxylic acid <2005CEO551, 2005CGD1683>, bipyridine-*N*-oxides with amino and nitrobenzoic acids <2005CGD727>, and bipyridine-*N*-oxides and diphenols <2005CGD1041>.

A further hydrogen-bonding example which has also been demonstrated with pyridine derivatives is the aromatic C-H...N interaction <2001T5791, 2002AXCo697>. These interactions are exemplified by the solid state of pyridine dicarboxylate esters, with the interactions supplemented by C-H...O=C contacts <2001CEO170>, and pyridine-lisoxazoles <2000TL5827>.

Nitrogen-halogen interactions, while mentioned above, have also been studied explicitly by considering co-crystals of bipyridines, bipyridyl systems, and phenanthrolines with both aryl and alkyl halides <2000T5535, 2001CGD165, 2005CEO302>. Perhaps the most interesting observation from these studies is that the nitrogen-halogen interaction is shown using quantum mechanical calculations to be of comparable energy to a hydrogen bond <2001CGD165>.

Pyridinium salts can also be used as synthons in crystal engineering, with the electron-deficient π -system interacting with electron-rich aromatic systems. Whether the interactions are either intermolecular or intramolecular is determined by the substituents on the pyridinium ring, as demonstrated by the bispyridinium salts **133** <2003EJO4528> and the pyridinium-appended calixarenes **134** <2006TL181>.



Another recently identified synthon involves the interaction between the C-H of a pyridinium ring and a carbonyl oxygen, which comes about due to the large positive charges on the pyridinium hydrogen atoms <2001EJO1519>. This is demonstrated in **Figure 10** for the pyridine derivative **135**.

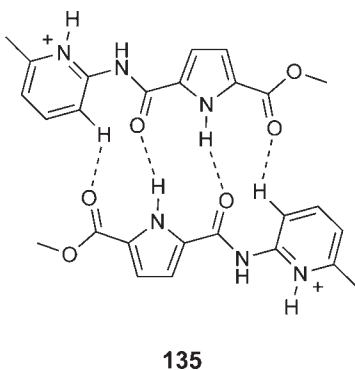
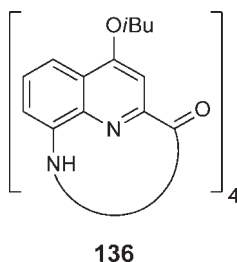


Figure 10

While much design is involved in the crystal engineering discussed, many interesting and unpredictable crystal structures of pyridine derivatives can also be obtained. For example, the crystal structures of the strained cyclic tetraquinolines **136** are particularly interesting given that they form rosettes consisting of twelve of the macrocyclic units <2004OL2985>.



7.01.4 Summary

At this point, it is worth returning to the equivalent section of the previous edition of this work <1996CHEC-II(5)1>. In it, the author identified the growing trend at the time toward increased expenditure (both in terms of money and personnel) in the related areas of supramolecular chemistry and the interface between biology and chemistry and predicted that “(results in these areas) will certainly occupy increasingly larger attention in any further discussion of pyridine architecture.” Clearly this review supports this statement as it has highlighted the change in focus of research involving the structure of pyridine and its derivatives over the last decade. While fundamental studies are still underway, structure at the level of a single molecule now no longer dominates the literature. The ongoing understanding of supramolecular interactions (based on the already well understood structure of the corresponding individual molecules) both in the solution and solid states has led to many research programs with the aim of using pyridine-based systems either to produce new materials, to mimic, or understand biological systems or as portions of functional ‘molecular machines’. It is anticipated that this direction will continue in the future, though with an ongoing emphasis on still more complex systems.

References

- 1960JA4433 E. Wasserman, *J. Am. Chem. Soc.*, 1960, **82**, 4433.
 1967JA5723 I. T. Harrison and S. Harrison, *J. Am. Chem. Soc.*, 1967, **89**, 5723.
 1969LA53 G. Schill and H. Zollenkopf, *Justus Liebigs Ann. Chem.*, 1969, 53.
 1974JA6762 R. C. Helgeson, J. M. Timko, P. Moreau, S. C. Peacock, J. M. Mayer, and D. J. Cram, *J. Am. Chem. Soc.*, 1974, **96**, 6762.
 1984CHEC(2)99 C. D. Jackson; in ‘Comprehensive Heterocyclic Chemistry I’, A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 2, p. 99.
 1990JA8902 J. S. Nowick, P. Ballester, F. Ebmeyer, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1990, **112**, 8902.
 1991AGE1036 P. L. Anelli, P. R. Ashton, N. Spencer, A. M. Z. Slawin, J. F. Stoddart, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1036.
 1991MI417 M. Born and H. Ritter, *Makromol. Chem., Rapid Commun.*, 1991, **12**, 471.
 1995JOC5291 M. A. V. Ribeiro da Silva, V. M. F. Morais, M. A. R. Matos, and C. M. A. Rio, *J. Org. Chem.*, 1995, **60**, 5291.
 1995JOC7411 M. Gdaniec, M. J. Milewska, and T. Polonski, *J. Org. Chem.*, 1995, **60**, 7411.
 1995JST(333)275 K. Szabo, S. Kunsagi-Mate, and N. Marek, *J. Mol. Struct.*, 1995, **333**, 275.
 1996AGE1815 M. Jaeger and H. B. Stegmann, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1815.
 1996AXC2538 D. Mrvos-Sermek, Z. Popovic, and D. Matkovic-Calogovic, *Acta Crystallogr., Sect. C*, 1996, **52**, 2538.
 1996CHEC-II(5)1 C. D. Jackson; in ‘Comprehensive Heterocyclic Chemistry II’, A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 1.
 1996CM961 H. Kihara, T. Kato, T. Uryu, and J. M. J. Frechet, *Chem. Mater.*, 1996, **8**, 961.
 1996CPH(207)19 M. S. Moghaddam, A. D. O. Bawagan, K. H. Tan, and W. von Niessen, *Chem. Phys.*, 1996, **207**, 19.
 1996JA8034 W. Lin, W. Lin, G. K. Wong, and T. J. Marks, *J. Am. Chem. Soc.*, 1996, **118**, 8034.
 1996JA10269 S. T. Howard, *J. Am. Chem. Soc.*, 1996, **118**, 10269.
 1996JA12012 D. B. Amabilino, P. R. Ashton, V. Balzani, C. L. Brown, A. Credi, J. M. J. Frechet, J. W. Leon, F. M. Raymo, N. Spencer, J. F. Stoddart, and M. Venturi, *J. Am. Chem. Soc.*, 1996, **118**, 12012.
 1996JOC6371 F. H. Beijer, R. P. Sijbesma, J. A. J. M. Vekemans, E. W. Meijer, H. Kooijman, and A. L. Huub, *J. Org. Chem.*, 1996, **61**, 6371.
 1996JOC6881 A. Arduini, W. M. McGregor, A. Pochini, A. Secchi, F. Uguzzoli, and R. Ungaro, *J. Org. Chem.*, 1996, **61**, 6881.
 1996JOC7018 J. A. Zoltewicz, N. M. Maier, and W. M. F. Fabian, *J. Org. Chem.*, 1996, **61**, 7018.
 1996JOC8391 Y. Habata, J. S. Bradshaw, J. J. Young, S. L. Castle, P. Huszthy, T. Pyo, M. L. Lee, and R. M. Izatt, *J. Org. Chem.*, 1996, **61**, 8391.
 1996JPC16141 J. Wang and R. J. Boyd, *J. Phys. Chem.*, 1996, **100**, 16141.
 1996JST(365)21 M. Ladika and N. G. Rondan, *J. Mol. Struct.*, 1996, **365**, 21.
 1996JST(385)23 W. Wysocka and T. Brukwicki, *J. Mol. Struct.*, 1996, **385**, 23.
 1996T8703 J. A. Zoltewicz, N. M. Maier, and W. M. F. Fabian, *Tetrahedron*, 1996, **52**, 8703.
 1996T9665 R. B. Palmer and N. H. Andersen, *Tetrahedron*, 1996, **52**, 9965.
 1996T12223 S. Goswami, K. Ghosh, Kumares, and S. Dasgupta, *Tetrahedron*, 1996, **52**, 12223.

- 1997AGE1904 M.-V. Martinez-Diaz, N. Spencer, and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1904.
1997BML2519 A. Straub, A. Goehrt, and L. Born, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2519.
1997CCCR1 S. J. Dunne, L. A. Summers, and E. I. von Nagy-Felsobuki, *Coord. Chem. Rev.*, 1997, **165**, 1.
1997CM2983 J. F. Malone, C. M. Murray, G. M. Dolan, R. Docherty, and A. J. Lavery, *Chem. Mater.*, 1997, **9**, 2983.
1997CRV1325 K. A. Connors, *Chem. Rev.*, 1997, **97**, 1325.
1997JA9804 M. Solum, K. L. Altman, M. Strohmeier, D. A. Berges, Y. Zhang, J. C. Facelli, R. J. Pugmire, and D. M. Grant, *J. Am. Chem. Soc.*, 1997, **119**, 9804.
1997JA10192 J. O. Morley, R. M. Morley, R. Docherty, and M. H. Charlton, *J. Am. Chem. Soc.*, 1997, **119**, 10192.
1997JA10587 Y. Hamuro, S. J. Geib, and A. D. Hamilton, *J. Am. Chem. Soc.*, 1997, **119**, 10587.
1997JAM1255 S. Mabie and C. Franot, *J. Am. Soc. Mass Spectrom.*, 1997, **8**, 1255.
1998JOC7258 A. L. Moraczewski, L. A. Banaszynski, A. M. From, C. E. White, and B. D. Smith, *J. Org. Chem.*, 1998, **61**, 7258.
1997JOC8063 P. A. Hunt, T. Fischer, and P. Schwerdtfeger, *J. Org. Chem.*, 1997, **62**, 8063.
1997J(P2)2099 C. E. Marjo, M. L. Scudder, D. C. Craig, and R. Bishop, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2099.
1997J(P2)2605 A. R. Katritzky, I. Ghiviriga, D. C. Oniciu, R. A. More O'Ferrall, and S. M. Walsh, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2605.
1997JST(389)105 R. Benassi, C. Bertarini, and F. Taddei, *J. Mol. Struct.*, 1997, **389**, 105.
1997JST(404)33 J. Hanuza, M. Maczka, A. Waskowska, W. Oganowski, M. Andruszkiewicz, H. Ban-Oganoswka, B. Lutz, and J. H. van der Mass, *J. Mol. Struct.*, 1997, **404**, 33.
1997T2817 G. Bringmann, M. Stahl, and K.-P. Gulden, *Tetrahedron*, 1997, **53**, 2817.
1997T3557 T. Katoh, K. Ogawa, Y. Inagaki, and R. Okazaki, *Tetrahedron*, 1997, **53**, 3557.
1997TL4503 S. Goswami and K. Ghosh, *Tetrahedron Lett.*, 1997, **38**, 4503.
1998AGE2838 S. J. Loeb and J. A. Wisner, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 2838.
1998CC2757 S. J. Loeb and J. A. Wisner, *Chem. Commun.*, 1998, 2757.
1998CEJ84 M. Lamsa, J. Huuskonen, K. Rissanen, and J. Pursiainen, *Chem. Eur. J.*, 1998, **4**, 84.
1998CJC686 C. Reichardt, S. Lobbecke, A. M. Mehranpour, and G. Schafer, *Can. J. Chem.*, 1998, **76**, 686.
1998JA2695 D. Ranganathan, V. Haridas, and I. L. Karle, *J. Am. Chem. Soc.*, 1998, **120**, 2695.
1998JA6458 D. A. Leigh, A. Murphy, J. P. Smart, M. S. Deleuz, and F. Zerbetto, *J. Am. Chem. Soc.*, 1998, **120**, 6458.
1998JA11932 P. R. Ashton, R. Ballardini, V. Balzani, I. Baxter, A. Credi, M. C. T. Fyfe, M. T. Gandolfi, M. Gomez-Lopez, M.-V. Martinez-Diaz, A. Piersanti, N. Spencer, J. F. Stoddart, M. Venturi, A. J. P. White, and D. J. Williams, *J. Am. Chem. Soc.*, 1998, **120**, 11932.
1998JCC961 L. Carballeira and I. Perez-Juste, *J. Comput. Chem.*, 1998, **19**, 961.
1998JOC3310 J. E. Anderson, A. I. Ijeh, C. Storch, D. Casarini, and L. Lunazzi, *J. Org. Chem.*, 1998, **63**, 3310.
1998JST(427)25 R. Kralj, B. Kojic-Prodic, S. Nikolic, and N. Trinajstic, *J. Mol. Struct.*, 1998, **427**, 25.
1998JST(427)87 E. D. Raczyńska, *J. Mol. Struct.*, 1998, **427**, 87.
1998JST(446)69 T. Brukwicki, *J. Mol. Struct.*, 1998, **446**, 69.
1999AGE2543 T. W. Bell, A. B. Khasanov, M. G. B. Drew, A. Filikov, and T. L. James, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 2543.
1999AJC71 G. Smith, C. E. Pascoe, C. H. L. Kennard, and K. A. Byriel, *Aust. J. Chem.*, 1999, **52**, 71.
1999AJC1047 V. T. Nguyen, A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *Aust. J. Chem.*, 1999, **52**, 1047.
1999CC181 L. R. MacGillivray and J. L. Atwood, *Chem. Commun.*, 1999, 181.
1999CC2389 A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *Chem. Commun.*, 1999, 2389.
1999CEG137 D. E. Lynch, S. Chatwin, and S. Parsons, *Cryst. Eng.*, 1999, **2**, 137.
1999CEJ449 A. M. Belostotskii, H. E. Gottlieb, P. Aped, and A. Hassner, *Chem. Eur. J.*, 1999, **4**, 449.
1999EJO2373 H. Scheytza, O. Rademacher, and H.-U. Reissig, *Eur. J. Org. Chem.*, 1999, 2373.
1999EJO2383 R. Wagner, B. Wiedel, W. Gunther, H. Gols, and E. Anders, *Eur. J. Org. Chem.*, 1999, 2383.
1999EJO2479 P. Cudic, J.-P. Vigneron, J.-M. Lehn, M. Cesario, and T. Prange, *Eur. J. Org. Chem.*, 1999, 2479.
1999JA1479 K. N. Houk, S. Menzer, S. P. Newton, F. M. Raymo, J. F. Stoddart, and D. J. Williams, *J. Am. Chem. Soc.*, 1999, **121**, 1479.
1999JOC3572 Z.-T. Li, G.-Z. Ji, C.-X. Zhao, S.-D. Yuan, H. Ding, C. Huang, A. L. Du, and M. Wei, *J. Org. Chem.*, 1999, **64**, 3572.
1999JOC7802 C. B. Martin, H. R. Mulla, P. G. Willis, and A. Cammers-Goodwin, *J. Org. Chem.*, 1999, **64**, 7802.
1999J(P2)801 V. Martinez-Merino and M. J. Gil, *J. Chem. Soc., Perkin Trans. 2*, 1999, 801.
1999JST(474)215 T. Brukwicki and W. Wysocka, *J. Mol. Struct.*, 1999, **474**, 215.
1999JST(476)139 J. F. Arenas, I. Lopez Tocon, J. C. Otero, and J. I. Marcos, *J. Mol. Struct.*, 1999, **476**, 139.
1999JST(482)371 B. Z. Jovanovic, M. Misic-Vukovic, A. D. Marinkovic, and J. Csanadi, *J. Mol. Struct.*, 1999, **482-483**, 371.
1999OL1001 W. S. Bryant, J. W. Jones, P. E. Mason, I. Guzei, A. L. Rheingold, F. R. Fronczek, D. S. Nagvekar, and H. W. Gibson, *Org. Lett.*, 1999, **1**, 1001.
1999T7835 M. Mazik, D. Bläser, and R. Boese, *Tetrahedron*, 1999, **55**, 7835.
1999T14501 T. Brukwicki, A. Przybyl, W. Wysocka, and J. Sosnicki, *Tetrahedron*, 1999, **55**, 14501.
2000CC359 L. R. MacGillivray, P. R. Diamante, J. L. Reid, and J. Ripmeester, *Chem. Commun.*, 2000, 359.
2000CC517 L. R. MacGillivray, H. A. Spinney, J. L. Reid, and J. Ripmeester, *Chem. Commun.*, 2000, 517.
2000CC845 S. J. Loeb and J. A. Wisner, *Chem. Commun.*, 2000, 845.
2000CC1939 S. J. Loeb and J. A. Wisner, *Chem. Commun.*, 2000, 1939.
2000CEG251 J. Bacsa, M. R. Caira, A. Jacobs, L. R. Nassimbeni, and F. Toda, *Cryst. Eng.*, 2000, **3**, 251.
2000CEJ2262 B. Cabezon, J. Cao, Jiang, F. M. Raymo, J. F. Stoddart, A. J. P. White, and D. J. Williams, *Chem. Eur. J.*, 2000, **6**, 2262.
2000CEJ2865 M. Mazik, D. Blaser, and R. Boese, *Chem. Eur. J.*, 2000, **6**, 2865.
2000CEO145 C. B. Aakeroy, A. M. Beatty, and D. S. Leinen, *CrystEngComm*, 2000, **27**, 145.
2000EJO1727 I. Higler, L. Grave, E. Breuning, W. Verboom, F. De Jong, T. Fyle, and D. N. Reinhoudt, *Eur. J. Org. Chem.*, 2000, 1727.
2000JA738 H. R. Mulla and A. Cammers-Goodwin, *J. Am. Chem. Soc.*, 2000, **122**, 738.
2000JA7817 L. R. MacGillivray, J. L. Reid, and J. A. Ripmeester, *J. Am. Chem. Soc.*, 2000, **122**, 7817.
2000JOC1924 V. Balzani, A. Credi, G. Mattersteig, O. A. Matthews, F. M. Raymo, J. F. Stoddart, M. Venturi, A. J. P. White, and D. J. Williams, *J. Org. Chem.*, 2000, **65**, 1924.

- 2000J(P2)1259 E. Kolehmainen, B. Osmialowski, T. M. Krygowski, R. Kauppinen, M. Nissinen, and R. Gawinecki, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1259.
- 2000J(P2)2185 E. Kolehmainen, B. Osmialowski, M. Nissinen, R. Kauppinen, Maija, and R. Gawinecki, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2185.
- 2000J(P2)2382 R. J. Abraham, N. Aboitiz, J. Merrett, B. Sherborne, and I. Whitcombe, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2382.
- 2000JST(552)233 L. Sobczyk, T. Lis, Z. Olejnik, and I. Majerz, *J. Mol. Struct.*, 2000, **552**, 233.
- 2000NAT720 V. Berl, I. Huc, R. G. Khoury, M. J. Krische, and J.-M. Lehn, *Nature*, 2000, **407**, 720.
- 2000OL239 B. Huang and J. R. Parquette, *Org. Lett.*, 2000, **2**, 239.
- 2000OL2947 T. Chang, A. M. Heiss, S. J. Cantrill, M. C. T. Fyfe, A. R. Pease, S. J. Rowan, J. F. Stoddart, A. J. P. White, and D. J. Williams, *Org. Lett.*, 2000, **2**, 2947.
- 2000PCP4682 M. Castella-Ventura, E. Kassab, G. Buntinx, and O. Poizat, *Phys. Chem. Chem. Phys.*, 2000, **2**, 4682.
- 2000T5535 P. Cardillo, E. Corradi, A. Lunghi, S. V. Meille, M. T. Messina, P. Metrangolo, and G. Resnati, *Tetrahedron*, 2000, **56**, 5535.
- 2000TL5827 M. Mazik, D. Blaser, and R. Boese, *Tetrahedron Lett.*, 2000, **41**, 5827.
- 2001ACR433 A. R. Pease, J. O. Jeppesen, J. F. Stoddart, Y. Luo, C. P. Collier, and J. R. Heath, *Acc. Chem. Res.*, 2001, **34**, 433.
- 2001AGE3240 C. B. Aakeroy, A. M. Beatty, and B. A. Helfrich, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3240.
- 2001CEJ2798 V. Berl, I. Huc, R. G. Khoury, and J.-M. Lehn, *Chem. Eur. J.*, 2001, **7**, 2798.
- 2001CEJ2810 V. Berl, I. Huc, R. G. Khoury, and J.-M. Lehn, *Chem. Eur. J.*, 2001, **7**, 2810.
- 2001CEJ3482 P. R. Ashton, V. Baldoni, V. Balzani, A. Credi, H. D. A. Hoffmann, M.-V. Martinez-Diaz, F. M. Raymo, J. F. Stoddart, and M. Venturi, *Chem. Eur. J.*, 2001, **7**, 3482.
- 2001CEJ4715 A. M. Belostotskii, M. Shokhen, H. E. Gottlieb, and A. Hassner, *Chem. Eur. J.*, 2001, **7**, 4715.
- 2001CEJ5727 B. Ma, Y. Zhang, and P. Coppens, *CrystEngComm*, 2001, **3**, 78.
- 2001CEO107 S. F. Alshahateet, R. Bishop, D. C. Craig, and M. L. Scudder, *CrystEngComm*, 2001, **3**, 107.
- 2001CEO170 M. C. Grossel, C. A. Golden, J. R. Gomm, P. N. Horton, D. A. S. Merkel, M. E. Oszer, and R. A. Parker, *CrystEngComm*, 2001, **3**, 170.
- 2001CEO225 S. F. Alshahateet, R. Bishop, D. C. Craig, and M. L. Scudder, *CrystEngComm*, 2001, **3**, 225.
- 2001CEO265 S. F. Alshahateet, R. Bishop, D. C. Craig, and M. L. Scudder, *CrystEngComm*, 2001, **3**, 265.
- 2001CGD47 C. B. Aakeroy, A. M. Beatty, and D. S. Leinen, *Cryst. Growth. Des.*, 2001, **1**, 47.
- 2001CGD165 R. B. Walsh, C. W. Padgett, P. Metrangolo, G. Resnati, T. W. Hanks, and W. T. Pennington, *Cryst. Growth. Des.*, 2001, **1**, 165.
- 2001CGD271 B.-Q. Ma, Y. Zhang, and P. Coppens, *Cryst. Growth. Des.*, 2001, **1**, 271.
- 2001EJO1519 C. Schmuck and J. Lex, *Eur. J. Org. Chem.*, 2000, 1519.
- 2001EJO2343 C. Reichardt, D. Che, G. Heckenkemper, and G. Schafer, *Eur. J. Org. Chem.*, 2001, 2343.
- 2001EJO3255 H. Bauer, F. Stier, C. Petry, A. Knorr, C. Stadler, and H. A. Staab, *Eur. J. Org. Chem.*, 2001, 3255.
- 2001EJO4041 Q. Y. Li, E. Vogel, A. H. Parham, M. N. Nieger, M. Bolte, R. Frohlich, P. Saarenketo, K. Rissanen, and F. Vogtle, *Eur. J. Org. Chem.*, 2001, 4041.
- 2001JA7154 R. G. Hicks, M. T. Lemaire, L. Oehrstroem, J. F. Richardson, L. Thompson, and Z. Xu, *J. Am. Chem. Soc.*, 2001, **123**, 7154.
- 2001JA9264 F. M. Raymo, M. D. Bartberger, K. N. Houk, and J. F. Stoddart, *J. Am. Chem. Soc.*, 2001, **123**, 9264.
- 2001JHC1387 I. Alkorta and J. Elguero, *J. Heterocycl. Chem.*, 2001, **38**, 1387.
- 2001JOC5987 M. B. Zaman, M. Tomura, and Y. Yamashita, *J. Org. Chem.*, 2001, **66**, 5987.
- 2001JOC8883 A. Abbotto, S. Bradamante, and G. A. Pagani, *J. Org. Chem.*, 2001, **66**, 8883.
- 2001JP11785 A. C. Spivey, A. Maddaford, D. P. Leese, and A. J. Redgrave, *J. Chem. Soc., Perkin 1*, 2001, 1785.
- 2001JPO201 R. Gawinecki, B. Osmialowski, E. Kolehmainen, and R. Kauppinen, *J. Phys. Org. Chem.*, 2001, **14**, 201.
- 2001JST(542)1 G. Ramirez-Galicia, G. Perez-Caballero, and M. Rubio, *J. Mol. Struct.*, 2001, **542**, 1.
- 2001JST(563)545 Y. Buyukmurat and S. Akyuz, *J. Mol. Struct.*, 2001, **563–564**, 545.
- 2001SAA2659 H. I. Abdulla and M. F. El-Bermani, *Spectrochim. Acta, Part A*, 2001, **57**, 2659.
- 2001T5791 M. Mazik, D. Blaser, and R. Boese, *Tetrahedron*, 2001, **57**, 5791.
- 2002ARK198 L. Forlani, G. Cristoni, C. Boga, P. E. Todesco, E. Del Vecchio, S. Selva, and M. Monari, *ARKIVOC*, 2002, xi, 198.
- 2002AXCo697 U. H. Patel, C. G. Dave, M. M. Jotani, and H. C. Shah, *Acta Crystallogr., Sect. C*, 2002, **58**, o697.
- 2002CCS578 I. Huc, V. Maurizot, H. Gornitzka, and J.-M. Léger, *Chem. Commun.*, 2002, 578.
- 2002CEG9 N. Shan, A. D. Bond, and W. Jones, *Cryst. Eng.*, 2002, **5**, 9.
- 2002CEO194 J. Ashmore, R. Bishop, D. C. Craig, and M. L. Scudder, *CrystEngComm*, 2002, **4**, 194.
- 2002CEO510 A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *CrystEngComm*, 2002, **4**, 510.
- 2002CEO585 S. F. Alshahateet, A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *CrystEngComm*, 2002, **4**, 585.
- 2002CGD325 B. R. Bhogala, P. Vishweshwar, and A. Nangia, *Cryst. Growth Des.*, 2002, **2**, 325.
- 2002CGD421 A. N. M. M. Rahman, R. Bishop, D. C. Craig, C. E. Marjo, and M. L. Scudder, *Cryst. Growth. Des.*, 2002, **2**, 421.
- 2002IJQ534 R. J. Doerksen and A. J. Thakkar, *Int. J. Quantum Chem.*, 2002, **90**, 534.
- 2002JA1860 M. J. Rashkin and M. L. Waters, *J. Am. Chem. Soc.*, 2002, **124**, 1860.
- 2002JA12469 J. A. Wisner, P. D. Beer, M. G. B. Drew, and M. R. Sambrook, *J. Am. Chem. Soc.*, 2002, **124**, 12469.
- 2002JA13088 G. Cuevas and E. Juaristi, *J. Am. Chem. Soc.*, 2002, **124**, 13088.
- 2002JA14425 C. B. Aakeroy, A. M. Beatty, and B. A. Helfrich, *J. Am. Chem. Soc.*, 2002, **124**, 14425.
- 2002JA14486 C. Mueller, F. Talbot, and S. Leutwyler, *J. Am. Chem. Soc.*, 2002, **124**, 14486.
- 2002JOC161 P. Bour, H. Navratilova, V. Setnicka, M. Urbanova, and K. Volka, *J. Org. Chem.*, 2002, **67**, 161.
- 2002JOC556 P. Vishweshwar, A. Nangia, and V. M. Lynch, *J. Org. Chem.*, 2002, **67**, 556.
- 2002JOC1515 I. Alkorta and J. Elguero, *J. Org. Chem.*, 2002, **67**, 1515.
- 2002JOC2065 A. Moghimi, M. F. Rastegar, M. Ghandi, M. Taghizadeh, A. Yari, M. Shamsipur, G. P. A. Yap, and H. Rahbarnoohi, *J. Org. Chem.*, 2002, **67**, 2065.
- 2002JOC9061 D. Moran, K. Sukcharoenphon, R. Puchta, H. F. Schaefer, III, P. V. R. Schleyer, and C. D. Hoff, *J. Org. Chem.*, 2002, **67**, 9061.
- 2002JOC9175 A. M. Elizarov, S.-H. Chiu, and J. F. Stoddart, *J. Org. Chem.*, 2002, **67**, 9175.
- 2002J(P2)393 T. Satou and T. Shinmyozu, *J. Chem. Soc., Perkin Trans. 2*, 2002, 393.
- 2002J(P2)1081 R. J. Abraham and M. Reid, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1081.

- 2002J(P2)1882 R. D. Webster, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1882.
- 2002JST(578)249 I. Yavari, S. Moradi, H. K. Fard, F. Nourmohammadian, and D. Tahmassebi, *J. Mol. Struct.*, 2002, **578**, 249.
- 2002JST(617)189 P. Dapporto, A. Guerri, P. Paoli, P. Rossi, M. Altamura, F. R. Calabri, and A. Guidi, *J. Mol. Struct.*, 2002, **617**, 189.
- 2002JSU409 A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *J. Supramol. Chem.*, 2002, **2**, 409.
- 2002OL1791 W. Ong, M. Gómez-Kaifer, and A. E. Kaifer, *Org. Lett.*, 2002, **4**, 1791.
- 2002PNA4972 S.-I. Tamaru, S. Shinkai, A. B. Khasanov, and T. W. Bell, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 4972.
- 2002PNA5007 H.-J. Kim, W. S. Jeon, Y. H. Ko, and K. Kim, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 5007.
- 2003AGE2164 W. Ong and A. E. Kaifer, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 2164.
- 2003AGE2738 C. Dolain, V. Maurizot, and I. Huc, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 2738.
- 2003AXE0913 N. Vembu, M. Nallu, J. Garrison, and W. J. Youngs, *Acta Crystallogr., Sect. E*, 2003, **59**, o913.
- 2003CC2751 D. Braga, *Chem. Commun.*, 2003, 2752.
- 2003CEJ2982 J. O. Jeppesen, K. A. Nielsen, J. Perkins, S. A. Vignon, A. Di Fabio, R. Ballardini, M. T. Gandolfi, M. Venturi, V. Balzani, J. Becher, and J. F. Stoddart, *Chem. Eur. J.*, 2003, **9**, 2982.
- 2003CEO414 P. Grosshans, A. Jouaiti, V. Bulach, J.-M. Planeix, M. W. Hosseini, and J.-F. Nicoud, *CrystEngComm*, 2003, **5**, 414.
- 2003CEO417 S. F. Alshahateet, A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *CrystEngComm*, 2003, **5**, 417.
- 2003CEO422 A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *CrystEngComm*, 2003, **5**, 422.
- 2003CGD547 B. R. Bhogala and A. Nangia, *Cryst. Growth Des.*, 2003, **3**, 547.
- 2003CGD799 R. Liantonio, P. Metrangolo, T. Pilati, G. Resnati, and A. Stevenazzi, *Cryst. Growth. Des.*, 2003, **3**, 799.
- 2003EJO72 A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *Eur. J. Org. Chem.*, 2003, 72.
- 2003EJO4528 T.-a. Koizumi, K. Tsutsui, and K. Tanaka, *Eur. J. Org. Chem.*, 2003, 4528.
- 2003JA19272 F. Huang, F. R. Fronczek, and H. W. Gibson, *J. Am. Chem. Soc.*, 2003, **125**, 9272.
- 2003JA9367 F. Huang, H. W. Gibson, W. S. Bryant, D. S. Nagvekar, and F. R. Fronczek, *J. Am. Chem. Soc.*, 2003, **125**, 9367.
- 2003JA9699 K. J. Wallace, W. J. Belcher, D. R. Turner, K. F. Syed, and J. W. Steed, *J. Am. Chem. Soc.*, 2003, **125**, 9699.
- 2003JA10125 R. A. Olsen, L. Liu, N. Ghaderi, A. Johns, M. E. Hatcher, and L. J. Mueller, *J. Am. Chem. Soc.*, 2003, **125**, 10125.
- 2003JA14014 I. V. Alabugin, O. Ikkala, and L.-O. Pietila, *J. Am. Chem. Soc.*, 2003, **125**, 14014.
- 2003JOC1529 P. Acharya, O. Plashkevych, C. Morita, S. Yamada, and J. Chattopadhyaya, *J. Org. Chem.*, 2003, **68**, 1529.
- 2003JOC6304 B. Laleu, C. Herse, B. W. Laursen, G. Bernardinelle, and J. Lacour, *J. Org. Chem.*, 2003, **68**, 6304.
- 2003JOC8697 A. Conejo-Garcia, J. M. Campos, A. Entrena, R. M. Sanchez-Martin, M. A. Gallo, and A. Espinosa, *J. Org. Chem.*, 2003, **68**, 8697.
- 2003JOC9177 K. K. Arora and V. R. Pedireddi, *J. Org. Chem.*, 2003, **68**, 9177.
- 2003JPO626 K. Herodes, J. Koppel, C. Reichart, and I. A. Koppel, *J. Phys. Org. Chem.*, 2003, **16**, 626.
- 2003JST(623)263 C. Malardier-Jugroot, A. C. Spivey, and M. A. Whitehead, *J. Mol. Struct.*, 2003, **623**, 263.
- 2003JST(663)91 O. Lehtonen, O. Ikkala, and L.-O. Pietila, *J. Mol. Struct.*, 2003, **663**, 91.
- 2003OBC1435 A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *Org. Biomol. Chem.*, 2003, **1**, 1435.
- 2003OBC4329 V. M. F. Morais, M. S. Miranda, and M. A. R. Matos, *Org. Biomol. Chem.*, 2003, **1**, 4329.
- 2003PCA1486 A. L. Mattioda, D. M. Hudgins, C. W. Bauschlicher, M. Rosi, and L. J. Allamandola, *J. Phys. Chem. A*, 2003, **107**, 1486.
- 2003PCA4669 A. C. Benniston, M. Davies, A. Harriman, and C. Sams, *J. Phys. Chem. A*, 2003, **107**, 4669.
- 2004AXCo284 M. Hemamalini, P. T. Muthiah, G. Bocelli, and A. Cantoni, *Acta Crystallogr., Sect. C*, 2004, **60**, o284.
- 2004CC62 I. Odriozola, N. Kyritsakas, and J.-M. Lehn, *Chem. Commun.*, 2004, 62.
- 2004CC138 A. L. Hubbard, G. J. E. Davidson, R. H. Patel, J. A. Wisner, and S. J. Loeb, *Chem. Commun.*, 2004, 138.
- 2004CC1480 J. M. Heemstra and J. S. Moore, *Chem. Commun.*, 2004, 1480.
- 2004CCA391 I. Ghiviriga, E. W. Czerwinski, and A. T. Balaban, *Croat. Chem. Acta*, 2004, **77**, 391.
- 2004CEO207 S. H. Dale, M. R. J. Elsegood, M. Hemming, and A. L. Wilkinson, *CrystEngComm*, 2004, **6**, 207.
- 2004CEO484 L. T. Higham, U. P. Kreher, J. L. Scott, and C. R. Strauss, *CrystEngComm*, 2004, **6**, 484.
- 2004CEO618 J. Ashmore, R. Bishop, D. C. Craig, and M. L. Scudder, *CrystEngComm*, 2004, **6**, 618.
- 2004CGD545 S. Banerjee and S. Murugavel, *Cryst. Growth. Des.*, 2004, **4**, 545.
- 2004CGD837 S. F. Alshahateet, R. Bishop, D. C. Craig, and M. L. Scudder, *Cryst. Growth. Des.*, 2004, **4**, 837.
- 2004EJS683 W.-N. Wu and M. D. Moyer, *Eur. J. Mass Spec.*, 2004, **10**, 683.
- 2004JA6135 M. Winkler, B. Cakir, and W. Sander, *J. Am. Chem. Soc.*, 2004, **126**, 6135.
- 2004JA9669 M. C. Letzel, B. Decker, A. B. Rozhenko, W. W. Schoeller, and J. Mattay, *J. Am. Chem. Soc.*, 2004, **126**, 9669.
- 2004JA9862 S. Yamada, T. Misono, and S. Tsuzuki, *J. Am. Chem. Soc.*, 2004, **126**, 9862.
- 2004JA14738 F. Huang and H. W. Gibson, *J. Am. Chem. Soc.*, 2004, **126**, 14738.
- 2004JAM862 F. Lepine, S. Milot, E. Deziel, J. He, and L. G. Rahme, *J. Am. Soc. Mass Spectrom.*, 2004, **15**, 862.
- 2004JCP11112 S. Kokubo, N. Ando, K. Koyasu, M. Misui, and A. Nakajima, *J. Chem. Phys.*, 2004, **121**, 11112.
- 2004JOC536 A. T. Balaban, I. Ghiviriga, E. W. Czerwinski, P. De, and R. Faust, *J. Org. Chem.*, 2004, **69**, 536.
- 2004JOC1383 W. Ong and A. E. Kaifer, *J. Org. Chem.*, 2004, **69**, 1383.
- 2004JOC5005 I. Novak and B. Kovac, *J. Org. Chem.*, 2004, **69**, 5005.
- 2004JOC7448 M. Mazik, W. Radunz, and R. Boese, *J. Org. Chem.*, 2004, **69**, 7448.
- 2004JST(679)53 N. Mariet, M. Ibrahim-Ouali, J.-L. Parrain, and M. Santelli, *J. Mol. Struct.*, 2004, **679**, 53.
- 2004JST(709)129 A. Ladjarafi, H. Meghezzi, and A. Boucekkine, *J. Mol. Struct.*, 2004, **709**, 129.
- 2004JTC557 O. V. Shishkin and R. I. Zubatyuk, *J. Struct. Chem.*, 2004, **45**, 557.
- 2004OBC175 A. N. M. M. Rahman, R. Bishop, D. C. Craig, and M. L. Scudder, *Org. Biomol. Chem.*, 2004, **2**, 175.
- 2004OBC337 J. S. Lock, B. L. May, P. Clements, S. F. Lincoln, and C. J. Easton, *Org. Biomol. Chem.*, 2004, **2**, 337.
- 2004OBC2335 T. Yamada, T. Ichino, M. Hanyu, D. Ninomiya, R. Yanagihara, T. Miyazawa, Toshifumi, and T. Murashima, *Org. Biomol. Chem.*, 2004, **2**, 2335.
- 2004OBC2751 N. Georges, S. J. Loeb, J. Tiburcio, and J. A. Wisner, *Org. Biomol. Chem.*, 2004, **2**, 2751.
- 2004OL185 K. Moon and A. E. Kaifer, *Org. Lett.*, 2004, **6**, 185.
- 2004OL659 J. M. Heemstra and J. S. Moore, *Org. Lett.*, 2004, **6**, 659.
- 2004OL2665 S. Vladimir, K. Moon, and A. E. Kaifer, *Org. Lett.*, 2004, **6**, 2665.

- 2004OL2985 H. Jiang, J.-M. Leger, P. Guionneau, and I. Huc, *Org. Lett.*, 2004, **6**, 2985.
- 2004SCI1845 J. D. Badji, V. Balzani, A. Credi, S. Silvi, and J. F. Stoddart, *Science*, 2004, **303**, 1845.
- 2004T10029 H. Jiang, V. Maurizot, and I. Huc, *Tetrahedron*, 2004, **60**, 10029.
- 2005AGE477 C. A. Schalley, C. Verhaelen, F.-G. Klaerner, U. Hahn, and F. Voegtler, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 477.
- 2005AGE1954 J. Garric, J. M. Leger, and I. Huc, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 1954.
- 2005CEJ6135 C. Dolain, A. Grelard, M. Laguerre, H. Jiang, V. Maurizot, and I. Huc, *Chem. Eur. J.*, 2005, **11**, 1635.
- 2005CEO108 B. Venkataraman, Z. Ning, J. J. Vittal, and S. Valiyaveetil, *CrystEngComm*, 2005, **7**, 108.
- 2005CEO139 S. F. Alshahateet, R. Bishop, M. L. Scudder, C. Y. Hu, E. H. E. Lau, F. Kooli, Z. M. A. Judeh, P. S. Chow, and R. B. H. Tan, *CrystEngComm*, 2005, **7**, 139.
- 2005CEO193 C. B. Aakeröy, J. Desper, and J. F. Urbina, *CrystEngComm*, 2005, **7**, 193.
- 2005CEO302 J. L. Syssa-Magale, K. Boubekeur, P. Palvadeau, A. Meerschaut, and B. Schoellhorn, *CrystEngComm*, 2005, **7**, 302.
- 2005CEO551 B. R. Bhogala, S. Basavoju, and A. Nangia, *CrystEngComm*, 2005, **7**, 551.
- 2005CEJ5889 M. Vetrichelvan and S. Valiyaveetil, *Chem. Eur. J.*, 2005, **11**, 5889.
- 2005CGD727 J. R. Bowers, G. W. Hopkins, G. P. A. Yap, and K. A. Wheeler, *Cryst. Growth Des.*, 2005, **5**, 727.
- 2005CGD1041 Q. Zeng, D. Wu, C. Liu, H. Ma, J. Lu, S. Xu, Y. Li, C. Wang, and C. Bai, *Cryst. Growth Des.*, 2005, **5**, 1041.
- 2005CGD1575 A. Jayaraman, V. Balasubramaniam, and S. Valiyaveetil, *Cryst. Growth Des.*, 2005, **5**, 1575.
- 2005CGD1683 B. R. Bhogala, S. Basavoju, and A. Nangia, *Cryst. Growth Des.*, 2005, **5**, 1683.
- 2005CGD1767 D. Kong, A. Clearfield, and J. Zon, *Cryst. Growth Des.*, 2005, **5**, 1767.
- 2005CGD1889 Q. Zeng, D. Wu, C. Wang, H. Ma, J. Lu, C. Liu, S. Xu, Y. Li, and C. Bai, *Cryst. Growth Des.*, 2005, **5**, 1889.
- 2005EJO162 Y. Liu, D.-S. Guo, E.-C. Yang, H.-Y. Zhang, and Y.-L. Zhao, *Eur. J. Org. Chem.*, 2005, 162.
- 2005EJO869 J. Hartung, K. Spehar, I. Svoboda, H. Fuess, M. Arnone, and B. Engels, *Eur. J. Org. Chem.*, 2005, 869.
- 2005EJO3801 G. Dyker, M. Mastalers, and I. M. Müller, *Eur. J. Org. Chem.*, 2005, 3801.
- 2005EJO4338 B. A. Trofimov, A. M. Vasil'tsov, E. Y. Schmidt, N. V. Zorina, A. V. Afonin, A. I. Mikhaleva, K. B. Petrushenko, I. A. Ushakov, L. B. Krivdin, V. K. Belsky, and L. I. Bryukvin, *Eur. J. Org. Chem.*, 2005, 4338.
- 2005EJO4581 Y. Liu, E.-C. Yang, Y. Chen, D.-S. Guo, and F. Ding, *Eur. J. Org. Chem.*, 2005, 4581.
- 2005JA4033 L. J. Scherer, L. Merz, E. C. Constable, C. E. Housecroft, M. Neuburger, and B. A. Hermann, *J. Am. Chem. Soc.*, 2005, **127**, 4033.
- 2005JA5490 J. van Gestel, A. R. A. Palmans, B. Titulaer, J. A. J. M. Vekemans, and E. W. Meijer, *J. Am. Chem. Soc.*, 2005, **127**, 5490.
- 2005JA9745 Y. Liu, A. H. Flood, P. A. Bonvallet, S. A. Vignon, B. H. Northrop, H.-R. Tseng, J. O. Jeppesen, T. J. Huang, B. Brough, M. Baller, S. Magonov, S. D. Solares, W. A. Goddard, C.-H. Ho, and J. F. Stoddart, *J. Am. Chem. Soc.*, 2005, **127**, 9745.
- 2005JOC1993 K. Hassall, S. Lobachevsky, and J. M. White, *J. Org. Chem.*, 2005, **70**, 1993.
- 2005JOC3231 F. Huang, K. A. Switek, L. N. Zakharov, F. R. Fronczek, C. Slebodnick, M. Lam, J. A. Golen, W. S. Bryant, P. E. Mason, A. L. Rheingold, M. Ashraf-Khorassani, and H. W. Gibson, *J. Org. Chem.*, 2005, **70**, 3231.
- 2005JOC9115 M. Mazik, D. Blaeser, and R. Boese, *J. Org. Chem.*, 2005, **70**, 9115.
- 2005JPO1013 K. Herodes, I. Leito, J. Koppel, C. Reichardt, and I. A. Koppel, *Eur. J. Org. Chem.*, 2005, **18**, 1013.
- 2005JST(713)245 M. Z. Kassae, B. N. Haerizade, and Z. S. Hossaini, *J. Mol. Struct.*, 2005, **713**, 245.
- 2005JST(752)68 A. Moghimi, B. Maddah, A. Yari, M. Shamsipur, M. Boostani, M. F. Rastegar, and A. R. Ghaderi, *J. Mol. Struct.*, 2005, **752**, 68.
- 2005T10242 F. Huang, A. L. Rheingold, C. Slebodnick, A. Ohs, K. A. Switek, and H. W. Gibson, *Tetrahedron*, 2005, **61**, 10242.
- 2005TL2411 S. Varughese and V. R. Pedireddi, *Tetrahedron Lett.*, 2005, **46**, 2411.
- 2005TL6499 Z. Li, J. Ding, G. Robertson, M. Day, and Y. Tao, *Tetrahedron Lett.*, 2005, **46**, 6499.
- 2005TL7187 S. Goswami, S. Dey, H.-K. Fun, S. Anjum, and Atta-ur-Rahman, *Tetrahedron Lett.*, 2005, **46**, 7187.
- 2006TL181 S. Ishihara and S. Takeoka, *Tetrahedron Lett.*, 2006, **47**, 181.
- 2006JA637 V. Balzani, H. Bandmann, P. Ceroni, C. Giansante, U. Hahn, F.-G. Klaerner, U. Mueller, W. M. Mueller, C. Verhaelen, V. Vicinelli, and F. Voegtler, *J. Am. Chem. Soc.*, 2006, **128**, 637.

Biographical Sketch



Jason Harper is a graduate of the University of Adelaide and the Australian National University. After positions at the University of Cambridge (as an NHMRC C. J. Martin Postdoctoral Fellow) and the Open University, he was appointed to the academic staff in the School of Chemistry, University of New South Wales in 2002. His research interests fall broadly in the area of mechanistic and physical organic chemistry with a particular focus on understanding the outcome of organic processes in ionic liquids. Outside the lab, he tries to keep up with a diverse range of activities ranging from cycling ridiculous distances periodically (his last big trip was around the east coast of Tasmania) to learning Taiko (Japanese drumming).

7.02

Pyridines and their Benzo Derivatives: Reactivity at the Ring

D. L. Comins

North Carolina State University, Raleigh, NC, USA

S. O'Connor

Clemson University, Clemson, SC, USA

R. S. Al-awar

Eli Lilly and Company, Indianapolis, IN, USA

© 2008 Elsevier Ltd. All rights reserved.

7.02.1 Introduction: General Reactivity Patterns	42
7.02.2 Electrophilic Attack at Nitrogen	42
7.02.2.1 Protonation and Salt Formation	42
7.02.2.2 Lewis Acids	43
7.02.2.3 Alkyl Halides and Related Compounds	43
7.02.2.4 Acyl Halides and Related Compounds	43
7.02.2.5 Activated Alkenes	46
7.02.2.6 Halogens	47
7.02.2.7 N-Oxidation	49
7.02.2.8 Carbenes	50
7.02.3 Electrophilic Attack at Carbon	52
7.02.3.1 Halogenation	52
7.02.3.1.1 Chlorination	53
7.02.3.1.2 Bromination	54
7.02.3.1.3 Iodination	54
7.02.3.1.4 Fluorination	55
7.02.3.2 Nitration and Sulfonation	56
7.02.3.3 Diazo Coupling	59
7.02.3.4 Acylation and Alkylation	61
7.02.3.5 Oxidation	61
7.02.4 Nucleophilic Attack at Carbon	63
7.02.4.1 Halogenation: Formation of a Carbon–Halogen Bond	63
7.02.4.1.1 Chlorination	63
7.02.4.1.2 Bromination	64
7.02.4.1.3 Iodination	64
7.02.4.1.4 Fluorination	64
7.02.4.2 Organometallics, Enolates, and Cyanide	64
7.02.4.2.1 On neutral molecules	64
7.02.4.2.2 Via pyridinium salts	66
7.02.4.2.3 Cross-coupling reactions	70
7.02.4.3 Heteroatom Nucleophiles	75
7.02.4.3.1 Nucleophilic addition	75
7.02.4.3.2 Nucleophilic substitution	78
7.02.4.3.3 Metal-catalyzed coupling reactions	78
7.02.4.4 Chemical Reduction	80
7.02.4.4.1 Hydride reduction	80

7.02.4.4.2	Dithionite reduction	80
7.02.4.4.3	With free electrons	81
7.02.4.4.4	Hydrogenation	82
7.02.5	Free Radical Attack at Carbon	84
7.02.5.1	Halogenation	84
7.02.5.2	Alkylation, Arylation, and Acylation	85
7.02.6	Thermal and Photochemical Reactions and Those Involving Cyclic Transition States	87
References		91

7.02.1 Introduction: General Reactivity Patterns

Substitution reactions of pyridines and their benzo derivatives continue to attract considerable attention as they play an important role in the preparation of biologically active compounds and new materials. In general, pyridine derivatives are thermally and photochemically stable, but can be attacked by electrophiles at ring nitrogen and certain carbon atoms. Strong nucleophiles can also react, generally at the α - or γ -ring carbon atoms of the pyridine ring. Patterns of general reactivity for electrophilic and nucleophilic attack are depicted in [Figures 1 and 2](#). For a detailed discussion on reactivity, the reader is referred to the corresponding sections in CHEC(1984) and CHEC-II(1996).

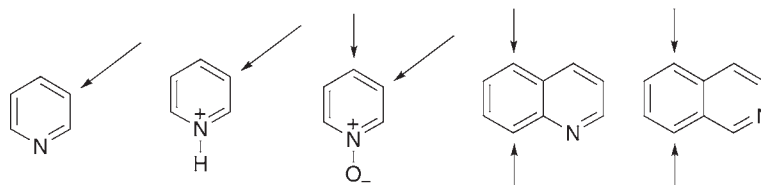


Figure 1 General reactivity pattern for electrophilic substitution.

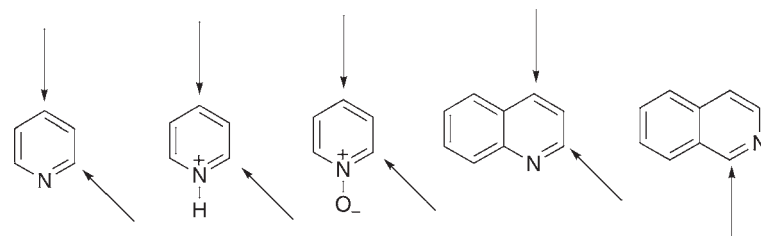


Figure 2 General reactivity pattern for nucleophilic substitution.

Pyridines undergo radical substitution reactions preferentially at the 2-position. Yields and regioselectivity are generally higher if the reaction is carried out in an acid medium. The presence of a strongly electron-donating substituent (OH, OR, NR₂) on the pyridine ring can alter the reactivity pattern of electrophilic and radical substitution.

7.02.2 Electrophilic Attack at Nitrogen

7.02.2.1 Protonation and Salt Formation

Simple pyridines and their benzo derivatives are weak bases that form salts with strong acids. This is a very common reaction which is sufficiently described in CHEC(1984) and CHEC-II(1996) <1984CHEC(2)165, 1996CHEC-II(5)41>.

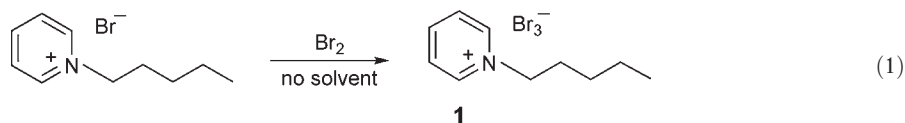
7.02.2.2 Lewis Acids

Various Lewis acids including alkylboranes, arylboranes, and borane hydrides form complexes with pyridine and its benzo derivatives <2000ICA128, 2002JOM205, 2004TL3913, 2004AGE4902, 2005IC601, 2005ICA2996, 1984CHEC(2)165, 1996CHEC-II(5)37>.

7.02.2.3 Alkyl Halides and Related Compounds

The quaternization of pyridine and its benzo derivatives using alkyl halides is well documented and these compounds have been used as versatile synthetic intermediates or as final products <2006OBC1071, 2005TL1137, 2005CHE771, 2004RCB2233, 2004CHE1124, 2003COR995, 2002TL7379, 2002S1530, 2001JHC909, 2001AHC269, 1997T14687>, have served as intermediates to biologically active compounds, and at times been studied for their own activity <2004OBC220, 2003JME4273, 2002CHE1098>. Chiral pyridinium-based ionic liquids have been prepared by N-alkylation of pyridines with chloromethyl-(–)-menthyl ether <2006TA1728>. A review on quaternary salts of pyridines and related compounds describing their synthesis, physicochemical properties, possible applications, and their biological activities has been published <2003COR995>.

Pyridinium hydrobromide perbromide salt was introduced by Djerassi and Scholz as an alternative brominating agent to bromine in 1948. Salazar and Dorta rationalized that since alkylpyridinium salts are well documented and commercially available room temperature ionic liquids, a combination of an alkylpyridinium cation with tribromide anion **1** should therefore lead to a room temperature ionic liquid bromine analogue (Equation 1).



When tested on several organic substrates, the reagent was capable of selectively monobrominating ketones along with aromatics and phenols (Table 1). Anisole, for example (entry iii), required the addition of Na₂CO₃ to prevent the hydrolysis of the methoxy group whereas alkenes and alkynes were also susceptible to bromination by the reagent (entries v–vii) <2004SL1318>.

The versatility of γ -thioquinolinium salts was effectively demonstrated by Vaseux who was able to prepare, using an Eschenmoser approach, N-substituted 4-alkylidenequinolines such as **3** <1995S56>. Starting with 4(1*H*)-quinolinethione, the alkylation of sulfur was accomplished using K₂CO₃ as the base, and quaternization of the quinoline nitrogen with various reactive alkyl bromides produced the desired quinolinium salts **2**. A combination of R¹, R², and R³ were investigated with variable yields. The extrusion of sulfur from the intermediates **2** using a phosphite reagent gave the desired final products **3** in reasonable yields (Scheme 1).

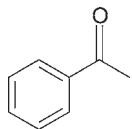
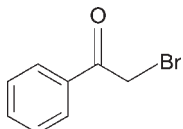
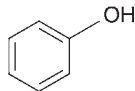
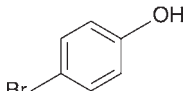
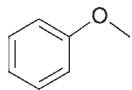
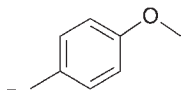
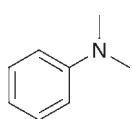
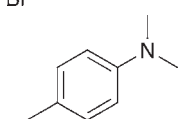
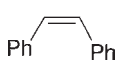
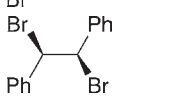
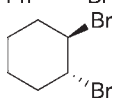
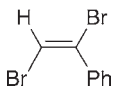
Several chiral *N*-alkylpyridinium and related salts (Figure 3) have been prepared and studied as electrophiles for asymmetric nucleophilic addition reactions <2001CC1166, 2003TA1691, 1996CPB267, 2001TL6109, 2000EJO1391, 2004TA3919, 1998JOC1767>.

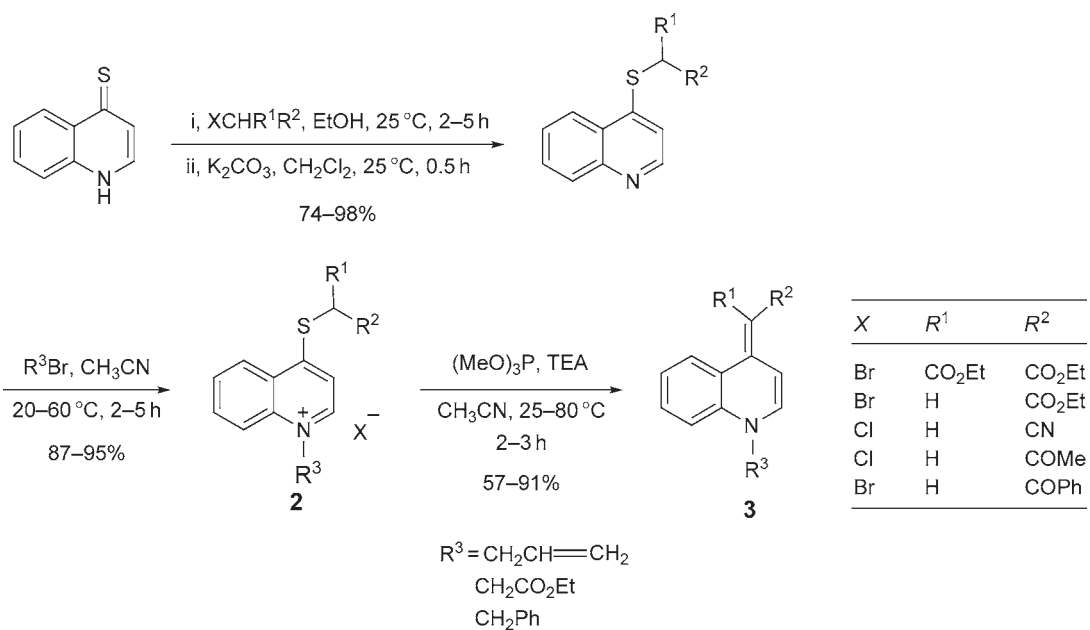
7.02.2.4 Acyl Halides and Related Compounds

N-Acylpyridinium salts are prepared *in situ* by the reaction of a pyridine with an acyl halide. These intermediates are more reactive than their *N*-alkyl counterparts and are attacked at the 2- or 4-position by various nucleophiles. The yields are frequently high and the method has been widely used in the preparation of substituted pyridines, piperidine derivatives, and natural products. Several reviews have covered many of the recent contributions in this area <B-1996MI251, 1999JHC1491, 2002MI870, 2002J(P1)1141>. Asymmetric versions of this chemistry continue to be developed using *N*-acyl salts containing a chiral auxiliary. Several chiral *N*-acylpyridinium and related salts are depicted in Figure 4 (**4** <1994AXC25, 1999JHC1491, 1996TL3807, 2002J(P1)1141, 2002MI870>, **5** <1995HCA61>, **6** <2002T6757>, **7** <1994TL7343>, **8** <2002TL5853>, **9** <1996TL1599>, **10** <2001T8939>, **11** <1999TL6241>).

Expanding on established chemistry using *N*-acylpyridinium salts as intermediates for the preparation of *N*-acyldihydropyridines and dihydropyridones, Wanner and co-workers examined a method using a bicyclic lactone

Table 1 Solvent-free bromination using pentylpyridiniumtribromide **1** at room temperature

Entry	Substrate	Product	Yield (%)
i			85
ii			93
iii			90
iv			81
v			90
vi			84
vii			92

**Scheme 1**

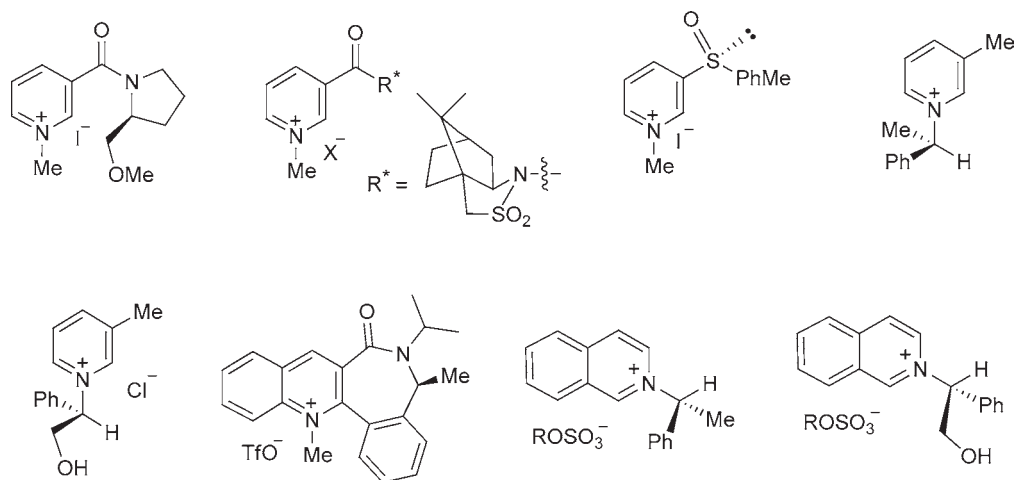


Figure 3 Chiral *N*-alkylpyridinium salts.

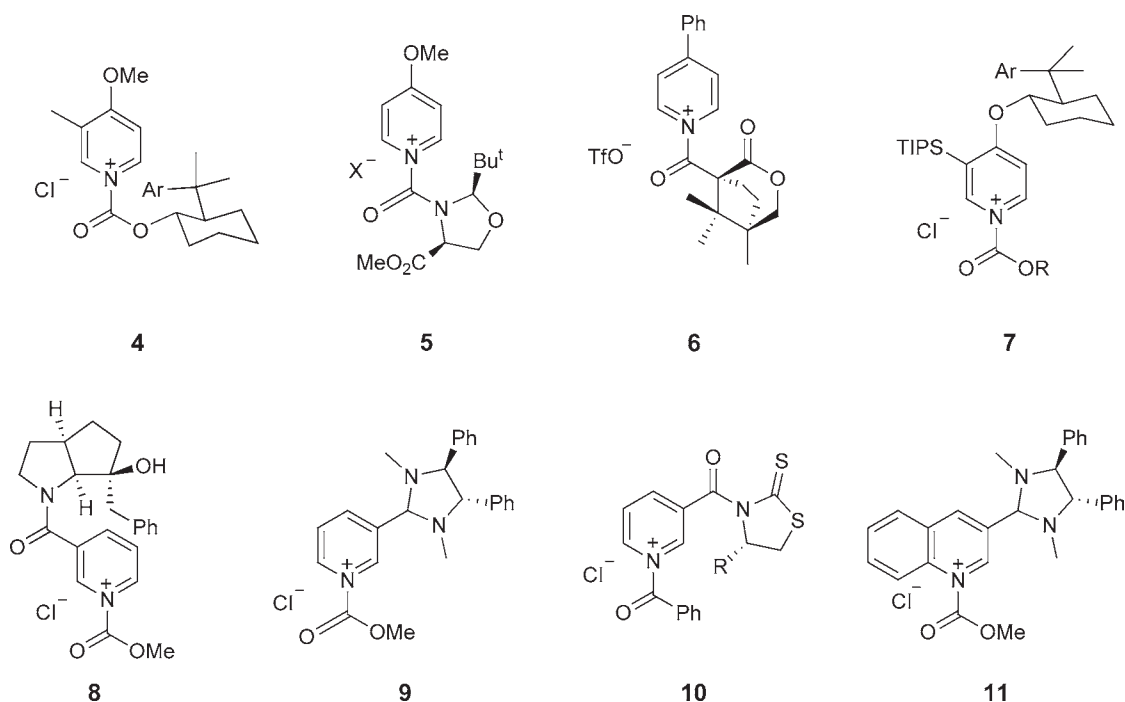
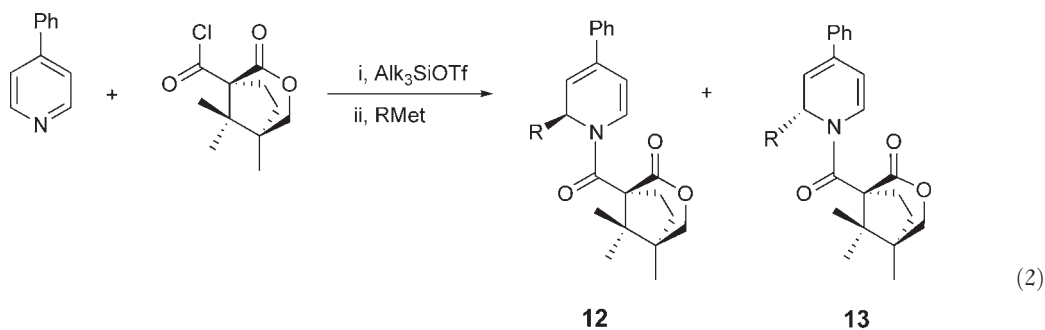


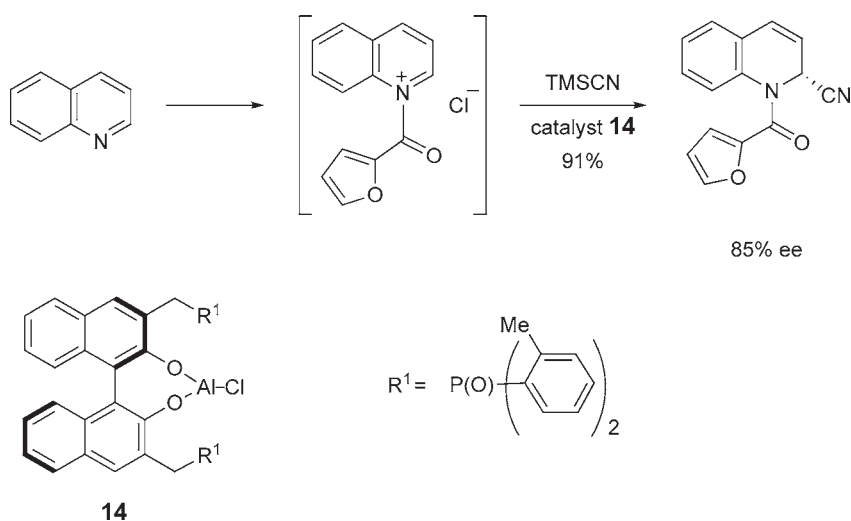
Figure 4 Various chiral *N*-acylpyridinium salts.

acid as the chiral auxiliary [\[2002T6757\]](#). Using ^1H NMR spectroscopy to track the formation of the *N*-acylpyridinium salt, it was revealed that in addition to reaction concentration a great improvement in salt formation was achieved by employing trialkylsilyl triflates as additives. These conditions improved the yields of the subsequent addition reactions (Equation 2) [\[2000JOC9272\]](#). Yamaguchi *et al.* had previously reported that certain additives such as AgOTf , NaOTf , LiOTf , AgBF_4 , and Me_3SiOTf increased the reactivity of *N*-acyl salt ions generated from quinoline and chloroformates [\[1997TL403, 1998CL547\]](#). They also demonstrated that addition reactions of allylsilanes to *N*-acylquinolinium salts are promoted by a catalytic amount of triflate ion to give 2-allyl-1,2-dihydroquinoline derivatives in good yields [\[2001T109\]](#).



<i>R</i> Met	<i>Alk</i> ₃ <i>SiOTf</i>	Yield 12 + 13 (%)	d.s. 12/13
PhMgBr	ⁱ Pr ₃ SiOTf	89	38/62
	Me ₃ SiOTf	72	93/7

When first reported in 1905, the Reissert reaction demonstrated the addition of KCN to quinoline in the presence of benzoyl chloride, but many new modifications since then have employed other nucleophiles and catalytic promotion by a Lewis acid. Shibasaki reported in 2001 the first catalytic enantioselective Reissert-type reaction. Optimized reaction conditions involving an electron-rich aromatic acid chloride in a low-polarity solvent, and use of catalyst **14**, were found to suppress the racemic pathway and resulted in good enantioselectivity (Scheme 2) <2001JA6801>.



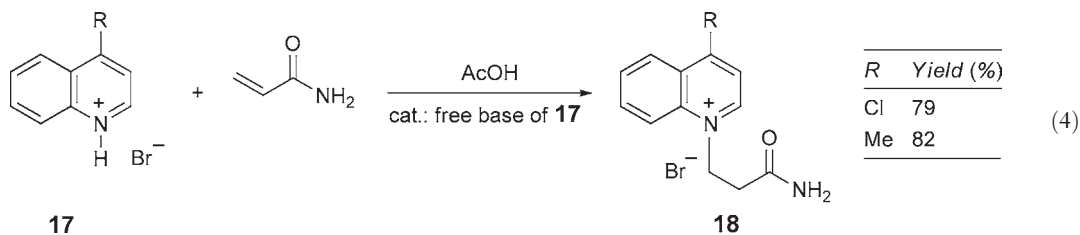
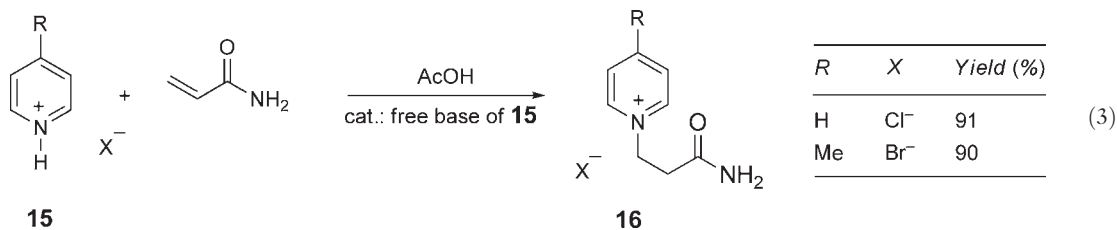
Scheme 2

Transfer of the dimethylcarbamoyl group from *N*-acyloxypyridinium salts to pyridines and from *N*-acylpyridinium salts to pyridine *N*-oxides was studied in acetonitrile. Equations relating the reaction rates and equilibria in the *N*-O and O-*N* acyl-transfer series to the basicity of the nucleophile and leaving group were obtained. The reactions all are single stage and occur by the forced concerted S_N2 mechanism <2004RJC1597>. Studies on the influence of *N*-acylpyridinium salt formation on the observed reaction rate have been reviewed <1997MI67>.

7.02.2.5 Activated Alkenes

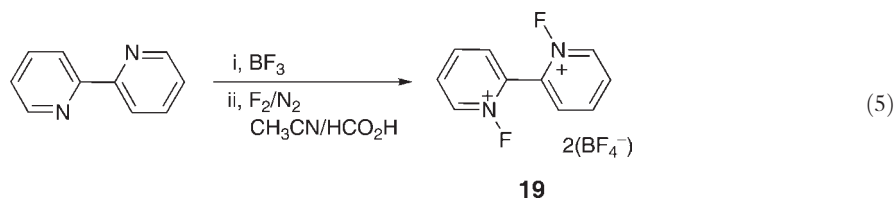
An improved preparation of precursors to cyanine dyes by means of the 1,4-addition of pyridines and quinolines to acrylamide was recently described by Deligeorgiev (Equations 3 and 4) <2005DP21>. The reaction of the

pyridinium **15** or quinolinium salt **17** in acetic acid in the presence of a catalytic amount of the respective base of the substrate with acrylamide under reflux produced salts **16** and **18** in good yield. These conditions allowed the reaction to be run in the absence of water. In all these cases, acetic acid does not only serve as a solvent but rather effectively inhibits the polymerization of the acrylamide.

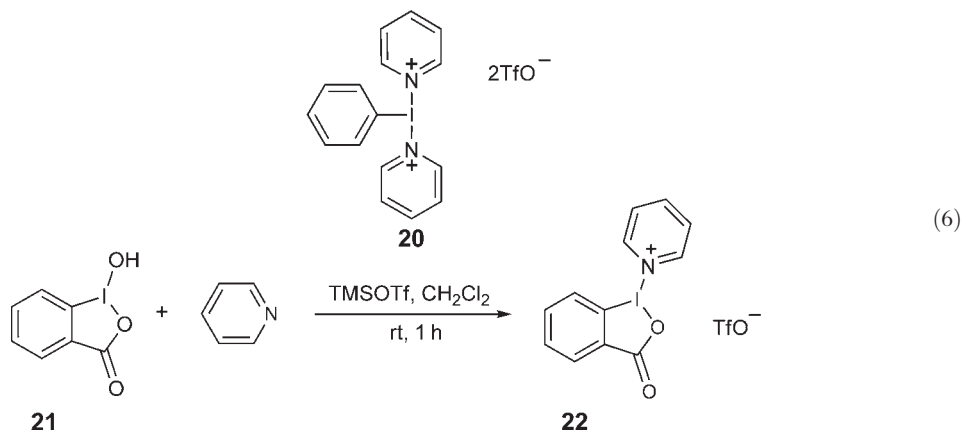


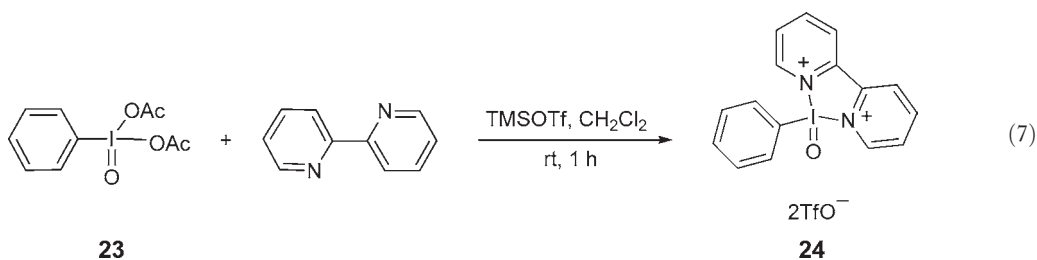
7.02.2.6 Halogens

N',N'-Difluoro-2,2'-bipyridinium bis(tetrafluoroborate) **19**, prepared in one pot by introducing BF₃ gas into 2,2'-bipyridine at 0°C followed by fluorine gas diluted with nitrogen, was shown to be a highly reactive electrophilic fluorinating agent (Equation 5) <2003JFC173>.

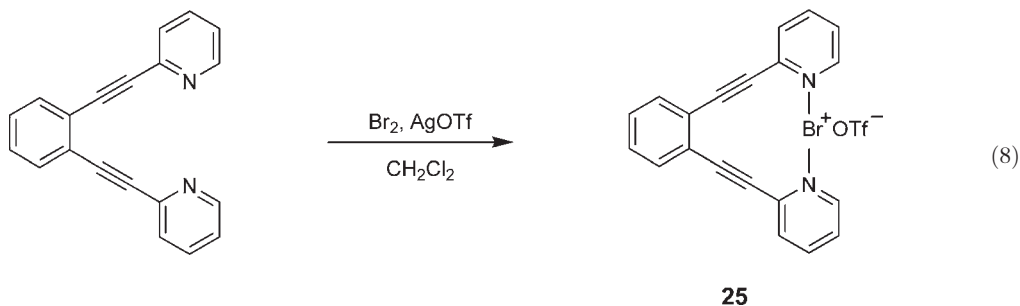


Synthetically useful phosphorane-derived phenyliodonium triflates have been synthesized from the highly electrophilic pyridinium complex **20** <2002TL2359>. Similarly, benziodoxole **21** reacts with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and pyridine to form a precipitate of complex **22** (Equation 6) <2002TL5735>. The first example of a pentavalent iodine complex with a chelating polydentate nitrogen ligand **24** was obtained from diacetate **23** under similar conditions (Equation 7) <2002TL5735>.

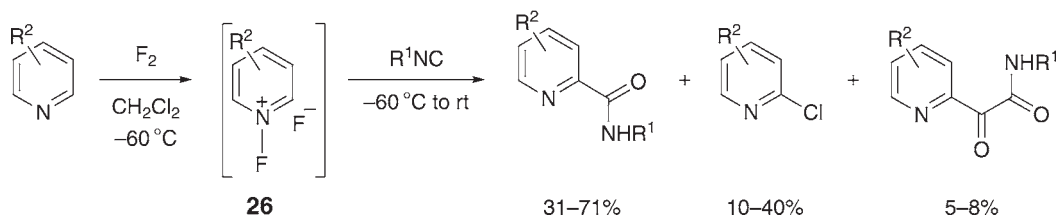




1,2-Bis(2'-pyridylethynyl)benzenebromonium triflate **25** was prepared as shown in Equation (8) to study the transfer of Br^+ to various olefinic acceptors <2001IC3097, 2003JOC3802>.

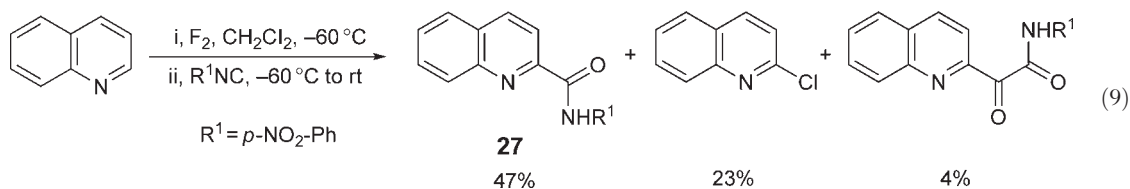


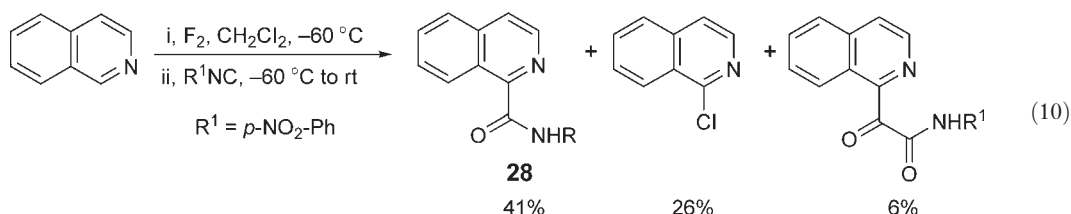
N-Fluoropyridinium salts, readily generated from pyridine and elemental fluorine, react with isonitriles to produce 2-pyridylglyoxamides in good yield. The best yields were obtained with weak electron-donating or -withdrawing groups on pyridine. Speculating that the ring substituents influence the degree of fluorination of the pyridyl ring or the stability of the resulting *N*-fluoropyridinium salt **26** can explain the observed overall yields of the reaction. As would be expected, the pyridines substituted at the 3-position gave a mixture of the respective 2- and 6-regioisomers in a 1.5:1 ratio (Scheme 3) <2005TL2279>.



Scheme 3

Similarly, the fluorine salts of 2-quinoline and 1-isoquinoline can also be harnessed to generate carboxamides **27** and **28** albeit in moderate yields (Equations 9 and 10) <2005TL2279>.

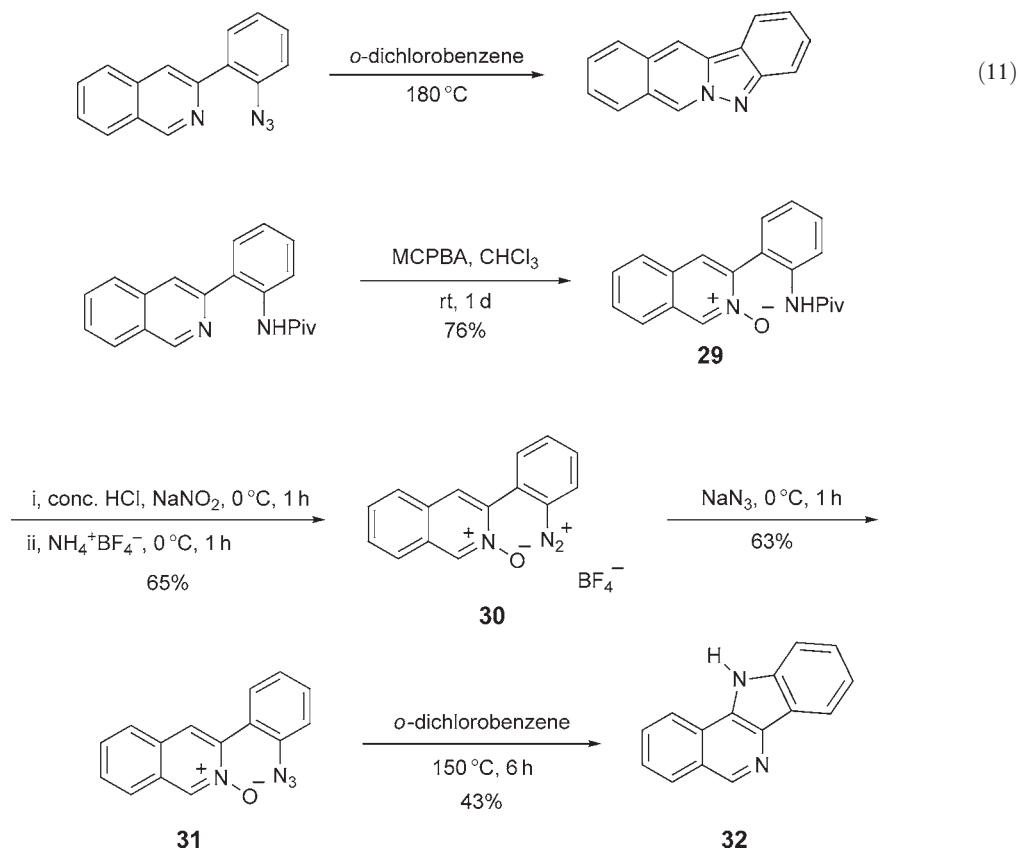




7.02.2.7 N-Oxidation

N-Oxides, obtained by the oxidation of pyridine and its benzo analogues, are versatile intermediates in organic synthesis <2005BML883, 2003TL6643, 2003DP223, 2003CHE1263>. Reagents used for *N*-oxide formation include peracids, $\text{H}_2\text{O}_2/\text{AcOH}$, $\text{H}_2\text{O}_2/\text{manganese tetrakis(2,6-dichlorophenyl)porphyrin}$, $\text{H}_2\text{O}_2/\text{methyltrioxorhenium}$, dimethyldioxirane, bis(trimethylsilyl) peroxide, Caro's acid, oxaziridines <2001ARK242>, trifluoroacetic anhydride (TFAA)/ H_2O_2 -urea complex <2000TL2299>, HOF/ CH_3CN <1999S1427>, $\text{O}_2/\text{ruthenium}$, <2002CC1040>, $\text{H}_2\text{O}_2/\text{molecular sieves}$ <2002JMO109>, O_2/cobalt <2003AGE1265>, trichloroisocyanuric acid/ AcOH <2004SC247>, bromamine-T/ RuCl_3 <2004TL4281>, and TBHP/ MoCl_5 <2006RCB331>.

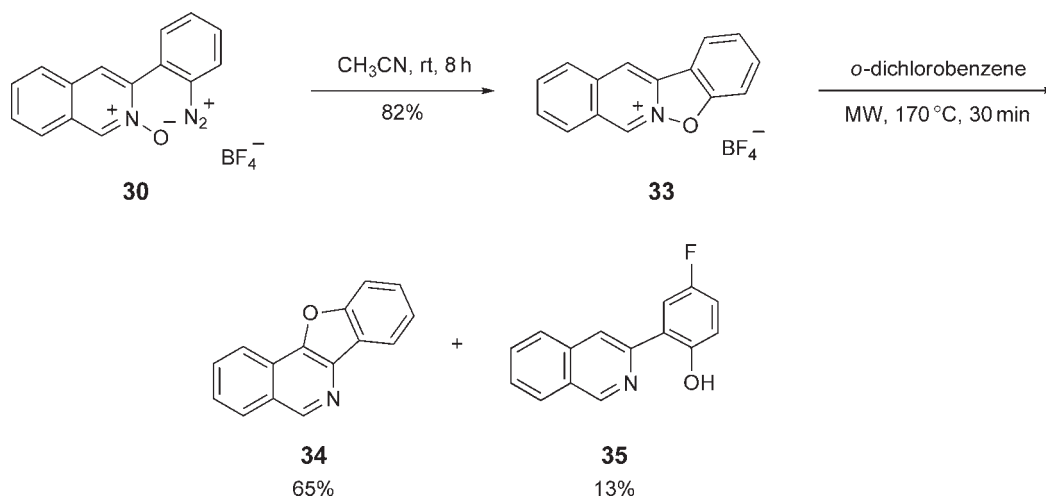
Besides activating the ring for substitution reactions, the *N*-oxide moiety can serve as an effective nitrogen-protecting group. For example, in order to suppress the product of N–N bond formation (Equation 11) in favor of the desired C–4 reaction product **32**, azide **31** was prepared from *N*-oxide **29** in two steps (Scheme 4) <2002TL6035>.



Scheme 4

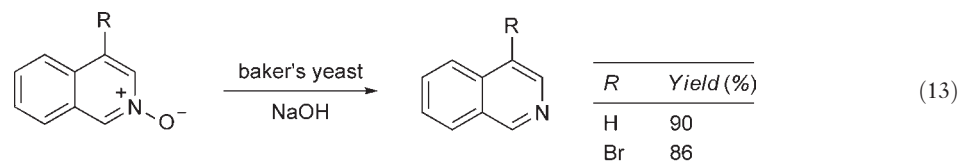
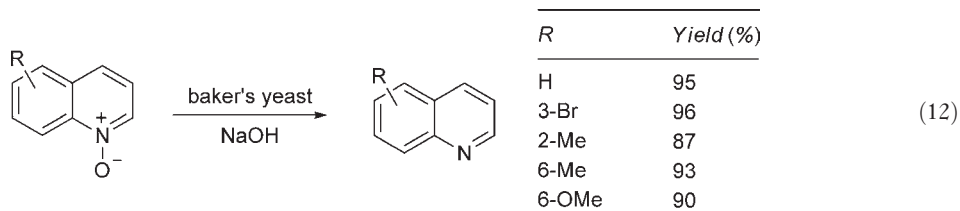
When subjected to the same reaction conditions as used in Equation (11), *N*-oxide **31** gave the desired product **32** in a moderate yield, presumably by cyclization of the azido compound followed by thermal deoxygenation of the *N*-oxide intermediate (Scheme 4).

Alternatively, nucleophilic attack of the *N*-oxide **30** at the electrophilic carbon atom followed by nitrogen elimination results in formation of benzisoxazolo[2,3-*b*]isoquinoline **33** which in turn under thermolysis reaction conditions gives product **34** in 65% yield along with ca. 15% of the *p*-fluorophenol derivative **35** (Scheme 5). The latter product was successfully eliminated when the BF_4^- anion of **30** was replaced by HSO_4^- .



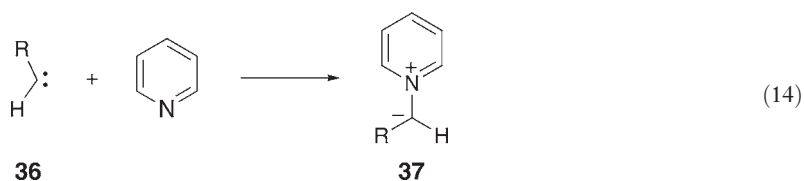
Scheme 5

Although the reduction of pyridyl *N*-oxides with baker's yeast has been reported, the reaction has not been readily employed due to the low yields and long reaction times. Baik *et al.* found that addition of NaOH greatly increased the efficiency of the reaction, thus producing the desired products in high yield (Equations 12 and 13) <1997TL845>. Several methods are available for the reduction of heteroaromatic *N*-oxides <2001ARK242>.

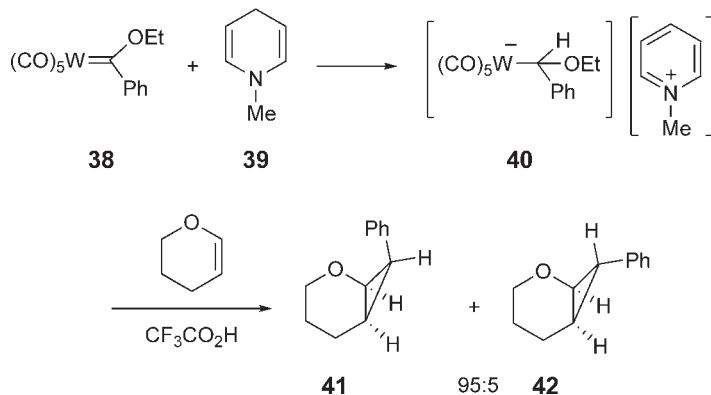


7.02.2.8 Carbenes

Pyridine effectively stabilizes the short-lived organic carbenes **36** by forming the corresponding pyridinium ylides **37** that are far more stable than the starting carbene (Equation 14).

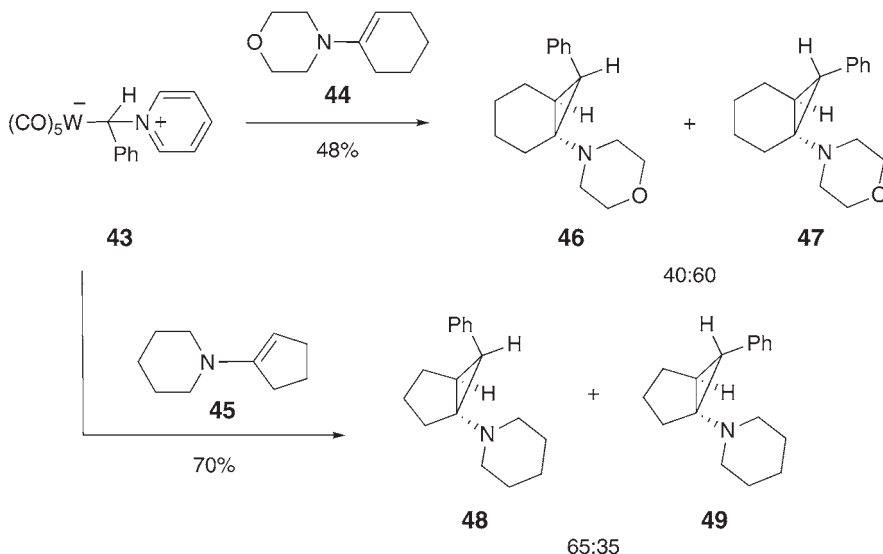


Pyridinium tungstate **40**, prepared from phenyl ethoxy carbene **38** and dihydropyridine **39**, serves as an effective cyclopropanation reagent to give products **41** and **42** in 95:5 ratio and in 35% yield (Scheme 6) [\[1998JOM119\]](#).



Scheme 6

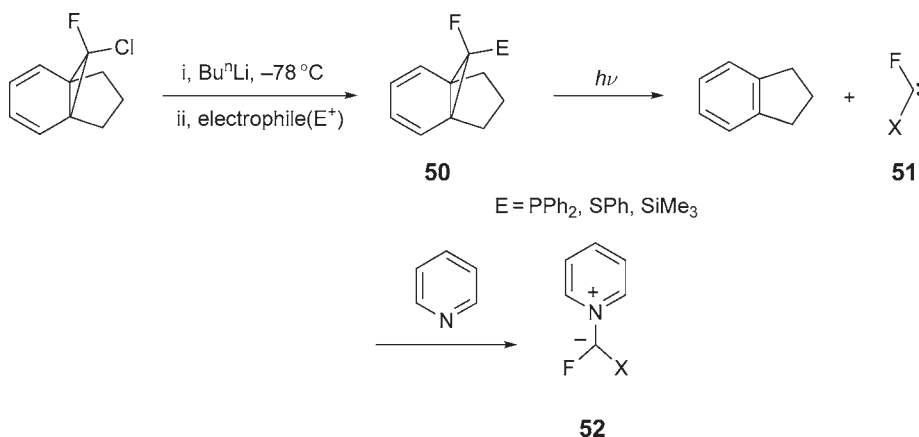
Similarly, enamines **44**, and **45**, react with complex **43** to give the corresponding cyclopropyl amines **46–49** (Scheme 7).



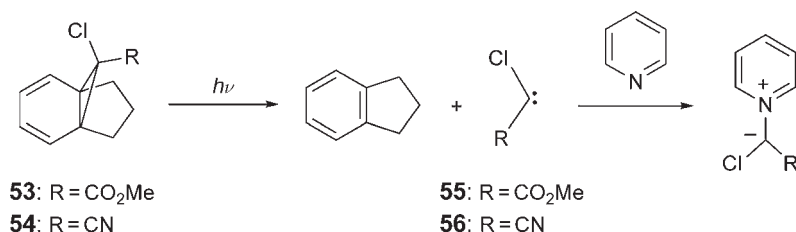
Scheme 7

Singlet fluorocarbenes **51** substituted with diphenylphosphoryl, phenylsulfanyl, and TMS groups were generated from *endo*-10-fluoro-*exo*-10-substituted tricyclo[4.3.1.0]decadienes **50** under photolysis conditions to produce the ultraviolet–visible (UV–Vis) active ylides **52** on reaction with pyridine (Scheme 8) <2004PCA1033>.

Similarly, pyridine traps both carbenes **55** and **56** which are effectively generated under laser flash photolysis from precursors **53** and **54**, respectively. Carbene **56** was found to have greater bimolecular reactivity than analogue **55**. Since singlet carbene **55** is nonplanar, the filled hybrid orbital of the carbene can now interact with the π^* -system of the carbonyl. This additional stability can be attributed to the lone pairs of the carbonyl coordinating with the empty p orbital of the carbene (**Scheme 9**) <2001JA6061, 2002TL7>.



Scheme 8

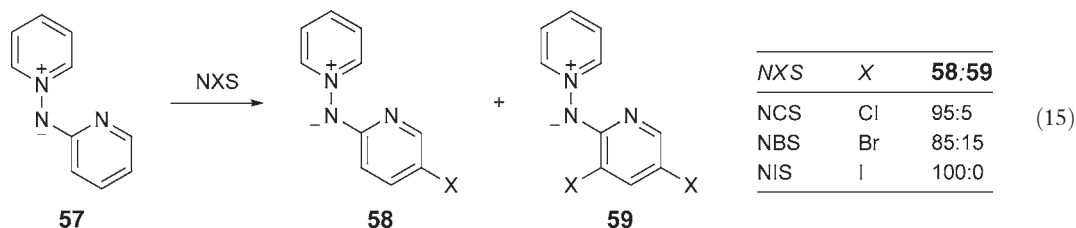


Scheme 9

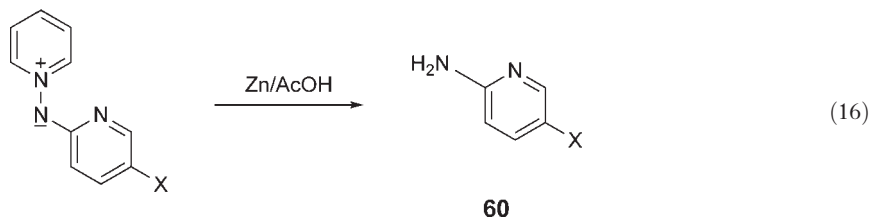
7.02.3 Electrophilic Attack at Carbon

7.02.3.1 Halogenation

Halogenation of pyridines can be effected using a variety of reagents which are not always mild and compatible with other functionalities in the molecule. As a rule, electrophilic substitution in the pyridine ring is more facile if electron-releasing substituents are present. An indirect method of monohalogenating 2-aminopyridine at the 5-position has been reported. Pyridinium *N*-(2'-pyridyl)aminide **57**, prepared from 2,4-dinitrophenylpyridinium halide and 2-pyridylhydrazine [<1994T4995>](#), undergoes halogenation at the 5-position when subjected to 1 equiv of *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), or *N*-iodosuccinimide (NIS) in 78%, 71%, and 90% yield, respectively ([Equation 15](#)) [<1995T8649>](#).

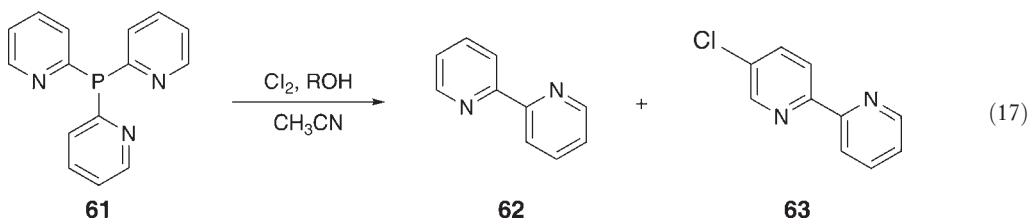


The 2-amino-5-halopyridines **60** were then produced from the corresponding aminides using Zn/acetic acid for the N–N bond fission ([Equation 16](#)).



7.02.3.1.1 Chlorination

An interesting electrophilic substitution of the pyridyl ring through a pentacovalent phosphorane was discovered and optimized by Uchida *et al.* Although the treatment of tris(2-pyridyl)phosphine **61** with chlorine in CH₃CN or CH₂Cl₂ gives the crystalline product Py₃P⁺Cl[−] Cl[−], it was found that the addition of methanol under refluxing conditions resulted in the formation of the coupling product **62** along with trace amounts of 5-chloro-2,2'-bipyridyl **63**. Upon additional evaluation of several protic solvents, including H₂O, MeOH, EtOH, *i*-PrOH, and *t*-BuOH, it was found that when the chlorination of **61** was carried out in CH₃CN in the presence of any of these solvents the yield of the 5-chloro coupling product **63** could be increased to 61–85% (Equation 17) <1995TL4077>.



Furthermore, the chlorination and bromination of the substituted starting material **64** along with tris(2-pyridyl)phosphine oxide **65** were examined (Equation 18), and the results are summarized in Table 2.

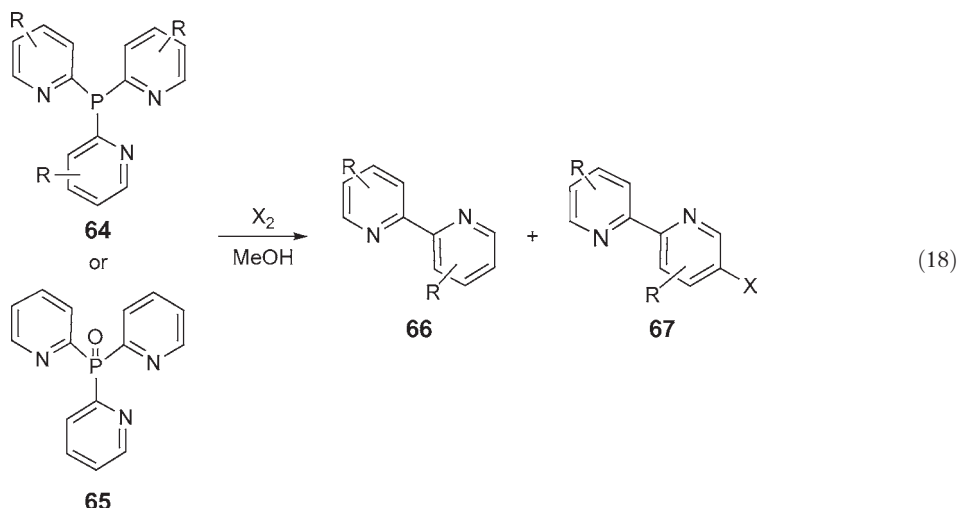


Table 2 Halogenation of phosphine **64** or phosphine oxide **65** in methanol

Entry	(64 or 65) ^a	R	X ₂	66 and 67	Yield ^b (%)
i	64	H	Cl ₂	3	77
ii	65	H	Cl ₂	8	62
iii	64	4-Me	Cl ₂	6	63
iv	64	6-Me	Cl ₂	2	73
v	64	6-Br	Cl ₂	0	0
vi	64	H	Br ₂	14	76
vii	65	H	Br ₂	15	74
viii	64	4-Me	Br ₂	36	48
ix	64	6-Me	Br ₂	22	69

^aStarting material (SM).

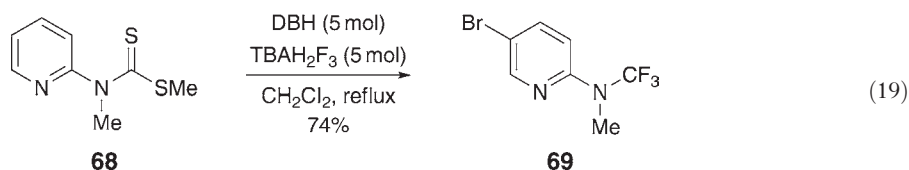
^bDetermined by gas chromatography.

Reaction of *N*-fluoropyridinium triflate with a base in methylene chloride affords 2-chloropyridine as the major product along with 2-pyridyl triflate and 2-fluoropyridine. This conversion may be explained by a singlet carbene produced through proton abstraction of the *N*-fluoropyridinium salt <1996JFC161>.

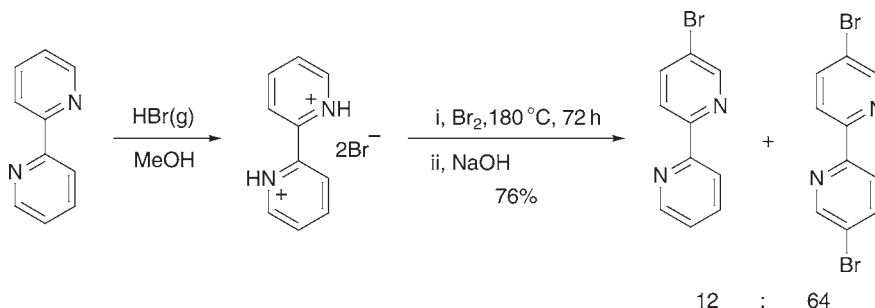
7.02.3.1.2 Bromination

A study by Brown and Gouliarov looking at the bromination of quinoline and isoquinoline found it highly dependent on the brominating agent, the acid used, the temperature and reaction concentration, with the monobromination of isoquinoline being much more regioselective than that of quinoline. Under optimal conditions, using NBS/H₂SO₄ or *N,N*-dibromoisocyanuric acid (DBI)/CF₃SO₃H, 5-bromoisoquinoline can be isolated in 72% yield. The use of 2.3 equiv of NBS in concentrated H₂SO₄ leads to a 76% isolated yield of 5,8-dibromoisoquinoline. Using this procedure, 5-bromoquinoline was obtained in a modest 44% yield, while using excess reagent led to 61% yield of 5,8-dibromoquinoline <2002S83>. Regioselective bromination of 2-methoxy-6-methylpyridine using 1,3-dibromo-5,5-dimethylhydantoin (DBH) provided a high yield (85%) of 5-bromo-2-methoxy-6-methylpyridine under mild conditions. Bromination of 4-dimethylaminopyridine (DMAP) and quinoline with DBH under similar conditions afforded the C-3 brominated products in 80% and 20% yield, respectively <1997TL4415>. Regioselective mono- and dihalogenations of amino, hydroxy, and methoxy pyridines with NBS in different solvents have been studied. In most cases, the monobrominated derivatives can be obtained regioselectively and in high yields <2001S2175, 2003SL1678>.

The valuable intermediate 5-bromo-2-trifluoromethylaminopyridine **69** was prepared in one step from pyridyl methyl dithiocarbamate **68** by reaction with tetrabutylammonium dihydrogentrifluoride (TBAH₂F₃) and DBH in boiling dichloromethane (Equation 19) <1995TL563>.



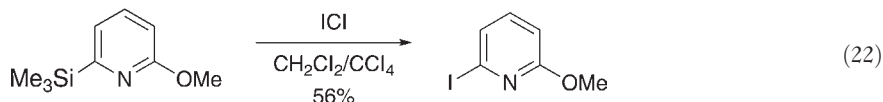
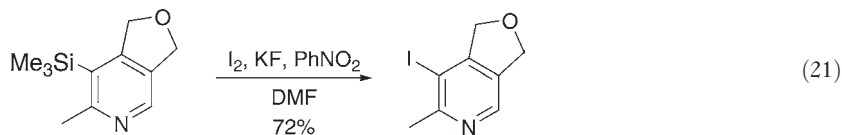
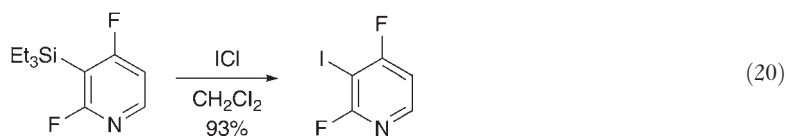
Preparation of 5-monobromo- and 5,5'-dibromo-2,2'-bipyridine (bipy) occurs in moderate yields from bipy and simple, common reagents in two steps (Scheme 10) <1995TL6471>.

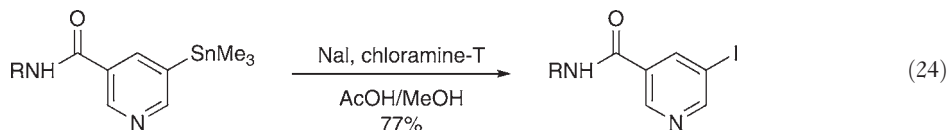
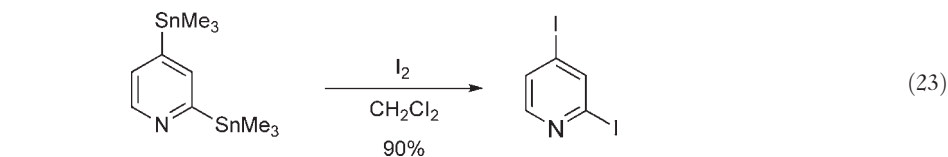


Scheme 10

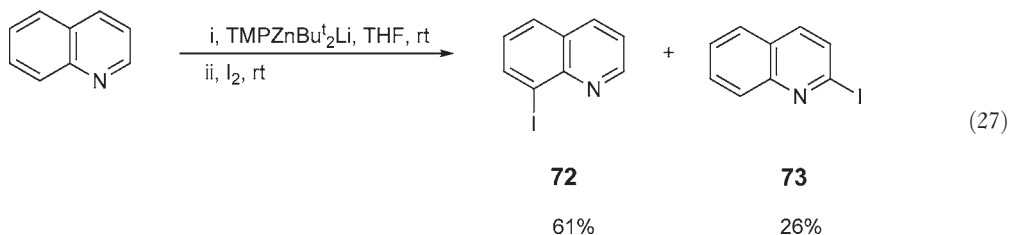
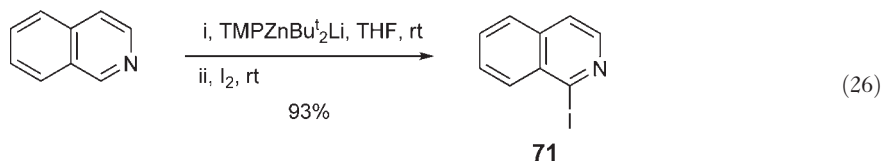
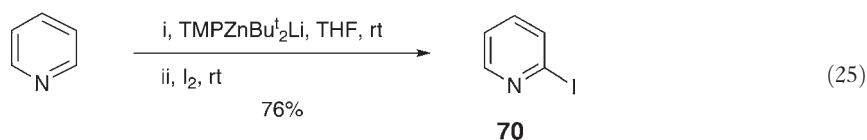
7.02.3.1.3 Iodination

Direct electrophilic iodination of simple pyridines is difficult <1996CHEC-II(5)37>; however, regioselective introduction of an iodine on a pyridine derivative can be easily accomplished via iododesilylation or iododestannylation. A few examples are given in Equations (20–24) <2005JOC2494, 2005SL1188, 1998CEJ67, 1982CPB1731, 2005CAR15>.

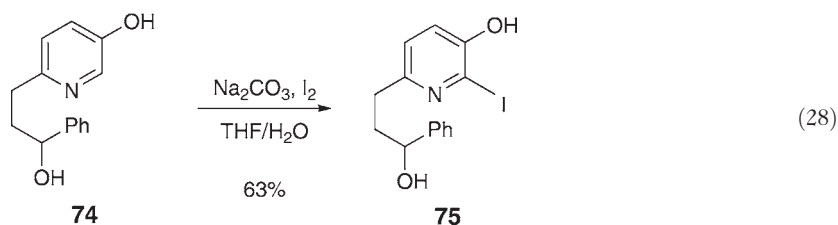




The iodination of pyridine, quinoline, and isoquinoline via α -metalation using lithium di-*tert*-butyltetramethylpiperidinozincate (TMP-zincate) proceeds smoothly at room temperature using iodine as the electrophile. The chemoselective deprotonative zincation generated 2-iodopyridine **70** and 1-iodoisoquinoline **71** in 76% and 93% yield, respectively. Quinoline metalated preferentially at the 8-position to give 61% yield of the 8-iodo derivative **72** and 26% yield of 2-iodoisoquinoline **73** (Equations 25–27) <1999JA3539>.



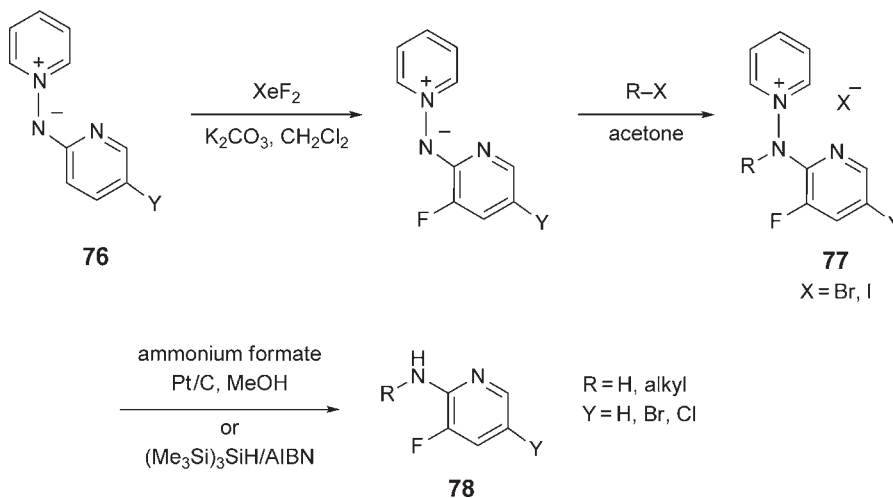
Pyridinol **74** undergoes regiospecific iodination at C-2 with iodine under mild basic conditions to afford diol **75** in good yield (Equation 28) <2004T11751>. The iodination of various bromohydroxypyridines with NIS in acetonitrile is completely regioselective <2003SL1678>.



7.02.3.1.4 Fluorination

The preparation of fluorinated pyridine derivatives continues to be of considerable importance due to the effect that the fluorine atom can have on the physical, chemical, and biological properties of the heterocycle. Despite this, there are few reports on the direct electrophilic fluorination of pyridines. The treatment of various quinoline derivatives with elemental fluorine in acidic reaction media afforded mono- and difluorinated products where the halogenation occurred on the benzene ring of the heterocycles <2004JFC661>.

An interesting electrophilic fluorination of azinyl-*N*-aminides **76** with XeF_2 , followed by alkylation of the exocyclic nitrogen, gave pyridine derivatives **77**. Reductive fission of the N–N bond provided 3-fluoro-2-aminopyridines **78** (Scheme 11) <1999JOC1007>.



Scheme 11

7.02.3.2 Nitration and Sulfonation

Pyridine undergoes nitration at least 10^{22} times slower than benzene whereas pyridine *N*-oxide, pyridones, and pyridinamines can be nitrated more easily <1992H(34)2179>. The sluggish reactivity of pyridines toward electrophilic substitution can be attributed to their protonation under the reaction conditions <2005OBC538>. The first reported nitration of pyridines with dinitrogen pentoxide in sulfur dioxide solution was shown by Bakke to give 3-nitropyridines **79** in good yield (Equation 29; Table 3) <1994ACS1001, 2003PAC1403, 2005JHC463>. He proposed that this reaction proceeds by a [1,5]-sigmatropic shift of the nitro group from the 1- to the 3-position of the ring via a dihydropyridine intermediate rather than an electrophilic aromatic substitution.

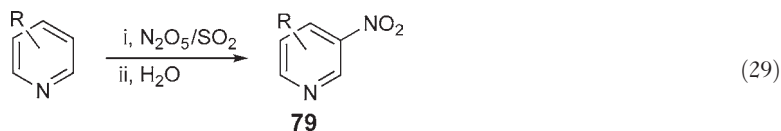


Table 3 Nitration of pyridine and substituted pyridine with $\text{N}_2\text{O}_5/\text{SO}_2$

<i>R</i>	Yield 79 (%)
H	63
2-Me	42
3-Me	29
4-Me	70
4-Ph	31
3-Ac	19
4-Ac	75
3-Cl	15
4-CN	35
Quinoline ^a	16 ^b
Isoquinoline ^a	28 ^c

^aStarting material.

^b3-nitroquinoline.

^c4-nitroisoquinoline.

More recently, Katritzky *et al.* were able to effectively avoid the handling of the unstable and difficult-to-obtain dinitrogen pentoxide reagent by preparing it *in situ* and reacting it immediately with pyridines. Since an equilibrium concentration of dinitrogen pentoxide has been proposed to exist in the nitric acid–acetic anhydride system <1972CPB2678, 1973JOC2271>, a nitric acid–TFAA system was tested as a viable alternative <2005OBC538>. The direct nitration of pyridine and substituted pyridines was successful by treatment of a substrate with nitric acid in TFAA (usually 12 h at 0–24 °C) followed by sodium metabisulfite solution (Equation 30; Table 4).

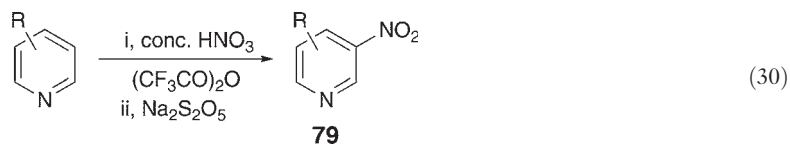


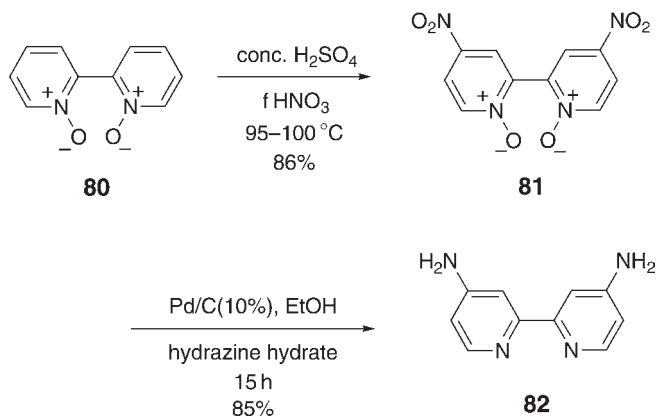
Table 4 Nitration of pyridine and substituted pyridines with nitric acid/TFAA and sodium metabisulfite

<i>R</i>	Yield 79 (%)
H	83
2-Me	68
3-Me	62
4-Me	86
4-Et	25
3-Ac	20
4-Ac	83
3-Cl	76
4-NMe ₂	32
Isoquinoline ^a	37 ^b

^aStarting material.

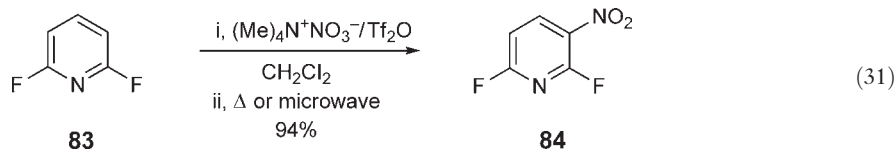
^b4-nitroisoquinoline.

Nitration of 3,5-dichloro- and 3,5-difluoropyridine can be carried out via their *N*-oxides to provide the 4-nitro derivative as the major product <1998J(P1)1705>. Leech reported an improved yield for the preparation of diamine **82**. Using sulfuric acid and fuming nitric acid produces 4,4'-dinitro-2,2'-bipyridine-*N,N'*-dioxide **81** in 86% yield versus a previously reported yield for the nitration of **80** of 54%. The reduction of the resulting dinitro groups and the *N*-oxides was accomplished with 10% Pd/C and hydrazine hydrate to give **82** in 85% yield (Scheme 12) <2004TL121>. Conversion of 2-nitroaminopyridine *N*-oxides to 2-amino-5-nitropyridine *N*-oxides occurs in the presence of sulfuric acid at 80 °C <1998RJO271>.

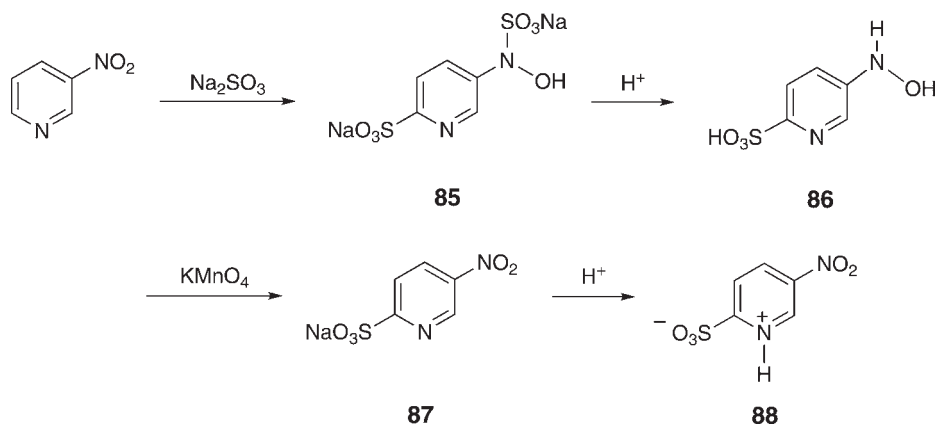


Scheme 12

A new mild nitration employing tetramethylammonium nitrate and trifluoromethanesulfonic anhydride in CH_2Cl_2 was found to effectively mononitrate aromatics and heteroaromatics in high yields. Although pyridine **84** had been synthesized from its corresponding 2,6-dichloro-3-nitropyridine or from the direct nitration of **83** using conc. H_2SO_4 and HNO_3 , using the milder nitronium triflate nitrating agent was equally effective but required the optimization of the reaction conditions. The conditions were modified from room temperature to reflux under a more concentrated solution in order to achieve complete conversion. Applying the reaction to microwave-assisted conditions proved fruitful but first the nitrating agent had to be prepared over 1.5 h at room temperature before its addition to the substrates and irradiation. The best conditions for converting pyridine **83** to **84** required 1.3 equiv of the nitrating agent and two irradiations, one for 10 min followed by magnetic stirring to ensure adequate reaction suspension mixing, and then by an additional 5 min of irradiation, all at 80°C (Equation 31) <2003JOC267>.

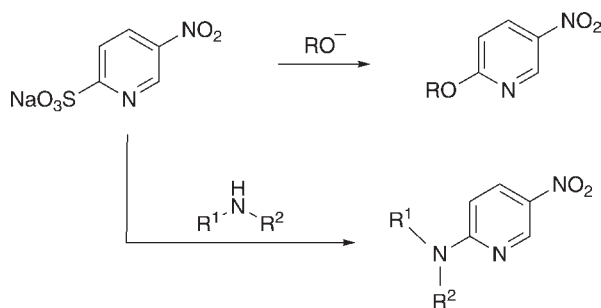


Interestingly, 3-nitropyridine can be sulfonated with Na_2SO_3 to give 2,5-disubstituted pyridine **88** (Scheme 13) <2000J(P1)1241>. The reaction proceeds through the sulfonic acid salt **85**, which when treated with an acidic ion-exchange resin generates 5-hydroxyaminopyridine-2-sulfonic acid **86**. Subsequent oxidation results in the nitro analogues **87** and **88** (Scheme 13) <2003OBC2710>.



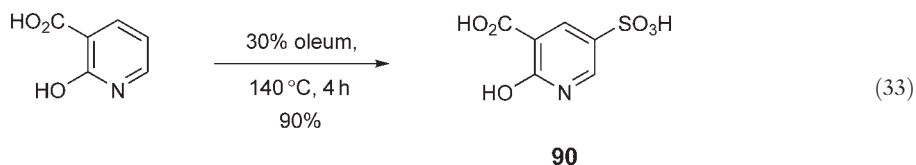
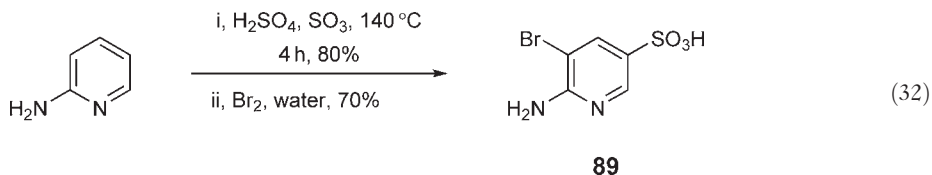
Scheme 13

In addition, the sulfonate group was found to be a good leaving group susceptible to both oxygen and nitrogen nucleophiles (Scheme 14).



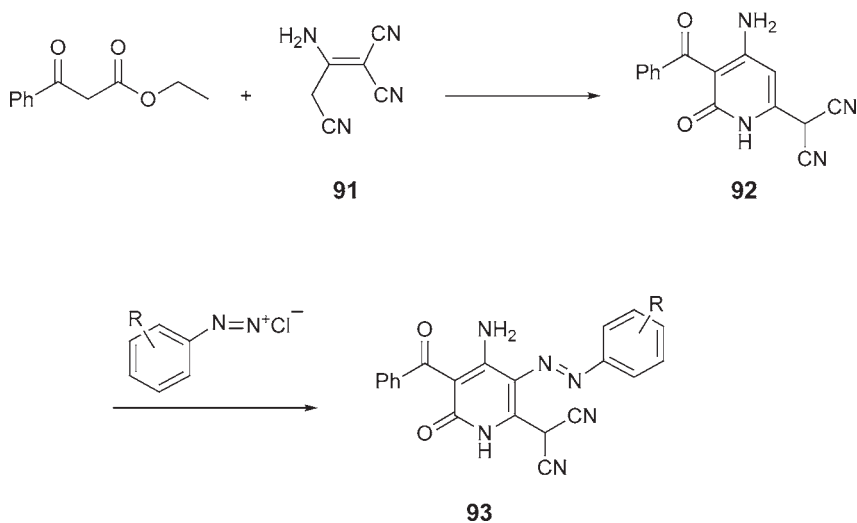
Scheme 14

Sulfonylation of 2-aminopyridine occurs at the 5-position under fairly harsh (140 °C) conditions of sulfur trioxide in sulfuric acid. Subsequent C-3 bromination under mild conditions affords **89**. Similarly 2-hydroxy nicotinic acid when subjected to stoichiometric 30% oleum at 140 °C gave sulfonic acid **90** in 90% yield (Equations 32 and 33) <2002OPD767>.



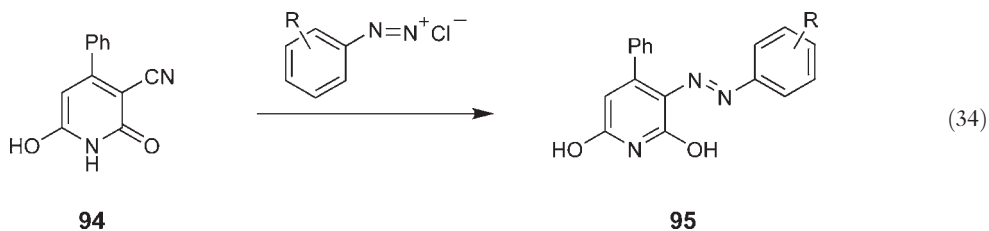
7.02.3.3 Diazo Coupling

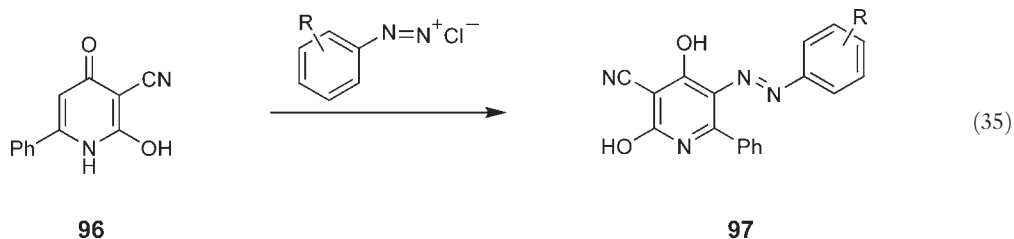
The 4-aminopyridine derivative **92**, prepared from the reaction of ethyl benzoylacetate and malononitrile dimer **91**, undergoes the coupling reaction with aromatic diazonium salts to afford azo derivatives such as **93**. Under refluxing conditions in ethanolic sodium hydroxide, these azo compounds cyclize to pyrido[3,2-*c*]pyridazines and pyrido[3,2-*c*]-pyridazino[2',3'-*a*]quinazolines (Scheme 15) <2005AP329>.



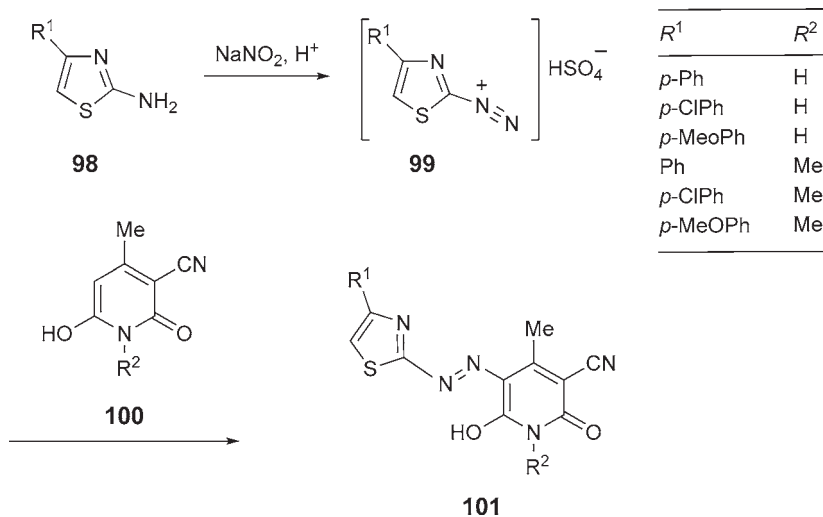
Scheme 15

Similarly, pyridones **94** and **96** underwent coupling with various diazonium salts to generate the azo derivatives **95** and **97** (Equations 34 and 35) <2001T6787>.

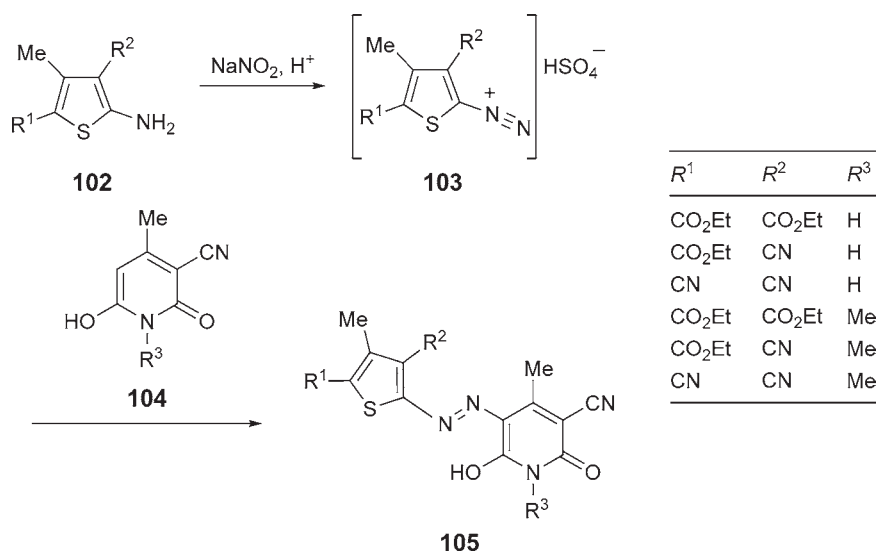




Bis-hetaryl monoazo dyes **101** and **105** were prepared respectively from pyridones **100** and **104** and the diazo analogues of thiazole **98** and thiophene **102** (Schemes 16 and 17) <2004DP1, 2004DP173>.



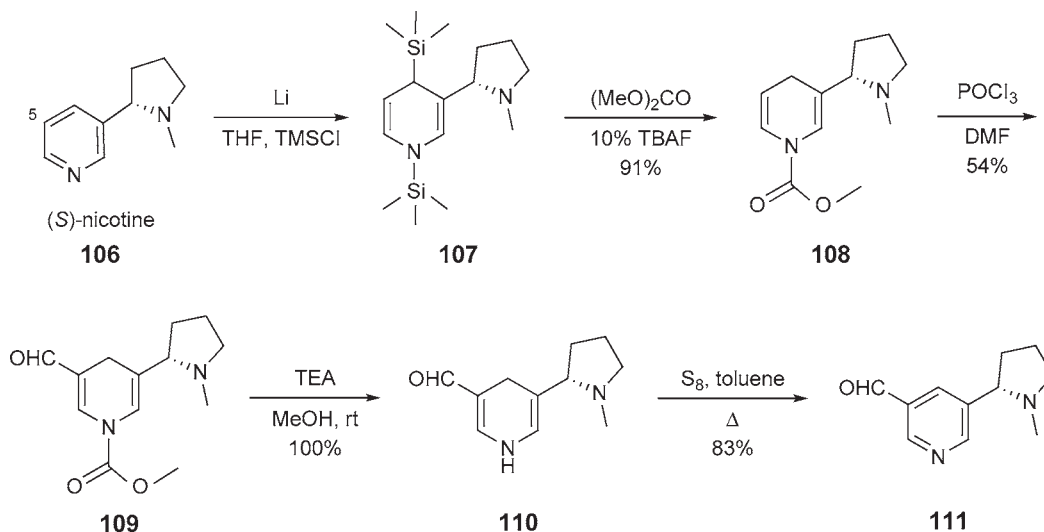
Scheme 16



Scheme 17

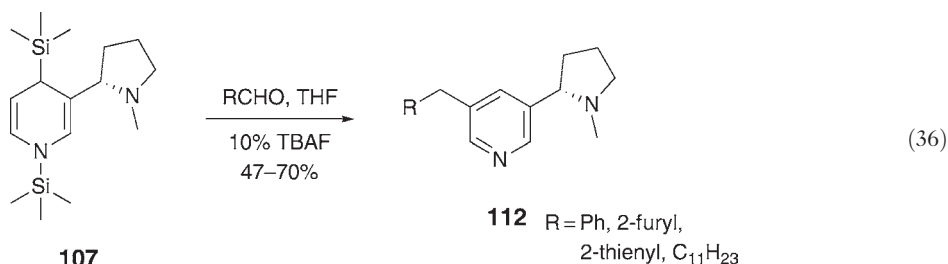
7.02.3.4 Acylation and Alkylation

Since the Friedel–Crafts acylation/alkylation fails with most pyridines, methods which utilize electron-rich dihydropyridine intermediates have been developed. After the dihydropyridine undergoes electrophilic substitution, it can be readily aromatized to afford the corresponding 3-substituted pyridine <1998CHE871>. Comins and co-workers demonstrated an indirect C-5 formylation of nicotine **106** via the disilylated 1,4-dihydropyridine **107**. Treatment of **107** with methyl carbonate in the presence of tetrabutylammonium fluoride (TBAF) readily acylated the nitrogen to give **108**. Under Vilsmeier–Haack acylation conditions, 1-acyl-1,4-dihydropyridine **108** underwent electrophilic substitution at C-5 to give aldehyde **109**. Aromatization of **109** was carried out by removal of the *N*-carbomethoxy group to give **110**, which when subjected to elemental sulfur in refluxing toluene provided the desired nicotine-5-carbaldehyde **111** in 83% yield (Scheme 18) <2006OL179, 2006TL1449>. An entry to 3,5-disubstituted pyridines from 3-substituted pyridines via the acylation of an *N*-alkyl-1,4-dihydropyridine intermediate has been reported <2003TL4711>.



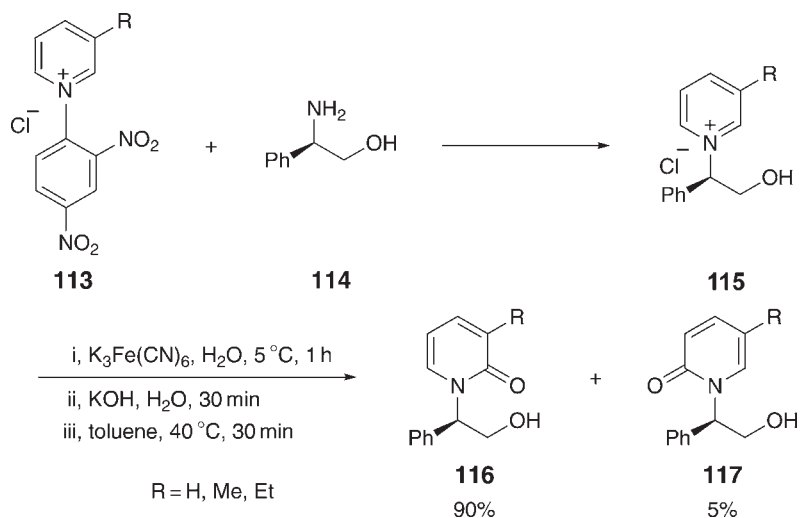
Scheme 18

Nicotine can be alkylated at C-5 via the disilyl-1,4-dihydropyridine **107** using a modification of the Tsuge reaction. Addition of an aldehyde and a catalytic amount of TBAF to **107** affords the C-5 alkylnicotines **112** in moderate to good yield (Equation 36) <2006OL179>.



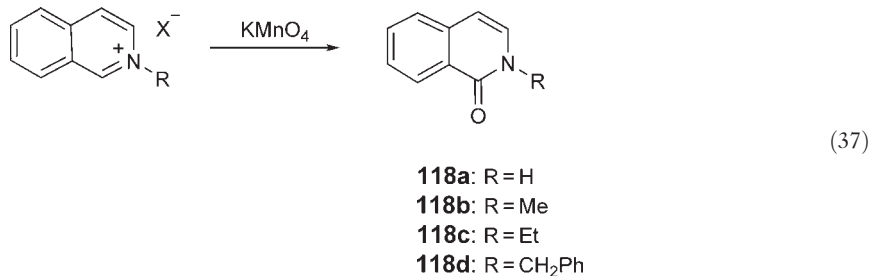
7.02.3.5 Oxidation

Chiral pyridinium salt **115**, prepared from the reaction of Zincke salt **113** with (*R*)-(-)-2-phenylglycinol **114** <1992SL431, 1997JOC729>, underwent oxidation to afford 2- and 6-pyridones in high yield when treated for 1 h with potassium ferricyanide followed by potassium hydroxide. The regioselectivity was also good favoring pyridone **116** over **117** in a 90:10 ratio (Scheme 19) <1998TA2027>. Generally, an increasing percentage of oxidation at C-6 is observed when the bulkiness of the C-3 substituent increases <2000MOL1175>.

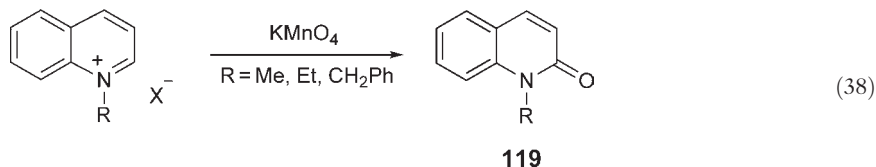


Scheme 19

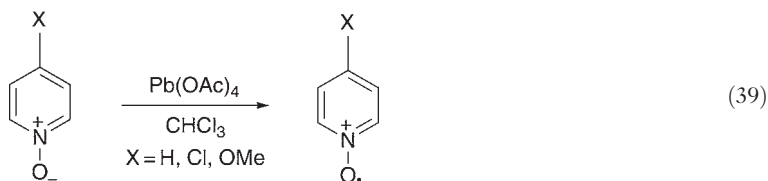
Although a number of reagents such as Fremy's salt, lead(II) and mercuric acetates, chromic acid, and peracids effectively oxidize isoquinoline and quinoline *N*-alkyl salts, potassium permanganate and active manganese dioxide are some of the mildest and most selective. Oxidation of *N*-methylisoquinolinium iodide in dichloroethane in the presence of KMnO_4 and a catalytic amount of 18-crown-6 for 3 h at room temperature led to 2-methyl-1-(2*H*)-isoquinolinone **118b** in 50% yield whereas running the reaction in CH_3CN afforded the desired product in 82% yield. The same procedure afforded the corresponding products **118c** and **118d** in good yields from the isoquinoline salts of ethyl iodide and benzyl chloride. The oxidation of the salts from acetyl chloride or ethyl chloroformate afforded upon workup the hydrolyzed pyridone **118a** (Equation 37) <1996T1451>.



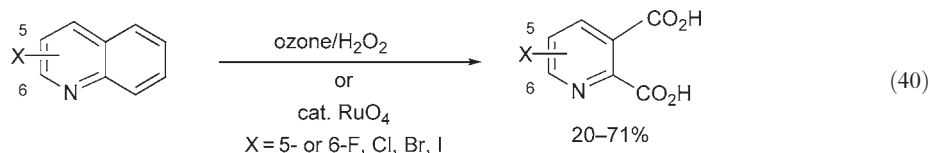
Similarly, treatment of the *N*-alkyliminium salts of quinoline under the same oxidizing conditions resulted in formation of 1-alkyl-2(2*H*)-quinolinones **119** (Equation 38) <1996T1451>.



One-electron oxidation of pyridine *N*-oxides with lead tetraacetate gives *N*-oxide radical cations (Equation 39) <2002RJC729>.



Pyridine-2,3-dicarboxylic acids containing a halogen in the 5- or 6-position were prepared by oxidation of the corresponding quinolines using either ozone/H₂O₂ or catalytic RuO₄. Diacids substituted in the 6-position by Cl or Br, or in the 5-position by F, Cl, or Br, respectively, were isolated in 46–71% yields. The yields of 6-fluoro and 6- or 5-iodo diacids were low (<30%) (Equation 40) <2001S2495>.

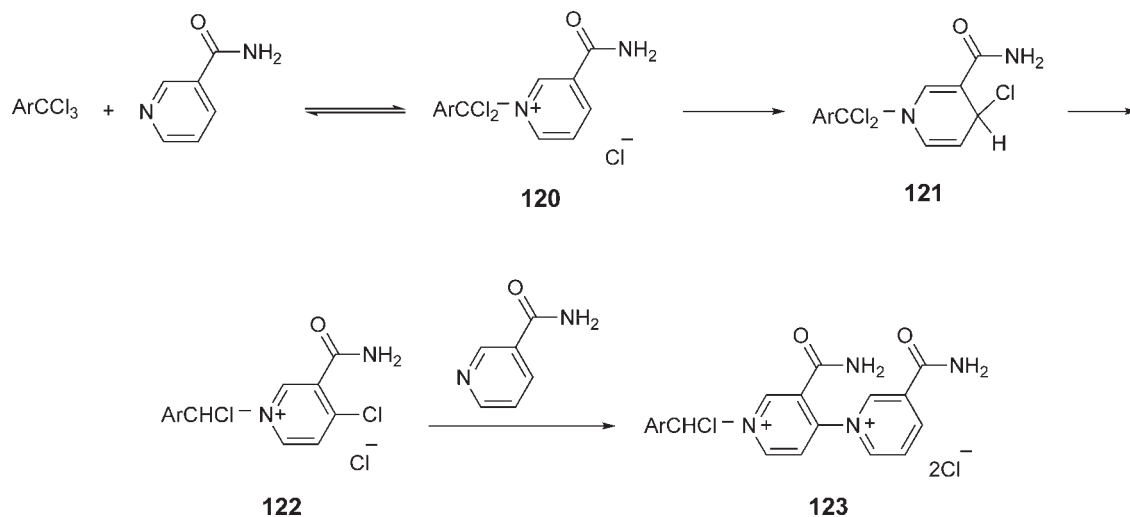


7.02.4 Nucleophilic Attack at Carbon

7.02.4.1 Halogenation: Formation of a Carbon–Halogen Bond

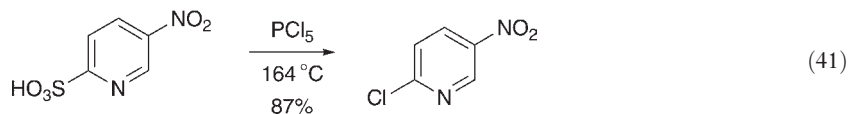
7.02.4.1.1 Chlorination

Trichloromethylarenes are found to activate the pyridine ring via N-alkylation such that 4-chloropyridines are formed (Scheme 20) <1995TL5075>. In the case of nicotinamide, the dihydropyridine intermediate **121** undergoes an intermolecular redox reaction with hydride transferred to the benzylic position to give **122**. Subsequent displacement of the C-4 chloride with nicotinamide affords the bipyridinium salts **123**.

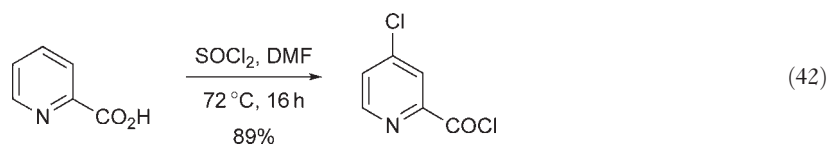


Scheme 20

Conversion of 2-hydroxypyridines to 2-chloropyridines has been effected using triphenylphosphine and NCS <1999TL7477, 2001HCA1112>. Interestingly, 5-nitropyridine-2-sulfonic acid is converted to 2-chloro-5-nitropyridine in 87% yield when treated with phosphorus pentachloride (Equation 41). This reaction provides a new pathway to chloronitropyridines <2003OBC2710>.



An improved procedure for the preparation of 4-chloropicolinyl chloride from picolinic acid and thionyl chloride has been developed (Equation 42) <2002OPD777>. Phosphoryl chloride in the presence of triethylamine converts pyridine *N*-oxide into 2-chloropyridine in 90% yield <2001SC2507>.



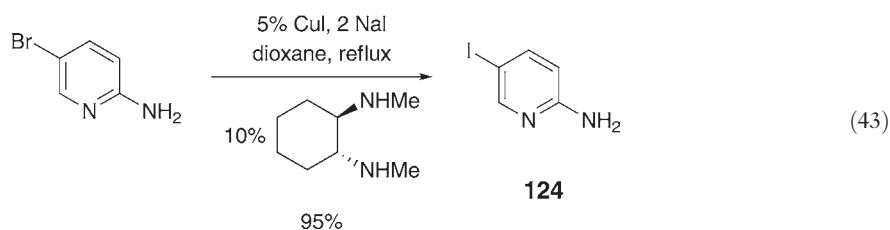
7.02.4.1.2 Bromination

As with the reaction of 2-hydroxypyridines with NCS and triphenylphosphine cited above, the use of NBS as the halogenation reagent results in 2-bromopyridines [<1999TL7477, 2001HCA1112>](#). This reaction is also effective for the conversion of 2-quinolone to 2-bromoquinoline. In a similar fashion, the use of P_2O_5/Bu_4NBr proceeds under mild conditions to convert hydroxyheteroarenes to various bromoheteroarenes [<2001TL4849>](#). Treatment of 2-chloro-3-(hydroxymethyl)quinoline with PBr_3 afforded 2-bromo-3-(bromomethyl)quinoline in high yield [<1992JA10971>](#). Bromotrimethylsilane in refluxing propionitrile converts 2-chloropyridines into 2-bromopyridines [<2002EJO4181>](#).

7.02.4.1.3 Iodination

Heteroaromatic compounds including pyridyl, quinolyl, and isoquinolyl chlorides have been converted to their corresponding iodides via acid-mediated nucleophilic halogen exchange with sodium iodide in refluxing acetonitrile [<2003SL1801>](#). Both 2-chloro- and 2-bromopyridines give the corresponding iodo derivative on treatment with *in situ*-generated iodotrimethylsilane [<2002EJO4181>](#). These conditions are also effective for converting 2- or 4-chloroquinoline and 1-chloroisoquinoline to their iodo derivatives.

Klapars and Buchwald developed a method for the conversion of heteroaryl bromides into the corresponding iodides using a catalyst system comprising CuI and a 1,2- or 1,3-diamine ligand. In this manner, 5-bromo-2-aminopyridine was converted to the iodopyridine **124** (Equation 43) [<2002JA14844>](#).



7.02.4.1.4 Fluorination

Nucleophilic fluorination such as halogen-fluorine exchange or Balz-Schiemann reactions of diazonium salts are common methods used to prepare various fluoropyridines [<1984CHEC\(2\)216, 1996CHEC-II\(5\)68>](#). A one-pot deaminative fluorination of aminoarenes via diazonium salts was developed using hydrogen fluoride combined with base solutions. Using this procedure, several fluoropyridines were prepared in high yield [<1996T23>](#). Selective fluorination of various pyridines and quinolines to afford the corresponding 2-fluoro derivatives can be achieved using elemental fluorine-iodine mixtures at room temperature. The reaction is suggested to proceed by fluoride attack on an *N*-iodo intermediate [<1999J\(P1\)803>](#).

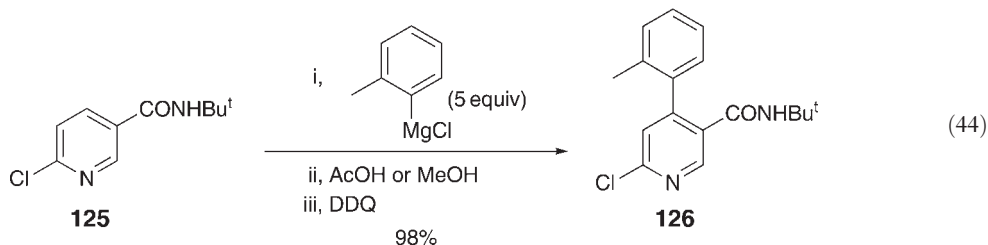
Fluorination of 2,3,5-trichloropyridine with KF and CsF in an ionic liquid afforded 3,5-dichloro-2-fluoropyridine and 5-chloro-2,3-difluoropyridine in good yield [<2004SC4301>](#). Spray-dried KF in hot dimethyl sulfoxide (DMSO) containing a small amount of tetramethylammonium chloride is effective for the displacement of chlorine by fluorine in certain polyhalopyridines [<2005CEJ1903>](#). The conversion of several chloropyridines to their fluoro derivatives has been carried out at room temperature using anhydrous TBAF in DMSO [<2006AGE2720>](#) or KF in sulfolane [<2002BML411>](#).

7.02.4.2 Organometallics, Enolates, and Cyanide

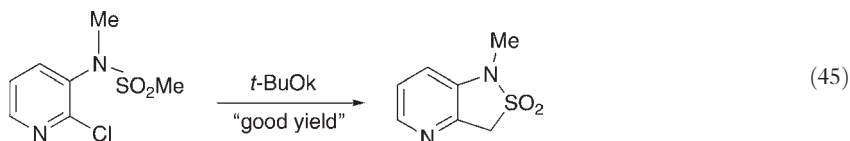
7.02.4.2.1 On neutral molecules

Certain pyridines react with Grignard reagents in the 1,4-manner when substituted by electron-withdrawing groups such as a carboxamide [<2000J\(P1\)4245, 2005JOC2000>](#). The intermediate dihydropyridine can conveniently be oxidized to the pyridine structure. An example of this is seen in the reaction of 6-chloronicotinic acid derivative **125** with an excess of *o*-tolylmagnesium chloride, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

(DDQ), yielding the product **126** in excellent yield (Equation 44) <1995T9531>. Trimethylsilyl anion (Me_3Si^-), generated from hexamethyldisilane and sodium methoxide, reacts with pyridine in hexamethylphosphoramide (HMPA) to afford 4-trimethylsilylpyridine in 92% yield <2001OL1197>.

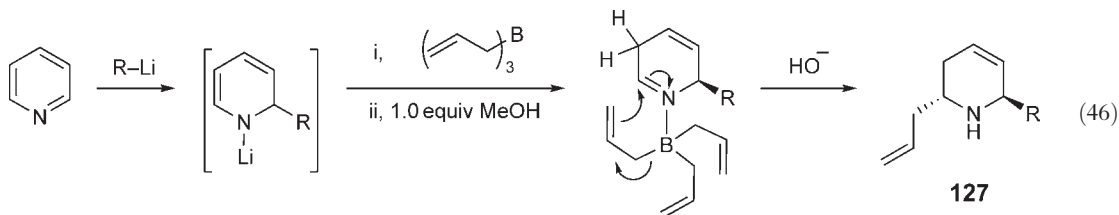


Reactions of enolates with 2-halogenated pyridines incorporate useful functionality into the molecule. An intramolecular version is shown below (Equation 45). This is recognized as an important procedure due to the mild base required, preventing undesirable side reactions <1997TL4667, 2005JOC10186>. Malonate anion reacts with 2,3,4-trichloroquinoline to afford the C-4-substituted derivative <2006JHC117>. Displacement reactions of halopyridines with lithiated nitriles occur by aromatic nucleophilic substitution <2000SL1488, 1997H(45)1929>. Microwave irradiation assists the substitution of 2- and 3-halopyridines with the anion of phenylacetonitrile <2002T4931>. Nitro-substituted quinolines are activated toward nucleophilic addition. The anion of chloromethyl phenyl sulfone adds to a variety of nitroquinolines to give [(phenylsulfonyl)methyl]nitroquinolines <1996LA641>.

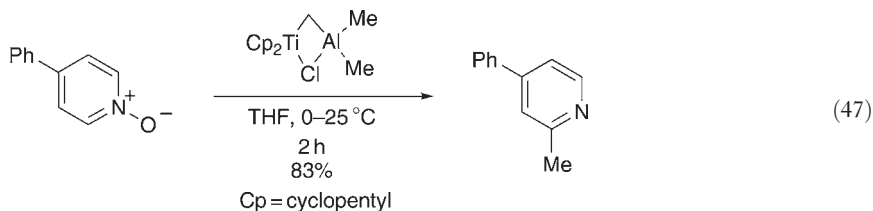


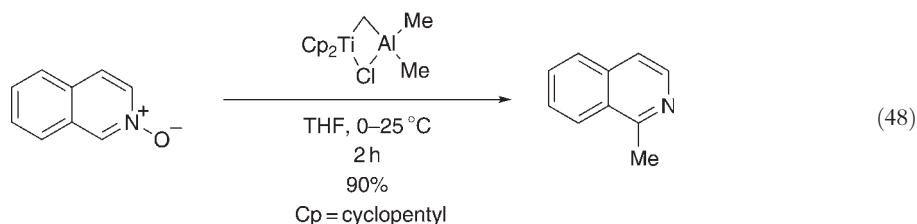
The palladium-catalyzed, microwave-assisted conversion of 3-bromopyridine to 3-cyanopyridine using zinc cyanide in dimethylformamide (DMF) has been reported <2000JOC7984>. Substoichiometric quantities of copper or zinc species improve both conversion rate and efficiency of Pd-catalyzed cyanation reactions <1998JOC8224>. A modification of this procedure uses a heterogeneous catalyst prepared from a polymer-supported triphenylphosphine resin and $\text{Pd}(\text{OAc})_2$; the nitriles were obtained from halopyridines in high yields <2004TL8895>. The successful cyanation of 3-chloropyridine is observed with potassium cyanide in the presence of palladium catalysts and tetramethylethylenediamine (TMEDA) as a co-catalyst <2001TL6707>.

A novel route to unsymmetrical *trans*-2-allyl-6-alkyl(alkyl)-1,2,3,6-tetrahydropyridines **127** was developed using the known 1,2-addition of RLi to pyridine followed by an allylboration of an intermediate imine formed on addition of methanol (Equation 46) <1996TL1317>.

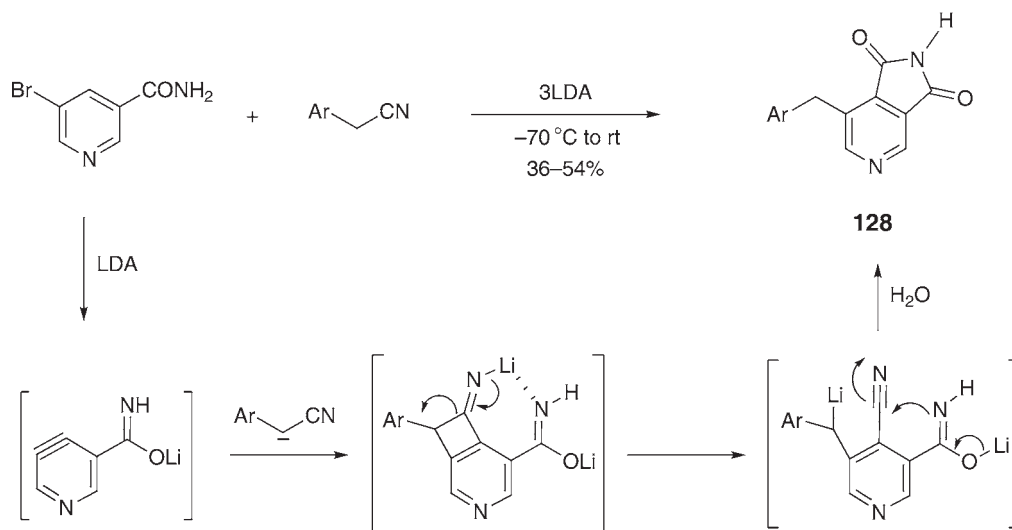


In the Tebbe reaction with pyridine *N*-oxides and their benzo derivatives, regioselective attack at the α -position occurs along with the expected deoxygenation (Equations 47 and 48) <2000AGE2529>. The presumed organometallic intermediate is the titanocene methylenide complex $[\text{Cp}_2\text{Ti}=\text{CH}_2]$.

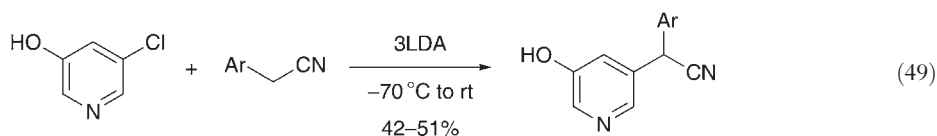




Preparation of 7-arylmethyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3-(2*H*)-diones **128** from 5-bromonicotinamide, arylacetonitriles, and lithium diisopropylamide (LDA) occurs via a pyridyne mechanism (Scheme 21). Under similar conditions, 5-chloro-3-pyridinol and arylacetonitriles afford the C-5 substitution products (Equation 49) <1998T3391>.



Scheme 21

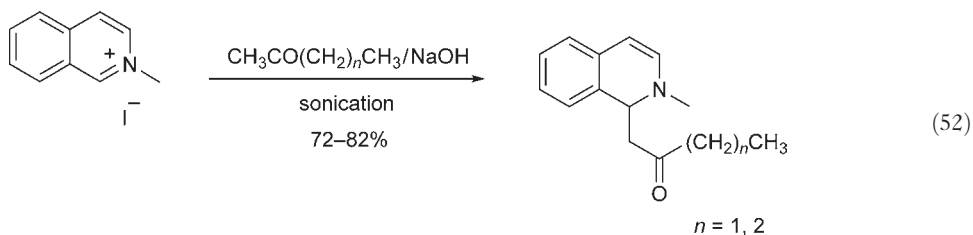
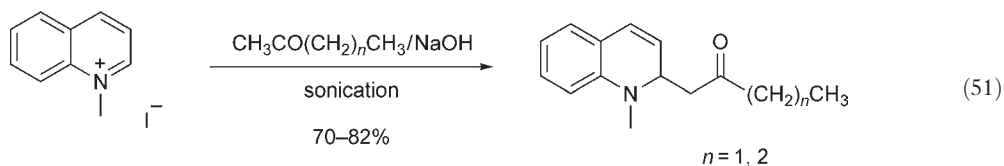
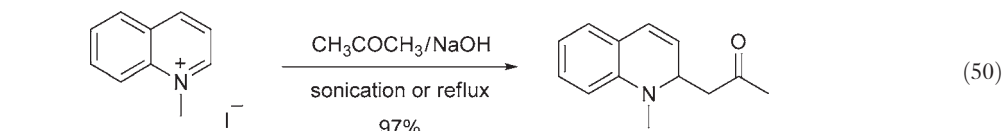


7.02.4.2.2 Via pyridinium salts

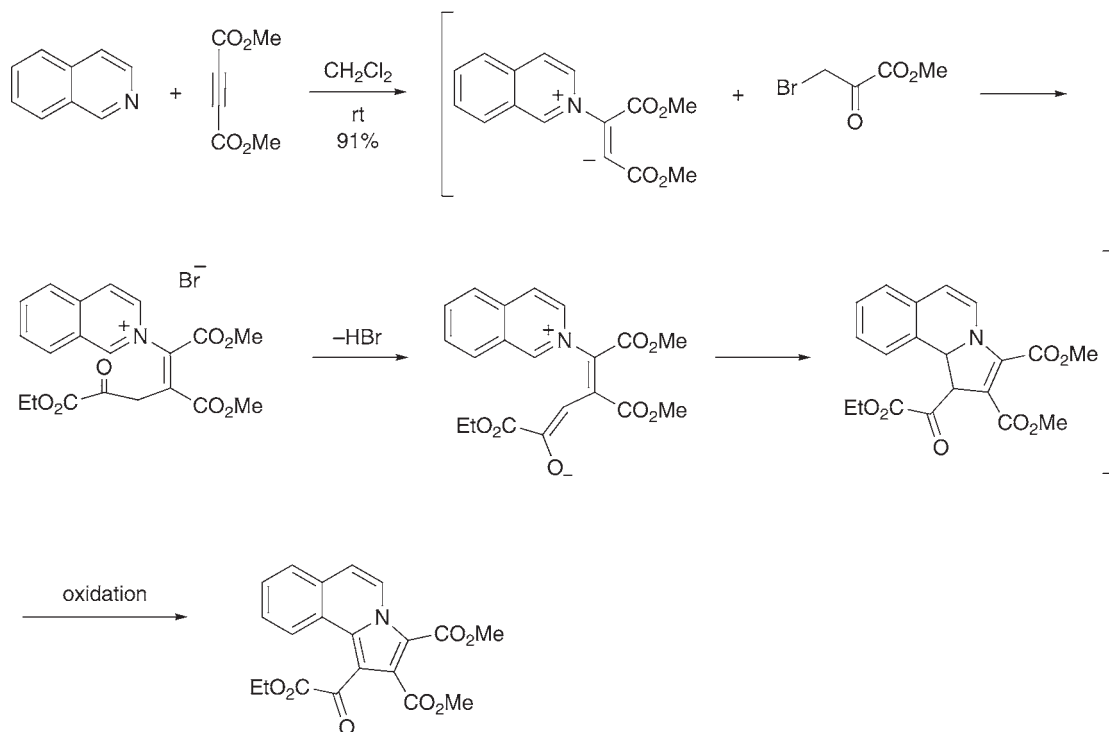
Organometallics add to *N*-acyl- and *N*-alkyl-pyridinium salts to yield 2- and 4-substituted products. Reagents include Grignards <1996TL3807, 1998SL649, 1999OL657, 1999TL6241, 2003COR995, 2006OL2985>, organolithiums <1998H(48)1313, 2001OL469, 2006TL531>, organocuprates <1998TL9275, 2002BML411, 2005TL8905>, metalo enolates <2005OL5227>, silyl enol ethers, organotins, and organosilanes <1997TL403>. Certain heterocycles, such as imidazole, pyrrole, and indole, have been added to *N*-alkyl- and *N*-acylpyridinium, quinolinium, or isoquinolinium salts <1996JCM380, 1997CEJ410, 1997T13959, 2004JOC2863>.

The addition of nucleophiles to *N*-alkylpyridinium and related salts has been used extensively for the preparation of various dihydropyridines and in the synthesis of natural products <2003T2953, 2002J(P1)1141, 2001AHC269>. *N*-Methylquinolinium and *N*-methylisoquinolinium salts undergo attack by the sodium enolate of acetone at the α -carbon regioselectively (>80%) with sonochemical activation. Other methyl ketones give the desired regioisomers exclusively, though in more moderate yields (Equations 50–52) <1996JOC4830>. The C-4 addition of enolates, indolesodium, and cyanide to 1-alkyl-3-(2-quinolyl)quinolinium salts has been investigated <1998CHE1045>. Reaction of 1-methyl, 1-benzyl, and 1-benzoyl-4-ethoxycarbonylpyridinium salts with zinc and benzyl bromide

produce 4,4-disubstituted 1,4-dihydropyridines regioselectively <1996J(P1)2545>. Regioselective cyanomethylation of methylquinolinium and methylisoquinolinium iodides occurs using trimethylsilylacetonitrile in the presence of cesium fluoride <2000JOC907>.



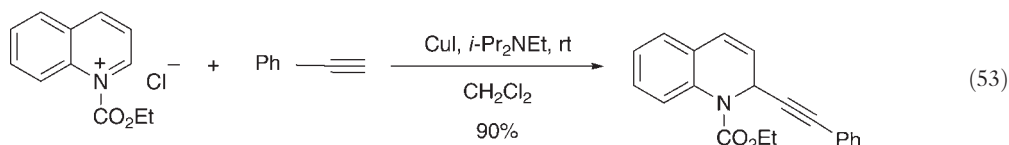
Dimethyl acetylenedicarboxylate (DMAD) reacts with isoquinoline in the presence of ethyl bromopyruvate to yield pyrrole[2,1-*a*]isoquinolines in excellent yields <2006TL6037>. A zwitterionic mechanism is proposed, and implies an enolate intermediate (Scheme 22). The oxidation in the final step occurs spontaneously without addition of any reagent.



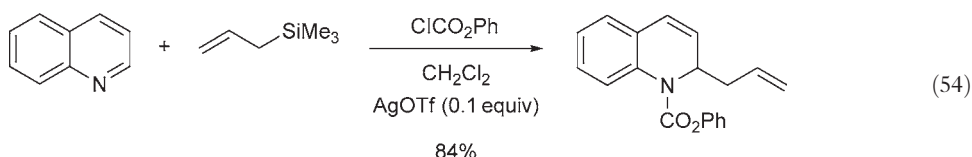
Scheme 22

The reaction of methyl nicotinate with *tert*-butyldimethylsilyl triflate gave the *N*-silylpyridinium salt which on treatment with phenyl Grignard followed by TBAF afforded the *N*-unsubstituted 4-phenyl-1,4-dihydropyridine <1998TL9275>. An improved preparation of *N*-(trimethylsilyl)pyridinium triflate, *N*-(triphenylsilyl)pyridinium triflate, and *N*-(triisopropylsilyl)pyridinium triflate involves the reaction of the corresponding allyl silanes with triflic acid followed by pyridine <1997S744>.

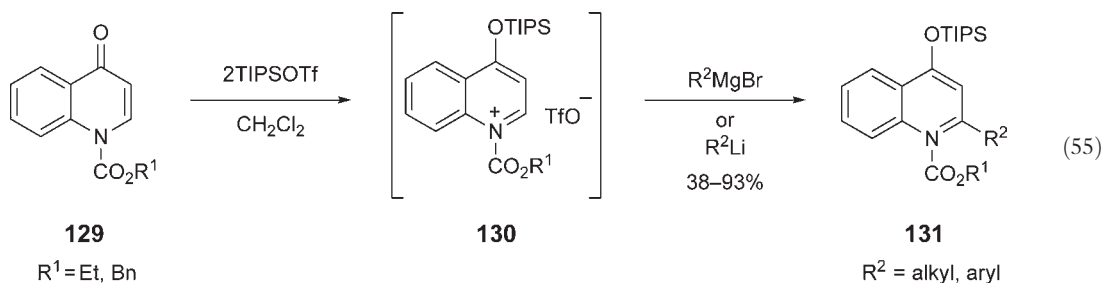
N-Acylpyridinium salts are more reactive than the *N*-alkyl derivatives and afford more stable dihydropyridine products on addition of nucleophiles. Organocuprates are utilized for entry into 2-alkynyl-substituted quinoline systems (Equation 53) <2005TL8905>. They have the advantage of superior selectivity over Grignard reagents, which yield a mixture of the 2- and 4-substituted products. The reaction has been expanded to include isoquinolines and pyridines.



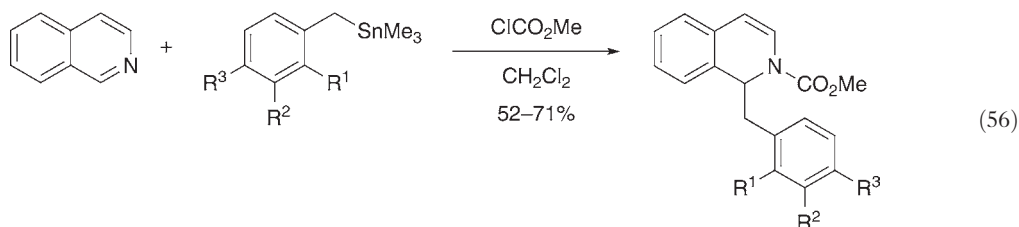
The popular activation method of pyridine rings by reaction with chloroformates was not observed for reaction of *N*-acylated quinoline with allyltrimethylsilane until a catalytic amount of silver triflate was added. It was shown that the triflate counterion increases the electrophilicity of the *N*-acylquinolinium salt (Equation 54) <1997TL403, 2001T109>.

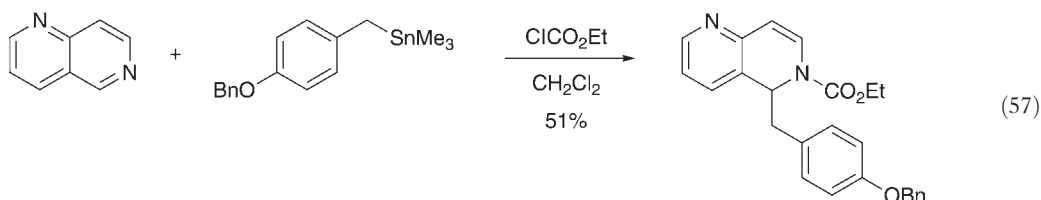


The 4-silyloxyquinolinium triflates **130** are prepared *in situ* by reaction of *N*-acyl-4-quinolones **129** with TIPSOTf (TIPS = 1,1,3,3-tetraisopropylidisiloxane). Addition of various Grignard or lithium reagents provide the C-2 adducts **131** (Equation 55) <1997SL313>.



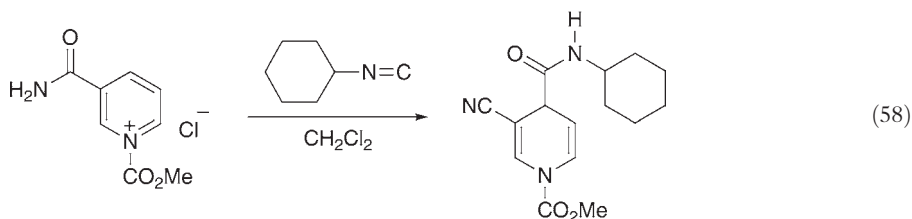
Benzyltrimethylstannanes react with isoquinolines and 1,6-naphthyridines in the presence of a chloroformate to afford 1-benzyl-1,2-dihydro derivatives (Equations 56 and 57) <1998TL1721, 2000TL8053>. An allyl group can be introduced at C-1 of isoquinoline using a mixture of phenyl chloroformate, indium, and allyl bromide <2004OBC2170>. Yamaguchi and co-workers previously reported the addition of benzylstannanes to *N*-acylpyridinium salts <1986TL211>. The CuCN·2LiBr-catalyzed organozinc addition to *N*-acylpyridinium salts was studied. Both dialkylzinc reagents and alkylzinc halides almost exclusively gave the C-4 addition products, with only trace amounts of the 2-substituted isomers <2003EJO4586>.



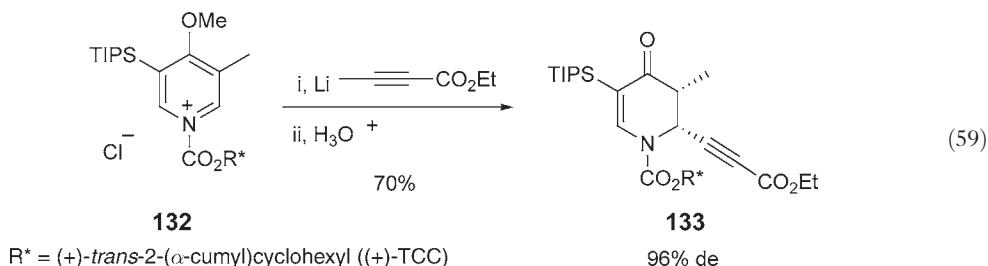


The reaction of pyridines with triflic anhydride affords *N*-trifluoromethylsulfonylpyridinium triflates *in situ*. These reactive pyridinium salts add phosphines, phosphates, ketones (via the enol), and electron-rich aromatics. The 1,4-dihydropyridine intermediates can be converted to 4-substituted pyridines on treatment with base [1998S195](#), [1999S2071](#), [2001OL2807](#), [2005OL5535](#). Reaction of *N*-fluoropyridinium fluoride generated *in situ* with a series of isonitriles led to the formation of the corresponding picolinamides in good yields. A similar reaction sequence for quinoline and isoquinoline afforded the α -acylated products at C-2 and C-1, respectively [2005TL2279](#).

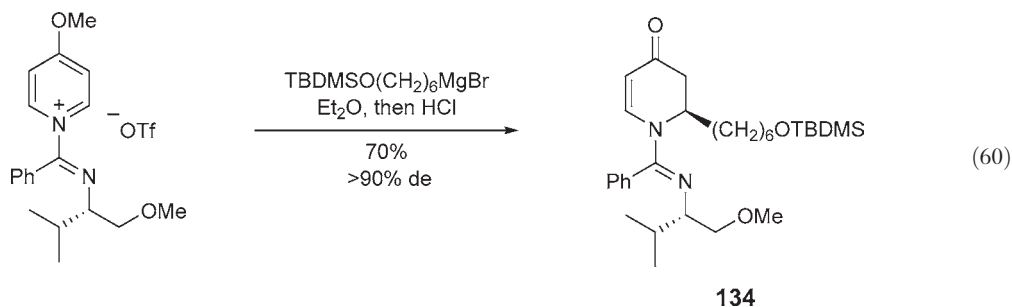
With *N*-alkyl- or *N*-acylpyridinium salts, the addition of isonitriles takes place efficiently when a carboxamido group is present in the 3-position. The outcome of the reaction involves the stabilization of the nitrilium intermediates by the amide, which suffers a mild dehydration providing 3-cyano-4-carbamoyl-1,4-dihydropyridines. This method also works with the corresponding *N*-acylquinolinium and *N*-acylisoquinolinium salts (Equation 58) [2006OL5789](#), [2004JOC3550](#).



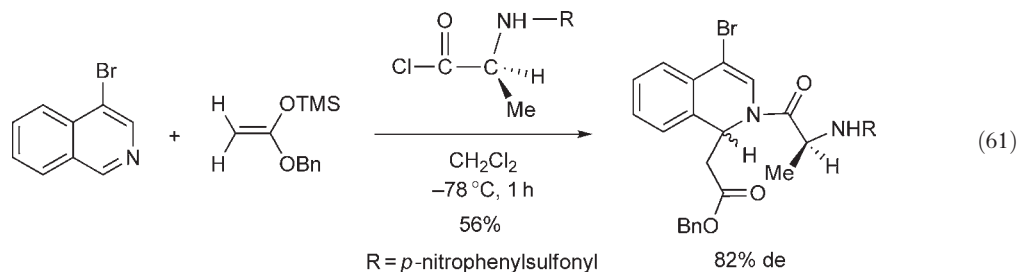
Asymmetric synthesis using *N*-acyl salts of pyridine and derivatives continues to be developed. The chiral *N*-acylpyridinium salt **132** reacts with lithiated ethyl propiolate to provide the diastereomer **133** in 70% yield and >96% de (Equation 59) [2001OL469](#). The stereochemistry at C-3 is presumably due to axial protonation of the intermediate enol ether during workup.



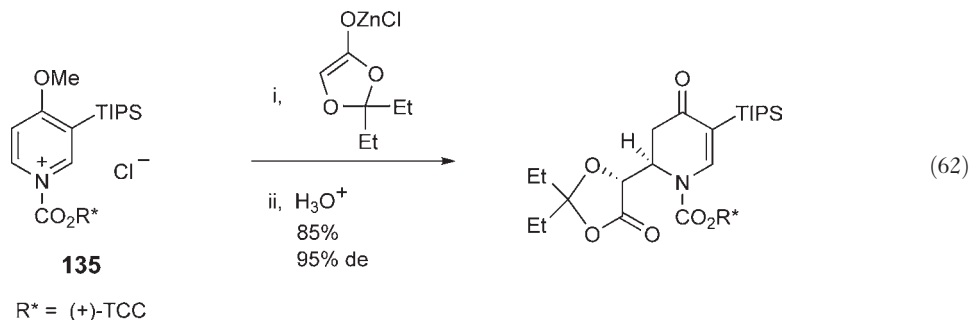
A related example is shown by 4-methoxypyridine activated by a chiral amidine auxiliary, which on attack by a Grignard reagent provides dihydropyridone **134** (Equation 60) [2006OL2985](#). Charette and co-workers have nicely developed this methodology to include the asymmetric syntheses of various substituted piperidines and natural products [2005OL2747](#), [2005JOC2368](#), [2005OL5773](#).



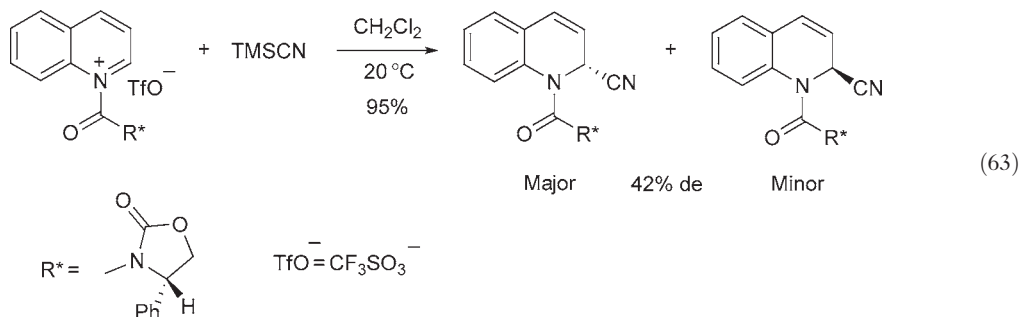
With an amino acid-derived chiral auxiliary employed in the chloroformate, reaction of silyl enol ethers with isoquinolinium salts showed not only regioselectivity, but some stereoselectivity as well (Equation 61) <1999SL1154>. The addition of ketene silyl acetals to an *N*-acylpyridinium salt containing a chiral 2,2-dimethyloxazolidine at C-3 gave 1,4-dihydropyridines with excellent stereoselectivity <2002JA8184>.



The diastereoselective addition of prochiral metallo enolates to chiral *N*-acylpyridinium salt **135** has been studied <1999JA2651>. Addition of the zinc enolate of 2,2-diethyl-1,3-dioxolan-4-one to a pyridine activated by a chiral chloroformate proceeded in 85% yield and with >95% de. The fixed stereochemistry of the cyclic enolate is a determining factor in the resulting relative configuration of the two new chiral centers. An acyclic transition state is proposed (Equation 62) <2004JOC5219>. Chiral *N*-acylpyridinium salt **135** has been used as starting material for numerous asymmetric syntheses of natural products <2002J(P1)1141, 2002MI870, 2004JOC5219, 2005OL5227>. Certain indolyl and pyrrolyl Grignard reagents add to 1-acyl salts of 4-methoxy-3-(triisopropylsilyl)pyridine to give the corresponding 1-acyl-2-heteroaryl-2,3-dihydro-4-pyridones in good to high yield <2004JOC2863>. The addition of triphenylsilyl- or dimethylphenylsilylmagnesium bromide to chiral *N*-acyl-4-methoxypyridinium salts affords C-2-silylated 2,3-dihydro-4-pyridones in good yield and high diastereoselectivity <2002H(58)505>.



A chiral auxiliary-mediated Reissert reaction has been demonstrated. Though the diastereomeric ratios are not as high as hoped, the conditions are simple and the products are easily separated by flash chromatography (Equation 63) <2005TL2983>. A catalytic version of the asymmetric Reissert reaction with quinolines, isoquinolines, and pyridines has been developed by Shibasaki and co-workers <2005PAC2047, 2004JA11808>.

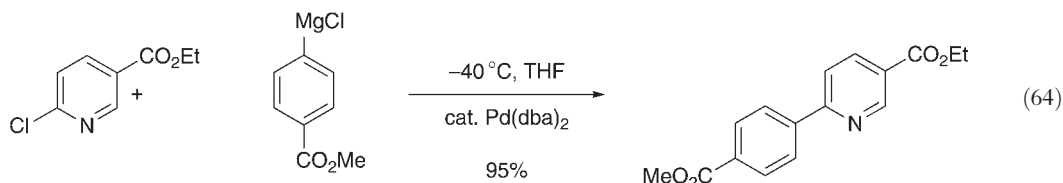


7.02.4.2.3 Cross-coupling reactions

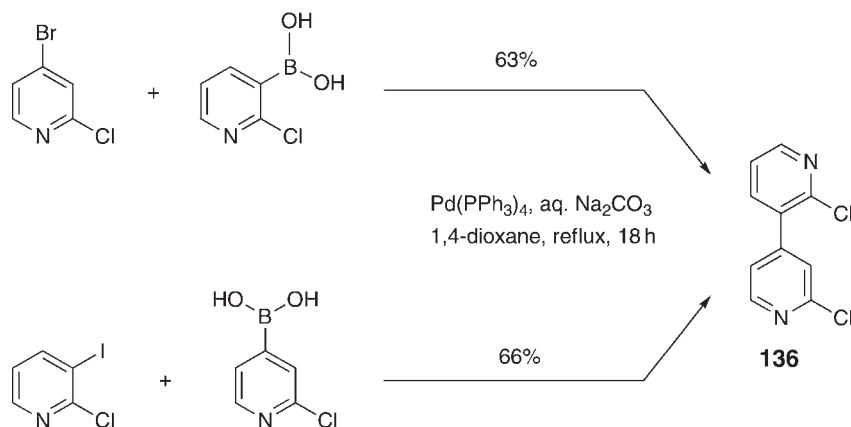
Transition metal-catalyzed cross-coupling methods are increasingly important for the synthesis of substituted pyridines and their benzo derivatives. The popular Negishi, Kumada, Suzuki, Stille, Heck, Hiyama, Sonogashira, and Kharasch cross-couplings have been utilized to prepare numerous azine derivatives. This subject has been extensively reviewed <1995CRV2457, 1998T263, B-2000MI183, 2002T9633, 2002J(P1)1921, 2002COR507,

2002JOM58, 2002AGE4176, 2003COR629, 2004S2419, 2004CCR2337, 2004CRV2667, B-2004MI41, B-2004MI125, B-2004MI163, B-2004MI815, 2005T2245, 2005CJC266, 2005CL624, 2005AGE4442, 2005S2989, 2006CEJ4954, 2006THC(1)155>; only selected examples are given below.

The Negishi and Kumada cross-coupling reactions have been carried out on 3,5- and 2,6-dibromopyridine. Monosubstitution can be achieved in good yield <2001TL7787, 2001TL5717, 2006OL5853>. Several substituted pyridyl amino acids have been prepared by palladium-catalyzed cross-coupling of serine-derived organozinc reagents with various halopyridines <2003OBC4254>. Polyfunctional pyridines can be prepared by Pd(0)-catalyzed cross-coupling of functionalized arylmagnesium halides with chloro- or bromopyridines at temperatures as low as -40°C (Equation 64) <2001TL5717>. *N,N*-Diethyl pyridyl *O*-sulfamates were found to be effective cross-coupling partners for Kumada–Corriu reactions <2005OL2519>.

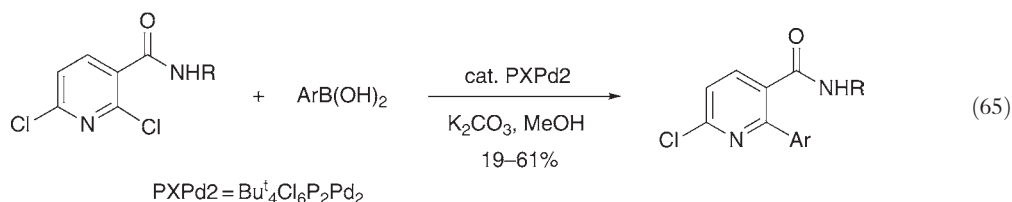


In the Suzuki reactions of pyridine systems, the heterocycle can be used both as the electrophile and the organoborate nucleophile <B-2000MI183, 2003JOC3352, 2003JOC7379, 2005TL3573>. Selectivity is such that either coupling partner can carry a chlorine atom on the pyridine ring as is demonstrated in the formation of bipyridyl **136** by two different routes (Scheme 23) <2003JOC10178>. Suzuki cross-coupling reactions of 2,4-dibromopyridine are regioselective at the 2-position with several alkenyl(aryl)boronic acids affording 2-substituted-4-bromopyridines <2006T11063>.

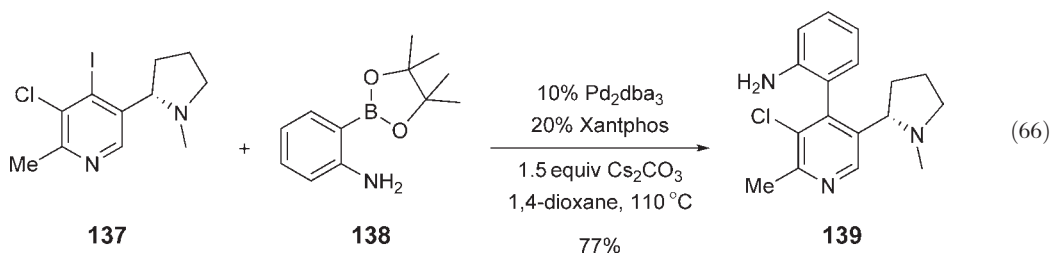


Scheme 23

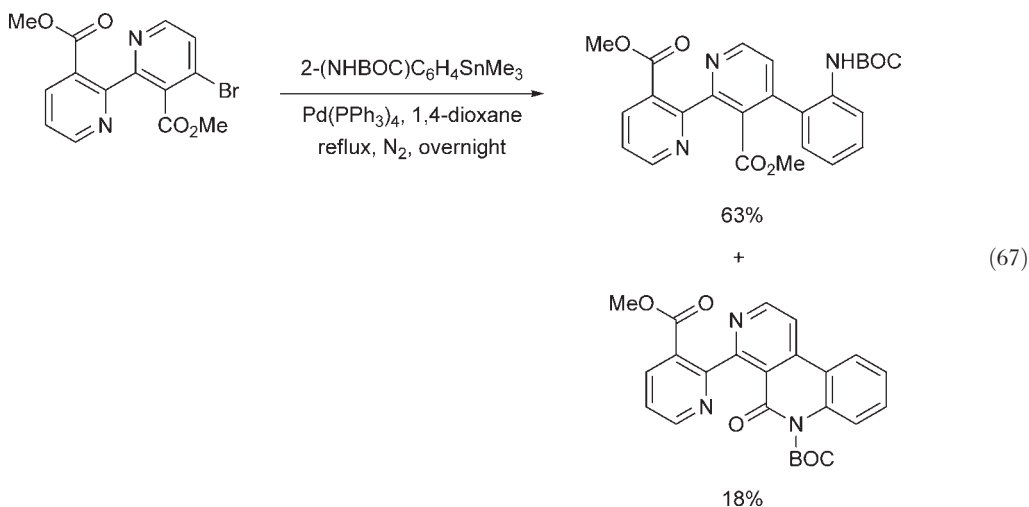
A short synthesis of 2-aryl-6-chloronicotinamides via regioselective Suzuki coupling of 2,6-dichloronicotinamide with aryl boronic acids was reported. Regioselectivity was attributed to chelation of the palladium(0) species to the carbonyl of the amide group (Equation 65) <2003OL3131>. The Suzuki coupling reaction has been applied to the preparation of small combinatorial libraries using 5-bromonicotinic acid as a scaffold on three different types of solid support <2005TL581>. Alkyl groups can be introduced by the *B*-alkyl Suzuki–Miyaura reaction using an alkyl borane and a pyridyl halide <2001AGE4544, 2004TL6125>. Methylation can be carried out using methylboron reagents such as methylboronic acid, methylboranes derived from 9-borabicyclo[3.3.1]nonane (9-BBN), and trimethylboroxine <2000TL6237, 2006OL3549>.



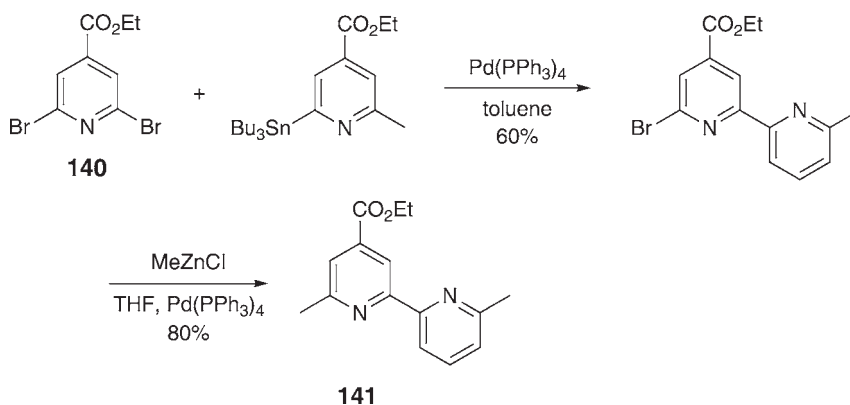
Suzuki cross-coupling with 2,3-dibromoquinoline shows preferential reaction at C-2 providing 2-aryl-3-bromoquinolines <1999SC3959>. Palladium-catalyzed coupling of arylboronic acids to 1,3-dichloroisoquinoline takes place exclusively at the 1-position to give 1-aryl-3-chloroisoquinolines <1997J(P1)927>. The cross-coupling at C-4 of 4-iodonicotine derivative **137** and amino boronate ester **138** afforded **139** which is an intermediate in a short synthesis of (*S*)-brevicolline (Equation 66) <2006OL3549>.



The Stille reaction is very tolerant of most functional groups, making it effective for the preparation of complex pyridine derivatives (Equation 67) <2004EJO1891>. It is possible to generate the organostannane *in situ* through the palladium-mediated reaction of a pyridyl halide or triflate with hexamethylditin <1995TL9085, 2001JOC1500>.

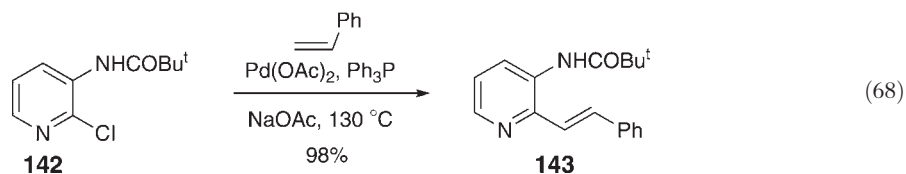


The dibromopyridine **140** underwent successive Stille and Negishi cross-couplings to afford bipyridine **141** (Scheme 24) <2002S1564>. Several 6-heteroaryl-3-methylpyridines were prepared from 3-picoline by a one-pot lithiation–stannylation–Stille reaction sequence <2001TL1879>. The Stille cross-coupling reaction has been used profusely for the preparation of substituted pyridines, bipyridines, poly(bipyridines), and terpyridines <2004CRV2667>. Conditions have been found for the Stille and Heck cross-couplings of 4-chloroquinolines <2003JOC7077, 2003JOC7551>.

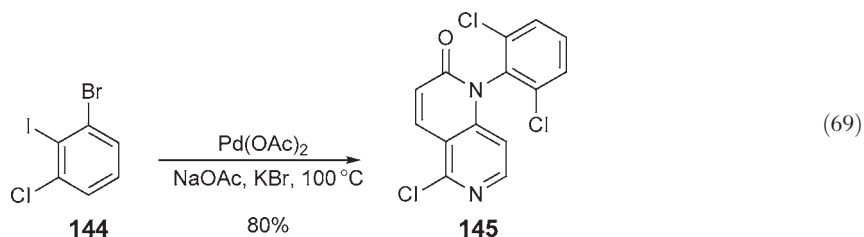


Scheme 24

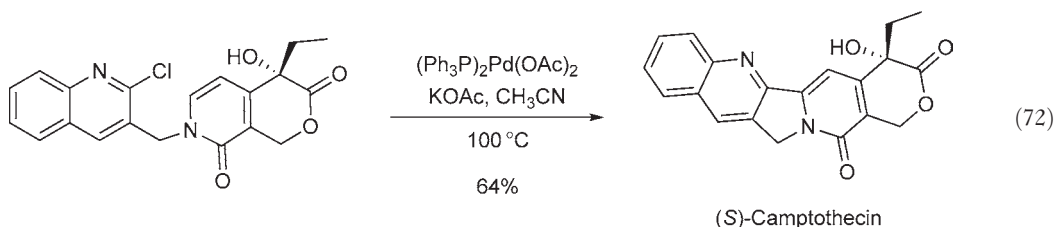
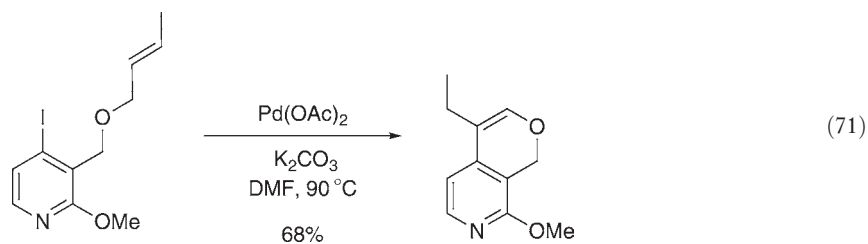
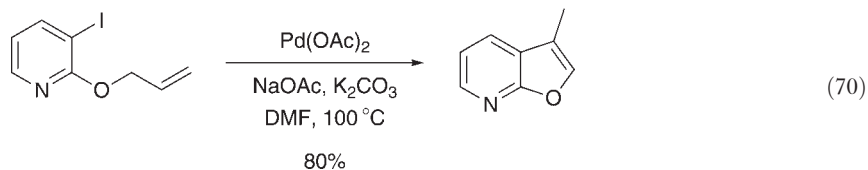
The inter- and intramolecular Heck reactions provide other routes to substituted pyridines <B-2000MI183>. Although electron-deficient 2-bromopyridines are resistant to substitution under Heck conditions, the aminopyridine **142** affords a high yield of the adduct **143** (Equation 68) <1998T6311>. The intermolecular Heck reaction of a 3-pyridyltriflate with ethyl acrylate is accelerated by LiCl <1999SL804>. An efficient Heck vinylation of 3-substituted-2-bromo-6-methylpyridines with methyl acrylate has been developed <2005T4569>.



A regioselective tandem Heck-lactamization was developed for a multi-kilogram preparation of drug intermediate **145** from trihalopyridine **144** (Equation 69) <2006JOC8602>.



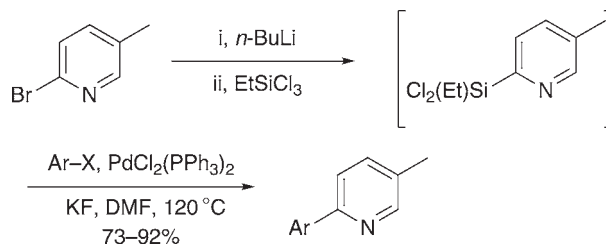
The intramolecular Heck reaction is a versatile method for the formation of pyridine-containing heterocycles, synthetic intermediates, and natural products <2004COR781, 2003CRV2945, 1999H(51)1957>. A few examples are depicted in Equations (70)–(72) <1996H(43)1641, 1999JOC3461, 2001OL4255>.



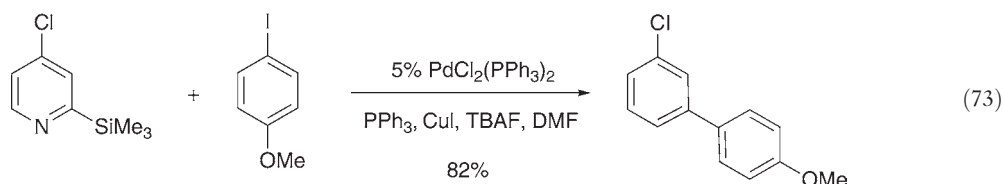
The Hiyama cross-coupling of organosilanes is attractive as the intermediates are often easy to prepare and the silicon by-products are environmentally benign. A one-pot synthesis of 2-aryl-3-methylpyridines from 2-bromo-3-methylpyridine was developed (Scheme 25) <2003JOM58>. Both 2- and 3-bromopyridine cross-couple with phenyltrimethoxysilane to afford the corresponding phenylpyridines in good yield <1999OL2137>.

Gros and co-workers have shown that the presence of electron-withdrawing substituents on the pyridine ring of 2-trimethylsilylpyridines provides sufficient activation to allow them to be useful partners in the Hiyama cross-coupling.

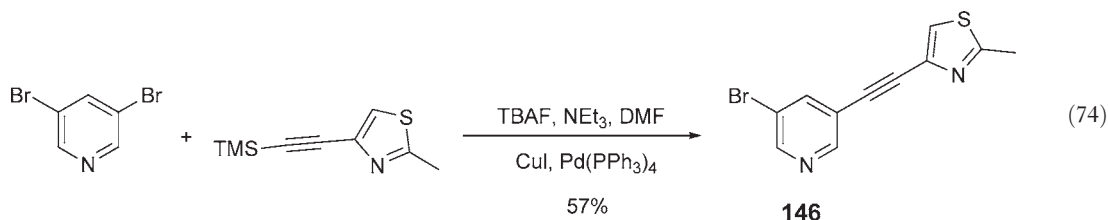
The reaction can be performed at room temperature with various heteroaryl halides (Equation 73) <2005OL697>. It was found that (2-pyridyl)allyldimethylsilanes are pyridyl-transfer reagents in palladium-catalyzed coupling reactions of aryl iodides in the presence of silver oxide as an activator <2006OL729>.



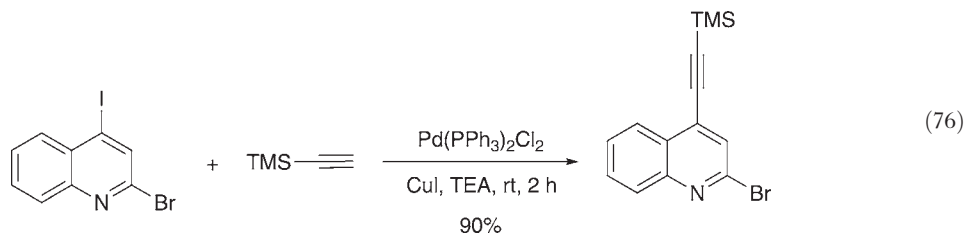
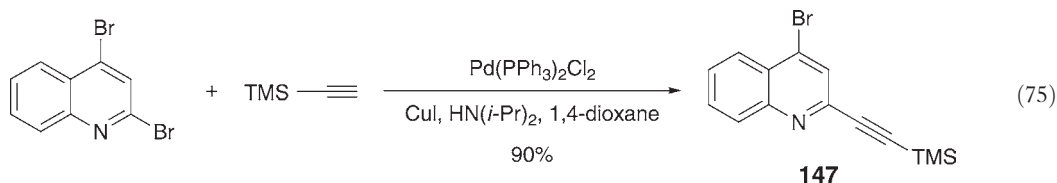
Scheme 25



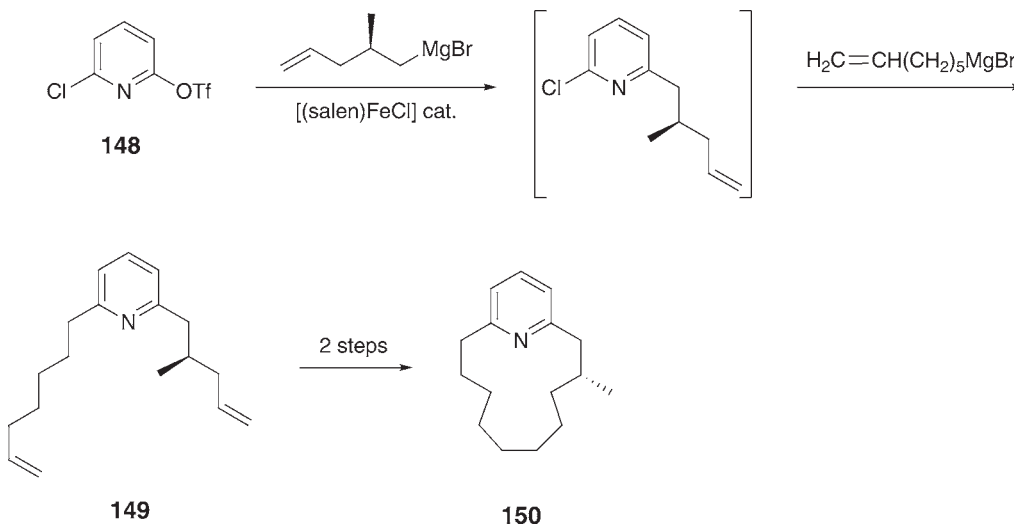
The Sonogashira reaction has been routinely used to prepare alkynylpyridine derivatives <B-2000MI183, 1997J(P1)709, 1998BML2169, 2005OL1793>. With dihalopyridines, bisalkynylation is easily achieved using excess alkyne. There have been several examples of regioselective monoacetylenation of polyhalopyridines with the α -position being preferentially substituted in most cases <2005T2245>. A modification of the Sonogashira reaction starting with a TMS-substituted alkyne was used to prepare pyridine derivative **146** (Equation 74) <2003BML351>. A copper-free Sonogashira alkynylation of 3-amino-2-chloropyridines was used in an efficient azaindole synthesis <2006OL3307>.



The Sonogashira coupling reaction of 2,4-dibromoquinoline with trimethylsilylacetylene is regioselective for the 2-position affording quinoline derivative **147** in high yield (Equation 75) <2003JOC3736>. The regioselectivity is reversed with 2-bromo-4-iodoquinoline due to the greater reactivity of the aryl-iodide bond toward oxidative addition with palladium (Equation 76) <2005TL6697>. Conditions were found for the regioselective Sonogashira alkynylation of 4-chloro-6-iodo(bromo)quinolines to afford 6-alkyl-4-chloroquinolines in high yields <2004RCB189>.



There have been several advances in iron-catalyzed cross-coupling reactions [<2005CL624>](#). This method works very well for the coupling of alkyl Grignard reagents to electron-deficient aryl- and heteroaryl chlorides and tosylates as well as electron-rich heteroaryl triflates. In their synthesis of muscopyridine **150**, Fürstner and Leitner prepared intermediate **149** from pyridyl triflate **148** by the iron-catalyzed sequential addition of two different Grignard reagents (**Scheme 26**) [<2003AGE308>](#).



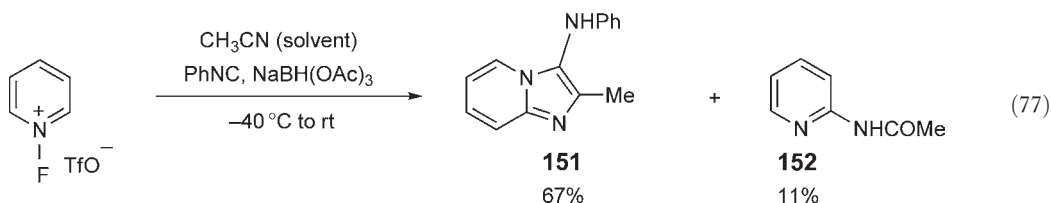
Scheme 26

Stille and Suzuki couplings of bromopyridines are effective in the synthesis of various bipyridines and terpyridines [<2006TL3471>](#). By use of various palladium-catalyzed coupling reactions, 2,6-dichloro-4-iodopyridine can be converted to a number of 2,4,6-trisubstituted pyridines [<2001OL4263>](#). Palladium-catalyzed cross-couplings can be carried out on halopyridine *N*-oxides and halo-*N*-alkylpyridinium salts in good yields [<2005SOS\(15\)11>](#). Bipyridines are conveniently prepared by palladium- or nickel-catalyzed homocoupling of halopyridines [<1998T13793, 1999SC3341, 2005T4289>](#).

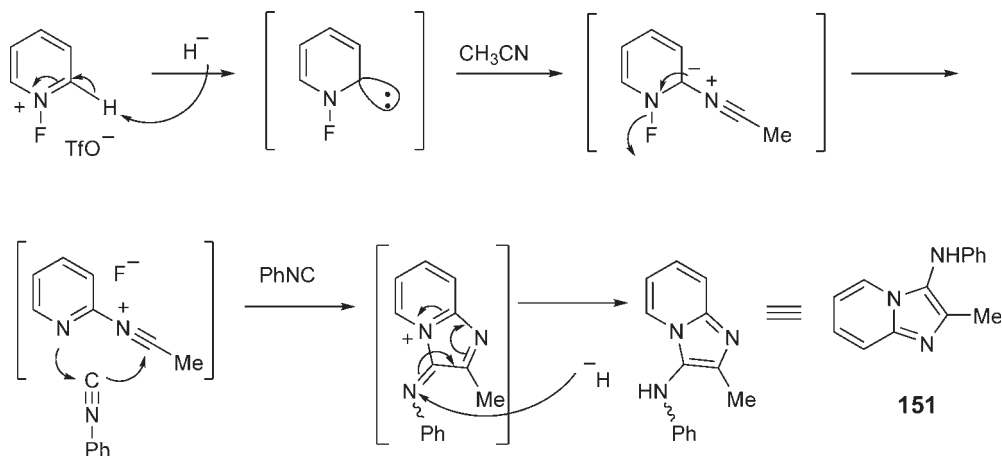
7.02.4.3 Heteroatom Nucleophiles

7.02.4.3.1 Nucleophilic addition

Heteroatom nucleophiles react with pyridine in its neutral or activated pyridinium form. When the nitrogen has been fluorinated, the product of nitrile/isonitrile addition is an imidazopyridine [<2005TL4487>](#) (**Equation 77**).

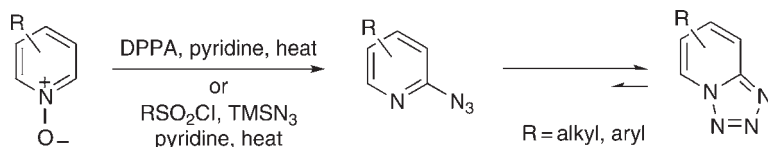


The proposed mechanism for formation of **151** is shown in (**Scheme 27**). Proton abstraction by the hydride base from the activated 2-position of the *N*-fluoropyridinium triflate yields a highly reactive carbene which undergoes attack by the acetonitrile solvent. The resulting nitrilium ylide eliminates fluoride and subsequently adds the isocyanide with cyclization. Finally, reduction by the hydride reagent and aromatization provide the imidazopyridine **151**. The undesired amide **152** is a product of hydrolysis of the intermediate nitrilium compound.



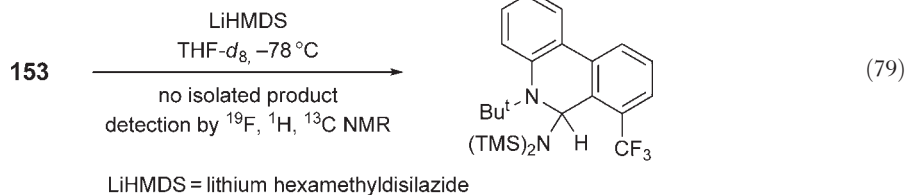
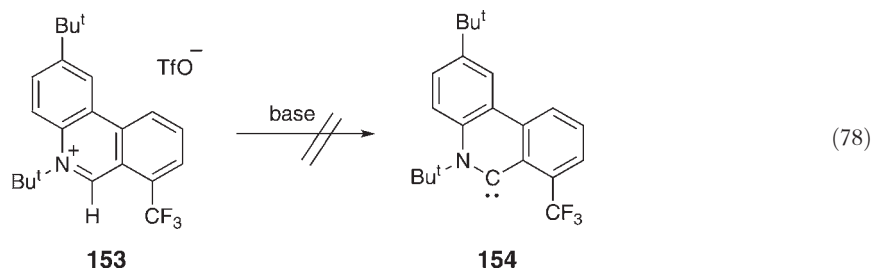
Scheme 27

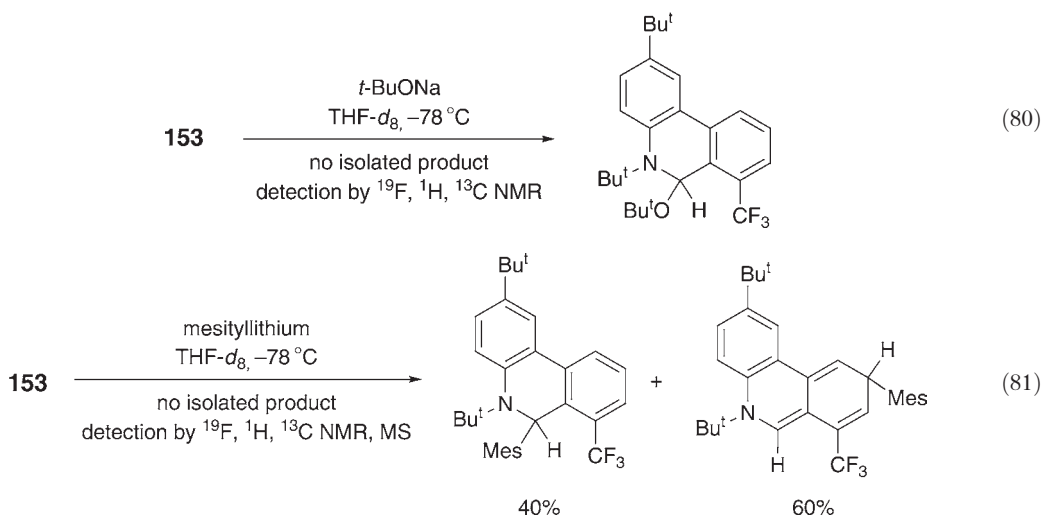
Pyridine *N*-oxides are converted to tetrazolo[1,5-*a*]pyridines in good to excellent yield by heating a pyridine and sulfonyl or phosphoryl azide in the absence of solvent (Scheme 28) <2006JOC9540>.



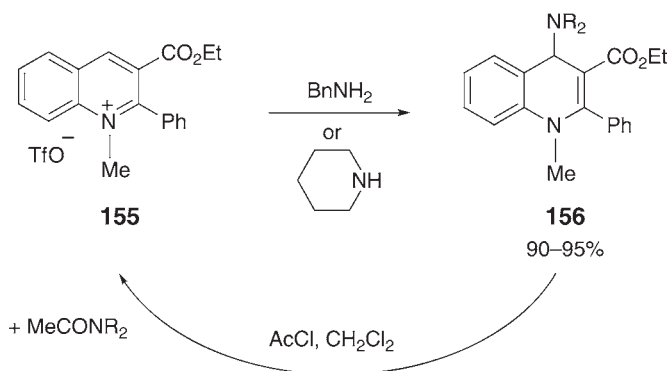
Scheme 28

An attempt to generate an amino-aryl carbene **154** from the alkylated phenanthridinium salt **153** (Equation 78) <2006TL531> was unsuccessful due to steric interactions. The actual reaction with a variety of strong, sterically hindered bases/nucleophiles is shown (Equations 79–81). The mesityllithium products proved that a carbene intermediate is not possible. Unlike *t*-butyl alcohol and hexamethyldisilazane, trimethylbenzene, the conjugate acid of mesityllithium, is not prone to carbene insertion reactions. Electronically this is explained by the planar nature of **153** which serves to lower the lowest unoccupied molecular orbital (LUMO) energy of the iminium moiety.



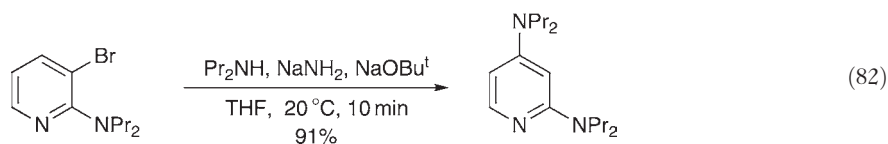


Under biphasic conditions, the reaction of benzylamine or piperidine with the quinolinium salt **155** gave adducts **156** in high yields. Addition of the amine nucleophile takes place exclusively at the C-4 position of the quinolinium salt. On treatment of **156** with acetyl chloride, the corresponding carboxamides are produced in near quantitative yields along with the regeneration of quinolinium salt **155** (Scheme 29) <2004TA3919>. Intramolecular attack of a C-3-tethered amine onto pyridinium salts provides a novel route to nitrogen heterocycles via a ring-opening mechanism <2006AGE7803>. An oxidative double phosphorylation of *N*-alkylpyridinium salts was effected through the use of dialkyl phosphates, DDQ, and triethylamine. Moderate to good yields of 2,6-diphosphonylated-1,2-dihydropyridines were obtained in a one-pot reaction involving tandem nucleophilic addition/oxidation processes <2000OL1533>.

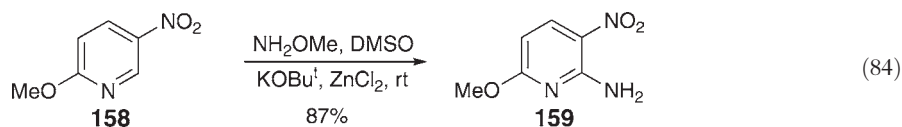
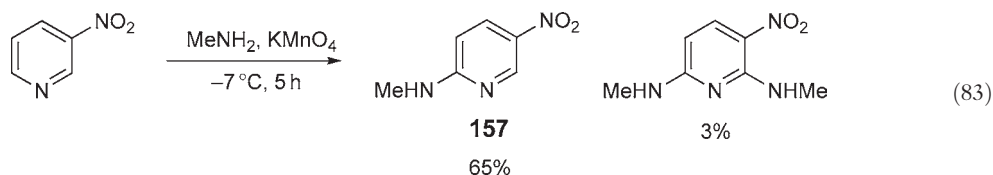


Scheme 29

The base combination of sodium amide and sodium *tert*-butoxide in tetrahydrofuran (THF) containing a secondary amine converts halopyridines into aminopyridines via a pyridyne intermediate (Equation 82) <1997H(45)2113>. The regioselectivity varies depending upon the position and type of pyridine substituents.

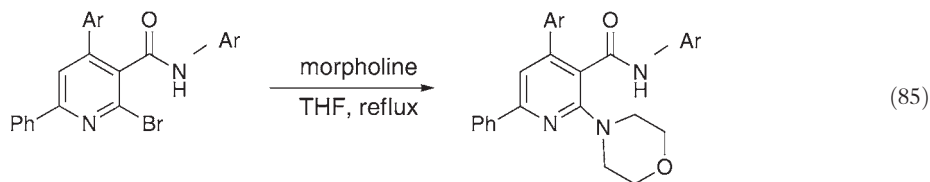


Amination of 3-nitropyridine with potassium permanganate in liquid ammonia, or an aliphatic amine, affords the 2-amino-pyridine **157** (Equation 83) <1999JPR75>. The nitropyridine **158** is aminated at C-6 with *O*-methylhydroxylamine in the presence of ZnCl_2 to give **159** in high yield (Equation 84) <1998CC1519>.



7.02.4.3.2 Nucleophilic substitution

Substitution reactions of halopyridines with heteroatom nucleophiles have been commonly used for the preparation of numerous pyridine derivatives. A number of monographs and review articles have covered this useful chemistry <1984CHEC(2)220, 1996CHEC-II(5)78, 1996CHEC-II(5)98, 2005SOS(15)11, 1999AHC295, 1994HOU(E7b)286>. The order of reactivity is position 4 > 2 > 3. The halide in 2- and 4-halopyridines is quite easily substituted by nucleophiles such as hydrazine, thiolate anions, and alkoxides. Reaction at the 3-position is more difficult, but use of a higher temperature in DMSO or DMF often effects substitution <1985JHC1419, 1990JOC69, 2004USP6706844, 2006T6000>. The substitution reactions are more facile if an activating group is present on the ring. For example, treatment of 2-bromonicotinamides with secondary amines in refluxing THF affords the corresponding 2-amino derivatives in good yields (Equation 85) <2006BMC4466>. The reactions of halopyridines with sulfur and oxygen nucleophiles under microwave irradiation afford high yields of substitution products <2002T4931>.

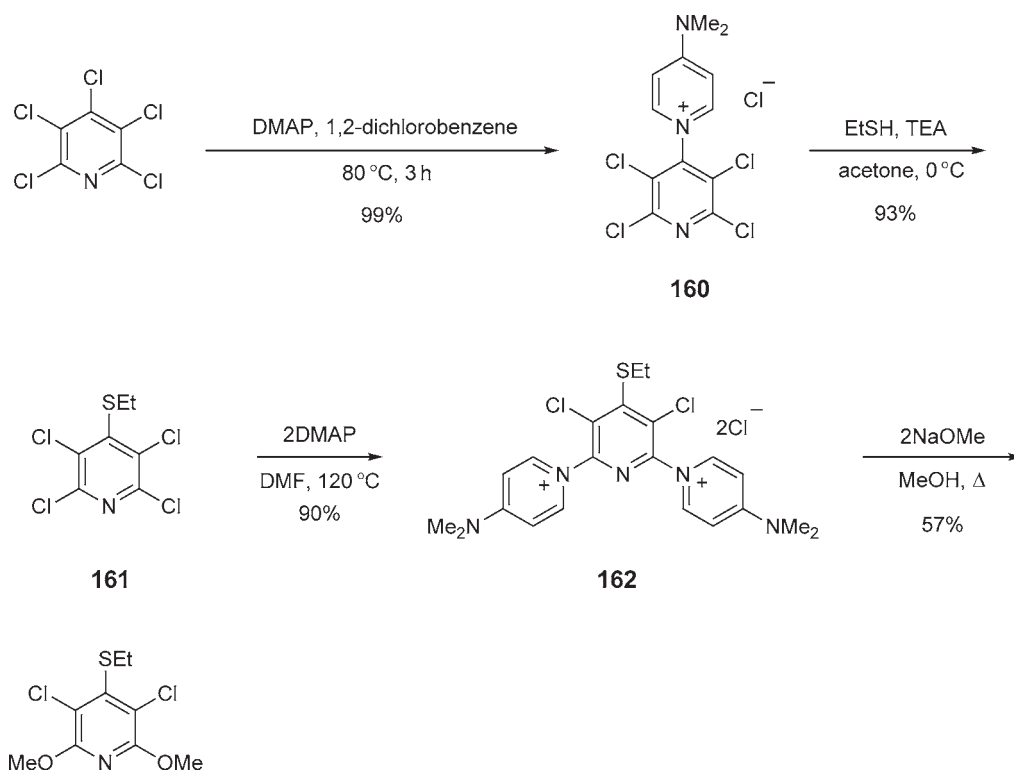


The heteroarenium salts **160** and **162** are readily available in quantitative yield by treating pentachloropyridine, or tetrachloropyridine **161**, and DMAP in 1,2-dichlorobenzene at 80 °C. Activation of chloropyridines by heteroarenium substituents allows sequential substitutions by O-, N-, and S-nucleophiles (Scheme 30) <2005ZNB683, 2006S3987, 2006T1667, 2006T6893>.

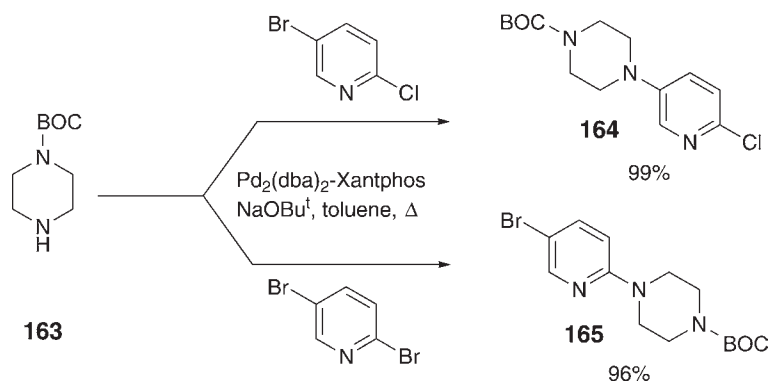
7.02.4.3.3 Metal-catalyzed coupling reactions

The palladium-catalyzed amination of halopyridines has been developed into a useful method for the preparation of various aminopyridine derivatives <2002AGE4176, 2002TCC131, B-2000MI183, 1996JOC7240, 1997SL329, 1999T11399>. Excellent regioselectivity can be obtained on amination of polyhalopyridines. Reaction of piperazine derivative **163** and 5-bromo-2-chloropyridine catalyzed by a palladium–Xantphos complex predominantly gives the 5-amino-2-chloropyridine **164** in high yield. The corresponding amination of 2,5-dibromopyridine exclusively affords the 2-amino-5-bromopyridine **165** (Scheme 31) <2003OL4611>. Palladium-catalyzed cross-coupling reactions of bromopyridines and amines can be efficiently performed using KF-alumina in place of strong bases such as sodium *tert*-butoxide <2002TL7967>. Benzophenone imine and allylamine can be used as ammonia equivalents in the C–N coupling reactions of halopyridines <1996JOC7240, 1998TL1313>. The synthesis of macrocycles containing two pyridine and two polyamine fragments was carried out by the Pd-catalyzed amination of 2,6-dihalopyridines <2005HCA1983, 2006TL2691>.

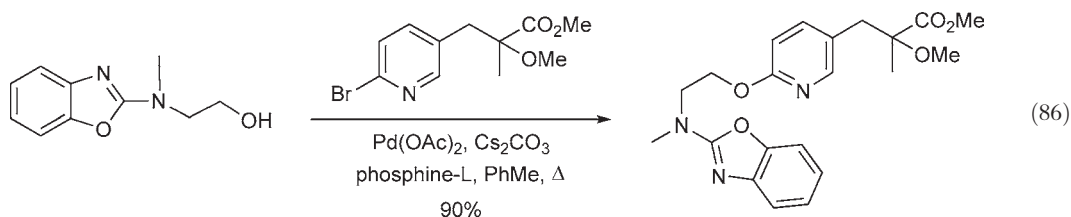
Intermolecular palladium-catalyzed coupling of halopyridines and alcohols is a mild and versatile method for the preparation of pyridine ethers <2002AGE4176>. Complex molecules containing heterocycles and sensitive functionality can be prepared in high yield (Equation 86) <2006TL5333>. A general palladium-catalyzed coupling of aryl bromides and thiols is also effective in the pyridine series <2004OL4587>.



Scheme 30



Scheme 31



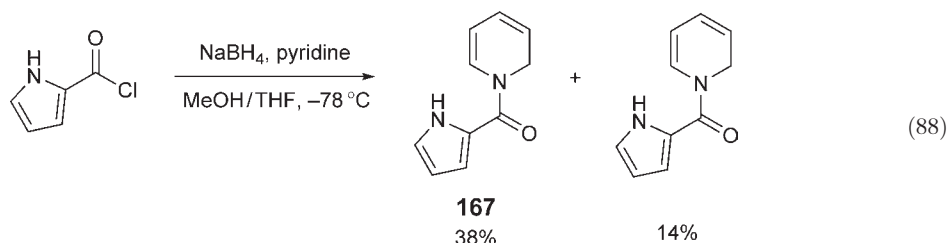
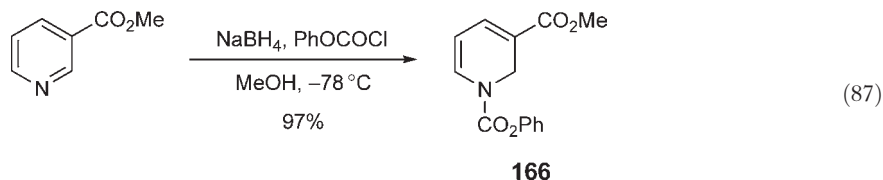
The copper-mediated C(aryl)–O, C(aryl)–N, and C(aryl)–S bond formation can be used as an alternative to many palladium-catalyzed transformations <2003AGE5400, 2006T4435>.

7.02.4.4 Chemical Reduction

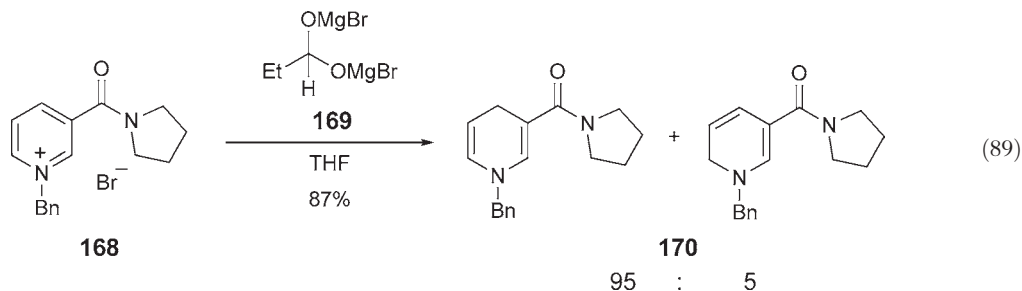
Chemical reduction of pyridines can be achieved with hydride, dithionite, dissolving metal reagents, or hydrogenation. The pyridine nucleus can be activated to reduction by conversion to a pyridinium species <1984CHEC(2)165, 1996CHEC-II(5)80>.

7.02.4.4.1 Hydride reduction

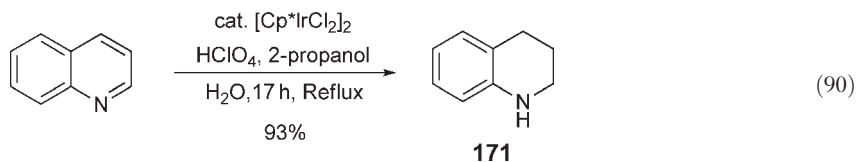
The methyl ester of nicotinic acid is selectively reduced to the 1,2-dihydropyridine **166** in a vast improvement over previous methods (Equation 87) <2001OL201>. Low temperatures and choice of pyridinium-activating agent are crucial to avoid 1,4-dihydropyridine formation. A modification of Fowler's dihydropyridine synthesis was used to prepare the *N*-acyldihydropyridine **167** (Equation 88) <2006OL2961>.



Kanomata *et al.* carried out the reduction of *N*-alkylpyridinium salt **168** via hydride transfer from diolate **169** to afford mainly the 1,4-dihydropyridine **170** (Equation 89) <1998AGE1410>.



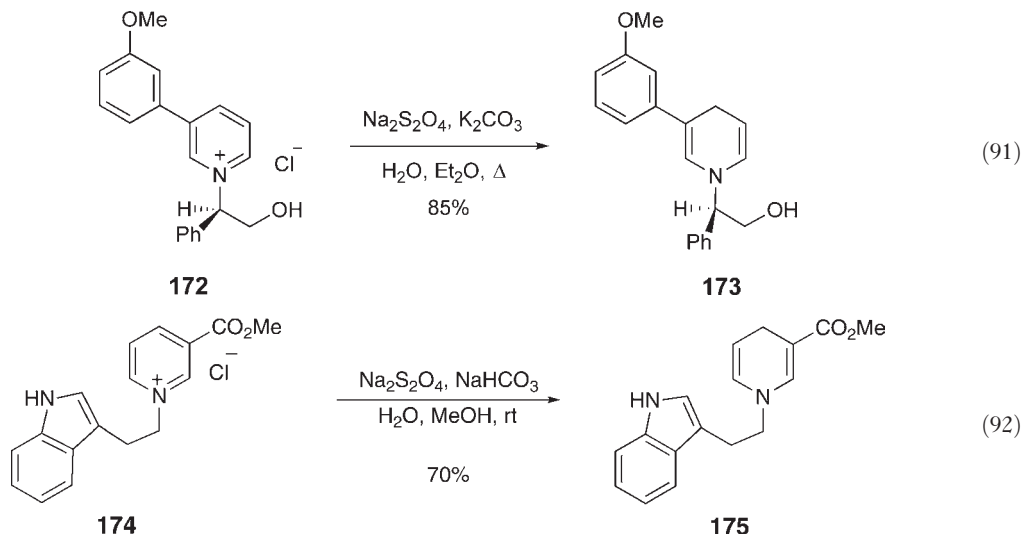
Hydride transfer by isopropanol to quinoline is catalyzed by a pentamethylcyclopentadienyl (Cp*) iridium complex, resulting in regioselective reduction to 1,2,3,4-tetrahydroquinoline **171**. The yield is optimized by use of acid, and *N*-alkylation by the isopropyl group is eliminated by including water (Equation 90) <2004TL3215>. A possible mechanism is thought to involve iridium hydride as the reducing agent.



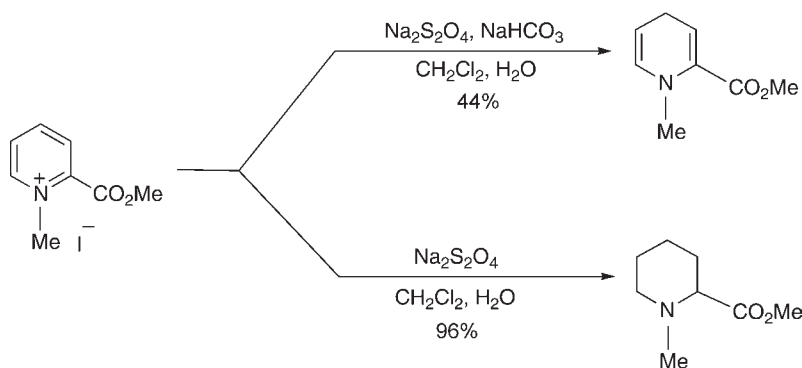
7.02.4.4.2 Dithionite reduction

Sodium dithionite reduction of pyridinium salts, usually substituted with electron-withdrawing groups in the 3- or 3,5-positions, chiefly affords the corresponding 1,4-dihydropyridines. The regioselectivity of formation of the dithionite adducts and mechanisms of decomposition have been studied <2005T10331, 2000TL1235>. The sodium

dithionite reduction of pyridinium salts **172** and **174** gave the 1,4-dihydropyridines **173** and **175**, respectively (Equations 91 and 92) <1997JOC729, 2002T7869>.



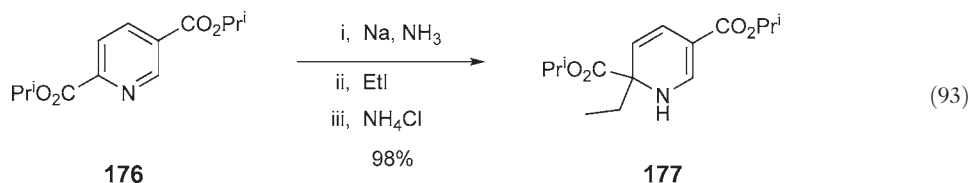
Lavilla and co-workers developed a dithionite reduction of α -substituted *N*-alkylpyridinium salts to afford the corresponding 1,4-dihydropyridines or piperidines. In the absence of NaHCO_3 , full reduction occurred to give the piperidine derivatives in high yield (Scheme 32) <2005TL3513>.



Scheme 32

7.02.4.4.3 With free electrons

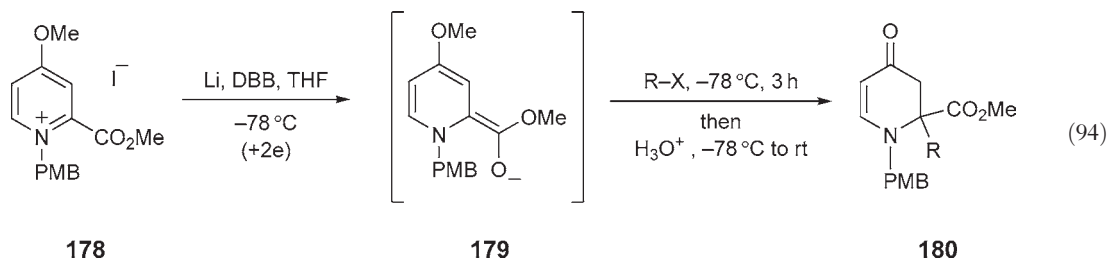
Pyridines are readily reduced under dissolving metal conditions to provide dihydro or perhydro derivatives <B-2000MI217, 1996CHEC-II(5)82>. Donohoe *et al.* have examined the partial reduction of a series of pyridines containing electron-withdrawing groups. Conditions were found such that the intermediate anion from the reduction of **176** could be alkylated with electrophiles to afford 1,2-dihydropyridines **177** containing a quaternary center at C-2 (Equation 93) <2001J(P1)1435>.



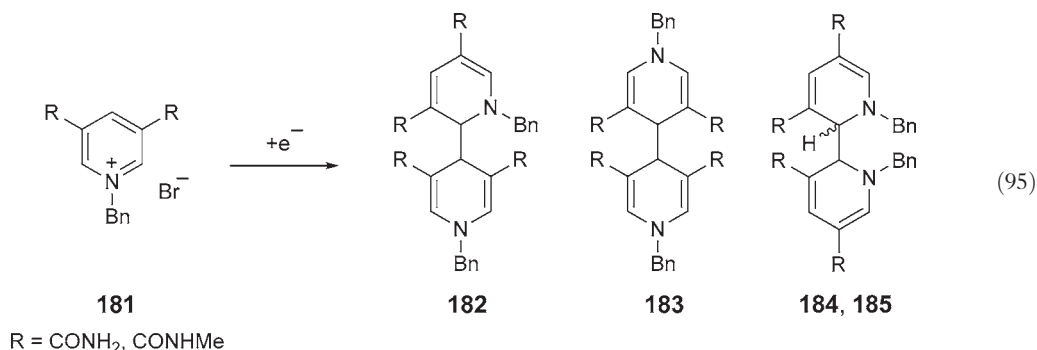
A two-electron reduction of activated pyridinium salt **178** forms an intermediate enolate **179**, which, upon quenching with a number of electrophiles, yields dihydro-4-pyridones **180** after hydrolysis. These compounds are notable because they contain a variety of groups α to the nitrogen (Table 5; Equation (94) <2005OL435, 2006OBC1071>).

Table 5 2-Substituted pyridones prepared using two-electron reduction

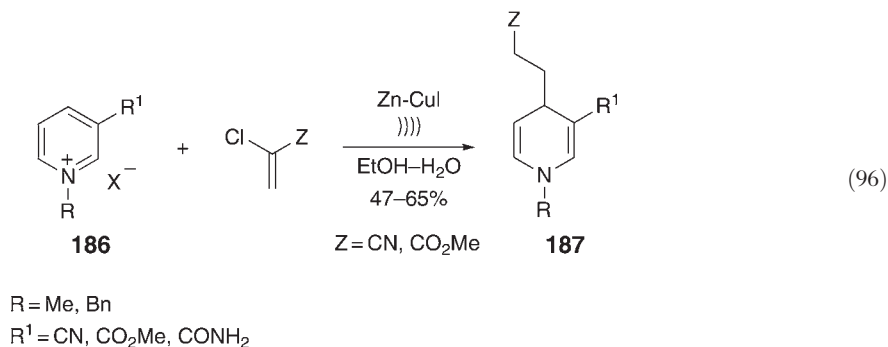
<i>R</i>	Yield (%)
H	65
Me	74
Bu ⁱ	67
<i>n</i> -BuCl	65
CO ₂ Me	70



One-electron electrochemical reduction of pyridinium salts **181** yields mixtures of four isomeric dimers **182–185**. The two most abundant products are **182** and **183** (Equation 95) <2002J(P1)542>.



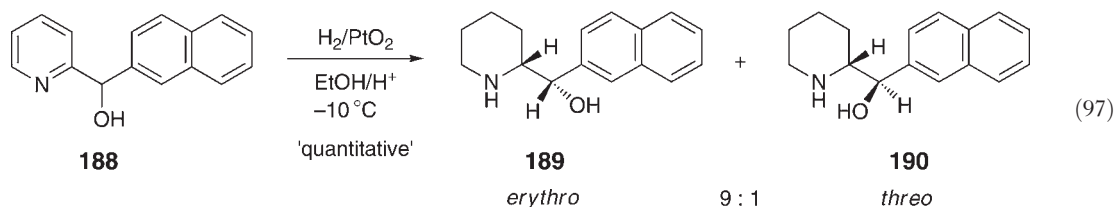
In the presence of Zn/CuI couple in a protic medium under sonochemical activation, pyridinium salt **186** and α -chloroacrylates afford the 4-substituted 1,4-dihydropyridines **187**. The mechanism likely involves the one-electron reduction of **186**, and addition of the radical to the olefin to generate a new radical whose reduction, proton abstraction, and Zn-promoted reductive cleavage of the C–Cl bond complete the conversion (Equation 96) <2004COR715>.



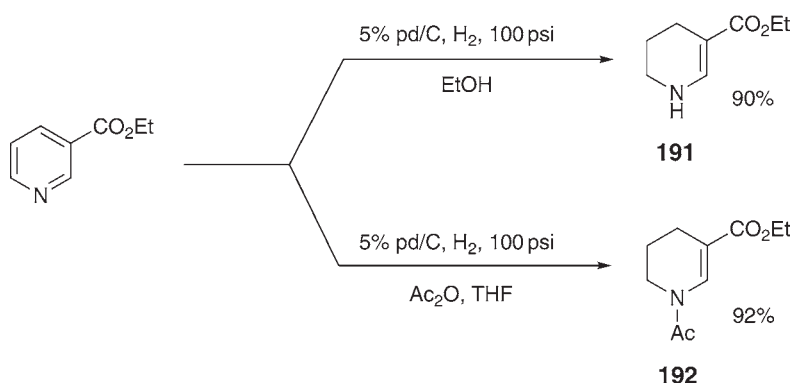
7.02.4.4.4 Hydrogenation

A common and often efficient method for the preparation of saturated piperidines is the catalytic reduction of pyridines, pyridine *N*-oxides, or pyridinium salts <2001CHE797, 2003T2953>. Reduction of the naphthylpyridyl alcohol **188**

with molecular hydrogen over PtO_2 yields a 90:10 mixture of *erythro*- **189** and *threo*- **190** piperidines in quantitative yield (Equation 97) <2003JOC7308>. Activation of the ring is achieved with HCl and optimal *erythro* formation is observed at lower temperature (-10°C). Recrystallization from diethyl ether gives pure *erythro* in 60% yield.

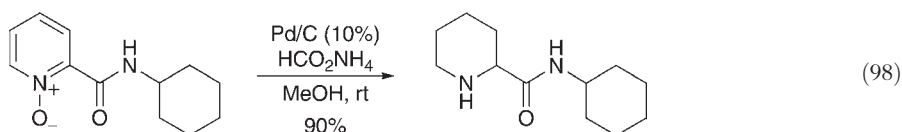


Partial hydrogenation of ethyl nicotinate under heterogeneous catalytic conditions in EtOH, or in THF/ Ac_2O , affords the corresponding vinylogous amides **191** and **192**, respectively. This method can also be applied to 3-acetyl- and 3-benzoylpyridine (Scheme 33) <2006EJO4343>.

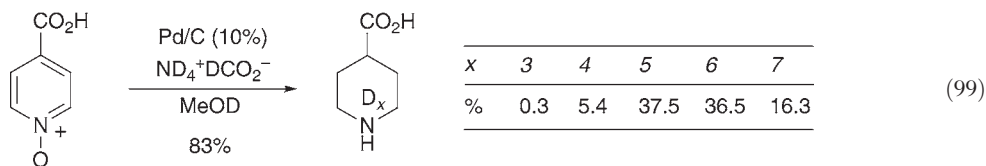


Scheme 33

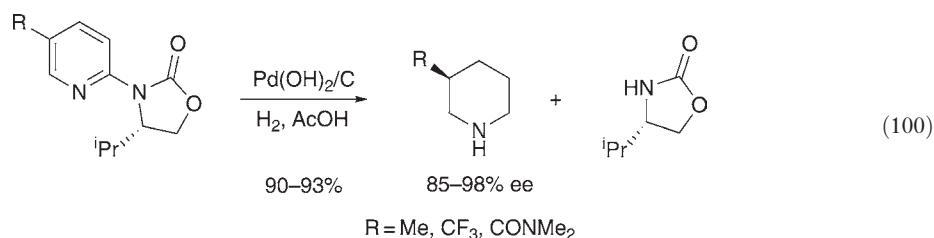
An efficient procedure for the reduction of pyridine *N*-oxides to piperidines using ammonium formate and palladium on carbon has been developed (Equation 98) <2001JOC5264>. The reaction conditions are mild and can also be applied to the *N*-oxides of quinoline and isoquinoline.



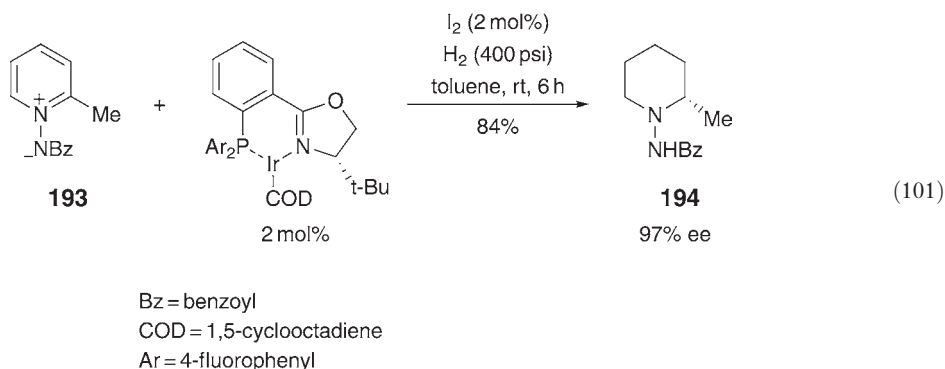
Deuterated ammonium formate is found to reduce 4-carboxypyridine *N*-oxide in the presence of a palladium catalyst. Incorporation of a minimum of five deuteriums in the ring is achieved in good yield (Equation 99) <2004TL8889>.



In recent years, a few stereoselective methods for the asymmetric hydrogenation of pyridines and related heterocycles have been developed <2005OBC4171>. A chiral auxiliary method starts with an oxazolidinone-substituted pyridine which on reduction with $\text{H}_2/\text{Pd}(\text{OH})_2$ in acetic acid affords the corresponding piperidine in good yield and high enantiopurity. The chiral auxiliary is cleaved during the reaction and can be recovered (Equation 100) <2004AGE2850>.



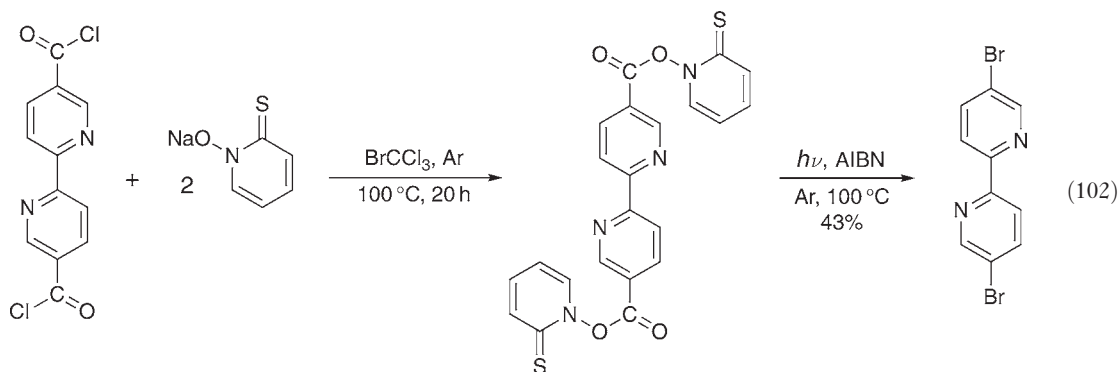
Application of the known iridium-catalyzed hydrogenation of imines to the pyridine system results in excellent yields and good enantiomeric excess when reaction conditions, catalysts, and activated pyridines are optimized. Among the findings are the use of molecular iodine to oxidize the Ir(I) to Ir(III) *in situ*, choice of ligand, and that of a variety of 2-methylpyridines, activated and unactivated, only the *N*-acyliminopyridinium ylide **193** was hydrogenated (Equation 101) <2005JA8966>. The conditions shown for synthesis of **194** are optimal.

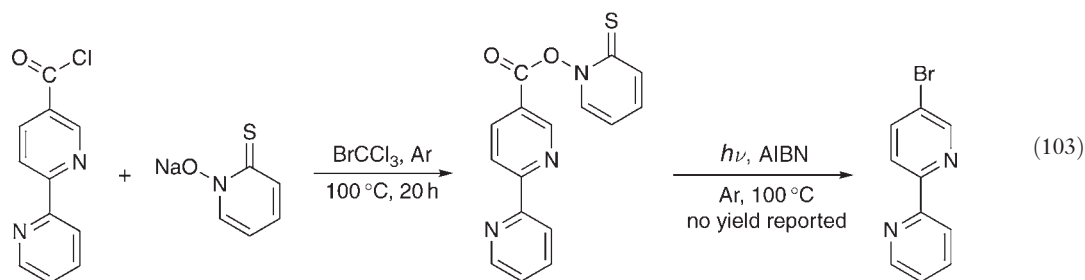


7.02.5 Free Radical Attack at Carbon

7.02.5.1 Halogenation

The direct free radical chlorination or bromination of pyridines is effected at high temperatures (220–500 °C) or by irradiation <1996CHEC-II37, B-2000MI217>. Attack at the α -position predominates. A recent process for producing 2-chloropyridine combines pyridine with chlorine in the vapor phase in the presence of a catalyst which generates free radicals <2002USP6369231>. Free radical bromination of bipyridyl using Barton chemistry is used in order to unambiguously assign the structures purported to be 5,5'-dibromo-2,2'-bipyridine and 5-bromo-2,2'-bipyridine (Equations 102 and 103) <1995TL6471>. This method employs a radical decarboxylative bromination. Azobisisobutyronitrile (AIBN) is the radical initiator and BrCCl_3 is the chain carrier. The reaction is performed in one pot as isolation of the intermediate thiohydroxamic ester is not necessary.

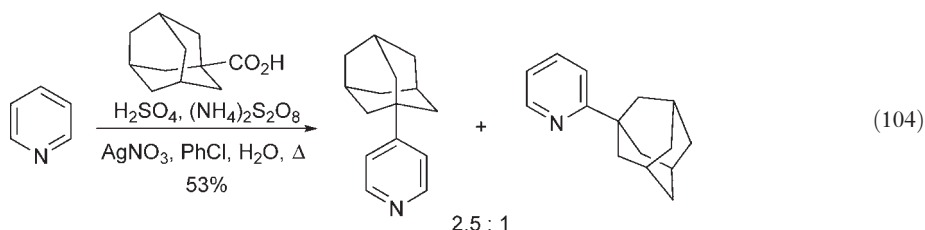




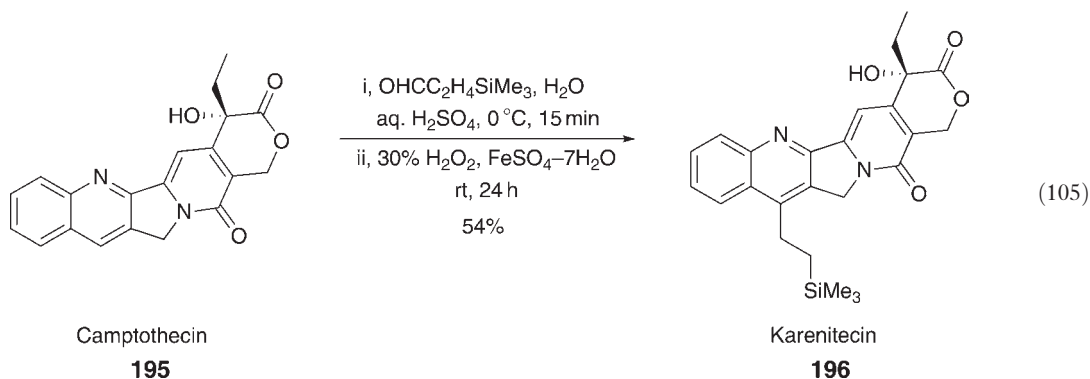
7.02.5.2 Alkylation, Arylation, and Acylation

Radical alkylations of pyridines and quinolines preferentially occur at positions 2 and 4. Protonation of the ring nitrogen influences the regioselectivity by favoring C-4 substitution.

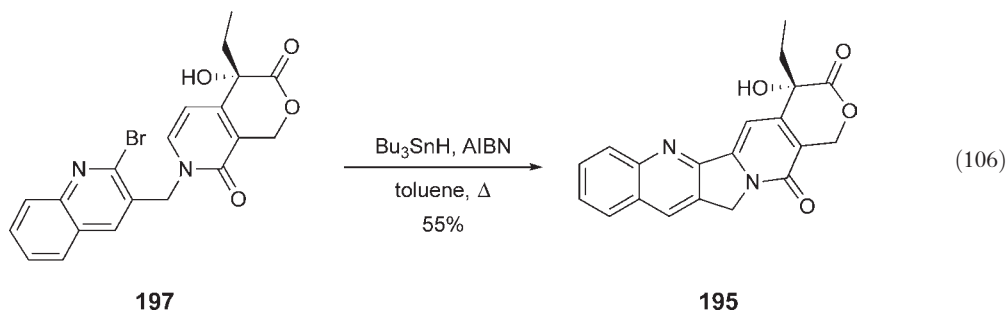
Pyridine is attacked by the adamantyl radical to give a mixture of C-2 and C-4 isomers (Equation 104) <1995ZOR670>. The analogous reaction of ethyl isonicotinate gave mainly the 2-substituted derivative.



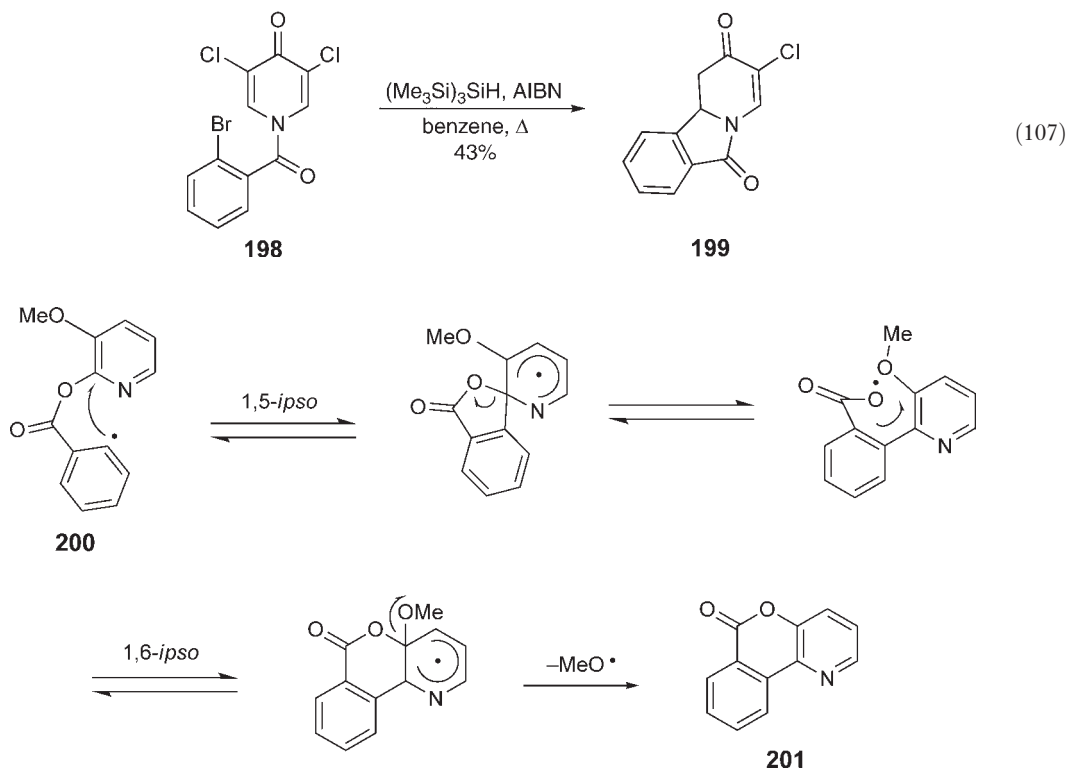
Using a modified Minisci reaction, the 4-position of the quinoline ring in alkaloid **195** (camptothecin) was substituted to afford the highly active antitumor agent **196** (karenitecin) (Equation 105) <2001USP6194579>.



Various intramolecular aryl radical reactions of pyridine derivatives have been developed <2004COR757, 2001J(P1)2885>. An early example of this type is found in a short synthesis of camptothecin **195**. The tetracyclic intermediate **197** was cyclized by a free radical reaction to afford the natural product (Equation 106) <1994TL5331>.

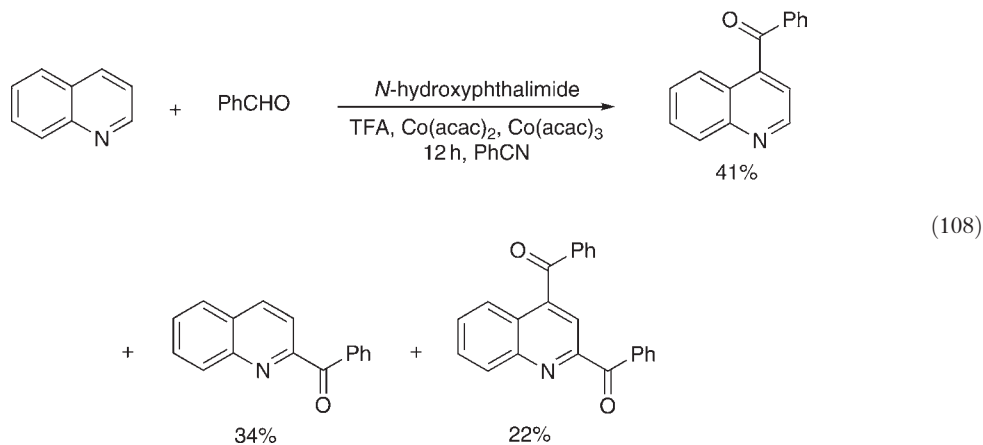


Radical cyclization of the 4-pyridone **198** occurs to give isoindolinone **199** with loss of a chlorine atom (Equation 107) <2003T3009>. Intramolecular free radical arylations of isoquinolin-1-ones have been reported <2000OL2535>. Various intramolecular radical additions to pyridines and quinolines at the 2-, 3-, and 4-positions have been shown to be facile processes <1997TL137, 2000J(P2)1809, 2001TL9061, 2001TL2907, 2001JOC2197, 2003T3009, 2004OL3671>. Occasionally, rearrangements are observed. The free radical cyclization of **200** produced the product **201** via the *ipso*-substitution mechanism proposed in Scheme 34 <2003T3009>.



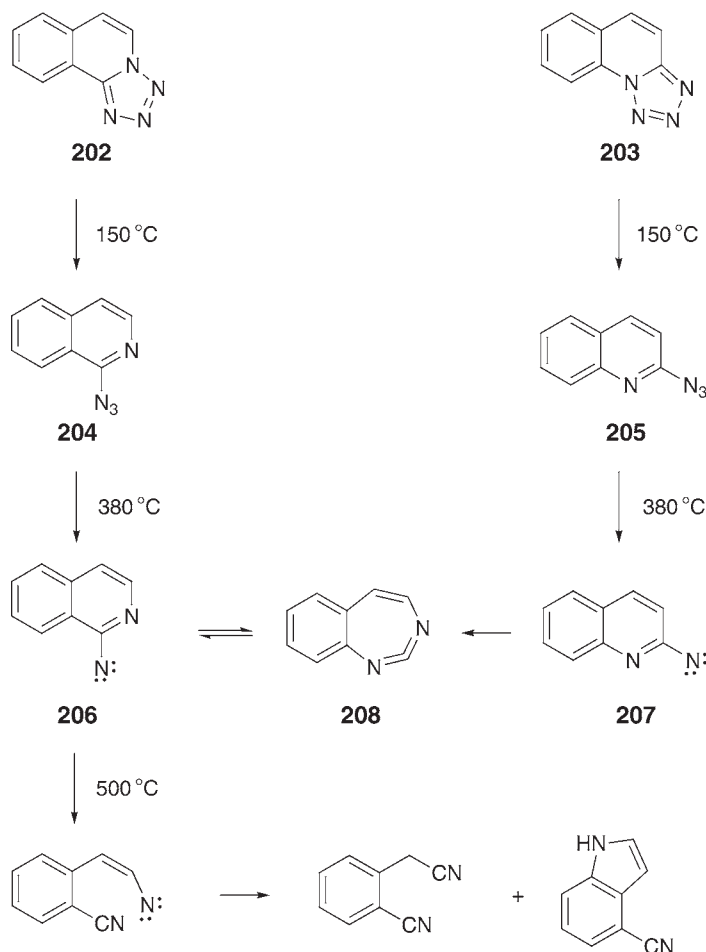
Scheme 34

A new process for the homolytic acylation of protonated heteroaromatic bases has been developed by Minisci *et al.* An *N*-oxyl radical generated from *N*-hydroxyphthalimide by oxygen and Co(II) abstracts a hydrogen atom from an aldehyde. The resulting nucleophilic acyl radical adds to the heterocycle which is then rearomatized via a chain process. Under these conditions, quinoline and benzaldehyde afford three products (Equation 108) <2003JHC325>. A similar reaction with 4-cyanopyridine gives 2-benzoyl-4-cyanopyridine in 96% yield.



7.02.6 Thermal and Photochemical Reactions and Those Involving Cyclic Transition States

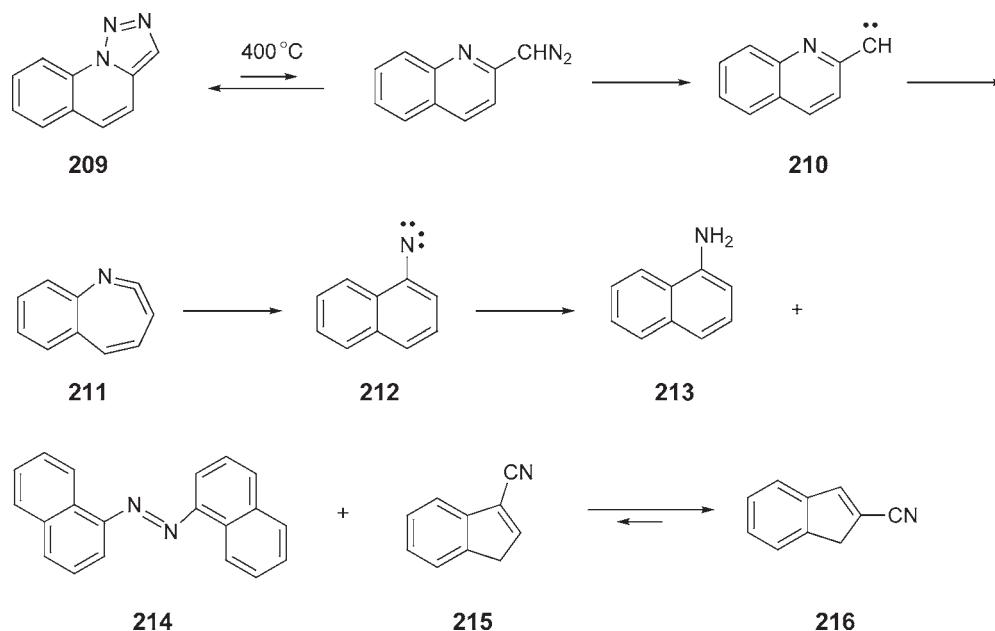
The mechanisms of ring-expansion and ring-opening reactions of quinolyl and isoquinolyl nitrenes generated by flash vacuum thermolysis (FVT) are proposed <2003JOC1470>. Tetrazoles **202** and **203** were used as the starting materials. The subsequent decomposition to and observation of azides **204** and **205** and nitrenes **206** and **207** through a common carbodiimide **208** was achieved through the use of different, and subsequently increasing, FVT temperatures (Scheme 35). The intermediates were isolated in an argon matrix and characterized by infrared spectroscopy. Interestingly, the same nitrenes were observed for the matrix photolysis reactions of tetrazoles **202** and **203**.



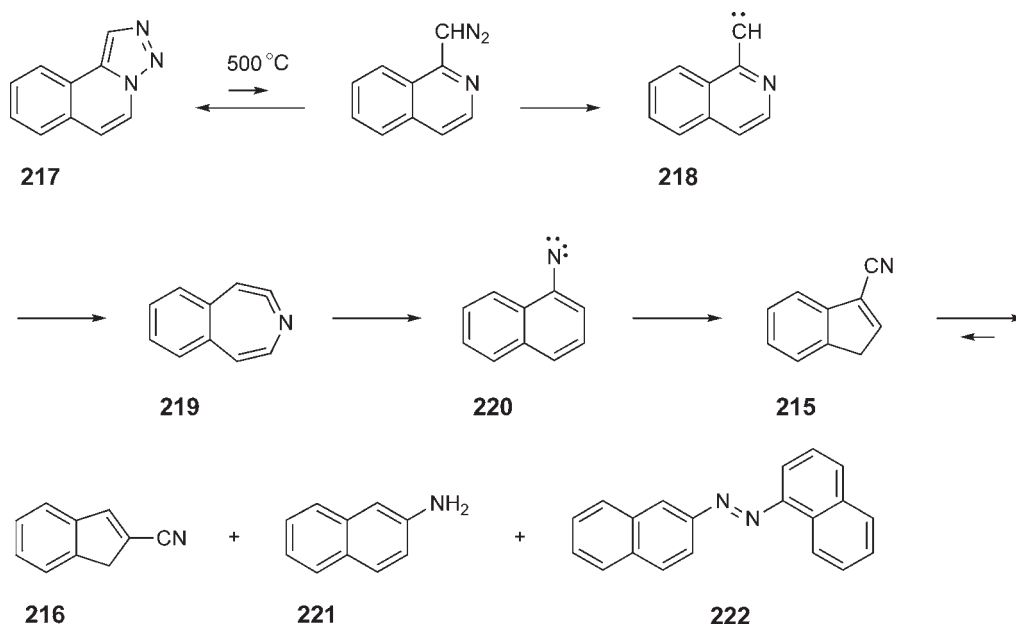
Scheme 35

Carbenes **210** generated from the triazoloquinoline **209** by FVT rearrange into a seven-membered ring ketenimine **211**, similar to carbodiimide **208**. The ketenimine similarly rearranges to 1-naphthyl nitrene **212** and nitrene derivatives **213**, **214**, **215**, and **216** (Scheme 36) <2004JOC2033>.

Similar products were found in the thermolysis of triazoloisoquinoline **217**, again through carbene **218**, ketenimine **219**, and nitrene **220**, to the cyanoindenes **215** and **216** as well as 2-aminonaphthalene **221** and 1,2'-azonaphthalene **222** (Scheme 37).



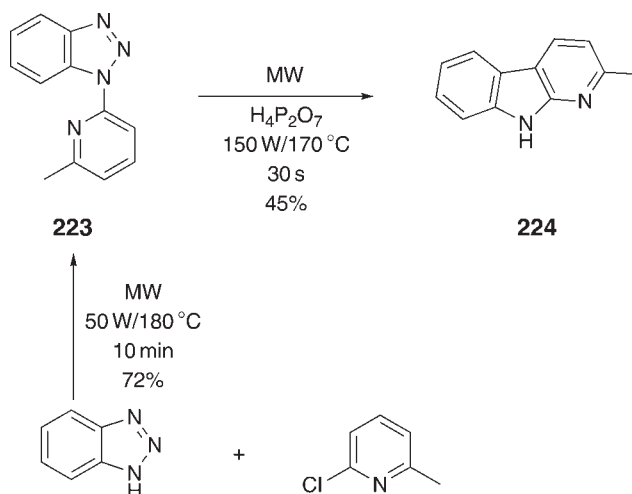
Scheme 36



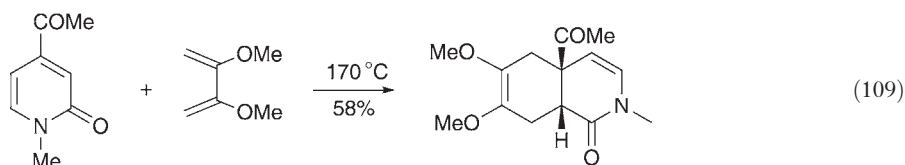
Scheme 37

In a modified Graebe–Ullman reaction, pyridylbenzotriazole **223** was converted to α -carboline **224** in an efficient manner but in moderate yield (Scheme 38) <2006OL415>. Microwave irradiation was the energy source for both α -carboline synthesis and the preparation of **223**. The advantages of this procedure are that the starting materials are commercially available and lower reaction times are used resulting in fewer undesirable side products. The style of microwave oven, amount of pyrophosphoric acid, power level, and time were all optimized.

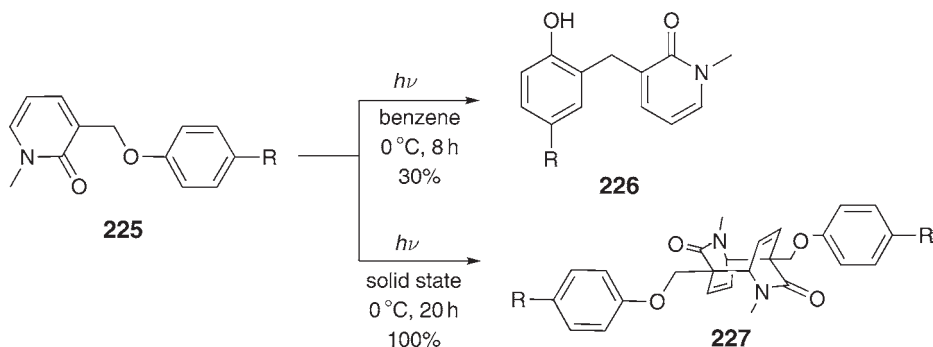
A 2-pyridone ring can be a building block for the synthesis of isoquinoline derivatives by acting as a dienophile in a Diels–Alder reaction. An electron-withdrawing group at C-4 is necessary for reaction with various substituted 1,3-butadienes (Equation 109) <2000CPB1814>.



Scheme 38



A phase-selective photochemical reaction of 2-pyridones is observed. Irradiation of **225** in benzene gives mainly rearrangement products **226**, whereas, in the solid state, [4+4] photocycloaddition to the photodimer **227** occurred in quantitative yield (Scheme 39) <2004OL683>. The stereochemistry of the photodimer was exclusively the *trans-anti*-configuration, as shown. This is presumably due to π - π -stacking and dipole-dipole interactions between the pyridones. Intermolecular photocycloaddition of 2-pyridone mixtures can be selective and lead to useful quantities of [4+4] cycloaddition cross-products <1999JOC950>.

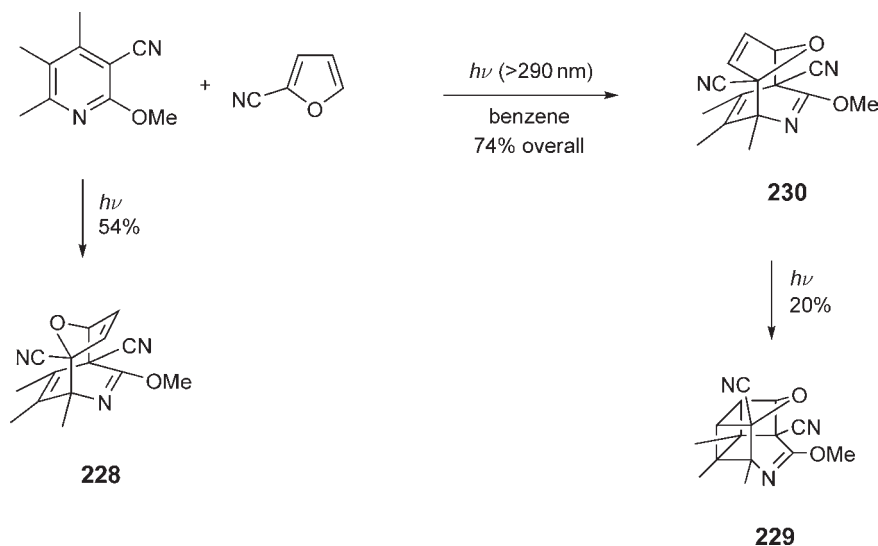


Scheme 39

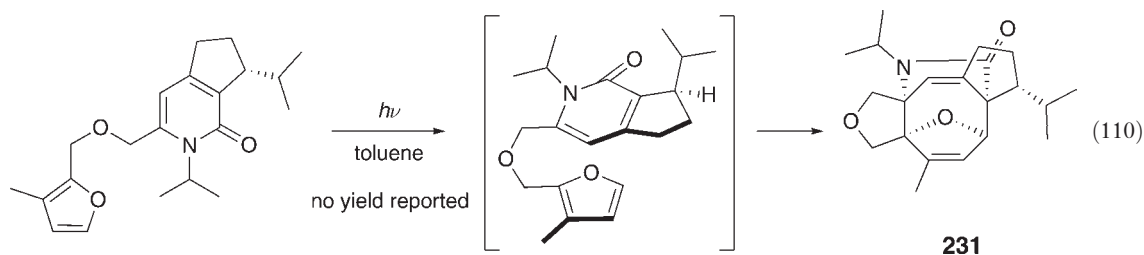
Photochemical cycloaddition of 2-cyanofuran with 2-alkoxy-3-cyanopyridine results in the formation of [4+4] photoadducts **228** and **229**. The latter compound is seen to arise through the intermediate **230** (Scheme 40) <2004TL4437>. Mechanistic studies show that the photoadditions proceed from the singlet-excited state of the pyridine. The preference for the formation of **228** over **229** is explained by the two heteroaromatics approaching each other such as to avoid proximity of their electronegative heteroatoms.

An intramolecular [4+4] photocycloaddition of a 2-pyridone with a furan ring yields the complex 1,5-cyclooctadiene **231** <2006OL3367>. The proposed transition state conformation leading to the realized (and desired) *cis,syn*-product is shown (Equation 110). The isopropyl group on the cyclopentane of the pyridone demonstrated stereocontrol and the

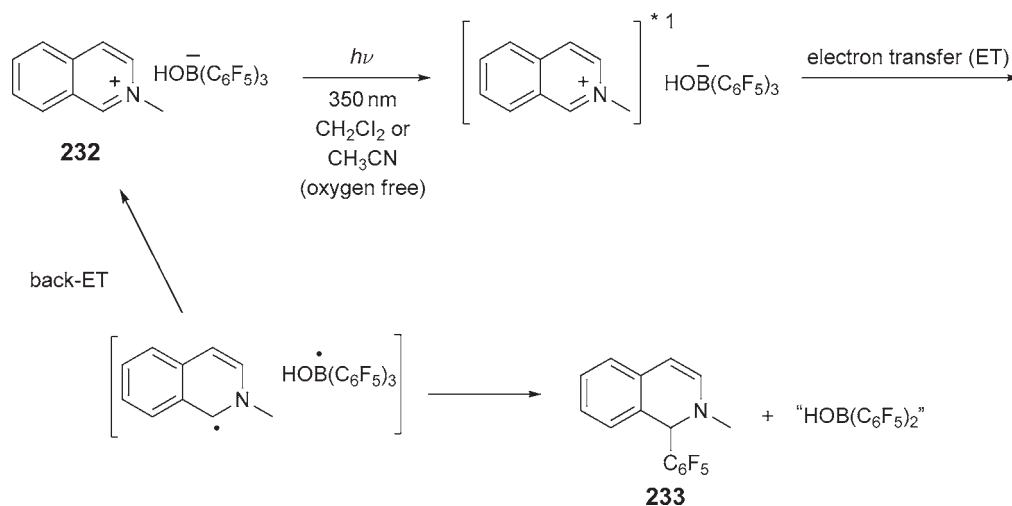
isopropyl group on the nitrogen of the pyridone was found to be necessary. The *N*-unsubstituted pyridine yielded only 25% of the desired *cis,syn*-product, the majority being the *trans,syn*-isomer.



Scheme 40

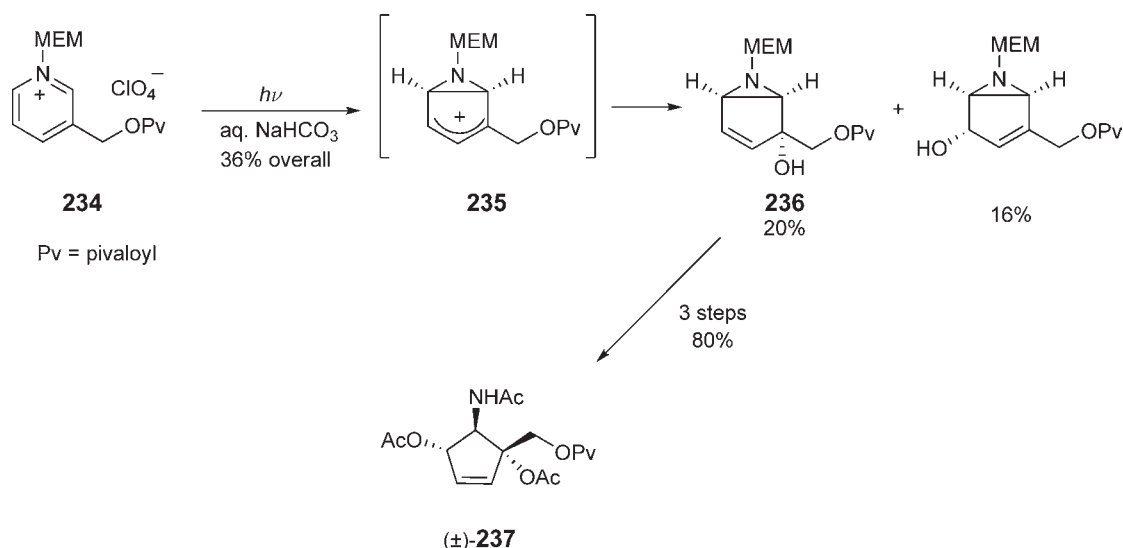


Irradiation of isoquinolinium hydroxytris(pentafluorophenyl)borate **232** resulted in C_6F_5 transfer to the isoquinolinium cation to yield 2-methyl-1-(2,3,4,5,6-pentafluorophenyl)-1,2-dihydroisoquinoline **233** [<2005JOC10653>](#). The mechanism is proposed to be due to a photoinduced electron transfer from the singlet state of the *N*-methylisoquinolinium cation, confirmed using fluorescence quenching (Scheme 41).



Scheme 41

Photolysis of 3-substituted pyridinium salt **234** in aqueous base provides the highly functionalized bicyclic aziridine **236**, albeit in low yield (20%) <2005JOC5618>. Fortunately, the two regioisomers can be separated chromatographically. The reaction presumably proceeds through indiscriminant hydroxide addition onto an intermediate allylic cation **235**. Compound **236** can be carried on to the desired acetamidocyclopentene derivative **237** in three steps and 80% yield (Scheme 42).



Scheme 42

References

- 1972CPB2678 Y. Ito, Y. Hamada, and M. Hirota, *Chem. Pharm. Bull.*, 1972, **20**, 2678.
 1973JOC2271 M. E. Kurz, L. T. A. Yang, E. P. Zahora, and R. C. Adams, *J. Org. Chem.*, 1973, **38**, 2271.
 1982CPB1731 Y. Yamamoto and A. Yanagi, *Chem. Pharm. Bull.*, 1982, **30**, 1731.
 1984CHEC(2)165 E. F. V. Scriven; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 2, p. 165.
 1985JHC1419 D. L. Comins and E. D. Stroud, *J. Heterocycl. Chem.*, 1985, **22**, 1419.
 1986TL211 R. Yamaguchi, M. Moriyasu, and M. Kawanisi, *Tetrahedron Lett.*, 1986, **27**, 211.
 1990JOC69 D. L. Comins and M. O. Killpack, *J. Org. Chem.*, 1990, **55**, 69.
 1992H(34)2179 A. R. Katritzky and W.-Q. Fan, *Heterocycles*, 1992, **34**, 2179.
 1992JA10971 D. L. Comins, M. F. Baevsky, and H. Hong, *J. Am. Chem. Soc.*, 1992, **114**, 10971.
 1992SL431 Y. Genisson, C. Marazano, M. Mehmandoust, D. Gnecco, and B. C. Das, *Synlett*, 1992, 431.
 1994ACS1001 J. M. Bakke, I. Hegbom, E. Overeide, and K. Aaby, *Acta Chem. Scand.*, 1994, **48**, 1001.
 1994AXC25 P. Singh, D. L. Comins, and S. P. Joseph, *Acta Crystallogr., Sect. C*, 1994, **50**, 25.
 1994HOU(E7b)286 D. Spitzner; in 'Houben-Weyl Methoden der Organischen Chemie' Solidus *Science of Synthesis*, E. Kreher, Ed.; Thieme, Stuttgart, 1994, vol. E7b, p. 286.
 1994T4995 R. Carceller, J. L. Garcia-Navio, M. L. Izquierdo, J. Alvarez-Builla, M. Fajardo, P. Gomez-Sal, and F. Gago, *Tetrahedron*, 1994, **50**, 4995.
 1994TL5331 D. L. Comins, H. Hong, and G. Jianhua, *Tetrahedron Lett.*, 1994, **35**, 5331.
 1994TL7343 D. L. Comins and D. H. LaMunyon, *Tetrahedron Lett.*, 1994, **35**, 7343.
 1995SCRV2457 N. Miyaara and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
 1995HCA61 J. Streith, A. Boiron, J.-L. Paillaud, E.-M. Rodriguez-Perez, T. Sifferlen, C. Strehler, and T. Tschamber, *Helv. Chim. Acta*, 1995, **78**, 61.
 1995S56 J. Levillain and M. Vazeux, *Synthesis*, 1995, 56.
 1995T8649 C. Burgos, F. Delgado, J. L. Garcia-Navio, M. L. Izquierdo, and J. Alvarez-Builla, *Tetrahedron*, 1995, **51**, 8649.
 1995T9531 W. Schlecker, A. Huth, and E. Ottow, *Tetrahedron*, 1995, **51**, 9531.
 1995TL563 M. Kuroboshi, K. Mizuno, K. Kanie, and T. Hiyama, *Tetrahedron Lett.*, 1995, **36**, 563.
 1995TL4077 Y. Uchida, R. Kajita, Y. Kawasaki, and S. Oae, *Tetrahedron Lett.*, 1995, **36**, 4077.
 1995TL5075 L. I. Belen'kii, I. S. Poddubnyi, and M. M. Krayushkin, *Tetrahedron Lett.*, 1995, **36**, 5075.
 1995TL6471 F. M. Romero and R. Ziesel, *Tetrahedron Lett.*, 1995, **36**, 6471.
 1995TL9085 S. A. Hitchcock, D. R. Mayhugh, and G. S. Gregory, *Tetrahedron Lett.*, 1995, **36**, 9085.
 1995ZOR670 I. A. Rybakova, E. N. Prilezhaeva, and V. P. Litvinov, *Zh. Org. Khim.*, 1995, **31**, 670 (*Chem. Abstr.*, 1996, **124**, 232219).

- 1996CHEC-II(5)37 D. L. Comins and S. P. Joseph; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Elsevier, Oxford, 1996, vol. 5, p. 37.
- 1996CPB267 T. Inanishi, S. Obika, T. Nishiyama, M. Nishimoto, Y. Hamano, K. Miyashita, and C. Iwata, *Chem. Pharm. Bull.*, 1996, **44**, 267.
- 1996H(43)1641 S. Y. Cho, S. S. Kim, K.-H. Park, S. K. Kang, J.-K. Choi, K.-J. Hwang, and E. K. Yum, *Heterocycles*, 1996, **43**, 1641.
- 1996JCM380 R. Lavilla, T. Gotsens, J. M. Gavalda, M. C. Santano, and J. Bosch, *J. Chem. Res.(S)*, 1996, 380.
- 1996JFC161 T. Umemoto, G. Tomizawa, H. Hachisuka, and M. Kitano, *J. Fluorine Chem.*, 1996, **77**, 161.
- 1996JOC4830 F. Diaba, I. Lewis, M. Grignon-Dubois, and S. Navarre, *J. Org. Chem.*, 1996, **61**, 4830.
- 1996JOC7240 S. Wagner and S. L. Buchwald, *J. Org. Chem.*, 1996, **61**, 7240.
- 1996J(P1)2545 J. MacTavish, G. R. Proctor, and J. Redpath, *J. Chem. Soc., Perkin Trans 1*, 1996, 2545.
- 1996LA641 M. Grzegozek, M. Wozniak, and H. C. van der Plas, *Liebigs Ann. Chem.*, 1996, 641.
- B-1996MI251 D. L. Comins and S. P. Joseph; in 'Advances in Nitrogen Heterocycles', C. J. Moody, Ed.; JAI Press Inc., Greenwich, CT, 1996, vol. 2, p. 251.
- 1996T23 N. Yoneda and T. Fukuhara, *Tetrahedron*, 1996, **52**, 23.
- 1996T1451 A. P. Venkov and S. M. Statkova-Abeghe, *Tetrahedron*, 1996, **52**, 1451.
- 1996TL1317 Y. N. Bubnov, E. V. Klimkina, A. V. Ignatenko, and I. D. Gridnev, *Tetrahedron Lett.*, 1996, **37**, 1317.
- 1996TL1599 S. Raussou, N. Urbain, P. Mangeney, A. Alexakis, and N. Platzter, *Tetrahedron Lett.*, 1996, **37**, 1599.
- 1996TL3807 D. L. Comins and L. Guerra-Weltzien, *Tetrahedron Lett.*, 1996, **37**, 3807.
- 1997CEJ410 J. Winter and J. Rétey, *Chem. Eur. J.*, 1997, **3**, 410.
- 1997H(45)1929 A. Wang and E. R. Biehl, *Heterocycles*, 1997, **45**, 1929.
- 1997H(45)2113 K. Vinter-Pasquier, B. Jamart-Gregoire, and P. Caubère, *Heterocycles*, 1997, **45**, 2113.
- 1997JOC729 Y.-S. Wong, C. Marazano, D. Gnecco, Y. Génisson, A. Chiaroni, and B. C. Das, *J. Org. Chem.*, 1997, **62**, 729.
- 1997J(P1)709 J. G. Rodriguez, R. Martin-Villamil, F. H. Cano, and I. Fonseca, *J. Chem. Soc., Perkin Trans. 1*, 1997, 709.
- 1997J(P1)927 A. Ford, E. Sinn, and S. Woodward, *J. Chem. Soc., Perkin Trans. 1*, 1997, 927.
- 1997MI67 J. A. King, *Trends Org. Chem.*, 1997, **6**, 67.
- 1997S744 G. A. Olah and D. A. Klumpp, *Synthesis*, 1997, 744.
- 1997SL313 U. Beifuss and S. Ledderhose, *Synlett*, 1997, 313.
- 1997SL329 J. F. Hartwig, *Synlett*, 1997, 329.
- 1997T13959 R. Lavilla, T. Gotsens, M. Guerrero, C. Masdeu, M. C. Santano, C. Minguillón, and J. Bosch, *Tetrahedron*, 1997, **53**, 13959.
- 1997T14687 K. Marx and W. Eberbach, *Tetrahedron*, 1997, **53**, 14687.
- 1997TL137 M. Lucília, E. N. da Mata, W. B. Motherwell, and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 137.
- 1997TL403 R. Yamaguchi, B. Hatano, T. Nakayasu, and S. Kozima, *Tetrahedron Lett.*, 1997, **38**, 403.
- 1997TL845 W. Baik, D. I. Kim, S. Koo, J. U. Rhee, S. H. Shin, and B. H. Kim, *Tetrahedron Lett.*, 1997, **38**, 845.
- 1997TL4415 C. Chassaing, A. Haudrechy, and Y. Langolis, *Tetrahedron Lett.*, 1997, **38**, 4415.
- 1997TL4667 K. Wojciechowski and S. Kosinski, *Tetrahedron Lett.*, 1997, **38**, 4667.
- 1998AGE1410 N. Kanomata, M. Suzuki, M. Yoshida, and T. Nakata, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1410.
- 1998BML2169 A. B. Dyatkina, J. R. Brickwood, and J. R. Proudfoot, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2169.
- 1998CC1519 S. Seko and K. Miyake, *J. Chem. Soc., Chem. Commun.*, 1998, 1519.
- 1998CEJ67 H. Josien, S.-B. Ko, D. Bom, and D. P. Curran, *Chem. Eur. J.*, 1998, **4**, 67.
- 1998CHE871 M. A. Yurovskaya, O. D. Mit'kin, and F. V. Zaitseva, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, **34**, 871.
- 1998CHE1045 A. V. Aksenov, O. N. Nadein, I. V. Borovlev, and Y. I. Smushkevich, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, **34**, 1045.
- 1998CL547 R. Yamaguchi, Y. Omoto, M. Miyake, and K.-I. Fujita, *Chem. Lett.*, 1998, **27**, 547.
- 1998H(48)1313 D. L. Comins, C. J. Foti, and A. H. Libby, *Heterocycles*, 1998, **48**, 1313.
- 1998JOC1767 D. Barbier, C. Marazano, C. Riche, B. C. Das, and P. Potier, *J. Org. Chem.*, 1998, **63**, 1767.
- 1998JOC8224 B. A. Anderson, E. C. Bell, F. O. Ginah, N. K. Harn, L. M. Pagh, and J. P. Wepsiec, *J. Org. Chem.*, 1998, **63**, 8224.
- 1998JOM119 B. Martin-Vaca, H. Rudler, M. Audouin, M. Nicolas, T. Durand-Reville, and B. Vissiere, *J. Organomet. Chem.*, 1998, **567**, 119.
- 1998J(P1)1705 R. D. Chambers, C. W. Hall, J. Hutchinson, and R. W. Millar, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1705.
- 1998RJO271 A. A. Matreiev, I. V. Koblik, A. F. Popov, V. A. Savelova, and V. N. Matvienko, *Russ. J. Org. Chem.*, 1998, **34**, 271 (*Chem. Abstr.*, 1998, **129**, 330358e).
- 1998S195 M. Haase, H. Goerls, and E. Anders, *Synthesis*, 1998, 195.
- 1998SL649 U. Beifuss, G. Feder, T. Bes, and I. Uson, *Synlett*, 1998, 649.
- 1998T263 S. P. Stanforth, *Tetrahedron*, 1998, **54**, 263.
- 1998T3391 A. Wang, S. Tandel, H. Zhang, Y. Huang, T. C. Holdeman, and E. R. Biehl, *Tetrahedron*, 1998, **54**, 3391.
- 1998T6311 C. Niu, J. Li, T. W. Doyle, and S.-H. Chen, *Tetrahedron*, 1998, **54**, 6311.
- 1998T13793 J. Hassan, V. Penalva, L. Lavenot, C. Gozzi, and M. Lemaire, *Tetrahedron*, 1998, **54**, 13793.
- 1998TA2027 D. Gnecco, C. Marazano, R. G. Enriquez, J. L. Teran, M. R. Sanchez, and A. Galindo, *Tetrahedron Asymmetry*, 1998, **9**, 2027.
- 1998TL1313 S. Jaime-Figueroa, Y. Liu, J. M. Muchowski, and D. G. Putnam, *Tetrahedron Lett.*, 1998, **39**, 1313.
- 1998TL1721 J. E. Deline and R. B. Miller, *Tetrahedron Lett.*, 1998, **39**, 1721.
- 1998TL9275 M.-L. Bannasar, C. Juan, and J. Bosch, *Tetrahedron Lett.*, 1998, **39**, 9275.
- 1999AHC295 L. I. Belen'kii, N. D. Kruchkovskaya, and V. N. Gramenitskaya, *Adv. Heterocycl. Chem.*, 1999, **73**, 295.
- 1999H(51)1957 M. Ikeda, S. A. A. El Bialy, and T. Yakura, *Heterocycles*, 1999, **51**, 1957.
- 1999JA2651 D. L. Comins, J. T. Kuethe, H. Hong, and F. J. Lakner, *J. Am. Chem. Soc.*, 1999, **121**, 2651.
- 1999JA3539 Y. Kondo, M. Shilai, M. Uchiyama, and T. Sakamoto, *J. Am. Chem. Soc.*, 1999, **121**, 3539.
- 1999JHC1491 D. L. Comins, *J. Heterocycl. Chem.*, 1999, **36**, 1491.
- 1999JOC950 S. McN. Sieburth, C.-H. Lin, and D. Rucando, *J. Org. Chem.*, 1999, **64**, 950.
- 1999JOC1007 A. G. de Viedma, V. Martínez-Barrasa, C. Burgos, M. L. Izquierdo, and J. Alvarez-Builla, *J. Org. Chem.*, 1999, **64**, 1007.
- 1999JOC3461 D. Bankston, F. Fang, E. Huie, and S. Xie, *J. Org. Chem.*, 1999, **64**, 3461.
- 1999J(P1)803 R. D. Chambers, M. Parsons, G. Sandford, C. J. Skinner, M. J. Atherton, and J. S. Moilliet, *J. Chem. Soc., Perkin Trans 1*, 1999, 803.
- 1999JPR75 B. Szpakiewicz and M. Wozniak, *J. Prakt. Chem.*, 1999, **341**, 75.
- 1999OL657 D. L. Comins, Y.-m. Zhang, and S. P. Joseph, *Org. Lett.*, 1999, **1**, 657.

- 1999OL2137
 1999S1427
 1999S2071
 1999SC3341
 1999SC3959
 1999SL804
 1999SL1154
 1999TL11399
 1999TL6241
 1999TL7477
 2000AGE2529
 2000CPB1814
 2000EJO1391
 2000ICA128
 2000JOC907
 2000JOC7984
 2000JOC9272
 2000J(P1)1241
 2000J(P1)4245
 2000J(P2)1809
 B-2000MI183
 B-2000MI217
 2000MOL1175
 2000OL1533
 2000OL2535
 2000SL1488
 2000TL1235
 2000TL2299
 2000TL6237
 2000TL8053
 2001AGE4544
 2001AHC269
 2001ARK242
 2001CC1166
 2001IC3097
 2001CHE797
 2001HCA1112
 2001JA6061
 2001JA6801
 2001JHC909
 2001JOC1500
 2001JOC2197
 2001JOC5264
 2001J(P1)1435
 2001J(P1)2885
 2001OL201
 2001OL469
 2001OL1197
 2001OL2807
 2001OL4255
 2001OL4263
 2001S2175
 2001S2495
 2001SC2507
 2001T109
 2001T6787
 2001T8939
 2001TL1879
 2001TL2907
 2001TL4849
 2001TL5717
 2001TL6109
 2001TL6707
 2001TL7787
 2001TL9061
 2001USP6194579
 2002AGE4176
- M. E. Mowery and P. DeShong, *Org. Lett.*, 1999, **1**, 2137.
 S. Dayan, M. Kol, and S. Rozen, *Synthesis*, 1999, 1427.
 M. Haase, W. Gunther, H. Gorls, and E. Anders, *Synthesis*, 1999, 2071.
 C. Janiak, S. Deblon, and H.-P. Wu, *Synth. Commun.*, 1999, **29**, 3341.
 D. Csanyi, G. Timari, and G. Hajos, *Synth. Commun.*, 1999, **29**, 3959.
 J. Namyslo and D. E. Kaufman, *Synlett*, 1999, 804.
 T. Itoh, K. Nagata, M. Miyazaki, and A. Ohsawa, *Synlett*, 1999, 1154.
 A. J. Belfield, G. R. Brown, and A. J. Foubister, *Tetrahedron*, 1999, **55**, 11399.
 F. Rezgui, P. Mangeney, and A. Alexakis, *Tetrahedron Lett.*, 1999, **40**, 6241.
 O. Sugimoto, M. Mori, and K.-i. Tanji, *Tetrahedron Lett.*, 1999, **40**, 7477.
 K. C. Nicolaou, A. E. Koumbis, S. A. Snyder, and K. B. Simonsen, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 2529.
 R. Fujita, M. Hoshino, H. Tomisawa, and H. Hongo, *Chem. Pharm. Bull.*, 2000, **48**, 1814.
 B. Guilloteau-Bertin, D. Compere, L. Gil, C. Marazano, and B. C. Das, *Eur. J. Org. Chem.*, 2000, 1391.
 E. W. Ainscough, A. M. Brodie, A. D. Lowe, and J. M. Water, *Inorg. Chim. Acta*, 2000, **303**, 128.
 F. Diaba, C. LeHoyerou, M. Grignon-Dubois, and P. Gervail, *J. Org. Chem.*, 2000, **65**, 907.
 M. Alterman and A. Hallberg, *J. Org. Chem.*, 2000, **65**, 7984.
 J. Pabel, C. E. Hosl, M. Maurus, M. Ege, and K. T. Wanner, *J. Org. Chem.*, 2000, **65**, 9272.
 J. M. Bakke, E. Ranes, C. Romming, and I. Sletvold, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1241.
 V. Bonnet, F. Mongin, F. Trécourt, and G. Quéguiner, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4245.
 S. Mukhopadhyay, G. Rothenberg, D. Gitis, M. Baidossi, D. E. Ponde, and Y. Sasson, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1809.
 J. J. Li and G. W. Gribble, in 'Palladium in Heterocyclic Chemistry', Pergamon, Oxford, 2000, p. 183.
 A. R. Katritzky, in 'Handbook of Heterocyclic Chemistry', 2nd edn, Pergamon, Oxford, 2000, p. 217.
 J. L. Terán, D. Gnecco, A. Galindo, J. R. Juárez, R. G. Enríquez, M. Soriano, and W. F. Reynolds, *Molecules*, 2000, **5**, 1175.
 R. Lavilla, A. Spada, and J. Bosch, *Org. Lett.*, 2000, **2**, 1533.
 K. Orito, Y. Satoh, H. Nishizawa, R. Harada, and M. Tokuda, *Org. Lett.*, 2000, **2**, 2535.
 R. T. Skerlj, D. Bogucki, and G. J. Bridger, *Synlett*, 2000, 1488.
 V. Carelli, F. Liberatore, L. Scipione, R. Musio, and O. Sciacovelli, *Tetrahedron Lett.*, 2000, **41**, 1235.
 S. Caron, N. M. Do, and J. E. Sieser, *Tetrahedron Lett.*, 2000, **41**, 2299.
 M. Gray, I. P. Andrews, D. F. Hook, J. Kitteringham, and M. Voyle, *Tetrahedron Lett.*, 2000, **41**, 6237.
 V. J. Colandrea and E. M. Naylor, *Tetrahedron Lett.*, 2000, **41**, 8053.
 S. R. Chemler, D. Trauner, and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 4544.
 R. Kuwar and R. Chandra, *Adv. Heterocycl. Chem.*, 2001, **78**, 269.
 S. Youssif, *ARKIVOC*, 2001, 242.
 M.-L. Bennasar, E. Zulaica, Y. Alonso, I. Mata, E. Molins, and J. Bosch, *J. Chem. Soc., Chem. Commun.*, 2001, 1166.
 E. Bosch and C. L. Barnes, *Inorg. Chem.*, 2001, **40**, 3097.
 R. V. Seller, P. V. Reshetov, and A. P. Kriven'ko, *Chem. Heterocycl. Compd. (Engl. Trans.)*, 2001, **37**, 797.
 O. Sugimoto, M. Mori, K. Moriya, and K. Tanji, *Helv. Chim. Acta*, 2001, **84**, 1112.
 Y. Likhovotvorik, Z. Zhu, E. L. Tae, E. Tippmann, B. T. Hill, and M. S. Platz, *J. Am. Chem. Soc.*, 2001, **123**, 6061.
 M. Takamura, K. Funabashi, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 6801.
 M. S. Wittemore, N. D. Heindel, I. Jabiou, C. Guillon, T. E. McNeel, R. D. Rapp, D. E. Heck, and J. D. Laskin, *J. Heterocycl. Chem.*, 2001, **38**, 909.
 N. Zhang, L. Thomas, and B. Wu, *J. Org. Chem.*, 2001, **66**, 1500.
 Y.-T. Park, C.-H. Jung, M.-S. Kim, K.-W. Kim, N. W. Song, and D. Kim, *J. Org. Chem.*, 2001, **66**, 2197.
 B. Zacharie, N. Moreau, and C. Dockendorff, *J. Org. Chem.*, 2001, **66**, 5264.
 T. J. Donohoe, A. J. McRiner, M. Helliwell, and P. Sheldrake, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1435.
 W. R. Bowman, M. O. Cloonan, and S. L. Krintel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2885.
 G. Zhao, U. C. Deo, and B. Ganem, *Org. Lett.*, 2001, **3**, 201.
 D. L. Comins, S. Huang, C. L. McArdle, and C. L. Ingalls, *Org. Lett.*, 2001, **3**, 469.
 A. Postigo and R. A. Rossi, *Org. Lett.*, 2001, **3**, 1197.
 A. R. Katritzky, S. Zhang, T. Kurz, M. Wang, and P. J. Steel, *Org. Lett.*, 2001, **3**, 2807.
 D. L. Comins and J. M. Nolan, *Org. Lett.*, 2001, **3**, 4255.
 J. V. Mello and N. S. Finney, *Org. Lett.*, 2001, **3**, 4263.
 V. Cañibano, J. F. Rodríguez, M. Santos, M. A. Sanz-Tejedor, M. C. Carreño, G. González, and J. L. García-Ruano, *Synthesis*, 2001, 2175.
 M.-D. Le Bas, C. Gueret, C. Perrio, M.-C. Lasne, and L. Barre, *Synthesis*, 2001, 2495.
 J.-C. Jung, Y.-J. Jung, and O.-S. Park, *Synth. Commun.*, 2001, **31**, 2507.
 R. Yamaguchi, T. Nakayasu, B. Hatano, T. Nagura, S. Kozima, and K. Fujita, *Tetrahedron*, 2001, **57**, 109.
 F. M. Abdelrazek, A. M. Salah El-Din, and A. E. Mekky, *Tetrahedron*, 2001, **57**, 6787.
 S. Yamada, T. Misono, M. Ichikawa, and C. Morita, *Tetrahedron*, 2001, **57**, 8939.
 J. Mathieu, P. Gros, and Y. Fort, *Tetrahedron Lett.*, 2001, **42**, 1879.
 D. C. Harrowven, B. J. Sutton, and S. Coulton, *Tetrahedron Lett.*, 2001, **42**, 2907.
 Y. Kato, S. Okada, K. Tomimoto, and T. Mase, *Tetrahedron Lett.*, 2001, **42**, 4849.
 V. Bennet, F. Mongin, F. Trécourt, G. Guéguiner, and P. Knochel, *Tetrahedron Lett.*, 2001, **42**, 5717.
 D. C. dos Santos, R. P. de Freitas Gil, L. Gil, and C. Marazano, *Tetrahedron Lett.*, 2001, **42**, 6109.
 M. Sundermeier, A. Zapf, M. Beller, and J. Sans, *Tetrahedron Lett.*, 2001, **42**, 6707.
 P. Nshimyumukiza, D. Cahard, J. Rouden, M.-C. Lasne, and J.-C. Plaquevent, *Tetrahedron Lett.*, 2001, **42**, 7787.
 D. C. Harrowven, B. J. Sutton, and S. Coulton, *Tetrahedron Lett.*, 2001, **42**, 9061.
 F. H. Hauseer (BioNumerik Pharmaceuticals, Inc.), *US Pat.* 6 194 579 (2001).
 A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 4176.

- 2002BML411 K. Brachwitz and A. Hilgeroth, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 411.
2002CC1040 S. L. Jain and B. Sain, *J. Chem. Soc., Chem. Commun.*, 2002, 1040.
2002CHE1098 V. I. Bozhanov and S. P. Ivonin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2002, **38**, 1098.
2002COR507 M. Ishikura, *Curr. Org. Chem.*, 2002, **6**, 507.
2002EJO4181 M. Schlosser and F. Cottet, *Eur. J. Org. Chem.*, 2002, 4181.
2002H(58)505 D. L. Comins, M. O. Killpack, E. Despagne, and E. Zeller, *Heterocycles*, 2002, **58**, 505.
2002JA184 S. Yamada and C. Morita, *J. Am. Chem. Soc.*, 2002, **124**, 8184.
2002JA1484 A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 14844.
2002JMO109 M. Prasad, G. Kamalakar, G. Madhavi, S. J. Kulkarni, and K. V. Raghavan, *J. Mol. Catal. A*, 2002, **186**, 109.
2002JOM58 T. Hiyama, *J. Organomet. Chem.*, 2002, **653**, 58.
2002JOM205 C. Bauer, D. Gabel, T. Borrmann, J. D. Kennedy, C. A. Kilner, M. Thornton-Pett, and U. Dorfler, *J. Organomet. Chem.*, 2002, **657**, 205.
2002JP1542 V. Carelli, F. Liberatore, S. Tortorella, B. Di Rienzo, and L. Scipione, *J. Chem. Soc., Perkin Trans. 1*, 2002, 542.
2002JP1141 R. Lavilla, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1141.
2002JP11921 I. Collins, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1921.
2002MI870 S. Joseph and D. L. Comins, *Curr. Opin. Drug Discov. Dev.*, 2002, **5**, 870.
2002OPD767 D. J. Dale, J. Draper, P. J. Dunn, M. L. Hughes, F. Hussain, P. C. Levett, G. B. Ward, and A. S. Wood, *Org. Process Res. Dev.*, 2002, **6**, 767.
2002OPD777 D. Bankston, J. Dumas, R. Natero, B. Riedl, M.-K. Monahan, and R. Sibley, *Org. Process Res. Dev.*, 2002, **6**, 777.
2002RJC729 A. V. Ryzhakov, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2002, **72**, 729.
2002S83 W. D. Brown and A. H. Gouliarov, *Synthesis*, 2002, 83.
2002S1530 S. Lall, V. Behaj, D. Mancheno, R. Casiano, M. Thomas, A. Rikin, J. Gaillard, R. Raju, A. Scumpia, S. Castro, *et al. Synthesis*, 2002, 1530.
2002S1564 S. Bedel, G. Ulrich, C. Picard, and P. Tisnes, *Synthesis*, 2002, 1564.
2002T4931 Y.-J. Cherng, *Tetrahedron*, 2002, **58**, 4931.
2002T6757 C. E. Hoesl, M. Maurus, J. Pabel, K. Polborn, and K. T. Wanner, *Tetrahedron*, 2002, **58**, 6757.
2002T7869 T. Putkonen, E. Yalkonen, A. Tolvanen, and R. Jokela, *Tetrahedron*, 2002, **58**, 7869.
2002T9633 S. Kotha, K. Lahiri, and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633.
2002TCC131 A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131.
2002TL7 Y. Sun, I. Likhovotvorik, and M. Platz, *Tetrahedron Lett.*, 2002, **43**, 7.
2002TL2359 V. V. Zhdankin, O. Maydanovich, J. Herschbach, J. Bruno, E. D. Matveeva, and N. S. Zefirov, *Tetrahedron Lett.*, 2002, **43**, 2359.
2002TL5735 V. V. Zhdankin, A. Y. Kopysov, and N. V. Yashin, *Tetrahedron Lett.*, 2002, **43**, 5735.
2002TL5853 S. Yamada, M. Saitoh, and T. Misono, 2002, **43**, 5853.
2002TL6035 M. Beres, G. Timari, and G. Hajós, *Tetrahedron Lett.*, 2002, **43**, 6035.
2002TL7379 T. N. Lambert, S. Chittamuru, H. K. Jacobs, and A. S. Gopalan, *Tetrahedron Lett.*, 2002, **43**, 7379.
2002TL7967 B. Basu, S. Jha, N. K. Mridha, and Md. M. H. Bhuiyan, *Tetrahedron Lett.*, 2002, **43**, 7967.
2002USP6369231 R. Walravens, J. Franklin, and P. Trouillet (Reilly Industries), *US Pat.* 6 369 231 (2002).
2003AGE308 A. Fürstner and A. Leitner, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 308.
2003AGE1265 S. L. Jain and B. Sain, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 1265.
2003AGE5400 S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 5400.
2003BML351 N. D. P. Cosford, J. Roppe, L. Tehrani, E. J. Schweiger, T. J. Seiders, A. Chaudary, S. Rao, and M. A. Varney, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 351.
2003CHE1263 A. B. Borisov, V. K. Osmanov, I. G. Sokolov, V. Matsulevich, and G. N. Borisova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 1263.
2003COR629 P. Gros and Y. Fort, *Curr. Org. Chem.*, 2003, **7**, 629.
2003COR995 W. Śliwa, *Curr. Org. Chem.*, 2003, **7**, 995.
2003CRV2945 A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945.
2003DP223 A. C. Razus, L. Birzan, S. Nae, L. Cristian, F. Chiraleu, and V. Cimpeanu, *Dyes Pigments*, 2003, **57**, 223.
2003EJO4586 X. Wang, A. M. Kauppi, R. Olsson, and F. Almqvist, *Eur. J. Org. Chem.*, 2003, 4586.
2003JFC173 K. Adachi, Y. Ohira, G. Tomizawa, S. Ishihara, and S. Oishi, *J. Fluorine Chem.*, 2003, **120**, 173.
2003JHC325 F. Minisci, F. Recupero, A. Cecchetto, C. Punta, C. Gambarotti, F. Fontana, and G. F. Pedulli, *J. Heterocycl. Chem.*, 2003, **40**, 325.
2003JME4273 Y. Cao, M. Zhang, C. Wu, S. Lee, M. E. Wroblewski, T. Whipple, P. I. Nagy, K. Takacs-Novak, A. Balazs, S. Toros, *et al. J. Med. Chem.*, 2003, **46**, 4273.
2003JOC267 S. A. Shackelford, M. B. Anderson, L. C. Christie, T. Goetzen, M. C. Guzman, M. A. Hananel, W. D. Kornreich, H. Li, V. P. Pathak, A. K. Rabinovich, *et al. J. Org. Chem.*, 2003, **68**, 267.
2003JOC1470 C. Addicott, A. Reisinger, and C. Wentrup, *J. Org. Chem.*, 2003, **68**, 1470.
2003JOC3352 A. Sutherland and T. Gallagher, *J. Org. Chem.*, 2003, **68**, 3352.
2003JOC3736 J. M. Nolan and D. L. Comins, *J. Org. Chem.*, 2003, **68**, 3736.
2003JOC3802 A. A. Neverov, H. X. Feng, K. Hamilton, and R. S. Brown, *J. Org. Chem.*, 2003, **68**, 3802.
2003JOC7077 C. Wolf and R. Lerebours, *J. Org. Chem.*, 2003, **68**, 7077.
2003JOC7308 A. Solladie-Cavallo, C. Marsol, M. Yaakoub, K. Azyat, A. Klein, M. Roje, C. Suteu, T. B. Freedman, X. Cao, and L. A. Nafie, *J. Org. Chem.*, 2003, **68**, 7308.
2003JOC7379 A. C. Spivey, F. Zhu, M. B. Mitchell, S. G. Davey, and R. L. Jarvest, *J. Org. Chem.*, 2003, **68**, 7379.
2003JOC7551 C. Wolf and R. Lerebours, *J. Org. Chem.*, 2003, **68**, 7551.
2003JOC10178 A. Bouillon, A. S. Voisin, A. Robic, J.-C. Lancelot, V. Collot, and S. Rault, *J. Org. Chem.*, 2003, **68**, 10178.
2003JOM58 D. Bravo-Zhivotovskii, G. Korogodsky, and Y. Apeloig, *J. Organomet. Chem.*, 2003, **686**, 58.
2003OBC2710 J. M. Bakke, E. Ranes, C. Romming, and I. Sletvold, *Org. Biomol. Chem.*, 2003, **1**, 2710.
2003OBC4254 S. Tabanella, I. Valancogne, and R. F. W. Jackson, *Org. Biomol. Chem.*, 2003, **1**, 4254.
2003OL3131 W. Yang, Y. Wang, and J. R. Corte, *Org. Lett.*, 2003, **5**, 3131.

- 2003OL4611 J. Ji, T. Li, and W. H. Bunnelle, *Org. Lett.*, 2003, **5**, 4611.
- 2003PAC1403 J. M. Bakke, *Pure Appl. Chem.*, 2003, **75**, 1403.
- 2003SL1678 A. Meana, J. F. Rodríguez, M. A. Sanz-Tejedor, and J. L. García-Ruano, *Synlett*, 2003, 1678.
- 2003SL1801 C. Wolf, G. E. Tumambac, and C. N. Villalobos, *Synlett*, 2003, 1801.
- 2003T2953 P. M. Weintraub, J. S. Sabol, J. M. Kane, and D. R. Bercherding, *Tetrahedron*, 2003, **59**, 2953.
- 2003T3009 W. Zhang and G. Pugh, *Tetrahedron*, 2003, **59**, 3009.
- 2003TA1691 M. Amat, M.-D. Coll, N. Llor, C. Escolano, E. Molins, C. Miravittles, and J. Bosch, *Tetrahedron Asymmetry*, 2003, **14**, 1691.
- 2003TL4711 M.-L. Bannasar, E. Zulaica, T. Roca, Y. Alonso, and M. Moneris, *Tetrahedron Lett.*, 2003, **44**, 4711.
- 2003TL6643 F. C. Krebs, *Tetrahedron Lett.*, 2003, **44**, 6643.
- 2004AGE2850 F. Glorius, N. Spielkamp, S. Holle, R. Goddard, and C. W. Legmann, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 2850.
- 2004AGE4902 N. Giuseppone, J.-L. Schmitt, and J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 4902.
- 2004CCR2337 I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337.
- 2004CHE1124 A. A. Bogolyubov, N. B. Chernysheva, and V. V. Semenov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1124.
- 2004CRV2667 R. Chinchilla, C. Nájera, and M. Yus, *Chem. Rev.*, 2004, **104**, 2667.
- 2004COR715 R. Lavilla, *Curr. Org. Chem.*, 2004, **8**, 715.
- 2004COR757 W. Zhang, *Curr. Org. Chem.*, 2004, **8**, 757.
- 2004COR781 P. J. Guiry and D. Kiely, *Curr. Org. Chem.*, 2004, **8**, 781.
- 2004DP1 M. S. Yen and I. J. Wang, *Dyes Pigments*, 2004, **63**, 1.
- 2004DP173 M. S. Yen and I. J. Wang, *Dyes Pigments*, 2004, **62**, 173.
- 2004EJO1891 L. Bijere, L. Legentil, J. Bastide, F. Darro, C. Rochart, and E. Delfourne, *Eur. J. Org. Chem.*, 2004, 1891.
- 2004JA11808 E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 11808.
- 2004JFC661 R. D. Chambers, D. Holling, G. Sandford, A. Batsanov, and J. A. K. Howard, *J. Fluorine Chem.*, 2004, **125**, 661.
- 2004JOC2033 N. M. Lan, R. Burgard, and C. Wentrup, *J. Org. Chem.*, 2004, **69**, 2033.
- 2004JOC2863 J. T. Kuethe and D. L. Comins, *J. Org. Chem.*, 2004, **69**, 2863.
- 2004JOC3550 J. L. Díaz, M. Miguel, and R. Lavilla, *J. Org. Chem.*, 2004, **69**, 3550.
- 2004JOC5219 J. T. Kuethe and D. L. Comins, *J. Org. Chem.*, 2004, **69**, 5219.
- B-2004MI41 N. Miyaura; in 'Metal-Catalyzed Cross-Coupling Reactions', 2nd edn, A. DeMeijere and F. Diederich, Eds.; Wiley-VCH, Weinheim, 2004, p. 41.
- B-2004MI125 T. N. Mitchell; in 'Metal-Catalyzed Cross-Coupling Reactions', 2nd edn, A. DeMeijere and F. Diederich, Eds.; Wiley-VCH, Weinheim, 2004, p. 125.
- B-2004MI163 S. E. Denmark and R. F. Sweis; in 'Metal-Catalyzed Cross-Coupling Reactions', 2nd edn, A. DeMeijere and F. Diederich, Eds.; Wiley-VCH, Weinheim, 2004, p. 163.
- B-2004MI815 E. Negishi, X. Zeng, Z. Tan, M. Qian, Q. Hu, and Z. Huang; in 'Metal-Catalyzed Cross-Coupling Reactions', 2nd edn, A. DeMeijere and F. Diederich, Eds.; Wiley-VCH, Weinheim, 2004, p. 815.
- 2004OBC220 I. Hutchinson, A. J. McCarroll, R. A. Heald, and M. F. G. Stevens, *Org. Biomol. Chem.*, 2004, **2**, 220.
- 2004OBC2170 S. H. Lee, Y. S. Park, M. H. Nam, and C. M. Yoon, *Org. Biomol. Chem.*, 2004, 2170.
- 2004OL683 S. Kohmoto, T. Noguchi, H. Masu, K. Kishikawa, M. Yamamoto, and K. Yamaguchi, *Org. Lett.*, 2004, **6**, 683.
- 2004OL3671 E. Bacque, M. E. Qacemi, and S. Z. Zard, *Org. Lett.*, 2004, **6**, 3671.
- 2004PCA1033 C. Buron, E. M. Tippmann, and M. S. Platz, *J. Phys. Chem. A*, 2004, **108**, 1033.
- 2004OL4587 T. Itoh and T. Mase, *Org. Lett.*, 2004, **6**, 4587.
- 2004RCB189 I. P. Beletskaya, G. V. Latyshev, A. V. Tsvetkov, and N. V. Lukashev, *Russ. Chem. Bull.*, 2004, **53**, 189.
- 2004RCB2233 A. V. Lesiev, S. L. Ioffe, Y. A. Strelenko, and V. M. Danilenko, *Russian Chem. Bull., Int. Ed.*, 2004, **53**, 2233.
- 2004RJC1597 V. I. Rybachenko, G. Shreder, V. M. Gokhfel'd, K. Yu. Chotii, V. V. Kovalenko, and B. Lenska, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2004, **74**, 1597.
- 2004S2419 F. Bellina, A. Carpita, and R. Rossi, *Synthesis*, 2004, 2419.
- 2004SC247 P. Zhong, S. Guo, and C. Song, *Synth. Commun.*, 2004, **34**, 247.
- 2004SC4301 P. Zhong, H. Hu, and S. Guo, *Synth. Commun.*, 2004, **34**, 4301.
- 2004SL1318 J. Salazar and R. Dorta, *Synlett*, 2004, **7**, 1318.
- 2004TL1751 D. B. Gotchev and D. L. Comins, *Tetrahedron*, 2004, **60**, 11751.
- 2004TA3919 S. Leleu, C. Papamicaël, F. Marsais, G. Dupas, and V. Levacher, *Tetrahedron Asymmetry*, 2004, **15**, 3919.
- 2004TL121 P. Kavanagh and D. Leech, *Tetrahedron Lett.*, 2004, **45**, 121.
- 2004TL3215 K. Fujita, C. Kitatsuji, S. Furukawa, and R. Yamaguchi, *Tetrahedron Lett.*, 2004, **45**, 3215.
- 2004RCB3913 M. K. Uddin, R. Fujiyama, S.-I. Kiyooka, M. Fujio, and Y. Tsuno, *Tetrahedron Lett.*, 2004, **45**, 3913.
- 2004TL4281 V. B. Sharma, S. L. Jain, and B. Sain, *Tetrahedron Lett.*, 2004, **45**, 4281.
- 2004TL4437 M. Sakamoto, T. Yagi, S. Kobaru, T. Mino, and T. Fujita, *Tetrahedron Lett.*, 2004, **45**, 4437.
- 2004TL6125 C. J. Cowden, D. C. Hammond, B. C. Bishop, K. M. J. Brands, A. J. Davies, U. Dolling, and S. E. Brewer, *Tetrahedron Lett.*, 2004, **45**, 6125.
- 2004TL8889 V. Derdau, *Tetrahedron Lett.*, 2004, **45**, 8889.
- 2004TL8895 R. R. Srivastava and S. E. Collibee, *Tetrahedron Lett.*, 2004, **45**, 8895.
- 2004USP6706844 D. L. Comins and S. Huang, *US Pat.* 6 706 844 (2004).
- 2005AGE4442 K. C. Nicolaou, P. G. Bulger, and D. Sarlah, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 4442.
- 2005AP329 F. M. Abdelrazek and A. E. M. Fathy, *Arch. Pharm. (Weinheim, Ger.)*, 2005, **338**, 329.
- 2005BML883 S. Marchais-Oberwinkler, B. Nowicki, V. W. Pike, C. Halldin, J. Sandell, Y.-H. Chou, B. Gulyas, L. T. Brennum, L. Farde, and H. V. Wikstrom, *Biorg. Med. Chem.*, 2005, **13**, 883.
- 2005CAR15 S. Ghirmai, E. Mume, V. Tolmachev, and S. Sjöberg, *Carbohydr. Res.*, 2005, **340**, 15.
- 2005CEJ1903 C. Bobbio, T. Rausis, and M. Schlosser, *Chem. Eur. J.*, 2005, **11**, 1903.
- 2005CHE771 A. B. Borisov, V. K. Belsky, T. V. Goncharova, G. N. Borisova, V. K. Osmanov, Z. V. Matsulevich, N. G. Frolova, and E. D. Savin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2005, **41**, 771.
- 2005CJC266 R. Franzen and Y. Xu, *Can. J. Chem.*, 2005, **83**, 266.

- 2005CL624 A. Fuerstner and R. Martin, *Chem. Lett.*, 2005, **34**, 624.
- 2005DP21 T. Deligeorgiev, A. Vasilev, and K.-H. Drexhage, *Dyes Pigments*, 2005, **67**, 21.
- 2005HCA1983 A. D. Averin, O. A. Ulanovskaya, I. A. Fedotenko, A. A. Borisenko, M. V. Serebryakova, and I. P. Beletskaya, *Heck. Chim. Acta*, 2005, **88**, 1983.
- 2005IC601 Y. Cui, Q.-D. Liu, D.-R. Bai, W.-L. Jia, Y. Tao, and S. Wang, *Inorg. Chem.*, 2005, **44**, 601.
- 2005ICA2996 G. Vargas, N. Farfan, R. Santillan, A. Gutierrez, E. Gomez, and V. Barba, *Inorg. Chim. Acta*, 2005, **358**, 2996.
- 2005JA8966 C. Y. Legault and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 8966.
- 2005JHC463 J. M. Bakke, *J. Heterocycl. Chem.*, 2005, **42**, 463.
- 2005JOC2000 F. Hoffmann-Emery, H. Hilpert, M. Scalone, and P. Waldmeier, *J. Org. Chem.*, 2005, **71**, 2000.
- 2005JOC2368 A. Lemire, D. Beaudoin, M. Grenon, and A. B. Charette, *J. Org. Chem.*, **70**, 2368.
- 2005JOC2494 M. Schlosser, C. Bobbio, and T. Rausis, *J. Org. Chem.*, 2005, **70**, 2494.
- 2005JOC5618 X. Feng, E. N. Duesler, and P. S. Mariano, *J. Org. Chem.*, 2005, **70**, 5618.
- 2005JOC10186 A. Klapars, J. H. Waldman, K. R. Campos, M. S. Jensen, M. McLaughlin, J. Y. L. Chung, R. J. Cvetovich, and C.-y. Chen, *J. Org. Chem.*, 2005, **70**, 10186.
- 2005JOC10653 P. Hewavitharane, E. O. Danilov, and D. C. Neckers, *J. Org. Chem.*, 2005, **70**, 10653.
- 2005OBC538 A. R. Katritzky, E. F. V. Scriven, S. Majumder, R. G. Akhmedova, A. V. Vakulenko, N. G. Akhmedov, R. Murugan, and K. A. Abboud, *Org. Biomol. Chem.*, 2005, **3**, 538.
- 2005OBC4171 F. Glorius, *Org. Biomol. Chem.*, 2005, **3**, 4171.
- 2005OL435 T. J. Donohoe, D. J. Johnson, L. H. Mace, M. J. Bamford, and O. Ichihara, *Org. Lett.*, 2005, **7**, 435.
- 2005OL697 P. Pierrat, P. Gros, and Y. Fort, *Org. Lett.*, 2005, **7**, 697.
- 2005SL1188 P. Belmont and T. Helhadj, *Org. Lett.*, 2005, **7**, 1793.
- 2005OL2519 T. K. Macklin and V. Snieckus, *Org. Lett.*, 2005, **7**, 2519.
- 2005OL2747 A. Lemire and A. B. Charette, *Org. Lett.*, 2005, **7**, 2747.
- 2005OL5227 D. L. Comins and J. J. Sahn, *Org. Lett.*, 2005, **7**, 5227.
- 2005OL5535 E. J. Corey and Y. Tian, *Org. Lett.*, 2005, **7**, 5535.
- 2005OL5773 M. Sales and A. B. Charette, *Org. Lett.*, 2005, **7**, 5773.
- 2005PAC2047 M. Karai, N. Kato, E. Ichikawa, and M. Shibasaki, *Pure Appl. Chem.*, 2005, **77**, 2047.
- 2005S2989 B. A. Friedman, B. R. Taft, C.-T. Lee, T. Butler, and B. H. Lipshutz, *Synthesis*, 2005, 2989.
- 2005SL1188 A. Gutnov, V. Abaev, D. Redkin, C. Fischer, W. Bonrath, and B. Heller, *Synlett*, 2005, 1188.
- 2005SOS(15)11 D. Spitzner; in 'Science of Synthesis', D. Black, Ed.; Thieme, New York, 2005, vol. 15, p. 11.
- 2005T2245 S. Schroeter, C. Stock, and T. Bach, *Tetrahedron*, 2005, **61**, 2245.
- 2005T4289 S. Goswami, A. K. Adak, R. Mukherjee, S. Jana, S. Dey, and J. F. Gallagher, *Tetrahedron*, 2005, **61**, 4289.
- 2005T4569 N. Robert, C. Hoarau, S. Célanire, P. Ribéreau, A. Godard, G. Quéguiner, and F. Marsais, *Tetrahedron*, 2005, **61**, 4569.
- 2005T10331 V. Carelli, F. Liberatore, L. Scipione, B. D. Rienzo, and S. Tortorella, *Tetrahedron*, 2005, **61**, 10331.
- 2005TL581 J. C. Fernandez, L. Sole-Feu, D. Fernandez-Former, N. Figuera, P. Forns, and F. Alberico, *Tetrahedron Lett.*, 2005, **46**, 581.
- 2005TL1137 J. Baudoux, P. Judeinstein, D. Cahard, and J.-C. Plaquevent, *Tetrahedron Lett.*, 2005, **46**, 1137.
- 2005TL2279 A. S. Kiselyov, *Tetrahedron Lett.*, 2005, **46**, 2279.
- 2005TL2983 M. Pauvert, S. C. Collet, M.-J. Bertrand, A. Y. Guingant, and Michel Evain, *Tetrahedron Lett.*, 2005, **46**, 2983.
- 2005TL3513 E. Gómez, M. Miguel, O. Jiménez, G. de la Rosa, and R. Lavilla, *Tetrahedron Lett.*, 2005, **46**, 3513.
- 2005TL3573 T. Itoh and T. Mase, *Tetrahedron Lett.*, 2005, **46**, 3573.
- 2005TL4487 A. S. Kiselyov, *Tetrahedron Lett.*, 2005, **46**, 4487.
- 2005TL6697 D. L. Comins, J. M. Nolan, and I. D. Bori, *Tetrahedron Lett.*, 2005, **46**, 6697.
- 2005TL8905 J. S. Yadav, B. V. S. Reddy, M. Sreenivas, and K. Sathiah, *Tetrahedron Lett.*, 2005, **46**, 8905.
- 2005ZNB683 A. Schmidt and T. Mordhorst, *Z. Naturforsch., B*, 2005, **60**, 683.
- 2006AGE2720 H. Sun and S. G. DiMaggio, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**, 2720.
- 2006AGE7803 A. M. Kearney and C. D. Vanderwal, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**, 7803.
- 2006BMC4466 A. S. Girgis, H. M. Hosni, and F. F. Barsoum, *Bioorg. Med. Chem.*, 2006, **14**, 4466.
- 2006CEJ4954 S. E. Denmark and J. D. Baird, *Chem. Eur. J.*, 2006, **12**, 4954.
- 2006EJO4343 A. Lei, M. Chen, M. He, and X. Zhang, *Eur. J. Org. Chem.*, 2006, 4343.
- 2006JHC117 W. Stadlbauer, A. E. Taeubl, H. V. Dang, C. Reidlinger, and K. Zangger, *J. Heterocycl. Chem.*, 2006, **43**, 117.
- 2006JOC8602 J. Y. L. Chung, R. J. Cvetovich, M. McLaughlin, J. Amato, F.-R. Tsay, M. Jensen, S. Weissman, and D. Zewge, *J. Org. Chem.*, 2006, **71**, 8602.
- 2006JOC9540 J. M. Keith, *J. Org. Chem.*, 2006, **71**, 9540.
- 2006OBC1071 T. J. Donohoe, D. J. Johnson, L. H. Mace, R. E. Thomas, J. Y. K. Chiu, J. S. Rodrigues, R. G. Compton, C. E. Banks, P. Tomcik, M. J. Bamford, *et al. Org. Biomol. Chem.*, 2006, **4**, 1071.
- 2006OL179 E. D. Smith, F. C. Fevrier, and D. L. Comins, *Org. Lett.*, 2006, **8**, 179.
- 2006OL415 P. Vera-Luque, R. Alajarin, J. Alvarez-Builla, and J. J. Vaquero, *Org. Lett.*, 2006, **8**, 415.
- 2006OL729 T. Nokami, Y. Tomida, T. Kamei, K. Itami, and J. Yoshida, *Org. Lett.*, 2006, **8**, 729.
- 2006OL2961 C. Schroif-Gregoire, N. Traver, A. Zaparucha, and A. Al-Mourabit, *Org. Lett.*, 2006, **8**, 2961.
- 2006OL2985 T. Focken and A. B. Charette, *Org. Lett.*, 2006, **8**, 2985.
- 2006OL3307 M. McLaughlin, M. Palucki, and I. W. Davies, *Org. Lett.*, **8**, 3307.
- 2006OL3367 P. Chen, Y. Chen, P. J. Carroll, and S. McNSieburth, *Org. Lett.*, 2006, **8**, 3367.
- 2006OL3549 F. F. Wagner and D. L. Comins, *Org. Lett.*, 2006, **8**, 3549.
- 2006OL5789 N. A. O. Williams, C. Masdeu, J. L. Díaz, and R. Lavilla, *Org. Lett.*, 2006, **8**, 5789.
- 2006OL5853 A. Labonne, T. Kribber, and L. Hintermann, *Org. Lett.*, 2006, **8**, 5853.
- 2006RCB331 L. A. Musina, E. E. Shul'ts, L. A. Kricherskii, S. M. Adekenov, M. M. Shakirov, and G. A. Tolstikov, *Russ. Chem. Bull.*, 2006, **55**, 331.
- 2006S3987 A. Schmidt, T. Mordhorst, and M. Nieger, *Synthesis*, 2006, 3987.
- 2006T1667 A. Schmidt, T. Mordhorst, and M. Nieger, *Tetrahedron*, 2006, **62**, 1667.

- 2006T4435 Z. Zhang, J. Mao, D. Zhu, F. Wu, H. Chen, and B. Wan, *Tetrahedron*, **62**, 4435.
- 2006T6000 A. S. Voisin, A. Bouillon, J.-C. Lancelot, A. Lesnard, and S. Rault, *Tetrahedron*, 2006, **62**, 6000.
- 2006T6893 A. Schmidt, J. C. Namyslo, and T. Mordhorst, *Tetrahedron*, 2006, **62**, 6893.
- 2006T11063 C. Sicre, J.-L. Alonso-Gómez, and M. M. Cid, *Tetrahedron*, 2006, **62**, 11063.
- 2006TA1728 J. Pernak and J. Feder-Kubis, *Tetrahedron Asymmetry*, 2006, **17**, 1728.
- 2006THC(1)155 B. U. W. Maes; in 'Topics in Heterocyclic Chemistry', R. R. Gupta, Ed.; Springer-Verlag, Berlin, 2006, vol. 1, p. 155.
- 2006TL531 X. Cattoen, D. Bourissou, and G. Bertrand, *Tetrahedron Lett.*, 2006, **47**, 531.
- 2006TL1449 D. L. Comins and E. D. Smith, *Tetrahedron Lett.*, 2006, **47**, 1449.
- 2006TL2691 A. D. Averin, O. A. Ulanovskaya, A. A. Borisenko, M. V. Serebryakova, and I. P. Beletskaya, *Tetrahedron Lett.*, 2006, **47**, 2691.
- 2006TL3471 P. Gaviña and S. Tatay, *Tetrahedron Lett.*, 2006, **47**, 3471.
- 2006TL5333 P. S. Humphries, S. Bailey, Q.-Q. T. Do, J. H. Kellum, G. A. McClellan, and D. M. Wilhite, *Tetrahedron Lett.*, 2006, **47**, 5333.
- 2006TL6037 I. Yavari, Z. Hossaini, and M. Sabbaghan, *Tetrahedron Lett.*, 2006, **47**, 6037.

Biographical Sketch



Professor Daniel L. Comins received his B.A. degree in chemistry in 1972 from the State University of New York at Potsdam and his Ph.D. in 1977 from the University of New Hampshire under the direction of Robert E. Lyle. During 1977–79, he was a postdoctoral associate in the laboratories of Professor A. I. Meyers at Colorado State University working on the total synthesis of the antitumor alkaloids *N*-methylmaysenine and maysine. He joined the faculty of Utah State University in 1979, became an associate professor in 1984, and moved to North Carolina State University as a full professor in 1989. His research interests include heterocyclic chemistry, synthetic methodology, and total synthesis of natural products. In 1995 and again in 1999, he was elected to the Advisory Board of the International Society of Heterocyclic Chemists. He is or has been a member of the editorial advisory boards of *Progress in Heterocyclic Chemistry*, *Letters in Organic Chemistry*, *ARKIVOC*, and *Current Topics in Medicinal Chemistry*. Professor Comins is currently an associate editor of the *Journal of Organic Chemistry*. In 1998, he became a Japan Society Promotion of Science (JSPS) Research Fellow. Recently, he was the recipient of the 2005 North Carolina ACS Distinguished Lecturer Award.



Sean O'Connor was born in Portsmouth, New Hampshire (United States), in 1947. He received his B.S. with special attainments in chemistry from Washington and Lee University. He completed his M.S. at the University of South Carolina with Professor R. L. Cargill and his Ph.D. from Clemson University with Professor R. A. Abramovitch. He has been a postdoctoral associate in the laboratories of Professor D. L. Comins (Utah State University) and Professor R. E. Gawley (University of Miami). He worked as an industrial chemist for 20 years in the aerospace, biotechnology, and pharmaceutical fields and relocated to Clemson University in August 2005, where he is a lecturer in the chemistry department.



Rima S. Al-awar earned her B.S (1988) and Ph.D. (1993) degrees from North Carolina State University under the direction of Prof. Daniel L. Comins. Upon completing her postdoctoral studies with Prof. Michael T. Crimmins at the University of North Carolina at Chapel Hill, she joined Eli Lilly and Company as a senior organic chemist in 1995. As a Research Scientist in Discovery Chemistry Research and Technologies, she contributed to oncology targets including the natural product cryptophycin. She is currently a head in Chemistry Product Research and Development.

7.03

Pyridines and their Benzo Derivatives: Reactivity of Substituents

V. Caprio

University of Auckland, Auckland, New Zealand

© 2008 Elsevier Ltd. All rights reserved.

7.03.1	Introduction	102
7.03.2	Fused Benzene Rings	102
7.03.2.1	Substitution Reactions in Fused Benzene Rings	102
7.03.2.1.1	Deuteration and tritiation	103
7.03.2.1.2	Nitration	103
7.03.2.1.3	Halogenation	104
7.03.2.1.4	Sulfonation	105
7.03.2.1.5	Alkylation	105
7.03.2.1.6	Acylation and Carboxylation	107
7.03.2.1.7	Alkenylation	108
7.03.2.1.8	Alkynylation	109
7.03.2.1.9	Arylation	109
7.03.2.1.10	Nucleophilic displacement	111
7.03.2.1.11	Formation of organometallic species	112
7.03.2.2	Oxidation at the Fused Benzene Ring	113
7.03.2.3	Reduction of Fused Benzene Rings	114
7.03.3	C-Linked Substituents	115
7.03.3.1	Alkyl Groups	115
7.03.3.1.1	Alkyl substituents attached to carbon	115
7.03.3.1.2	Alkyl substituents attached to nitrogen	120
7.03.3.2	Aryl Groups	123
7.03.3.3	Acyl Groups	126
7.03.3.4	Carboxylic Acids and Derivatives	129
7.03.4	N-Linked Substituents	132
7.03.4.1	Amino Groups and Related Functions	132
7.03.4.1.1	Amino groups attached to carbon	132
7.03.4.1.2	Amino groups attached to nitrogen	135
7.03.4.2	Nitro Groups	136
7.03.5	O-Linked Substituents	137
7.03.5.1	Pyridones and Hydroxypyridines	137
7.03.5.2	Alkylation of Hydroxypyridines, Pyridones, and their Benzo Derivatives	138
7.03.5.3	Acylation of Hydroxypyridines, Pyridones, and their Benzo Derivatives	140
7.03.5.4	Ethers	140
7.03.5.5	N-Oxides and their Derivatives	141
7.03.6	S-Linked Substituents	143
7.03.6.1	Thiols, their Tautomers and Related Compounds	143
7.03.6.2	Sulfonic Acids and Related Compounds	146
7.03.7	Halogen Substituents	148
7.03.7.1	Nucleophilic Displacement	148

7.03.7.1.1	Oxygen and sulfur nucleophiles	148
7.03.7.1.2	Nitrogen nucleophiles	149
7.03.7.1.3	Other nucleophiles	152
7.03.7.2	Reductive Dehalogenation	153
7.03.7.3	Halogens Attached to Nitrogen	153
7.03.8	Metals	154
7.03.9	Further Developments	161
References		161

7.03.1 Introduction

The aromatic ring of pyridine and the benzo derivatives is electron deficient due to the presence of the electro-negative nitrogen atom with positions 2, 4, and 6 on the pyridine ring most affected. In a similar manner, positions 2 and 4 of the quinoline ring and carbons 1 and 3 of the isoquinoline ring are especially electron deficient. The π -deficiency affects the reactivity of substituents on these heterocycles especially those at the more electron-deficient sites. Many examples of this effect are discussed in CHEC-II(1996) <1996CHEC-II(5)91>. For example, benzylic anions of 2- and 4-picolines are stabilized by resonance and induction and the methyl group is readily deprotonated by strong bases. 2-Hydroxypyridines exist predominantly as the 2-pyridone tautomer and thus behave as in lactams. In a similar manner, 2-pyridinethiols are in equilibrium with the thione tautomer. Furthermore, halopyridines undergo nucleophilic substitution in the absence of electron-withdrawing groups. While many of the transformations presented in CHEC-II(1996) are still routinely employed this chapter will focus on a discussion of the many new methods developed for manipulating substituents on the hetarene ring of pyridines, quinolines, and isoquinolines. Much of this new methodology proceeds via the generation of heteroaryl-based organometallic species and significant progress has been made in this area during the last decade. In the past the generation of organolithium reagents was limited by the propensity of the heteroarene ring to undergo nucleophilic attack and very few reports of the preparation of pyridylmagnesium halides existed. Either species may now be accessed without difficulty and the formation of carbon-carbon bonds to the hetarene ring is a routine procedure. Furthermore, there are numerous examples of the palladium(0)-mediated formation of both carbon-carbon and carbon-heteroatom bonds at the hetarene ring of pyridines, quinolines, and isoquinolines.

The on-going discovery of pyridine and quinoline alkaloids, some of potent bioactivity <2000NPR131, 2004NPR752>, no doubt provides much impetus for the development of new transformations in this area. The isolation and chemistry of new pyridine alkaloids is the subject of regular review <2000NPR435, 1997NPR637> and the discovery of new quinoline alkaloids is also covered on an annual basis <2005NPR627, 2004NPR650, 2003NPR476, 2002NPR742, 2001NPR543, 2000NPR603, 1999NPR697, 1998NPR595, 1997NPR605, 1997NPR11, 1995NPR465, 1995NPR77>.

The chemistry of pyridines and benzo derivatives is also reviewed elsewhere. The literature in this area is covered on an annual basis in the review series *Progress in Heterocyclic Chemistry* <2005PHC261, 2004PHC309, 2003PHC284, 2002PHC257, 2001PHC238, 2000PHC237, 1999PHC230, 1998PHC226, 1997PHC222, 1996PHC209, 1995PHC195> and has been the subject of review in the recent edition of *Science of Synthesis* <2005SOS11, 2005SOS389>.

7.03.2 Fused Benzene Rings

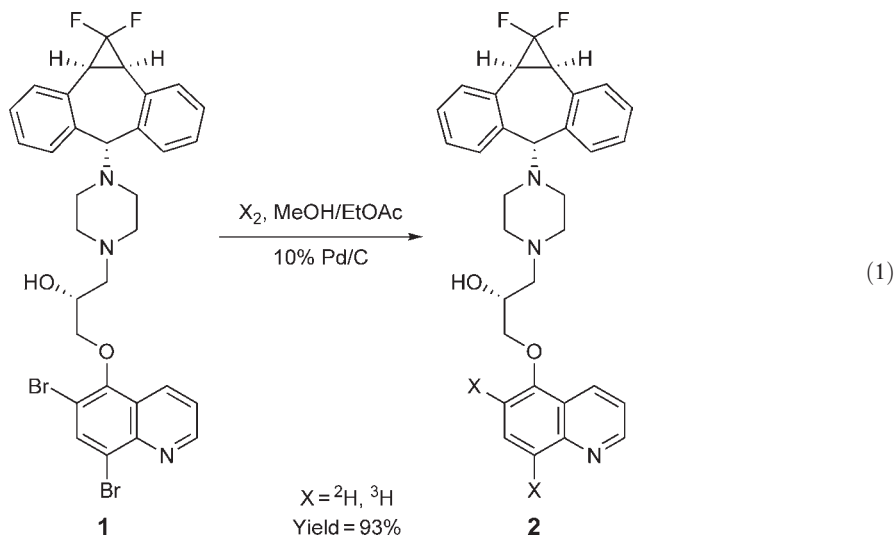
7.03.2.1 Substitution Reactions in Fused Benzene Rings

As expected the carbocyclic ring of quinolines undergoes more facile electrophilic substitution than the heterocyclic ring especially in strongly acidic media when the pyridine ring is further deactivated by protonation. In general, electrophilic substitution occurs predominantly at the 5- and 8-positions, but the regiochemistry of addition is also influenced by the presence of any electron-donating groups. While substituents at the 2- and 4-positions of quinolines are most activated toward nucleophilic attack, the S_NAr reaction can occur at the carbocyclic ring especially when substituents are activated by *ortho* or *para* electron-withdrawing groups. The formation of carbon-carbon bonds to the carbocyclic ring of quinolines is mainly achieved by metal-mediated processes from the corresponding haloquinoline, either via metal-halogen exchange or using transition metal-catalyzed procedures.

7.03.2.1.1 Deuteration and tritiation

Much recent research in this area has been driven by the need for radiolabeled quinoline-based pharmaceuticals for use in pharmacokinetic and mechanistic studies. The classical method for the synthesis of 8-deuterioquinolines is by hydrogen exchange of a quinoline precursor at the carbocyclic ring using deuteriosulfuric acid at high temperature. This method has been applied to the conversion of 4,7-dichloroquinoline to 8-deuterio-4,7-dichloroquinoline – a compound used in the synthesis of deuterium-labeled ferrochloroquine <1998JLCR911>.

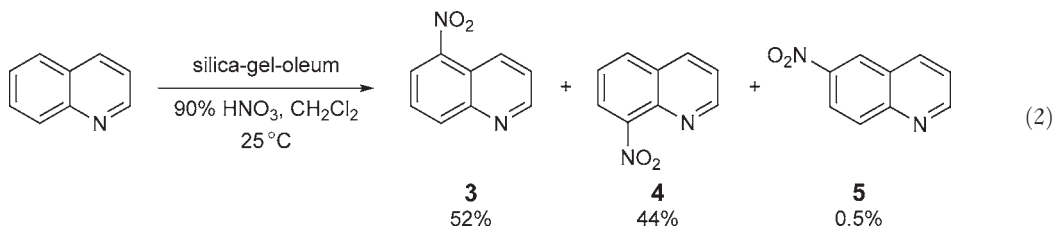
Regioselective deuteration/tritiation can be achieved by treatment of the corresponding bromide with deuterium or tritium gas in the presence of palladium on carbon. This method can be performed on relatively complex substrates. For example, dibromoquinoline **1** was converted to the labeled multidrug resistance modulator, compound **2** in high yield (Equation 1) <1997JLCR49>. In a similar manner, the 6-bromoquinolyl moiety of bromosaquinavir was converted to tritiated saquinavir on treatment with tritium in the presence of palladium on carbon in ethanol <1998JLCR1103>.



A number of modifications to the classical, acid-catalyzed hydrogen–deuterium exchange have been made and applied to the synthesis of polydeuterated quinolines. Quinoline- d_7 may be prepared by treating quinoline with deuterium oxide and a polymer-supported sulfonic acid Deloxan[®] in a stainless steel pressure reactor at 325 °C <1999TL4433>. A deuteration that proceeds under more mild conditions can be achieved using a microwave-enhanced procedure performed on the hydrochloride salt. Irradiating 5-aminoquinolin-8-ol hydrochloride in a conventional microwave oven in deuterium oxide led to 95% deuterium incorporation at the 6-position and 30% deuterium incorporation at the 7-position <2000J(P2)2208>. Access to quinoline- d_7 can also be achieved under microwave irradiation. Almost complete base-catalyzed deuterium exchange occurs when a solution of quinoline-4-ol in 40% NaOD- D_2O is subjected to four microwave treatments in a conventional microwave oven at high setting <2000ISJ301>.

7.03.2.1.2 Nitration

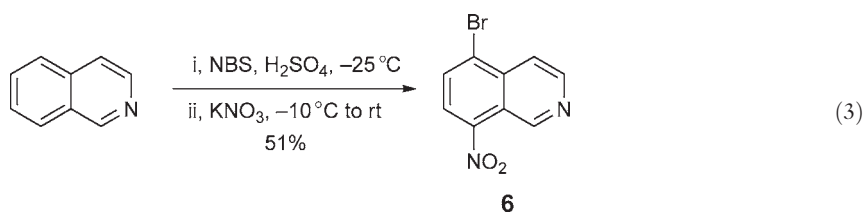
Quinoline undergoes nitration at the 5- and 8-positions using strongly acidic media such as nitric acid/sulfuric acid and yields 3-nitroquinoline under more weakly acidic conditions. While the former remains the method of choice for effecting nitration of the carbocyclic ring, some research has been directed toward reducing the amount of sulfuric acid used in this process by the use of solid supported acid catalysts. Soaking silica gel in 20% oleum provides solid-supported sulfuric acid that catalyzes the nitration of quinoline in nitric acid to give a mixture of 5-nitroquinoline **3** and 8-nitroquinoline **4** along with small quantities of the 6-isomer **5** (Equation 2) <1996TL513>.



The rate of nitration is greatly increased under microwave irradiation. While 8-hydroxyquinoline is nitrated in 3.5 h using copper(II) nitrate and glacial acetic acid, the same reaction is effected in 1 min under microwave irradiation in a conventional microwave oven to give the 5-nitro-8-hydroxyquinoline in 70% yield <1997IJB1071>.

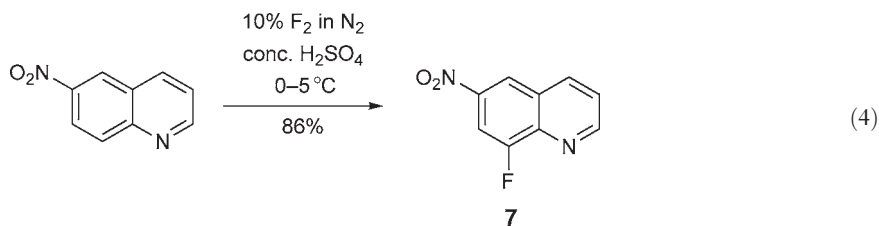
Quinoline-1-oxide undergoes nitration at the 2-, 5-, and 8-positions. While it is known that isomer ratios are temperature dependent, it has been recently shown that the orientation of nitration is also dependent on the acidity of the reaction medium <1997CPB279>. 2-Nitroquinoline 1-oxide, arising from nitration of unprotonated substrate, predominates under weakly acidic conditions. Nitration in stronger acidic media occurs on the hydroxyquinolinium ion and yields 5- and 8-nitroquinoline 1-oxide as the major products with increasing amounts of the 5-isomer formed in very highly acidic media.

The nitration of isoquinoline also occurs predominantly at the 5- and 8-positions and may be achieved in tandem with bromination to give access to bromonitroisoquinolines in a one-pot procedure <2005OS98>. Isoquinoline is selectively brominated at the 5-position using *N*-bromosuccinimide (NBS) in sulfuric acid and nitration, without isolation of 5-bromoisoquinoline, occurs on addition of potassium nitrate to afford moderate yields of 5-bromo-8-nitroisoquinoline **6** (Equation 3).



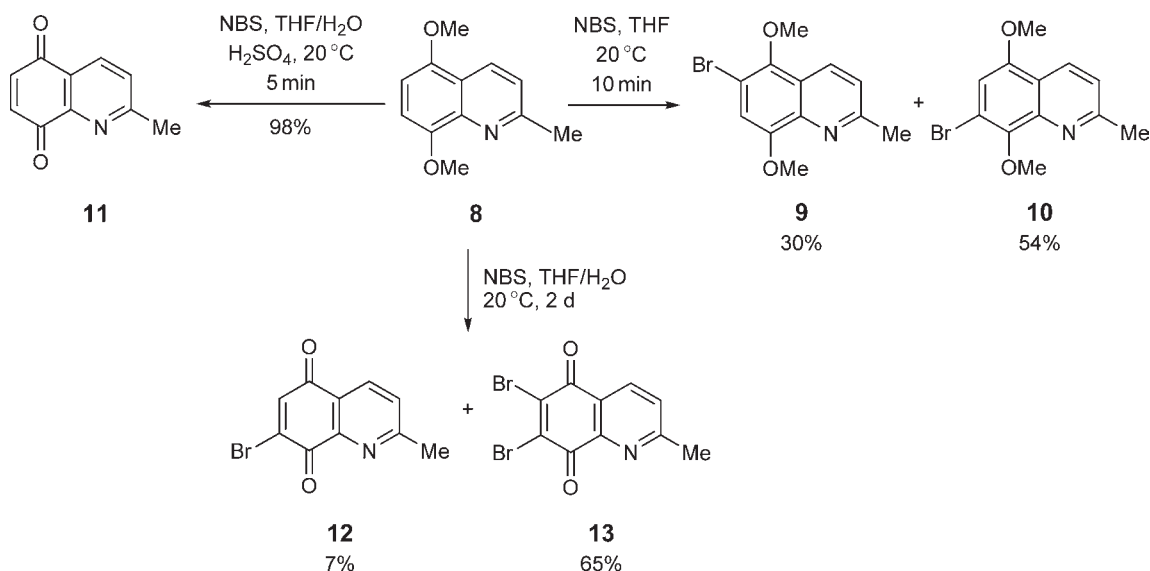
7.03.2.1.3 Halogenation

The medicinal importance of fluorinated compounds has prompted some research into the fluorination of quinolines. A variety of quinolines undergo direct fluorination at the carbocyclic ring using elemental fluorine in acidic media. Passing fluorine gas through a solution of the quinoline in sulfuric acid at 0–5 °C results in the formation of fluorinated quinolines in good yield <2002JFC99, 2004JFC661>. While quinoline gives a mixture of 5-, 6-, and 8-fluoroquinolines, derivatives substituted with electron-donating groups yield products substituted at the *ortho*- and *para*-positions. Fluorination at the *meta*-position occurs on quinolines bearing electron-withdrawing substituents. For example, 6-nitroquinoline undergoes fluorination at C-8 to give fluoroquinoline **7** in good yield (Equation 4).



Direct bromination of quinoline and isoquinoline often results in mixtures of products and some recent research has been directed toward developing more regioselective reaction conditions. Isoquinoline may be regioselectively brominated at C-5 using NBS in sulfuric acid at –18 to –25 °C <2005OS98> or using *N,N'*-dibromoisocyanuric acid (DBI) in triflic acid <2002S83>. Quinoline undergoes sluggish bromination, at the 5-position, using NBS at –20 °C but is brominated at room temperature using DBI/triflic acid to give 5-bromoquinoline in 44% yield.

In contrast to the parent compound, activated quinolines undergo high yielding, regioselective bromination. 6-Haloquinolin-8-ols are chlorinated or brominated at the 5- and then the 7-positions using either *N*-chlorosuccinimide (NCS) or NBS, respectively, in sulfuric acid and undergo dibromination using 2 equiv of either halogenating agent in acetic acid <2001M1075>. 5,8-Dimethoxyquinolines readily undergo bromination using NBS in tetrahydrofuran (THF) at room temperature to give mixtures of 6- and 7-monobrominated quinolines **9** and **10** (Scheme 1). Performing this reaction in aqueous THF, in the presence of sulfuric acid, results in rapid acid-catalyzed oxidative demethylation giving quinoline-5,8-diones **11**. As bromination is faster than oxidation, in the absence of acid, performing the reaction in the presence of water, without sulfuric acid, leads to the isolation of a mixture of 6- and 7-bromoquinolinediones **12** and **13**.

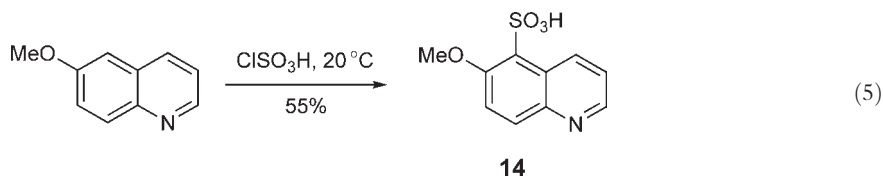


Scheme 1

It has recently been shown that direct iodination of quinoline using iodine in the presence of potassium periodate and sulfuric acid gives access to 3,6-diiodoquinoline rather than the 5,8-diiodo isomer predicted [<2002MM1563>](#).

7.03.2.1.4 Sulfonation

Chlorosulfonation of a variety of electron-rich quinolines and isoquinolines occurs *ortho* or *para* to an electron-donating substituent using neat chlorosulfonic acid at 20°C [<2003SC3427>](#). The product may be isolated as the sulfonic acid or sulfonyl chloride. 6-Methoxyquinoline, for example, is sulfonated at the 5-position under these conditions to give sulfonic acid **14** in moderate yield (Equation 5). Heating is required to effect sulfonation of less activated substrates and the reaction fails to proceed with quinolines and isoquinolines bearing electron-withdrawing groups. The sulfonyl chlorides are converted to sulfonamides on treatment with resin-bound 1-dimethylaminopyridine (DMAP), diisopropylethylamine, and a primary or secondary amine.



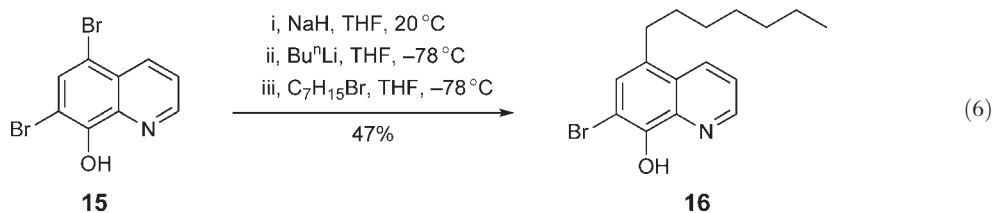
Quinoline- and isoquinolinesulfonic acids may also be accessed from the corresponding bromides by lithiation and sulfonation [<1999BML2753>](#). A range of 2-chloroquinolines and 1-chloroisoquinolines, brominated at the carbocyclic ring, undergo lithium–bromine exchange on treatment with *n*-BuLi in THF at -78°C . The lithio-derivatives are then sulfonated using sulfur dioxide gas and the resulting sulfonic acids converted to the sulfonyl chlorides using thionyl chloride.

7.03.2.1.5 Alkylation

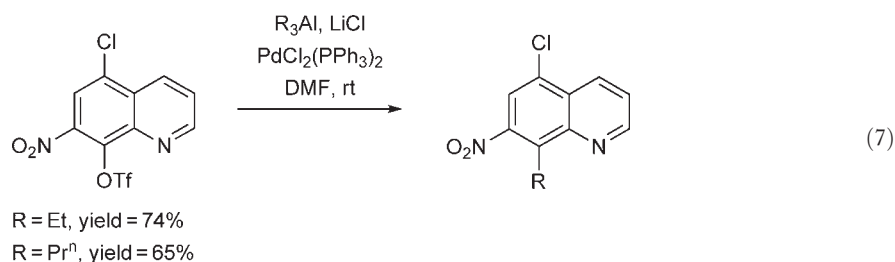
Almost all alkylations at the carbocyclic rings of quinolines are effected by metal-mediated processes; either by quenching of a quinolyl organometallic species with a suitable electrophile or by transition metal-mediated coupling of a haloquinoline or quinolyltriflate with an alkylmetal derivative.

8-Quinolylcyanocuprates undergo coupling with propargyl- and allylbromides to give the corresponding 8-allyl- and 8-propargyl-substituted quinolines in good yield [<2003S233>](#). 7-Lithio and 5-lithio derivatives of 8-hydroxyquinolines react with alkyl bromides, aldehydes, and epoxides to allow introduction of substituted and unsubstituted alkyl

groups at the 5- or 7-position [<1995TL8415>](#). For example, 5-lithio-7-bromo-8-hydroxyquinoline reacts with 1-bromoheptane in THF at -78°C to give 5-heptylquinoline **16** in moderate yield (Equation 6).

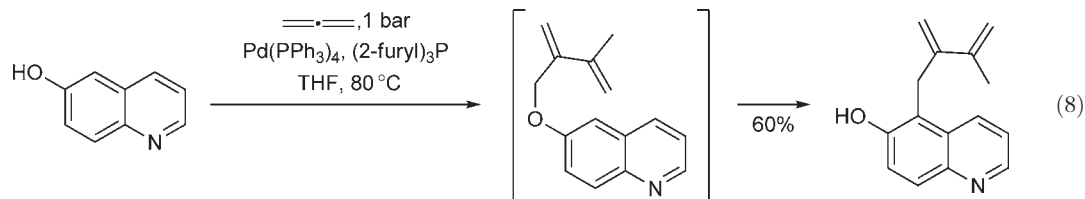


A popular method for carbon–carbon bond formation at the carbocyclic ring of quinolines is by cross-coupling of a suitably functionalized quinoline with an alkylmetal reagent. A decyl group has been introduced to the 5-position of the quinoline ring by Suzuki coupling of 5-bromo-8-alkoxyquinolines with 9-decyl-9-BBN, obtained by hydroboration of 1-decene. 5-Bromo-8-benzyloxyquinoline undergoes cross-coupling with 9-decyl-9-BBN in 64% yield using $\text{Pd}(\text{PPh}_3)_4$ as catalyst in the presence of sodium hydroxide [<1997S1425>](#), while 5-bromo-3-decyl-8-methoxyquinoline undergoes coupling with the same organoborane, prepared *in situ*, in 84% yield using $(\text{dppf})\text{PdCl}_2$ as catalyst in the presence of potassium carbonate [<1999EJOC3165>](#). 8-Hydroxyquinolines may be alkylated at the 8-position via conversion to the corresponding triflate derivative. These triflates, when activated by the presence of an *ortho* nitro group, undergo cross-coupling with tetraethyltin and tetrabutyltin in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ under reflux to give 8-ethyl- and 8-butylquinolines in good yield [<2002SC2027>](#). This cross-coupling occurs, in comparable yields, with triethylaluminium and tripropylaluminium at room temperature (Equation 7).

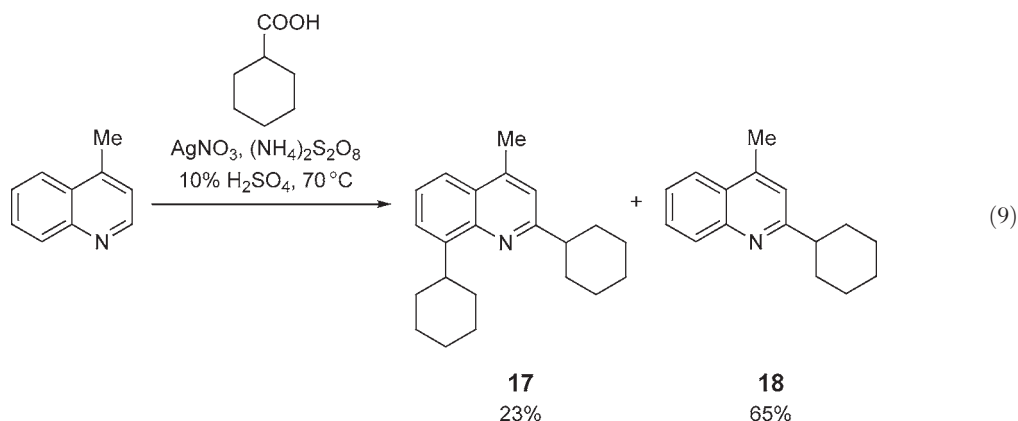


Quinolyl triflates and tosylates also undergo cross-coupling with alkyl Grignard reagents. In a relatively economical coupling process 6-quinolyl triflate, chloride and tosylate undergo coupling to tetradecylmagnesium bromide in the presence of cheap iron(II) salts at room temperature to give the 6-alkylquinoline in good yield [<2002AGE609>](#), [<2002JA13856>](#).

A 1,3-diene moiety has been introduced to the 5-position of 6-hydroxyquinoline by palladium-catalyzed addition of allene [<2001T7965>](#). It is thought that the reaction proceeds by initial *O*-alkylation followed by Claisen rearrangement to give the C-alkylated product (Equation 8).



Alkylation at the carbocyclic ring of quinolines may be achieved by radical-mediated means. 4-Methylquinoline undergoes alkylation with a range of cyclic and acyclic alkyl radicals generated by silver-catalyzed oxidative decarboxylation of carboxylic acids using ammonium persulfate [<2003BML1051>](#). The overall yield of this process is high in some cases and the reaction proceeds to give separable mixtures of 2-alkylquinolines as the major products and 2,8-dialkylquinolines. For example, 4-methylquinoline is alkylated using cyclohexanecarboxylic acid to give a mixture of alkylated products **17** and **18** in 88% overall yield (Equation 9).

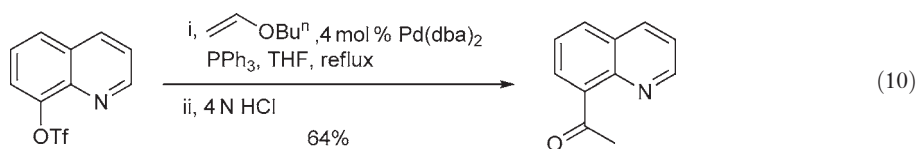


Another radical-mediated alkylation of the carbocyclic ring of quinoline is achieved on generation of polyfluoroalkyl radicals by sulfinate dechlorination of per(poly)fluoroalkyl chlorides in the presence of the reductant sodium dithionite in DMSO [\[2001JFC107\]](#). Quinoline is alkylated, in moderate yield, at the relatively electron-rich 5-position using 1-chlorooctafluorobutane or 1-chloroheptadecafluorooctane as alkylating agent and sodium dithionite in dimethyl sulfoxide (DMSO) at 75°C .

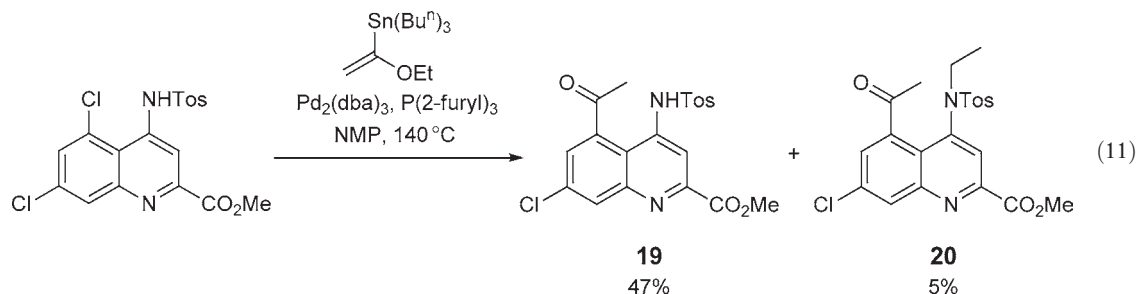
Quinolines activated with electron-donating substituents do undergo Friedel–Crafts alkylation with highly reactive electrophiles. 5-Amino- and 8-aminoquinoline react with neat hexafluoroacetone sesquihydrate, in the absence of Lewis acids, to give products possessing a *para*-1,1,1,3,3,3-hexafluoropropan-2-ol moiety in moderate to good yields [\[2003EJO4286\]](#).

7.03.2.1.6 Acylation and Carboxylation

The main method for the preparation of acylquinolines is by palladium-catalyzed substitution of a haloquinoline or quinolyl triflate precursor. Stille coupling of 8-trifluoromethanesulfonylquinoline with (1-ethoxyvinyl)tri(*n*-butyl)stannane in the presence of $\text{Pd}(\text{dba})_2$ followed by hydrolysis with 4 M HCl proceeds to give 8-acetylquinoline in moderate yield [\[2001T2507\]](#). The reaction with 1-ethoxyvinylzinc or tri(1-ethoxyvinyl)indium proceeds with similar efficiency. Utilizing *n*-butylvinyl ether as coupling partner in a Heck reaction gives 8-acetylquinoline in an improved yield of 64% (Equation 10).



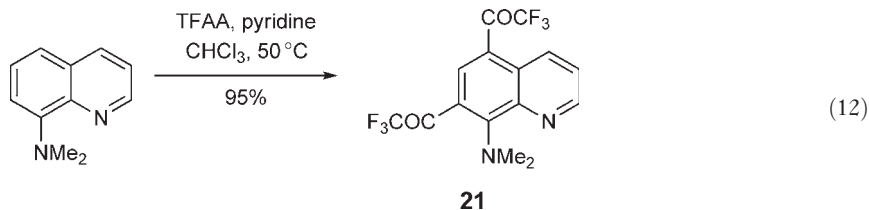
Regioselective cross-coupling of 5,7-dichloroquinolines with (1-ethoxyvinyl)tri(*n*-butyl)stannane occurs at the 5-position in the presence of a neighboring tosylamide group to give the corresponding 5-acylquinoline **19** and also small amounts of *N*-ethyl product **20** (Equation 11) [\[1997SL473\]](#).



Benzoylation at the 8-position of quinoline can be achieved by transformation of the corresponding quinolinecarbaldehyde. Treatment of 8-quinolinecarbaldehyde with $[\text{Ru}_3(\text{CO})_{12}]$ gives an acylruthenium hydride that undergoes

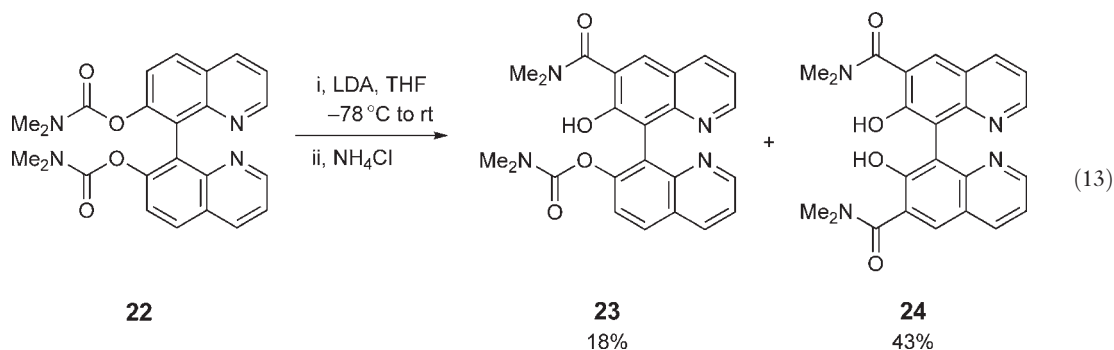
cross-coupling with a variety of aryl iodides in the presence of catalytic amounts of $[\text{Pd}_2(\text{dba})_3]$ to give a range of benzoylated quinolines in good to excellent yield [<2005AGE455>](#).

Quinolines undergo acetylation by electrophilic aromatic substitution when the carbocyclic ring is activated by the presence of electron-donating groups. *N,N*-Dimethyl-8-quinolylamine undergoes diacetylation with trifluoroacetic anhydride (TFAA) in pyridine to give the corresponding 5,7-bistrifluoroacetate **21** in excellent yield (Equation 12) [<1999S237>](#).



The most popular method for the introduction of ketone and formyl functional groups to the carbocyclic ring of quinolines is by quenching of an organolithium precursor with a suitable electrophile. 5-Lithioquinolines [<1995TL8415>](#) and 7-lithioquinolines [<1995S1159>](#) may be formylated by the addition of *N*-formylpiperidine at -78°C . A wide variety of 6-quinolylalkanones are accessed, albeit in low to moderate yield, by quenching of the corresponding 6-lithioquinoline with a Weinreb amide [<2005JME2134>](#).

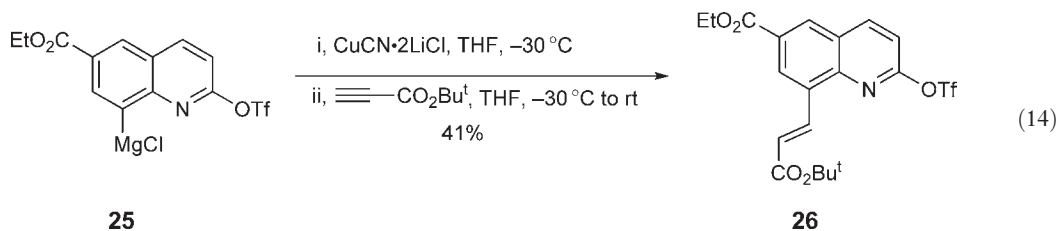
Alkoxy carbonyl groups may be introduced onto the carbocyclic ring of quinolines by palladium-catalyzed carbonylation. Heating 4,7-dichloroquinoline in methanol in an autoclave, in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ under an atmosphere of carbon monoxide gives a mixture of 4-methoxycarbonyl and 4,7-dimethoxycarbonylquinoline in 60% and 40% yield, respectively [<1999TL3719>](#). 6-Diethylaminocarbonyl-substituted quinolines may be synthesized by anionic *ortho*-Fries rearrangement of carbamate precursors. 7,7'-bis(((dimethylamino)carbonyl)oxy)-8,8'-biquinolyl **22** undergoes rearrangement on *ortho*-deprotonation using lithium diisopropylamide (LDA) to give a mixture of amides **23** and **24** (Equation 13) [<2005JOC373>](#).



7.03.2.1.7 Alkenylation

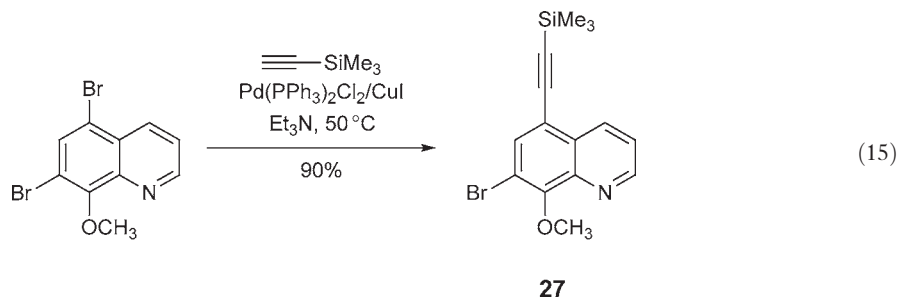
Alkenyl groups have been introduced onto the carbocyclic rings of quinolines by Heck or Stille reaction of the corresponding haloquinoline. Heck reaction of 5- and 7-bromoquinolines with ethyl acrylate [<2005TL2201>](#) and (*E*)-ethyl crotonate, respectively [<2003BML2291>](#), in the presence of $\text{Pd}(\text{OAc})_2$ and phosphine ligands has been used to introduce enoate moieties onto the quinoline ring. Ethenylpyridine groups may be introduced to the 7-position of quinolines under similar conditions utilizing 3-ethenylpyridine as coupling partner [<2004BML2155>](#).

Enoate moieties may be introduced to the 8-position of quinolines by conjugate addition of the corresponding quinolylcuprate with ethyl propiolate [<2003S233>](#). Transmetalation of Grignard reagent **25** with $\text{CuCN}\cdot 2\text{LiCl}$ followed by addition of alkynoate gives enoate **26** in moderate yield (Equation 14).



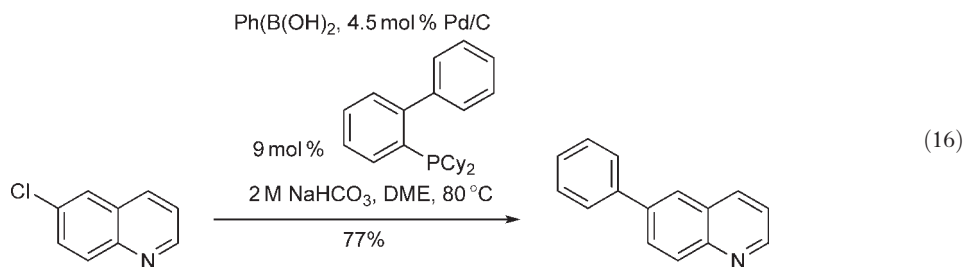
7.03.2.1.8 Alkynylation

Sonogashira coupling of 5- and 7-bromoquinolines with alkynes in the presence of palladium(0) and copper(I) iodide gives alkynyl-substituted quinolines in good yield. 7-Bromoquinolines have been coupled with ethynylpyridines and ethynylbenzene using $\text{Pd}(\text{PPh}_3)_4$ as catalyst in the presence of CuI in dimethylformamide (DMF) to give the 7-ethynylquinoline <2004BOMC2155>. 5-Bromoquinolines also undergo Sonogashira coupling with ethynylarenes and trimethylsilylthyne using Pd(0) catalysts and CuI in THF in good yield <2003OL2769>. 5,7-Dibromo-8-methoxyquinoline undergoes regioselective coupling with trimethylsilylthyne to give the corresponding 5-(trimethylsilylthyne)quinoline **27** in high yield (Equation 15) <1995JHC1261>.



7.03.2.1.9 Arylation

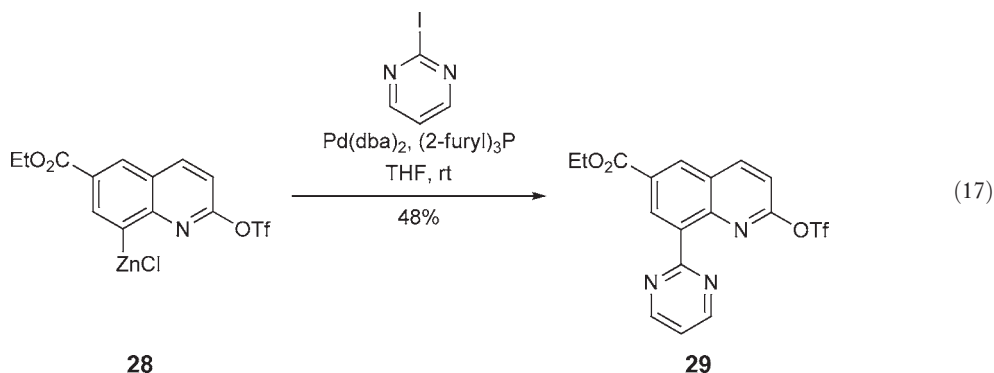
Arylation at the carbocyclic ring of quinolines is achieved by Suzuki–Miyaura coupling of a variety of arylboronic acids with the corresponding chloro-, bromo-, or iodoquinoline. An 8-iodoquinoline has been coupled with a range of *para*-substituted boronic acids in the presence of $\text{Pd}(\text{PPh}_3)_4$ and sodium carbonate in benzene/ethanol/water <2003BML3375>. 5-Bromo-8-hydroxyquinoline undergoes coupling with a wide range of arylboronic acids, including pyridinyl and triazinyl boronic acids using $\text{Pd}(\text{PPh}_3)_4$ in the presence of potassium carbonate in toluene <2004JOC1723>. A Suzuki coupling of 6-chloroquinoline with phenylboronic acid utilizing relatively inexpensive palladium on charcoal as catalyst in the presence of phosphine ligands in 1,2-dimethoxyethane (DME) has been developed <2003JOC9412>. While the reaction does not proceed using triphenylphosphine as ligand, coupling occurs in good yield in the presence of the sterically hindered phosphine 2-(dicyclohexylphosphino)biphenyl that is thought to promote reductive elimination (Equation 16). The catalyst is more easily handled than conventional palladium catalysts and may be separated from the reaction mixture by filtration and purified for reuse.



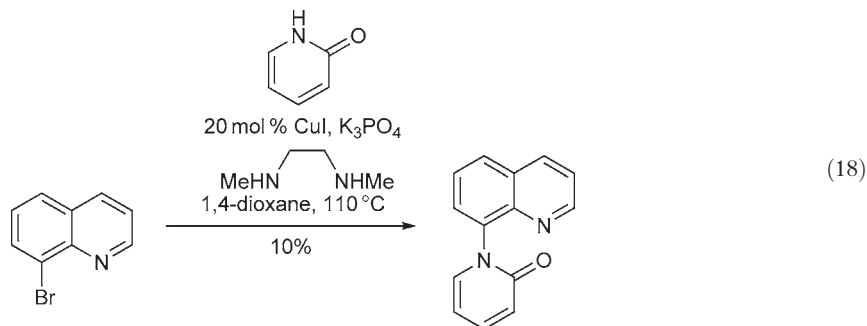
Cross-couplings are generally performed on haloquinolines and quinolyl triflates. Suzuki reactions of the more easily handled and relatively unreactive tosylquinolines are now also possible using bulky biaryl monophosphines as supporting ligands in the presence of palladium(II) acetate <2003JA11818>. 6-Tosyloxyquinoline undergoes coupling with 4-acetylphenylboronic acid in the presence of 5 mol % of such ligands and catalytic $\text{Pd}(\text{OAc})_2$.

The arylation of quinolines may be achieved using arylzinc species as cross-coupling partner. 8-Quinolyl nonaflate (nonaflate = $\text{OSO}_2(\text{CF}_2)_3\text{CF}_3$) undergoes high-yielding cross-coupling with 1-naphthylzinc bromide in the presence of catalytic quantities of nickel(II) chloride and diethyl phosphite and DMAP as ligands at 25°C <2005OL4871>. The use of arylmagnesium halides as coupling partners has allowed the introduction of relatively unreactive fluoroquinolines in the cross-coupling process. 2-Methyl-6-fluoroquinoline undergoes cross-coupling with phenylmagnesium chloride in the presence of $\text{Ni}(\text{acac})_2$ and 1,1'-bis(diphenylphosphino)ferrocene to give 2-methyl-6-phenylquinoline in 91% yield <2002JOC8991>.

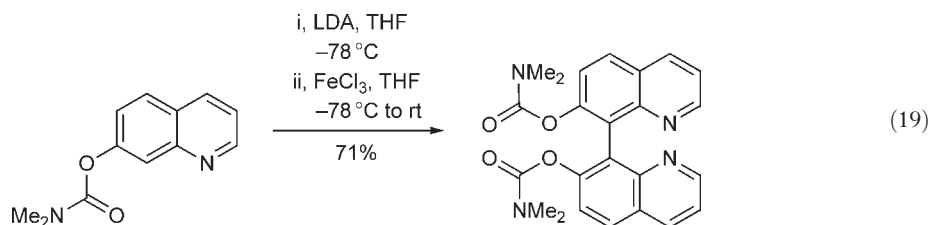
While the general strategy for arylation of quinolines centers on the use of haloquinolines in combination with arylmetal derivatives, aryl and heteroaryl moieties have been introduced to the carbocyclic ring of quinolines by coupling of aryl halides with a quinolylmetal reagent [<2003S233>](#). 8-Quinolylzinc chlorides undergo Negishi cross-coupling with aryl halides in moderate to good yield in the presence of $\text{Pd}(\text{dba})_2$ and *tris*-*o*-furylphosphine. For example, quinolylzinc chloride **28** couples with 2-iodopyrimidine to give adduct **29** in moderate yield ([Equation 17](#)).



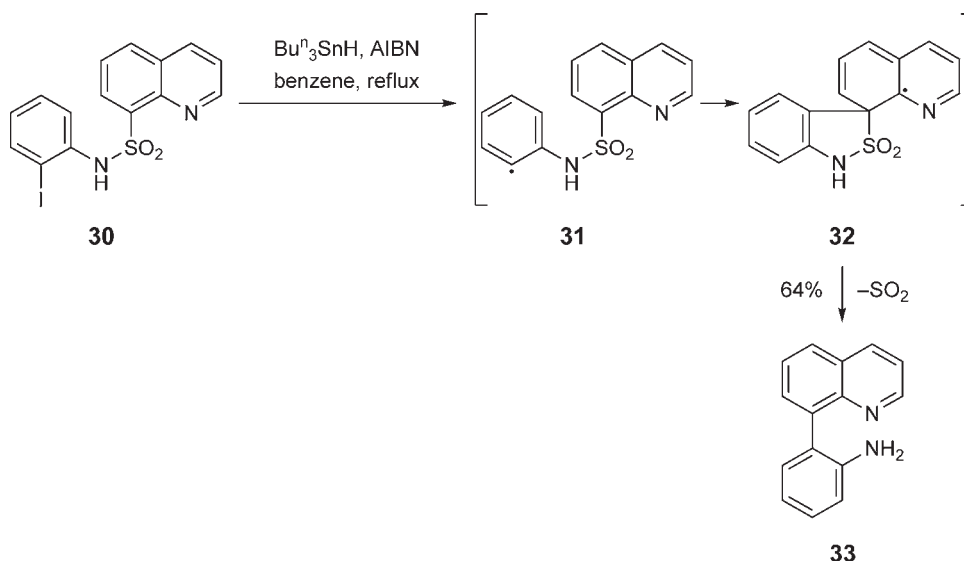
Low-yielding introduction of heteroaryl groups onto the carbocyclic ring of quinolines via the heteroatom has been achieved using the copper-catalyzed aryl amination procedure developed by Buchwald [<2001JA7727>](#). Heating a mixture of 8-bromoquinoline and 2-pyridone, in the presence of CuI , *N,N'*-dimethylethylenediamine and potassium phosphate in dioxane gives the *N*-quinolylpyridone in only 10% yield [<2004TL4257>](#). The low yield is attributed to coordination of the quinoline nitrogen with the copper catalyst ([Equation 18](#)).



8,8'-Biquinolyls and 6,6'-biquinolines may be accessed by metal-mediated homocoupling. 8-Lithioquinolines, obtained by metallation of the carbocyclic ring using LDA, undergo oxidative dimerization using FeCl_3 to give the 8,8'-biquinolyl in good yield ([Equation 19](#)) [<2005JOC373>](#) while 6-bromoquinolines undergo reductive dimerization in the presence of $\text{Ni}(0)$, generated by treatment of NiCl_2 with zinc and triphenylphosphine, to give the 6,6'-biquinolyl in good to moderate yields [<2003OL2251>](#).



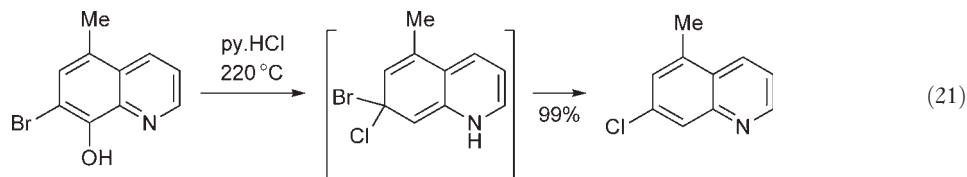
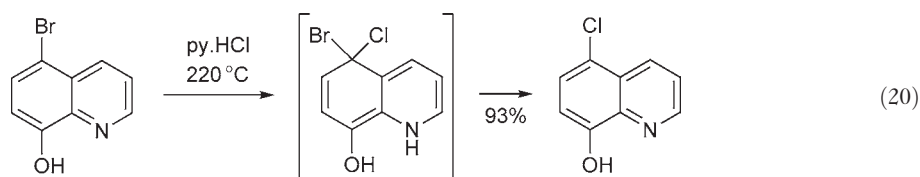
An alternative approach to the introduction of aryl groups onto quinolines has been developed and centers on the *ipso*-substitution of a sulfonyl group by an aryl radical [<1997TL137>](#). Compound **30**, possessing an *ortho*-iodoaryl moiety linked to the quinoline ring via a sulphonamide tether, is converted into radical **31** on treatment with tributyltin hydride and 2,2'-azobisisobutyronitrile (AIBN) in benzene. Intramolecular [1,5]-*ipso* substitution gives spiro intermediate **32** that rearomatizes, by extrusion of SO_2 to give biaryl **33** in good yield ([Scheme 2](#)). While this transformation can also be performed on substrates possessing a sulfonate tether only low yields of arylated products are obtained.



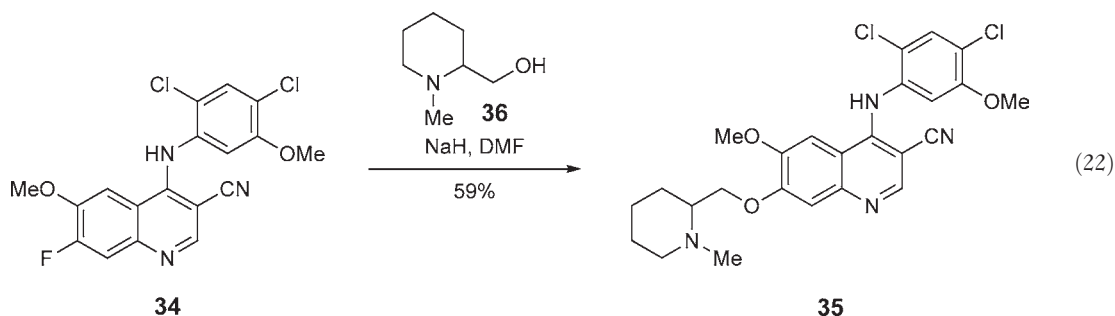
Scheme 2

7.03.2.1.10 Nucleophilic displacement

Nucleophilic substitution most readily occurs at the 2- and 4-position of the more electron-deficient heterocyclic ring of quinolines. However, $\text{S}_{\text{N}}\text{Ar}$ reactions at the carbocyclic ring can occur, mainly at positions 5 and 7. 5,7-Dibromo-8-hydroxyquinoline, 5-bromo-8-hydroxyquinoline, and 7-bromo-8-hydroxy-5-methylquinoline undergo conversion to the corresponding chloroquinolines on treatment with neat pyridine hydrochloride at 220°C in a process that is postulated to proceed via the formation of stabilized Meisenheimer complexes [<1996TL6695>](#) (Equations 20 and 21).



The reaction of a variety of polychloroquinolines with cesium fluoride in DMSO at 100°C has been monitored by ^{19}F NMR spectroscopy [<1998JFC203>](#). While this process is not preparatively useful, owing to the inseparable mixtures of polychloropolyfluoroquinolines formed, these studies do show that the 5-position and 7-position undergo initial nucleophilic attack followed by the 6-position and then the 8-position. Alkylamino and alkoxy moieties may also be introduced to the 5- and/or 7-positions of quinolines by nucleophilic displacement of a haloquinoline precursor. 5,7-Dibromo-8-hydroxyquinoline is converted to the corresponding diaminoquinoline, in moderate to good yield, on treatment with neat cyclic and acyclic secondary amines at elevated temperatures [<2001JHC1213>](#). The fluoro-substituent in 7-fluoro-3-quinolinecarbonitriles may be substituted by alkoxides [<2004JMC1599>](#). For example, fluoroquinoline **34** is converted to 7-alkoxyquinoline **35** in moderate yield using alcohol **36** in the presence of sodium hydride (Equation 22).

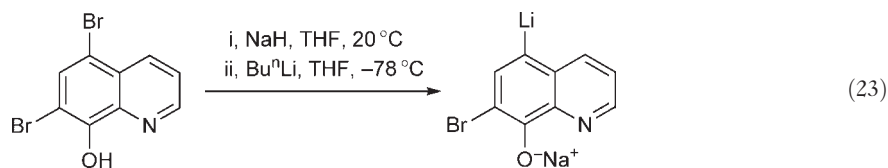


Substituents at other positions of the carbocyclic ring undergo nucleophilic displacement if activated by the presence of *ortho* and/or *para* electron withdrawing substituents. 5,7-Dinitro-8-hydroxyquinoline reacts with 2-methyl-2-propanethiol in the presence of sodium hydride in DMF to give the corresponding 8-(*t*-butylthio)quinoline in good yield. While amino groups are rarely displaced by nucleophiles, the *N,N*-dimethylamino group in *N,N*-dimethylamino-5,7-bis(trifluoroacetyl)quinoline undergoes reaction with a variety of amines, alcohols, and thiols in acetonitrile under reflux to give 8-amino, 8-alkoxy, and 8-mercaptoquinolines in good yield <2000S237>.

The Sandmeyer procedure for the synthesis of aryl halides from arylamines has been applied, with modification, to the conversion of 5- and 8-aminoquinolines to the iodo and bromo derivative. 8-Aminoquinoline is converted to 8-bromoquinoline in good yield on treatment with *t*-butyl nitrite in the presence of CuBr in acetonitrile at 60 °C <2003JOC5123> and 5-amino-6-nitroquinoline is converted to the 5-iodo derivative under equally mild conditions using potassium nitrite and copper iodide in DMSO at 60 °C <2005JOC2445>.

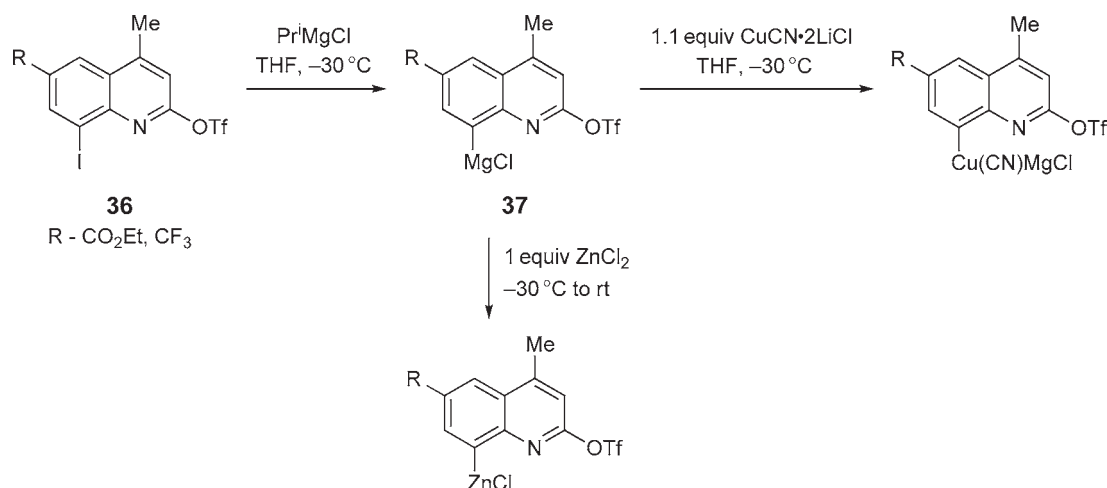
7.03.2.1.11 Formation of organometallic species

Lithioquinolines may be accessed by lithium–halogen exchange of bromoquinolines with alkyllithiums. However, this procedure is limited by the propensity of the electron-deficient heterocyclic ring to undergo nucleophilic attack by the organometallic reagent. 8-Hydroxybromoquinolines, as the sodium salts, undergo clean lithium–bromine exchange <1995TL8415>. Nucleophilic addition is suppressed by the higher electron density of the salts. Treatment of 7-bromo-8-hydroxyquinoline with sodium hydride in THF followed by *n*-butyllithium at –78 °C gives the 7-lithio derivative that is quenched by electrophiles in moderate yield. Furthermore, this method can be performed in a regioselective manner on dibromoquinolines. 5,7-Dibromo-8-hydroxyquinoline is regioselectively lithiated at C-5 under these conditions (Equation 23).



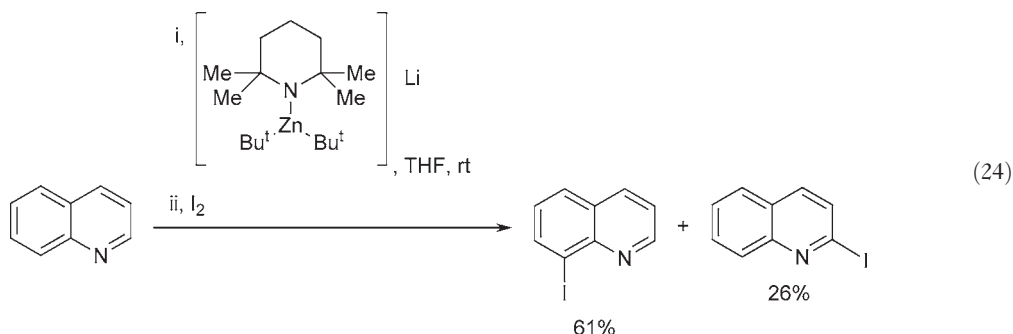
The regioselectivity of this lithiation is reversed when performed on 5,7-dimethoxy-8-hydroxyquinoline, to give the 7-lithioquinoline, owing to the *ortho* directing effect of the methoxy group <1995S1159>. In this case, nucleophilic attack is suppressed by the use of phenyllithium to effect lithium–bromine exchange in diethyl ether at –75 °C. The nitrogen atom can also play a role in the regioselectivity of lithiation at the carbocyclic ring when the C-2 position is blocked. For example, 2-trifluoromethylquinoline undergoes lithiation by lithium 2,2,6,6-tetramethylpiperide (LITMP) in diethyl ether at C-8 owing to coordination of the organometallic reagent with the nitrogen lone pair <2003EJO1569>. While bromine–lithium exchange is generally rapid using organometallic reagents such as *n*-butyllithium, hydrogen–metal exchange (metallation) of bromoquinolines at the carbocyclic ring can be effected, using bulky bases such as LITMP and LDA, without affecting the bromine atom <2004EJO1008>.

The preparation of organolithium and Grignard reagents by the traditional, oxidative insertion technique is limited in scope owing to functional group intolerance. A functionalized quinolylmagnesium reagent **37** can now be prepared by iodine–magnesium exchange of 8-iodoquinoline **36** with *i*-PrMgCl at –30 °C <2003S233>. Furthermore, this reagent undergoes transmetalation with CuCN·2LiCl or ZnCl₂ to give access to the corresponding cyanocuprate or arylzinc species, respectively (Scheme 3).



Scheme 3

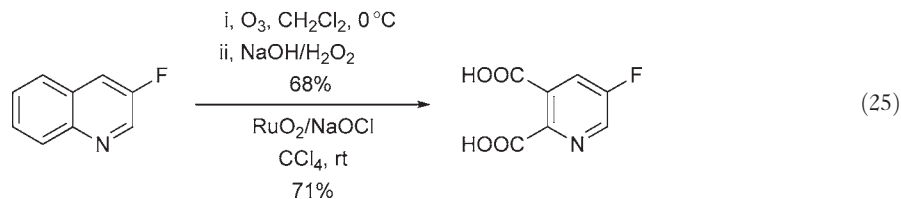
An alternative route to quinolylyl zinc reagents centers on the chemoselective deprotonative zincation of quinoline with the zincate complex prepared from LITMP and di-*tert*-butylzinc [<1999JA3539>](#). Deprotonation occurs to give a mixture of the 2- and 8-metallated species that undergoes iodination to give 8-iodoquinoline as the major product ([Equation 24](#)). In a similar manner to the lithiation of quinoline using LITMP, regioselectivity in the zincation most likely arises from prior complexation of the base with the ring nitrogen.



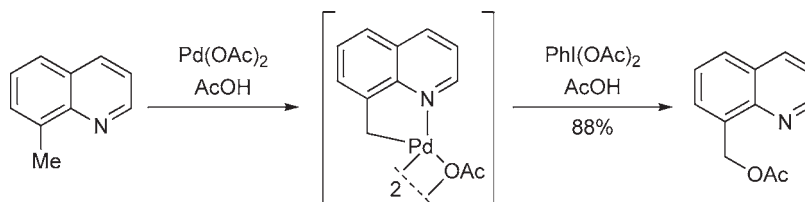
The selective halomercuration and acetoxymercuration of the carbocyclic ring of quinolines can be achieved using mercury salts. However, no new work has occurred in this area since publication of CHEC-II [<1996CHEC-II\(5\)91>](#).

7.03.2.2 Oxidation at the Fused Benzene Ring

Oxidative cleavage of the carbocyclic ring of quinolines may be achieved with a variety of oxidants to yield pyridine-2,3-dicarboxylic acids. There are few methods to access halogeno-substituted pyridine-2,3-dicarboxylic acids but this has been recently achieved using ozone and hydrogen peroxide or ruthenium tetroxide. Oxidation using either reagent proceeds in good yield on a variety of halogenated quinolines except 2-iodo and 2-fluoroquinoline [<2001S2495>](#). For example, 3-fluoroquinoline is converted to the 5-fluoropyridine-2,3-dicarboxylic acid in 68% yield using ozone/H₂O₂ and is oxidatively cleaved in comparable yields using ruthenium tetroxide ([Equation 25](#)).



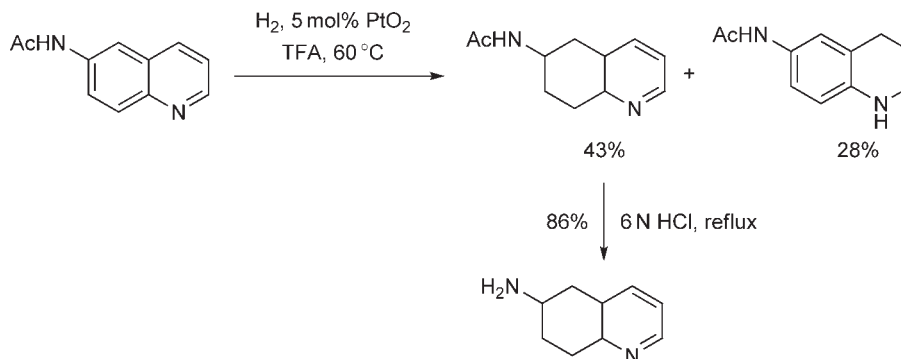
8-Methoxyquinoline is regioselectively oxidized at the methyl group by a chelate-directed palladium-catalyzed C–H bond activation <2004JA2300>. 8-Methylquinoline is selectively oxidized at the methyl position on treatment with palladium(II) acetate followed by the oxidant phenyliodine diacetate in acetic acid. The reaction proceeds via formation of a palladacycle (Scheme 4). Performing the reaction in methanol leads to isolation of 8-(methoxymethyl)quinoline in 77% yield.



Scheme 4

7.03.2.3 Reduction of Fused Benzene Rings

Both the heterocyclic and carbocyclic rings of quinoline undergo hydrogenation with selectivity dependent on the pH of the reaction medium. Hydrogenation in neutral or weakly acidic media takes place at the pyridine ring while reduction of quinolines in strongly acidic pH proceeds to give the 5,6,7,8-tetrahydroquinoline. The hydrogenation of aminoquinolines has proved problematic owing to hydrogenolysis of the amine substituent. This transformation has now been achieved by hydrogenation of the *N*-acetylamino-protected quinoline or isoquinoline in the presence of PtO_2 as catalyst in neat TFA followed by hydrolysis <2002JOC7890>. As an example, 6-acetamidoquinoline is reduced under these conditions to give a mixture of acetamido-substituted reduction products (Scheme 5). This transformation can also be applied to the reduction of other substituted quinolines and isoquinolines. The presence of electron-donating groups on the pyridine ring enhances the selectivity in favor of the 5,6,7,8-tetrahydroquinoline. Hydrogenation of 3-methoxyquinoline under these conditions gives the 5,6,7,8-tetrahydroquinoline as the sole product in 65% yield.



Scheme 5

The use of PtO_2/H_2 can also effect the reduction of quinolines, 2-substituted with a carbonyl group, or substituted with alkyl groups at C-8 <2003TL8501>. The former systems are cleanly hydrogenated at both the carbonyl functionality and heterocyclic ring in ethanol, in the presence of 1 equiv of HCl, but undergo reduction at the carbonyl group and carbocyclic ring using concentrated HCl or neat TFA as solvent to give complex mixtures. However, alkyl-substituted quinolines undergo more clean reduction in strongly acidic media. Hydrogenation of 2-methyl-8-isopropylquinoline occurs in neat TFA, under 10 bar H_2 to give the 5,6,7,8-tetrahydroquinoline in quantitative yield.

Acidic media in the hydrogenation of quinolines may be avoided by the use of $\text{Rh}/\text{Al}_2\text{O}_3$ as catalyst. Selective reduction may then be effected in hexafluoroisopropanol or methanol <2004SL2827>. Use of methanol leads to the isolation of the corresponding 1,2,3,4-tetrahydroquinoline while performing the hydrogenation in hexafluoroisopropanol results in total reduction to the decahydro product.

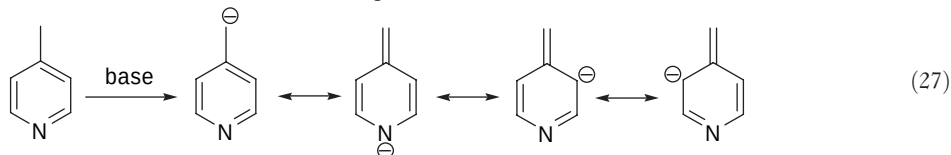
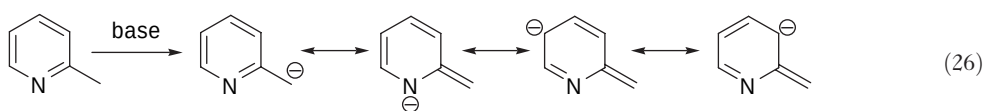
The thermal hydrogenolysis of quinoline at elevated temperature (773–1173 K) and pressure (20–30 bar) has been recently studied and shown to be an efficient method for degrading this compound <2004EJO3011>. The nitrogen atoms are converted to HCN and NH_3 and both the benzene and pyridine rings are decomposed via the formation of radicals induced by reaction with hydrogen atoms.

7.03.3 C-Linked Substituents

7.03.3.1 Alkyl Groups

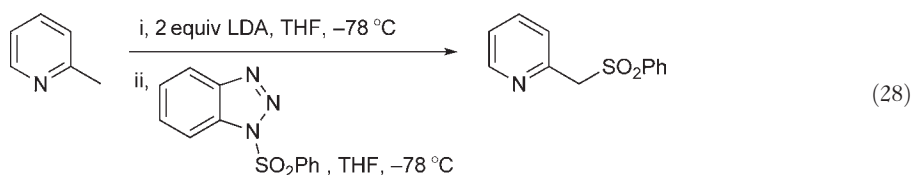
7.03.3.1.1 Alkyl substituents attached to carbon

Alkyl groups at the 2- and 4-positions of the pyridine ring are electron deficient due to loss of electron density to the ring nitrogen by resonance and induction. A consequence of this effect is the relative ease of deprotonation at the 2- and 4-methyl position to give resonance-stabilized anions (Equations 26 and 27).



Alkylpyridines may be deprotonated at the benzylic position using strong bases such as organolithium compounds, metal amide bases, and sodium amide. The regioselectivity of deprotonation of 2,4-dialkylpyridines such as 2,4-lutidine is influenced by the reaction conditions. The 4-methyl position is the more reactive and the corresponding anion of greater thermodynamic stability. However, deprotonation using organolithiums, such as *n*-butyllithium, under kinetic control, results in the formation of the 2-lithiomethylpyridine. The selectivity of this process arises from prior coordination of the base to the neighboring nitrogen <1974JOC3834>. The use of noncoordinating amide bases results in the formation of the 4-lithiomethylpyridine. It has recently been shown that this selectivity arises from rapid equilibration of the lithiated regioisomers mediated by the presence of free amine. As a result, the introduction of diethylamine to the anion of 2,4-lutidine generated with *n*-butyllithium results in a complete reversal of selectivity to give the more thermodynamically stable 4-methyl anion <1999OL87>.

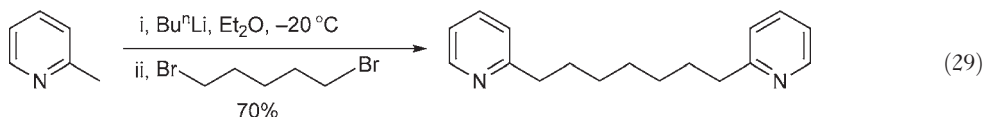
The ready deprotonation of the pyridylmethyl group allows selective functionalization of this moiety as the benzylic anions undergo addition to a wide variety of electrophiles. A range of hetero-substituted 2- and 4-methylpyridines have been synthesized in such a manner; this section concentrates only on those transformations reported since the publication of CHEC-II(1996). Optically pure pyridylmethylsulfoxides can be obtained by quenching of pyridylmethyl anions with *p*-toluenesulfinates <1997J(P1)1763> and trialkylsilyl groups can be introduced onto 2- and 4-methyl pyridines in good yield by quenching of the corresponding anions with trimethylsilyl chloride (TMSCl), triisopropylsilylchloride chloride (TIPSCl), and tert-butyldimethylsilyl chloride (TBDMSCl) <2005JOC1993>. Benzylic sulfonation of 2-picoline may be achieved in moderate yield by quenching of 2-lithiomethylpyridine with 1-(phenylsulfonyl)benzotriazole at -78°C in THF <2005JOC9191> (Equation 28).



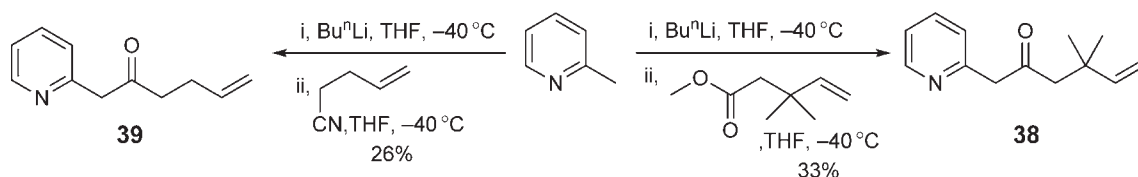
Phosphine groups are introduced to the benzylic position by addition of chlorophosphines to 2-lithiomethylpyridines <2003JCD1419>. Selenation at the benzylic position of 2-methylpyridines has been achieved in low yield by

quenching of the 2-methyl anion, prepared using *n*-BuLi, with freshly powdered selenium metal in frozen THF <2003JOM38>. In a more operationally simple procedure relatively complex (2-methylpyridin-3-yl)cyclohexanols are selenated at the benzylic position in good yield on treatment with *t*-BuLi at -78°C in the presence of DMPU followed by phenylselenium chloride <2006TL553>.

Benzylic anions derived from 2- and 4-methylpyridines react with a variety of carbon-based electrophiles and there are numerous recent examples of their reactions with aldehydes <1995T13089, 2001T1771>, ketones <2000EJO2735, 2004JHC443>, and epoxides <2002JOC9354>. Alkylation of pyridines is possible by treatment of 2- and 4-methyl pyridines with base followed by allyl bromides <2002JOC741, 2005OL315> or alkyl halides <2004EJO835, 1999JOC9658>. For example, 2-picoline is converted to 1,8 bis(2-pyridyl)octane on treatment with *n*-BuLi followed by 1,6-dibromohexane <2003JOC7651> (Equation 29).

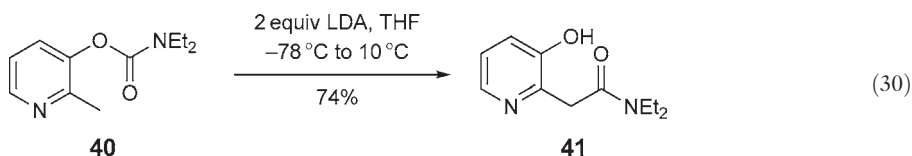


The reaction of pyridylmethyl anions with nitriles, esters, and amides leads to the synthesis of pyridylmethyl-ketones <1998BCJ285>. For example, the methyl anion derived from 2-methylpyridine reacts with methyl 3,3-dimethylpentenoate to give ketone **38** and with 1-cyano-3-butene to give ketone **39** in moderate yields (Scheme 6).

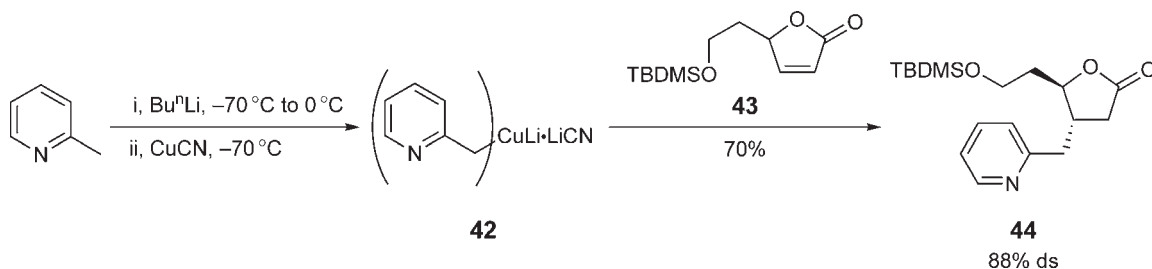


Scheme 6

Ethoxycarbonyl moieties may be introduced at the benzylic position by reaction of pyridylmethyl anions with diethyl carbonate <1997S949> or ethyl chloroformate <2004BML1795>. Fries rearrangement of *O*-(2-methylpyridyl)carbamates has been used to introduce an acetamide group to the benzylic position of 2-methylpyridines <1997SL839>. Treatment of *O*-pyridylmethylcarbamate **40** with 2.2 equiv of LDA at -78°C leads to the formation of pyridylacetamide **41** in 70% yield (Equation 30).

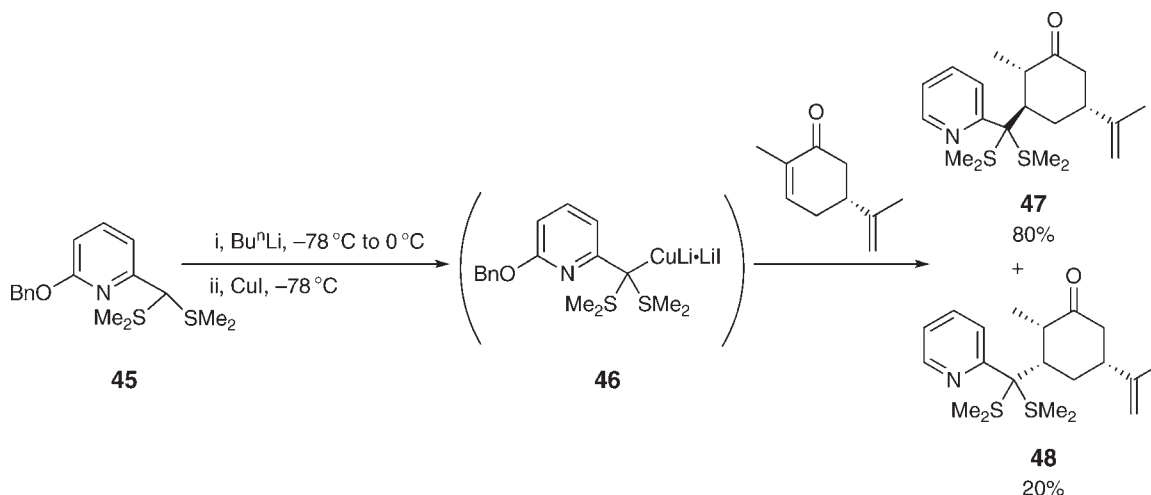


Pyridylmethyl lithium species generally react as hard anions giving rise to 1,2-addition products when coupled with α,β -unsaturated carbonyl derivatives. It has been found that the corresponding cyano-Gilman cuprates such as **42** also undergo 1,2-addition to α,β -unsaturated ketones but do add in a conjugate fashion to α,β -unsaturated esters and lactones such as **43** in good yield and stereoselectivity <2003H(60)1843> (Scheme 7).



Scheme 7

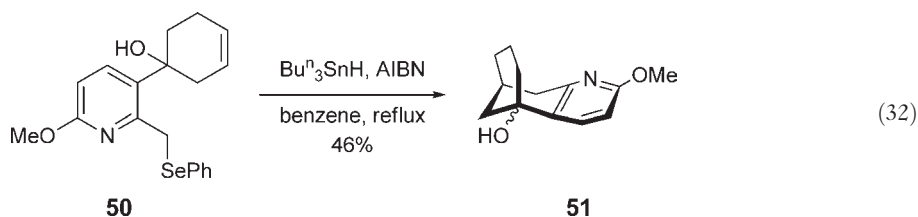
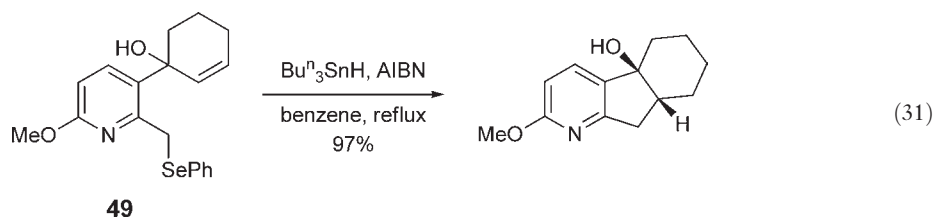
The conjugate addition of pyridylmethylcuprates to α,β -unsaturated ketones can be effected when the benzylic position has been functionalized with anion stabilizing groups <1995T1337>. The Gilman cuprate **46**, derived from 2-bismethylthiomethylpyridine **45**, undergoes conjugate addition with carvone in excellent yield to give a mixture of diastereomers **47** and **48** (Scheme 8). Cuprate **46** also undergoes conjugate addition with simple, acyclic ketones and 2-cyclohexenone.



Scheme 8

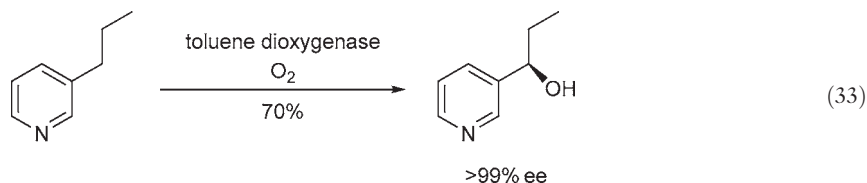
Methyl anions formed by deprotonation of 3-methylpyridines are only stabilized by induction and, as a consequence, the benzylic position is less reactive than that of the 2- and 4-methyl isomers. Nevertheless, deprotonation at the methyl group of 3-methylpyridines does occur using strong bases. These anions react in a similar manner to the 2- and 4-methyl analogues undergoing addition to aldehydes <1995SC2963>, esters <2005BML3296>, and alkyl halides <2003OL2611, 2005T1127>.

While the reactions of pyridylmethyl anions is well documented, the generation and use of pyridylmethyl radicals to form C–C bonds has only been recently reported. Pyridylmethylphenylselenide **49** is converted to the benzylic radical, on treatment with *n*-Bu₃SnH and AIBN, and undergoes 5-*exo*-trig cyclization in high yield <2006TL553> (Equation 31). Selenide **50** undergoes 6-*exo*-trig cyclization in lower yield to give the bicycle[3.3.1]nonane core of hupzine A **51** (Equation 32).

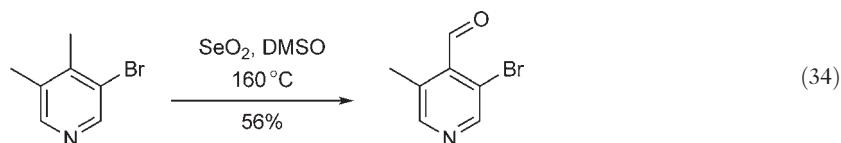


The benzylic position of methylpyridines undergoes direct oxidation to give hydroxymethylpyridines, pyridine carbaldehydes, and nicotinic acid derivatives. The enzyme toluene dioxygenase in the mutant soil bacterium *Pseudomonas putida* catalyzes the asymmetric hydroxylation of 2- and 3-alkylpyridines to give chiral nonracemic 2-pyridylalkanols in high ee <2002TA2201>. 3-Ethyl- and 3-propylpyridine undergoes selective oxidation at the side chain. As an example 3-propylpyridine is oxidized in high yield and enantioselectivity to give

(*R*)-1-(3-pyridyl)propan-1-ol in 70% yield and greater than 99% ee (Equation 33). 2-Alkylpyridines undergo some ring hydroxylation and this mode of oxidation predominates with 4-alkylpyridines.

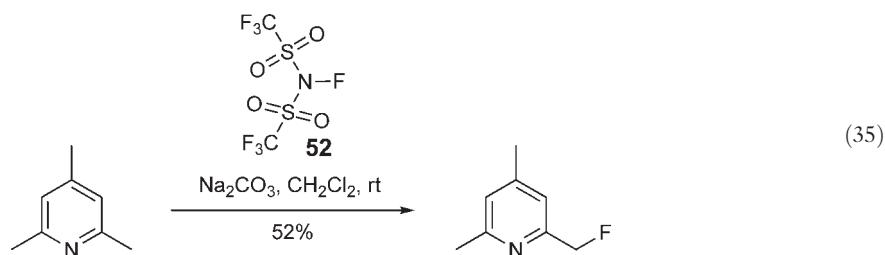


The most common method for side chain oxidation of methylpyridines utilizes selenium dioxide as oxidant to give access to the corresponding carbaldehyde. This reagent can selectively oxidize more reactive 2- and 4-methyl groups in the presence of 3-methyl groups. For example, 3-bromo-4, 5-dimethylpyridine undergoes oxidation using SeO₂ in DMSO at 160 °C to give 3-bromo-4-formyl-5-methylpyridine in moderate yield (Equation 34).



The 3-methyl group can also be oxidized using SeO₂ despite the relatively lower reactivity of this substituent. 3,5-Dimethylpyridine can be converted into pyridine-3,5-dicarbaldehyde in 20% yield using SeO₂ in dioxane/water at 80 °C <2004OL1033>. This oxidation can be performed under mild conditions with microwave assistance. Irradiation of 2,6-lutidine for 25 min in the presence of SeO₂ under solvent-free conditions using a 450 W domestic microwave oven gives 2-methyl-6-pyridinecarbaldehyde in 40% yield <2003SC475>.

It is possible to halogenate selectively at the methyl position of alkylpyridines to give halogenoalkylpyridines. Low to moderate yields of fluoromethylpyridines are obtained on fluorination of 2- and 4-methyl pyridines with *N*-fluoro-bis[(trifluoromethyl)sulfonyl]imide **52** in the presence of sodium carbonate in dichloromethane <1996T15>. 2-Methylpyridine is fluorinated in 20% yield and 4-methylpyridine in 72% yield under these conditions. Reagent **52** also effects the selective fluorination of 2,4,6-collidine to give the 2-fluoromethylated product in moderate yield (Equation 35).

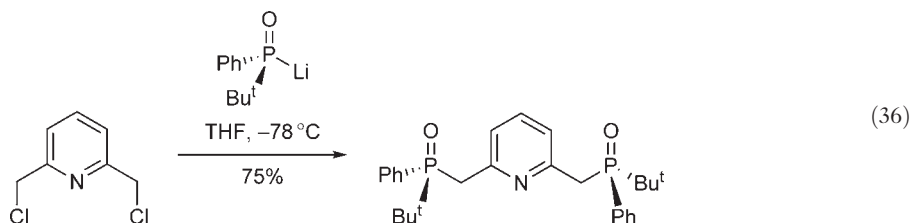


The traditional method for the formation of chloromethylpyridines is treatment of the corresponding methylpyridine with phosphoryl chloride <2004OL4527, 1998BML453>. This transformation can also be achieved using trichloroisocyanuric acid in chloroform under reflux <2005JME1367> or using NCS in combination with benzoyl peroxide in acetonitrile in a radical-catalyzed procedure <2000JOC7718>.

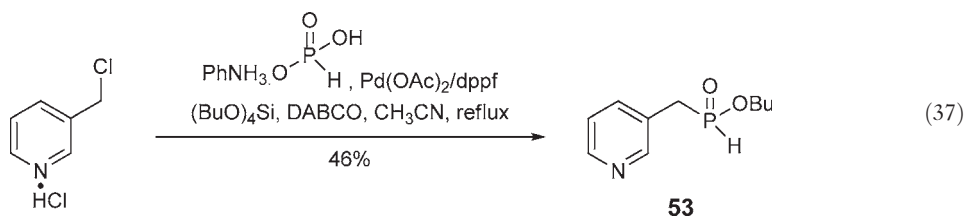
Radical-based processes, generally using NBS in combination with a radical initiator, are the most common methods for effecting benzylic bromination of methylpyridines. Bromination of a 2-methylpyridine can be achieved in low yield using NBS in the presence of catalytic amounts of benzoyl peroxide in carbon tetrachloride under thermal conditions <2002JOC741> and has been achieved in near quantitative yield under irradiation using a sun lamp <2003BML3979>. AIBN also functions as a radical initiator in this process <2001OL3895, 2003OBC2865>. One disadvantage of this procedure is the formation of dibromomethyl products. This can be minimized by the use of dichloromethane or benzene in place of carbon tetrachloride as solvent or by radical bromination in biphasic media <2002TL1697>. Side-chain bromination of 2-methylpyridine can also be effected using a solvent-free microwave-assisted procedure that proceeds rapidly without radical initiator. Irradiation of a ground mixture of 2-methylpyridine and NBS in a 450 W microwave oven leads to the formation of 2-bromomethylpyridine in 40% yield in 9 min <2004CL916>.

The direct iodination of methylpyridines is rare and iodomethylpyridines are generally obtained by nucleophilic displacement of existing benzylic substituents.

The halogen substituents of halogenomethylpyridines undergo substitution reactions with carbon-based nucleophiles such as allylmagnesium bromide <2002JOC741> and enolates <1997JA656>. These halogen substituents are also readily displaced by heteroatom-based nucleophiles. A number of recent investigations have focused on the formation of carbon–phosphorus bonds at the benzylic position of methyl pyridines. 2-Bromomethylpyridines undergo Michaelis–Arbuzov reaction with tris-trimethylsilyl phosphite in toluene at 95 °C to give pyridylmethylphosphites in high yield <2001TL5393>. 2-Pyridylmethylphosphine oxides can be prepared by reaction of bis(2-bromomethyl)pyridine with magnesiated diphenylphosphine oxide <2003JCD153> and bis(2-chloromethyl)pyridines can be converted to the corresponding optically pure bis(phosphine oxides) by reaction with chiral nonracemic-lithiated dialkylphosphine oxides <2000EJOC3205> (Equation 36).



Pyridylmethylphosphinates can be accessed, albeit in low isolated yield, by palladium-catalyzed cross-coupling of 2- and 3-pyridylmethyl chlorides with anilinium hypophosphites <2005T6315>. For example, 3-chloromethylpyridine hydrochloride reacts with anilinium hypophosphite in the presence of Pd(OAc)₂, dppf, 1,4-diazabicyclo[2.2.2]octane (DABCO), and (BuO)₄Si as esterification agent to give butyl (pyridine-3-ylmethyl)phosphinate **53** in 46% yield (Equation 37). This transformation proceeds in 24% yield when performed on 2-chloromethylpyridine.

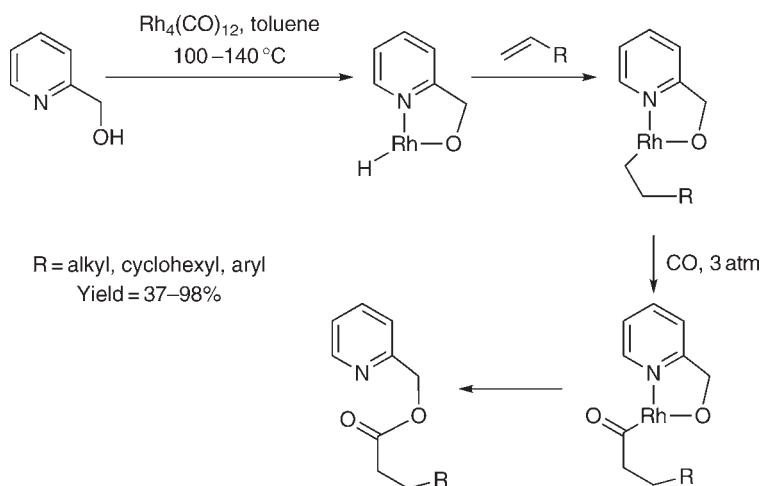


2-Chloromethylpyridine is converted to 2-picolylarsonic acid in quantitative yield by Meyer reaction with arsenic(III) oxide in an aqueous sodium hydroxide solution <2002PS2773>.

The conversion of 2- and 4-chloromethyl and 2-bromomethylpyridines to the corresponding hydroxymethylpyridine is possible under basic hydrolysis conditions <1995JHC675, 1998BML1909, 2000JOC7718>.

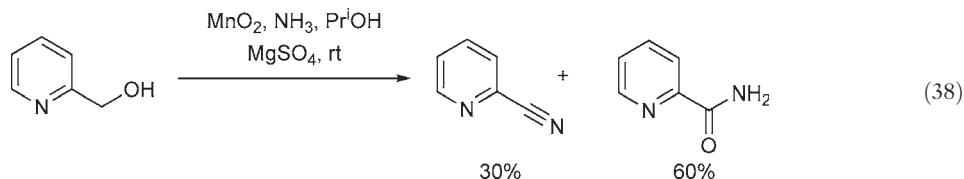
Hydroxymethylpyridines undergo the reactions typical of alkyl alcohols. In addition, 2-hydroxymethylpyridines are converted to a wide variety of ester derivatives, in moderate to excellent yield, by hydroesterification of alkenes in the presence of carbon monoxide and catalytic quantities of Ru₄(CO)₁₂. The reaction requires prior coordination of the ring nitrogen to rhodium and proceeds by oxidative insertion of the OH group followed by insertion of alkene and CO. Migratory insertion followed by reductive elimination gives the product ester and regenerates the catalyst (Scheme 9). This hydroesterification proceeds in high yield in the absence of carbon monoxide using of 2-pyridylmethyl formate as substrate and Rh₃(CO)₁₂ as catalyst <2002JA750>.

Hydroxymethyl pyridines are converted into aldehydes and ketones using the same oxidants that effect the oxidation of alkanols. In addition, they may be oxidized using MnO₂ in chlorinated solvents and there are a number of recent examples of the oxidation of 2-, 3-, and 4-hydroxymethylpyridines to aldehydes using this oxidant <1999JHC445, 2003OL2397, 2003T4873>. Hydroxymethylpyridines are also oxidized to aldehydes using cumylhydroperoxide (CHP) in the presence of catalytic quantities of Zr(OBu)₄ and 4 Å mol sieves in dichloromethane <1996JOC1467>. In this process, oxidation occurs by hydride transfer within a mixed zirconium complex formed by interaction of the catalyst with *t*-butyl hydroperoxide (TBHP) and substrate alcohol. Oxidation proceeds poorly with alcohols capable of strong chelation to the zirconium center and while 3- and 4-hydroxymethyl pyridine undergo rapid and quantitative conversion to the corresponding aldehyde, 2-hydroxymethylpyridine is only oxidized slowly in 60% yield. Oxidation also proceeds using TBHP as hydride acceptor to give a mixture of aldehyde and *tert*-butyl ester. Hydroxymethyl pyridines may be directly oxidized to carboxylic acid derivatives in the presence of excess MnO₂. 2-Hydroxymethylpyridine is converted to a mixture of the nitrile and amide using 15 equiv of MnO₂ in the presence of ammonia in isopropanol and anhydrous magnesium sulfate <2002SL1291> (Equation 38). The reaction proceeds



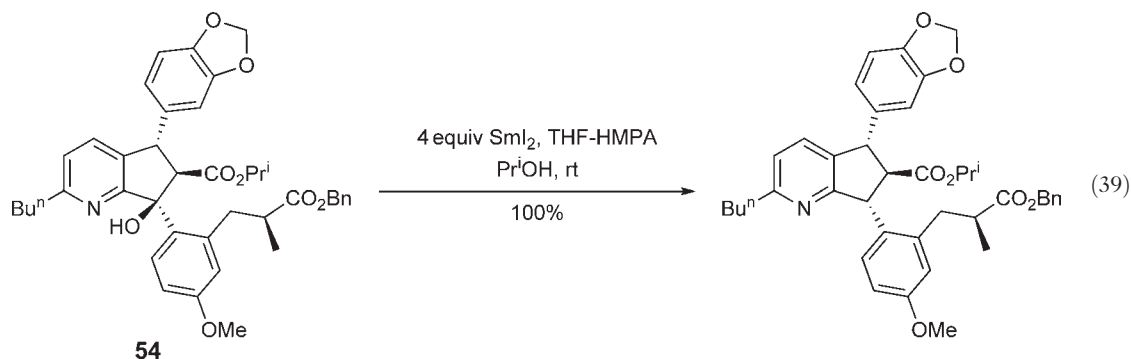
Scheme 9

via formation of the aldehyde followed by the imine in the presence of ammonia followed by further oxidation to the nitrile. Hydrolysis of the nitrile results in the formation of the amide.



3-Hydroxymethylpyridine undergoes oxidation to the corresponding methyl ester in 64% yield in the presence of excess MnO_2 and NaCN in methanol [<2002SL1293>](#). In this case, the reaction proceeds via formation of the cyanohydrin. Further oxidation gives an acyl cyanide that is converted to the methyl ester on reaction with methanol. Reaction of the acyl cyanide intermediate with an amine gives rise to an amide and oxidation of 4-hydroxymethylpyridine in the presence of *iso*-butylamine rather than methanol gives the corresponding amide in 65% yield.

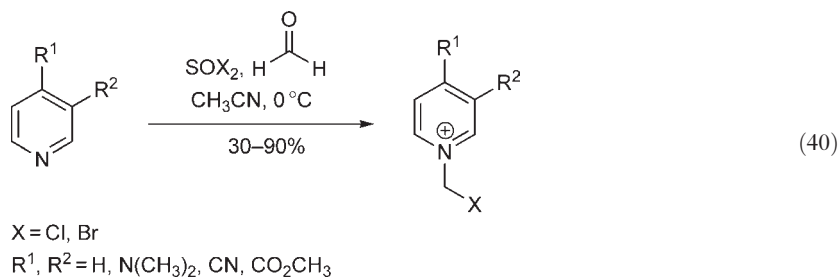
The deoxygenation of pyridinemethanol derivatives, readily obtained by nucleophilic addition to pyridinecarbaldehydes, provides access to a range of alkylpyridines substituted at the benzylic position. While the reduction of benzylic hydroxyl groups using iodotrimethylsilane (TMSI) is incompatible with the presence of a pyridine ring, 2- and 4-hydroxymethylpyridine are reduced under mild conditions using a 1 M solution of SmI_2 in THF in the presence of hexamethylphosphoramide (HMPA) and pivalic acid as a proton source at rt [<1999TL8823>](#). 3-Hydroxymethylpyridines require prior conversion to the acetoxy derivative before reduction takes place. This reduction can be performed on complex substrates. For example, alcohol **54** undergoes stereoselective reduction in quantitative yield (Equation 39).



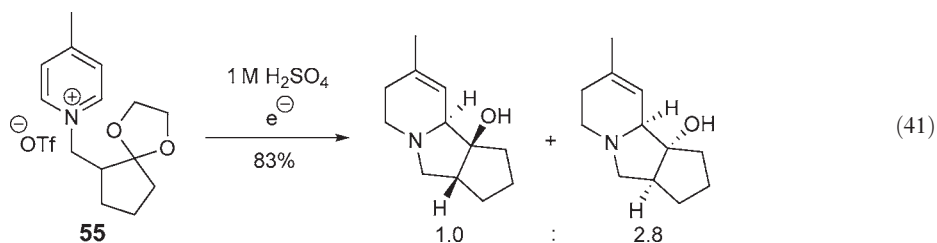
7.03.3.1.2 Alkyl substituents attached to nitrogen

A variety of *N*-halomethylpyridinium salts may be accessed by condensation of pyridines with thionyl halides and formaldehyde [<1999JOC3113>](#) (Equation 40). While it is predicted that such salts should undergo displacement of

pyridine by nucleophiles in the gas phase, these salts undergo reaction with nitrogen heterocycles in MeCN via displacement of the halogen substituent to give 1,1-bis(heteroarylium)methyl salts in good yield.



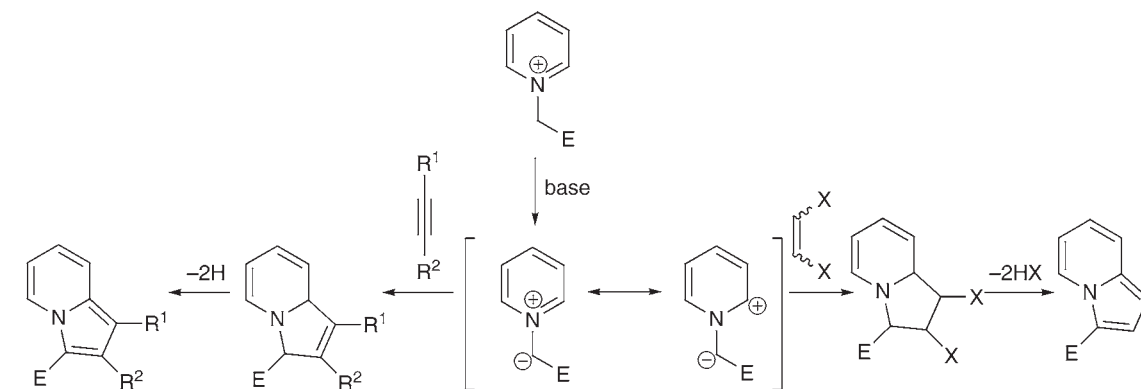
The presence of an alkyl substituent on nitrogen activates the 2- and 6-positions of the pyridine ring to nucleophilic attack and cyclizations can occur when the alkyl group is substituted with nucleophilic groups. *N*-(Oxoalkyl)pyridinium salts undergo cyclization on electrolysis in 1 M aqueous sulfuric acid to give a variety of indolizidine and quinolizidine alkaloid skeleta in good yield <2003EJO2919>. The reaction proceeds at the cathode by cyclization of a hydroxyalkyl radical, formed by reduction of the protonated ketone. As an example, pyridinium salt **55** undergoes deprotection and cyclization on cathodic reduction to give a diastereoisomeric mixture of cyclopenta[*a*]indolizidinols in high yield (Equation 41).



Conversion of *N*-(oxoalkyl)pyridinium salts to the corresponding *O*-methyloximes and subsequent cyclization of the oxime nitrogen onto the pyridinium ring gives access to imidazo[1,2-*a*]pyridines <1996S927>.

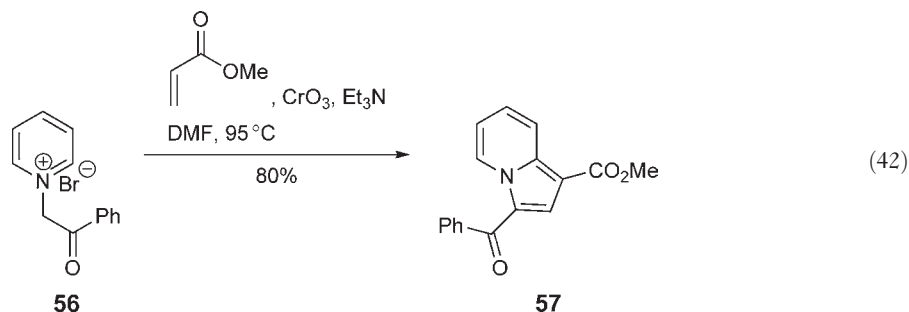
The base-induced cyclization of *N*-(oxoethyl)pyridinium salts of 2-picolines, known as the Tschitschibabin indolizine synthesis, is a classical method of preparation of indolizines from pyridines. The ready isolation of the products by decanting or filtration has allowed for the recent development of a parallel synthesis of a wide range of 2-substituted indolizines <2003SL2086>.

N-Alkylpyridinium salts possessing electron-withdrawing functionality on the alkyl side chain are readily deprotonated at carbon adjacent to nitrogen to give pyridinium *N*-ylides that undergo 1,3-dipolar cycloaddition with alkenes and alkynes to give indolizines (Scheme 10). This cycloaddition chemistry of pyridinium *N*-ylides has been the subject of a recent review <1996H(49)2005>.

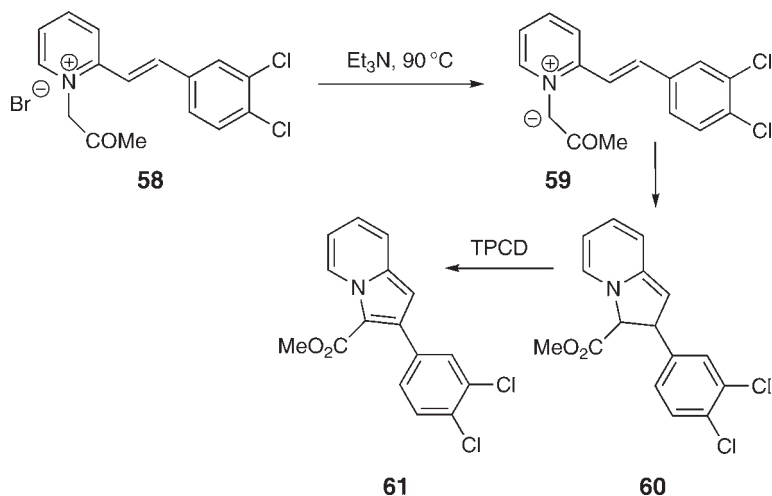


Scheme 10

The cycloaddition with alkynes yields cycloadducts that may undergo aromatization on air oxidation. This procedure has recently been applied to the synthesis of perfluoroalkylated indolizinyolphosphonates by 1,3-dipolar cycloaddition of pyridinium *N*-ylides with perfluoroalkynylphosphonates [<2002SL714>](#). The cycloaddition with alkenes only proceeds with dipolarophiles bearing leaving groups X, such as halides, that are eliminated during aromatization. *N*-(Cyanomethyl)pyridinium and isoquinolinium salts undergo 1,3-dipolar cycloaddition with fluorinated alkenes, formed *in situ* from polyfluoroalkanoates in the presence of triethylamine and potassium carbonate to give fluorinated cycloadducts in moderate to good yield [<1998JFC13>](#). 1-Fluoroalkylindolizines are conveniently accessed by cycloaddition of 2-bromo-3,3,3-trifluoropropene with pyridinium *N*-ylides in the presence of triethylamine and potassium carbonate in DMF in moderate to good yield [<1999S51>](#). Fluorinated indolizines can also be obtained by 1,3-dipolar cycloaddition of pyridinium, quinolinium, and isoquinolinium salts with gaseous fluoroalkenes [<2003S35>](#). As the dipolarophiles are readily soluble in DMF, these cycloadditions may be conveniently carried out using standard glassware. Nitro-substituted indolizines and pyrrolo[2,1-*a*]isoquinolines are accessed by 1,3-dipolar cycloaddition of pyridinium and isoquinolinium *N*-ylides with 1,1-diiodo-2,2-dinitroethylene in dichloromethane [<2002SL1547>](#). An oxidant-promoted 1,3-dipolar cycloaddition process uses oxidizing agents to effect aromatization by dehydrogenation. This modification allows the use of a variety of electron-deficient alkenes as dipolarophiles. Oxidants include CrO_3 [<2000JHC1527>](#), tetrakis(pyridine)cobalt(II) dichromate (TPCD) [<1997SC1395>](#), and MnO_2 [<2000S1733>](#). For example, pyridinium salt **56** reacts with methyl acrylate in the presence of triethylamine and CrO_3 in DMF at 95 °C to give indolizine **57** in 80% yield (Equation 42).



Indolizines can also be accessed from *N*-alkylpyridinium salts in intramolecular fashion. 2-(2-Arylethynyl)pyridinium ylides undergo 1,5-dipolar cyclization to give 2-aryindolizines. This reaction can now be performed in moderate yield using the corresponding 2-(2-arylethenyl) derivative in the presence of oxidants such as TPCD that effect aromatization of the initially formed dihydroindolizine. For instance, pyridinium salt **58** is converted in triethylamine to the ylide **59** that undergoes cyclization to give dihydroindolizine **60**. *In situ* oxidation with TPCD gives the indolizine **61** in moderate yield (Scheme 11).

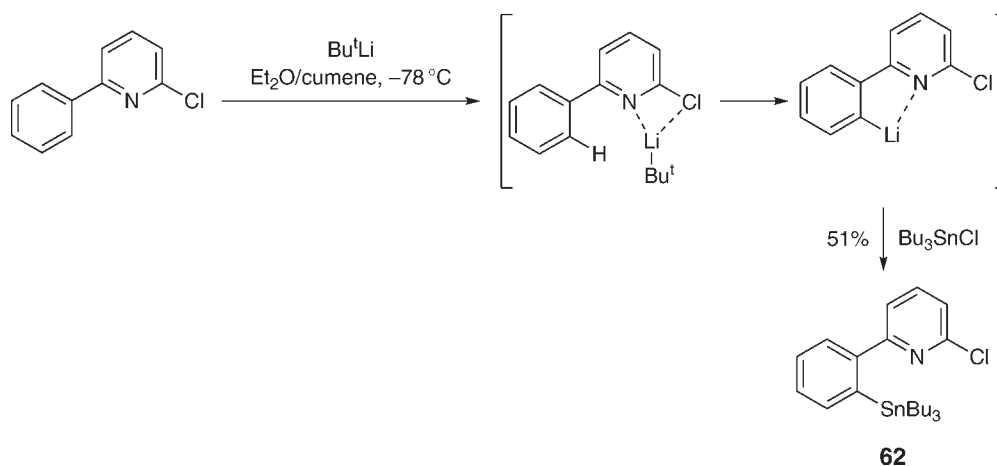


Scheme 11

Ring-closing metathesis (RCM) reactions of *N*-alkenylpyridinium salts are possible using Grubbs' catalyst and this strategy has been used to access dihydroquinolizinium cations from *N*-(2'-butenyl)- α -vinylpyridinium triflates in good yield <2004OL4125>.

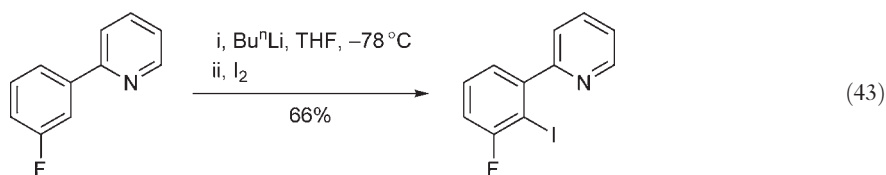
7.03.3.2 Aryl Groups

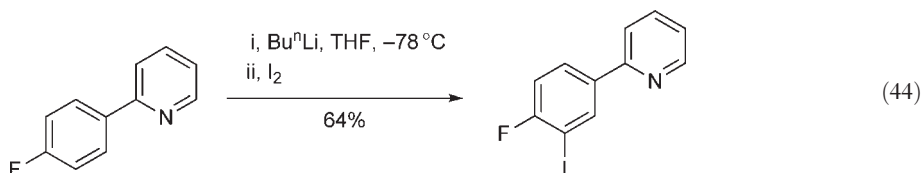
Much of the recent research on phenylpyridines has focused on studying the regioselective functionalization of the phenyl ring via pyridine-directed *ortho*-lithiation and C–H bond activation. 2-Phenylpyridine undergoes nucleophilic attack of the organolithium when using *n*-BuLi or *t*-BuLi while lithiation at C-2 occurs using the superbase *n*-BuLi-lithium dimethylaminoalkoxide (LiDMAE) <2003JOC2028>. Lithiation at the phenyl ring does occur when the C-2 position of the pyridine moiety is blocked with a chlorine atom. Lithiation of 2-chloro-6-phenylpyridine using *t*-BuLi in Et₂O/cumene at –78 °C leads to selective lithiation at the C-2' position of the phenyl ring <2003JOC4918>. No lithium–chlorine exchange or lithiation *ortho* to the chlorine atom is observed. Treatment of 2-chloro-6-phenylpyridine with *t*-BuLi results in *ortho*-lithiation via coordination of the pyridine nitrogen and chlorine atom with the lithiating reagent. The metallated species is stabilized by chelation with nitrogen and reacts with a variety of electrophiles. For instance, quenching the reaction with Bu₃SnCl gives stannane **62** in 51% yield (Scheme 12).



Scheme 12

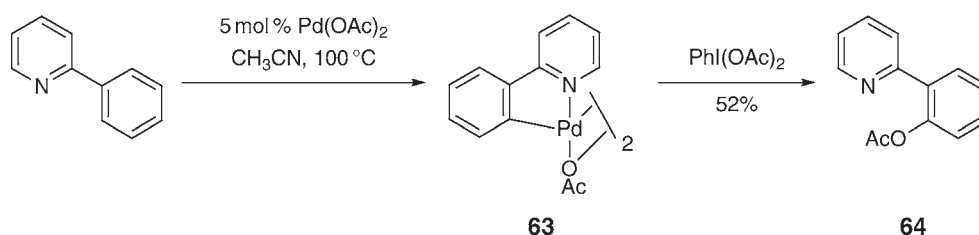
Regioselective lithiation at the phenyl group of 2-phenylpyridines is also possible in the presence of unsubstituted pyridine rings when there are additional directing groups on the phenyl ring. Lithiation of 2(3-fluorophenyl)pyridines and 2(3-chlorophenyl)pyridines) at C-2 of the phenyl ring occurs under kinetic control using *n*-BuLi in THF at –75 °C and also be can effected under thermodynamic control on the corresponding bromide, albeit in low yield, using lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at –75 °C <2004JOC6766>. In the latter example, the stabilizing effect of the nitrogen atom prevents the elimination of lithium bromide to give a benzyne. In this study the directing effect of the pyridine moiety was shown to be weaker than that of a fluorine atom. Lithiation of 2-(3-fluorophenyl)pyridine with *n*-BuLi followed by quenching with iodine gives the C-2' iodinated product (Equation 43) while lithiation of 2(4-fluorophenyl)pyridine with the superbase *n*-BuLi-*t*-BuOK (LICKOR) followed by an iodine quench results in iodination at the C-3' position (Equation 44).





The 2-pyridyl moiety can also direct the position of lithiation of heterocyclic substituents. 2,2'-Bipyridine and 2,4'-bipyridine undergo lithiation at the position *ortho* to the 2-pyridyl substituent using LTMP in THF at -40 or -70 °C <1996T14469>.

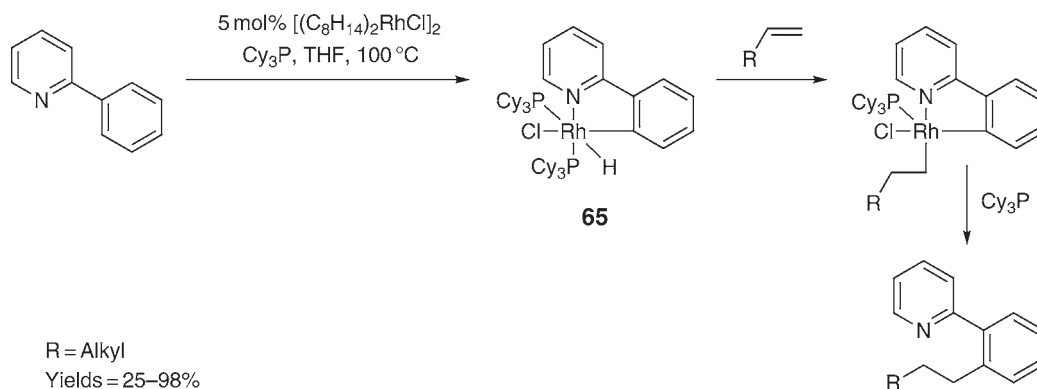
The 2-pyridyl moiety can be used to direct regioselective catalytic C–H bond activation. Chelate-directed electrophilic aromatic substitution of 2-phenylpyridine with 5 mol% Pd(OAc)₂ leads to the formation of a palladacycle **63** that undergoes oxidation with PhI(OAc)₂ followed by carbon–heteroatom bond formation and reductive elimination to give acetylated phenol **64** <2004JA2300> (Scheme 13). Use of 2.3–2.5 equiv of oxidant leads to dioxygenation in 83% yield. This palladium-catalyzed C–H bond activation can also be applied to the formation of C–C bonds *ortho* to the 2-pyridyl moiety. Treatment of palladacycle **63** with [Ph₂I]BF₄ leads to arylation at the C-2'-position of the benzene ring <2005JA7330>. The 2-quinolyl group also functions as a directing group in this transformation.



Scheme 13

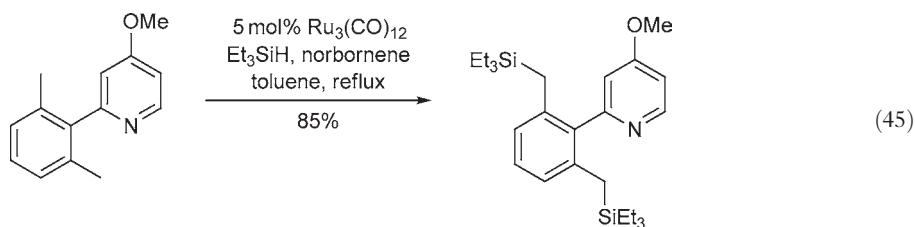
These palladacycles also undergo addition to iodobenzenes. 2-Phenylpyridine is arylated at the *ortho*-position with *para*-substituted iodobenzenes in good yield in the presence of 5 mol% Pd(OAc)₂ and stoichiometric amounts of AgOAc <2005OL3657>.

The 2-pyridyl substituent also directs C–H bond cleavage by rhodium and ruthenium complexes to give cyclometallated hydride complexes that undergo further organometallic reactions. Reaction of 2-phenylpyridine with the rhodium complex formed *in situ* from [(C₈H₁₄)₂RhCl]₂ and tricyclohexylphosphine proceeds via insertion of rhodium across the *ortho* C–H bond to give a hydride complex **65**. Hydrometallation of alkenes followed by reductive elimination gives alkylated products in moderate to good yield (Scheme 14).

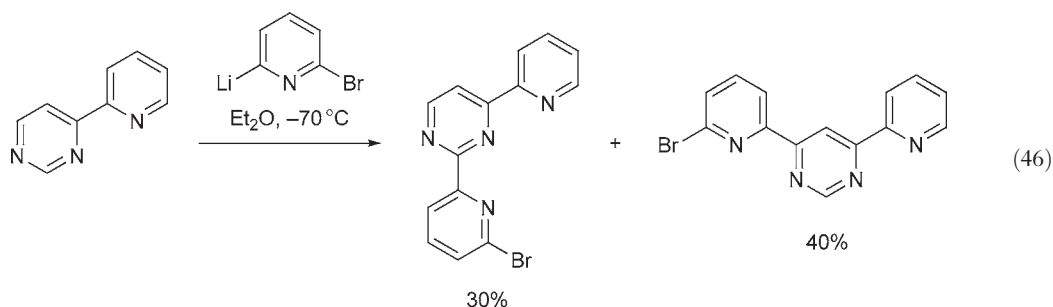


Scheme 14

A similar process, performed using the ruthenium complex $\text{Ru}_3(\text{CO})_{12}$ in the presence of ethene and carbon monoxide, leads to the formation of C-2' propionylated products <1997JOC2604>. This process fails when applied to the coupling of other alkenes and, at present, is limited to the use of ethene. Arylation *ortho* to the pyridyl group in 2-phenylpyridines and 2-naphthylpyridines occurs in the presence of 2.5 mol% $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$ and aryl bromides to give *ortho* aryl products in high yield. In this case the reaction is postulated to proceed via $\text{S}_{\text{E}}\text{Ar}$ reaction of an arylated ruthenium(IV) complex, formed *in situ*, to give a ruthenacycle that undergoes reductive elimination to yield the product. The 2-pyridyl group also directs activation of neighboring benzylic C–H bonds. Treatment of 2-(2,6-dimethylphenyl)pyridines with $\text{Ru}_3(\text{CO})_{12}$ and triethylsilane in the presence of norbornene as a hydrogen acceptor in toluene leads to silylation at the benzylic position. The reaction is enhanced by the presence of electron-donating groups on the pyridine ring. For example, 2-(2,6-dimethylphenyl)-4-methoxypyridine undergoes silylation at both benzylic positions to give the product in 85% yield (Equation 45).

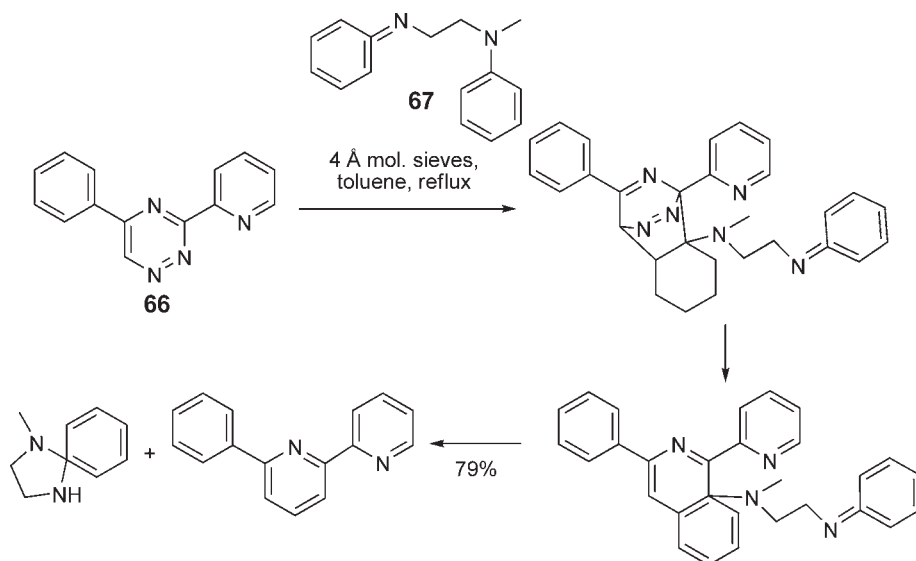


The presence of a 2-pyridyl substituent on a pyrimidine ring influences the regioselectivity of nucleophilic attack of organolithium reagents. While 4-substituted pyrimidines undergo addition of organolithium reagents to give the 4,6-disubstituted isomer as the major compound, 4-(2-pyridyl)pyrimidine reacts with 6-lithio-2-bromopyridine to give the 2,4- and 4,6-isomers in near equimolar quantities owing to prior chelation of the organolithium with the 2-pyridyl moiety <2000EJOC3505> (Equation 46).



Triazines undergo inverse electron demand aza-Diels–Alder reactions with enamines to give cycloadducts that undergo retro-Diels–Alder reaction followed by elimination, sometimes requiring a separate step, to give substituted pyridines. Application of this process to pyridyl-substituted triazines is a useful method for the synthesis of functionalized bipyridines <2005TL1791>. Taylor and co-workers have circumvented the need to use preformed enamines and the requirement for a separate aromatization step in this procedure by utilizing tethered imine-enamines, formed *in situ*. The intermediates arising from cycloaddition then readily undergo elimination to give highly substituted bipyridines <2004CC508>. As an example, triazine **66** undergoes cycloaddition with the tethered imine–enamine **67**, formed *in situ* from cyclohexanone and *N*-methylethylenediamine, to give a cycloadduct that undergoes retro-Diels–Alder reaction and elimination in one pot to give a 2,2'-bipyridine in good yield (Scheme 15).

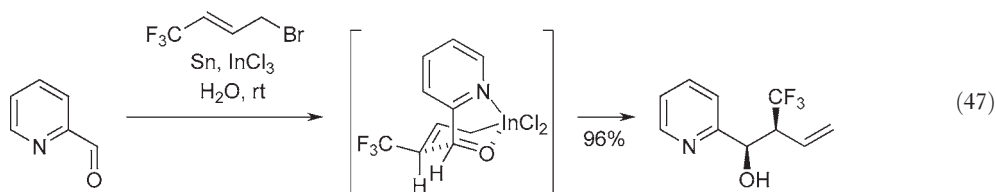
Microbial oxidation of phenylpyridines and phenylquinolines occurs selectively at the benzene ring to give catechols. Treatment of 2-phenylpyridine, 2-benzylpyridine, and 2-phenylquinoline with *Escherichia coli* cells expressing genes for biphenyl dioxygenase and dihydrodiol dehydrogenase results in oxidation of the benzene ring to give the 2,3-diol in low yield <2005T195>.



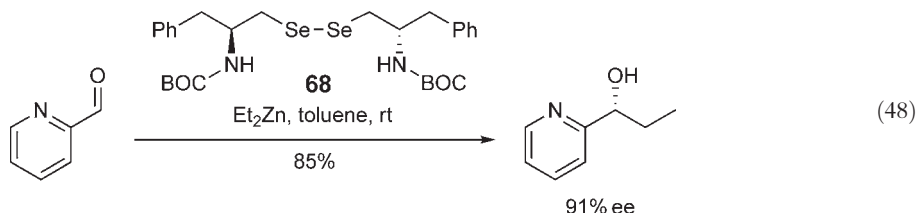
Scheme 15

7.03.3.3 Acyl Groups

Pyridinecarbaldehydes undergo addition with a wide variety of carbon-based nucleophiles in an analogous manner to benzaldehydes. The majority of recent progress in this area has been made in the development of stereoselective variants. Pyridine-2-carbaldehyde undergoes addition with the allylindium reagent derived from 1,1,1-trifluoro-4-bromobut-2-ene to give the *syn*-allyl alcohol as the major product in high yield <1997AGE980>. The reaction proceeds by initial formation of an allyltin reagent that undergoes transmetalation with InCl_3 and, in general, proceeds to give the *anti*-product owing to an equatorial orientation of the aldehyde substituent in the six-membered transition state. However, the pyridine substituent prefers to sit in an axial position to maximize chelation with indium (Equation 47). The reaction also proceeds using pyridine-3-carbaldehyde to give the *anti*-allyl alcohol in high yield.



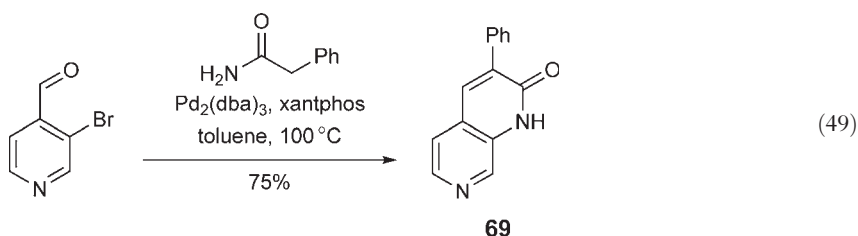
Diethyl zinc undergoes enantioselective addition to 2-pyridinecarbaldehyde in 91% ee in the presence of 0.5 mol% optically pure diselenide **68** in toluene at room temperature <2003OL2635> (Equation 48). The reaction is postulated to proceed by *in situ* formation of a chiral zinc selenolate formed by nucleophilic attack of Et_2Zn on diselenide **68**.



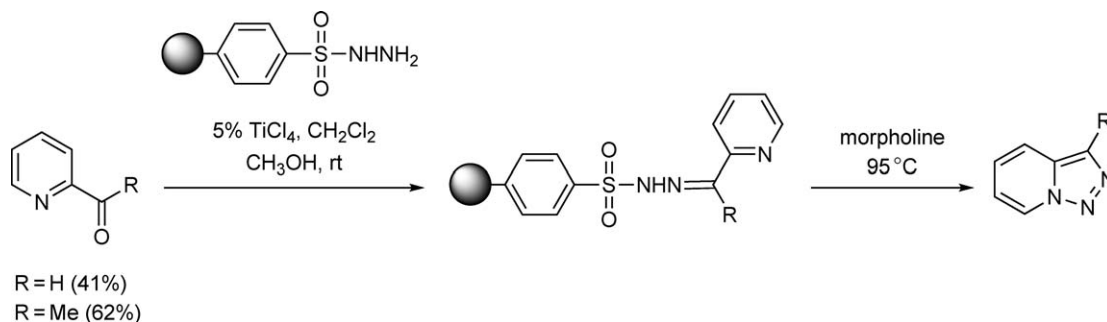
3-Pyridinecarbaldehyde reacts with trimethylsilyl cyanide in the presence of the catalysts derived from either enantiomer of 3,3'-bis(diethylaminomethyl)-substituted binaphthol or 1,1'-bi-2-naphthol (BINOL) and

dimethylaluminium dichloride to give the cyanohydrin in high yield and enantiomeric ratio [<2004T10487>](#). 3-Pyridinecarbaldehyde undergoes enantioselective conversion to the corresponding (*R*)-cyanohydrin on treatment with acetonecyanohydrin in the presence of the biocatalyst hydroxynitrile lyase extracted from seeds of the Japanese apricot *Prunus mume* [<2005T10908>](#). Biocatalysts have been applied to effect enantioselective C–C bond-forming reactions of pyridinecarbaldehydes. 2-Pyridinecarbaldehyde undergoes the benzoin reaction in the presence of benzoylformate decarboxylase in DMSO at room temperature to give the (*R*)-acyloin in 70% yield and 94% ee [<1999TA4769>](#). Asymmetric aldol reaction of 2-pyridinecarbaldehydes has also been effected using asymmetric catalysis. Mukaiyama aldol reaction of 6-chloro-5-hydroxypyridinecarbaldehyde with methyl trimethylsilyl ketene acetal occurs in 90% yield and 94% ee in the presence of Carreira's binaphthyl ligand $\text{Ti}(\text{OPr}^i)_4$ and 3,5-di-*tert*-butylsalicylic acid [<2002AGE1062>](#).

Synthetic manipulation of pyridinecarbaldehydes gives access to a variety of fused heterocycles. Palladium-catalyzed cross-coupling of *ortho*-bromopyridinecarbaldehydes and enolisable amides in the presence of $\text{Pd}_2(\text{dba})_3$ and xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) leads to the formation of naphthyridinones in moderate to good yield [<2004OL2433>](#). For example, 3-bromopyridine-4-carbaldehyde undergoes coupling with 2-phenylacetamide followed by *in situ* cyclodehydration to give 1, 7-naphthyridone **69** (Equation 49).

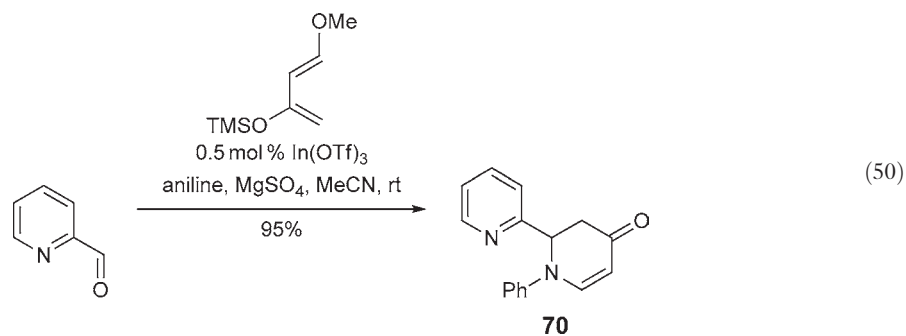


In an alternative approach to naphthyridines, *ortho*-ethynylpyridinecarbaldehydes undergo cyclization in the presence of ammonia in ethanol in a sealed tube at 80 °C to give the fused heterocycle in low to good yield [<1999S306>](#). Solid-phase synthesis of fused triazoles may be achieved using polystyrene-sulfonyl hydrazide resin in combination with 2-acetylpyridine or pyridine-2-carbaldehyde [<2004TL6129>](#). Treatment of the initial hydrazone with morpholine leads to the generation of the corresponding diazo intermediate and cyclization to the triazole (Scheme 16).



Scheme 16

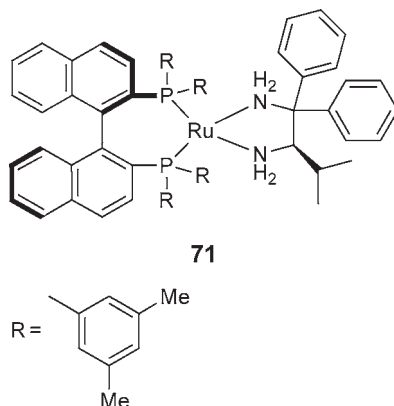
Lewis acid-catalyzed Diels–Alder reaction of pyridinecarbaldehydes and Danishefsky's diene and derivatives provides access to pyridyl-substituted dihydropyranones. The reaction of 2-pyridinecarbaldehyde and Danishefsky's diene occurs in 65% yield in the presence of 2 mol% of the lanthanide catalyst $[\text{Cp}_2\text{Ce}][\text{BPh}_4]$ and 5 mol% proton sponge [<2000JOC1215>](#). The cycloaddition can be performed in the presence of amines and Lewis acids such as indium(III) triflate [<1999TL5621>](#) or ytterbium(III) triflate [<2003TL6629>](#) to give access to tetrahydropyridine derivatives such as **70** (Equation 50).



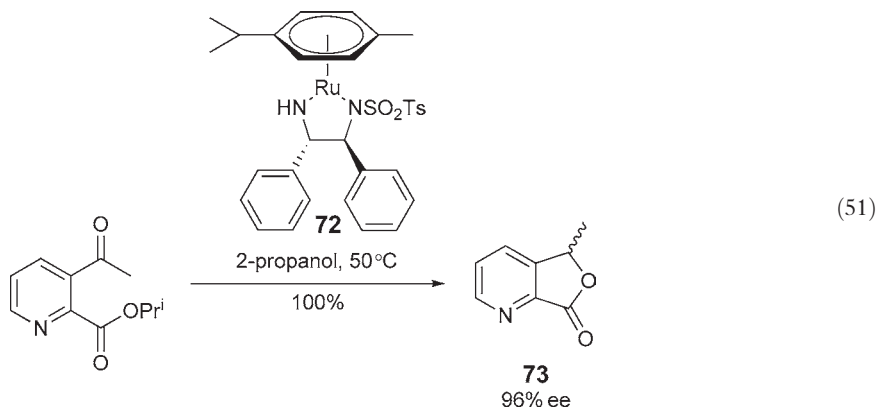
This Diels–Alder reaction proceeds in an enantioselective fashion in the presence of chiral, nonracemic Lewis acid catalysts. 2-Pyridinecarbaldehyde and 3-pyridinecarbaldehyde undergo high-yielding addition with Danishefsky's diene in the presence of [(*R*)-BINOL]₂-Ti(OPrⁱ)₄ complex in 99% and 98% ee, respectively <2005T5822>.

Pyridinecarbaldehyde may be selectively oxidized at nitrogen using dimethyldioxirane (DMDO) in acetone at room temperature <1999T12557>. 3-Pyridinecarbaldehyde is oxidized to the *N*-oxide in 60% yield, while the 4-substituted isomer is oxidized in 98% yield. 3-Pyridinecarboxaldehyde is converted in 98% yield to the corresponding dihydroxy-methyl-substituted *N*-oxide that undergoes dehydration to the aldehyde upon heating to 60 °C under vacuum.

A number of methods have been developed for the asymmetric reduction of acetylpyridines. Asymmetric hydrogenation of 2- and 3-acetylpyridine occurs in high yield and ≥94% ee to give the (*S*)-alcohol product using 2.5 mol% chiral ruthenium complex **71** in 2-propanol in an autoclave pressurized with 50 atm of hydrogen gas <2000OL1749>.



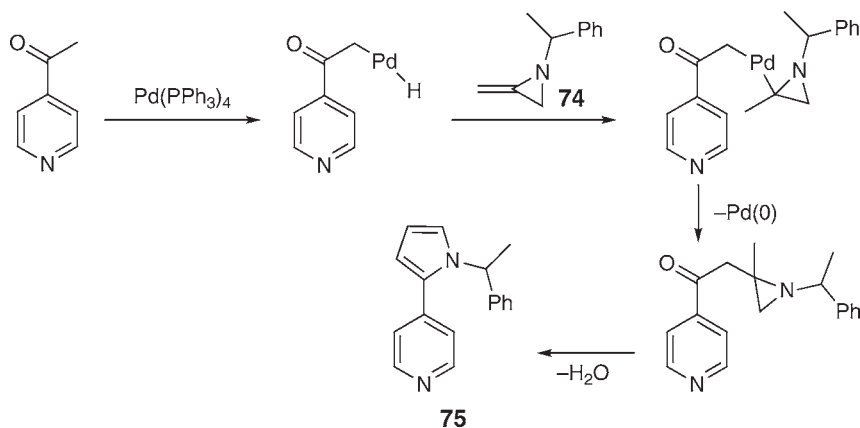
Asymmetric transfer hydrogenation of acetylpyridines is possible in the presence of chiral ruthenium catalysts and 2-propanol. Treatment of 2-propyl 3-acetylpyridine-2-carboxylate with 1 mol% ruthenium catalyst **72** in a 0.1 M 2-propanol solution results in asymmetric reduction followed by cyclization to give pyridinyl lactone **73** in quantitative yield <2001TL1899> (Equation 51). While the reduction proceeds in 96% ee, the absolute configuration of the product was not determined.



(*R,R*)-2,6-Bis(1-hydroxyethyl)pyridine effects asymmetric reduction of 2,6-diacetylpyridine in the presence of $\text{Zn}(\text{OTf})_2$ and sodium triacetoxyborohydride and *para*-nitrophenol to produce more of the diol with the same configuration <2003OL3947>. Using 20 mol% of the catalyst in dichloromethane at room temperature results in >80% conversion to the diol in 47% de and 40% ee. The asymmetric reduction of diacetylpyridines can also be effected with chlorodiisopinocamporylborane <1996TL3795>. Reduction of 2,6-diacetylpyridine with Ipc_2BCl gives 36% of the mono-reduction product and 59% of the diol. The low yields of diol are proposed to arise from coordination of nitrogen with the boron reagent, and 3,5-diacetyl-2,6-lutidine, with a noncoordinating nitrogen, is converted to the (*R,R*)-diol using (+)- Ipc_2BCl in 97% yield and $\geq 99\%$ ee. 2,6-Diperfluoracetylpyridines are converted to the (*S,S*)-diols using (–)- Ipc_2BCl in 72% yield and $\geq 99\%$ ee. Acetylpyridines also undergo biocatalytic reductions. 2,6-Diacetylpyridine is reduced to the (*S*)-monoalcohol in 91% yield and 95% ee using baker's yeast in the presence of sucrose and phosphate buffer <1997TA3467> and 3- and 4-acetylpyridine are reduced to the corresponding (*S*)-alcohols in 99% yield and 99% ee using whole cells obtained from the spores of *G. Candidum* in the presence of the hydrophobic polymer Amberlite™ XAD <2000J(P1)3205>.

Friedländer reaction of 2-acetylpyridine with 2-aminobenzaldehydes gives access to 2-(pyridin-2-yl)quinolines. This process is now possible using the more stable 2-aminobenzylalcohols in the presence of oxidants. 2-(Pyridin-2-yl)quinoline is synthesized in 88% yield from 2-acetylpyridine and 2-aminobenzylalcohol in the presence of a ruthenium-grafted hydrocalcite under 1 atm of oxygen in toluene at 100 °C <2004TL6029> and is accessed in 89% yield using 1 mol% of the ruthenium catalyst $\text{RuCl}_2(\text{=CHPh})\text{PCy}_3)_2$ in the presence of KOH in dioxane at 80 °C <2001CC2576>.

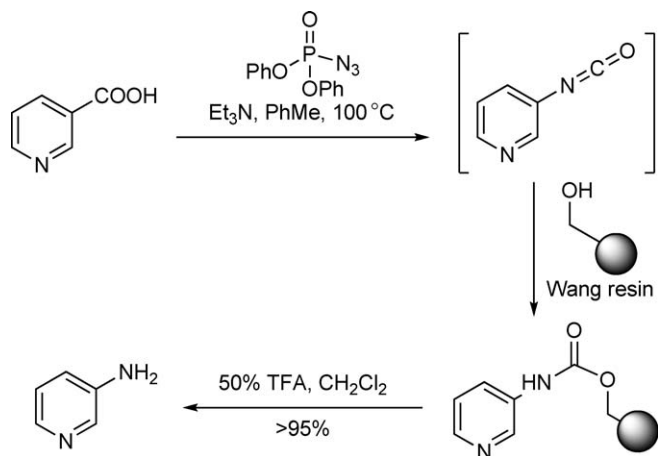
Acetylpyridines are found to undergo oxidative insertion into the alpha carbon–hydrogen bond of the acyl moiety in the presence of Pd(0) to give hydridopalladium intermediates. These species undergo hydropalladation with methyleneaziridines followed by reductive elimination and cyclisation to give pyridylpyrroles in good to excellent yield <2004JA13898>. For example, 4-acetylpyridine reacts with methyleneaziridine **74** in the presence of 30 mol% $\text{Pd}(\text{PPh}_3)_4$ to give pyridylpyrrole **75** in 88% yield (Scheme 17).



Scheme 17

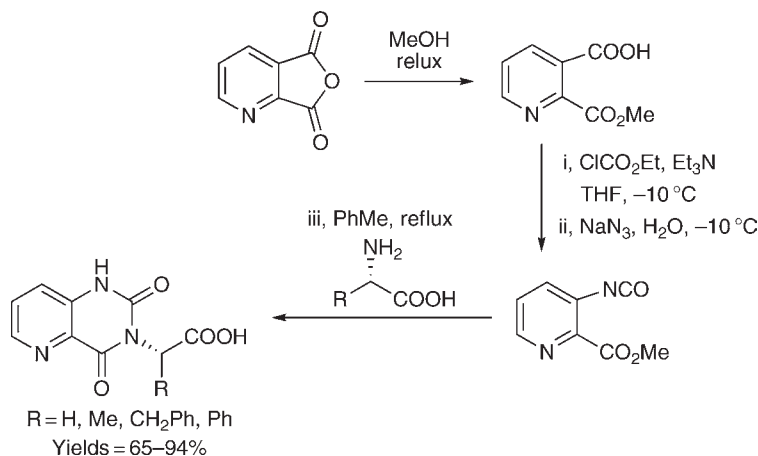
7.03.3.4 Carboxylic Acids and Derivatives

A new procedure for the esterification of pyridine dicarboxylic acids has been developed that proceeds via *in situ* generation of the acid fluoride <2004S2485>. Treatment of 2-pyridinecarboxylic acid with a stoichiometric amount of *N,N,N,N*-tetramethylfluoroformamidinium hexafluorophosphate (TFFH) in dichloromethane and triethylamine leads to the generation of the acid fluoride that undergoes coupling with (3-methyloxetan-3-yl)methanol to give the corresponding ester in 95% yield. Libraries of 2-, 3-, and 4-aminopyridines may be prepared by performing Curtius rearrangement of the corresponding carboxylic acid in the presence of Wang resin <1999TL1721>. For example, 3-pyridinecarboxylic acid is converted on treatment with diphenylphosphoryl azide in toluene at 100 °C to the corresponding isocyanate that is transformed to the carbamate on reaction with *in situ* Wang resin. Cleavage from the resin is achieved using 50% TFA to give the amine in >95% yield (Scheme 18). The resin-bound carbamate may be *N*-alkylated in high yield using sodium hydride and either ethyl iodide or allylbromide to give the *N*-alkylated aminopyridine on cleavage.



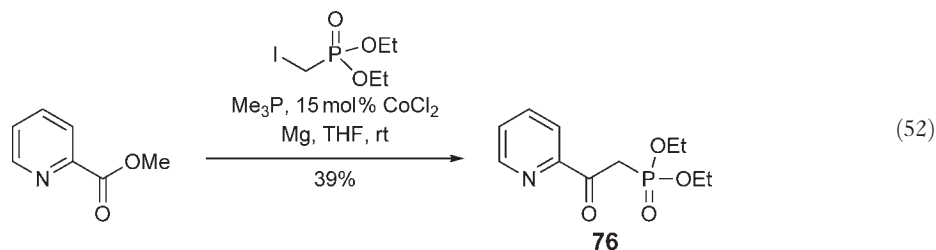
Scheme 18

Pyridopyrimidine systems may also be accessed by *in situ* generation of pyridylisocyanates [<2003TL2745>](#). Treatment of 2,3-pyridinecarboxylic anhydride with methanol leads to the formation of 2-(methoxycarbonyl)nicotinic acid that undergoes Curtius rearrangement on conversion to the 3-acyl azide with sodium azide and ethyl chloroformate. Condensation of the resulting isocyanate with a series of amino acids leads to the synthesis of pyrido[3,2-*d*]-pyrimidines in good to excellent yield (Scheme 19).



Scheme 19

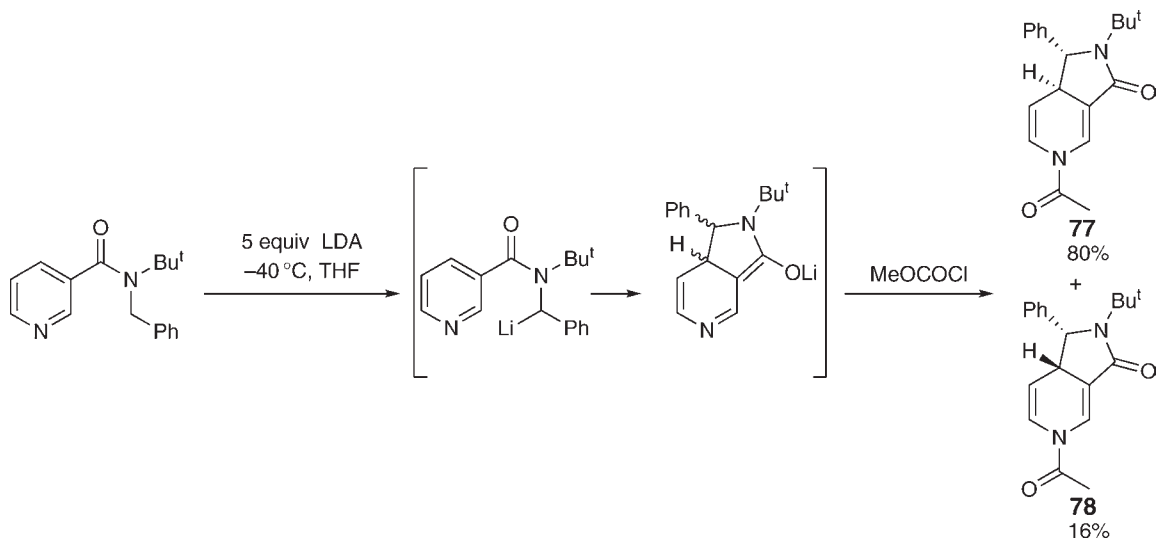
Picolinate esters may be converted to the corresponding β -ketophosphonate by metal-mediated coupling with α -halophosphonates. Methyl picolinate is converted to the β -ketophosphonate **76** on treatment with 15% CoCl₂ in the presence of magnesium metal to regenerate Co(0) and trimethylphosphine ligands in THF in 39% yield [<2002S1683>](#) (Equation 52). The reaction can also be carried out in the absence of magnesium using stoichiometric amounts of cobalt complex to give the phosphonate in 34% yield with a 55% yield of recovered starting material.



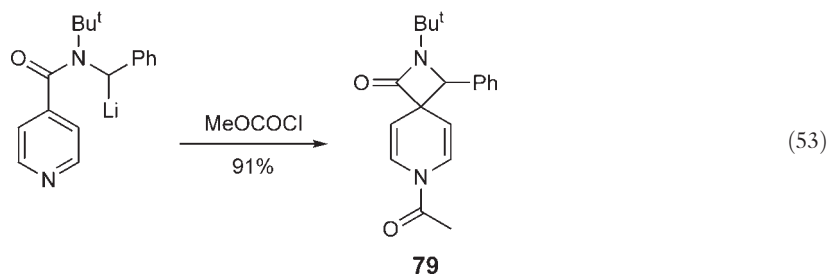
The same reaction can be carried out in the presence of 2.2 equiv of samarium iodide in THF to give the compound **76** in 30% yield and recovered starting material in 60% yield <2002TL7259>.

Methyl pyridinecarboxylates can be converted to the corresponding amide on treatment with MgCl_2 or MgBr_2 in the presence of a range of primary and secondary amines <2001TL1843>. The reaction of the dimethyl pyridine-2,3-dicarboxylate with the 2,5-isomer occurs selectively at the 2-position.

Pyridinecarboxamides undergo lithiation α to the amide nitrogen and the resulting anions undergo cyclization onto the pyridine ring giving access to partially saturated pyrrolopyridines and spirocyclic β -lactams <2005OL3673>. For example, *N*-benzyl-*N*-(*tert*-butyl)pyridine-3-carboxamide undergoes lithiation on treatment with LDA followed by cyclization and *N*-acylation with methyl chloroformate to give a diastereomeric mixture of dihydropyridines **77** and **78** (Scheme 20). In contrast, the lithium anion obtained from the pyridine-4-carboxamide undergoes cyclization to give the 2,7-diazaspiro[3,5]-nonane **79** in high yield (Equation 53).



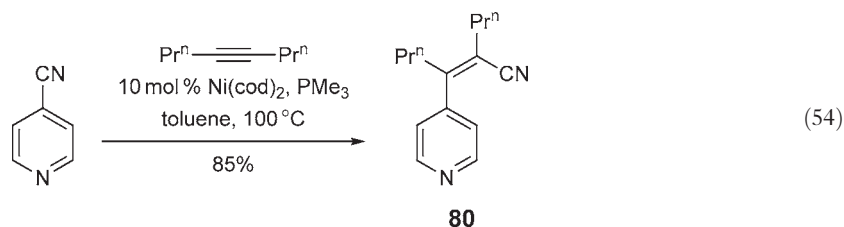
Scheme 20



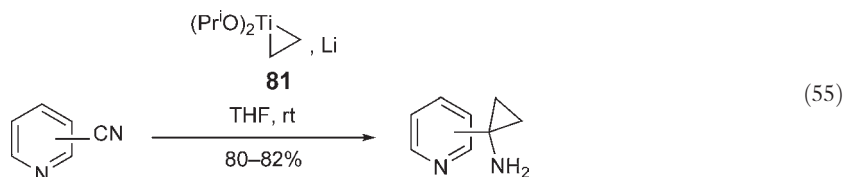
The reductive cleavage of pyridinecarboxamides generally occurs only under forcing conditions. However, it has been found that conversion of *N*-benzylpyridinecarboxamides to the corresponding *tert*-butyl acylcarbamate by reaction with BOC_2O and DMAP allows mild reduction in high yield by controlled potential electrolysis, activated aluminium, or sodium borohydride in ethanol to give the hydroxymethylpyridine and BOC-protected amine <2001OL2021>.

Cyanopyridines have been shown to be good coupling partners in transition metal-mediated C–C bond-forming reactions. The C–CN bond is readily activated by oxidative insertion of nickel catalysts, and the resulting nickel(II) complexes undergo transmetalation with other organometallic species and carbometallation across alkynes. Treatment of 2- and 3-cyanopyridines with aryl Grignard reagents, 5 mol% dichlorobis(trimethylphosphine)nickel, and sterically bulky alkoxides, that prevent the formation of imines and homo-coupled products,

leads to the synthesis of biaryls in good yield [\[2003SI1643\]](#). This cross-coupling can also be performed with alkenyl Grignard reagents to give alkenyl-substituted pyridines. An alternative approach to the synthesis of alkenylpyridines from cyanopyridines centers on the carbometallation of alkynes with pyridylnickel complexes [\[2004JA13904\]](#). For example, treatment of 4-cyanopyridine and oct-4-yne with 10 mol% bis(1,5-cyclooctadiene)-nickel(0) and trimethylphosphine in toluene gives alkenylpyridine **80** in good yield (Equation 54). The reaction proceeds by oxidative insertion of nickel(0) into the C–CN bond followed by cyanonickelation and reductive elimination.



Cyanopyridines undergo titanium-mediated reductive cyclopropanation to give pyridylcyclopropylamines in good yield [\[2003OL753\]](#). Both 2- and 3-cyanopyridine react with the titanium species **81** formed from diethylzinc and methyltriisopropoxytitanium in the presence of lithium isopropoxide to give the cyclopropylamine product in 80% and 82% yield, respectively (Equation 55).



2- and 4-Cyanopyridines are activated toward nucleophilic attack and undergo displacement with a variety of lithium amides derived from secondary amines and *n*-butyllithium in the presence of 1.5 equiv of cesium fluoride to give the corresponding aminopyridine in moderate to high yield [\[2004TL2667\]](#).

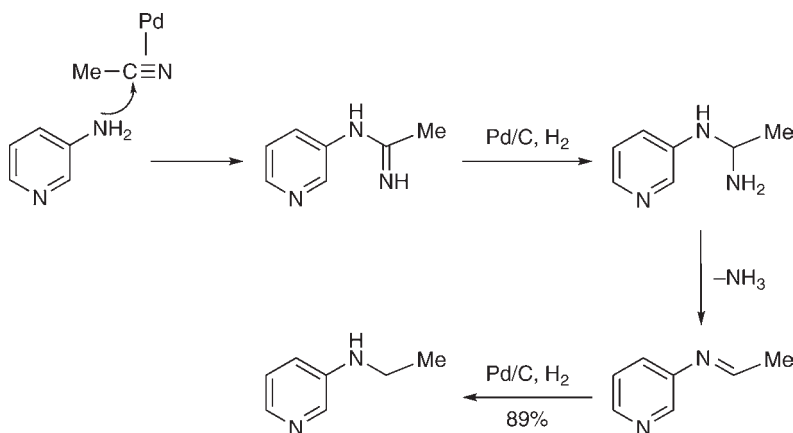
7.03.4 N-Linked Substituents

7.03.4.1 Amino Groups and Related Functions

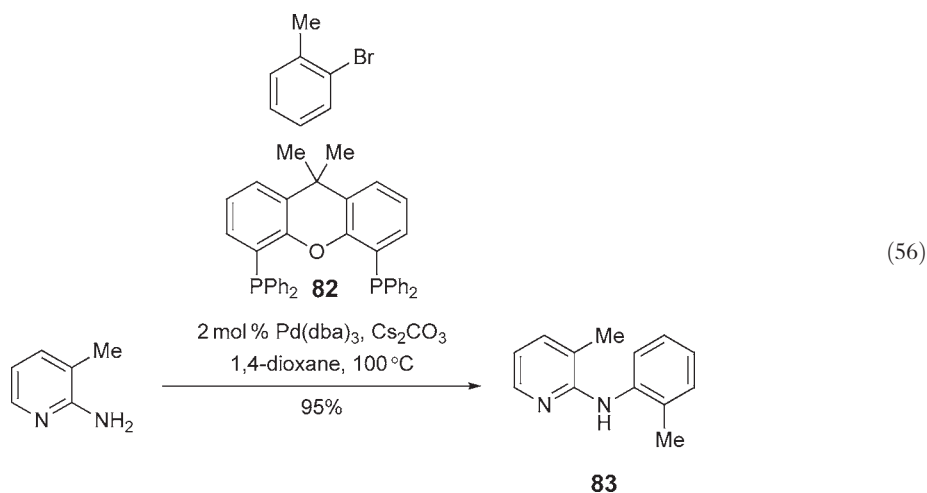
7.03.4.1.1 Amino groups attached to carbon

Several new methods have been developed for the *N*-alkylation and *N*-arylation of aminopyridines. 4-Aminopyridine undergoes alkylation with *N*-(2-chloroethyl)morpholine in 90% yield in the presence of catalytic quantities of potassium iodide in acetonitrile under microwave irradiation [\[2004TL8797\]](#). 3-Aminopyridine undergoes mild, reductive alkylation using acetonitrile as alkylating agent in the presence of Pd/C in MeOH under an atmosphere of hydrogen [\[2004OL4977\]](#). It is postulated that Pd(0) acts as an activating agent for alkylation and also as a reduction catalyst in this procedure (Scheme 21).

Transition metal-mediated C–N bond formation has also been applied to the *N*-arylation of aminopyridines. 2-Aminopyridine undergoes coupling with *para*-tolylboronic acid in the presence of 1.5 equiv of Cu(OAc)₂, pyridine, and 4 Å mol sieves to the *N*-arylated product in 70% yield [\[2000S674\]](#). The arylation of 2-aminopyridines can also be effected using aryl bromides in the presence of palladium(0) catalysts [\[2002OL3481\]](#). For example, 2-amino-3-methylpyridine reacts with 1-bromo-2-methylbenzene in the presence of 2 mol% Pd(dba)₃, xantphos **82**, and CsCO₃ in 1,4-dioxane at 100 °C to give the *N*-arylated product **83** in high yield (Equation 56).

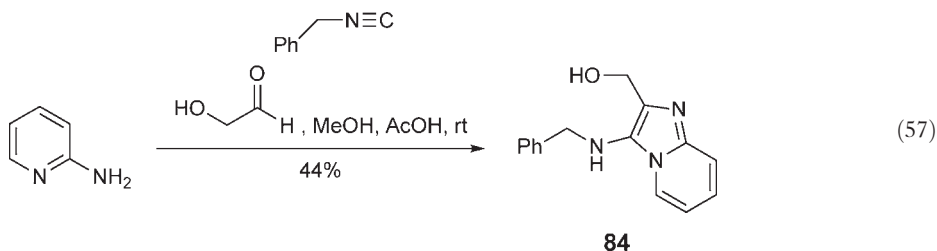


Scheme 21

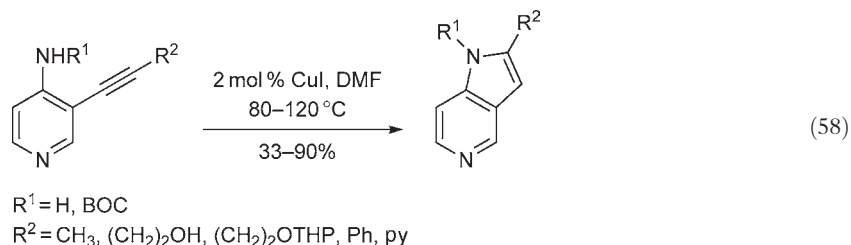


Aminopyridines undergo condensation with *N,N*-dialkylformamides to give *N,N*-dialkylformamidines. The reaction of 2-aminopyridine with DMF can be achieved rapidly in the presence of 2-pyridinesulfonyl chloride to give the *N,N*-dimethylformamidine in 87% yield [<1997TL5423>](#). 2- and 4-Aminopyridines undergo condensation with isothiocyanates in THF under 0.6 GPa pressure in the absence of catalysts to give *N*-pyridinothiourea derivatives in good to high yield [<2002TL1035>](#). Imines of 4-aminopyridine can be prepared by condensation with dimethylacetals in the presence of 10 mol% of the relatively easily handled Lewis acid scandium triflate in toluene using a Dean–Stark apparatus [<1998SL640>](#).

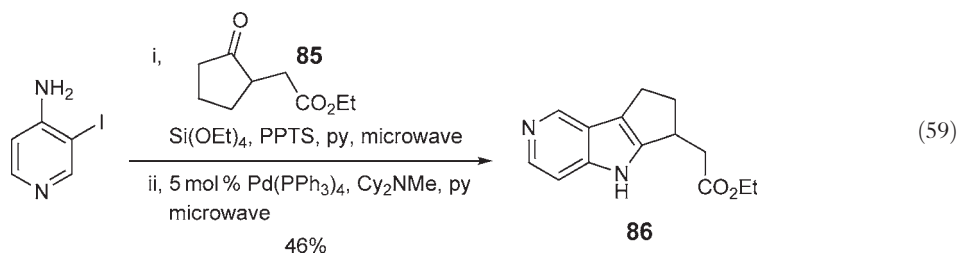
Aminopyridines are useful substrates for the preparation of fused heterocycles. Imidazo[1,2-*a*]pyridines may be prepared in moderate to good yield by three-component coupling of 2-aminopyridine, aldehydes and isocyanides [<1998S661>](#). The reaction proceeds by nucleophilic attack of the isocyanide onto an iminium species formed by condensation of 2-aminopyridine with the aldehyde component followed by 1,3-H shift. For example, 2-aminopyridine reacts with benzylisocyanide and 2-hydroxyacetaldehyde in the presence of 2 equiv of glacial acetic acid in methanol to give imidazo[2-*a*]pyridine **84** in 44% yield (Equation 57).



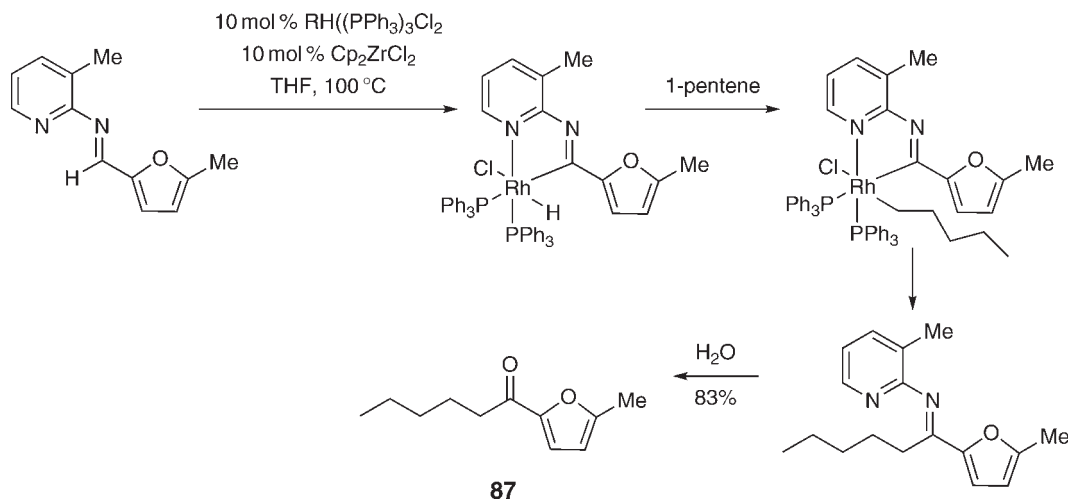
Imidazo[2-*a*]pyridines bound to solid supports via acid or base labile linkers can be prepared by reaction of resin-bound α -bromoketones with 2-aminopyridines <2003TL6265>. 5-Azaindoles may be prepared by cyclization of *ortho*-alkynyl aminopyridines in moderate to high yield in the presence of catalytic amounts of CuI <1998TL5159> (Equation 58).



A range of imines and enamines, formed from *ortho*-haloaminopyridines and ketones, may be converted to a variety of substituted 4-, 5-, 6-, and 7-azaindoles by microwave-assisted intramolecular Heck reaction <2005S2571>. As an example, 4-amino-3-iodopyridine is converted to azaindole **85** in 46% yield by condensation with ketone **86** followed by Heck reaction of the resulting enamine (Equation 59).

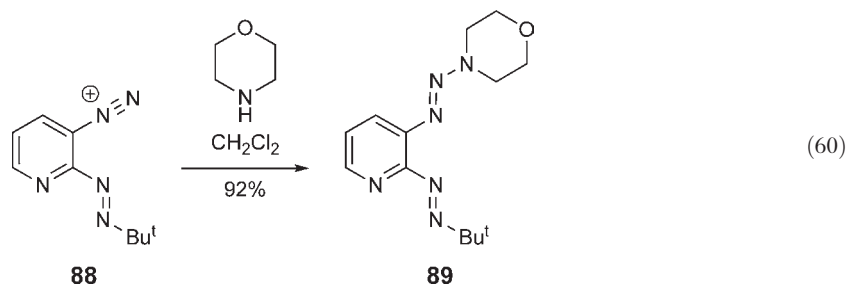


Aldimines, formed from 2-amino-3-picoline and a variety of heteroaromatic aldehydes, may be converted to ketimines by reaction with 1-pentene in the presence of 10 mol % Wilkinson's catalyst (Rh(PPh₃)₃Cl) and 10 mol % bis(cyclopentadienyl)zirconium or titanium dichloride <1997TL6673>. Activation of the aldimine C–H bond, hydrometallation of the resulting rhodium complex with 1-pentene followed by migratory insertion and reductive elimination gives the ketimine. As the product is readily hydrolyzed to the ketone, this process represents a novel method for the conversion of aldehydes to ketones. For example, the imine formed from 2-amino-3-picoline and 5-methylfuran-2-carbaldehyde reacts with 1-pentene in the presence of Wilkinson's catalyst and Cp₂ZrCl₂ to give the ketone **87** in 83% yield (Scheme 22).

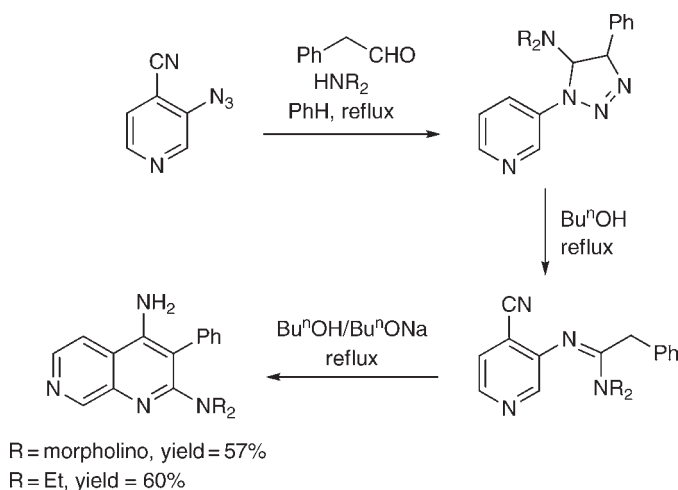


Scheme 22

Pyridinediazonium salts react with nucleophiles at the terminal nitrogen of the diazo group <2004EJO4794>. For example, diazonium salt **88** reacts with morpholine to give triazene **89** in high yield (Equation 60).

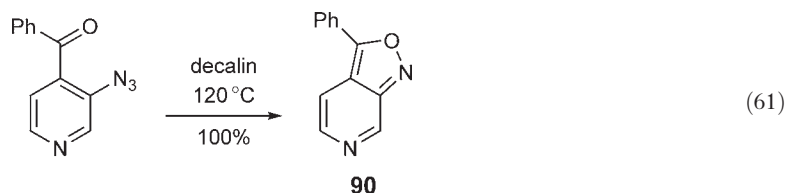


Azidopyridines undergo 1,3-dipolar cycloaddition with alkynes to give pyridyl-substituted triazoles, typically as a mixture of regioisomers. The regioselectivity of this process can be controlled by the presence of a trimethylsilyl group on the alkyne to give the 1-pyridyl-4-trimethylsilyl triazole as sole product <2005OL1469>. 3-Azido-4-cyanopyridine is converted to the corresponding amino-triazoline on reaction with arylacetaldehydes and secondary amines. The triazine undergoes rearrangement to an amidine that then undergoes cyclocondensation to give a naphthyridine <1996J(P1)1359> (Scheme 23).



Scheme 23

The rate of thermolysis of azidopyridines is enhanced by the presence of a neighboring benzoyl group such that 3-azido-4-benzoylpyridine thermolyzes 152 times faster than 3-azidopyridine to give isoxazolo[3,4-*c*]pyridine **90** in quantitative yield <1996AJC761> (Equation 61).

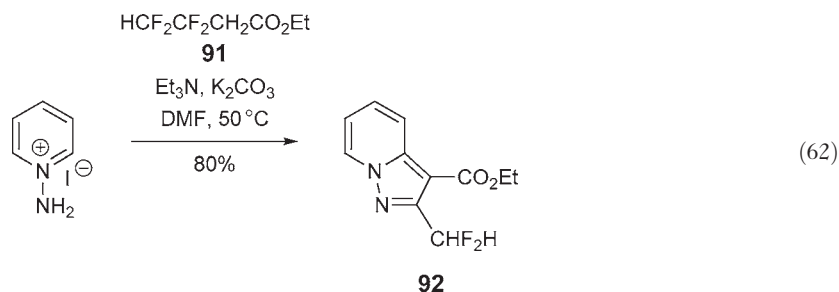


The azide moiety of azidopyridines can be reduced to the corresponding amine in good yield using indium powder, in the presence of conc. HCl, in 3:1 H₂O:THF <2001S81>.

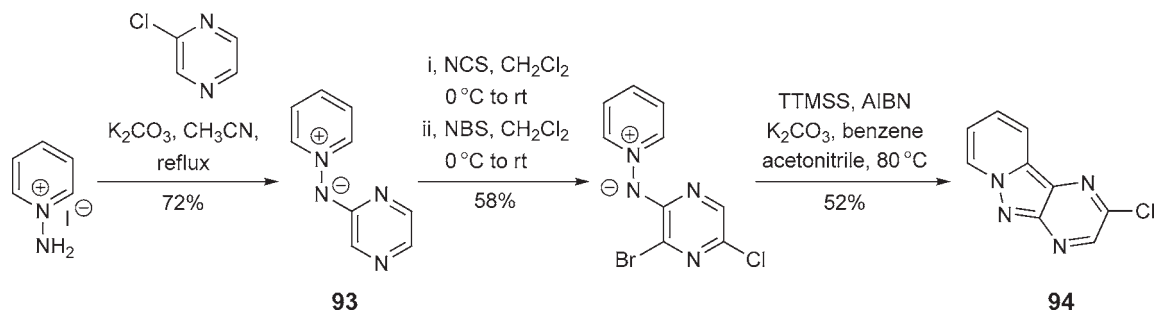
7.03.4.1.2 Amino groups attached to nitrogen

The recent chemistry of *N*-aminopyridinium halides is dominated by the reactions of the corresponding pyridinium ylides generated by deprotonation of the amino group. These 1,3-dipoles undergo cycloaddition with dipolarophiles and react with electrophiles at the nitrogen of the amino group.

N-Aminopyridinium and isoquinolinium iodides react with ethyl-2,2-dihydropolyperfluoroalkanoates in the presence of base to give polyfluorosubstituted pyrazolo[1,5-*a*]pyridines in moderate to good yield <1998JFC57>. Elimination of HF from the alkenoate precursors generates the alkenoate that undergoes 1,3-dipolar cycloaddition with the pyridinium ylide followed by loss of HF and HCl to give the fluorinated pyrazolopyridine. As an example, *N*-aminopyridinium iodide reacts with alkenoate **91** to give pyrazolopyridine **92** in 80% yield (Equation 62).



Pyridinium *N*-heteroarylamidines have been previously prepared by a three-step sequence from *N*-arylpyridinium salts. A one-step sequence has now been devised and centers on the *N*-arylation of the pyridinium ylide with a π -deficient chloroheteroaryl compound <2004T1093>. *N*-Aminopyridinium iodide undergoes $\text{S}_{\text{N}}\text{Ar}$ reaction with chloropyridines, chloropyrimidines, and chloropyrazines in good to high yield in the presence of potassium carbonate in acetonitrile at room temperature or under reflux to give pyridinium-*N*-heteroarylamidines such as **93**. These products may be regioselectively chlorinated then brominated using NCS followed by NBS <1995T8649> and the products undergo intramolecular radical arylation on treatment with AIBN and tris(trimethylsilyl)silane (TTMSS) in the presence of potassium carbonate in acetonitrile/benzene at 80 °C <2002SL1093>. For example, pyridinium(*N*-(2'-pyrazinyl)amidine) is converted to pyrazolo[1,5-*a*]pyridine **94** using this procedure (Scheme 24).

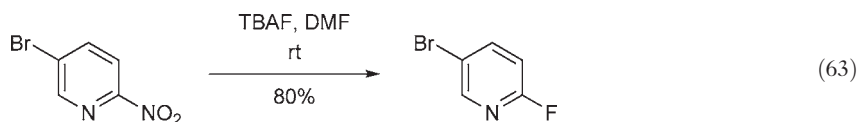


Scheme 24

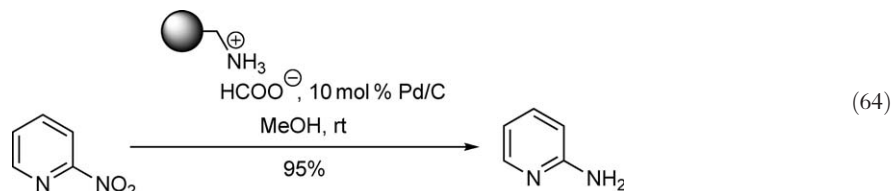
N-Aminopyridinium iodide may also be alkylated on nitrogen with *N*-benzoylthioureas in the presence of base and thiophiles such as bismuth nitrate and mercury chloride to give pyridinium *N*-benzoylguanidines in moderate to good yields <2005T10536>.

7.03.4.2 Nitro Groups

The nitro substituent in 2- and 4-nitropyridines may be displaced by a number of nucleophiles. Reaction of 2-methyl-4-nitropicolinic acid with 37% $\text{HCl}_{(\text{aq})}$ under reflux leads to the formation of 2-methyl-4-chloropicolinic acid in 80% yield <2002SC1715>. Reaction of 2-chloro-4-nitropyridine with a variety of alcohols or thiols in the presence of sodium hydride in 1,4-dioxane occurs in moderate to good yield to give the corresponding 4-alkoxy or 4-alkylthio-pyridine <2004EJO3477>. A variety of 2- and 4-nitropyridines undergo fluorodenitration in the presence of tetrabutylammonium fluoride (TBAF) in DMF to give the corresponding fluoropyridine in moderate to high yield <2005OL577>. This procedure tolerates the presence of bromine substituents. For example, 5-bromo-2-nitropyridine is converted to the 2-fluoro derivative in 80% yield (Equation 63). Fluorodenitration of 3-nitropyridines is also possible when the pyridine ring is substituted with electron-withdrawing substituents.



The nitropyridines can be reduced to the corresponding aminopyridine and several new methods have been developed to achieve this transformation. 3-Nitropyridine is reduced in excellent yield by the mixed borohydride prepared from 1 equiv of ZrCl_4 and 4 equiv of NaBH_4 in THF under reflux [<2000SL683>](#). 3-Nitropyridines may be reduced to the aminopyridine using sodium hydrosulfite in THF/ H_2O at room temperature [<2005JME5104>](#). 2-Nitropyridine can be reduced to the amine in near quantitative yield by transfer hydrogenation in the presence of 10% Pd/C and recyclable polymer-supported formate, prepared from aminomethylpolystyrene resin and ammonium formate [<2005SC223>](#) (Equation 64). The resin is easily recovered by filtration and may be used up to 10 times.

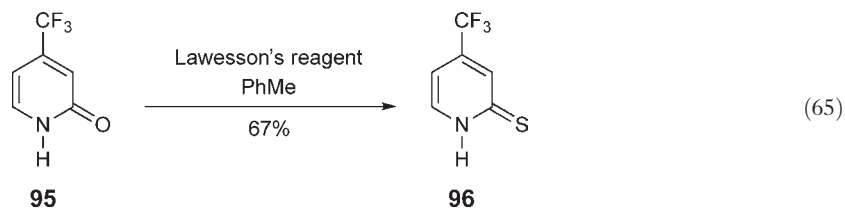


7.03.5 O-Linked Substituents

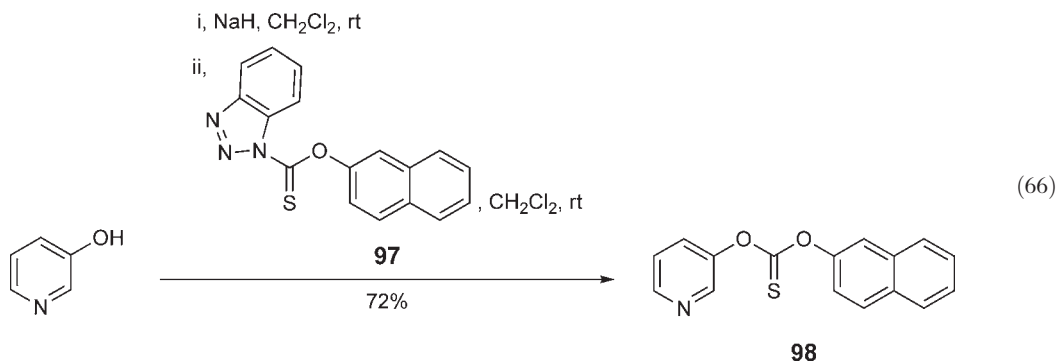
7.03.5.1 Pyridones and Hydroxypyridines

2-Pyridones may be directly converted to the 2-chloropyridine on treatment with phosphoryl chloride at elevated temperatures [<2005JOC6204, 2004JA12232, 2003H\(60\)1461, 2000JHC1253>](#).

2-Pyridones may be converted to pyridine thiones by treatment with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent). For example, pyridone **95** gives pyridine thione **96** on treatment with Lawesson's reagent in dry toluene (Equation 65) [<1999JFC153>](#).

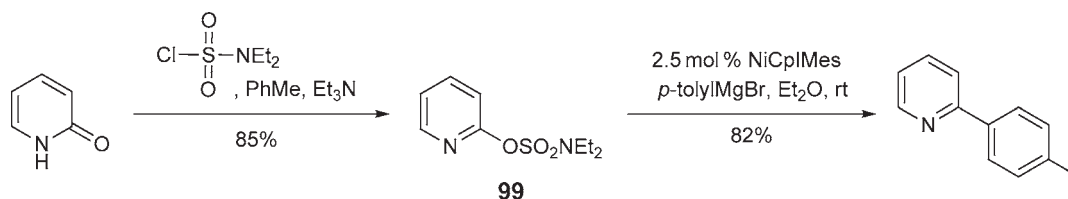


3-Hydroxypyridines may be thioacylated using benzotriazole reagents. The sodium salt of 3-hydroxypyridine reacts with aryloxythiobenzotriazole **97** to give thiocarbonate **98** in good yield [<2005JOC7866>](#) (Equation 66).



Hydroxypyridines are readily converted to the corresponding *O*-sulfamates and triflates and these derivatives undergo transition metal-catalyzed C–C bond formation. *O*-Sulfamates can be obtained by treatment of 2- and

3-hydroxypyridines with *N,N*-diethylsulfamoyl chloride in the presence of triethylamine. These compounds undergo Kumada–Corriu cross-coupling with aryl Grignard reagents to give biaryls in good yield <2005OL2519>. As an example, 2-pyridone is converted to sulfamate **99** that undergoes cross-coupling with *para*-tolylmagnesium bromide in the presence of NiClCpIMes (IMes = bis-(1,3-(2,4,6-trimethylphenyl))imidazol-2-ylidene) (Scheme 25).



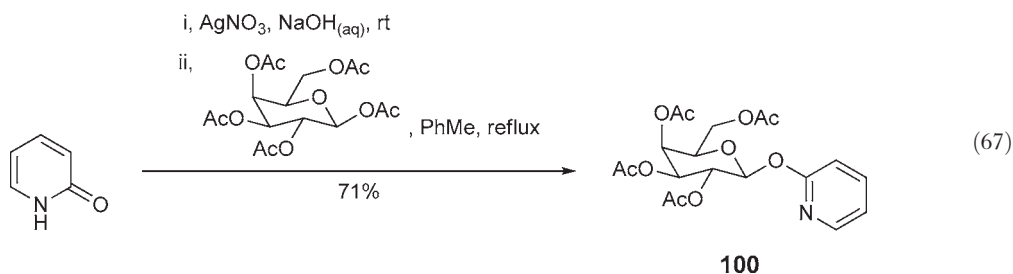
Scheme 25

Using TiF_2O in the presence of lutidine, 2- and 3-hydroxypyridines are converted to the corresponding triflates, that undergo Stille coupling in high yield with vinyltributyltin in the presence of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ <1996JOC4623>. 3-Hydroxypyridines react with TiF_2O in pyridine to give the triflate that undergoes Suzuki–Miyaura coupling with 2-pivaloylaminophenylboronic acid in the presence of $\text{Pd}(\text{PPh}_3)_4$ and potassium carbonate in 95% yield <2001JOC2654>.

2-Pyridones are converted to the 2-trimethylsilyloxy derivative using bis(trimethylsilyl)acetamide (BSA) in acetonitrile <1999T11985> while 3-hydroxypyridines have been converted to the *tert*-butyldimethylsilyl ether in high yield on treatment with TBSCl in DMF in the presence of imidazole <2004T11751> and have been transformed to the triisopropylsilyl ether on treatment with TIPSCl and imidazole in DMF <2005SL2080>.

7.03.5.2 Alkylation of Hydroxypyridines, Pyridones, and their Benzo Derivatives

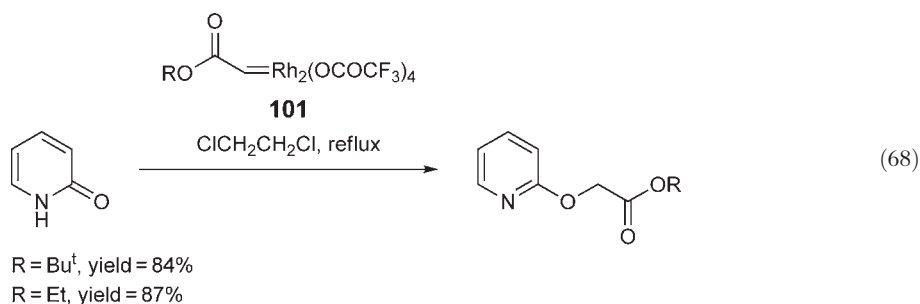
Attempted alkylation of 2-pyridones often leads to mixtures of *N*- and *O*-alkylated products with the selectivity dependent on the reaction conditions. Alkylation of the sodium salt of 2-pyridone often leads to *N*-alkylation while alkylation of the silver salt results in *O*-alkylation. For example, β -D-galactopyranose pentaacetate reacts with silver 2-pyridoxide in toluene under reflux to give the pyridylgalactopyranoside **100** in good yield (Equation 67) <2001T3267>.



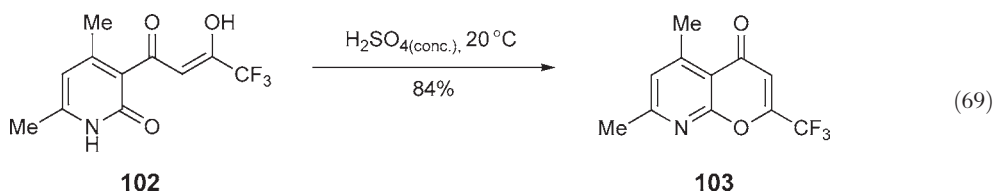
O-Alkylation is also favored using more sterically hindered electrophiles such as secondary alkyl halides. Alkylation of 2-pyridone with isopropyl iodide under mild conditions in the presence of CsF in DMF at room temperature leads to the formation of a mixture of *N*- and *O*-alkylated products in a 11:89 ratio, respectively, and 62% overall yield <1995SL845>. 2-Pyridone may be alkylated with primary and secondary alcohols under Mitsunobu conditions using PPh_3 and DEAD. This procedure favors formation of the *O*-alkylated product when performed in THF and DME, although use of benzyl alcohol and 2-naphthalenemethanol results in predominantly *O*-alkylation <1994TL2819>. The selectivity of alkylation of 2-benzyloxy-2(1*H*)-quinolinone has been recently studied <1999TL6999>. In contrast to 2-pyridone, alkylation using benzyl bromide in the presence of sodium hydride in DMF occurs at oxygen while *N*-alkylation predominates under solid–liquid phase transfer conditions using toluene in the presence of KOH and tetrabutylammonium iodide.

Selective *O*-alkylation of 2-pyridones is effected by reaction with diazoacetic esters in the presence of 2 mol% $\text{Rh}_2(\text{OCOCF}_3)_4$ <2000OL1641>. The reaction proceeds by selective transfer of the carbene from rhodium–carbene

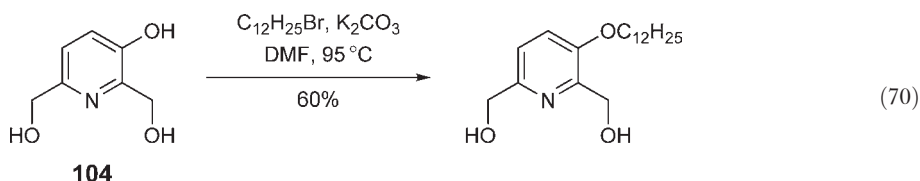
complex **101** to the oxygen of 2-pyridone followed by 1,4-hydrogen shift of the resulting oxygen ylide to give the acetic ester ether in high yield (Equation 68).



2-Pyridones such as **102** possessing polyfluoroalkylated β -diketone substituents at the 3-position undergo intramolecular condensation on treatment with conc. H_2SO_4 to give 8-aza-2-polyfluoroalkylchromones such as **103** <2003JFC25> (Equation 69).

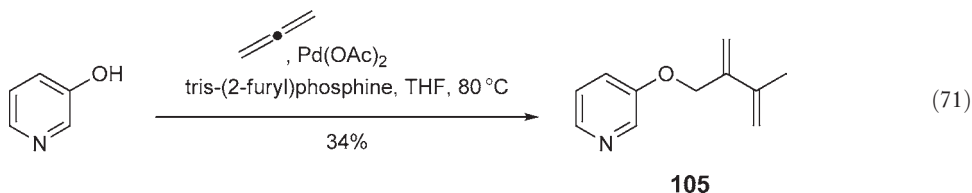


3-Hydroxypyridines are readily alkylated under a variety of conditions. Mitsunobu reaction with alcohols occurs selectively at oxygen in the presence of PPh_3 and DEAD in THF at room temperature <2003TL725>. The 3-hydroxy group may be selectively alkylated in the presence of aliphatic hydroxyl groups. Pyridine **104** is alkylated at the aromatic position with dodecyl bromide in the presence of potassium carbonate in DMF at 95°C <2003OBC644> (Equation 70).



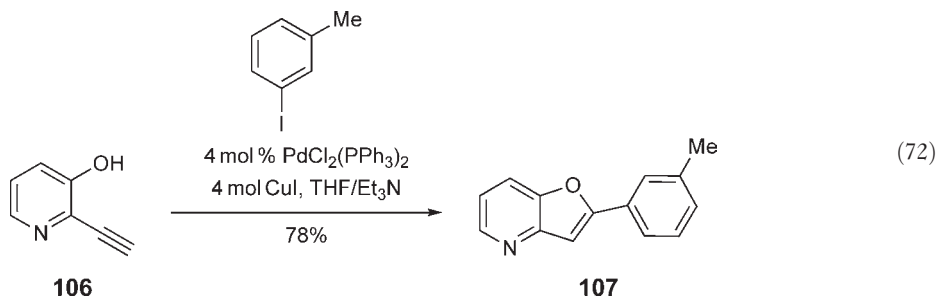
The 3-hydroxy group may be methylated in high yield using trimethylsilyldiazomethane in methanol and dichloromethane at 20°C <2005BML1721>. Alkylation of the 3-hydroxy group can be effected by reaction of polymer-bound nucleophiles allowing the preparation of pyridyl ethers free from salts. A column of the quaternary ammonium exchange resin Amberlite® IRA-900 loaded with 3-hydroxypyridine can be treated with a solution of *n*-butyl bromide in THF to give the corresponding butyl ether <1996TL5257>.

3-Hydroxypyridine may be allylated by Pd(0)-catalyzed nucleophilic attack of oxygen onto allene <2001T7965>. Reaction with 2 equiv of allene in THF in the presence of $\text{Pd}(\text{OAc})_2$ and tris-(2-furyl)phosphine gives 1,3-dienyl ether **105** in 34% yield (Equation 71). This process occurs in similar yield when performed on 3-hydroxyisoquinoline.



2-Ethynyl-3-pyridinols undergo coupling with iodoarenes, aryl triflates, and enol triflates in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ and CuI. Nucleophilic attack of oxygen onto the arylated alkyne product occurs *in situ* to give

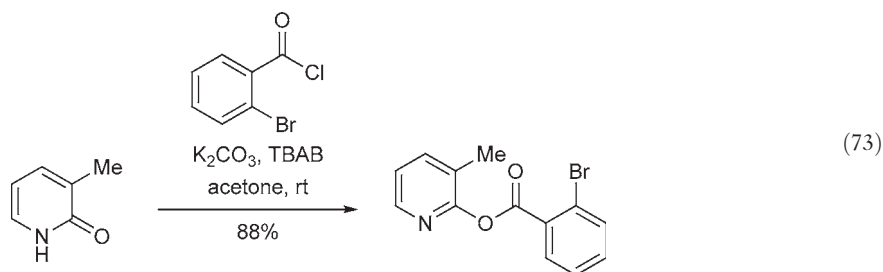
2-substituted furo[3,2-*b*]pyridines <2002SL453>. For example, ethynylpyridinol **106** can be converted to furopyridine **107** (Equation 72).



A similar process can also be performed on the corresponding 3-ethynyl-2-pyridinol but only proceeds in 12–38% yield.

7.03.5.3 Acylation of Hydroxypyridines, Pyridones, and their Benzo Derivatives

2-Pyridones may be selectively acylated at oxygen by treatment with acetyl chloride in acetone in the presence of potassium carbonate <2001JOC3646>. 2-Pyridones are also selectively *O*-acylated with 2-bromobenzoyl chlorides in high yield using potassium carbonate and tetrabutylammonium bromide (TBAB) in acetone <2003T3009>. For example 3-methoxy-2(1*H*)-pyridone is acylated in 88% yield by 2-bromobenzoyl chloride under these conditions (Equation 73).



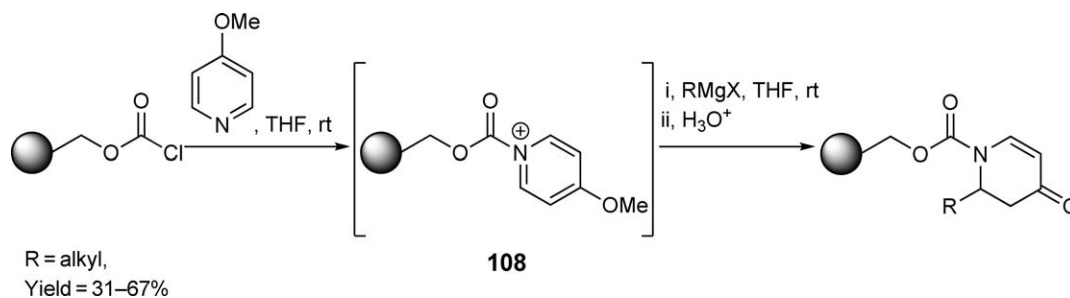
2-Pyridone may also be acylated on oxygen using acetic anhydride in the presence of catalytic quantities of sulfuric acid <1999T12797>. 4-Pyridones have been acylated at oxygen in moderate yield using acetic anhydride in pyridine at 80 °C <2002JME1079>.

3-Hydroxypyridines may be *O*-acylated using acetyl chloride in triethylamine <2000TL8053> and with a variety of acid chlorides in moderate to good yields in acetone in the presence of potassium carbonate at 0 °C <2003JME2631>. Acetylation of 2-bromo-3-hydroxypyridine has been achieved in 91% yield by heating in acetic anhydride <2000OL2291>.

7.03.5.4 Ethers

Alkyl ethers of 2- and 4-pyridones are readily deprotected under a variety of acidic conditions. 2-Methoxypyridines may be dealkylated to give the corresponding pyridone in moderate yield on heating with 12*N* HCl <2005JME1948>. The deprotection of 2-methoxy-6-pentylpyridine has been effected in 95% yield in 48% HBr <2001BMC2863>. The *O*-deprotection of methoxypyridines is also achieved in high yield using TMSI in chloroform <2003EJO4445> or using a combination of TMSCl and NaI in acetonitrile at 80 °C <1996T11385, 2001SL765>. An alternate, high-yielding demethylation of 2-methoxypyridines utilizes stoichiometric quantities of boron tribromide in dichloromethane at –20 °C <2004H(63)2735>. A variety of 4-alkoxypyridines may be deprotected by stirring in DMSO under reflux or utilizing aluminium trichloride in dichloromethane at room temperature <2002JME1079>. Demethylation of 4-methoxypyridines can also be effected in good yield using conc. HCl in ethanol <1998JME4408>. *N*-Acylpyridinium salts substituted with alkoxy groups at the 4-position undergo nucleophilic attack by Grignard reagents followed by cleavage of the alkyl ether to give substituted dihydropyridones. This

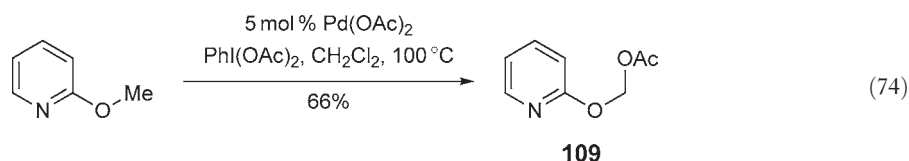
process has been performed on resin-linked acylpyridinium complex **108**, formed by reaction of 4-methoxypyridine with chloroformate solid support, to provide a variety of dihydropyridone scaffolds <1998TL217> (Scheme 26).



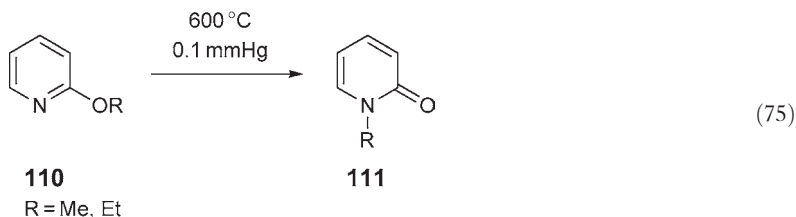
Scheme 26

3-Alkoxy pyridines undergo deprotection under relatively forcing conditions, typically requiring the use of strong Brønsted or Lewis acids at elevated temperatures <2004T11751>. Alternatively, rapid and high-yielding deprotection of 3-methoxypyridines can be effected using aluminium trichloride and sodium chloride at 150 °C <1996JOC4623>. This procedure is not tolerant of the presence of an ester functionality and a more selective demethylation occurs using AlCl₃ in dichloromethane under reflux over 2 days. High-yielding *O*-dealkylation of 3-methoxypyridines can be effected at room temperature over 3 days using 3 equiv of boron tribromide in dichloromethane <2004TL3607>.

The sp³ C–H bond adjacent to oxygen in 2-alkoxy pyridines undergoes selective oxidation in moderate yield in the presence of catalytic Pd(OAc)₂ and stoichiometric amounts of PhI(OAc)₂ in dichloromethane <2004JA9542>. Selectivity in this process arises from chelation of Pd(II) to the pyridine nitrogen. 2-Methoxypyridine undergoes regioselective oxidation to acetal **109** in 66% yield on treatment with 5 mol% Pd(OAc)₂ and 1.1 equiv of PhI(OAc)₂ in dichloromethane at 100 °C (Equation 74) while *n*-butoxypyridine is oxidized in 44% yield and isopropoxy pyridine is oxidized in 42% yield.



2-Alkoxy pyridines such as **110** undergo thermally induced rearrangement to *N*-alkylpyridones such as **111** under flash vacuum pyrolysis <2003AJC913> (Equation 75). 2-Methoxy-4-methylquinoline and 1-methoxyisoquinoline also undergo rearrangement in 35% and 70% yield, respectively.



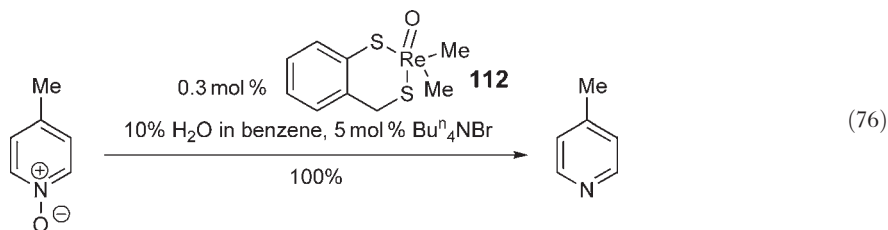
7.03.5.5 *N*-Oxides and their Derivatives

A variety of new methods for the selective reduction of pyridine *N*-oxides to the corresponding pyridine have been developed. A procedure that is limited to the reduction of relatively electron-rich pyridine *N*-oxides utilizes hexamethyldisilane in the presence of methyl lithium in THF/HMPA <1999JOC2211>. This reduction can also be performed on quinoline and isoquinoline *N*-oxides. Tris(2-carboxyethyl)phosphine (TCEP) can be used to

deoxygenate pyridine *N*-oxides in high yield in dioxane under reflux <2003SC3503>. The relatively high water solubility of this phosphine helps circumvent some of the purification problems associated with the use of more conventional phosphines in this reduction. An environmentally benign deoxygenation that utilizes only sodium hydroxide or sodium ethoxide in benzyl alcohol as reaction medium at 30 °C has been developed <2005JOC3218>. This procedure has been applied to the high-yielding deoxygenation of pyridine *N*-oxide, isoquinoline *N*-oxide, and a number of quinoline *N*-oxides. The process is thought to proceed via a series of both ionic and radical steps and results in partial oxidation of the solvent alcohol. The reaction can be performed in other short alkyl chain alcohols at elevated temperatures.

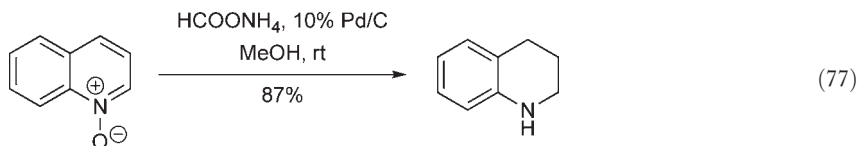
Many deoxygenation processes utilize metal salts or complexes. A range of pyridine *N*-oxides can be reduced at nitrogen in high yield using iron powder in acetic acid/water under reflux <2004JME6749>, nickel(II) chloride, lithium powder and 10 mol% 4,4'-di-*tert*-butylbiphenyl <2000T8673>, titanium tetrachloride and 0.5 equiv of indium powder <2003SC4185> or anhydrous indium trichloride <2002TL1877>.

Oxomolybdenum and oxorhenium complexes function as efficient oxo-transfer catalysts in combination with stoichiometric quantities of triphenylphosphine, to effect the deoxygenation of pyridine *N*-oxides. A range of pyridine *N*-oxides, quinoline, and isoquinoline *N*-oxides are deoxygenated in high yield using 1 mol% of the dichlorodioxomolybdenum(VI) catalyst $\text{MoO}_2\text{Cl}_2(\text{DMF})_2$ in the presence of 1 equiv of triphenylphosphine in THF under reflux <2005SL1389> or 0.3% oxorhenium catalyst **112** in the presence of 1 equiv of triphenylphosphine in benzene or 10% water with benzene containing 5 mol% tetrabutylammonium bromide <2000OL3525>. For example, 4-methylpyridine *N*-oxide is reduced in quantitative yield using this process (Equation 76).

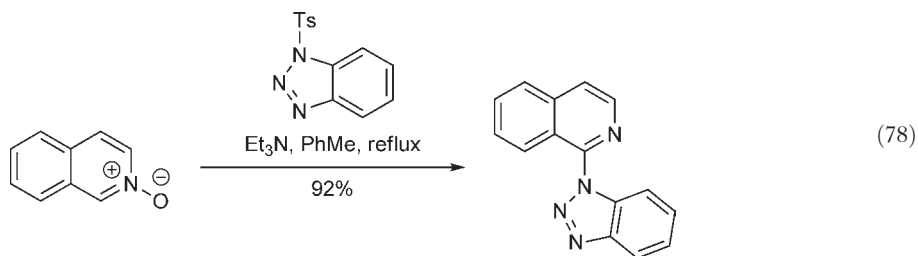


Some recent efforts have been directed toward developing deoxygenation of pyridine *N*-oxides using relatively cheap and more easily handled reagents. One method utilizes aluminium hexahydrate in the presence of potassium iodide in acetonitrile/water at room temperature <2001SL795>. Higher yields of deoxygenation have been achieved by simply heating the pyridine *N*-oxide in the presence of 1 equiv of readily available molybdenum hexacarbonyl in ethanol <2006TL125>. Deoxygenation of a range of pyridine *N*-oxides has also been achieved using 1 equiv of water-tolerant zinc or copper triflate in acetonitrile at 80 °C <2006SL395>.

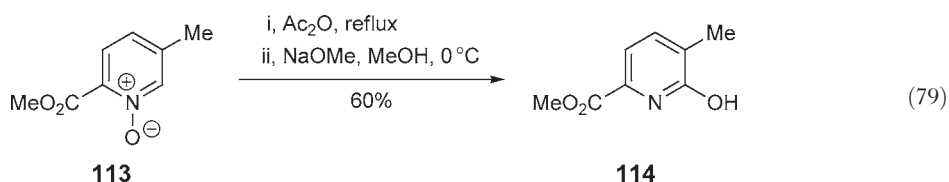
Pyridine *N*-oxides may be reduced at nitrogen and the aromatic ring in high yield under mild conditions by catalytic transfer hydrogenation using ammonium formate as the hydrogen source in the presence of 10 mol% palladium on carbon <2001JOC5264>. Quinoline and isoquinoline *N*-oxide are also reduced to the piperidine derivative in high yield. For example, quinoline *N*-oxide is reduced to 1,2,3,4-tetrahydroquinoline in 87% yield on stirring with ammonium formate in the presence of Pd/C in methanol overnight (Equation 77).



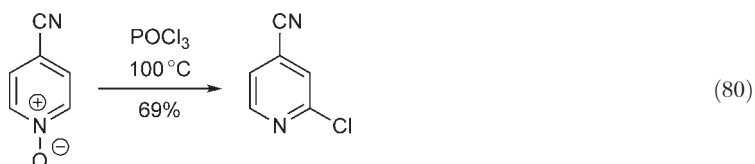
Oxidation of the pyridine nitrogen increases the propensity of the aromatic ring for nucleophilic attack at the 2- and 4-positions. α -Benzotriazolyl-substituted pyridines, quinolines, and isoquinolines may be prepared by treatment of the *N*-oxide with 1-tosylbenzotriazole in the presence of triethylamine in toluene or xylene under reflux <2001H1703> (Equation 78).



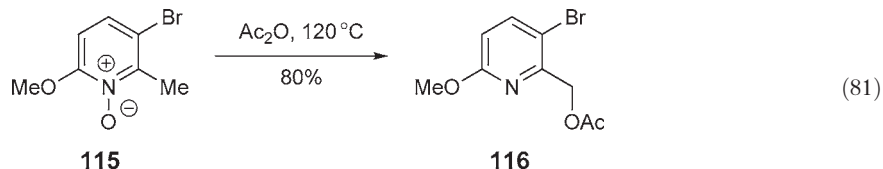
Pyridine *N*-oxides undergo isomerism to the 2-pyridone when heated under reflux in acetic anhydride. In a recent application of this methodology, pyridine *N*-oxide **113** was treated with acetic anhydride followed by sodium methoxide to give 6-hydroxypyridine **114** in 60% yield <2002T6951> (Equation 79). 3-Acetylpyridine *N*-oxide can be converted to the 2-pyridone under similar conditions in 28% yield <2001T8841>.



Pyridine *N*-oxides also provide access to 2-chloropyridines. Treatment of 4-cyanopyridine *N*-oxide with phosphorus oxychloride under reflux for 24 h results in the formation of 2-chloro-4-cyanopyridine in 69% yield <2001TL6815> (Equation 80).



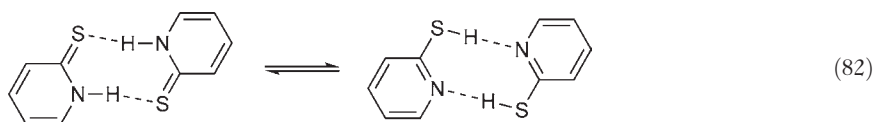
It is possible to convert 2-picoline *N*-oxides directly to 2-chloromethylpyridines using tosyl chloride. It has been found that this method cannot be extended to the transformation of highly substituted pyridine *N*-oxides and an improved procedure, utilizing a combination of 1.5 equiv of both TsCl and Et₃N, has been developed to overcome this problem <2002SC1211>. Alternatively, treatment of pyridine *N*-oxides such as **115** with acetic anhydride at elevated temperature results in formation of the related 2-acetoxymethylpyridine such as **116** <2000CPB1514, 2003JA5186, 2003OBC2865> (Equation 81).



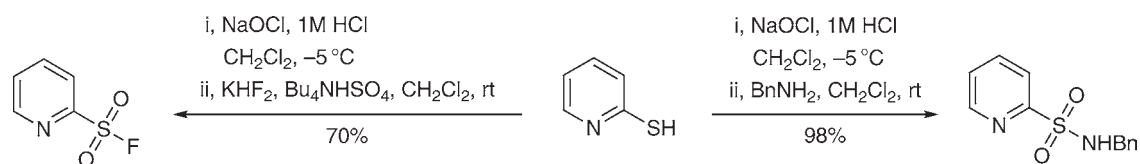
7.03.6 S-Linked Substituents

7.03.6.1 Thiols, their Tautomers and Related Compounds

2-Pyridinethiol is in equilibrium with 2-pyridinethione and it has been previously thought that the thiol is more stable in nonpolar solvents while the thione is more stable in polar solvents. Recent variable temperature Fourier transform IR experiments and computational studies calculated at the B3LYP/6-311 level of theory indicate that the thione is more thermodynamically stable than the thiol in nonpolar solvents and that tautomerism occurs via the dimer <2002JOC9061> (Equation 82).

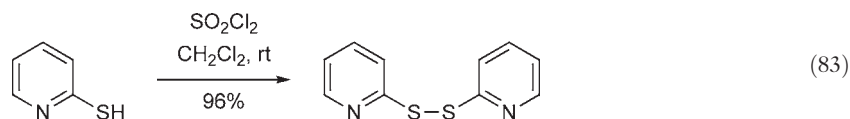


A number of new procedures have been developed for the oxidation of sulfur-linked substituents on the pyridine ring at sulfur. 2- and 4-Pyridinethiols may be oxidized to the corresponding sulfonyl chloride at low temperature using sodium hypochlorite in a mixture of dichloromethane and 1 M aqueous HCl [\[2006JOC1080\]](#). Treatment of the crude solution of sulfonyl chloride in dichloromethane with benzylamine results in rapid conversion to the sulfonamide. Carrying out the oxidation in the presence of KHF₂ and tetrabutylammonium sulfate results in conversion to the sulfonyl fluoride. For example, 2-pyridinethiol is converted to the sulfonamide in 98% yield and the sulfonyl fluoride in 70% yield using this procedure ([Scheme 27](#)). In the same manner, 4-pyridinethiol is converted to the sulfonyl chloride in 39% yield and 2-quinolinethiol is converted to the sulfonyl chloride and sulfonyl fluoride in 80% and 49% yield, respectively.

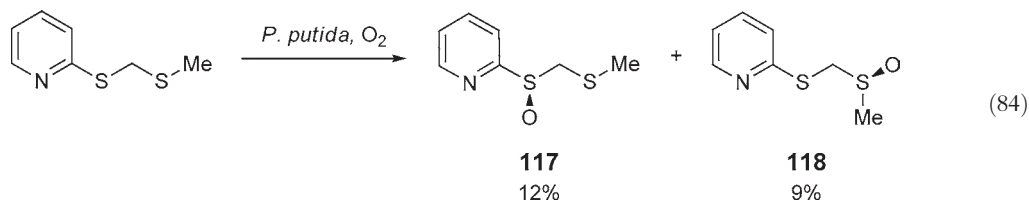


Scheme 27

Controlled oxidation of thiols may lead to oxidative coupling to give disulfides. This transformation can now be achieved using solid-phase reagents. 2-Pyridinethiol is converted to 2,2'-dipyridyl disulfide in 75% yield on treatment with the quaternary ammonium resin Dowex 1-X8, in which Cl[−] has been replaced with Cr₂O₇^{2−} and HSO₄[−], in acetonitrile under reflux [\[2003SC1833\]](#). The same transformation can be effected rapidly in 96% yield under solvent-free conditions using quinolinium fluorochromate, prepared from quinoline, 40% HF, and chromium trioxide, on silica gel [\[2003M1571\]](#). The oxidative coupling of 2-pyridinethiol can also be effected in near quantitative yield using sulfuryl chloride in dichloromethane ([Equation 83](#)). As this cheap and facile procedure generates SO₂ and HCl as the only by-products, no workup or purification is required and in some cases the reaction may be carried out on a rotary evaporator.

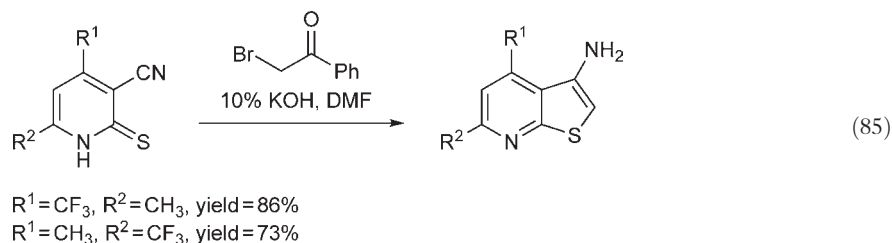


A number of new biotransformations utilizing whole-cell or enzymatic procedures for the oxidation of alkylthio-pyridines to optically pure sulfoxides have been developed. 4-(Methylthio)pyridine is oxidized to give the (*R*)-sulfoxide in 69% ee using vanadium bromoperoxidase isolated from the brown seaweed *Ascophyllum nodosum* [\[1999TA4563\]](#). However, only a low conversion of 10% is observed. Moderate conversions of 2-methylthiopyridine to the sulfoxide in >99% ee have been achieved using aqueous hydrogen peroxide in the presence of microencapsulated chloroperoxidase, isolated from *Caldariomyces fumago* [\[2004AGE4097\]](#). Naphthalene dioxygenase-catalyzed oxidation of methylsulfanylmethyl-2-pyridyl sulfide occurs using whole cells of *Pseudomonas putida* NCIMB 8859 to give a mixture of (*S*)-alkyl aryl sulfoxide **117** in 12% yield and ≥98% ee and 9% of the dialkyl sulfoxide **118** in 73% ee [\[2001J\(P1\)3288\]](#) ([Equation 84](#)).

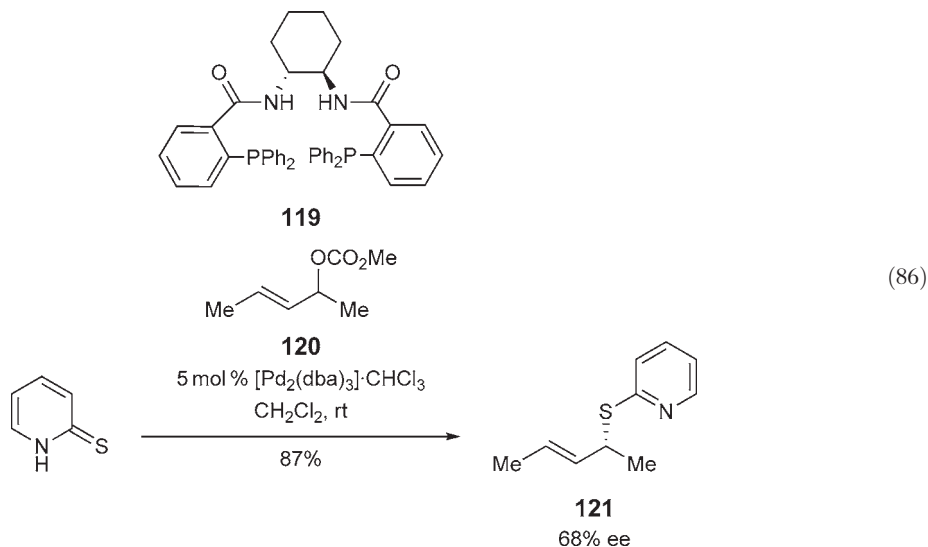


2-(Alkylthio)pyridines can also be oxidized to sulfoxides using sodium periodate in methanol <2002SL1404> or MCPBA in dichloromethane <2001TL8845>.

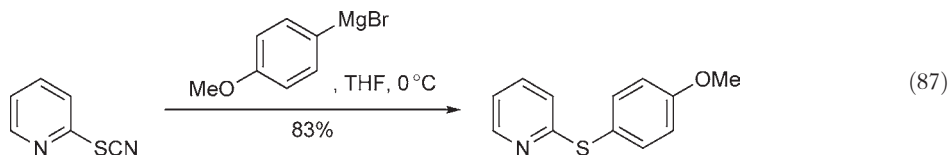
The sulfur atom of pyridinethiols is sufficiently nucleophilic to undergo reaction with carbon-based electrophiles in the presence of base or via metal-mediated means to give access to *S*-alkyl, allyl, and aryl derivatives. 3-Cyano-2-pyridinethiones react with methyl iodide in DMF in the presence of 10% aqueous KOH to give the *S*-methyl derivative in good yield <1996T10841>. Similar alkylation with bromoacetophenone is followed by *in situ* condensation to give 3-aminothieno[2,3-*b*]pyridines in good yield (Equation 85). Alkylation of 2-pyridinethiones with α -bromoacetates has also been achieved using triethylamine as base in acetonitrile <2001T8845>.



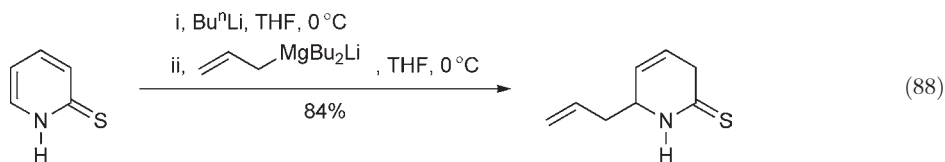
2-Pyridinethiones undergo palladium(0)-catalyzed enantioselective allylation with cyclic and acyclic allylcarbonates in the presence of the Trost ligand **119** to give allylic sulfides with moderate enantiomeric selectivity <2003CEJ4202>. For example, reaction with allyl carbonate **120** in the presence of 5 mol% $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ and 11 mol% **114** in dichloromethane at room temperature gives allyl sulfide **121** in 87% yield and 68% ee (Equation 86).



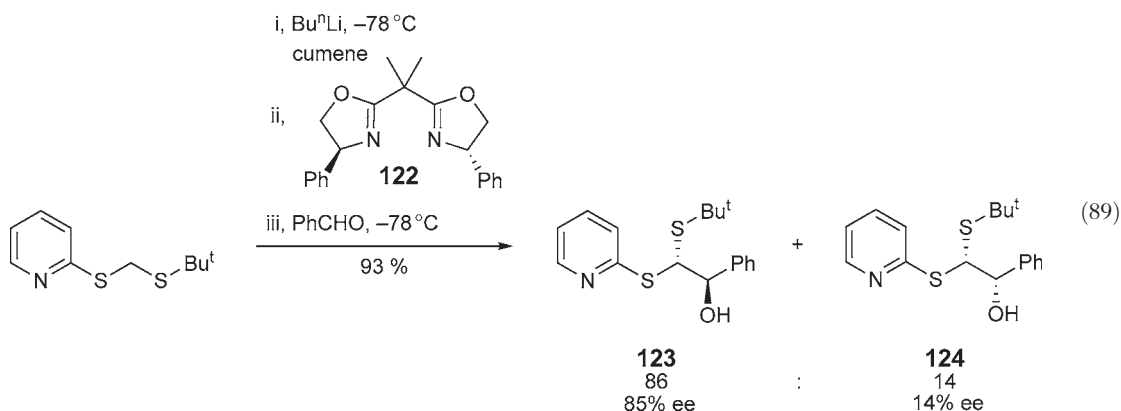
Alkylthio- and arylthiopyridines can also be synthesized from the thiopyridine by nucleophilic attack of Grignard reagents at electrophilic sulfur. In this umpolung-based strategy, 2-pyridinethiones are first converted to the thiocyanato derivative that undergoes reaction with alkyl and aryl Grignard reagents in THF at 0°C to give alkyl- or arylthiopyridines in good to excellent yield <1999H(50)1015>. For example, 2-thiocyanatopyridine reacts with 4-methoxyphenylmagnesium bromide to give the arylthiopyridine in 83% yield (Equation 87). Regioselectivity in this process is thought to arise from chelation of the Grignard reagent with both the ring nitrogen and sulfur atoms and thus proceeds poorly with 4-thiocyanatopyridines giving products arising from attack of the Grignard reagent at the pyridine ring.



The pyridine ring of pyridinethiones is activated to nucleophilic attack but does not undergo addition with allylmagnesium chloride. Good yields of ring allylated products have been obtained from the reaction of *N*-lithiated or *N*-methylated pyridine-2-thione with the 'ate' complex derived from treatment of allylmagnesium chloride with 2 equiv of *n*-BuLi <2005TL4295>. *N*-Methyl-2-pyridinethione reacts with lithium allyldibutylmagnesate in THF at 0 °C to give 6-allyl-3,4-dihydro-1*H*-pyridine-2-thione as the major product. *N*-Lithio-2-pyridinethione also initially reacts at the 4-position but the intermediate undergoes Cope rearrangement to give the C-6 allylated product (Equation 88).



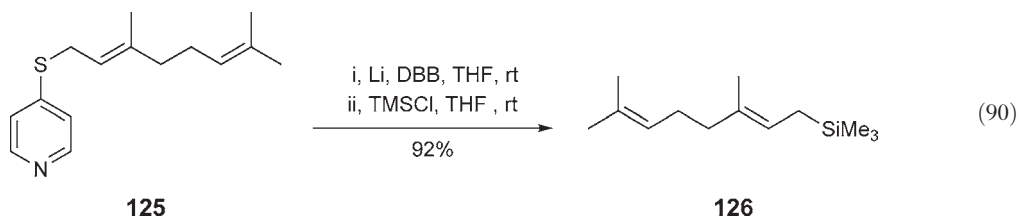
The thioacetal-*tert*-butylthio(2-pyridylthio)methane is deprotonated adjacent to sulfur on treatment with *n*-BuLi and the anion undergoes diastereoselective and enantioselective addition to a range of aromatic and alkylaldehydes in the presence of the chiral bis(oxazoline) **122**. For example, reaction with benzaldehyde proceeds to give *anti*- and *syn*-adducts **123** and **124** in 93% yield and 86:14 ratio, respectively <2004JOC1581> (Equation 89).



α -(2-Pyridylsulfonyl)acetate is dialkylated in moderate yield using benzyl bromide and potassium carbonate as base in the presence of tetrabutylammonium bromide in acetonitrile <2001T8845>.

Mono-fluorination of 2- and 4-pyridylsulfides bearing electron-withdrawing groups on sulfur has been achieved in moderate to good yields at the carbon adjacent to sulfur by anodic fluorination using platinum electrodes in an acetonitrile solution of $\text{Et}_3\text{N} \cdot 3\text{HF}$ as supporting electrolyte and fluorine source <1995JOC7654, 2001T8817>.

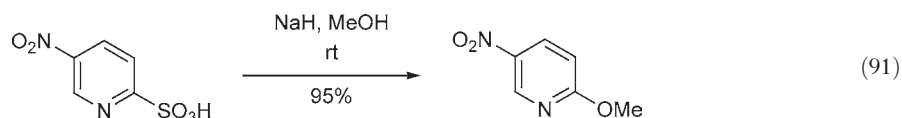
4-Allylthiopyridines such as compound **125** undergo reductive lithiation on treatment with lithium and 4,4'-di-*tert*-butyldiphenyl (DBB) and the resulting allyllithium reacts with TMSCl to give allylsilanes such as **126** <2004JOC7592>. (Equation 90).



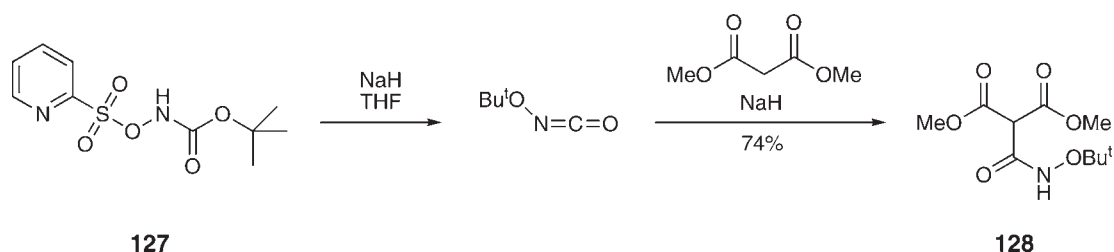
7.03.6.2 Sulfonic Acids and Related Compounds

The sulfonate group of pyridine-2-sulfonic acids is readily displaced by nucleophiles when activated by a *para*-electron withdrawing group. 5-Nitropyridine-2-sulfonic acids are substituted at the 2-position with a variety of nitrogen-, oxygen-, and halogen-based nucleophiles <2003OBC2710, 2004OBC2671>. For example, 5-nitropyridine-2-sulfonic acid

reacts with sodium methoxide in methanol at room temperature to give 2-methoxy-5-nitropyridine in 95% yield (Equation 91).

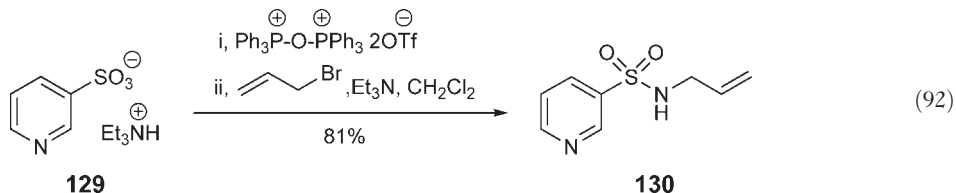


The leaving group ability of the 2-pyridylsulfonate group is exploited in the use of *N*-butoxycarbonyl(2-pyridylsulfonyl)hydroxylamine **127** as a reagent to prepare hydroxamic acid derivatives from soft enolates <1999JOC5896>. For example, reagent **127** reacts with dimethylmalonate in the presence of sodium hydride in THF to give hydroxamic acid derivative **128** in 76% yield (Scheme 28). The reaction is thought to proceed via base-induced rearrangement of **127** to generate the *t*-butoxycyanate that then acylates the malonate enolate.

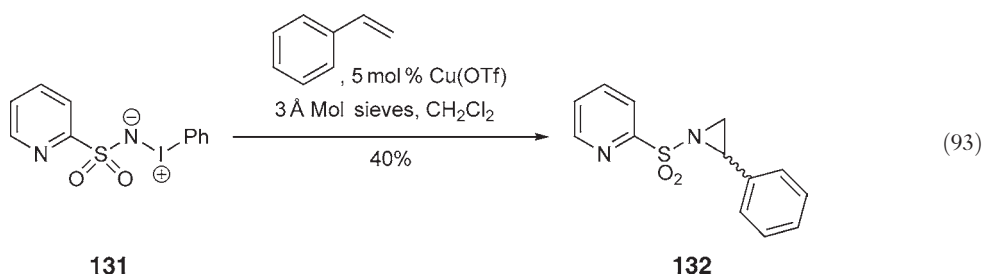


Scheme 28

Sulfonamides may be directly synthesized from sulfonic acid salts by treatment with triphenylphosphine ditriflate followed by an amine <2004JA1024>. This procedure, that avoids the generation of sulfonic acids, converts sulfonic acid salt **129** to sulfonamide **130** in 81% yield (Equation 92). Problems associated with the removal of triphenylphosphine oxide by-products can be alleviated by performing the reaction with polystyrene-supported phosphine.



Pyridinesulfonamides are converted to (pyridylsulfonylimino)iodobenzenes such as **131** by reaction with phenyliodonium diacetate. These compounds function as effective nitrene transfer reagents and react with styrene in the presence of catalytic copper(I) triflate to give aziridine **132** in 40% yield <1999T5459> (Equation 93). It has been discovered that chelation of copper to the pyridine nitrogen is a driving force for this process and that use of the iminoiodobenzene derived from 5-methyl-2-pyridinesulfonamide in combination with 3 mol% copper(II) trifluoroacetylacetonate can be used to effect the aziridination of a range of olefins in moderate to high yield <2004OL4109>.

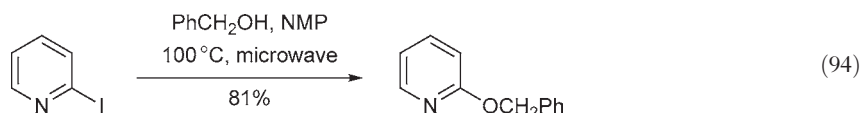


7.03.7 Halogen Substituents

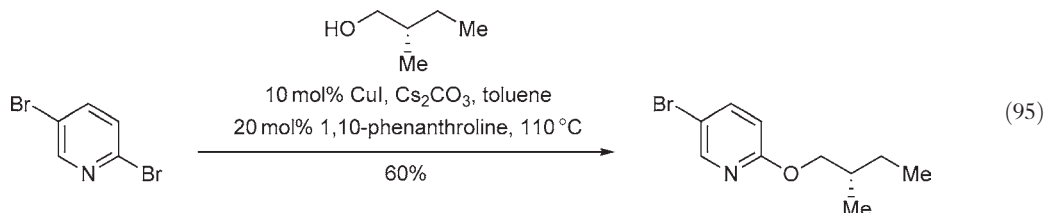
7.03.7.1 Nucleophilic Displacement

7.03.7.1.1 Oxygen and sulfur nucleophiles

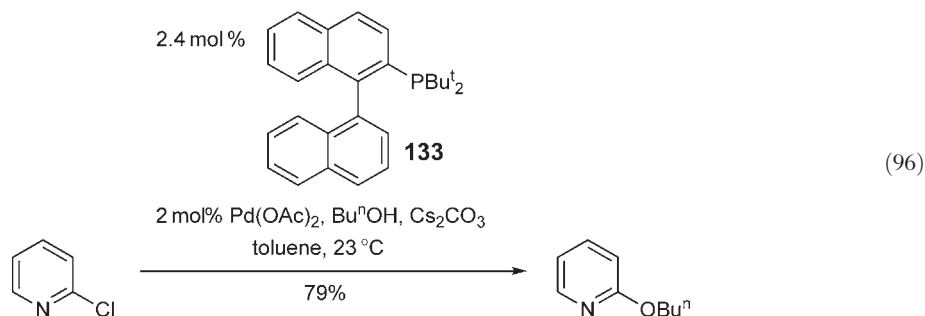
While halogen substituents on the electron-deficient pyridine ring may be displaced by oxygen-based nucleophiles, this transformation often requires harsh conditions such as use of strong bases in polar aprotic solvents under reflux. A wide range of heteroatom-based nucleophiles and nitriles undergo reaction with 2-, 3-, and 4-halopyridines in minutes at elevated temperature in polar solvents such as HMPA, DMSO, and *N*-methylpyrrolidine (NMP) under microwave irradiation [\[2002T4931\]](#). For example, 2-iodopyridine undergoes displacement with benzyl alcohol in NMP in 1 min at 100 °C under irradiation ([Equation 94](#)). Halogenated quinolines and pyridines also undergo efficient nucleophilic substitution with potassium methoxide and phenoxide under microwave irradiation in the presence of catalytic amounts of phase-transfer catalyst and small quantities of nonpolar solvent such as nonane [\[2004SC297\]](#).



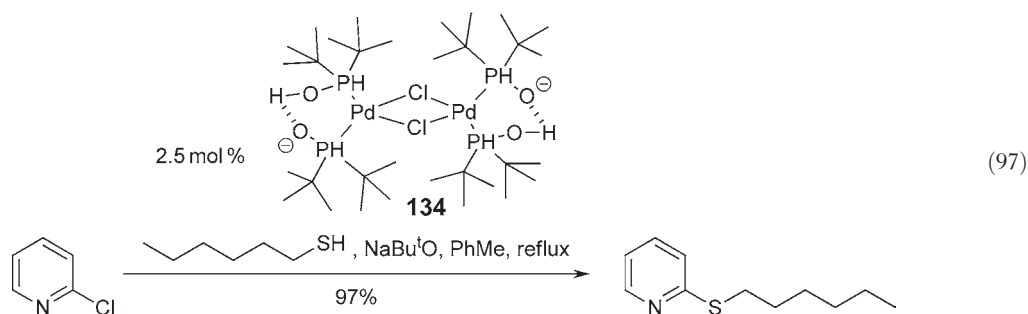
A method for the synthesis of pyridyl ethers from halides that does not require the use of strong base involves transition metal-mediated coupling of halopyridines with alcohols using methods developed by the group of Buchwald. 3-Iodopyridine undergoes cross-coupling with *n*-butanol and isopropanol to give the corresponding 2-alkoxypyridine in 87% and 92% yield, respectively, in the presence of 10 mol% CuI, 20 mol% 1,10-phenanthroline, and cesium carbonate at 110 °C in a sealed tube [\[2002OL973\]](#). This Buchwald protocol also proceeds in a regioselective manner when applied to dihalopyridines. 2, 5-Dibromopyridine undergoes coupling with (*S*)-2-methyl-1-butanol selectively at the 2-position in 70% yield in toluene at 110 °C in a sealed tube ([Equation 95](#)).



This cross-coupling can also be mediated by catalytic quantities of palladium(0) species. 3-Bromopyridine may be converted to the 3-*tert*-butoxy derivative in 30% yield using 6 mol% Pd(OAc)₂, P(*t*-Bu)₃ and sodium *tert*-butoxide in xylene at 120 °C [\[1999TL8837\]](#). This cross-coupling procedure proceeds efficiently under very mild conditions using Pd(OAc)₂ in the presence of binaphthyl-based ligands such as **133** in toluene. 2-Chloropyridine is coupled with *n*-butanol at room temperature under these conditions in 79% yield ([Equation 96](#)).

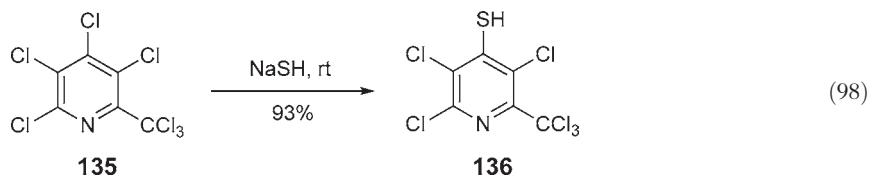


Palladium-catalyzed methods have also been applied to the synthesis of thiopyridines from halopyridines. 3-Chloropyridine undergoes cross-coupling with 1-hexanethiol to give the thiopyridine in 97% yield using 2.5 mol% of the air-stable palladium(II) complex **134** in the presence of sodium *tert*-butoxide in toluene under reflux [\[2001JOC8677\]](#) ([Equation 97](#)).

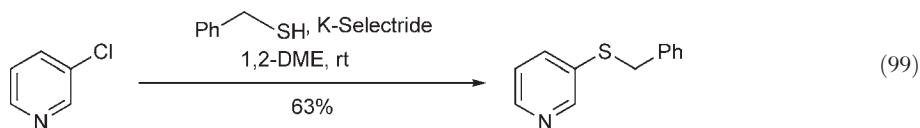


4-Methoxythiophenol couples with 2- and 3-iodopyridines in 77% and 87% yield, respectively, using 1 mol% $\text{Pd}(\text{dba})_3$ as catalyst in the presence of 2 mol% bis[2-(diphenylphosphino)phenyl] ether (DPEphos) and *t*-BuOK in toluene at 100 °C [\[2001T3069\]](#) and 2-methyl-5-bromopyridine undergoes cross-coupling with aryl-, benzyl-, and alkylthiols in excellent yield in the presence of 2.5 mol% $\text{Pd}_2(\text{dba})_3$, 5 mol% xantphos, and diisopropylethylamine in 1,4-dioxane under reflux [\[2004OL4587\]](#).

The most common method for the synthesis of thiopyridines from halopyridines is by nucleophilic displacement with thiolate anions. This occurs under relatively mild conditions when the halogen is activated by the presence of an *ortho* or *para* electron-withdrawing group. For instance, 2-chloro-3-nitropyridine reacts with 1-propanethiol in the presence of sodium hydroxide in ethanol at room temperature to give the alkylthiopyridine in 94% yield [\[2004JOC2551\]](#). 2-Chloropyridine is effectively converted to the 2-pyridinethiol using thiourea in 25% $\text{HCl}_{(\text{aq})}$ [\[1997BMCL2223\]](#). Halogen substituents at the 2- and 4-positions are most reactive to displacement by sulfur nucleophiles with the 4-position being the most activated. Thus, polychloropyridines such as chloride **135** undergo displacement selectively at the 4-position on treatment with sodium hydrogen sulfide to give 4-thiopyridine **136** in 93% yield [\[2002BML3593\]](#) (Equation 98).



Unactivated halopyridines including 3-halopyridines undergo substitution at room temperature using thioborates prepared *in situ* from K-Selectride and phenylethanethiol in 1,2-DME in moderate to good yield. 3-Chloropyridine is converted to the thiol in 63% yield using these conditions [\[1999TL5565\]](#) (Equation 99).



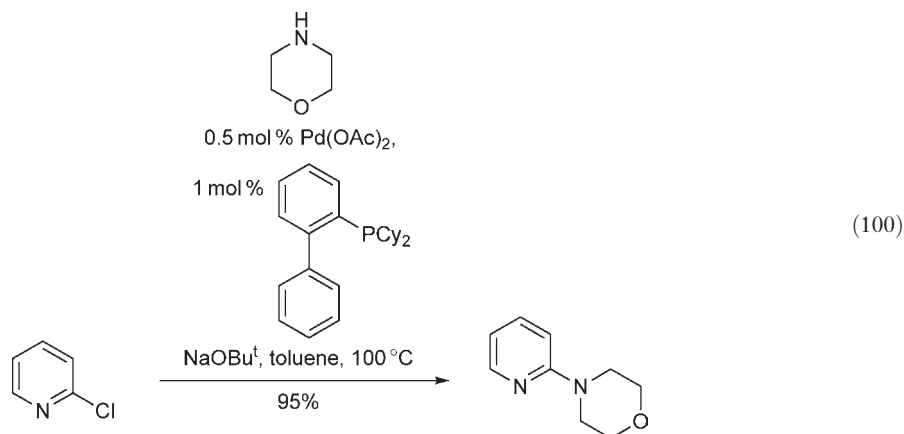
The displacement of halogens with thiolate anions is much accelerated under microwave irradiation. 2-, 3-, and 4-Halopyridines react with the sodium anion of thiophenol and ethanethiol in high yield in HMPA or NMP in a matter of minutes under microwave irradiation at 110 °C [\[2002T4931\]](#).

2- and 3-Chloropyridines may also be converted to the corresponding thiopyridine by radical mediated means. Irradiation of a mixture of halopyridine and the potassium anion of thiourea in DMSO at 350 nm using an Hg lamp leads to formation of the 2- or 3-pyridyl radical which reacts with thiourea to give an arene thiolate anion. Quenching of this anion with methyl iodide gives the 2- or 3-methylthiopyridine in 87% or 58% yield, respectively [\[2003OL4133\]](#).

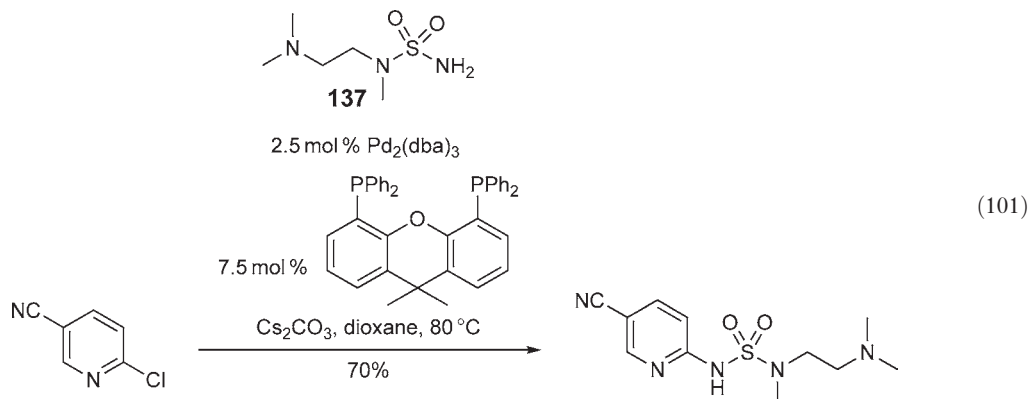
7.03.7.1.2 Nitrogen nucleophiles

Nitrogen nucleophiles, in a similar manner to oxygen- and sulfur-based functionality, undergo transition metal-catalyzed cross-coupling with halopyridines. The use of palladium(0) catalysts is most effective in combination with chelating bis-(phosphine) ligands such as BINAP that prevent the formation of pyridine–palladium complexes that

terminate the catalytic cycle <1996JOC7240, 2005SL87>. Under these conditions, utilizing 2 mol% Pd(dba)₃, 4 mol% (±)-BINAP, and sodium *tert*-butoxide in toluene at 70 °C, a variety of primary and secondary amines cross-couple with 2-, 3-, and 4-bromopyridines in high yield. Higher catalyst loadings were required to effect amination of chloropyridines. This loading is much reduced when using catalytic quantities of the efficient bis(phosphines) (*o*-biphenyl)P(*t*-Bu)₂ or (*o*-biphenyl)PCy₂ <2000JOC1158>. For example, 2-chloropyridine undergoes cross-coupling with morpholine in the presence of 0.5 mol% Pd(OAc)₂, 1 mol% bis(phosphine) and sodium *tert*-butoxide in toluene at 100 °C to give the 2-aminopyridine in 95% yield (Equation 100).

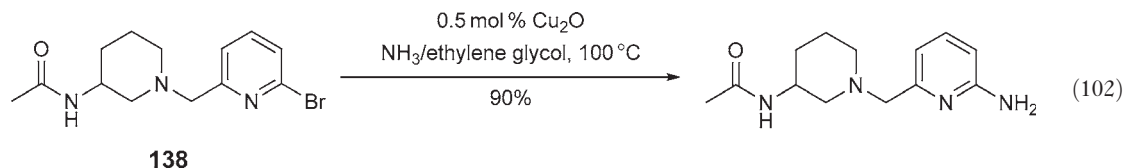


The Pd(0)/BINAP-catalyzed amination is much accelerated under microwave irradiation. The cross-coupling of 5- and 6-bromobenzyloxy pyridines with a range of cyclic and acyclic amines utilizing Buchwald's conditions occurs in high yield in 10 min on microwave irradiation at 120 °C in toluene <2005TL4621>. The cross-coupling of bromopyridines with secondary acyclic amines is problematic under standard Buchwald conditions employing bis(phosphine) ligands but does occur in good to high yield in the presence of ferrocenylphosphine ligands <1997JOC1568>. The coupling of 2-chloropyridine with secondary amines occurs in good yield in the presence of 10 mol% Ni(OAc)₂ and 2,2'-bipyridine <1999T12829>. This transformation can also be performed on 2-chloropyridine in 64% yield. The cross-coupling procedure can also be performed with other nitrogen-based substrates. 2-Chloropyridines undergo palladium-catalyzed substitution with both aryl and aliphatic ureas in good yield in the presence of catalytic quantities of Pd(OAc)₂ and xantphos as ligand with sodium *tert*-butoxide or NaOH as base in dioxane <2005S915>. 2-Chloropyridines activated by electron-withdrawing groups at the 5-position undergo cross-coupling with secondary sulfamides in good yield using Pd₂(dba)₃ as catalyst in dioxane in the presence of cesium carbonate <2004OL2705>. For example, 6-chloronicotinonitrile undergoes coupling to sulfamide **137** in 70% yield using 7.5 mol% xantphos as ligand (Equation 101).



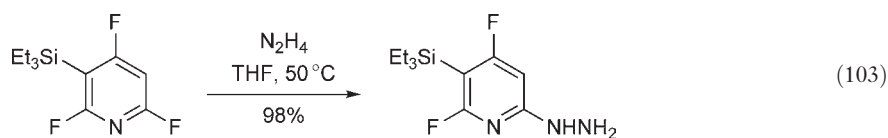
N-(2-Pyridyl)sulfoximines may be prepared by palladium-catalyzed coupling of the halopyridine with *N*-H sulfoximines in a microwave-assisted procedure <2004TL5233>. For example, 2-chloropyridine couples with sulfoximines in moderate yield in the presence of 10 mol% Pd(OAc)₂, BINAP, and cesium carbonate under microwave irradiation. This cross-coupling does not occur using ammonia and thus direct conversion to the primary

aminopyridine has been problematic. This has been overcome by the use of lithium bis(trimethylsilylamide) as an ammonia equivalent in the cross-coupling. Treatment of 2-bromopyridine with 2 mol% $\text{Pd}(\text{dba})_2$, $\text{P}(t\text{-Bu})_3$, and lithium bis(trimethylsilyl)amide in toluene leads to formation of 2-aminopyridine in 87% yield with no concomitant formation of the pyridine <2001OL2729>. The direct conversion of 2-bromopyridines to primary aminopyridines can be more conveniently achieved using copper(I) catalysts. For example 2-bromopyridine **138** is converted to the corresponding 2-aminopyridine in 90% yield using 5 mol% copper(I) oxide in ammonia saturated ethylene glycol <2001TL3251> (Equation 102).

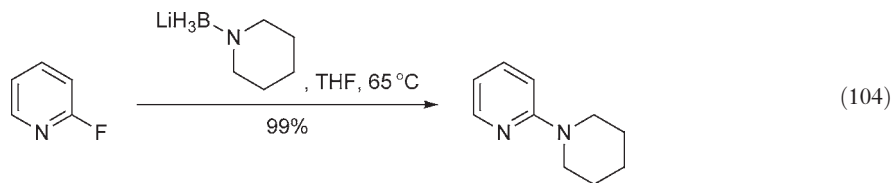


Copper(I) salts are also effective in the coupling of primary amines and halopyridines. 2-Iodopyridine is converted to 2-butylaminopyridine in 80% yield on treatment with *n*-butylamine and 0.5 equiv of relatively inexpensive copper(I) iodide and cesium acetate in DMF <2003OL4987>. While many of the above methods can only be performed under inert atmosphere, a copper-catalyzed amination has been developed, utilizing copper(I) iodide as catalyst in the presence of ethylene glycol as supporting ligand and potassium phosphate as base, that proceeds in air <2002OL581>. Under these conditions, 3-bromopyridine couples with *n*-hexylamine in 85% yield at 80 °C.

Aminopyridines may be synthesized by conventional nucleophilic displacement of halide substituents. In general, 4-halo substituents are more easily displaced than those at the 2-position. It has been discovered that this order of reactivity is reversed in the presence of a bulky trialkylsilyl group at the 3- or 5-position <2005OL127>. For instance, 2,4,6-trifluoro(3-triethylsilyl)pyridine undergoes reaction with hydrazine monohydrate exclusively at the 6-position (Equation 103).



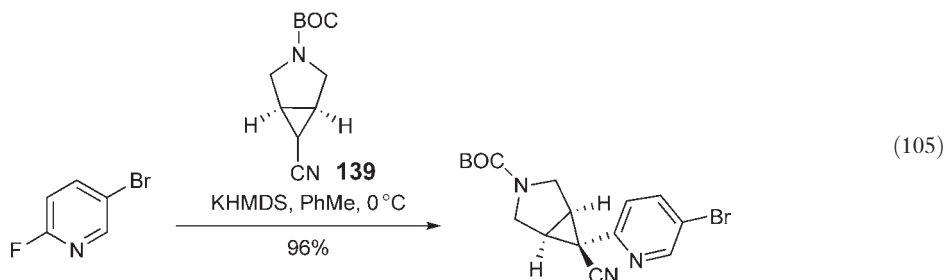
2-Fluoropyridines undergo amination in good yield on treatment with lithium aminoborohydride reagents in THF at 65 °C <2003OL3867>. As an example, reaction with 1.1 equiv of lithium piperidinyl borohydride in THF at 65 °C gives 2-piperidinylpyridine in 99% yield (Equation 104). 2-Chloropyridine can also be used as a substrate in the presence of excess borohydride.



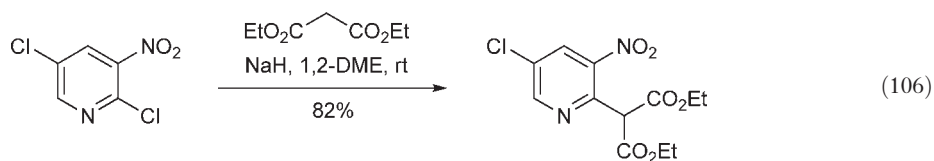
It is thought that coordination of the pyridine nitrogen with boron activates the ring to nucleophilic attack. However, 2-fluoropyridine also reacts with a range of primary and secondary lithium amides in THF at room temperature in the absence of boron reagents to give the 2-aminopyridine in moderate to high yield <2004TL6417>. This methodology is restricted to fluoropyridines and leads to ring opening of the aromatic ring when applied to chloro- and bromopyridines. The reaction of 5-chloro-3-methoxypyridine with lithium amides has also been studied and is thought to proceed via formation of a pyridine intermediate followed by nucleophilic attack to give 5-amino products <1999H(50)843>. This reaction proceeds using THF or the free amine as solvent and can also be performed on 5-chloro-3-hydroxypyridine. Nucleophilic displacement using the free amine often requires harsh reaction conditions and can proceed in low yield. A variety of primary and secondary amines in 20% $\text{NaOH}_{(\text{aq})}$ under 0.8 GPa pressure can lead to the related 4-aminopyridine <2000S116>.

7.03.7.1.3 Other nucleophiles

The halogen of 2-halopyridines undergoes displacement with a variety of carbon-based nucleophiles. 2-Halopyridines undergo S_NAr reaction with secondary nitriles under mild conditions in the presence of NaHMDS or KHMDS <2005JOC10186>. The reaction can be performed with a range of halogen substituents but highest yields are achieved with 2-fluoropyridines. For example, treatment of a mixture of 2-fluoro-5-bromopyridine and nitrile **139** with KHMDS 0 °C gives the α -arylated nitrile in 96% yield (Equation 105).

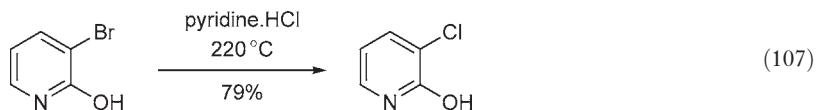


2-Halopyridines such as 2,5-dichloro-3-nitropyridine undergo regioselective nucleophilic displacement at the 2-position in high yield with the sodium salt of diethyl malonate in DME at room temperature (Equation 106).

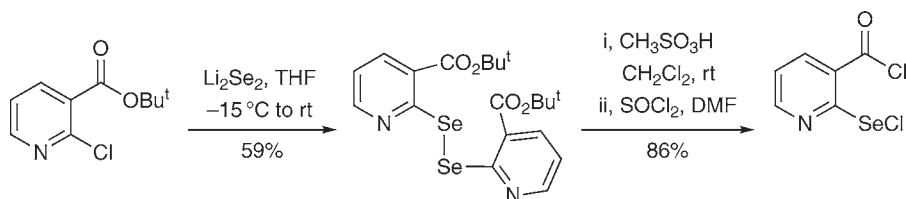


2-Bromopyridine undergoes photoassisted $S_{RN}1$ reaction with a variety of stabilized carbanions <1997JOC6152>. The reaction is carried out in the presence of potassium amide in liquid ammonia at -33 °C under photoirradiation at 350 nm and proceeds in moderate to good yield with anions derived from 2-benzyl-4,4-dimethyloxazoline, 2,4-dialkylthiazoles, and dimethyl methylphosphonate and also with carboxamide and ester enolates.

2-Chloropyridines are readily converted into the related 2-iodo- or 2-bromopyridine using iodotrimethylsilane or bromotrimethylsilane via the intermediacy of an *N*-silylpyridinium salt that activates the ring to nucleophilic attack <2002EJO4181, 2003EJO1559>. The displacement is effected in propionitrile under reflux and occurs in moderate to good yield with 2-chloropyridines and 2,4-dichloropyridine but does not proceed with 2- or 3-chloropyridine or less basic fluoropyridines. Chlorine is also displaced from the 2- and 4-positions of quinolines and the 1-position of isoquinoline in high yield using this process. While direct bromination of hydroxypyridines and hydroxyquinolines is often regioselective, direct chlorination is not. Thus, a good strategy for the synthesis of the chlorohydroxypyridine or quinoline proceeds via displacement of the corresponding bromo derivative. This can be achieved in good yield using pyridine hydrochloride at high temperature <1996TL6695>. Heating a mixture of 3-bromo-2-hydroxypyridine and pyridine hydrochloride at 220 °C for 10 min leads to the formation of the chloropyridine in 79% yield (Equation 107).



The chlorine atom in *tert*-butyl-2-chloronicotinate can be displaced with a diselenide group in moderate yield using dilithium diselenide in THF <2003SC3805>. The resulting diselenide is hydrolyzed and cleaved to the chloroselenide on treatment with thionyl chloride and catalytic amounts of DMF (Scheme 29).

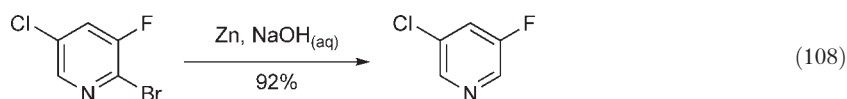


Scheme 29

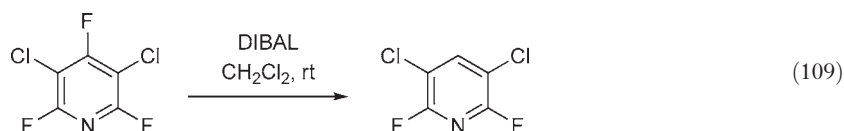
2,2'-Dipyridyldiselenides and tellurides can be prepared by treatment of 2-bromopyridines and 2-bromopicolines in ethanol or 2-ethoxyethanol with sodium hydrogen selenide or sodium hydrogen telluride, prepared *in situ* from elemental selenium or tellurium with sodium borohydride <2003SC977>. The diselenides and tellurides are reductively cleaved with sodium borohydride to give sodium selenolates or tellurolates that may be quenched with methyl iodide to give 2-methylseleno and 2-methyltelluropyridines.

7.03.7.2 Reductive Dehalogenation

Hydrodehalogenation of 2-, 3-, and 4-halopyridines can be achieved using a variety of reducing agents. In general, halogens at the 4-positions are more readily displaced than those at the 2-position with 3-halo substituents being the least reactive. It is also possible to distinguish between heavy and light halogens. The bromine atom in 2-bromo-5-chloro-3-fluoropyridine is selectively displaced using zinc powder in aqueous sodium hydroxide to give 5-chloro-3-fluoropyridine in high yield (Equation 108). The use of nucleophilic reducing agents favors displacement of fluorine atoms while reduction by hydrogenation results in replacement of heavier halogens selectively. Thus, the chlorine atom in 3-chlorodifluoropyridines can be selectively removed by transfer hydrogenation using ammonium formate in the presence of catalytic quantities of palladium on carbon while the fluorine atom at the 4-position in 3-chlorotetrafluoropyridine is selectively removed using sodium borohydride in ethanol <2005CEJ1903>.



Replacement of fluorine by hydrogen can be achieved selectively in the presence of chlorine atoms using DIBAL <1998J(P1)1705>. For example, 3,5-dichloro-2,4,6-trifluoropyridine is selectively reduced at the 4-position using DIBAL in dichloromethane at room temperature (Equation 109). Pentafluoropyridine is reduced to give mixtures of 2,3,5,6-tetrafluoropyridine and 2,3,5-trifluoropyridine using lithium aluminium hydride in diethyl ether in the presence of 12-crown-4 <1998J(P1)1705>.

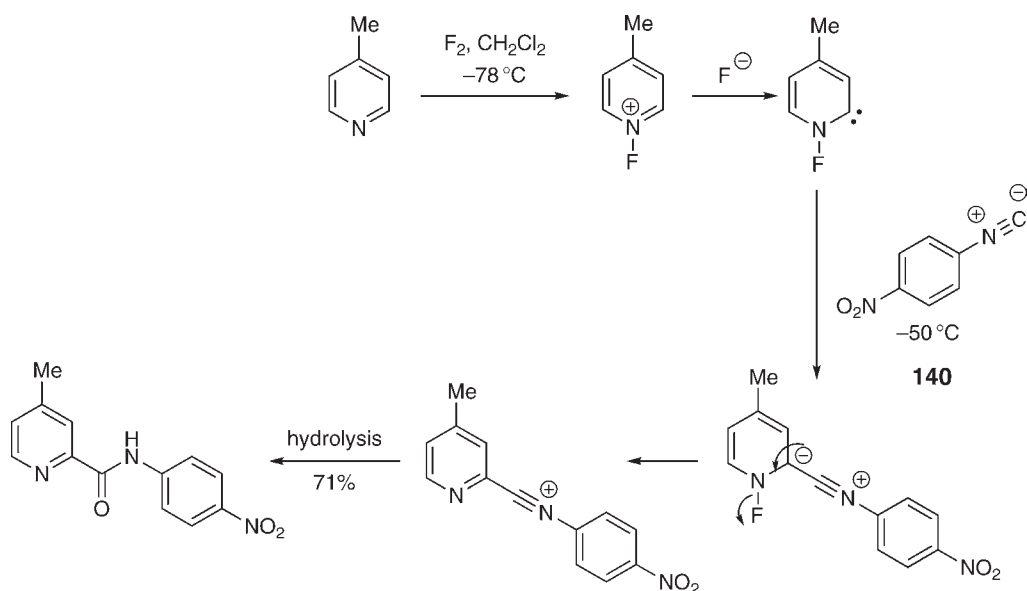


Halopyridines can also be reduced using transition metal catalysts in the presence of reductants. The chlorine atom in 2-chloropyridines can be replaced by hydrogen in high yield using 5 mol% (PPh)₃NiCl₂, PPh₃ and 1.2 equiv of Me₂NH·BH₃ and potassium carbonate in acetonitrile at 40 °C <2001TL7737> and 2-, 3-, and 4-chloropyridine can be reduced to pyridine in high yield using 5 mol% Pd(OAc)₂ in the presence of polymethylhydrosiloxane (PMHS) and potassium fluoride in THF <2002TL8823>.

7.03.7.3 Halogens Attached to Nitrogen

Research in this area has concentrated on the generation and reactions of *N*-fluoropyridinium salts. *N*-Fluoropyridinium fluorides, generated *in situ* by reaction of pyridines with fluorine gas, undergo reaction with a variety of isonitriles to give 2-picolinamides in moderate to good yield <2005TL2279>. For example, treatment of 4-methylpyridine with fluorine gas at -78 °C followed by isonitrile **140** at -50 °C to 0 °C leads to formation of the corresponding picolinamide in 71% yield. The reaction is postulated to proceed by initial formation of a carbene that undergoes addition to the isonitrile followed by aromatization and hydrolysis (Scheme 30). This reaction can also be performed in acetonitrile or propionitrile with sodium triacetoxyborohydride as base. In this case the initial step is addition to a molecule of solvent to the generated carbene. Attack of the isonitrile onto the resulting nitrilium ylide followed by cyclization provides access to imidazo[1,2-*a*]pyridines <2005TL4487>.

The main use of *N*-fluoropyridinium salts is as fluorinating agents. A recent study of *N*-fluoropyridinium-2-sulfonates substituted with alkyl or trifluoromethyl groups reveals them to be powerful and selective fluorinating

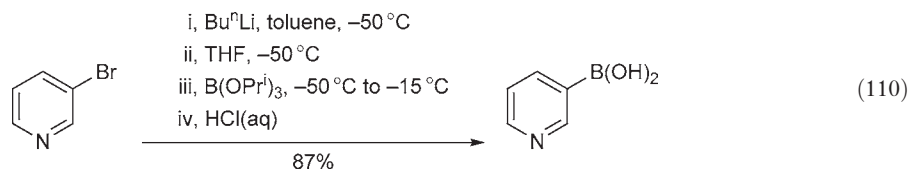


Scheme 30

agents [<1995JOC6563>](#). While the lipophilic alkyl groups help solubilize these fluorinating salts and hence improve yields, they act to decrease reactivity by electron donation. The trifluoromethyl group aids solubility and also increases reactivity. Thus, judicious placing of substituents on the pyridine ring allows the development of selective fluorinating agents. Regioselectivity is also influenced by interactions of the sulfonate group of the fluorinating agent with functional groups on the substrate.

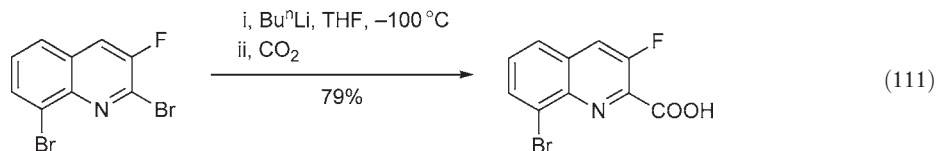
7.03.8 Metals

The lithiation of pyridines, either by metallation or by lithium–halogen exchange, has traditionally proved difficult owing to competing ring deprotonation and also nucleophilic attack of the lithiating agent onto the π -deficient pyridine ring. Nevertheless, the reaction of pyridyllithium species with electrophiles is now one of the most common ways of functionalizing the pyridine ring. Performing lithium–halogen exchange in THF by inverse addition and at very low temperature minimizes competing deprotonation. This process may be performed at higher temperature using toluene as solvent making large-scale preparations more convenient [<2002TL4285>](#). For instance, addition of 3-bromopyridine to *n*-BuLi in toluene at $-50^\circ C$ gives the lithiopyridine as a yellow solid that is dissolved on addition of THF. Quenching of this mixture with triisopropyl borate gives the boronic acid in 87% yield (Equation 110). 3-Lithiopyridine also undergoes reaction with aldehydes and ketones in high yield.



It is also possible to mono-lithiate 2,6-dibromopyridine using *n*-BuLi in a reverse addition technique in THF at $-78^\circ C$ [<1996TL2537>](#). In this procedure, the dilithio derivative initially formed undergoes halogen–metal exchange with dibromopyridine to give 2 equiv of 2-bromo-6-lithiopyridine that reacts with DMF and ketones in good yield. Dibromohydroxypyridines are effectively mono-lithiated in a regioselective manner using the normal mode of addition of 2 equiv of *n*-BuLi in THF at $-90^\circ C$ [<2003SL1678>](#). It was found that metal–halogen exchange at C-2 and C-6 and at positions *ortho* to the hydroxyl group is hindered owing to the relative instability of anions at this site. The resulting pyridyllithium species may be quenched with water to give debrominated products in good yield and also react with iodine to give iodinated pyridines in moderate yield. Lithium–bromine exchange can be

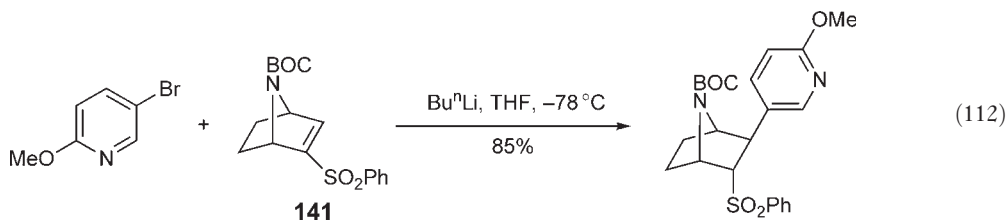
performed in the presence of fluorine atoms. A study into the metallation of substituted 2-bromo-3-fluoroquinolines revealed that bromine–lithium exchange takes place in the presence of fluorine atoms and that lithiation occurs preferentially at the electron-deficient heterocyclic ring [<2005T717>](#). For instance, 2,8-dibromo-3-fluoroquinoline undergoes selective lithiation using *n*-BuLi at -100°C in THF. Addition of CO_2 gives the 2-carboxylic acid in 79% yield ([Equation 111](#)). Lithium–halogen exchange using alkylolithium reagents is generally limited to bromo and iodo-pyridines. Metal–halogen exchange of 2-, 3-, and 4-chloropyridines and 2-chloroquinolines can be effected by naphthalene-catalyzed reductive lithiation using lithium powder in the presence of catalytic quantities of naphthalene in THF at -78°C [<2000T4043>](#). Quenching of the lithium anion with electrophiles such as aldehydes and ketones proceeds in moderate to high yield. These anions also react with imines in low yield.



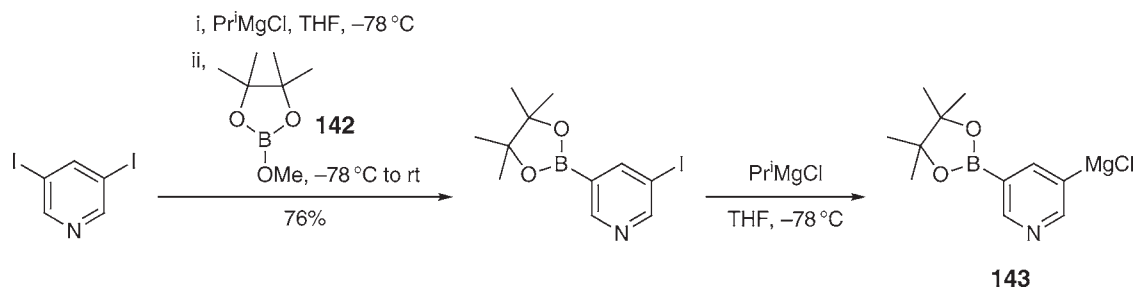
Barbier-type conditions can be used to convert 2- and 3-halopyridines to the pyridyllithium *in situ* in the presence of electrophiles. Sonication of the bromo- or iodo-pyridine with lithium powder containing 0.5% sodium in the presence of aldehydes or diphenyldisulfide as electrophile in THF at room temperature gives the pyridyl alcohol or sulfide in moderate to good yield [<2000T3709>](#).

An alternative method for the regioselective formation of pyridyllithium reagents is by direct deprotonation of the pyridine using a strong base (also known as metallation). The deprotonation is usually effected using lithium amide or alkylolithium bases at low temperature. Lithiation on the pyridine often occurs *ortho* to substituents containing heteroatoms in a process known as a directed *ortho*-metallation or DoM. Directing groups include halogens and a wide variety of oxygen-, sulfur-, and nitrogen-containing functional groups. As such a detailed discussion of this process is beyond the scope of this account. Readers seeking an in-depth discussion of the directed metallation of pyridines and benzo derivatives are directed to the recent review in this area [<2001T4059>](#). When halogen substituents are present on the pyridine, there is competition between metallation and metal–halogen exchange. In general, use of alkylolithiums favors metal–halogen exchange while the use of lithium amides favors metallation. However, lithiation of 3-bromopyridines using *t*-BuLi can proceed via either route with selectivity being electrophile and addition order dependent [<2004SL2319>](#). Reverse addition and use of D_2O or dimethyldisulfide as electrophiles results in products arising from initial metal–halogen exchange while a normal mode of addition and use of TMSCl as electrophile results in 3-bromo-4-silylated pyridines. Pyridine *N*-oxides are readily deprotonated at C-2 using LDA or *n*-butyllithium as base in THF and these reagents react in high yield with a variety of electrophiles including iodine, alkyl halides, aldehydes, and ketones [<1995J\(P1\)2503>](#). Regioselectivity arises from an enhanced acidity of the 2-position and the chelating effect of the oxygen.

In general, pyridyllithium species undergo the wide range of carbon–carbon bond forming additions typical of other organolithium reagents and such methodology is a convenient means of replacing halogens with carbon-based functionality complementary to the chemistry discussed in [Section 7.03.7.1.3](#). 3-Lithiopyridines have been observed to undergo Michael addition with vinyl sulfones. As a key step in a synthetic route to the analgesic alkaloid epibatidine, Simpkins and co-workers obtained the carbon skeleton of the target by Michael addition of the lithiopyridine derived from 5-bromo-2-methoxypyridine to vinyl sulfone **141** [<1998J\(P1\)3689>](#) ([Equation 112](#)). Lithiopyridines may be converted to trialkylsilylpyridines and pyridine boronic acids as described above. In addition, 2-lithiopyridines react with dichlorophenylphosphane to give bis(2-pyridyl)phenylphosphanes [<2000EJOC3505>](#) and 4-pyridyllithium reacts with gaseous dinitrogen tetroxide in frozen THF to give 4-nitropyridine in 57% yield [<1997JA1476>](#).

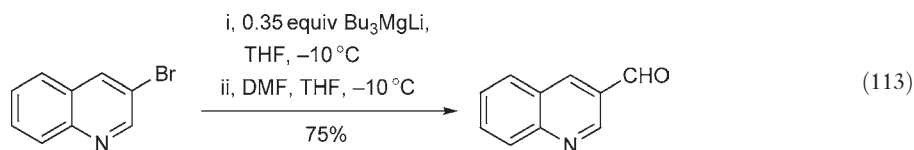


Pyridylmagnesium halides are generally prepared by metal–halogen exchange of halopyridines with alkyl Grignard reagents rather than by the more standard technique based on oxidative insertion of magnesium. However, oxidative magnesiation of 2-iodo-, bromo-, and even 2-chloropyridines has been found to occur between -20 and 30°C using activated magnesium prepared from lithium, naphthalene, and magnesium dichloride [\[2003JOC2054\]](#). The resultant Grignard species react with nonbulky aldehydes to give the corresponding alcohols in moderate yield. Reaction with more sterically hindered aldehydes does occur when the Grignard reagent is generated in the presence of the electrophile under Barbier-type conditions. The most common method for the generation of pyridylmagnesium halides is by metal–halogen exchange of bromo- and iodopyridines with isopropylmagnesium chloride in THF at room temperature [\[1999TL4339\]](#). Grignard reagents prepared in this manner from 2- and 3-bromopyridine react with aldehydes and iodine in high yield and disulfides and ketones in moderate yield. Dibromopyridines undergo a single exchange with bromine substituents at the 3-position being the most readily replaced. This mono-exchange can be applied to the synthesis of mixed bimetallic pyridines [\[2005AGE3133\]](#). Treatment of diiodopyridines such as 2,5-diiodopyridine with $i\text{-PrMgCl}\cdot\text{LiCl}$ in THF at -78°C followed by quenching with dioxaborolane **142** gives the boronic ester that undergoes a second metal–halogen exchange giving access to bimetallic reagents of type **143** (Scheme 31). These reagents react with benzaldehyde in good yield and a variety of other electrophiles after conversion to the corresponding cyanocuprate.



Scheme 31

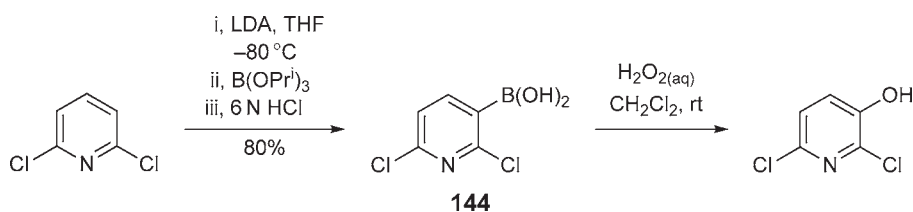
This metal–halogen exchange takes place preferentially with iodides and is functional group tolerant. Thus, 5-bromo-2-iodopyridine can be converted into 5-bromopyridylmagnesium chloride on treatment with $i\text{-PrMgCl}$ in THF at 0°C [\[2004OL4905\]](#). Iodopyridines functionalized with nitrile, ester, and chloride substituents also undergo smooth metal–halogen exchange with $i\text{-PrMgBr}$ in THF at -40°C to give functionalized Grignard reagents that react with aldehydes in high yield [\[2000JOC4618\]](#). Applying this methodology to the preparation of quinolylmagnesium halides has proved problematic owing to competing nucleophilic attack of isopropylmagnesium chloride onto the quinoline ring. The bromine–magnesium exchange of 2-, 3-, and 4-bromoquinolines can be achieved using the ate complex Bu_3MgLi in THF at -10°C to give lithium tri(quinolyl)magnesates [\[2003T8629\]](#). These species can be quenched with aldehydes, CO_2 , disulfides, and iodine in moderate to good yield. For example, treatment of 3-bromoquinoline with 0.35 equiv of lithium tributylmagnesate at -10°C followed by DMF gives quinoline-3-carbaldehyde in good yield (Equation 113).



Lithium tributyl magnesate can also be used to prepare lithium tripyridylmagnesates from iodopyridines at -78°C [\[2001JOC4333\]](#). The more reactive ate complex lithium dibutylisopropylmagnesate can be used to prepare tripyridylmagnesates from bromopyridines at this temperature. This metal–halogen exchange is also functional group tolerant and metal–halogen exchange takes place in the presence of ester, amide, nitrile, and other halogen substituents to give functionalized arylmagnesium reagents that react with aldehydes in moderate to good yield. Lithium tributylmagnesate does undergo effective metal–bromine exchange at elevated temperature and can be used

to mono-metalate 2,6-dibromopyridine at -10°C in THF <2001TL4841>. Halo-2-picolines are often poor substrates for this metal–halogen exchange procedure using isopropylmagnesium chloride owing to competing deprotonation of the methyl group. This limitation has been overcome using lithium dibutylisopropylmagnesium. 5-Bromo-2-picoline undergoes smooth exchange with this reagent at -10°C to give the picolylmagnesium complex that reacts with aldehydes, acid chlorides, and allyl bromide in moderate to good yield <2006TL1877>.

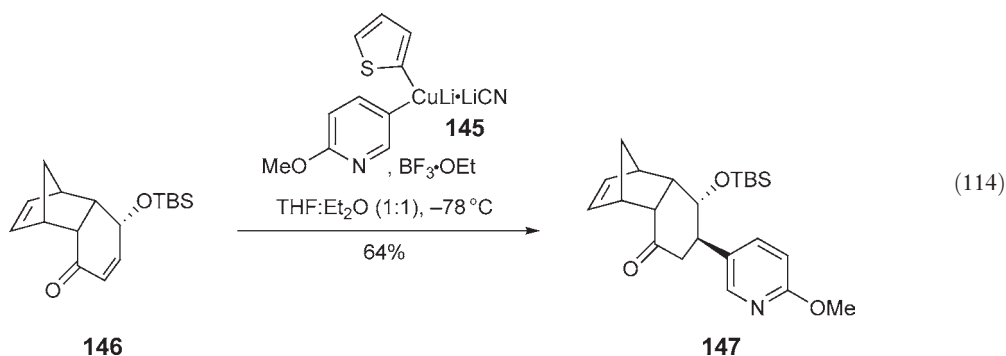
Pyridylboronic acids have been conveniently synthesized by quenching of pyridyllithium reagents with triisopropylborate <2002TL4285>. Boronate ester moieties may be introduced by reaction of pyridylmagnesium halides with dioxaboralanes <2005AGE3133>. The most important use of pyridinyl boronic acids and esters is as coupling partners in transition metal-mediated cross-coupling processes, described in more detail below. These compounds undergo hydroxydeboronation on treatment with aqueous hydrogen peroxide or MCPBA <2005T1417>. For example, treatment of 2,6-dichloropyridine with LDA followed by triisopropylborate gives boronic acid **144** that is converted to the hydroxypyridine under biphasic conditions using aqueous hydrogen peroxide and dichloromethane (Scheme 32).



Scheme 32

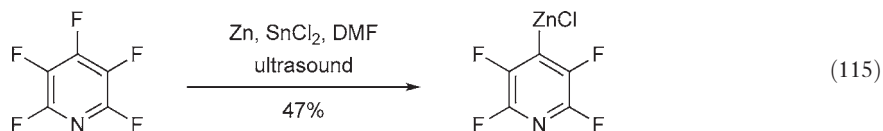
Pyridylstannanes are accessed by transmetalation of pyridyllithium reagents with trialkyltin halides such as tributyltin chloride <2000OL3373, 1998JA2805> and typically utilized as coupling partners in Stille reactions with aryl and alkenyl halides.

Organocopper derivatives of pyridine can be prepared by transmetalation of pyridyllithium and magnesium derivatives with copper(I) salts and these reagents undergo the C–C bond-forming reactions typical of organocuprates. Treatment of pyridylmagnesium halides, prepared by transmetalation of halopyridines with isopropylmagnesium chloride or bromide, with 1 equiv of $\text{CuCN}\cdot 2\text{LiCl}$ effects transmetalation to the cyanocuprate derivatives that couple with allyl bromide and acid chlorides in good yield <2005AGE3133, 2000JOC4618>. 3-Bromopyridines have been converted to cyano-Gilman cuprates incorporating the thienyl group as a dummy ligand by transmetalation of 3-lithiopyridines with lithium 2-thienylcyanocuprate and these cuprates have been observed to undergo highly diastereoselective addition to α,β -unsaturated ketones <1998J(P1)3151>. For example, pyridylcuprate **145** reacts with ketone **146** to give the 1,4-adduct **147** in good yield as a single diastereoisomer <1999SL1405> (Equation 114).



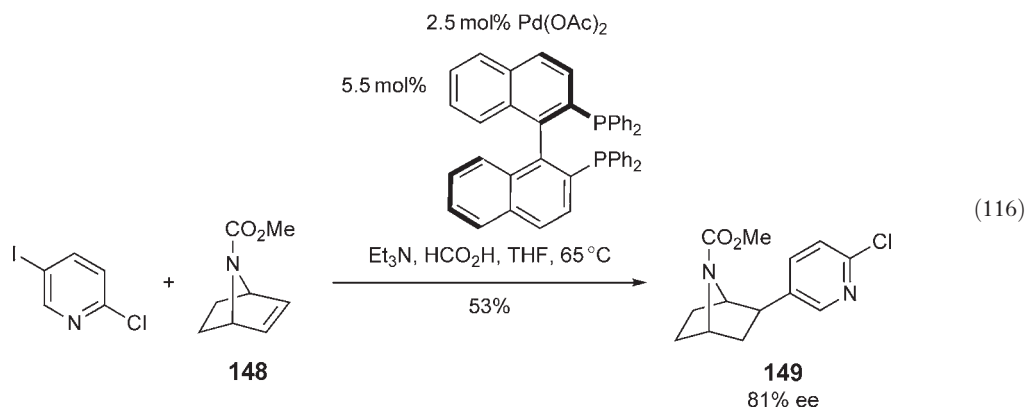
Pyridylzinc chlorides may be accessed by transmetalation of the corresponding pyridyllithium with anhydrous zinc chloride <2001EJO4207>. The regioselective preparation of 2-pyridylzinc species may be achieved by deprotonation of pyridine with lithium zincates <1999JA3539>. Pyridylzinc reagents have been prepared by direct insertion of zinc into carbon–halogen bonds. This has been achieved by stirring 2-bromopyridine in the presence of Rieke zinc in THF under reflux <2003SL852> and by treatment of fluoropyridines with zinc in the presence of tin(II) chloride in a

process accelerated by ultrasound [<2000TL3817>](#). For example, sonication of a mixture of tetrafluoropyridine, zinc and SnCl_2 in DMF results in 47% conversion to the 4-pyridylzinc chloride ([Equation 115](#)).

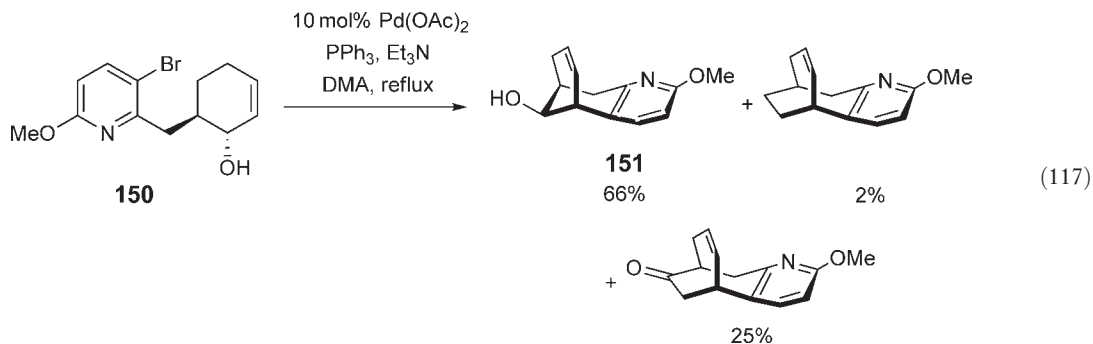


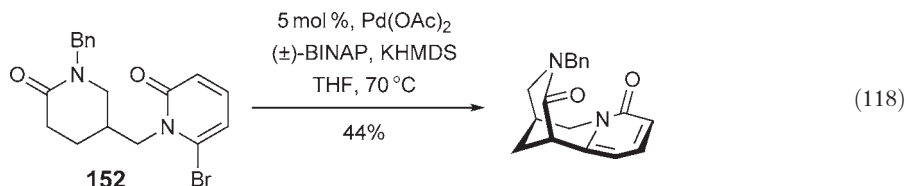
Pyridylzinc compounds react with halogens such as iodine to give halopyridines [<1999JA3539>](#) and are most commonly employed as substrates in the palladium(0)-mediated cross-coupling known as Negishi coupling described in more detail below [<2001EJO4207, 2003SL852>](#).

The palladium(0)-mediated coupling of halopyridines with olefins, known as the Mizoroki–Heck reaction, is one of the most widely used methods for the formation of C–C bonds to the pyridine ring and for the sake of brevity only recent highlights in this area will be discussed. Readers seeking a more detailed discussion of this methodology and developments in the general field should consult the many recent reviews [<2005T11771, 2005AGE4442, 2003CRV2945, 2002OR157, 2000PHC37>](#). The intermolecular coupling of 2-, 3-, and 4-bromo or iodopyridines with mono-substituted alkenes is most commonly achieved by heating in the presence of catalytic quantities of palladium(II) acetate, triarylphosphines, and a base such as triethylamine [<2005OL363, 2004JOC1959, 2002JME3558, 1998JHC717>](#) or potassium carbonate [<2005S2193, 2002T3525>](#). 3-Bromopyridine can be coupled to 1,2-disubstituted alkenes in high yield to give the (*E*)-product using allylpalladium chloride dimer as catalyst and 1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (tedicyp) as ligand [<2003TL8487>](#). The intermolecular reaction can proceed with enantioselectivity when performed in the presence of a reductant and an optically pure ligand. For example, azabicyclo[2.2.1]heptene **148** undergoes reductive arylation with 2-chloro-5-iodopyridine in the presence of 2.5 mol% $\text{Pd}(\text{OAc})_2$ and 5.5 mol% (*R*)- or (*S*)-BINAP ligands, triethylamine and formic acid to give the core structure of epibatidine **149** in moderate yield but high ee, although the absolute configuration was not determined ([Equation 116](#)).

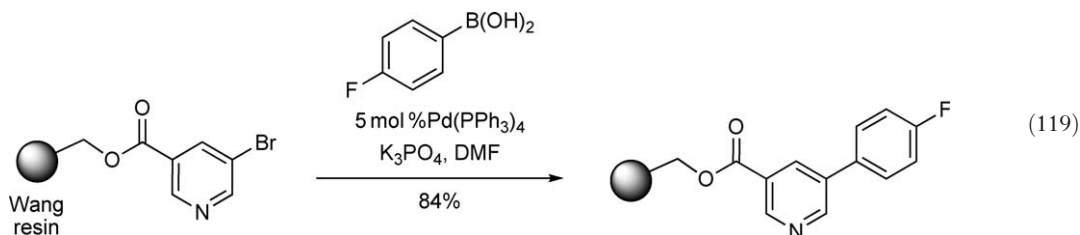


The intramolecular Heck reaction is a powerful method for the synthesis of constrained tertiary and quaternary carbon centers and has been applied as a key step in the synthesis of a number of pyridine alkaloids. Mann *et al.* have accessed the bicyclononane core structure of huperzine A **150** in moderate yield by intramolecular Heck reaction of bromopyridine **151** ([Equation 117](#)). Another notable application of this methodology is the intramolecular α -arylation of the amide enolate generated from **152** to give the carbon skeleton of cytosine [<2004OBC1825>](#) ([Equation 118](#)).



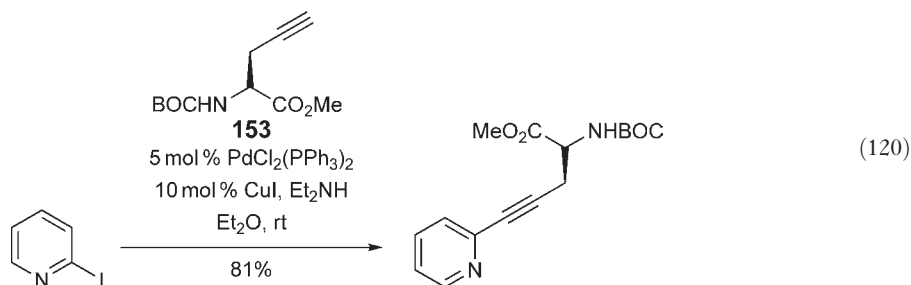


The cross-coupling of halopyridines with aryl and alkenyl organometallic reagents in the presence of palladium(0) catalysts is also a common method for the formation of carbon–pyridine and carbon–quinoline bonds. Suzuki–Miyaura cross-coupling of alkenylboronates occurs with 2-, 3-, and 4-iodo and bromopyridines to give alkenyl-substituted pyridines. This reaction is typically achieved using tetrakis(triphenylphosphine)palladium(0) as catalyst in the presence of oxygen bases such as potassium carbonate in DME [<2002TL4935>](#) and has also been achieved using potassium *tert*-butoxide, potassium hydroxide, or silver oxide as base in THF [<2005SL529>](#). This reaction has recently been applied to the preparation of combinatorial libraries using nicotinic acid as a scaffold [<2005TL581>](#). 5-Bromonicotinic acid on Wang, Rink, or BAL resin reacts with a variety of arylboronic acids in the presence of 5 mol% $\text{Pd}(\text{PPh}_3)_4$ and potassium phosphate in DMF or sodium carbonate in toluene in high yield. For example, the reaction on Wang resin with 4-fluorophenylboronic acid proceeds in 84% yield (Equation 119).



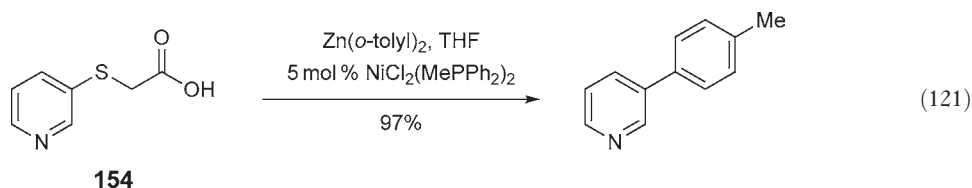
The Stille coupling of halopyridines and tributylvinyltin is again generally achieved in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(0) in toluene under reflux [<2005JOC1698, 2004JA2>](#) and also proceeds using $\text{PdCl}_2(\text{PPh}_3)_2$ [<2000TL8053>](#). A variety of 2-bromopyridines undergo cross-coupling with 2-tributylstannylpyridines in moderate to good yield using $\text{Pd}(\text{PPh}_3)_4$ to give symmetrical and unsymmetrical 2,2'-bipyridines [<2000JOC167>](#). The arylation of bromopyridines with phenyltrimethyltin can be achieved in good yield in water using air-stable and water-soluble palladium–phosphinous acid complexes [<2003JOC7551>](#). This reaction can also be extended to the arylation of 3-chloropyridines and also 3-chloroquinolines.

The alkynylation of halopyridines can be achieved by Sonogashira reaction with alkynes in the presence of catalytic amounts of palladium(0) and CuI and stoichiometric quantities of base. In common with other cross-coupling protocols, this reaction may be achieved using $\text{Pd}(\text{PPh}_3)_4$ as catalyst [<2004OL2209, 2004JA10389>](#). However, the reaction is more commonly performed using $\text{PdCl}_2(\text{PPh}_3)_2$ as catalyst [<2006OL167, 2005JME1721, 2004OL4253>](#). For example, 2-iodopyridine reacts with propargylglycine derivative **153** to give the alkynylpyridine in 85% yield (Equation 120). 3-Bromopyridines have been coupled in moderate to good yield with a variety of alkynes, in a more economical procedure, using 10% palladium on carbon as catalyst in the presence of catalytic CuI [<2005JME1721>](#).



These cross-coupling processes can proceed in a regioselective sense when performed on dihalopyridines, quinolines, and isoquinolines. Generally, oxidative addition of palladium occurs preferentially at the most electrophilic position. Thus, halogens at the 2- or 6-positions of pyridines are substituted in preference to those at the 3- or 5-positions while halogens at the 2- and 1-positions are preferentially replaced in quinolines and isoquinolines, respectively. The regioselective cross-coupling of polyhaloheterocycles, including halopyridines, haloquinolines, and haloisoquinolines, has been recently reviewed [<2005T2245>](#). Directing groups on the pyridine ring may also be used to achieve regioselectivity in the cross-coupling process. 2,6-Dichloronicotinamide undergoes regioselective cross-coupling with arylboronic acids at the 2-position owing to chelation of the palladium(0) catalyst to the adjacent amide moiety [<2003OL3131>](#).

The cross-coupling reactions of pyridines are certainly not restricted to the use of halopyridines. 2- and 4-Methylthiopyridines undergo Pd(0)-mediated Negishi cross-coupling with benzylzinc bromide to give the corresponding benzylpyridine. 2-Methylthiopyridine and 4-methylthiopyridine undergo cross-coupling with benzylzinc bromide in the presence of 1 mol% Pd(PPh₃)₄ in 80% and 70% yield, respectively [<2000SL905>](#). 3-Methylthiopyridine is unreactive under these conditions possibly due to the extra electron density at the 3-position that hinders oxidative insertion of Pd(0) into the C–S bond. Activation of this substrate using 1 equiv of BF₃·Et₂O does allow cross-coupling to take place and 3-ethylpyridine can be accessed in moderate yield on treatment with ethylzinc iodide in the presence of 5 mol% PdCl₂(PPh₃)₂ and BF₃·Et₂O in THF at 55 °C [<2002JOC9304>](#). However, 3-thiopyridine **154** undergoes cross-coupling with Zn(*o*-tolyl)₂ in the presence of the more reactive nickel catalyst NiCl₂(MePh₂P)₂ with no additional activation to give the cross-coupled product in 97% yield [<1999JA9449>](#) (Equation 121).

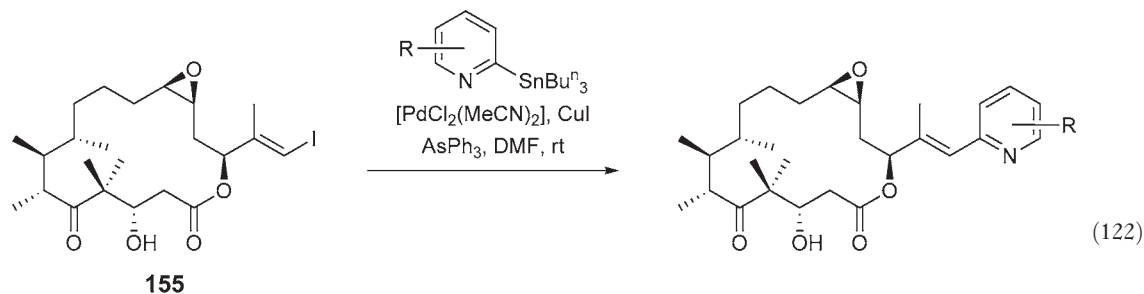


Pyridyltriflates and *O*-sulfamates also undergo cross-coupling reactions in the presence of palladium(0) and these processes have been covered in more detail in [Section 7.03.5.1](#).

Organometallic derivatives of pyridines are excellent coupling partners in cross-coupling reactions. 3-Pyridylmagnesium chloride, prepared by transmetalation of 3-bromopyridine with isopropylmagnesium chloride, undergoes cross-coupling with haloarenes including chloroarenes in good yield in the presence of 5 mol% nickel(II) acetylacetonate and diphenylphosphinoethane as ligand in THF at room temperature [<2002SL1008>](#). Triquinolylmagnesium salts also undergo cross-coupling with chloro- and bromoheteroarenes in the presence of 5 mol% Pd(dba)₂ and 5 mol% dppf as ligand to give biaryl products in low to moderate yield [<2003T8629>](#). There are numerous examples of the use of pyridylboronic acids and esters in Suzuki–Miyaura cross-couplings. 2-Pyridylboronic acids cross-couple with aryl bromides and iodides in the presence of 4 mol% tetrakis(triphenylphosphine)palladium(0) as catalyst and aqueous potassium carbonate as base [<2003T10043>](#). The coupling of pyridylboronic acids with halobenzenes can also be achieved using bis(triphenylphosphine)palladium dichloride (PdCl₂(PPh₃)₂) and sodium carbonate [<2005JOC388, 2005T5131>](#) or with Pd₂(dba)₃ and potassium phosphate [<2005JA4685>](#).

2-Pyridylzinc chlorides, prepared by treatment of the pyridyllithium with zinc chloride, undergo Negishi cross-coupling with iodobenzenes in good yield using 5 mol% bis(triphenylphosphine)palladium dichloride or tetrakis(triphenylphosphine)palladium(0) [<2001EJO4207>](#). 2,2'-Bipyridines can be accessed in high yield by Negishi coupling of 2-pyridylzinc bromides with 2-chloro- and 2-bromopyridines [<2003SL852>](#).

Pyridylstannanes readily undergo Stille cross-coupling with alkenyl and aryl halides on heating in the presence of palladium(0) catalysts. Again, tetrakis(triphenylphosphine)palladium(0) is commonly employed as a catalyst in this procedure [<2006JOC1254, 2005T5475, 2004JOC2953>](#), and bipyridines and terpyridines have been accessed by cross-coupling of 2-chloropyridines with 2-tributylstannylpyridines in the presence of bis(triphenylphosphine)palladium dichloride in xylene under reflux [<2006JOC566>](#). In a notable application of this methodology a range of epothilone B analogues were accessed in good yield by Stille reaction of a variety of stannylpyridines with vinyl iodide **155** in good yield to give pyridine analogues of epothilone B [<2003AGE3515>](#) (Equation 122).



R = 3-Br, yield = 74%

R = 3-Cl, yield = 46%

R = 3-SMe, yield = 78%

R = 3-CF₃, yield = 41%

R = 2-SMe, yield = 69%

These cross-coupling procedures are not limited to the construction of C–C bonds. The halogen atoms in halopyridines can be substituted with a variety of oxygen-, sulfur-, and nitrogen-based functionality via transition metal-mediated procedures discussed in some detail in [Section 7.03.7.1](#).

7.03.9 Further Developments

3-Hydroxypyridines and 8-hydroxyquinolines undergo selective copper-mediated *O*-arylation with aryl bromides in high yield using 1 mol% CuI as catalyst in the presence of 2,2,6,6-tetramethylheptane-3,5-dione as ligand [<2007OL643>](#).

The scope of 2- and 4-pyridylcuprates has been studied and these species were shown to react smoothly with a variety of enoates [<2007OL891>](#). The reactivity of 2-pyridylcuprates is dependant on the nature of the C-3 substituent and only those with hydrogen or a methyl group at this position reacted successfully.

References

- 1974JOC3834 R. Levine, D. A. Dimmig, and W. M. Kadunce, *J. Org. Chem.*, 1974, **39**, 3834.
 1996CHEC-II(5)91 N. Dennis, in 'Comprehensive Heterocyclic Chemistry II', A. McKillop, Ed.; Pergamon, Oxford, 1996, vol.5, p. 91.
 1994TL2819 D. L. Comins and G. Jianhua, *Tetrahedron Lett.*, 1994, **35**, 2819.
 1995J(P1)2503 O. Mongin, P. Rocca, L. Thomas-dit-Dumont, F. Trécourt, F. Marsais, A. Godard, and G. Quéguiner, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2503.
 1995JHC675 M. V. Papadopolou, S. Goswami, and A. D. Hamilton, *J. Heterocycl. Chem.*, 1995, **32**, 675.
 1995JHC1261 F. Trécourt, F. Mongin, M. Mallet, and G. Quéguiner, *J. Heterocycl. Chem.*, 1995, **32**, 1261.
 1995JOC6563 T. Umemoto and G. Tomizawa, *J. Org. Chem.*, 1995, **60**, 6563.
 1995JOC7654 A. W. Erian, A. Konno, and T. Fuchigami, *J. Org. Chem.*, 1995, **60**, 7654.
 1995NPR77 J. P. Michael, *Nat. Prod. Rep.*, 1995, **12**, 77.
 1995NPR465 J. P. Michael, *Nat. Prod. Rep.*, 1995, **12**, 465.
 1995PHC195 J. E. Toomey and R. Murugan, *Prog. Heterocycl. Chem.*, 1995, **7**, 195.
 1995S1159 F. Trécourt, M. Mallet, F. Mongin, and G. Quéguiner, *Synthesis*, 1995, 1159.
 1995SC2963 M. U. Koller, K. L. Peariso, T. S. Guion, S. S. Martinez, and C. F. Beam, *Synth. Commun.*, 1995, **25**, 2963.
 1995SL845 T. Sato, K. Yoshimatsu, and J. Otera, *Synlett*, 1995, 845.
 1995T1337 G. A. Kraus, D. R. Vines, and J. H. Malpert, *Tetrahedron*, 1995, **51**, 1337.
 1995T8649 C. Burgoc, F. Delgado, J. L. Garcia-Navio, M. L. Izquierdo, and J. Alvarez-Builla, *Tetrahedron*, 1995, **51**, 8649.
 1995T13089 B. Seiller, C. Bruneau, and P. H. Dixneuf, *Tetrahedron*, 1995, **51**, 13089.
 1995TL8415 F. Mongin, J.-M. Fourquez, S. Rault, V. Levacher, A. Godard, F. Trécourt, and G. Quéguiner, *Tetrahedron Lett.*, 1995, **36**, 8415.
 1996AJC761 L. K. Dyall, D. W. Maloney, J. J. Harvey, and B. E. Fulloon, *Aust. J. Chem.*, 1996, **49**, 761.
 1996H(49)2005 W. Sliwa, *Heterocycles*, 1996, **49**, 2005.
 1996J(P1)1359 E. M. Becalli, E. Erba, M. L. Gelmi, and D. Pocar, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1359.
 1996JOC1467 K. Krohn, I. Vinke, and H. Adam, *J. Org. Chem.*, 1996, **61**, 1467.
 1996JOC4623 T. R. Kelly and F. Lang, *J. Org. Chem.*, 1996, **61**, 4623.
 1996JOC7240 S. Wagaw and S. L. Buchwald, *J. Org. Chem.*, 1996, **61**, 7240.
 1996PHC209 J. E. Toomey and R. Murugan, *Prog. Heterocycl. Chem.*, 1996, **8**, 209.
 1996S927 V. A. Artyomov, A. M. Shestopalov, and V. P. Livinov, *Synthesis*, 1996, 927.

- 1996T15 W. Ying, D. D. DesMarteau, and Y. Gotoh, *Tetrahedron*, 1996, **52**, 15.
- 1996T10841 V. P. Kislyi, K. G. Nikishin, E. Y. Kruglova, A. M. Shestopalov, and V. V. Semenov, *Tetrahedron*, 1996, **52**, 10841.
- 1996T11385 D. P. Curran, H. Liu, H. Josien, and S.-B. Ko, *Tetrahedron*, 1996, **52**, 11385.
- 1996T14469 J. A. Zoltewicz and C. D. Dill, *Tetrahedron*, 1996, **52**, 14469.
- 1996TL513 J. M. Riego, Z. Sedin, J. M. Zaldívar, N. C. Marziano, and C. Tortato, *Tetrahedron Lett.*, 1996, **37**, 513.
- 1996TL2537 D. Cai, D. L. Hughes, and T. R. Verhoeven, *Tetrahedron Lett.*, 1996, **37**, 2537.
- 1996TL3795 P. V. Ramachandra, G.-M. Chen, Z.-H. Lu, and H. C. Brown, *Tetrahedron Lett.*, 1996, **37**, 3795.
- 1996TL5257 J. J. Parlow, *Tetrahedron Lett.*, 1996, **37**, 5257.
- 1996TL6695 F. Mongin, O. Mongin, F. Trécourt, A. Godard, and G. Quéguiner, *Tetrahedron Lett.*, 1996, **37**, 6695.
- 1997AGE980 T.-P. Loh and X.-R. Li, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 980.
- 1997BMCL2223 W. Neidhart, V. Breu, K. Burri, M. Clozel, G. Hirth, U. Klinkhammer, T. Giller, and H. Ramuz, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2223.
- 1997CPB279 A. Yokoyama, T. Ohwada, S. Saito, and K. Shudo, *Chem. Pharm. Bull.*, 1997, **45**, 279.
- 1997IJB1071 M. Kidwai and S. Kohli, *Indian J. Chem., Sect. B*, 1997, 1071.
- 1997JA656 A. G. Meyers, J. L. Gleason, T. Yoon, and D. W. Kung, *J. Am. Chem. Soc.*, 1997, **119**, 656.
- 1997JA1476 K. Tani, K. Lukin, and P. E. Eaton, *J. Am. Chem. Soc.*, 1997, **119**, 1476.
- 1997J(P1)1763 Y. Kita, N. Shibata, S. Fukui, M. Bando, and S. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1763.
- 1997JLCR49 B. A. Czeskis, *J. Labelled Compd. Radiopharm.*, 1997, **39**, 49.
- 1997JOC2604 N. Chatani, Y. Ie, F. Kakiuchi, and S. Murai, *J. Org. Chem.*, 1997, **62**, 2604.
- 1997JOC1568 J.-F. Marcoux, S. Wagaw, and S. L. Buchwald, *J. Org. Chem.*, 1997, **62**, 1568.
- 1997JOC6152 J. W. Wong, K. J. Natalie, Jr., G. C. Nwokogu, J. S. Pisipati, P. T. Flaherty, T. D. Greenwood, and J. F. Wolfe, *J. Org. Chem.*, 1997, **62**, 6152.
- 1997NPR11 J. P. Michael, *Nat. Prod. Rep.*, 1997, **14**, 11.
- 1997NPR605 J. P. Michael, *Nat. Prod. Rep.*, 1997, **14**, 605.
- 1997NPR637 D. O'Hagan, *Nat. Prod. Rep.*, 1997, **14**, 637.
- 1997PHC222 D. L. Comins and S. O'Connor, *Prog. Heterocycl. Chem.*, 1997, **9**, 222.
- 1997S949 D. H. Bremner, A. D. Dunn, K. A. Wilson, K. R. Sturrock, and G. Wishart, *Synthesis*, 1997, 949.
- 1997S1425 Y. Nakano and D. Imai, *Synthesis*, 1997, 1425.
- 1997SL395 X. Zhang, W. Cao, X. Wei, and H. Hu, *Synth. Commun.*, 1997, **27**, 1395.
- 1997SL473 W. E. Hume and R. Nagata, *Synlett*, 1997, 473.
- 1997SL839 A. V. Kalinin, M. A. J. Miah, S. Chattopadhyay, M. Tsukazaki, M. Wicki, T. Nguen, A. L. Coelho, M. Kerr, and V. Snieckus, *Synlett*, 1997, 839.
- 1997TA3467 M. Uchiyama, N. Katoh, R. Mimura, N. Yokota, Y. Shimogaichi, M. Shimazaki, and A. Ohta, *Tetrahedron Asymmetry*, 1997, **8**, 3467.
- 1997TL137 M. Lucflia, E. N. da Mata, W. B. Motherwell, and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 137.
- 1997TL5423 Y. Han and L. Cai, *Tetrahedron Lett.*, 1997, **38**, 5423.
- 1997SL6673 C.-H. Jun, D.-Y. Lee, and J.-B. Hong, *Tetrahedron Lett.*, 1997, **38**, 6673.
- 1998BCJ285 N. Fujii, F. Kakiuchi, A. Yamada, N. Chatani, and S. Murai, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 285.
- 1998BML453 D. Guay, G. C. Duresne, T. R. Jones, M. McAuliffe, C. McFarlane, K. M. Metters, P. Prasit, C. Rochette, P. Roy, N. Sawyer, and R. Zamboni, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 453.
- 1998BMCL1909 S.-H. Yoon, S. Seo, Y. Lee, S. Hwang, and D. Y. Kim, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1909.
- 1998JA2805 Y. Yao, J. J. S. Lamba, and J. M. Tour, *J. Am. Chem. Soc.*, 1998, **120**, 2805.
- 1998J(P1)1705 R. D. Chambers, C. W. Hall, J. Hutchinson, and R. W. Millar, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1705.
- 1998J(P1)3151 V. Caprio and J. Mann, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3151.
- 1998J(P1)3689 G. M. P. Giblin, C. D. Jones, and N. S. Simpkins, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3689.
- 1998JFC13 X.-C. Zhang and W.-Y. Huang, *J. Fluorine Chem.*, 1998, **92**, 13.
- 1998JFC57 X.-C. Zhun and W. Y. Huang, *J. Fluorine Chem.*, 1998, **87**, 57.
- 1998JFC203 R. S. Matthews, *J. Fluorine Chem.*, 1998, **91**, 203.
- 1998JHC717 S. W. Wright, D. L. Hageman, and L. Mc Clure, *J. Heterocycl. Chem.*, 1998, **35**, 717.
- 1998JLCR911 C. Biot, S. Caron, L. A. Maciejewski, and J. S. Brocard, *J. Labelled Compd. Radiopharm.*, 1998, **41**, 911.
- 1998JLCR1103 H. R. Wiltshire, K. J. Prior, J. Dhesi, F. Trach, M. Schlageter, and H. Schönenberger, *J. Labelled Compd. Radiopharm.*, 1998, **41**, 1103.
- 1998JME4408 A. Tanaka, T. Terasawa, H. Hagihara, N. Ishibe, M. Sawada, Y. Sakuma, M. Hashimoto, H. Takasugi, and H. Tanaka, *J. Med. Chem.*, 1998, **41**, 4408.
- 1998NPR595 J. P. Michael, *Nat. Prod. Rep.*, 1998, **15**, 595.
- 1998PHC226 R. D. Larsen, *Prog. Heterocycl. Chem.*, 1998, **10**, 226.
- 1998S661 K. Groebke, L. Weber, and F. Mehlh, *Synthesis*, 1998, 661.
- 1998SL640 H. Heaney, M. T. Simcox, A. M. Z. Slawin, and R. G. Giles, *Synlett*, 1998, 640.
- 1998TL217 C. Chen, I. A. McDonald, and B. Munoz, *Tetrahedron Lett.*, 1998, **39**, 217.
- 1998TL5159 L. Xu, I. R. Lewis, S. K. Davidsen, and J. B. Summers, *Tetrahedron Lett.*, 1998, **39**, 5159.
- 1999BML2753 M. R. Becker, W. R. Ewing, R. S. Davis, H. W. Pauls, C. Ly, A. Li, H. J. Mason, Y. M. Choi-Sledeski, A. P. Spada, V. Chu, *et al.*, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2753.
- 1999EJO3165 M. Albrecht, O. Blau, and J. Zauner, *Eur. J. Org. Chem.*, 1999, 3165.
- 1999H(50)843 S. Tandel and E. R. Biehl, *Heterocycles*, 1999, **50**, 843.
- 1999H(50)1015 I. Nagasaki, M. Matsumoto, M. Yamashita, and A. Miyashita, *Heterocycles*, 1999, **50**, 1015.
- 1999JA3539 Y. Kondo, M. Shilai, M. Uchiyama, and T. Sakamoto, *J. Am. Chem. Soc.*, 1999, **121**, 3539.
- 1999JA9449 J. Srogl, W. Liu, D. Marshall, and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1999, **121**, 9449.
- 1999JFC153 A. D. Dunn, *J. Fluorine Chem.*, 1999, **93**, 153.
- 1999JHC445 P. A. Krapcho and T. Gilmore, *J. Heterocycl. Chem.*, 1999, **36**, 445.

- 1999JOC2211 J. R. Hwu, W. N. Tseng, H. V. Patel, F. F. Wong, D.-N. Horng, B. R. Liaw, and L. C. Lin, *J. Org. Chem.*, 1999, **64**, 2211.
- 1999JOC3113 E. Anders, A. Opitz, K. Wermann, B. Wiedel, M. Walther, W. Imhof, and H. Görls, *J. Org. Chem.*, 1999, **64**, 3113.
- 1999JOC5896 S. Hanessian and S. Johnstone, *J. Org. Chem.*, 1999, **64**, 5896.
- 1999JOC9658 Z. J. Song, M. Zhao, R. Desmond, P. Devine, D. M. Tschäen, R. Tillyer, L. Frey, L. Heid, F. Xu, B. Foster, *et al.*, *J. Org. Chem.*, 1999, **64**, 9658.
- 1999NPR697 J. P. Michael, *Nat. Prod. Rep.*, 1999, **16**, 697.
- 1999OL87 D. A. Evans, V. J. Cee, T. E. Smith, and K. J. Santiago, *Org. Lett.*, 1999, **1**, 87.
- 1999PHC230 R. D. Larsen and I. W. Davies, *Prog. Heterocycl. Chem.*, 1999, **11**, 230.
- 1999S51 X.-C. Zhang and W.-Y. Huang, *Synthesis*, 1999, 51.
- 1999S237 E. Okada, N. Tsukushi, and N. Shimomura, *Synthesis*, 2000, 237.
- 1999S306 A. Numata, Y. Kondo, and T. Sakamoto, *Synthesis*, 1999, 306.
- 1999SL1405 H. Nakashima, K. Hiroya, T. Taniguguchi, and K. Ogasawara, *Synlett*, 1999, 1405.
- 1999T5459 B. V. Mephrath, S. Diltz, P. J. Walsh, and J. D. Protasiewicz, *Tetrahedron*, 1999, **40**, 5459.
- 1999T11985 T. Searls and L. W. McLaughlin, *Tetrahedron*, 1999, **55**, 11985.
- 1999T12557 G. Dyker and B. Hölzer, *Tetrahedron*, 1999, **55**, 12557.
- 1999T12797 Y. L. Janin, J. Chiki, M. LeGraverend, C. Huel, and E. Bisagni, *Tetrahedron*, 1999, **55**, 12797.
- 1999T12829 E. Brenner, R. Schneider, and Y. Fort, *Tetrahedron*, 1999, **55**, 12829.
- 1999TA4563 H. B. ten Brink, H. L. Holland, H. E. Schoemaker, H. Van Lingen, and R. Weaver, *Tetrahedron Asymmetry*, 1999, **10**, 4563.
- 1999TA4769 A. S. Demir, T. Dünwald, H. Iding, M. Pohl, and M. Müller, *Tetrahedron Asymmetry*, 1999, **10**, 4769.
- 1999TL1721 S. Sunami, T. Sagara, M. Ohkubo, and H. Morishima, *Tetrahedron Lett.*, 1999, **40**, 1721.
- 1999TL3719 D. Najiba, J.-F. Carpentier, Y. Castanet, C. Biot, J. Brocard, and A. Motreux, *Tetrahedron Lett.*, 1999, **40**, 3719.
- 1999TL4339 F. Trecourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais, and G. Quéguiner, *Tetrahedron Lett.*, 1999, **40**, 4339.
- 1999TL4433 C. Boix and M. Poliakoff, *Tetrahedron Lett.*, 1999, **40**, 4433.
- 1999TL5565 E. Takashiro, Y. Nakamura, and K. Fujimoto, *Tetrahedron Lett.*, 1999, **40**, 5565.
- 1999TL5621 T. Ali, K. K. Chauhan, and C. G. Frost, *Tetrahedron Lett.*, 1999, **40**, 5621.
- 1999TL6999 Z.-X. Guo, A. N. Cammidge, A. McKillop, and D. C. Horwell, *Tetrahedron Lett.*, 1999, **40**, 6999.
- 1999TL8823 Y. Kato and T. Mase, *Tetrahedron Lett.*, 1999, **40**, 8823.
- 1999TL8837 M. Watanabe, M. Nishiyama, and Y. Koie, *Tetrahedron Lett.*, 1999, **40**, 8837.
- 2000CPB1514 M. Tamura, U. Y. Urano, K. Kikuchi, T. Higuchi, H. Masaaki, and T. Nagano, *Chem. Pharm. Bull.*, 2000, **48**, 1514.
- 2000EJO2735 B. Koning, J. Buter, R. Hulst, R. Stroetinga, and R. M. Kellogg, *Eur. J. Org. Chem.*, 2000, 2735.
- 2000EJOC3205 R. K. Haynes, T. Lok, A. Yueng, W.-K. Chan, W.-L. Lam, Z.-Y. Li, L.-L. Yueng, A. S. C. Chan, P. Li, M. Koen, *et al.*, *Eur. J. Org. Chem.*, 2000, 3205.
- 2000EJOC3505 R. Krämer and I. O. Fritsky, *Eur. J. Org. Chem.*, 2000, 3505.
- 2000ISJ301 K. Monde, Y. Tomita, L. Gilchrist, Jr., A. E. McDermot, and K. Nakanishi, *Isr. J. Chem.*, 2000, **40**, 301.
- 2000JP13205 K. Nakamura, M. Fujii, and Y. Ida, *J. Chem. Soc., Perkin Trans. 1.*, 2000, 3205.
- 2000JP22208 S. Anto, G. S. Getvoldsen, J. R. Harding, J. R. Jones, S.-Y. Lu, and J. C. Russell, *J. Chem. Soc., Perkin Trans. 2*, 2002, 2208.
- 2000JHC1527 Wang, J. Hu, X. Zhang, Y. Hu, and H. Hu, *J. Heterocycl. Chem.*, 2000, **37**, 1527.
- 2000JHC1253 W. Stadbauer, W. Fiala, M. Fischer, and G. Hojas, *J. Heterocycl. Chem.*, 2000, **37**, 1253.
- 2000JOC1158 J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1158.
- 2000JOC1215 G. A. Molander and R. M. Rzasa, *J. Org. Chem.*, 2000, **65**, 1215.
- 2000JOC4618 M. Abarbri, J. Thibonnet, L. Berillon, F. Dehmel, M. Rottlander, and P. Knochel, *J. Org. Chem.*, 2000, **65**, 4618.
- 2000JOC7718 J. A. Pesti, G. F. Huhn, J. Yin, Y. Xing, and J. M. Fortunak, *J. Org. Chem.*, 2000, **65**, 7718.
- 2000NPR131 J. W. Daly, G. H. Martin, T. F. Spande, M. W. Decker, J. P. Sullivan, and M. Williams, *Nat. Prod. Rep.*, 2000, **17**, 131.
- 2000NPR435 D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435.
- 2000NPR603 J. P. Michael, *Nat. Prod. Rep.*, 2000, **17**, 603.
- 2000OL1641 J. Busch-Peterson and E. J. Corey, *Org. Lett.*, 2000, **2**, 1641.
- 2000OL1749 T. Ohkuma, M. Koizumi, M. Yoshida, and R. Noyori, *Org. Lett.*, 2000, **2**, 1749.
- 2000OL2291 S. Lindstrom, L. Ripa, and A. Hallberg, *Org. Lett.*, 2000, **2**, 2291.
- 2000OL3373 U. S. Schubert, C. Eschbaumer, and M. Heller, *Org. Lett.*, 2000, **2**, 3373.
- 2000OL3525 Y. Wang and J. H. Espenson, *Org. Lett.*, 2000, **2**, 3525.
- 2000PHC37 J. J. Li, *Prog. Heterocycl. Chem.*, 2000, **12**, 37.
- 2000PHC237 R. D. Larsen and J.-F. Marcoux, *Prog. Heterocycl. Chem.*, 2000, **12**, 237.
- 2000S116 H. Kotsuki, H. Sakai, and T. Shinohara, *Synlett*, 2000, 116.
- 2000S237 E. Okada, N. Tsukushi, and N. Shimomura, *Synthesis*, 2000, 237.
- 2000S674 P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, K. M. Averill, D. M. T. Chan, and A. Combs, *Synlett*, 2000, 674.
- 2000S1733 L. Zhang, F. Liang, L. Sun, Y. Hu, and H. Hu, *Synthesis*, 2000, 1733.
- 2000SL683 K. P. Chary, S. R. Ram, and D. S. Iyengar, *Synlett*, 2000, 683.
- 2000SL905 M. E. Angiolli, A. L. Casalnuovo, and T. P. Selby, *Synlett*, 2000, 905.
- 2000T3709 A. Leprêtre, A. Turck, N. Plé, and G. Quéguiner, *Tetrahedron*, 2000, **56**, 3709.
- 2000T4043 I. Gómez, E. Alonso, D. J. Ramón, and M. Yus, *Tetrahedron*, 2000, **56**, 4043.
- 2000T8673 F. Alonso, G. Radivoy, and M. Yus, *Tetrahedron*, 2000, **56**, 8673.
- 2000TL3817 A. O. Miller, V. I. Krasnov, D. Peters, V. E. Platonov, and R. Miethchen, *Tetrahedron Lett.*, 2000, **41**, 3817.
- 2000TL8053 V. J. Colandrea and E. M. Naylor, *Tetrahedron Lett.*, 2000, **41**, 8053.
- 2001BMC2863 J. W. Huffman, J. Lu, G. Hynd, J. L. Wiley, and B. R. Martin, *Bioorg. Med. Chem.*, 2001, **9**, 2863.
- 2001CC2576 C. S. Cho, B. T. Kim, T.-J. Kim, and S. C. Shim, *Chem. Commun.*, 2001, 2576.
- 2001EJO4207 M. Alami, J.-F. Peyrat, L. Belachmi, and J.-D. Brion, *Eur. J. Org. Chem.*, 2001, 4207.
- 2001H1703 A. R. Katritzky, T. Kurz, S. Zhang, and M. Voronkov, *Heterocycles*, 2001, **55**, 1703.
- 2001JA7727 A. Klapars, J. Antilla, C. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727.

- 2001J(P1)3288 D. R. Boyd, N. D. Sharma, S. A. Haughey, J. F. Malone, A. W. T. King, B. T. McMurray, A. Alves-Areias, C. C. R. Allen, R. Holt, and H. Dalton, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3288.
- 2001JFC107 X.-T. Huang, Z.-Y. Long, and Q.-Y. Chen, *J. Fluorine Chem.*, 2001, **111**, 107.
- 2001JHC1213 G. B. Okide, *J. Heterocycl. Chem.*, 2001, **38**, 1213.
- 2001JOC2654 E. Pasquinet, P. Rocca, S. Richalot, F. Guéritte, D. Guénard, A. Godard, F. Marsais, and G. Quéguiner, *J. Org. Chem.*, 2001, **66**, 2654.
- 2001JOC3646 D. K. Rayabarapu, K. K. Majumdar, T. Sambaiiah, and C.-H. Cheng, *J. Org. Chem.*, 2001, **66**, 3646.
- 2001JOC4333 A. Inoue, K. Kitagawa, H. Shinokubo, and K. Oshima, *J. Org. Chem.*, 2001, **66**, 4333.
- 2001JOC5264 B. Zacharie, N. Moreau, and C. Dockendorff, *J. Org. Chem.*, 2001, **66**, 5264.
- 2001JOC8677 G. Y. Li, G. Zheng, and A. F. Noonan, *J. Org. Chem.*, 2001, **66**, 8677.
- 2001M1075 H. Gershon, D. D. Clarke, and M. Gershon, *Monatsh. Chem.*, 2001, **132**, 1075.
- 2001NPR543 J. P. Michael, *Nat. Prod. Rep.*, 2001, **118**, 543.
- 2001OL2021 U. Ragnarsson, L. Grehn, H. L. S. Maia, and L. Monteiro, *Org. Lett.*, 2001, **3**, 2021.
- 2001OL2729 S. Lee, M. Jørgensen, and J. F. Hartwig, *Org. Lett.*, 2001, **3**, 2729.
- 2001OL3895 T. R. Kelly, M. Caverio, and Y. Zhao, *Org. Lett.*, 2001, **3**, 3895.
- 2001PHC238 D. S. Coffey, S. A. May, and A. M. Ratz, *Prog. Heterocycl. Chem.*, 2001, **13**, 238.
- 2001S81 J. G. Lee, K. I. Choi, H. Y. Koh, Y. Kim, Y. Kang, and Y. S. Cho, *Synthesis*, 2001, 81.
- 2001S2495 M.-D. Le Bas, C. Guéret, C. Perriot, M.-C. Lasne, and L. Barré, *Synthesis*, 2001, 2495.
- 2001SL765 W. R. Bowman, C. F. Bridge, M. O. Cloonan, and D. C. Leach, *Synlett*, 2001, 765.
- 2001SL795 M. Boruah and D. Konwar, *Synlett*, 2001, 795.
- 2001T1771 T. Nicola, D. Schwarzrock, M. Keller, and W. Eberbach, *Tetrahedron*, **57**, 1771.
- 2001T2507 J.-Y. Legros, G. Primault, and J.-C. Fiaud, *Tetrahedron*, 2001, **57**, 2507.
- 2001T3069 U. Schöpfer and A. Sclapbach, *Tetrahedron*, 2001, **57**, 3069.
- 2001T3267 S. Hanessian, O. M. Saavedra, V. Mascitti, W. Marterer, R. Oehrlin, and C.-P. Mak, *Tetrahedron*, 2001, **57**, 3267.
- 2001T4059 F. Mongin and G. Quéguiner, *Tetrahedron*, 2001, **57**, 4059.
- 2001T7965 R. Grigg, N. Kongkathip, B. Kongkathip, S. Luangkamin, and H. A. Dondas, *Tetrahedron*, 2001, **57**, 7965.
- 2001T8817 S. M. Riyadh, H. Ishii, and T. Fuchigami, *Tetrahedron*, 2001, **57**, 8817.
- 2001T8841 R. Fujita, K. Watanabe, W. Ikeura, Y. Ohtake, H. Hongo, Y. Harigaya, and H. Matzuzaki, *Tetrahedron*, 2001, **57**, 8841.
- 2001T8845 D. A. Alonso, C. Nájera, and M. Varea, *Tetrahedron*, 2001, **42**, 8845.
- 2001TL1843 Z. Guo, E. D. Dowdy, W.-S. Li, R. Polniaszek, and E. Delaney, *Tetrahedron Lett.*, 2001, **42**, 1843.
- 2001TL1899 K. Everaere, J.-L. Scheffler, A. Mortreux, and F.-F. Carpentier, *Tetrahedron Lett.*, 2001, **42**, 1899.
- 2001TL3251 F. Lang, D. Zewge, I. N. Houpi, and R. P. Volante, *Tetrahedron Lett.*, 2001, **42**, 3251.
- 2001TL4841 T. Iida, T. Wada, K. Tomimoto, and T. Mase, *Tetrahedron Lett.*, 2001, **42**, 4841.
- 2001TL5393 A. K. Battacharya, F. Stolz, and R. R. Schmidt, *Tetrahedron Lett.*, 2001, **42**, 5393.
- 2001TL6815 L. F. Frey, K. Marcantonio, D. E. Frantz, J. A. Murry, R. D. Tillyer, E. J. J. Grabowski, and P. J. Reider, *Tetrahedron Lett.*, 2001, **42**, 6815.
- 2001TL7737 B. H. Lipshutz, T. Tomioka, and S. S. Pfeiffer, *Tetrahedron Lett.*, 2001, **42**, 7737.
- 2001TL8845 D. A. Alonso, C. Nájera, and M. Varea, *Tetrahedron Lett.*, 2001, **42**, 8845.
- 2002AGE609 A. Fürstner and A. Leitner, *Angew. Chem., Int. Ed.*, 2002, **41**, 609.
- 2002AGE1062 A. G. Meyers, P. C. Hogan, A. R. Hurd, and S. D. Goldberg, *Angew. Chem., Int. Ed.*, 2002, **41**, 1062.
- 2002BML3593 A. Tiwari, W. R. Waud, and R. F. Struck, *Bioorg. Med. Chem. Lett.*, 2002, **10**, 3593.
- 2002EJO4181 M. Schlosser and F. Cottet, *Eur. J. Org. Chem.*, 2002, 4181.
- 2002JA13856 A. Fürstner, A. Leitner, M. Méndez, and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856.
- 2002JMC1079 A. Tiwari, J. M. Riordan, W. R. Waud, and R. F. Struck, *J. Med. Chem.*, 2002, **45**, 1079.
- 2002JFC99 R. D. Chambers, D. Holling, G. Sandford, H. Puschmann, and J. A. K. Howard, *J. Fluorine Chem.*, 2002, **117**, 99.
- 2002JOC7890 K. A. Skupinska, E. J. McEachern, R. T. Skerlj, and G. J. Bridger, *J. Org. Chem.*, 2002, **67**, 7890.
- 2002JOC9304 I. Gosh and P. A. Jacobi, *J. Org. Chem.*, 2002, **67**, 9304.
- 2002MM1563 C. G. Banguy, M. E. Rampey-Vaughn, L. T. Quan, S. M. Angel, M. D. Smith, and U. H. F. Bunz, *Macromolecules*, 2002, **35**, 1563.
- 2002JA750 S. Ko, Y. Na, and S. Chang, *J. Am. Chem. Soc.*, 2002, **124**, 750.
- 2002JME1079 A. Tiwari, J. M. Riordan, W. R. Waud, and R. F. Struck, *J. Med. Chem.*, 2002, **45**, 1079.
- 2002JME3558 Y.-Q. Wu, D. E. Wilkinson, D. Limburg, J.-H. Li, H. Sauer, D. Ross, S. Liang, D. Spicer, H. Valentine, M. Fuller, *et al.*, *J. Med. Chem.*, 2002, **45**, 3558.
- 2002JOC741 P. S. Dragovich, R. Zhou, and T. J. Prins, *J. Org. Chem.*, 2002, **67**, 741.
- 2002JOC8991 F. Mongin, L. Mojovic, B. Guillet, F. Trécourt, and G. Quéguiner, *J. Org. Chem.*, 2002, **67**, 8991.
- 2002JOC9061 D. Moran, K. Sukcharoenphon, R. Puchta, H. F. Schaefer, III, P. V. R. Schleyer, and C. D. Hoff, *J. Org. Chem.*, 2002, **67**, 9061.
- 2002JOC9354 K. R. Gibson, L. Hitzel, R. J. Mortshire-Smith, U. Gerhard, R. A. Jelley, A. J. Reeve, M. Rowley, A. Nadin, and A. P. Owens, *J. Org. Chem.*, 2002, **67**, 9354.
- 2002NPR742 J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 742.
- 2002OL581 F. Y. Kwong, A. Klapars, and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 581.
- 2002OL973 M. Wolter, G. Nordmann, G. E. Job, and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 973.
- 2002OL3481 J. Yin, M. M. Zhao, M. A. Huffman, and J. M. McNamara, *Org. Lett.*, 2002, **4**, 3481.
- 2002OR157 J. T. Link, *Org. React.*, 2002, **60**, 157.
- 2002PS2773 P. V. Ioannou, P. A. Afroudakis, and M. G. Siskos, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 2773.
- 2002PHC257 S. D. Coffey, S. P. Kolis, and S. A. May, *Prog. Heterocycl. Chem.*, 2002, **14**, 257.
- 2002S83 W. D. Brown and A. H. Gouliarov, *Synthesis*, 2002, 83.
- 2002S1683 F. Orsini, E. Di Teodoro, and M. Ferrari, *Synthesis*, 2002, 1683.
- 2002SC1211 R. A. Rane, R. K. Pathak, C. P. Kaushik, K. V. V. Prasad Rao, and A. Kumar, *Synth. Commun.*, 2001, **32**, 1211.
- 2002SC1715 S. Guery, Y. Rival, and C. G. Wermuth, *Synth. Commun.*, 2002, **32**, 1715.

- 2002SL453 A. Arcadi, S. Cacchi, S. Di Giuseppe, G. Fabrizi, and F. Marinelli, *Synlett*, 2002, 453.
- 2002SL714 Y. Shen, Y. Zhang, and G.-F. Jiang, *Synlett*, 2002, 714.
- 2002SL1008 V. Bonnet, F. Mongin, F. Trécourt, G. Breton, F. Marsais, P. Knochel, and G. Quéguiner, *Synlett*, 2002, 1008.
- 2002SL1291 G. D. McAllister, C. D. Wilfred, and R. J. K. Taylor, *Synlett*, 2002, 1291.
- 2002SL1293 J. S. Foot, H. Kanno, G. M. P. Giblin, and R. J. K. Taylor, *Synlett*, 2002, 1293.
- 2002SL1547 E. Bouladakis, B. Chung, M. R. J. Elsegood, and G. W. Weaver, *Synlett*, 2002, 1547.
- 2002SC2027 N. Nikolaides, S. E. Bogdan, and J. S. Szalma, *Synth. Commun.*, 2002, **32**, 2027.
- 2002SL1404 Z. Appelbe, M. Casey, C. M. Keaveney, and C. J. Kelly, *Synlett*, 2002, 1404.
- 2002SL1093 A. Nuñez, A. García de Viema, V. Martínez-Barrasa, C. Burgos, and J. Alvarez-Builla, *Synlett*, 2002, 1093.
- 2002T3525 G. Pandey, J. K. Laha, and G. Lakshmaiah, *Tetrahedron*, 2002, **58**, 3525.
- 2002T4931 Y.-J. Cherng, *Tetrahedron*, 2002, **58**, 4931.
- 2002T6951 M. Adamczyk, S. R. Akireddy, and R. E. Reddy, *Tetrahedron*, 2002, **58**, 6951.
- 2002TA2201 M. D. Garret, R. Scott, and G. N. Sheldrake, *Tetrahedron Asymmetry*, 2002, **13**, 2201.
- 2002TL1035 K. Kumamoto, Y. Misawa, S. Tokita, Y. Kubo, and H. Kotsuki, *Tetrahedron Lett.*, 2002, **43**, 1035.
- 2002TL1697 S. Bedel, G. Ulrich, and C. Picard, *Tetrahedron Lett.*, 2002, **43**, 1697.
- 2002TL1877 M. Ilias, D. C. Barman, D. Prajapati, and J. S. Sandhu, *Tetrahedron Lett.*, 2002, **43**, 1877.
- 2002TL4285 D. Cai, R. D. Larsen, and P. J. Reider, *Tetrahedron Lett.*, 2002, **43**, 4285.
- 2002TL4935 F. Berrée, P. G. Bleis, and B. Carboni, *Tetrahedron Lett.*, 2002, **43**, 4935.
- 2002TL7259 F. Orsini and A. Caselli, *Tetrahedron Lett.*, 2002, **43**, 7259.
- 2002TL8823 R. J. Rahaim Jr., and R. E. Maleczka, Jr., *Tetrahedron Lett.*, 2002, **43**, 8823.
- 2003AGE3515 K. C. Nicolaou, P. K. Sasmal, G. Rassias, M. V. Reddy, K.-H. Altmann, M. Wartmann, A. O'Brate, and P. Giannakakou, *Angew. Chem., Int. Ed.*, 2003, **42**, 3515.
- 2003AJC913 T. Lister, R. H. Prager, M. Tsaconas, and K. L. Wilkinson, *Aust. J. Chem.*, 2003, **56**, 913.
- 2003BML1051 R. Jain, B. Vaitilingam, A. Nayyar, and P. B. Palde, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1051.
- 2003BML2291 U. J. Ries, H. W. M. Priepe, N. H. Hauel, E. E. J. Haaksma, J. M. Stassen, W. Wienen, and H. Nar, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2291.
- 2003BML3375 C. Q. Huang, K. Wilcoxon, J. R. McCarthy, M. Haddach, T. R. Webb, J. Gu, Y.-F. Xie, D. E. Grigoriadis, and C. Chen, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3375.
- 2003BML3979 L. Liu, J. E. Stelmach, S. R. Natarajan, M.-H. Chen, S. B. Singh, C. D. Schwartz, C. E. Fitzgerald, S. J. O'Keefe, D. M. Zaller, D. M. Schmatz, *et al.*, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3979.
- 2003CEJ4202 H.-J. Gais, T. Jagush, N. Spalthoff, F. Gerhards, M. Frank, and G. Raabe, *Chem. Eur. J.*, 2003, **9**, 4202.
- 2003CRV2945 A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945.
- 2003EJO1559 F. Cottet, M. Murall, O. Lefebvre, and M. Schlosser, *Eur. J. Org. Chem.*, 2003, 1559.
- 2003EJO1569 M. Schlosser and M. Marull, *Eur. J. Org. Chem.*, 2003, 1569.
- 2003EJO2919 J. Heimann, H. J. Schäfer, R. Frölich, and B. Wibbeling, *Eur. J. Org. Chem.*, 2003, 2919.
- 2003EJO4286 R. Masciadri, M. Kamer, and N. Nock, *Eur. J. Org. Chem.*, 2003, 4286.
- 2003EJO4445 N. Wild and U. Groth, *Eur. J. Org. Chem.*, 2003, 4445.
- 2003H(60)1461 Y. Azuma, M. Morone, K. Nagayama, Y. Kawamata, and A. Sato, *Heterocycles*, 2003, **60**, 1461.
- 2003H(60)1843 F. Sánchez-Sancho and B. Herradón, *Heterocycles*, 2003, **60**, 1843.
- 2003JA5186 M. J. Henson, M. A. Vance, C. X. Zhang, H. C. Liang, and K. D. Karlin, *J. Am. Chem. Soc.*, 2003, **125**, 5186.
- 2003JA11818 H. N. Nguyen, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11818.
- 2003JCD153 X.-M. Gan, R. T. Paine, E. N. Duesler, and H. Nöth, *J. Chem. Soc., Dalton Trans.*, 2003, 153.
- 2003JCD1419 H.-P. Chen, Y.-H. Liu, S.-M. Peng, and S.-T. Liu, *J. Chem. Soc., Dalton Trans.*, 2003, 1419.
- 2003JFC25 V. Y. Sosnovsikh and M. A. Barbatov, *J. Fluorine Chem.*, 2003, **120**, 25.
- 2003JME2631 Q.-L. Luo, J.-Y. Li, Z. Y. Li, L.-L. Chen, J. Li, Z. Qian, Q. Shen, Y. Li, G. H. Lushington, Q.-Z. Ye, *et al.*, *J. Med. Chem.*, 2003, **46**, 2631.
- 2003JOC2028 P. Gros and Y. Fort, *J. Org. Chem.*, 2003, **68**, 2028.
- 2003JOC2054 O. Sugimoto, S. Yamada, and K. Tanji, *J. Org. Chem.*, 2003, **68**, 2054.
- 2003JOC4918 P. Gros and Y. Fort, *J. Org. Chem.*, 2003, **68**, 4918.
- 2003JOC5123 K. Wada, T. Mizutani, and S. Kitagawa, *J. Org. Chem.*, 2003, **68**, 5123.
- 2003JOC7551 C. Wolf and R. Lerebours, *J. Org. Chem.*, 2003, **68**, 7551.
- 2003JOC7651 P. Quagliotto, G. Viscardi, C. Barolo, E. Barni, S. Bellinvia, E. Fiscaro, and C. Compari, *J. Org. Chem.*, 2003, **68**, 7651.
- 2003JOC9412 T. Tagata and M. Nishida, *J. Org. Chem.*, 2003, **68**, 9412.
- 2003JOM38 B. W. Skelton, V.-A. Tolhurst, A. H. White, A. M. Williams, and A. J. Wilson, *J. Organomet. Chem.*, 2003, **674**, 38.
- 2003M1571 M. Tajbakhsh, I. Mohammad-Baltork, and K. Alimohammadi, *Monatsh. Chem.*, 2003, **134**, 1571.
- 2003NPR476 J. P. Michael, *Nat. Prod. Rep.*, 2003, **20**, 476.
- 2003OBC644 R. Hovland, C. Glogard, A. J. Aasen, and J. Klaveness, *Org. Biomol. Chem.*, 2003, **1**, 644.
- 2003OBC2710 J. M. Bakke and I. Sletvold, *Org. Biomol. Chem.*, 2003, **1**, 2710.
- 2003OBC2865 S. A. Kelly, Y. Foricher, J. Mann, and J. Bentley, *Org. Biol. Chem.*, 2003, **1**, 2865.
- 2003OL753 S. Wiedmann, D. Frank, H. Winsel, and A. de Meijere, *Org. Lett.*, 2003, **5**, 753.
- 2003OL2251 Y.-Z. Hu, G. Zhang, and R. P. Thummel, *Org. Lett.*, 2003, **5**, 2251.
- 2003OL2397 R. Ziesel and C. Stroh, *Org. Lett.*, 2003, **5**, 2397.
- 2003OL2611 Y. Morimoto, S. Kitao, T. Okita, and T. Shoji, *Org. Lett.*, 2003, **5**, 2611.
- 2003OL2635 A. L. Braga, M. W. Paixao, D. S. Ludtke, C. S. Silveira, and O. E. D. Rodrigues, *Org. Lett.*, 2003, **5**, 2635.
- 2003OL2769 R. Pohl and P. Anzenbacher, Jr., *Org. Lett.*, 2003, **16**, 2769.
- 2003OL3131 W. Yang, Y. Wang, and J. R. Corte, *Org. Lett.*, 2003, **5**, 3131.
- 2003OL3867 S. Thomas, S. Roberts, L. Pasumansky, S. Gamsey, and B. Singaram, *Org. Lett.*, 2003, **5**, 3867.
- 2003OL3947 F. B. Panosyan and J. Chin, *Org. Lett.*, 2003, **5**, 3947.
- 2003OL4133 J. E. Arguello, L. C. Schmidt, and A. B. Peñéñory, *Org. Lett.*, 2003, **5**, 4133.

- 2003OL4987 K. Okano, H. Tokuyama, and T. Fukuyama, *Org. Lett.*, 2003, **5**, 4987.
2003PHC284 D. S. Coffey, S. P. Kolis, and S. A. May, *Prog. Heterocycl. Chem.*, 2003, **15**, 284.
2003S35 K. Wu and Q.-Y. Chen, *Synthesis*, 2003, 35.
2003S233 A. Staubitz, W. Dohle, and P. Knochel, *Synthesis*, 2003, 233.
2003S1643 J. A. Miller, J. W. Dankwardt, and J. M. Penney, *Synthesis*, 2003, 1643.
2003SC475 S. Goswami and A. K. Adak, *Synth. Commun.*, 2003, **33**, 475.
2003SC977 K. K. Bhasin, V. K. Jain, H. Kumar, S. Sharma, S. K. Mehta, and J. Singh, *Synth. Commun.*, 2003, **33**, 977.
2003SC1833 F. Shirini, M. M. Lakouraj, I. Mohammadpour-Baltork, and D. Asadi, *Synth. Commun.*, 2003, **33**, 1833.
2003SC3427 J. Y. Q. Lai, Y. Ferguson, and M. Jones, *Synth. Commun.*, 2003, **33**, 3427.
2003SC3503 A.-M. Faucher and C. Grand-Maitre, *Synth. Commun.*, 2003, **33**, 3503.
2003SC3805 K. Kloc, I. Maliszewska, and J. Młochowski, *Synth. Commun.*, 2003, **33**, 3805.
2003SC4185 B. W. Yoo, K. H. Choi, K. I. Choi, and J. H. Kim, *Synth. Commun.*, 2003, **33**, 4185.
2003SL852 Y.-Q. Fang and G. S. Hanan, *Synlett*, 2003, 852.
2003SL1678 A. Meana, J. F. Rodríguez, M. A. Sanz-Tejedor, and J. L. García-Ruano, *Synlett*, 2003, 1678.
2003SL2086 W. Chai, A. Kwok, V. Wong, N. I. Carruthers, and J. Wu, *Synlett*, 2003, 2086.
2003T3009 W. Zhang and G. Pugh, *Tetrahedron*, 2003, **59**, 3009.
2003T4873 K. Miyashita, H. Murafuji, H. Iwaki, E. Yoshioka, and T. Imanishi, *Tetrahedron*, 2003, **59**, 4873.
2003T8629 S. Demouchel, F. Mongin, F. Trecourt, and G. Quéguiner, *Tetrahedron*, 2003, **59**, 8629.
2003T10043 A. Bouillon, J.-C. Lancelot, J. S. O. Santos, V. Collot, P. R. Bovy, and S. Rault, *Tetrahedron*, 2003, **59**, 10043.
2003TL725 B. M. Mathes and S. A. Filla, *Tetrahedron Lett.*, 2003, **44**, 725.
2003TL2745 R. Mamouni, M. Aadil, M. Akssira, J. Lsri, and J. Sepulveda-Arues, *Tetrahedron Lett.*, 2003, **44**, 2745.
2003TL6265 S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib, and G. Guillaumet, *Tetrahedron Lett.*, 2003, **44**, 6265.
2003TL6629 B. Furman and M. Dziedzic, *Tetrahedron Lett.*, 2003, **44**, 6629.
2003TL8487 I. Kondolff, H. Doucet, and M. Santelli, *Tetrahedron Lett.*, 2003, **44**, 8487.
2003TL8501 A. Solladié-Cavallo, M. Roje, A. Baram, and V. Šunjić, *Tetrahedron Lett.*, 2003, **44**, 8501.
2004AGE4097 V. Trevisan, M. Signoretto, S. Colonna, V. Pironti, and G. Strukul, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 4097.
2004BML1795 J. Jiang, R. J. DeVita, M. T. Goulet, M. J. Wyvratt, J.-L. Lo, N. Ren, J. B. Yudkovitz, J. Cui, Y. T. Yang, K. Cheng, *et al.*, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1795.
2004BML2155 A. C. B. Sosa, D. H. Boschelli, F. Yei, J. M. Golas, and F. Boschelli, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2155.
2004CC508 S. A. Raw and R. J. K. Taylor, *Chem. Commun.*, 2004, 508.
2004CL916 S. Goswami, S. Dey, S. Jana, and A. K. Adak, *Chem. Lett.*, 2004, **33**, 916.
2004EJO835 R. Hulst, I. Muizebelt, P. Oosting, C. van der Pol, A. Wagenaar, J. Smisterovam, E. Bulten, C. Driessen, D. Hoekstram, and J. B. F. N. Engberts, *Eur. J. Org. Chem.*, 2004, 835.
2004EJO3477 S. J. Connon and A. F. Hegarty, *Eur. J. Org. Chem.*, 2004, 3477.
2004EJO1008 M. Marull and M. Schlosser, *Eur. J. Org. Chem.*, 2004, 1008.
2004EJO3011 M. K. Cieplik and R. Louw, *Eur. J. Org. Chem.*, 2004, 3011.
2004EJO4794 D. L. Lipilin, O. Y. Smirnov, A. M. Churakov, Y. A. Strelenko, A. Y. Tyurin, S. L. Ioffe, and V. A. Tartkovsky, *Eur. J. Org. Chem.*, 2004, 4794.
2004H(63)2735 Y. Yonezawa, A. Konn, and C. Shin, *Heterocycles*, 2004, **63**, 2735.
2004JA2 L. A. Estroff, C. D. Incarvito, and A. D. Hamilton, *J. Am. Chem. Soc.*, 2004, **126**, 2.
2004JA1024 S. Caddick, J. D. Wilden, and D. B. Judd, *J. Am. Chem. Soc.*, 2004, **126**, 1024.
2004JA2300 A. R. Dick, K. L. Hull, and M. S. Sandford, *J. Am. Chem. Soc.*, 2004, **126**, 2300.
2004JA9542 L. V. Desai, K. L. Hull, and M. S. Sandford, *J. Am. Chem. Soc.*, 2004, **126**, 9542.
2004JA10389 A. Orita, T. Nakano, D. L. An, K. Tanikawa, K. Wakamatsu, and J. Otera, *J. Am. Chem. Soc.*, 2004, **126**, 10389.
2004JA12232 D. B. Grotjahn and D. A. Lev, *J. Am. Chem. Soc.*, 2004, **126**, 12232.
2004JA13898 A. I. Siriwardana, K. K. A. D. S. Kathirarachchi, I. Nakamura, I. D. Gridnev, and Y. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 13898.
2004JA13904 Y. Nakao, S. Oda, and T. Hiyama, *J. Am. Chem. Soc.*, 2004, **126**, 13904.
2004JHC443 K. Sato, S. Okazaki, T. Yamagishi, and S. Arai, *J. Heterocycl. Chem.*, 2004, **41**, 443.
2004JMC1599 D. H. Boschelli, Y. D. Wang, S. Johnson, B. Wu, F. Ye, A. C. B. Sosa, J. M. Golas, and F. Boschelli, *J. Med. Chem.*, 2004, **47**, 1599.
2004JME6749 F. Julemont, X. de Leval, C. Michaux, J.-F. Renard, J.-Y. Winum, J.-L. Montero, J. Damas, J.-M. Dogné, and B. Pirotte, *J. Med. Chem.*, 2004, **47**, 6749.
2004JFC661 R. D. Chambers, D. Holling, G. Sandford, A. S. Batsanov, and J. A. K. Howard, *J. Fluorine Chem.*, 2004, **125**, 661.
2004JOC1581 S. Nakamura, Y. Ito, L. Wang, and T. Toru, *J. Org. Chem.*, 2004, **69**, 1581.
2004JOC1723 R. Pohl, V. A. Montes, J. Shinar, and P. Anzenbacher, Jr., *J. Org. Chem.*, 2004, **69**, 1723.
2004JOC1959 N. Yasua, Y. Hsiao, M. S. Jensen, N. R. Rivera, C. Yang, K. M. Wells, J. Yau, M. Palucki, L. Tan, P. G. Dormer, *et al.*, *J. Org. Chem.*, 2004, **69**, 1959.
2004JOC2551 J. Zienkiewicz, P. Kaszynski, and V. G. Young, Jr., *J. Org. Chem.*, 2004, **69**, 2551.
2004JOC2953 M. Akhtaruzzaman, M. Tomura, J. Nishida, and Y. Yamashita, *J. Org. Chem.*, 2004, **69**, 2953.
2004JOC6766 F. Mongin, A.-S. Rebstock, F. Trécourt, G. Quéguiner, and F. Marsais, *J. Org. Chem.*, 2004, **69**, 6766.
2004JOC7592 S. Strieff, N. Ribeiro, and L. Désaubry, *J. Org. Chem.*, 2004, **69**, 7592.
2004NPR650 J. P. Michael, *Nat. Prod. Rep.*, 2004, **21**, 650.
2004NPR752 X. Ma and D. R. Gang, *Nat. Prod. Rep.*, 2004, **21**, 752.
2004OBC2671 E. J. Andreassen, J. M. Bakke, I. Sletvold, and H. Svenson, *Org. Biomol. Chem.*, 2004, **2**, 2671.
2004OBC1825 C. Botuha, C. M. S. Galley, and T. Gallagher, *Org. Biomol. Chem.*, 2004, **2**, 1825.
2004OL1033 J. P. Collman, R. A. Decréau, and S. Costanzo, *Org. Lett.*, 2004, **6**, 1033.
2004OL2209 M. R. Tracey, Y. Zhang, M. O. Frederick, J. A. Mulder, and R. P. Hsung, *Org. Lett.*, 2004, **6**, 2209.
2004OL2433 P. J. Manley and M. T. Bilodeau, *Org. Lett.*, 2004, **6**, 2433.

- 2004OL2705 L. Alcaraz, C. Bennion, J. Morris, P. Meghani, and S. M. Thom, *Org. Lett.*, 2004, **6**, 2705.
2004OL4109 H. Han, I. Bae, E. J. Yoo, J. Lee, Y. Do, and S. Chang, *Org. Lett.*, 2004, **6**, 4109.
2004OL4125 A. Núñez, A. M. Cuadro, J. Alvarez-Builla, and J. J. Vaquero, *Org. Lett.*, 2004, **6**, 4125.
2004OL4253 Y. Takayama, T. Haazawa, T. Andou, K. Maraoka, H. Ohtani, M. Takahashi, and F. Sato, *Org. Lett.*, 2004, **6**, 4253.
2004OL4527 W. J. Sanders, X. Zhang, and R. Wagner, *Org. Lett.*, 2004, **6**, 4527.
2004OL4587 T. Itoh and T. Mase, *Org. Lett.*, 2004, **6**, 4587.
2004OL4905 J. J. Song, N. K. Yee, Z. Tan, J. Xu, S. R. Kapadia, and C. H. Senanayake, *Org. Lett.*, 2004, **6**, 4905.
2004OL4977 H. Sajiki, T. Ikawa, and K. Hirota, *Org. Lett.*, 2004, **6**, 4977.
2004PHC309 D. L. Comins, J. Dinsmore, and S. O'Connor, *Prog. Heterocycl. Chem.*, 2004, **16**, 309.
2004S2485 M. Pittelkow, F. S. Kamounah, U. Boas, B. Pederson, and J. B. Christensen, *Synthesis*, 2004, 2485.
2004SC297 M. Lloung, A. Loupy, S. Marque, and A. Petit, *Synth. Commun.*, 2004, **63**, 297.
2004SL2319 P. Pierrat, P. Gros, and Y. Fort, *Synlett*, 2004, 2319.
2004SL2827 F. Fache, *Synlett*, 2004, 2827.
2004T1093 M. J. Reyes, C. Burgos, M. L. Izquierdo, and J. Alvarez-Builla, *Tetrahedron*, 2004, **60**, 1093.
2004T10487 J. Casas, C. Nájera, J. M. Sansano, and J. M. Saá, *Tetrahedron*, 2004, **60**, 10487.
2004T11751 D. B. Gotchev and D. L. Comins, *Tetrahedron*, 2004, **60**, 11751.
2004TL2667 J. M. Penney, *Tetrahedron*, 2004, **45**, 2667.
2004TL3607 E. Brenner, R. M. Baldwin, and G. Tamagnan, *Tetrahedron Lett.*, **45**, 3607.
2004TL4257 C. S. Li and D. D. Dixon, *Tetrahedron Lett.*, 2004, **45**, 4257.
2004TL5233 M. Harmata, X. Hong, and S. K. Ghosh, *Tetrahedron Lett.*, 2004, **45**, 5233.
2004TL6029 K. Motokura, T. Mizugaki, K. Ebitani, and K. Kaneda, *Tetrahedron Lett.*, 2004, **45**, 6029.
2004TL6129 M. S. Raghavendra and Y. Lam, *Tetrahedron Lett.*, 2004, **45**, 6129.
2004TL6417 L. Pasumansky, A. R. Hernández, S. Gamsey, C. T. Goralski, and B. Singaram, *Tetrahedron Lett.*, 2004, **45**, 6417.
2004TL8797 J. L. Romera, J. M. Cid, and A. A. Trabanco, *Tetrahedron Lett.*, 2004, **45**, 8797.
2005AGE455 S. Ko, B. Kang, and S. Chang, *Angew. Chem., Int. Ed.*, 2005, **44**, 455.
2005AGE4442 K. C. Nicolaou, P. G. Bulger, and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442.
2005AGE3133 O. Baron and P. Knochel, *Angew. Chem., Int. Ed.*, 2005, **44**, 3133.
2005BML1721 C. Klumpp, A. Burger, G. L. Mislin, and M. A. Abdallah, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1721.
2005BML3296 T. Biftu, D. Feng, M. Ponpipom, N. Girotra, G.-B. Liang, X. Qian, R. Bugianesi, J. Simeone, L. Chang, A. Gurnett, *et al.*, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3296.
2005CEJ1903 C. Bobbio, T. Rausis, and M. Schlosser, *Chem. Eur. J.*, 2005, **11**, 1903.
2005JA4685 T. E. Barder, S. D. Walker, J. R. Martinelli, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685.
2005JA7330 D. Kalyani, N. R. Deprez, L. V. Desai, and M. S. Sandford, *J. Am. Chem. Soc.*, 2005, **127**, 7330.
2005JME1367 M. G. N. Russell, R. W. Carling, J. R. Atack, F. A. Bromidge, S. M. Cook, P. Hunt, C. Isted, M. Lucas, R. M. McKernan, A. Mitchinson, *et al.*, *J. Med. Chem.*, 2005, **48**, 1367.
2005JME1948 A. Benjahad, M. Croisy, C. Monneret, E. Bisagni, D. Mabire, S. Coupa, A. Poncelet, I. Csoka, J. Guillemont, C. Meyer, *et al.*, *J. Med. Chem.*, 2005, **48**, 1948.
2005JME2134 D. Mabire, S. Coupa, C. Adelinet, A. Poncelet, Y. Simonnet, M. Venet, R. Wouters, A. S. J. Lesage, L. Van Beijsterveldt, and F. Bischoff, *J. Med. Chem.*, 2005, **48**, 2134.
2005JME5104 Z. Guo, J. E. Tellew, R. S. Gross, B. Dyck, J. Grey, M. Haddach, M. Kiankarimi, M. Lanier, B. -F. Li, Z. Luo, J. R. McCarthy, *et al.*, *J. Med. Chem.*, 2005, **48**, 5104.
2005JME1721 Z.-L. Wei, Y. Xiao, H. Yuan, M. Baydyuk, P. A. Petukhov, J. L. Musachio, K. J. Kellar, and A. P. Kozikowski, *J. Med. Chem.*, 2005, **48**, 1721.
2005JOC373 P. R. Blakemore, C. Kilner, and S. D. Milicevic, *J. Org. Chem.*, 2005, **70**, 373.
2005JOC388 A. E. Thompson, G. Hughes, A. S. Batsanov, M. R. Bryce, P. R. Parry, and B. Tarbit, *J. Org. Chem.*, 2005, 388.
2005JOC1698 S. Inokuma, H. Ide, T. Yonekura, T. Funaki, S. Kondo, S. Shiobara, T. Yoshihara, S. Tobita, and J. Nishimura, *J. Org. Chem.*, 2005, **70**, 1698.
2005JOC1993 K. Hassall, S. Lobachevsky, and J. M. White, *J. Org. Chem.*, 2005, **70**, 1993.
2005JOC2445 I. Sapountzis, H. Dube, R. Lewis, N. Gommerman, and P. Knochel, *J. Org. Chem.*, 2005, **70**, 2445.
2005JOC3218 H.-R. Bjørsvik, C. Gambarotti, V. R. Jensen, and R. R. González, *J. Org. Chem.*, 2005, **70**, 3218.
2005JOC6204 R. J. Anderson, J. B. Hill, and J. C. Morris, *J. Org. Chem.*, 2005, **70**, 6204.
2005JOC7866 A. R. Katritzky, R. M. Witek, V. Rodriguez-Garcia, P. P. Mohapatra, J. W. Rogers, J. Cusido, A. A. A. Abdel-Fattah, and P. J. Steel, *J. Org. Chem.*, 2005, **70**, 7866.
2005JOC9191 A. R. Katritzky, A. A. A. Abdel-Fattah, A. V. Vakulenko, and H. Tao, *J. Org. Chem.*, 2005, **70**, 9191.
2005JOC10186 A. Klapars, J. H. Waldman, K. R. Campos, M. S. Jensen, M. McLaughlin, J. Y. L. Chung, R. J. Cvetovich, and C.-Y. Chen, *J. Org. Chem.*, 2005, **70**, 10186.
2005NPR627 J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 627.
2005OS98 W. D. Brown and A. H. Gouliaev, *Org. Synth.*, 2005, **81**, 98.
2005OL127 M. Schlosser, T. Rausis, and C. Bobbio, *Org. Lett.*, 2005, **7**, 127.
2005OL363 J. Le Notre, J. J. Firet, L. A. J. M. Leo, B. J. van Steen, G. van Koten, and R. M. K. Gebbink, *Org. Lett.*, 2005, **7**, 363.
2005OL577 S. D. Kuduk, R. M. DiPardo, and M. G. Bock, *Org. Lett.*, 2005, **7**, 577.
2005OL1469 S. J. Coats, J. S. Link, D. Gauthier, and D. J. Hlasta, *Org. Lett.*, 2005, **7**, 1469.
2005OL2519 T. K. Macklin and V. Snieckus, *Org. Lett.*, 2005, **7**, 2519.
2005OL3673 J. Clayden, S. D. Hamilton, and R. T. Mohammed, *Org. Lett.*, 2005, **7**, 3673.
2005OL4871 A. Gavryushin, C. Kofink, G. Manolikakes, and P. Knochel, *Org. Lett.*, 2005, **7**, 4871.
2005OL315 A. B. Smith, III, B. S. Freeze, M. J. LaMarche, T. Hirose, I. Brouard, M. Xian, K. F. Sundermann, S. J. Shaw, M. A. Burlingame, S. B. Horwitz, *et al.*, *Org. Lett.*, 2005, **7**, 315.
2005OL3657 D. Shabashov and O. Daugulis, *Org. Lett.*, 2005, **7**, 3657.
2005PHC261 H. L. Fraser, M. B. Floyd, and A. C. B. Sosa, *Prog. Heterocycl. Chem.*, 2005, **17**, 261.

- 2005S915 A. Abad, C. Agulló, A. C. Cuñat, and C. Vilanova, *Synthesis*, 2005, 915.
- 2005S2193 J.-H. Li, D.-P. Wang, and Y.-X. Xie, *Synthesis*, 2005, 2193.
- 2005S2571 N. Lachance, M. April, and M.-A. Joly, *Synthesis*, 2005, 2571.
- 2005SC223 K. Abiraj, G. R. Srinivasa, and D. C. Gowda, *Synth. Commun.*, 2005, **35**, 223.
- 2005SL87 I. P. Beletskaya, A. D. Averin, N. A. Pleshkova, A. A. Borisenko, M. V. Serebryakova, F. Denat, and R. Guillard, *Synlett*, 2005, 87.
- 2005SL529 A. P. Lightfoot, S. J. R. Twiddle, and A. Whiting, *Synlett*, 2005, 529.
- 2005SL1389 R. Sanz, J. Escribano, Y. Fernández, R. Aguado, M. R. Pedrosa, and F. J. Arnáiz, *Synlett*, 2005, 1389.
- 2005SL2080 T. Lomberget, S. Radix, and R. Barret, *Synlett*, 2005, 2080.
- 2005SOS11 D. Spitzner; in 'Science of Synthesis', D. StC. Black, Ed.; Georg Thieme Verlag, Stuttgart, 2005, vol.15, p. 11.
- 2005SOS389 R. D. Larsen; in 'Science of Synthesis', D. StC. Black, Ed.; Georg Thieme Verlag, Stuttgart, 2005, vol.15, p. 389.
- 2005T195 N. Misawa, R. Nakamura, Y. Kagiya, H. Ikenaga, K. Furukawa, and K. Shindo, *Tetrahedron*, 2005, **61**, 195.
- 2005T717 L. Ondi, J.-N. Volle, and M. Schlosser, *Tetrahedron*, 2005, **61**, 717.
- 2005T1127 S. P. Romeril, V. Lee, J. E. Baldwin, and T. D. W. Claridge, *Tetrahedron*, 2005, **61**, 1127.
- 2005T1417 A. S. Voisin, A. Bouillon, J.-C. Lancelot, and S. Rault, *Tetrahedron*, 2005, **61**, 1417.
- 2005T2245 S. Schröter, C. Stock, and T. Bach, *Tetrahedron*, 2005, **61**, 2245.
- 2005T5131 A. E. Thompson, A. S. Batsanov, M. R. Bryce, N. Saygili, P. R. Parry, and B. Tarbit, *Tetrahedron*, 2005, **61**, 5131.
- 2005T5475 V. Patroniak, M. Kubicki, S. Maciej, A. R. Stefankiewicz, and A. M. Grochowska, *Tetrahedron*, 2005, **61**, 5475.
- 2005T5822 B. Gao, Z. Fu, Z. Yu, L. Yu, Y. Hunag, and X. Feng, *Tetrahedron*, 2005, **61**, 5822.
- 2005T6315 K. Bravo-Altamirano, Z. Huang, and J.-L. Montchamp, *Tetrahedron*, 2005, **61**, 6315.
- 2005T10536 S. Cunha, M. T. Rodrigues, C. C. da Silva, H. B. Napolitano, I. Vencato, and C. Lariucci, *Tetrahedron*, 2005, **61**, 10536.
- 2005T10908 S. Nana, Y. Kato, and Y. Asano, *Tetrahedron*, 2005, **61**, 10908.
- 2005T11771 F. Alonso, I. P. Beletskaya, and M. Yus, *Tetrahedron*, 2005, **61**, 11771.
- 2005TL581 J.-C. Fernández, L. Solé-Feu, D. Fernandez-Forner, N. de la Figuera, P. Forns, and F. Albericio, *Tetrahedron Lett.*, 2005, **46**, 581.
- 2005TL1791 V. N. Kozhevnikov, D. N. Kozhevnikov, O. V. Shabunina, V. L. Rusinov, and O. N. Chupakhin, *Tetrahedron Lett.*, 2005, **46**, 1791.
- 2005TL2201 F. Zouhiri, M. Danet, C. Bénard, M. Normand-Bayle, J.-F. Mouscadet, H. Leh, C. M. Thomas, G. Mbemba, J. d'Angelo, and D. Desmaële, *Tetrahedron Lett.*, 2005, **46**, 2201.
- 2005TL2279 A. S. Kiselyov, *Tetrahedron Lett.*, 2005, **46**, 2279.
- 2005TL4295 J. G. Sośnicki, *Tetrahedron Lett.*, 2005, **46**, 4295.
- 2005TL4487 A. S. Kiselyov, *Tetrahedron Lett.*, 2005, **46**, 4487.
- 2005TL4621 J.-N. Heo, Y. S. Song, and B. T. Kim, *Tetrahedron Lett.*, 2005, **46**, 4621.
- 2006JOC167 R. Zong, D. Wang, R. Hammitt, and R. P. Thummel, *J. Org. Chem.*, 2006, **71**, 167.
- 2006JOC566 D. Martineau, M. Beley, and P. C. Gros, *J. Org. Chem.*, 2006, **71**, 566.
- 2006JOC1080 S. W. Wright and K. N. Hallstrom, *J. Org. Chem.*, 2006, **71**, 1080.
- 2006JOC1254 J. Mendoia, I. Castellote, J. Alvarez-Builla, J. Fernandez-Gadea, A. Gomez, and J. J. Vaquero, *J. Org. Chem.*, 2006, **71**, 1254.
- 2006SL395 A. Saini, S. Kumar, and J. S. Sandhu, *Synlett*, 2006, 395.
- 2006TL125 B. W. Yoo, J. W. Choi, and C. M. Yoon, *Tetrahedron Lett.*, 2006, **47**, 125.
- 2006TL553 J. Ward and V. Caprio, *Tetrahedron Lett.*, 2006, **47**, 553.
- 2006TL1877 S. Kii, A. Akao, T. Iida, T. Mase, and N. Yasuda, *Tetrahedron Lett.*, 2006, **47**, 1877.
- 2007OL643 R. A. Altman and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 643.
- 2007OL891 A. C. Spivey, I. Shukla, and J. F. Hayler, *Org. Lett.*, 2007, **9**, 891.

Biographical Sketch



Vittorio Caprio was born in Welshpool, Powys, UK, studied at Reading University, where he obtained a B.Sc in 1994, and received his Ph.D. in 1998 under the direction of Prof. J. Mann. He then spent 2 years as a postdoctoral fellow in the laboratories of Margaret Brimble at the University of Auckland, New Zealand. Vittorio was appointed as a lecturer in organic and medicinal chemistry at the University of Auckland in 2001 and a senior lecturer in 2006. His research interests center on the design of novel synthetic routes to bioactive alkaloids.

7.04

Pyridines and their Benzo Derivatives: Reactivity of Reduced Compounds

D. Barker

The University of Auckland, Auckland, New Zealand

© 2008 Elsevier Ltd. All rights reserved.

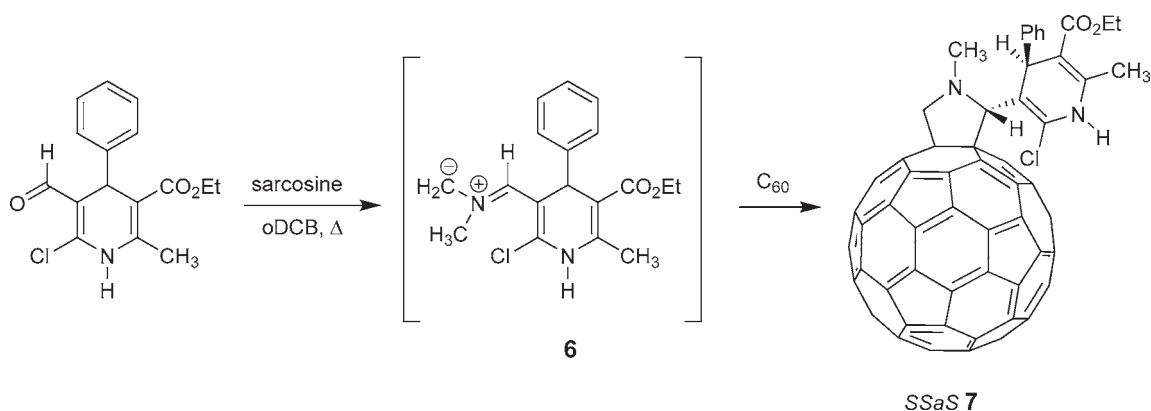
7.04.1	Introduction	171
7.04.1.1	Theoretical Methods	171
7.04.1.2	Experimental Structural Methods and Thermodynamic Aspects	172
7.04.2	Reactivity of Dihydropyridines	175
7.04.2.1	2,3-Dihydropyridines and their Iminium Salts	175
7.04.2.2	2,5-Dihydropyridines	177
7.04.2.3	3,4-Dihydropyridines and their Iminium Salts	178
7.04.2.4	1,2-Dihydropyridines	179
7.04.2.5	1,4-Dihydropyridines	188
7.04.3	Reactivity of Tetrahydropyridines	194
7.04.3.1	2,3,4,5-Tetrahydropyridines and their Iminium Salts	194
7.04.3.2	1,2,3,4-Tetrahydropyridines	199
7.04.3.3	1,2,3,6-Tetrahydropyridines	205
7.04.4	Reactivity of Piperidines	207
7.04.4.1	Piperidines	208
7.04.5	Important Compounds and Applications	210
7.04.6	Further Developments	211
	References	212

7.04.1 Introduction

Reduced pyridines, namely tetrahydropyridines, dihydropyridines, and piperidines, are found in numerous natural and synthetic compounds. Interest in investigating the synthesis and reactivity of these compounds has often been driven by the fact that many of these compounds have interesting and unique pharmacological properties. This chapter highlights recent advances in the synthetic manipulations of reduced pyridines and where relevant highlights the development of asymmetric methods upon these compounds.

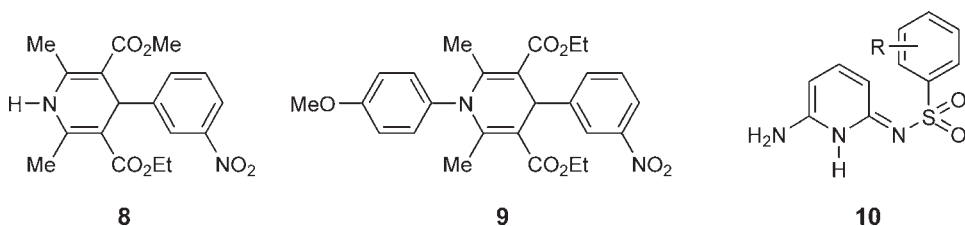
7.04.1.1 Theoretical Methods

Numerous theoretical investigations on the formation, structure, and reactivity of reduced pyridines have been reported since 1995. The ring expansion of *N*-methylene pyrrole, 2-methylene pyrrole, and 3-methylene pyrrole radicals to dihydropyridines was studied using *ab initio* methods (B3LYP) <2000PCA530>. Investigations showed that the expansion of *N*-methylene pyrrole radical was the fastest and gave 1,2-dihydropyridine while the other two isomers gave 1,4-dihydropyridine. Using the same molecular methods, the thermal rearrangement of 4-aza-1,2-hexadiene-5-yne was studied. It was discovered that the formation of 3-methylpyrrole was more favorable than the expected 1,4-dihydropyridine <2003OL4871>. An *ab initio* study into the Diels–Alder reaction of ethene and nitrogen-containing aromatic heterocycles found that during the reaction between ethylene and 1,2,3-triazine, 2,3-dihydropyridine would be produced along with the elimination of nitrogen gas <2005JST195>. A study using density functional calculations (B3LYP) showed that the [4+2] cycloaddition reaction of 2-aza-1,3-butadiene cation **1** and



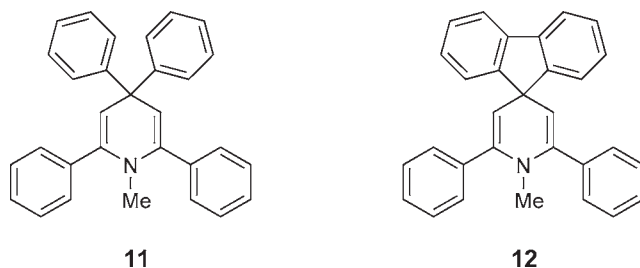
Scheme 2

10 determined that while many different stacking arrangements were formed only the unsubstituted ($R=H$) or 4-methyl ($R=4\text{-Me}$) aryl derivatives were polymorphic [\[2004CGD701\]](#). Raman spectroscopy has also been used to study polymorphism in 1,4-dihydropyridines and determined humidity to be an important factor in the crystallization of these compounds [\[2004JRS353, 2005MI2\]](#).



Piperidine was found to form a stable complex with carbon dioxide and water and this was examined by X-ray diffraction [\[2003JST177\]](#). It was determined that the complex was formed only in the gas phase, with piperidine vapor complexing with CO_2 and water in air and that silver ions were not required for formation as previously noted in the crystallization of 4-methylpiperidine.

Numerous NMR studies have been reported on the structure of 1,4-dihydropyridines used for the treatment of hypertension [\[2000MRC680, 2001MRC406, 2005JBS112\]](#). These studies show that many compounds, whose structures had previously been assigned by comparison with similar 1,4-dihydropyridines, had often been incorrectly characterized and that small structural changes in these classes of chemicals can lead to compounds having widely different physical properties and spectroscopic data. A good example of this is the spectroscopic study of the two photoactive compounds, 1-methyl-2,4,4,6-tetraphenyl-1,4-dihydropyridine **11** and 4,4-(biphenyl-2,2'-diyl)-2,6-diphenyl-1-methyl-1,4-dihydropyridine **12** [\[2002PJC235\]](#). The study concluded that two isomers of **12** existed in both solution and the solid state while these features were not exhibited in **11** and this was attributed to the one extra C–C bond between the two phenyl rings giving **12** enhanced rigidity.



NMR and ultraviolet (UV) methods have been used to study the interesting adducts formed between the antituberculous drug isoniazid and cofactor NAD (nicotinamide adenine dinucleotide) [\[2005OBC670\]](#). Studies

showed that the bathochromic effects observed in the ultraviolet–visible (UV–Vis) spectrum of the dehydrated adduct **13** were due to the highly conjugated species having two mesomeric forms (Figure 1). The conformational equilibrium and nitrogen inversion barriers have been determined for numerous *N*-chloro- and *N*-bromopiperidines using ^{13}C NMR spectroscopy <2002HCO391>.

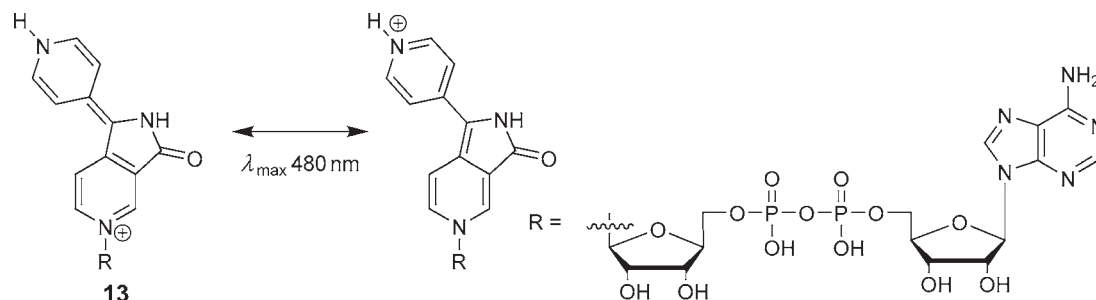
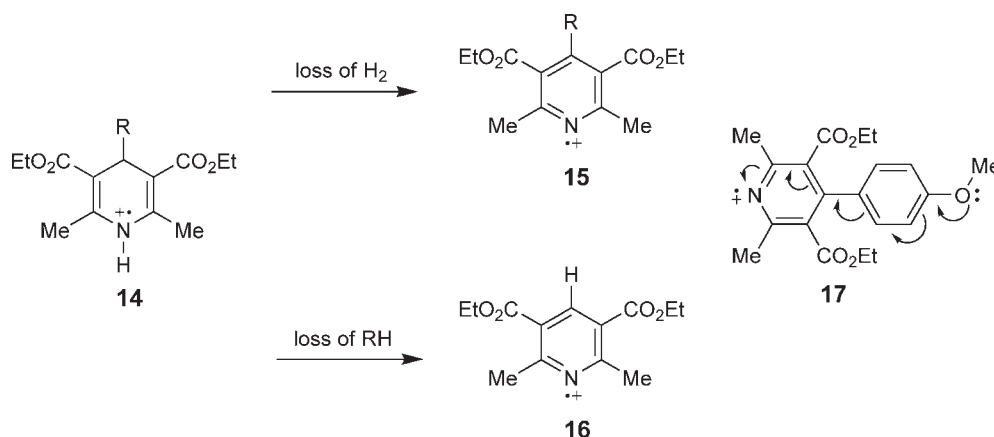


Figure 1

UV methods have been used to study the inclusion complexes formed between 1,4-dihydropyridine calcium antagonists such as nitrendipine **8** and β -cyclodextrins <2003MI1>. The study showed that one molecule of β -cyclodextrin encapsulated the aromatic substituent and the solubility of the drug was greatly enhanced. A study on the fragmentation during mass spectrometry (MS) of 1,4-dihydropyridines determined that two main pathways of fragmentation of the molecular ion **14** exist (Scheme 3). The first involves 1,4-elimination of H_2 to give pyridine **15** while the other involves 1,4-elimination of RH to give pyridine **16**. The elimination of H_2 is favored when the pyridine **15** is stabilized by resonance, for example, when $\text{R} = 4$ -methoxyphenyl as in compound **17** <2004RCM590>.



Scheme 3

A photochemical investigation of 4-substituted-1,4-dihydropyridines has shown that exposure to UV light induced photooxidation with 1,4-elimination of H_2 or R-H . It was determined that the light sensitivity of solid samples of 1,4-dihydropyridines was far less than that for samples in solution <2005BML3423>. Most solid samples showed only trace oxidation after 50 h continuous exposure while, on average, in solution 100% oxidation took 10–15 h.

A thermodynamic and kinetic investigation into the hydride transfer of 1,4- and 1,2-dihydropyridines, mimicking NADH/NAD^+ has been reported <2003CEJ3937>. The study determined that the oxidation potential of 1,2-dihydropyridines **18** was generally lower than that of 1,4-dihydropyridines **19** and the $\text{C}_4\text{-H}$ dissociation energy was higher than the $\text{C}_2\text{-H}$ energy, seemingly indicating that H-2 is the more likely hydride source. However, when **18** and **19** were treated with hydride substrate **20** to form pyridinium **21**, it was found that activation energy of the reaction with 1,2-dihydropyridines **18** was far higher than with the 1,4-isomer **19** (Figure 2). Also, in the reverse reaction, the addition of hydride to the 2-position of pyridinium **21** is far less favored than at the 4-position.

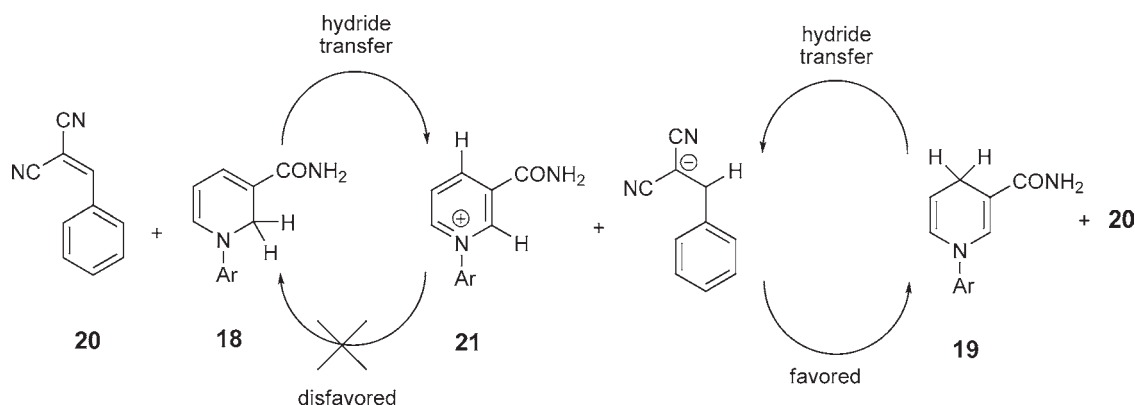


Figure 2

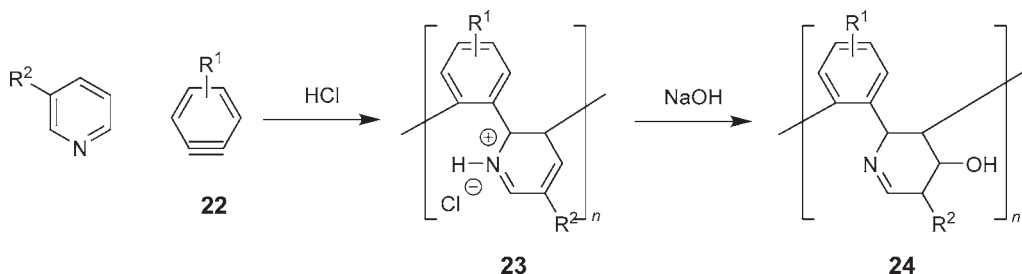
7.04.2 Reactivity of Dihydropyridines

By far the most widely studied area of dihydropyridine chemistry since 1995 has been that dealing with 1,4-dihydropyridines, generally due to this class containing numerous biologically active compounds and the similarity of these compounds to the biological NAD(P)/NAD(P)H system. A review published in 1997 highlights the use of 1,4-dihydropyridines in synthesis, especially in their utility as reducing agents <1997MI1>.

Of the other isomers, the more stable 1,2-dihydropyridines are the most studied. The latest general review of the chemistry of dihydropyridines was published in 2002 <2002J(P1)1141> while a review published in 2004 focused on the redox chemistry of dihydropyridines <2004COR715>.

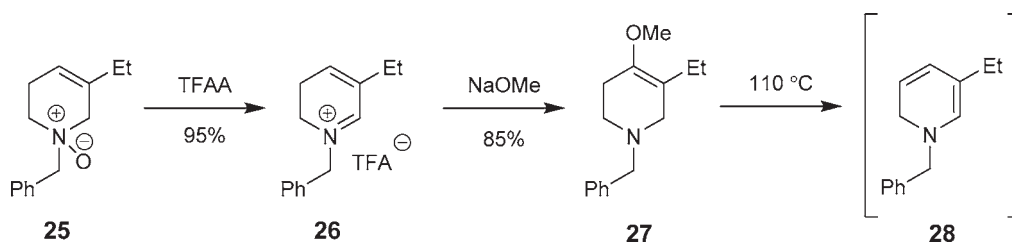
7.04.2.1 2,3-Dihydropyridines and their Iminium Salts

In general, 2,3-dihydropyridines are highly unstable compounds susceptible to 1,2- or 1,4-addition. Very few stable 2,3-dihydropyridines have been reported, one exception being 2-thiosubstituted derivatives which can be prepared from lithiated allenes and isothiocyanates <2004TL5881, 2004S735, 1997TL6905>. Another stable 2,3-dihydropyridine, albeit as the iminium salt, is formed from the copolymerization of pyridine and substituted benzynes **22** (Scheme 4). Treatment of the polymer **23** with aqueous sodium hydroxide resulted in neutralization of the iminium salt and 1,4-addition of hydroxide ion to give 4-hydroxy-1,2,3,4-tetrahydropyridine copolymers **24** <2005MM2167>.



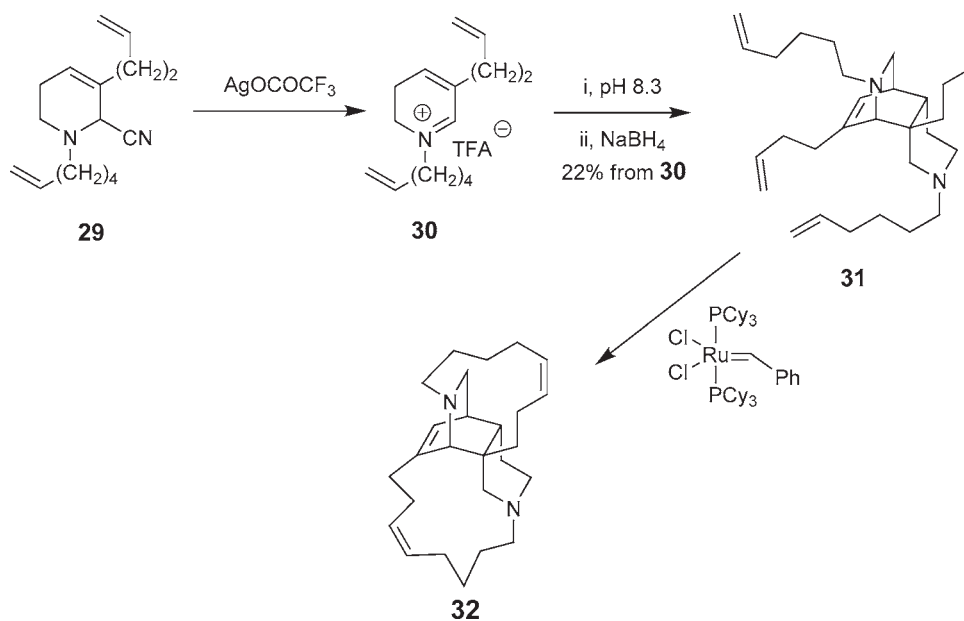
Scheme 4

The iminium salts of 2,3-dihydropyridines are far more stable than the free bases and have been used extensively in the synthesis of alkaloids. *N*-Benzyl iminium salt **26**, formed from the Polonovski–Potier reaction of *N*-oxide **25**, was transformed into enol ether **27**, which is a synthon for the unstable *N*-benzyl-1,2-dihydropyridine **28** (Scheme 5) <2004LOC168>. The same transformation on a similar iminium salt has been used in the formation of macrocyclic marine alkaloids <1995TL2059>. Carbon nucleophiles, such as the silylenol ethers of esters, have been shown to undergo 1,2-addition rather than 1,4-addition to 2,3-dihydropyridinium salts <1999T14995>.



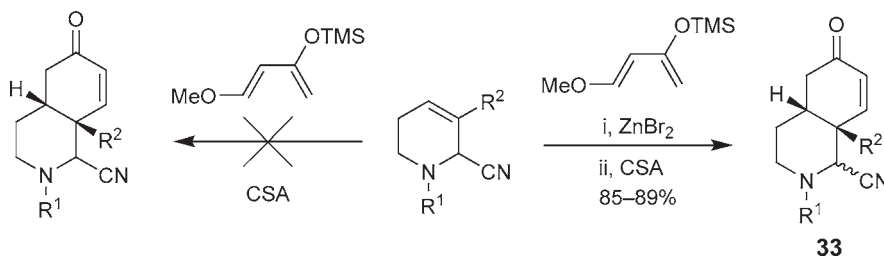
Scheme 5

Of even greater stability, and therefore greater synthetic utility, are the α -aminonitriles, which are formed by trapping the 2,3-dihydropyridinium salt with cyanide ion. These α -aminonitriles are easily converted back to the more reactive 2,3-dihydropyridinium salts with Lewis acids. 2,3-Dihydropyridinium salt **30** formed from the α -aminonitrile **29** undergoes a Diels–Alder reaction with another molecule of **30** to give the tricyclic product **31**, which then undergoes double ring-closing metathesis to form the natural product keramaphidin **32** (Scheme 6) <1999CEJ3154, 1997T2271>.



Scheme 6

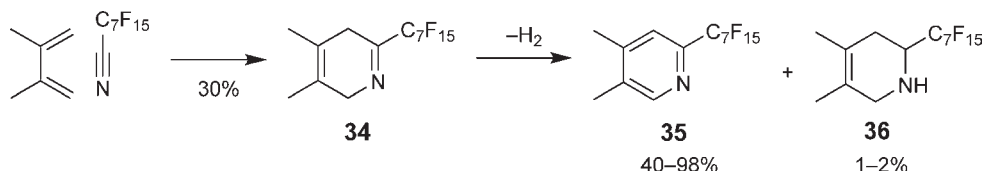
The Diels–Alder reactions of α -aminonitriles with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene in the presence of a Lewis acid gave, after acidic hydrolysis, cyanohydroisoquinolines **33** <1998TL5417>. When no Lewis acid was used, the reaction did not proceed apparently showing that the 2,3-dihydropyridinium salt is the active species and that cyanide ion is reintroduced after the Diels–Alder reaction (Scheme 7).



Scheme 7

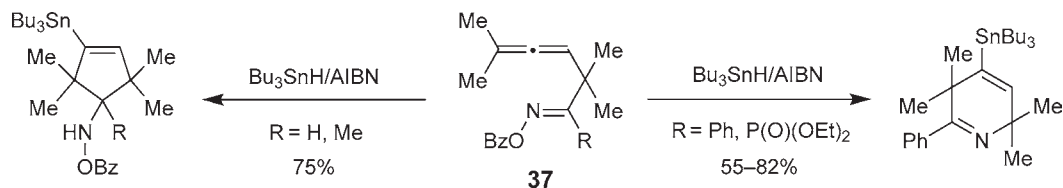
7.04.2.2 2,5-Dihydropyridines

2,5-Dihydropyridines are highly unstable, quickly isomerizing to the more stable 1,2-dihydropyridines. 3,4-Dimethyl-6-perfluoroheptyl-2,5-dihydropyridine **34** has been formed from the Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene with perfluorooctanitrile (Scheme 8) <1998T11027>. The 2,5-dihydropyridine **34** was found to be transiently stable; in the solid state, loss of H₂ to form pyridine **35** was 98% complete in 23 h at 50 °C, whereas in solution only 40% of **35** is produced after 2 weeks. It was noticed that in solution some of the hydrogen extruded from **34** hydrogenates other molecules of **34** to form tetrahydropyridine **36**, though the hydrogen transfer was not found to be stoichiometric.



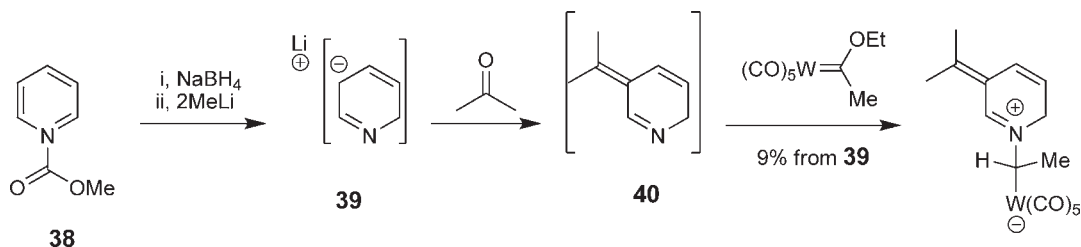
Scheme 8

Stable 2,5-dihydropyridines have also been formed from the tin-mediated radical cyclization of β -allenylbenzoxyloximes **37** but only when the oxime substituent was electron withdrawing (R = Ph or P(O)(OEt)₂). When the substituent is not electron withdrawing (e.g., R = H, Me) the 5-*exo*-cyclization occurs to form cyclopentenones (Scheme 9) <2000EJO275>. The cyclization has also been reported utilizing the tosyl radical as a substitute for the tributyltin radical <1999TL4547>.



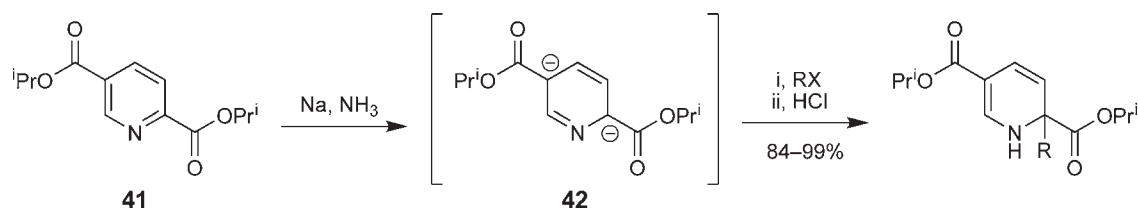
Scheme 9

5-Lithio-2,5-dihydropyridine **39**, formed from pyridinium chloroformate **38**, reacts with acetone to form 5-isopropylidene-2,5-dihydropyridine **40**, which can be trapped with alkoxycarbene complexes of tungsten to form stable complexes (Scheme 10) <1996JA12045, 1998OM361, 1998JOM119>.



Scheme 10

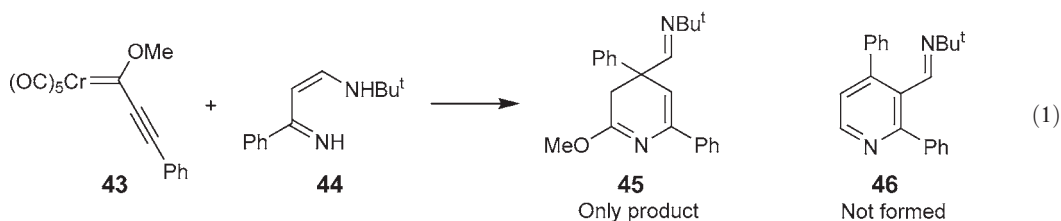
2,5-Dihydropyridine dianion **42**, generated from the Birch reduction of pyridine **41**, was found to undergo alkylation only at the 2-position with no 5-substituted products being isolated (Scheme 11) <2001J(P1)1435, 2000OL3861>.



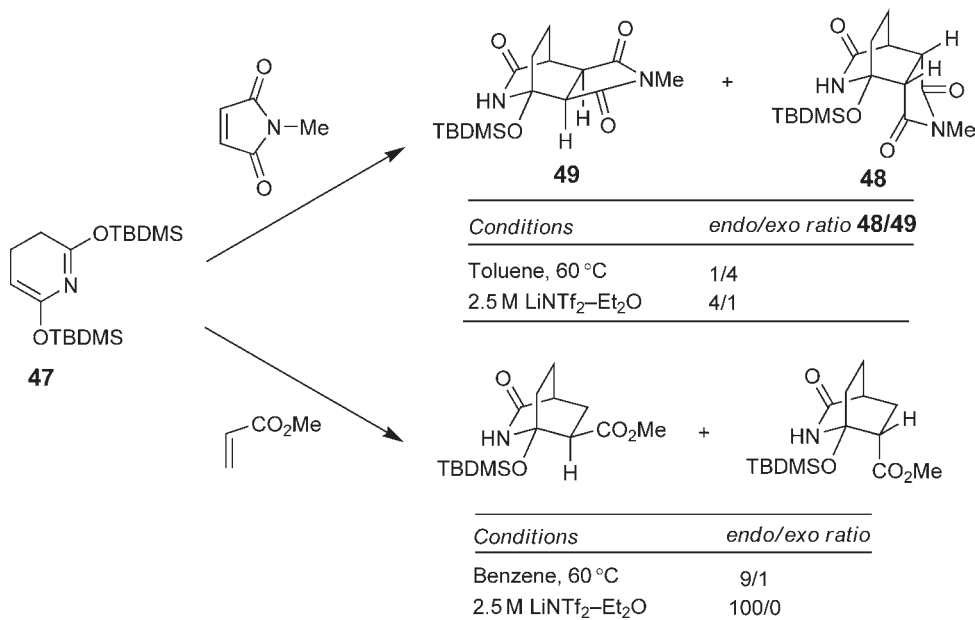
Scheme 11

7.04.2.3 3,4-Dihydropyridines and their Iminium Salts

3,4-Dihydropyridines are inherently unstable and rapidly isomerize to other dihydropyridine isomers; many also rapidly eliminate H_2 to form pyridines. The exceptions are 3,4-dihydropyridines substituted at the 2- and 5-positions with electron-donating groups. However, even stable 3,4-dihydropyridines can be oxidized to the corresponding pyridine by the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [\(<1995T7161>\)](#). An example of the stability of these substituted 3,4-dihydropyridines is in the unexpected formation of 2-methoxy-3,4-dihydropyridine **45** rather than the expected pyridine **46** from the [3+3] cyclization of 4-amino-1-azabutadiene **44** with Fischer alkynylcarbene complex **43** (Equation 1) [\(<2001NJC8>\)](#). The 2-methoxy group was proposed to stabilize an intermediate and result in elimination of the metal without aromatization.



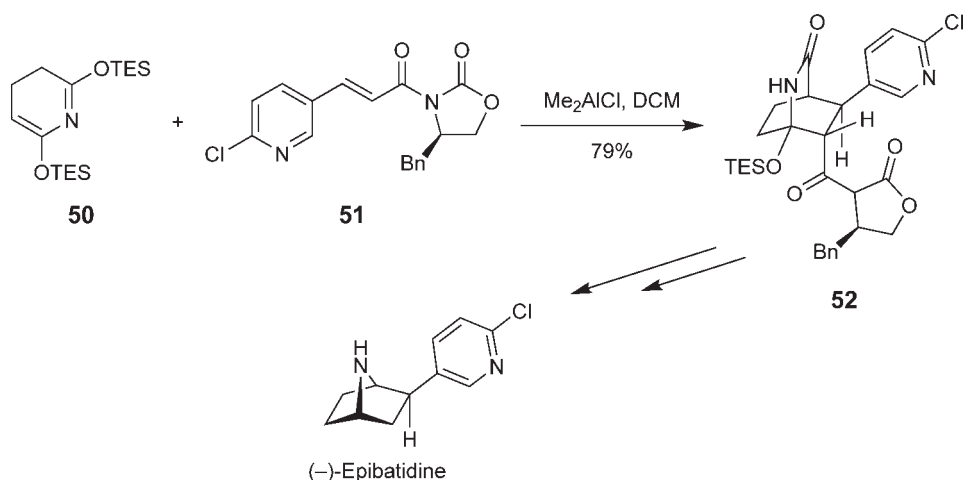
2,6-Bis-silyloxy-3,4-dihydropyridines are stable dienes easily synthesized from glutarimide. The Diels–Alder reaction of azadiene **47** with *N*-methylmaleimide in benzene at 60°C gives predominantly the *endo*-adduct **48**, whereas the selectivity is reversed in reaction with lithium trifluoromethanesulfonimide in ether giving predominantly the *exo*-adduct **49** (Scheme 12) [\(<1995SL565>\)](#). When methyl acrylate is used as the dienophile, the reaction



Scheme 12

under either set of conditions is *exo*-selective; however, use of lithium trifluoromethanesulfonimide in ether as the solvent increased the *exo/endo*-selectivity by a factor of 10.

A similar 2,6-bis-silyloxy-3,4-dihydropyridine **50** has been reported to undergo a Diels–Alder reaction with chiral dienophile **51** (Scheme 13) <2001OL3009>. The benzyl group on the oxazolidinone ring of **51** ensures complete facial selectivity, while interaction of the silyloxy groups on the diene **50** with the methyl groups on the chelating Lewis acid disfavors the *endo*-product and leads to a 20:1 diastereoselectivity for the *exo*-adduct **52** (Figure 3), which was eventually converted to the alkaloid (–)-epibatidine.



Scheme 13

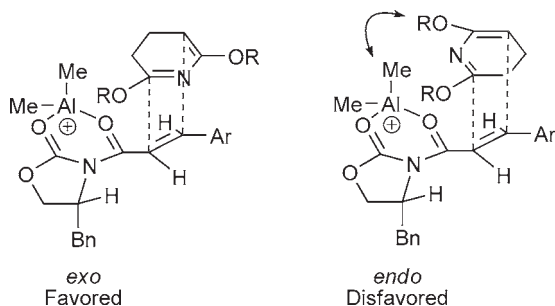
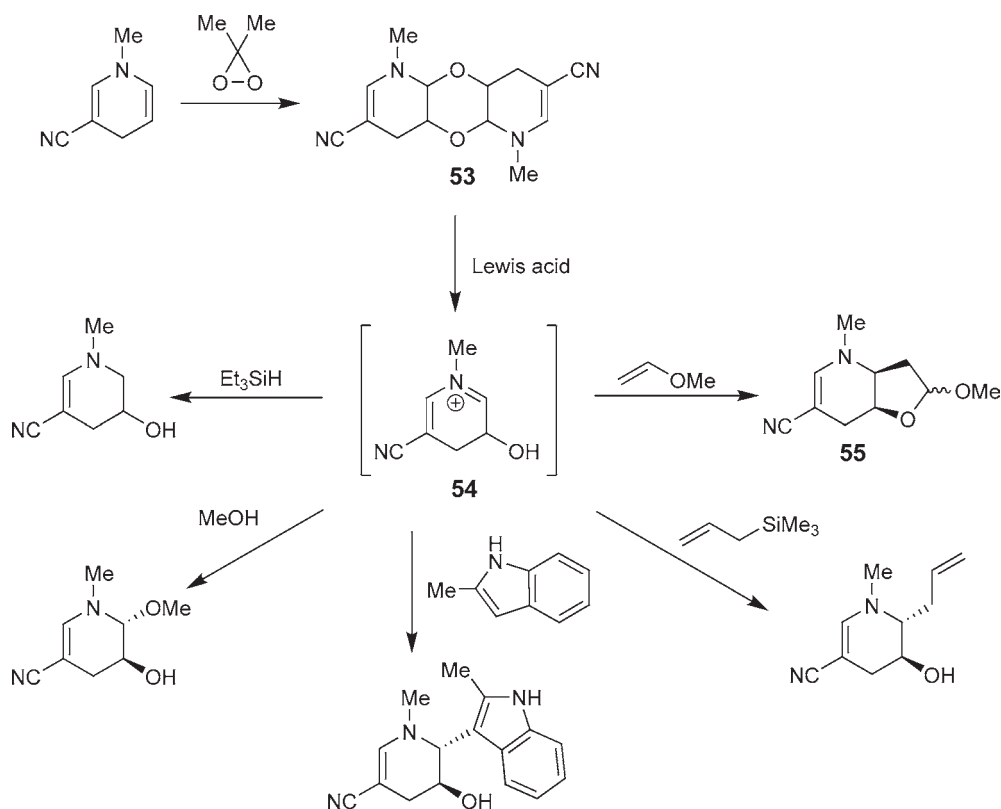


Figure 3

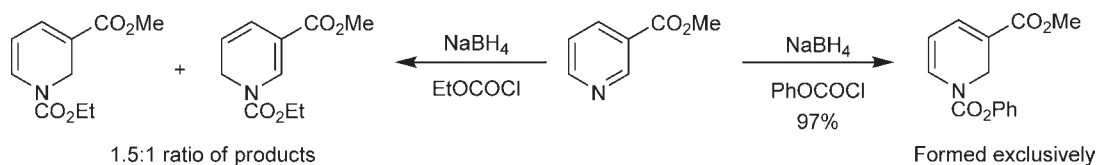
Dioxane **53**, synthesized by the treatment of a 1,4-dihydropyridine with dimethyldioxirane, can be considered a stable synthon of the 3,4-dihydropyridinium salt **54**. Addition of a Lewis acid caused the double fragmentation of the dioxane ring to form two molecules of the salt **54**, which readily undergoes nucleophilic attack at the 2-position (Scheme 14) <1997CC213>. In general, a 3:1 ratio of *trans*- over the *cis*-product is formed except in the case of the addition of vinyl enol ethers where only the *cis*-tetrahydrofuran product **55** is formed. This suggests that the initial addition of the enol ether generates a stable carbocation, of which only the *cis*-arrangement can undergo the intramolecular cyclization to form the tetrahydrofuran, and the *trans*-intermediate must equilibrate to the *cis* before cyclization can occur.

7.04.2.4 1,2-Dihydropyridines

1,2-Dihydropyridines are far more stable than the previously mentioned dihydropyridine isomers and have been used in numerous synthetic transformations. In particular, *N*-alkoxycarbonyl-1,2-dihydropyridines, which can be obtained from the Fowler reduction of pyridines, are widely used. The use of phenyl chloroformate rather than ethyl or benzyl chloroformate in the Fowler reduction of 3-substituted pyridines, where the substituent is an electron-withdrawing group, was found to increase the yield and selectivity of the 3-substituted-1,2-dihydropyridine (Scheme 15) <2001OL201>.

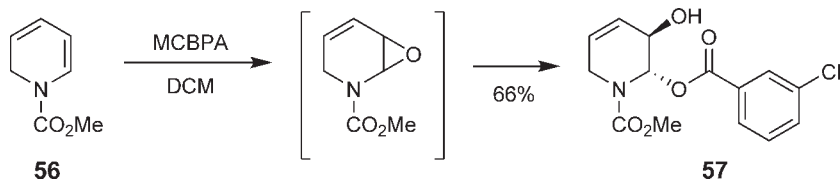


Scheme 14



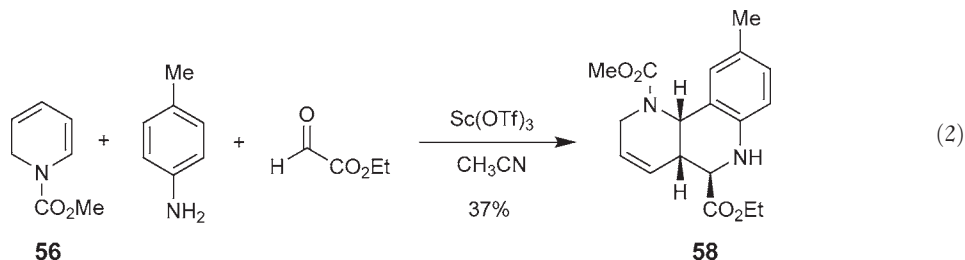
Scheme 15

The oxidation of *N*-methoxycarbonyl-1,2-dihydropyridine **56** with *meta*-chloroperbenzoic acid results in *trans*-dioxygenation of the 5,6-alkene to give the allylic alcohol **57** [\[1998JOC10001\]](#) (Scheme 16). The reaction is thought to proceed via an unstable aminoepoxide which is regio- and stereoselectively trapped by *m*-chlorobenzoic acid.

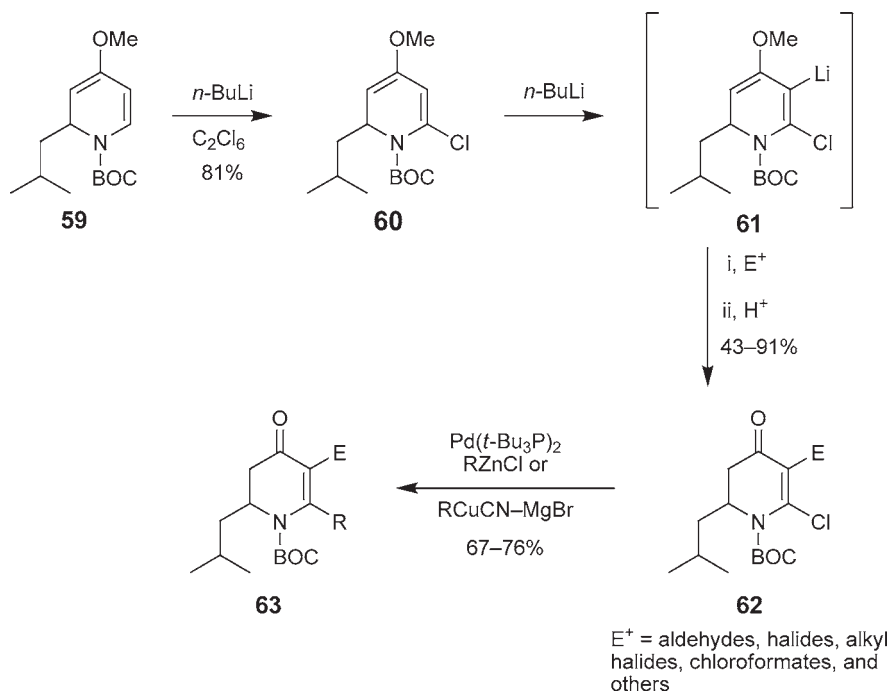


Scheme 16

Dihydropyridines such as **56** have recently been reported to undergo Lewis acid-catalyzed multicomponent reactions with anilines and aldehydes to form pyrido-fused tetrahydroquinolines **58** (Equation 2) <2005JCO33>. A wide variety of dihydropyridines, aldehydes, and anilines are tolerated, and the reaction proceeds well on numerous solid supports allowing the reaction to be performed combinatorially.

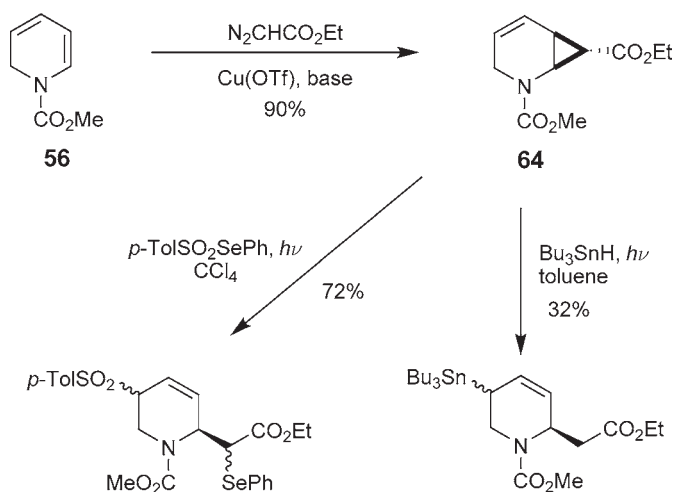


Directed lithiation of *N*-BOC-2-isobutyl-4-methoxy-1,2-dihydropyridine **59** followed by the addition of hexachloroethane gives 6-chloro-1,2-dihydropyridine **60** <2005OL5661>. Directed *ortho*-metalation of **60** by *n*-butyllithium results in lithiate **61**, which undergoes addition to numerous electrophiles and, following acidic hydrolysis, results in the formation of 5-substituted-6-chloro-4-piperidones **62**. These chloropiperidones **62** can undergo Negishi or Stille couplings and also react with cyanocuprates, with concomitant loss of HCl, to give 5,6-disubstituted piperidones **63** (Scheme 17). Lithiation at the 6-position and reaction with alkyl halides has also been reported for numerous 2-substituted-*N*-BOC-1,2-dihydropyridines to give 2,6-disubstituted-1,2-dihydropyridines <2000TL7779>.



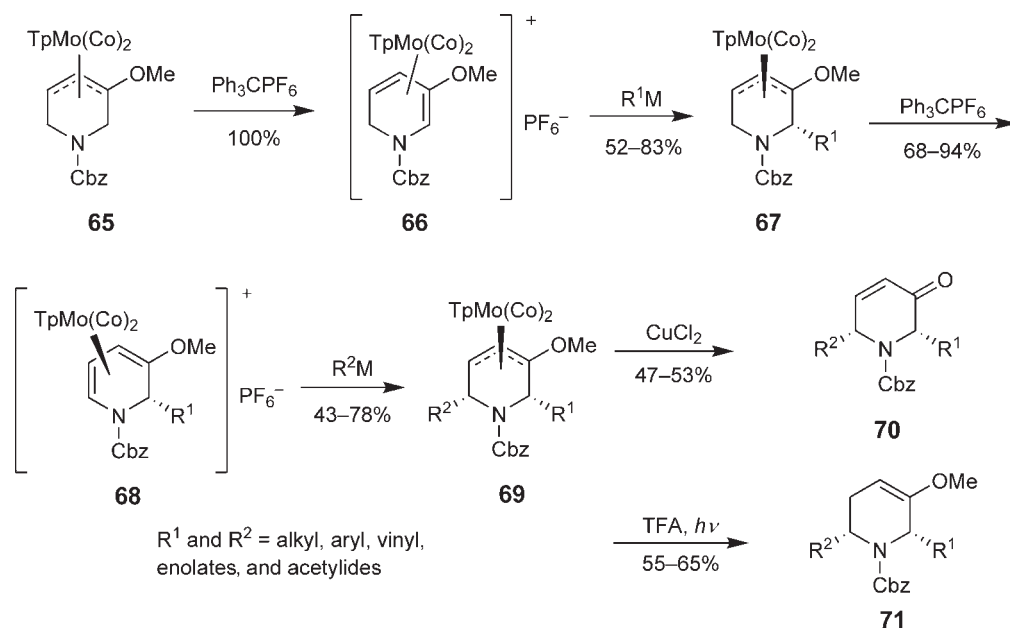
Scheme 17

Hydrogenation of 2,4-disubstituted-1,2-dihydropyridines has been shown to give *cis*-2,4-disubstituted piperidines when the C-4 substituent is bulky. When the group at C-4 is a methyl group, however, mixtures of *cis*- and *trans*-piperidine products are formed <1998SL1337>. Cyclopropanation of 1,2-dihydropyridines, such as **56**, with ethyl diazoacetate occurs only at the electron-rich alkene to give a single cyclopropane diastereomer **64**, which can undergo radical-induced ring opening with either tributyltinhydride or *p*-TolSO₂SePh to give 3,6-disubstituted-1,2,3,6-tetrahydropyridines (Scheme 18) <2003T8543>. The addition is not stereoselective and results in formation of a 1:1 mixture of diastereomers. The use of thiophenol, a common radical initiator in cyclopropane ring-opening reactions, gave no reaction in this case.



Scheme 18

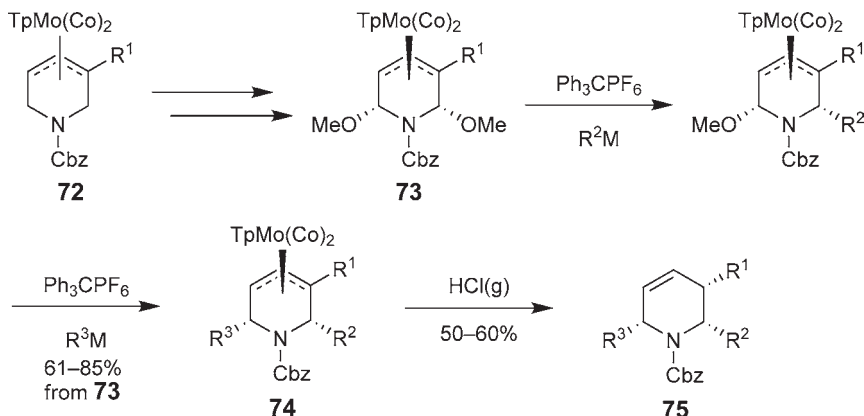
The cationic molybdenum 1,2-dihydropyridine complex **66** can be generated from the regioselective hydride abstraction of molybdenum complex **65**. The methoxy group is critical for selective abstraction to give complex **66**, which can then undergo nucleophilic addition with Grignard reagents or alkyllithiums to give 6-substituted complexes **67** (Scheme 19) [\[2000JOC7445\]](#). The nucleophilic addition is regio- and stereospecific giving the product from attack of the nucleophile at the end of the diene adjacent to the nitrogen atom and *anti* to the molybdenum moiety. The resultant complexes **67** can be further deprotonated to give the isomeric 1,2-dihydropyridine complexes **68**, which can undergo another nucleophilic addition to give 2,6-disubstituted products **69**. Oxidative or photolytic demetalation of complexes **69** give enones **70** or enol ethers **71**, respectively.



Scheme 19

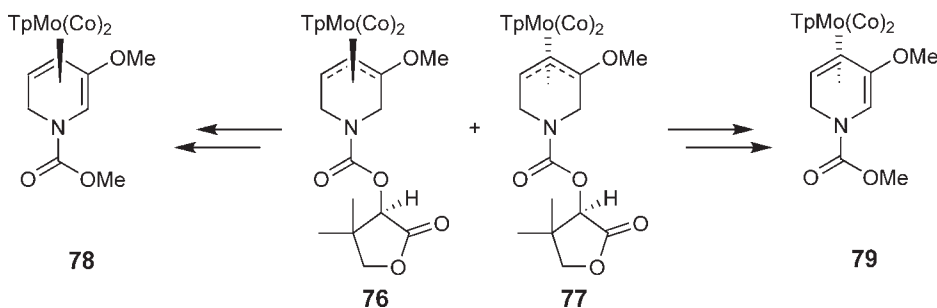
Complex **72**, where the methoxy group of complex **65** is replaced with a methyl or phenyl group, showed poor regioselectivity in the initial proton abstraction, leading to a mixture of dihydropyridine isomers. An alternative procedure was developed in which complex **72** is converted into 2,6-dimethoxy complex **73**, which then undergoes highly regio- and

stereospecific nucleophilic substitution of the methoxy group adjacent to the 3-substituent. Further deprotonation and subsequent addition of a second nucleophile replaces the remaining methoxy group to give the 2,3,6-trialkyl-substituted-1,2,3,6-tetrahydropyridine product **75** after decomplexation of complex **74** (Scheme 20) <2001JA12477>.



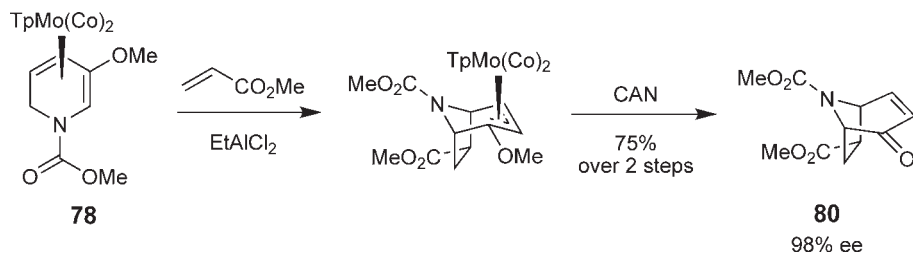
Scheme 20

Replacing the benzyl carbamate in **65** with a chiral carbamate derived from (*R*)-pantolactone generates diastereomeric molybdenum 1,2-dihydropyridine complexes **76** and **77**, which are easily separable by crystallization <2000OL3909>. Once separated, these chiral complexes **76** and **77** are easily converted to the more reactive methyl carbamate molybdenum 1,2-dihydropyridine complexes **78** and **79**, respectively, and allow the synthesis of enantiopure 2,6-disubstituted tetrahydropyridines (Scheme 21).



Scheme 21

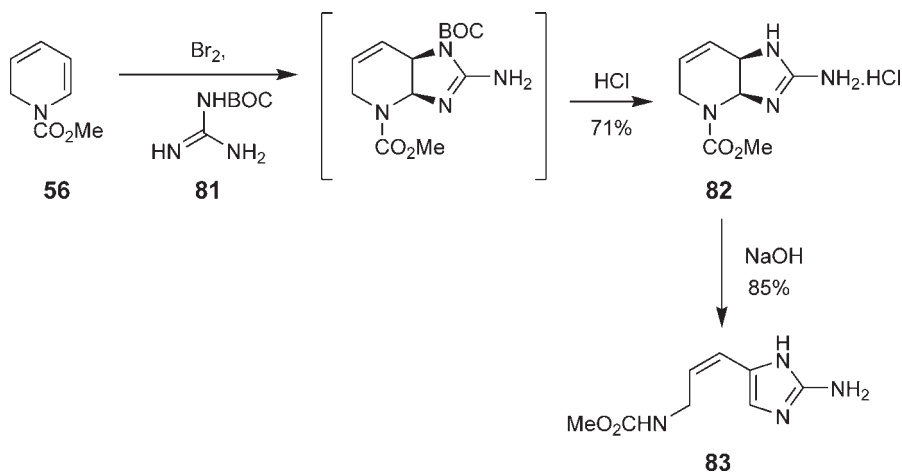
Chiral 1,2-dihydropyridine complex **78** has been shown to undergo Lewis acid-initiated [5+2] cycloadditions with electron-deficient alkenes, such as methyl acrylate, to give, after demetalation using ceric ammonium nitrate, functionalized tropanes **80** (Scheme 22) <2000OL3909, 1999JA5811>. Short reaction times and substoichiometric amounts of Lewis acid are sufficient to ensure regio- and enantioselectivity. It is thought that excess Lewis acid mediates a slow reversal



Scheme 22

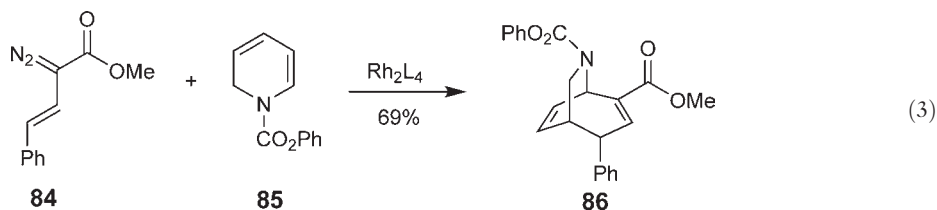
of the cycloaddition leading to poor overall selectivity when reaction times are extended. Molybdenum complexes such as **65** and **78** have also been shown to undergo Lewis-catalyzed [5+3] cycloadditions to give bridged heterocycles where, again, the molybdenum ligand is critical in controlling the regio- and enantioselectivity <2003JA9026>.

Selective bromine-mediated addition of BOC-protected-guanidine **81** to dihydropyridine **56** occurs across the electron-rich 5,6-alkene to give, after acid deprotection, *cis*-2-amino-1,3a,5,7a-dihydroimidazo[4,5-b]pyridine **82** (Scheme 23). Amino bond cleavage under basic conditions affords substituted 2-aminoimidazole **83** <2004OL3933>. Replacement of guanidine **81** with urea or thiourea leads, similarly, to 2-aminooxazoles or 2-aminothiazoles, respectively; however, the yields are considerably lower than that of **82** due to the sensitivity of the ureas to bromine oxidation <2005JOC8208>.

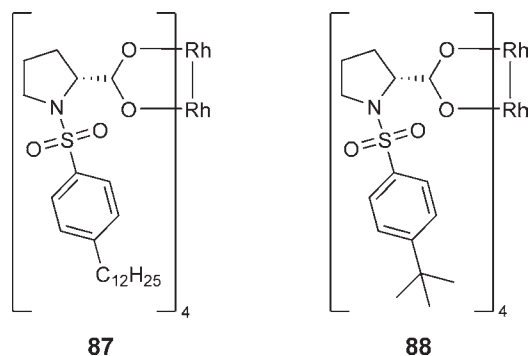


Scheme 23

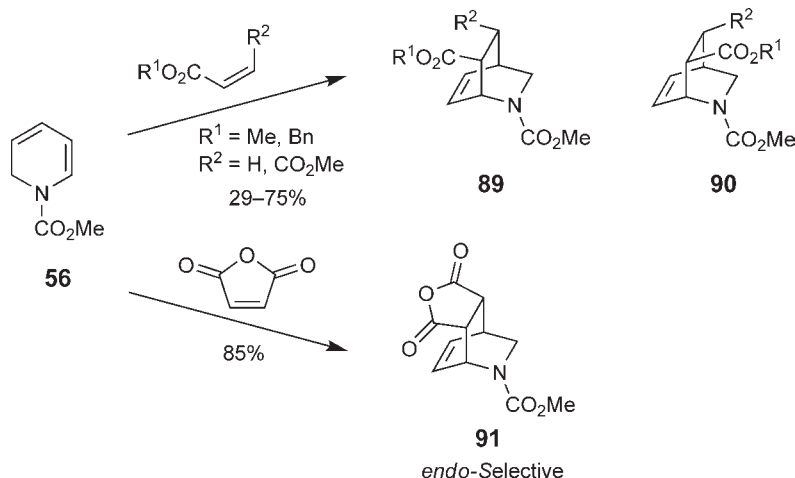
Rhodium(II)-catalyzed decomposition of vinyldiazoacetates **84** in the presence of *N*-phenoxy carbonyl-1,2-dihydropyridine **85** gives 6-azabicyclo[3.2.2]nonanes **86** (Equation 3). The overall reaction is a [3+4] cycloaddition which occurs by a tandem cyclopropanation/Cope rearrangement <1998TL2707, 2001JOC7898>.



The use of chiral dirhodium tetraproline catalysts, such as **87** and **88**, allows asymmetric induction resulting in formation of azabicyclo[3.2.2]nonane products with high enantiomeric excess <2002JOC5683>.

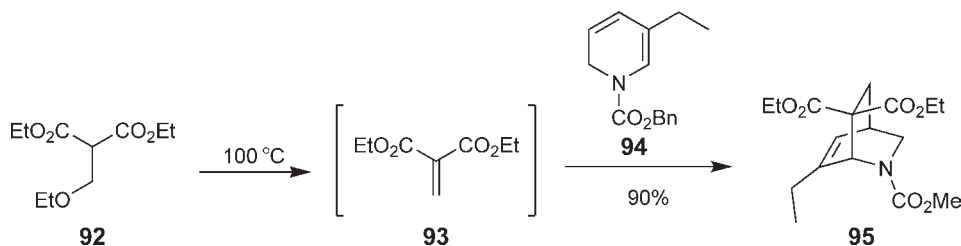


The Diels-Alder reaction of 1,2-dihydropyridines is still actively studied with research mainly focused on developing highly regio- and enantioselective methods for the formation of isoquinuclidines. While the Diels-Alder reaction between dihydropyridine **56** and numerous acrylic acid esters or dimethyl maleate resulted in variable yields of both the *endo*-**89** and *exo*-**90** 2-azabicyclo[2.2.2]octene products, the reaction with maleic anhydride yielded only the *endo*-product **91** (Scheme 24) <2003T7555>. The *endo*-**89** and *exo*-**90** isomers generated when using acrylic acid esters ($R_1 = \text{Me}$, $R_2 = \text{H}$) are usually difficult to separate. However, hydrolysis of the esters and subjection of the *endo/exo*-acid mixture to iodolactonization conditions results in lactonization of only the *endo*-isomer. The *exo*-acid is easily separated from the *endo*-lactone, which can be easily converted back to the *endo*-acid, thereby allowing complete separation of the two isomers <2005BML3501>.



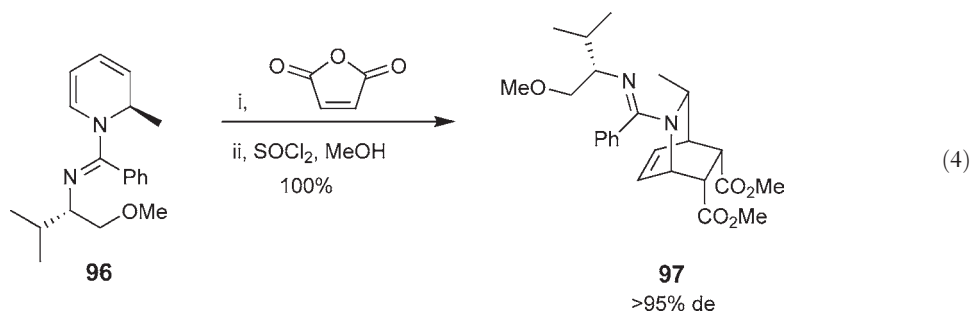
Scheme 24

A study of the reactivity of disubstituted dihydropyridines in Diels-Alder reactions found that 2,3-disubstituted-1,2-dihydropyridines were unreactive when compared with 2,5-disubstituted-1,2-dihydropyridines <2001S1784>. High regioselectivity in the Diels-Alder reaction of 1,2-dihydropyridines has been achieved by the use of 1,1-homodisubstituted acrylate dienophiles such as **93**. Dienophiles of this nature are highly unstable and rapidly polymerize but can be formed *in situ* from the high-temperature elimination of ethanol from the stable ethoxymethylmalonate **92**. Reaction of **93** with 1,2-dihydropyridine **94** was completely regioselective giving bicyclic product **95** (Scheme 25) <1999OL973>. The Diels-Alder reaction of 1,2-dihydropyridines with 1,1-disubstituted dienophiles that act as ketene equivalents has also been reported <1997SL786>.

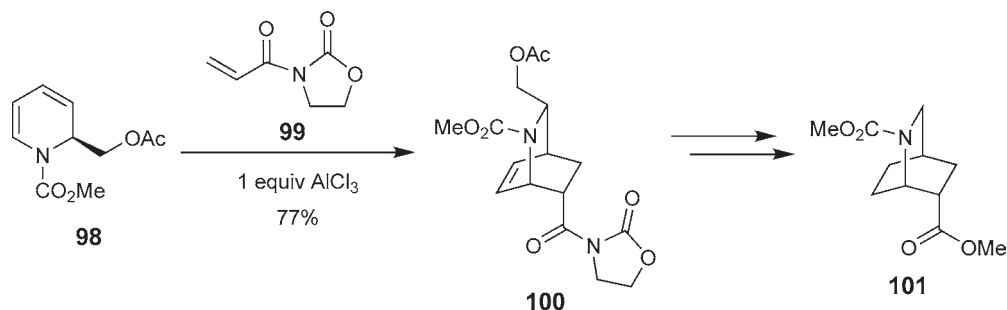


Scheme 25

The development of chiral Diels-Alder reactions to form enantiomerically enriched isoquinuclidines has been of considerable interest. Older examples focused on the use of chiral auxiliaries, generally attached to the nitrogen of the 1,2-dihydropyridine, the best of which were carbohydrate based <1990TL1995>. Recently, amidines have been shown to be very efficient chiral auxiliaries with 1-*N*-amidine-1,2-dihydropyridine **96** undergoing [4+2] cycloaddition with maleic anhydride to give only the *endo*-product **97** with >95% diastereomeric excess (Equation 4) <2005OL5773>.



The Diels–Alder reaction of chiral 1,2-dihydropyridine **98**, which can be prepared as a single enantiomer from L-lysine, with *N*-acryloyloxazolidinone **99** gave 2-azabicyclo[2.2.2]octene product **100**, which was converted into isoquinuclidine **101** with 97% ee (Scheme 26) <2000TL7685>.



Scheme 26

The rationale for the high enantioselectivity of the reaction when compared to 1,2-dihydropyridines bearing a chiral auxiliary on nitrogen is that the chiral center at the 2-position on the dihydropyridine **98** is positioned closer than an auxiliary to the reaction center in the transition state of the Diels–Alder reaction (Figure 4).

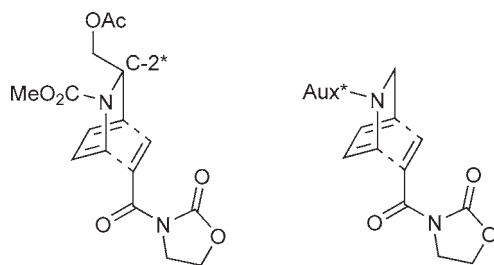
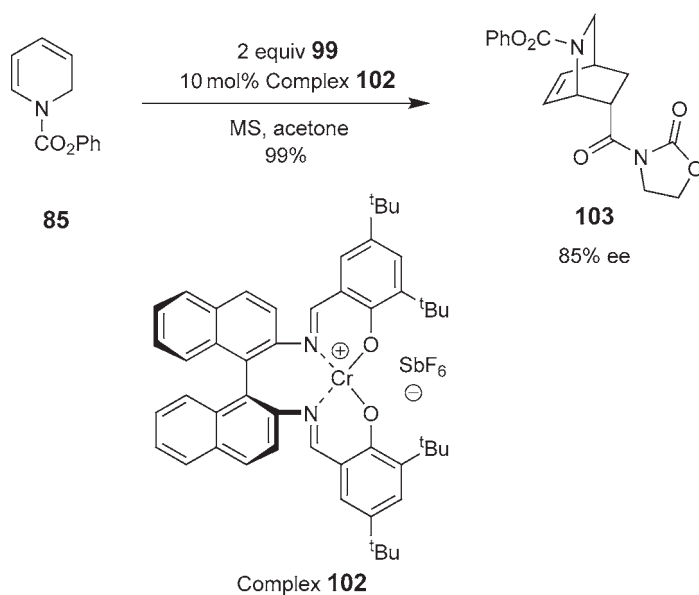


Figure 4

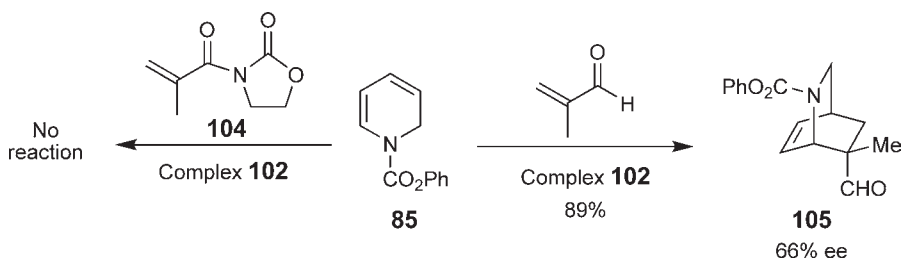
Chiral catalysts have recently been developed to allow the enantioselective Diels–Alder reactions of 1,2-dihydropyridines. The weakly Lewis-acidic chromium(III) complex **102** was found to catalyze the reaction between *N*-phenoxy carbonyl-1,2-dihydropyridine **85** and *N*-acryloyloxazolidinone **99** to give 2-azabicyclo[2.2.2]octene product **103** in near-quantitative yield and 85% ee (Scheme 27) <2002T8299>.

The reaction of **85** with other dienophiles, however, proved to be less effective: *N*-methacryloyloxazolidinone **104** gave no reaction whereas methacrolein gave product **105** in lower yield and ee (Scheme 28).

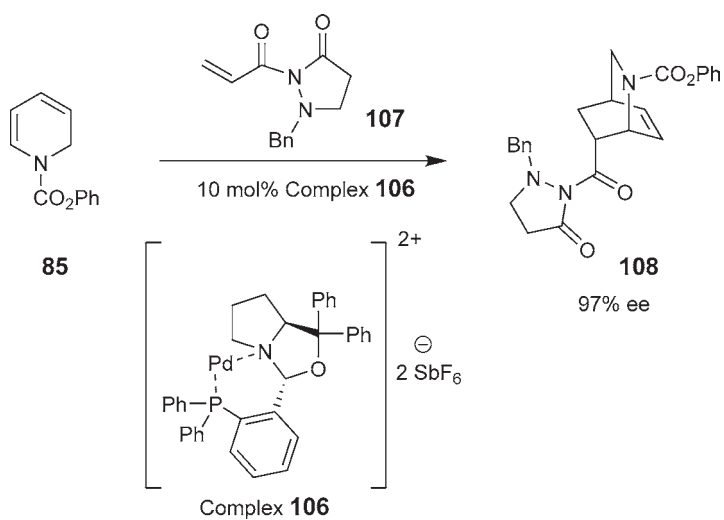
Proline-based palladium complex **106** has been shown to catalyze the Diels–Alder reaction of 1,2-dihydropyridine **85** and oxazolidinone **99** to give **103** in similar enantiomeric excess as the chromium(III) complex **102** <2005TL5677>. Alteration of the dienophile to pyrazolidin-3-one **107** improves the enantioselectivity of the reaction and gives product **108** in 97% ee (Scheme 29).



Scheme 27

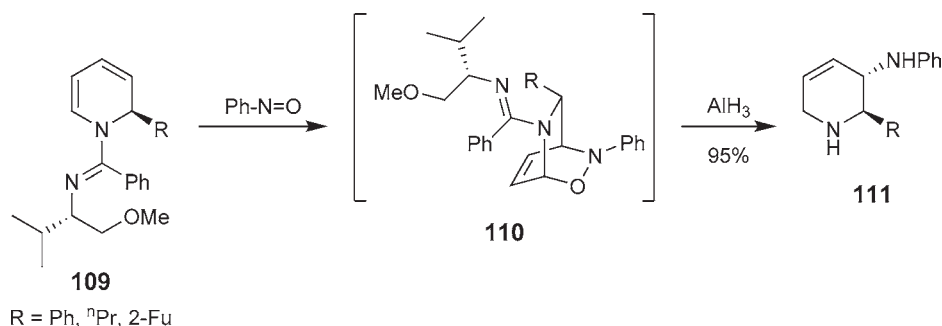


Scheme 28



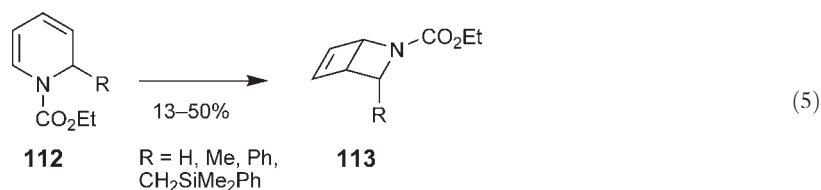
Scheme 29

The [4+2] cycloaddition of 2-substituted-1,2-dihydropyridines **109** with heterodienophile nitrosobenzene gives unstable cycloadducts **110** as single diastereomers in 98% ee. Adducts **110** can be reduced with alane to give 3-aminosubstituted-1,2,3,6-tetrahydropyridines **111** with a *trans*-relationship between the 2-substituent and 3-amino group (Scheme 30) <2005JOC2368>.



Scheme 30

Photoirradiation at 300 nm of *N*-alkoxycarbonyl-1,2-dihydropyridines results in ring closure and the formation of 2-azabicyclo[2.2.0]hex-5-enes. Substituents are tolerated at the 2-, 3-, and 4-positions; however, the yields are significantly lower than those for unsubstituted dihydropyridines. Irradiation of 2-substituted-1,2-dihydropyridines **112** proceeds via a torquoselective process to give only the *endo*-product **113** (Equation 5) <2001JOC1805, 2000T9227>.

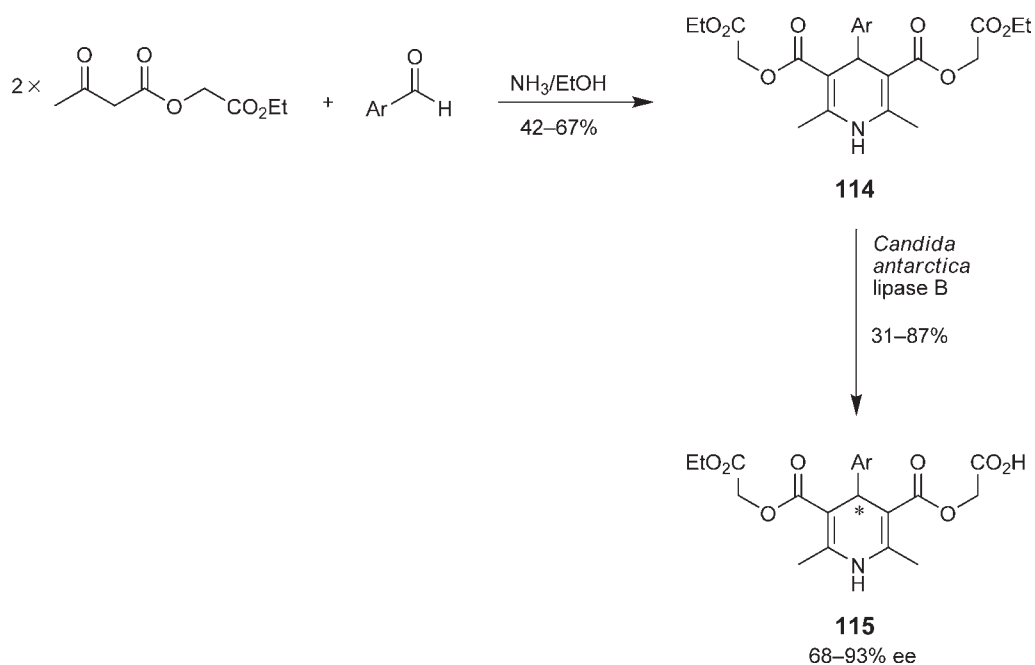


7.04.2.5 1,4-Dihydropyridines

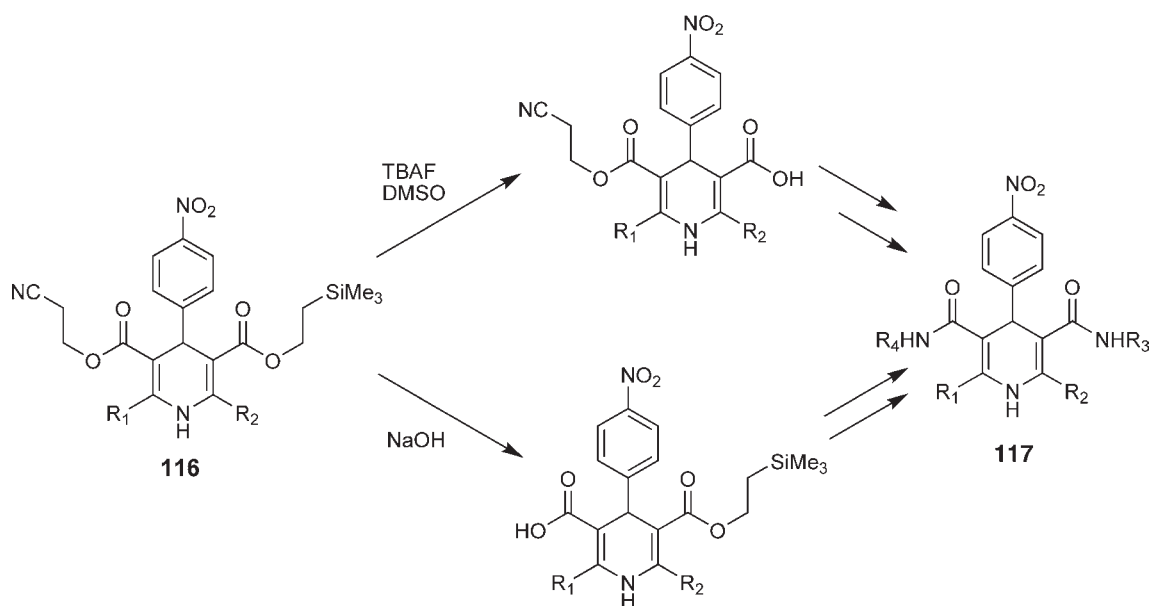
4-Aryl-1,4-dihydropyridine-3,5-dicarboxylates are widely studied due to their use in the treatment of cardiovascular diseases. Most of these compounds are synthesized using the Hantzsch method which is unsuitable for the synthesis of unsymmetrical or chiral derivatives. Enzymatic desymmetrization of bis(ethoxycarbonylmethyl)-1,4-dihydropyridine-3,5-dicarboxylates **114**, generated by the Hantzsch method, using *Candida antarctica* lipase B has generated enantiopure 1,4-dihydropyridines **115** in reasonable to high yields with good enantiomeric selectivity (Scheme 31) <2000TA4559>. Conversion of the dihydropyridine nitrogen from a free amine to an *N*-methoxymethyl derivative has been shown to reverse the selectivity of lipase AK (*Pseudomonas* sp.) desymmetrization completely <1997TA857>.

Using the Fax modification of the Hantzsch procedure, unsymmetrical 1,4-dihydropyridine-3,5-dicarboxylates **116** can be generated (Scheme 32) <1951JOC1259>. The esters of these 3,5-dicarboxylates are resistant to basic hydrolysis and a range of esters have been developed such that they each require differing hydrolysis conditions. Selective deprotection of one ester allows functionalization of a single carboxylate, and numerous unsymmetrical 1,4-dihydropyridine-3,5-diamides **117** can be generated <1998TL5293>.

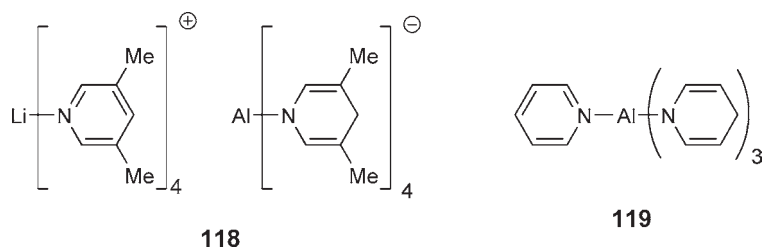
1,4-Dihydropyridine metal complexes, which can be formed from the reaction of pyridines with aluminium hydrides, can act as selective reducing agents. One such ionic complex **118** was formed from the 3,5-dimethylpyridine and lithium aluminium hydride, while the neutral dihydropyridyl complex **119** is formed from pyridine and aluminium hydride-trimethylamine complex <1999IC4700>. The neutral complex **119**, in comparison to **118**, has high solubility in organic solvents and is potentially a useful reducing agent.



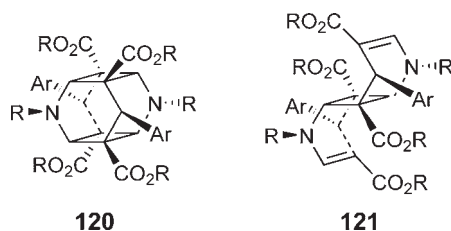
Scheme 31



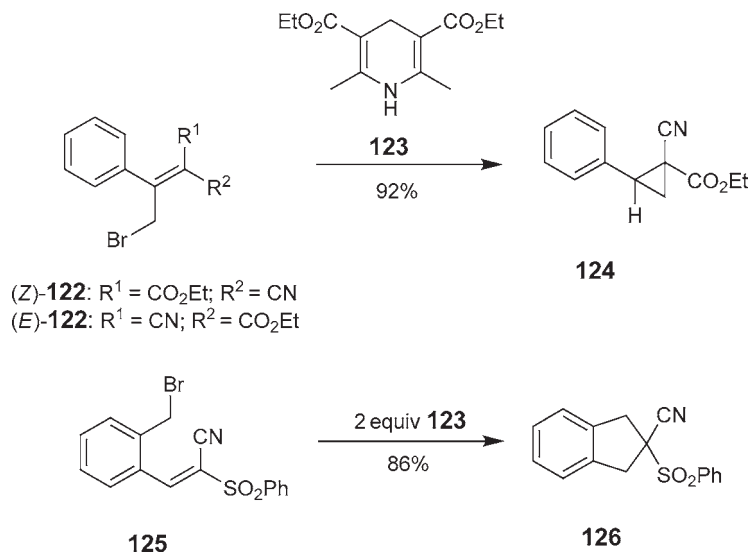
Scheme 32



Irradiation of 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates with unfiltered light ($\lambda \geq 270$ nm) results in the formation of highly crystalline 3,9-diazatetraasterane-1,5,7,11-tetracarboxylates **120**. When the dimerization occurs in the solution phase, small amounts of *anti*-cyclobutane dimers **121** are also formed <2000EJO245>. The dimerization can also be undertaken in the solid state, to give only the diazatetraasterane **120** product, although some substrates that react in solution are unreactive in the solid phase <1998EJO1213>.

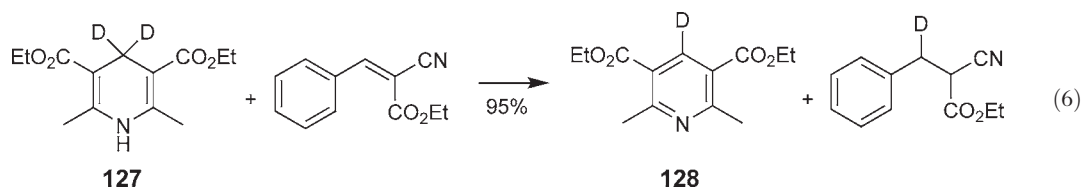


A major synthetic use of 1,4-dihydropyridine-3,5-dicarboxylates is as reducing agents. In particular, the so-called Hantzsch dihydropyridine **123** is frequently used, and an interesting example is formation of cyclopropane **124** from bromomethylcinnamates **122** (Scheme 33) <2001JOC344>. It was found that the reaction of either (*E*)-**122** or (*Z*)-**122** gave identical yields of only the (*E*)-isomer of cyclopropane **124**. The same conditions can also be used to form indanes **126** from benzylic bromides **125**.

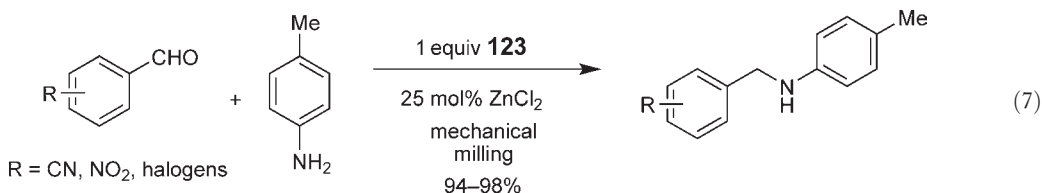


Scheme 33

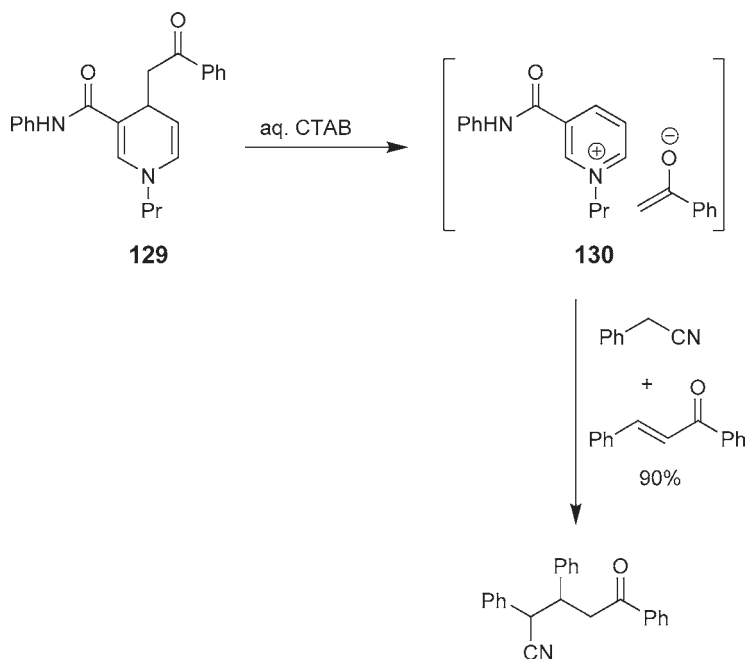
The reduction of α -cyanocinnamates with 4,4-dideutero Hantzsch dihydropyridine **127** gave a product that was singly deuterated at only the benzylic position (Equation 6) together with the oxidized pyridine product **128**. This shows that reductions of this type result from a hydride transfer from the 4-position of the 1,4-dihydropyridine followed by proton extraction from the nitrogen of the dihydropyridine <2000J(P2)1857>. This oxidative conversion of dihydropyridine **127** to pyridine **128** was not inhibited by the presence of an electron-transfer inhibitor showing that the reaction does not involve electron transfer <2000JOC8158, 2000JOC3853>.



The reductive aminations of various benzaldehydes with 4-methylaniline, using Hantzsch dihydropyridine **123** as the hydrogen source, have been achieved under mechanical milling, solvent-free conditions (Equation 7) <2005OBC1617>. The reaction was found not to proceed unless Lewis acid catalysts were added, the best results being obtained when ZnCl_2 was used. The reduction of imines to amines using dihydropyridine **123** has recently been reported to proceed in high yields, and again the reaction requires the presence of an acidic catalyst: in this case diphenyl phosphate gave the best results <2005SL2367>.



1,4-Dihydropyridine **129** has been shown to catalyze Michael reactions in aqueous cationic micelles of cetyltrimethylammonium bromide (Scheme 34) <2003CL1064>. In the micelles, dihydropyridine **129** ionizes to form an acetophenone enolate salt **130**. The highly basic enolate deprotonates the Michael donor which then rapidly reacts with the Michael acceptor. The use of anionic surfactants did not promote Michael reactions, suggesting that the cationic micelles promote the dissociation of salt **130**.

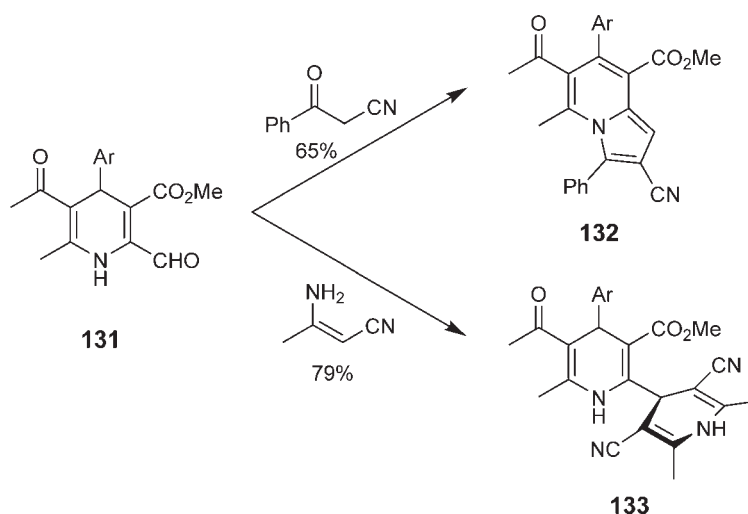


Scheme 34

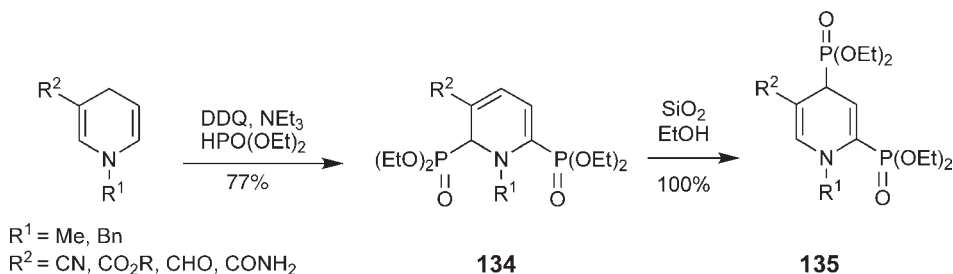
2-Formyl-1,4-dihydropyridines **131** can be converted to either indolizines **132** or bis-1,4-dihydropyridines **133** with benzoylacetonitrile or 3-aminocrotononitrile, respectively (Scheme 35) <2002T5747>. Broadening of the signals in both the ¹H and ¹³C NMR spectra showed that bis-1,4-dihydropyridine **133** exists in a restricted conformation with very slow rotation about the bond between the two 1,4-dihydropyridine rings.

1,4-Dihydropyridines bearing an electron-withdrawing group at the 3-position undergo oxidative diphosphonylation to give 1,2-dihydropyridines **134** (Scheme 36) <2000OL1533>. Refluxing 1,2-dihydropyridine **134** in SiO_2 results in a 1,3-phosphonate shift to give the corresponding 1,4-dihydropyridine isomer **135**.

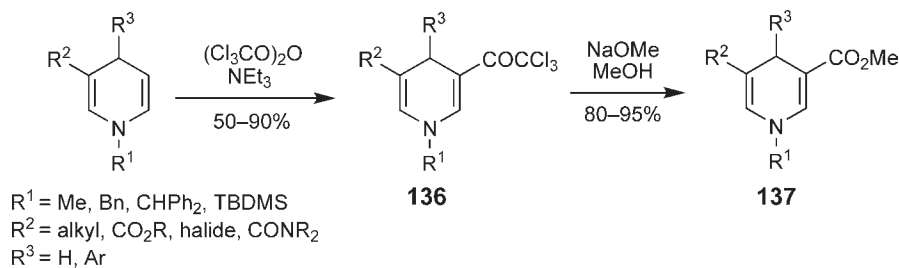
1,4-Dihydropyridines substituted at the 3- and/or 4-positions undergo selective acylation with trichloroacetic anhydride to give 5-trichloroacetyl-1,4-dihydropyridines **136**, which are easily converted by the haloform reaction to esters **137** (Scheme 37) <1998TL9275, 2002T8099, 2003TL4711>. Hydrogenation, over platinum oxide, of



Scheme 35



Scheme 36

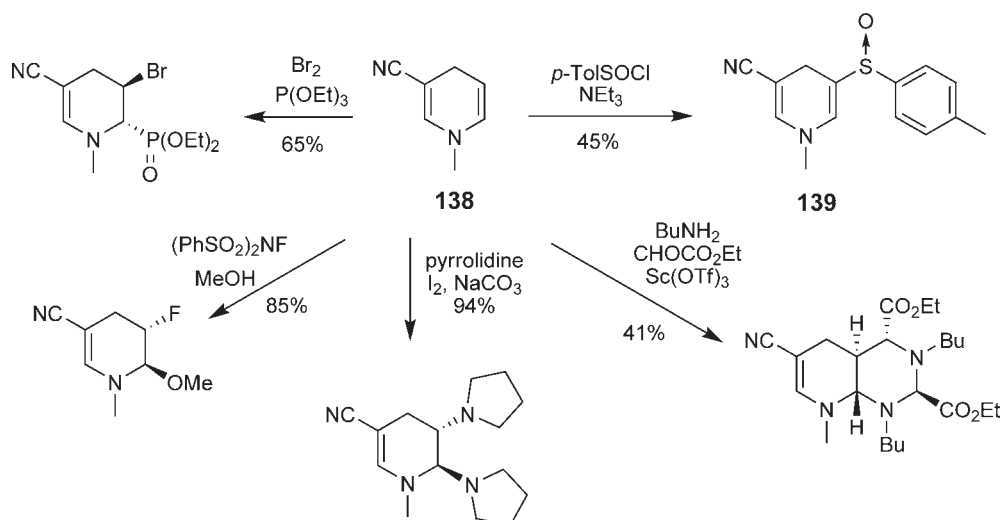


Scheme 37

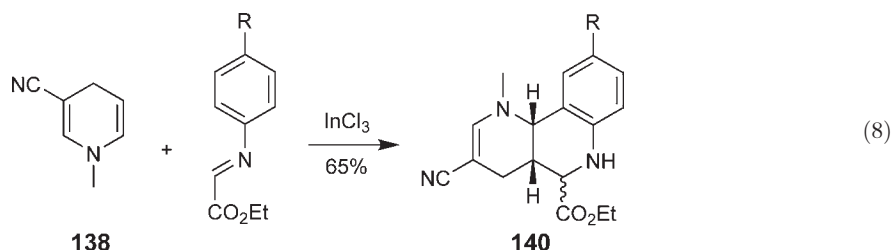
3,4-disubstituted-1,4-dihydropyridines selectively reduces the 2,3-alkene to give the 3,4-disubstituted-1,2,3,4-tetrahydropyridine, where the relationship between the 3- and 4-substituents is *cis* [<1999TL3961>](#).

There has been extensive research into electrophilic additions to 3-substituted-1,4-dihydropyridines, such as *N*-methyl-3-cyano-1,4-dihydropyridine **138**, which readily undergoes addition across the more reactive enamine-like 5,6-alkene to give 2,3,5-trisubstituted-1,2,3,4-tetrahydropyridines (Scheme 38) [<1998JOC2728, 2000CEJ1763, 2003TL8449>](#). In an unusual example, the reaction with sulfinyl chlorides and triethylamine results in the formation of the 1,4-dihydropyridine sulfoxide **139**, where in the absence of an additional nucleophile, the iminium intermediate is deprotonated to yield the monosubstituted 1,4-dihydropyridine product **139**.

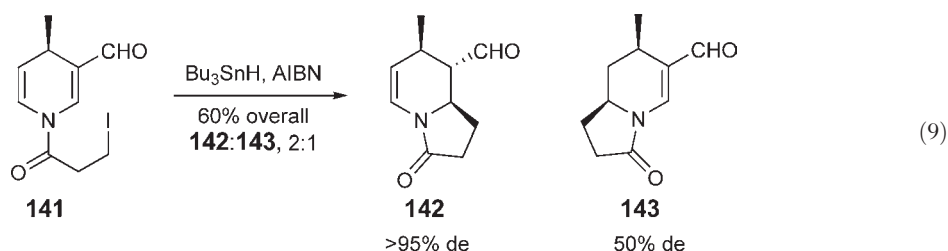
N-Methyl-3-cyano-1,4-dihydropyridine **138** has also been shown to undergo Diels–Alder reactions with aromatic iminiums to give benzonaphthyridine adducts **140** (Equation 8) [<2003OL717>](#).



Scheme 38

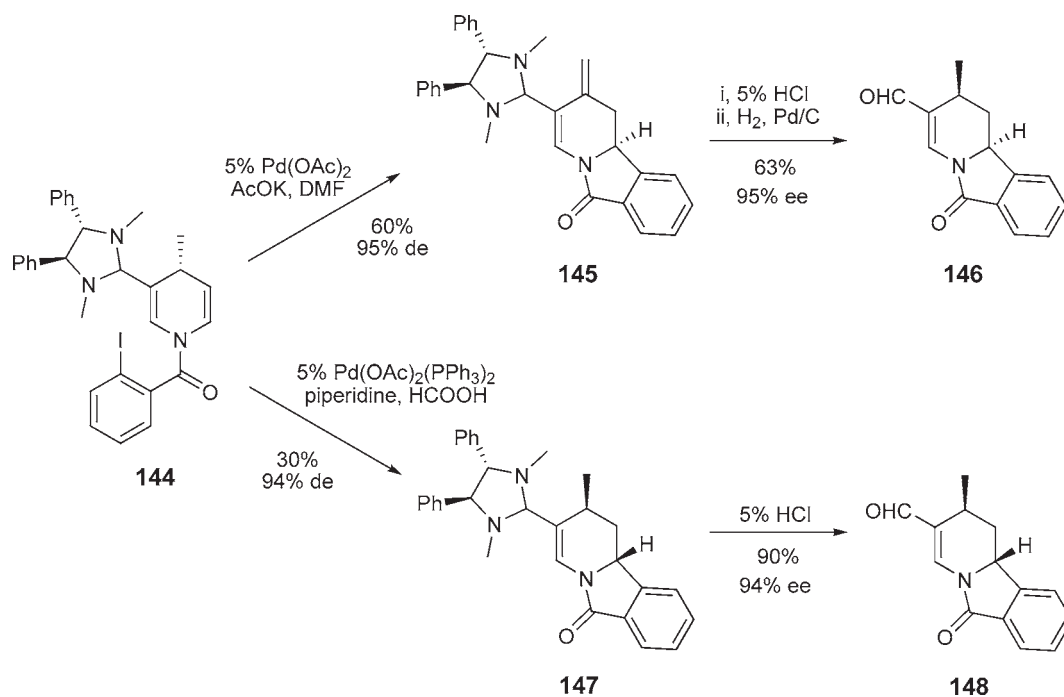


N-7-Iodopropanamide-3-formyl-1,4-dihydropyridine **141** undergoes radical cyclization to give a 2:1 mixture of quinolizinones **142** and **143**, respectively (Equation 9) <1998T10349>. It was discovered that when the 3-formyl group was reduced to the primary alcohol the radical cyclization did not proceed at all and neither **142** nor **143** were obtained. Whilst the absence of the C-2 cyclized product **142** was predicted with the removal of the electron-withdrawing formyl group, it is unsure why the production of the C-6 cyclized product **143** is affected.

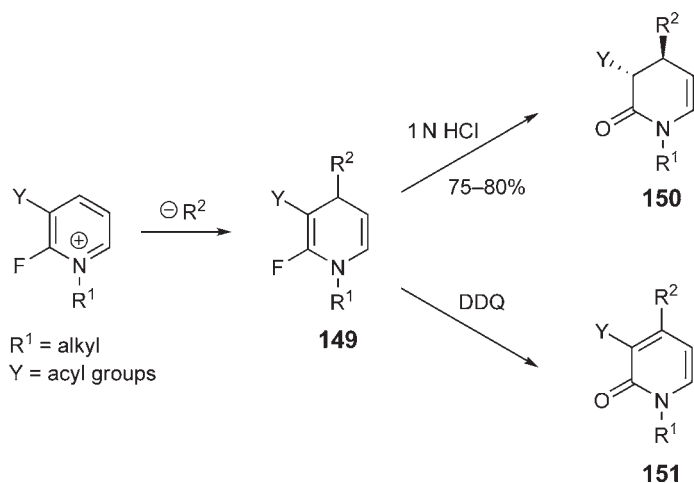


N-2-Iodobenzamide-1,4-dihydropyridine **144** bearing a 3-chiral aminal as a formyl synthon has been shown to undergo intramolecular Heck reactions <2001TL589>. Under normal Heck conditions, an *exo*-methylene compound **145** is the sole product, which, after hydrolysis of the aminal and hydrogenation of the methylene group, gives the tricyclic product **146** with high enantiomeric selectivity. Under reductive Heck conditions, the tricyclic aminal **147** is generated with the opposite stereochemistry at the newly formed carbon–carbon bond. Aminal **147** can also be hydrolyzed to give the tricyclic product **148** with similarly high enantiomeric selectivity (Scheme 39).

3-Acyl-2-fluoro-1,4-dihydropyridines **149**, easily synthesized by alkylation of 2-fluoropyridinium salts, undergo hydrolysis to form dihydro-2-pyridones **150** in which only the more stable 3,4-*trans*-isomer is formed. 1,4-Dihydropyridines **149** can also be oxidized with DDQ to form 2-pyridones **151** (Scheme 40) <2002JOC7465, 2000CC2459>.



Scheme 39



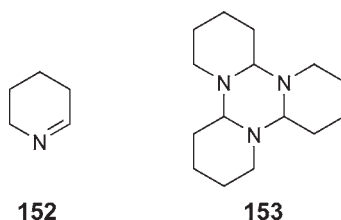
Scheme 40

7.04.3 Reactivity of Tetrahydropyridines

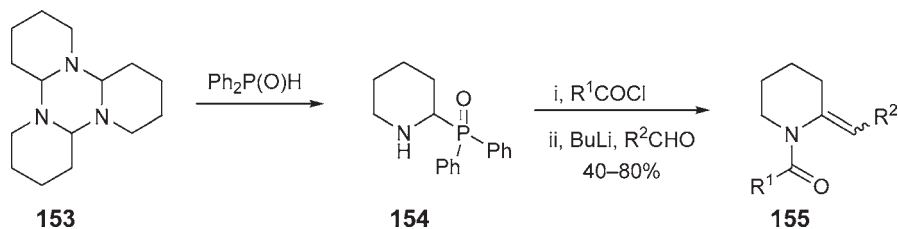
When comparing the chemistry of the three tetrahydropyridine isomers, the reactivities of 1,2,3,4- and 2,3,4,5-tetrahydropyridines are similar and these two isomers are often interconvertable. The chemistry of 1,2,3,6-tetrahydropyridines is somewhat different, and in particular the influence of the nitrogen atom has the least effect on the reactivity of the alkene, which behaves more like an alkene in a nonheterocyclic system.

7.04.3.1 2,3,4,5-Tetrahydropyridines and their Iminium Salts

Unsubstituted 2,3,4,5-tetrahydropyridine **152** exists as a monomer in solution where it is somewhat unstable and highly reactive but conveniently exists in air as a stable crystalline solid in its trimeric form **153** <1977OS118>.

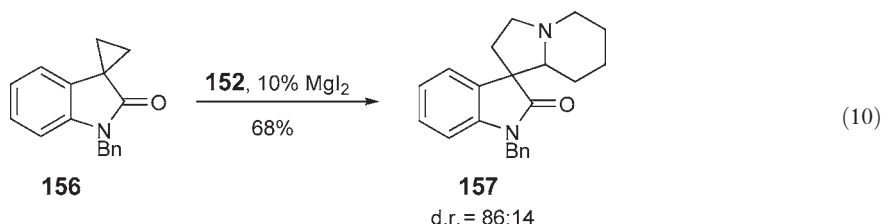


Triazine **153** reacts with diphenylphosphine oxide to form phosphinoyl piperidine **154**, which, after acylation of the nitrogen, can be condensed with numerous aldehydes to form 2-methylene piperidines **155** (Scheme 41) <1996TL7749, 1999T2659>.

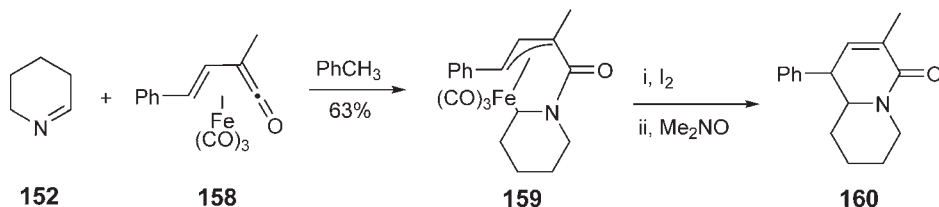


Scheme 41

2,3,4,5-Tetrahydropyridine **152**, handled as triazine **153**, in the presence of metal catalysts, undergoes insertion into spiro-fused cyclopropane **156** to give the tetracyclic adduct **157** in an 86:14 mixture of diastereoisomers. (Equation 10) <1999AG3186>.

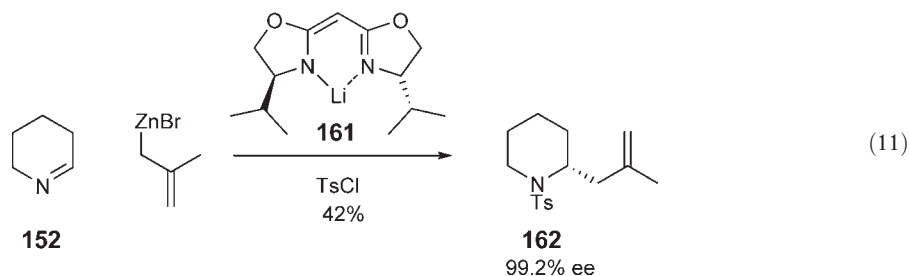


2,3,4,5-Tetrahydropyridine **152** can be inserted into the iron–acyl carbon bond of the $\text{Fe}(\text{CO})_3$ -bound vinyl ketene **158** to give the iron complex **159**, which can be oxidatively cleaved to give bicyclic lactam **160** (Scheme 42) <1995OM1586>.

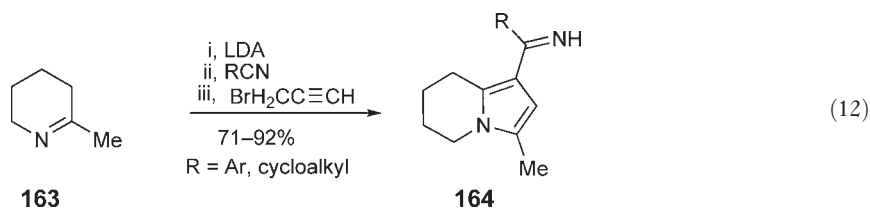


Scheme 42

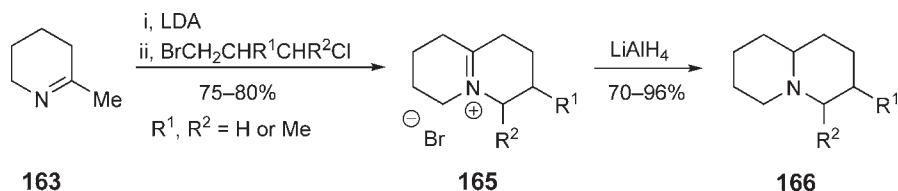
The enantioselective allylation of 2,3,4,5-tetrahydropyridine **152** can be achieved with high enantiomeric excess using allyl zinc reagents in combination with the chiral lithiated bisoxazoline catalyst **161** to give the 2-substituted piperidine **162** (Equation 11) <1996JA8489>. Allylation of 2,3,4,5-tetrahydropyridine **152** and other *cis*-imines has also been reported using chiral π -allylpalladium complexes, utilizing allyltributyltin as the allyl species; however, the enantioselectivity was shown to be poor <2003JA14133>.



The use of 6-methyl-2,3,4,5-tetrahydropyridine **163** has been widely reported in the synthesis of heterocycles due to its ability to be deprotonated selectively on the *exo*-methyl group using lithium diisopropylamide (LDA). Deprotonation of tetrahydropyridine **163** with LDA followed by addition of a nitrile and propargyl bromide give tetrahydroindolizines **164** in moderate to high yields (Equation 12) <1996JOC2185>.

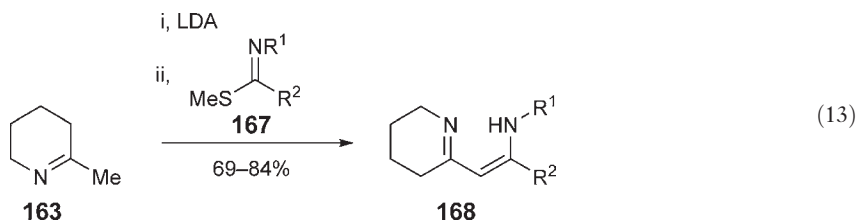


Deprotonation of **163** followed by addition of 1-bromo-3-chloropropanes results in the high-yielding formation of quinolizidinium salts **165**, which are easily reduced to give quinolizidines **166** (Scheme 43) <2003T3099>. Replacing the 1-bromo-3-chloropropane with a 1,4-dibromobutane similarly gave the 1-azabicyclo[5.4.0]undecane product; however, using longer dihaloalkyl reagents did not provide the corresponding bicyclic product. Alkylation of the deprotonated **163** with allylic bromides has also been reported <2000T7969>.

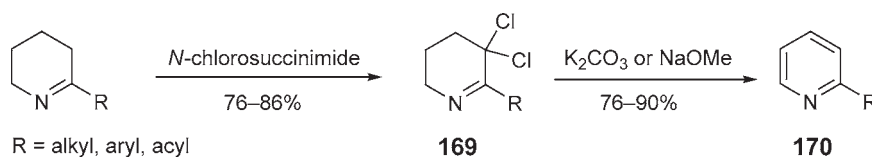


Scheme 43

Unsymmetrical diketimines **168**, which are widely used as bidentate metal ligands, can be synthesized by deprotonation of 6-methyl-2,3,4,5-tetrahydropyridine **163** followed by addition of imidothioethers **167** (Equation 13) <2005JOC2075>.

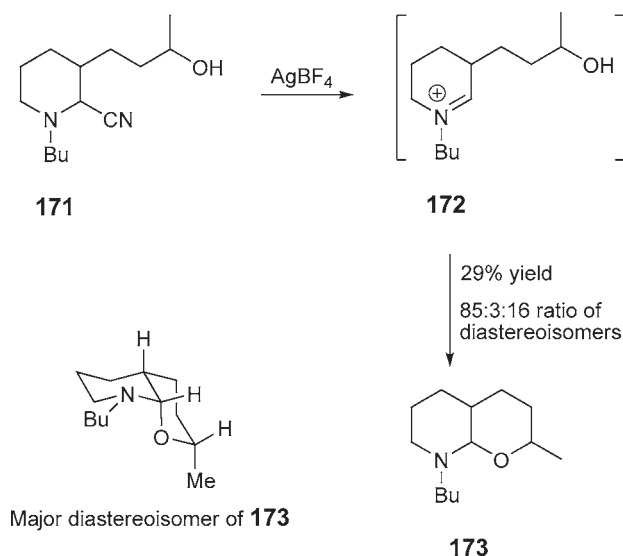


6-Substituted-2,3,4,5-tetrahydropyridines are selectively chlorinated at the 5-position using *N*-chlorosuccinimide to give 5,5-dichloro-2,3,4,5-tetrahydropyridines **169**, which can be dehydrochlorinated under mild basic conditions to give 2-substituted pyridines **170** (Scheme 44). This two-step procedure removes the need for the previously harsh conditions required for dehydrogenation of substituted-2,3,4,5-tetrahydropyridines <1996CC653>. 5-Chloro-5,6-disubstituted-2,3,4,5-tetrahydropyridines can be similarly dehydrochlorinated to give 2,3-disubstituted pyridines <2001JOC53>.



Scheme 44

1-Substituted-2-cyanopiperidines are stable compounds that upon treatment with $AgBF_4$ eliminate HCN to generate reactive 2,3,4,5-tetrahydropyridine iminium salts. Iminium salt **172**, generated from 2-cyanopiperidine **171**, undergoes intramolecular attack of an appended hydroxyl group to form octahydropyrano[2,3-*b*]pyridine **173** as a mixture of diastereoisomers, where the major diastereoisomer has a stabilizing *exo*-anomeric effect (Scheme 45) <2004EJO1057>.



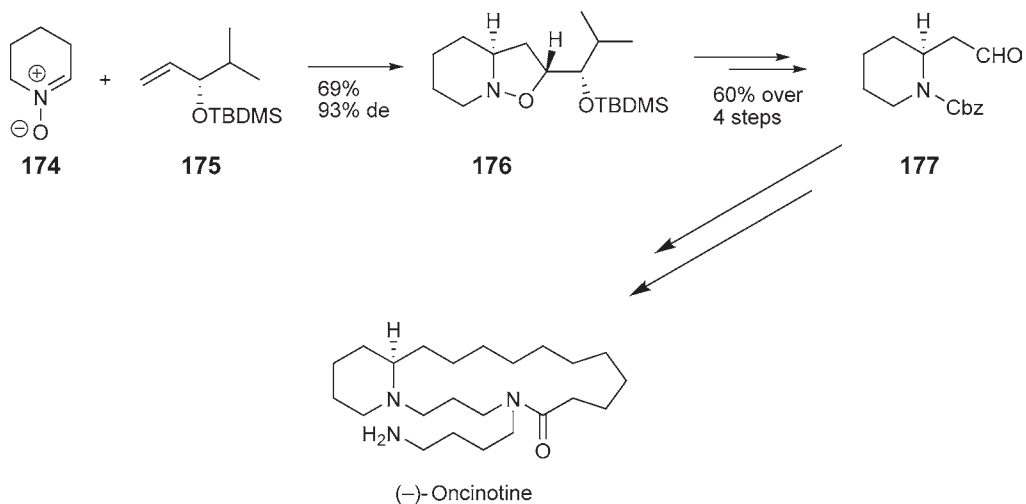
Scheme 45

2,3,4,5-Tetrahydropyridine *N*-oxide **174** readily undergoes 1,3-dipolar cycloadditions with a variety of substrates, often with very high stereoselectivity, and two reviews have been published on this area <1998CHE387, 2000JIC637>. A recent study of cycloadditions involved chiral substrates in order to control the enantioselectivity of the addition. Allyl-silylether **175** derived from (*S*)-valine undergoes 1,3-dipolar cycloaddition with 2,3,4,5-tetrahydropyridine *N*-oxide **174** to give isoxazolidine **176**, which is easily separable from a minor diastereoisomer (Scheme 46) <1996JOC1023>. Isoxazolidine **176** can be transformed over several steps into 2-(formylmethyl)piperidine **177**, which is a useful chiral building block and has been used in the synthesis of the alkaloid (–)-oncinotine.

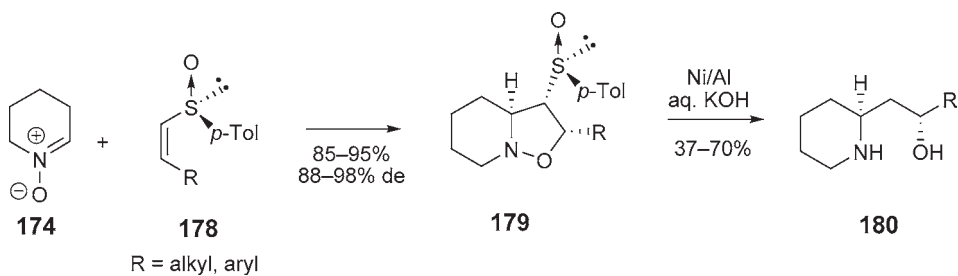
2,3,4,5-Tetrahydropyridine *N*-oxide **174** undergoes 1,3-dipolar cycloaddition with (*Z*)-vinyl sulfoxides **178** to give isoxazolidines **179**, which can be desulfurized to give amino alcohols **180** with high enantiomeric selectivity (Scheme 47) <1997TA109>.

Recent work has focused on developing catalytically controlled asymmetric 1,3-dipolar cycloadditions of cyclic nitrones such as 2,3,4,5-tetrahydropyridine *N*-oxide **174**. The Lewis acid iron complex **181** catalyzes the cycloaddition of 2,3,4,5-tetrahydropyridine *N*-oxide **174** with methacrolein to give (3*S*,5*S*)-isoxazolidine **182** in good yield and high enantiomeric selectivity (Scheme 48) <2002JA4968>. The same catalyst **181** however gave (3*R*,4*S*,5*R*)-isoxazolidine **183** with much lower selectivity when crotonaldehyde was used.

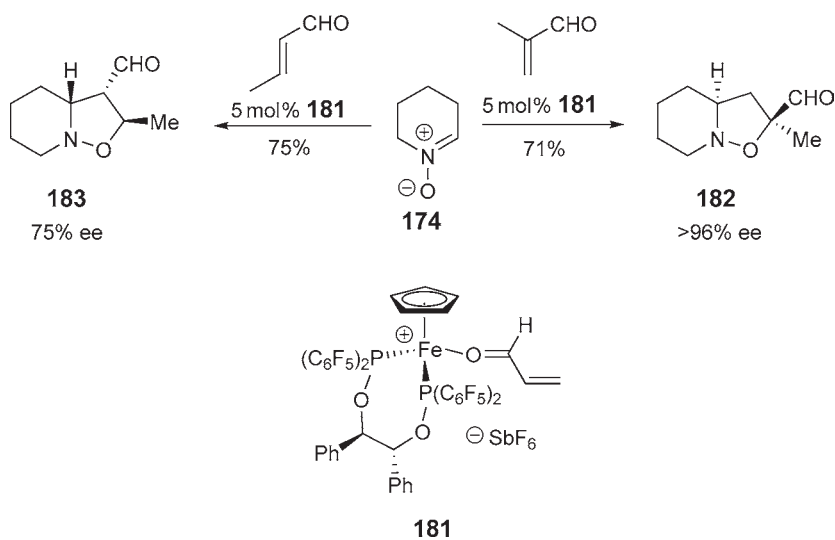
Rhodium complex **184** catalyzes the cycloaddition of 2,3,4,5-tetrahydropyridine *N*-oxide **174** with methacrolein to give the (3*R*,5*R*)-isoxazolidine **185** in quantitative yield and high enantiomeric selectivity (Equation 14) <2005JA13386>.



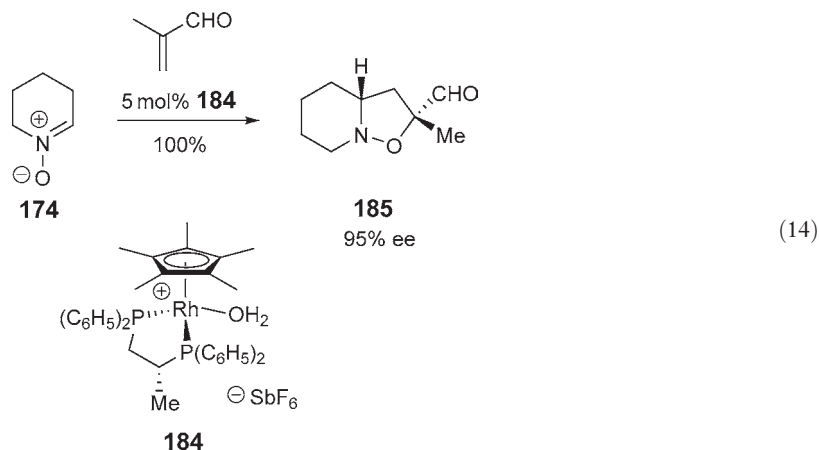
Scheme 46



Scheme 47

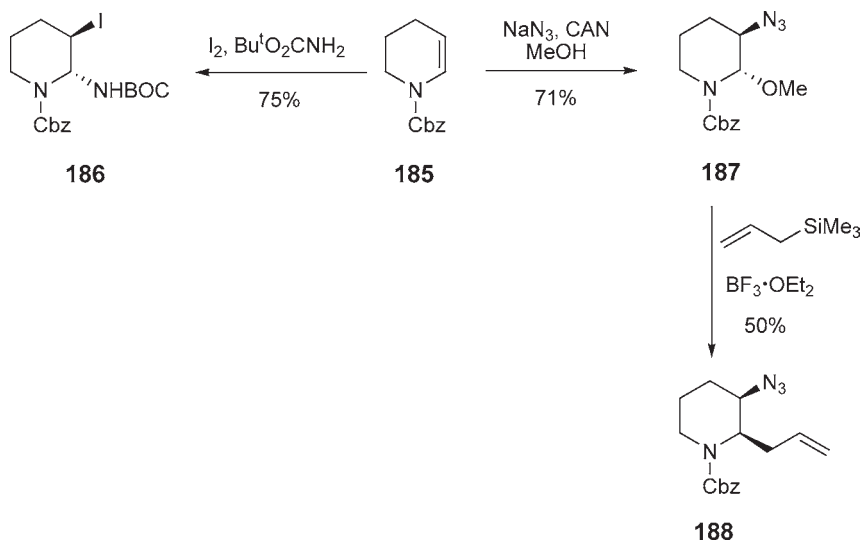


Scheme 48



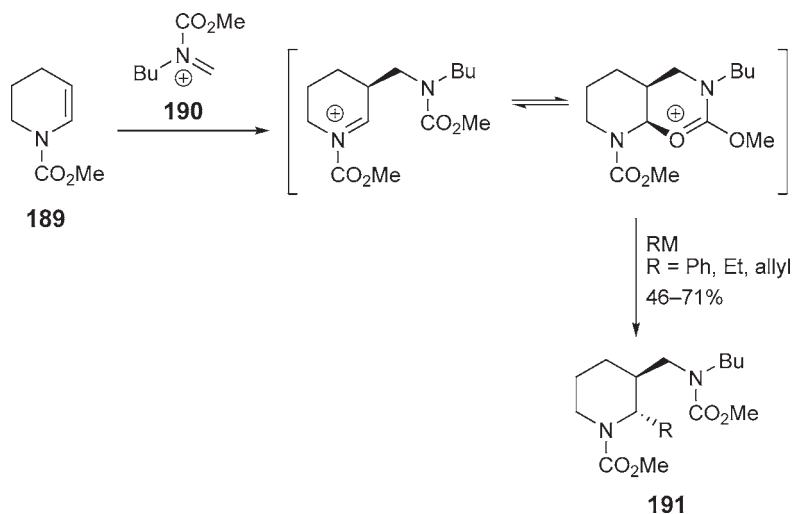
7.04.3.2 1,2,3,4-Tetrahydropyridines

1,2,3,4-Tetrahydropyridines are endocyclic enamines and can react readily with numerous electrophiles at the 5-position and nucleophiles at the 6-position. An example of this reactivity is a three-component reaction of *N*-benzyloxycarbonyl-1,2,3,4-tetrahydropyridine **185**, which reacts with primary carbamates in the presence of iodine to give 2-amino-3-iodopiperidines **186**, with a *trans*-relationship between the substituents (Scheme 49). Tetrahydropyridine **185** also reacts with sodium azide in methanol in the presence of ceric ammonium nitrate to give 3-azido-2-methoxypiperidine **187**, which can be isolated or reacted with nucleophiles in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give 3-azido-2-alkylpiperidines **188** in which the relationship between the substituents is *cis* <2005T1221>.



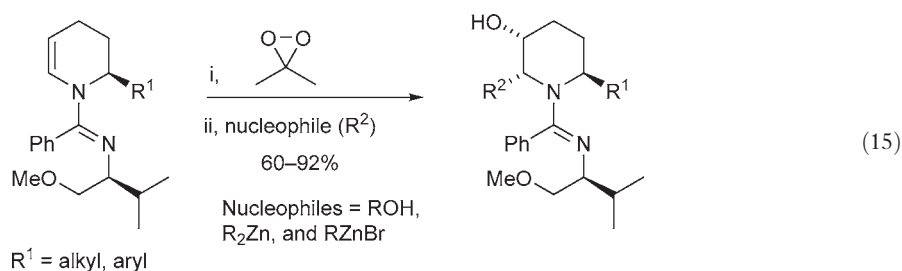
Scheme 49

N-Methoxycarbonyl-1,2,3,4-tetrahydropyridine **189** reacts with the *N*-acyliminium ion **190** followed by an organo-metallic reagent to give 2,3-disubstituted piperidines **191**. The reaction proceeds in high diastereoselectivity to give the 2,3-*trans* product. This is thought to be due to a cyclic intermediate being formed. This intermediate is hindered on one face and leads to attack of the nucleophile on the opposite face from the original iminium addition (Scheme 50) <2004JA14338>.

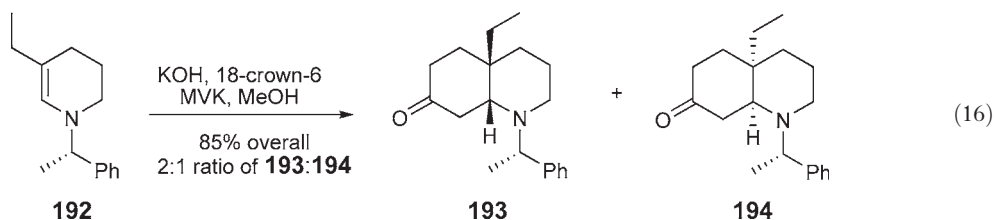


Scheme 50

Chiral *N*-amidino-1,2,3,4-tetrahydropyridines undergo a stereoselective epoxidation–nucleophilic opening sequence with either alcohols or organozinc reagents to give 2,3,6-trisubstituted piperidines where the relationship between the 2- and 3-positions is *cis* (Equation 15) <2005OL2747>.

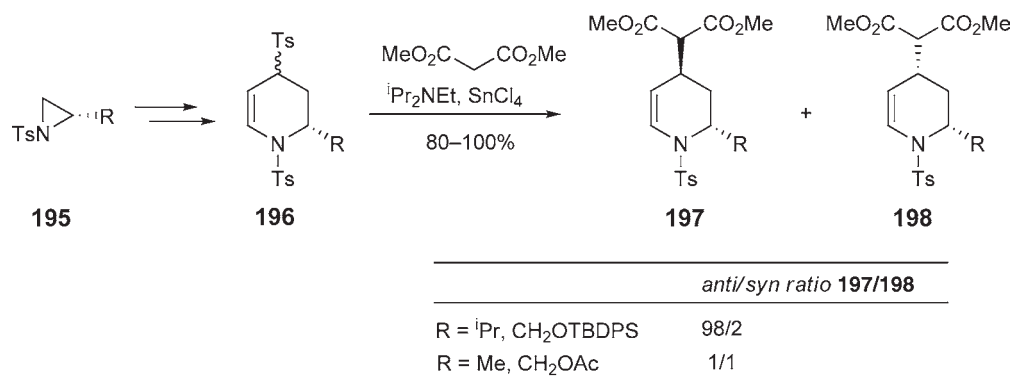


Chiral 1,2,3,4-tetrahydropyridine **192** derived from (*S*)-1-phenylethylamine undergoes base-induced addition of methyl vinyl ketone to give a 2:1 separable diastereomeric mixture of *cis*-fused octahydro-quinolin-7-ones **193** and **194** (Equation 16) <2001TA2099>.

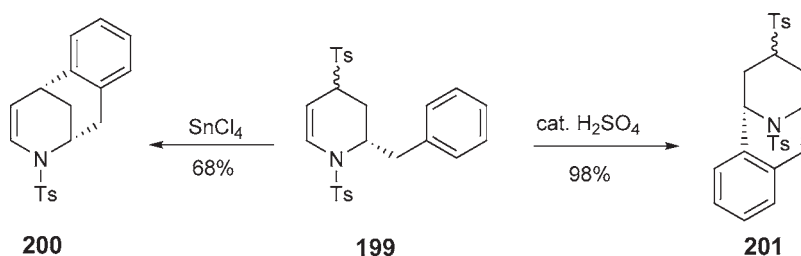


2-Alkyl-1,4-bis(4-tolylsulfonyl)-1,2,3,4-tetrahydropyridines **196**, which can be synthesized from chiral *N*-tosylaziridines **195**, are versatile compounds that can be converted into numerous piperidine and tetrahydropyridine species (Scheme 51). Nucleophilic substitution of the 4-tosyl group of **195** requires addition of a Lewis acid. Bulky substituents at the 2-position give 2,4-*anti*-1,2,3,4-tetrahydropyridine **197** while with smaller substituents a mixture of *syn*- and *anti*-isomers is formed <2001TL8369>.

Addition of a Lewis acid to a dilute solution of 2-benzyl-1,4-bis(4-tolylsulfonyl)-1,2,3,4-tetrahydropyridines **199** results in an intramolecular reaction to give benzomorphan **200**, while exposure of tetrahydropyridines **199** to a catalytic amount of concentrated acid results in an alternative intramolecular cyclization to give tropine **201** (Scheme 52) <1998SL58>.

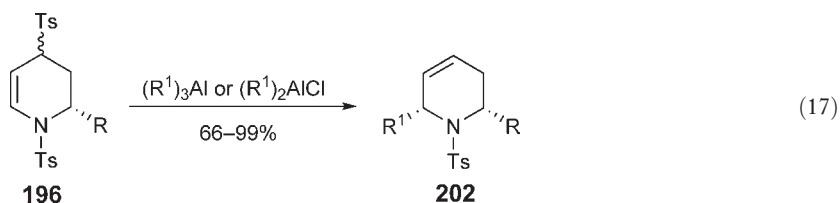


Scheme 51

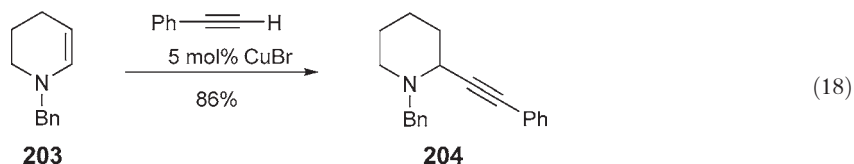


Scheme 52

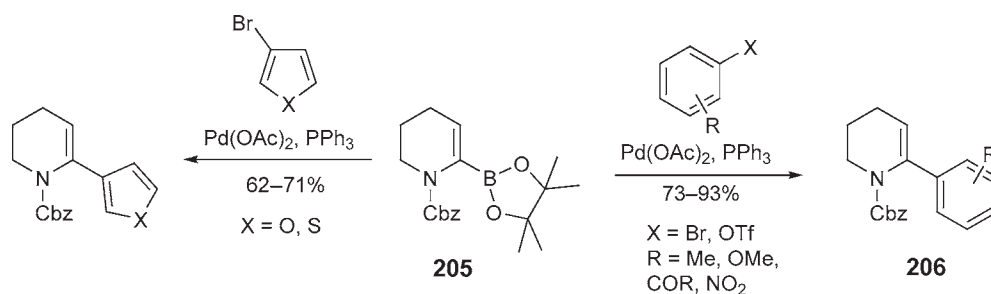
Treatment of 2-alkyl-1,4-bis(4-tolylsulfonyl)-1,2,3,4-tetrahydropyridines **196** with nucleophilic Lewis-acidic organometallic reagents results in addition of the nucleophile at the 6-position and elimination of the 4-tosyl group with concomitant isomerization of the alkene to give 2,6-*syn*-disubstituted-1,2,3,6-tetrahydropyridines **202** (Equation 17) <1998SL55, 2001JOM380>.



Terminal alkynes undergo copper-catalyzed additions to enamines such as *N*-benzyl-1,2,3,4-tetrahydropyridine **203** to give 2-alkynyl-piperidines **204** in high yield (Equation 18). A wide variety of functionalities can be tolerated on the alkyne and the reaction can be performed enantioselectively to give products with moderate (54–90%) enantiomeric selectivity <2002AGE2535>.

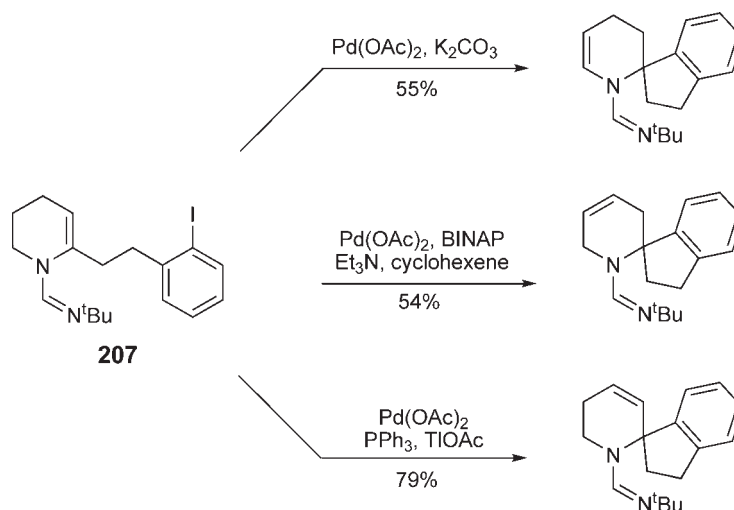


The 1,2,3,4-tetrahydropyridine boronate **205** undergoes Suzuki–Miyaura coupling with numerous aryl halides and triflates to give 6-aryl-1,2,3,4-tetrahydropyridines **206** in high yield (Scheme 53) <2005JOC7324>. The coupling of heteroaryl bromides, vinyl iodides, and acid chlorides has also been achieved using similar conditions but the yields are generally lower.



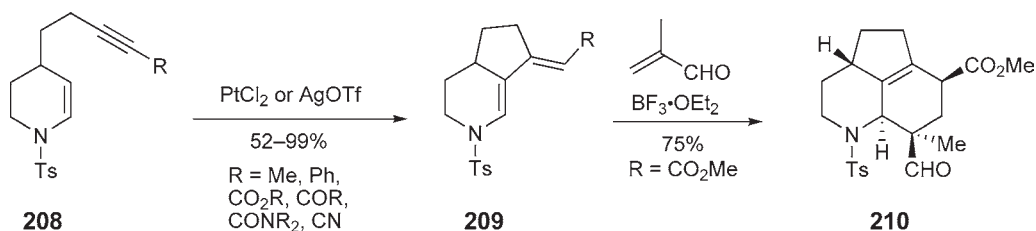
Scheme 53

6-[2-(2-Iodophenyl)ethyl]-1,2,3,4-tetrahydropyridine **207** undergoes intramolecular Heck arylations and, due to double bond migration, gives different isomers of tetrahydropyridine-dihydrospiroindanes. In all cases, the reaction is catalyzed by palladium acetate, but by changing the ligands and additives a particular tetrahydropyridine isomer can be formed preferentially (Scheme 54) <1996JOC7147>. When a chiral phosphine ligand is employed, products with high enantioselectivity can be obtained <1997JOC595>.



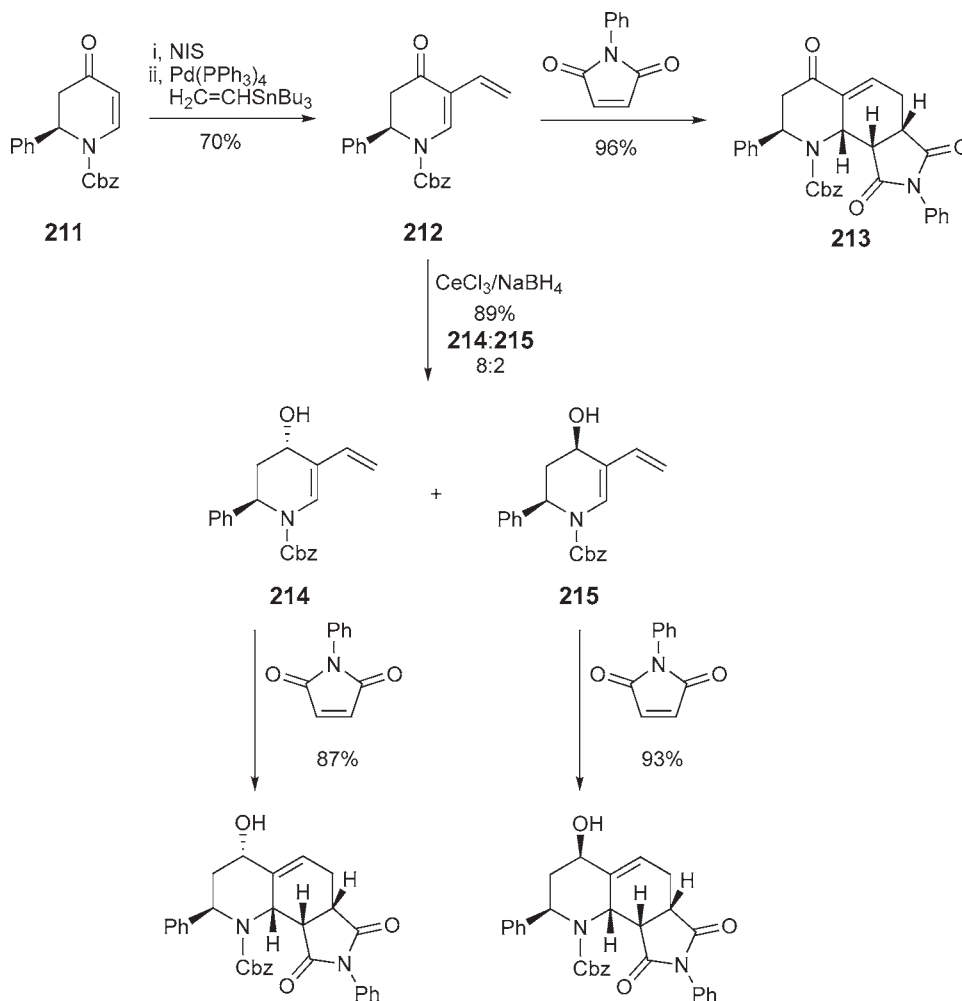
Scheme 54

N-Tosyl-1,2,3,4-tetrahydropyridines **208**, which have at the 4-position a tethered electron-deficient alkyne, undergo metal-catalyzed cycloisomerization to give 2-azahydrindans **209**, which can undergo Diels–Alder reactions with acroleins to give highly functionalized 1-azadecalins **210** (Scheme 55) <2004OL5023>.



Scheme 55

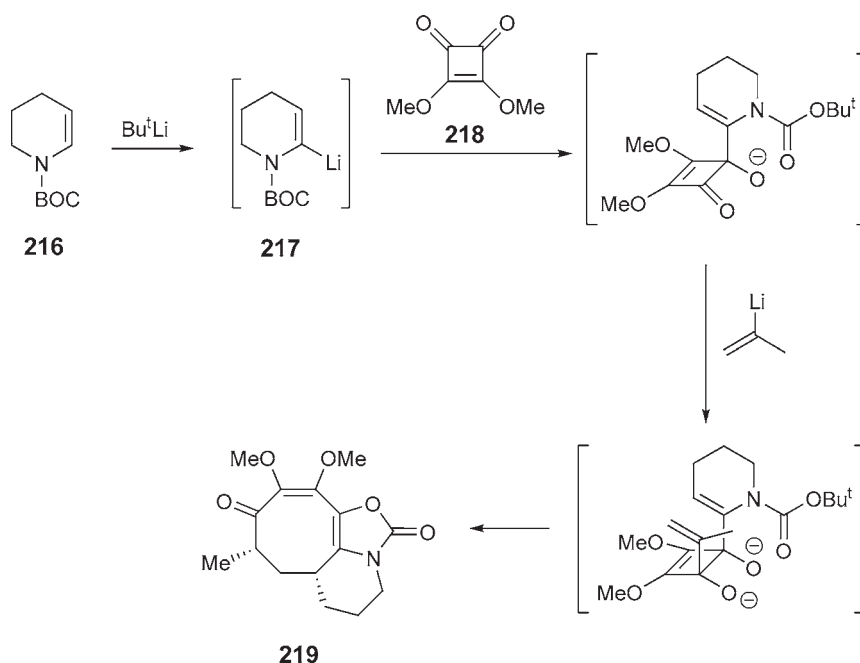
2-Phenyl-4-oxo-5-vinyl-1,2,3,4-tetrahydropyridine **212**, which can be synthesized by iodination and Stille coupling of 4-oxo-1,2,3,4-tetrahydropyridine **211**, also undergoes Diels–Alder reactions with numerous dienophiles, for example, *N*-phenylmaleimide, to give octahydroquinoline cycloadducts **213** (Scheme 56) <2003OL321, 2005JOC5221>. The cycloaddition is highly *endo*-selective and addition occurs on the α -face, opposite from the 2-phenyl substituent. When the 2-substituent is changed to a less sterically demanding group, a minor amount of cycloadduct is also formed from addition of the dienophile to the β -face. Cycloaddition of alcohols **214** or **215**, which are obtained by Luche reduction of **212**, also gave *endo*-cycloadduct resulting from addition that occurs to the α -face, showing the addition is controlled by stereochemistry at the 2-position.



Scheme 56

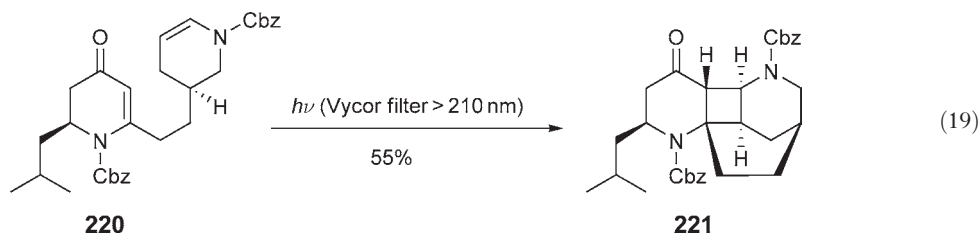
1-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydropyridine **216** is deprotonated at the vinylic 6-position to give 6-lithio-1,2,3,4-tetrahydropyridine **217** which can undergo addition to numerous electrophiles <2000OL155>. In an unusual example, addition of dimethyl squarate **218** to tetrahydropyridine **217**, followed by addition of 2-propenyllithium, results in formation of cyclooctadienone **219** (Scheme 57) <1997TL3151>. Cyclooctadienone **219** is formed via electrocyclic ring opening, with high stereoselectivity, presumably due to the stereoselective addition of the 2-propenyllithium under chelation control.

Cycloadditions on 1,2,3,4-tetrahydropyridines are usually limited to those bearing an electron-withdrawing group at the 5-position or with a 4-oxo group to activate the enamine-like alkene. For example, di-1,2,3,4-tetrahydropyridine **220** in which one of the two 1,2,3,4-tetrahydropyridine units has a 4-oxo group undergoes [2+2] photocycloaddition

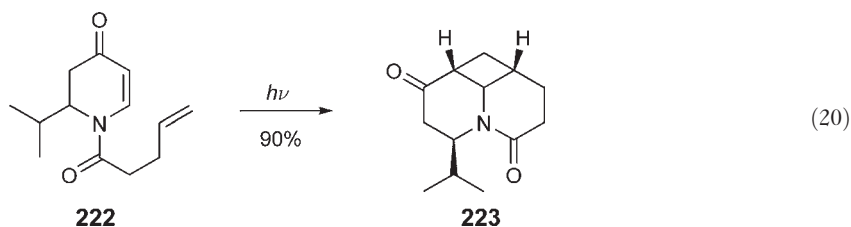


Scheme 57

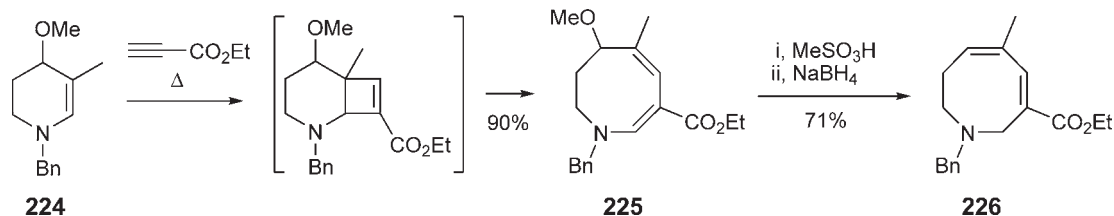
when irradiated with light >210 nm to give cycloadduct **221** as a single diastereoisomer (Equation 19) <2001OL3217>. Here again the facial selectivity is determined by the stereochemistry of the 2-position.



Irradiation of the 1,2,3,4-tetrahydropyridine **222** results in formation of quinolizidine **223** in high yield, as a single diastereoisomer (Equation 20) <2002OL1611>. Photoirradiation of N-tethered allenes has also been shown to result in a good yield of the corresponding [2+2] cycloadduct <1997T16253>.



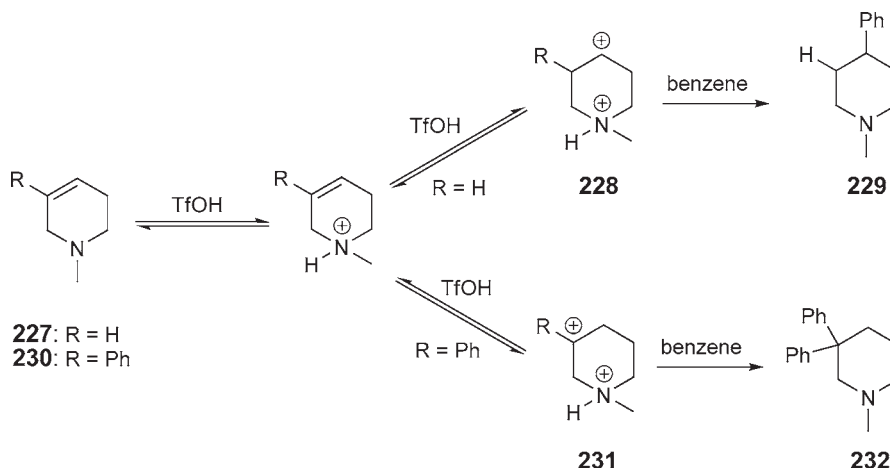
The 4-methoxy-1,2,3,4-tetrahydropyridine **224** undergoes thermal [2+2] cycloaddition to ethyl propiolate to give 1,6,7,8-tetrahydroazocine **225** which can be isomerized under acidic reducing conditions to 1,2,7,8-tetrahydroazocine **226** with concomitant elimination of methanol (Scheme 58) <2000TL6067>. Replacement of sodium borohydride with an alkyl Grignard reagent in the isomerization procedure results in formation of 2-alkyl-substituted products <2005EJO1052>.



Scheme 58

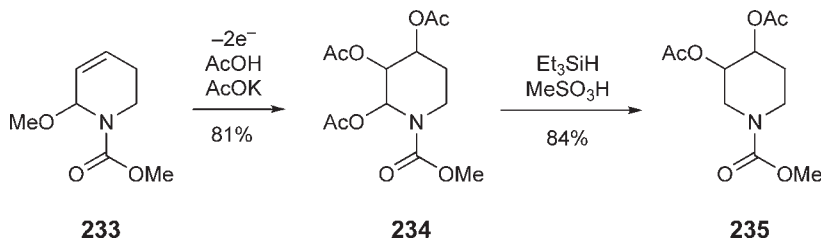
7.04.3.3 1,2,3,6-Tetrahydropyridines

Triflic acid catalyzes the arylation of *N*-methyl-1,2,3,6-tetrahydropyridine **227** to give 4-phenylpiperidine **229** (Scheme 59) <2001TL5821>. The reaction is believed to proceed by initial formation of a 1,4-dication **228**, which forms in preference to the 1,3-dication **231**. When *N*-methyl-5-phenyl-1,2,3,6-tetrahydropyridine **230** is arylated under the same conditions, 3,3-diphenylpiperidine **232** is formed as the sole product showing the stabilization of the 1,3-dication intermediate **231** by the tertiary 5-position. Intramolecular arylation of 2- and 6-benzyl-substituted 1,2,3,6-tetrahydropyridines can also be catalyzed by triflic acid <2005OL4309>.



Scheme 59

Electrochemical oxidation of the 6-methoxy-1,2,3,6-tetrahydropyridine **233** in acetic acid gives 2,3,4-triacetoxypiperidine **234** which can be easily reduced to 3,4-diacetoxypiperidine **235** in which the two acetoxy groups are predominantly equatorial (Scheme 60) <2004TL8177>.

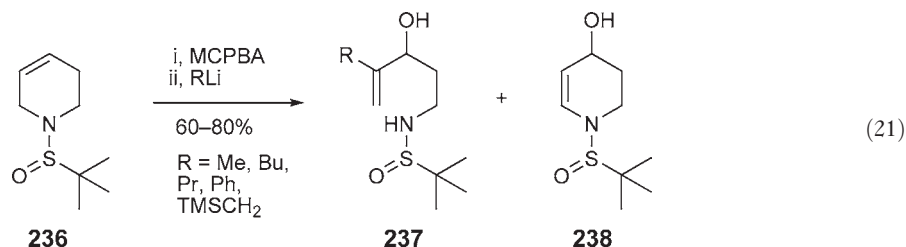


Scheme 60

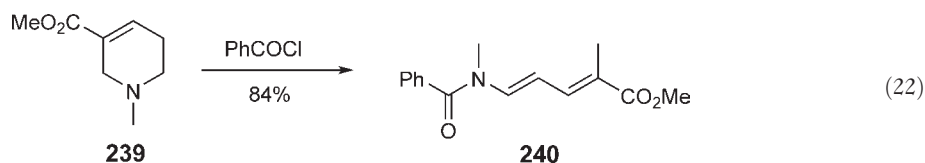
These oxygenated piperidines, or aza-sugars, are of considerable interest due to their wide-ranging biological activities. Diequatorial hydroxylation of the alkene of 1,2,3,6-tetrahydropyridines has also been achieved by

epoxidation of the alkene, followed by ring opening of the epoxide with benzoate and acetate salts. An axial hydroxyl substituent at the 3-position on the 1,2,3,6-tetrahydropyridine allows stereoselective epoxidation on the same face as the hydroxyl group <2005T8888>.

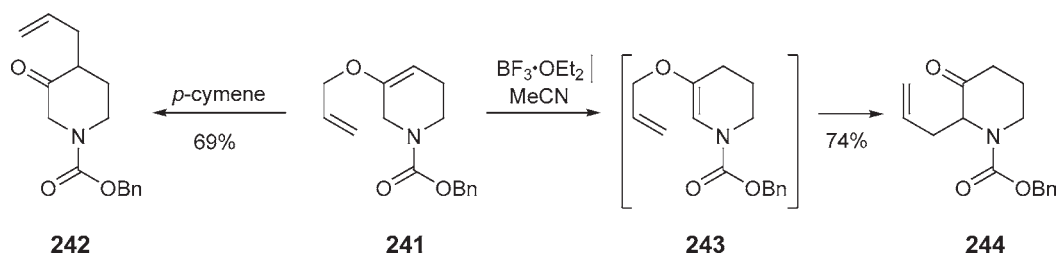
Epoxidation of *N*-*tert*-butylsulfonyl-1,2,3,6-tetrahydropyridine **236** followed by addition of alkyllithium reagents gives a mixture of allylic alcohols **237** and 4-hydroxy-1,2,3,4-tetrahydropyridines **238** (Equation 21) <2003T9729>. Exchange of the *N*-sulfonyl group for a carbamate results in formation of tetrahydropyridines **238** and little or no allylic alcohol is formed.



Benzoylation of arecoline (methyl *N*-methyl-1,2,3,6-tetrahydropyridine-3-carboxylate) **239** gives the unusual stable enamide-diene **240** in high yield (Equation 22) <1997JOC2298>.

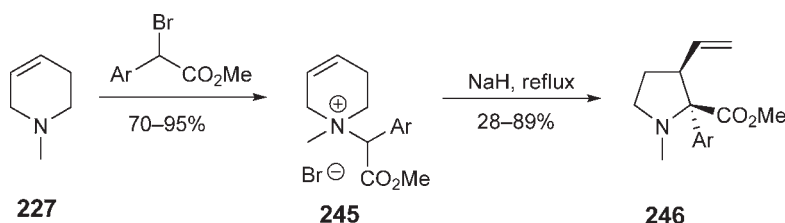


5-Allyloxy-1,2,3,6-tetrahydropyridine **241** undergoes Claisen rearrangement in *cymene* to give 4-allyl-3-oxo-piperidine **242**. The boron trifluoride etherate-mediated Claisen rearrangement gives only the 2-allyl isomer **244** due to the initial isomerization of tetrahydropyridine **241** into 1,2,3,4-tetrahydropyridine **243** by the Lewis acid (Scheme 61) <1999S1814>.



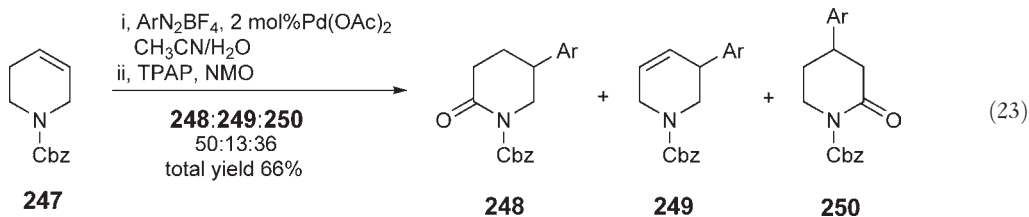
Scheme 61

Tetrahydropyridinium salts **245**, formed in high yield from the alkylation of *N*-methyl-1,2,3,6-tetrahydropyridine **227** with aryl-substituted bromoacetates, undergo [2,3]-sigmatropic rearrangements to give 3-vinyl-pyrrolidine-2-carboxylates **246** (Scheme 62). Replacement of the aryl substituent with electron-donating alkyl groups disfavors the rearrangement and leads to elimination by-products <2002T10113>.

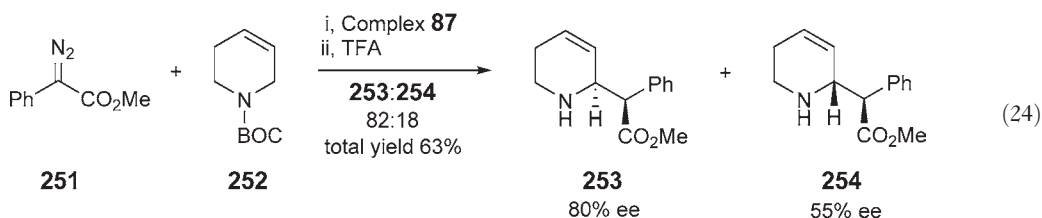


Scheme 62

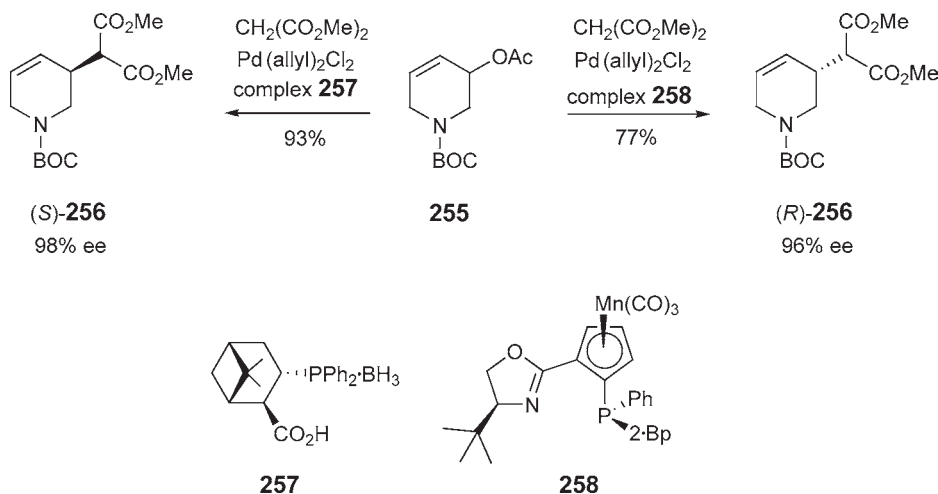
Heck arylation of *N*-benzyloxycarbonyl-1,2,3,6-tetrahydropyridine **247** with aryldiazonium salts results in formation of a mixture of unstable α -hydroxy carbamates, which can be isolated, after oxidation, as the stable lactam derivatives. Arylation occurs preferentially at the 5-position to give lactam **248** and tetrahydropyridine **249** with 4-aryl lactam **250** being formed to a lesser extent (Equation 23) <2002TL741>.



Chiral dirhodium complex **87** (see Section 7.04.2.4) catalyzes the diastereo- and enantioselective insertion of phenyldiazoacetate **251** into 1,2,3,6-tetrahydropyridine **252** to give predominantly the *erythro* 6-substituted-1,2,3,6-tetrahydropyridine **253** with high enantiomeric selectivity. The *threo*-isomer **254** is a minor product and was formed with much lower selectivity (Equation 24) <1999JA6509, 2001TL3149>.



Racemic 3-acetoxy-1,2,3,6-tetrahydropyridine **255** undergoes palladium-catalyzed asymmetric allylic alkylations with malonates to give 3-substituted-1,2,3,6-tetrahydropyridines **256**, which are useful chiral precursors for alkaloid synthesis, in very high yield and enantiomeric excess (Scheme 63) <1999EJO2515>. Chiral phosphanes are used as the palladium ligands with borane complex **257** giving (*S*)-**256**, while manganese complex **258** gives the (*R*)-**256**.



Scheme 63

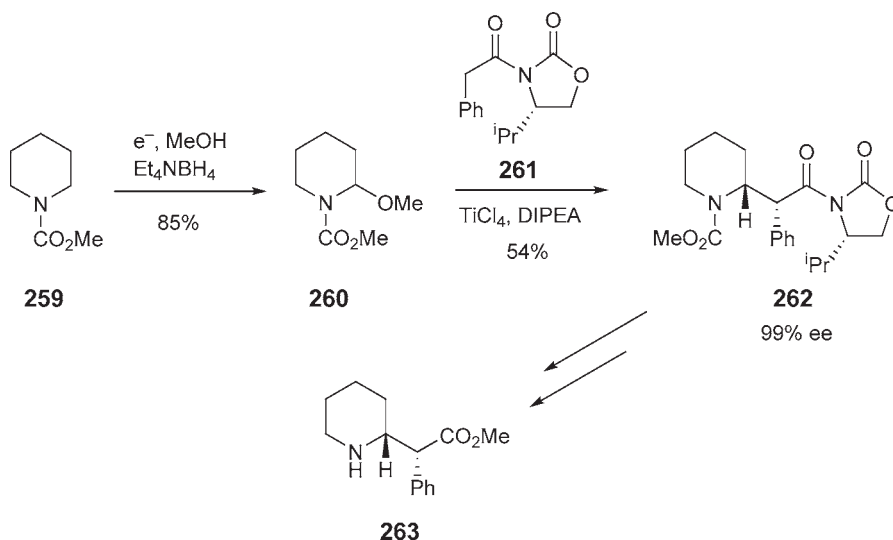
7.04.4 Reactivity of Piperidines

The vast majority of the reactions of piperidines occur either at nitrogen or at the α -carbons to the nitrogen atom. With no ring alkene, the types of manipulations that can be carried out upon piperidines are fewer than those of the dihydro- and tetrahydropyridines.

The piperidine ring system is found in numerous biologically active alkaloids and a number of reviews have been published on synthetic methods to form piperidines, generally from acyclic starting materials <2000S1781, 2003EJO3693, 2003T2953, 2004T1701>.

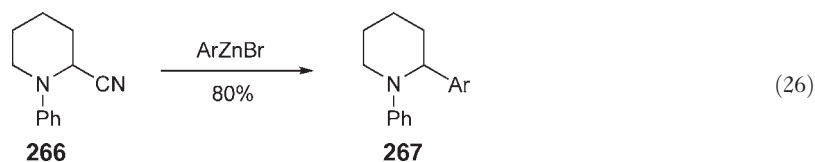
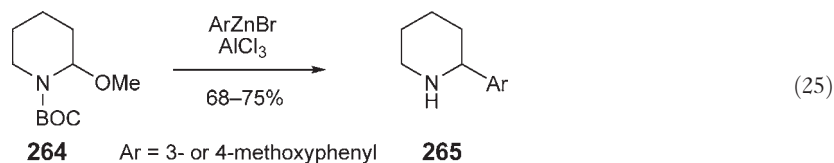
7.04.4.1 Piperidines

N-Methoxycarbonyl-2-methoxypiperidine **260**, generated in high yield from electrochemical oxidation of *N*-methoxycarbonylpiperidine **259**, undergoes stereoselective coupling of the titanium enolates of imides **261** to give the *threo*-isomer of 2-substituted piperidines **262** with high enantiomeric excess (Scheme 64) <1999OL175>. Cleavage of the imide and carbamate gives *threo*-methylphenidate **263**.

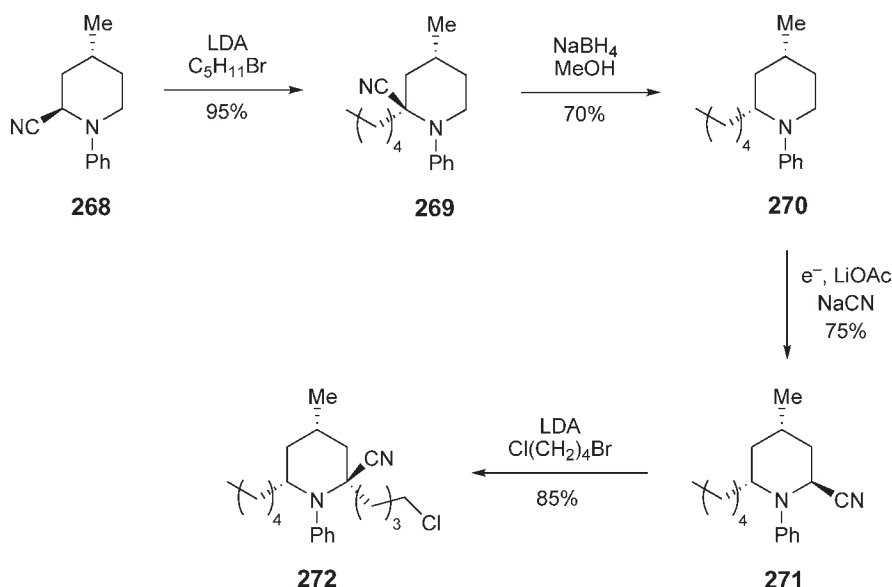


Scheme 64

N-*tert*-Butoxycarbonyl-2-methoxypiperidine **264** reacts with aromatic organozinc reagents, with concomitant hydrolysis of the carbamate, to give 2-arylpiperidines **265** (Equation 25), while *N*-phenyl-2-cyanopiperidine **266** undergoes the same reaction to give *N*-phenyl-2-arylpiperidines **267** (Equation 26) <2006TL455>.



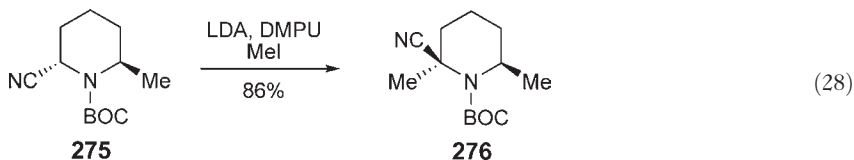
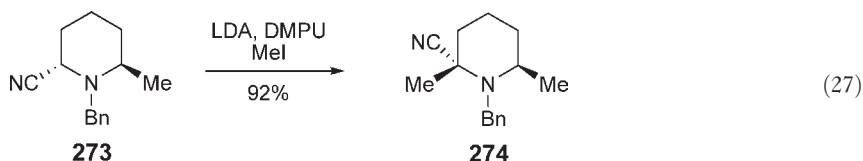
2-Cyanopiperidines are useful reagents that allow stereoselective alkylation at the 2-position and can be decyanated with predictable outcomes. Alkylation of 2,4-*trans*-*N*-phenyl-2-cyano-4-methylpiperidine **268** results in formation of the 2,4-*cis*-dialkyl product **269** (Scheme 65) <2002SL895>. A wide variety of alkyl halides can be employed



Scheme 65

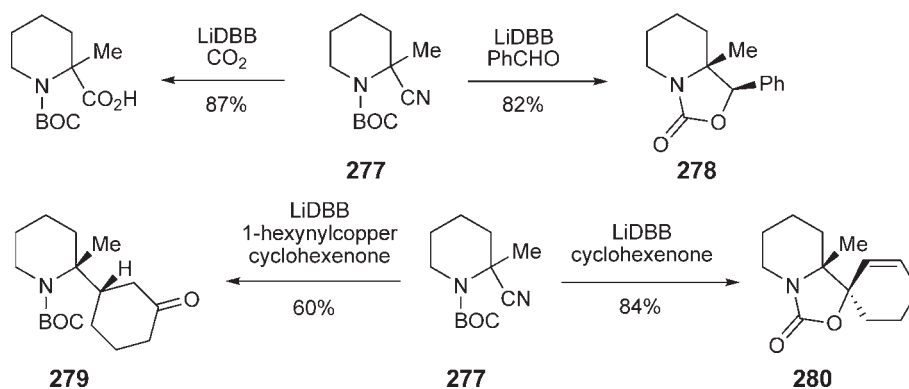
and the yields are generally very high. Decyanation of **269** with sodium borohydride gives dialkyl piperidine **270** with retention of configuration at the 2-position. Anodic cyanation of substituted piperidines such as **270** gives 6-cyano-piperidine **271** with a *trans*-relationship between the 2- and 6-positions <2003OBC547>. Further stereoselective alkylation is then possible at the 6-position to give 2,4,6-*syn*-trialkyl piperidines **272**.

The stereochemistry of alkylation in 2-cyano-6-alkylpiperidines is controlled by the substituent on nitrogen. When the N-substituent is a group such as phenyl or benzyl, such as in *N*-benzylpiperidine **273**, alkylation gives predominantly the 2,6-*cis*-dialkyl product **274**, with retention of stereochemistry with regard to the cyano group (Equation 27). However, when the N-substituent is a carbamate, such as in *tert*-butoxycarbonylpiperidine **275**, alkylation results in the formation of the 2,6-*trans*-dialkyl product **276** (Equation 28) <2005T3371>.

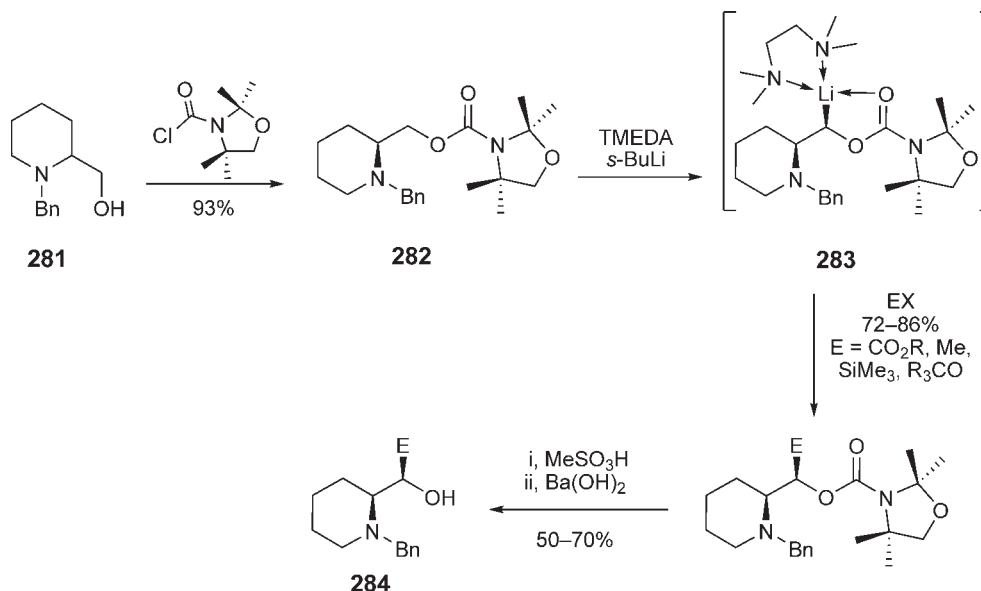


N-*tert*-Butoxycarbonyl-2-cyanopiperidines such as **277** undergo reductive decyanation–lithiation with lithium di-*tert*-butylbiphenylide (LiDBB) to give α -lithiopiperidines which can then undergo addition of numerous electrophiles, to give 2-substituted piperidines. The addition of aldehydes and ketones results in formation of bicyclic carbamates such as **278**. Transmetalation of the initial lithiate, with hexynylcopper, forms the cuprate which results in the formation of the 1,4-addition product **279** upon addition of enones, such as cyclohexenone, while the lithiate gives only 1,2-addition product **280** (Scheme 66) <2004OL2745>.

Carbamate **282**, derived from *N*-benzylpiperidine-2-methanol **281**, undergoes stereoselective deprotonation when treated with *sec*-butyllithium and tetramethylethylenediamine to give lithiate **283**, which can be trapped with numerous electrophiles to give, after hydrolysis of the carbamate, a single diastereoisomer of β -hydroxy piperidines **284** (Scheme 67) <1999S1915>.



Scheme 66

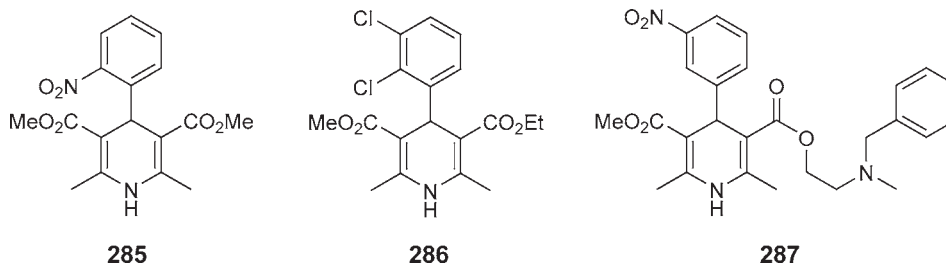


Scheme 67

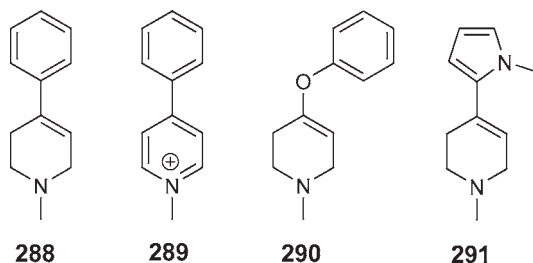
7.04.5 Important Compounds and Applications

The dihydropyridine, tetrahydropyridine, and piperidine ring systems are found in numerous natural and synthetic compounds, many of which have interesting pharmacological properties. This section discusses a small selection of compounds that have been synthesized and studied because of their interesting biological properties.

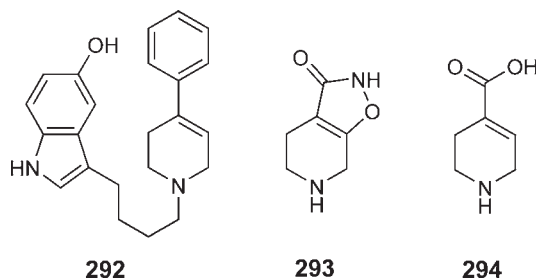
1,4-Dihydropyridines continue to be widely studied and clinically used as calcium channel antagonists. Compounds such as nifedipine **285**, felodipine **286**, and nicardipine **287** are standard clinically used medicines for the treatment of cardiovascular diseases such as hypertension. 1,4-Dihydropyridines have been discovered to have numerous other biological activities and a review of their diverse use as medicinal compounds was published in 2003 [\[2003MI2\]](#).



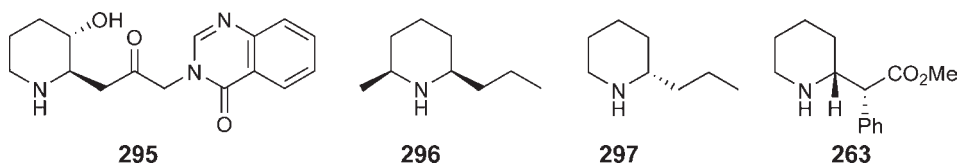
The tetrahydropyridine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) **288** is a well-known neurotoxin that induces symptoms like those for Parkinson's disease. The toxic effects of this compound have been attributed to its oxidation by monoamine oxidase (MAO) to form the pyridine MPP⁺ **289**. MPP⁺ migrates into the mitochondria of neural cells inhibiting the production of ATP and results in cell death <2000MI1, 2001MI1>. Numerous compounds, such as 4-phenoxy- **290**<1997BMC1519> and 4-pyrrole-tetrahydropyridines **291** <2002BMC3031>, have been modelled on MPTP in an attempt to inhibit MAO without exhibiting neurotoxic effects.



Many other 1,2,3,6-tetrahydropyridines that have neural activity have been synthesized. For example, oxindole **292** <1992JMC4020> is a potent dopamine autoreceptor agonist and was originally developed for the treatment of schizophrenic syndromes. Gaboxadol (also known as THIP) **293**, an analogue of isoguvacine **294**, is a powerful GABA-A receptor agonist and is currently being investigated as a new treatment for sleep disorders <2006MI2>. A review on other medicinal tetrahydropyridines was published in 2005 <2005CME551>.



The piperidine skeleton is found in hundreds of natural alkaloids and synthetic compounds, and an in-depth summary of these compounds is beyond the scope of this work. It has been noticeable that in the past 10 years the synthetic endeavours toward these piperidine alkaloids have focused on asymmetric methods to develop these compounds. Recent examples of the asymmetric synthesis of piperidine alkaloids include the synthesis of the potent antimalarial compound (+)-febrifugine **295**, using 1,3-dipolar cycloadditions of 2,3,4,5-tetrahydropyridine *N*-oxides (see Section 7.04.3.1) <2002JMC2563, 2005SL346>, pine weevil antifeedant dihydropinidine **296**<1998T13505, 2006TA1074, 2003JA2878>, and neurotoxin coniine **297**<2000TL8769, 2004CC2324>. Recently, asymmetric synthesis has allowed the sale of pure (+)-*threo* methylphenidate **263**, which is the pharmacologically active isomer <1998JME591, 1999JOC1750> used for the treatment of attention-deficit hyperactivity disorder (ADHD).

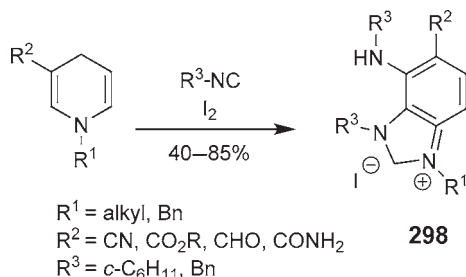


7.04.6 Further Developments

Recently reported has been a comprehensive experimental and theoretical study of the Diels-Alder reaction of 1,2-dihydropyridines such as **56**, **94** and **112** with numerous dienophiles to form 2-azabicyclo[2.2.2]octenes <2007JOC3458>. It was discovered that in all cases the kinetic preference was for the *endo*-adduct. Theoretical calculations showed that for the dienophile methyl vinyl ketone the total transition state energy favored the

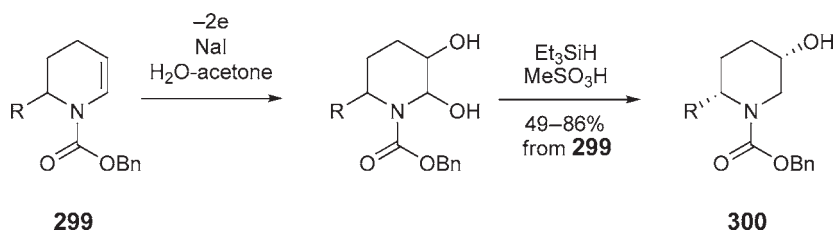
exo-adduct however total entropy effects, which favor the *endo*-adduct, dominate resulting in an overall preference for the *endo* product.

A recent discovery has been the unprecedented double insertion of isocyanides into 1,4-dihydropyridines, bearing an electron-withdrawing group at the 3-position, resulting in the formation of substituted benzimidazolium salts **298** (Scheme 68) <2007AGE3043>.



Scheme 68

Electrochemical oxidation of 2-substituted-1,2,3,4-tetrahydropyridines **299** allows access to the 2-substituted-5-hydroxypiperidines **300** where the relationship between the two substituents is *cis* (Scheme 69) <2007JES(E)31>. Conventional oxidation of **299** using a range of standard reagents gave predominately the 2,5-*trans* isomer.



Scheme 69

References

- 1951JOC1259 H. H. Fax, J. I. Lewis, and W. Wenner, *J. Org. Chem.*, 1951, **16**, 1259.
 1977OS118 G. P. Claxton, L. Allen, and J. M. Grisar, *Org. Synth.*, 1977, **56**, 118.
 1990TL1995 C. Marazano, Y. Yannie, M. Mehmandoust, and B. C. Das, *Tetrahedron Lett.*, 1990, **31**, 1995.
 1992JMC4020 H. Boettcher, G. Barnickel, H. H. Hausberg, A. F. Haase, C. A. Seyfried, and V. Eiermann, *J. Med. Chem.*, 1992, **35**, 4020.
 1995OM1586 A. C. Reduto dos Reis and L. S. Hegedus, *Organometallics*, 1995, **14**, 1586.
 1995SL565 S. T. Handy, P. A. Grieco, C. Mineur, and L. Ghosez, *Synlett*, 1995, 565.
 1995T7161 D. W. Bell and E. V. Anslyn, *Tetrahedron*, 1995, **51**, 7161.
 1995TL2059 L. Gil, A. Gateau-Olesker, Y.-S. Wong, L. Chernatova, C. Marazano, and B. C. Das, *Tetrahedron Lett.*, 1995, **36**, 2059.
 1996CC653 N. De Kimpe, M. Keppens, and G. Fonck, *J. Chem. Soc., Chem. Commun.*, 1996, 635.
 1996JA12045 H. Rudler, M. Audouin, A. Parlier, B. Martin-Vaca, R. Goumont, T. Durand-Réville, and J. Vaissermann, *J. Am. Chem. Soc.*, 1996, **118**, 12045.
 1996JA8489 M. Nakamura, A. Hirai, and E. Nakamura, *J. Am. Chem. Soc.*, 1996, **118**, 8489.
 1996JOC1023 H. Ina, M. Ito, and C. Kibayashi, *J. Org. Chem.*, 1996, **61**, 1023.
 1996JOC2185 J. Barluenga, M. Tomás, V. Kouznetsov, A. Suárez-Sobrinho, and E. Rubio, *J. Org. Chem.*, 1996, **61**, 2185.
 1996JOC7147 L. Ripa and A. Hallberg, *J. Org. Chem.*, 1996, **61**, 7147.
 1996TL7749 A. Couture, E. Deniau, P. Grandelaudon, and S. Lebrun, *Tetrahedron Lett.*, 1996, **37**, 7749.
 1997BMC1519 C. Franot, S. Mabie, and N. Castagnoli, *Bioorg. Med. Chem.*, 1997, **5**, 1519.
 1997CC213 R. Lavilla, F. Gullón, X. Barón, and J. Borsch, *J. Chem. Soc., Chem. Commun.*, 1997, 213.
 1997JOC595 L. Ripa and A. Hallberg, *J. Org. Chem.*, 1996, **62**, 595.

- 1997JOC2298 G. Zhai and B. Ganem, *J. Org. Chem.*, 1996, **62**, 2298.
1997MI1 M. Fuji, K. Nakamura, and A. Ohno, *Trends Heterocycl. Chem.*, 1997, **5**, 17.
1997SL786 D. I. MacGee and M. L. Lee, *Synlett*, 1997, 786.
1997T2271 J. E. Baldwin, L. Bischoff, T. D. W. Claridge, F. A. Heupel, D. R. Spring, and R. C. Whitehead, *Tetrahedron*, 1997, **53**, 2271.
1997TL6253 M. S. Shepard and E. M. Carreira, *Tetrahedron*, 1997, **53**, 16253.
1997TA109 C. Louise and C. Hootele, *Tetrahedron Asymmetry*, 1997, **8**, 109.
1997TA857 M. S. de Castro, L. Salazar, and J. V. Sinisterra, *Tetrahedron Asymmetry*, 1997, **8**, 857.
1997TL3151 L. A. Paquette and J. Tae, *Tetrahedron Lett.*, 1997, **38**, 3151.
1997TL6905 L. Brandsma, N. A. Nedolya, H. D. Verkruijsse, N. L. Owen, D. Li, and B. A. Trofimov, *Tetrahedron Lett.*, 1997, **38**, 6905.
1998CHE387 M.-G. A. Shvekhgheimer, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, **34**, 387.
1998CPH1 D. B. Chesnut, *Chem. Phys.*, 1998, **231**, 1.
1998EJO1213 A. Hilgeroth, U. Baumeister, and F. W. Heinemann, *Eur. J. Org. Chem.*, 1998, 1213.
1998TL2707 D. L. Thai, M. T. Sapko, C. T. Reiter, D. E. Bierer, and J. M. Perel, *J. Med. Chem.*, **41**, 591.
1998JOC2728 R. Lavilla, O. Coll, R. Kumar, and J. Borsch, *J. Org. Chem.*, 1998, **63**, 2728.
1998JOC10001 R. Lavilla, X. Barón, O. Coll, F. Gullón, C. Masdeu, and J. Borsch, *J. Org. Chem.*, 1998, **63**, 10001.
1998JOM119 B. Martin-Vaca, H. Rudler, M. Audouin, M. Nicolas, T. Durand-Réville, and B. Vissière, *J. Organomet. Chem.*, 1998, **567**, 119.
1998JST217 O. V. Shishkin, *J. Mol. Struct.*, 1998, **447**, 217.
1998SL55 D. Craig, R. McCaque, G. A. Potter, and M. R. V. Williams, *Synlett*, 1998, 55.
1998SL58 D. Craig, D. R. McCaque, G. A. Potter, and M. R. V. Williams, *Synlett*, 1998, 58.
1998OM361 H. Rudler, B. Martin-Vaca, M. Nicolas, M. Audouin, and J. Vaissermann, *Organometallics*, 1998, **17**, 361.
1998SL1337 A. Nazih, M.-R. Schneider, and A. Mann, *Synlett*, 1998, 1337.
1998T10349 P. Mangeney, L. Hamon, S. Raussou, N. Urbain, and A. Alexakis, *Tetrahedron*, 1998, **54**, 10349.
1998T11027 H. Junge and G. Oehme, *Tetrahedron*, 1998, **54**, 11027.
1998T13505 H. Takahata, Y. Yotsui, and T. Momose, *Tetrahedron*, 1998, **54**, 13505.
1998TL2707 M. B. L. Davies, L. M. Hodges, and C. T. Thornley, *Tetrahedron Lett.*, 1998, **39**, 2707.
1998TL5293 M. R. Marzabadi, X. Hong, and C. Gluchowski, *Tetrahedron Lett.*, 1998, **39**, 5293.
1998TL5417 J. E. Baldwin, D. R. Spring, and R. C. Whitehead, *Tetrahedron Lett.*, 1998, **39**, 5417.
1998TL9275 M.-L. Bannasar, C. Juan, and J. Bosch, *Tetrahedron Lett.*, 1998, **39**, 9275.
1999AG3186 B. Alper, C. Meyers, A. Lerchner, D. R. Siegel, and E. M. Carreira, *Angew. Chem.*, 1999, **38**, 3186.
1999EJO2515 S. Schleich and G. Helmchen, *Eur. J. Org. Chem.*, 1999, 2515.
1999CEJ3154 J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, and R. C. Whitehead, *Chem. Eur. J.*, 1999, **5**, 3154.
1999IC4700 K. Hensen, A. Lemke, and T. Stumpf, *Inorg. Chem.*, 1999, **38**, 4700.
1999JA5811 J. Yin and L. S. Liebskind, *J. Am. Chem. Soc.*, 1999, **121**, 5811.
1999JA6509 H. M. L. Davies, T. Hansen, D. W. Hopper, and S. A. Panaro, *J. Am. Chem. Soc.*, 1996, **121**, 6509.
1999JOC1750 M. Prashard, H. Y. Kim, Y. Lu, Y. Liu, D. Har, O. Repic, T. J. Blacklock, and P. Giannousis, *J. Org. Chem.*, 1999, **64**, 1750.
1999MI1 P. B. Cherkasov, M. Jonsson, and V. Galkin, *J. Mol. Graphics Model.*, 1999, **17**, 28.
1999OL175 Y. Matsumura, Y. Kanda, K. Shirai, O. Onomura, and T. Maki, *Org. Lett.*, 1999, **1**, 175.
1999OL973 M. T. Reding and T. Fukuyama, *Org. Lett.*, 1999, **1**, 973.
1999S1814 Y. Takeuchi, M. Hattori, H. Abe, and T. Harayama, *Synthesis*, 1999, 1814.
1999S1915 B. Weber, J. Schwerdtfeger, R. Frohlich, A. Gohrt, and D. Hoppe, *Synthesis*, 1999, 1915.
1999T2659 S. Lebrun, A. Couture, E. Deniau, and P. Grandelaudon, *Tetrahedron*, 1999, **55**, 2659.
1999T14995 D. Passarella, M. Martinelli, N. Llor, M. Amat, and J. Bosch, *Tetrahedron*, 1999, **55**, 14995.
1999TL3961 M.-L. Bannasar, E. Zulaica, C. Juan, L. Llauger, and J. Bosch, *Tetrahedron Lett.*, 1999, **40**, 3961.
1999TL4547 M. Depature, D. Siri, J. Grimaldi, and J. Hatem, *Tetrahedron Lett.*, 1999, **40**, 4547.
2000CC2459 M.-L. Bannasar, C. Juan, and J. Bosch, *J. Chem. Soc., Chem. Commun.*, 2000, 2459.
2000CEJ1763 R. Lavilla, R. Kumar, O. Coll, C. Maseu, A. Spada, J. Bosch, E. Espinosa, and E. Molins, *Chem. Eur. J.*, 2000, **6**, 1763.
2000EJO245 A. Hilgeroth, U. Baumeister, and F. W. Heinemann, *Eur. J. Org. Chem.*, 2000, 245.
2000EJO275 M. Depature, J. Diewok, J. Grimaldi, and J. Hatem, *Eur. J. Org. Chem.*, 2000, 275.
2000JP21857 X.-Q. Zhu, H.-L. Zou, P.-W. Yuan, Y. Lie, L. Cao, and J.-P. Cheng, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1857.
2000JC637 A. Banerji, *J. Indian Chem. Soc.*, 2000, **77**, 637.
2000JOC3853 J.-P. Cheng, X.-Q. Zhu, Y. Sun, F. Bi, and J. He, *J. Org. Chem.*, 2000, **65**, 3853.
2000JOC7445 A. F. Moretto and L. S. Liebskind, *J. Org. Chem.*, 2000, **65**, 7445.
2000JOC8158 X.-Q. Zhu, B.-J. Zhao, and J.-P. Cheng, *J. Org. Chem.*, 2000, **65**, 8158.
2000MI1 A. Nicotra and S. Parvez, *Toxicology*, 2000, **153**, 157.
2000PCA530 F. Dubnikova and A. Lifshitz, *J. Phys. Chem. A*, 2000, **104**, 530.
2000OL155 T. J. Wilkinson, N. W. Stehle, and P. Beak, *Org. Lett.*, 2000, **2**, 155.
2000OL1533 R. Lavilla, A. Spada, and J. Bosch, *Org. Lett.*, 2000, **2**, 1533.
2000OL3861 T. Donohoe, A. J. McRiner, and P. Sheldrake, *Org. Lett.*, 2000, **2**, 3861.
2000OL3909 H. C. Malinakova and L. S. Liebskind, *Org. Lett.*, 2000, **2**, 3909.
2000MRC680 M. S. Morales-Rios, A. Medina, V. Pérez-Alvarez, and P. Joseph-Nathan, *Magn. Reson. Chem.*, 2000, **38**, 680.
2000S1781 S. Laschat and T. Dickner, *Synthesis*, 2000, 1781.
2000T7969 T. N. Van and N. De Kimpe, *Tetrahedron*, 2000, **56**, 7969.
2000T9227 G. R. Krow, J. Yuan, Y. Fang, M. D. Meyer, D. J. Anderson, J. E. Campbell, and P. J. Carroll, *Tetrahedron*, 2000, **56**, 9227.
2000TA4559 A. Sobolev, M. C. R. Franssen, N. Makarova, G. Duburs, and A. de Groot, *Tetrahedron Asymmetry*, 2000, **11**, 4559.
2000TL6067 L. Gil, R. P. de F. Gil, D. C. dos Santos, and C. Marazano, *Tetrahedron Lett.*, 2000, **41**, 6067.
2000TL7685 Y. Matsumura, Y. Nakamura, T. Maki, and O. Onomura, *Tetrahedron Lett.*, 2000, **41**, 7685.
2000TL7779 T.-P. Loh, P.-L. Lye, R.-B. Wang, and K. Y. Sim, *Tetrahedron Lett.*, 2000, **41**, 7779.
2000TL8769 F. Bois, D. Gardette, and J.-C. Gramain, *Tetrahedron Lett.*, 2000, **41**, 8769.

- 2001CEJ4715 A. M. Belostotkii, M. Shokhen, H. E. Gottlieb, and A. Hassner, *Chem. Eur. J.*, 2001, **7**, 4715.
- 2001JA12477 C. Shu, A. Alcudia, J. Yin, and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2001, **123**, 12477.
- 2001(P1)1435 T. Donohoe, A. J. McRiner, M. Helliwell, and P. Sheldrake, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1435.
- 2001JOC53 W. Aelterman, N. De Kimpe, V. Tyvorskii, and O. Kulinkovich, *J. Org. Chem.*, 2001, **66**, 53.
- 2001JOC344 X.-Q. Zhu, H.-Y. Wang, J.-S. Wang, and Y.-C. Liu, *J. Org. Chem.*, 2001, **66**, 344.
- 2001JOC1805 G. R. Krow, Y. B. Lee, W. S. Lester, N. Liu, J. Yuan, J. Duo, S. B. Herzon, Y. Nguyen, and D. Zacharias, *J. Org. Chem.*, 2001, **66**, 1805.
- 2001JOC7898 H. M. L. Davies, M. Hodges, and T. M. Gregg, *J. Org. Chem.*, 2001, **66**, 7898.
- 2001JOM380 S. Carballares and D. Craig, *J. Organomet. Chem.*, 2001, **624**, 380.
- 2001MI1 S. Przedborski, V. Jackson-Lewis, A. B. Naini, M. Jakowec, G. Petzinger, R. Miller, and M. Akram, *J. Neurochem.*, 2001, **76**, 1265.
- 2001MRC406 J. Jung, L. Kim, C. K. Lee, Y. H. Cho, S.-H. Ahn, and Y. Lim, *Magn. Reson. Chem.*, 2001, **39**, 406.
- 2001NJC8 J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaria, R. Corzo-Suárez, and S. Garcia-Granda, *New J. Chem.*, 2001, **25**, 8.
- 2001OL201 G. Zhao, U. C. Deo, and B. Ganem, *Org. Lett.*, 2001, **3**, 201.
- 2001OL3009 D. A. Evans, K. A. Scheidt, and C. W. Downey, *Org. Lett.*, 2001, **3**, 3009.
- 2001OL3217 D. L. Comins and A. L. Williams, *Org. Lett.*, 2001, **3**, 3217.
- 2001SI784 D. J. Wallace, A. D. Gibb, I. F. Cottrell, D. J. Kennedy, K. M. J. Brands, and U. H. Dolling, *Synthesis*, 2001, 1784.
- 2001TA2099 E. Vázquez, A. Galindo, D. Gnecco, and S. Bernes, *Tetrahedron Asymmetry*, 2001, **12**, 2099.
- 2001TL589 C. Pays and P. Mangeney, *Tetrahedron Lett.*, 2001, **42**, 589.
- 2001TL3149 H. M. L. Davies and P. Ren, *Tetrahedron Lett.*, 2001, **42**, 3149.
- 2001TL5821 D. A. Klumpp, P. S. Beauchamp, G. V. Sanchez, S. Aguirre, and S. de Leon, *Tetrahedron Lett.*, 2001, **42**, 5821.
- 2001TL8369 J.-C. Adelbrecht, D. Craig, and S. Thorimbert, *Tetrahedron Lett.*, 2001, **42**, 8369.
- 2002AGE2535 C. Koradin, K. Polborn, and P. Knochel, *Angew. Chem., Int. Ed.*, 2002, **41**, 2535.
- 2002BMC3031 P. Bissel, M. C. Bigley, K. Castagnoli, and N. Castagnoli, *Bioorg. Med. Chem.*, 2002, **10**, 3031.
- 2002HCO391 J. V. Correia, M. N. Simoes, A. C. Ferreira, L. R. Galveia, and F. M. S. Brito Palma, *Heterocycl. Commun.*, 2002, **8**, 391.
- 2002JA4968 F. Viton, G. Bernardinelli, and E. P. Kündig, *J. Am. Chem. Soc.*, 2002, **124**, 4968.
- 2002(JP1)1141 R. Lavilla, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1141.
- 2002JMC2563 H. Kikuchi, H. Tasaka, S. Hirai, Y. Takaya, Y. Iwabuchi, H. Ooi, S. Hatakeyama, H.-S. Kim, Y. Wataya, and Y. Oshima, *J. Med. Chem.*, 2002, **45**, 2563.
- 2002JOC5683 H. M. L. Davies and L. M. Hodges, *J. Org. Chem.*, 2002, **67**, 5683.
- 2002JOC7465 M.-L. Bannasar, E. Zulaica, C. Juan, Y. Alonso, and J. Bosch, *J. Org. Chem.*, 2002, **67**, 7465.
- 2002OL1611 D. L. Comins, X. Zheng, and R. R. Goehring, *Org. Lett.*, 2002, **4**, 1611.
- 2002PJC235 E. Sliwinska, K. Palewska, A. Lewanowicz, J. Lipinski, J. Sworakowski, R. Gancarz, and S. Nespurek, *Pol. J. Chem.*, 2002, **76**, 235.
- 2002T5747 S. Marchalin, M. Chudik, K. Cvopová, J. Kozišek, J. Leško, and A. Dačh, *Tetrahedron*, 2000, **58**, 5747.
- 2002SL895 R. Malassene, L. Toupet, J.-P. Hurvois, and C. Moinet, *Synlett*, 2002, 895.
- 2002T8099 M.-L. Bannasar, T. Roca, M. Moneris, C. Juan, and J. Bosch, *Tetrahedron*, 2002, **58**, 8099.
- 2002T8299 N. Takenaka, Y. Huang, and V. H. Rawal, *Tetrahedron*, 2000, **58**, 8299.
- 2002T10113 J. B. Sweeny, A. Tavassoli, N. B. Carter, and J. F. Hayes, *Tetrahedron*, 2002, **58**, 10113.
- 2002TL741 M. J. S. Carpes and C. R. D. Correia, *Tetrahedron Lett.*, 2002, **43**, 741.
- 2003CL1064 S. H. Mashraqui and M. A. Karnik, *Chem. Lett.*, 2003, **32**, 1064.
- 2003CPB929 M. L. Jimeno, I. Alkorta, C. Cano, N. Jagerovic, P. Goya, J. Elguero, and C. Foces-Foces, *Chem. Pharm. Bull.*, 2003, **51**, 929.
- 2003EJO3693 F.-X. Felpin and J. Lebreton, *Eur. J. Org. Chem.*, 2003, 3693.
- 2003JA2878 C. Shu and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2003, **125**, 2878.
- 2003JA9026 R. G. Arrayás and L. S. Liebskind, *J. Am. Chem. Soc.*, 2003, **125**, 9026.
- 2003JA14133 R. A. Fernandes, A. Stimac, and Y. Yamamoto, *J. Am. Chem. Soc.*, 2003, **125**, 14133.
- 2003JOC4382 T.-Q. Ding and D.-C. Fang, *J. Org. Chem.*, 2003, **68**, 4382.
- 2003JST177 I. Novak and H. Jiang, *J. Mol. Struct.*, 2003, **645**, 177.
- 2003MI1 C. Yáñez, J. Núñez-Vergara, and J. A. Squella, *Electroanalysis*, 2003, **15**, 1771.
- 2003MI2 D. J. Triggle, *Mini-Rev. Med. Chem.*, 2003, **3**, 215.
- 2003CEJ3937 X.-Q. Zhu, L. Cao, Y. Yang, J.-Y. Lu, J.-S. Wang, and J.-P. Cheng, *Chem. Eur. J.*, 2003, **9**, 3937.
- 2003OBC547 R. Malassene, E. Vanquelef, L. Toupet, J.-P. Hurvois, and C. Moinet, *Org. Biomol. Chem.*, 2003, **1**, 547.
- 2003OL321 J. T. Kuethe, C. A. Brooks, and D. L. Comins, *Org. Lett.*, 2003, **5**, 321.
- 2003OL717 R. Lavilla, M. C. Bernabeu, I. Carranco, and J. L. Diaz, *Org. Lett.*, 2003, **5**, 717.
- 2003OL4871 B. H. Bui and P. R. Schreiner, *Org. Lett.*, 2003, **5**, 4871.
- 2003T2953 P. M. Weintraub, J. S. Sabol, J. M. Kane, and D. R. Borcherting, *Tetrahedron*, 2003, **59**, 2953.
- 2003T3099 K. A. Tehrani, M. D'hooghe, and N. De Kimpe, *Tetrahedron*, 2003, **59**, 3099.
- 2003T7555 Y. Arakawa, T. Murakami, F. Ozawa, Y. Arakawa, and S. Yoshifuji, *Tetrahedron*, 2003, **59**, 7555.
- 2003T8543 O. Andrey, B. Camuzat-Dedenis, L. Chabaud, K. Julienne, Y. Landais, L. Parra-Rapado, and P. Renaud, *Tetrahedron*, 2003, **59**, 8543.
- 2003T9179 M. Suarez, Y. Verdecia, B. Illezcas, R. Martinez-Alvarez, A. Alvarez, E. Ochoa, C. Seoana, N. Kayali, and M. Martin, *Tetrahedron*, 2003, **59**, 9179.
- 2003T9729 D. M. Hodgson, T. J. Miles, and J. Witherington, *Tetrahedron*, 2003, **59**, 9729.
- 2003TL4711 M.-L. Bannasar, E. Zulaica, T. Roca, Y. Alonso, and M. Moneris, *Tetrahedron Lett.*, 2003, **44**, 4711.
- 2003TL8449 I. Carranco, J. L. Diaz, O. Jimenez, and R. Lavilla, *Tetrahedron Lett.*, 2003, **44**, 8449.
- 2004CC2324 N. Gommermann and P. Knochel, *J. Chem. Soc., Chem. Commun.*, 2004, 2324.
- 2004CGD701 M. T. Kirchner, L. S. Reddy, G. R. Desiraju, R. K. R. Jetti, and R. Boese, *Crystal Growth and Design*, 2004, **4**, 701.
- 2004COR715 R. Lavilla, *Curr. Org. Chem.*, 2004, **8**, 715.
- 2004EJO1057 A. A. Maia, S. Mons, R. P. de, F. Gil, and C. Marazano, *Eur. J. Org. Chem.*, 2004, 1057.
- 2004JA14338 S. Suga, T. Nishisa, D. Yamada, A. Nagaki, and J. Yoshida, *J. Am. Chem. Soc.*, 2004, **126**, 14338.
- 2004JRS353 K. L. A. Chan, O. S. Fleming, S. G. Kazarian, D. Vassou, G. D. Chryssikos, and V. Gionis, *J. Raman Spectrosc.*, 2004, **35**, 353.

- 2004JST171 E. Vessally, H. Kavian, S. Arshadi, and H. Pirelahi, *J. Mol. Struct.*, 2004, **678**, 171.
- 2004JTC557 O. V. Shishkin and R. I. Zubatyuk, *J. of Struct. Chem.*, 2004, **45**, 557.
- 2004LOC168 A. A. Maia, R. P. Freitas-Gil, L. F. Gil, and C. Marazano, *Lett. Org. Chem.*, 2004, **1**, 168.
- 2004OL2745 S. A. Wolckenhauer and S. D. Rychnovsky, *Org. Lett.*, 2004, **6**, 2745.
- 2004OL3933 R. Abou-Jneid, S. Ghoulami, M.-T. Martin, E. T. H. Dau, N. Travert, and A. Al-Mourabit, *Org. Lett.*, 2004, **6**, 3933.
- 2004OL5023 T. J. Harrison and G. R. Dake, *Org. Lett.*, 2004, **6**, 5023.
- 2004RCM590 H. Salehi, Q. Li, H. Yin, and Q. Guo, *Rapid Commun. Mass Spectrom.*, 2004, **18**, 590.
- 2004S735 L. Brandsma and N. A. Nedolya, *Synthesis*, 2004, 735.
- 2004T1701 M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701.
- 2004TL5881 O. A. Tarasova, N. A. Nedolya, L. Brandsma, and A. I. Albanov, *Tetrahedron Lett.*, 2004, **45**, 5881.
- 2004TL8177 S. Furukubo, N. Moriyama, O. Onomura, and Y. Matsumura, *Tetrahedron Lett.*, 2004, **45**, 8177.
- 2005CME551 N. N. Mateeva, L. L. Winfield, and K. K. Redda, *Curr. Med. Chem.*, 2005, **12**, 551.
- 2005BML3423 H. R. Memarian and A. Mirjafari, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3423.
- 2005BML3501 Z. Ye, L. Guo, K. J. Barakat, P. G. Pollard, B. L. Palucki, I. K. Sebhat, R. K. Bakshi, R. Tang, R. N. Kalyani, A. Vongs, *et al.*, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3501.
- 2005JBS112 J. A. DaSilva, C. S. Barria, C. Jullian, P. Navarrete, L. N. Vergara, and J. A. Squella, *J. Braz. Chem. Soc.*, 2005, **16**, 112.
- 2005EJO1052 A. C. L. B. Trindade, D. C. dos Santos, L. Gil, C. Marazano, and R. P. de F. Gil, *Eur. J. Org. Chem.*, 2005, 1052.
- 2005JA13386 D. Carmona, M. P. Lamata, F. Viguri, R. Rodriguez, L. A. Oro, F. J. Lahoz, A. I. Balana, T. Tejero, and P. Merino, *J. Am. Chem. Soc.*, 2005, **127**, 13386.
- 2005JCO33 I. Carranco, J. L. Diaz, O. Jiménez, M. Vendrell, F. Albericio, M. Royo, and R. Lavilla, *J. Comb. Chem.*, 2005, **7**, 33.
- 2005JOC2075 K.-H. Park and W. J. Marshall, *J. Org. Chem.*, 2005, **70**, 2075.
- 2005JOC2368 A. Lemire, D. Beaudoin, M. Grenon, and A. B. Charette, *J. Org. Chem.*, 2005, **70**, 2368.
- 2005JOC3256 A. Alvarez, E. Ochoa, Y. Verdecia, M. Suárez, M. Solá, and N. Martin, *J. Org. Chem.*, 2005, **70**, 3256.
- 2005JOC5221 D. L. Comins, J. T. Kuethe, T. M. Miller, F. C. Févriér, and C. A. Brooks, *J. Org. Chem.*, 2005, **70**, 5221.
- 2005JOC7324 E. G. Occhiato, F. L. Galbo, and A. Guarna, *J. Org. Chem.*, 2005, **70**, 7324.
- 2005JOC8208 M. de R. S. Salvatori, R. Abou-Jneid, S. Ghoulami, M.-T. Martin, A. Zaparucha, and A. Al-Mourabit, *J. Org. Chem.*, 2005, **70**, 8208.
- 2005ST195 H.-O. Ho and W.-K. Li, *J. Mol. Struct.*, 2005, **723**, 195.
- 2005MI1 I. Novak, *J. Chem. Inf. Model.*, 2005, **45**, 334.
- 2005MI2 D. Vassou, V. Gionis, and G. D. Chryssikos, *Phys. Chem. Glasses*, 2005, **46**, 144.
- 2005MM2167 E. Ihara, A. Kurokawa, T. Koda, T. Muraki, T. Itoh, and K. Inoue, *Macromolecules*, 2005, **38**, 2167.
- 2005OBC670 S. Broussey, V. Bernardes-Génisson, Y. Coppel, A. Quémard, J. Bernadou, and B. Meunier, *Org. Biomol. Chem.*, 2005, **3**, 670.
- 2005OBC1617 Z. Zhang, J. Gao, J.-J. Xia, and G.-W. Wang, *Org. Biomol. Chem.*, 2005, **3**, 1617.
- 2005OL2747 A. Lemire and A. B. Charette, *Org. Lett.*, 2005, **7**, 2747.
- 2005OL4309 N. D. Smith, J. Hayashida, and V. H. Rawal, *Org. Lett.*, 2005, **7**, 4309.
- 2005OL5661 D. W. Young and D. L. Comins, *Org. Lett.*, 2005, **7**, 5661.
- 2005OL5773 A. B. Charette and M. Sales, *Org. Lett.*, 2005, **7**, 5773.
- 2005SL346 A. Ashoorzadeh and V. Caprio, *Synlett*, 2005, 346.
- 2005SL2367 M. Rueping, C. Azap, E. Sugiono, and T. Theissmann, *Synlett*, 2005, 2367.
- 2005T1221 M. N. Matos, C. A. Afonso, and R. A. Batey, *Tetrahedron*, 2005, **61**, 1221.
- 2005T3371 S. A. Wolckenhauer and S. D. Rychnovsky, *Tetrahedron*, 2005, **61**, 3371.
- 2005T8888 Z. Zhao, L. Song, and P. S. Mariano, *Tetrahedron*, 2005, **61**, 8888.
- 2005TL5677 H. Nakano, N. Tsugawa, and R. Fujita, *Tetrahedron Lett.*, 2005, **46**, 5677.
- 2006MI1 M. Mahendra, B. H. Doreswamy, M. A. Sridhar, J. Shashidhara Prasad, A. R. Parecha, J. A. Patel, D. Manvar, K. Dholaria, and A. Shah, *Cryst. Res. Technol.*, 2006, **41**, 92.
- 2006MI2 K. A. Wafford and B. Ebert, *Curr. Opin. Pharmacol.*, 2006, **6**, 30.
- 2006TA1074 C. Eriksson, K. Sjoedin, F. Schlyter, and H.-E. Hoegberg, *Tetrahedron Asymmetry*, 2006, **17**, 1074.
- 2006TL455 E. L. Gall, C. Gosmini, and M. Troupel, *Tetrahedron Lett.*, 2006, **47**, 455.
- 2007AGE3043 C. Masdeu, E. Gómez, N. A. O. Williams, and R. Lavilla, *Angew. Chem., Int. Ed.* 2007, **46**, 3043.
- 2007JOC3458 G. R. Krow, Q. Huang, S. W. Szczepanski, F. H. Hausheer, and P. J. Carroll, *J. Org. Chem.*, 2007, **72**, 3458.
- 2007JES(E)31 S. S. Libendi, T. Ogino, O. Onomura, and Y. Matsumura, *J. Electrochem. Soc.*, 2007, **154**(2), 2007, E31.

Biographical Sketch



David Barker was born in 1974 in Altrincham, UK, and immigrated to Sydney, Australia, in 1983. In 1997, he graduated from the University of Sydney with a B.Sc. degree in organic chemistry with first class honours. He completed his Ph.D. in 2001 from the same university while under the supervision of Professor Margaret Brimble and Dr. Malcolm McLeod. He then spent three years at the School of Medical Sciences at the University of New South Wales working with Larry Wakelin. In 2004, he was appointed as lecturer in medicinal chemistry at the University of Auckland. His research interests center on the synthesis of biologically active natural products recently focusing on complex dincolignans, DNA minor groove binding ligands, and neuroactive alkaloids.

7.05

Pyridines and their Benzo Derivatives: Synthesis

P. A. Keller

University of Wollongong, Wollongong, NSW, Australia

© 2008 Elsevier Ltd. All rights reserved.

7.05.1	Introduction	217
7.05.2	Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component	218
7.05.2.1	Formation of One Bond	218
7.05.2.1.1	Bond formation adjacent to nitrogen	218
7.05.2.1.2	Bond formation between α - and β -carbons	230
7.05.2.1.3	Bond formation between β - and γ -carbons	234
7.05.2.2	Formation of Two Bonds	246
7.05.2.2.1	From [5+1] and [9+1] atom fragments	246
7.05.2.2.2	From [4+2] atom fragments and [8+2] fragments	254
7.05.2.2.3	From [3+3] and [7+3] fragments	273
7.05.2.3	Formation of Three Bonds	282
7.05.2.3.1	From a fragment containing four atoms and two one-atom fragments	282
7.05.2.3.2	From fragments containing one, two, and three atoms	282
7.05.2.3.3	From three two-atom fragments	287
7.05.2.4	Formation of Four Bonds	288
7.05.2.4.1	From two two-atom and two one-atom fragments	288
7.05.2.4.2	From three one-atom and, one three-atom fragment	289
7.05.3	Ring Syntheses by Transformations of Another Ring	289
7.05.3.1	From Three-Membered Rings	289
7.05.3.2	From Four-Membered Rings	291
7.05.3.3	From Five-Membered Rings	291
7.05.3.3.1	Carbocyclic rings	291
7.05.3.3.2	From furans, pyrroles, and their benzologues	292
7.05.3.3.3	From oxazoles, isoxazoles, and their benzologues	293
7.05.3.3.4	Other five-membered heterocycles	295
7.05.3.4	From Six-Membered Rings	295
7.05.3.4.1	Pyrans, pyrones, pyrylium salts, and their benzologues	295
7.05.3.4.2	Oxazines, diazines, and their benzologues	297
7.05.3.4.3	Triazines	298
7.05.3.5	From Seven-Membered Rings	298
References		299

7.05.1 Introduction

Chapters entitled 'Pyridines and Their Benzo Derivatives: Synthesis' appear in CHEC(1984) <1984CHEC(2)395> and CHEC-II(1996) <1996CHEC-II(5)167>. Additional reviews are listed throughout this chapter within the relevant sections.

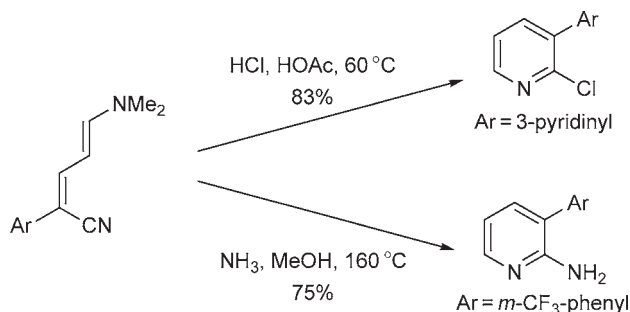
Within each section of this chapter, the syntheses are arranged starting with the completely unsaturated rings, then partially unsaturated, and then through to those that are fully saturated. Within classes, cyclizations are grouped according to mechanism wherever possible. Lactams are classed as tetrahydro derivatives.

7.05.2 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

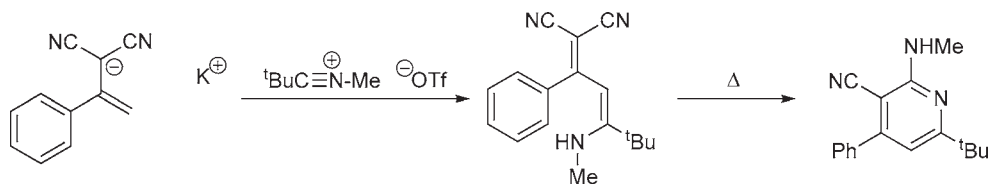
7.05.2.1 Formation of One Bond

7.05.2.1.1 Bond formation adjacent to nitrogen

The cyclization of enamines under acidic and basic conditions gives the 2-chloro and 2-amino derivatives, respectively (**Scheme 1**) <1995JOC3750>. Other cyclizations of enamines include thermal reactions (**Scheme 2**) <1996ACS623>.

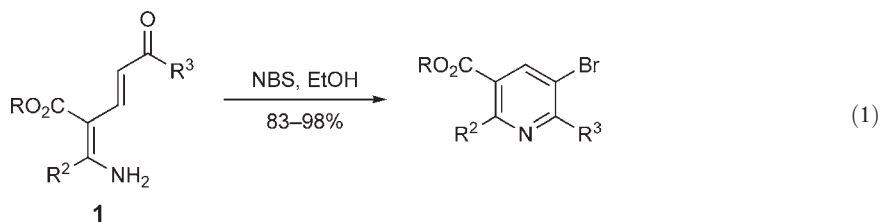


Scheme 1

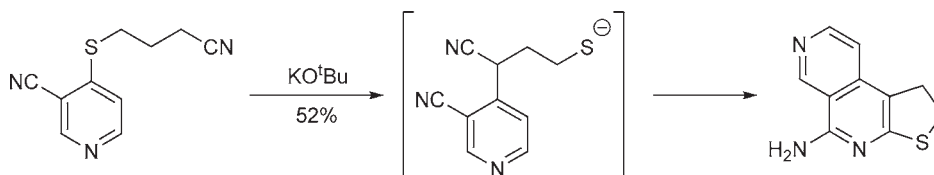


Scheme 2

A bromo cyclization of dienone **1** gives rise to excellent yields of tetrasubstituted pyridines (**Equation 1**) <2004SL811>.

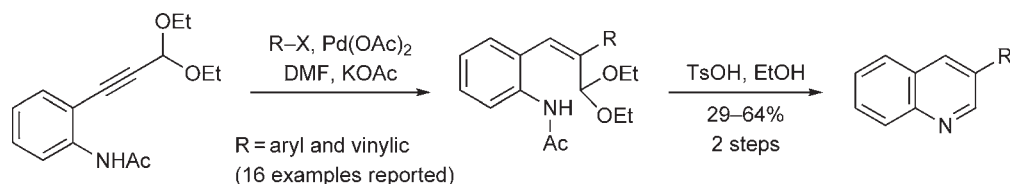


In an interesting reaction, furo- and thieno[2,3-*b*]pyridine derivatives have been synthesized via a facile Smiles rearrangement under basic conditions followed by a cyclization forming the pyridine ring in modest yields (**Scheme 3**) <2001H(55)741>.

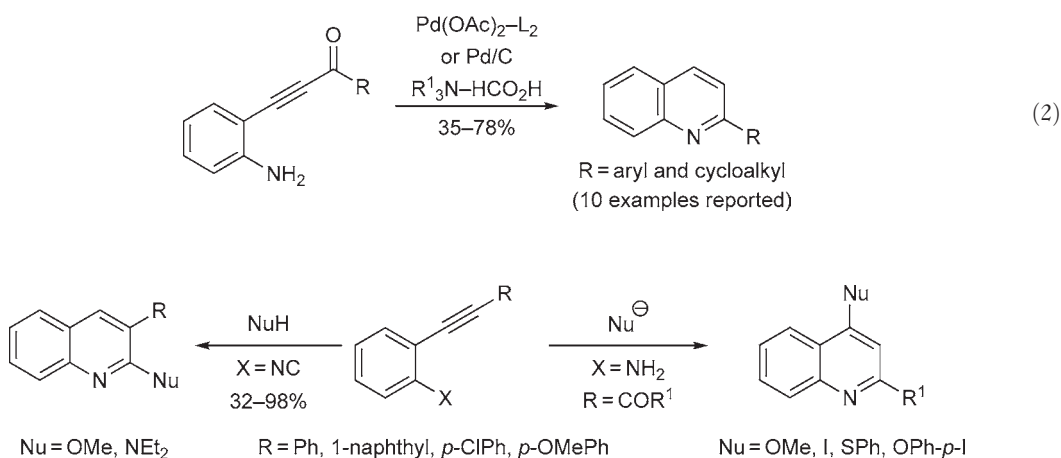


Scheme 3

Palladium-catalyzed reactions of aryl and vinyl halides to suitably substituted aniline alkynes yields alkenes that can be cyclized to quinolines using TsOH in ethanol (**Scheme 4**) <1996T10225>. Similar systems can undergo a hydrogenation/heterocyclization also yielding quinolines (**Equation 2**) <1999SL401>. Similar alkyne systems with unprotected *o*-amino substituents cyclized in the presence of nucleophiles yielding quinolines with 4-substituents (**Scheme 5**) <1999OL1977, 1999T13233>. Exchange of the amino substituent with an isocyanate produces the 2-substituted quinoline in a parallel reaction.

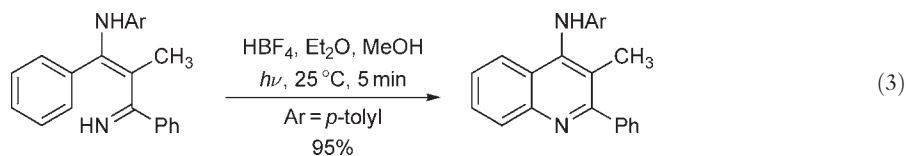


Scheme 4

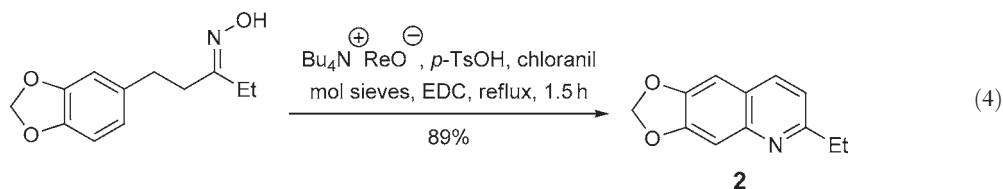


Scheme 5

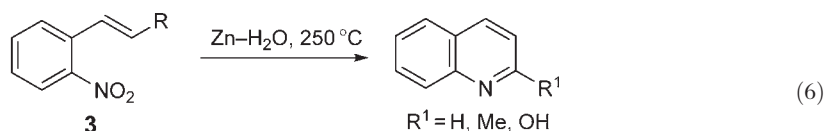
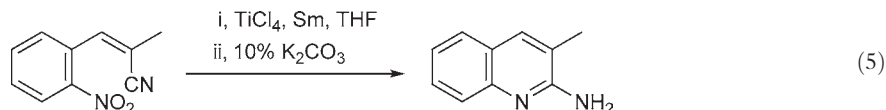
Irradiation of azadienes in the presence of fluoroboric acid gave an excellent yield of the 4-aminoquinoline (**Equation 3**) <1994S1155>.



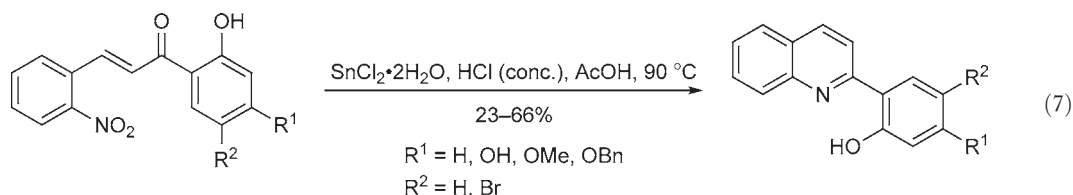
The cyclization of oximes under acid conditions is well documented. Lewis acid-catalyzed conditions prevail in the synthesis of quinoline **2** (**Equation 4**) <1995CL5>.



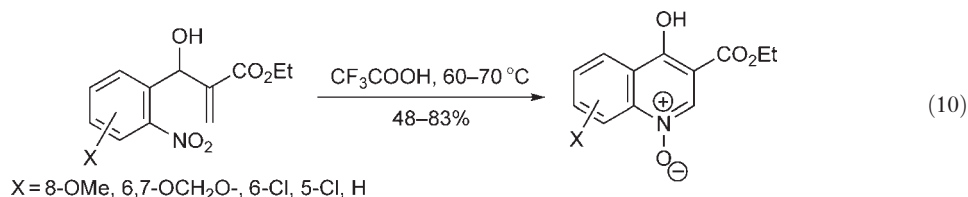
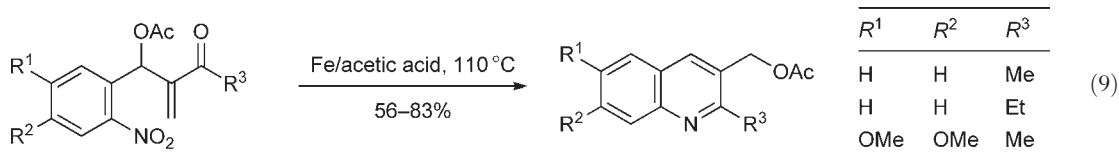
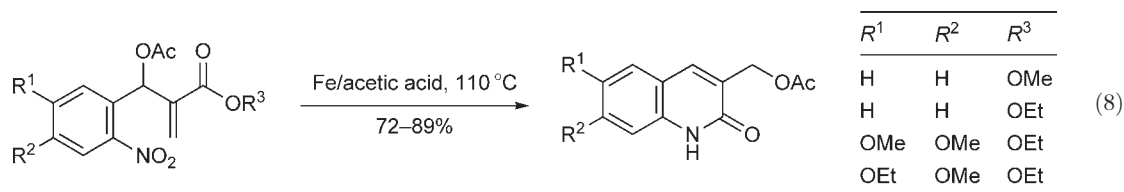
Reductive ring closures to quinolines are also common. An intramolecular reductive coupling of nitrile and nitro groups with low-valent titanium gave the aminoquinoline (Equation 5) <1998JCM398, 1998SC3249, 1998J(P1)2899>. Often it is the preparation of the precursor to reductive ring closure that dictates the final reaction outcome, for example, an initial 1,3-dipolar cycloaddition followed by reductive cyclization yields a quinoline analogue of phenylalanine <1998JCM796>. The Baylis–Hillman reaction of a vinyl ketone with *o*-nitrobenzaldehyde followed by reduction gives rise to quinolines <1998CC2563>. Zinc in near-critical water has been used as the reducing agent in the reduction of the nitro substituent in the cinnamic acid derivative **3** leading to the 2-substituted quinolines (Equation 6) <1999NJC641>. Reductive coupling of 2'-hydroxy-2-nitrochalcones yields in a limited number of examples the quinoline in a one-pot reaction (Equation 7) <2003TL5893>. Quinoline *N*-oxides are side products formed in this reaction.

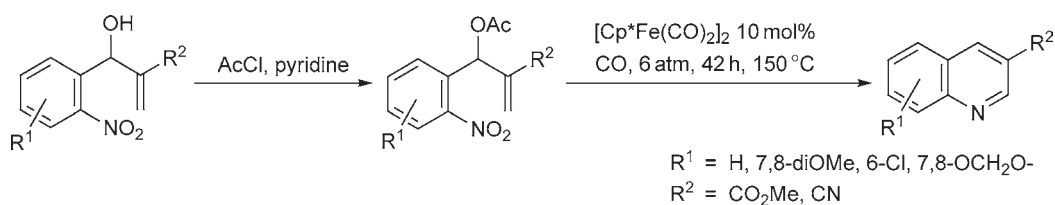


R = CHO, COMe, CO₂H, COMe



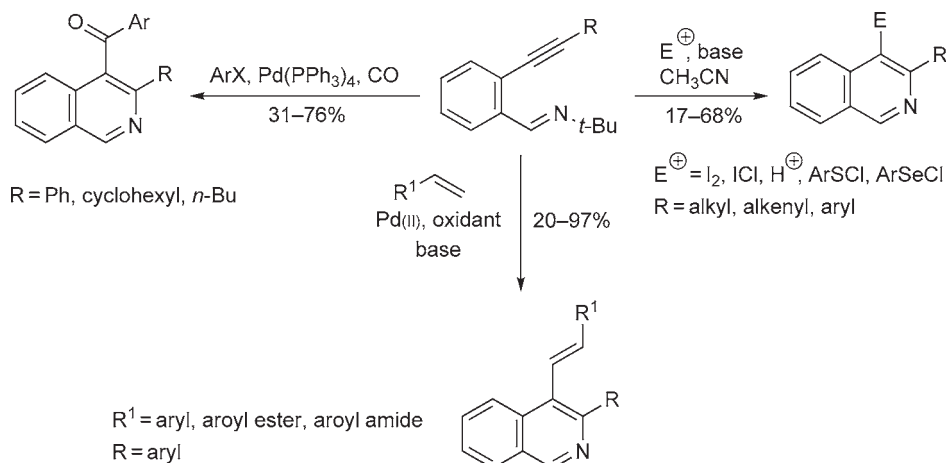
Additional variations to the reduction–cyclization strategies involve Baylis–Hillman adducts of *o*-nitrobenzaldehydes reacting with iron in acetic acid to yield the quinolone (Equation 8) or the quinoline (Equation 9) <2002T3693>, depending on the use of an ester or ketone starting material, respectively. Minor manipulations in the reagents used, for example, trifluoroacetic acid, can give directly the quinoline *N*-oxide (Equation 10) <2000OL343>. The synthesis of 3-carboxyquinolines has been successful whereas previous attempts using this strategy have only produced indoles, 2-quinolines, 4-quinolines, unsubstituted quinolines, and dihydroquinolines (Scheme 6) <2003JOC6427>.





Scheme 6

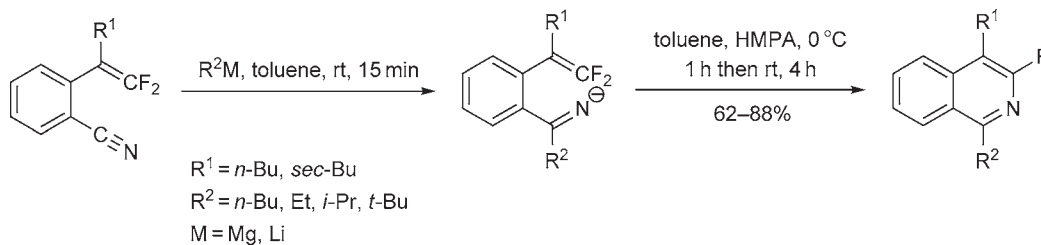
Alkynylbenzaldimines can produce isoquinolines (Scheme 7). The use of electrophiles and base yielded 3,4-disubstituted quinolines [<2002JOC3437, 2001OL2973>](#), whereas the palladium-catalyzed carbonylation gave 4-arylquinolines [<2002OL193, 2002JOC7042>](#). Cyclization followed by Heck reaction gave rise to 4-alkenyl-substituted quinolines [<2002TL3557>](#).



Scheme 7

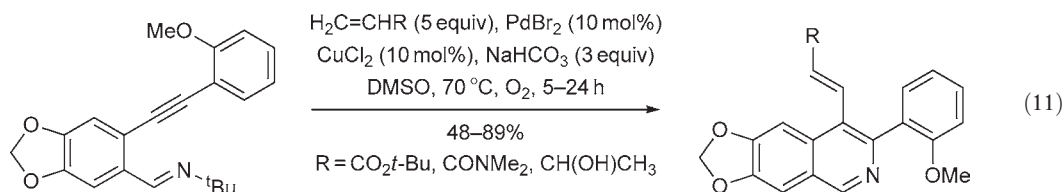
The palladium-catalyzed intramolecular annulation of alkynes and *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals to produce isoquinoline and quinolines has been reported [<2001JOC8042>](#).

Different β,β -difluoro-*o*-isocyanostyrenes react with organolithiums to yield quinolines with isoquinolines being produced from the corresponding *o*-cyano- β,β -difluorostyrenes (Scheme 8) [<2003OL1455>](#).

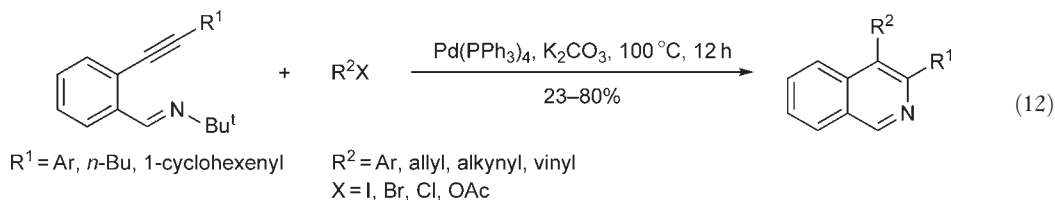


Scheme 8

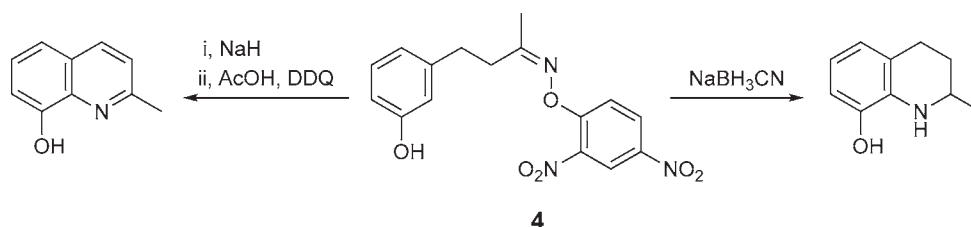
The same reaction has been developed that allows for *in situ* olefination in the synthesis of isoquinoline derivatives (Equation 11) [<2003JOC980>](#). Although numerous examples were reported, it was found that the aryl methoxy substituent was necessary for the reaction to be successful.



This cyclization/*in situ* addition reaction was extended in a general process to alkylation (Equation 12) <2003JOC920, 2001OL4035>. Numerous examples were presented but poorer yields were obtained when electron-rich or *o*-substituted aryl halides were used. The 1,4-diallyl-1,2-dihydroisoquinoline derivatives can be formed with the same strategy using allyltributylstannanes and allyl chloride with Cu(II) acetate cocatalyst <2004TL7339>. Further, the intramolecular Pd-catalyzed coupling between aryl halides and amide enolates gave 4-aryl-3-isoquinolone derivatives which were subsequently converted to 4-arylisquinolines <2001OL631>.

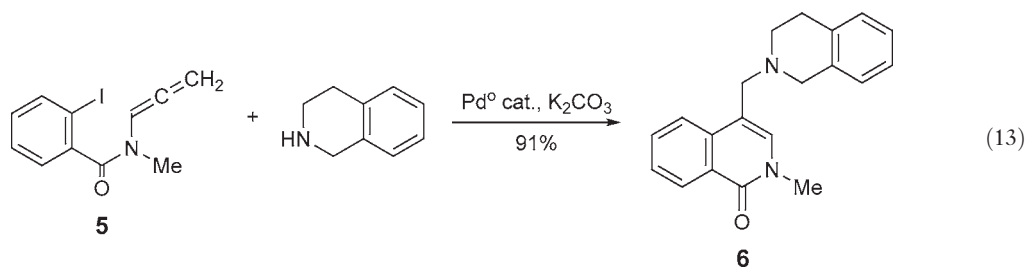


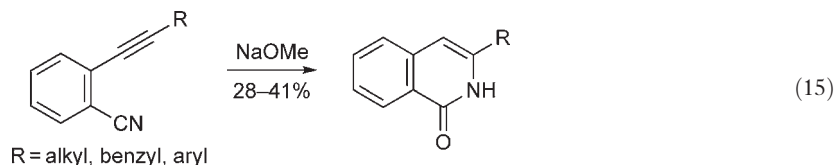
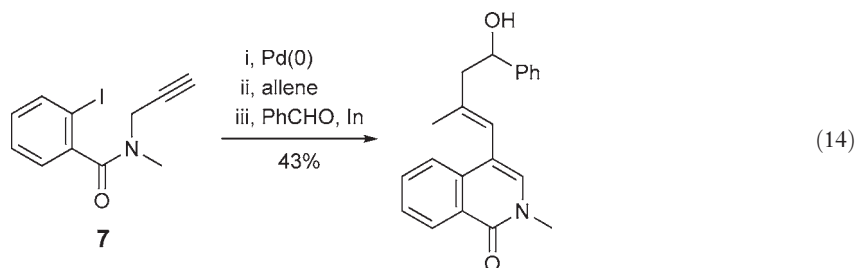
Oximes are good precursors to reductive cyclization. A reductive base-induced cyclization of *O*-aryl oxime **4** will yield the tetrahydroquinoline <1998CL437>. The reduction prevented the normal dihydro-cyclization product from disproportionating to the quinoline and tetrahydroquinoline <1998BCJ2945>. By adding 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) after cyclization, the quinoline is the sole product (Scheme 9).



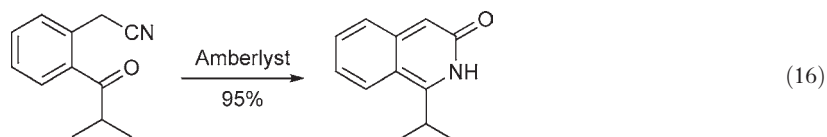
Scheme 9

Palladium-based reactions continue to be a valuable strategy in ring cyclization. The *o*-iodoallene system **5** undergoes Pd-catalyzed cyclisation in the presence of tetrahydroisoquinoline to give the isoquinoline **6** in 91% yield (Equation 13) <1995CC1903>. In an analogous reaction, the *o*-iodoalkyne **7**, in the presence of benzaldehyde, was cyclized to produce the isoquinoline in moderate yield (Equation 14) <2000CC933>. Similar systems can be accessed by direct anionic cyclization of 2-alkynylbenzonitriles (Equation 15) <1999T13193>. Phenanthridines can also be produced with this strategy <1999OL767>.

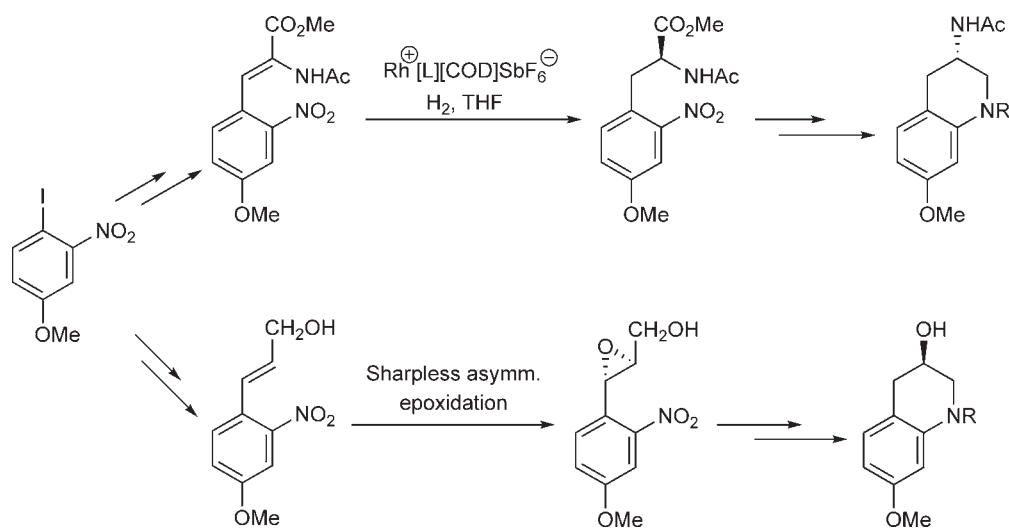




The synthesis of 1-substituted 2*H*-isoquinolin-3-ones has been reported from 2-acylphenylacetonitriles under acidic conditions (Equation 16) <2004JHC979>. The use of Amberlyst ion-exchange resins was found to give improved yields over the use of sulfuric acid or methanesulfonic acid.

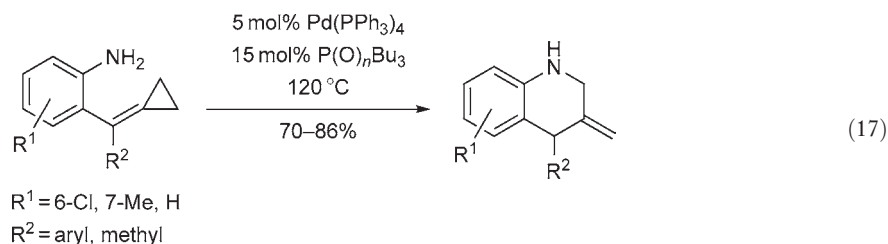


The enantioselective synthesis of 3-substituted tetrahydroquinolines was achieved with ~98% ee starting from *o*-nitrocinnamyl intermediates and using rhodium-catalyzed asymmetric hydrogenation, with subsequent cyclization yielding the heterocycle (Scheme 10) <2001OL2053>. In an analogous fashion, Sharpless epoxidation of similar *o*-nitrocinnamyl alcohols yields 3-substituted tetrahydroquinolines with ~90% ee.

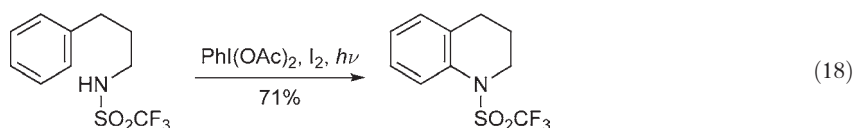


Scheme 10

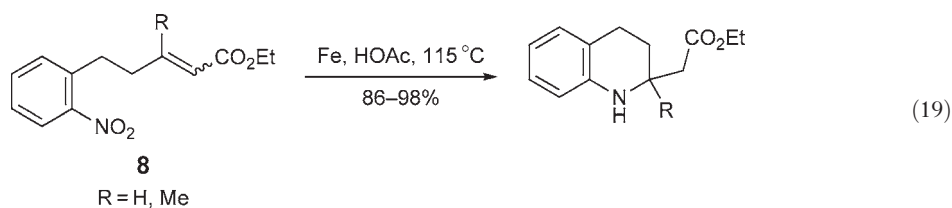
An interesting variation on the Heck reaction is the intramolecular hydroamination to produce the tetrahydroquinoline with an exocyclic alkene substituent in the 3-position (Equation 17) <2005JOC5932>.



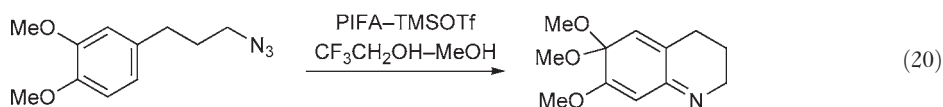
Reactions based on irradiation to produce tetrahydroquinolines are frequently reported. The reaction premise is ring closure by the nitrogen atom onto an aromatic ring. Therefore, cyclization of 3-(naphthylamino)-2-alkenimines produces benzoquinolines [<1998T6929, 1998T14113>](#), while irradiation of α -dehydronaphthylalanine yields the quinolinone [<1998TL4083>](#). In order for the sulfonamide to oxidize as a prelude to cyclization, irradiation is required with no reaction in the dark ([Equation 18](#)) [<1998JOC5193>](#). Further, the reaction of nitroarenes with TiO_2 as a photocatalyst in the presence of alcohols leads to the formation of the tetrahydroquinoline [<1999TL1145>](#).



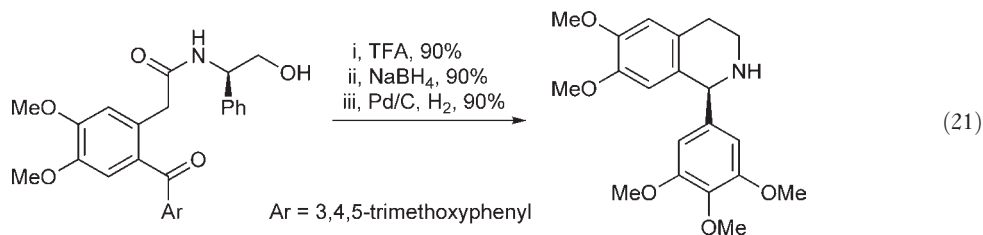
Reduction of *o*-nitro substituents is also a popular method for the synthesis of tetrahydroquinolines. For example, acrylates such as **8** go through tandem reduction–Michael addition under standard conditions [<2000JOC2847>](#) ([Equation 19](#)).



An interesting report on the synthesis of quinone imines was the oxidative cyclization of phenylalkylazides with phenyliodine(III) bis(trifluoroacetate) (PIFA) ([Equation 20](#)) [<1999CPB241>](#).

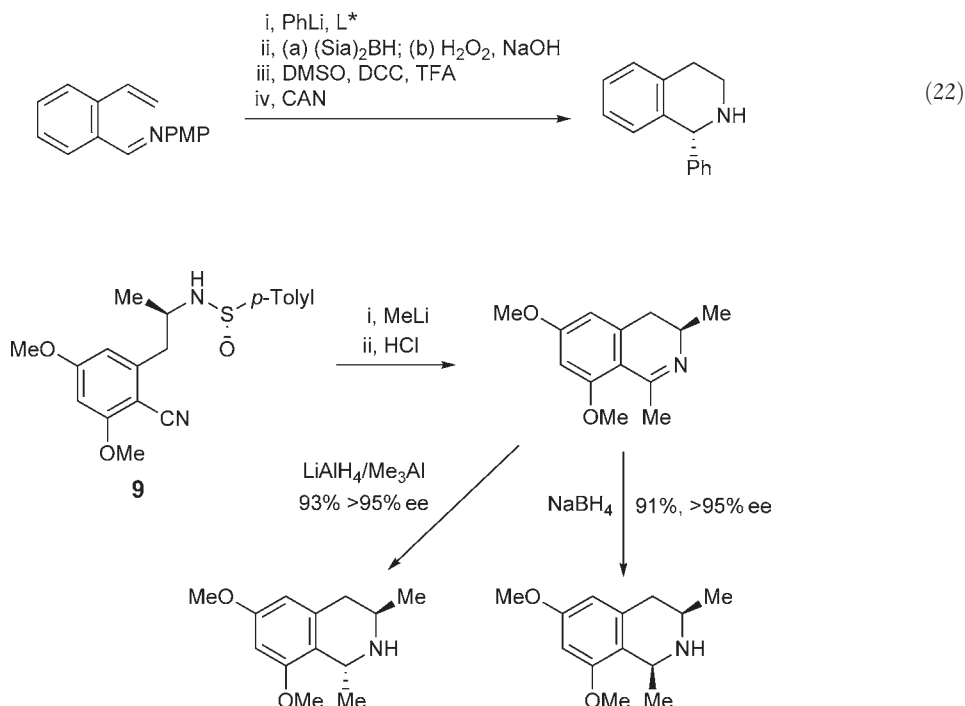


In a reductive amination-based reaction, 1-aryltetrahydroisoquinolines can be synthesized stereoselectively starting from chiral amides ([Equation 21](#)) [<1996TL4369>](#). A modification of this procedure also yields the *cis*- and *trans*-1,3-disubstituted tetrahydroisoquinolines in a stereoselective manner.



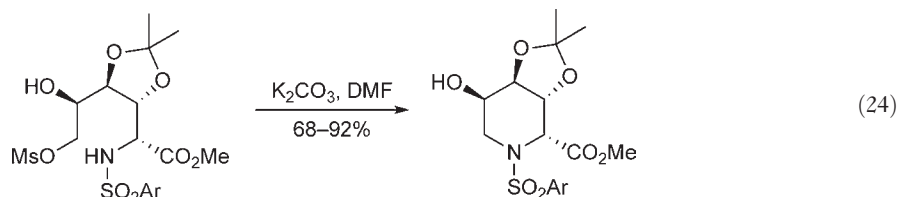
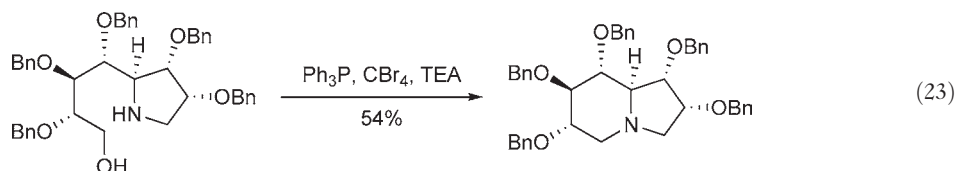
The Heck reaction continues to be a popular route to tetrahydroisoquinolines. Intramolecular reaction of 2-iodo-*N*-phenylbenzamide with methyl acrylate yields 1-oxotetrahydroisoquinoline-3-carboxylic acids [<1997J\(P1\)2577>](#), while the intramolecular reaction of an aryl bromide with an enaminone also forms the tetrahydroisoquinoline ring [<1997TL2829>](#).

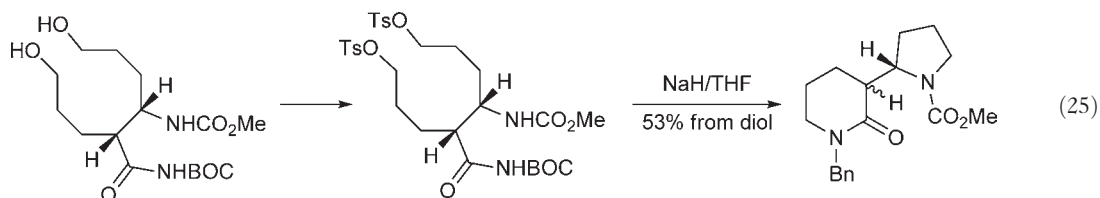
New chiral methods for the preparation of tetrahydroisoquinolines are becoming available. The two-step reaction of an imine in a chiral ligand-mediated addition of an organolithium species yields chiral 1-substituted tetrahydroisoquinolines (Equation 22) <1999TA221>. Internal chiral induction can be achieved by using sulfonamide-substituted systems (Scheme 11). Reaction of **9** with MeLi followed by acidification yielded the cyclic imine – reduction of this imine with $\text{LiAlH}_4/\text{Me}_3\text{Al}$ gives the *trans*-1,3 derivatives whereas reduction using NaBH_4 results in the *cis*-1,3 derivative <2000OL3901>.



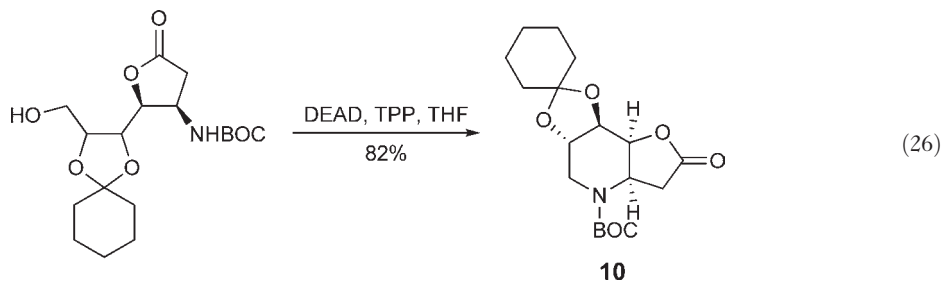
Scheme 11

Cyclization to form piperidines by attack of a nitrogen nucleophile onto an electrophilic carbon continues to generate reports. Recent examples include a polyhydroxylated indolizidine scaffold synthesis (Equation 23) <2004JOC3139>, the synthesis of azasugar-type compounds (Equation 24) <2004JME1930>, a new synthesis of nicotine via a double regioselective intramolecular cyclization <2004HCA2712> (Equation 25), and a base-induced cyclization <2006AGE932>.

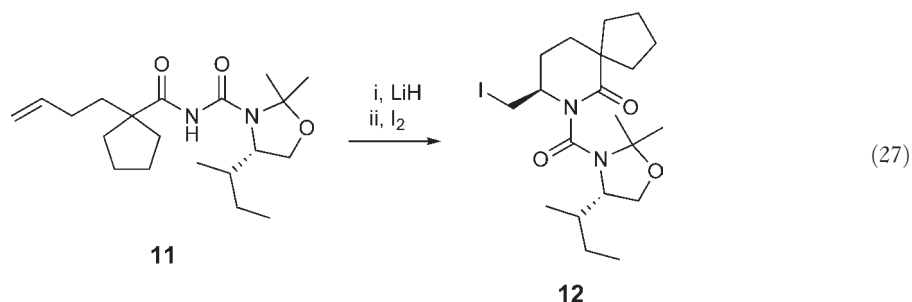




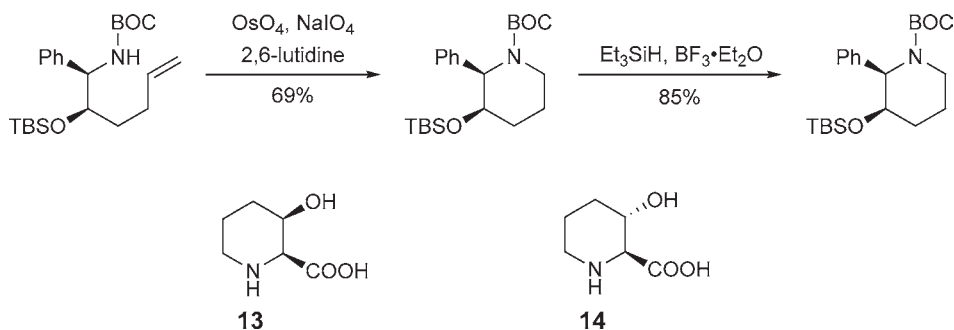
Similarly, *N*-BOC-aminoalcohols can be subjected to Mitsunobu reaction conditions to yield the piperidine structure **10** (Equation 26) <2004JOC2229>, which is an intermediate in the synthesis of galactohomonojirimycin (BOC = *t*-butoxycarbonyl). Cyclization of an *N*-BOC derivative of an aminoalcohol mesylate was reported in the synthesis of enantiopure 3-hydroxy-4-phenylpiperidine derivatives starting from L-phenylglycine <2004TL987>.



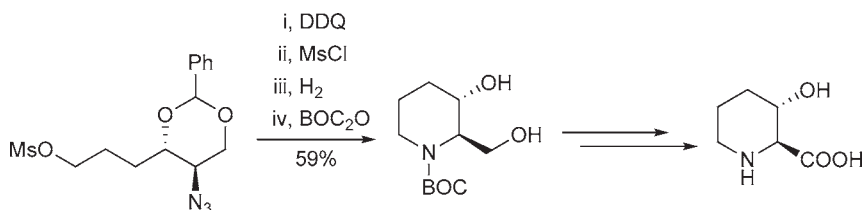
N-Nucleophilic attack onto olefinic electrophiles has also been reported <2004JOC7906>. An iodolactamization of chiral **11** using LiH followed by iodine yielded **12** in 90% yield with a de of 97% (Equation 27).



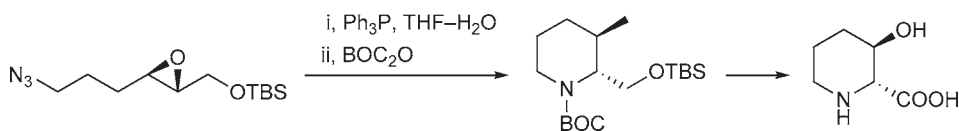
Dihydroxylation of olefins followed by oxidation with periodate leads to cyclization and the corresponding carbinolamine. This can then be reduced to the piperidine <2005JOC10182> (Scheme 12). The strategy was used in the synthesis of both the (2*S*,3*R*)-3-hydroxypipicolinic acid **13** and (2*S*,3*S*)-3-hydroxypipicolinic acid **14** from D-serine. Variations in this strategy toward both *trans*-isomers of the 3-hydroxypipicolinic acid moiety are shown in Schemes 13 and 14. The initial stereochemistry was introduced using Sharpless method <2005JOC360>.



Scheme 12

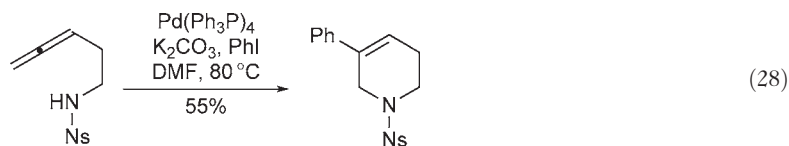


Scheme 13

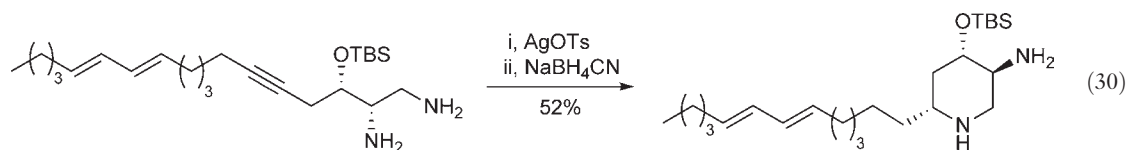
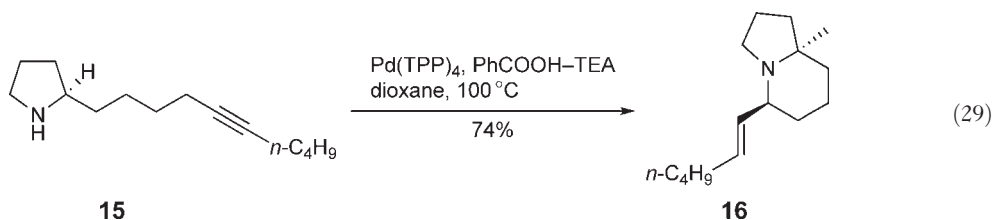


Scheme 14

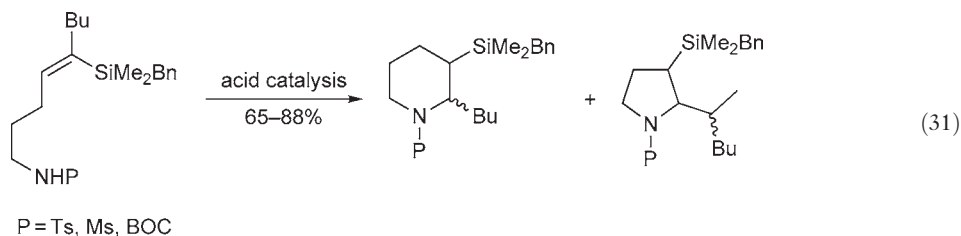
The cyclization of alleneamines under palladium catalysis proceeds with coupling at the 3-position with aryl iodides and vinyl triflates [<1999OL717, 1999SL324>](#). The cyclization can also proceed by the 4-*exo-trig*-pathway, and, under suitable conditions, piperidines are produced exclusively ([Equation 28](#)).



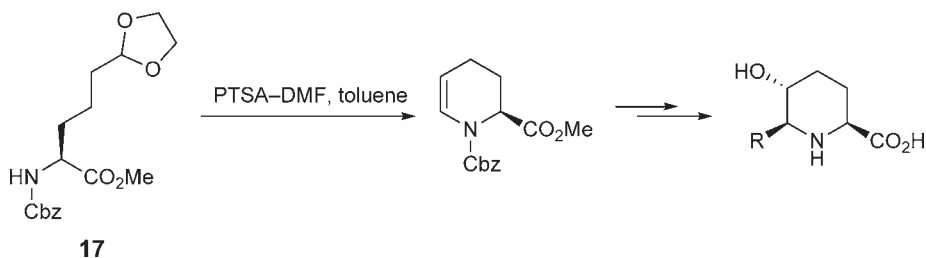
An intramolecular Pd(0)/benzoic acid-catalyzed hydroamination of the pyrrolidinealkyne **15** gave the indolizidine **16** as a single diastereomer – subsequent saturation of the alkene yielded the alkaloid (–)209D ([Equation 29](#)) [<2005TL2101>](#). A similar strategy was used in the first total synthesis of pseudodistomin D by the sequential hydroamination and *in situ* imine reduction ([Equation 30](#)) [<2005OL823>](#). Deprotection of *tert*-butyldimethylsilyl (TBS) to the free alcohol occurs in 100% yield. A high-yielding intramolecular hydroamination strategy has been reported using sulfonyl-protected primary aminoalkynes to produce piperidines [<2005JOC4883>](#). A catalytic quantity of Pd(TPP)₄ and triphenylphosphine (TPP) is required and no carboxylic acid proton source is necessary.



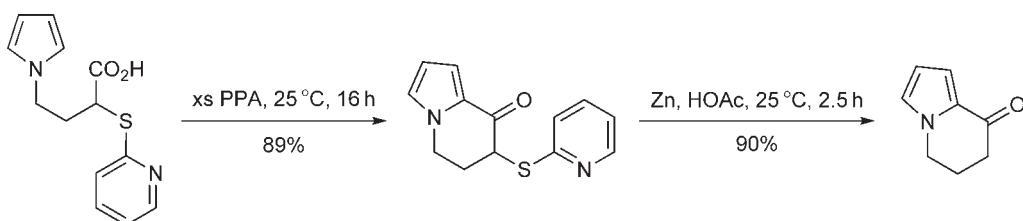
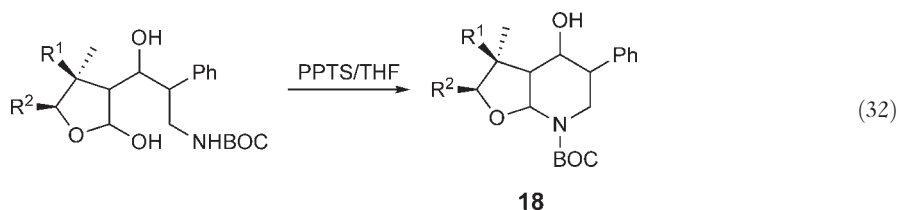
An intramolecular cyclization of vinylsilanes with acyl amines yields substituted piperidines ([Equation 31](#)) [<2003SL143>](#). Pyrrolidines are produced as by-products and the ratio of formation was dependent on the acid used, and the time and temperature.



Further acid-catalyzed reactions include the use of *p*-toluene sulfonic acid–DMF in a cyclization of the protected amino acid **17** (DMF = dimethylformamide; [Scheme 15](#)) [<2004OL4941>](#). This was the key step in the stereo-selective synthesis of 5-hydroxypipercolic acid. A similar acid-catalyzed ring closure of a hemiacetal yielded the fused piperidine **18** [<2004JOC1872>](#) ([Equation 32](#)). The indolizidine alkaloid can be accessed by a Barton–Ester method utilizing a polyphosphoric acid (PPA) cyclization ([Scheme 16](#)) [<1994T19157>](#).

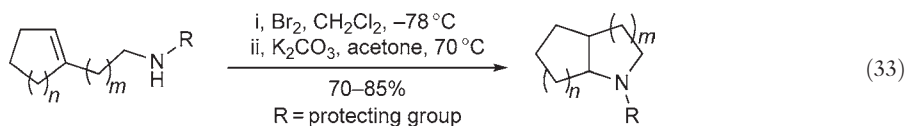


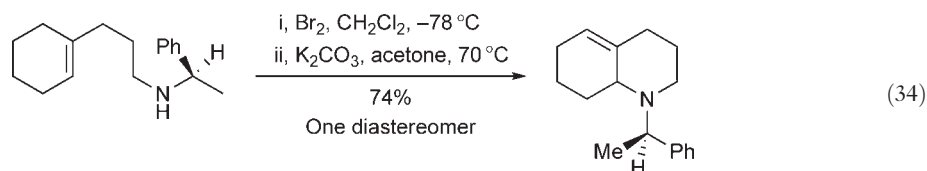
Scheme 15



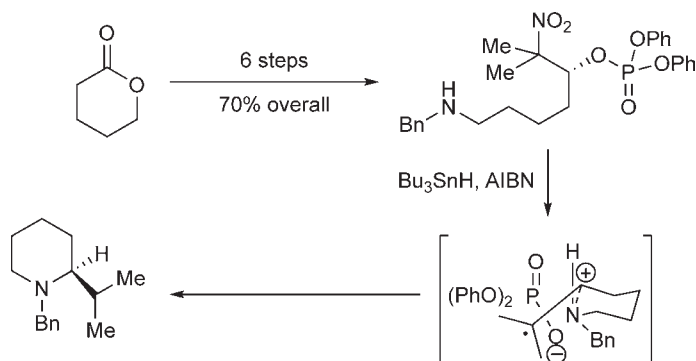
Scheme 16

Application of the halogenation of γ -aminoolefins preceding intramolecular cyclization has been applied to the synthesis of fused piperidines ([Equation 33](#)) [<2003CC1918>](#). The presence of chiral substituents (e.g., via the nitrogen protecting group) generates a diastereoselective reaction ([Equation 34](#)).



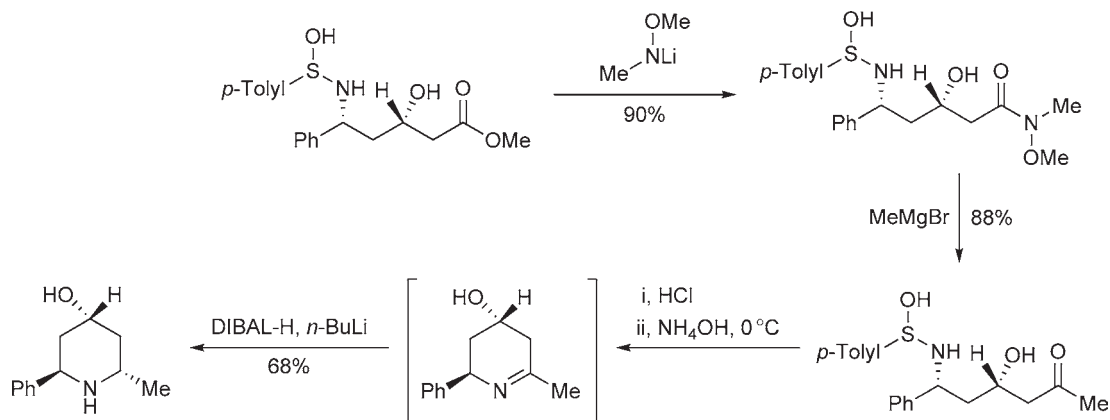


Enantioselective synthesis of 2-substituted piperidines with 60% ee has been reported via radical precursors being trapped in an intramolecular reaction (**Scheme 17** <2003OL3767>). These cyclizations were rationalized in terms of chair-like transition states, with the maximum number of pseudoequatorial substituents, in which the nucleophilic amine attacks the alkene radical cation on the face opposite to the phosphate anion.



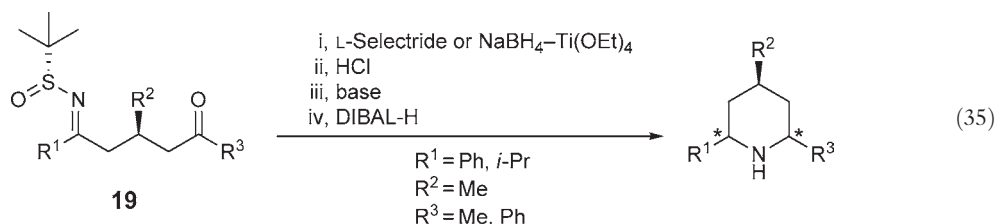
Scheme 17

Diastereoselectivity in functionalized piperidine synthesis has also been reported using chiral sulfinimines (**Scheme 18** <2003OL3855>). It was postulated that the observed selectivity arose from an intermediate alkoxy aluminium species shielding one face of the imine during reduction.

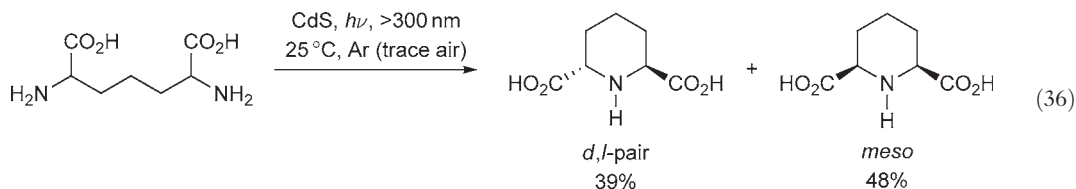


Scheme 18

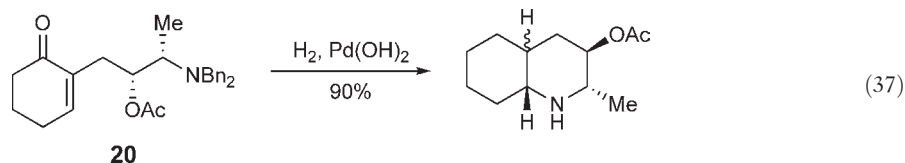
The conjugate addition of *N*-sulfinyl metalloeneamines to enones gave **19**, which is converted in a facile manner to the corresponding piperidine in good diastereoselectivity after sequential stereoselective reduction, N-deprotection, cyclization, and imine reduction (**Equation 35** <2005JOC7342>).



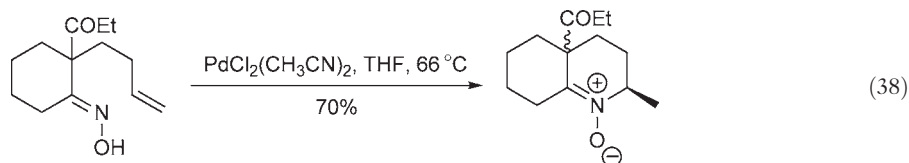
Irradiation of 2,6-diaminopimelic acid in CdS suspension gave the enantiomeric *trans*-2,6-piperidinedicarboxylic acids as well as the single *cis*-isomer <1995TL3189> (Equation 36).



The cyclohexenone **20**, when subjected to hydrogenation, undergoes debenzoylation followed by reductive amination to give the perhydroquinoline as a 1:1 mixture of *cis*- and *trans*-isomers (Equation 37) <2005T8264>.

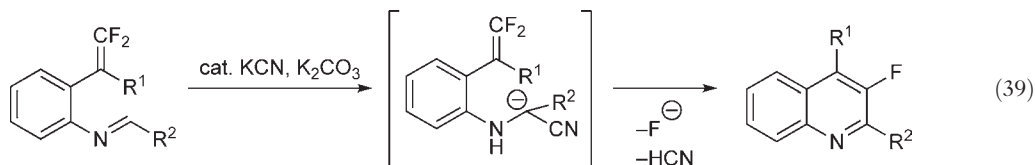


A palladium-catalyzed cyclization of alkenyloximes yields the nitron derivative of the perhydroquinoline (Equation 38) <1997T15051>.

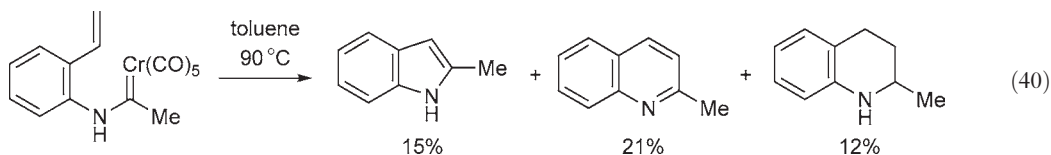


7.05.2.1.2 Bond formation between α - and β -carbons

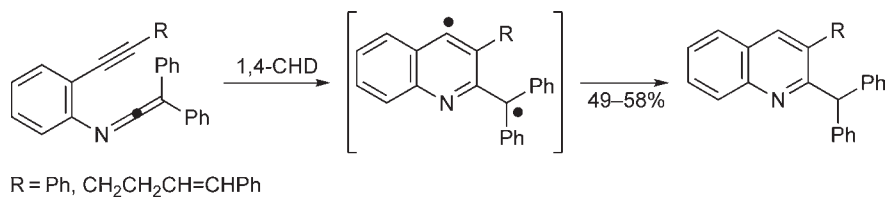
Examples of β,β -difluorostyrenes in cyclization reactions where the α,β -bond of quinolines is formed have been reported (Equation 39) <2003OL1455, 2004CL590, 2004SL1219>.



Cyclization of chromium carbenes to quinolines is inefficient with low yields and mixtures of products (Equation 40) <2003T8775>.

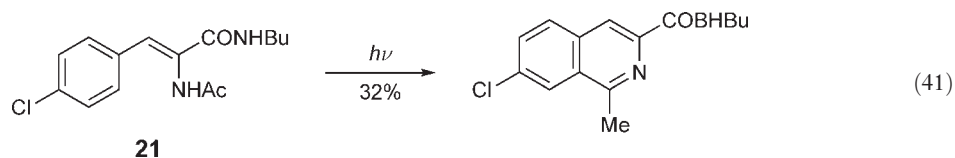


Enyne-ketenimines can form biradicals which upon cycloaromatization will form the quinoline (**Scheme 19**) <1998AGE1562, 1998JOC3517, 1998AGE2371>.

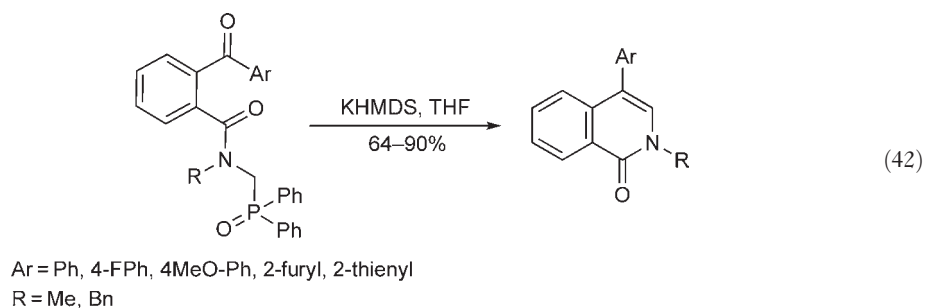


Scheme 19

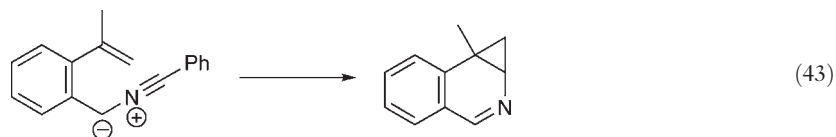
Typical irradiation reactions have been utilized in the synthesis of isoquinolines; for example, the phenylalanine derivative **21** yields the substituted isoquinoline as the major product (**Equation 41**) <1996TL5917>.



The base-promoted cyclization of phosphorylated *o*-aroylbenzamides is a new route to 2-alkyl-4-aryl-1(2*H*)-isoquinolines (**Equation 42**) <1996T4433>.



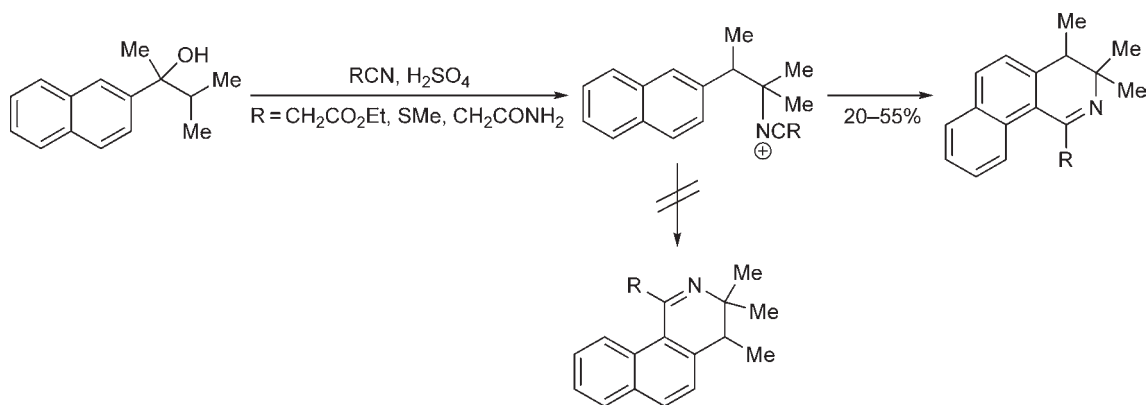
Intramolecular cyclization of nitrile ylides produces the cyclopropyl-fused quinolines (**Equation 43**) <1998J(P1)807>.



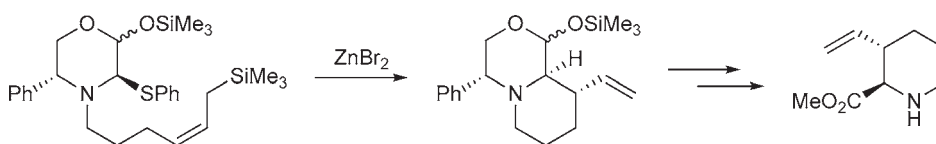
The use of the Ritter reaction and α -naphthylcarbinols and nitriles results in the formation of a single product, the 3,4-dihydrobenzo[*h*]isoquinoline with no regioisomer detected (**Scheme 20**) <2003CHE184>.

Reaction of an allylsilane on a chiral iminium provides the substituted pipecolic acid derivatives after oxidation and hydrolysis (**Scheme 21**) <1997SL799, 1997TA2975>. In an analogous reaction, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ can be used as the Lewis acid resulting in an asymmetric synthesis of desoxoprosopinine (**Equation 44**) <1997TL7469>.

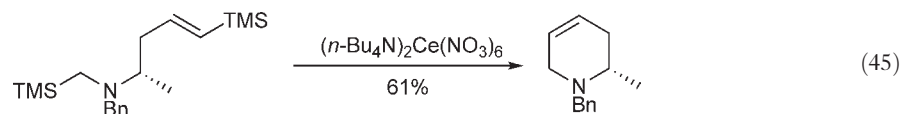
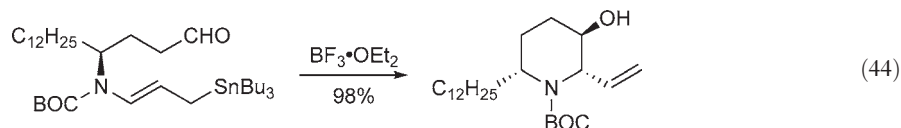
The use of allylsilane cyclization onto iminium or acyl iminium ions is well reported <1998T10309, 1998SL921, 1998H(48)507, 1998EJO2461>. One example shows the iminium moiety generated by oxidation of a trimethylsilyl (TMS) group (**Equation 45**) <1998JOC841>.



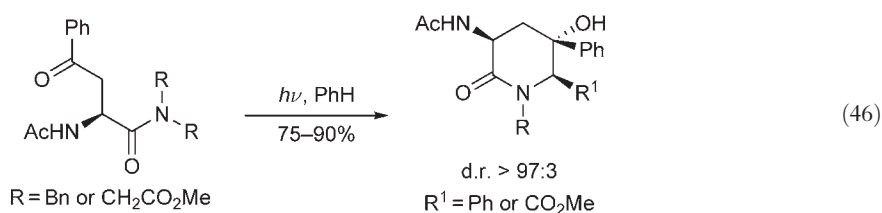
Scheme 20



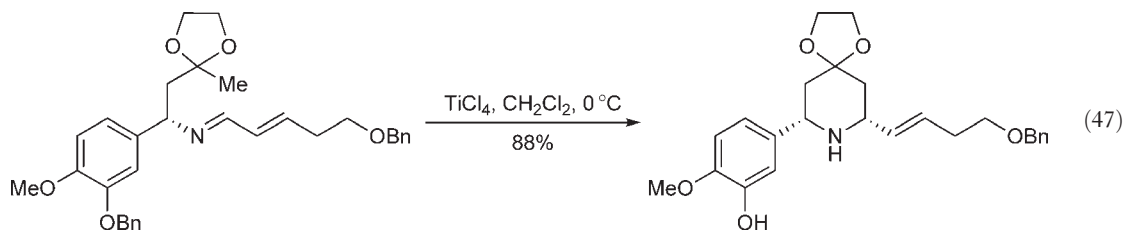
Scheme 21



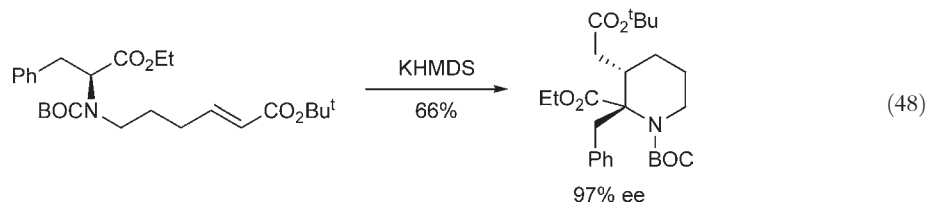
The photochemical cyclization of γ -ketoamides results in a stereoselective reaction to piperidines (Equation 46) <1999TL3137>. Utilization of the γ -ketoamide of proline yields the corresponding indolizone ring <1999TL5987>.



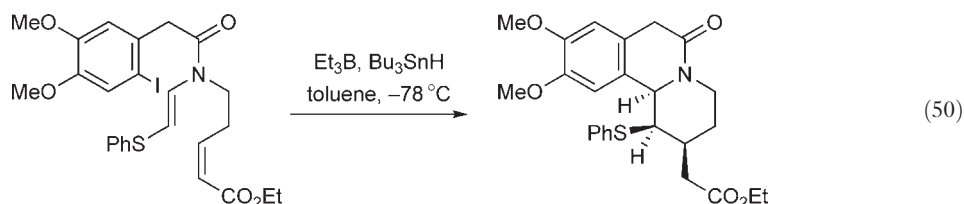
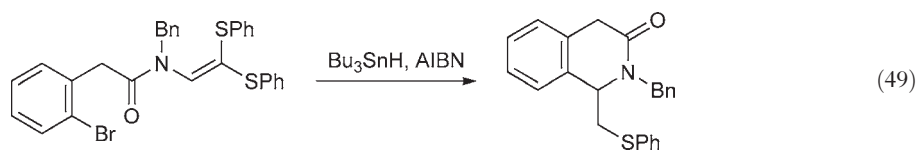
Chiral imines have been reported as undergoing intramolecular Mannich reaction to give 4-piperidones <2005JA8398>. Equation (47) illustrates the synthesis of the *cis*-2,6-disubstituted 4-piperidone, which was a key step in the synthesis of (+)-abresoline <2005TL2669>.



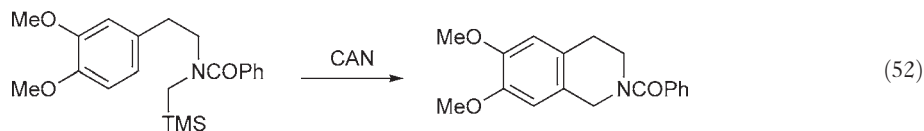
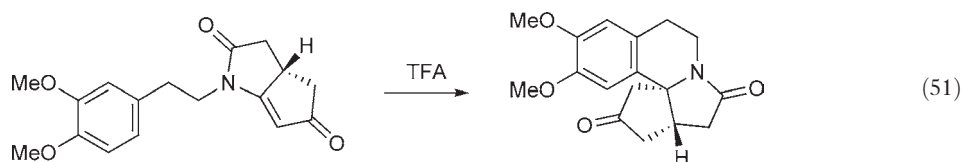
The intramolecular conjugate addition of enolates derived from α -amino acids gives rise to piperidines with adjacent stereogenic ring atoms with an axially chiral enolate intermediate being proposed <2005OBC1609>. Equation (48) illustrates an example where the starting material is generated from phenylalanine.



A radical cyclization controlled by sulfur yields the tetrahydroisoquinoline (Equation 49) <1997J(P1)2291>. In the absence of the sulfur groups, only the reduced product is isolated. Further reactions that utilize radical cyclizations with vinylsulfides show a cascade reaction eventually forming the benzo[*a*]quinolizine system <1999TL1149> (Equation 50).

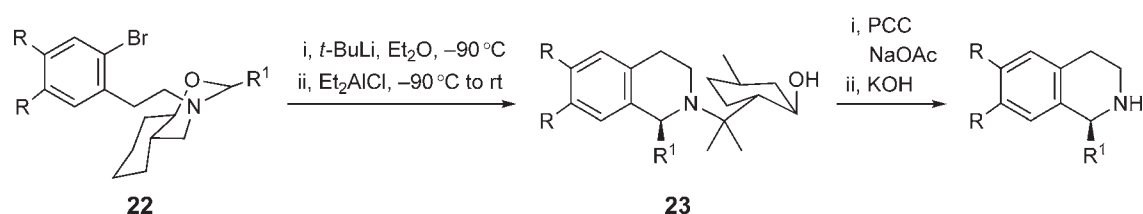


A variation on the traditional acid-catalyzed approach is illustrated in Equation (51) where the stereoselective introduction of a quaternary carbon in the *N*-acyliminium cyclization of a chiral enamide results in an asymmetric synthesis of tetrahydroisoquinolines <1997T2449, 1997T3045>. Oxidative Pictet–Spengler reaction using ceric ammonium nitrate (CAN) to produce the tetrahydroisoquinoline is a new application of a traditional reaction (Equation 52) <1998JOC860>. An interesting route to chiral 1-substituted tetrahydroisoquinolines utilizes a ring opening of the *N,O*-acetal moiety of perhydrobenzoxazine **22** to yield **23** as a single diastereoisomer. Subsequent removal of the auxiliary resulted in enantiopure isoquinoline (Scheme 22) <2001JOC243, 2001JA1817>.

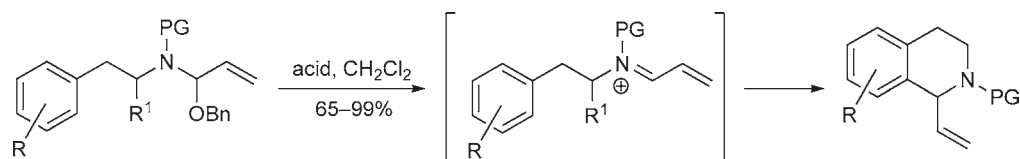


An acid-catalyzed reaction of an allylic *N,O*-acetal leads to allylic iminium ions which allows a subsequent cyclization to the α -vinyltetrahydroisoquinoline (Scheme 23) <2005JOC5519>.

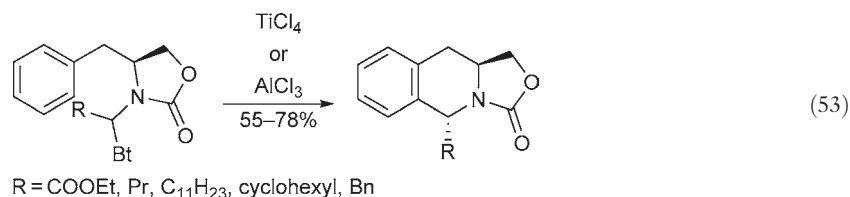
A Friedel–Crafts-type reaction can be utilized in a Lewis acid-mediated reaction to yield tetrahydroquinolines (Equation 53) <1999J(P1)179, 1999TA255>.



Scheme 22

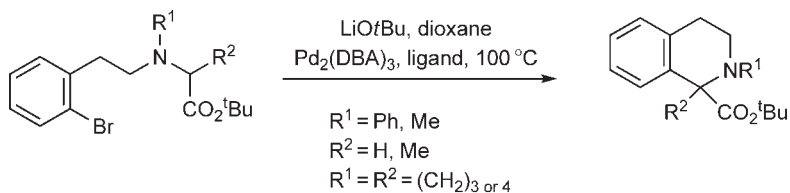


Scheme 23

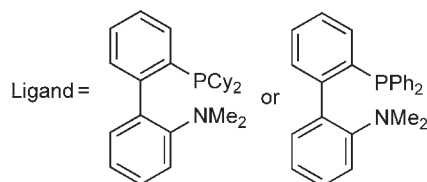


(53)

The palladium-based coupling to 1-substituted tetrahydroisoquinolines has been reported using standard conditions (Equation 54) <2002JOC465>, with the asymmetric versions reported to be part of ongoing studies.



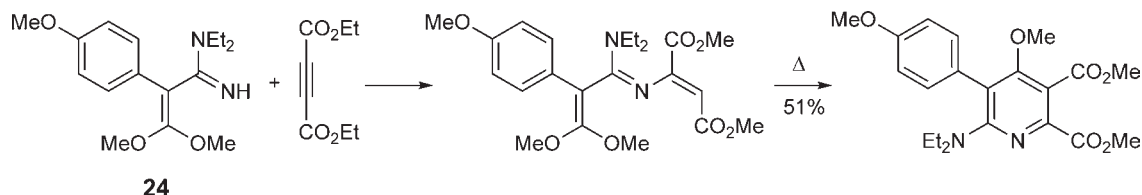
(54)



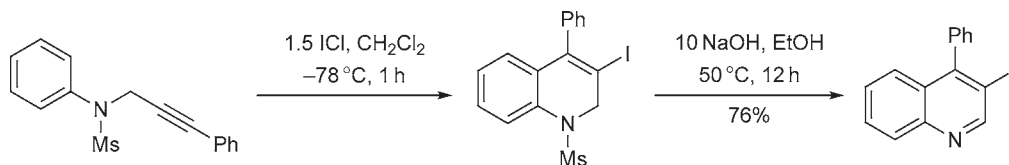
7.05.2.1.3 Bond formation between β - and γ -carbons

Pyridines have been formed by the cyclization of azadienes, themselves obtained by a conjugate addition between **24** and alkyne diesters (Scheme 24) <2000T4817>.

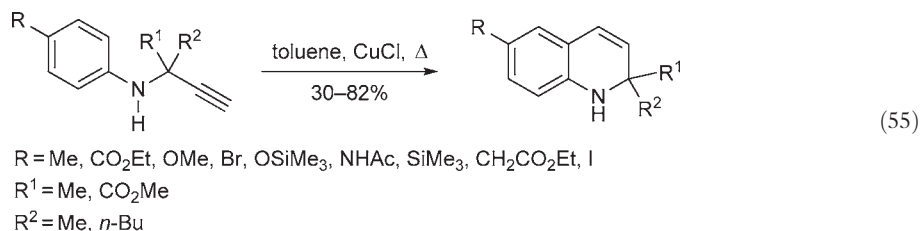
Intramolecular cyclization of N -propargyl anilines in the presence of ICl yields the dihydroquinoline, which is easily transformed into the fully saturated quinoline in high yield (Scheme 25) <2005OL763>. This process was intentionally developed as a facile route to a variety of substituted quinolines. The use of N -propargyl anilines in the presence of cuprous chloride yields the dihydroquinoline (Equation 55) <1995TL7721>.



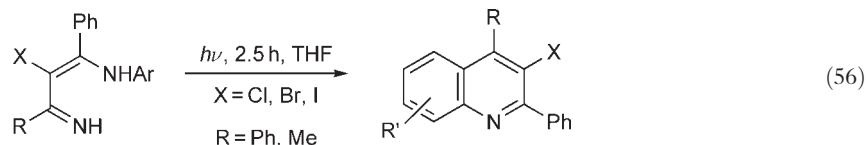
Scheme 24



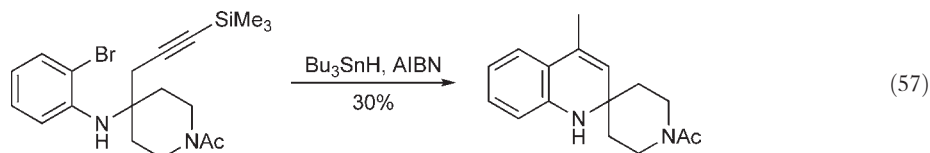
Scheme 25



The irradiation of haloalkenimines gives 3-haloquinolines (Equation 56) <1996JOC7195>.

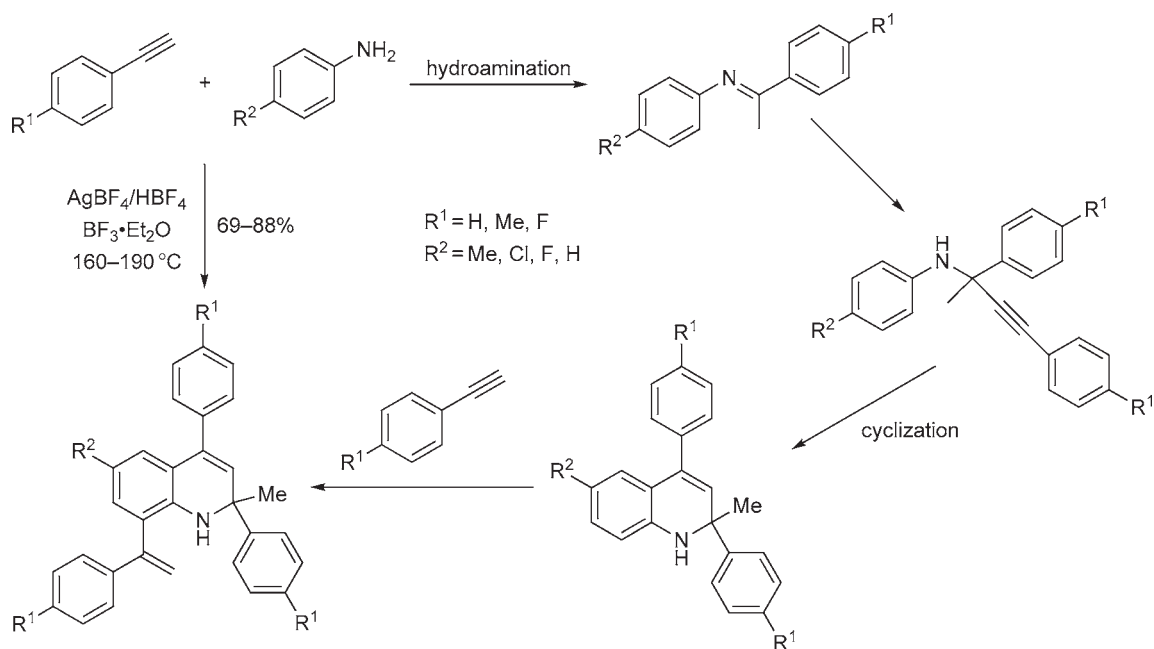


Intramolecular radical cyclization of an aryl bromide and an alkyne can be used to produce dihydroquinolines (Equation 57) <1998TL2965>. An analogous reaction setup utilizes a Lewis acid-catalyzed novel one-pot domino pathway using silver catalysis in high regioselectivity (Scheme 26) <2005OL2675>. Three mole equivalents of the alkyne are used with the final cyclization step arising from alkynic addition.

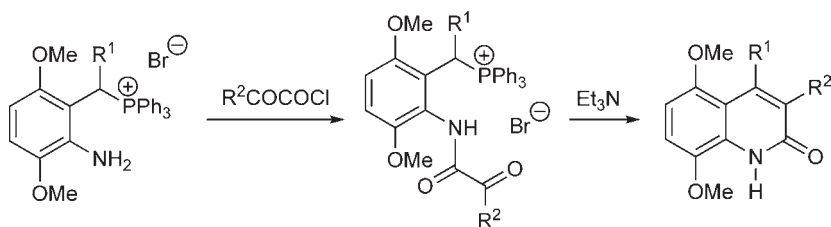
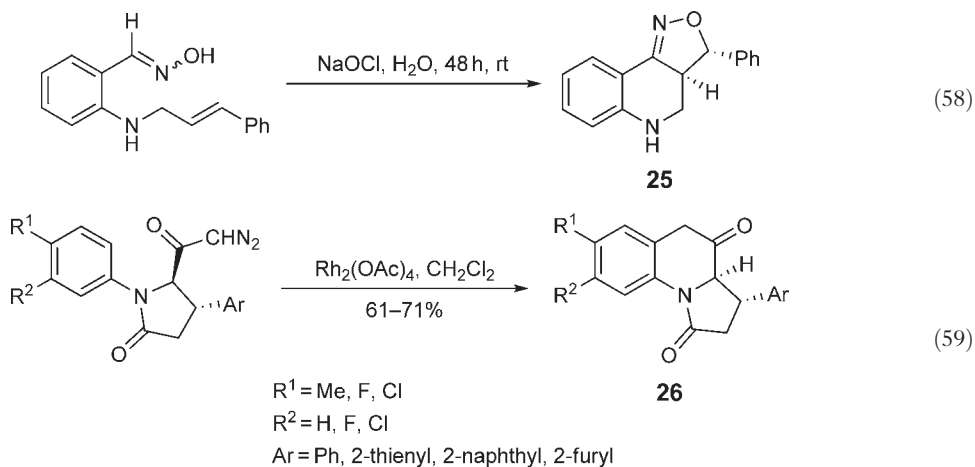


A 1,3-dipolar cycloaddition using oxime derivatives yielded the tetrahydroquinoline derivative **25** (Equation 58) <2005S3423>. It was advantageous that the product precipitated out of the aqueous reaction medium in excellent yield. Carbenoid-insertion reactions have been demonstrated to produce the ring-extended quinolone structure **26** from simple substituted anilines (Equation 59) <2003TL7433>. The C–H insertion onto the aromatic ring can vary.

An intramolecular Wittig reaction has been used to produce 2(1*H*)-quinolinones (Scheme 27) <1995LA1895>. The use of the ketoester **27** and anilines under different reaction conditions led to either 2-quinolones or 4-quinolones (Scheme 28) <2003S2005>. In a variation on this theme, an acid-catalyzed cyclization of the cyclopropyl anilide derivative **28** yielded the fused quinolone following a ring-opening/ring-closing sequence (Equation 60) <2006SC693>.

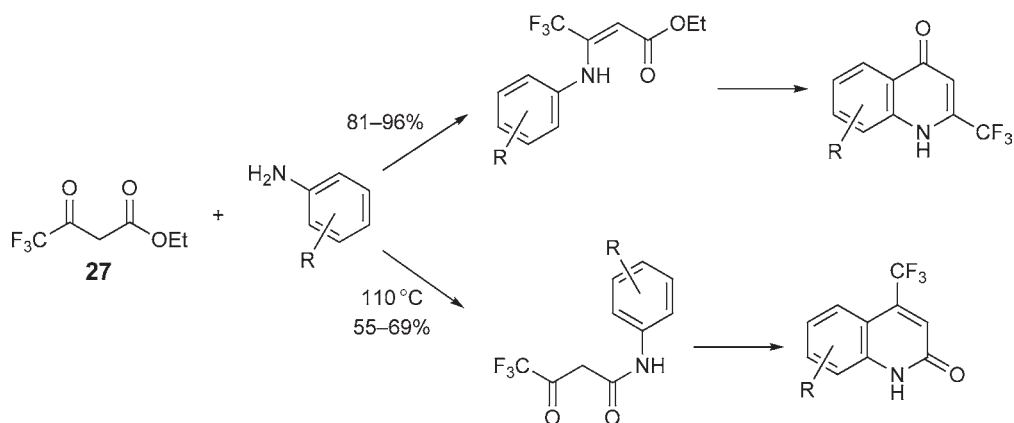


Scheme 26

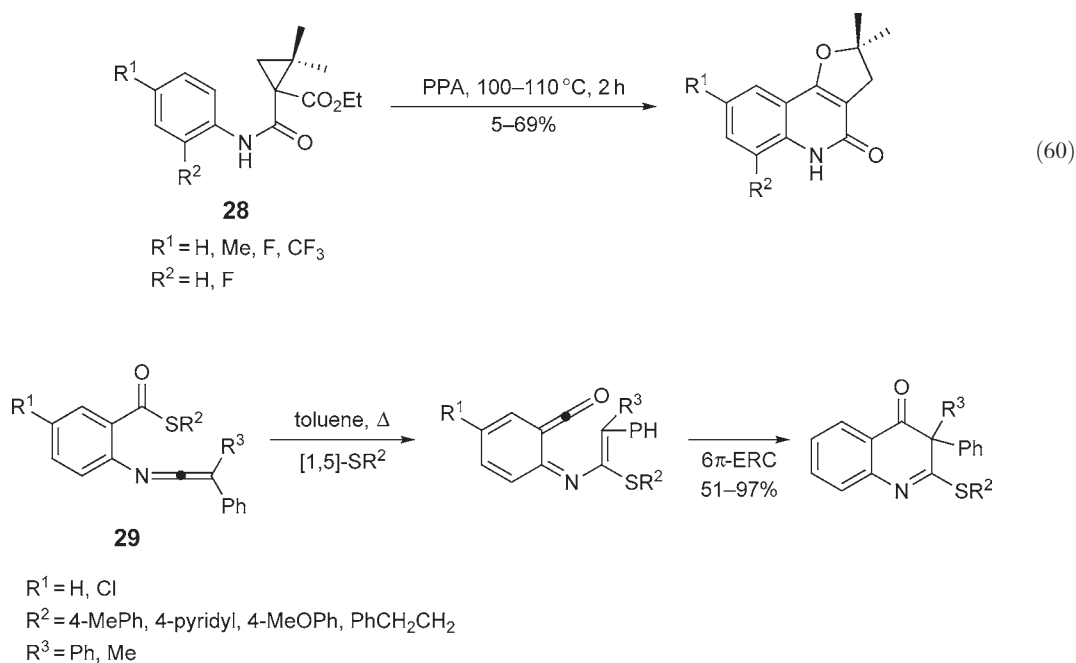


Scheme 27

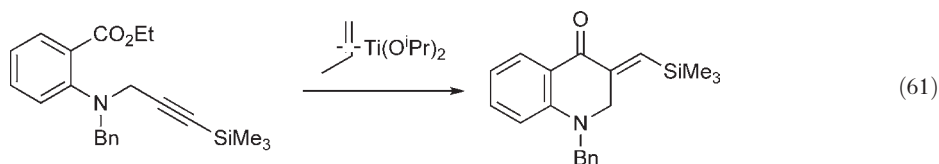
The thermally induced cyclization of the ketenimine **29** invoked a [1,5]-sigmatropic migration of the alkyl-aryl-thio group and then followed a 6 π -electrocyclic ring-closing reaction to give the 4-quinolone (**Scheme 29**) <2005OL5281>. The titanium(II)-alkene complex reacts with the *N*-propargylaniline leading to 4-quinolones (**Equation 61**) <1997JA6984>. The same reaction can be used to produce tetrahydroquinolines using *N*-allyl derivatives.



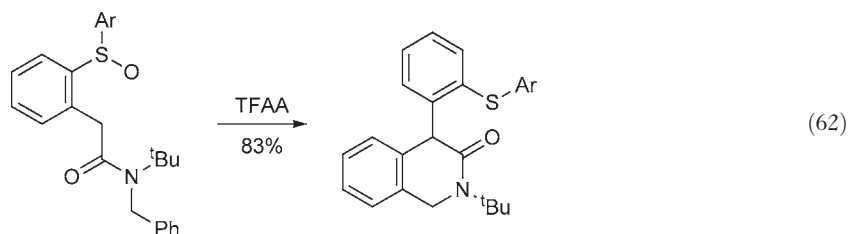
Scheme 28



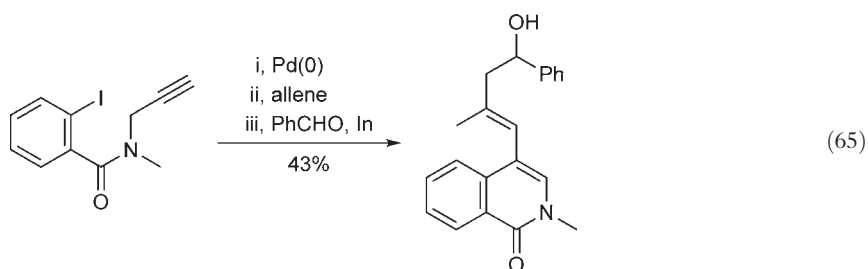
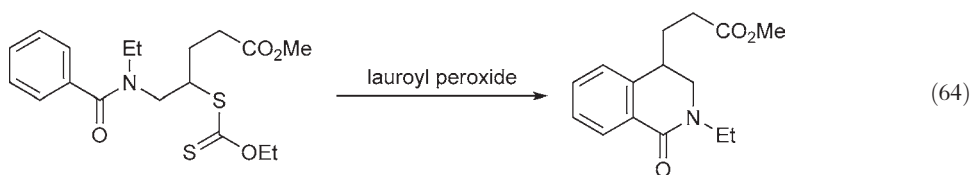
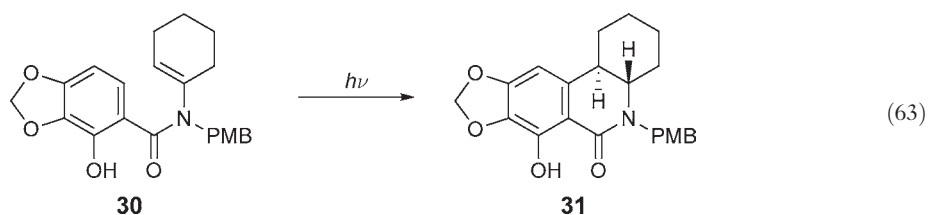
Scheme 29



The vinylogous Pummerer reaction of an amido-substituted sulfoxide produces the tetrahydroisoquinoline (Equation 62) <1995JOC7082>. Benzoyltetrahydroisoquinolinones have also been synthesized under Pummerer-type conditions on polymer support <2005H(65)1881>. Additional later examples highlighted the same reaction incorporating a fluorous-phase cyclative-capture method <2005AGE452>.

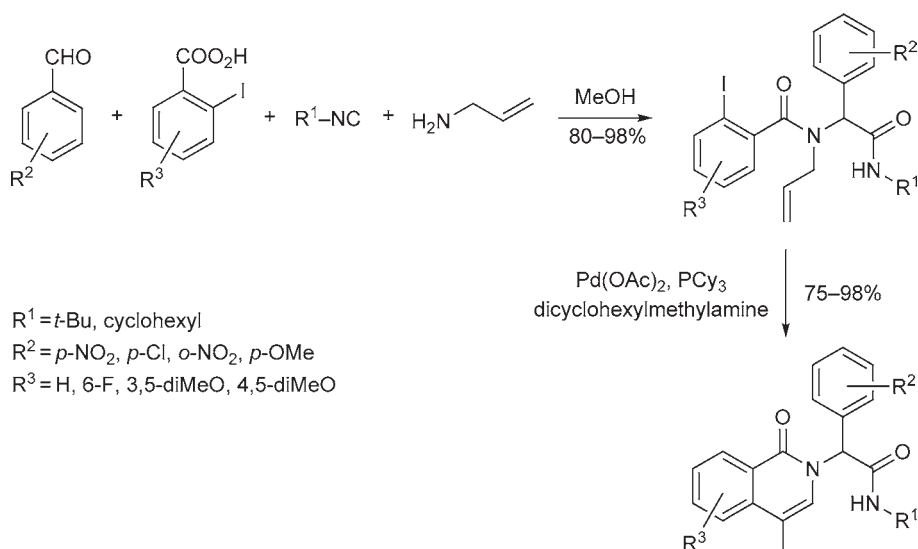


An H-bond-controlled photocyclization of **30** leads to the extended quinolone ring system **31** (Equation 63) <1997SL547>. Radical-based reactions can also be used for simple cyclizations (Equation 64) <1998TL7295>. Palladium-based reactions to the same scaffold include a typical intramolecular aryl halide–alkyne cyclization from the appropriate starting amide – in this example, the addition of benzaldehyde in the final stage allows for additional substitution at the C-4 position (Equation 65) <2000CC933>. A four-component one-pot reaction sequence utilizes the same cyclization strategy invoking the use of allyl substitutes (Scheme 30) <2004OL3155>, with additional examples shown <2004TL417>.

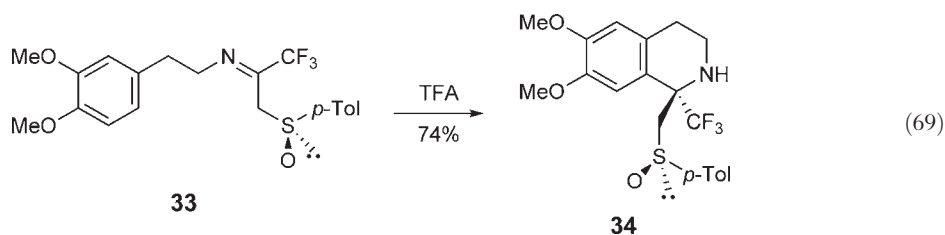
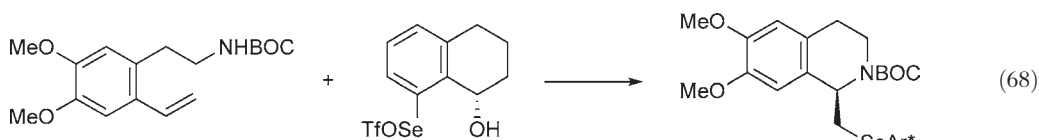
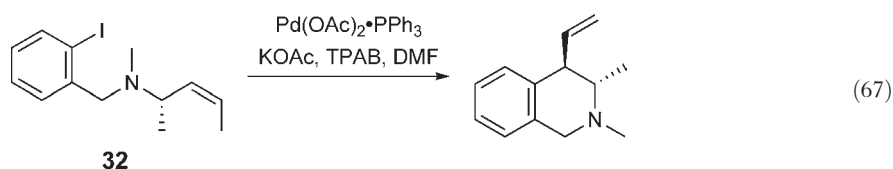
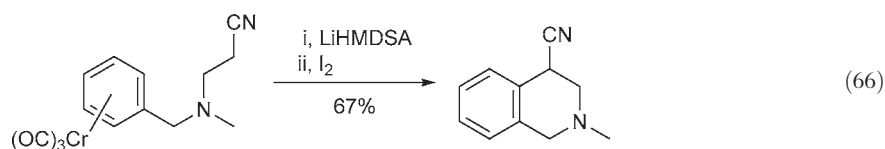


Tetrahydroisoquinolines can be produced by a nucleophilic attack on a chromium-activated aromatic ring (Equation 66) <1997TL7387>. The chromium is subsequently removed by oxidation. A highly diastereomeric ring-closing reaction occurs by the Pd-catalyzed reaction of the chiral *N*-allylbenzylamine derivative **32** <1997LA1407> (Equation 67).

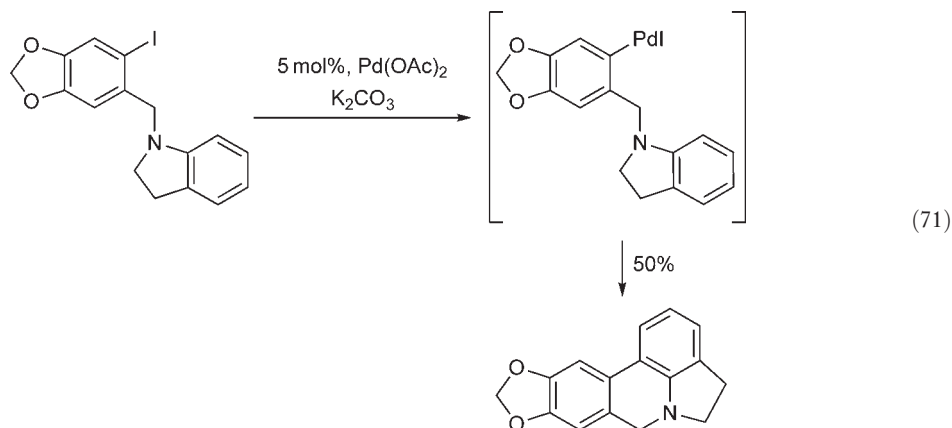
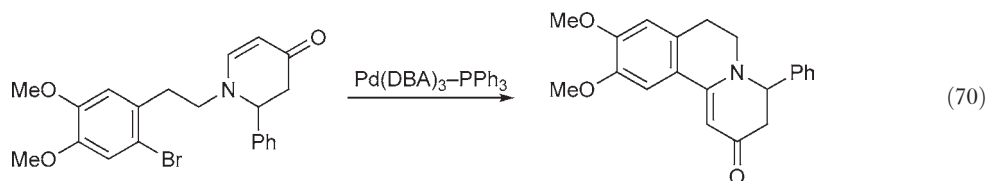
Chirality can be induced at the C-1 position by the cyclization of *o*-vinylphenethylamine in the presence of a chiral selenium reagent (Equation 68) <1998S162>. Removal of the selenide gives the 2-methyltetrahydroisoquinoline. The use of the Pictet–Spengler reaction in the asymmetric synthesis of tetrahydroisoquinolines remains active. Therefore the intramolecular reaction of β -iminosulfoxide **33** yields the chiral product **34** (Equation 69) <1998EJO435>.



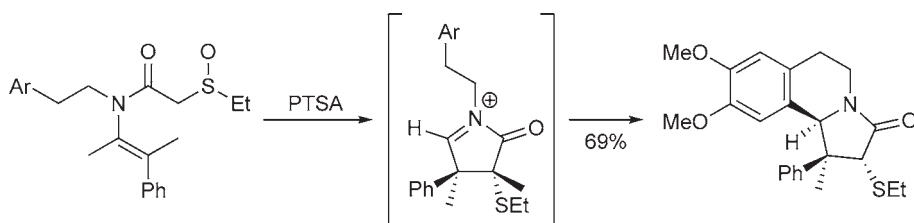
Scheme 30



Extended ring systems can also be formed using intramolecular Heck coupling reactions. Equation (70) shows the preparation of the isoquinoline-based tricyclic benzo[*a*]quinolizine under typical Heck conditions, whereas Equation (71) shows the synthesis of anhydrolycorine, a member of the Amaryllidaceae alkaloid class [2004T1611](#), using a typical palladium-catalyzed biaryl bond-formation reaction. The same group used a similar strategy to optimize the synthesis of benzonaphthazepines [2004S1446](#).



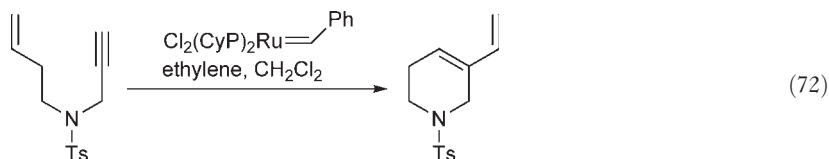
The Pummerer reaction has been shown to give ring closure at the C-1/aryl bond via an *N*-acyliminium intermediate (**Scheme 31**) <1998JOC6778, 1998JOC1144>. Other acids reported include trifluoroacetic anhydride (TFAA) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ <1999H(51)119>. Also reported is the ring closure at the C4/aryl bond to yield tetrahydroisoquinolines <1998CPB430, 1998H(48)981>.

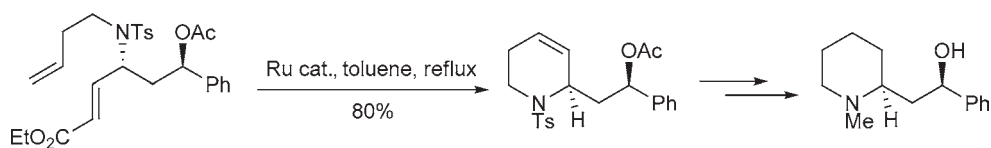


Scheme 31

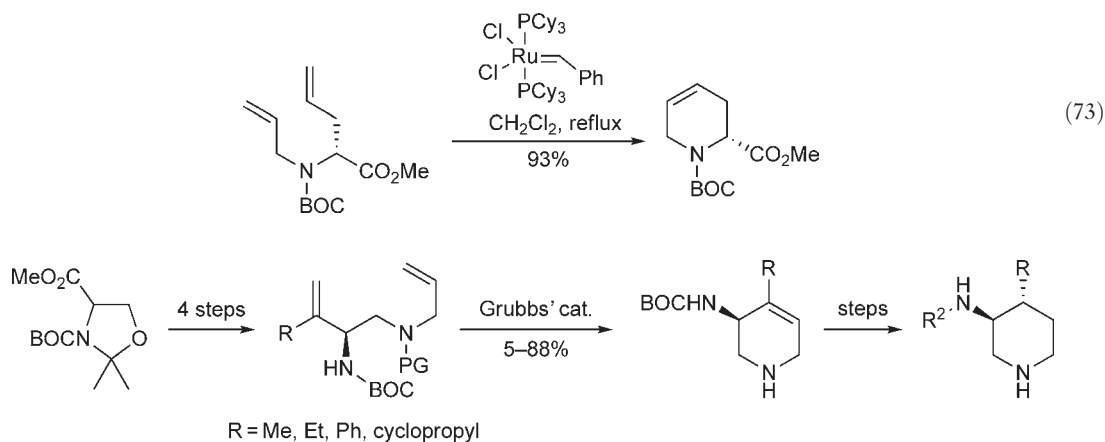
Two examples of the aza-Wittig reaction to produce isoquinolines have also been reported <1997JOC1146, 1997S963>.

Metathesis-based reactions to produce dihydropiperidines is one of the most significant methodologies to emerge in the previous decade <1998TL9563, 1998TL6711, 1998EJO2583, 1998TL6175, 1998CC2053, 1998JOC3158, 2001T5393>. The variety and versatility of examples establish this strategy as one of the simplest and most useful to produce this class of compounds. Occasionally, further development of the reaction is required in order to obtain acceptable yields, for example, the addition of ethylene (**Equation 72**), or the extrusion of ethyl acetate (**Scheme 32**) <2004TL1919>. Numerous chiral examples have been reported (**Equation 73**) <1997TL677, 1997AGE2036>, with a range of chiral sources, for example, amino acids including protected serine derivatives (**Scheme 33**) <2002OL4499>.



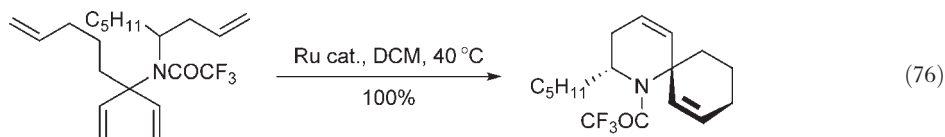
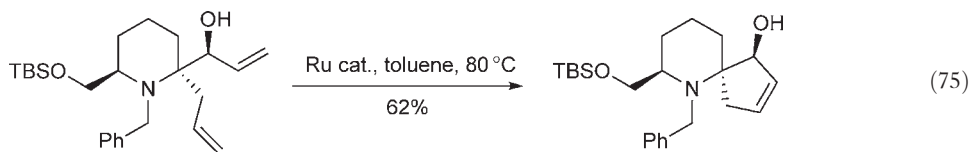
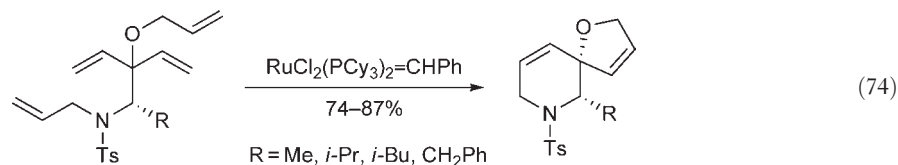


Scheme 32



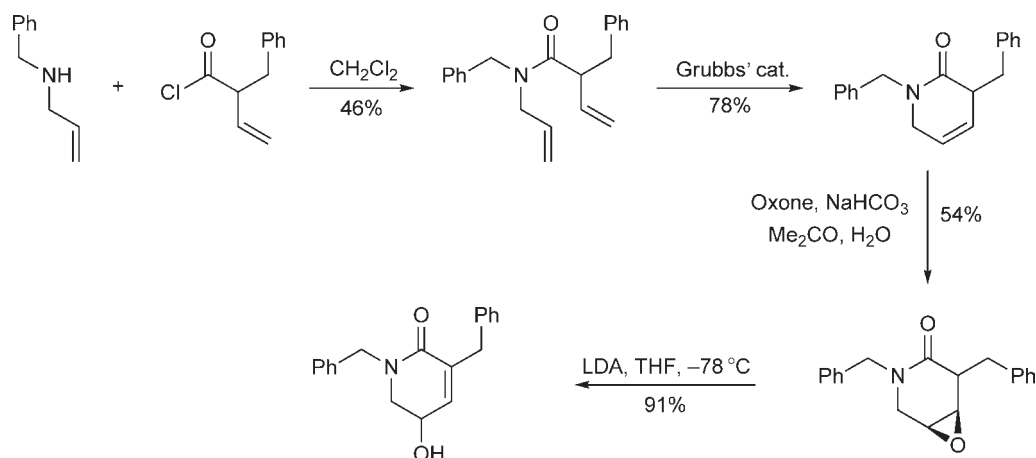
Scheme 33

Variations in the use of ring-closing metathesis (RCM) include the synthesis of spiro-based piperidines with high diastereoselectivity (Equations 74 and 75) <2000TL2027, 2004SL2295>, including a tandem RCM of the tetralene to an azaspirocycle (Equation 76) <2004T8869>. Piperidin-2-ones can also be synthesized by this strategy (Scheme 34) <2003JOC2432>.

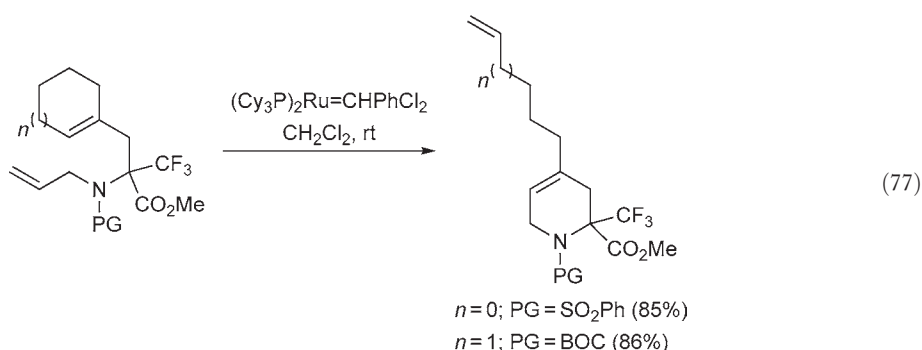


The tolerance of functional groups to the RCM reaction conditions broadens the scope of this strategy. Equation (77) shows an example of a multifunctionalized precursor yielding high yields during a ring-opening–ring-closing metathesis reaction <2001SL621>.

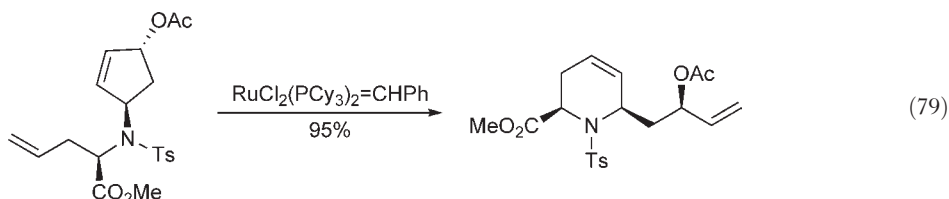
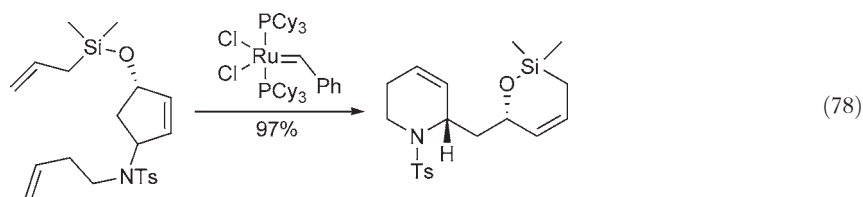
RCM reactions are particularly prominent in the synthesis of natural products. In addition to those already illustrated here, many additional examples have been reported <2000OL1847, 2000CPB1593, 2000CC1027, 2000TL4113>. Some notable natural product classes which utilize RCM as key reactions include the indolizidine and quinolizidine alkaloids <2000OL3971, 2000CC1501>, the asymmetric synthesis of fagomine and its congeners <2001TA817>, pipermethysine <2001OL3381>, coniine <2001TA2269, 2001JOM(624)359>, solenopsin A <2001TA2269>, and (–)-pipercoline <2001JOM(624)359>.



Scheme 34



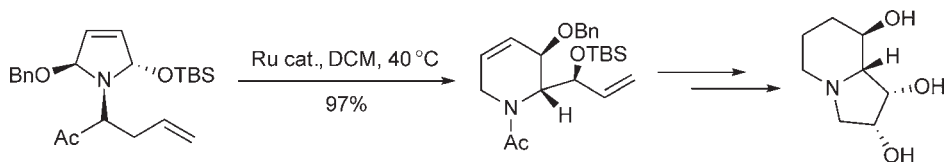
Combination ring-closing and ring-opening reactions are also common, for example, in the synthesis of (–)-halosaline (Equation 78) [<1999T8179>](#) and a transformation involving the generation of stereogenic atoms (Equation 79) [<2000S893>](#).



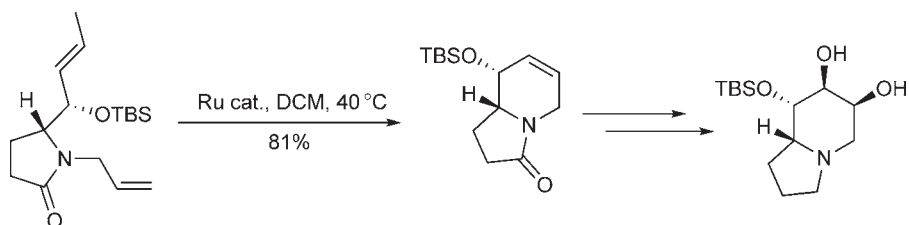
A review on the use of the RCM reaction toward the synthesis of azasugars and alkaloids has been published [<1999EJO959>](#).

The combination of RCM with additional reactions provides excellent strategies for the synthesis of highly functionalized products in short periods of time, often with multiple stereogenic atoms present. For example, a synthesis of (–)-swainsonine utilized a ring-rearrangement metathesis reaction to produce the key tetrahydropyridine which was subsequently converted to the natural product (Scheme 35) [<2004JOC7284>](#). Alternative stereoisomers of the same scaffold can be made using RCM and different starting materials (Scheme 36) [<2004OBC3128>](#),

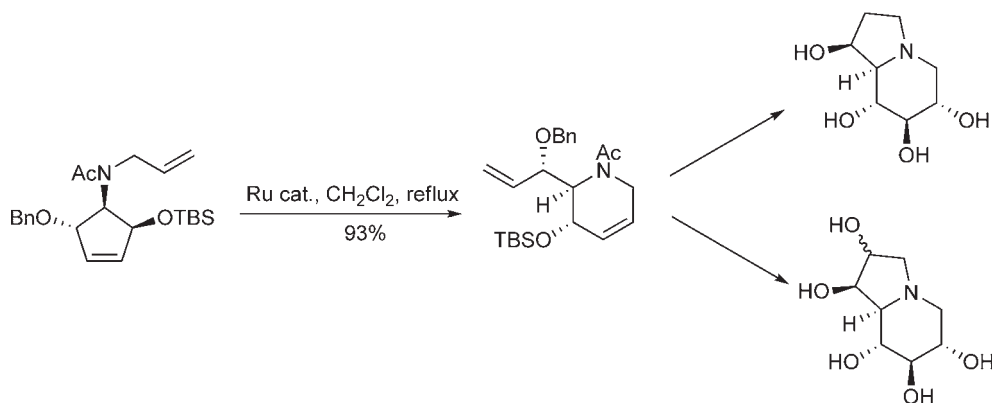
including castanospermine and both isomers of uniflorine A (**Scheme 37**) <2005T8888>. The further use of asymmetric dihydroxylation on products arising from RCM is illustrated in **Scheme 38** <2004TL761> and **Scheme 39** <2004SL2776>, where the highly functionalized piperidines each contain four stereogenic atoms, emphasizing the usefulness of the RCM strategy.



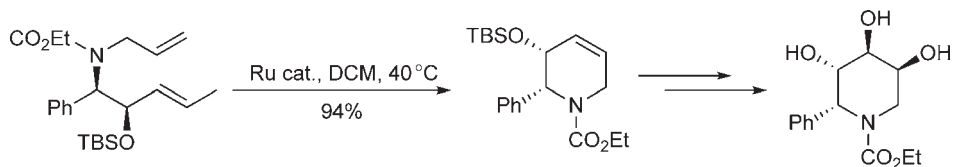
Scheme 35



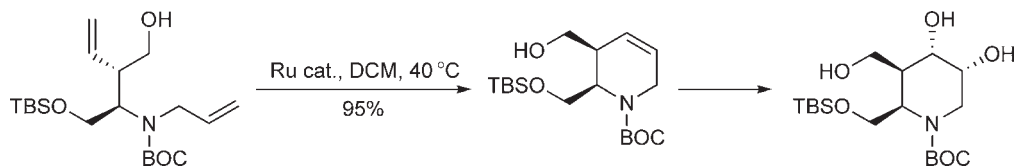
Scheme 36



Scheme 37

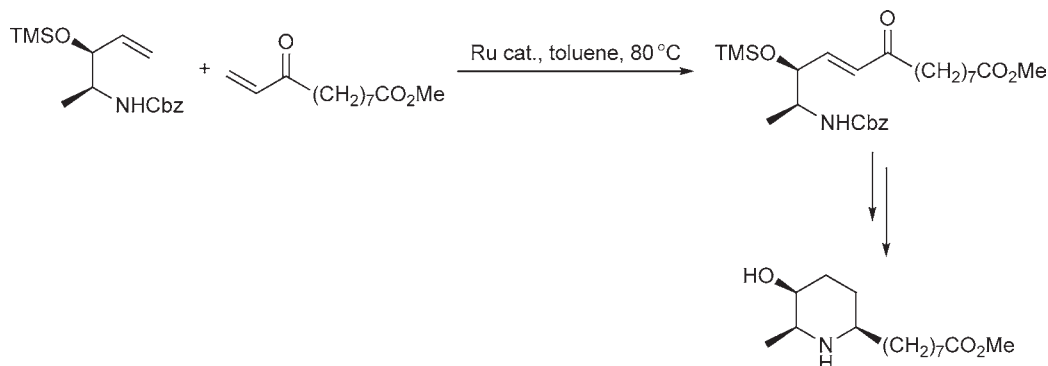


Scheme 38

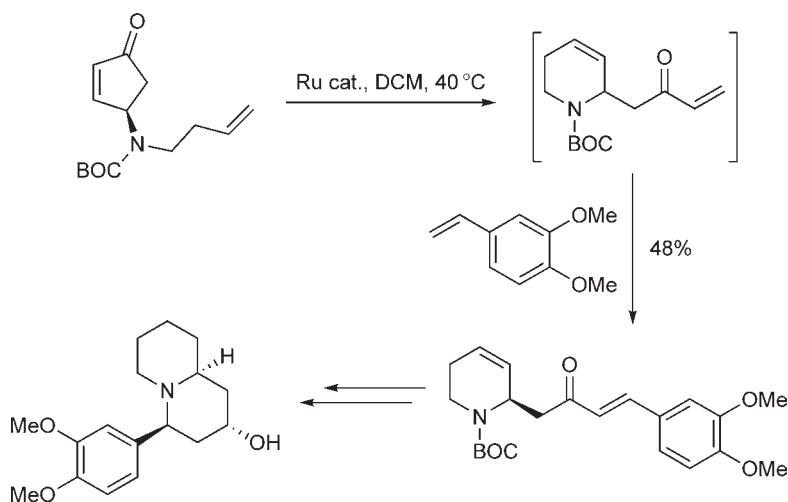


Scheme 39

Cross metathesis (CM) reactions can also be used as the key step in a piperidine synthesis (**Scheme 40**) <2004TL1167> or in sequence with ring-rearrangement metathesis, for example, in the synthesis of (–)-lasubine (**Scheme 41**) <2004T9629>.



Scheme 40

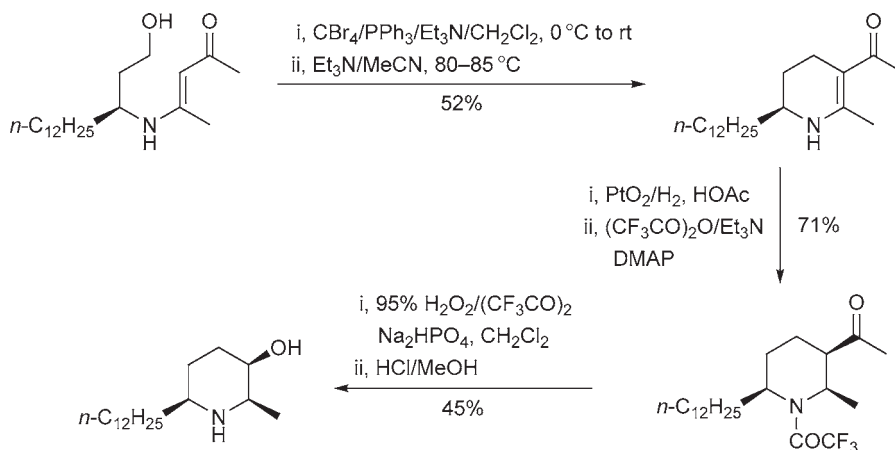


Scheme 41

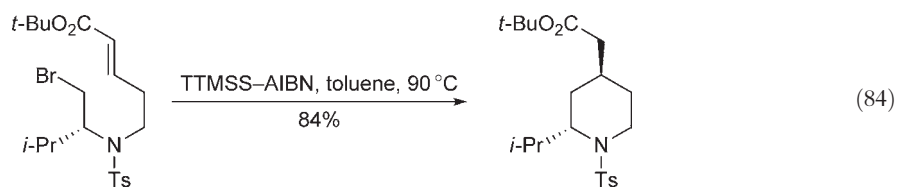
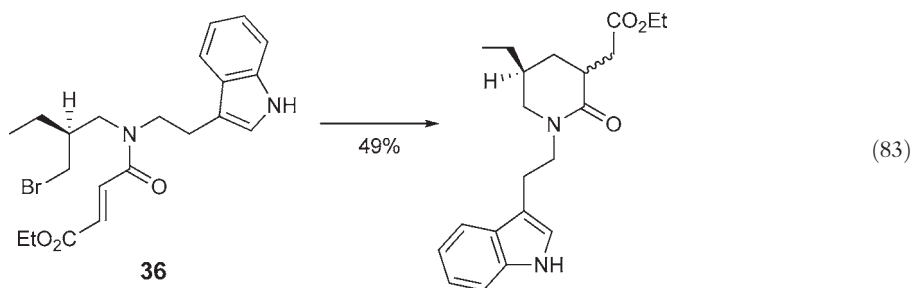
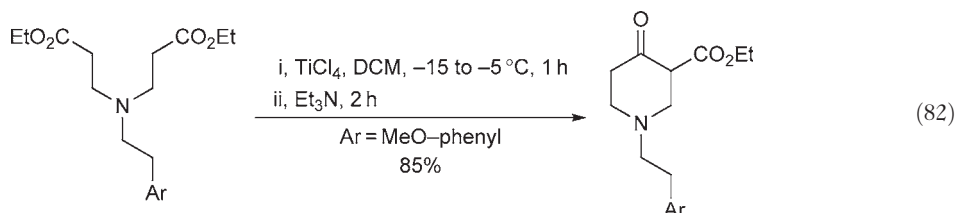
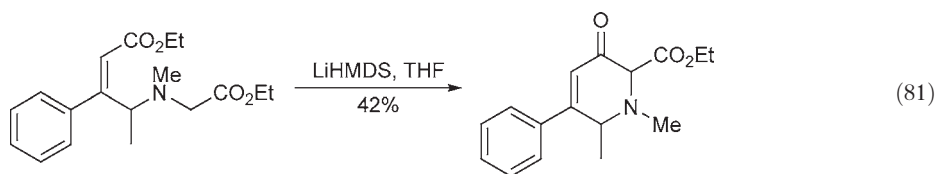
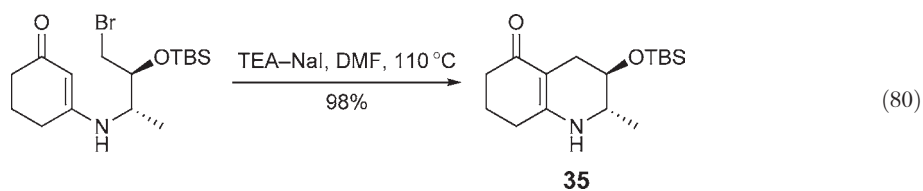
A stereospecific route to enantiopure all-cis-2,3,6-trisubstituted piperidines relies on a cyclization step that is dependent upon temperature, and choice and quantity of base (**Scheme 42**) <2003TL3963>. Further intramolecular alkylation reactions reported include that of the chiral enaminone to the bicyclic structure **35**, a key intermediate toward the synthesis of lepadin alkaloids (**Equation 80**) <2004AGE4222>.

Dieckmann condensation under basic conditions yields 3-piperidones (**Equation 81**) <2004JME5620>. Substituted 4-piperidones are also reported in a Ti(IV)-mediated Dieckmann condensation of diesters (**Equation 82**) <1995SC177>. The electroreduction of the alkenyl bromide **36** under [Ni(cyclam)](ClO₄)₂-catalyzed conditions leads to the piperidone in moderate yields (**Equation 83**) <1996JOC677>.

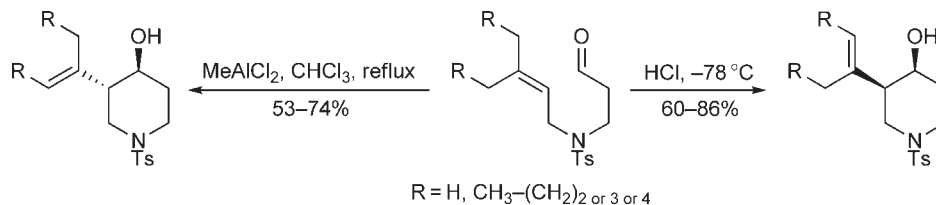
The radical cyclization to piperidines continues to be reported. 2,2'-Azobisisobutyronitrile (AIBN) can be used with a variety of substrates including chiral substrates which give products with enhanced diastereoselectivity (**Equation 84**) <2004OBC2270>. Other substrates used include an intramolecular diene in a 6-*endo-trig*-process, a 5-*exo-trig*-process <2004T8181>, the cyclization of an oxime ether and aldehyde to give cyclic amino alcohols <1999JOC2003, 1999H(51)2711>, and an alkene–aldehyde cyclization <1997TL5907>.



Scheme 42

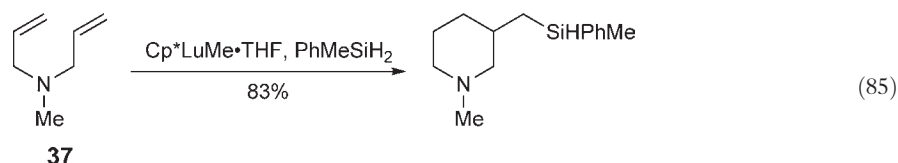


A traditional acid-catalyzed cyclisation to piperidines can control the stereo-outcome by the judicious choice of acid (**Scheme 43**) <2002OL3727>. Stereoselectivities of up to 98:2 were achieved with a Lewis acid giving the *trans*-isomer and Brønsted acids yielding the *cis*-isomers.

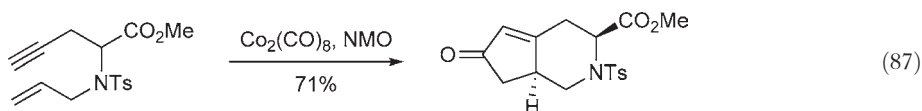
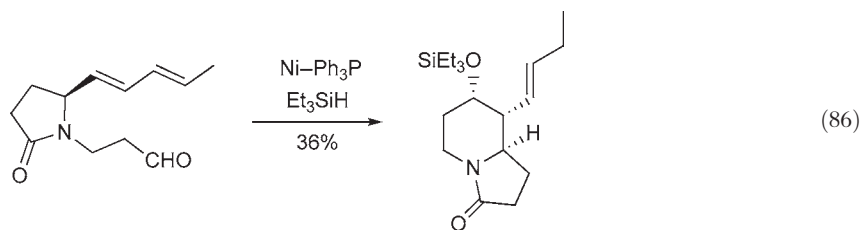


Scheme 43

Organolanthanide-catalyzed silylation has recently been developed and is a significant new strategy for the synthesis of piperidines. For example, the diallyl compound **37** was cyclized in 83% yield with 5 mol% catalyst in the presence of a suitable silyl terminator (**Equation 85**) <2005T2631>.



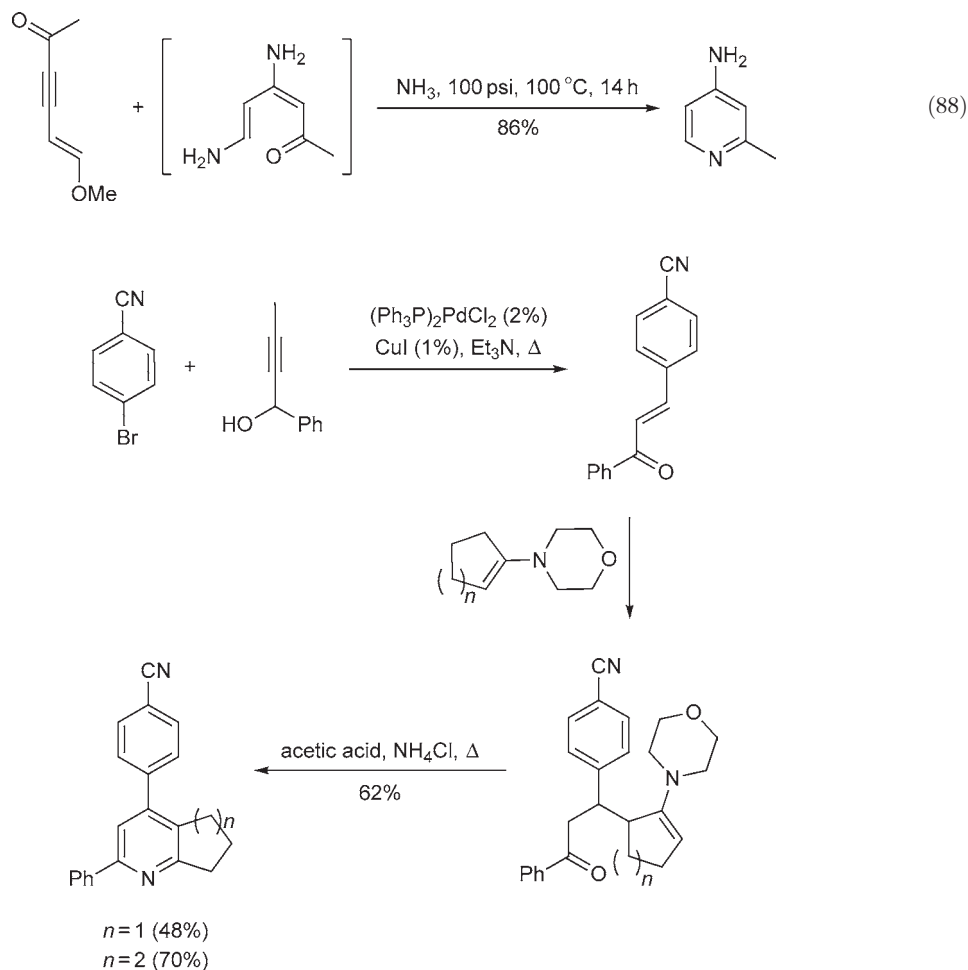
Nickel-catalyzed cyclization of a 1,3-diene side chain of the substituted pyrrolidones yields a precursor to the indolizidine alkaloid (–)-elaeokanine C (**Equation 86**) <1997TL3931>. Other metal-catalyzed reactions include the Rh-induced *in situ* carbene generation and subsequent cyclization onto the heteroatom to yield piperidines <1997T16565, 1997JOC67>. Pauson–Khand cyclizations have also been used (**Equation 87**) <1997T6611>.



7.05.2.2 Formation of Two Bonds

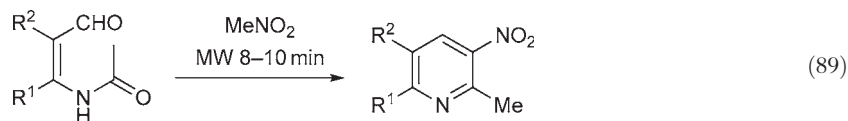
7.05.2.2.1 From [5+1] and [9+1] atom fragments

The insertion of a nitrogen-containing fragment is a traditional strategy for the synthesis of pyridines. Reported examples include the amination of acetylenic ketones (**Equation 88**) <2001TL1847>, and as part of a four-component, one-pot synthesis the insertion of ammonium ion following a multistep sequence (**Scheme 44**) <2002TL6907>. Additional multicomponent strategies to pyridines have also been reported <2002RCB362, 2002SC3493, 2002T9709>.

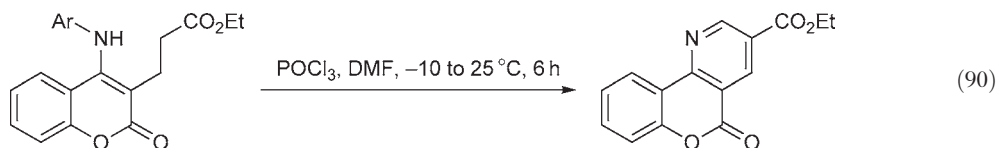


Scheme 44

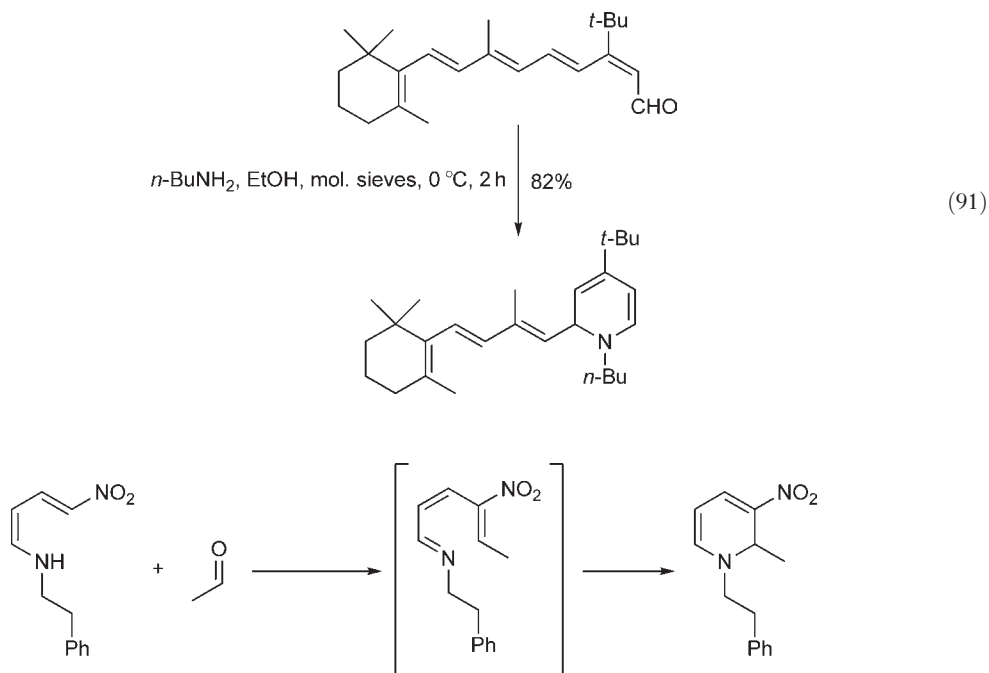
The insertion of a one-carbon unit into a β -formylenamide under microwave irradiation yields the pyridine (Equation 89) <2004SL1309>.



Ring closure under Vilsmeier conditions leads to the pyridine structure (Equation 90) <1995JHC505>.

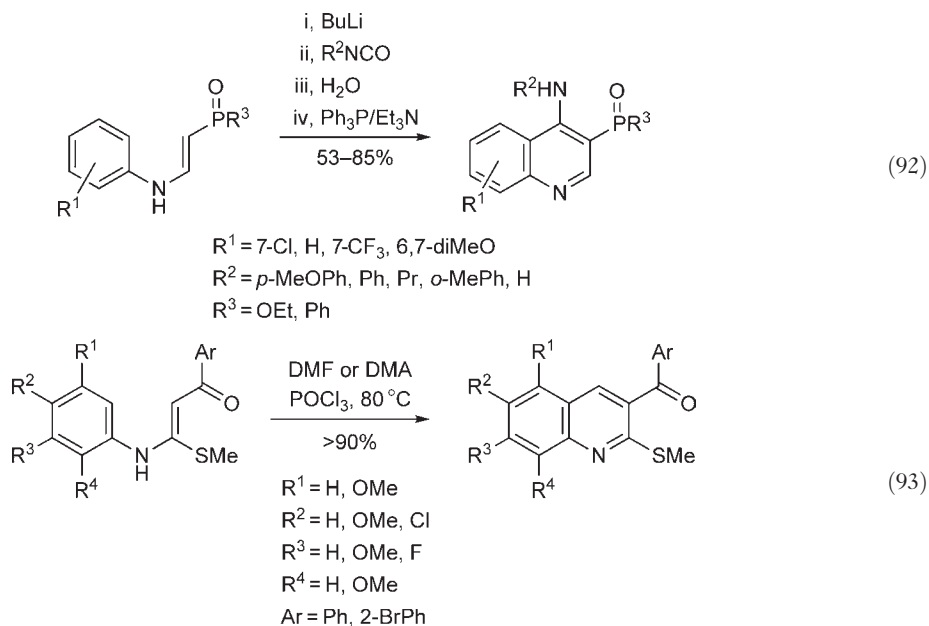


Dihydropyridines have also been reported with a nitrogen fragment insertion <1995JOC1763>, in this case reported as a general method that possessed unprecedented steric acceleration of a 6π -electrocyclization (Equation 91). Dihydropyridines have also been reported with insertion of a carbon fragment (Scheme 45) <2000CPB436>. In this example, the novel insertion of aldehydes into amino 1,2-butadienes leads to the heterocycle.

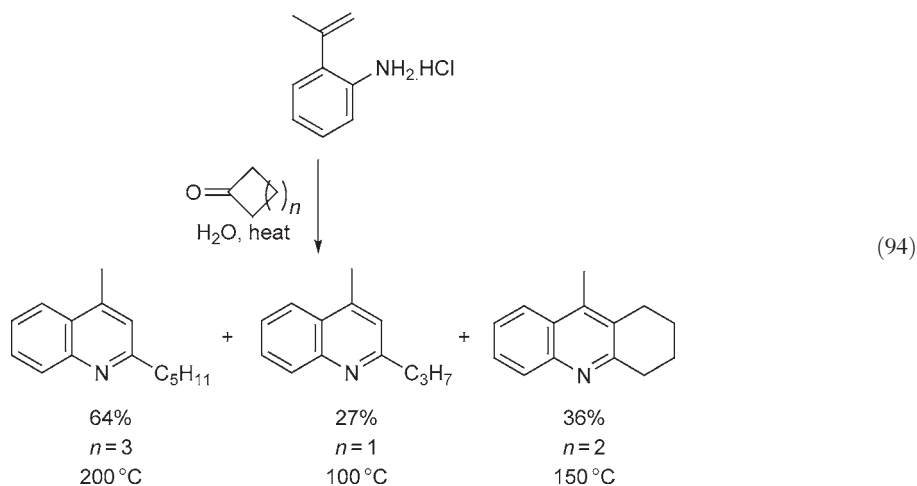


Scheme 45

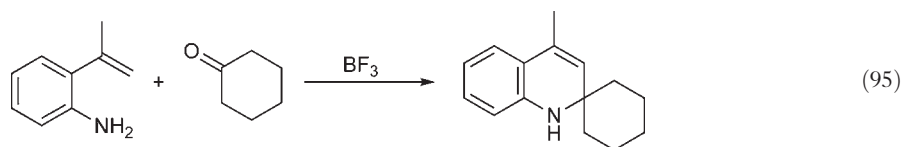
Reaction of lithiated β -enaminophosphonates of aniline and isocyanates with subsequent cyclization of the resulting amides with triphenylphosphine/triethylamine leads to the 3-phosphonyl-4-aminoquinolines (Equation 92) <1999T5947>. Aniline reaction with β -diketones <1999H(51)2171> and ethoxymethylenemalonates <1999JFC(94)7> also leads to quinoline formation. The Vilsmeier reaction conditions can also be applied to the synthesis of quinolines with the use of α -oxoketene *N,S*-anilinoacetals (Equation 93) <2003JOC3966>.



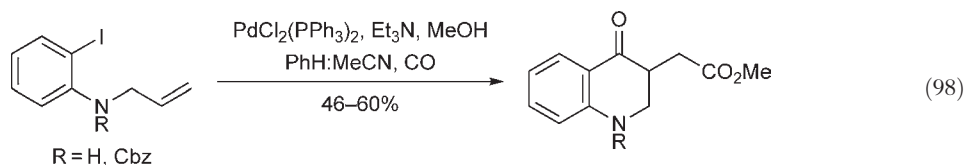
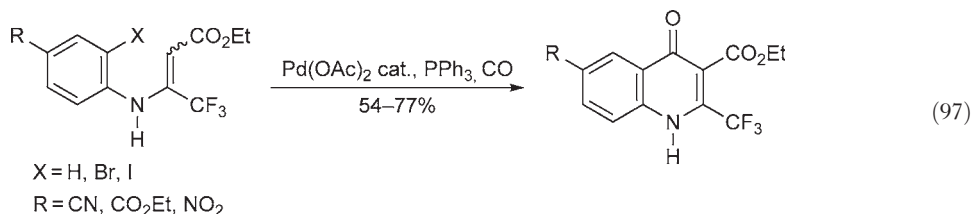
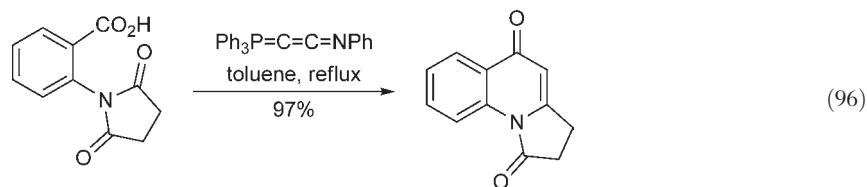
In a novel approach, the hydrothermal process in the absence of organic solvents of 2-isoprenylaniline with cyclic ketones leads to quinoline synthesis (Equation 94) <2003OL1605>. The product distribution is heavily dependent on the temperature of reaction.



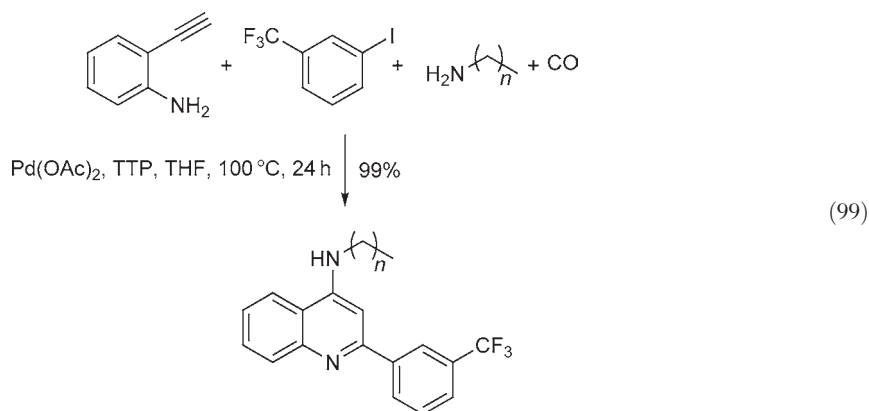
The dihydroquinoline structure can be accessed by the reaction of 2-isoprenylaniline with ketones in a condensation reaction in the presence of a Lewis acid (Equation 95) <1998JPR309, 1998TL5139>.



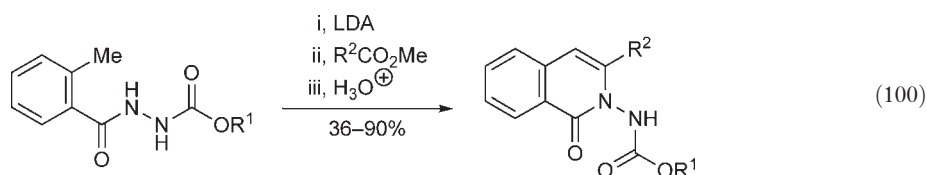
The aza-Wittig ring-closing reaction can be utilized in the synthesis of quinol-4-ones in excellent yield (Equation 96) <1995TL59>. The same heterocyclic scaffold can be accessed by the palladium-catalyzed reaction of vinylogous amide derivatives in a carbon monoxide atmosphere (Equation 97) <1996CC2253>. The analogous reaction using *N*-allylanilines produces the quinolone structure (Equation 98) <2001JOC2175>.



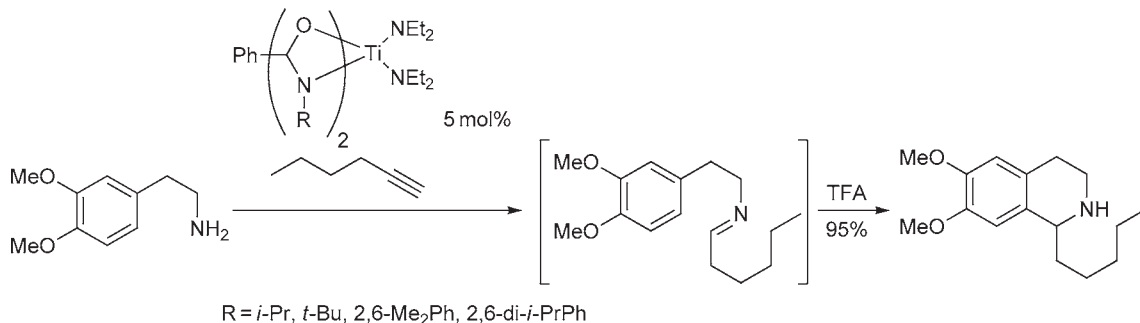
The usefulness of palladium-based chemistry is highlighted by the multicomponent cascade reaction sequence that uses *o*-ethylanilines, aryl iodides, primary amines, and carbon monoxide (Equation 99) <2005JOC6454>.



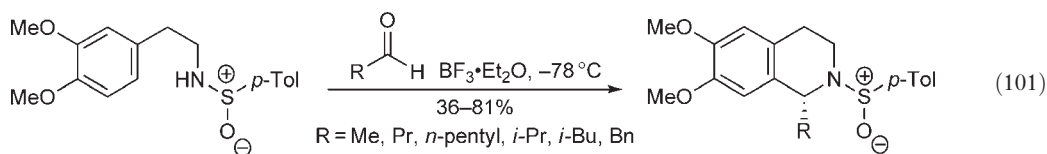
Esters of 2-(2-methylphenyl)hydrazinecarboxylic acids can be metallated with lithium diisopropylamide (LDA) and the resulting polyanions condensed with aromatic esters and lead to acid-catalysed cyclization to 1-isoquinolones (Equation 100) <1996SC1763>.



The Pictet–Spengler reaction continues to be reported in the synthesis of tetrahydroisoquinolines. In some unusual variations, the titanium ‘precatalyst’ illustrated in Scheme 46 was used in a one-pot reaction using phenylethylamines and alkynes (Scheme 46) <2003OL4733>. The use of *N*-sulfinylamine precursors gave reported diastereomeric ratios as high as 96:4, with the chiral auxiliary being removed in a facile manner using HCl in ethanol (Equation 101) <2001TL8885>.

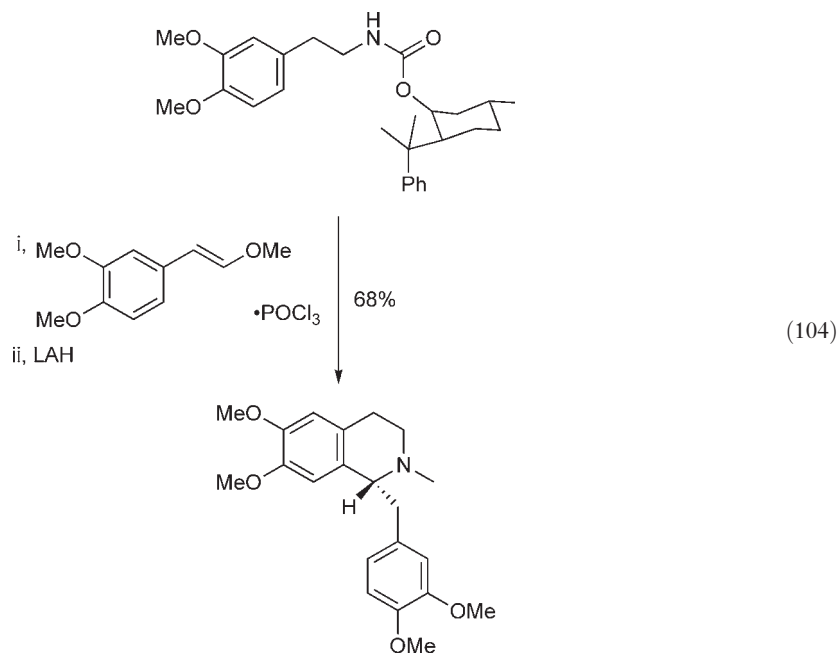
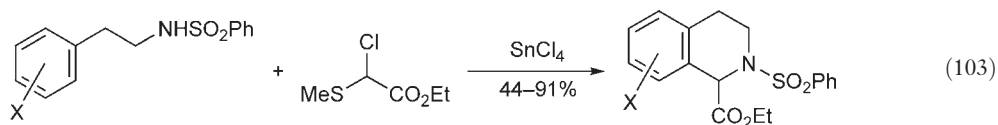
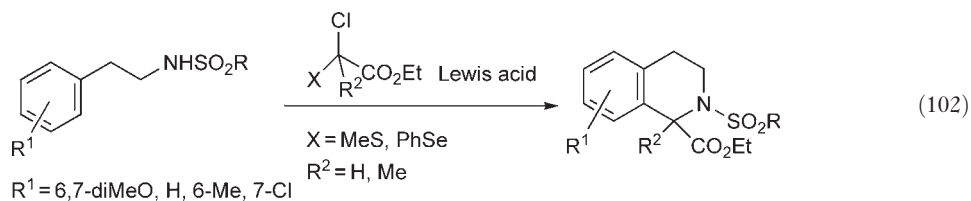


Scheme 46

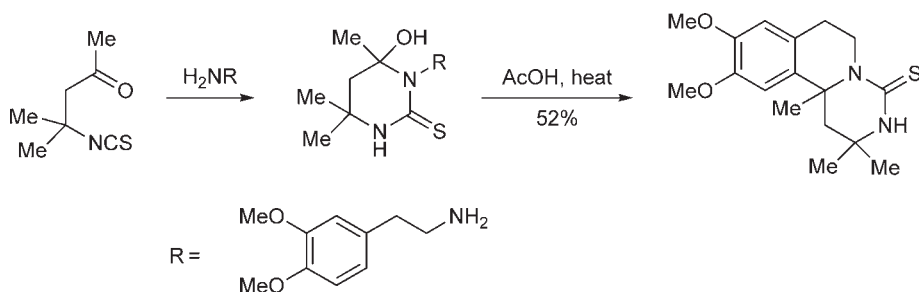


Reported improvements in conditions allows for the synthesis of tetrahydroisoquinolines in good yield by condensation reactions using reagents with strongly electron withdrawing substituents present (Equation 102) <1999H(51)103, 1999TL4969>. This has been extended to the reaction of the electron-deficient *N*-benzenesulfonyl- β -phenethylamines

with ethyl chloro(methylthio)acetate to give moderate to high yields of the tetrahydroisoquinolines (Equation 103) <1996H(42)141>. POCl₃-catalyzed reactions have also been reported with the enantioselectivity being induced by the chiral urethane (Equation 104) <1997T16327>.

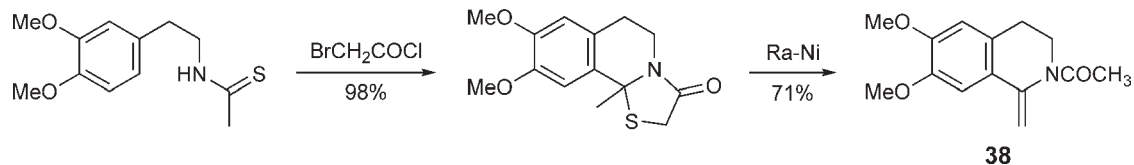


The intramolecular cyclization toward tetrahydroisoquinolines can lead to some interesting chemistry. The reaction of isothiocyanatocarbonyls with aromatic ethyl amines gives the fused systems under mild conditions (Scheme 47) <2003CHE277>. Reaction of thioamide derivatives with bromoacetyl chloride upon cyclization leads to *S,N*-acetal tetrahydroisoquinoline derivatives, which can be treated with Raney nickel to produce 38

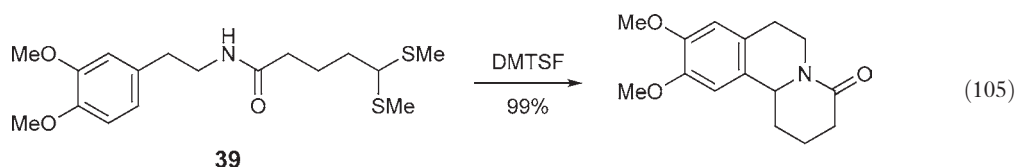


Scheme 47

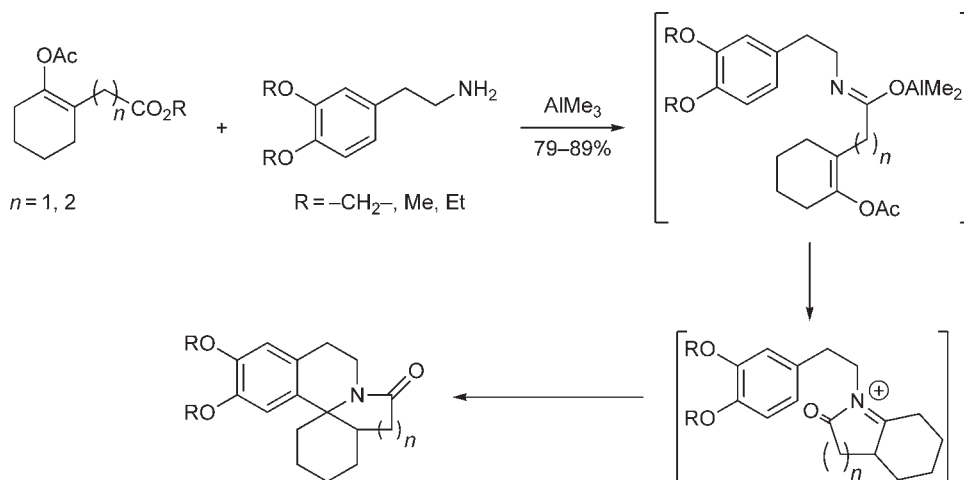
(**Scheme 48**) <1998TL4761>. Further examples of this strategy were also reported <2000JOC2684>. A thionium ion-promoted Mannich reaction of the amide **39** upon treatment with dimethyl(methylthio)sulfonium tetrafluoroborate yields the extended tetrahydroisoquinoline in excellent yield (**Equation 105**) <2000JOC235>.



Scheme 48

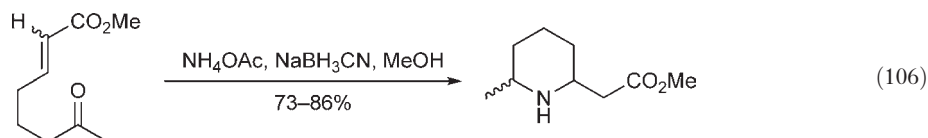


A domino reaction catalyzed by AlMe_3 leads to the skeleton of the *Erythrina* and β -homo-*Erythrina* alkaloids (**Scheme 49**) <2004AGE5391>. The mechanism is believed to proceed via an *N*-acyliminium ion and a metallated amide.

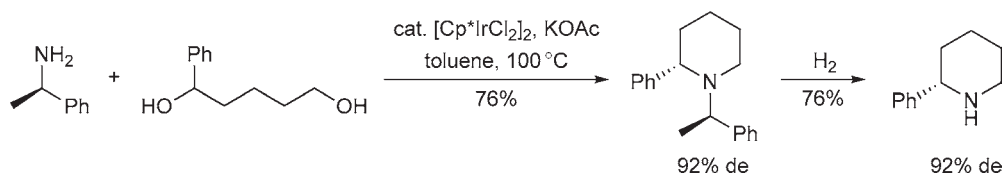


Scheme 49

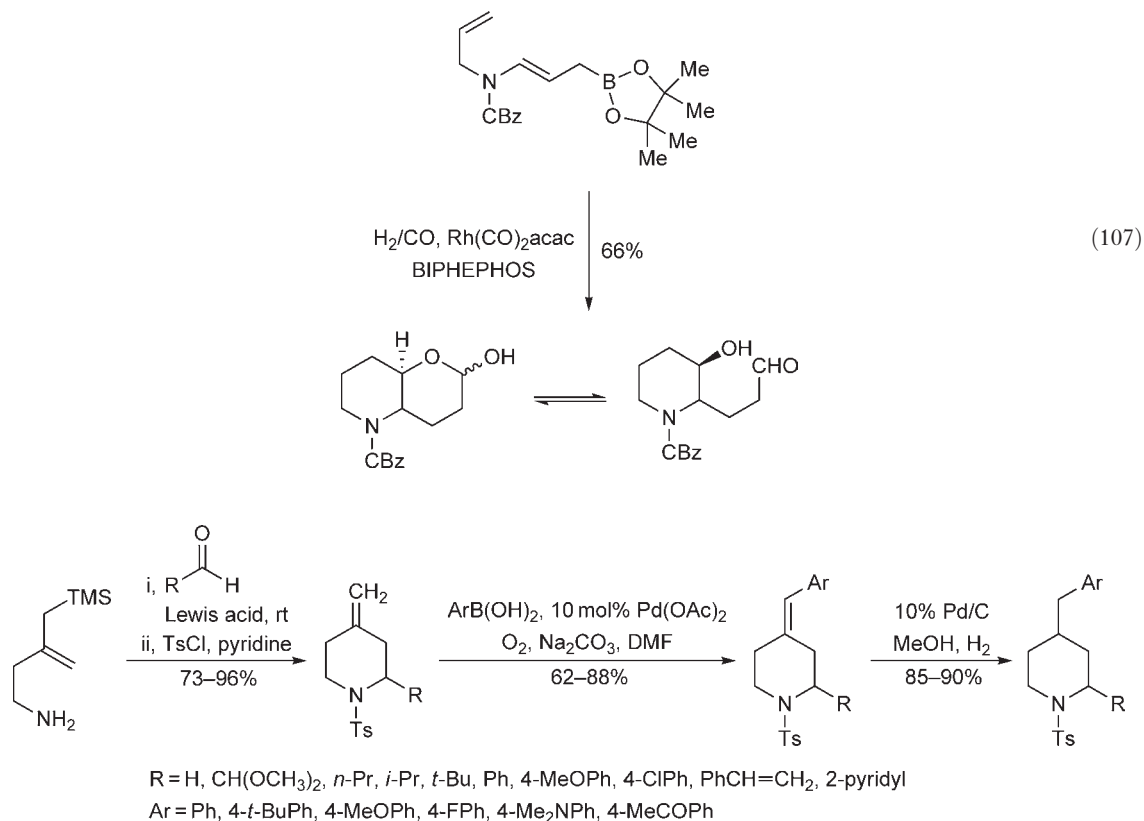
The strategy of nitrogen-fragment insertions leading to piperidines continues to be reported. In addition to the usual ammonium ion insertion <1996J(P1)967> (**Equation 106**), the reaction can be stereoselective; for example, **Scheme 50** shows the iridium complex with pentamethylcyclopentadienyl ligands acting as the catalyst in the *N*-heterocyclization of a diol and (*R*)-phenylethylamine <2004OL3525>. Further stereoselective reactions of the same type have been reported <1998SL652>.



The insertion of carbon fragments is another common strategy for the synthesis of piperidines. Hydroformylation of an allyl-substituted aminoallylboronate in the presence of a rhodium catalyst produces a reasonable yield of piperidine (**Equation 107**) <2000H(52)121>. Aldehydes have also been used in the cyclization of imines in a one-pot multistep synthesis of piperidines that allowed further functionalization to take place (**Scheme 51**) <2003TL8249>.

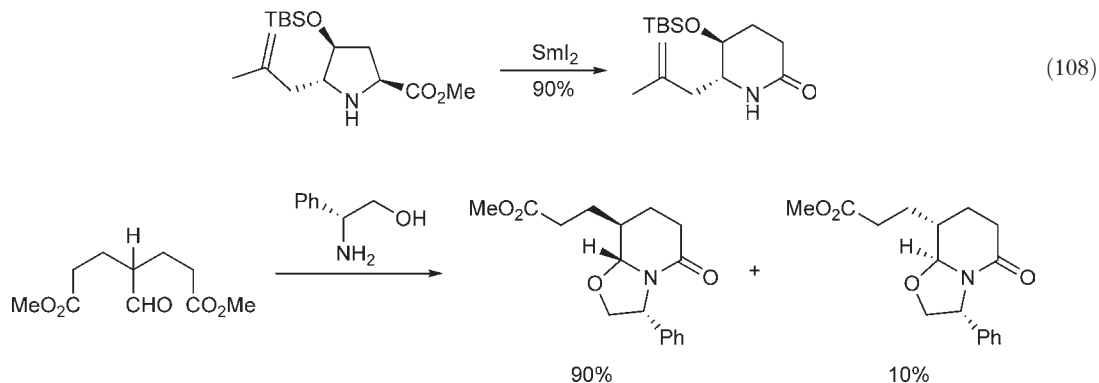


Scheme 50



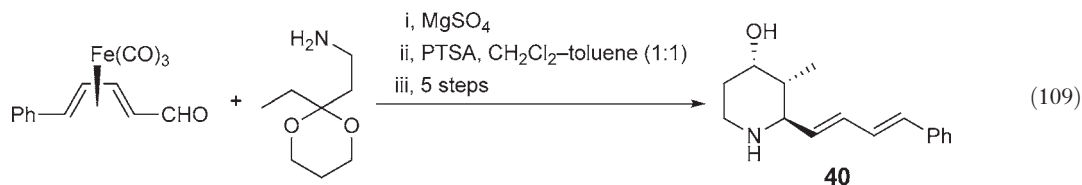
Scheme 51

Piperidin-2-ones have also been prepared by the insertion of ammonium ion [<2004TL6221>](#) (Equation 108), with chiral versions also being reported ([Scheme 52](#)) [<2002CC526>](#).



Scheme 52

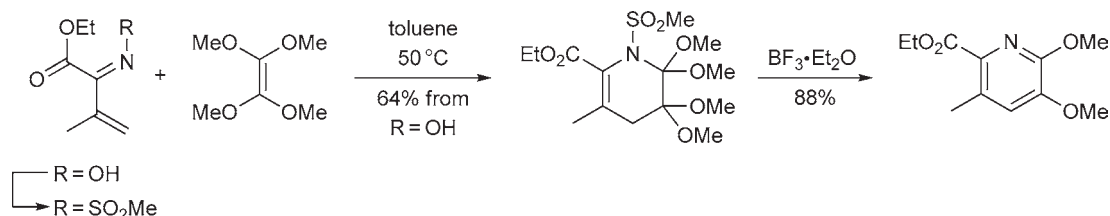
A novel reaction that transfers chirality from an enantiopure tricarbonyl(dienal)iron complex in a Schiff base condensation reaction is followed by an intramolecular Mannich reaction to yield a piperidine which was then manipulated in additional five steps to dienomyacin C **40** (Equation 109) <1999EJO1517>.



7.05.2.2.2 From [4+2] atom fragments and [8+2] fragments

The application of Diels–Alder methodology to pyridine formation can take different approaches. The heteroatom can be sourced from the diene or the dienophile and by varying its position in the starting materials can lead to strategies for different substitution patterns in the pyridine product. While such approaches are well documented, recent reports have both extended the range of derivatives available and incorporated new technology to assist in the optimization of reactions.

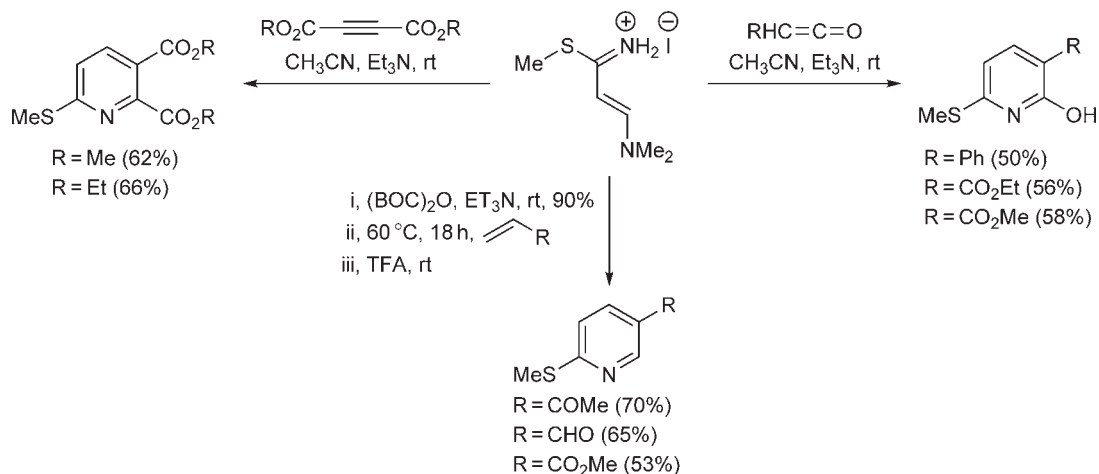
An N-1-diene-1-aza-1,3-butadiene was employed in a Diels–Alder reaction to synthesize the key intermediate, a tetrasubstituted pyridine, in the total synthesis of the pyridine-base natural product, piericidin (**Scheme 53**) <2005JA15704>. The concerted cyclization conditions were surprisingly mild, considering the steric demand of the dienophile and that the aromatization was not successful under a variety of basic conditions, but the Lewis acid cleanly affected the transformation.



Scheme 53

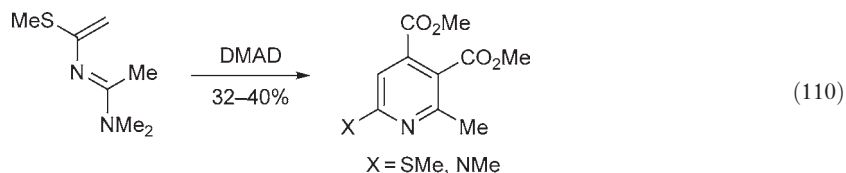
1-Azabutadienes have also been reported to react with dimethylmaleate <1995TL8977> with significant rate enhancement using LiNTf₂. However, it has been noted that the use of lanthanide triflates as catalysts can be preferable to the unstable lithium perchlorate <1995SL233>.

An extension to the aza-diene method is the use of diazadienium iodide - its reaction with acetylenes, ketenes, and acrylic dienophiles yields pyridines of varying substitution patterns (**Scheme 54**) <2004TL9557>. Similarly,

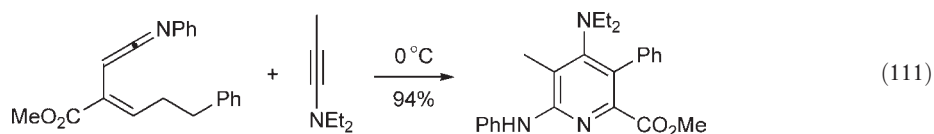


Scheme 54

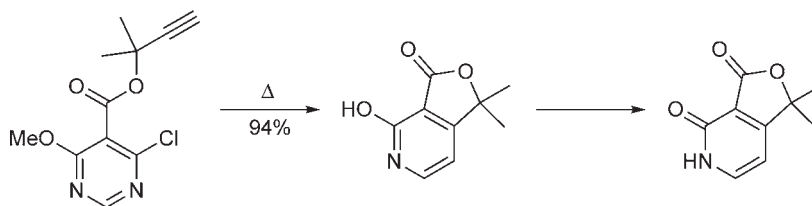
substituted 2-aza-1-(dimethylamino)-3-(methylthio)-1,3-dienes react with electron-deficient dieneophiles to give pyridine derivatives (Equation 110) <1996T10095>.



Conjugated heterocumulenes can act as heterodimers in [4+2] cycloadditions, reacting with aminoalkynes to give tetrasubstituted pyridines (Equation 111) <1997T4521>. The corresponding isoquinoline is formed if the reaction is heated to 140 °C.

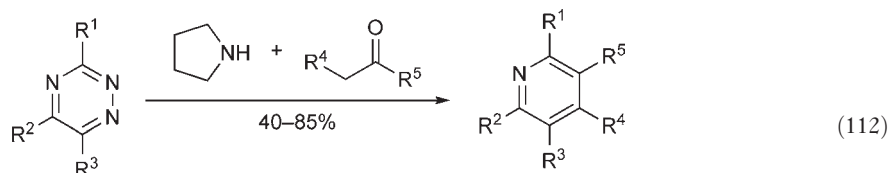


Acetylenic pyrimidines undergo hetero-Diels–Alder reactions yielding pyrido-fused lactams with recent reports of improved yields using microwave-assisted conditions <2005TL3423>. The use of alkynes as dieneophiles has also been reported in an intramolecular reaction with chloropyrimidine (Scheme 55) <2000SL625>, in this case toward the total synthesis of cerpegin via demethylation.



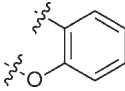
Scheme 55

The typical reaction of 1,2,4-triazines with alkenes has been recently extended to include medium-sized cyclic alkenes, for example, cycloheptene and cyclododecene, giving the fused pyridines <1996J(P1)519>. Recent extensions of enamine reactions with 1,2,4-triazines allow a facile formation of a wide range of substituted pyridines. The enamines can be generated *in situ* and under solvent-free microwave conditions (Equation 112) <2005JOC10086>, giving yields of 40–85% for highly substituted pyridines and fused analogues (Table 1). The same authors also report a thermal tethered imine–enamine reaction with triazines which replaces the amine with a diamine and which was thought to aid in the elimination–aromatization steps. This was successful for a range of cyclic ketones and 1,2,4-triazines of 33–100%, and required reaction in toluene at reflux <2005JOC10086>.



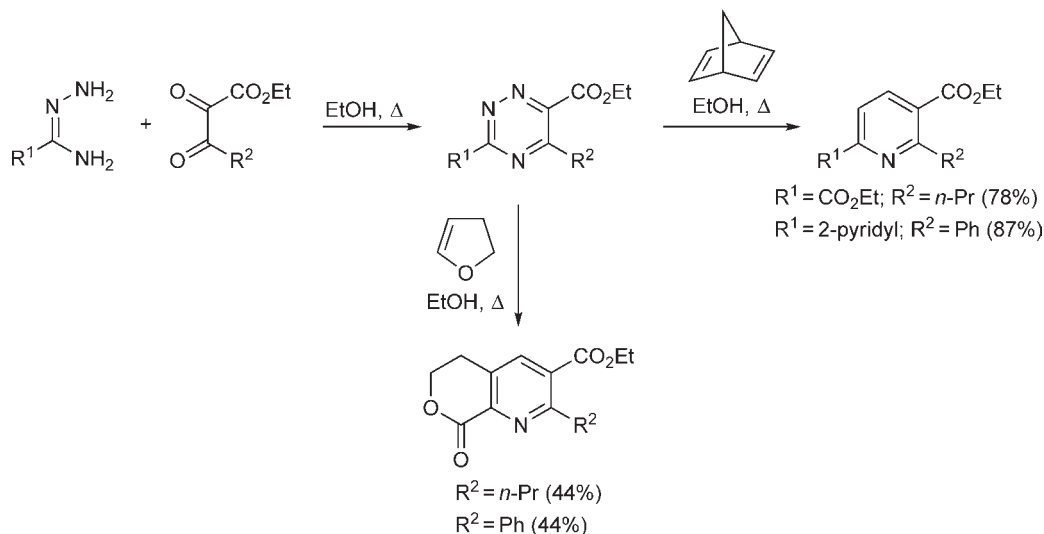
Conditions: triazine (0.1 mmol), ketone or aldehyde (0.2 mmol), pyrrolidine (0.2 mmol), MW irradiation 150–200 W

Table 1 Solvent-free microwave reaction of *in situ*-generated enamines with 1,2,4-triazines (Equation 112) <2005JOC10086>

R^1	R^2	R^3	R^4	R^5	Yield (%)
Py	H	H	Pr	H	67
Py	Fur	Fur	H	Ph	82
Py	Ph	H	Pr	H	85
Py	Ph	H	Pr	H	81
Py	Ph	H			66

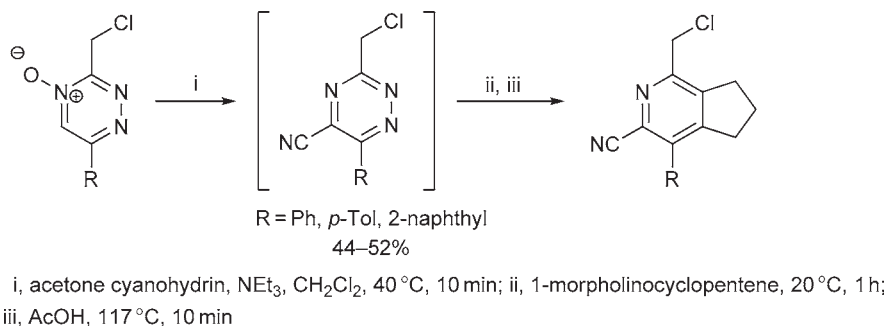
5,5'-Dimeric versions of these triazines have also been reported to undergo the Diels–Alder reaction with preformed enamines to give 2,2'-bipyridines <2005MOL265>. It is possible to carry out the reaction stepwise or in one pot; however, the yields are variable for both sequences (10–64%).

It is also possible to generate the same triazine *in situ* as part of a one-pot reaction starting from ethyl thioamido oxalate followed by generation of the hydrazone and then addition of an α,β -diketone ester and either norbornadiene or 2,3-dihydrofuran. The former diene yields the pyridine skeleton in 59–87% yield, while the latter gives fused pyridolactones in 39–44% yield (Scheme 56) <2004T8893>.

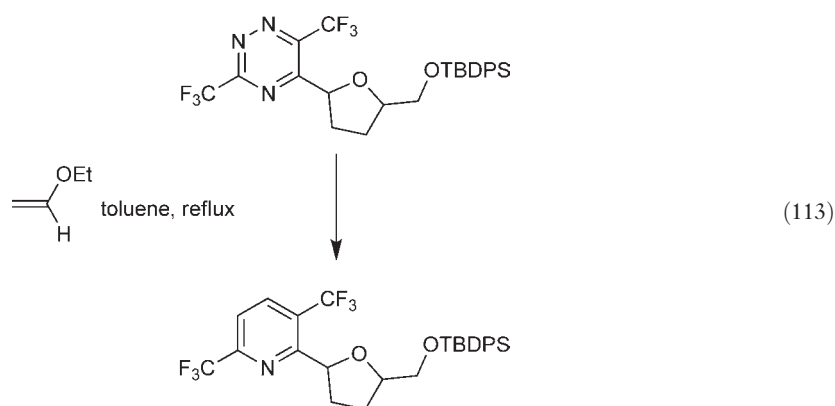
**Scheme 56**

Additionally, triazines have been used in the same manner to produce terpyridines <2005TL1521> and bipyridines <2005TL1791>, and an encompassing report on the reaction of 1,2,4-triazines with enamines producing cycloalkylpyridines using a Diels–Alder–*retro*-Diels–Alder strategy has also been presented <2005T8148>. Further triazine-based [4+2] reactions include the generation of thienopyridines in an intramolecular reaction <2002JCM60, 2002CPB463> and the generation of 4-stannylpyridine when ethynyltributyltin is used <1998TL2549>. Enamines have also been utilized with 2-azabutadienes generating fluoroalkyl ring-fused pyridines <2005T2779>.

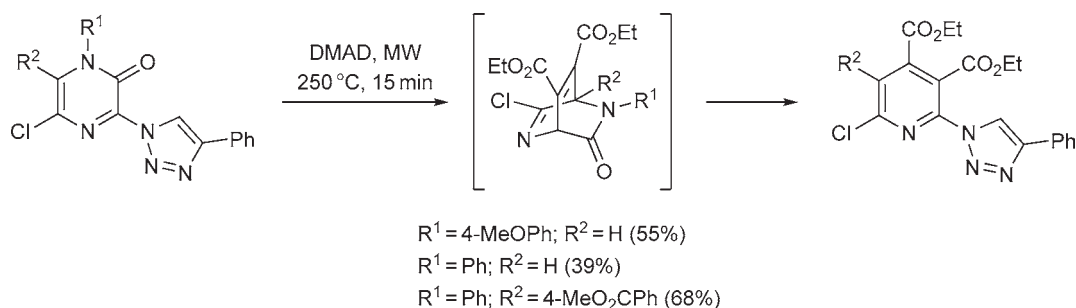
An analogous reaction can be undertaken starting from the corresponding 4-*N*-oxide of the triazine (Scheme 57) <2005RCB2187>. This involves an inverse electron-demand Diels–Alder cycloaddition and utilizes a morpholine substituent as a leaving group to promote the aromatization to the pyridine. Additional analogous reactions include the use of electron-rich nucleophiles (e.g., Equation 113) giving rise to a pyridine nucleoside <1997ZNB851> and 3-pyridylindoles <1997H(45)1551>. Using the same strategy of triazines in inverse electron-demand reactions with a variety of electron-rich strained dienophiles gives pyridines, branched oligopyridines, and ‘super-branched’ pyridines <1998TL6687, 1998TL6691, 1998TL8817, 1998TL8821, 1998TL8825>.



Scheme 57

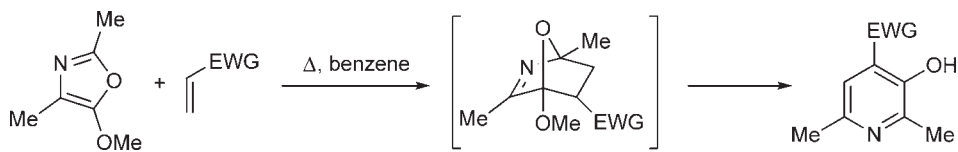


Diels–Alder reaction strategies to pyridines can also utilize 2(1*H*)-pyrazinones as the heteroatom source, requiring alkynes as the dienophile (**Scheme 58**) <2005JCO490>. This is enhanced by microwave irradiation, with elimination of isocyanate yielding the pyridine. Also possible from the same intermediate is elimination of cyanogen chloride giving rise to the corresponding pyridone. Both outcomes are usually observed; however, selectivity is possible through substitution of the pyrazinone at the C-1 position, with alkyl substituents favoring pyridone formation and aryl substitution promoting pyridine formation.



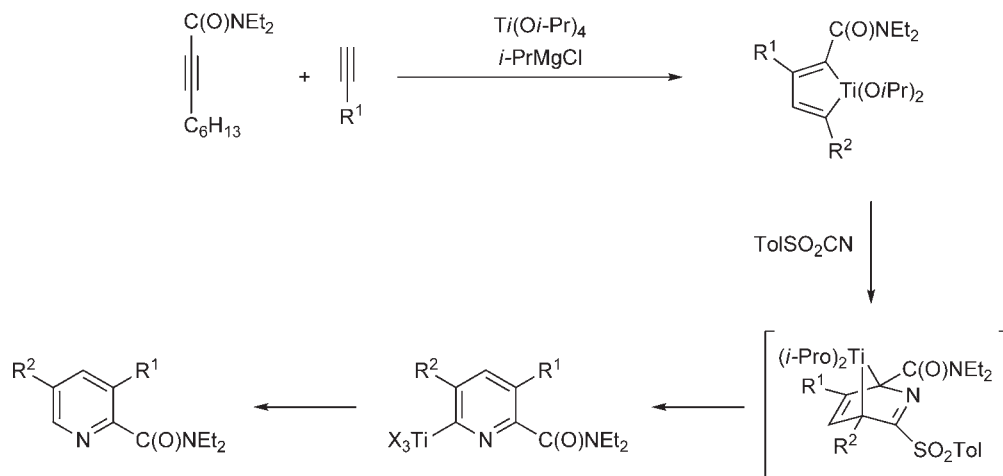
Scheme 58

A further strategy is the addition of alkenes with electron-withdrawing groups (EWGs) attached to 2,4-dimethyl-5-methoxyoxazole to produce 3-hydroxy-2,6-dimethylpyridines (**Scheme 59**) <2005HAC49>. Acyclic alkenes give 60–90% yields while cyclic alkenes produce the corresponding fused pyridines in 70–96% yields. Recent intramolecular examples, also resulting in fused products, show yields of 23–37% <2000TL10251>.



Scheme 59

The generation of an unsymmetrical titaniumcyclopentadiene from different acetylenes can then be subjected to a [4+2] cycloaddition with a sulfonylnitrile to form an intermediate complex which collapses under acidic conditions to yield substituted pyridines (Scheme 60; Table 2) <2002JA3518>. A similar reaction using zirconium has been reported <2002JA5059>.

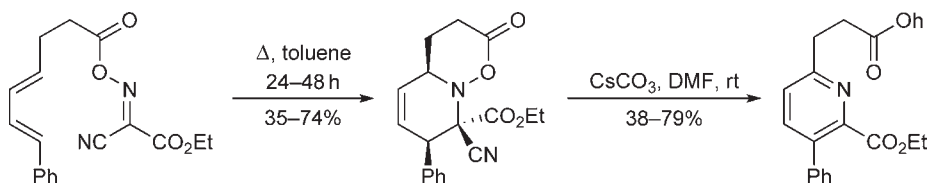


Scheme 60

Table 2 Pyridine synthesis by [4+2] cycloadditions using titanium (Scheme 60)

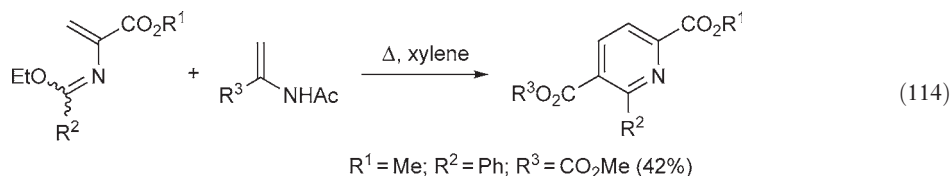
R^1	R^2	Yield (%)
C_6H_{13}	C_6H_{13}	62
C_6H_{13}	$BnO-CH_2-CH_2-$	68
C_6H_{13}	Ph	70
C_6H_{13}	$SiMe_3$	55

Intramolecular oximino malonate hetero-Diel–Alder reactions give the regioselective synthesis of pyridines in a two-step process in modest to good yields (Scheme 61) <2000OL4007>.

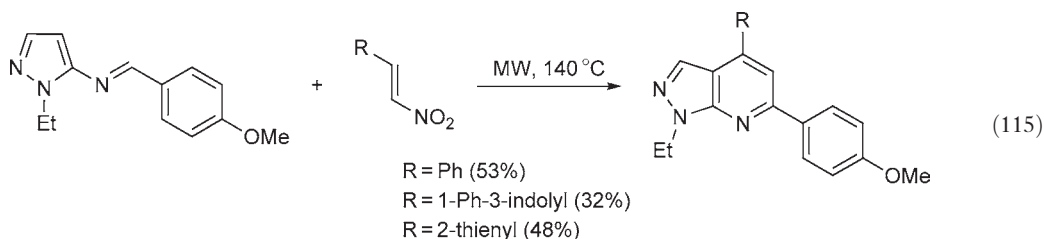


Scheme 61

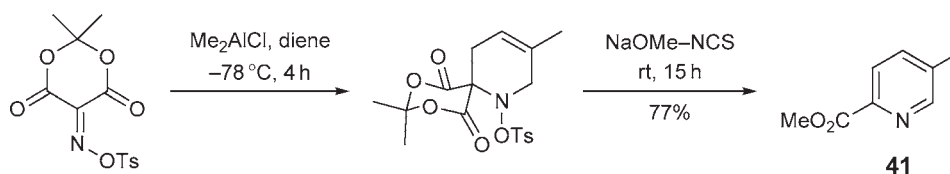
Hetero-Diels–Alder reactions using 2,3-dimethyl-1,3-butadiene and perfluorooctanonitrile at high pressure gives dihydropyridine that is then slowly oxidized to the pyridine <1998T11027>. 2-Azadienes react with dienophiles under typical thermal Diels–Alder reaction conditions to produce the corresponding pyridines in reasonable yield, for example, 42% (Equation 114) <2005JA15644>. Interestingly, the same product was made in 79% by heating the diene alone, indicating that the same reagent was additionally acting as the dienophile. Microwave conditions resulted in modest yields of pyridines.



Diels–Alder cyclizations are thermal reactions, and recent significant developments in the use of microwave irradiation to pyridine synthesis have been reported, including a series of pyrazolo[3,4-*b*]pyridines from nitroalkenes and pyrazolylimines with reaction times of 5–10 min (Equation 115) <2000T1569>. This method appears to be general to this bicyclic class; for example, replacement of the substituent on the imine allows for a C-2-unsubstituted pyridine. A range of cyclic and acyclic dienes have also been reported.



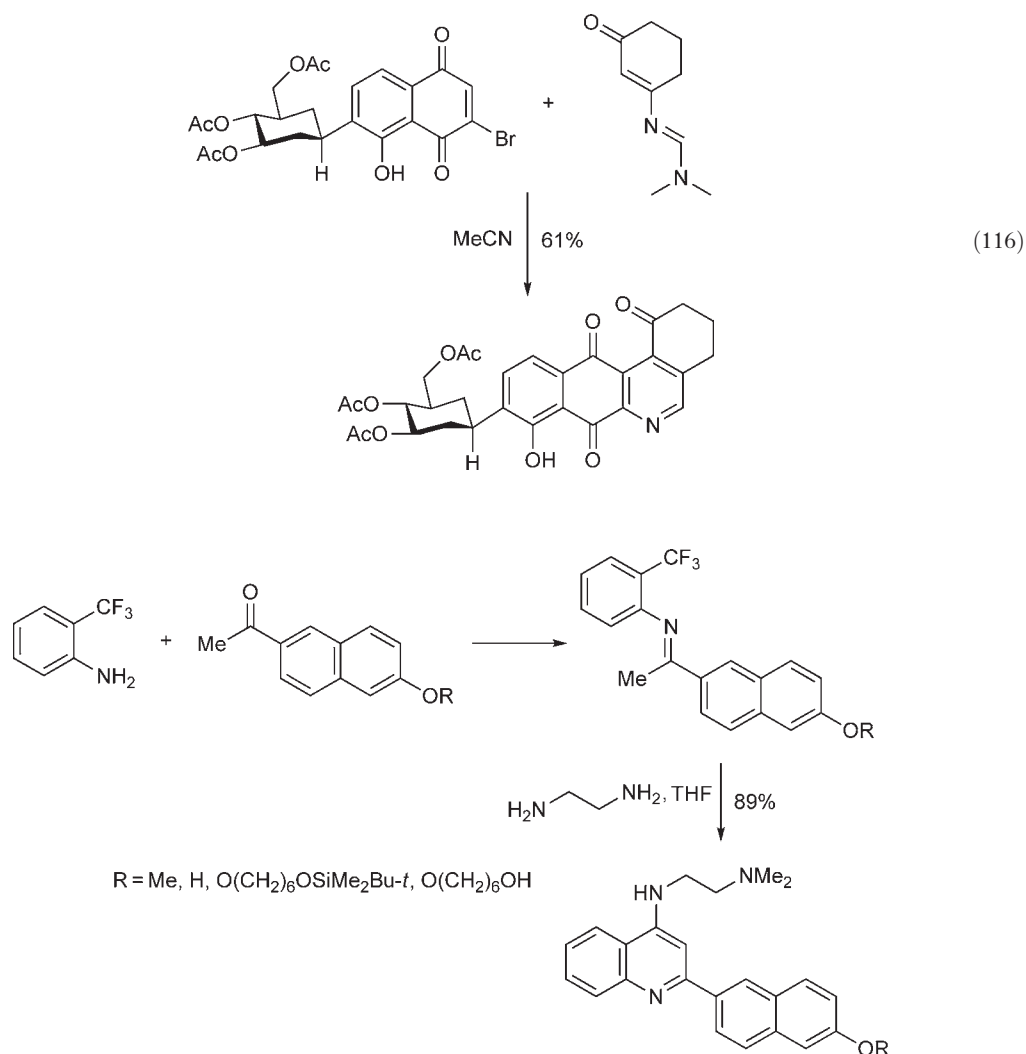
Diels–Alder reactions utilizing oximino sulfonates and a variety of dienes proceed with a regiocontrol that is opposite to that observed when traditional dienophiles are used <1998JOC7840>. This gives rise to pyridines of the type **41** (Scheme 62).



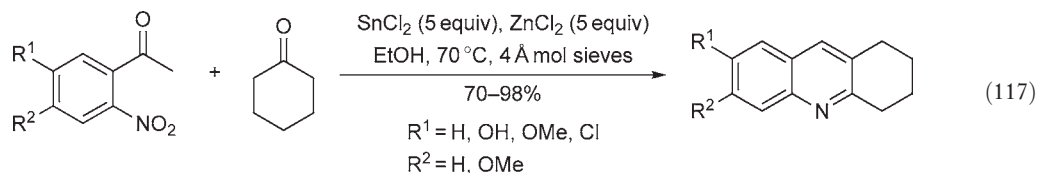
Scheme 62

Pyridine-fused quinones have also been generated by [4+2] cycloaddition reactions <2005TL7669, 2005EJO1903>. Equation (116) shows an example where the key step is cycloaddition of a 2-aza-1,3-diene with 2-bromonaphthylquinone yielding a pyridine-fused naphthoquinone in a convergent synthesis of an angucycline derivative <2005TL7669>.

Condensation reactions continue to be reported as routes to quinolines. A series of 2-naphthyl-4-aminoquinolines were synthesized for studies to support DNA binding (Scheme 63) <2003JA7272>, and an *in situ* arylnitro reduction using SnCl_2 with the subsequent use of symmetrical ketones (Equation 117) <2003OL4257> is one of a few select examples. Other typical variations include the use of enolate chemistry <1996TL4655>, and solvent-free condensation conditions <2005TL4539>. The Friedlander synthesis also continues to be reported <1997SL285, 1995JOC7369, 2005TL767, 2005TL3493, 2005TL7249, 2005TL1647, 2007OBC61>, and some newer variations include the use of copper-catalyzed protocols <2006TL6781> and gold-catalyzed reaction conditions <2007T2811>.

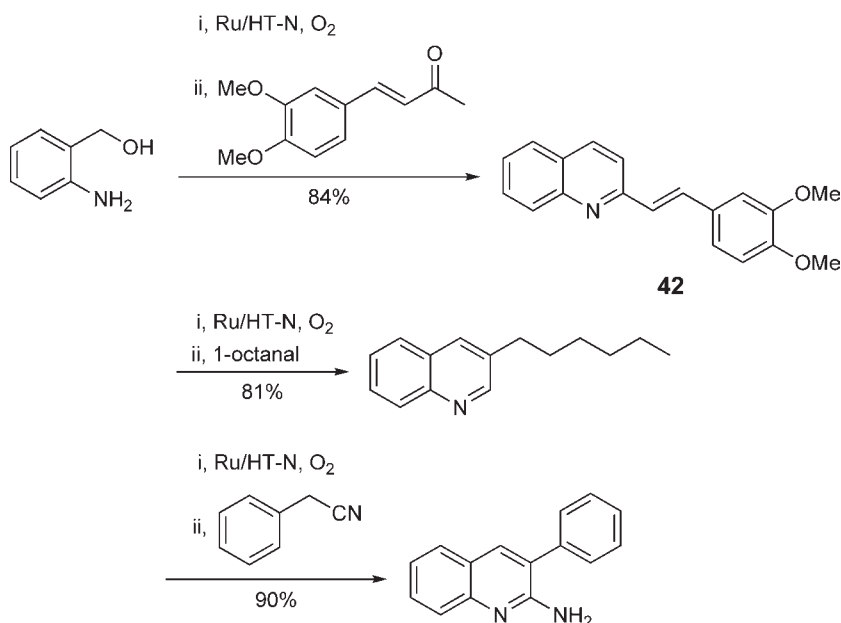


Scheme 63

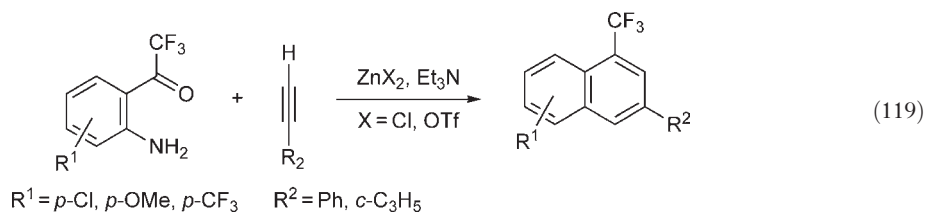
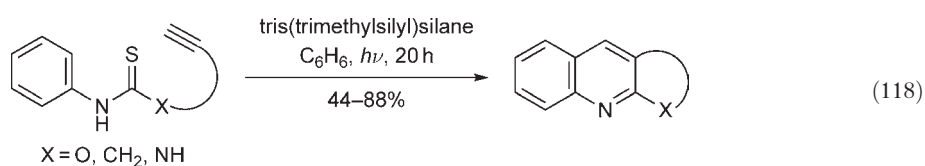


A one-pot quinoline synthesis starting with 2-aminobenzyl alcohol and α,β -unsaturated ketones using ruthenium-grafted hydrotalcites as a heterogeneous catalyst has been reported (Scheme 64) <2004TL6029>. Molecular oxygen was used for the oxidation of ruthenium and the styryl quinoline **42** was produced in good yield. The use of other donors, for example, octanal and phenylacetonitrile, yielded 3-amylquinoline and 2-amino-3-phenylquinoline, respectively.

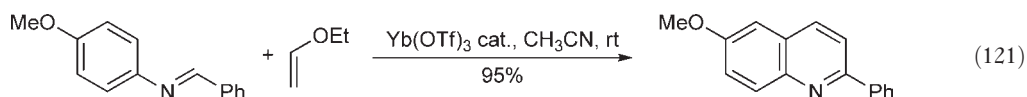
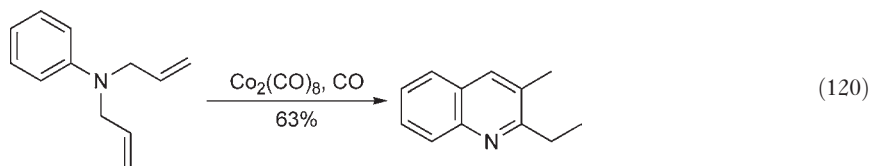
Alkynes continue to be used as a reactive functionality in quinoline synthesis. The readily available thiocarbamates, thioamides, and thioureas allow intramolecular cyclization of pendant alkynes to give modest to good yields of the quinolines (Equation 118) <2003OL1765>. An intermolecular reaction involving a zinc-mediated alkynylation–cyclization provides an efficient route to 4-trifluoromethyl-substituted quinolines (Equation 119) <2002JOC9449>.



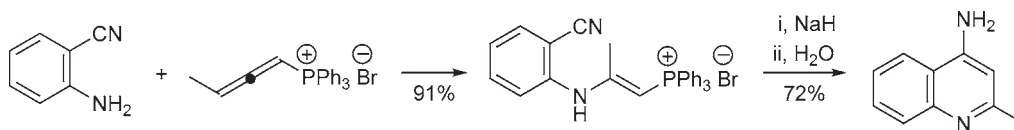
Scheme 64



Diallylaniline is converted exclusively into 2-ethyl-3-methylquinoline when heated with a catalytic amount of Co₂(CO)₈ under an atmosphere of CO (Equation 120) <2003JOC3563>. A [4+2] cycloaddition of *N*-aryldimines with vinyl ethers catalysed by ytterbium(III) triflate gave quinoline derivatives in good yields (Equation 121) <1995S801>.

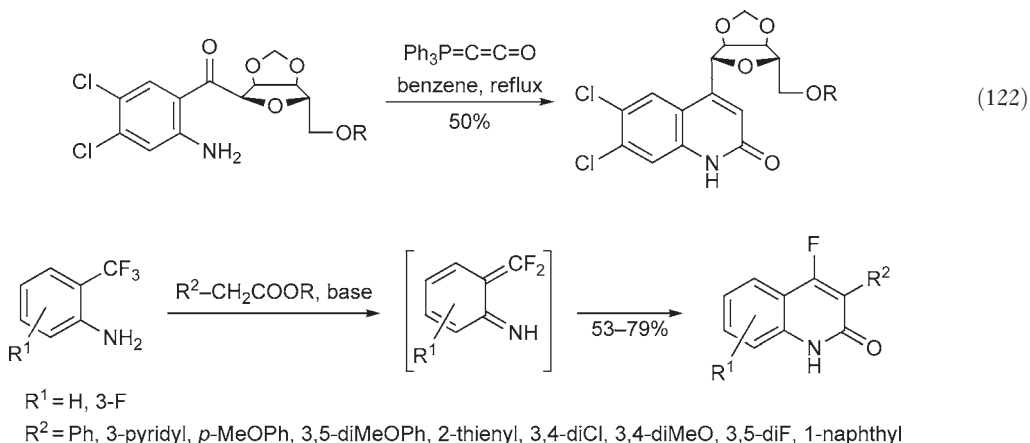


The Wittig reaction can be used to generate quinolines after initial addition of allenes to anilines (Scheme 65) <1998T1647>.



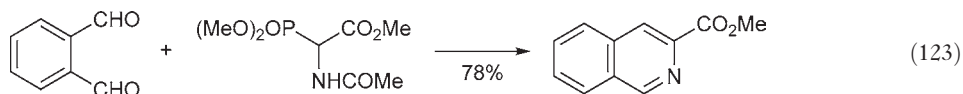
Scheme 65

Quinolinones can be made by the reaction of 2-aminophenones with a ketene ylide via an intramolecular Wittig reaction (Equation 122) <2003JOC4170>. The nucleoside unit in this example survives the reaction conditions. The reaction of (2-fluoromethyl)aniline with esters of arylacetic acid yielded 4-fluorinated 2-quinolinones (Scheme 66) <2004OL4061>.

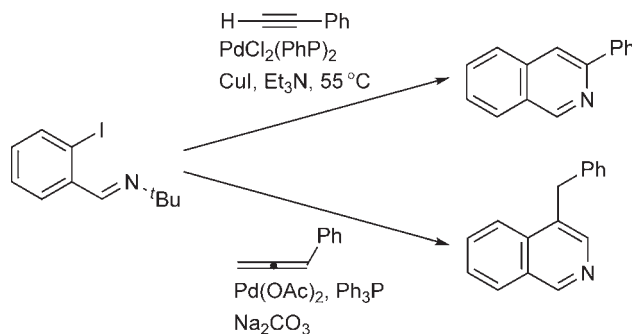


Scheme 66

The addition of the N(2)–C(3) unit to isoquinolines is reported using *o*-diformylbenzene and phosphoglycine (Equation 123) <1999TL7935>.

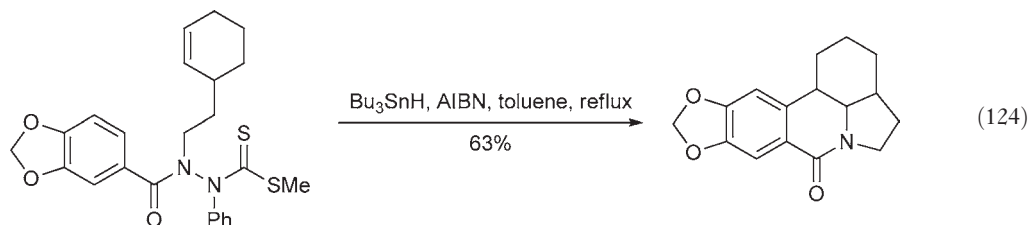


More commonly reported is the insertion of the C3–4 unit. Palladium-catalyzed conditions can utilize iodobenzalimine with alkynes <1999OL553, 1998JOC5306, 2005JOC10172> or allenes <1999TL4255> (Scheme 67). Alternative metal catalysts include nickel <2005OL5179>.

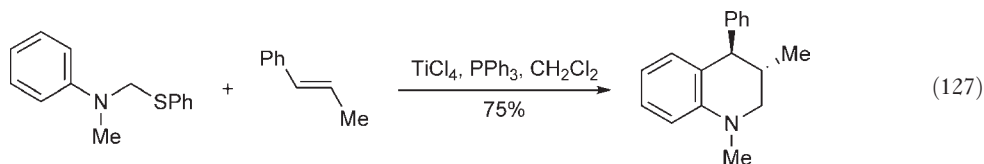
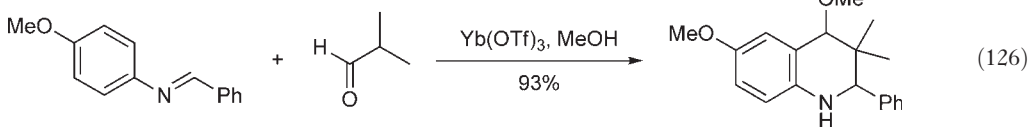
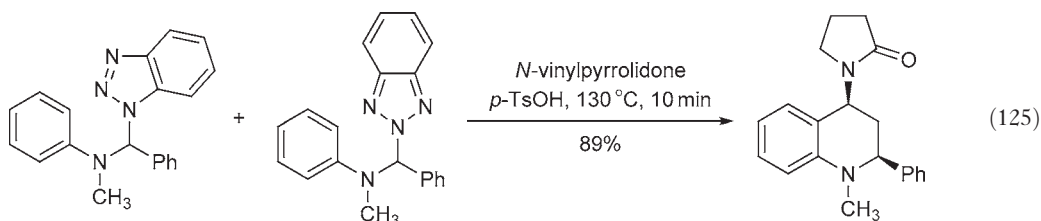


Scheme 67

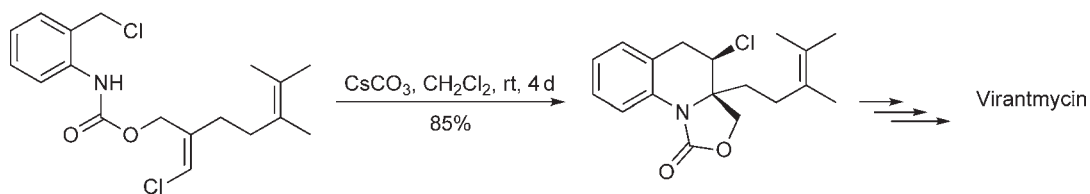
Radical cyclization of suitably substituted benzamides yields the reduced 1-isoquinolinone (Equation 124) <1999TL2125>. In the illustrated example, the reactive intermediate was formed on the nitrogen as an amidyl radical, and this was followed by tandem cyclization.



Stereospecific reactions of tetrahydroquinolines reported include a C3-4 insertion using *N*-vinylpyrrolidinone with 1*H*-benzotriazole used as a leaving group (Equation 125) <1995JOC2588, 1995JOC3993>. Other examples of C3-4 insertions include a three-component reaction under the influence of a Lewis acid (Equation 126) <1997T9715>. Different nucleophiles can be used including alcohols, anilines, thiols, and water, all producing 4-substituted products with only mild diastereoselectivity being observed with chiral aldehydes or imines. The intermolecular [4+2] cycloaddition of cationic 2-azabutadienes and different dieneophiles (Equation 127) <1995CC2137, 1996SL34> is a further example of a similar 2-carbon insertion.

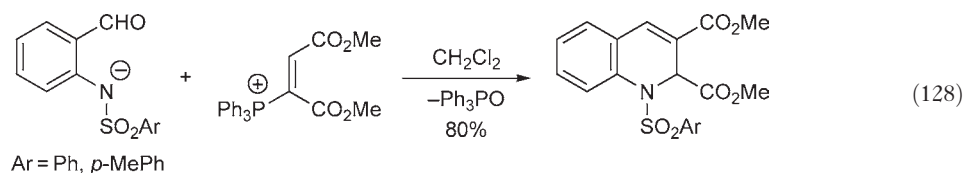


The [4+2] intramolecular cyclization of *ortho*-substituted chloromethylanilides has led to the synthesis of the tetrahydroquinoline alkaloid virantmycin (Scheme 68) <2006EJO4916>.

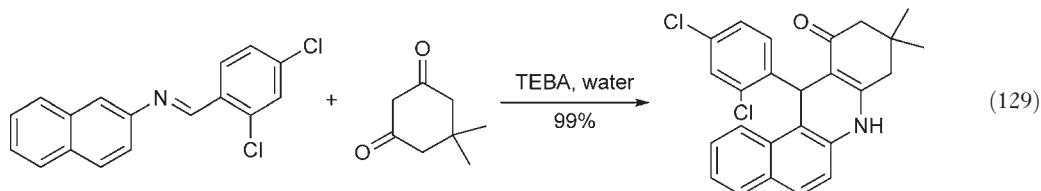


Scheme 68

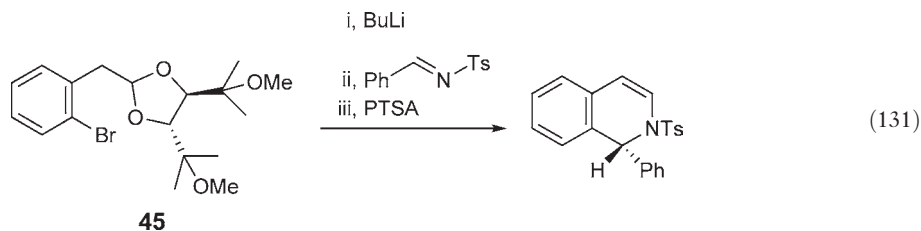
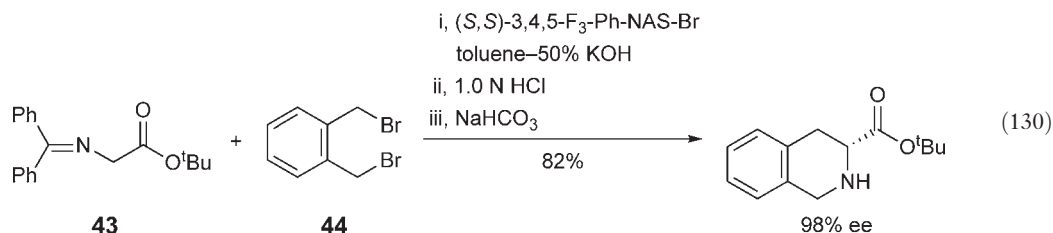
The use of traditional condensation reactions continues to be reported with vinylphosphonium salts and *N*-sulfonylanilines (Equation 128) <1997M927>.



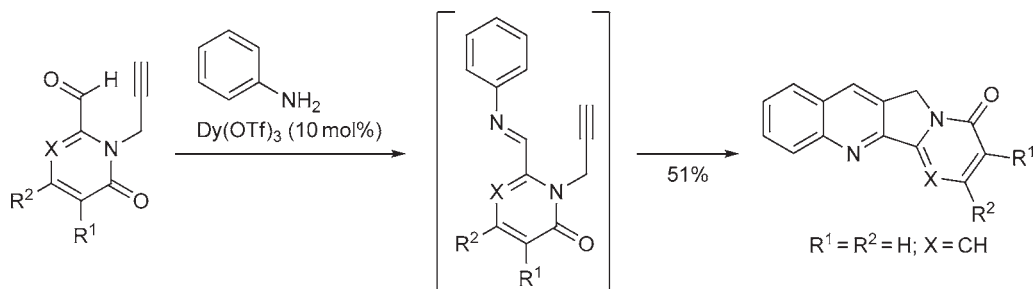
An example of a reaction of a Schiff base to give an extended dihydroquinoline structure that used water as the reaction solvent is shown in Equation (129) <2005TL7169>. Benzyltriethylammonium chloride (TEBA) was used as a catalyst and good to excellent yields were obtained.



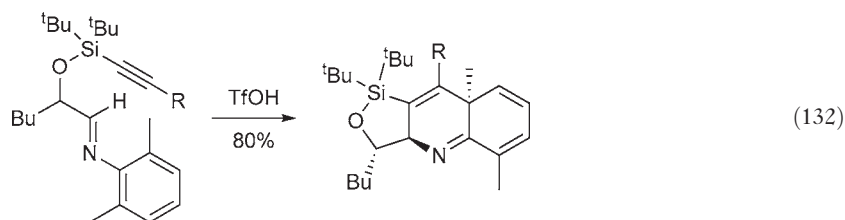
The insertion of the N(2)–C(3) unit in reduced isoquinolines remains a topic of interest, especially stereoselective examples. The iminoglycinate **43** undergoes reaction with the dibromo **44** in the presence of the *C*₂-symmetric chiral quaternary ammonium bromide phase-transfer catalyst (Equation 130) <2001S1716>. A high-yielding tetrahydroisoquinoline resulted in excellent enantioselectivity. Reaction of the chiral anion generated from **45** with benzylidene also produces chiral tetrahydroisoquinolines (Equation 131) <1999EJO503>.



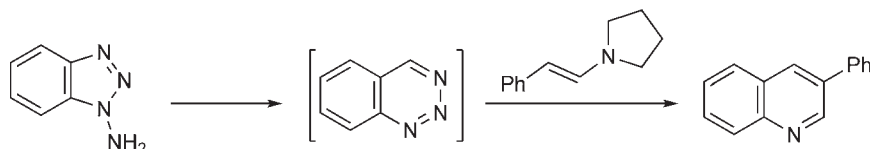
An intramolecular cyclization of *N*-anilino- and *N*-benzyl-substituted propargyl trimethylsilyl ethers with Lewis acid catalysis provides the quinolines and isoquinolines, respectively <2004OL2361>. An intramolecular aza-Diels–Alder reaction has been used as a key step in the synthesis of luotonin (Scheme 69) <2004OL4913>. An analogous reaction afforded the dihydroquinoline as a single diastereomer (Equation 132) <2000TL5715>.



Scheme 69



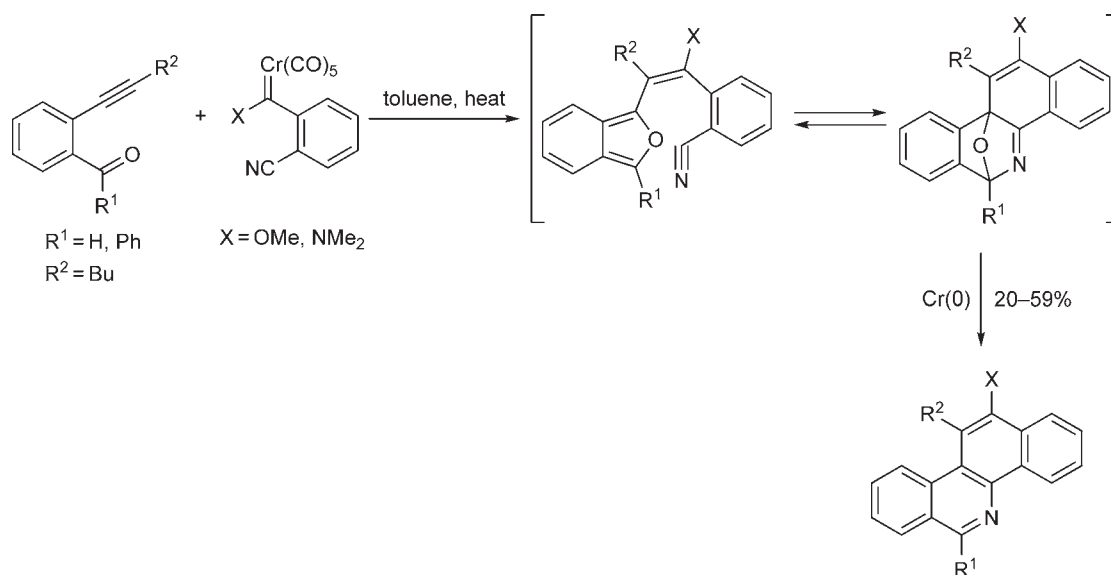
Oxidative rearrangement of 1-aminobenzotriazole yields the reactive 1,2,3-benzotriazine which reacts with dienophiles to produce quinolines (**Scheme 70**) <1998CPB332>.



Scheme 70

Quinoline-fused C_{60} derivatives are formed by the reaction with *o*-azaxylylene <1998JOC8074>.

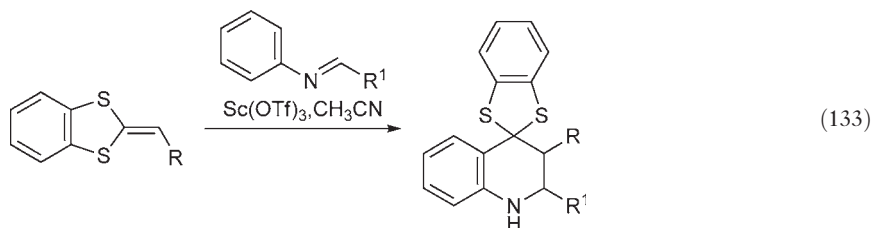
Coupling of a cyanocarbene complex with an alkyne–aldehyde yielded isoquinolines (**Scheme 71**) <2003OL4261>. The key reaction step is an intramolecular Diels–Alder reaction; however, overall yields are at best moderate with product mixtures often occurring – the preparation of the benzo analogues was more successful.



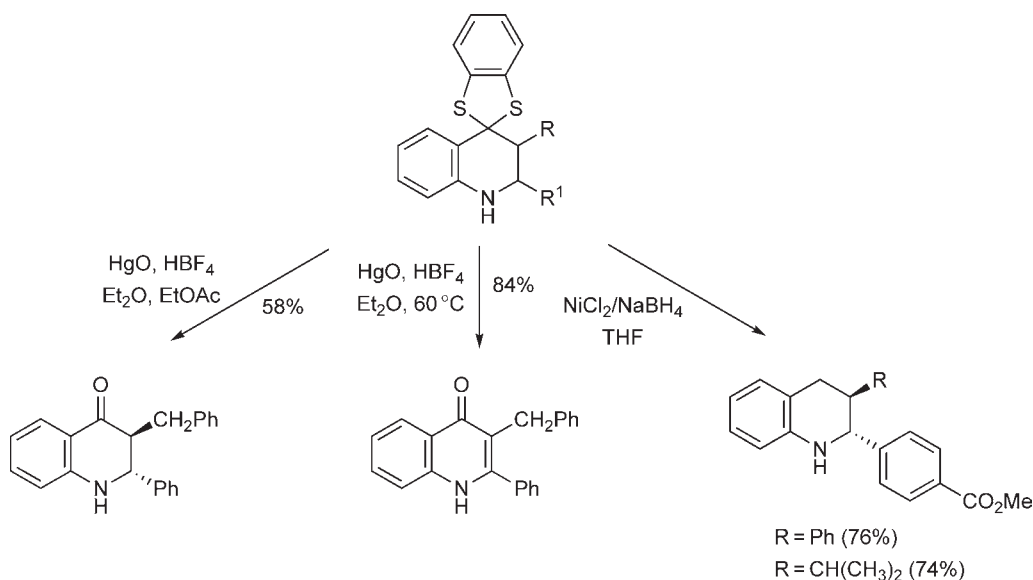
Scheme 71

Diels–Alder reactions mediated by $FeCl_3$ –NaI <2004TL3507> or sulfamic acid <2004S69, 2004S949> yield tetrahydroquinolines while the use of polyethylene glycol 4000 (PEG 4000) as a soluble polymer support in a three-step one-pot aza-Diels–Alder reaction also gives tetrahydroisoquinolines <2004SL1175>.

An aza-Diels–Alder reaction to give tetrahydroquinolines involves an intermediate ketene diacetal as a dienophile reacting with *N*-arylimines in selectivities varying from 1:1 to 100:0 *anti:syn* (Equation 133; **Table 3**) <2002OL4411>. Further manipulations yield different quinolones (**Scheme 72**).

**Table 3** Tetrahydroquinoline synthesis using an aza-Diels–Alder approach (Equation 133)

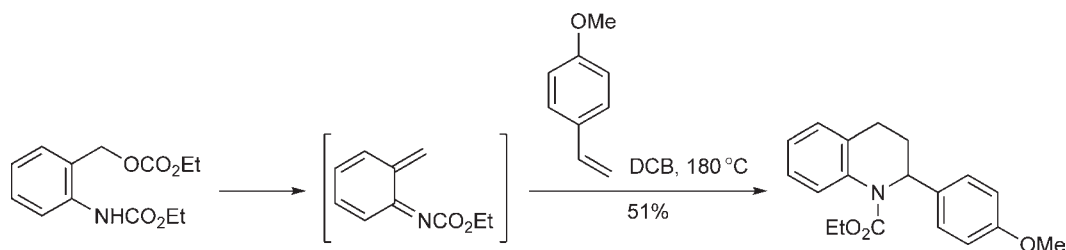
<i>R</i>	<i>R</i> ¹	Yield (%)	<i>anti:syn</i>
Ph	<i>p</i> -(C ₆ H ₄)CO ₂ Me	81	23:1
CH ₂ Ph	Ph	82	28:1
CH(CH ₃) ₂	<i>p</i> -(C ₆ H ₄)CO ₂ Me	38	100:0

**Scheme 72**

An InCl₃-catalyzed domino reaction of aromatic amines and cyclic enol ethers has been reported and gives rise in good yields to a range of 2,3,4-trisubstituted 1,2,3,4-tetrahydroquinolines <2002JOC3969>.

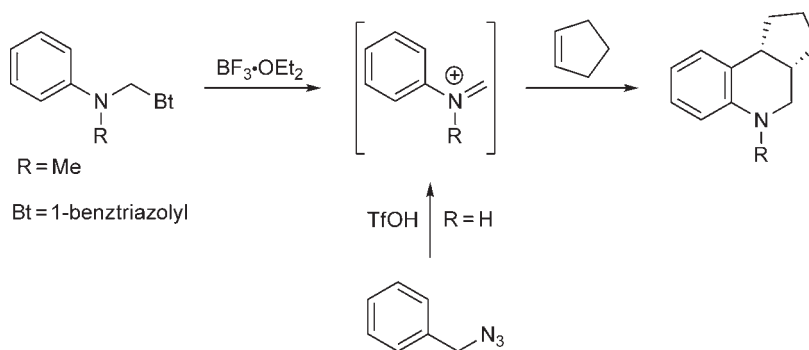
The dysprosium(III) catalyzed reaction between anilines and dihydrofurans forms an intermediate 2-azadiene before reacting with an additional equivalent of dihydrofuran in a formal Diels–Alder reaction producing hexahydrofuro[3,2-*c*]quinolines <2001TL7935>. In a complementary fashion, 4-arylhexahydropyrroloquinolines were synthesized in a [4+2] cycloaddition between enamides and imines derived from aromatic amines <2001T5615>. The utilization of anilines reacting with glyoxylates containing chiral auxiliaries to produce imines which are subsequently reacted with cyclopentadiene in an aza-Diels–Alder reaction produces tetrahydroquinolines in an enantioselective fashion <2001T6399>. Further asymmetric reactions to produce tetrahydroquinolines have been reported using an inverse electron-demand Diels–Alder reaction and chiral Ti(IV) catalysis <2001OL1973>.

The hetero-Diels–Alder reaction continues to be a popular method of producing the tetrahydroquinoline ring structure. The generation of *o*-azaxylylene allows for the subsequent cycloaddition with dienophiles to produce the corresponding quinoline ring structure (Scheme 73) <1998H(48)1103, 1998JHC467>.



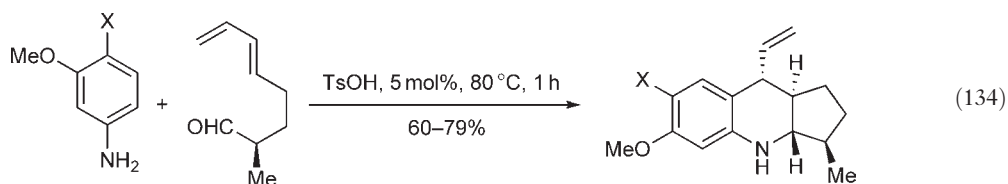
Scheme 73

Lewis acid-assisted reaction of α -aminobenzotriazole yields an iminium ion which reacts with unreactive olefins to produce tetrahydroquinolines (**Scheme 74**) <1997JHC1259>.

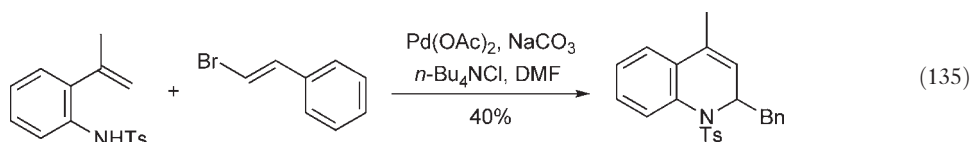


Scheme 74

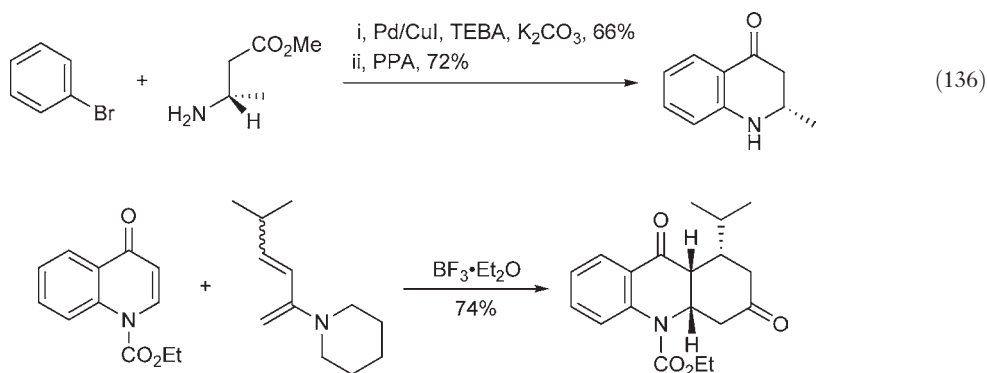
An intramolecular hetero-Diels–Alder reaction has been used to produce the cyclopentaquinoline core of a series of alkaloids <2003OL2509>. They form in high diastereoselectivity, generating up to four contiguous stereogenic atoms (**Equation 134**).



Dihydroquinolines can be synthesized by the palladium-catalyzed reaction of *o*-allyl- or *o*-isoprenyl-*N*-tosylanilides with vinyl halides or triflates (**Equation 135**) <1998TL1885, 1998TL2515, 1998T9961, 1998TL2965, 1998JOC4554>. By-products can be formed in the instance of *o*-vinylanilide, including indoles and extended chains.

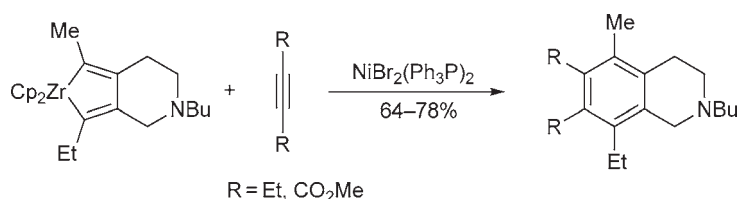


Chiral quinolinones can be accessed by the palladium-catalyzed coupling between aryl bromides and β -amino acids, followed by intramolecular acid-catalyzed cyclisation (**Equation 136**) <1998TA1137>. The reaction of 2-amino-1,3-diene with quinolinone yields the acridine derivative directly (**Scheme 75**) <1997J(P1)2807>.



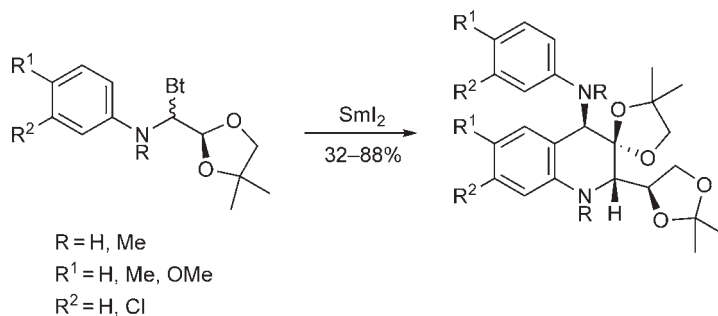
Scheme 75

In a Ni-couple reaction, the benzo ring of tetrahydroisoquinolines is formed by reaction of acetylenes with piperidine-fused zirconocyclopentadienes (**Scheme 76**) <1999JA11093>.



Scheme 76

Benzotriazoles derived from anilines and (*R*)-glyceraldehydes dissociate in the presence of SmI₂ and undergo cycloaddition to give the optically active tetrahydroisoquinoline (**Scheme 77**) <2000JOC3148>.



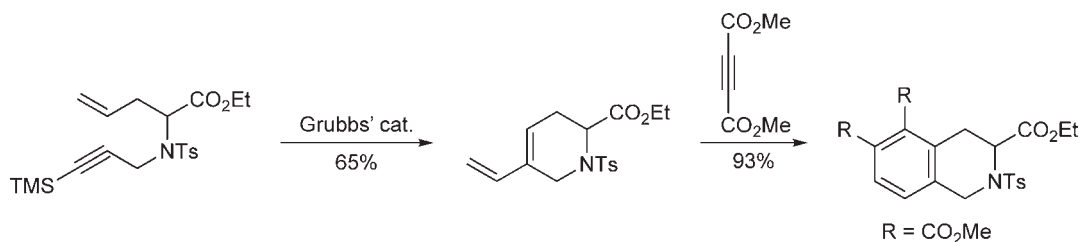
Scheme 77

The use of aromatic imines to produce tetrahydroquinolines has been shown to be promoted by the use of bismuth(III) chloride and triflate catalysts <2000SL1160>.

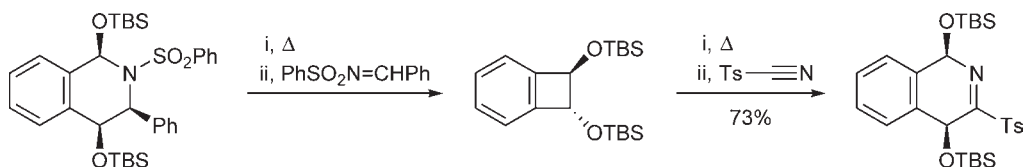
Sequential Grubbs' metathesis/Diels–Alder strategies can be used to produce tetrahydroquinolines. For example, intramolecular enyne metathesis followed by reaction with alkynes followed by oxidation serves as a useful route to multisubstituted systems (**Scheme 78**) <2000CC503>.

Benzocyclobutanes can undergo [4+2] reactions using toluenesulfonyl cyanide or *N*-benzylidenephenyisulfonamide leading to tetrahydroisoquinolines and dihydroisoquinolines, respectively (**Scheme 79**) <2000AGE1937>.

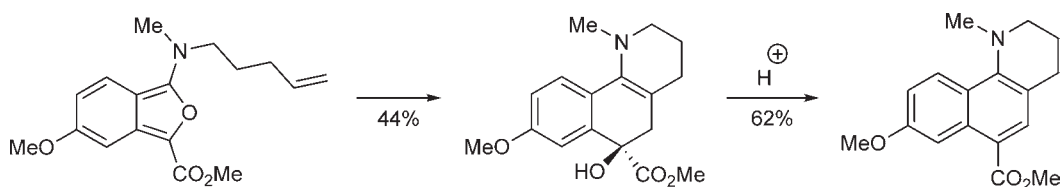
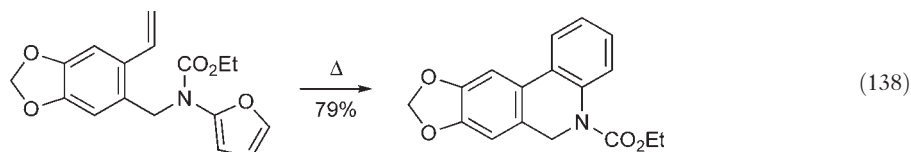
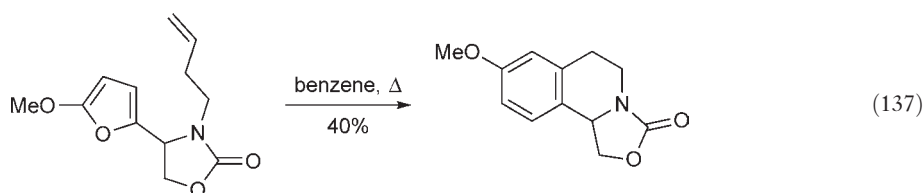
Intramolecular [4+2] reactions to give tetrahydroquinolines have been reported using substituted furans (Equations 137 and 138) <1995J(P1)2393, 1999JOC3595>, isobenzofurans (**Scheme 80**) <1995TL8581>, and diene alkynes catalyzed by Ni (**Scheme 81**) <1996JOC824>.



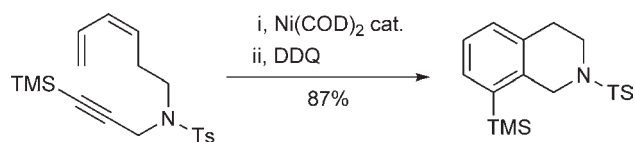
Scheme 78



Scheme 79

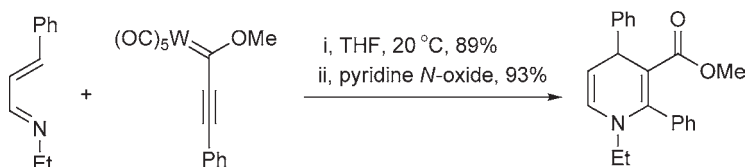


Scheme 80

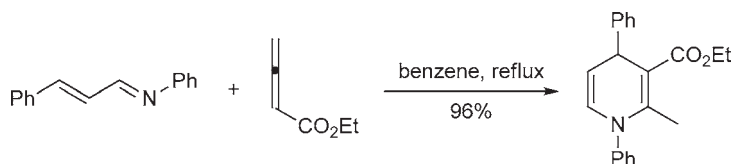


Scheme 81

In a [4+2] cycloaddition reaction that proceeds via a Michael addition, an azadiene has been shown to react with Fischer carbenes yielding the 1,4-dihydropyridine after removal of the metal (Scheme 82) <1997TL3981>. Reactions of 1-azadienes with allenic esters yield the 1,4-dihydropyridine in excellent yield (Scheme 83) <2001OL2133>.

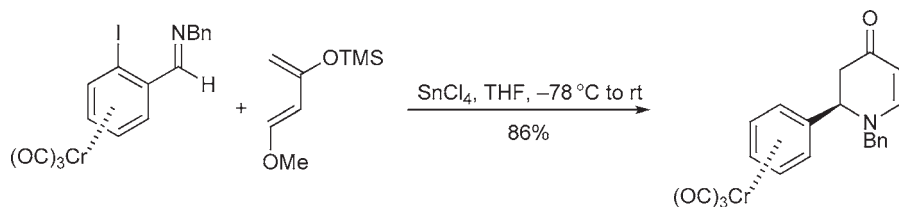


Scheme 82

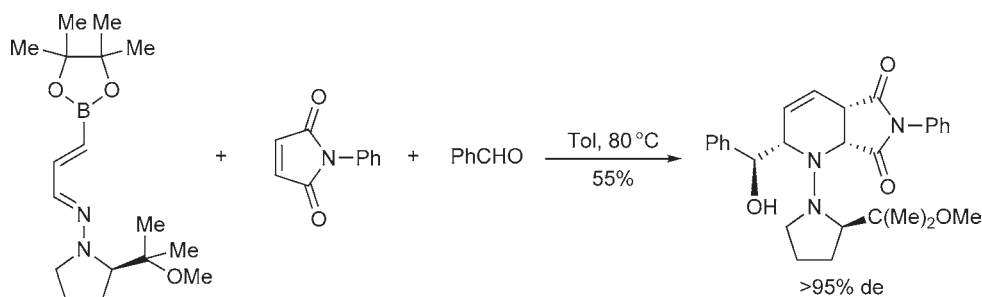


Scheme 83

The hetero-Diels–Alder reaction has long been recognized as a useful method to produce dihydropyridines [<2000SL242>](#). Chiral selectivity in tetrahydropyridine synthesis can be achieved if planar chiral CO complexes of imines are reacted with dienes ([Scheme 84](#)) [<1999SL626, 1999OL1997>](#). High selectivity was also achieved using a tandem aza-[4+2]/allylboration process by reaction of a hydrazonodiene with *N*-phenylmaleimide and benzaldehyde ([Scheme 85](#)) [<2000OL3715>](#).

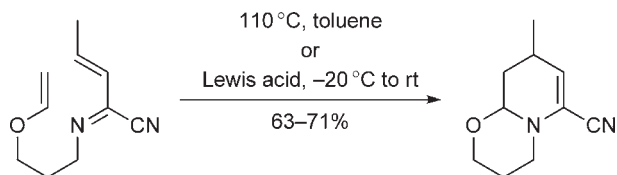


Scheme 84



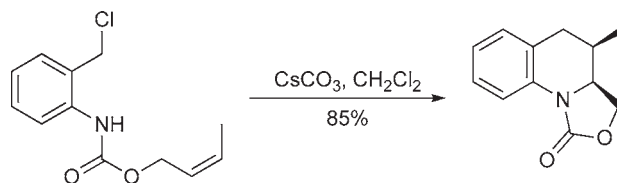
Scheme 85

An intramolecular hetero-Diels–Alder reaction of activated azadienes gives rise to the fused tetrahydropyridines by heating or catalysis ([Equation 139](#)) [<1999TL7211, 1999TL7215>](#).



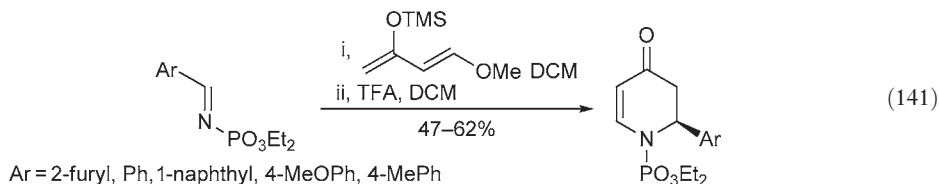
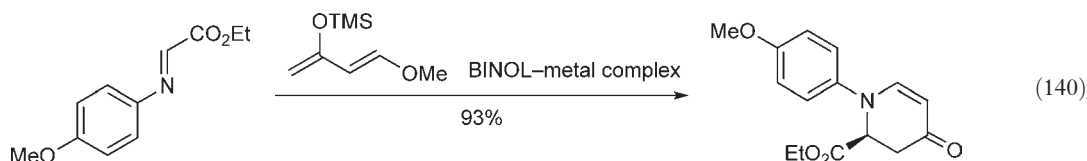
(139)

Intra- and intermolecular aza-Diels–Alder reactions of *o*-azaxylenes give rise to hydroquinoline (Scheme 86) <1999AG(E)1928>.

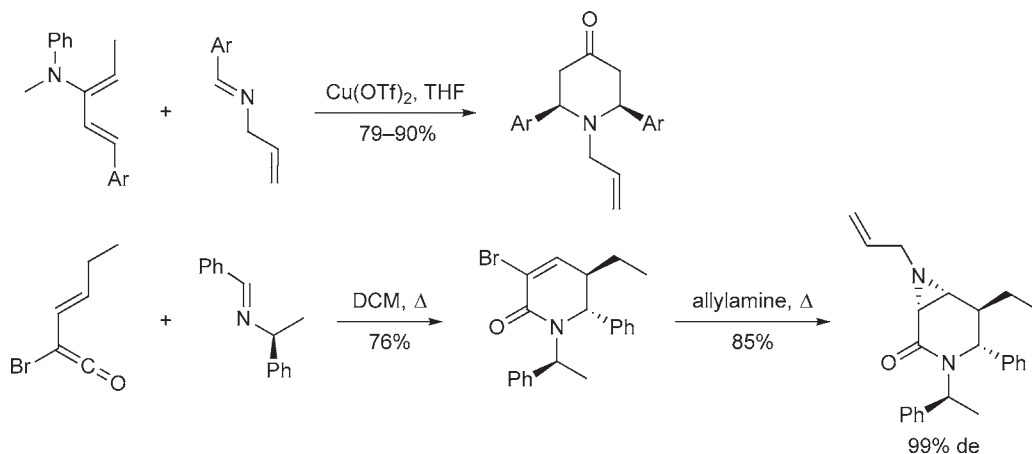


Scheme 86

Danishefsky's diene has been utilized in conjunction with *N*-functionalized imines to produce 4-piperidones (Equation 140). The use of (*S*)-BINOL–zinc complexes gives rise to moderate to high enantioselectivity <2004SL711>, and was the only chiral additive to give a stereoselective outcome (77% ee) when the *N*-phosphoryl-arylimines were used (BINOL = 1,1'-bi-2-naphthol) <2004SL708>. Danishefsky's diene has also been used in reactions with *N*-arylimines in supercritical CO₂ <2004T6163> and with chiral imines derived from tartaric acid to provide 2,3-dihydropiperidin-4-ones in excellent yield and selectivity (Equation 141) <2000H(52)137>.

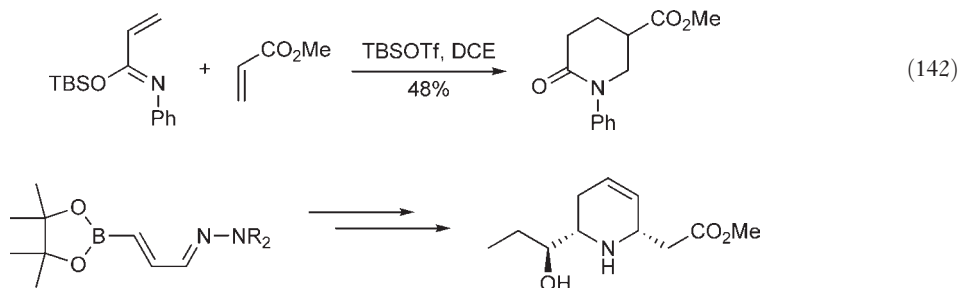


meso-2,6-Diaryl-4-piperidones were produced in a [4+2] cycloaddition reaction using aryl-*N*-allylimines and a diene in the presence of Cu(OTf)₂ in high yield and de (>99%) (Scheme 87) <2004TL4357>. Reaction of imines with β,γ -unsaturated α -bromoketenes yields dihydro-2-pyridones some of which were reacted with allylamines producing aziridines with 99% de in generally high yield <2004TL5031>.



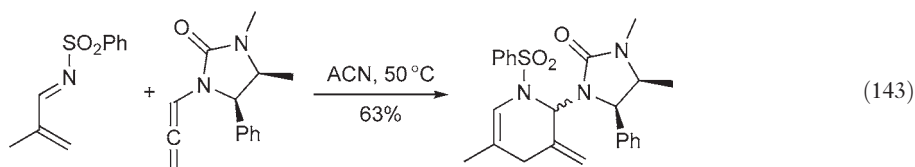
Scheme 87

Tetrahydro-2-pyridones are also produced by a [4+2] cycloaddition of 1-aza-2-siloxydiene with simple dienes in a Lewis acid-catalyzed reaction (Equation 142) <2004S2222>. In an analogous manner, hydrazone derivatives have been in aza-[4+2] cycloadditions with reactive dienophiles which can be trapped with aldehydes to form highly functionalized piperidines (Scheme 88) <2004AGE2001, 2004JOC8429>.

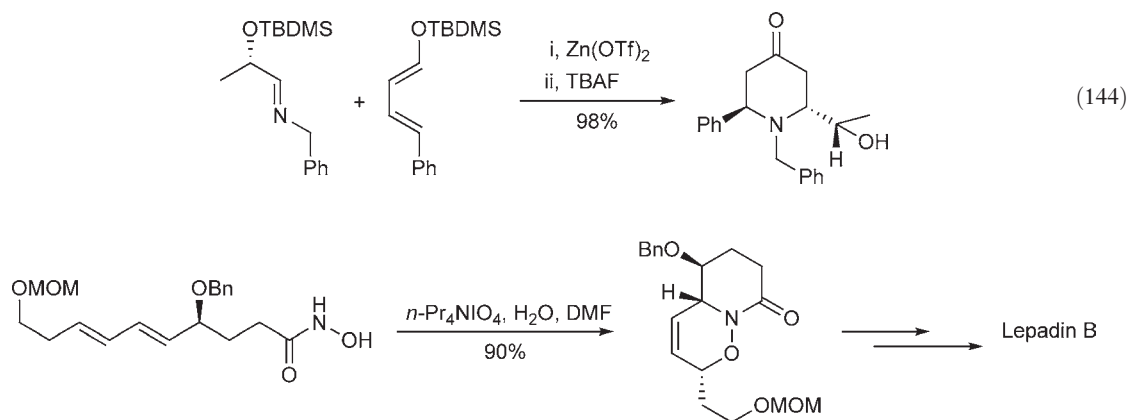


Scheme 88

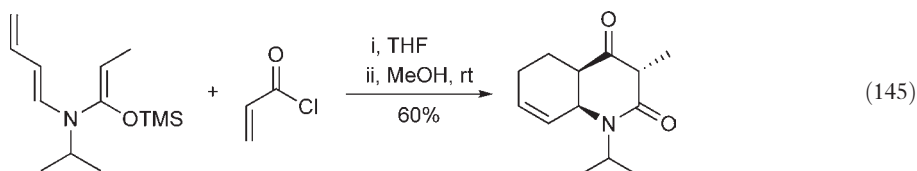
N-Sulfonyl vinylimines and allenamides undergo inverse electron-demand cycloadditions, giving rise to tetrahydropyridines (Equation 143) <2004T7629>. The mechanism, stereochemistry, and synthetic limitations were all reported.



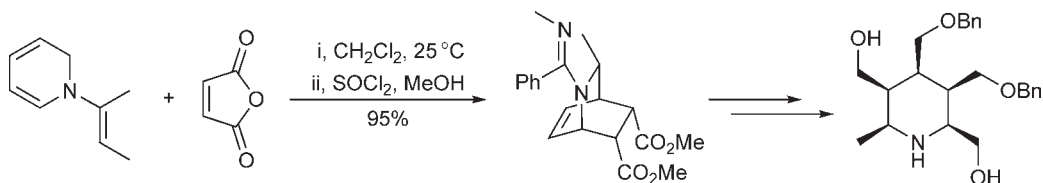
Access to chiral piperidines can be achieved using a hetero-Diels–Alder reaction of chiral imines and is particularly useful toward the synthesis of natural products (Equation 144) <1997TL2547, 1997T5423, 1997S1151>. An aqueous intramolecular version using an acylnitroso derivative produced the piperidone which was the key step toward the enantioselective total synthesis of the natural product lepadin B (Scheme 89) <2000OL2955>. Cascade Diels–Alder acylation reaction of a ketene acetal generates the corresponding piperidine dione (Equation 145) <1996T11643>.



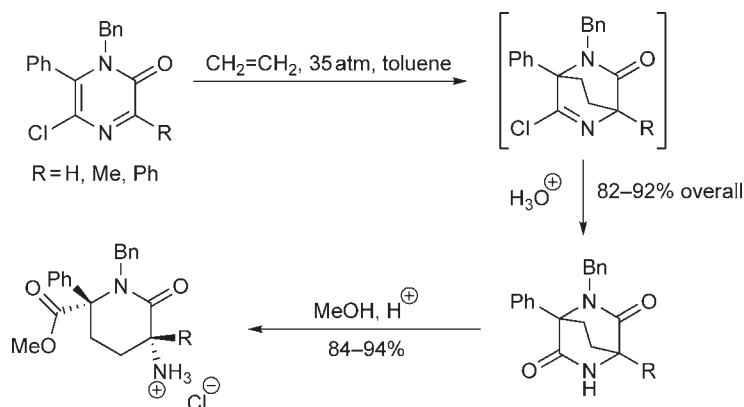
Scheme 89



A stereoselective synthesis of 2,3,4,5-tetra- and 2,3,4,5,6-pentasubstituted piperidines was reported via the oxidative cleavage of Diels–Alder adducts derived from a dihydropyridine (**Scheme 90**) <2005OL5773>. Subsequent functional group transformation gave rise to highly functionalized piperidines. Other strategies toward highly functionalized piperidines have been reported using the readily available pyrazinones (**Scheme 91**). Only single stereoisomers were reported <2003T5047>.

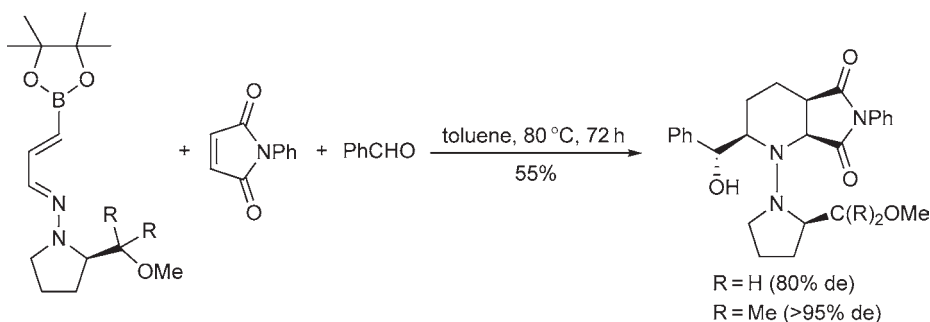


Scheme 90



Scheme 91

Piperidines can be produced stereoselectively with diastereomeric excess of >95% and in moderate yield using a three-component Diels–Alder strategy. A chiral auxiliary is required as part of a 1-aza-4-borono-1,3-diene and the reaction was reported as a solid-phase synthesis with acceptable outcomes (**Scheme 92**) <2003CEJ466>.

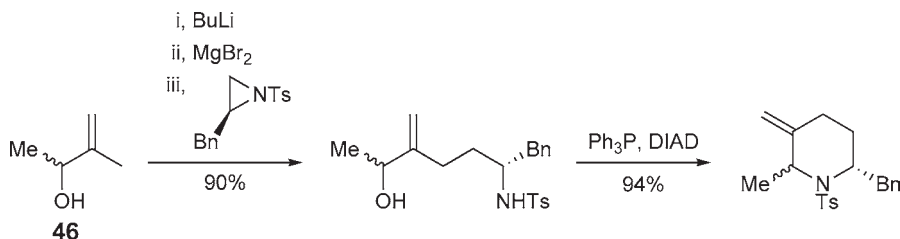
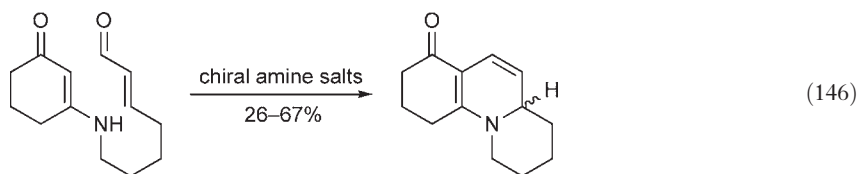


Scheme 92

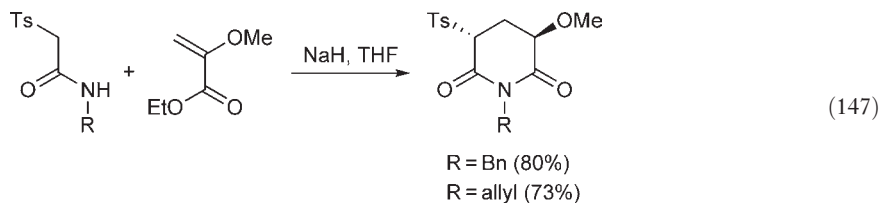
7.05.2.2.3 From [3+3] and [7+3] fragments

A formal [3+3] cycloaddition reaction of a vinylogous amide was used in the presence of chiral amine salts and yielded the fused piperidine derivative enantioselectively (**Equation 146**) <2005JOC4248>. A stepwise [3+3] cycloaddition sequence starting from a dianion of **46**, transmetalation, and addition of aziridine allowed for the

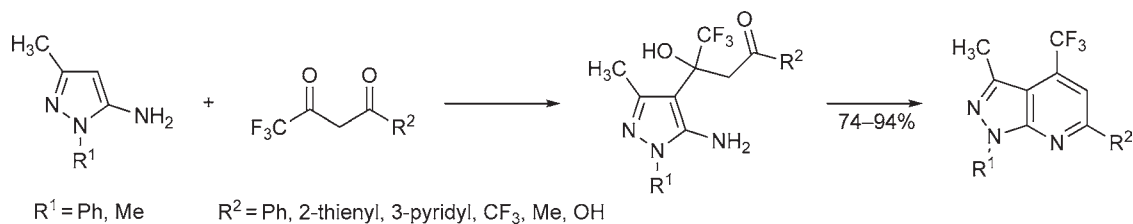
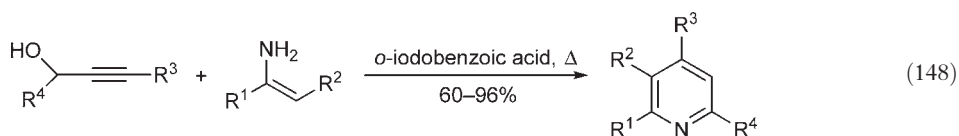
subsequent intermediate to be treated to Mitsunobo conditions resulting in over 90% of the piperidine product (**Scheme 93**) <2005OL2993>. This strategy has been applied to a number of aziridines <2005JOC207>. Annulation resulting from initial anion generation by NaH was found to be effective for piperidine synthesis (**Equation 147**) <2004T10223>. Reviews based on [3+3] cycloaddition reactions for piperidine synthesis <2005OBC1349> and generally six-membered nitrogen-containing heterocycles <2005EJO23> have been published.



Scheme 93



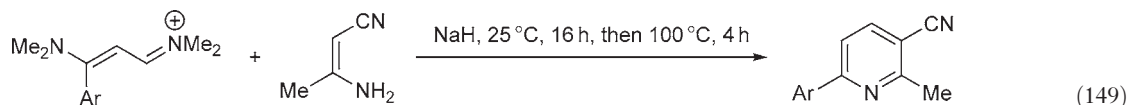
Examples of nitrogen-containing heterocycle syntheses based on condensation reactions continue to be forthcoming. Examples include a tandem oxidation–annulation of propargyl alcohols in a one-pot synthesis of pyridines (**Equation 148**) <2003SL1443>, trifluoromethyl-substituted pyridines (**Scheme 94**) <2003S1531>, and standard malononitrile additions to α,β -unsaturated ketones <1995JCM392>.



Scheme 94

The reaction of vinylogous iminium salts with β -aminocrotonitriles yields the corresponding pyridine (**Equation 149**) <1995T1575>. The analogous reaction using vinyliminophosphoranes with aldehydes leads to

betaines which undergo either intra- or intermolecular reaction to give pyridines or dihydropyridines (Equation 150); Table 4) <1995TL8283, 1996JOC8094>. In an aza-Wittig reaction, similar substrates gives rise to 3-azatrienes which upon heating are transformed into the pyridines (Equation 151) <1996TL6379>.



Ar = 4-MeOPh (80%), 4-MePh (74%), 4-ClPh (58%), 4-BrPh (49%), Ph (67%), 4-NO₂Ph (52%), 4-FPh (67%), 3,4-(OMe)₂Ph (65%), 3-NO₂Ph (55%)

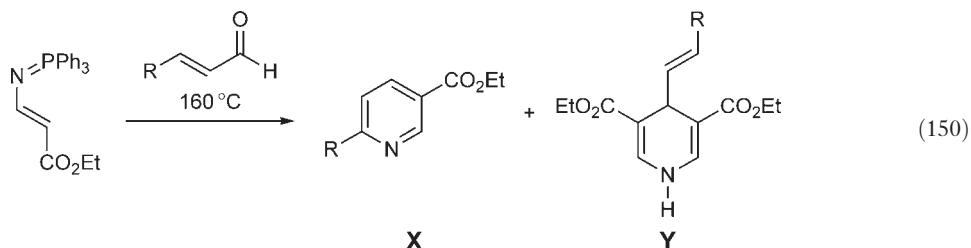
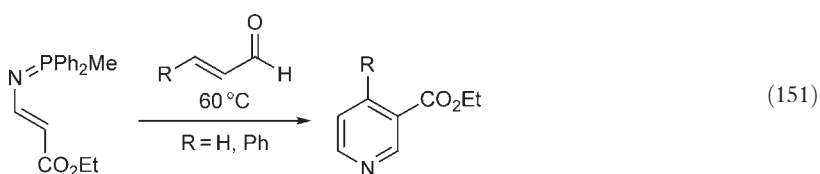
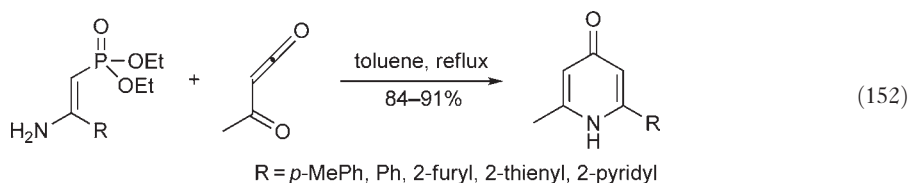


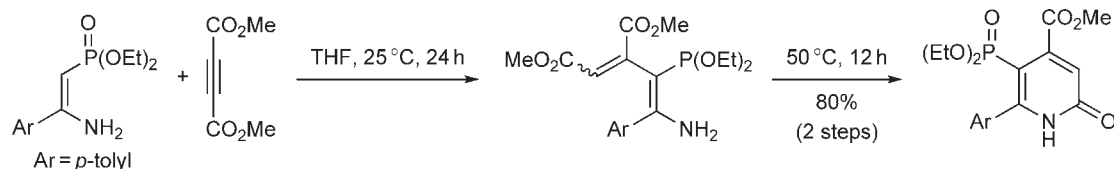
Table 4 The reaction of vinyliminophosphoranes with aldehydes leading to the synthesis of dihydropyridines (Equation 150)

R	Yield (%)	
	X	Y
Ph	33	44
4-ClPh	30	40
2-NO ₂ Ph	30	46
2-OMePh	31	38
H	42	—

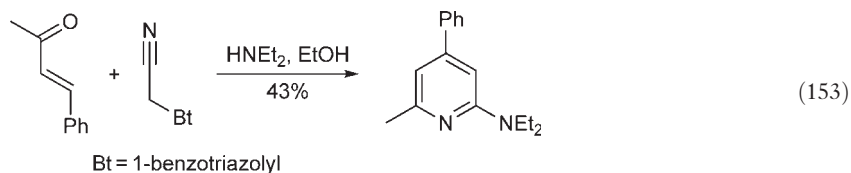


Some variations on reagents include the use of iminophosphoranes and acetylenic esters leading to a mixture of regioisomeric pyridines <1998H(48)2551> and the addition of β -enaminophosphoranes to an acetylketene yielding 4-pyridones <1998H(47)517> (Equation 152). Alkynes and enamines can produce 2-pyridones with 5-phosphonate ester substituents (Scheme 95) <1995H(41)1915>. Pyridine rings without a 3-substituent can be prepared in a base-promoted reaction with elimination of the benzotriazolyl unit being key (Equation 153) <1997JOC6210>.

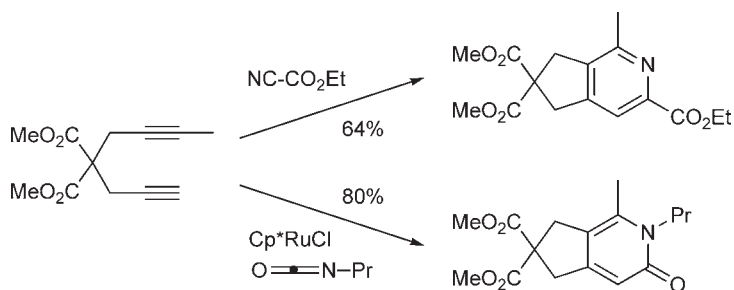




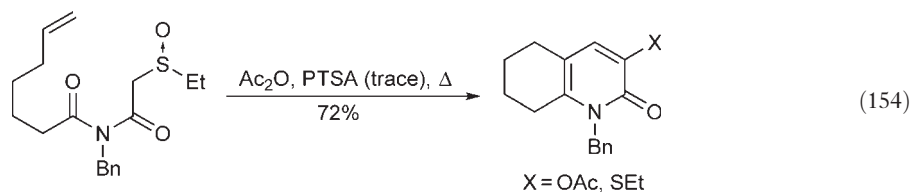
Scheme 95



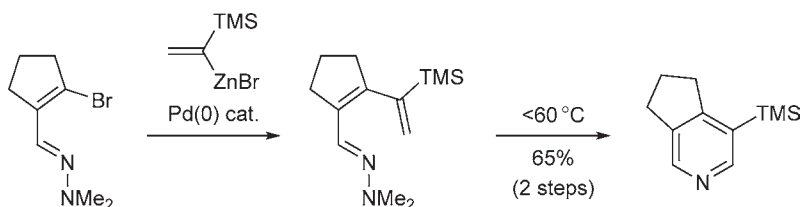
Other cycloaddition reactions to give pyridines include the [2+2+2] reaction of diynes with both nitriles and isocyanates to yield fused pyridines and 2-pyridones, respectively (Scheme 96) <2005JA605>. Other [2+2+2] cycloaddition reactions reported include those catalyzed by cobalt <2005JA3473, 2005SL1188, 2005SL1758>, nickel <2005JA5030>, ruthenium <2005JA605>, and rhodium <2005OL4737>. A [3+2] cycloaddition with methyl acrylate leads to 2-pyridinone after ring cleavage and elimination of phenylsulfonic acid (Equation 154) <1997TL15051>.



Scheme 96

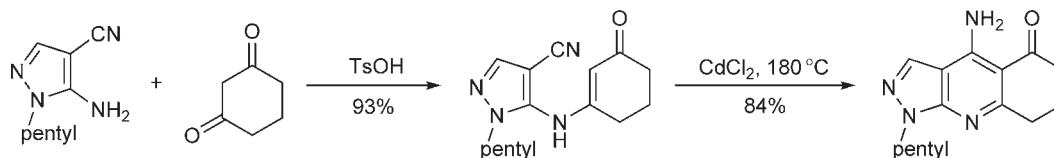


The palladium-catalyzed reaction of 2-bromocyclopentene-1-carbaldehyde derivatives with vinylzinc, 2-furyl, or 2-thienylzinc halides leads to the dimethylhydrazones which cyclize thermally to pyridines (Scheme 97) <1995T9119>. Palladium-catalyzed hetero-annulation reactions of internal alkynes to pyridines were reported

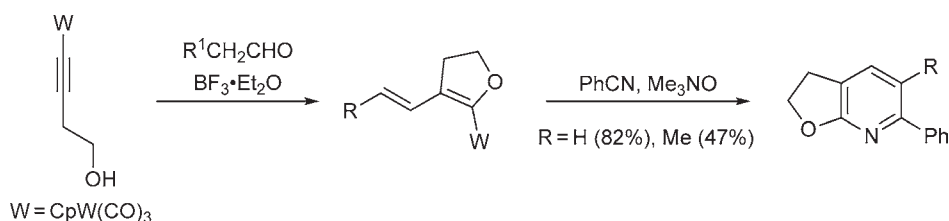


Scheme 97

<1998TL627>. Other metal-catalyzed reactions include the CdCl_2 -mediated cyclization of enamines in the presence of a cyano substituent (**Scheme 98**) <1995JOC5243>. Zinc and copper (I) salts can be used in place of the cadmium; however, organocadmium promoters allow room temperature cyclization. A two-step process involving tungsten alkynols, aldehydes, and nitriles in the presence of a Lewis acid yields pyridines (**Scheme 99**) <1998JA4520>.

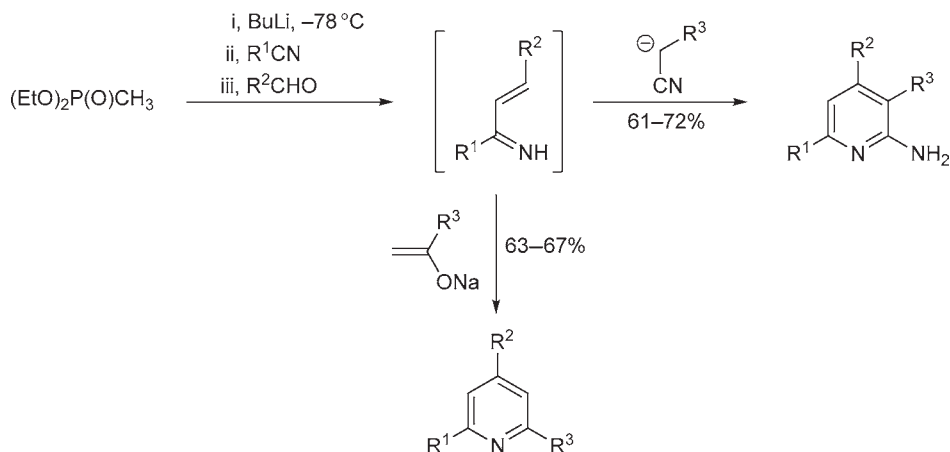


Scheme 98



Scheme 99

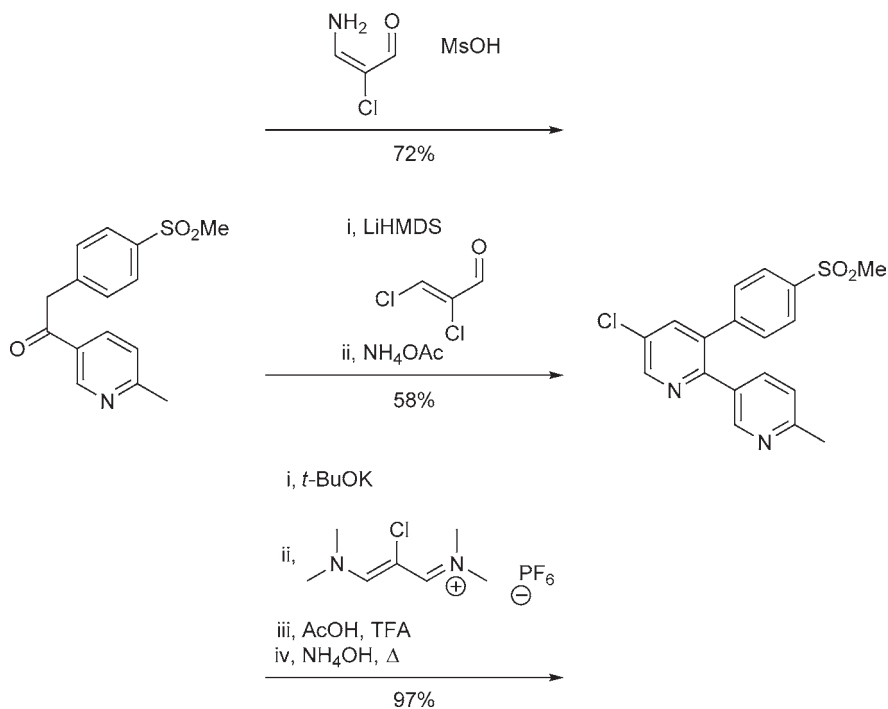
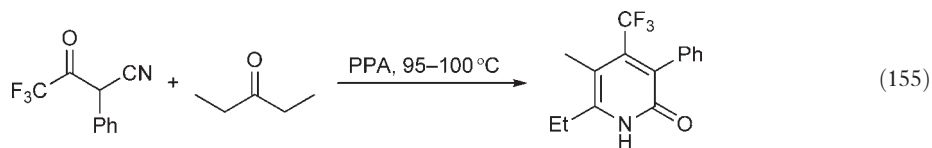
Condensation reactions continue to be reported and include those forming highly substituted pyridines (**Scheme 100**; **Table 5**) <1995TL9297>. Variations in the acid or base conditions from the identical starting ketone give the 2,3-diaryl-5-chloropyridine as part of a program to synthesize this cyclooxygenase-2 (COX-2)-specific inhibitor (**Scheme 101**) <2000JOC8415>. PPA-promoted reactions are also still being reported (**Equation 155**) <1995JCM476>.



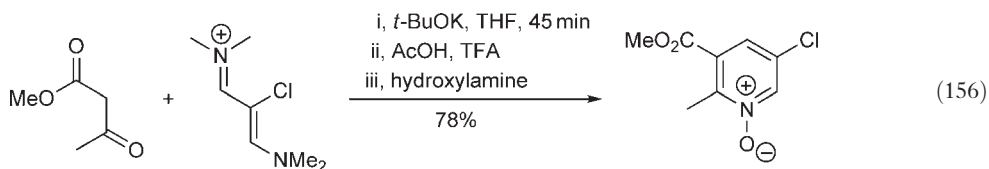
Scheme 100

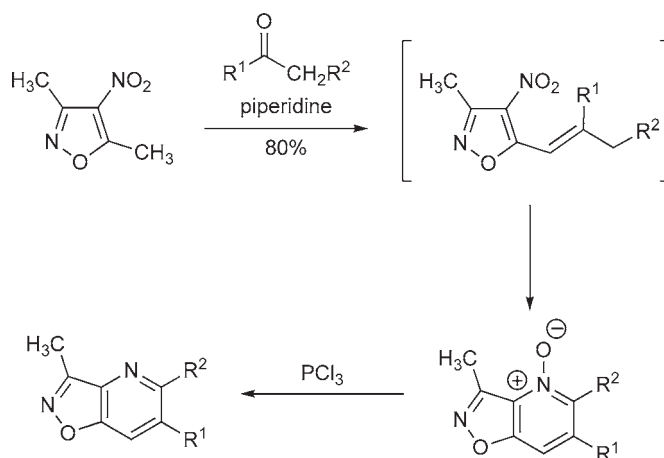
Table 5 Condensation reactions yielding pyridines (**Scheme 100**)

R^1	R^2	R^3	Yield (%)
Ph	4-FPh	4-ClPh	72
Ph	4-MeOPh	2-naphthyl	61
2-Quinoliny	4-MeOPh	4-ClPh	68

**Scheme 101**

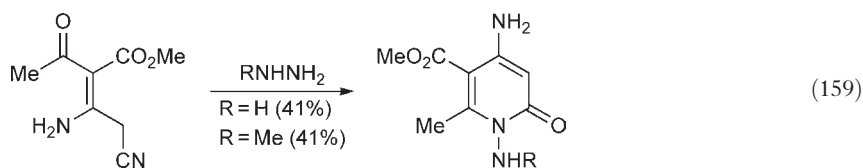
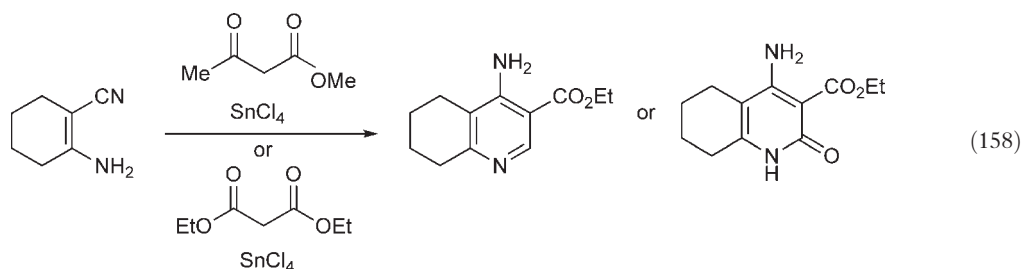
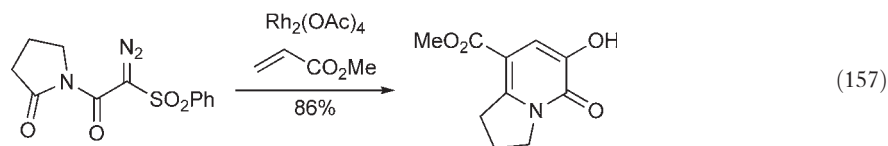
Synthesis of pyridine *N*-oxides has been reported by a direct cyclization in a [3+2+1] annulation reaction (**Equation 156**) <2001OL209>. A one-step synthesis of fused isoxazolo[4,5-*b*]pyridine *N*-oxides was reported. Deoxygenation to the pyridine was achieved using PCl_3 (**Scheme 102**) <2003IJB1742>.



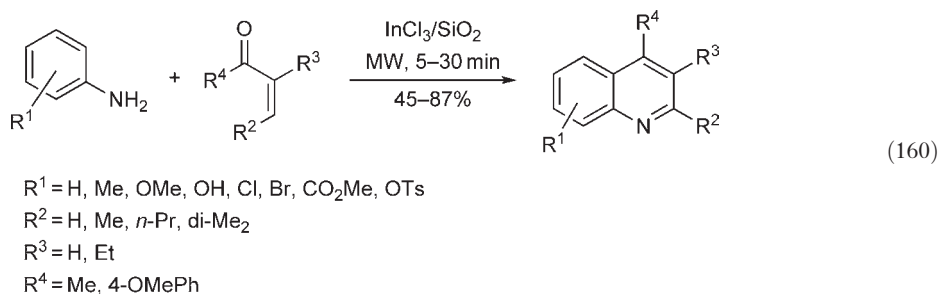


Scheme 102

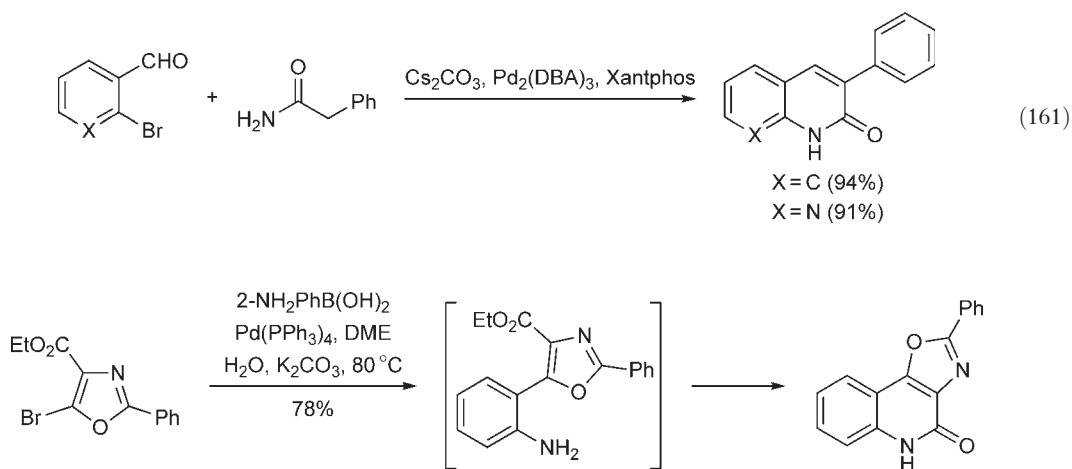
The pyridinone ring was reported to be constructed by the reaction of a carbenoid structure, generated from the reaction of a diazoimide with rhodium catalyst, undergoing an intramolecular cyclization (Equation 157) <1997JOC438>. Other pyridinone syntheses rely on typical condensation reactions, for example, in the presence of stoichiometric amounts of tin(IV) chloride (Equation 158) <1995T12277>, or by reaction with cyanoenamino ketoester (Equation 159) <1999H(50)791>, or the reaction of acetohydrazides with arylidenecyanoacetate derivatives <1999JCM6>.



Condensation reactions remain popular for the synthesis of quinolines <2006JOC6592>. Some modern variations on these classic reactions include an example of a solventless system, and the use of indium(III) chloride on silica gel under microwave conditions (Equation 160) <2003T813>. These fast, clean, high-yielding reactions gave aromatized products under indium(III) catalysis after a typical Michael addition of aniline to vinyl ketone.

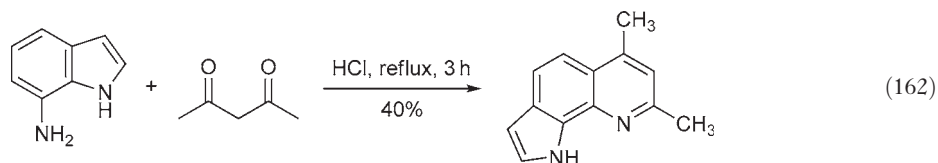


Dihydroquinolinones have been formed in a convergent one-pot cascade sequence that utilized a palladium-catalyzed cross-coupling reaction of 2-bromonicotinamide or 2-bromobenzaldehyde with 2-phenylacetamide. Dehydration of the amide intermediate gave good yields of the product (Equation 161) <2004OL2433>. Palladium chemistry can be utilized in a different strategy to give the same heterocycles, for example, a two-step synthesis to the fused quinolines-4-ones (Scheme 103) <2003OL2911>. Additional reports of 2-aryl-2,3-dihydroquinolinone synthesis were from 2-aminochalcones using indium(III) chloride supported on silica gel in a solvent-free system <2004S63>.

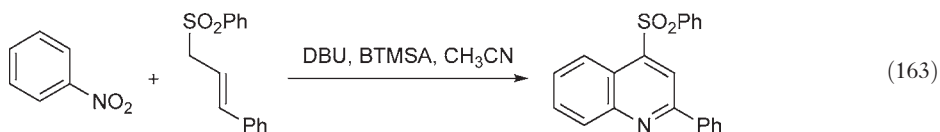


Scheme 103

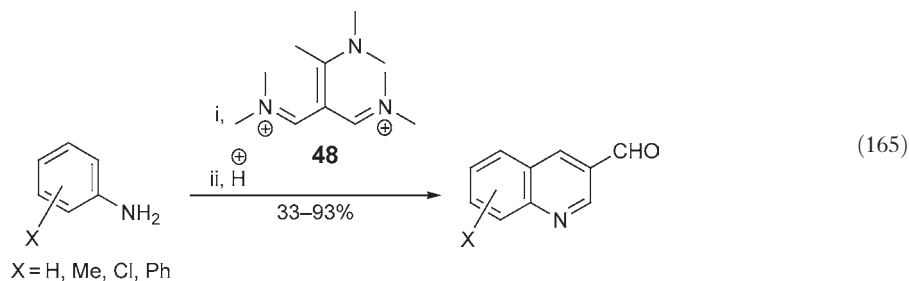
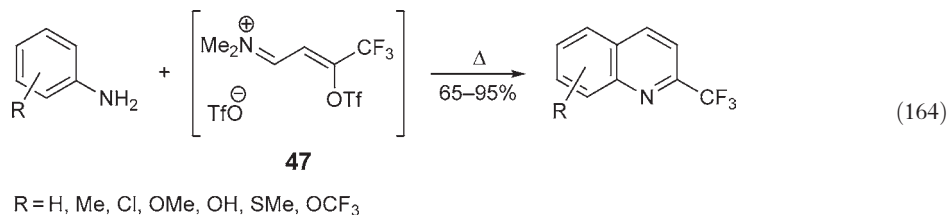
Corrections to condensation products have been made with 2,4-dimethylpyrroloquinoline arising from the reaction of 7-aminoindoles with acetylacetone <1995SC1601, 1995CHE50> and not pyrrolobenzodiazepine as originally reported (Equation 162) <1957PCS354>.



A DBU-silane or DBU-Lewis acid double condensation of aryl nitro compounds with cinnamyl phenyl sulfones leads to the corresponding quinolines (1,8-diazabicyclo[5.4.0]undec-7-ene; Equation 163) <1998T2607>. This approach utilizes the opposite polarity that is normally observed in aniline condensations with electrophiles.



Reactions with iminium salts are also reported. The triflate **47** reacts with anilines to yield 2-trifluoroquinolines (Equation 164) <1999EJO937>, whereas condensation of the vinamidinium salt **48** with anilines leads to 3-formylquinoline derivatives (Equation 165) <2001S1351>.



The piperidine dione structure can be generated by acylation of Meldrum's acid with N-protected β -amino acids followed by thermolysis of the resulting N-protected δ -amino- β -ketoacid (Equation 166; Table 6) <2004JOC130>.

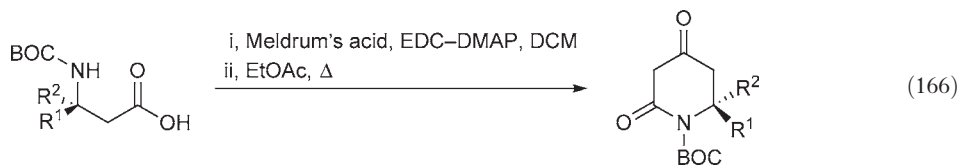
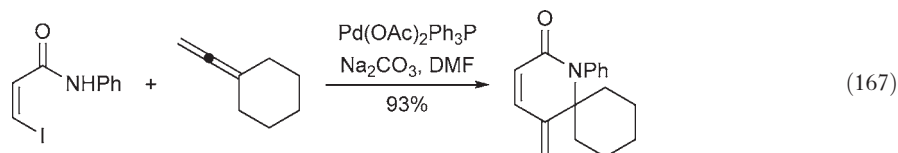


Table 6 Piperidine dione synthesis from N-protected β -amino acids (Equation 166)

R^1	R^2	Yield (%)
CO ₂ <i>t</i> -Bu	H	77
CO ₂ Bn	H	85
H	<i>t</i> -Bu	68
H	Bn	87
H	<i>i</i> -Pr	63
H	Me	93

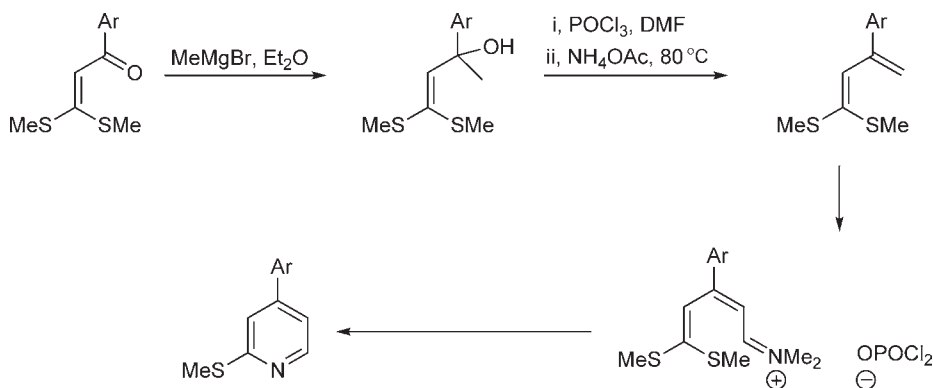
Palladium-mediated intramolecular aminations onto an allylic alcohol <1998TL5971> or allene <1998TL5421> are reported for the synthesis of piperidines. An intermolecular version of the allene-based reactions has been reported in the synthesis of spiro-piperidines (Equation 167) <1998JOC2154>.



7.05.2.3 Formation of Three Bonds

7.05.2.3.1 From a fragment containing four atoms and two one-atom fragments

Pyridines have been synthesized from an unusual Vilsmeier–Haack reaction where POCl_3 dehydrates the appropriate enol to give a diene which in turn reacts with the Vilsmeier reagent leading to an iminium salt which subsequently cyclizes (**Scheme 104**; **Table 7** <2002TL2273>).

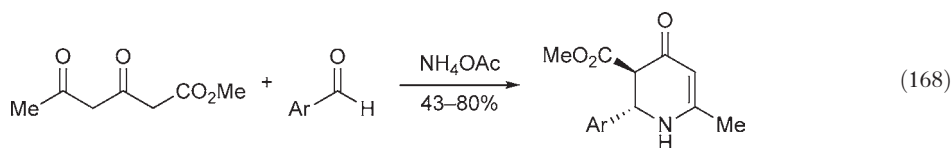


Scheme 104

Table 7 Pyridine synthesis using Vilsmeier reagent (**Scheme 104**)

Ar	Yield (%)
Ph	51
4-BrPh	56
2-Naphthyl	41

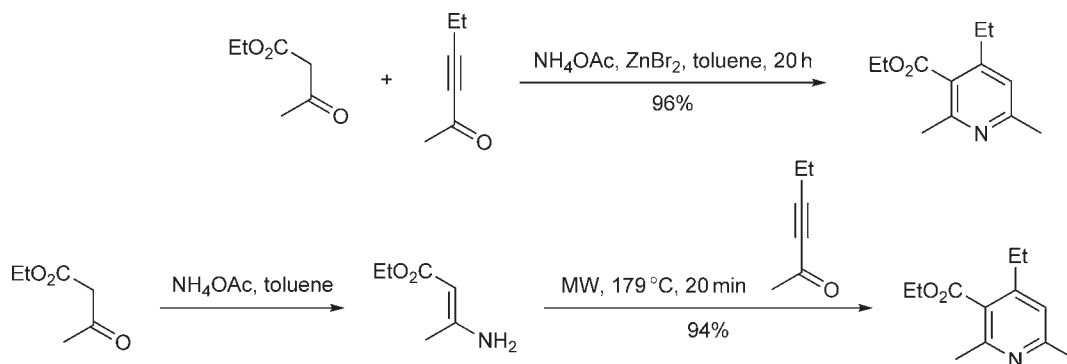
A simple diastereoselective route to 2,3,6-trisubstituted-2,3-dihydro-4-pyridones from a diketoeester, aryl aldehydes, and ammonium acetate has been reported (**Equation 168**) <2005TL5511>.



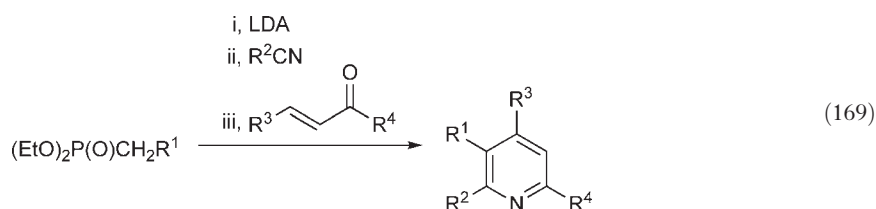
7.05.2.3.2 From fragments containing one, two, and three atoms

One of the most common methods of pyridine synthesis is condensation-based reactions. In the more traditional reactions with acid-catalyzed dehydrations in the final steps <2002J(P1)1663, 2002CC1682>, the use of microwave generators has been an advantage. The microwave conditions are simply thermal and facilitate the same reactions, for example, dehydration. An instance is the treatment of ethyl acetoacetate with ethyl β -aminocrotonate with an alkyne in a microwave reactor, which yields the 2,3,4,6-tetrasubstituted pyridine (**Scheme 105**) <2002TL8331>. The same pyridine can be synthesized under Lewis acid conditions <2002TL8331> and similarly substituted analogues using normal thermal conditions <2005JOC1389>.

Polysubstituted pyridines can be generated by the regioselective addition of lithiated β -enaminophosphonates to unsaturated carbonyl compounds. This variation on the classic condensation reaction can also be obtained using a one-pot reaction of metallated phosphonates and sequential addition of nitriles and unsaturated carbonyl compounds (**Equation (169)**; **Table 8**) <1996TL4977>.



Scheme 105

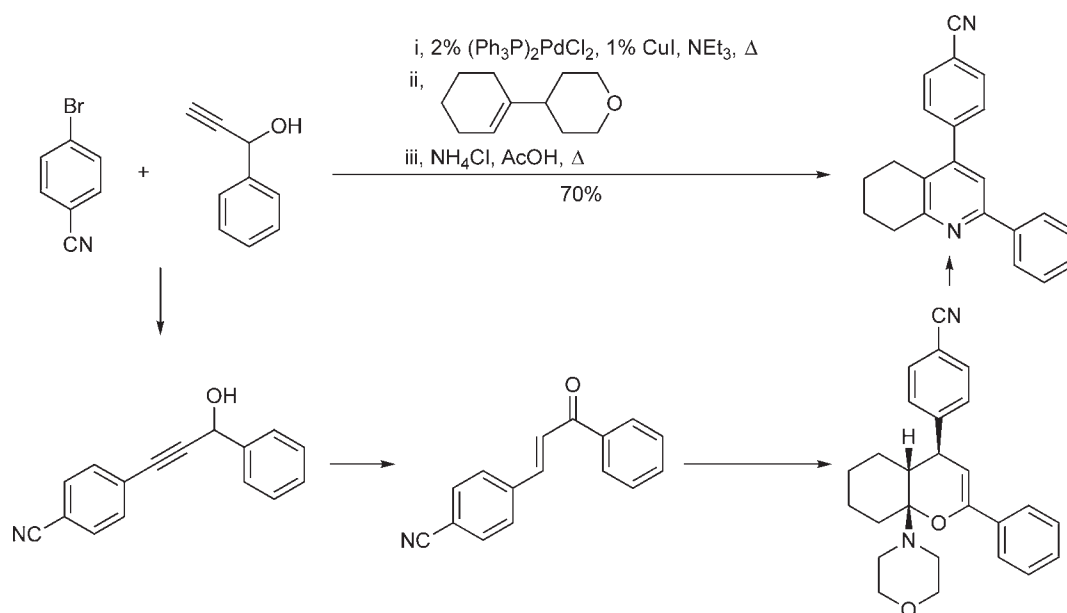
**Table 8** Pyridine synthesis using β -enaminophosphonates (Equation 169)

R^1	R^2	R^3	Yield (%)
H	<i>p</i> -MePh	Ph	90
H	2-Pyridyl	Ph	87
H	2-Furyl	Ph	81
H	<i>p</i> -MePh	Me	62
Me	<i>p</i> -MePh	Ph	65
Me	2-Pyridyl	Ph	60
Ph	<i>p</i> -MePh	Ph	91
Ph	<i>p</i> -MePh	Me	55

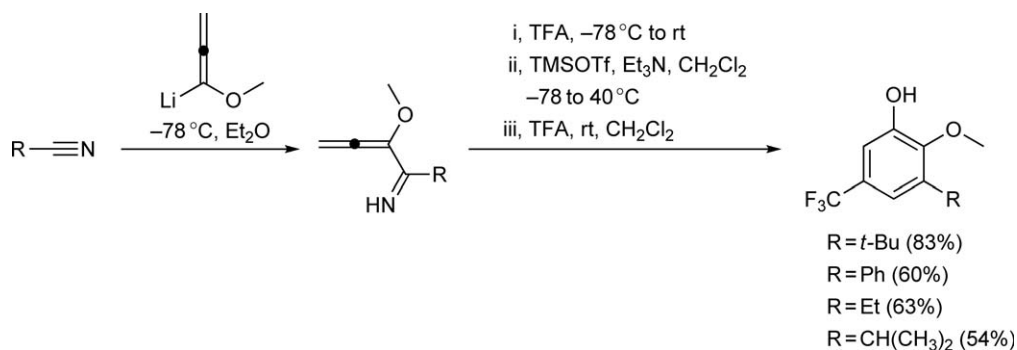
The use of palladium-based chemistry continues to generate methods for heterocyclic synthesis. In a four-component reaction, ring-fused pyridines can be synthesized in one pot, referred to as a coupling–isomerization–enamine addition–cyclocondensation sequence (Scheme 106) <2005EJO1834>.

In a recently reported synthesis of pyridines, lithiated methoxyallenes react with nitriles in the presence of trifluoroacetic acid (Scheme 107) <2004CEJ4283>. The mechanism is postulated to proceed via initial protonation followed by nucleophilic addition of the trifluoroacetate ion with subsequent intramolecular acyl transfer and aldol condensation to give the pyridine. An additional pyridine formation starting from azaenynes allenes forms α -5-didehydro-3-picoline diradicals, which can be trapped by 1,4-cyclohexadiene, chloroform, and methanol to produce various pyridines <2004OL2059>.

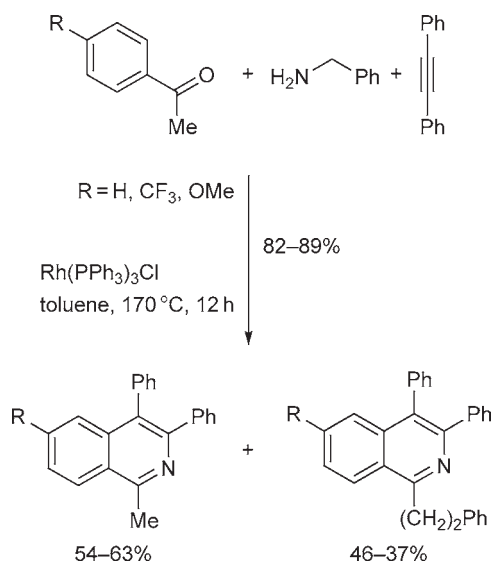
Condensation reactions to produce isoquinolines continue to be reported. In a rhodium-catalyzed example, the three-component reaction (Equation 170) produces a modest quantity of the target with a notable quantity of the phenethyl-substituted by-product <2003OL2759>.



Scheme 106

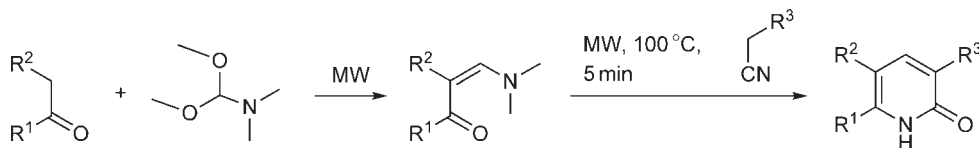


Scheme 107



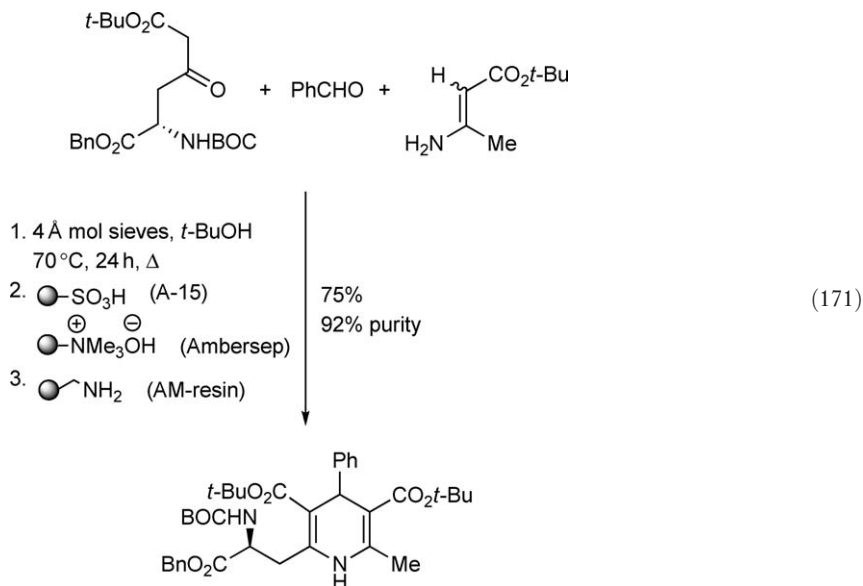
(170)

Microwave reaction conditions have been reported for the synthesis of 2-pyridones in a modern version of the traditional three-component condensation reaction (**Scheme 108**) <2004T8633>. A library of 18 3,5,6-trisubstituted pyridines was generated and includes aryl, alkyl, and fused derivatives.



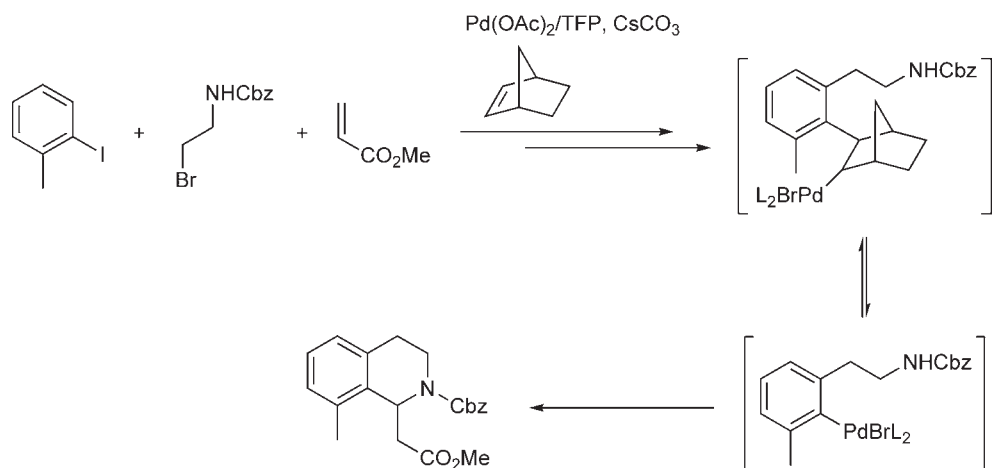
Scheme 108

The synthesis of 1,4-dihydropyridines is still of interest because of their biological activity. The well-used Hantzsch synthesis is often the choice <2004JME3180, 2004JME2688, 2004JME254, 2004JME3163>, while a more recently developed mild solvent-free approach has improved yields <2004SL827>. Further reports include the use of phase-transfer catalysis and diethylene glycol as solvent <2004TL9011>. Highly functionalized 1,4-dihydropyridines are produced in one pot under thermal conditions with a simplified purification due to the presence of polymer-supported scavengers to remove excess reagents (**Equation 171**) <2004T2311>.

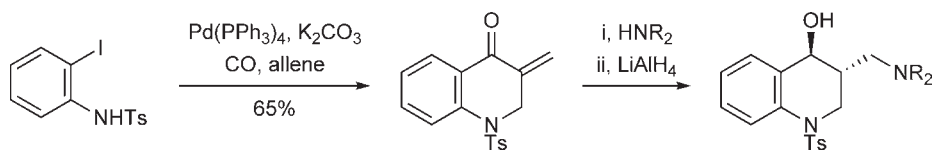
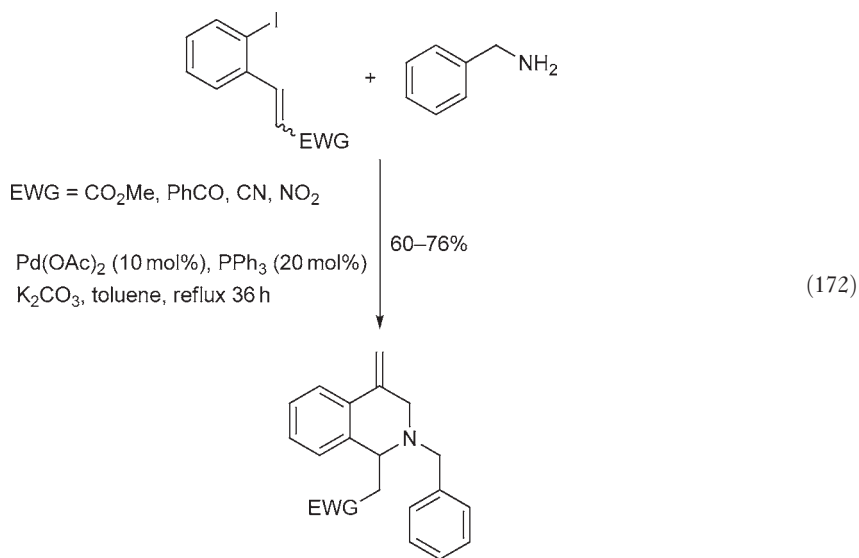


Palladium chemistry has been used in the synthesis of tetrahydroisoquinolines. Different combinations of iodoaryl-amine-alkene can be used in these multicomponent reactions. For example, the metal-mediated *o*-alkylated/alkenylation and intramolecular aza-Michael reaction (**Scheme 109**) give moderate yields of heterocycle <2004TL6903>, whereas the palladium-catalyzed allene insertion–nucleophilic incorporation–Michael addition cascade (**Equation 172**) produces good yields of tetrahydroisoquinolines in 15 examples <2003TL7445> with further examples producing tetrahydroquinolines (**Scheme 110**) <2000TL7125>.

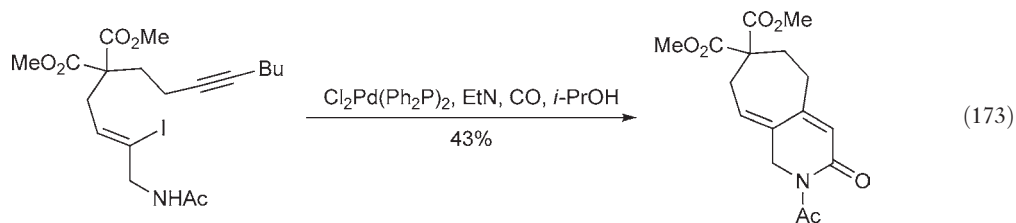
Termination of cyclic carbopalladation of alkynes using carbonylative lactamization can be achieved with alkenyl or aryl halides containing an ω -carboxamido or ω -sulfonamido group and can be used in the synthesis of piperidines (**Equation 173**) <1996T11529>.



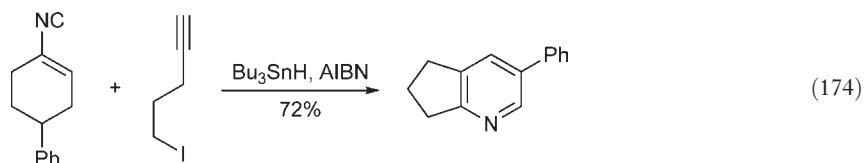
Scheme 109



Scheme 110

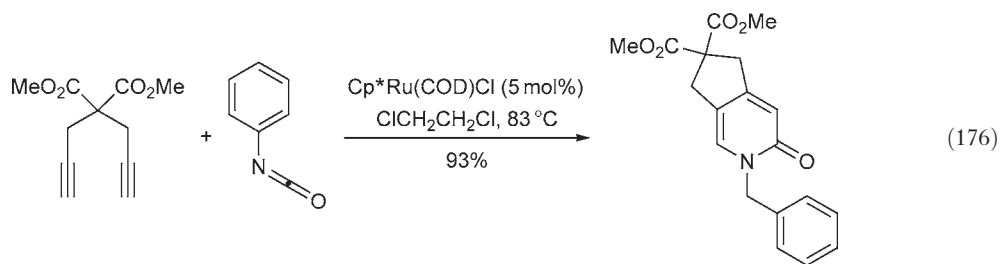
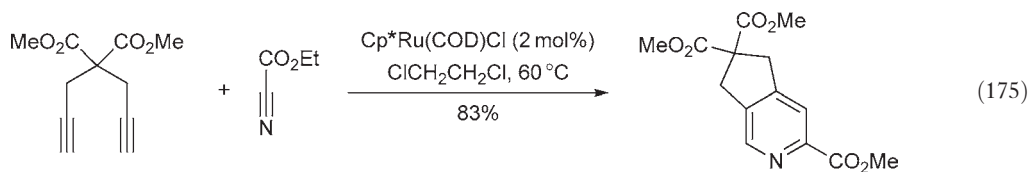


A [4+1] radical annulation approach was used in a reaction between isonitriles and 1-iodoalkynes to produce fused pyridines (Equation 174) <2000J(P1)641>.

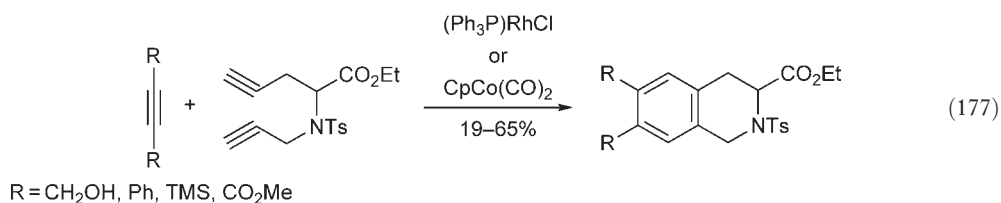


7.05.2.3.3 From three two-atom fragments

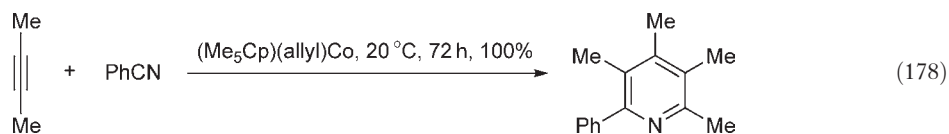
Strategies to pyridines include a ruthenium-mediated [2+2+2] cycloaddition to produce annulated products <2001OL2117>. Reaction of 1,6-heptadiynes with electron-deficient nitriles yields the pyridine (Equation 175), whereas the same strategy using isocyanates leads to the 2-pyridone (Equation 176).

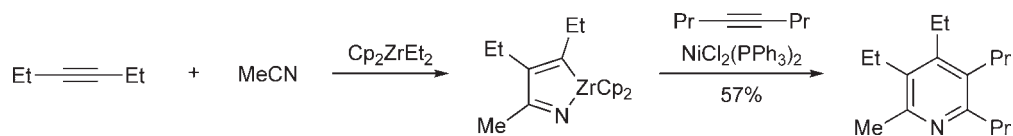


In an extension of the 3 × triple-bond approach, tetrahydroisoquinolines were derived from a [2+2+2] cycloaddition in the presence of either Ph- or Co-catalysts (Equation 177) <2000BML1413>.



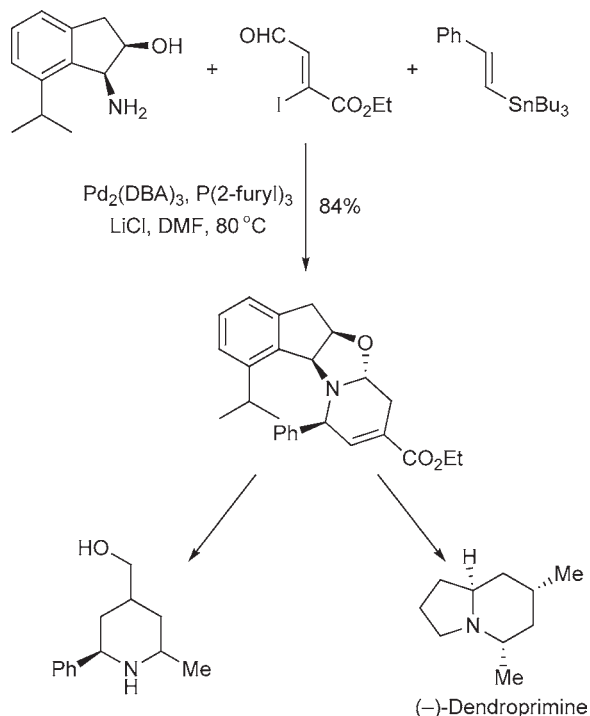
Selective cyclotrimerization of alkynes with nitriles leads to pentasubstituted pyridines with minimal formation of benzenoid by-products (Equation 178) <1994CB2535, 2000OL3131>. Similar reaction of nonsymmetrical alkynes and aliphatic nitriles using irradiation required longer reaction times and produces lower, but still good, yields <1995JOM(488)47>. Different alkynes can be utilized in the same strategy if a sequential approach is used <2000JA4994> (Scheme 111).





Scheme 111

The synthesis of 2,4,6-trisubstituted piperidines has been reported via the generation of a fused cyclic intermediate in a three-component reaction using typical palladium-based chemistry (**Scheme 112**) <2006OL3813, 2006OL3809>. Stereocontrol was observed and the same intermediate was used in the stereoselective synthesis of the indolizidine alkaloid (–)-dendroprimine.

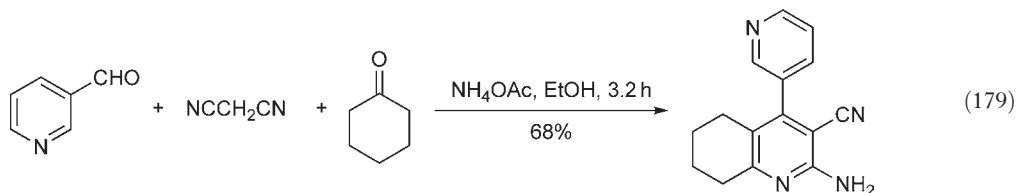


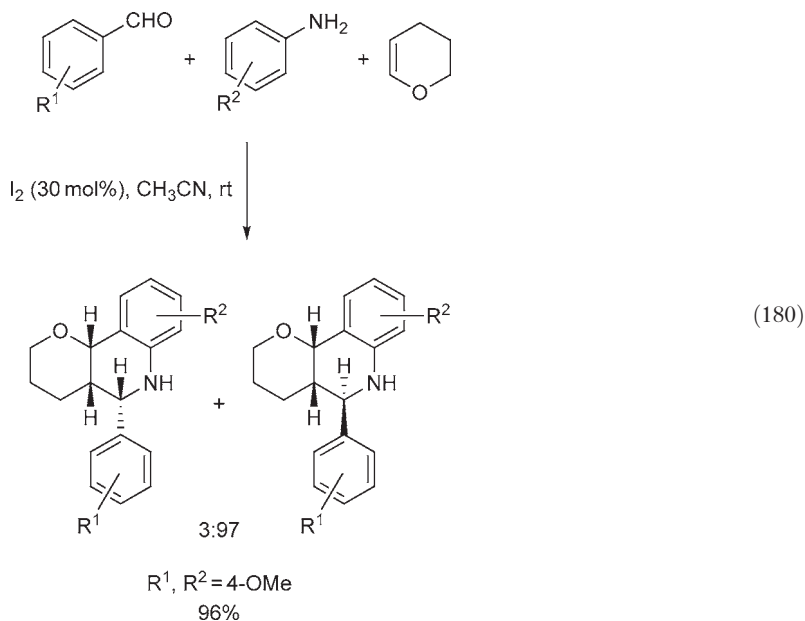
Scheme 112

7.05.2.4 Formation of Four Bonds

7.05.2.4.1 From two two-atom and two one-atom fragments

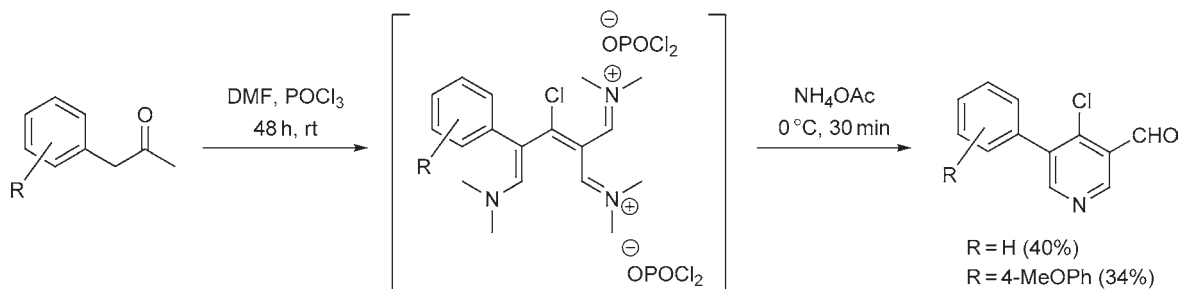
Multicomponent one-pot reactions continue to be the focus of heterocyclic synthesis when multi-bonds are formed. Malononitrile condenses with 3-pyridinecarbaldehyde and a ketone to form a substituted bipyridine (**Equation 179**) <1995JCM146>. In another condensation, with aniline being the ultimate source of the tetrahydroquinoline nitrogen atom, iodine is used as a catalyst in a reaction that was optimized for yield and diastereoselectivity (**Equation 180**) <2005SL2357>.





7.05.2.4.2 From three one-atom and, one three-atom fragment

A 4-bond synthesis of pyridines from carbonyl compounds, which were subjected to Vilsmeier–Haack conditions giving the conjugated iminium salts, has been achieved by reaction with ammonium acetate (**Scheme 113**) <2004T5069>.

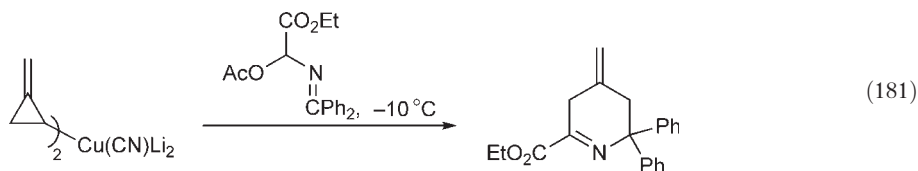


Scheme 113

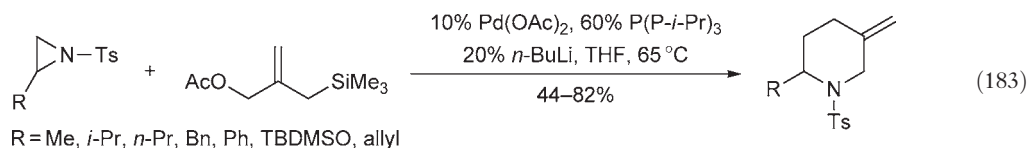
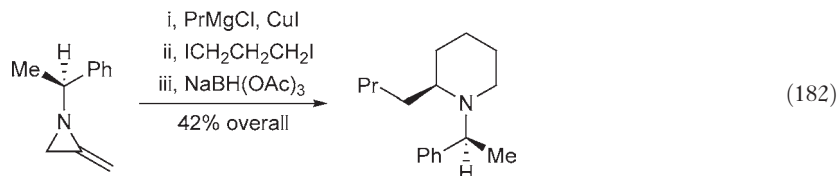
7.05.3 Ring Syntheses by Transformations of Another Ring

7.05.3.1 From Three-Membered Rings

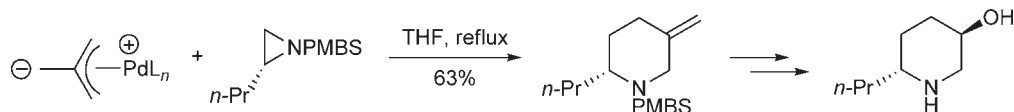
Methylenecyclopropanecuprate addition to electrophilic glycine derivatives leads to an intermediate that undergoes ring expansion to the piperidine (**Equation 181**) <1997LA2197>.



A novel one-pot ring expansion of 2-methyleneaziridine led to piperidines in four steps with stereocontrol (Equation 182) <2001CC1784>. The example illustrated resulted in a short synthesis of (*S*)-coniine. The reaction of *N*-Ts aziridines with silylpropenyl acetate in the presence of a palladium catalyst yielded piperidines in a [3+3] cycloaddition (Equation 183) <2003JOC4286>. Vinylaziridines also undergo aza-[2,3]-Wittig rearrangement to piperidines <1997ACS1024>. Optically active aziridines gave rise to enantiomerically pure piperidines. Thermolysis of 2(*H*)-aziridines that possess cyclopropyl substituents yield pyridines <1995H(40)511> although some steric inhibition was noted. Aza-Wittig reaction of aziridines yields tetrahydropyridines <1995TL3557>.

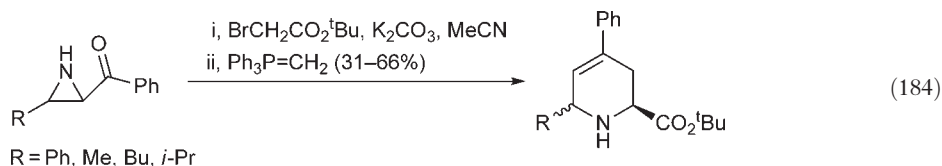


In a variation on the two-component cycloaddition reaction, a [3+3] strategy was reported whereby reaction of enantiomerically pure aziridines, generated from amino acids, with palladium trimethylenemethane complexes leads to a piperidine (Scheme 114). Yields ranged from 63% to 82% and the efficiency of the methodology was demonstrated by the four-step synthesis of (–)-pseudoconhydrin <2001SL1596>.

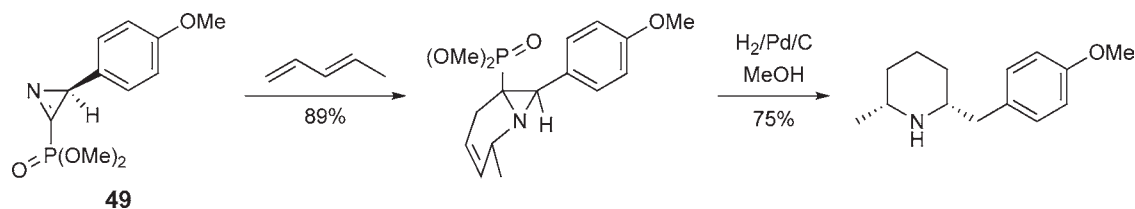


Scheme 114

The *N*-alkylation of 2-benzoyl-2-alkylaziridines followed by the Wittig olefination yielded directly piperidine derivatives (Equation 184) <1995J(P1)2739>.



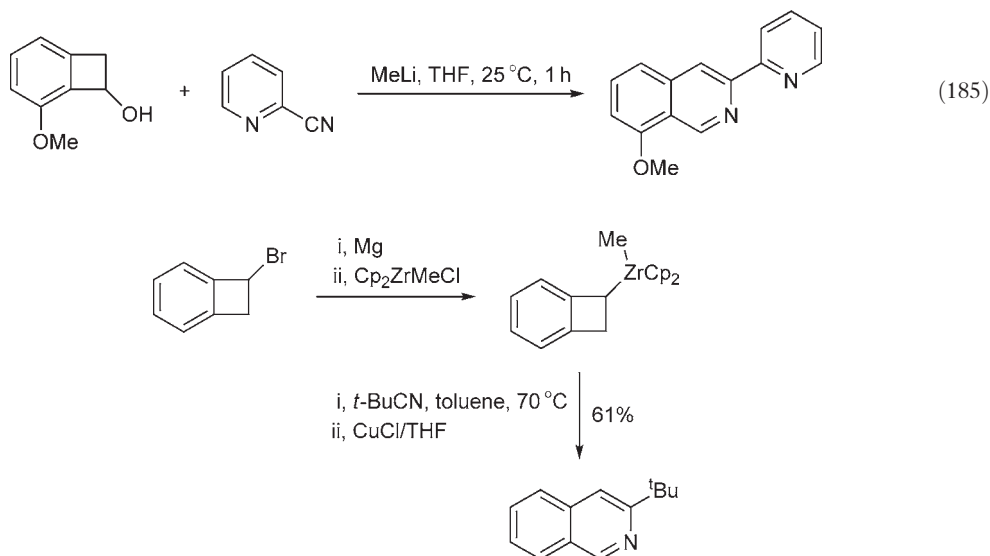
A novel route to optically active piperidines is the imino Diels–Alder reaction between the chiral 2*H*-azirine **49** and *trans*-1,3-pentadiene (Scheme 115) <2002OL655>. The resulting strained intermediate was a single diastereomer and subsequent halogenation produced the 2,6-disubstituted piperidine.



Scheme 115

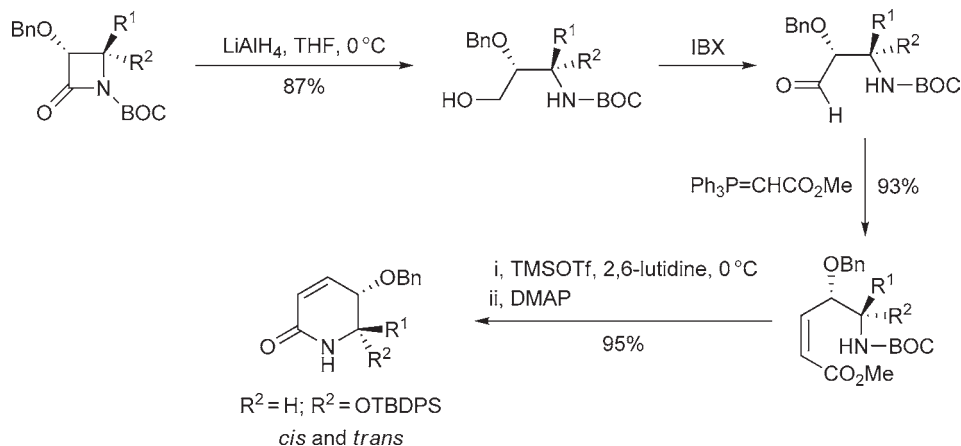
7.05.3.2 From Four-Membered Rings

Isoquinolines can be generated from benzocyclobutanol and 2-cyanopyridine [<1994TL9191>](#) (Equation 185). Zirconocene–copper-mediated coupling of benzocyclobutanes in the presence of nitriles gives the isoquinoline, albeit with only select examples of 3-substitution ([Scheme 116](#)) [<2003OL877>](#).



Scheme 116

In a novel application of 2-azetidinanes, the ready availability of chiral versions enables their reductive ring opening and subsequent functional group manipulation to give chiral versions of 2-pyridones in excellent yields ([Scheme 117](#)) [<2003T6445>](#).

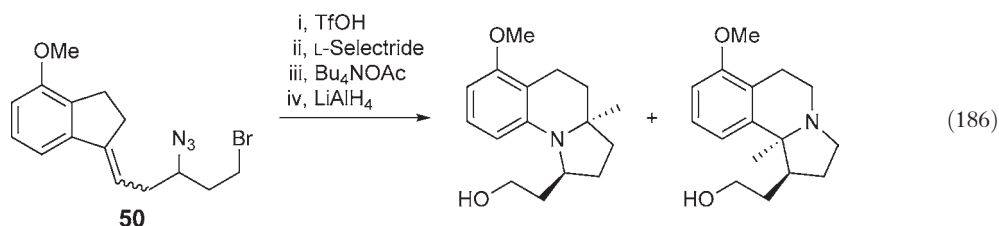


Scheme 117

7.05.3.3 From Five-Membered Rings

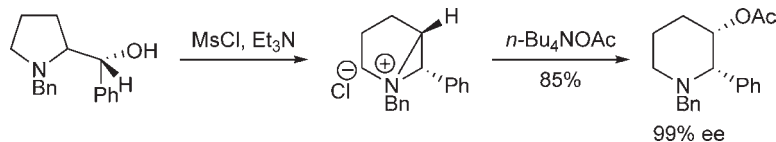
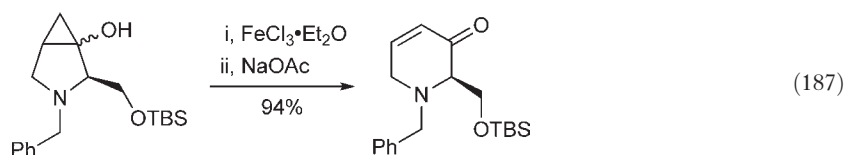
7.05.3.3.1 Carbocyclic rings

The alkyl azide [50](#) can be treated with TfOH followed by reduction to give the corresponding benzoindolizine structures (Equation 186) [<2000JOC7158>](#). The major product was isolated in 45% yield while the minor regioisomer was isolated in 10% yield. Further examples of this strategy were also reported.

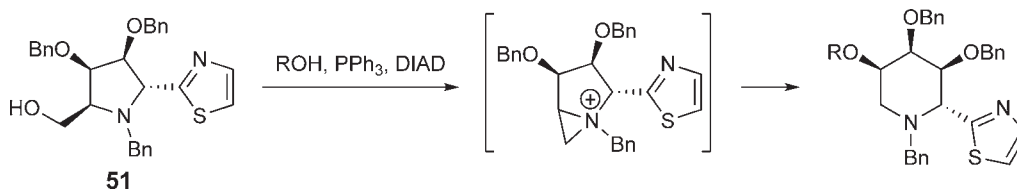


7.05.3.3.2 From furans, pyrroles, and their benzologues

A chiral fused pyrrolidine, derived from serine, undergoes FeCl_3 -induced ring expansion to a piperidine which is a precursor to azasugars (Equation 187) <1999TL5331>. Other ring-enlargement reactions of pyrrolidines led to enantioselective syntheses of 2,3-disubstituted piperidines (Scheme 118) <1998TL9447, 2001TL6223> with other piperidine substitution patterns obtained by starting from the appropriate starting material; for example, chiral 2,4-disubstituted pyrrolidines yield 2,5-disubstituted piperidines <1997LA573>. Analogous reaction pathways using different reagents can be achieved; for example, Mitsunobu conditions on **51** led to ring expansion and the corresponding piperidine (Scheme 119; Table 9) <2004SL1711>. Optically active 3-hydroxypiperidines are prepared by pyrrolidine methanol ring expansions <1999EJO1693>.



Scheme 118

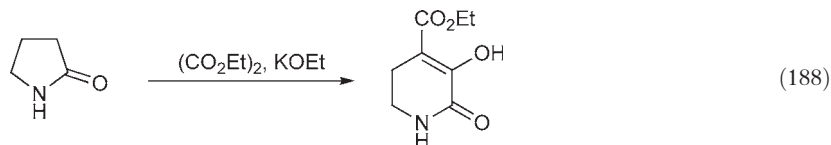


Scheme 119

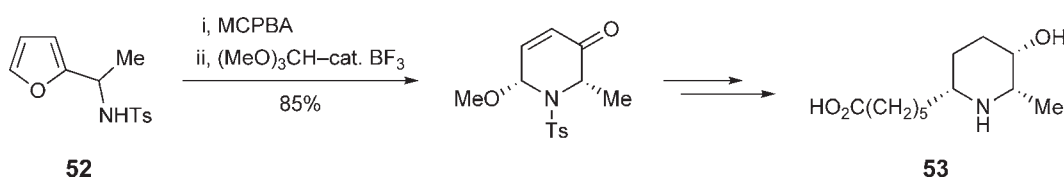
Table 9 Piperidine synthesis by ring expansion (Scheme 119)

<i>R</i>	Yield (%)
<i>p</i> -MeOPh	46
PhCO	48
Ph ₂ CHCO	74
<i>t</i> BuCO	13

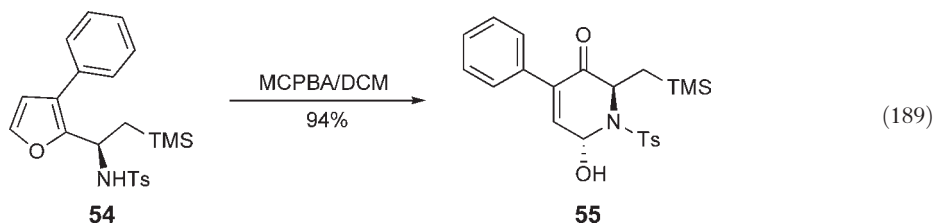
Cyclopentanones and 2-indanone undergo ring expansion by reaction with alkylazides to give the piperidinones and isoquinolinones, respectively, via a Schmidt reaction [<1997TA2893, 1997T16241>](#). The use of pyrrolidinone in ring expansions by reaction with diethyl oxalate has been reported to give the dihydropyridinone ([Equation 188](#)) [<1997OPP330>](#).



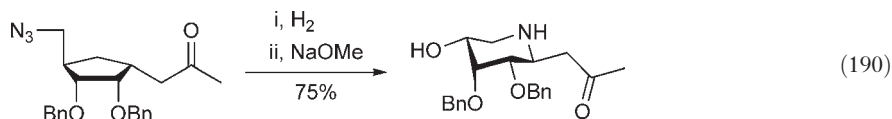
Oxidation of (2-furinylcarbonyl)amines is a valuable strategy for the synthesis of highly substituted piperidines [<1997J\(P1\)741, 1999TA3649, 1999S1889, 1999TL6869>](#). For example, the *m*-chloroperbenzoic acid (MCPBA) reaction of furan **52** yielded the methoxy-substituted tetrahydropiperidine, *en route* to a synthesis of the racemic azimic acid **53** ([Scheme 120](#)) [<2004OL4029>](#). Additional examples of the same reaction give excellent yields of a piperidine natural product [<2003JOC4371>](#). In an analogous reaction, treatment of **54** with MCPBA in dichloromethane (DCM) gave **55** ([Equation 189](#)) [<2004JOC2892>](#).



Scheme 120



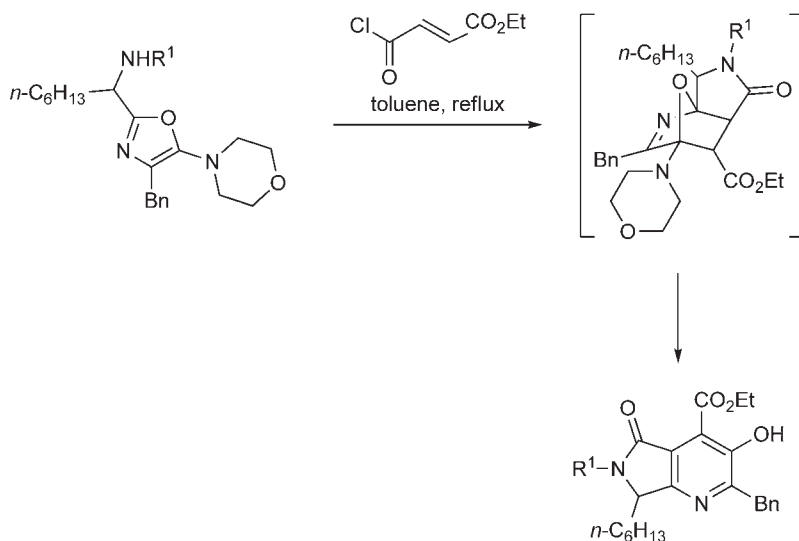
The synthesis of aza-*C*-glycosides has been reported ([Equation 190](#)) [<2005T11716>](#). The primary amine generated undertakes a conjugate addition to an enone intermediate.



7.05.3.3.3 From oxazoles, isoxazoles, and their benzologues

Annulated pyridines are reported to be synthesized via a [4+2] cycloaddition involving oxazoles ([Scheme 121](#); [Table 10](#)) [<2001OL877>](#). The reaction mechanism is classified as a domino process with an intramolecular Diels-Alder cycloaddition followed by a retro-Michael reaction.

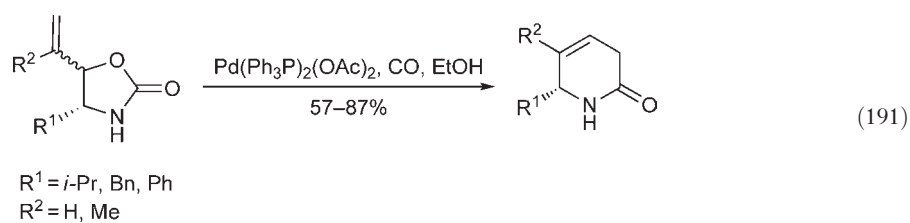
Oxazolidines can be converted into 3,6-dihydro-1*H*-pyridin-2-ones in a new synthesis ([Equation 191](#)) [<2000JA2944>](#) involving a palladium-catalyzed decarboxylative carbonylation.



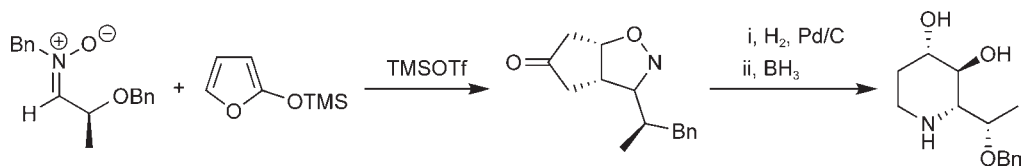
Scheme 121

Table 10 The synthesis of annulated pyridines via a [4+2] cycloaddition involving oxazoles ([Scheme 121](#))

R^1	Yield (%)
	65
	58



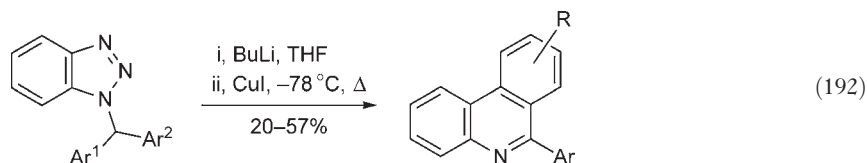
A Mukaiyama-type reaction of trimethylsilyloxyfuran with the nitron of lactaldehyde leads to hydroxylated piperidines following reduction of the isoxazolidine intermediates ([Scheme 122](#)) <1997OPP485>.



Scheme 122

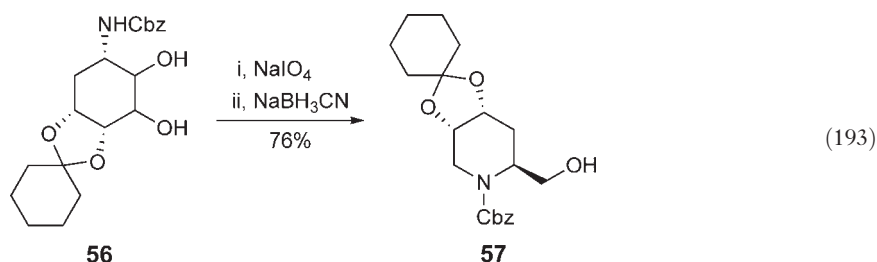
7.05.3.3.4 Other five-membered heterocycles

Lithiation of diarylbenzotriazolylmethanes with subsequent addition of copper(I) iodide yielded phenanthridines in moderate yield (Equation 192) <1996JHC607>. It was proposed that the mechanism involved radical intermediates.



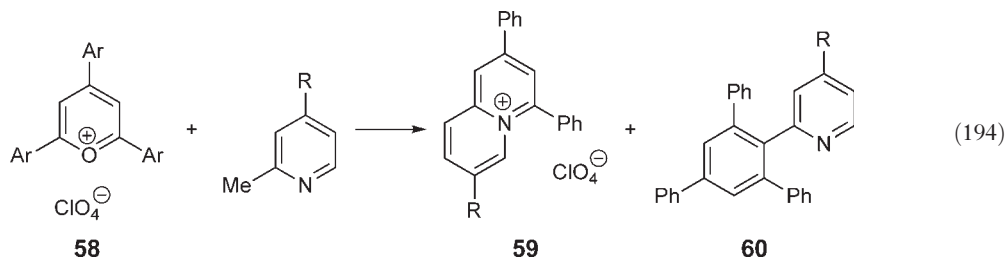
7.05.3.4 From Six-Membered Rings

Ring formation by reaction of N-nucleophiles onto carbonyl groups is well established and continues to be reported. For example, reductive amination following ring opening of the diol **56** gave the azasugar **57** (Equation 193) <2004TL5751>.

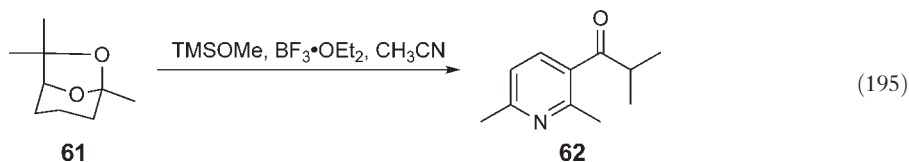


7.05.3.4.1 Pyrans, pyrones, pyrylium salts, and their benzologues

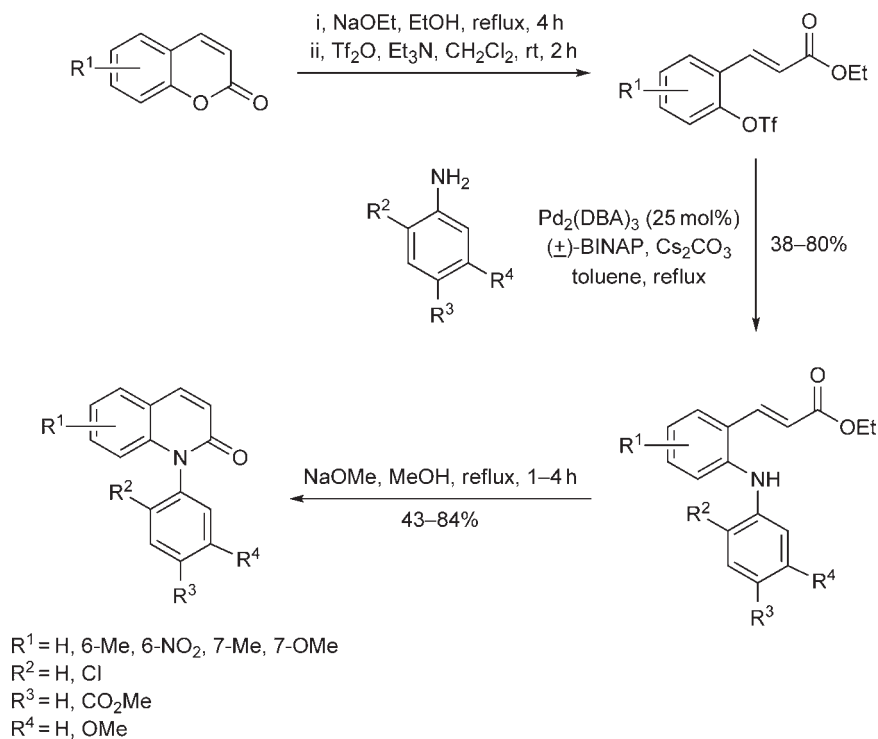
The triphenylpyrylium perchlorate **58** undergoes reaction with α -methyl heterocycles to give fused pyridinium derivatives **59** and low yields of the aryl by-product **60** (Equation 194).



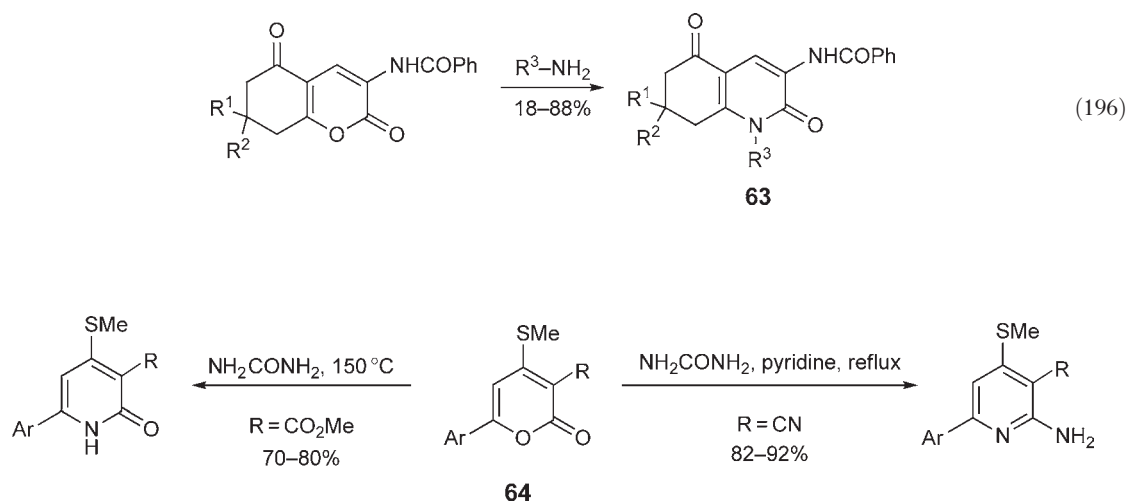
The bicyclic ketal **61** is converted cleanly into the pyridine **62** in the presence of an alkylnitrile and TMSOMe (Equation 195) <1997JHC325>. The active reagent, boron difluoromethanesulfonate, is generated *in situ*.



In a variation of a well-utilized strategy, the Buchwald–Hartwig palladium-catalyzed reaction was applied to the synthesis of N-substituted 2-quinolones starting from lactones (Scheme 123) <2003TL4207>. In an analogous reaction, benzopyrans can be used as the starting material in reaction with nitrogen nucleophiles <1996H(43)809>, in this instance generating the quinoline-4(*H*)-one **63** (Equation 196). Pyridines or pyridones can be selectively synthesized from the 2-pyranone **64** (Scheme 124) <2005SL623> by simple manipulation of the substituents present.

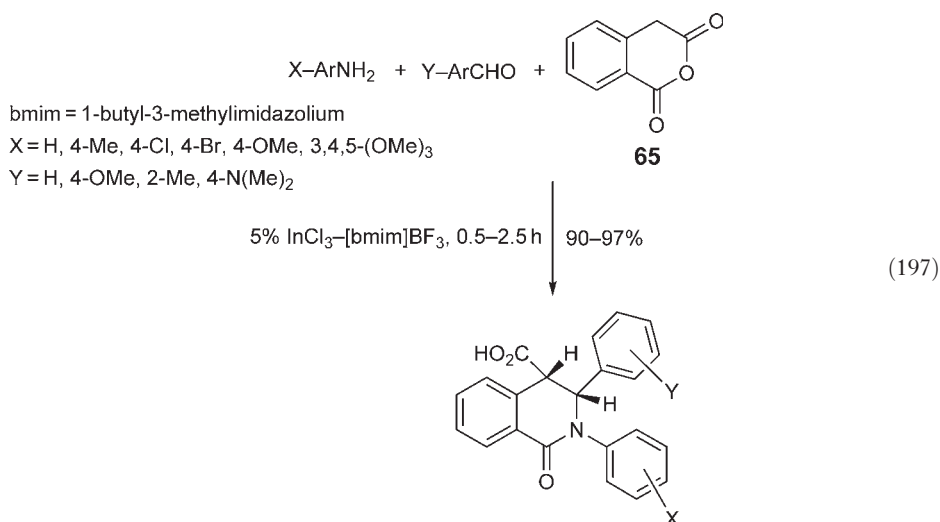


Scheme 123



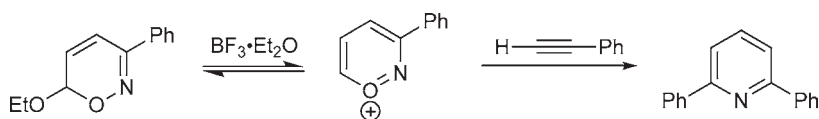
Scheme 124

Tetrahydroisoquinolonic acids were generated in good to excellent yields by the multicomponent reaction of benzaldehydes, amines, and the cyclic anhydride **65** (Equation 197) <2003T1805>. The key element in this example is the use of ionic liquids and in other examples of the same reaction strategy, the high diastereoselectivity achieved <2005JOC350>.

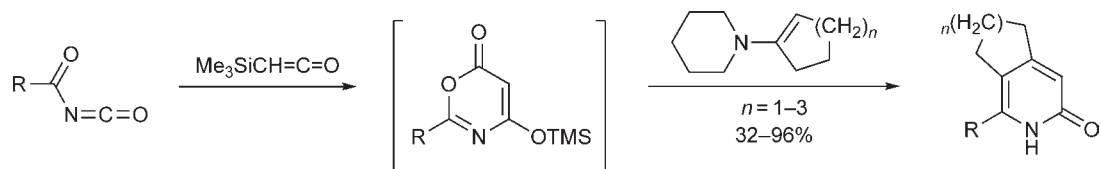
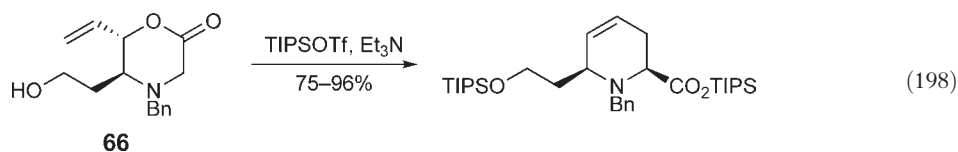


7.05.3.4.2 Oxazines, diazines, and their benzologues

Under Lewis acid catalysis, azapyrylium salts react to form 2,6-disubstituted pyridines (**Scheme 125**) <1995H(40)531>. As part of the synthesis of (–)-methyl palustamate, the oxazinone **66** undergoes a conformationally restricted Claisen rearrangement to the piperidine structure (**Equation 198**) <1998JOC7490>, with additional examples of the same strategy also reported <1997JOC8549>. Fused 2-pyridone structures have been reported from the *in situ* preparation of 1,3-oxazin-6-ones when reacted with the enamines of cycloalkanones (**Scheme 126**) <1996TL4977> – the same intermediate undergoes Diels–Alder reactions to give 2-pyridones <1996TL4973>. Activated methylene chemistry continues to play an important role in heterocycle formation.

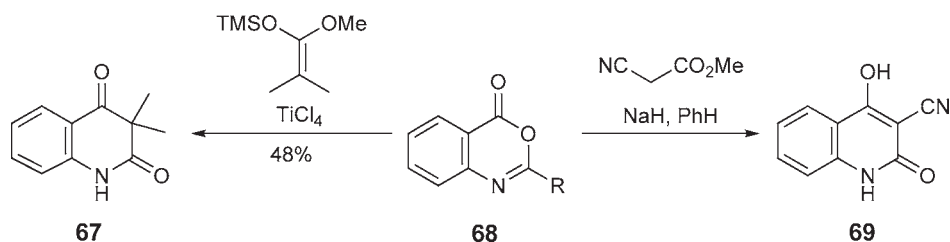


Scheme 125

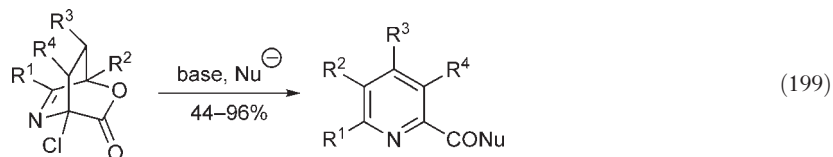


Scheme 126

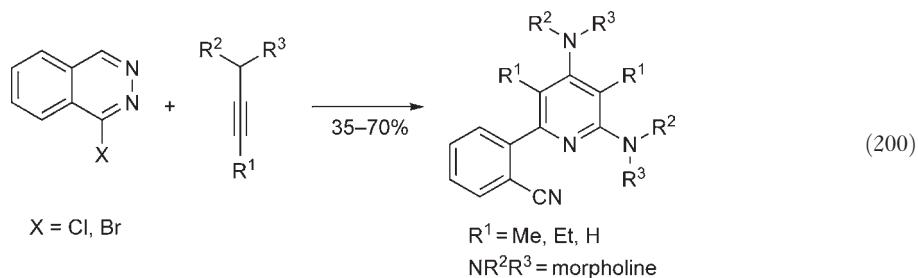
The benzoxazin-2-one **68** reacts with a β -cyano ester to form the 2-quinolone **69** <1999H(51)1543>, whereas the same starting material will react with silyl esters in the presence of Lewis acids leading to quinolinediones of the type **67** <1999OL1953> (**Scheme 127**). Equivalent bicyclic starting materials continue to be used in the synthesis of pyridines by reaction with nucleophiles (**Equation 199**) <1996T2591, 1996T6997, 1996T12529>. In this report, 13 examples are illustrated with substituents including alkyl, aryl, and hetero-functionalities.



Scheme 127

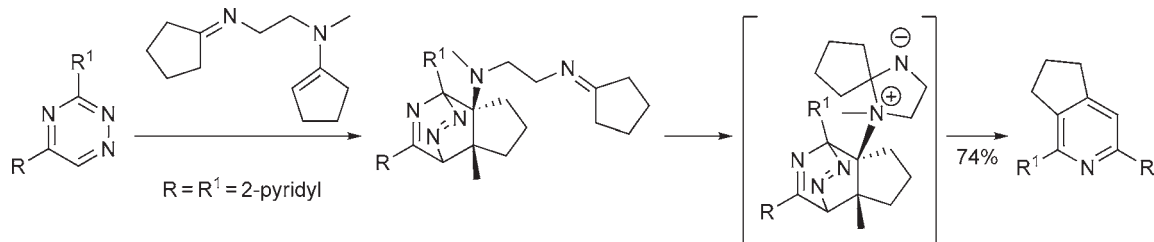


Phthalazines containing halo substituents react with 2 equiv of alkyne and undergo N–N bond cleavage leading to pentasubstituted pyridines (Equation 200) <1996H(43)199>.



7.05.3.4.3 Triazines

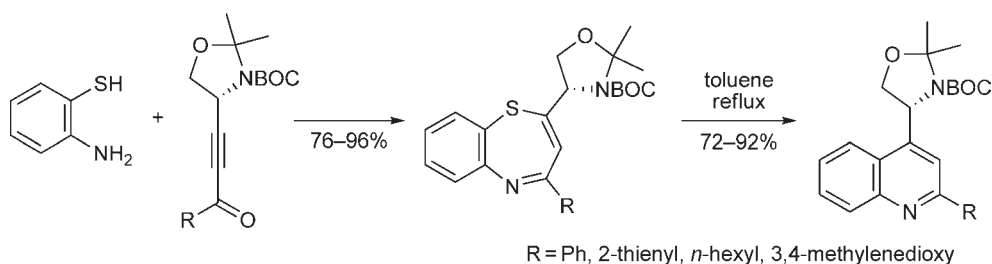
In reaction with cyclic enamines, 1,2,4-triazines have been used to prepare 2,2'-bispyridines <2004T6021> with extensions of this strategy to include a tethered imine–enamine, facilitating the direct conversion of the triazine to the pyridine without the requirement of a separate aromatization step (Scheme 128) <2004CC508>.



Scheme 128

7.05.3.5 From Seven-Membered Rings

Typical sulfur-extrusion reactions can lead to quinolines after an initial cyclocondensation producing the intermediate seven-membered ring (Scheme 129) <2000SL595>. Additional examples generated 2-trifluoromethyl-4-formyl derivatives <1997T641>.



Scheme 129

References

- 1957PCS354 P. M. Maitlis, *Proc. Chem. Soc.*, 1957, 354.
 1984CHEC(2)395 G. Jones; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 2, p. 395.
 1994CB2535 H. Nehl, *Chem. Ber.*, 1994, **127**, 2535.
 1994S1155 P. J. Campos, C.-Q. Tan, J. M. Gonzalez, and M. A. Rodriguez, *Synthesis*, 1994, 1155.
 1994TL9157 D. H. R. Barton, M. M. M. Araújo Pereira, and D. K. Taylor, *Tetrahedron Lett.*, 1994, **35**, 9157.
 1994TL9191 J. J. Fitzgerald, F. E. Michael, and R. A. Olofson, *Tetrahedron Lett.*, 1994, **35**, 9191.
 1995CC1903 R. Grigg, V. Sridharan, and L.-H. Xu, *J. Chem. Soc., Chem. Commun.*, 1995, 1903.
 1995CC2137 U. Beifuss and S. Ledderhose, *J. Chem. Soc., Chem. Commun.*, 1995, 2137.
 1995CHE50 S. A. Yamashkin and I. A. Batanov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1995, **31**, 50.
 1995CL5 H. Kusama, Y. Yamashita, and K. Narasaka, *Chem. Lett.*, 1995, 5.
 1995H(40)511 K. Isomura, H. Kawasaki, K. Takehara, and H. Taniguchi, *Heterocycles*, 1995, **40**, 511.
 1995H(40)531 K. Homann, R. Zimer, and H.-U. Reissig, *Heterocycles*, 1995, **40**, 531.
 1995H(41)1915 F. Palacios, J. Garcia, A. M. Ochoa de Retana, and J. Oyarzabal, *Heterocycles*, 1995, **41**, 1915.
 1995JCM146 F. F. Abdel-Latif and R. M. Shaker, *J. Chem. Res. (S)*, 1995, 146.
 1995JCM392 F. Al-Omran and N. Al-Awadi, *J. Chem. Res. (S)*, 1995, 392.
 1995JCM476 H. Kikukawa and T. Nishiwaki, *J. Chem. Res. (S)*, 1995, 476.
 1995JHC505 D. Heber, I. C. Ivanov, and S. K. Karagiosov, *J. Heterocycl. Chem.*, 1995, **32**, 505.
 1995JOC1763 D. F. Maynard and W. H. Okamura, *J. Org. Chem.*, 1995, **60**, 1763.
 1995JOC2588 A. R. Katritzky, B. Rachwal, and S. Rachwal, *J. Org. Chem.*, 1995, **60**, 2588.
 1995JOC3750 R. Church, R. Trust, J. D. Albright, and D. W. Powell, *J. Org. Chem.*, 1995, **60**, 3750.
 1995JOC3993 A. R. Katritzky, B. Rachwal, and S. Rachwal, *J. Org. Chem.*, 1995, **60**, 3993.
 1995JOC5243 J. B. Campbell and J. W. Firor, *J. Org. Chem.*, 1995, **60**, 5243.
 1995JOC7082 J. T. Kuethe, J. E. Cochran, and A. Padwa, *J. Org. Chem.*, 1995, **60**, 7082.
 1995JOC7369 D. L. Boger and J.-H. Chen, *J. Org. Chem.*, 1995, **60**, 7369.
 1995JOM(488)47 M. Costa, F. S. Dias, G. P. Chiusoli, and G. L. Gazzola, *J. Organomet. Chem.*, 1995, **488**, 47.
 1995JP(1)2393 T. Hudlicky, G. Butora, S. P. Fearnley, A. G. Gum, P. J. Persichini, III, M. R. Stabile, and J. S. Merola, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2393.
 1995JP(1)2739 I. Coldham, A. J. Collis, R. J. Mould, and R. E. Rathmell, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2739.
 1995LA1895 P. Ferrer, C. Avendaño, and M. Söllhuber, *Liebigs Ann. Chem.*, 1995, 1895.
 1995S801 Y. Makioka, T. Shindo, Y. Taniguchi, K. Takaki, and Y. Fujiwara, *Synthesis*, 1995, 801.
 1995SC177 M. N. Deshmukh, U. S. Kumar, and A. V. R. Rao, *Synth. Commun.*, 1995, **25**, 177.
 1995SC1601 M. Elouar, N. Knouzi, A. Elkihel, E. M. Essassi, M. Benchidimi, J. Hamelin, R. Carrié, and R. Danion-Bougot, *Synth. Commun.*, 1995, **25**, 1601.
 1995SL233 S. Kobayashi, M. Araki, H. Ishitani, S. Nagayama, and I. Hachiya, *Synlett*, 1995, 233.
 1995T1575 S. A. Petrich, F. A. Hicks, D. R. Wilkinson, J. G. Tarrant, S. M. Bruno, M. Vargas, K. N. Hosein, J. T. Gupton, and J. A. Sikorski, *Tetrahedron*, 1995, **51**, 1575.
 1995T9119 T. L. Gilchrist, P. D. Kemmitt, and A. L. Germain, *Tetrahedron*, 1995, **51**, 9119.
 1995T12277 A. C. Veronese, R. Callegari, and C. F. Moreli, *Tetrahedron*, 1995, **51**, 12277.
 1995TL59 J. A. R. Rodrigues, G. C. Leiva, and J. D. F. Desousa, *Tetrahedron Lett.*, 1995, **36**, 59.
 1995TL3189 B. Ohtani, S. Kusakabe, K. Okada, S. Tsuru, K. Izawa, Y. Amino, and S.-I. Nishimoto, *Tetrahedron Lett.*, 1995, **36**, 3189.
 1995TL3557 I. Coldham, A. J. Collis, R. J. Mould, and R. E. Rathmell, *Tetrahedron Lett.*, 1995, **36**, 3557.
 1995TL7721 N. M. Williamson, D. R. March, and A. D. Ward, *Tetrahedron Lett.*, 1995, **36**, 7721.
 1995TL8283 P. Molina, A. Pastor, and M. J. Vilaplana, *Tetrahedron Lett.*, 1995, **36**, 8283.
 1995TL8581 O. Peters and W. Friedrichsen, *Tetrahedron Lett.*, 1995, **36**, 8581.
 1995TL8977 R. Tamion, C. Mineur, and L. Ghosez, *Tetrahedron Lett.*, 1995, **36**, 8977.
 1995TL9297 A. S. Kiselyov, *Tetrahedron Lett.*, 1995, **36**, 9297.
 1996ACS623 P. Kolsaker, H. Karlson, and C. Rømming, *Acta Chem. Scand.*, 1996, **50**, 623.
 1996CC2253 E. J. Latham and S. P. Stanforth, *J. Chem. Soc., Chem. Commun.*, 1996, 2253.
 1996CHEC-II(5)167 G. Jones; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 167.

- 1996H(42)141 H. Kohno and Y. Sekine, *Heterocycles*, 1996, **42**, 141.
1996H(43)199 K. Iwamoto, S. Suzuki, E. Oishi, A. Miyashita, and T. Higashino, *Heterocycles*, 1996, **43**, 199.
1996H(43)809 P. Trebse, S. Polanc, M. Kocevar, and T. Solmajer, *Heterocycles*, 1996, **43**, 809.
1996JHC607 A. R. Katritzky and B. Yang, *J. Heterocycl. Chem.*, 1996, **33**, 607.
1996JOC677 M. Ihara, A. Katsumata, F. Setsu, Y. Tokunagu, and F. Fukumoto, *J. Org. Chem.*, 1996, **61**, 677.
1996JOC824 M. F. Gordeev, D. V. Patel, and E. M. Gordon, *J. Org. Chem.*, 1996, **61**, 824.
1996JOC7195 P. J. Campos, C.-Q. Tan, M. A. Rodriguez, and E. Anon, *J. Org. Chem.*, 1996, **61**, 7195.
1996JOC8094 P. Molina, A. Pastor, and M. J. Vilaplana, *J. Org. Chem.*, 1996, **61**, 8094.
1996(JP1)519 M. G. Barlow, L. Sibous, N. N. E. Suliman, and A. E. Tipping, *J. Chem. Soc., Perkin Trans. 1*, 1996, 519.
1996(JP1)967 M. G. Banwell, C. T. Bui, H. T. T. Pham, and G. W. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1996, 967.
1996SC1763 M. U. Koller, A. C. Church, C. L. Griffith, M. A. Hines, R. J. Lachicotte, R. A. Taylor, and C. F. Beam, *Synth. Commun.*, 1996, **26**, 1763.
1996SL34 U. Beifuss, O. Kunz, S. Ledderhose, M. Taraschewski, and C. Tonko, *Synlett*, 1996, 34.
1996T2591 K. J. Dubois, C. C. Fannes, F. Compennolle, and G. J. Hoornaert, *Tetrahedron*, 1996, **52**, 2591.
1996T4433 A. Couture, E. Deniau, P. Grandclaoudon, and P. Woisel, *Tetrahedron*, 1996, **52**, 4433.
1996T6997 K. J. Dubois and G. J. Hoornaert, *Tetrahedron*, 1996, **52**, 6997.
1996T10095 G. Morel, E. Marchand, J.-P. Pradère, L. Toupet, and S. Sinbandhit, *Tetrahedron*, 1996, **52**, 10095.
1996T10225 S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro, and P. Pace, *Tetrahedron*, 1996, **52**, 10225.
1996T11529 C. Copéret, S. Ma, T. Sugihara, and E. Negishi, *Tetrahedron*, 1996, **52**, 11529.
1996T11643 A. Franz, P.-Y. Eschler, M. Tharin, and R. Neier, *Tetrahedron*, 1996, **52**, 11643.
1996T12529 K. J. Dubois, C. C. Fannes, S. M. Toppet, and G. J. Hoornaert, *Tetrahedron*, 1996, **52**, 12529.
1996TL4369 G. Gosmann, D. Guillaume, and H.-P. Husson, *Tetrahedron Lett.*, 1996, **37**, 4369.
1996TL4655 L. Strekowski, S.-Y. Lin, H. Lee, and J. C. Mason, *Tetrahedron Lett.*, 1996, **37**, 4655.
1996TL4973 K. Takaoka, T. Aoyama, and T. Shioiri, *Tetrahedron Lett.*, 1996, **37**, 4973.
1996TL4977 K. Takaoka, T. Aoyama, and T. Shioiri, *Tetrahedron Lett.*, 1996, **37**, 4977.
1996TL5917 K. Kubo, S. Yaegashi, K. Susaki, T. Sakurai, and H. Inoue, *Tetrahedron Lett.*, 1996, **37**, 5917.
1996TL6379 F. Palacios and G. Rubiales, *Tetrahedron Lett.*, 1996, **37**, 6379.
1997ACS1024 P. Somfai, T. Jarevang, U. M. Lindstrom, and A. Svensson, *Acta Chem. Scand.*, 1997, **51**, 1024.
1997AGE2036 M. Schuster and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2036.
1997H(45)1551 K. I. Iwamoto, E. Oishi, T. Sano, A. Tsuchiya, Y. Suzuki, T. Higashino, and A. Miyashita, *Heterocycles*, 1997, **45**, 1551.
1997JA6984 S. Okamoto, M. Iwakubo, K. Kobayashi, and F. Sato, *J. Am. Chem. Soc.*, 1997, **119**, 6984.
1997JHC325 J.-G. Jun and T. H. Ha, *J. Heterocycl. Chem.*, 1997, **34**, 325.
1997JHC1259 A. R. Katritzky, D. A. Nichols, M. Qi, and B. Yang, *J. Heterocycl. Chem.*, 1997, **34**, 1259.
1997JOC67 A. Padwa, M. A. Brodney, J. P. Marino, Jr., M. H. Osterhout, and A. T. Price, *J. Org. Chem.*, 1997, **62**, 67.
1997JOC438 S. M. Sheehan and A. Padwa, *J. Org. Chem.*, 1997, **62**, 438.
1997JOC1146 F. Palacios, C. Alonso, and G. Rubiales, *J. Org. Chem.*, 1997, **62**, 1146.
1997JOC6210 A. R. Katritzky, M. Belyakov, A. E. Sorochinsky, S. A. Henderson, and J. Chen, *J. Org. Chem.*, 1997, **62**, 6210.
1997JOC8549 S. R. Angle and R. M. Henry, *J. Org. Chem.*, 1997, **62**, 8549.
1997(JP1)741 Y.-M. Xu and W.-S. Zhou, *J. Chem. Soc., Perkin Trans. 1*, 1997, 741.
1997(JP1)2291 H. Ishibashi, H. Kawanami, H. Nagakawa, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2291.
1997(JP1)2577 J. S. Mahantky, M. De, and N. G. Kundu, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2577.
1997(JP1)2807 U. Beifuss and M. Taraschewski, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2807.
1997LA573 J. Wilken, M. Kosseljans, W. Saak, D. Haase, S. Pohl, and J. Martens, *Liebigs Ann. Chem.*, 1997, 573.
1997LA1407 L. F. Tietze, O. Burkhardt, and M. Henrich, *Liebigs Ann. Chem.*, 1997, 1407.
1997LA2197 S. I. Kozhushkov, M. Brandl, D. S. Yufit, R. Machinek, and A. de Meijere, *Liebigs Ann. Chem.*, 1997, 2197.
1997M927 I. Yavari, A. A. Esmaili, A. Ramazani, and A. R. Bolbol-Amiri, *Monatsh. Chem.*, 1997, **128**, 927.
1997OPP330 S. D. Barrett, J. C. Jaen, B. W. Caprathe, A. J. Thomas, and H. Tecle, *Org. Prep. Proced. Int.*, 1997, **29**, 330.
1997OPP485 F. Degiorgis, M. Lombardo, and C. Trombini, *Org. Prep. Proced. Int.*, 1997, **29**, 485.
1997S963 P. Molina, A. Vidal, and F. Tovar, *Synthesis*, 1997, 963.
1997S1151 M. Weymann, W. Pfrengle, D. Schollmeyer, and H. Kunz, *Synthesis*, 1997, 1151.
1997SL285 J. I. Ubeda, M. Villacampa, and C. Avendano, *Synlett*, 1997, 285.
1997SL547 J. H. Rigby and V. Gupta, *Synlett*, 1997, 547.
1997SL799 C. Agami, D. Bihan, R. Morgentin, and C. Puchot-Kadouri, *Synlett*, 1997, 799.
1997T641 T. Masquelin and D. Obrecht, *Tetrahedron*, 1997, **53**, 641.
1997T2449 J. Y. Lee, Y. S. Lee, B. Y. Chung, and H. Park, *Tetrahedron*, 1997, **53**, 2449.
1997T3045 Y. S. Lee, S. S. Kang, J. H. Choi, and H. Park, *Tetrahedron*, 1997, **53**, 3045.
1997T4521 J. Barluenga, M. Ferrero, and F. Palacios, *Tetrahedron*, 1997, **53**, 4521.
1997T5423 K. Ishimaru, Y. Yamamoto, and K.-Y. Akiba, *Tetrahedron*, 1997, **53**, 5423.
1997T6611 G. L. Bolton, J. C. Hodges, and J. R. Rubin, *Tetrahedron*, 1997, **53**, 6611.
1997T9715 R. Annunziata, M. Cinquini, F. Cozzi, V. Molteni, and O. Schupp, *Tetrahedron*, 1997, **53**, 9715.
1997T15051 M. Frederickson, R. Grigg, J. Markandu, M. Thornton-Pett, and J. Redpath, *Tetrahedron*, 1997, **53**, 15051.
1997T16241 V. Gracias, K. E. Frank, G. L. Milligan, and J. Aube, *Tetrahedron*, 1997, **53**, 16241.
1997T16327 D. L. Comins, P. M. Thakker, and M. F. Baevsky, *Tetrahedron*, 1997, **53**, 16327.
1997T16565 B. N. Naidu and F. G. West, *Tetrahedron*, 1997, **53**, 16565.
1997TA2893 G. Vidari, M. Tripolini, P. Novella, P. Allegrucci, and L. Garlaschelli, *Tetrahedron Asymmetry*, 1997, **8**, 2893.
1997TA2975 L. Battistini, F. Zanardi, G. Rassu, P. Spanu, G. Pelosi, G. G. Fava, M. B. Ferrari, and G. Casiraghi, *Tetrahedron Asymmetry*, 1997, **8**, 2975.
1997TL677 F. P. J. T. Rutjes and H. E. Schoemaker, *Tetrahedron Lett.*, 1997, **38**, 677.
1997TL2547 R. Badorey, C. Cativiela, M. D. Diaz-de-Villegas, and J. A. Galvez, *Tetrahedron Lett.*, 1997, **38**, 2547.

- 1997TL2829 S. Kirschbaum and H. Waldmann, *Tetrahedron Lett.*, 1997, **38**, 2829.
1997TL3931 Y. Sato, N. Saito, and M. Mori, *Tetrahedron Lett.*, 1997, **38**, 3931.
1997TL3981 J. Barluenga, M. Tomas, J. A. Lopez-Pelegrin, and E. Rubio, *Tetrahedron Lett.*, 1997, **38**, 3981.
1997TL5907 A. F. Parsons and R. M. Pettifer, *Tetrahedron Lett.*, 1997, **38**, 5907.
1997TL7387 M.-C. P. Yeh, C.-N. Chuang, and C.-H. Yiu, *Tetrahedron Lett.*, 1997, **38**, 7387.
1997TL7469 I. Kadota, M. Kawada, Y. Muramatsu, and Y. Yamamoto, *Tetrahedron Lett.*, 1997, **38**, 7469.
1997ZNB851 G. Seitz and J. Seigl, *Z. Naturforsch. B*, 1997, **52**, 851.
1998AGE1562 M. Schmittel, J.-P. Steffen, M. A. W. Angel, B. Engels, C. Lennartz, and M. Hanrath, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1562.
1998AGE2371 M. Schmittel, J.-P. Steffen, B. Engels, C. Lennartz, and M. Hanrath, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 2371.
1998BCJ2945 K. Uchiyama, A. Ono, Y. Hayashi, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 2945.
1998CC2053 S. N. Osipov, C. Bruneau, M. Picquet, A. F. Kolomiets, and P. H. Dixneuf, *J. Chem. Soc., Chem. Commun.*, 1998, 2053.
1998CC2563 O. B. Familoni, P. T. Kaye, and P. J. Klaas, *J. Chem. Soc., Chem. Commun.*, 1998, 2563.
1998CL437 A. Ono, K. Uchiyama, Y. Hayashi, and K. Narasaka, *Chem. Lett.*, 1998, 437.
1998CPB332 J. Koyama, I. Toyokuni, and K. Tagahara, *Chem. Pharm. Bull.*, 1998, **46**, 332.
1998CPB430 T. Shinohara, A. Takeda, J. Toda, and T. Sano, *Chem. Pharm. Bull.*, 1998, **46**, 430.
1998EJO435 P. Bravo, M. Crucianelli, A. Farina, S. V. Meille, A. Volonterio, and M. Zanda, *Eur. J. Org. Chem.*, 1998, 435.
1998EJO2461 C. Agami, D. Bihan, L. Hamon, C. Kadouri-Puchot, and M. Lusinch, *Eur. J. Org. Chem.*, 1998, 2461.
1998EJO2583 J. J. N. Veerman, J. H. van Maarseveen, G. M. Visser, C. G. Kruse, H. E. Schoemaker, H. Hiemstra, and F. P. J. T. Rutjes, *Eur. J. Org. Chem.*, 1998, 2583.
1998H(47)517 F. Palacios, A. M. O. de Retana, and J. Oyarzabal, *Heterocycles*, 1998, **47**, 517.
1998H(48)507 V. Bardot, D. Gardette, Y. Gelas-Mialhe, J.-C. Gramain, and R. Remuson, *Heterocycles*, 1998, **48**, 507.
1998H(48)981 T. Shinohara, A. Takeda, J. Toda, and T. Sano, *Heterocycles*, 1998, **48**, 981.
1998H(48)1103 K. Nishiyama, H. Kubo, T. Sato, K. Higashiyama, and S. Ohmiya, *Heterocycles*, 1998, **48**, 1103.
1998H(48)2551 N. Kanomata and T. Nakata, *Heterocycles*, 1998, **48**, 2551.
1998JA4520 W. T. Lai, F.-C. Lai, G.-H. Lee, S.-M. Ping, and R.-S. Liu, *J. Am. Chem. Soc.*, 1998, **120**, 4520.
1998JCM398 L. Zhou, S. Tu, D. Shi, and G. Dai, *J. Chem. Res. (S)*, 1998, 398.
1998JCM796 M. Hadden and P. J. Stevenson, *J. Chem. Res. (S)*, 1998, 796.
1998JHC467 A. R. Katritzky, D. Semenzin, B. Yang, and D. P. M. Pleyner, *J. Heterocycl. Chem.*, 1998, **35**, 467.
1998JOC841 X.-D. Wu, S.-K. Khim, X. G. Zhang, E. M. Cederstrom, and P. S. Mariano, *J. Org. Chem.*, 1998, **63**, 841.
1998JOC860 H. J. Kim, U. C. Yoon, Y.-S. Jung, N. S. Park, E. M. Cederstrom, and P. S. Mariano, *J. Org. Chem.*, 1998, **63**, 860.
1998JOC1144 A. Padwa, R. Hennig, C. O. Kappe, and T. S. Reger, *J. Org. Chem.*, 1998, **63**, 1144.
1998JOC2154 R. C. Larock, Y. He, W. W. Leong, X. Han, M. D. Refvik, and J. M. Zenner, *J. Org. Chem.*, 1998, **63**, 2154.
1998JOC3158 J. F. Miller, A. Termin, K. Koch, and A. D. Piscopio, *J. Org. Chem.*, 1998, **63**, 3158.
1998JOC3517 C. Shi and K. K. Wang, *J. Org. Chem.*, 1998, **63**, 3517.
1998JOC4554 J. Cossy, C. Poitevin, D. G. Pardo, J.-L. Peglion, and A. Dessinges, *J. Org. Chem.*, 1998, **63**, 4554.
1998JOC5193 H. Togo, Y. Hoshina, T. Muraki, H. Nakayama, and M. Yokoyama, *J. Org. Chem.*, 1998, **63**, 5193.
1998JOC5306 K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 1998, **63**, 5306.
1998JOC6778 A. Padwa, T. M. Heidelbaugh, J. T. Kuethe, and M. S. McClure, *J. Org. Chem.*, 1998, **63**, 6778.
1998JOC7490 S. R. Angle and R. M. Henry, *J. Org. Chem.*, 1998, **63**, 7490.
1998JOC7840 A. R. Renslo and R. L. Danheiser, *J. Org. Chem.*, 1998, **63**, 7840.
1998JOC8074 N. Martin, A. Martinez-Grau, L. Sanchez, C. Seoane, and M. Torres, *J. Org. Chem.*, 1998, **63**, 8074.
1998J(P1)807 J.-P. Strachan, J. T. Sharp, and S. Parsons, *J. Chem. Soc., Perkin Trans. 1*, 1998, 807.
1998J(P1)2899 L. Zhou and Y. Zhang, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2899.
1998JPR309 H. Walter, *J. Prakt. Chem.*, 1998, **340**, 309.
1998S162 T. Wirth and G. Fragale, *Synthesis*, 1998, 162.
1998SC3249 L. Zhou and Y. Zhang, *Synth. Commun.*, 1998, **28**, 3249.
1998SL652 C. Schneider and C. Borner, *Synlett*, 1998, 652.
1998SL921 K.-T. Kang, E. H. Kim, W. J. Kim, N. S. Song, J. K. Shin, and B. Y. Cho, *Synlett*, 1998, 921.
1998T1647 F. Palacios, D. Aparicio, and J. Garcia, *Tetrahedron*, 1998, **54**, 1647.
1998T2607 Z. Wrobel, *Tetrahedron*, 1998, **54**, 2607.
1998T6929 P. J. Campos, E. Anon, M. C. Malo, C.-Q. Tan, and M. A. Rodriguez, *Tetrahedron*, 1998, **54**, 6929.
1998T9961 R. C. Larock, P. Pace, H. Yang, C. E. Russell, S. Cacchi, and G. Fabrizi, *Tetrahedron*, 1998, **54**, 9961.
1998T10309 C. Agami, D. Bihan, L. Hamon, and C. Puchot-Kadouri, *Tetrahedron*, 1998, **54**, 10309.
1998T11027 H. Junge and G. Oehme, *Tetrahedron*, 1998, **54**, 11027.
1998T14113 P. J. Campos, E. Anon, M. C. Malo, and M. A. Rodriguez, *Tetrahedron*, 1998, **54**, 14113.
1998TA1137 D. Ma and J. Jiang, *Tetrahedron Asymmetry*, 1998, **9**, 1137.
1998TL627 S. S. Park, J.-K. Choi, E. K. Yum, and D.-C. Ha, *Tetrahedron Lett.*, 1998, **39**, 627.
1998TL1885 R. C. Larock, H. Yang, P. Pace, S. Cacchi, and G. Fabrizi, *Tetrahedron Lett.*, 1998, **39**, 1885.
1998TL2515 R. C. Larock, P. Pace, and H. Yang, *Tetrahedron Lett.*, 1998, **39**, 2515.
1998TL2549 J. Sauer and D. K. Heldmann, *Tetrahedron Lett.*, 1998, **39**, 2549.
1998TL2965 J. Cossy, C. Poitevin, D. G. Pardo, J.-L. Peglion, and A. Dessinges, *Tetrahedron Lett.*, 1998, **39**, 2965.
1998TL4083 K. Kubo, Y. Ishii, T. Sakurai, and M. Makino, *Tetrahedron Lett.*, 1998, **39**, 4083.
1998TL4761 S. M. Sheehan, L. S. Beall, and A. Padwa, *Tetrahedron Lett.*, 1998, **39**, 4761.
1998TL5139 J. P. Edwards, J. D. Ringgenberg, and T. K. Jones, *Tetrahedron Lett.*, 1998, **39**, 5139.
1998TL5421 M. Meguro and Y. Yamamoto, *Tetrahedron Lett.*, 1998, **39**, 5421.
1998TL5971 H. Yokoyama, K. Otake, S. Yamaguchi, and Y. Hirai, *Tetrahedron Lett.*, 1998, **39**, 5971.
1998TL6175 J.-M. Campagne and L. Ghosez, *Tetrahedron Lett.*, 1998, **39**, 6175.
1998TL6687 G. R. Pabst and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 6687.

- 1998TL6691 G. R. Pabst, K. Schmid, and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 6691.
1998TL6711 H. Sauriat-Dorizon and F. Guibe, *Tetrahedron Lett.*, 1998, **39**, 6711.
1998TL7295 N. Cholleton and S. Z. Zard, *Tetrahedron Lett.*, 1998, **39**, 7295.
1998TL8817 O. C. Pfüller and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 8817.
1998TL8821 O. C. Pfüller and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 8821.
1998TL8825 G. R. Pabst, O. C. Pfüller, and J. Sauer, *Tetrahedron Lett.*, 1998, **39**, 8825.
1998TL9447 O. Calvez, A. Chiaroni, and N. Langlois, *Tetrahedron Lett.*, 1998, **39**, 9447.
1998TL9563 A. D. Abell, J. Gardiner, A. J. Phillips, and W. T. Robinson, *Tetrahedron Lett.*, 1998, **39**, 9563.
1999AG(E)1928 H. Steinhagen and E. J. Corey, *Angew. Chem. Int. Ed. Engl.*, 1999, **38**, 1928.
1999CPB241 Y. Kita, M. Egi, M. Ohtsubo, T. Saiki, A. Okajima, T. Takada, and H. Tohma, *Chem. Pharm. Bull.*, 1999, **47**, 241.
1999EJO503 B. Wunsch and S. Nerdinger, *Eur. J. Org. Chem.*, 1999, 503.
1999EJO937 I. L. Baraznenok, V. G. Nenajdenko, and E. S. Balenkova, *Eur. J. Org. Chem.*, 1999, 937.
1999EJO959 U. K. Pandit, H. S. Overkleef, B. C. Borer, and H. Bieräugel, *Eur. J. Org. Chem.*, 1999, 959.
1999EJO1517 I. Ripoché, J.-L. Canet, J. Gelas, and Y. Troin, *Eur. J. Org. Chem.*, 1999, 1517.
1999EJO1693 J. Cossy, C. Dumas, and D. G. Pardo, *Eur. J. Org. Chem.*, 1999, 1693.
1999H(50)791 C. B. Vicentini, M. Manfrini, M. Mazzanti, and A. C. Veronese, *Heterocycles*, 1999, **50**, 791.
1999H(51)103 H. Kohno and K. Yamada, *Heterocycles*, 1999, **51**, 103.
1999H(51)119 T. Shinohara, A. Takeda, J. Toda, M. Kohno, and T. Sano, *Heterocycles*, 1999, **51**, 119.
1999H(51)1543 C. Mitsos, A. Zografos, and O. Igglessi-Markopoulou, *Heterocycles*, 1999, **51**, 1543.
1999H(51)2171 P. Sanna, A. Carta, and G. Paglietti, *Heterocycles*, 1999, **51**, 2171.
1999H(51)2711 T. Kiguchi, M. Okazaki, and T. Naito, *Heterocycles*, 1999, **51**, 2711.
1999JA11093 T. Takahashi, F.-Y. Tsai, Y. Li, K. Nakajima, and M. Kitora, *J. Am. Chem. Soc.*, 1999, **121**, 11093.
1999JCM6 G. H. Elgemeie, A. H. H. Elghandour, H. A. Ali, and H. M. Abdel-Azzez, *J. Chem. Res. (S)*, 1995, 6.
1999JFC(94)7 E. Leyva, E. Monreal, and A. Hernández, *J. Fluorine Chem.*, 1999, **94**, 7.
1999JOC2003 T. Naito, K. Nakagawa, T. Nakamura, A. Kasei, I. Ninomiya, and T. Kiguchi, *J. Org. Chem.*, 1999, **64**, 2003.
1999JOC3595 A. Padwa, M. A. Brodney, B. Liu, K. Satake, and T. Wu, *J. Org. Chem.*, 1999, **64**, 3595.
1999(JP)179 C. Locher and N. Peerzada, *J. Chem. Soc., Perkin Trans. 1*, 1999, 179.
1999NJC641 C. Boix, J. M. de la Fuente, and M. Poliakoff, *New J. Chem.*, 1999, **23**, 641.
1999OL553 K. R. Roesch and R. C. Larock, *Org. Lett.*, 1999, **1**, 553.
1999OL717 F. P. J. T. Rutjes, K. C. M. F. Tjen, L. B. Wolf, W. F. J. Karstens, H. E. Schoemaker, and H. Hiemstra, *Org. Lett.*, 1999, **1**, 717.
1999OL767 M.-J. Wu, C.-F. Lin, and S.-H. Chen, *Org. Lett.*, 1999, **1**, 767.
1999OL1953 A. L. Zografos, C. A. Mitsos, and O. Igglessi-Markopoulou, *Org. Lett.*, 1999, **1**, 1953.
1999OL1977 M. Sugimoto, T. Fukuda, and Y. Ito, *Org. Lett.*, 1999, **1**, 1977.
1999OL1997 H. Ratni and E. P. Kündig, *Org. Lett.*, 1999, **1**, 1997.
1999S1889 S. D. Koulocheri and S. A. Haroutounian, *Synthesis*, 1999, 1889.
1999SL324 S.-K. Kang, T.-G. Baik, and A. N. Kulak, *Synlett*, 1999, 324.
1999SL401 S. Cacchi, G. Fabrizi, and F. Marinelli, *Synlett*, 1999, 401.
1999SL626 H. Ratni, B. Crousse, and E. P. Kündig, *Synlett*, 1999, 626.
1999T5947 F. Palacios, A. M. O. de Ratana, and J. Oyarzabal, *Tetrahedron*, 1999, **55**, 5947.
1999T8179 R. Stragies and S. Blechert, *Tetrahedron*, 1999, **55**, 8179.
1999T13193 M.-J. Wu, L.-J. Chang, L.-M. Wei, and C.-F. Lin, *Tetrahedron*, 1999, **55**, 13193.
1999T13233 A. Arcadi, F. Marinelli, and E. Rossi, *Tetrahedron*, 1999, **55**, 13233.
1999TA221 D. Taniyama, M. Hasegawa, and K. Tomioka, *Tetrahedron Asymmetry*, 1999, **10**, 221.
1999TA255 A. R. Katritzky, J. Cobo-Domingo, B. Yang, and P. J. Steel, *Tetrahedron Asymmetry*, 1999, **10**, 255.
1999TA3649 L.-X. Liao, Z.-M. Wang, H.-X. Zhang, and W.-S. Zhou, *Tetrahedron Asymmetry*, 1999, **10**, 3649.
1999TL1145 K. H. Park, H. S. Joo, S. W. Kim, M. S. Park, and P. S. Shin, *Tetrahedron Lett.*, 1999, **40**, 1145.
1999TL1149 H. Ishibashi, M. Inomata, M. Ohba, and M. Ikeda, *Tetrahedron Lett.*, 1999, **40**, 1149.
1999TL2125 X. Hoang-Cong, B. Quiclet-Sire, and S. Z. Zard, *Tetrahedron Lett.*, 1999, **40**, 2125.
1999TL3137 A. G. Griesbeck, H. Heckroth, and H. Schmickler, *Tetrahedron Lett.*, 1999, **40**, 3137.
1999TL4255 J. J. H. Diederer, R. W. Sinkeldam, H. W. Frijhauf, H. Hiemstra, and K. Vrieze, *Tetrahedron Lett.*, 1999, **40**, 4255.
1999TL4969 C. C. Silveira, C. R. Bernardi, A. L. Braga, and T. S. Kaufman, *Tetrahedron Lett.*, 1999, **40**, 4969.
1999TL5331 M. Shirai, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, 1999, **40**, 5331.
1999TL5987 P. Wessig, *Tetrahedron Lett.*, 1999, **40**, 5987.
1999TL6869 S. D. Koulocheri and S. A. Haroutounian, *Tetrahedron Lett.*, 1999, **40**, 6869.
1999TL7211 I. A. Motorina and D. S. Grierson, *Tetrahedron Lett.*, 1999, **40**, 7211.
1999TL7215 I. A. Motorina and D. S. Grierson, *Tetrahedron Lett.*, 1999, **40**, 7215.
1999TL7935 J. Hiebl, H. Kollmann, S. H. Levinson, P. Offen, S. B. Shetzline, and R. Badlani, *Tetrahedron Lett.*, 1999, **40**, 7935.
2000AGE1937 M. F. Hentemann, J. G. Allen, and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 1937.
2000BML1413 S. Kotha and N. Sreenivasachary, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1413.
2000CC503 S. Kotha and N. Sreenivasachary, *J. Chem. Soc., Chem. Commun.*, 2000, 503.
2000CC933 U. Anwar, R. Grigg, and V. Sridharan, *J. Chem. Soc., Chem. Commun.*, 2000, 933.
2000CC1027 M. D. Groaning and A. I. Meyers, *J. Chem. Soc., Chem. Commun.*, 2000, 1027.
2000CC1501 H. Ovaa, G. A. van der Marel, J. H. van Boom, R. Stragies, and S. Blechert, *J. Chem. Soc., Chem. Commun.*, 2000, 1501.
2000CPB436 T. Koike, Y. Shinohara, N. Ishibashi, N. Takeuchi, and S. Tobinaga, *Chem. Pharm. Bull.*, 2000, **48**, 436.
2000CPB1593 M. Arisawa, M. Takahashi, E. Takezawa, T. Yamaguchi, Y. Torisawa, A. Nishida, and M. Nakagawa, *Chem. Pharm. Bull.*, 2000, **48**, 1593.
2000H(52)121 R. W. Hoffmann and D. Bruckner, *Heterocycles*, 2000, **52**, 121.
2000H(52)137 M. Shimizu, A. Arai, and T. Fujisawa, *Heterocycles*, 2000, **52**, 137.

- 2000JA2944 J. G. Knight, S. W. Ainge, A. M. Harm, S. J. Harwood, H. I. Maughan, D. R. Armour, D. M. Hollinshead, and A. A. Jaxa-Chamiec, *J. Am. Chem. Soc.*, 2000, **122**, 2944.
- 2000JA4994 T. Takamura, F.-Y. Tsai, and M. Kitora, *J. Am. Chem. Soc.*, 2000, **122**, 4994.
- 2000JOC235 A. Padwa and A. G. Waterson, *J. Org. Chem.*, 2000, **65**, 235.
- 2000JOC2684 A. Padwa, L. S. Beall, T. M. Heidelbaugh, B. Liu, and S. M. Sheehan, *J. Org. Chem.*, 2000, **65**, 2684.
- 2000JOC2847 R. A. Bunce, D. M. Herron, and M. L. Ackerman, *J. Org. Chem.*, 2000, **65**, 2847.
- 2000JOC3148 S. Talukdar, C.-T. Chen, and J.-M. Fang, *J. Org. Chem.*, 2000, **65**, 3148.
- 2000JOC7158 W. H. Pearson and W.-K. Fang, *J. Org. Chem.*, 2000, **65**, 7158.
- 2000JOC8415 I. W. Davies, J. F. Marcoux, E. G. Corley, M. Jourmet, D.-W. Cai, M. Palucki, J. Wu, R. D. Larsen, K. Rossen, P. J. Pye, L. DiMichele, P. Dormer, and P. J. Reider, *J. Org. Chem.*, 2000, **65**, 8415.
- 2000J(P1)641 I. Lenoir and M. L. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2000, 641.
- 2000OL343 J. N. Kim, K. Y. Lee, H. S. Kim, and T. Y. Kim, *Org. Lett.*, 2000, **2**, 343.
- 2000OL1847 D. L. Wright, J. P. Schulte, II, and M. A. Page, *Org. Lett.*, 2000, **2**, 1847.
- 2000OL2955 T. Ozawa, S. Aoyagi, and C. Kibayashi, *Org. Lett.*, 2000, **2**, 2955.
- 2000OL3131 A. W. Fatland and B. E. Eaton, *Org. Lett.*, 2000, **2**, 3131.
- 2000OL3715 J. Tailor and D. G. Hall, *Org. Lett.*, 2004, 3715.
- 2000OL3901 F. A. Davis, P. K. Mohanty, D. M. Burns, and Y. W. Andemichael, *Org. Lett.*, 2000, **2**, 3901.
- 2000OL3971 U. Voightmann and S. Blechert, *Org. Lett.*, 2000, **2**, 3971.
- 2000OL4007 D. C. Bland, B. C. Raudenbush, and S. M. Weinreb, *Org. Lett.*, 2000, **2**, 4007.
- 2000S893 U. Voightmann and S. Blechert, *Synthesis*, 2000, 893.
- 2000SL242 F. Minassian, N. Pelloux-Leon, and Y. Vallee, *Synlett*, 2000, 242.
- 2000SL595 G. Cabarrocas, S. Rafel, M. Ventura, and J. M. Villagordo, *Synlett*, 2000, 595.
- 2000SL625 E. V. Tarasov, A. Henckens, and E. Ceulemans, *Synlett*, 2000, 625.
- 2000SL1160 H. Laurent-Robert, B. Garrigues, and J. Dubac, *Synlett*, 2000, 1160.
- 2000T1569 A. Diaz-Ortiz, J. R. Carrillo, F. P. Cossio, M. J. Gómez-Escalonilla, A. de la Hoz, A. Moreno, and P. Prieto, *Tetrahedron*, 2000, **56**, 1569.
- 2000T4817 E. M. Beccalli, F. Clerici, and M. L. Gelmi, *Tetrahedron*, 2000, **56**, 4817.
- 2000TL2027 D. J. Wallace, C. J. Cowden, D. J. Kennedy, M. S. Ashwook, I. F. Cottrell, and U.-H. Dolling, *Tetrahedron Lett.*, 2000, **41**, 2027.
- 2000TL4113 C. Agami, F. Couty, and N. Rabasso, *Tetrahedron Lett.*, 2000, **41**, 4113.
- 2000TL5715 T. Shimizu, K. Tanino, and I. Kuwajima, *Tetrahedron Lett.*, 2000, **41**, 5715.
- 2000TL7125 R. Grigg, A. Liu, D. Shaw, S. Suganthan, D. E. Woodall, and G. Yoganathan, *Tetrahedron Lett.*, 2000, **41**, 7125.
- 2000TL10251 M. Ohba, R. Izuta, and E. Shimizu, *Tetrahedron Lett.*, 2000, **41**, 10251.
- 2001CC1784 J. F. Hayes, M. Shipman, and H. Twin, *J. Chem. Soc., Chem. Commun.*, 2001, 1784.
- 2001H(55)741 T. Hirota, K.-I. Tomita, K. Sasaki, K. Okuda, M. Yoshida, and S. Kahino, *Heterocycles*, 2001, **55**, 741.
- 2001JA1817 R. Pedrosa, C. Andres, J. M. Iglesias, and A. Perez-Encabo, *J. Am. Chem. Soc.*, 2001, **123**, 1817.
- 2001JOC243 R. Pedrosa, C. Andres, and J. M. Iglesias, *J. Org. Chem.*, 2001, **66**, 243.
- 2001JOC2175 J. A. Nieman and M. D. Ennis, *J. Org. Chem.*, 2001, **66**, 2175.
- 2001JOC8042 K. R. Roesch, H. Zhang, and R. C. Larock, *J. Org. Chem.*, 2001, **66**, 8042.
- 2001JOM(624)359 K. Pachamuthu and Y. D. Vankar, *J. Organomet. Chem.*, 2001, **624**, 359.
- 2001OL209 I. W. Davies, J.-F. Marcoux, and P. J. Reider, *Org. Lett.*, 2001, **3**, 209.
- 2001OL631 T. Honda, H. Namika, and F. Satoh, *Org. Lett.*, 2001, **3**, 631.
- 2001OL877 X. S. Sun, P. Janvier, G. Zhao, H. Bienaymé, and J. Zhu, *Org. Lett.*, 2001, **3**, 877.
- 2001OL1973 G. Sundararajan, N. Prabakaran, and B. Varghese, *Org. Lett.*, 2001, **3**, 1973.
- 2001OL2053 I. Gallou-Dagommer, P. Gastaud, and T. V. RajanBabu, *Org. Lett.*, 2001, **3**, 2053.
- 2001OL2117 Y. Yamamoto, H. Takagishi, and K. Itoh, *Org. Lett.*, 2001, **3**, 2117.
- 2001OL2133 M. P. S. Ishar, K. Kumar, S. Kaur, S. Kumar, N. K. Girdhar, S. Sachar, A. Marwaha, and A. Kapoor, *Org. Lett.*, 2001, **3**, 2133.
- 2001OL2973 Q. Huang, J. A. Hunter, and R. C. Larock, *Org. Lett.*, 2001, **3**, 2973.
- 2001OL3381 R. G. Arayas, A. Alcudia, and L. S. Liebeskind, *Org. Lett.*, 2001, **3**, 3381.
- 2001OL4035 G. Dai and R. C. Larock, *Org. Lett.*, 2001, **3**, 4035.
- 2001S1351 N. J. Tom and E. M. Ruel, *Synthesis*, 2001, 1351.
- 2001S1716 T. Ooi, M. Takeuchi, and K. Maruoka, *Synthesis*, 2001, 1716.
- 2001SL621 S. N. Osipov, N. M. Kobelkova, G. T. Shchetnikov, A. F. Kolomiets, C. Bruneau, and P. H. Dixneuf, *Synlett*, 2001, 621.
- 2001SL1596 S. J. Hedley, W. J. Moran, A. H. G. P. Prenzel, D. A. Price, and J. P. A. Harrity, *Synlett*, 2001, 1596.
- 2001T5393 C. Agami, F. Couty, and N. Rabasso, *Tetrahedron*, 2001, **57**, 5393.
- 2001T5615 M. Hadden, M. Nieuwenhuyzen, D. Potts, P. J. Stevenson, and N. Thompson, *Tetrahedron*, 2001, **57**, 5615.
- 2001T6399 S. K. Bertilson, J. K. Ekegren, S. A. Modin, and P. G. Andersson, *Tetrahedron*, 2001, **57**, 6399.
- 2001TA817 Y. Banba, C. Abe, H. Nemoto, A. Kato, I. Adachi, and H. Takahata, *Tetrahedron Asymmetry*, 2001, **12**, 817.
- 2001TA2269 R. Kumareswaran and A. Hassner, *Tetrahedron Asymmetry*, 2001, **12**, 2269.
- 2001TL1847 V. B. Hegde, J. M. Renga, and J. M. Owen, *Tetrahedron Lett.*, 2001, **42**, 1847.
- 2001TL6223 J. Lee, T. Hoang, S. Lewis, S. A. Weissman, D. Askin, R. P. Volante, and P. J. Reider, *Tetrahedron Lett.*, 2001, **42**, 6223.
- 2001TL7935 R. A. Batey, D. A. Powell, A. Acton, and A. J. Lough, *Tetrahedron Lett.*, 2001, **42**, 7935.
- 2001TL8885 C. Gremmen, M. J. Wanner, and G.-J. Koomen, *Tetrahedron Lett.*, 2001, **42**, 8885.
- 2002CC526 M. Amat, M. Canto, N. Llor, and J. Bosch, *J. Chem. Soc., Chem. Commun.*, 2002, 526.
- 2002CC1682 M. C. Bagley, J. W. Dale, and J. Bower, *J. Chem. Soc., Chem. Commun.*, 2002, 1682.
- 2002CPB463 D. Branowska, S. Ostrowski, and A. Rykowski, *Chem. Pharm. Bull.*, 2002, **50**, 463.
- 2002JA3518 D. Suzuki, R. Tanaka, H. Urabe, and F. Sato, *J. Am. Chem. Soc.*, 2002, **124**, 3518.
- 2002JA5059 T. Takahashi, F.-Y. Tsai, Y. Li, H. Wang, Y. Kondo, M. Yamanaka, K. Nakajima, and M. Kitora, *J. Am. Chem. Soc.*, 2002, **124**, 5059.

- 2002JCM60 Y. A. Ibrahim and B. Al-Saleh, *J. Chem. Res. (S)*, 2002, 60.
2002JOC465 O. Gaertzen and S. L. Buchwald, *J. Org. Chem.*, 2002, **67**, 465.
2002JOC3437 Q. Huang, J. A. Hunter, and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 3437.
2002JOC3969 J. Zhang and C.-J. Li, *J. Org. Chem.*, 2002, **67**, 3969.
2002JOC7042 G. Dai and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 7042.
2002JOC9449 B. Jiang and Y.-G. Si, *J. Org. Chem.*, 2002, **67**, 9449.
2002J(P1)1663 M. C. Bagley, C. Brace, J. W. Dale, M. Ohnesorge, N. G. Phillips, X. Xiong, and J. Bower, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1663.
2002OL193 G. Dai and R. C. Larock, *Org. Lett.*, 2002, **4**, 193.
2002OL655 F. A. Davis, Y. Wu, H. Yan, K. R. Prasad, and W. McCoull, *Org. Lett.*, 2002, **4**, 655.
2002OL3727 J. T. Williams, P. S. Bahia, and J. S. Snaith, *Org. Lett.*, 2002, **4**, 3727.
2002OL4411 D. Cheng, J. Zhou, E. Saiah, and G. Beaton, *Org. Lett.*, 2002, **4**, 4411.
2002OL4499 X. E. Hu, N. K. Kim, and B. Ledoussal, *Org. Lett.*, 2002, **4**, 4499.
2002RCB362 V. V. Dotsenko, S. G. Krivolysko, V. P. Litvinov, and A. N. Chernega, *Russ. Chem. Bull.*, 2002, **51**, 362.
2002SC3493 F. A. Abu-Shanab, Y. M. Elkholy, and M. H. Elnagdi, *Synth. Commun.*, 2002, **32**, 3493.
2002T3693 D. Basavaiah, R. M. Reddy, N. Kumaragurubaran, and D. S. Sharada, *Tetrahedron*, 2002, **58**, 3693.
2002T9709 A. C. Veronese, C. F. Morelli, and M. Basato, *Tetrahedron*, 2002, **58**, 9709.
2002TL2273 A. D. Thomas and C. V. Asokan, *Tetrahedron Lett.*, 2002, **43**, 2273.
2002TL3557 Q. Huang and R. C. Larock, *Tetrahedron Lett.*, 2002, **43**, 3557.
2002TL6907 N. A. M. Yehia, K. Polborn, and T. J. J. Muller, *Tetrahedron Lett.*, 2002, **43**, 6907.
2002TL8331 M. C. Bagley, R. Lunn, and X. Xiong, *Tetrahedron Lett.*, 2002, **43**, 8331.
2003CC1918 Z. Shao, J. Chen, Y. Tu, L. Li, and H. Zhang, *J. Chem. Soc., Chem. Commun.*, 2003, 1918.
2003CEJ466 B. M. Toure, H. R. Hoveyda, J. Taylor, A. Ulaczyk-Lesanko, and D. G. Hall, *Chem. Eur. J.*, 2003, **9**, 466.
2003CHE184 Y. V. Shklyayev and Y. V. Nifontov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 184.
2003CHE277 A. S. Fisyuk and A. Y. Mukanov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 277.
2003IJB1742 T. J. M. Chary, A. K. Murthy, and E. Rajanarendar, *Indian J. Chem., Sect. B*, 2003, **42**, 1742.
2003JA7272 J. B. Chaires, J. Ren, M. Henary, O. Zegrocka, G. R. Bishop, and L. Strekowski, *J. Am. Chem. Soc.*, 2003, **125**, 7272.
2003JOC920 G. Dai and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 920.
2003JOC980 Q. Huang and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 980.
2003JOC2432 M. E. Humphries, J. Murphy, A. J. Phillips, and A. D. Abell, *J. Org. Chem.*, 2003, **68**, 2432.
2003JOC3563 J. Jacob and W. D. Jones, *J. Org. Chem.*, 2003, **68**, 3563.
2003JOC3966 P. K. Mahanta, C. Venkatesh, U. K. S. Kumar, H. Ila, and H. Junappa, *J. Org. Chem.*, 2003, **68**, 3966.
2003JOC4170 J. J. Chen, J. C. Drach, and L. B. Townsend, *J. Org. Chem.*, 2003, **68**, 4170.
2003JOC4286 S. J. Hedley, W. J. Moran, D. A. Price, and J. P. A. Harrity, *J. Org. Chem.*, 2003, **68**, 4286.
2003JOC4371 J. M. Harris and A. Padwa, *J. Org. Chem.*, 2003, **68**, 4371.
2003JOC6427 D. K. O'Dell and K. M. Nicholas, *J. Org. Chem.*, 2003, **68**, 6427.
2003OL877 T. V. V. Ramakrishna and P. R. Sharp, *Org. Lett.*, 2003, **5**, 877.
2003OL1455 J. Ichikawa, Y. Wada, H. Miyazaki, T. Mori, and H. Kuroki, *Org. Lett.*, 2003, **5**, 1455.
2003OL1605 B. K. Mehta, K. Yanagisawa, M. Shiro, and H. Kotsuki, *Org. Lett.*, 2003, **5**, 1605.
2003OL1765 W. Du and D. P. Curran, *Org. Lett.*, 2003, **5**, 1765.
2003OL2509 N. A. Magomedov, *Org. Lett.*, 2003, **5**, 2509.
2003OL2759 S.-G. Lim, J. H. Lee, C. W. Moon, J.-B. Hong, and C.-H. Jun, *Org. Lett.*, 2003, **5**, 2759.
2003OL2911 K. J. Hodgetts and M. T. Kershaw, *Org. Lett.*, 2003, **5**, 2911.
2003OL3767 D. Crich, M. Shirai, and S. Rumthao, *Org. Lett.*, 2003, **5**, 3767.
2003OL3855 F. A. Davis, A. Rao, and P. J. Carroll, *Org. Lett.*, 2003, **5**, 3855.
2003OL4257 B. R. McNaughton and B. L. Miller, *Org. Lett.*, 2003, **5**, 4257.
2003OL4261 B. K. Ghorai, D. Jiang, and J. W. Herndon, *Org. Lett.*, 2003, **5**, 4261.
2003OL4733 Z. Zhang and L. L. Schafer, *Org. Lett.*, 2003, **5**, 4733.
2003S1531 D. M. Volochnyuk, A. O. Pushechnikov, D. G. Krotko, D. A. Sibgatulin, S. A. Kovalyova, and A. A. Tolmachev, *Synthesis*, 2003, 1531.
2003S2005 D. O. Berbasov and V. A. Soloshonok, *Synthesis*, 2003, 2005.
2003SL143 K. Miura and A. Hosomi, *Synlett*, 2003, 143.
2003SL1443 M. C. Bagley, D. D. Hughes, H. M. Sabo, P. H. Taylor, and X. Siong, *Synlett*, 2003, 1443.
2003T813 B. C. Ranu, A. Hajra, S. S. Dey, and U. Jana, *Tetrahedron*, 2003, **59**, 813.
2003T1805 J. S. Yadav, B. V. S. Reddy, K. S. Rau, and A. R. Prasad, *Tetrahedron*, 2003, **59**, 1805.
2003T5047 J. Rogiers, W. M. De Borggraeve, S. M. Toppet, F. Compennolle, and G. J. Hoornaert, *Tetrahedron*, 2003, **59**, 5047.
2003T6445 H. K. Lee, J. S. Chun, and C. S. Pak, *Tetrahedron*, 2003, **59**, 6445.
2003T8775 B. C. G. Soderberg, J. A. Shriver, S. H. Cooper, T. L. Shrout, E. S. Helton, L. R. Austin, H. H. Odens, B. R. Hearn, P. C. Jones, T. N. Kouadio, T. H. Ngi, R. Baswell, H. J. Caprara, M. D. Meritt, and T. T. Mai, *Tetrahedron*, 2003, **59**, 8775.
2003TL3963 D. Ma and N. Ma, *Tetrahedron Lett.*, 2003, **44**, 3963.
2003TL4207 T. Ullrich and F. Giraud, *Tetrahedron Lett.*, 2003, **44**, 4207.
2003TL5893 A. I. R. N. A. Barros and A. M. S. Silva, *Tetrahedron Lett.*, 2003, **44**, 5893.
2003TL7433 P. Haldar, G. K. Kar, and J. K. Ray, *Tetrahedron Lett.*, 2003, **44**, 7433.
2003TL7445 X. Gai, R. Grigg, I. Koppen, J. Marchbank, and V. Sridharan, *Tetrahedron Lett.*, 2003, **44**, 7445.
2003TL8249 F. Furman and M. Dziedzic, *Tetrahedron Lett.*, 2003, **44**, 8249.
2004AGE2001 B. B. Toure and D. G. Hall, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 2001.
2004AGE4222 X. Pu and D. Ma, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 4222.
2004AGE5391 S. A. A. El Bialy, H. Braun, and L. F. Tietze, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 5391.
2004CC508 S. A. Raw and R. J. K. Taylor, *J. Chem. Soc., Chem. Commun.*, 2004, 508.

- 2004CEJ4283 O. Flögel, J. Dash, I. Brüdgam, H. Hartl, and H.-U. Reißig, *Chem. Eur. J.*, 2004, **10**, 4283.
2004CL590 T. Mori and J. Ichikawa, *Chem. Lett.*, 2004, 590.
2004HCA2712 T.-L. Ho and E. V. Kuzakov, *Helv. Chim. Acta*, 2004, **87**, 2712.
2004JHC979 A. S. Cănepa and R. D. Bravo, *J. Heterocycl. Chem.*, 2004, **41**, 979.
2004JME254 R. Shan, C. Velazquez, and E. E. Knaus, *J. Med. Chem.*, 2004, **47**, 254.
2004JME1930 H. Moriyama, T. Tsukida, Y. Inoue, K. Yokota, K. Yoshino, H. Kondo, N. Miura, and S.-I. Nishimura, *J. Med. Chem.*, 2004, **47**, 1930.
2004JME2688 S. Visentin, B. Rolando, A. Di Stilo, R. Fruttero, M. Novara, E. Carbone, C. Roussel, N. Vanthuyne, and A. Gasco, *J. Med. Chem.*, 2004, **47**, 2688.
2004JME3163 W. A. Carroll, K. A. Agrios, R. J. Altenbach, S. A. Buckner, Y. Chen, M. J. Coghlan, A. V. Daza, I. Drizin, M. Gopalakrishnan, R. F. Henry, M. E. Kort, P. R. Kym, I. Milicic, J. C. Smith, R. Tang, S. C. Turner, K. L. Whiteaker, H. Zhang, and J. P. Sullivan, *J. Med. Chem.*, 2004, **47**, 3163.
2004JME3180 W. A. Carroll, K. A. Agrios, R. J. Altenbach, S. A. Buckner, Y. Chen, M. J. Coghlan, A. V. Daza, I. Drizin, M. Gopalakrishnan, R. F. Henry, M. E. Kort, P. R. Kym, I. Milicic, J. C. Smith, R. Tang, S. C. Turner, K. L. Whiteaker, H. Zhang, and J. P. Sullivan, *J. Med. Chem.*, 2004, **47**, 3180.
2004JME5620 L. Héja, I. Kovács, É. Szárics, M. Incze, E. Temesváriné-Major, G. Dörnyei, M. Peredy-Kajtár, E. Gács-Baitz, C. Szántay, and J. Kardos, *J. Med. Chem.*, 2004, **47**, 5620.
2004JOC130 J. Marin, C. Didierjean, A. Aubry, J.-R. Casimir, J.-P. Briand, and G. Guichard, *J. Org. Chem.*, 2004, **69**, 130.
2004JOC1872 D. L. J. Clive and X. Huang, *J. Org. Chem.*, 2004, **69**, 1872.
2004JOC2229 M. Achmatowicz and L. S. Hegedus, *J. Org. Chem.*, 2004, **69**, 2229.
2004JOC2892 H.-K. Yim and H. N. C. Wong, *J. Org. Chem.*, 2004, **69**, 2892.
2004JOC3139 A. S. Davis, S. G. Pyne, B. W. Skelton, and A. H. White, *J. Org. Chem.*, 2004, **69**, 3139.
2004JOC7284 L. Song, E. N. Duesler, and P. S. Mariano, *J. Org. Chem.*, 2004, **69**, 7284.
2004JOC7906 M. Shen and C. Li, *J. Org. Chem.*, 2004, **69**, 7906.
2004JOC8429 B. B. Touré and D. G. Hall, *J. Org. Chem.*, 2004, **69**, 8429.
2004OBC2270 L. A. Gandon, A. G. Russell, and J. S. Snaith, *Org. Biomol. Chem.*, 2004, **2**, 2270.
2004OBC3128 F. Chevallier, E. Le Grogne, I. Beaudet, F. Fliegel, M. Evain, and J.-P. Quintard, *Org. Biomol. Chem.*, 2004, **2**, 3128.
2004OL2059 L. Feng, D. Kumar, D. M. Birney, and S. M. Kerwin, *Org. Lett.*, 2004, **6**, 2059.
2004OL2361 T. Ishikawa, S. Manabe, T. Aikawa, T. Kudo, and S. Saito, *Org. Lett.*, 2004, **6**, 2361.
2004OL2433 P. J. Manley and M. T. Bilodeau, *Org. Lett.*, 2004, **6**, 2433.
2004OL3155 Z. Xiang, T. Luo, K. Lu, J. Cui, X. Shi, R. Fathi, J. Chen, and Z. Yang, *Org. Lett.*, 2004, **6**, 3155.
2004OL3525 K. Fujita, T. Fujii, and R. Yamaguchi, *Org. Lett.*, 2004, **6**, 3525.
2004OL4029 M. P. Cassidy and A. Padwa, *Org. Lett.*, 2004, **6**, 4029.
2004OL4061 A. S. Kiselyov, E. L. Piatnitski, and J. Doody, *Org. Lett.*, 2004, **6**, 4061.
2004OL4913 H. Twin and R. A. Batey, *Org. Lett.*, 2004, **6**, 4913.
2004OL4941 P. N. M. Botman, F. J. Dommerholt, R. de Gelder, Q. B. Broxterman, H. E. Schoemaker, F. P. J. T. Rutjes, and R. H. Blaauw, *Org. Lett.*, 2004, **6**, 4941.
2004S63 K. H. Kumar, D. Muralidharan, and P. T. Perumal, *Synthesis*, 2004, 63.
2004S69 R. Nagarajan, C. J. Magesh, and P. T. Perumal, *Synthesis*, 2004, 69.
2004S949 R. S. Kumar, R. Nagarajan, and P. T. Perumal, *Synthesis*, 2004, 949.
2004S1446 T. Harayama, T. Sato, A. Hori, H. Abe, and Y. Takeuchi, *Synthesis*, 2004, 1446.
2004S2222 K. Takasu, N. Nishida, and M. Ihara, *Synthesis*, 2004, 2222.
2004SL708 L. Di Bari, S. Guilleme, S. Hermitage, J. A. K. Howard, D. A. Jay, G. Pescitelli, A. Whiting, and D. S. Yufit, *Synlett*, 2004, 708.
2004SL711 S. Guilleme and A. Whiting, *Synlett*, 2004, 711.
2004SL811 M. C. Bagley, C. Glover, E. A. Merritt, and X. Xiong, *Synlett*, 2004, 811.
2004SL827 M. A. Zolfigol and M. Safaie, *Synlett*, 2004, 827.
2004SL1175 Y.-G. Wang, X.-F. Lin, and S.-L. Cui, *Synlett*, 2004, **7**, 1175.
2004SL1219 J. Ichikawa, T. Mori, H. Miyazaki, and Y. Wada, *Synlett*, 2004, **7**, 1219.
2004SL1309 A. Chetia, M. Longchar, K. C. Lekhok, and R. C. Boruah, *Synlett*, 2004, 1309.
2004SL1711 A. Dondoni, B. Richichi, A. Marra, and D. Perrone, *Synlett*, 2004, 1711.
2004SL2295 T. Huxford and N. S. Simpkins, *Synlett*, 2004, 2295.
2004SL2776 N. J. Birch, P. J. Parsons, and D. I. C. Scopes, *Synlett*, 2004, 2776.
2004T1611 T. Harayama, A. Hori, H. Abe, and Y. Takeuchi, *Tetrahedron*, 2004, **60**, 1611.
2004T2311 A. Dondoni, A. Massi, E. Minghini, and V. Bertolasi, *Tetrahedron*, 2004, **60**, 2311.
2004T5069 A. D. Thomas, K. N. N. Josemin, and C. V. Asokan, *Tetrahedron*, 2004, **60**, 5069.
2004T6021 D. Branowska, *Tetrahedron*, 2004, **60**, 6021.
2004T6163 M. Shi, S.-C. Cui, and Q.-J. Li, *Tetrahedron*, 2004, **60**, 6163.
2004T7629 C. R. Berry and R. P. Hsung, *Tetrahedron*, 2004, **60**, 7629.
2004T8181 J. Flisińska-Luczak, S. Lesniak, and R. B. Nazarski, *Tetrahedron*, 2004, **60**, 8181.
2004T8633 N. Y. Gorobets, B. H. Yousefi, F. Belaj, and C. O. Kappe, *Tetrahedron*, 2004, **60**, 8633.
2004T8869 R. A. J. Wybrow, A. S. Edwards, N. G. Stevenson, H. Adams, C. Johnstone, and J. P. A. Harrity, *Tetrahedron*, 2004, **60**, 8869.
2004T8893 S. P. Stanforth, B. Tarbit, and M. D. Watson, *Tetrahedron*, 2004, **60**, 8893.
2004T9629 M. Zaja and S. Blechert, *Tetrahedron*, 2004, **60**, 9629.
2004T10223 B.-F. Chen, M.-R. Tasi, C.-Y. Yang, J.-K. Chang, and N.-C. Chang, *Tetrahedron*, 2004, **60**, 10223.
2004TL417 V. Gracias, J. D. Moore, and S. W. Djuric, *Tetrahedron Lett.*, 2004, **45**, 417.
2004TL761 F. Chevallier, I. Beaudet, E. Le Grogne, L. Toupet, and J.-P. Quintard, *Tetrahedron Lett.*, 2004, **45**, 761.
2004TL987 M. S. Bodas, P. K. Upadhyay, and P. Kumar, *Tetrahedron Lett.*, 2004, **45**, 987.
2004TL1167 S. Randl and S. Blechert, *Tetrahedron Lett.*, 2004, **45**, 1167.

- 2004TL1919 S. Raghavan and A. Rajender, *Tetrahedron Lett.*, 2004, **45**, 1919.
- 2004TL3507 A. Kamal, B. R. Prasad, A. V. Ramana, A. H. Babu, and K. S. Reddy, *Tetrahedron Lett.*, 2004, **45**, 3507.
- 2004TL4357 A. B. García, C. Valdés, and M.-P. Cabal, *Tetrahedron Lett.*, 2004, **45**, 4357.
- 2004TL5031 G. Cardillo, S. Fabbroni, L. Gentilucci, R. Perciacante, F. Piccinelli, and A. Tolomelli, *Tetrahedron Lett.*, 2004, **60**, 5031.
- 2004TL5751 T.-L. Shih, W.-S. Kuo, and Y.-L. Lin, *Tetrahedron Lett.*, 2004, **45**, 5751.
- 2004TL6029 K. Motokura, T. Mizugaki, K. Ebitani, and K. Kaneda, *Tetrahedron Lett.*, 2004, **45**, 6029.
- 2004TL6221 M. Katoh, R. Matsune, H. Nagase, and T. Honda, *Tetrahedron Lett.*, 2004, **45**, 6221.
- 2004TL6903 R. Ferraccioli, D. Carenzi, and M. Catellani, *Tetrahedron Lett.*, 2004, **45**, 6903.
- 2004TL7339 M. Ohtaka, H. Nakamura, and Y. Yamamoto, *Tetrahedron Lett.*, 2004, **45**, 7339.
- 2004TL9011 N. Tewari, N. Dwivedi, and R. P. Tripathi, *Tetrahedron Lett.*, 2004, **45**, 9011.
- 2004TL9557 A. Robin, K. Julienne, J.-C. Meslin, and D. Deniaud, *Tetrahedron Lett.*, 2004, **45**, 9557.
- 2005AGE452 L. A. McAllister, R. A. McCormick, S. Brand, and D. J. Procter, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 452.
- 2005EJO23 R. P. Hsung, A. V. Kurdyumov, and N. Sydorenko, *Eur. J. Org. Chem.*, 2005, 23.
- 2005EJO1834 O. G. Dediu, N. A. M. Yehia, T. Oeser, K. Polborn, and T. J. J. Müller, *Eur. J. Org. Chem.*, 2005, 1834.
- 2005EJO1903 F. Alvarez, A. Taleb, J. Gentili, P. Nebois, R. Terreux, M. Domard, A. Thozet, D. Merle, H. Fillion, and N. Walchshofer, *Eur. J. Org. Chem.*, 2005, 1903.
- 2005H(65)1881 H.-Y. Huang, R.-S. Hou, H.-M. Wang, and L.-C. Chen, *Heterocycles*, 2005, **65**, 1881.
- 2005HAC49 S. Bondock, *Heteroatom Chem.*, 2005, **16**, 49.
- 2005JA605 Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, and K. Itoh, *J. Am. Chem. Soc.*, 2005, **127**, 605.
- 2005JA3473 L. V. R. Boñaga, H.-C. Zhang, A. F. Moretto, H. Ye, D. A. Gauthier, J. Li, G. C. Leo, and B. E. Maryanoff, *J. Am. Chem. Soc.*, 2005, **127**, 3473.
- 2005JA5030 M. M. McCormick, H. A. Duong, G. Zuo, and J. Louie, *J. Am. Chem. Soc.*, 2005, **127**, 5030.
- 2005JA8398 F. A. Davis and B. Yang, *J. Am. Chem. Soc.*, 2005, **127**, 8398.
- 2005JA15644 R. A. Hughes, S. P. Thompson, L. Alcaraz, and C. J. Moody, *J. Am. Chem. Soc.*, 2005, **127**, 15644.
- 2005JA15704 M. J. Schermann and D. L. Boger, *J. Am. Chem. Soc.*, 2005, **127**, 15704.
- 2005JCO490 N. Kaval, D. Ermolat'ev, P. Appukkuttan, W. Dehaen, C. O. Kappe, and E. Van der Eycken, *J. Comb. Chem.*, 2005, **7**, 490.
- 2005JOC207 K. M. Goodenough, W. J. Moran, P. Raubo, and J. P. A. Harrity, *J. Org. Chem.*, 2005, **70**, 207.
- 2005JOC350 J. Azizian, A. A. Mohammadi, A. R. Karimi, and M. R. Mohammadizadeh, *J. Org. Chem.*, 2005, **70**, 350.
- 2005JOC360 P. Kumar and M. S. Bodas, *J. Org. Chem.*, 2005, **70**, 360.
- 2005JOC1389 M. C. Bagley, K. Chapaneri, J. W. Dale, X. Xiong, and J. Bower, *J. Org. Chem.*, 2005, **70**, 1389.
- 2005JOC4248 A. I. Gerasuto, R. P. Hsung, N. Sydorenko, and B. Slafer, *J. Org. Chem.*, 2005, **70**, 4248.
- 2005JOC4883 G. B. Bajracharya, Z. Huo, and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 4883.
- 2005JOC5519 S. S. Kinderman, M. M. T. Wekking, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, and F. P. J. T. Rutjes, *J. Org. Chem.*, 2005, **70**, 5519.
- 2005JOC5932 A. I. Siriwardana, M. Kamada, I. Nakamura, and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 5932.
- 2005JOC6454 G. Abbiati, A. Arcadi, V. Canevari, L. Capezzuto, and E. Rossi, *J. Org. Chem.*, 2005, **70**, 6454.
- 2005JOC7342 H. M. Peltier and J. A. Ellman, *J. Org. Chem.*, 2005, **70**, 7342.
- 2005JOC10086 Y. F. Sainz, S. A. Raw, and R. J. K. Taylor, *J. Org. Chem.*, 2005, **70**, 10086.
- 2005JOC10172 T. Konno, J. Chae, T. Miyabe, and T. Ishihara, *J. Org. Chem.*, 2005, **70**, 10172.
- 2005JOC10182 N. Liang and A. Datta, *J. Org. Chem.*, 2005, **70**, 10182.
- 2005MOL265 D. Branowska, *Molecules*, 2005, **10**, 265.
- 2005OBC1349 J. P. A. Harrity and O. Provoost, *Org. Biomol. Chem.*, 2005, **3**, 1349.
- 2005OBC1609 T. Kawabata, S. Majumdar, K. Tsubaki, and D. Monguchi, *Org. Biomol. Chem.*, 2005, **3**, 1609.
- 2005OL763 X. Zhang, M. A. Campo, T. Yao, and R. C. Larock, *Org. Lett.*, 2005, **7**, 763.
- 2005OL823 B. M. Trost and D. R. Fandrick, *Org. Lett.*, 2005, **7**, 823.
- 2005OL2675 Y. Luo, Z. Li, and C.-J. Li, *Org. Lett.*, 2005, **7**, 2675.
- 2005OL2993 K. M. Goodenough, P. Raubo, and J. P. A. Harrity, *Org. Lett.*, 2005, **7**, 2993.
- 2005OL4737 K. Tanaka, A. Wada, and K. Noguchi, *Org. Lett.*, 2005, **7**, 4737.
- 2005OL5179 R. P. Korivi and C.-H. Cheng, *Org. Lett.*, 2005, **7**, 5179.
- 2005OL5281 M. Alajarín, M.-M. Ortín, P. Sánchez-Andrada, Á. Vidal, and D. Bautista, *Org. Lett.*, 2005, **7**, 5281.
- 2005OL5773 M. Sales and A. B. Charette, *Org. Lett.*, 2005, **7**, 5773.
- 2005S3423 K. Bala and H. C. Hailes, *Synthesis*, 2005, 3423.
- 2005SL623 A. Goel, F. V. Singh, A. Sharon, and P. R. Maulik, *Synlett*, 2005, 623.
- 2005SL1188 A. Gutnov, V. Abaev, D. Redkin, C. Fischer, W. Bonrath, and B. Heller, *Synlett*, 2005, 1188.
- 2005SL1758 U. Groth, T. Huhn, C. Kesenheimer, and A. Kalogerakis, *Synlett*, 2005, 1758.
- 2005SL2357 M. Xia and Y.-D. Lu, *Synlett*, 2005, 2357.
- 2005RCB2187 V. N. Kozhevnikova, D. N. Kozhevnikov, O. V. Shaunina, N. N. Kataeva, S. A. Yuschuk, V. L. Rusinov, and O. N. Chupakhin, *Russ. Chem. Bull.*, 2005, **54**, 2187.
- 2005T2631 G. A. Molander and J. A. C. Romero, *Tetrahedron*, 2005, **61**, 2631.
- 2005T2779 F. Palacios, C. Alonso, G. Rubiales, and M. Villegas, *Tetrahedron*, 2005, **61**, 2779.
- 2005T8148 T. Lipinska, *Tetrahedron*, 2005, **61**, 8148.
- 2005T8264 M. Mena and J. Bonjoch, *Tetrahedron*, 2005, **61**, 8264.
- 2005T8888 Z. Zhao, L. Song, and P. S. Mariano, *Tetrahedron*, 2005, **61**, 8888.
- 2005T11716 T. Yi, A.-T. Wu, S.-H. Wu, and W. Zou, *Tetrahedron*, 2005, **61**, 11716.
- 2005TL767 G. Chelucci, I. Manca, and G. A. Pinna, *Tetrahedron Lett.*, 2005, **46**, 767.
- 2005TL1521 V. N. Kozhevnikov, D. N. Kozhevnikov, O. V. Shabunina, V. L. Rusinov, and O. N. Chupakhin, *Tetrahedron Lett.*, 2005, **46**, 1521.
- 2005TL1647 S. K. De and R. A. Gibbs, *Tetrahedron Lett.*, 2005, **46**, 1647.
- 2005TL1791 V. N. Kozhevnikov, D. N. Kozhevnikov, O. V. Shabunina, V. L. Rusinov, and O. N. Chupakhin, *Tetrahedron Lett.*, 2005, **46**, 1791.

- 2005TL2101 N. T. Patil, N. K. Pahadi, and Y. Yamamoto, *Tetrahedron Lett.*, 2005, **46**, 2101.
- 2005TL2669 M. Atobe, N. Yamazaki, and C. Kibayashi, *Tetrahedron Lett.*, 2005, **46**, 2669.
- 2005TL3423 B. Shao, *Tetrahedron Lett.*, 2005, **46**, 3423.
- 2005TL3493 G. Chelucci and G. Orrù, *Tetrahedron Lett.*, 2005, **46**, 3493.
- 2005TL4539 K. Taguchi, S. Sakaguchi, and Y. Ishii, *Tetrahedron Lett.*, 2005, **46**, 4539.
- 2005TL5511 J. Svetlik, V. Kettmann, and B. Zaleska, *Tetrahedron Lett.*, 2005, **46**, 5511.
- 2005TL7169 X.-S. Wang, M.-M. Zhang, Z.-S. Zeng, D.-Q. Shi, S.-J. Tu, X.-Y. Wei, and Z.-M. Zong, *Tetrahedron Lett.*, 2005, **46**, 7169.
- 2005TL7249 J. S. Yadav, P. P. Rao, D. Sreenu, R. S. Rao, V. N. Kumar, K. Nagaiah, and A. R. Prasad, *Tetrahedron Lett.*, 2005, **46**, 7249.
- 2005TL7669 N. Q. Vu, G. Dujardin, S. C. Collet, E.-A. Raiber, A. Y. Guingant, and M. Evain, *Tetrahedron Lett.*, 2005, **46**, 7669.
- 2006AGE932 B. B. Snider and Q. Che, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**, 932.
- 2006EJO4916 D. Keck, S. Vanderheiden, and S. Bräse, *Eur. J. Org. Chem.*, 2006, 4916.
- 2006JOC6592 Y.-C. Wu, L. Liu, H.-J. Li, D. Wang, and Y.-J. Chen, *J. Org. Chem.*, 2006, **71**, 6592.
- 2006OL3809 T. Kobayashi, M. Nakashima, and T. Hakogi, *Org. Lett.*, 2006, **8**, 3809.
- 2006OL3813 T. Kobayashi, F. Hasegawa, K. Tanaka, and S. Katsumura, *Org. Lett.*, 2006, **8**, 3813.
- 2006SC693 J. Su, J. Xiong, S. Liang, G. Qiu, X. Feng, H. Teng, L. Wu, and X. Hu, *Synth. Commun.*, 2006, **36**, 693.
- 2006TL6781 C. S. Cho, W. X. Ren, and S. C. Shim, *Tetrahedron Lett.*, 2006, **47**, 6781.
- 2007OBC61 A.-H. Li, E. Ahmed, X. Chen, M. Cox, A. P. Crew, H.-Q. Dong, M. Jin, L. Ma, B. Panicker, K. W. Siu, A. G. Steinig, K. M. Stolz, P. A. R. Tavares, B. Volk, Q. Weng, D. Werner, and M. J. Mulvihill, *Org. Biomol. Chem.*, 2007, **5**, 61.
- 2007T2811 S. Atechian, N. Nock, R. D. Norcross, H. Ratni, A. W. Thomas, J. Verron, and R. Masciadri, *Tetrahedron*, 2007, **63**, 2811.

Biographical Sketch



Paul Keller completed his B.Sc.(Hons) (1985) and Ph.D. at the University of New South Wales, Australia, before undertaking an Alexander von Humboldt funded post-doctoral fellowship at the University of Wuerzburg, Germany, working in collaboration with Gerhard Bringmann. Since 1994, he has worked at the University of Wollongong, Australia, and is currently Associate Professor in Organic and Medicinal Chemistry. His interests lie in the drug design and development of new generation anti-infectives and chiral ligand design for sterically hindered Suzuki reactions.

7.06

Pyridines and their Benzo Derivatives: Applications

C. H. McAteer

Vertellus Specialties Inc., Indianapolis, IN, USA

M. Balasubramanian

Pfizer Inc., Groton, CT, USA

R. Murugan

Vertellus Specialties Inc., Indianapolis, IN, USA

© 2008 Elsevier Ltd. All rights reserved.

7.06.1	Introduction	310
7.06.2	Natural Products	310
7.06.3	Reagents for Qualitative and Quantitative Analysis	313
7.06.4	Catalysts and Reagents in Organic Synthesis	314
7.06.5	Synthesis of Compounds with Pyridine Ring Opening	316
7.06.5.1	Nonheterocycles	316
7.06.5.2	Nonpyridine Heterocycles	317
7.06.6	Polymers	317
7.06.6.1	Linear Polymers	318
7.06.6.2	Cross-Linked Polymers	318
7.06.7	Dyes	318
7.06.8	Performance Applications	319
7.06.8.1	Flavors and Fragrances	319
7.06.8.2	Ionic Liquids	319
7.06.9	Agrochemicals	321
7.06.9.1	Fungicides	321
7.06.9.2	Herbicides	321
7.06.9.3	Insecticides	322
7.06.9.4	Plant Growth Regulators	322
7.06.10	Pharmaceuticals	323
7.06.10.1	Anti-Infective Agents	324
7.06.10.1.1	Antibacterial agents	324
7.06.10.1.2	Antibiotics	325
7.06.10.1.3	Antiviral agents (HIV/AIDS)	325
7.06.10.2	Anti-Inflammatory Agents – Nonsteroidal	326
7.06.10.3	Antineoplastic Agents	326
7.06.10.4	Cardiovascular Drugs	326
7.06.10.4.1	Antihypertensive agents	326
7.06.10.4.2	Vasodilator agents	327
7.06.10.5	Central Nervous System Agents	327
7.06.10.5.1	Analgesics	327
7.06.10.5.2	Anesthetics	327
7.06.10.5.3	Antidepressants	327
7.06.10.5.4	Anti-Parkinson agents	328
7.06.10.5.5	Antipsychotic agents	329

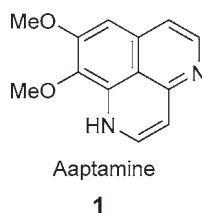
7.06.10.6	Dermatologic Agents – Antipsoriatics	329
7.06.10.7	Gastrointestinal Agents	329
7.06.10.7.1	Antiemetics	329
7.06.10.7.2	Antiulcer agents	330
7.06.10.8	Metabolic Diseases – Antidiabetic agents	330
7.06.10.9	Respiratory System Agents – Antiasthmatic agents	330
7.06.11	Veterinary Products	331
7.06.12	Miscellaneous	331
References		332

7.06.1 Introduction

The presence of pyridine compounds and their benzo derivatives in nature is well known, and their importance to humanity has been well discussed in earlier literature, including CHEC(1984) <1984CHEC(2)511> and CHEC-II(1996) <1996CHEC-II(5)245>. The applications of pyridine compounds and their benzo derivatives can be broadly divided into three areas: biological applications (based upon biological activity), chemical applications (based upon chemical properties), and performance applications (based upon physical properties). Discussion of biological applications appears in Sections 7.06.9, 7.06.10, and 7.06.11. Physical properties applications are subdivided into dyes and performance applications, while chemical properties applications are subdivided into analytical reagents, catalysts and reagents, and synthesis of other heterocycles and nonheterocycles by pyridine ring transformation. The subdivision in this chapter closely follows the contents given in CHEC-II(1996) <1996CHEC-II(5)245> with some modification. Pyridine-based polymers remain as a separate section but now with linear and cross-linked polymer subsections. The agrochemicals and pharmaceuticals sections have further classification by end use application. The performance applications section is similar to the additives section in CHEC-II(1996) <1996CHEC-II(5)245>, although a separate subsection on ionic liquids is now included due to the intense interest in the recent literature. Whenever possible, the authors refer to the earlier applications chapters of CHEC(1984) <1984CHEC(2)511> and CHEC-II(1996) <CHEC-II(5)245> for brevity.

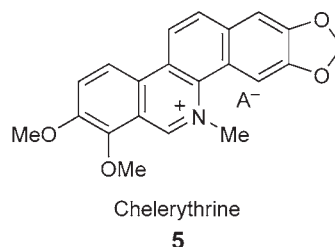
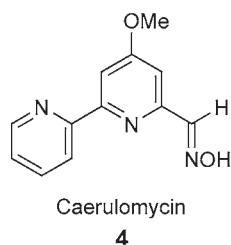
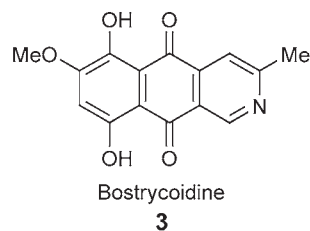
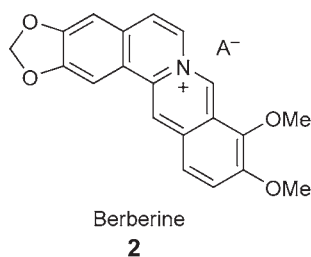
7.06.2 Natural Products

Natural products containing pyridines and their benzo derivatives continue to be isolated and characterized. The alkaloid aptamine **1** was isolated from the marine sponge *Aaptos aaptos*. Aptamine, 8,9-dimethoxy-1*H*-benzo[*d,e*][1,6]naphthyridine, was found to have biological properties including being an α -adrenoreceptor blocker and an antineoplastic agent <1999H(50)543, 2004JOC2251>.

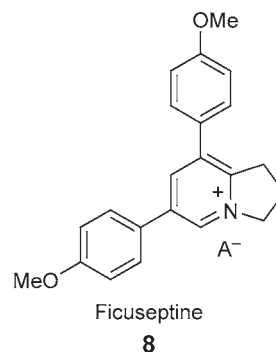
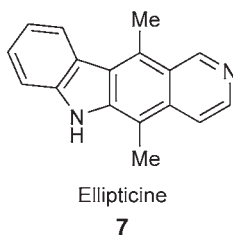
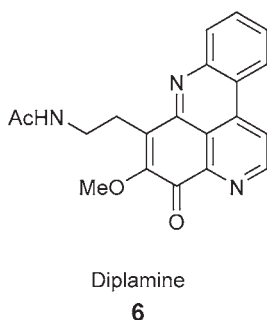


Berberine **2**, a quaternary alkaloid with a quinolizinium ring system, has been isolated from many types of berry and extensively studied for its pharmacological properties <1999MRC195, 2000JNP1638>. Bostrycoidine **3**, a pigment from *Fusarium solani* and *Fusarium bostrycoides*, contains an isoquinoline ring system and shows antibacterial and antitubercular activity <2000JOC640>. The 2,2'-bipyridine derivative, caerulomycin **4**, is an antibiotic isolated from *Streptomyces caerules* has been found also to be active against yeast, fungi, and *entamoeba histolytica* <2002JOC3272, 2002OL2385>. Chelerythrine **5**, a quaternary alkaloid with a phenanthridinium ring system, was

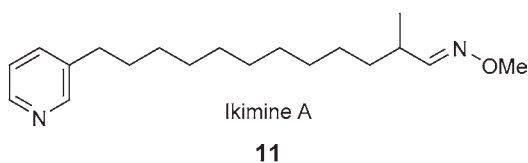
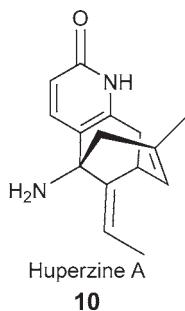
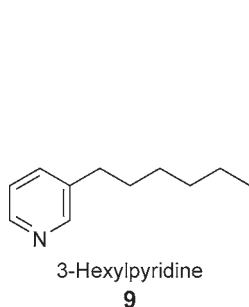
found to have diverse pharmacological applications displaying analgesic and antineoplastic properties as well as prolonging sleep <2001J(P1)523>.



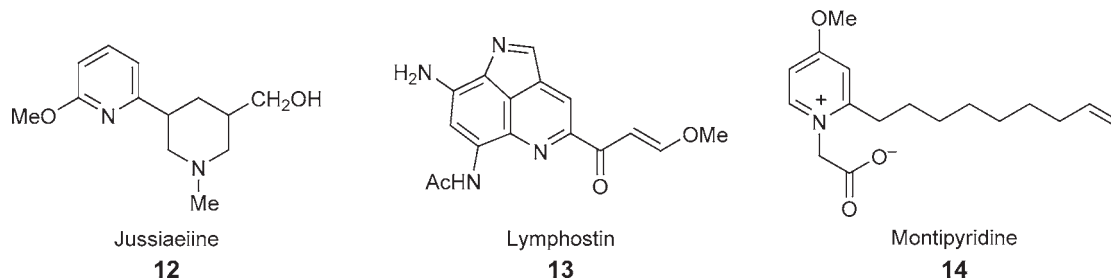
Diplamine **6**, an alkaloid from tunicate *Diplosoma* sp., containing the quinoline ring system, exhibits both antitussive and antitumor activity <2002T9779>. Ellipticine **7**, an alkaloid isolated from *Ochrosia elliptica*, contains a carbazole ring system and shows broad-spectrum antineoplastic activity. Ficuseptine **8**, a quaternary alkaloid containing an indolizinium ring system, was isolated from the leaves of *Ficus septica* and shows antimicrobial activity <2002EJO2288>.



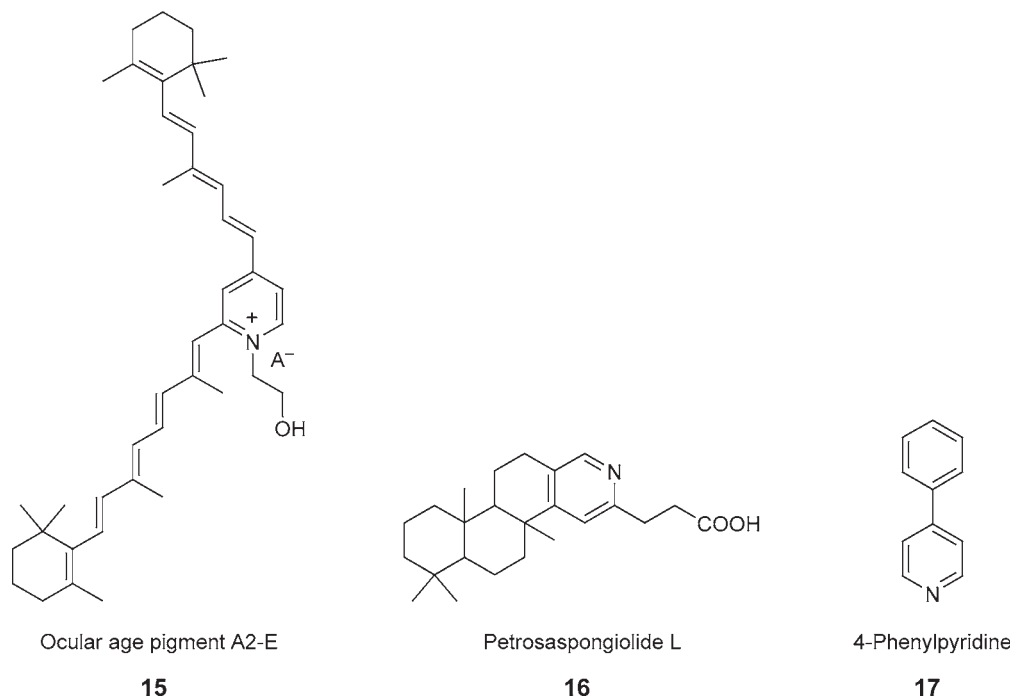
3-Hexylpyridine **9**, found in orange oil, is a liquid with a sweet fragrance that has found use in perfumery and as flavoring ingredient <2002JOC443>. Huperzine A **10**, an alkaloid with a quinolone ring system, has been isolated from *Lycopodium serratum* and found to show strong anticholinesterase activity and markedly increases efficiency for learning and memory in animals <2000T4541>. Ikimine A **11**, an alkaloid from an unidentified sponge, is a simple 3-substituted pyridine compound that is a cytotoxic agent showing antibacterial and antifungal activity <2000T2921>.



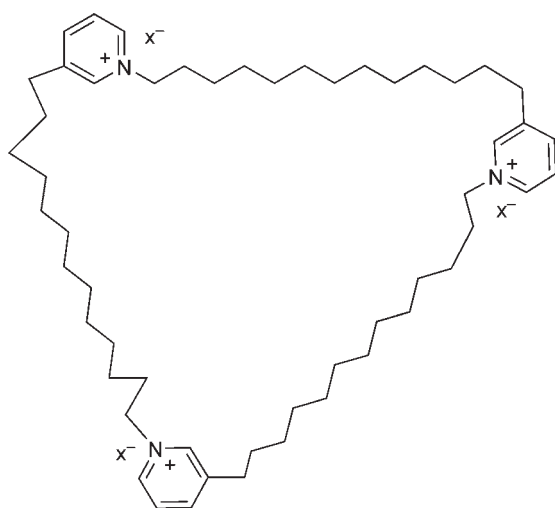
Jussiaeiine A **12**, an alkaloid from *Ulex jussiaei*, contains 2,3'-bipyridine ring system similar to anabasine <2000JNP201>. The antibiotic lymphostin **13** that contains a quinoline ring system is also an immunosuppressant and cytotoxic agent <1997JAN537>. Montipyridine **14**, a quaternary alkaloid containing a pyridine ring system, was isolated from stony coral *Montiora* sp. <2001JNP956>. Ocular age pigment A2-E **15**, an orange fluorescent pigment isolated from human eyes (>40 years), is a 1,2,4-trisubstituted pyridinium compound <2000OL373>.



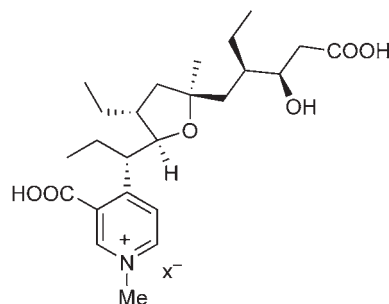
Petrosaspongiolide L **16**, an alkaloid isolated from the sponge *Petrosaspongia nigra*, contains an isoquinoline ring system and is a cytotoxic agent <2000JNP323>. 4-Phenylpyridine **17** was detected in both tea and peppermint <2002EJO4123>.



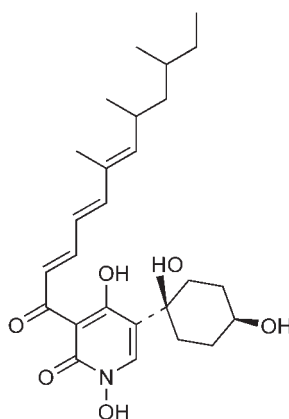
Viscosamine **18**, the first naturally occurring trimeric 3-alkyl pyridinium alkaloid, has been isolated from arctic sponge *Haliclona viscosa* <2003OL3567>. A unique 4-alkyl-substituted pyridinium alkaloid, simplakidine A **19**, has been isolated from the Caribbean sponge *Plakortis simplex* <2003OL673>. A new pyridone alkaloid, militarione A **20**, was isolated from the mycelium of the entomogenous fungus *Paecilomyces militaris* <2002OL197>.



Viscosamine

18

Simplakidine A

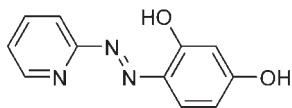
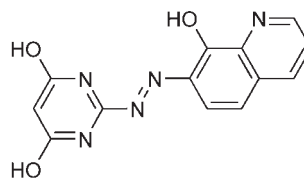
19

Militarinone A

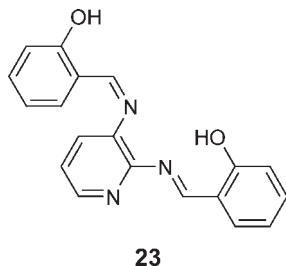
20

7.06.3 Reagents for Qualitative and Quantitative Analysis

In the photometric determination of copper, a coupling product formed between the diazonium salt from 2-amino-pyridine and resorcinol, or 4-(2-pyridinylazo)-1,3-benzenediol **21**, has been used. Here the formed copper complex under acetate buffer exhibits an absorption peak at 520 nm, which is measured photometrically [<2003KPU28>](#). Similarly for photometric determination of iron(II), a coupling product formed between the diazonium salt of 2-amino-4,6-dihydroxypyrimidine and 8-hydroxyquinoline, or 6-hydroxy-2-(8-hydroxy-7-quinolinyl)azo-4(1*H*)-pyrimidinone **22**, has been used. This reagent forms a blue complex with iron(II) ions with an absorption maximum at 625 nm that does not interfere with the presence of other metals [<2003KD95>](#).

**21****22**

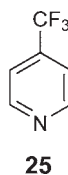
Schiff bases derived from an aminopyridine and an aromatic aldehyde find use in the spectrophotometric determination of metal ions. For example, *N,N'*-bis(salicylidene)-2,3-pyridinediamine **23** has been used in the determination of copper(II) ions. An advantage of Schiff bases derived from aminopyridines as analytical reagents lies in the simplicity of their preparative procedures <2000CCA81>.



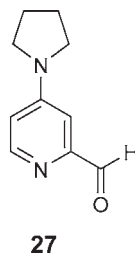
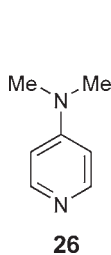
7.06.4 Catalysts and Reagents in Organic Synthesis

The lone pair of electrons on the pyridine nitrogen serves as a carrier for a wide range of Lewis acids. Many of the complexes and salts formed have become useful synthetic reagents. Use of pyridine and its derivatives as solvents and catalysts for condensation, dehydrohalogenation, and acylation reactions is well known in the literature and has been discussed in CHEC(1984) <1984CHEC(2)511> and CHEC-II(1996) <1996CHEC-II(5)245>.

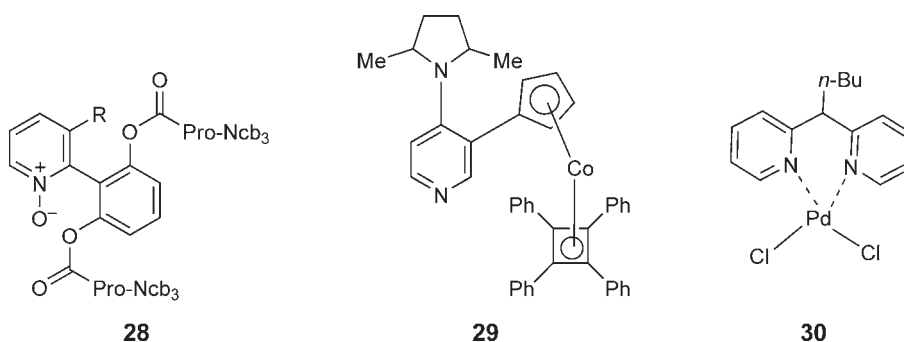
Pyridyldimethylsilane **24** is a reagent for the metal-catalyzed hydrosilylation of alkynes and alkenes <2004EROS1>. 4-(Trifluoromethyl)pyridine **25** has been used as a building block in heterocycle synthesis <2005EROS1>.



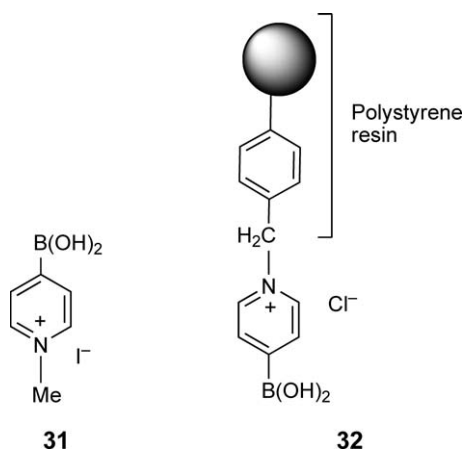
The uses of pyridine and its derivatives like 4-dimethylaminopyridine (DMAP) **26** have been introduced in CHEC(1984) <1984CHEC(2)511> and CHEC-II(1996) <1996CHEC-II(5)245>. 2-Formyl-4-pyrrolidinopyridine **27** is a catalyst for the selective methanolysis of α -hydroxy esters <2002EROS1>. Structurally simple pyridine *N*-oxides **28** function as efficient organocatalysts for the enantioselective allylation of aromatic aldehydes <2006JOC1458>. A highly active chiral metallocene-pyrrolopyridine **29**, prepared in three steps from [*S,S*]-hexane-2,5-diol, was applied to the asymmetric Steglich rearrangement of *O*-acylated azlactones <2006OL769>.



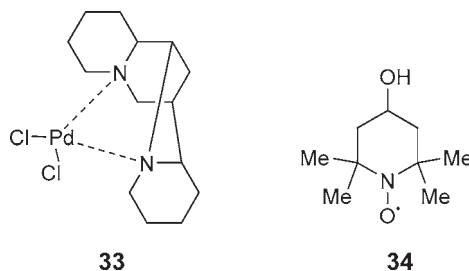
The (dipyridin-2-ylmethyl)amine-derived palladium(II) chloride complex **30** has been found to be a highly efficient catalyst for the synthesis of alkynes in water or in *N*-methylpyrrolidone and of diynes in the absence of reoxidant <2005EJOC4073>.



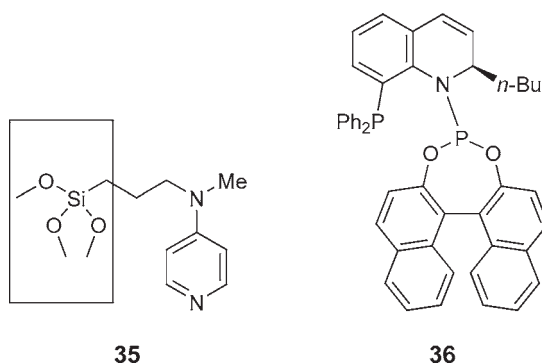
N-Alkyl-4-boronopyridinium halides such as **31** catalyze the esterification of α -hydroxycarboxylic acids <2005OL5047>. When the quaternized *N*-alkyl group is attached to a polystyrene resin, the supported *N*-alkyl-4-boronopyridinium salt **32** serves as a catalyst in amide formation reactions. These catalysts are thermally stable and easily recovered and recycled <2005OL5043>.



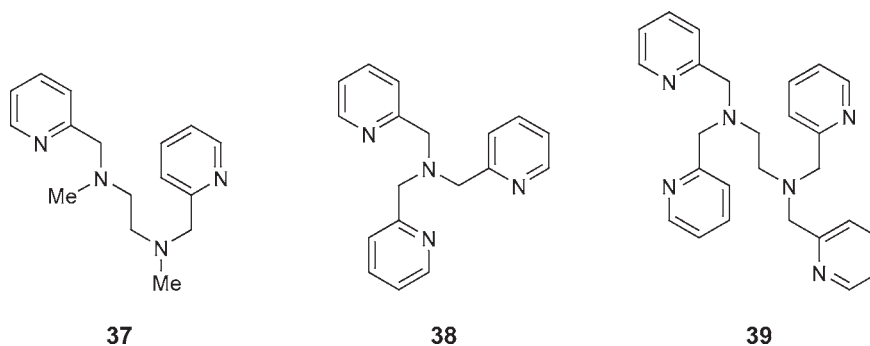
Optically active (–)-sparteine, a piperidine-derived alkaloid complexed with palladium chloride **33**, has been used in the enantioselective oxidation of benzyl alcohol derivatives <2005JA14817>. 4-Hydroxy-TEMPO **34** serves as an efficient catalyst for the continuous production of aldehydes from alcohols and bleach in a tube reactor (TEMPO = 2,2,6,6-tetramethyl-piperidine-1-oxyl) <2005OPD577>.



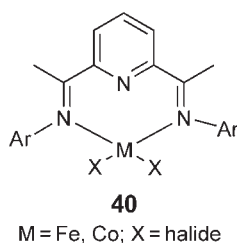
The dialkylaminopyridine-functionalized mesoporous silica nanosphere **35** is an efficient and highly stable heterogeneous nucleophilic catalyst <2005JA13305>. The bidentate ligand QUINAPHOS, possessing phosphine and phosphoramidite groups attached to a 1,2-dihydroquinoline derivative **36**, provides high enantiomeric excess for the rhodium-catalyzed hydrogenations of enamides to α -aminoesters and itaconic esters to α -substituted succinate esters <2006PMR54>.



Manganese-containing complexes with pyridine ligands based on picolylamines **37–39** have been patented for pulp bleaching <2006AGE206>. Neutral and cationic dendritic palladium complexes containing *N,N'*-iminopyridine chelating ligands have been used for the syndiospecific copolymerization of carbon monoxide and 4-*tert*-butylstyrene <2006OM3045>.



Metallocene-based catalysts that feature well-defined active sites are replacing traditional Ziegler–Natta olefin polymerization catalysts. The metallocene catalysts feature early-transition metals (Ti, Zr, Hf) and there is an intense research effort to find alternative single-site catalysts based upon less-expensive late-transition metals such as Fe, Co, and Ni. Highly active iron- and cobalt-based polymerization catalysts have been discovered that contain the 2,6-bis(arylimino)pyridine ligand **40** <1998JA4049>. Other notable reports of pyridine-containing ligands used for selective olefin oligomerization involve a hafnium pyridylamide catalyst <2006MI9> and chromium pyridylamine catalysts <2006WO096881>.



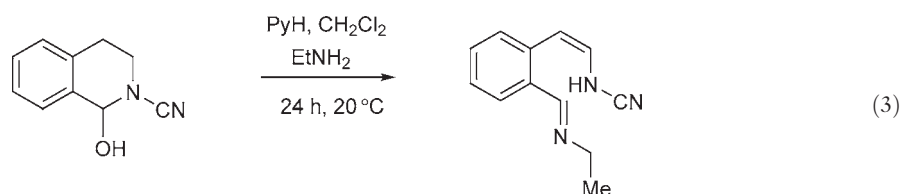
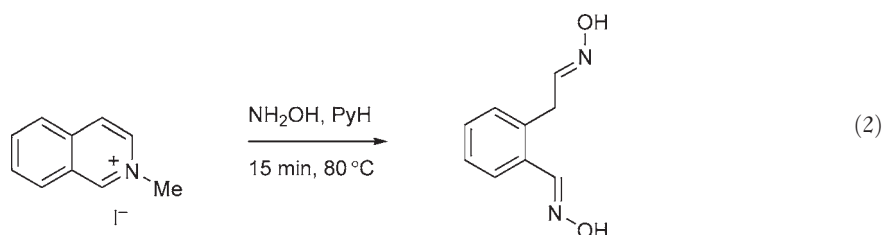
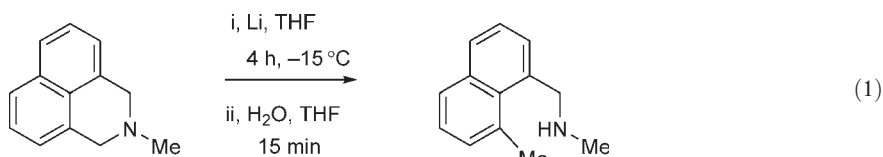
Both piperidine and pyridine serve as structure-directing agents in the commercial production of Ferrierite zeolite. More recently, use of DMAP has allowed preparation of novel metallo-aluminophosphate molecular sieves with both small- <2006WO2006037437> and large-pore architecture <2006USA074267>.

7.06.5 Synthesis of Compounds with Pyridine Ring Opening

7.06.5.1 Nonheterocycles

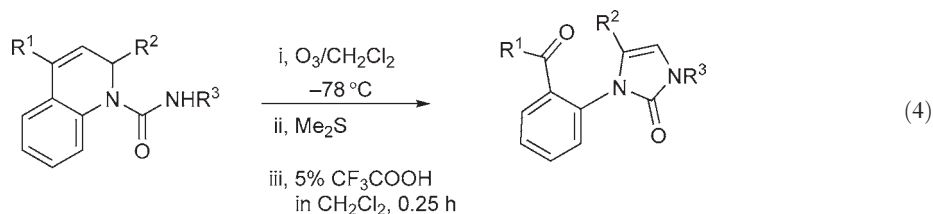
The C–N bond cleavage of a benzo tetrahydroisoquinoline compound with lithium metal followed by aqueous quenching formed a naphthalene derivative Equation (1) <2000T8375>. An isoquinolinium ring system has been converted into a highly functionalized 1,2-disubstituted benzene compound. Ring opening of the quaternary salt was

achieved using hydroxylamine [Equation \(2\)](#) [<1999ZNB532>](#). Similarly, the 1-hydroxy-2-cyanoisoquinoline compound underwent ring opening with ethylamine to give a 1,2-disubstituted benzene compound [Equation \(3\)](#) [<2000H\(53\)821>](#).



7.06.5.2 Nonpyridine Heterocycles

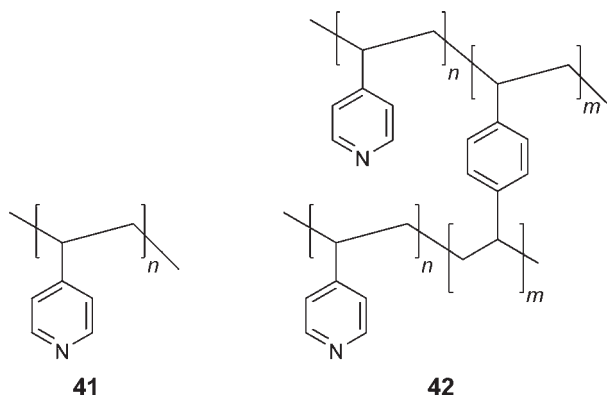
A novel approach to imidazol-2-one formation in four easy steps involves rearrangement of a quinoline compound. The quinoline is first converted into a 1,2-dihydro compound by adding a Grignard reagent in presence of a chloroformate and the important ring opening of the pyridine ring is achieved by ozonolysis [Equation \(4\)](#) [<2000TL6387>](#).



7.06.6 Polymers

The excellent review of pyridine polymers in CHEC-II(1996) [<1996CHEC-II\(5\)245>](#) not only discussed aromatic compounds such as polyvinylpyridines, polyalkylaminopyridines, polyviologen, polyquinolines, and polyvinylquinolines, but also saturated heterocycles such as polypiperidines. The subsection on ion-exchange resins in the same CHEC-II(1996) [<1996CHEC-II\(5\)245>](#) review gave good account of the applications of cross-linked polyvinylpyridines and pyridines supported on polystyrene.

A recent article summarized applications of both linear [41](#) and cross-linked [42](#) polyvinylpyridines, referring them as versatile polymers [<2001SCM19>](#). Linear polyvinylpyridine polymers have bactericidal activity. Commercial applications include use as a dye-transfer inhibitor in laundry detergent and as a pretreatment agent in reactive dyeing processes. Cross-linked polyvinylpyridines, due to their thermal and chemical stability, find use as catalyst supports, while their quaternary salts have been used as ion-exchange resins and in industrial chromatography for separation of fermentation acids like citric acid from their carbohydrate precursors.



Copolymers made using styrene, butadiene, and vinylpyridine find use in latex-based adhesives for bonding wood <1999PRC80>. Poly(ethylene oxide)-block-poly-2-vinylpyridine micelles filled with palladium nanoparticles have been used in the selective hydrogenation of dehydrolinalool <2004JM0273>. The sulfonation product of bead polymers prepared from styrene, vinylpyridine, acrylonitrile, and divinylbenzene gave oxidatively stable ion exchangers <2002USP6472479>. The palladium complex of poly(4-vinylpyridine-co-acrylic acid) has been found to be an excellent catalyst for homogeneous hydrogenation of aromatic nitro compounds <2003JM01>.

7.06.6.1 Linear Polymers

The ionic polymers, poly(pyridinium salts) containing bulky organic counter ions such as tosylate or triflimide ions and nine methylene units in their backbones, were prepared by either the ring-transmutation polymerization or the metathesis reaction. These polymers exhibit both thermotropic liquid-crystalline and light-emitting properties <2006PSA1028>. Polyvinylpyridine prepared by precipitation polymerization, which leads to small bead sizes (0.2–2 μm) and large surface area, can immobilize the Grubbs III catalyst by direct coordination with ruthenium <2005SL2948>.

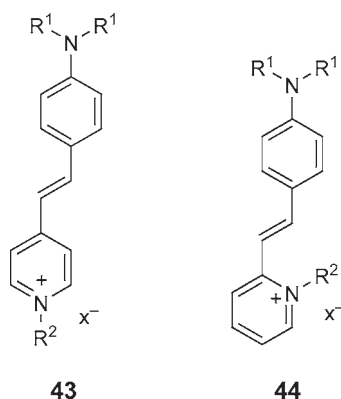
Vinylpyridine polymers encapsulating titanium-containing zeolites produce epoxidation catalysts with the propylene–hydrogen peroxide reaction giving high yields of propylene oxide. The catalysts can be easily recovered and reused and have shown low activity toward ring-opening reactions that form glycols <2005USP2005/0283009>.

7.06.6.2 Cross-Linked Polymers

Poly(4-vinylpyridine)-supported bromate in nonaqueous solution has been used in the bromination of aromatic compounds with potassium bromide <2005SC1947>. This bromination method is simple, efficient, mild, and selective for methoxyarenes, anilines, and phenols.

7.06.7 Dyes

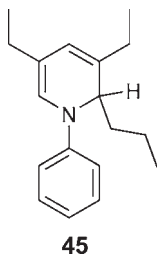
The uses of pyridine derivatives, such as aminopyridines, quinaldine, and acridine, together with quaternary salts and photochromic compounds are reviewed in CHEC-II(1996) <1996CHEC-II(5)245>. Pyridinium-based stilbazolium cationic dyes **43** and **44** were induced to give intense fluorescence by anionic peptide amphiphiles <2006CC1073>.



7.06.8 Performance Applications

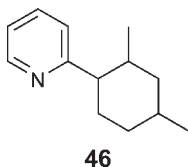
Performance applications focus on properties imparted by a particular compound. Whereas CHEC-II(1996) <1996CHEC-II(5)245> did not specifically cover performance applications, they were addressed under an additives section with subsections on antistatics, curing, inhibitors (for corrosion), stabilizers (against light), and others.

A dihydropyridine derivative **45** has been used as an adhesive activator for reactive acrylics <2006USA0178517>.



7.06.8.1 Flavors and Fragrances

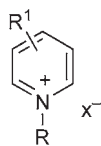
A European patent granted to Quest International Services BV involves use of pyridine derivatives as fragrance materials. 2-Alkyl-substituted pyridines are specifically mentioned, including all possible stereoisomers of 2-(2,4-dimethylcyclohexyl)pyridine **46**, which is made from 2-vinylpyridine and 2-methyl-1,3-pentadiene via the Diels–Alder reaction <2006EP01562904>.



7.06.8.2 Ionic Liquids

Ionic liquids, low melting point salts, are receiving considerable attention based upon a perception of being more environmentally benign compared to regular volatile organic solvents. Publications on the preparation and application of ionic liquids have grown at an astounding rate from 1996 to 2006. To date, a majority of the ionic liquids literature has focused on imidazolium-based materials with pyridinium-based materials receiving less attention.

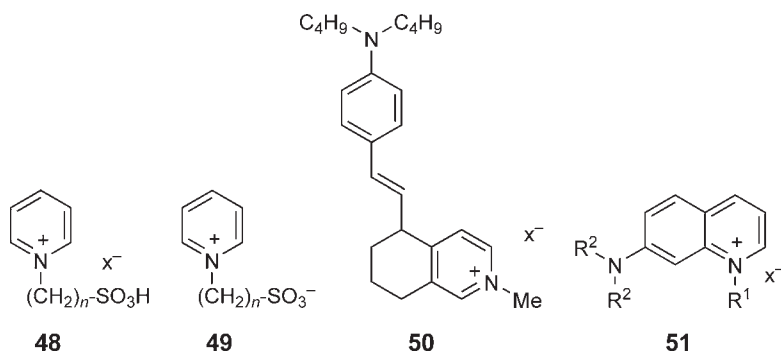
Pyridinium ionic liquids have a cationic entity containing a quaternized ring nitrogen that is charge-balanced with a suitable anion (usually a separate entity). Quaternary pyridinium salts such as paraquat, diquat, and cetylpyridinium chloride (see CHEC(1984) <1984CHEC(2)511> and CHEC-II(1996) <1996CHEC-II(5)245>) are solids well above room temperature and fall outside of the scope of being ionic liquids. Factors that contribute to determining whether a pyridine compound will be an ionic liquid at room temperature include choice of anion and N-substituent. The simplest cations such as *N*-alkylpyridinium and *N*-alkylpicolinium **47** provide ionic liquids with many applications.

**47**R = *n*-Bu; R¹ = H, CH₃

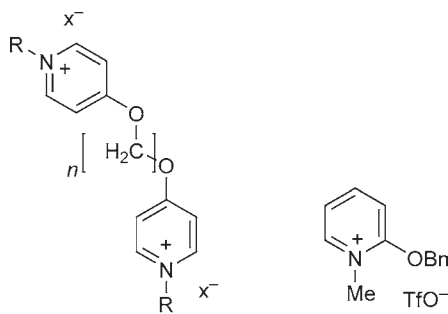
N-Butyl(4-methylpyridinium) tetrafluoroborate shows promise in the extraction of aromatic compound(s) from naphtha cracker feeds compared to sulfolane used in commercial practice <2005FP59>. Another refinery-based process involves the alkylation of isobutene by butanes using *N*-hydrocarbylpyridinium chloroaluminate ionic liquid catalysts <2006USA135839>.

N-Butylpyridinium tetrafluoroborate, containing dissolved phosphorus pentachloride, allows catalytic Beckmann rearrangement of cyclohexanone oxime giving ϵ -caprolactam with good conversion and selectivity <2001TL403>. The same ionic liquid containing dissolved ytterbium(III) trifluoromethanesulfonate was used to perform Friedel–Crafts acylation of furan and thiophene <2005JIC398>.

Ionic liquids based on sulfoalkylpyridinium salts **48** and **49** have been used in the application of esterification, Beckmann rearrangement, and carbonylation reactions <2004CN1594280>, as well as transesterification forming biodiesel <2006CX294>. Tetrahydroquinolinium salts are known to align with acceptor molecules on anionic surfaces to form molecular diodes. The quinoline derivative, *N*-methyl-5-(4-dibutylaminobenzylidene)-5,6,7,8-tetrahydroisoquinolinium **50**, is very similar to the stilbazolium salts seen earlier in the cationic dyes section <2006CC1404>. Quinolinium based ionic liquids, 7-dialkylamino-1-methylquinolinium salts **51**, are excellent color-shifting, mobility-sensitive fluorescent probes for polymer characterization and other demanding applications <2006JOC2666>.

**48****49****50****51**

Bicyclic pyridinium salts similar to 4,4'-(1,6-hexamethylenedioxy)-bis(1-octylpyridinium bromide) **52** have been found to have higher antibacterial and antifungal activity than benzalkonium chloride <2005JP2005325037>. Benzylation of a wide range of alcohols occurs in good to excellent yield under mild conditions using 2-benzyloxy-1-methylpyridinium triflate **53**, which is a stable, neutral organic salt <2006JOC3923>.

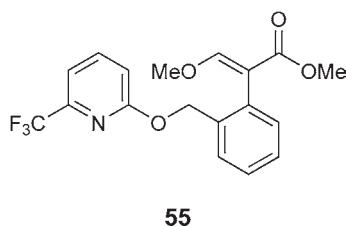
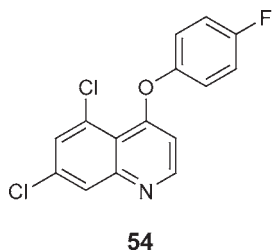
**52****53**

7.06.9 Agrochemicals

Use of pyridines and their benzo derivatives in agriculture is a consequence of their considerable bioactivity in herbicide, insecticide, and fungicide applications. The reader should refer to CHEC(1984) 1984CHEC(2)511> and CHEC-II(1996) <1996CHEC-II(5)245>, as many of the compounds discussed therein remain of great commercial importance. Interest continues in developing new products containing pyridine-based compounds, some of which are mentioned below.

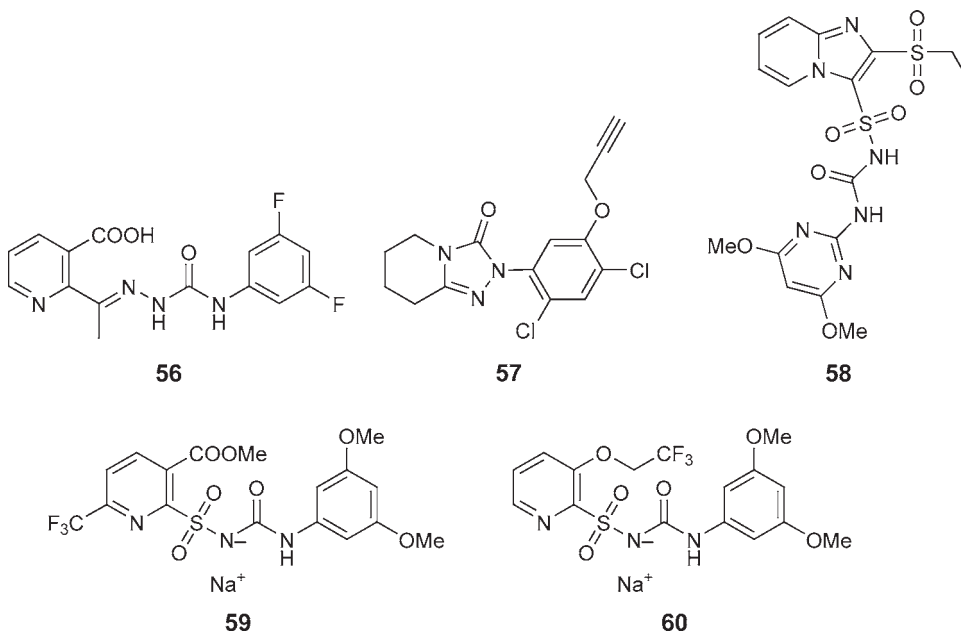
7.06.9.1 Fungicides

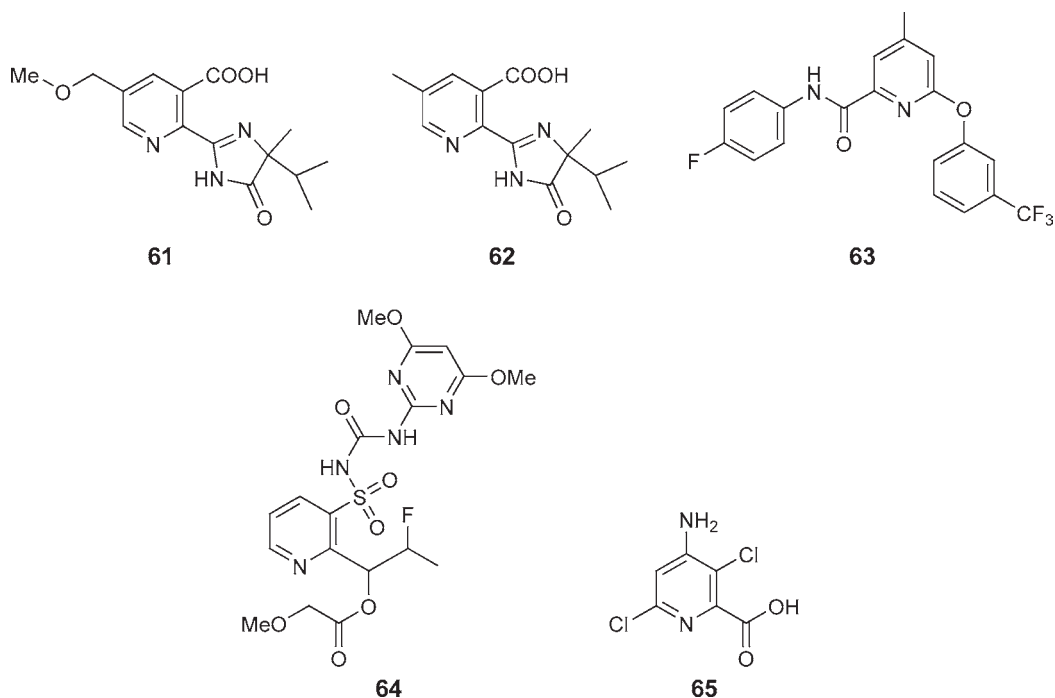
The quinoline-based quinoxifen **54** has been used as a fungicide for protection against cereal powdery mildew <1996MI(269)18>. Picoxystrobin **55** is also a newer fungicide making significant commercial impact <1999MI(324)27>.



7.06.9.2 Herbicides

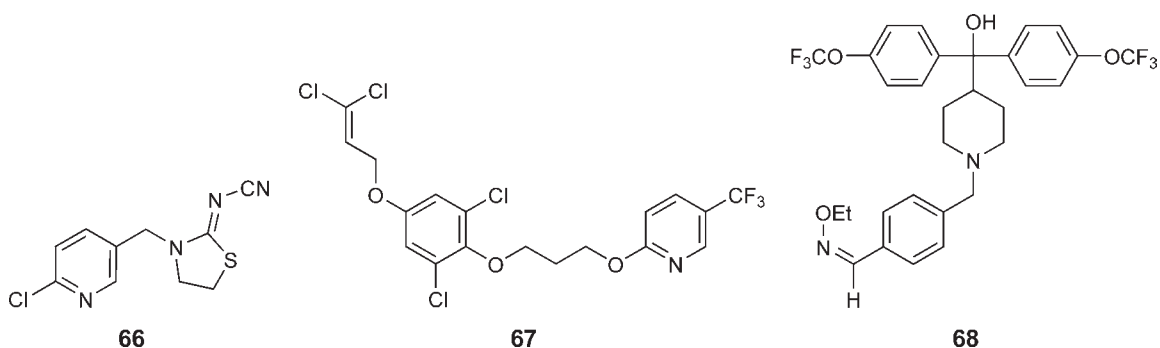
Numerous herbicides based on pyridine derivatives have been reported during the last decade and include diflu-fenzopyr **56** <1996MI(261)21>, azafenidin **57** <1996MI(247)19>, sulfosulfuron **58** <1996MI(261)22>, sulfonylurea flupyrsulfuron **59** <1995MI(244)26>, postemergent herbicide trifloxysulfuron sodium **60** <2001MI(389)23>, imazamox **61** <1995MI(244)26>, imazapic **62** <1997MI(287)21>, aryloxyphenylamide **63** <1999MI(341)19>, sulfonyl urea flucetosulfuron **64** <2003MI(436)20>, and aminopyralid **65** <2002MI(408)22>. Phenylpyridine derivatives similar to compound **63** can be made from a coupling reaction of 6-chloro-*N*-(4-fluorophenyl)-4-methylpyridin-2-carboxamide with 3-trifluoromethoxyphenylboronic acid, and showed herbicidal activity against *Monochoria vaginalis* <2006WO2006/0006569>.





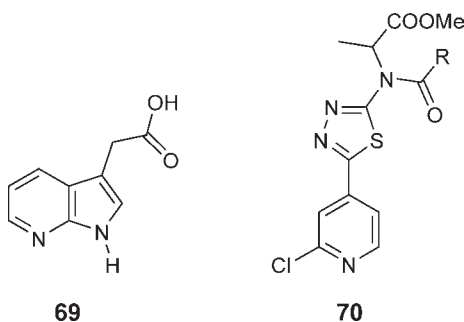
7.06.9.3 Insecticides

Thiacloprid **66** has been used as an insecticide and is the next generation after the industry standard imidacloprid <1997MI(287)21>. Pyridalyl **67** is also an insecticide used mainly with cotton and vegetable crops <2002MI(413)24>. Insecticides based on oximino and hydrazono derivatives of *N*-benzyl-4-benzhydryl- and *N*-benzyl-4-benzhydropiperidines have been reported. For example **68**, the condensation product of *N*-(4-formyl-benzyl)-4-[bis(4-trifluoromethoxyphenyl)-hydroxymethyl]piperidine with *O*-ethyl hydroxylamine-HCl showed good insecticidal activity against tobacco budworm <1999WO9914193>.



7.06.9.4 Plant Growth Regulators

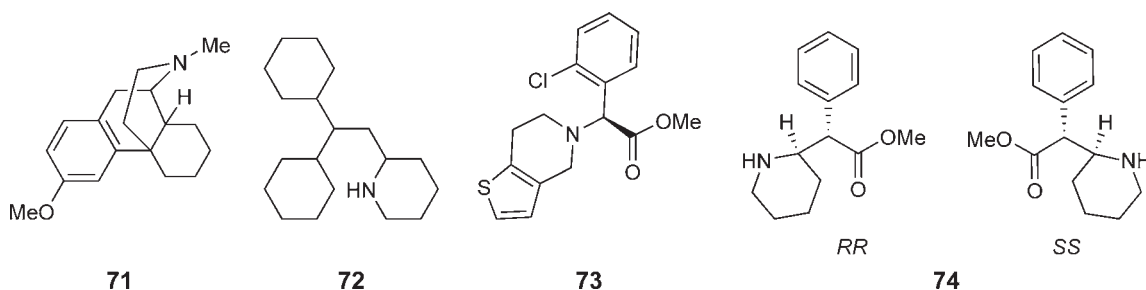
The pyridine compounds used as plant growth regulators include 1*H*-pyrrolo[2,3*b*]pyridine-3-acetic acid **69** <2004BPC247> and 2-amino-5[(2-chloropyridin-4-yl)-1,3,4-thiadiazole] **70** <2002YH795>, with the latter compound having additional fungicidal activity.



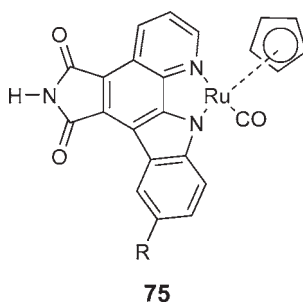
7.06.10 Pharmaceuticals

The commercial availability of pyridine derivatives and the biological activity of naturally occurring pyridine compounds has encouraged a tremendous amount of research on pharmaceutically active compounds containing pyridine and its derivatives ring systems. Pyridine-based pharmaceutical intermediates were described in CHEC(1984) <1984CHEC(2)511> according to the nature of ring substituent on the pyridine derivative, or its quaternary salt, and included carboxylic, alkyl, halo, and hydroxyl groups. The uses of pyridines and their derivatives in pharmaceuticals were described in CHEC-II(1996) <1996CHEC-II(5)245> with a focus on end use including analgesics, anesthetics, and psychopharmacologicals among others. This account continues the approach adopted in CHEC-II(1996) <1996CHEC-II(5)245>.

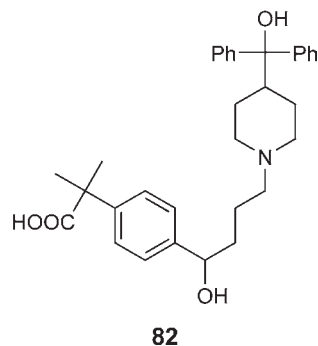
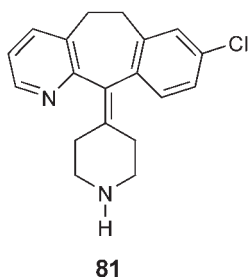
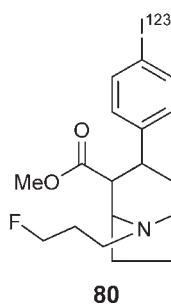
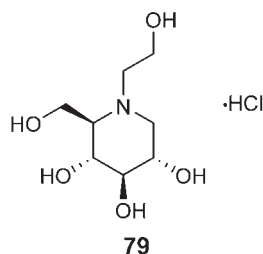
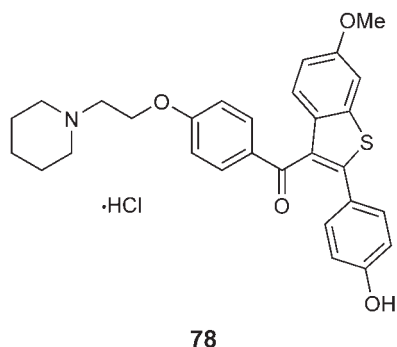
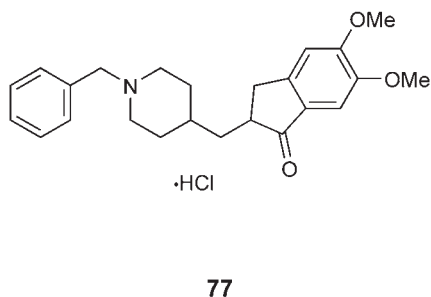
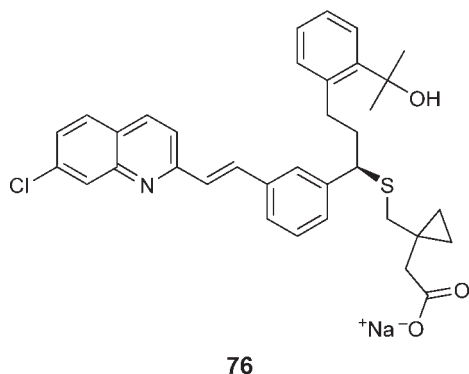
The importance of chiral isomers in pyridine-based drugs has recently emerged in several prominent cases. For example, the mirror image of the common cough suppressant **71** (dextromethorphan) is a potent narcotic. Perhexiline **72**, a drug used to treat abnormal heart rhythms, ultimately led to the deaths of many people due to the accumulation of a toxic stereoisomer in the body. Plavix® **73** or (*S*)-clopidogrel, a blockbuster drug used for thinning blood, is being battled in the courtroom where generic drug makers intend to invalidate a 1989 patent on the chiral version (the racemic version was originally patented in 1983). The stereoisomer of a drug may have other beneficial properties and such is the case with Ritalin **74**, where the (*R,R*)-configuration is used to treat ADHD whereas its mirror image (*S,S*)-isomer is found to have antidepressant properties <2003MI57>.



Organometallic compounds often show unique catalytic properties that may also allow their use as potential drug candidates. The cyclopentadienyl–ruthenium carbonyl catalyst **75**, that bears a quinoline-based bidentate ligand, was found to be a potent inhibitor of certain protein kinases <2006AGE1504>.



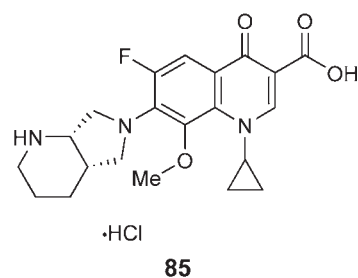
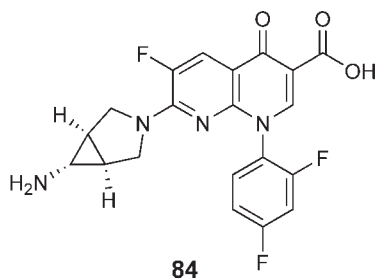
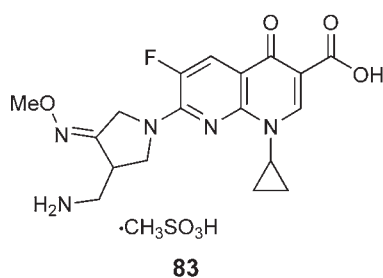
A 2,7-disubstituted quinoline derivative, montelukast sodium **76**, is used as an agent for rhinitis <1996USP5523477>. Donepezil hydrochloride **77**, a 1,4-disubstituted piperidine derivative, is used as treatment for cognition disorders <1990USP4895841>. A N-substituted piperidine derivative, keoxifene hydrochloride **78**, is an estrogen receptor modulator <2003EP0605193>. Miglitol **79**, a pentasubstituted piperidine derivative, is a glucosidase inhibitor <1977DE2758025>. Ioflupane **80**, a complex bicyclic compound that contains a substituted piperidine and an I¹²³ attached aryl ring, has been used a diagnostic agent <2000DDR478>. Desloratadine **81**, a 4-substituted piperidine derivative, is an antihistamine <1991EP0208855>. Fexofenadine **82**, a 1-substituted azacyclonol derivative, is a metabolite of terfenadine as well as an anti-inflammatory agent against allergic rhinitis <1993WO93/23047>.



7.06.10.1 Anti-Infective Agents

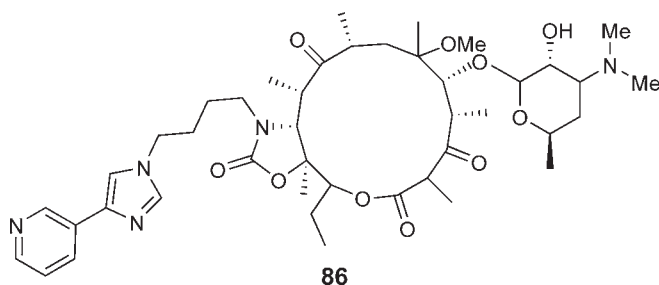
7.06.10.1.1 Antibacterial agents

Similar to quinolone antibiotics, the naphthyridone derivative gemifloxacin mesilate **83** is an antibacterial compound <1999EP688772>. Trovafloxacin **84**, another naphthyridone derivative, is also an active antibacterial <1998EP0676199>. A quinolone compound containing a disubstituted piperidine ring, moxifloxacin hydrochloride **85**, is an ophthalmic antibacterial agent <1992DE4208789>.



7.06.10.1.2 Antibiotics

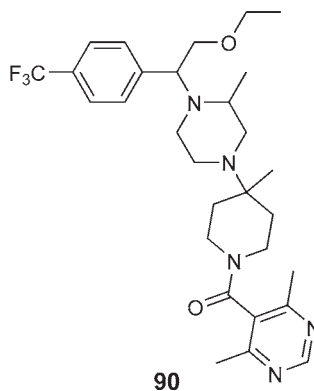
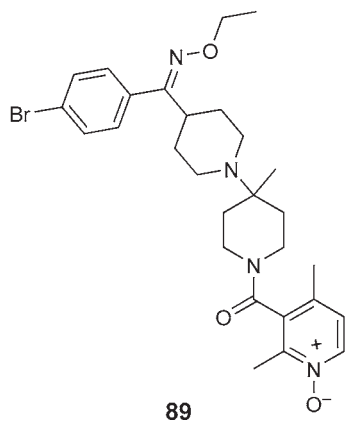
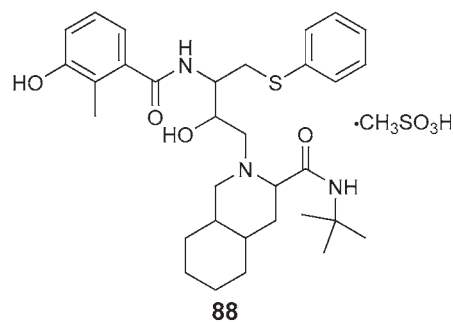
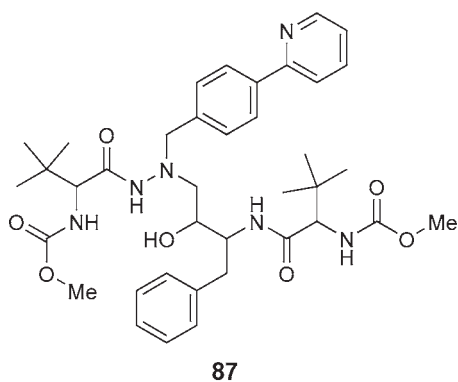
Telithromycin **86** is a macrolide containing a 3-substituted pyridine and is used as an antibiotic <1998EP0680967>.



7.06.10.1.3 Antiviral agents (HIV/AIDS)

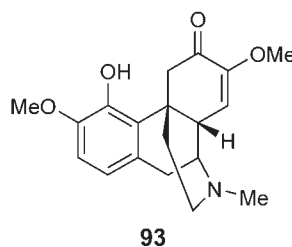
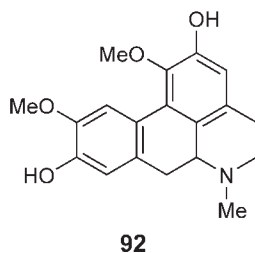
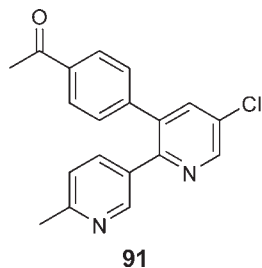
Atazanavir **87**, a 2-arylsubstituted pyridine derivative, is used as an antiviral AIDS drug <1998USP5849911>.

Nelfinavir mesilate **88** has found use as an antiviral agent <1994DDR1043>. Potential drugs for HIV inhibition that contain pyridine functionalities are Sch-C **89** and Sch-D **90** <2003MI30>.



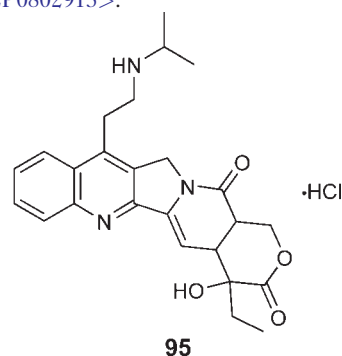
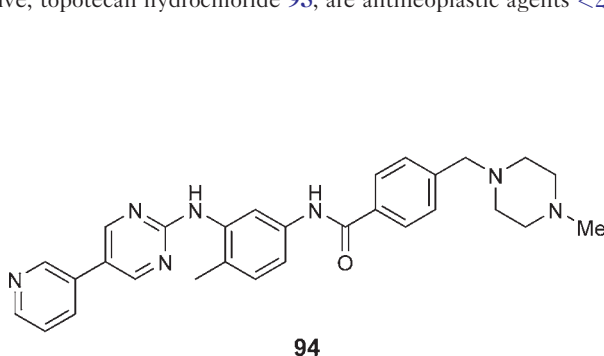
7.06.10.2 Anti-Inflammatory Agents – Nonsteroidal

2,3'-Bipyridines **91** have been used as nonsteroidal anti-inflammatories <2004ES2214130>. Two other nonsteroidal anti-inflammatory agents are boldine **92**, a dibenzoquinoline derivative, and sinomenine **93**, an isoquinoline derivative <B-2001MI1>.



7.06.10.3 Antineoplastic Agents

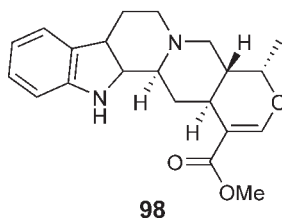
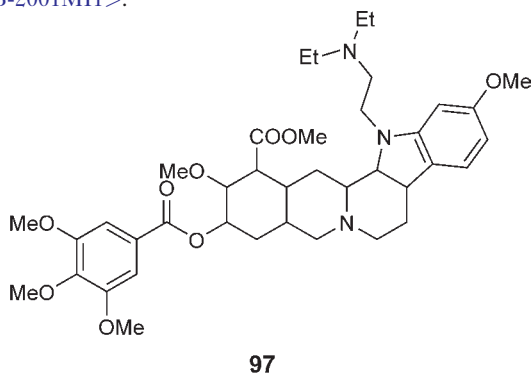
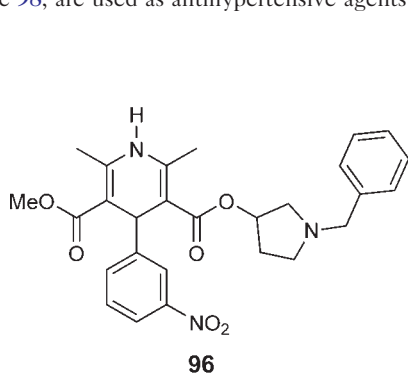
Imatinib mesylate **94** containing a 3-substituted pyridine ring <2000EP0564409>, and a trisubstituted quinoline derivative, topotecan hydrochloride **95**, are antineoplastic agents <2002EP0802915>.



7.06.10.4 Cardiovascular Drugs

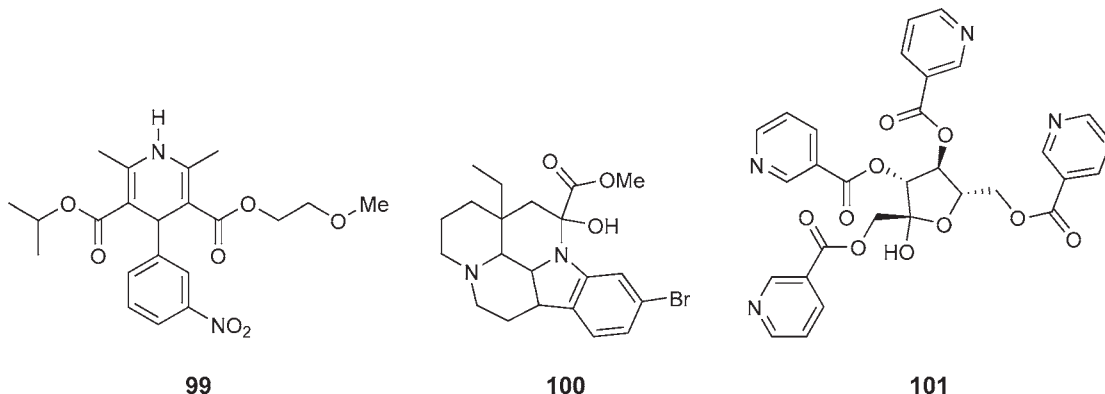
7.06.10.4.1 Antihypertensive agents

Barnidipine **96**, a 1,4-dihydropyridine derivative, and indole-fused piperidine derivatives, bictaserpine **97** and raubasine **98**, are used as antihypertensive agents <B-2001MI1>.



7.06.10.4.2 Vasodilator agents

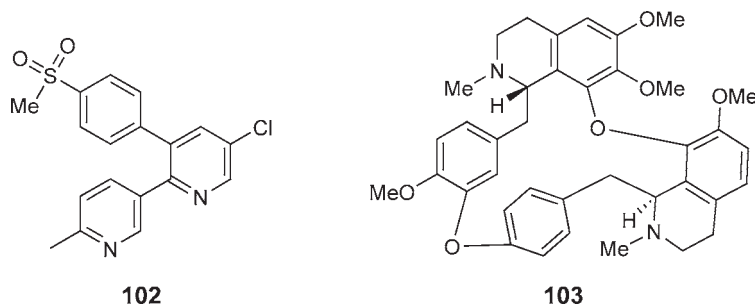
A 1,4-dihydropyridine derivative, nimodipine **99**, has been used as a cerebral vasodilator. The indolopiperidine derivative, brovincamine **100**, and furano-nicotinic ester derivative, nicofuranose **101**, are peripheral vasodilators <B-2001MI1>.



7.06.10.5 Central Nervous System Agents

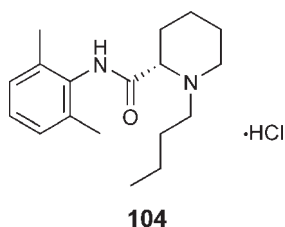
7.06.10.5.1 Analgesics

Etoricoxib **102**, a 2,3-bipyridine derivative, has been used as a nonopioid analgesic <2003EP0912518>. A bis-tetrahydroisoquinoline derivative, tetrandrine **103**, has been used as an analgesic and is present in the Chinese drug han-fang-chi <B-2001MI1>.



7.06.10.5.2 Anesthetics

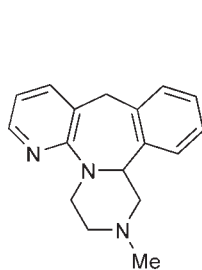
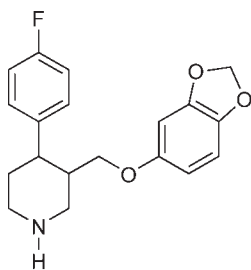
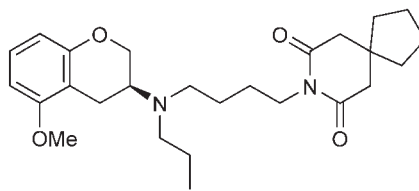
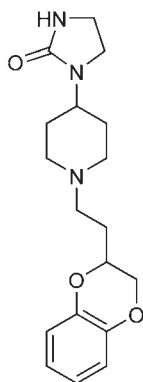
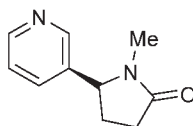
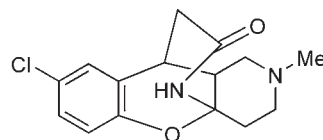
Levobupivacaine hydrochloride **104**, a 1,2-disubstituted piperidine derivative, is used as a local anesthetic <1997EP0723444>.



7.06.10.5.3 Antidepressants

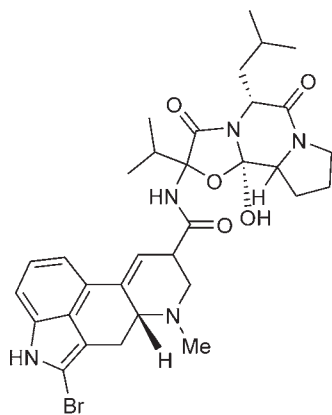
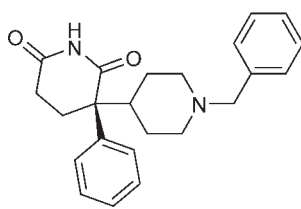
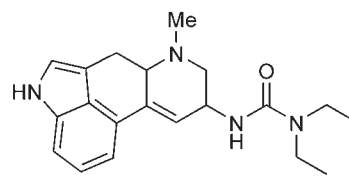
Mirtazapine **105**, a polycyclic pyridine derivative containing a pyridine ring fused with an azepine ring system, is an antidepressant <2006WO2006/008302>. The piperidine derivatives paroxetine **106**, alnespirone **107**, and Azaloxan

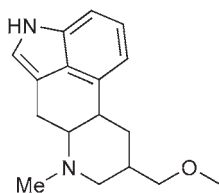
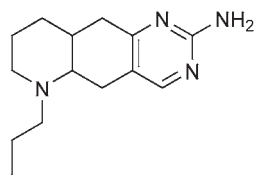
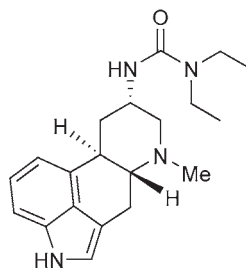
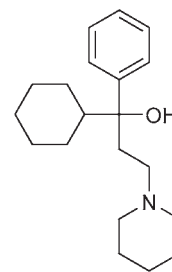
108 show antidepressant activity <2006OL1657>. Other compounds with antidepressant activity include cotinine **109**, a nicotine derivative, and lortalamine **110**, a tetracyclic heterocycle <B-2001MI1>.

**105****106****107****108****109****110**

7.06.10.5.4 Anti-Parkinson agents

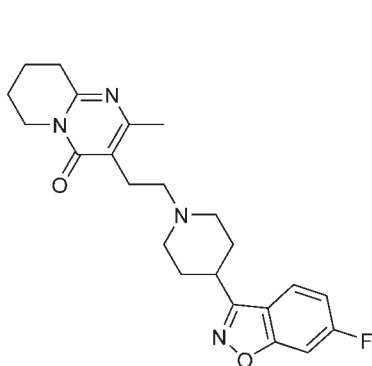
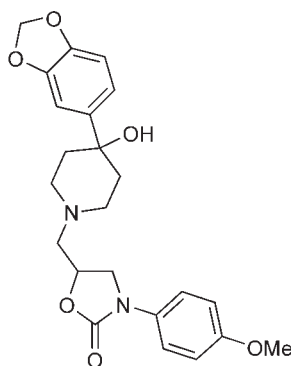
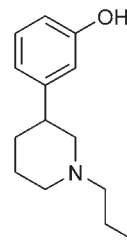
Many drugs based on pyridine derivatives treat symptoms of Parkinson disease. The various pyridine derivatives are bromocriptine **111**, an indole-fused quinoline derivative, dextemide **112**, a 4-substituted 1-benzylpiperidine derivative, lisuride **113**, an indole-fused quinoline derivative, pergolide **114**, another indole-fused quinoline derivative, quinlorane **115**, a pyrimidine-fused saturated quinoline derivative, terguride **116**, a saturated quinoline derivative, and trihexyphenidyl **117**, a 1-substituted piperidine derivative <B-2001MI1>.

**111****112****113**

**114****115****116****117**

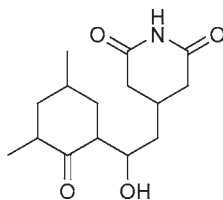
7.06.10.5.5 Antipsychotic agents

Risperidone **118** has been used to treat schizophrenia and bipolar disorder [<1997WO042940>](#). Piperidine derivatives such as panamesine **119**, a 1,4,4-trisubstituted piperidine, and preclamol **120**, a 1,3-disubstituted piperidine, have also been used as antipsychotic agents [<B-2001MI1>](#).

**118****119****120**

7.06.10.6 Dermatologic Agents – Antipsoriatics

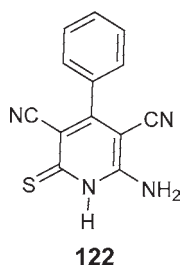
The 4-substituted glutarimide derivative cycloheximide **121** is an antipsoriatic agent [<B-2001MI1>](#).

**121**

7.06.10.7 Gastrointestinal Agents

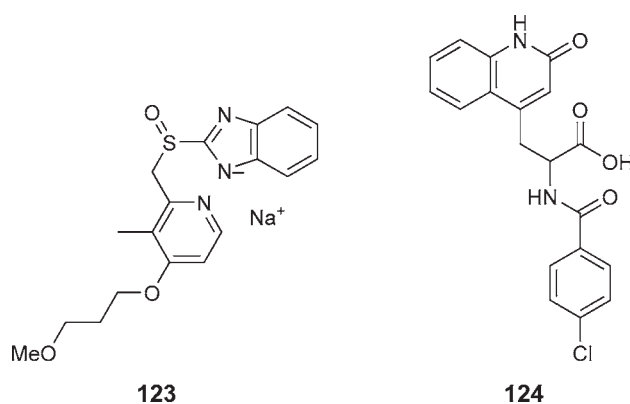
7.06.10.7.1 Antiemetics

Substituted 2-thio-3,5-dicyano-4-phenyl-6-aminopyridine **122** has been used in the treatment of nausea and vomiting [<2006WO2006/002823>](#).



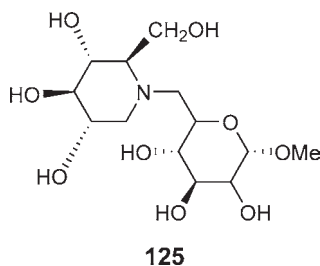
7.06.10.7.2 Antiulcer agents

Pariprazole **123**, a relative of omeprazole containing a trisubstituted pyridine ring, has been used as an antiulcer drug, an H^+/K^+ ATPase inhibitor, and an antihelicobacterpylori agent <1994EP268956>. A 4-substituted 2-quinolone derivative, rebamipide **124**, is an antiulcerative drug <B-2001MI1>.



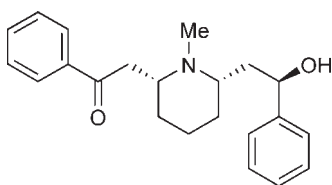
7.06.10.8 Metabolic Diseases – Antidiabetic agents

An azasugar derivative, camiglibose **125**, is an antidiabetic drug <B-2001MI1>.



7.06.10.9 Respiratory System Agents – Antiasthmatic agents

Lobeline **126**, a 2,6-disubstituted *N*-methylpiperidine, is used as a respiratory stimulant and is also found in the leaves and seeds of *Lobelia inflata* L. Lobeliaceae (or Indian tobacco) <B-2001MI1>.

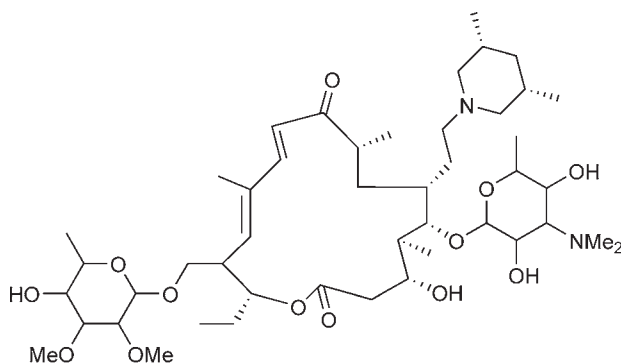


126

7.06.11 Veterinary Products

The use of pyridine and quinoline derivatives in the growth of poultry and related animal industries is described in CHEC(1984) <1984CHEC(2)511>. In CHEC-II(1996) <1996CHEC-II(5)245>, discussion of veterinary products had subsections covering anthelmintics, antiparasitics, and antibacterials. It is pointed out in CHEC-II(1996) <1996CHEC-II(5)245> that drugs developed for human use often find a place in veterinary medicine.

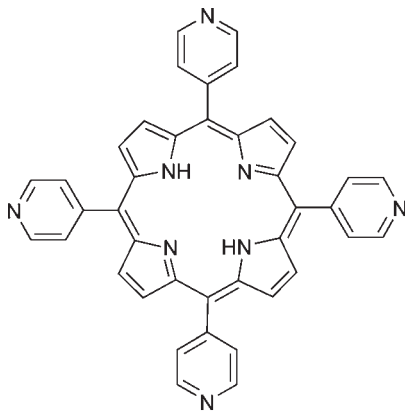
Micotil or Tilmicosin **127**, a 1-substituted 3,5-lupitidine (85:15 mixture of *cis/trans*-isomers), is used as an antibacterial agent against calf pneumonia. The macrolide component of micotil is structurally related to the antibacterial compound tylosin <1993JAVMA273>.

127
cis-Form

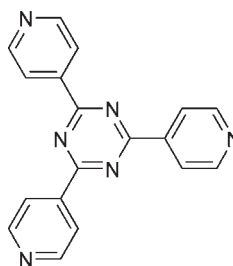
7.06.12 Miscellaneous

Some noteworthy reviews on applications of pyridines and their derivatives deal with oligopyridine liquid crystals as novel building blocks for supramolecular architectures based on metal coordination and hydrogen bonding <2000AGE2454>, enantioselective automultiplication of chiral pyridylalkanols by asymmetric autocatalysis <2000ACR382>, and photoactive mono- and polynuclear Cu(I)-phenanthrolines <2001CSR113>.

Coordination polymer nanotubes have been prepared using Hg²⁺-mediated coassembly of two ligands, tetrapyrroldiporphine (TPyP) **128** and tris(4-pyridyl)-1,3,5-triazine (TPyTa) **129** (which is readily formed by the trimerization of 4-cyanopyridine under acid- or base-catalyzed conditions), at the water–chloroform interface <2006CC3175>.



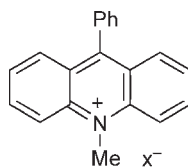
128



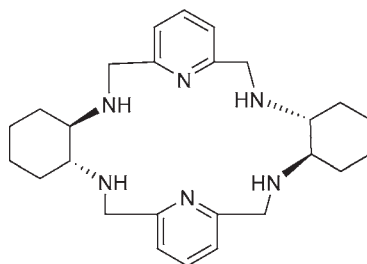
129

Recent reports of simple nitration methods using N_2O_5 , or its equivalents, led to the synthesis of nitropyridine derivatives in sufficient amounts to make them available for further reactions <2003SCM30>. An efficient synthesis of fluoro-, hydroxy-, and methoxy-pyridines starting from nitropyridines is reported. The reaction is mediated by tetrabutylammonium salts under mild conditions and is general for 2- and 4-nitro substituted pyridines. The 3-nitropyridines require additional electron-withdrawing groups on the pyridine ring for the reaction to proceed efficiently <2005OL577>.

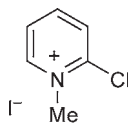
The acridinium salt **130** is a photocatalyst in the solvent-free selective photocatalytic oxidation of benzyl alcohol to benzaldehyde using molecular oxygen <2006CC2018>. Pyridine *N*-oxides and other *N*-heteroarene *N*-oxides undergo deoxygenation in basic conditions using benzyl alcohol that undergoes oxidation to benzaldehyde <2005JOC3218>.

**130**

The macrocycle **131**, containing a 2,6-dipicolyl fragment, has been used as a receptor for malate dianion in aqueous solution <2006CC1227>. 4-Aminopyridine coordinated to $\text{Ag}(\text{I})$ and hydrogen-bonded to nitrate forms a high-symmetry three- and four-connected hydrogen-bonded three-dimensional network <2006CC1082>.

**131**

Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide **132**, is of use in peptide synthesis. The dehydrothiolation step in the presence of Mukaiyama's reagent prevents Edman degradation from occurring <2006JC0237>. A method of converting pyridines into 3-acylpyridines using *N*-activated pyridinium salts is reported. The cyanide adducts of *N*-MOM pyridinium salts react with strong acylating reagents to provide 3-acyl-4-cyano-1,4-dihydropyridines, which are readily aromatized to 3-acylpyridines using zinc chloride in refluxing ethanol <2004CHE759>.

**132**

References

- 1977DEP2758025 B. Jungo, H. P. Krause, L. Müller and W. Puls (Bayer), DE 2758025 (1977).
 1984CHEC(2)511 F. S. Yates; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees Eds.; Pergamon Press, Oxford, 1984, vol. 2, p. 511.
 1990USP4895841 H. Sugimoto, Y. Tsuchiya, K. Higurashi, N. Karibe, Y. Iimura, A. Sasaki, Y. Yamanishi, H. Ogura, S. Araki, T. Kosasa, *et al.* (Eisai Co. Ltd.), *US Pat.* 4895841 (1990).
 1991EP0208855 D. P. Schumacher, F. J. Villani, J. K.-K. Wong, B. L. Murphy, and J. E. Clark (Schering Corp.), *Eur. Pat.* 0 208 855 (1991).
 1992DEA4208789 U. Peterson, A. Krebs, T. Schenke, T. Philipps, K. Grohe, K.-D. Bremm, R. Endermann, K. G. Metzger, and I. Haller (Bayer), DE 42 08 789 (A1) (1992).
 1993JAVMA273 D. W. Morck, J. K. Merrill, B. E. Thorlaksona, M. E. Olson, L. V. Tonkinson, and J. W. Costerton, *J. Am. Vet. Med. Assoc.*, 1993, **202**, 273.

- 1993WO93/23047 J. K. Woodward, R. R. Okerholm, M. G. Eller, and B. E. McNutt, WO 93/23047 (A1) 1993.
- 1994DDR1043 *Drug Data Rep.*, 1994, **16**(11), 1043.
- 1994EP268956 S. Souda, N. M. K. Ueda, S. Miyazawa, K. Tagami, S. Nomoto, M. Okita, N. Shimomura, I. S. K. Kaneko, M. Fujimoto, M. Murakami, *et al.* (Eisai Co., Ltd.), *Eur. Pat.* 0 268 956 (B2) (1994).
- 1995MI(244)26 *Agrow*, 1995, 244, p. 26, PJB Publications Ltd, 17. Nov.
- 1996MI(247)19 *Agrow*, 1996, 247, p. 19, PJB Publications Ltd, 5. Jan.
- 1996MI(261)21 *Agrow*, 1996, 261, p. 21, PJB Publications Ltd, 2 Aug.
- 1996MI(261)22 *Agrow*, 1996, 261, p. 22, PJB Publications Ltd, 2 Aug.
- 1996MI(269)18 *Agrow*, 1996, 269, p. 18, PJB Publications Ltd, 29. Nov.
- 1996CHEC-II(5)245 M. Balasubramanian and J. G. Keay in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 245.
- 1996USP5523477 S. King, B. Pipik, and D. A. Colon (Merck & Co.), *US Pat.* 5 523 477 (1996).
- 1997EP0723444 H. J. Bardsley and L. Mather (Chiro Science), *Eur. Pat.* 0 723 444 (B1) (1997).
- 1997JAN537 H. Nagata, K. Ochiai, Y. Aotani, K. Aniko, M. Yoshida, I. Takahashia, and T. Tamaoki, *J. Antibiot.*, 1997, **50**, 537.
- 1997MI(287)21 *Agrow*, 1997, 287, p. 21, PJB Publications Ltd, 29. Aug.
- 1997WO042940 P. A. Burke (Alkermes Inc.), WO 042 940 (1997).
- 1998EP0676199 A. E. Girard and T. D. Gootz (Pfizer Inc.), *Eur. Pat.* 0 676 199 (1998).
- 1998EP0680967 C. Agouridas, J.-F. Chantot, A. Denis, S. Gouin d'Ambrières, and O. Le Martret (Hoechst Marion Roussel), *Eur. Pat.* 0 680 967 (B1) (1998).
- 1998JA4049 B. L. Small, M. Brookhart, and A. M. A. Bennett, *J. Am. Chem. Soc.*, 1998, **120**, 4049.
- 1998USP5849911 A. Fässler, G. Bold, H.-G. Capraro, M. Lang, and S.C. Khanna (Novartis), *US Pat.* 5 849 911 (1998).
- 1999EP688772 J. H. Kwak, Y. N. Jeong, J. I. Oh, S. H. Kim, H. Choi, D.-H. Nam, C. Y. Hong, Y. K. Kim, J. H. Chang, and M.Y. Kim (LG Chemical Ltd.), *Eur. Pat.* 0 688 772 (B1) (1999).
- 1999H(50)543 E. Sugino, T. Chosi, and S. Hibino, *Heterocycles*, 1999, **50**, 543.
- 1999MI(341)19 *Agrow*, 1999, 341, p. 19, PJB Publications Ltd, 12. Mar.
- 1999MI(324)27 *Agrow*, 1999, 324, p. 27, PJB Publications Ltd, 12. Mar.
- 1999MRC195 R. Marek, O. Humpa, J. Dostál, J. Slavík, and V. Sklenár, *Magn. Reson. Chem.*, 1999, **37**, 195.
- 1999PRC80 N. John and R. Joseph, *Plast. Rubber Compos.*, 1999, **28**, 80.
- 1999WO9914193 W. H. Yeager, I. R. Silverman, R. N. Henrie, II, T. G. Cullen, and C. J. Peake (FMC Corporation), WO 99 14,193 (1999).
- 1999ZNB532 H. Moehrl, R. Niessen, and Z. Znsen, *Z. Naturforsch. B*, 1999, **54**, 532.
- 2000ACR382 K. Soai, T. Shibata, and I. Sato, *Acc. Chem. Res.*, 2000, **33**, 382.
- 2000AGE2454 C. Tschierske, *Angew. Chem., Int. Ed.*, 2000, **39**, 2454.
- 2000CCA81 Z. Cimerman, S. Miljanic, and N. Galic, *Croat. Chem. Acta.*, 2000, **73**, 81.
- 2000DDR478 *Drug Data Rep.*, 2000, **22** (05), 0478.
- 2000EP0564409 J. Zimmermann (Novartis), *Eur. Pat.* 0 564 409 (B1) (2000).
- 2000H(53)821 M. Sugiura, K. Asai, K. Hatano, Y. Kuroono, and Y. Hamada, *Heterocycles*, 2000, **53**, 821.
- 2000JNP201 P. Maximo and A. Lourencio, *J. Nat. Prod.*, 2000, **63**, 201.
- 2000JNP323 S. De Marino, M. Iorizzi, F. Zollo, C. Debitus, J.-L. Menou, L. F. Ospina, M. J. Alcaraz, and M. Paya, *J. Nat. Prod.*, 2000, **63**, 323.
- 2000JNP1638 C. W. Wright, S. J. Marshall, P. F. Russell, M. M. Anderson, J. D. Phillipson, G. C. Kirby, D. C. Warhurst, and P. L. Schiff, Jr., *J. Nat. Prod.*, 2000, **63**, 1638.
- 2000JOC640 B. Kesteleyn and N. De Kimpe, *J. Org. Chem.*, 2000, **65**, 640.
- 2000OL373 K. Tanaka and S. Katsumura, *Org. Lett.*, 2000, **2**, 373.
- 2000T2921 G. M. Nicholas and T. F. Molinski, *Tetrahedron*, 2000, **56**, 2921.
- 2000T4541 P. Camps, J. Contreras, R. El Achab, J. Morral, D. Muñoz-Torrero, M. Font-Bardia, X. Solans, A. Badiac, and N. M. Vivas, *Tetrahedron*, 2000, **56**, 4541.
- 2000T8375 V. Azzena, S. Demartis, L. Pilo, and E. Piras, *Tetrahedron*, 2000, **56**, 8375.
- 2000TL6387 S. Wendeborn, T. Winkler, and I. Foisy, *Tetrahedron Lett.*, 2000, **41**, 6387.
- 2001CSR113 N. Armaroli, *Chem. Soc. Rev.*, 2001, **30**, 113.
- 2001JNP956 N. Alam, J. Hong, C. O. Lee, K. S. Im, B. W. Son, J. S. Choi, W. C. Choi, and J. H. Jung, *J. Nat. Prod.*, 2001, **64**, 956.
- 2001J(P1)523 T. Harayama, H. Akamatsu, K. Okamura, T. Miyagoe, T. Akiyama, H. Abe, and Y. Takeuchi, *J. Chem. Soc., Perkin. Trans. I*, 2001, 523.
- 2001MI(389)23 *Agrow*, 2001, 389, p. 23, PJB Publications Ltd, 30 Nov.
- B-2001MI1 In 'Chiral Drugs', C. A. Challener Ed.; Ashgate Publishing, Aldershot, UK, 2001, pp. 175–472.
- 2001SCM19 M. P. Grendze, R. Murugan, and E. F. V. Scriven, *Speciality Chem. Mag.*, 19 Sep. 2001.
- 2001TL403 J. Peng and Y. Deng, *Tetrahedron Lett.*, 2001, **42**, 403.
- 2002MI(408)22 *Agrow*, 2002, 408, p. 22, PJB Publications Ltd, 13 Sep.
- 2002MI(413)24 *Agrow*, 2002, 413, p. 24, PJB Publications Ltd, 29 Nov.
- 2002EJO2288 F. Bracher and J. Daab, *Eur. J. Org. Chem.*, 2002, 2288.
- 2002EJO4123 S. P. Gromov and N. A. Kurchavov, *Eur. J. Org. Chem.*, 2002, 4123.
- 2002EP0802915 S. S. Jew, H. S. Lee, J. K. Kim, K. D. Ok, K. H. Cha, M. G. Kim, K. K. Lee, J. M. Kim, H. J. Kim, and J. M. Hah (Chong Kun Dang Corp.), *Eur. Pat.* 0 802 915 (B1), 2002.
- 2002EROS1 T. Sammakia; in 'Encyclopedia of Reagents for Organic Synthesis: 2-Formyl-4-pyrrolidinopyridine', John Wiley & Sons, 2002. October 15 online posting.
- 2002JOC443 P. F. H. Schwab, F. Fleischer, and J. Michl, *J. Org. Chem.*, 2002, **67**, 443.
- 2002JOC3272 F. Mongin, F. Trécourt, B. Gervais, O. Mongin, and G. Quéguiner, *J. Org. Chem.*, 2002, **67**, 3272.
- 2002OL197 K. Schmidt, W. Gunther, S. Stoyanova, B. Schubert, Z. Li, and M. Hamburger, *Org. Lett.*, 2002, **4**, 197.
- 2002OL2385 T. Sammakia, E. L. Stangeland, and M. C. Whitcomb, *Org. Lett.*, 2002, **4**, 2385.
- 2002T9779 D. R. Appleton, N. Pearce, G. Lambert, R. C. Babcock, and B. R. Coppa, *Tetrahedron*, 2002, **58**, 9779.

- 2002USP6472479 B. Köhler, R. Seidel, O. Halle, and E. Wenz (Bayer Aktiengesellschaft), *US Pat.* 6 472 479 (2002).
- 2002YH795 C. Che, S. F. Mao, and Z. H. Qin, *Yingyong Huaxue*, 2002, **19**, 795.
- 2003EP0605193 L. J. Black, H. U. Bryant, J. G. Cullinan, and R. F. Kauffman (Eli Lilly and Co.), *Eur. Pat.* 0 605 193 (B1), (2003).
- 2003EP0912518 D. Dube, R. Fortin, R. Friesen, Z. Wang, and J. Y. Gauthier (Merck Frost Canada & Co.), *Eur. Pat.* 0 912 518 (B1) (2003).
- 2003MI(436)20 *Agrow*, 2003, 436, p. 20, PJB Publications Ltd, 21 Nov.
- 2003MI30 *Chem. Eng. News* 2003, p. 30, May 26.
- 2003MI57 *Chem. Eng. News* 2003, p. 57, May 3.
- 2003JM01 X. Xi, Y. Liu, J. Shi, and S. Cao, *J. Mol. Catal. A*, 2003, **192**, 1.
- 2003KD95 G. M. Pisichenko, *Khim. Dizain*, 2003, 95.
- 2003KPU28 T. S. Reznik and L. D. Bugaeva, *Khim. Promislovist Ukraini (Kiev, Ukraine)*, 2003, 28.
- 2003OL3567 C. A. Volk and M. Kock, *Org. Lett.*, 2003, **5**, 3567.
- 2003OL673 C. Campagnuolo, C. Fattorusso, E. Fattorusso, A. Ianaro, B. Pisano, and O. Tagliatela-Scafati, *Org. Lett.*, 2003, **5**, 673.
- 2003SCM30 J. M. Bakke, *Speciality Chem. Mag.* p. 30 Jun. 2003.
- 2004BPC247 D. Caric, V. Tomisic, M. Kveder, N. Galic, G. Pifat, V. Magnus, and M. Saskic, *Biophys. Chem.*, 2004, **111**, 247.
- 2004CHE759 A. Klapars and E. Vedejs, *Chem. Heterocyclic Comp.*, 2004, **40**, 759.
- 2004CN1594280 T. Wang, H. Xing, Z. Zhou, and laY. Dai, *Chin. Pat.* 1 594 280 (2004).
- 2004EROS1 J. Yoshida and K. Itami; in 'Encyclopedia of Reagents for Organic Synthesis: 2-Pyridyldimethylsilane', John Wiley & Sons, 1996, April 15 online posting.
- 2004ES2214130 F. C. Javaloyes and G. Waneellow, *SP Pat.* 2 214 130 (A1) (2004).
- 2004JM0273 N. V. Seragina, A. V. Bykov, E. M. Sulman, V. G. Matveeva, S. N. Sidrov, L. V. Dubrovina, P. M. Valetsky, A. V. Kiselyova, A. R. Khoklov, B. Stein, *et al.*, *J. Mol. Cat. A*, 2004, **208**, 273.
- 2004JOC2251 G. R. Pettit, H. Hoffmann, D. L. Herald, J. McNulty, A. Murphy, K. C. Higgs, E. Hame, N. E. Lewin, L. V. Pearce, P. M. Blumberg, *et al.*, *J. Org. Chem.*, 2004, **69**, 2251.
- 2005EJOC4073 J. Gil-Molto and C. Najera, *Eur. J. Org. Chem.*, 2005, 4073.
- 2005EROS1 R. T. Taylor; in 'Encyclopedia of Reagents for Organic Synthesis', John Wiley & Sons, 2005, October 15 online posting.
- 2005FP59 G. W. Meindersma, A. J. G. Prodt, and A. B. De Haan, *Fuel Processing*, 2005, **87**, 59.
- 2005JA13305 H. T. Chen, S. Huh, J. W. Wiench, M. Pruski, and V. S. Y. Lin, *J. Am. Chem. Soc.*, 2005, **127**, 13305.
- 2005JA14817 J. A. Mueller, A. Cowell, B. D. Chandler, and M. S. Sigman, *J. Am. Chem. Soc.*, 2005, **127**, 14817.
- 2005JIC398 W. Su and Y. Wang, *J. Indian Chem. Soc.*, 2005, **82**, 398 (Chem. Abstracts 144: 331192r).
- 2005JOC3218 H. R. Bjorsvik, C. Gambarotti, V. R. Jensen, and R. R. Gonzalez, *J. Org. Chem.*, 2005, **70**, 3218.
- 2005JP2005325037 H. Koma, Y. Igarashi, and H. Nobeshima, *Jpn. Pat.* 2005 325 037 (2005).
- 2005OL577 S. D. Kuduk, R. M. DiPardo, and M. G. Bock, *Org. Lett.*, 2005, **7**, 577.
- 2005OL5043 T. Maki, K. Ishihara, and H. Yamamoto, *Org. Lett.*, 2005, **7**, 5043.
- 2005OL5047 T. Maki, K. Ishihara, and H. Yamamoto, *Org. Lett.*, 2005, **7**, 5047.
- 2005OPD577 E. Fitz-Langhals, *Org. Process Res. Dev.*, 2005, **9**, 577.
- 2005SC1947 H. Tajik, F. Shirini, P. Hassan-Zadh, and H. R. Rashtabadi, *Synth. Commun.*, 2005, **35**, 1947.
- 2005SL2948 K. Mennecke, K. Grela, U. Kunz, and A. Kirschning, *Synlett*, 2005, 2948.
- 2005USA2005/0283009 B. Le-Khac (Lyondell Chemical Company), *US Pat. Appl.* 2005/0 283 009 (A1) (2005).
- 2006AGE206 R. Hage and A. Lienke, *Angew. Chem. Int. Ed.*, 2006, **45**, 206.
- 2006AGE1504 U. Schatzschneider and N. Metzler-Nolte, *Angew. Chem., Int. Ed.*, 2006, **45**, 1504.
- 2006CC1073 H. Hachisako and R. Murakami, *Chem. Commun.*, 2006, 1073.
- 2006CC1082 M. A. M. Abu-Youssef, V. Langer, and L. Ohrstrom, *Chem. Commun.*, 2006, 1082.
- 2006CC1227 A. G. Alvarez, I. Alfanso, P. Diaz, E. G. Espana, and V. Gotor, *Chem. Commun.*, 2006, 1227.
- 2006CC1404 G. J. Ashwell and A. Chrialkowska, *Chem. Commun.*, 2006, 1404.
- 2006CC2018 K. Ohkubo, K. Suga, and S. Fukuzumi, *Chem. Commun.*, 2006, 2018.
- 2006CC3175 B. Liu, D. J. Qian, M. Chen, T. Wakayama, C. Nakamura, and J. Miyake, *Chem. Commun.*, 2006, 3175.
- 2006CX294 Q. Wu, H. Chen, M. Han, J. Wang, D. Wang, and Y. Jim, *Cuihua Xuebao*, 2006, **27**, 294 (Chem. Abstr. 2006: 535212).
- 2006MI9 *Chem. Eng. News*, 2006, p. 9, May 8.
- 2006EP01562904 D. Munro (Quest International Services BV), *Eur. Pat.* 01 562 904 (B1) (2006).
- 2006JC0237 J. I. Gavriluk, G. Evindar, and R. A. Batey, *J. Comb. Chem.*, 2006, **8**, 237.
- 2006JOC1458 L. Pignataro, M. Benaglia, R. Ammunziata, M. Cinquini, and F. Cozzi, *J. Org. Chem.*, 2006, **71**, 1458.
- 2006JOC2666 O. van den Berg, W. F. Jager, and S. J. Picken, *J. Org. Chem.*, 2006, **71**, 2666.
- 2006JOC3923 K. W. C. Poon and G. B. Dudley, *J. Org. Chem.*, 2006, **71**, 3923.
- 2006OL769 H. V. Nguyen, D. C. D. Butler, and C. J. Richards, *Org. Lett.*, 2006, **8**, 769.
- 2006OL1657 J. C. Pastre and C. R. D. Correia, *Org. Lett.*, 2006, **8**, 1657.
- 2006OM3045 J. M. Benito, E. de Jesus, F. J. de la Mata, J. C. Flores, and R. Gomez, *Organometallics*, 2006, **25**, 3045.
- 2006PMR54 D. J. Ager, A. H. M. de Vries, and J. G. de Vries, *Platinum Met. Rev.*, 2006, **50**, 54.
- 2006PSA1028 P. K. Bhowmik, H. Han, and A. K. Nedeltchev, *J. Polym. Sci., Polym. Chem., Part A*, 2006, **44**, 1028.
- 2006USA0074267 G. Cao, M. J. Shah, J. F. Brody, D. L. Dorset, and K. G. Strohmaier, (ExxonMobil Chemical), *US Pat. Appl.* 0074267 A1 (2006).
- 2006USA135839 S. Elomari, S. Trumbull, H. Timken, C. Kyung, and R. Cleverdon (Chevron), *US Pat. Appl.* 0135839 (2006)
- 2006USA0178517 M. Grendze, R. Murugan, L. M. Huckstep, and C. R. Hopper (Reilly Industries), *US Pat. Appl.* 0178517 (2006).
- 2006WO2006/008302 C. A. Aguilar (Medichem SA), *WO* 2006/008 302 (A3) (2006).
- 2006WO2006/002823 T. Krahn, W. Thielemann, U. Rosentreter, N. Diedrichs, and T. Kramer, *WO* 2006/002 823 (A1) (2006).
- 2006WO2006/006569 E. Takizawa, S. Kumata, and T. Kiyokawa (Nihon Nohyaku Co. Ltd.), *WO* 2006/006 569 (A1) (2006).
- 2006WO2006/037437 G. Cao and M. J. Shah (ExxonMobil Chemical), *WO* 2006/037 437 A1 (2006).
- 2006WO2006/096881 L. J. Ackerman, X. Bei, T. R. Boussie, G. M. Diamond, K. A. Hall, A. M. Lapointe, J. M. Longmire, V. J. Murphy, P. Sun, D. Verdugo, *et al.* (ExxonMobil Chemical), *WO* 2006/096881 A1 (2006).

Biographical Sketch



Colin H. McAteer was born in London, UK, and obtained B.Sc. (Hons) and Ph.D. degrees from the University of Warwick. In 1984, after postdoctoral fellowships at the University of Illinois, Champaign-Urbana, and Oxford University, UK, he joined British Petroleum PLC at the Sunbury Research Centre, UK. In 1991, he moved to Reilly Industries, Inc., Indianapolis, that in 2006 became Vertellus Specialties Inc. Trained in synthetic, kinetic, and mechanistic inorganic chemistry, his industrial expertise is in catalyzed processes to make transportation fuels, petrochemicals, and specialty chemicals. He has patents in areas including GTL, glycol ethers, pyridine derivatives, and ionic liquids. His ongoing research interests include the catalyzed synthesis of pyridine bases and their alkenyl and cyano derivatives, as well as the use of isotope substitution to investigate the mechanism of catalyzed processes.



Marudai Balasubramanian "BALU" obtained his Ph.D. degree in Organic Chemistry from the Indian Institute of Technology, Chennai, India in 1987. He carried out postdoctoral work with Dr. Alan R. Katritzky at the Department of Chemistry, University of Florida, Gainesville, Florida (1988–1992). He subsequently moved to Reilly Industries Inc., Indianapolis, Indiana, where he was a research chemist until 2002. His research interests include synthesis of heterocyclic compounds, particularly pyridine derivatives, and synthesis of intermediates for pharmaceuticals, agrochemicals, performance products and heterocyclic polymers. In 2002, he joined Research Informatics, Pfizer at Ann Arbor, Michigan, as information professional. Currently he works at Pfizer, Groton and manages content and vendor relationship for the chemical related commercial databases. He is author/co-author of more than fifty scientific papers and has written several reviews, chapters for monographs and comprehensive heterocyclic chemistry series. He currently serves as an international editorial board member of *Heterocyclic Communications* an international journal of heterocyclic chemistry.



Ramiah Murugan was born in Madurai, obtained B.Sc. (Chemistry) from American College, and M.Sc. (Chemistry) from Madurai University. After four years of Junior Scientist work at Madurai University, he joined Professor Alan R. Katritzky's group in the Department of Chemistry at University of Florida and obtained his Ph.D. in 1987. He continued in Professor Katritzky's group for two more years doing postdoctoral work in the area of high-temperature aqueous organic chemistry. He joined Reilly Industries in 1989 (currently, it is Vertellus Specialties Inc.) and grew within the ranks from research chemist to currently senior research associate. His research interests include synthesis of intermediates for pharmaceuticals, agrochemical products, and performance products; mechanistic studies; catalysis; polymer chemistry; and process development. He has many patents and publications to his credit in the above-mentioned areas of interest.

7.07

Pyrans and their Benzo Derivatives: Structure and Reactivity

A. J. Phillips, J. A. Henderson, and K. L. Jackson

University of Colorado, Boulder, CO, USA

© 2008 Elsevier Ltd. All rights reserved.

7.07.1	Introduction	338
7.07.1.1	Nomenclature	338
7.07.2	Theoretical Methods	340
7.07.3	Experimental Structural Methods	340
7.07.3.1	NMR Spectroscopy	340
7.07.3.1.1	¹ H NMR spectra	341
7.07.3.1.2	¹³ C NMR spectra	343
7.07.3.1.3	¹⁷ O NMR spectroscopy	344
7.07.3.2	Mass Spectrometry	344
7.07.3.3	X-Ray and Electron Diffraction Methods	344
7.07.3.4	Microwave Spectroscopy	346
7.07.3.5	UV Spectroscopy, IR/Raman, and Photoelectron Spectroscopy	346
7.07.3.6	Dipole Moments	346
7.07.4	Thermodynamic Aspects	347
7.07.4.1	Aspects of Aromaticity and Stability	347
7.07.4.2	Conformation	347
7.07.4.3	Tautomerism	348
7.07.5	Pyrylium Salts and Their Benzo Derivatives	349
7.07.5.1	Reactivity at Ring Atoms	349
7.07.5.1.1	Introduction	349
7.07.5.1.2	Photochemical reactions	350
7.07.5.1.3	Reactions with electrophiles	350
7.07.5.1.4	Reactions with nucleophiles	352
7.07.5.1.5	Reduction	357
7.07.5.1.6	Cycloadditions	358
7.07.6	2H- and 4H-Pyrans and Their Benzo Derivatives	359
7.07.6.1	Reactivity at the Ring Atoms	359
7.07.6.1.1	Photochemical reactions	359
7.07.6.1.2	Reactions with electrophiles	360
7.07.6.1.3	Reduction	361
7.07.6.1.4	Cycloadditions	361
7.07.6.2	Reactivity of Substituents	361
7.07.7	Pyran-2-ones and Their Benzo Derivatives	362
7.07.7.1	Introduction	362
7.07.7.2	Reactivity at Ring Atoms	363
7.07.7.2.1	Thermal and photochemical reactions	363
7.07.7.2.2	Reactions with electrophiles	364
7.07.7.2.3	Reactions with nucleophiles	366
7.07.7.2.4	Reductions	371
7.07.7.2.5	Radicals	371

7.07.7.2.6	Other reactions	373
7.07.7.3	Reactivity of Substituents	376
7.07.7.3.1	Fused benzene rings	376
7.07.7.3.2	C-Linked substituents	378
7.07.7.3.3	O-Linked substituents	379
7.07.8	Pyran-4-ones and Their Benzo Derivatives	380
7.07.8.1	Reactivity at Ring Atoms	380
7.07.8.1.1	Photochemical reactions	380
7.07.8.1.2	Reactions with electrophiles	383
7.07.8.1.3	Reactions with nucleophiles	385
7.07.8.1.4	Reductions	391
7.07.8.1.5	Other reactions	392
7.07.8.2	Reactivity of Substituents	395
7.07.8.2.1	Fused benzene rings	395
7.07.8.2.2	C-linked substituents	397
7.07.8.2.3	N-Linked substituents	398
7.07.9	Reduced Pyrans and Pyrones and Their Benzo Derivatives	399
7.07.9.1	Reactivity at Ring Atoms	399
7.07.9.1.1	Photochemical reactions	399
7.07.9.1.2	Reactions with electrophiles	400
7.07.9.1.3	Reactions with nucleophiles	405
7.07.9.1.4	Other reactions	407
References		410

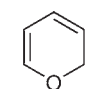
7.07.1 Introduction

7.07.1.1 Nomenclature

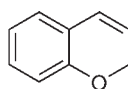
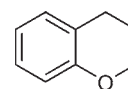
Six-membered oxygen-containing heterocycles are widespread through both the domains of ‘naturally occurring’ and ‘fully synthetic’ molecules. Many naturally occurring compounds containing pyrans and benzopyrans display interesting biological activity, which has, in part, motivated substantial attention from the chemical community at the levels of structure and reactivity, and synthesis and properties. A great deal of this material has been reviewed in CHEC(1984) and CHEC-II(1996), and the synthesis of pyrans and benzopyrans is covered in Chapter 7.08. The focus of this chapter is the structure and reactivity of this class of compounds.

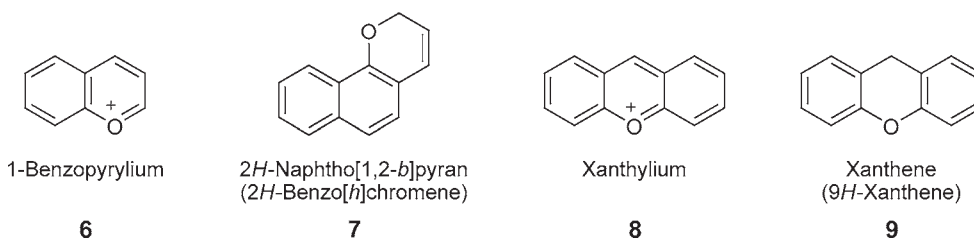
As was noted in CHEC-II(1996), a variety of names have been used for derivatives of pyrans and their benzo derivatives and many of these naming conventions have been reviewed in earlier works <1977HC(31), 1981HC(36)>. In the interests of continuity, and also because the use of common or trivial names is widespread in the literature, this chapter will also employ the nomenclature system that was employed in the corresponding chapter in CHEC-II(1996) <1996CHECII(5)301>. This material is reproduced for the readers’ benefit below.

Six-membered unsaturated oxygen heterocyclic compounds are based on three molecules: 2*H*-pyran **1**, 4*H*-pyran **2**, and the pyrylium ion **3**. Based on this, the benzo analog of 2*H*-pyran is named 2*H*-1-benzopyran (commonly 2*H*-chromene) and the benzo analog of 4*H*-pyran is called 4*H*-1-benzopyran (commonly 4*H*-chromene). The benzo analog of **3** is known as 1-benzopyrylium **6** (sometimes chromylum). Related naphthyl analogs are exemplified by 2*H*-naphtho[1,2-*b*]pyran **7**, the xanthylium ion **8**, and xanthene **9**.

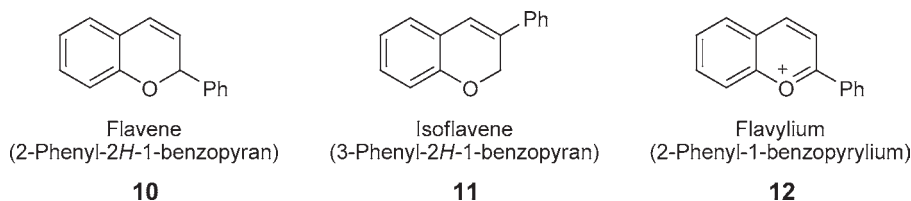
2*H*-Pyran**1**4*H*-Pyran**2**

Pyrylium

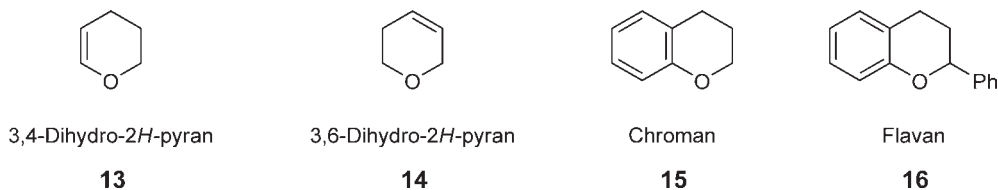
32*H*-1-Benzopyran
(2*H*-Chromene)**4**4*H*-1-Benzopyran
(4*H*-Chromene)**5**



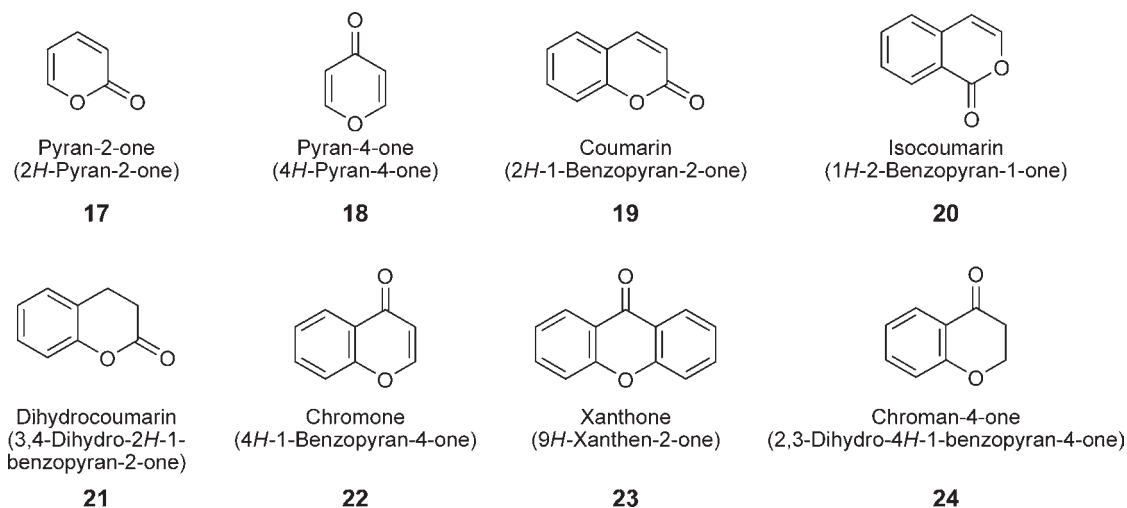
The widespread occurrence of flavonoids in nature has resulted in the adoption of a trivial nomenclature that is exemplified by the common names flavene **10** and isoflavene **11**. The corresponding benzopyrylium species is commonly called flavylum **12**.



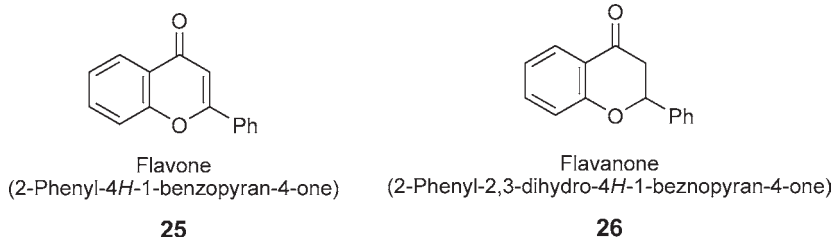
Partially reduced pyrans are named as derivatives of 2H-pyran, for example, 3,4-dihydro-2H-pyran **13** and 3,6-dihydro-2H-pyran **14**. The trivial name for the benzo analog **15** is chroman, and flavan is used for 2-phenyl derivative **16**.



Ketones derived from pyrans are called pyranones (also commonly pyrones), and the parent compounds are pyran-2-one **17** and pyran-4-one **18**. Trivial names are used for the related benzo analogs coumarin **19**, isocoumarin **20**, dihydrocoumarin **21**, chromone **22**, xanthone **23**, and chromanone **24**.



Naming of the ketone-containing flavanoids is exemplified by flavone **25** and flavanone **26**, respectively.



7.07.2 Theoretical Methods

The enormous progress in accessible computational power over the past decade has allowed for increased application of high-level *ab initio* quantum-chemical methods to questions of structure and reactivity, and this trend has been reflected in studies on pyrans and derivatives. As is the case with many computational studies, there has been substantial effort directed toward the comparison of data obtained by various computational methods with empirical data. **Table 1** provides a compilation of studies involving the applications of theoretical methods to pyrans and related molecules.

Table 1 Computational studies on pyrans and derivatives

<i>Compound type</i>	<i>Method</i>	<i>Information</i>	<i>Reference</i>
3,4-Dihydro-2H-pyran and 3,6-dihydro-2H-pyran	B3LYP/6-31G(d) and 6-31G(2d,p)	Relative stabilities	2006STC323
2H-Chromene	CASPT2/CASSCF	Structure, photochemical ring-opening mechanism	2005PCA8684
Tetrahydropyran	<i>Ab initio</i> and DFT with numerous basis sets	Conformational analysis	2001PCA10123
2-Methoxytetrahydro-2H-pyran	<i>Ab initio</i> and DFT with numerous basis sets and methods	Structure, gas-phase proton affinities	2001PCA8216
	MP2/6-31G(d,p) and B3LYP/6-31G(d,p)	Conformational analysis	2003ARK132
Tetrahydropyran	PM3	Thermodynamic properties	1997PCA2471
	<i>Ab initio</i> and DFT with several basis sets	Structure of radical cation	
3,4-Dihydro-2H-pyran	PM3	Thermodynamic properties	1997PCA2471
	B3LYP/6-31++G(d,p) and solvation models	Reactivity toward lithiation	2004T10899
3,6-Dihydro-2H-pyran	PM3	Thermodynamic properties	1997PCA2471
Isochroman	DFT (B3LYP) with various basis sets	Structure, geometry, and spectroscopic properties	2005CPH(313)279
3-Hydroxy-2-methyl-4H-pyranone	HF/6-31G*	Spectroscopic properties	2005VSP233
Pyran-2-ones	B3LYP/6-31G*	Cycloaddition reactivity	2003JOC7158, 2005JOC1122
Hydroxy pyran-4-ones	<i>Ab initio</i> and DFT with numerous basis sets	Stabilities	2003JMT(639)87
Anthocyanidins	DFT with B3LYP/6-31G(d)	Structures and stabilities	2005CPL(410)182
Flavones	HF/STO-3G	Conformation	2000JMT(504)77

7.07.3 Experimental Structural Methods

7.07.3.1 NMR Spectroscopy

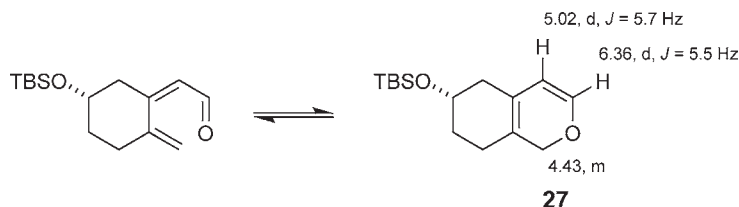
Essentially all publications published in the period since CHEC-II(1996) dealing with the synthesis, structural characterization, or properties of pyran-containing molecules are replete with nuclear magnetic resonance (NMR) data. While the empirical rules summarized in CHEC(1984) and CHEC-II(1996) remain of value for the

determination and assignment of structure, the prevalence of two-dimensional (2-D) NMR methods such as correlation spectroscopy (COSY), heteronuclear single quantum correlation (HSQC), and heteronuclear multiple bond correlation (HMBC) for the assignment of structure is abundantly apparent from the primary literature. Because of space constraints, the discussion in this section is confined to reports that provide significant new information or that illustrate particular features of NMR spectroscopy as it pertains to a class. Information guiding the reader to more extensive reviews is provided where possible.

7.07.3.1.1 ^1H NMR spectra

7.07.3.1.1(i) Pyrans, their benzologs and reduced derivatives

2*H*-Pyrans remains to be isolated, but ^1H data for the simple bicyclic derivative **27** have been reported <1999S1209>. Updated spectral data for 4*H*-pyran including coupling constants and analysis have been reported <2000JA287>.



Although tetrahydropyran (THP) **28** has been the subject of a number of previous NMR studies <1973JA4634, 1967JCB1203, 1982JA3635, 1976JOC1380>, a complete assignment of the ^1H NMR data has only recently been reported <1998J(P2)1751>. At room temperature, the 400 MHz spectrum of THP in 1:1 $\text{CDCl}_3:\text{CFCl}_3$ consists of three multiplets at δ 3.632, 1.637, and 1.568 in a ratio of 2:1:2 (H-2, H-4, and H-3, respectively). At -85°C , all the resonances are resolved, and the assignment of axial versus equatorial was possible on the basis of coupling constant analysis to give the information shown. These data, in conjunction with the previously reported study of the coupling constants of THP and comparison with cyclohexane data (Table 2) <1968JA6543, 1976JOC1380>, now provide a more complete picture of the NMR of tetrahydropyran.

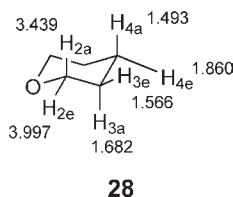
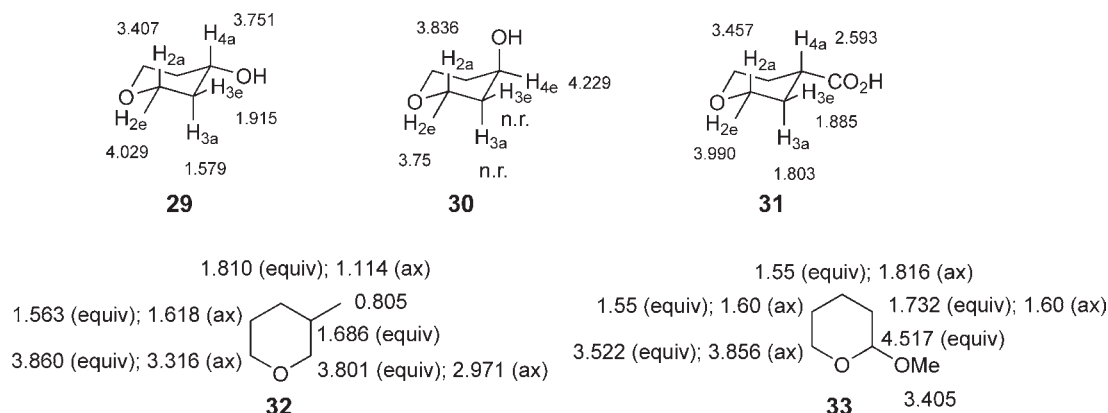


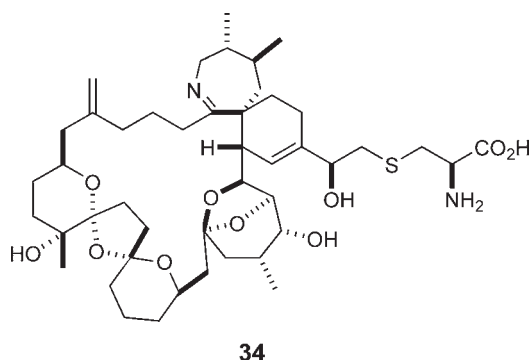
Table 2 ^1H NMR data for deuterated analogs of cyclohexane and THP

Compound	$J_{2a,3e}$	$J_{2e,3e}$	$J_{2a,3a}$	$J_{2e,3a}$	$\Delta\nu_{2e,2a}$	$\Delta\nu_{3e,3a}$	Reference
Cyclohexane- d_8	3.65	2.96	13.12	3.65	0.479	0.479	1968JA6543
Tetrahydropyran- d_4 or $-\text{d}_6$	1.9	1.5	12.4	4.5	0.527	0.074	1976JOC1380

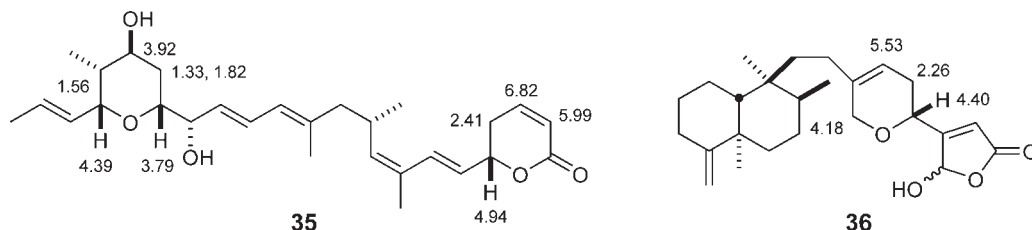
A number of pyrans, including 3-hydroxy-tetrahydropyran (both axial conformer, **29** and equatorial conformer, **30**), 2-methoxy-tetrahydropyran **33**, 3-methyl-tetrahydropyran **32**, and several 4-substituted tetrahydropyrans, along with 2-methyl-1,3-dioxolane and the rigid cyclic ethers 7-oxabicyclo[2.2.1]heptane and 1,8-cineole, were studied extensively by NMR. These empirical results, in conjunction with the literature data for a variety of acyclic and cyclic ethers, were used to examine the reliability of O-substituent chemical shift models in these systems. The empirical data correlate well with predictions made from the model and it is concluded that ethereal oxygen substituent chemical shifts are due to both steric and electrostatic terms <1998J(P2)1751>.



Some measure of the significant advances in NMR spectroscopy over the past two decades is provided by the ability to assign pyran-containing molecules of the complexity of, for example, pteriatoxin A, **34** <2006JA7742>, and maitotoxin <1996JA7946>.



Although no significant new NMR studies on dihydropyrans have been reported since CHEC-II(1996), several natural products that have dihydropyran and dihydropyranone ring systems have been isolated and fully characterized by NMR. For example, the antifungal metabolite ratjadone **35**, which was isolated from the mycobacterium *S. cellulosum* strain So ce360, is of polyketide origin and contains a 4-hydroxytetrahydropyran and a 5,6-dihydropyran-2-one ring <1995LA685>. Cacospongionolide B **36**, a marine-derived terpene, contains a dihydropyran ring <1995JNP1776>. The NMR assignments made as part of the structure elucidation of these two compounds have been confirmed by syntheses <2000AGE4364, 2002JA11584>.



As was noted in CHEC-II(1996), NMR spectroscopy has proved of great value in the structural identification of both natural and synthetic chromenes and chromans. Because of the volume of information accumulated, it is impractical to attempt a summary of trends in the space available, and the specialist review literature should be consulted <1990PHC(2)229, 2003PHC(15)360>.

7.07.3.1.1(ii) Pyranones, their benzologs and reduced derivatives

Few new studies describing significant advances in the ¹H NMR spectroscopy of this class have been reported since CHEC-II(1996); however, a number of useful reviews have appeared. A compilation of both ¹H and ¹³C NMR data

for the most common and important classes of xanthenes has been presented along with a discussion of the application of 1-D and 2-D NMR methods for the structure elucidation of these compounds <2005CME2481>. An earlier review also contains an extensive list of spectral data for oxygenated xanthenes <1979H(12)421>.

The vast literature associated with flavanoid chemistry precludes a discussion here but two valuable reviews have been published. The first reviews a number of spectroscopic techniques used for flavonoid analysis, with a strong emphasis on NMR spectroscopy (plus also mass spectrometry, vibrational spectroscopy, ultraviolet-visible (UV-Vis) spectroscopy, X-ray crystallography, and circular dichroism (CD)) <B-2006MI137>. The second review deals with NMR methods that have been successful in the characterization of phenolic acids and flavonoids from plant extracts that have not been separated or isolated as single components. The emphasis of the article is 2-D NMR methodology and a variety of experiments such as total correlated spectroscopy (TOCSY), COSY, nuclear Overhauser enhancement spectroscopy (NOESY) and heteronuclear multiple quantum correlation (HMQC) are discussed <B-2006MI125>.

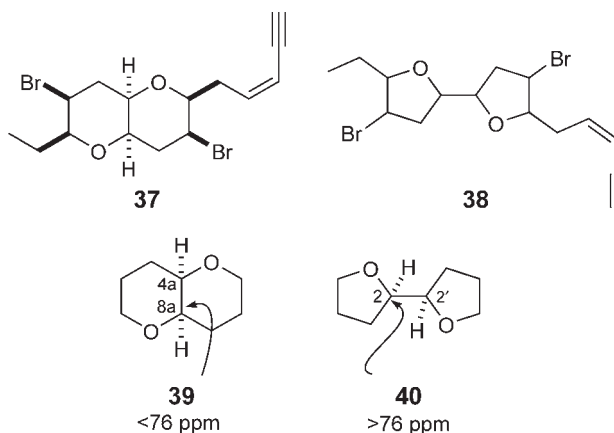
7.07.3.1.1(iii) Pyrylium salts

Few NMR studies that are of substantive value have appeared since CHEC-II(1996), and the reader should consult this earlier compendium for an extensive treatment.

7.07.3.1.2 ^{13}C NMR spectra

7.07.3.1.2(i) Pyrans, their benzologs and reduced derivatives

The difficulties associated with structure assignment of some pyran-containing molecules have been highlighted by the synthesis of the proposed structure of elatenyne, **37**. Careful analysis of the NMR data for a number of synthetic pyrano[3,2-*b*]pyrans and 2,2'-bifuranyl compounds showed that the ^{13}C NMR chemical shifts of the central oxygen-containing compounds could be separated into two groups: for the pyrano[3,2-*b*]pyrans the C-4a and C-8a ^{13}C NMR resonances fall upfield of 76 ppm (e.g., **37**), whereas for 2,2'-bifuranyl compounds the C-2 and C-2' resonances come downfield of 76 ppm (e.g., **40**). In conjunction with this, it has been proposed that elatenyne, **37**, is most likely the 2,2'-bifuranyl compound **38** <2006AGE7199>.



Calculations of the ^{13}C - ^{13}C coupling constants for all aldopyranoses of the D-series have allowed some general relationships with respect to stereochemistry and coupling constants to be postulated <2003RJO663, 2003RJO1194>. Data have been reported for the ^{13}C NMR substituent effects at the α , β , Ψ , and δ positions for 2-halomethyl-2-hydroxy-tetrahydrofurans and 2-halomethyl-5,6-tetrahydro-4*H*-pyrans. These studies showed that additivity rules allow the prediction of the chemical shifts for each carbon <1996SPL631>.

7.07.3.1.2(ii) Pyranones, their benzologs and reduced derivatives

A considerable volume of work has been carried out on these classes of compounds over the past few decades and the field has been well reviewed in CHEC-II(1996) and elsewhere <1982OMR55, B-1989MI1>. More recent reviews include a comprehensive review of the ^{13}C NMR of coumarins and derivatives <B-1996MI(18)971>.

7.07.3.1.2(iii) Pirylium salts

No new NMR studies that are of substantive value have appeared since CHEC-II(1996), and the reader should consult this earlier compendium for details.

7.07.3.1.3 ^{17}O NMR spectroscopy

Several reports describing the ^{17}O NMR of pyrans and derivatives have appeared, including a study in which the natural abundance ^{17}O NMR data for lactones such as pyranone were collected and the relationships between ^{17}O chemical shifts and structure were discussed of <1989H(29)301>. It is possible to distinguish between polyfunctionalized coumarins and chromones by ^{17}O NMR <1993CPB211>.

7.07.3.2 Mass Spectrometry

Almost all papers on pyrans and derivatives contain information such as peak listings for routine mass spectrometry; however, there have only been a handful of papers that describe new types of mass spectrometry or fragmentation patterns that have not previously been described in CHEC(1984) and CHEC-II(1996).

Extensive studies involving 57 aryl-substituted 4-hydroxycoumarins and using electrospray ionization (ESI) mass spectrometry have allowed the effect of the substituents in the aromatic ring on the fragmentation patterns to be determined. Deuterated compounds were used to prove some of the proposed fragmentation pathways, and the effect of tautomerism on the formation of quasimolecular ions and subsequent fragmentation was explained <2004EJS523>.

A number of papers have described analytical methods based on chromatography coupled to mass spectrometry for the analysis and determination of a variety of coumarins in biological samples <1995JAM132, 1997CHR197, 2006ANA201>.

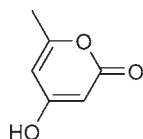
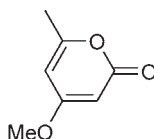
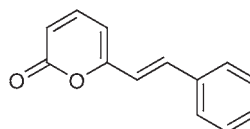
Mass spectrometric studies on a series of pyrylium perchlorates by both electron ionization (EI) and fast atom bombardment (FAB) methods showed that only some compounds give the expected formation of Py^+ and/or $[\text{Py-H}]^+$ ions, and this is followed by extensive fragmentation. Under FAB conditions, all the compounds show the formation of Py^+ without fragmentation products <1994RCM163>.

A detailed study of the fragmentation patterns of 5-hydroxy-2-isopropyl-7-methoxychromone has been described as part of the structure elucidation of this compound, which was isolated from the traditional Chinese medicinal plant *Baeckea frutescens* <2003JNP1144>.

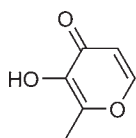
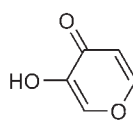
7.07.3.3 X-Ray and Electron Diffraction Methods

Several reviews describing structural features of heterocycles that include X-ray structure determinations have been published: <2005COR1287, B-2001MI(1)3>.

The crystal structure of 2-pyrone has been determined at 150 K <1994AXC1938>. The crystallographic data indicate that the C–C bond lengths exhibit substantial bond-length alternation. As such, it is concluded that the bonding can be described largely in terms of a localized bond model. The structures of several simple pyrones including 4-methoxy-6-methyl-2-pyrone **41**, 4-hydroxy-6-methyl-2-pyrone **42**, <2002ANS613>, and 6-styryl-2H-pyran-2-one **43** <2004AXE1515> have been determined.

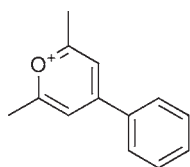
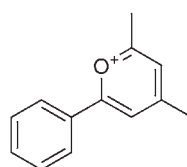
**41****42****43**

Maltol (3-hydroxy-2-methyl-4H-pyran-4-one, **44**) has attracted some attention from a crystallographic point of view and the structure of maltol hydrochloride has been determined <1996AXC2633>. The unit cell is composed of chloride anions and maltolium cations in which the carbonyl group is protonated. This results in lengthening of the C=O bond by ca. 0.06 Å. Greater delocalization in the π -system results in the double bonds being 0.02 Å longer and the single bonds being 0.02–0.03 Å shorter than in the parent compound. The structure of the related 3-hydroxy-4-pyrone **45**, isolated from *Erigeron annuus* and *E. strigosus*, has been determined by X-ray diffraction <1994SPL1431>.

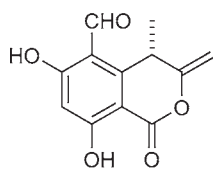
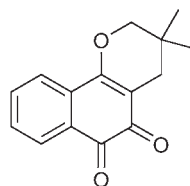
**44****45**

Crystal structures of two polymorphic forms of maltol **44** were also determined. The first form is orthorhombic and the second form is monoclinic, and the polymorphs exhibit different crystal-packing arrangements that are a function of intermolecular H-bonding. The first form consists of almost planar chains linked by H-bonds, whereas the second form has mutually H-bonded dimers [<1996AXC2917>](#).

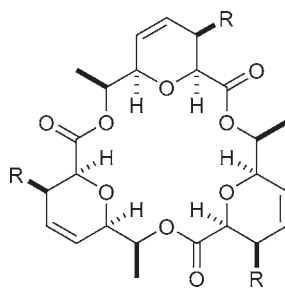
X-Ray structures of the isomeric phenyl-substituted pyrylium perchlorates, 2,6-dimethyl-4-phenylpyrylium **46** and 2,4-dimethyl-6-phenylpyrylium **47**, have been determined. Both pyrylium rings are planar in the crystal structures, and it is suggested that this facilitates the interaction of the electron-deficient pyrylium rings with the phenyl rings of adjacent molecules [<1997ZNB485>](#). The structure of 2,4,6-triphenylpyrylium trichloroacetate has also been determined [<1995AXC1180>](#). Although the three benzene rings are planar, they tilt from the plane of the pyrylium ring by 6.1°, 14.9°, and 23.7°, respectively.

**46****47**

The structures and stereochemistry of naturally derived pyran derivatives can be determined by a number of methods including X-ray. For example, the gross structure of (4*S*)-(+)-ascochin **48**, which was isolated from cultures of the endophytic fungus *Ascochyta* sp., was determined by X-ray diffraction. The absolute configuration was determined by quantum-mechanical calculation of the CD spectrum and comparisons with the experimentally determined spectrum [<2007EJO1123>](#). X-Ray crystallography was used to correct the structure of rhinacanthone from the previously claimed pyrano-1,4-naphthoquinone to pyrano-1,2-naphthoquinone **49** [<1995JNP1455>](#). The structures of a number of other pyran-containing natural products have been also been determined by X-ray.

**48****49**

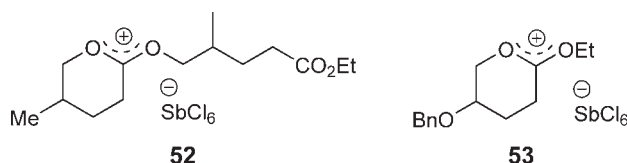
The structures of synthetic pyran-based ionophores have been investigated. *cis*-2-Alkyl-3-oxytetrahydropyrans form useful subunits for the preparation of new types of ionophores with C_2 symmetry [<2005T8177>](#). X-Ray crystallography of some of these compounds provided useful information on solid-state conformational preferences that can be related to the cation-complexation properties in solution. In a related study, the synthesis of 18–32-membered cyclic pyran-based compounds of the type shown (**50** and **51**) was described [<1996TL343, 1995JA12649>](#). Studies of these compounds focused on structural elements important for control of the shape and cation-binding ability and the structures of several of the compounds were determined by X-ray crystallography.



50: R = CH₂OPMB

51: R = CH₂OBn

Mechanistic studies into the nucleophilic substitution reactions of monosubstituted THP acetals that give opposite selectivities when a remote alkyl or alkoxy substituent is present at C-4 included the X-ray structure determination of **52** and **53** <2005JA5322>. Compound **52** exists in a conformation in which the C-4 methyl group is pseudoequatorial, whereas compound **53** exists in a conformation in which the C-4 alkoxy substituent is pseudoaxial. These results corroborate earlier computational studies <1997JOC7597, 1992JA859> that had indicated that electronegative substituents at C-4 or tetrahydropyrylium ions would prefer a pseudoaxial arrangement.



7.07.3.4 Microwave Spectroscopy

A detailed experimental investigation of the THP·H₂O complex (with molecular beam Fourier transform (FT) microwave spectroscopy, free-jet millimeter-wave spectroscopy, and *ab initio* calculations) revealed that the lowest energy species has the water in an axial position. <1998CEJ1974>. Similar studies into the THP·HCl complex allowed both the axial and equatorial hydrogen-bond complexes to be characterized; it was not possible to unequivocally determine which of the two is more stable <1999AGE1772>.

7.07.3.5 UV Spectroscopy, IR/Raman, and Photoelectron Spectroscopy

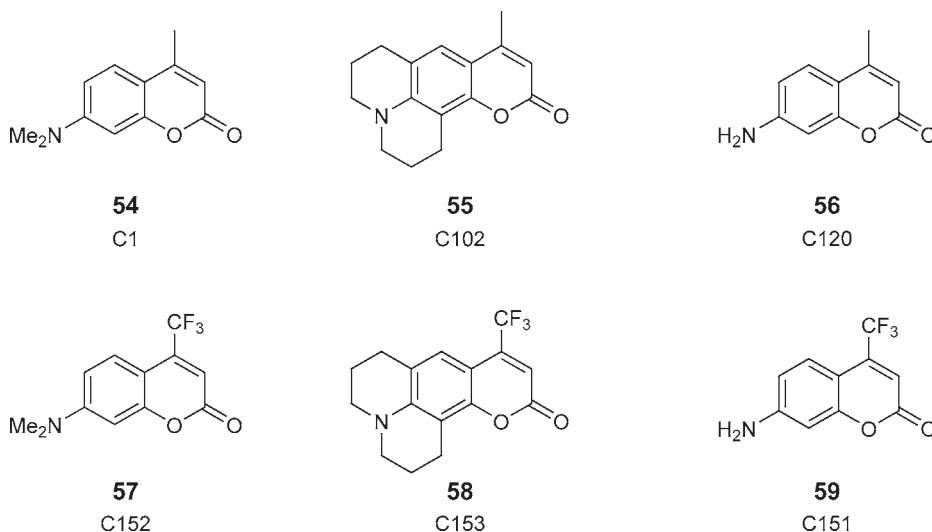
The absorption spectra of a group of 2,6-dimethyl-4-arylperrylium perchlorates were determined <2006PCA11338>. Changes in substituents on the aryl ring at the 4-position led to substantial changes in the absorption spectra. Computational studies provided results that were in good agreement with experiment, and for alkoxy- and alkyl-substituted systems, the spectra can be explained by Balaban's methods.

Investigations into the ability of computational methods to accurately predict λ_{max} for coumarins have shown that density functional theory (DFT) calculations using the B3LYP functional and the 6-311+G(2d,2p) basis set provide accurate λ_{max} when solvent effects are included <2005CPL(415)20>.

7.07.3.6 Dipole Moments

Reports on the determination of dipole moments of pyrans and derivatives have fallen off dramatically over the past two decades. This is probably a reflection of the facility with which this property can be calculated by high-level computational studies. Nonetheless, several papers describe important dipole moment determinations.

A number of structurally related 7-aminocoumarins **54–59** that are used as laser dyes and in nonlinear applications have had their dipole moments determined by following time-resolved changes in photoinduced microwave dielectric absorption. Dipole moments for these compounds range from 8.1 to 11.9 D and the changes in the dipole moment on electronic excitation range from 1.7 to 6.1 D. There is no significant change in benzene versus 1,4-dioxane, and these results unambiguously support the idea that these aminocoumarins fluoresce from the locally excited state and not from a zwitterionic or twisted intramolecular, charge-transfer state <2000PCA8577>. Other similar studies are available <2002JPH19, 2004SAA187, 2001JCP6702>.



The electric dipole moment components of the dipole of the THP·H₂O complex have been determined using Stark-effect FT microwave spectroscopy. Only a- and c-type spectra were observed, which is consistent with computational studies <1998CPL(297)543>.

7.07.4 Thermodynamic Aspects

7.07.4.1 Aspects of Aromaticity and Stability

A theoretical evaluation of the aromaticity of the pyrones pyromeconic acid, maltol, and ethylmaltol along with their anions and cations was carried out at several levels (Hartree–Fock, SVWN, B3LYP, and B1LYP) using the 6-311++G(d,p) basis set <2005JPO250>. The relative aromaticity of these compounds was evaluated by harmonic oscillator model of aromaticity (HOMA), nucleus-independent chemical shifts (NICSs), and *I*₆ indexes and decreases in the order cation > neutral molecule > anion.

Hydrogen bonding between pyrylium cations and water, and the effects on aromaticity, were studied by calculations (B3LYP with the 6-31+G(d,p) basis set) <2006JMT(760)59>.

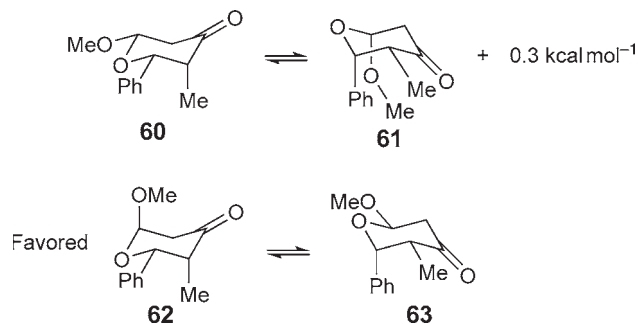
7.07.4.2 Conformation

The conformational analysis of pyrans has been reviewed twice recently <1998AHC217, 2004AHC(86)42>. The preferred conformation of the THP ring is a chair and this has been well established by a variety of methods including NMR, microwave spectroscopy, and electron diffraction <1973JA4634, 1967JCB1203, 1969CJC1289, 1979ACS(A)225>. An extensive compilation of conformational energies for THPs has been published <2004AHC(86)42> and reiterates the idea that with the exception of the 2-position, the conformational picture for monosubstituted pyrans is consistent with the patterns observed in cyclohexanes. Most substituents at the 2-position that are heteroatoms favor the anomeric effect-stabilized axial position. Exceptions that favor the equatorial position include amines and acetamides.

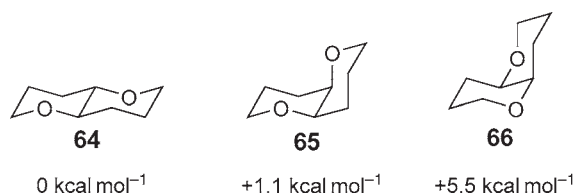
Several recent computational studies by Freeman and co-workers have addressed conformational aspects of pyrans <1999JMT(487)87, 2001PCA10123, 1999JMT(574)19>. *Ab initio* studies with a variety of basis sets and DFT were used to calculate energies of the chair, half-chair, twist, and boat conformers of THP. Similar calculations were applied to a number of alkyl-substituted pyrans including 3-trimethylsilylpyran. When second-order Møller–Plesset perturbation theory (MP2) was employed, the computational results were in good agreement with experimental results. Earlier efforts to examine the conformational energies of 2-monosubstituted pyrans have met with mixed success: while Hartree–Fock (HF)/6-31G* calculations generally provide numbers that agree with experimental results <1994JOC2138>; some methods such as AM1 do not <1991JCR(S)6>.

The conformational picture for some pyran-4-ones has also been investigated using variable-temperature NMR. Pyran-4-one **60** prefers the conformation in which the 2- and 6-position substituents prefer the equatorial position by ~0.3 kcal mol⁻¹ <1994JOC4895>. This is in contrast to earlier MM2 calculations, which predicted the diaxial conformer **61** to be favored by

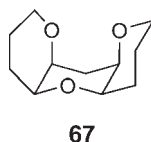
$0.51 \text{ kcal mol}^{-1}$ <1993JOC1367>. In contrast, the corresponding *anti*-diastereoisomer **62** favors the (anomERICALLY stabilized) 2-methoxy axial conformation. Further, *ab initio* computational studies using HF 6-31G* indicate that the parent tetrahydropyran-4-one ring system is relatively flat and that there is a small barrier to interconversion <1994JOC4899>.



The conformational preferences of 1,5-dioxo-*cis*-decalin **64–66** have been investigated both experimentally <1997LA1143> and computationally <1996JMT(370)221>. Calculations at the MM3-GE level (MM3 reparameterized to account for the *gauche*-effect) gave the relative stabilities shown. NMR investigations were consistent with this picture <1997LA1143> and even at -80°C none of the minor conformers could be detected.



In a similar vein, by NMR, 1,8,10-trioxo-*cis-syn-cis*-perhydroanthracene **67** also populates a single conformer in which the oxygen substituents are *gauche* with respect to each other.

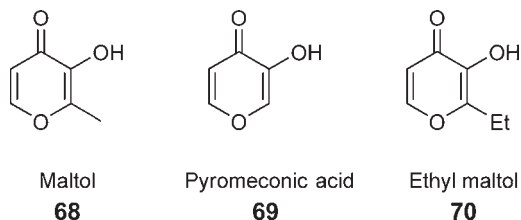


For substituted 2-benzopyrans, *peri*-type interactions have been shown to be of importance in influencing the conformation of the pyran ring <2003TL4535>.

An improved lanthanide-induced shift analysis technique that employs $\text{Yb}(\text{fod})_3$ was used to investigate the conformation of a number of lactones including 3,4-dihydrocoumarin (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadione). These studies indicate that both C-2 and C-3 are displaced from planarity to give a puckered conformation to the lactone ring <1997J(P2)1279>.

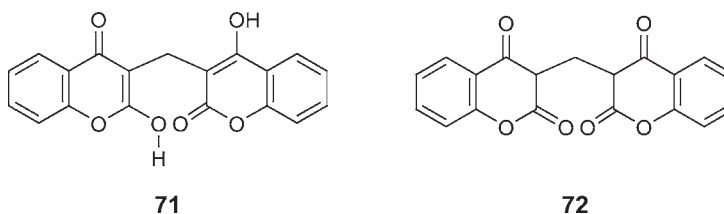
7.07.4.3 Tautomerism

Studies on the tautomerism of heterocycles, including pyrans and derivatives, have been extensively reviewed <2006AHC(91)1>. Computational studies have been used to examine a number of 3-hydroxy-4-pyranones such as maltol **68**, ethyl maltol **69**, and pyromeconic acid **70**, and it has been determined that the 3-hydroxy-4-oxo tautomer is the most stable <2003JMT(639)87>.

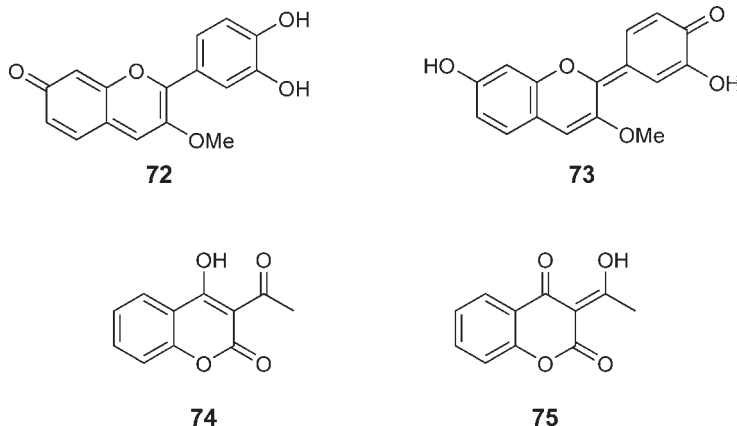


Tautomerism between 4-hydroxycoumarins and 2-hydroxychromones has been investigated extensively by deuterium labeling, ^{13}C NMR, and infrared (IR) spectroscopy <1982JHC385, 1982JHC475>. Computational studies now support the idea that 4-hydroxycoumarins are more stable than 2-hydroxy chromones <1997CJC377>.

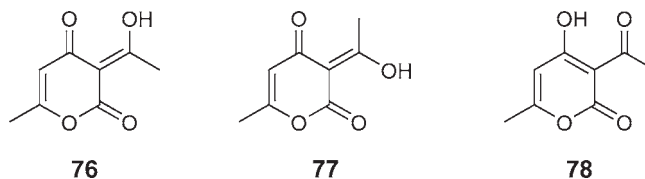
Dicoumarol, which can exist in a number of tautomers, has been studied using the PM3 method <2004JST(678)55>. Calculations in the gas phase predict the prevalence of the α,γ' -benzopyran tautomer **71**, whereas calculations that employed a continuum model of water predict that the α,α' -benzopyran tautomer **72** is favored.



Tautomerism in the benzopyranone **72** has been studied computationally, and tautomer **72** is calculated to be 1.4kcal mol^{-1} more stable than **73** <1994JCS(P2)2587>. 3-Acetyl-4-hydroxycoumarin has been studied using UV spectroscopy and by computational methods <1997CJC365, 2000JRO793>. Tautomer **74** is favored in nonpolar solvents such as CCl_4 or hexane. In polar solvents, **75** is favored. Computational studies at both semi-empirical and *ab initio* levels predict **74** and **75** to be of comparable stability, and significantly more stable than all other possible tautomers.



Dehydroacetic acid prefers tautomer **78** in a variety of solvents and also in the solid state <2000JST(554)225>.

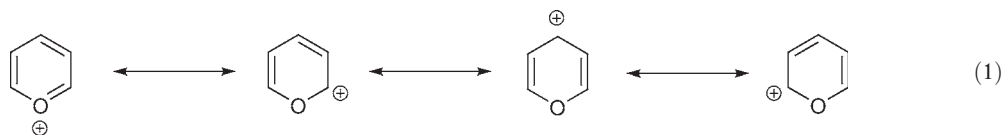


7.07.5 Pyrylium Salts and Their Benzo Derivatives

7.07.5.1 Reactivity at Ring Atoms

7.07.5.1.1 Introduction

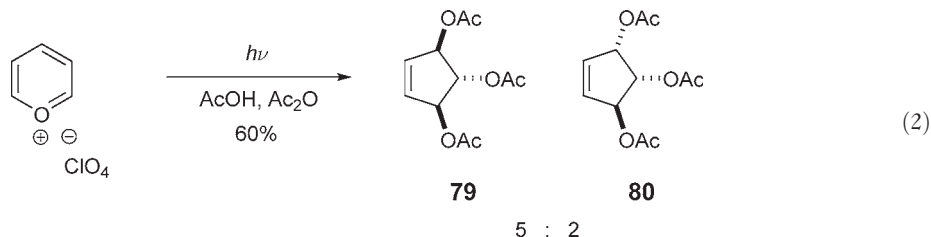
As is evident from the resonance structures shown in Equation (1), additions to the parent pyrylium salt would be expected to occur at the 2-, 4-, or 6-positions, and the great bulk of the literature describes reactivity of this general type, although the effects of structure in terms of determining regiochemistry are significant.



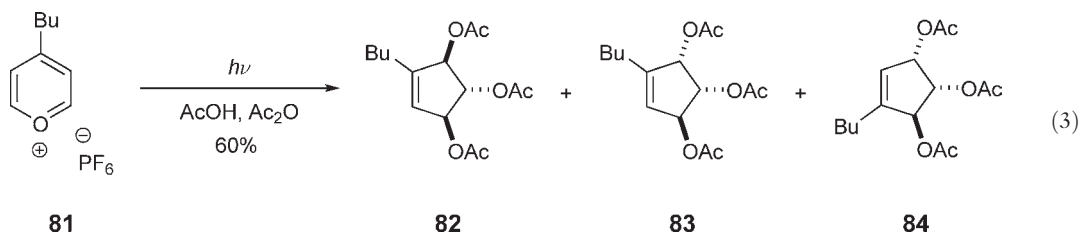
A substantial review describing the literature from 1980 to 1995 has been published [<1996AHC\(65\)283>](#), and only more recent advances are presented here.

7.07.5.1.2 Photochemical reactions

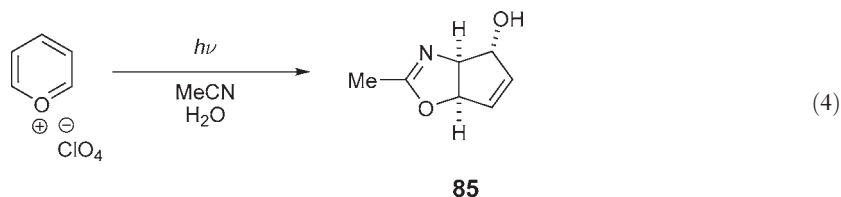
Ganem and co-workers have expanded earlier studies on the photochemistry of pyrylium salts to give functionalized cyclopentenones such as **79** and **80** (Equation 2) [<2001JA10425, 1973CC410, 1971CC1240, 1980S589>](#).



The 4-substituted isomers gave mixed results; however, **81** could be successfully converted to cyclopentenones (Equation 3).



Photolysis in wet acetonitrile led to bicyclic oxazolines such as **85** (Equation 4).

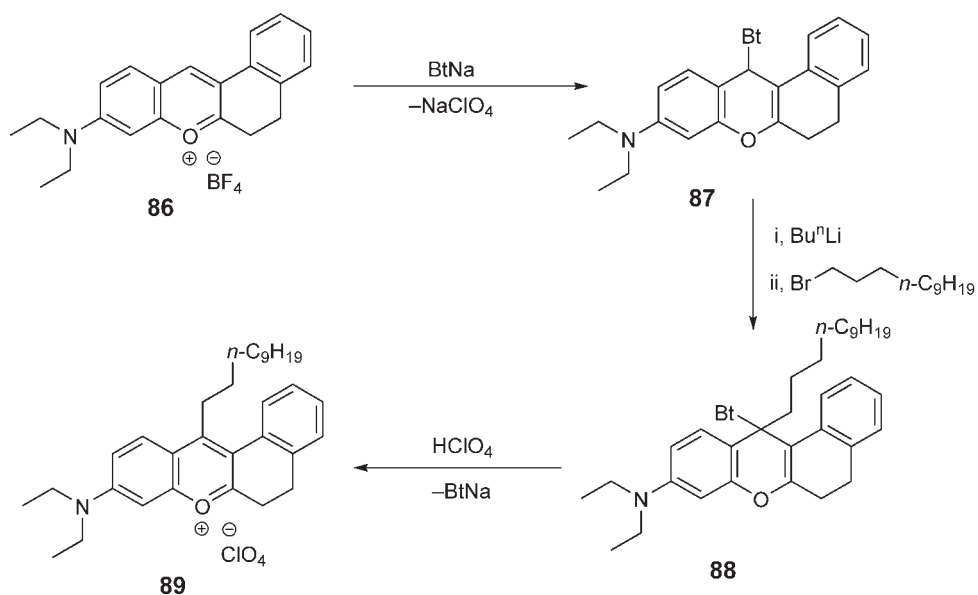


The photochemical behavior of a number of benzopyrylium salts has been studied [<2002JPH61>](#).

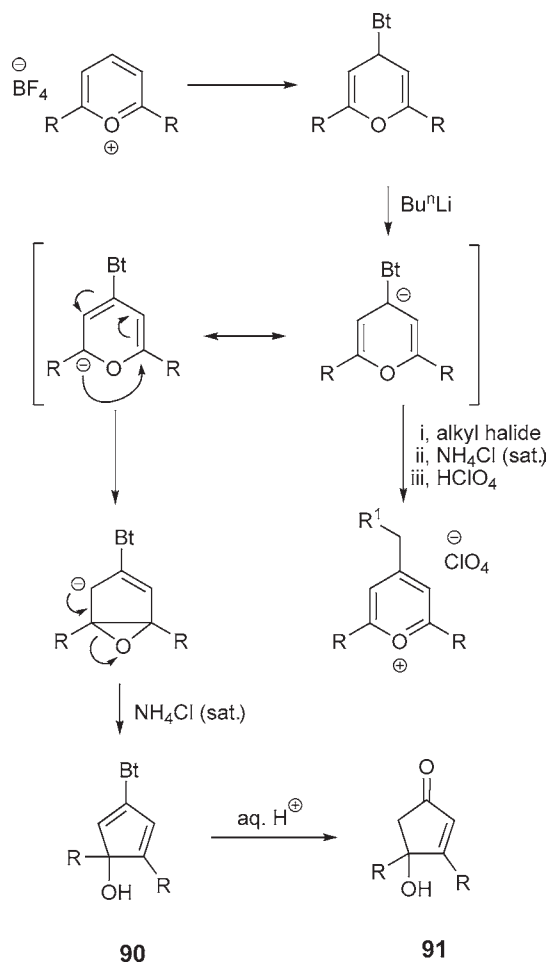
7.07.5.1.3 Reactions with electrophiles

Cursory inspection of pyrylium, benzopyrylium, and xanthylium salts suggests that these structures are less apt to react with electrophiles than nucleophiles, especially considering that each bears a formal positive charge. For this reason, examples of direct electrophilic substitution on the ring atoms of pyrylium are rare. There are, however, numerous examples of 'indirect' electrophilic substitution mediated by species such as benzotriazoles [<1997JOC8198, 1998EJO2623, 1999JPR152>](#). Benzotriazoles such as **86** add to pyryliums at the position *para* to the oxygen to give compounds (e.g., **87**) that can be deprotonated at C-4 to generate an anion that can be reacted with a variety of suitable electrophiles (**87** → **88**). Subsequent acid-mediated loss of the benzotriazole anion regenerates the pyrylium ion and gives formally the product of an electrophilic substitution reaction (Scheme 1). It should be emphasized that these reactions are obviously mechanistically very different from direct electrophilic substitution.

In an extension of this methodology, it was found that the anion formed could also lead to a ring rearrangement depending on the conditions it was subjected to. The mechanism for this transformation is shown in Scheme 2.



Scheme 1

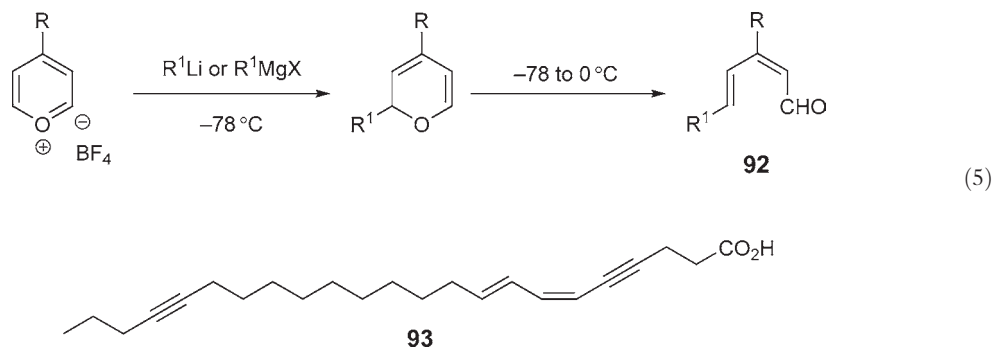


Scheme 2

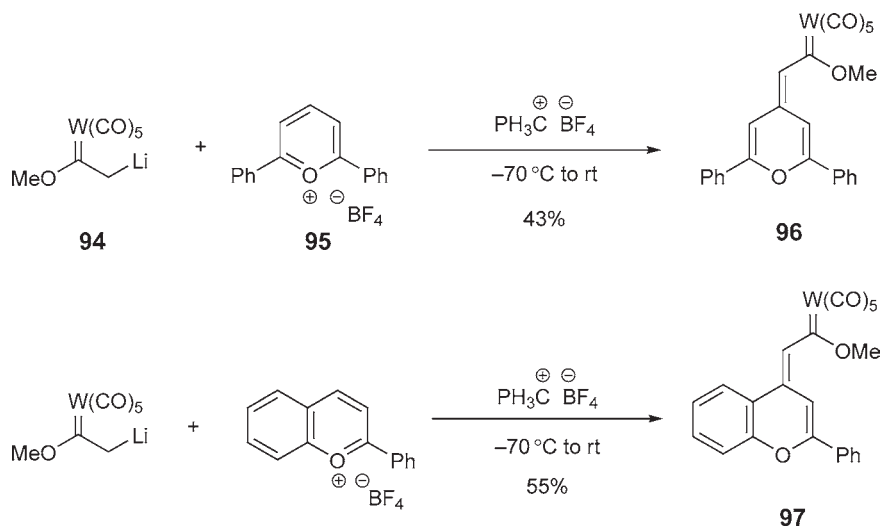
7.07.5.1.4 Reactions with nucleophiles

The electrophilicity of the C-2, C-4, and C-6 positions of pyryliums facilitates reaction to give either addition or substitution (if a suitable leaving group is present). Nucleophiles are also able to facilitate ring-transformation reactions during which the pyrylium ring is transformed into a new ring. An earlier review is available <1982AHC(suppl 2)1>.

The addition of organometallics to pyrylium salts has been investigated as a route to *2Z,4E*-dienals of general type **92** (Equation 5) <1989J(P1)683, 1991S320, 1995J(P1)2385, 1990JCM162, 1991J(P1)2725, 1992SL117, 1993CC1409>. This reaction has been employed in the total synthesis of complex compounds such as carduusyne A, **93** <1996TL1913>.

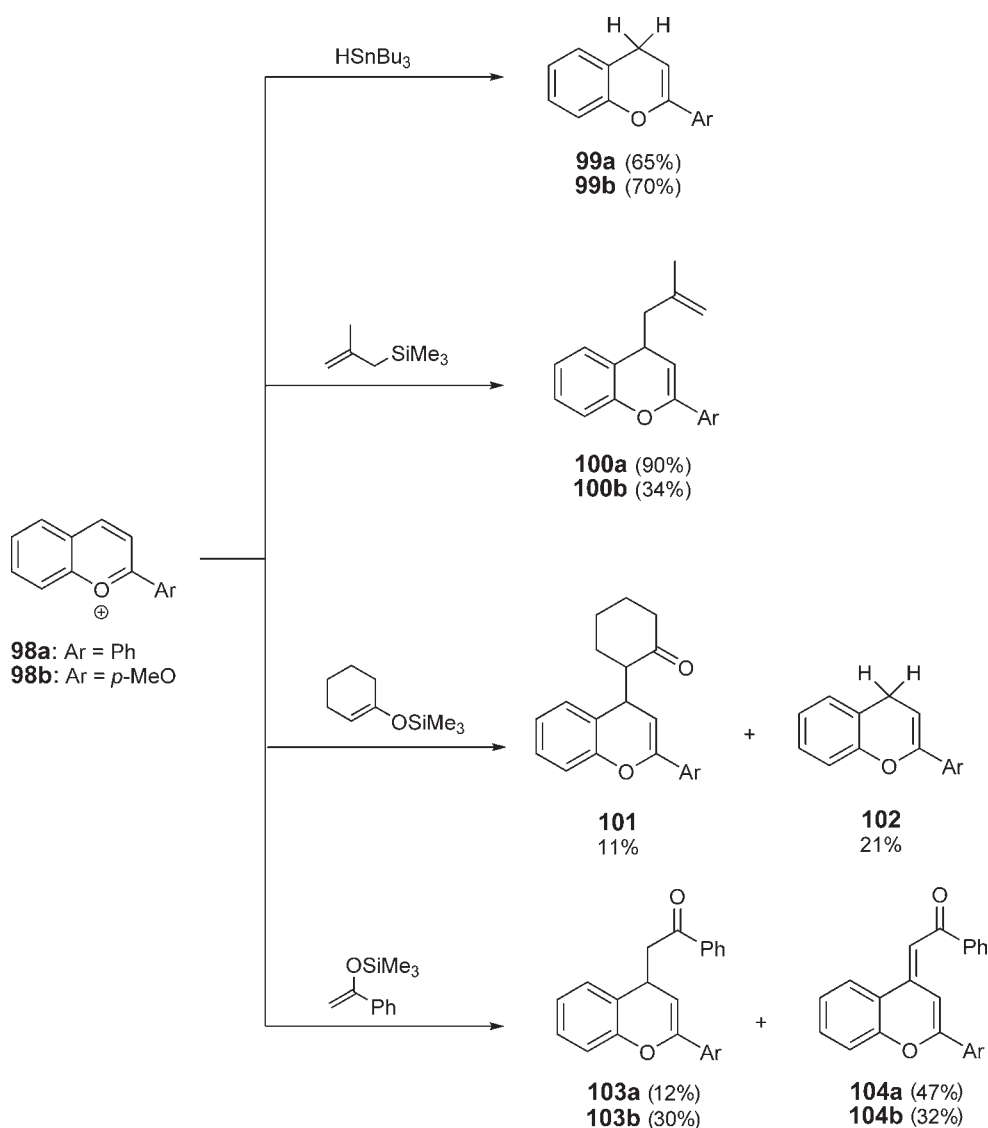


Pyrylium salts react with carbanions of Fischer carbene complexes to give γ -methylenepyran carbene complexes (e.g., 2,6-diphenylpyrylium **95** with **94** to give **96**). NMR data, X-ray analysis, and DFT calculations suggest that these complexes retain some pyrylium character (Scheme 3) <2002T7519, 1998TL557>.



Scheme 3

The kinetics of reactivity of 2-aryl-benzopyrylium ions (flavylium ions) with a variety of π -nucleophiles have been investigated photometrically (Scheme 4) <2001EJO4451>. As can be seen, flavylium ions such as **98a** and **98b** react readily with tributyltin hydride to give products such as **99a** and **99b** and methallyl trimethylsilane to give **100a** and **100b**. Although reactions with silyl enol ethers are possible, they are lower yielding and more complex mixtures are obtained. Electrophilicity parameters were extrapolated to allow the prediction of potential reaction partners for flavylium ions.



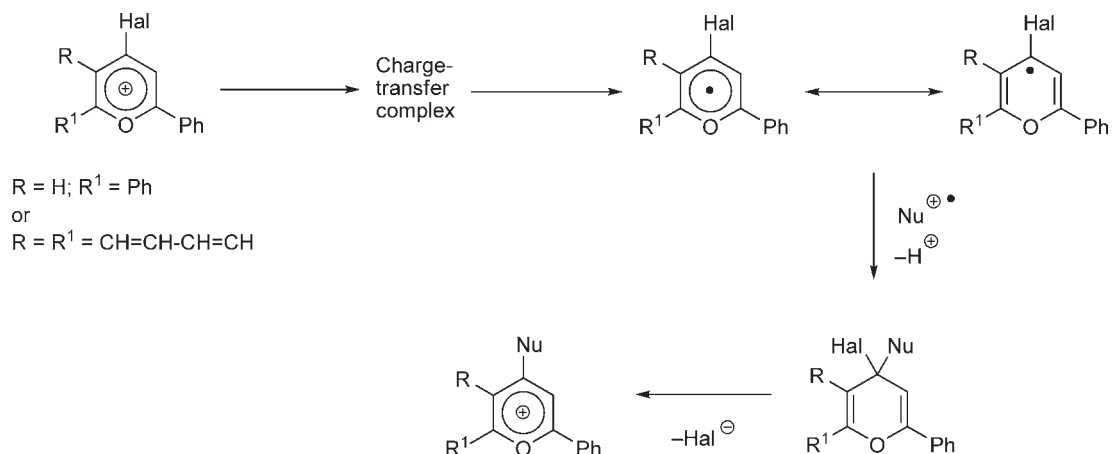
Scheme 4

2-Alkoxy-substituted chromones, which are readily prepared by ring-closing metathesis [<2000TL5979>](#), undergo facile ionization in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give benzopyrylium ions that are trapped by a variety of nucleophiles [<2001EJO4451>](#).

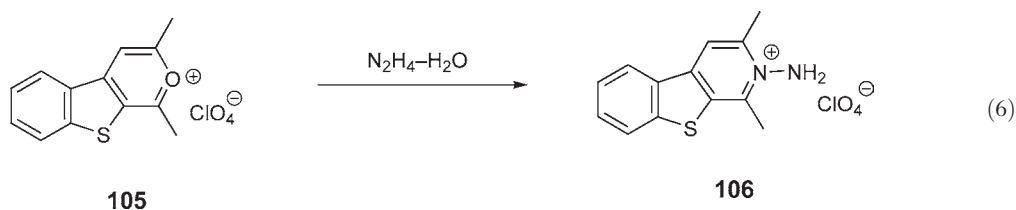
In the context of mechanistic studies, the electrochemical behavior and reactions with nucleophiles of 4-chloro-2,6-diphenylpyrylium and 4-chloro(bromo)flavylium have been studied [<1999CHE653>](#). The proposed mechanism for nucleophilic substitution in halogen-substituted pyrylium and flavylium salts passes through formation of a charge-transfer complex that is converted into an ion-radical pair by simple electron transfer. Heterocyclic cleavage of the *C*-halogen bond occurs at the stage of the radical or the adduct from the reaction of the pyrylium salt and the nucleophile. In this study, an amine nucleophile was used; however, the data are likely relevant for other types of nucleophiles as well ([Scheme 5](#)).

Reaction of hydroxylamine with tri- and tetrasubstituted pyrylium salts yields pyridine *N*-oxides and/or 2-isoxazolines via the intermediacy of keto-ketoximes [<1998T9747>](#). The regiochemistry of 2-isoxazoline formation from unsymmetrical pyryliums, and the Beckman rearrangement of the intermediate keto ketoximes have also been explored [<1998T9747, 1999T15011>](#).

The reaction of hydrazine with 1,3-disubstituted benzothieno[2,3-*c*]pyrylium salts (e.g., **105**) gives *N*-amino-1,3-dialkylbenzothieno[2,3-*c*]pyridines such as **106** (Equation 6) [<1998CHE983>](#).

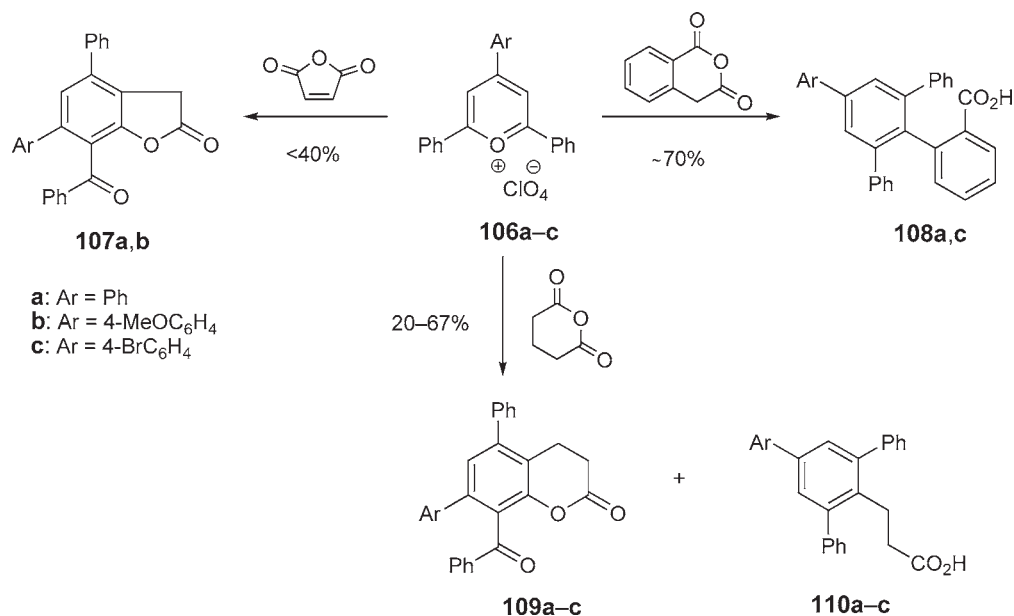


Scheme 5



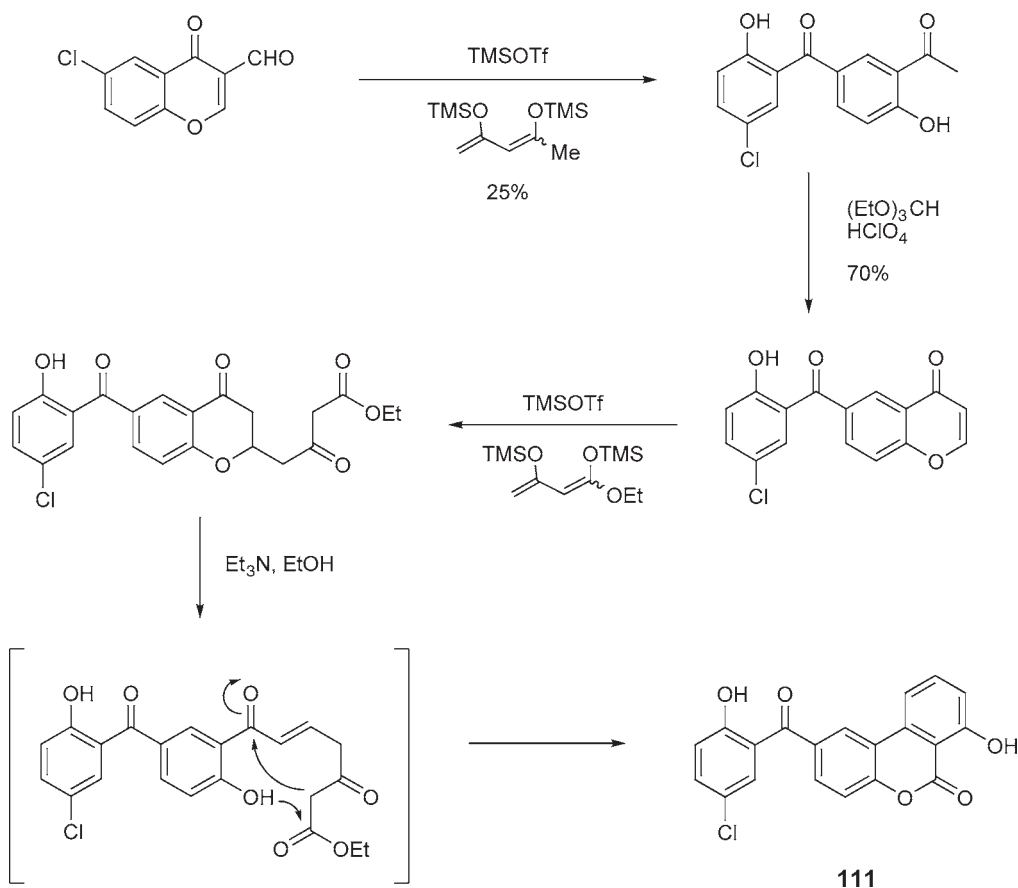
The reactions of a variety of other pyrylium, indolopyrylium, benzopyrylium, and flavylium salts with amines have been described [<1998T9747, 2002CHE741, 2002CHE743, 2003CHE386, 2004CHE1131, 2004CHE1300, 2004CHE1421, 2005CHE515>](#).

Pyrylium salts also react with cyclic anhydrides ([Scheme 6](#)) [<1995MC99>](#). Treatment of the salts **106a–c** with succinic anhydride gave lactones **107a** and **107b** in yields less than 40%, whereas reaction with homophthalic anhydride in dimethylformamide (DMF) gave benzoic acids **108a** and **108c** in ca. 70% yields. Reaction with glutaric anhydride gave lactones **109a–c** and acids **110a–c** when performed in toluene. In DMF, the yields were 20% and 67%, respectively. The scope of these reactions has been extensively studied [<1999PCJ480, 2000PCJ95>](#).



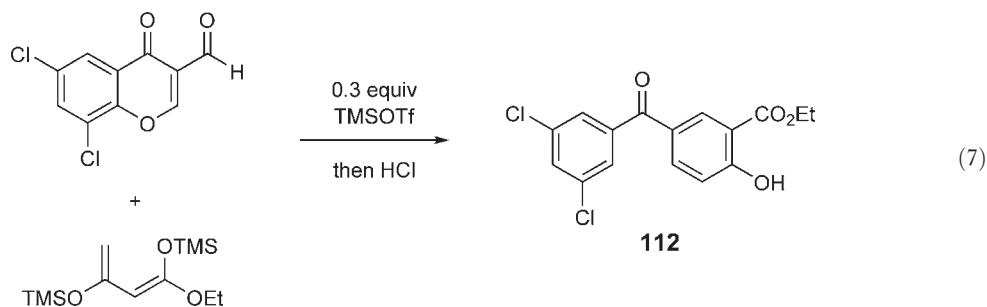
Scheme 6

Benzopyrylium triflates formed *in situ* from 3-formylchromones react in a sequential fashion with silyl enol ethers to give chromones such as **111** (Scheme 7) <2003TL7921, 2006T7674, 2002CC168, 2006CEJ1221, 2006T9694, 2006EJO3638>.

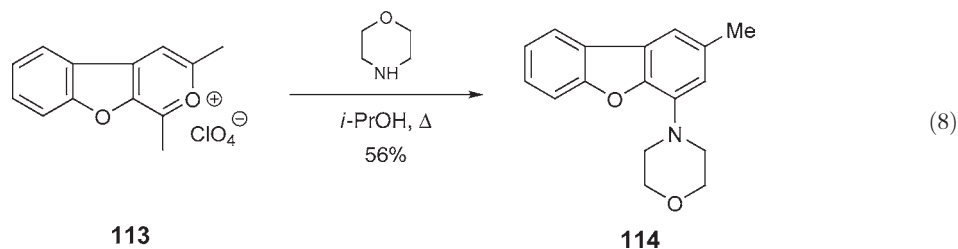


Scheme 7

Similarly, the reaction for formyl- and keto-chromones with silyloxydienes produced benzopyryliums which initiated a sequence that resulted in the formation of a 2,4-dihydroxybenzoquinone such as **112** (Equation 7) <2006EJO3638>.

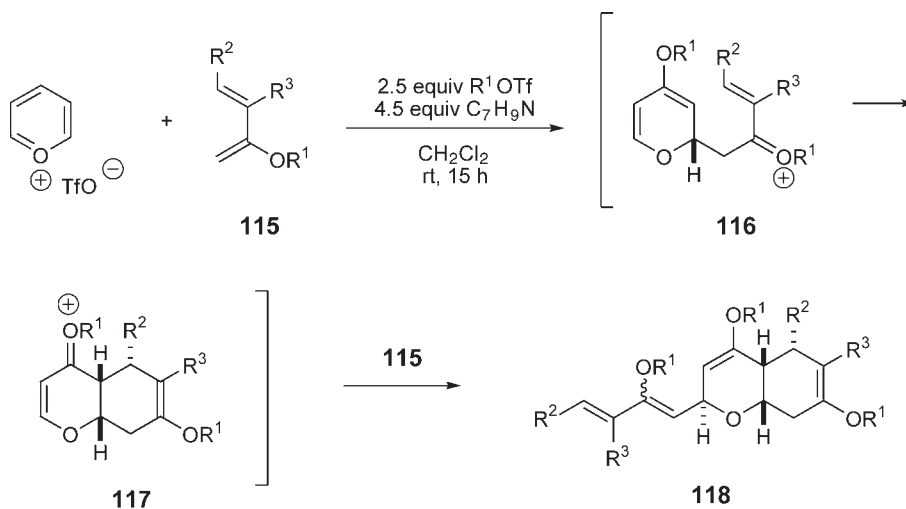


As is the case for the reaction of secondary amines with alkylpyrylium salts to give dialkylanilines, benzopyrylium and pyrylium salts react with amines to give similar products (e.g., **113** → **114**; Equation 8) <1982AHC(32)128, 1970KGS1308, 1981KGS1351, 1987KGS889, 1998CHE159>.



Multiple sequential functionalizations of pyryliums with silyl enol ethers gives rise to a variety of products, including tetrahydro-2*H*-chromenes and dicyclopenta[*a,j*]octahydroxanthene-9-ones, as shown in the tables below (Schemes 8 and 9) <2001AGE568>.

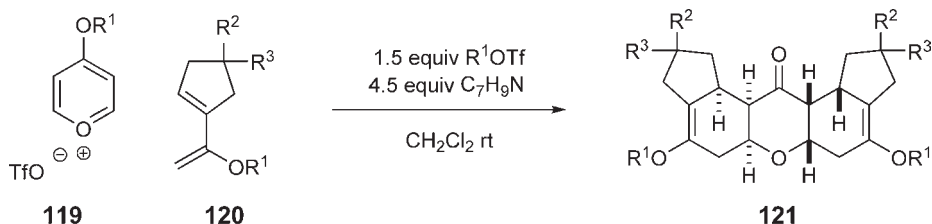
Benzopyrylium triflates (e.g., **122**) can be reacted with diazoesters to give cyclopropanes that are readily converted to 2,3-benzoxepins such as **123** and related heterocycles (Scheme 10) <2005TL4057>.



R^1	115	R^2	R^3	118	Yield (%)	E/Z
a	TBDMS	a	Ph	a	96	4.0:1.0
b	TES	b	Ph	b	98	4.1:1.0
c	TDMS	c	Ph	c	90	3.8:1.0
a	TBDMS	d	<i>p</i> -C ₆ H ₄ CN	d	80	11.0:1.0
a	TBDMS	e	<i>p</i> -C ₆ H ₄ Cl	e	35	1.3:1.0
a	TBDMS	f	(CH ₂) ₄	f	86	a
b	TES	g	(CH ₂) ₄	g	98	a
d	TIPS	h	(CH ₂) ₄	h	99	a
e	TMS	i	<i>p</i> -C ₆ H ₄ CO ₂ Me	i	62	3.4:1.0
e	TMS	j	<i>p</i> -C ₆ H ₄ NO ₂	j	56	Only <i>E</i>

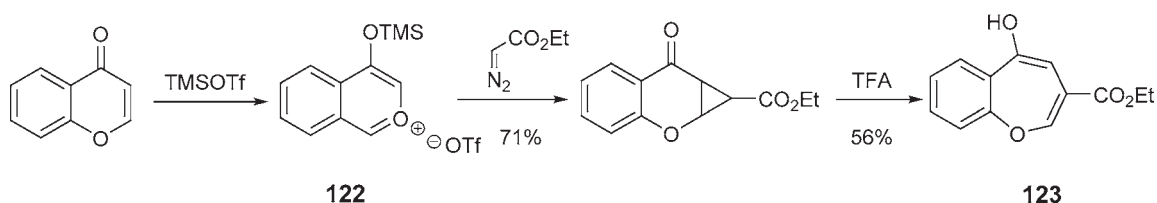
^aThe products **118f–h** were isolated as a mixture of two constitutional isomers.

Scheme 8



119	R^1	120	R^2	R^3	121	Yield (%)
a	TBDMS	a	H	H	a	85
e	TMS	b	H	H	b	75
d	TIPS	c	H	H	c	33
a	TBDMS	d	CO_2Me	CO_2Me	d	58
e	TMS	e	CO_2Me	CO_2Me	e	51
a	TBDMS	f	$=\text{CH}(\text{CH}_3)_2$		f	31
a	TBDMS	g	$\text{CH}(\text{CH}_3)_2$		g	61

Scheme 9

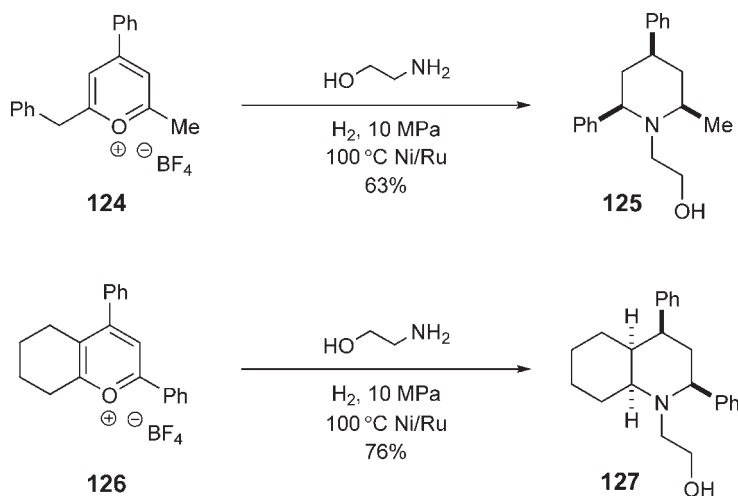


Scheme 10

7.07.5.1.5 Reduction

Although only a handful of catalytic reductions of pyryliums are known [<2002CHE1136>](#), the area (along with the reductions of pyridiniums and thiopyryliums) has been reviewed [<2001CHE797>](#).

The catalytic reduction of a variety of pyrylium salts in the presence of ethanolamine yields substituted piperidines [<2002CHE1136>](#). For example, pyryliums **124** and **126** are reduced to piperidines **125** and **127** in 63% and 76% yield, respectively ([Scheme 11](#)).

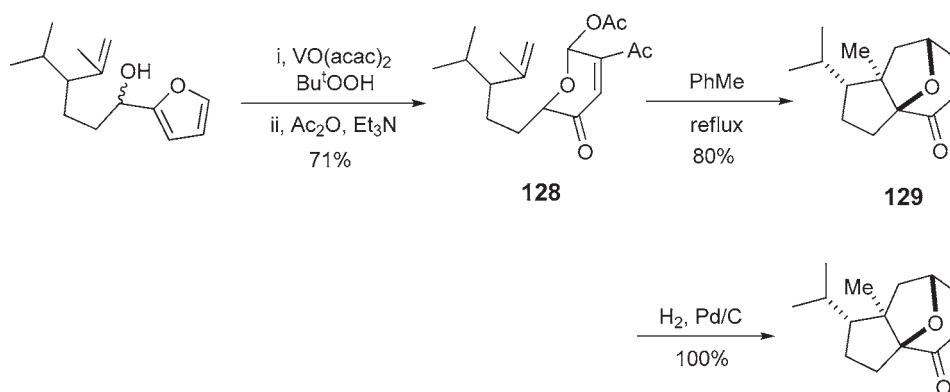


Scheme 11

Extensive mechanistic studies on the effect of substituents on hydride reductions of 2,4,6-triarylpyryliums with NaBH_4 and NaCNBH_3 have been described. These studies determined first- and second-wave reduction potentials and also rates for each reaction. Comparisons of the data sets leads to the conclusion that charge neutralization in the hydride addition transition state precedes B–H bonding changes <2002JPO689>.

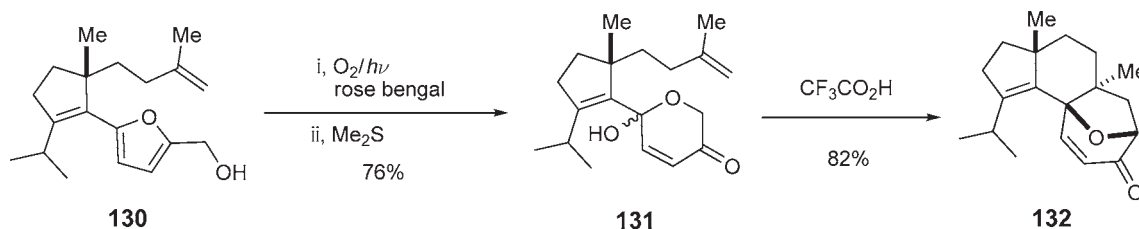
7.07.5.1.6 Cycloadditions

Cycloaddition reactions of pyrylium salts with alkenes continue to be explored in the context of natural products synthesis, as shown in Schemes 12–14. In the example shown in Scheme 12, a pyrylium–ylide [5+2] cycloaddition was performed (**128** → **129**), allowing access to intermediates reminiscent of the core framework of the diterpene antibiotic, guanacastepene <2001TL4947>.



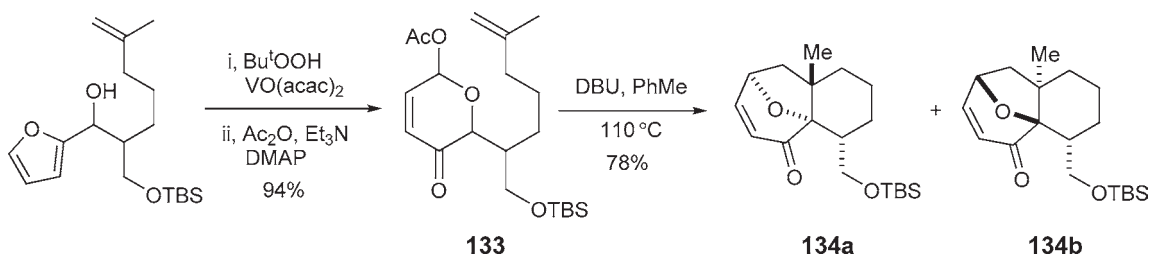
Scheme 12

In a study aimed at synthesizing the cyathin diterpene skeleton, another pyrylium ylide–alkene [5+2] cycloaddition was employed (as shown in Scheme 13) <1999T3553>.



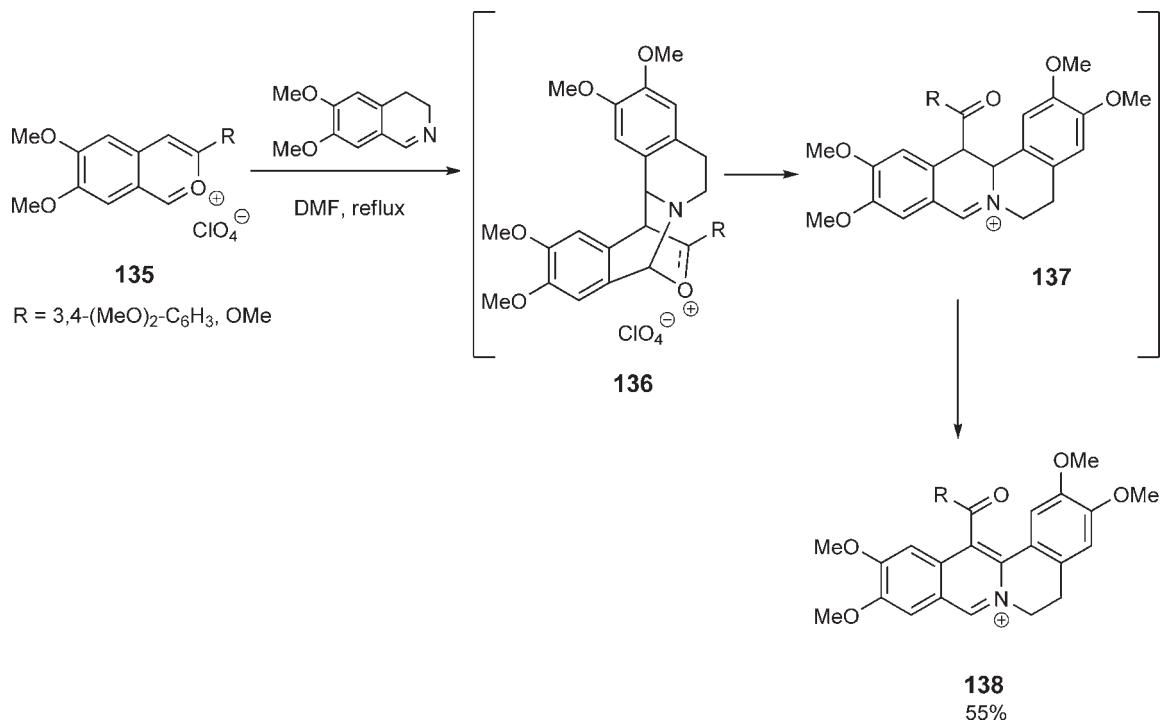
Scheme 13

A similar approach was employed en route to a synthesis of taxol precursors, as shown in Scheme 14 <1996T14081>. In this case, a [5+2] cycloaddition reaction of **133** yielded diastereoisomers **134a** and **134b**.



Scheme 14

Benzo[*c*]pyrylium salts (e.g., **135**) also undergo cycloadditions with azomethines via the intermediacy of **136** and **137** to give dihydroisoquinolinium salts such as **138** (Scheme 15) <1997MC204>.



Scheme 15

The catalytic asymmetric dipolar cycloaddition reactivity of *in situ*-formed 2-benzopyrylium-4-olates (e.g., **139**) with a variety of dipolarophiles including α -alkoxy ketones **140**, α -keto esters **141**, and acryloyl oxazolidinones **142** has been extensively studied (Scheme 16) <2000OL3145, 2002JA14836, 2003S1413, 2005JOC47, 2006T9218>.

The cycloaddition chemistry of transition metal-containing benzopyryliums has been reviewed <2006CL1082>.

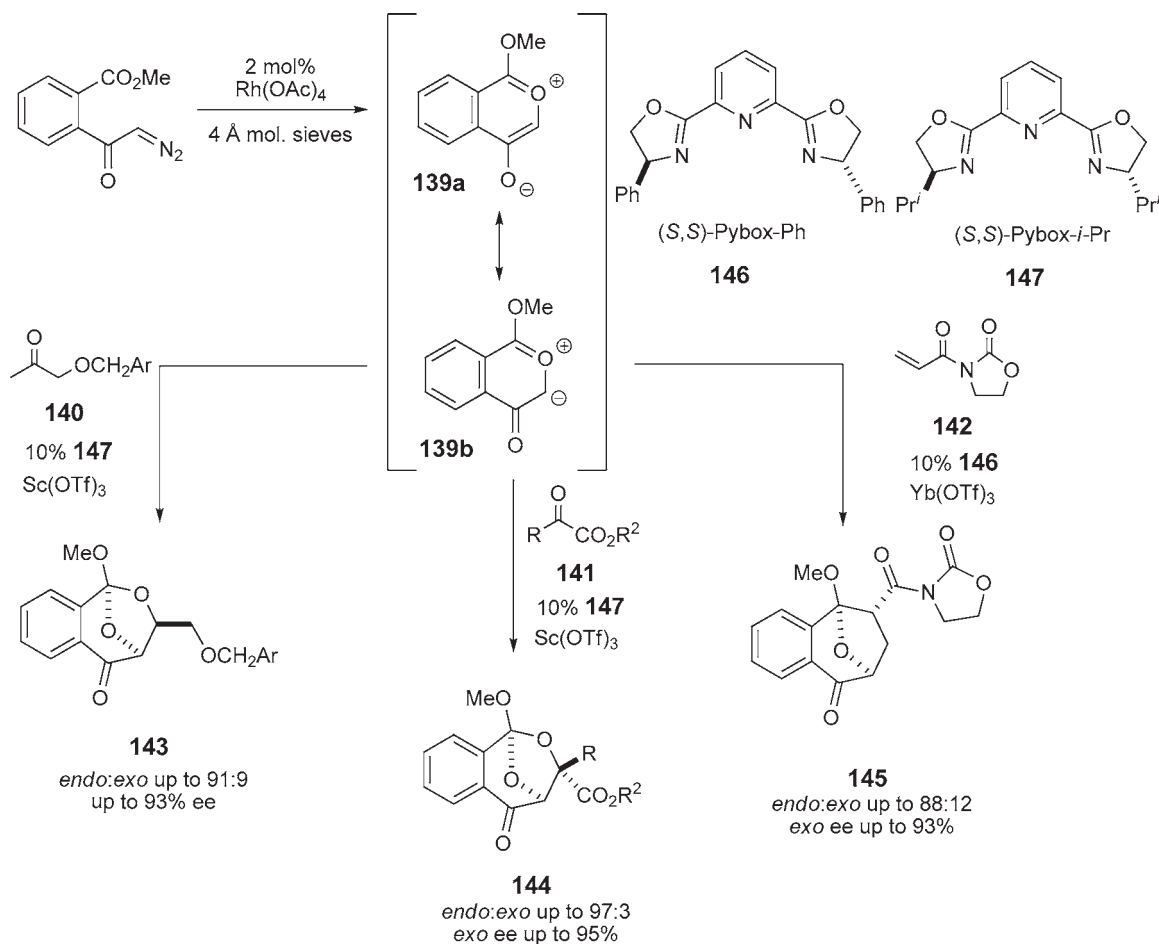
7.07.6 2*H*- and 4*H*-Pyrans and Their Benzo Derivatives

Relatively little new chemistry describing the reactivity of 2*H*- and 4*H*-pyrans has been described since CHEC(1984), and the reader is encouraged to review that earlier summary for this subject in addition to what is presented here.

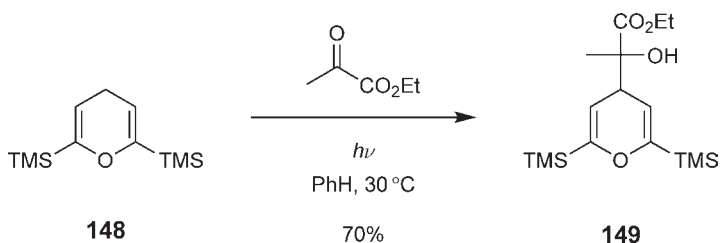
7.07.6.1 Reactivity at the Ring Atoms

7.07.6.1.1 Photochemical reactions

The photochemical reaction of 2,6-bis-(trimethylsilyl)-4*H*-pyran **148** with various ketoesters results in functionalization at the 4-position in moderate to good yields (61–73%) (Equation 9) <2000TL5199>.



Scheme 16

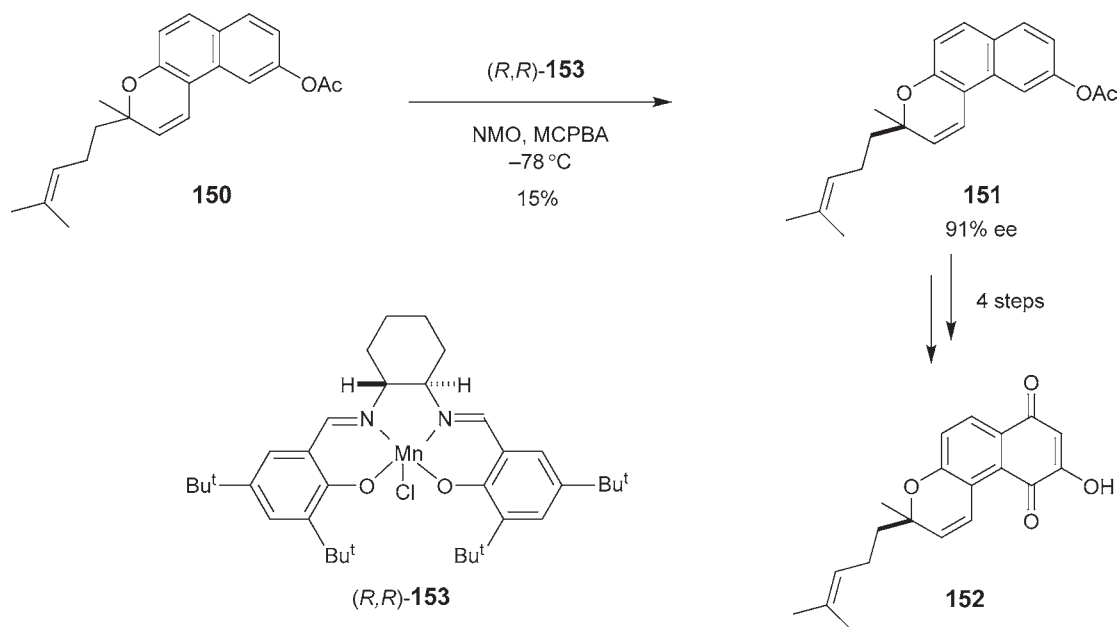


(9)

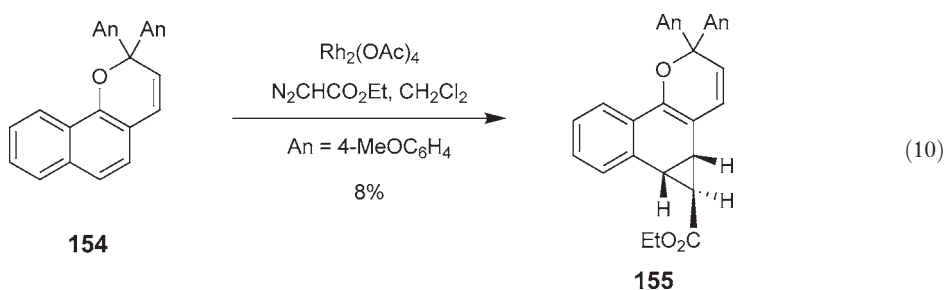
7.07.6.1.2 Reactions with electrophiles

The $\text{Mn}(\text{salen})$ -catalyzed asymmetric epoxidation of prochiral 2,2-dimethyl chromenes proceeds with high enantioselectivities (salen = *N,N'*-bis(salicylaldehyde)ethylenediamine) <1991JA7063, 1991TL7063, 1992SL407>, and this also allows for the kinetic resolution of chiral 2,2-dimethylchromenes (e.g., **150** $\rightarrow$ **151**; Scheme 17). The k_{rel} values of ~ 3 –10 (at -78°C) mean that the reaction must be run to substantially greater than 50% conversion. This however gives useful ee percentage (of recovered starting material) and the process has been applied to the synthesis of (+)-teretifolione B, **152** <1995JOC5380>.

Studies of the reactions of chromenes with carbene or carbenoid structures have been described, including zinc enolates of dibromoalkanones <2005RJO527>. Ring-opening reactions of naphthopyrans in the presence of ethyldiazoacetate and $\text{Rh}(\text{OAc})_4$ have also been recorded (Equation 10) <2004TL6151>.



Scheme 17



7.07.6.1.3 Reduction

Reduction of 4*H*-chromene-4-ylidene imines has been shown to lead to aminoalkyl phenols <2001T6809>.

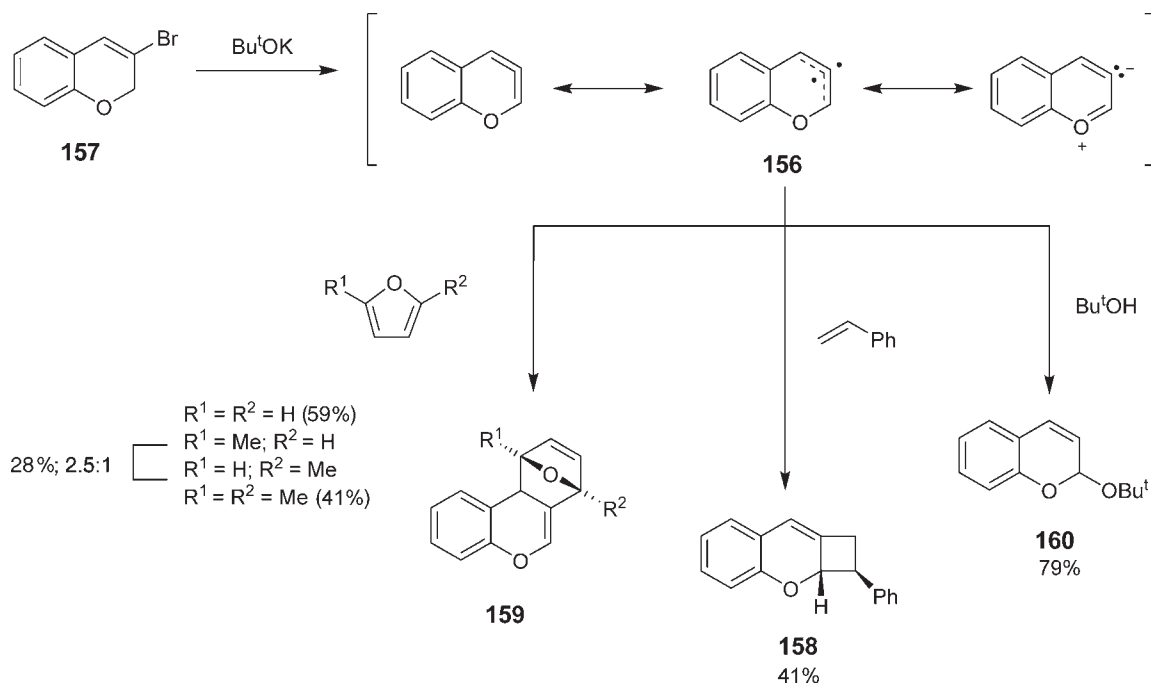
7.07.6.1.4 Cycloadditions

3 δ^2 -Chromene (2,3-didehydro-2*H*-1-benzopyran) **156** can be generated by treatment of 3-bromo-2*H*-chromene **157** with potassium *tert*-butoxide (Scheme 18). When done in the presence of styrene or furans, trapping is possible to give products such as **158** and **159**, respectively. 3 δ^2 -Chromene could be expected to behave as an allene, a diradical, or an ylide. In the absence of π -nucleophiles, acetal **160** was formed, which is suggestive of the importance of the ylide in terms of structure <1998EJO237>.

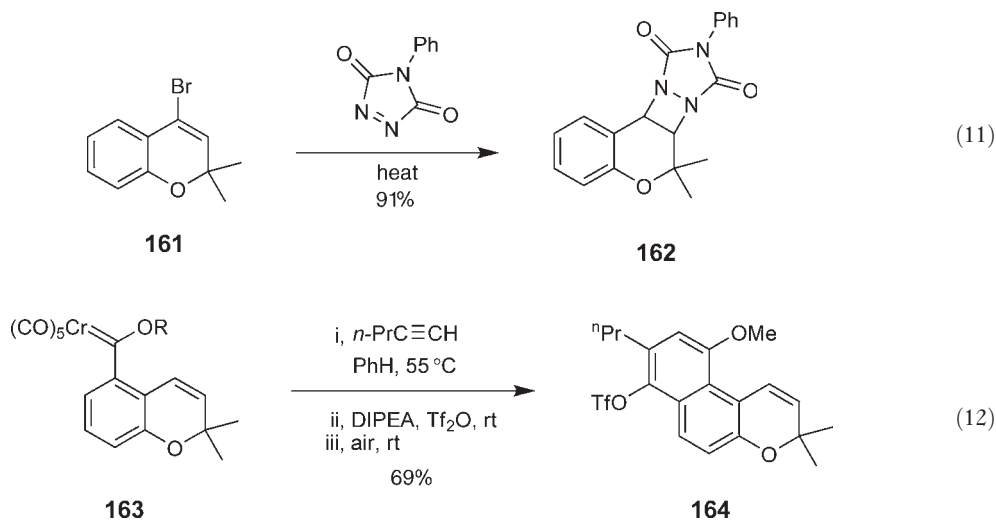
Simple 2*H*-chromenes produce [2+2] cycloaddition products upon reaction with triazolinones such as phenyl-triazolinone (PTAD) and methyl triazolinone (MTAD) (Equation 11) <1995T13277>.

7.07.6.2 Reactivity of Substituents

Chromium carbene complexes containing chromenes undergo benzannulation reactions with acetylenes to give 3*H*-naphtho[2,1-*b*]chromenes as products (Equation 12; **163** $\rightarrow$ **164**). The intermediate naphthols are air sensitive and are best trapped by protecting groups or further functionalization <2006JA11044>.



Scheme 18

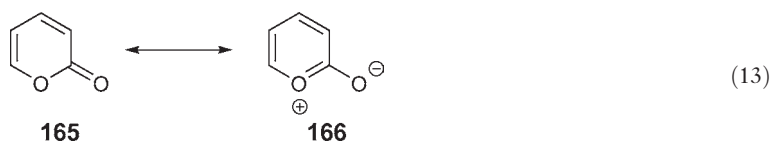


7.07.7 Pyran-2-ones and Their Benzo Derivatives

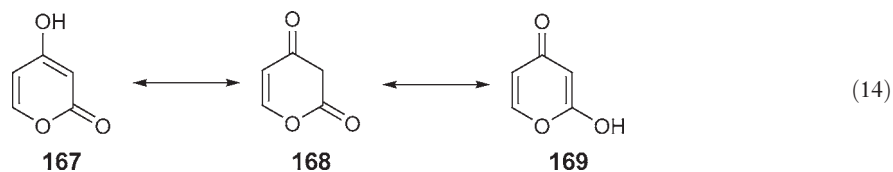
7.07.7.1 Introduction

The pyran-2-one motif is found in a large number of naturally occurring compounds, many of which have interesting pharmacological properties. For this reason, pyran-2-ones have long been recognized as important synthons for organic synthesis and medicinal chemistry and as such their reactivity has received substantial attention.

The structure of the pyran-2-one, **165**, is closely related to that of the pyrylium salt (Equation 13). One of the resonance structures of pyran-2-ones is the pyrylium betaine, **166**. As might be expected, pyran-2-one shows some aromaticity, which is manifested in some of its reactions; however, it also displays many of the reactivity patterns associated with 1,3-dienes and lactones, depending on the conditions it is subjected to.



Many of the pyran-2-ones discussed in this chapter possess a hydroxyl group at position 4. This feature allows them to behave as a 1,3-dicarbonyl as well as tautomerize to a pyran-4-one (Equation 14).

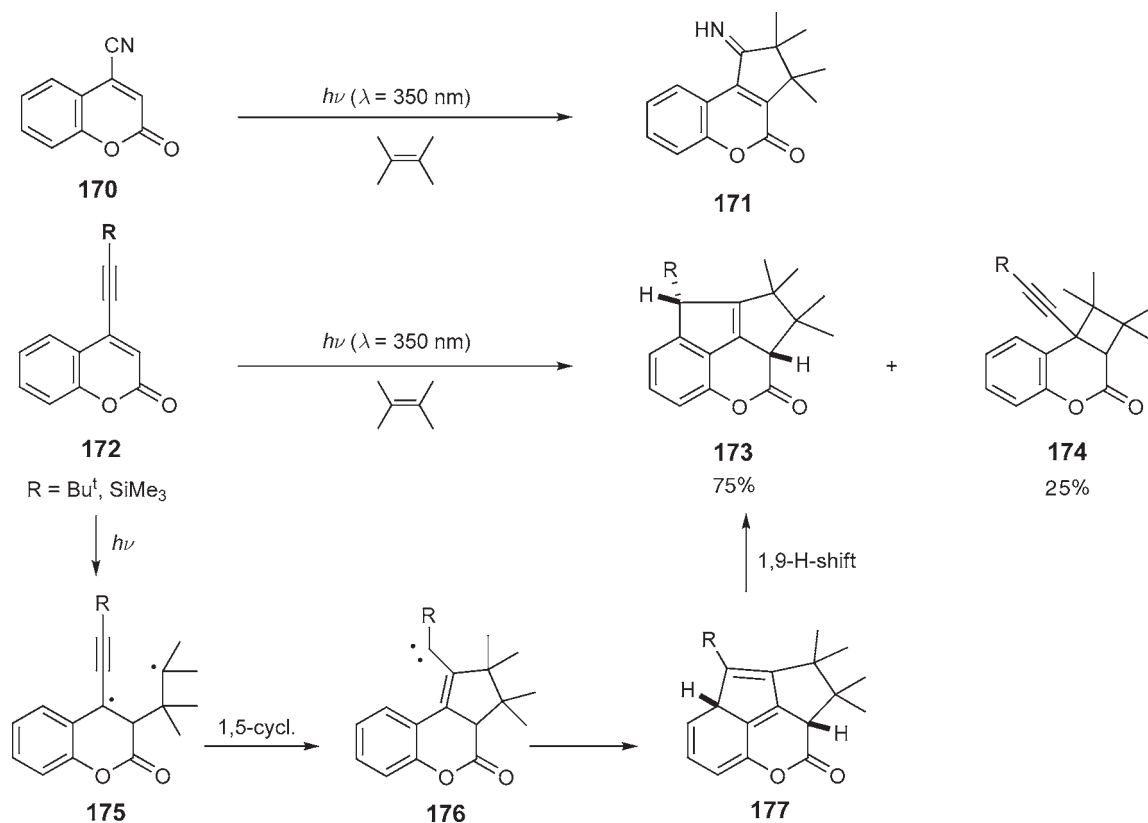


The coumarins are benzene-fused derivatives of pyran-2-ones. Many of the coumarins have interesting uses as drugs and antibiotics. The relatively less common isocoumarins and arylcoumarins are also members of the pyran-2-one family.

7.07.7.2 Reactivity at Ring Atoms

7.07.7.2.1 Thermal and photochemical reactions

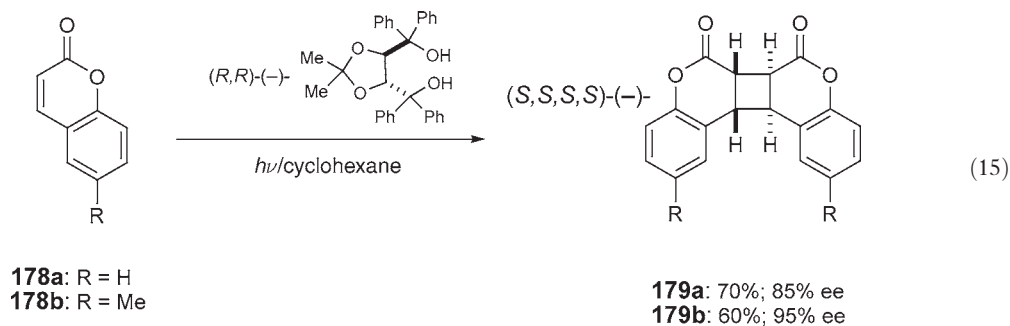
Many interesting photochemical reactions are possible with pyran-2-one and its various alkyl and benzo derivatives. For example, irradiation of 2-oxo-2*H*-1-benzopyran-4-carbonitrile **170** in the presence of excess 2,3-dimethylbut-3-ene in Ar-degassed benzene provided imino-substituted cyclopenta[*c*]annelated product **171** (Scheme 19)



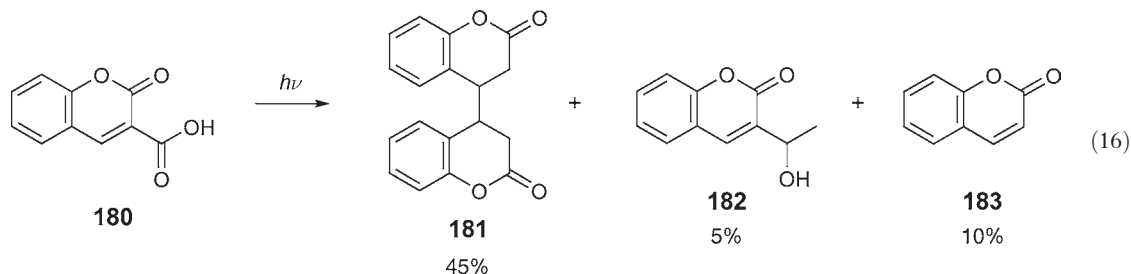
Scheme 19

<2001S1111>. In a similar vein, when 4-alkynylcoumarin **172** was irradiated under the same conditions, a mixture of **173** and [2+2] adduct **174** was obtained in a 3:1 ratio. The formation of **173** can be explained in terms of intermediates **175** $\rightarrow$ **177**. It is of interest that the cyclopentenylcarbene **176** undergoes electrocyclic ring closure efficiently whereas the corresponding cyclopentenyl nitrene formed in the conversion of **170** $\rightarrow$ **171** does not <2005OL5159>.

The [2+2] photodimerization of coumarin has been extensively studied and previously reviewed in this series <1984CHEC>. An enantioselective variant of this transformation has recently been described <2005OL1501>. Irradiation of coumarin or 6-methylcoumarin in the presence of an optically active host compound provided *anti*-head-to-head dimers with up to 98% ee (Equation 15).



A new type of photo-dimerization reaction for coumarin derivatives has also been described (Equation 16) <2002TL5161>. Irradiation of coumarin-3-carboxylic acid **180** in ethanol provided three different types of products: the 4,4'-dimer of chroman-2-one **181**, 3-(1'-hydroxyethyl)-coumarin **182**, and coumarin **183**. The authors postulated that for the formation of **181**, a ketyl radical is first formed, and the equilibrium between the 2-position and 4-position radical favors the latter. Dimerization of the 4-position radicals, followed by tautomerization and decarboxylation, provides dimer **181**.

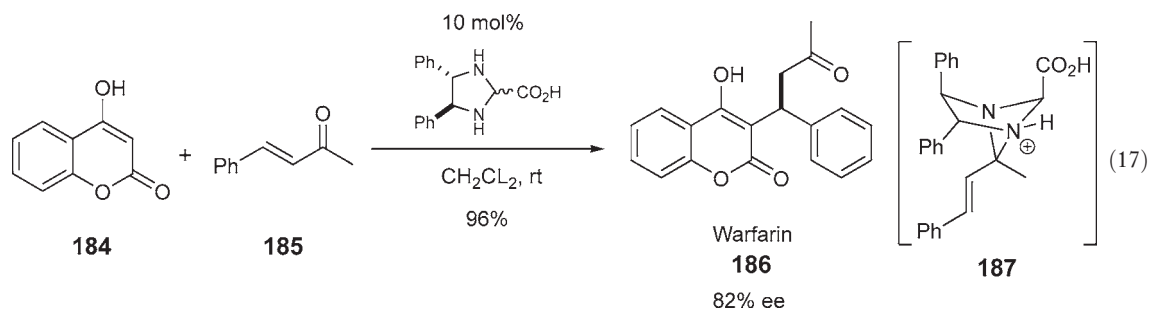


7.07.7.2.2 Reactions with electrophiles

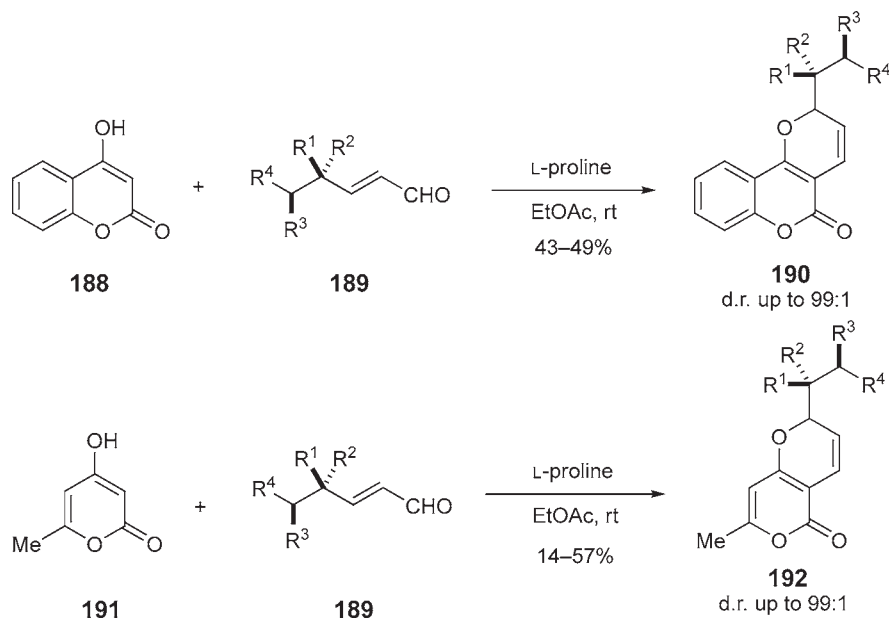
7.07.7.2.2(i) Addition and substitution

Epoxidation of coumarin at the C-3/C-4 double bond has been achieved using dimethyldioxirane (DMDO) <1997DMD1318>.

An organocatalytic asymmetric Michael addition of 4-hydroxycoumarins into α,β -unsaturated ketones has recently been reported <2003AGE4955>. This reaction was used en route to warfarin **186**, a well-known anticoagulant prescribed as a racemate despite the fact that the (*S*)-enantiomer has markedly better anticoagulant activity. 4-Hydroxycoumarins possessing either electron-withdrawing or electron-donating functionality were reacted in enantioselective Michael addition fashion with an array of enones to produce a broad range of Michael adducts, exemplified by the transformation shown to produce **186** (Equation 17). Aminal intermediate **187** was proposed to explain the observed stereochemical outcome.

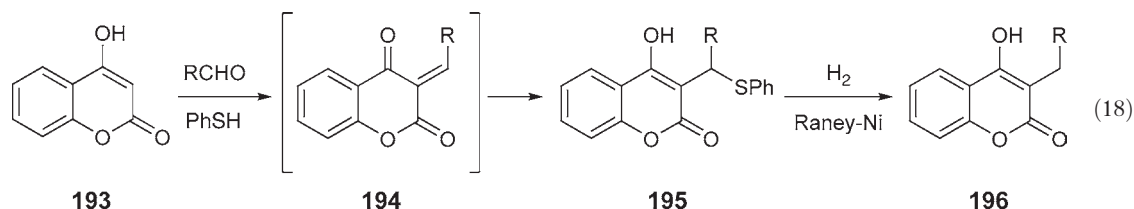


In an extension to the above methodology, a sequential 1,2-addition, dehydration, and *in situ* ring closure via a 6π -electron electrocyclic cyclization has been described in the context of the pharmacologically relevant natural products warfarin A, the arisugacins, merulidial, and isovelleral (**Scheme 20**) <2005CAR1287>. Carbohydrate-derived α,β -unsaturated enals were coupled with 4-hydroxycoumarin **188** and 4-hydroxy-6-methylpyran-2H-one **191** in the presence of proline catalysts to provide pyrone-annulated products of types **190** and **192**. Stereoselective electrocyclic ring closure was observed only when hydroxyl functionality (at any of R^1 – R^4) on the enal was acyl protected.

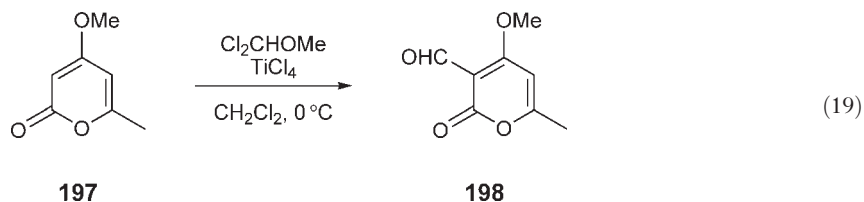


Scheme 20

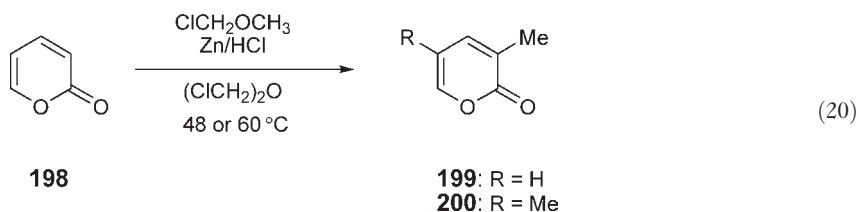
Several important natural compounds have an alkyl chain at the C-3 position of 4-hydroxycoumarins. In a synthesis of 3-geranyl-coumarin, 4-hydroxycoumarin was reacted with an aldehyde to generate intermediate **194**, which was trapped with thiophenol to produce **195**. Reduction of **195** under hydrogenation conditions in the presence of Raney-Ni catalyst afforded alkylated 4-hydroxycoumarin **196** <1997OPP223> (Equation 18).



Treatment of 4-methoxy-2H-pyran-2-one with a haloether in the presence of TiCl_4 provided 3-formyl-4-methoxy-2H-pyran-2-one, which is a useful synthon in natural products synthesis (Equation 19) <1998JOC8748, 2001COR571>.

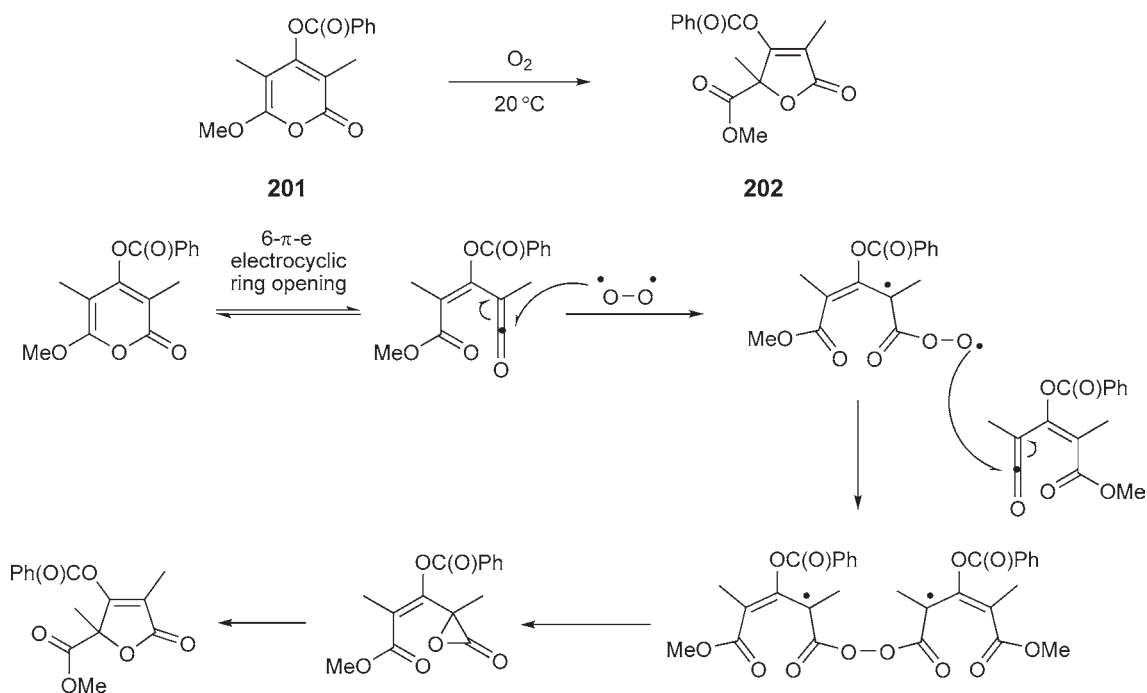


Electrophilic substitution at C-3 and C-5 of pyran-2-one, **198**, has been achieved by treatment of pyran-2-one with a haloether in the presence of Zn/HCl [<1992C457, 2001COR571>](#). 3,5-Disubstituted alkyl pyran-2-ones were the major products of this reaction ([Equation 20](#)).



7.07.7.2.2(ii) Oxidations

A novel and unusual oxidative rearrangement of 6-methoxypyran-2-ones to form highly functionalized α,β -butenolides has been reported [<2005OL3705>](#). The oxidation occurs at 20 °C in the presence of molecular oxygen. A mechanism was proposed for this transformation and is shown in [Scheme 21](#).



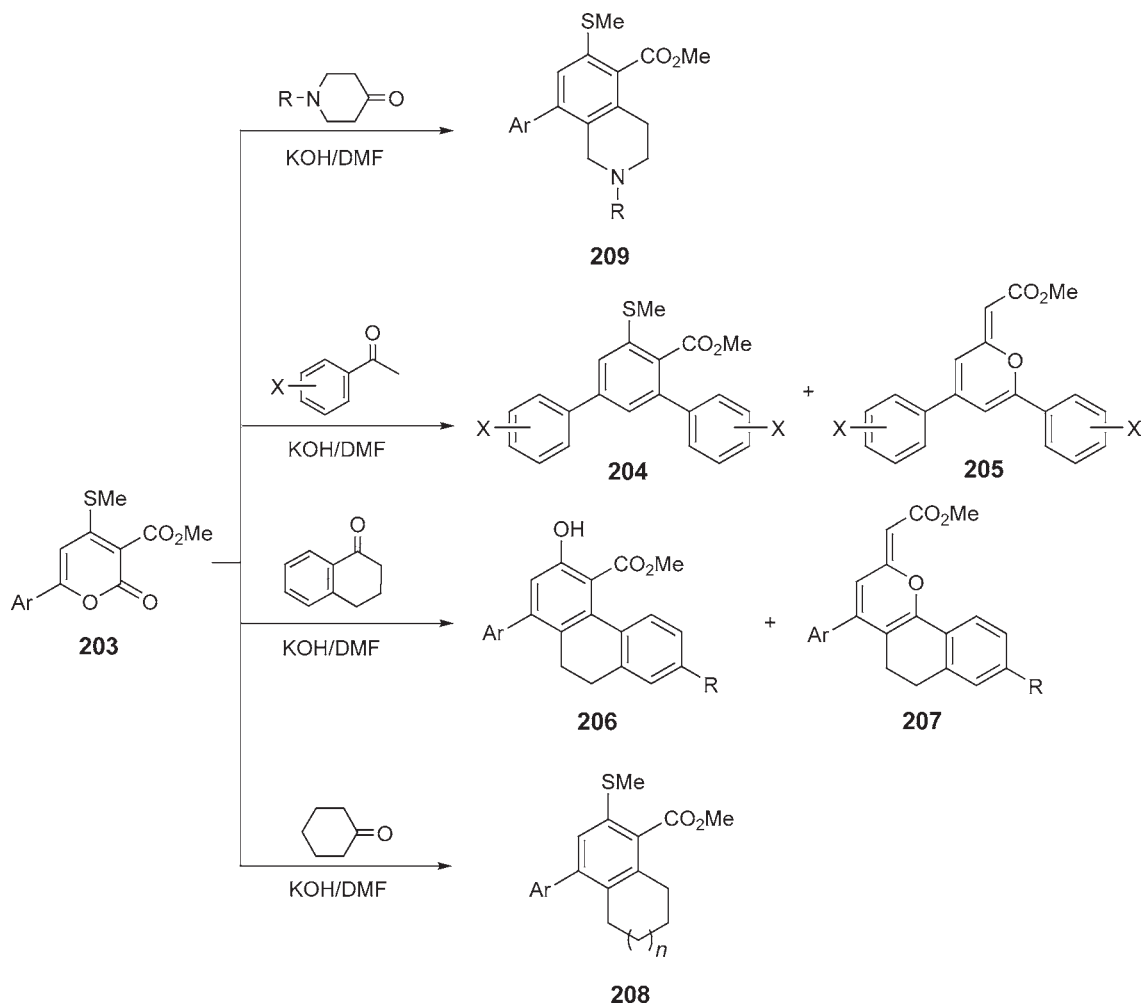
Scheme 21

7.07.7.2.3 Reactions with nucleophiles

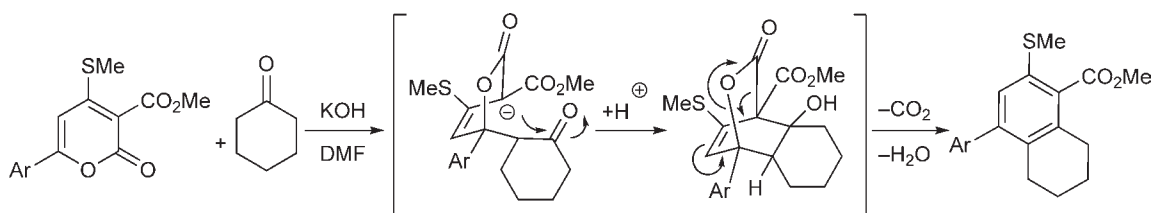
The pyran-2-one ring system has three electrophilic sites: C-2, C-4, and C-6. Among these sites, C-6 is the most susceptible to nucleophilic attack and subsequent ring transformation reactions. The ring-transformation process can be summarized in three steps: ring opening with a nucleophile, decarboxylation, and intramolecular recyclozation.

7.07.7.2.3(i) Carbon nucleophiles

A variety of carbanion-based nucleophiles that allow ring transformation of pyran-2-ones into a diverse array of benzene frameworks have recently been studied and reviewed <2001CUOC571>. Reaction of **203** with an enolate derived from an aryl ketone allows entry into a class of 1,3-terphenyls represented by **204**. In addition, a new minor product **205** was formed due to competing reactivity of the C-4 position <1996TL93, 1998S167>. In a similar vein, pyran-2-one **203** can be reacted with a variety of mono- and bicyclic ketones to generate bi- and tricyclic hydrocarbon structures **206–208** <1997JCM460, 1999S467>. In an extension of this methodology, aza analogs such as **209** were synthesized from **203** and N-substituted piperidones <1997CL1021, 1999JOC2387>. A generalized mechanism for the reactions in Scheme 22 is presented in Scheme 23.

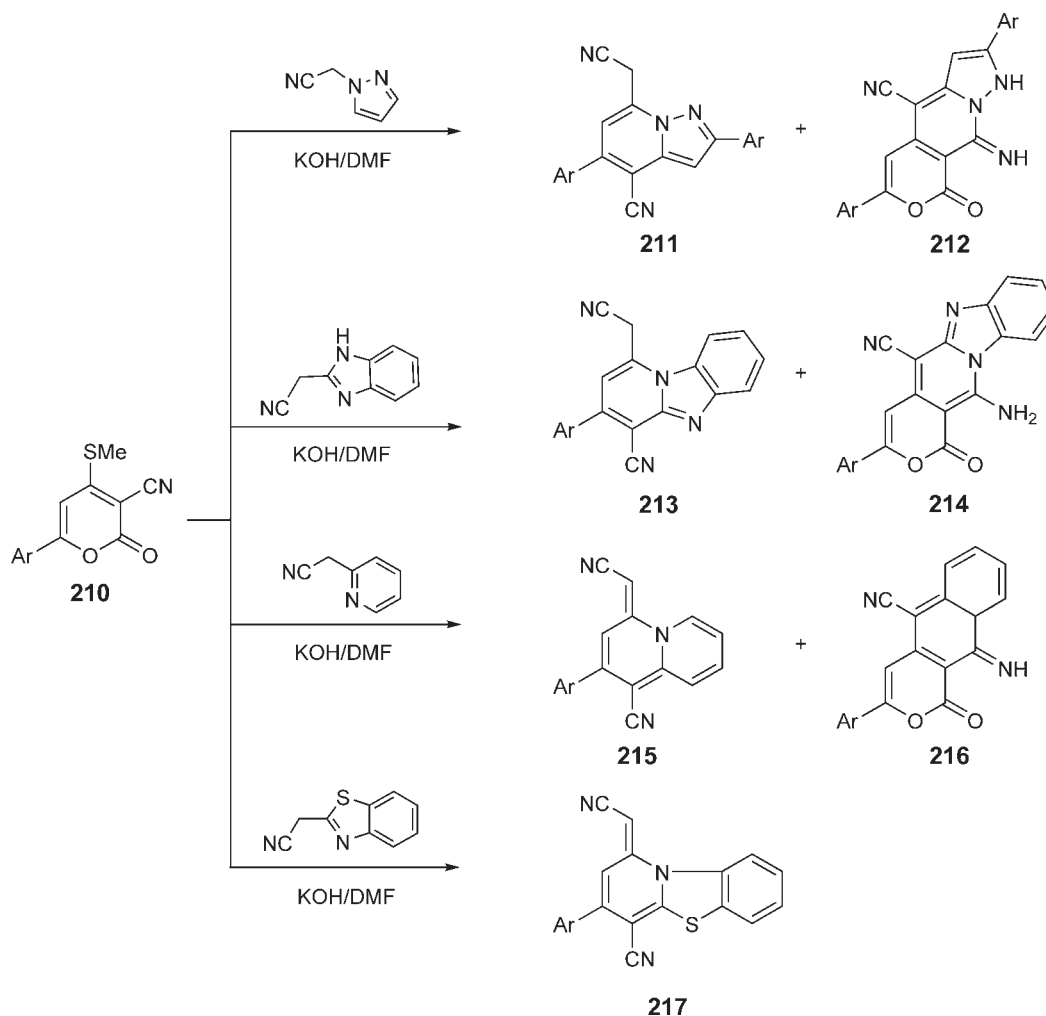


Scheme 22



Scheme 23

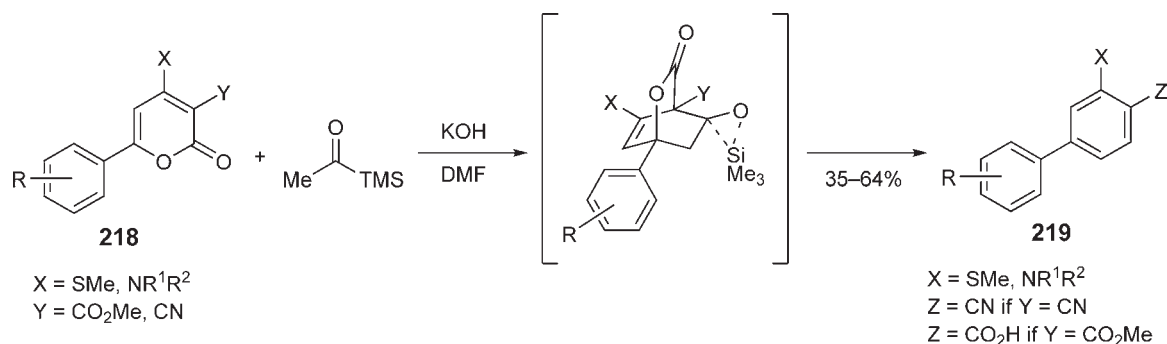
In an extension of the above methodology, reactions of pyran-2-ones with carbanions possessing pendant heterocycles were studied (Scheme 24 <2001COR571>. Treatment of pyran-2-one **210** with a carbanion of 5-aryl-3-cyanomethyl-1*H*-pyrazole provided pyrazolo[1,5-*a*]pyridine **211** along with the by-product **212** resulting from competing reaction at C-4 <1998EJO2083>. Similarly, reaction of **210** with an assortment of other cyanomethyl-bearing heterocycles including cyanomethylbenzimidazole, cyanomethylpyridine, and cyanomethylbenzthiazole followed the same reaction course to provide the respective heteroarenes shown in Scheme 24 <1998EJO2083, 1999S1884>.



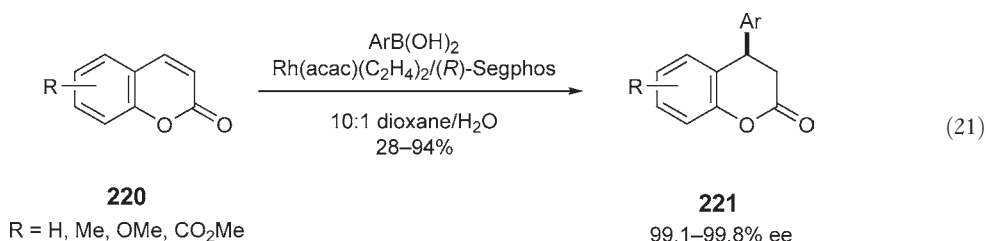
Scheme 24

Unsymmetrical biaryls (e.g., **219**) functionalized with electron-withdrawing or electron-donating substituents have been prepared from reaction of pyran-2-ones of type **218** with carbanions of acetyltrimethylsilane (Scheme 25) <2006JOC804>. Acetyltrimethylsilane serves as a useful reagent for two-carbon insertion, effectively transforming the pyran-2-one into a benzene ring. This mild method of biaryl preparation offers a potentially useful alternative to more expensive palladium-mediated cross-coupling strategies.

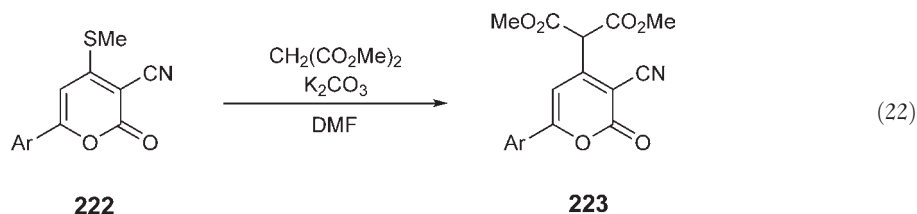
An asymmetric 1,4-addition of arylboronic acids to coumarins such as **220** catalyzed by rhodium has been achieved in greater than 99% ee (Equation 21) <2005OL2285>. This method should prove useful for the synthesis of enantiomerically enriched compounds that contain a stereogenic center between two aryl groups. This methodology was used in the total synthesis of (*R*)-tolterodine.



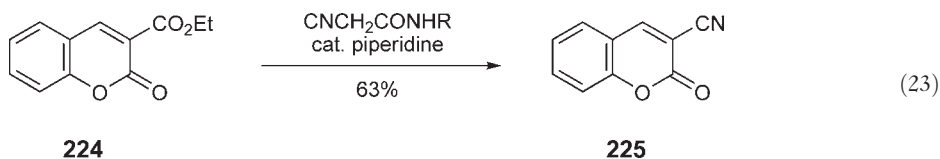
Scheme 25



A number of leaving groups at position C-4 of pyran-2-ones such 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-one **222** are able to permit substitution reactions with nucleophiles (Equation 22) <2001COR571>. Examples with a halogen leaving group are common <1996H(42)789>.



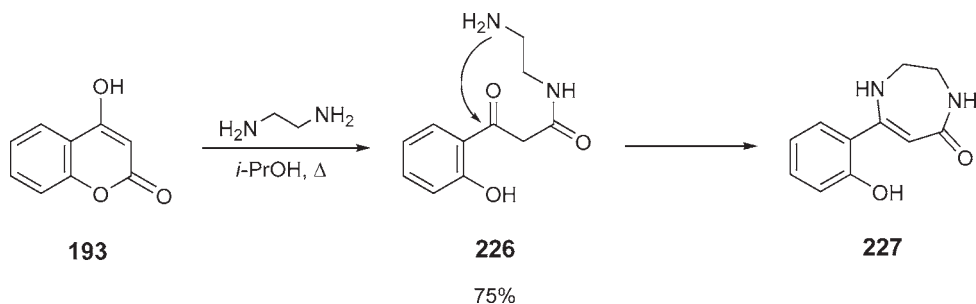
During efforts to perform a Michael addition on compounds of type **224**, an unusual ‘replacement’ of carbonyl-containing functionality at C-3 by a cyano group has been reported (Equation 23) <1998CHE1234>. A postulated mechanistic pathway for this conversion was described.



7.07.7.2.3(ii) Nitrogen nucleophiles

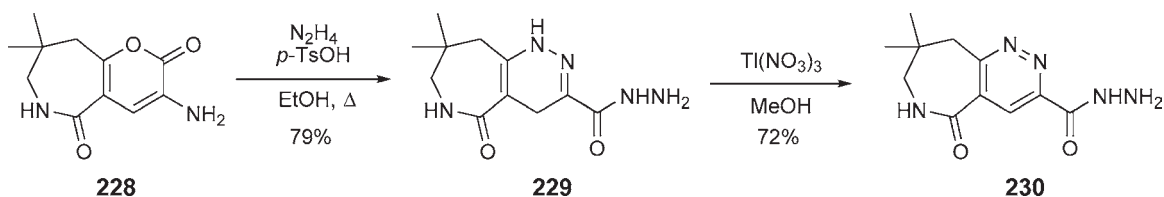
It is well known that nucleophiles such as ammonia and amines are able to open pyran-2-one rings. The resultant ring-opened products are often able to recyclize under acidic conditions to yield pyridone and benzene derivatives. This section is mainly concerned with ring-transformation reactions induced by nitrogen nucleophiles not previously discussed <1984CHEC>, as well as some novel chemistry involving nitrogen nucleophiles.

A synthetic route to 1,4-diazepin-5-ones such as **227** has been crafted by the reaction of 4-hydroxy coumarin **193** with 1,2-diamines under heating (Scheme 26) <1997JHC1821>. A variety of diamines were examined in this study, and obvious issues of regiochemistry arose with the use of unsymmetrical 1,2-diamines.

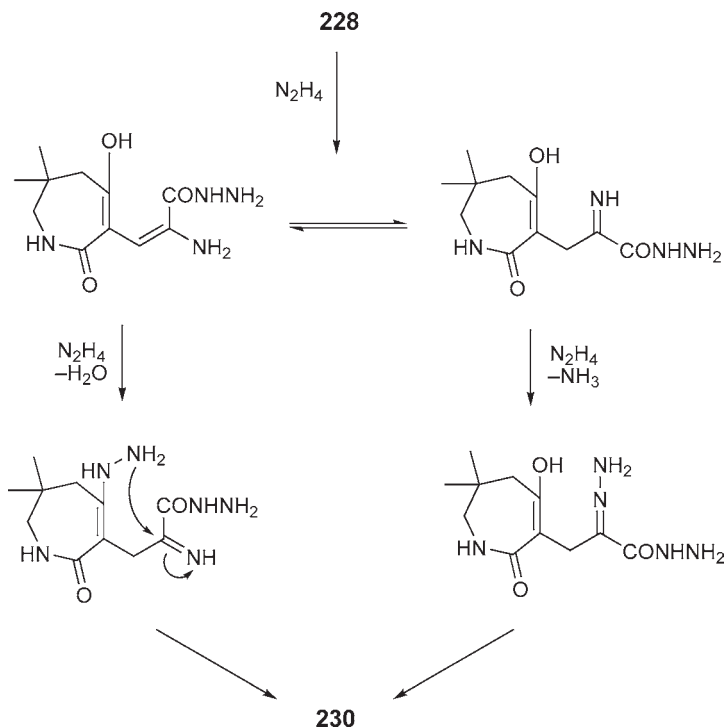


Scheme 26

A mechanistically novel reaction of pyrano[3,2-*c*]azepines **228** and hydrazine was used to prepare pyridazino[4,3-*c*]azepines such as **229**. Further oxidation of **229** yielded fused pyridazine derivatives (e.g., **230**; Scheme 27) <2000SL254>. Mechanistic insight was provided for this transformation and is shown in Scheme 28.

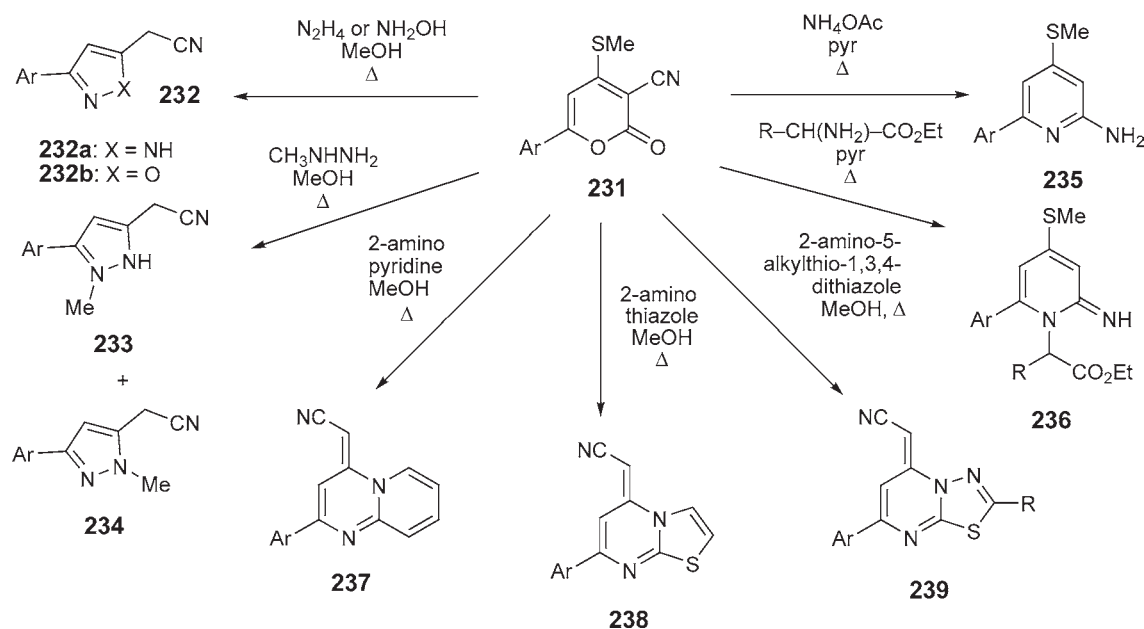


Scheme 27



Scheme 28

The synthesis of an assortment of nitrogen-containing heterocycles has been achieved by the action of nitrogen nucleophile-mediated ring transformations on functionalized pyran-2-ones such as **231** (Scheme 29) <2001COR571>. Treatment of **231** with hydrazine hydrate provided pyrazole **232a** <1991LA1229, 1994JCM86>, while reaction with methylhydrazine yielded two products, **233** and **234**. Use of hydroxylamine in an extension of this method afforded isoxazole **232b** <1993JCM110>. All of these products are formed by the attack of the nucleophile at C-6 of pyran-2-one followed by decarboxylation and recyclization involving elimination of methanethiol. On reaction with ammonia or amino acid ester with **231**, products **235** and **236** are formed, respectively <1994JCM354>. Fused bicyclic heterocycles such as pyrido[1,2-a]pyrimidines **237** <1999S1884>, thiazolo[3,2-a]pyrimidines **238**, and thia-diazolo[3,2-a]pyrimidines **239** have also been synthesized from the reaction of **231** with heterocyclic amines <2001COR571>.



Scheme 29

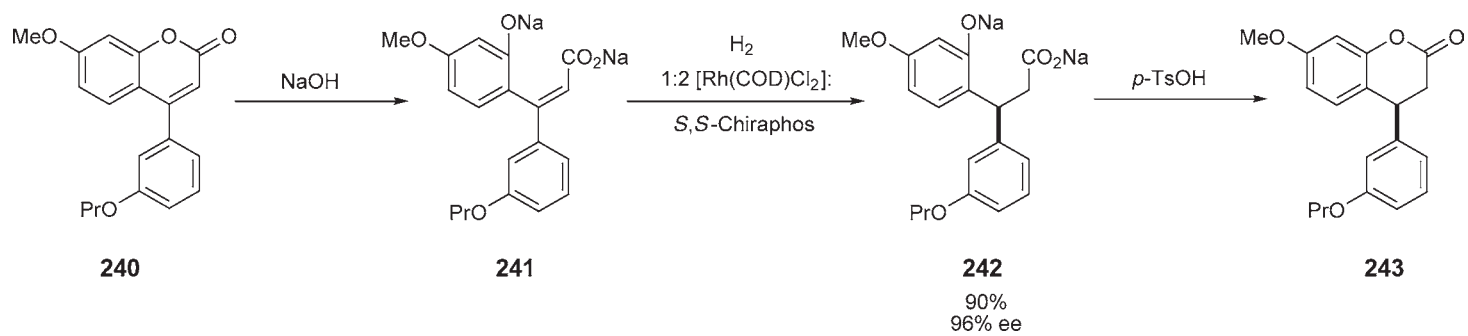
7.07.7.2.4 Reductions

The asymmetric catalytic hydrogenation of 4-aryl coumarins has been reported (Scheme 30) <1999TL3293>. Initial attempts to asymmetrically hydrogenate coumarin **240** directly proved unsuccessful. However, upon lactone opening, **241** was smoothly converted to hydrogenated product **242**, which would relactonize to **243** gradually on standing or more quickly under catalysis with *p*-toluenesulfonic acid.

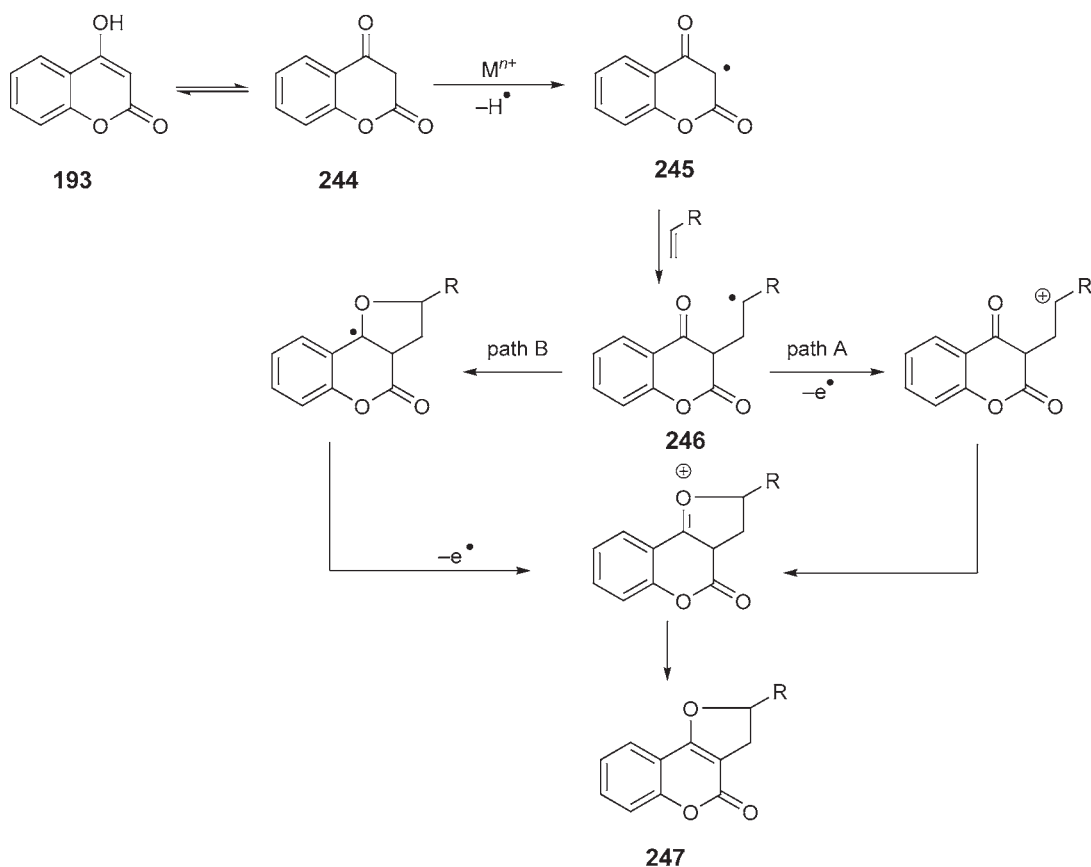
Enantioselective catalytic hydrogenations have also been accomplished with various substituted pyran-2-ones using ruthenium catalysts <1999JOC5768>. Hydrogenation was found to occur selectively at positions 5 and 6 with up to 97% ee. Substitution at position 3 influenced the selectivity and rendered further hydrogenation of the double bond at positions 3 and 4 much slower.

7.07.7.2.5 Radicals

It is well established that position 3 of coumarin is the most reactive with radicals. In keeping with this trend, 4-hydroxycoumarin **193** has been found to undergo addition to alkenes to generate 2,3-dihydro-4H-furo-[3,2-*c*][1]benzopyran-4-ones such as **247**, a common motif in natural products (Scheme 31). Cerium ammonium nitrate (CAN) and manganese(III) acetate hydrate (MAH) were the one-electron metal oxidants examined in this study <1996SC3359>. The reaction is triggered by the oxidation of the carbonyl substrate to an electrophilic α -oxo alkyl radical (**244** $\rightarrow$ **245**), which subsequently adds to the alkene (**245** $\rightarrow$ **246**). The exact mechanistic details beyond this point are unclear and may differ according to the oxidant employed, given that CAN and MAH have different oxidizing capacity toward alkyl radicals. The yields for this transformation are 10–94%, depending on the alkene used.



Scheme 30



Scheme 31

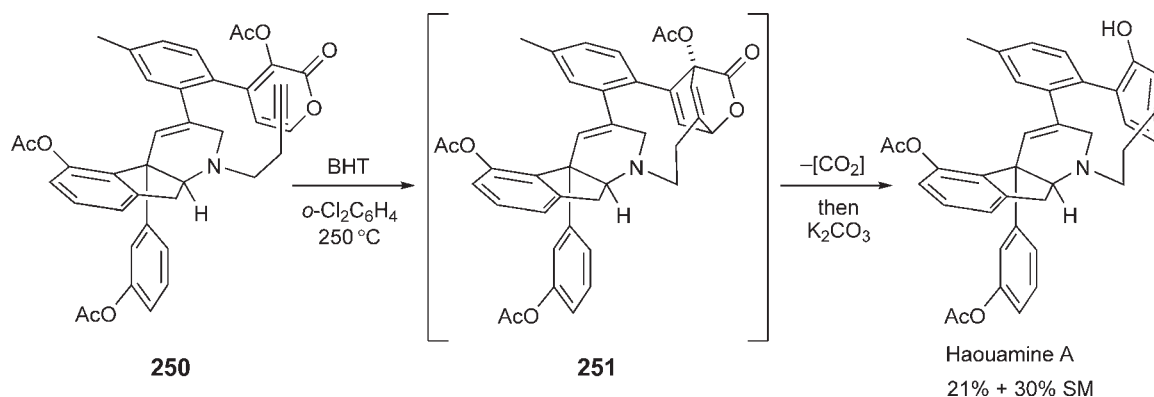
7.07.7.2.6 Other reactions

7.07.7.2.6(i) Cycloadditions

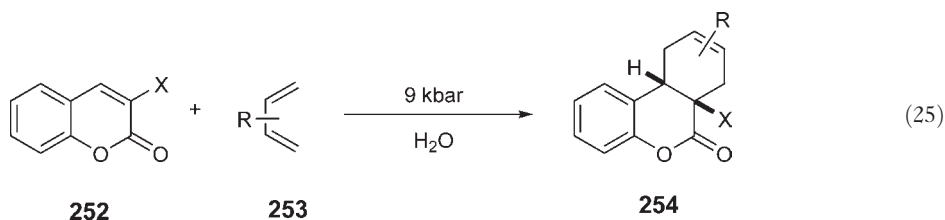
Pyran-2-ones are extraordinarily useful as Diels–Alder dienes, and therefore cycloadditions comprise much of the literature pertaining to pyran-2-ones. As one might expect, Diels–Alder reactions with pyran-2-one are facile with alkynes in addition to alkenes, exemplified by the transformation shown in Equation (24) <1997SC1123>. Using different sets of conditions, X can be anything from $-\text{CN}$ or $-\text{CO}_2\text{CH}_3$ to $-\text{OAc}$ to $-\text{H}$. A stunning application of this methodology has recently been used en route to an eight-step total synthesis of ($\pm$)-haouamine A <2006JA3908>, and is shown in Scheme 32.



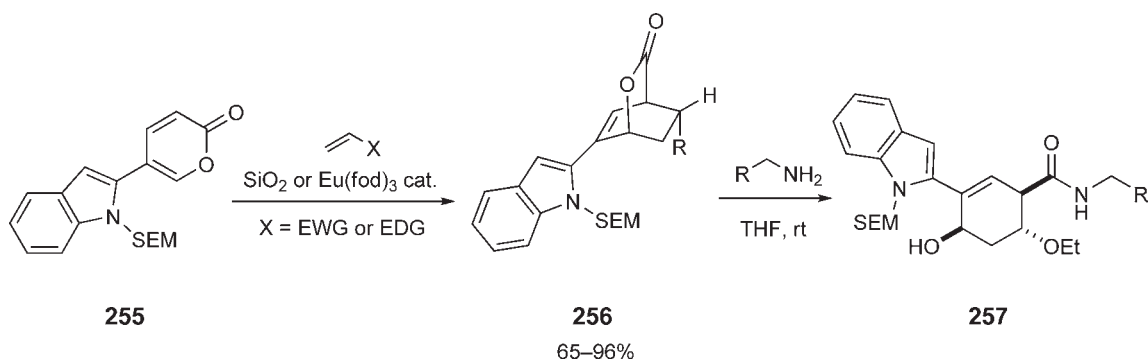
The use of coumarin in Diels–Alder reactions is, by comparison to pyran-2-ones, still largely unexplored. This is likely due to the low reactivity of the double bond at positions 3 and 4. Diels–Alder reactions with 3-substituted coumarins are rare, despite the potential to synthesize tetrahydro-6*H*-benzo[*c*]chromen-6-ones, important precursors to functionalized biphenyls and several natural products. Electron-withdrawing substitution at C-3 does not serve to efficiently activate the dienophilic system; thus, it has been found that high temperatures and pressures are necessary to effect the reaction (e.g., Equation 25) <2006JOC70>.



Scheme 32

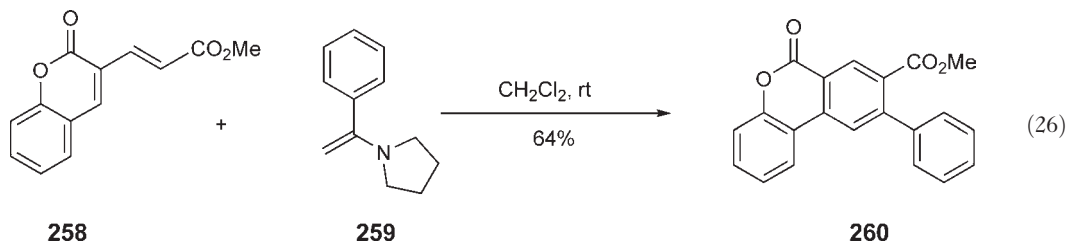


Some research groups have exploited the intrinsic reactivity of the bicycloadducts formed in the pyran-2-one Diels–Alder reactions. An example of this strategy is shown in [Scheme 33](#), where the pyran-2-one decorated with indole functionality **255** was reacted with an assortment of electron-rich and electron-poor dienes [<2000T5205>](#). The richly functionalized bicyclo[2.2.2]adduct **256** was then subjected to mild aminolysis to produce tetrasubstituted hexene **257** as single diastereoisomers.

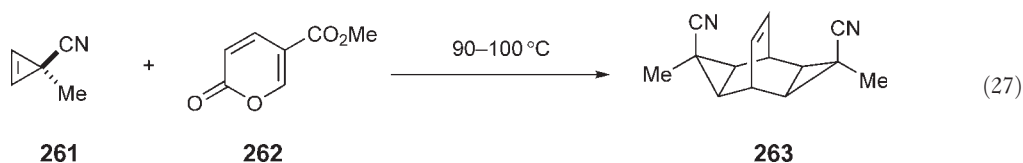


Scheme 33

It is also worth mentioning that inverse electron demand Diels–Alder reactions are possible with pyran-2-ones and coumarins. Shown in [Equation \(26\)](#) is one such reaction using an electron-deficient diene of coumarin **258** with enamine **259** to give **260** [<1999SL477>](#).



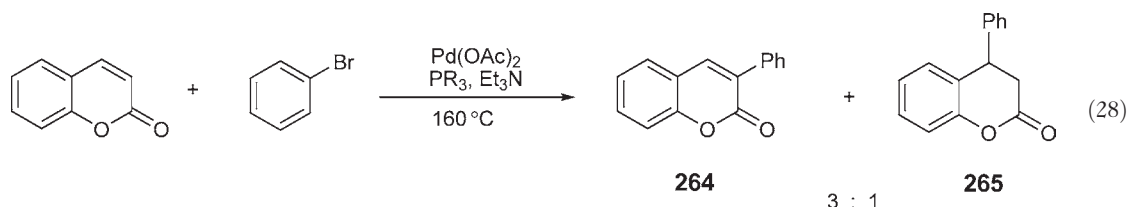
Cycloaddition reactions of several pyran-2-one derivatives with interesting outcomes include coumalic acid **262** and 1-methyleyclopropene-1-carbonitrile **261** to give **263** (Equation 27) <2006RJO969>.



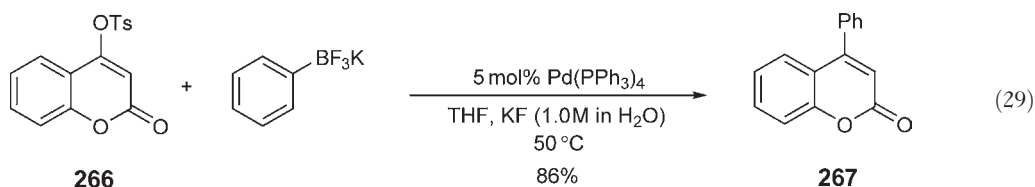
7.07.7.2.6(ii) Palladium-catalyzed reactions

Palladium-catalyzed reactions and cross-couplings are vital and widely used methods in the synthesis of organic compounds. Many examples have emerged utilizing pyran-2-ones and coumarins in palladium- and nickel-mediated reactions, and several of these are presented in this section.

A Pd-catalyzed Heck arylation with coumarin and bromobenzene has been reported (Equation 28) <1996IJB588>. Two products, **264** and **265**, were reported for this reaction in a 3:1 ratio. The major compound was formed by a Heck reaction at the C-3 position, and mechanistic discussion was included for both products.



Suzuki–Miyaura cross-couplings have been described for tosylated 4-hydroxycoumarins (e.g., **266**) with aryl trifluoroborates in the presence of Pd(PPh₃)₄ (Equation 29). Excellent yields have been reported for aryl trifluoroborates <2006TL1525>, while yields with aryl boronic acids are slightly lower <2002TL4395>. In a similar vein, Negishi couplings and Sonagashira reactions have also been reported for direct substitution of the pyran-2-one ring at position 4 <2003S2564>.



In a fascinating study, it was shown that regioselective Stille couplings can be accomplished on 3,5-dibromo-2-pyrones (Equation 30; Table 3) <2003JA14288>. Between the C-3 and C-5 positions, C-3 has lower electron density; therefore, oxidative addition of Pd(0) is predicted to proceed faster at this position. The coupling of tributyl(phenyl)stannane and **268** in the presence of 10% CuI in refluxing toluene provided the expected 3-phenyl-5-bromo-2-pyrone **269** in 94% yield. Surprisingly, however, the Stille coupling gave rise to the unpredicted 3-bromo-5-phenyl-2-pyrone **270** as the sole product in 75% yield when the reaction was performed with 1.0 equiv of CuI in DMF. The trend was maintained for a variety of stannanes, as shown in Table 4. The exact nature of the CuI effect on oxidative addition in polar solvents is not completely understood. This study should, however, be of great value given that the Stille coupling can be made to occur at either of two chemically different bromides, depending on the reaction conditions.

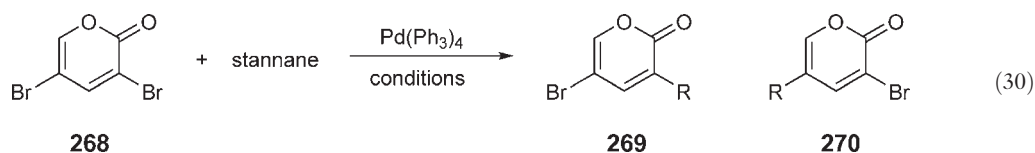


Table 3 Stille cross couplings on 3,4-dibromo-2-pyrone

Entry	Stannane	Condition	269	270
1		A (0.5 h) B (0.5 h)	50% Trace	Trace 50%
2		A (10 min) B (6 h)	67% Trace	0% Trace
3		A (20 min) B (0.5 h)	61% Trace	Trace 60%
4		A (20 min) B (20 min)	72% Trace	Trace 68%
5		A (10 min) B (12 h)	51% Trace	Trace 33%
6		A (1 h) B (20 min)	80% Trace	Trace 79%
7		A (1.5 h) B (0.5 h)	79% Trace	Trace 75%
8		A (7 h) B (0.5 min)	61% Trace	Trace 55%
9		A (2 h) C (2 h)	57% Trace	Trace 52%

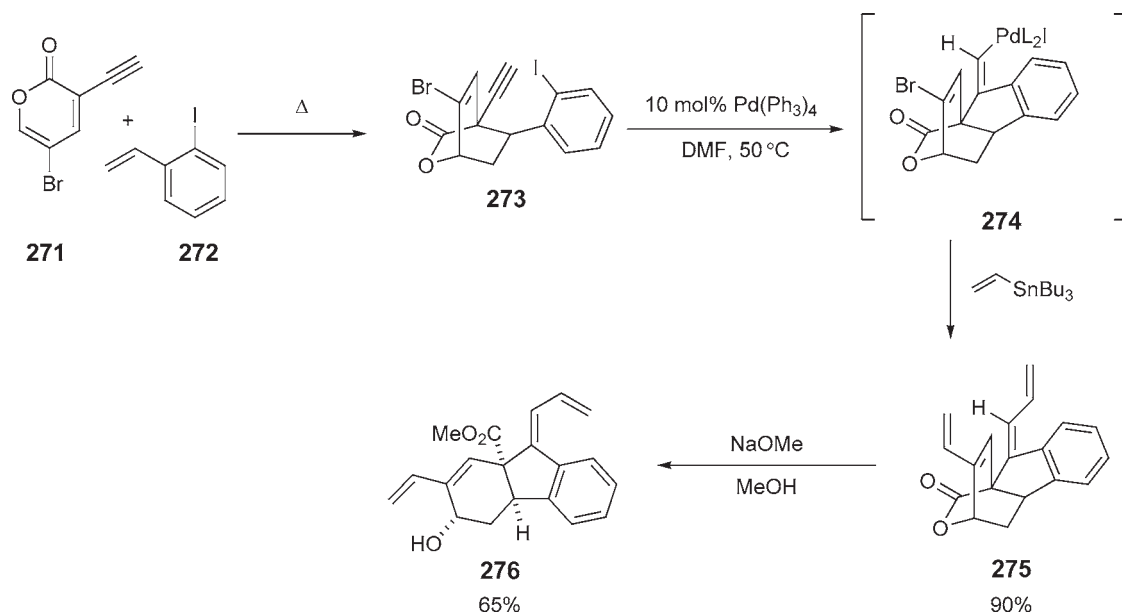
A: Pd(Ph₃)₄/Cul (0.1 equiv)/PhMe/100 °C.B: Pd(Ph₃)₄/Cul (0.1 equiv)/DMF/50 °C.C: Pd₂DBA₃/P(*t*-Bu)₃/PhMe/rt.

A clever synthesis of tetrahydrofluorenes has been reported and utilizes both cycloaddition and palladium-mediated chemistry (**Scheme 34**) <2003TL4439>. The initial reaction in this approach was a Diels–Alder reaction between alkynyl-substituted pyranones, for example, **271** (generated by Sonagashira reaction), and substituted styrenes to generate intermediates of type **273**. A palladium source was added, and the alkyne and aryl halide of the cycloadduct **273** were poised for immediate addition of the aryl palladium species into the alkyne to generate intermediate **274**. Upon addition of a stannane, product **275** was formed. Cleavage of the lactone bridge of **275** provides entry into a class of tetrahydrofluorenes (e.g., **276**) that vary according to the stannane used.

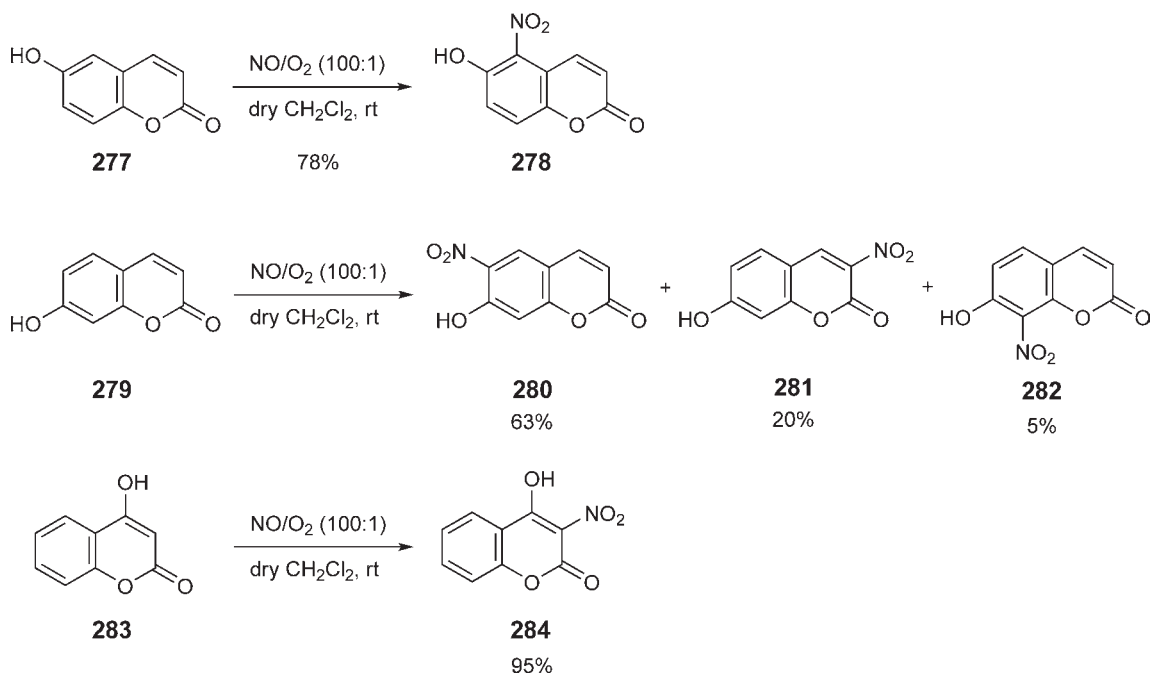
7.07.7.3 Reactivity of Substituents

7.07.7.3.1 Fused benzene rings

A novel method for the mononitration of 4-, 6-, or 7-hydroxycoumarins has been reported using gaseous nitric oxide with a small amount of oxygen in methylene chloride or acetonitrile (**Scheme 35**) <2004SC985>. The method is much milder than strong acid methods, and is more selective for mononitration products than those using thallium salts, CAN, or hydrogen peroxide-based methods. The reported yields are moderate to good to excellent for this transformation.



Scheme 34



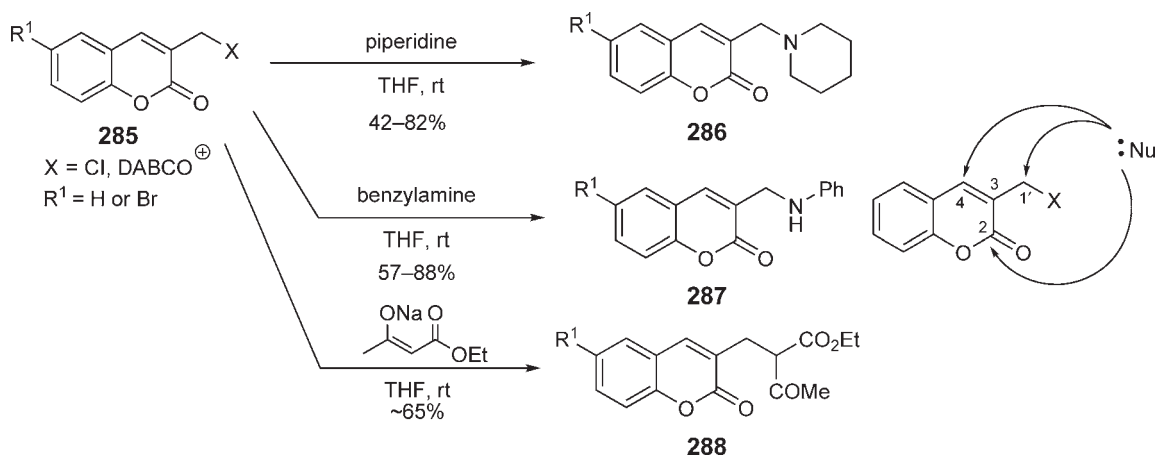
Scheme 35

Fluorescence and reverse-phase chromatography have been used to examine the reaction of coumarin with the OH radical in water <2005RPCA119>. In this study, coumarin was used as a probe to trap the OH radical, and it was found that 7-hydroxycoumarin (umbelliferone) was the major product. 3OH-, 4OH-, 5OH-, 8OH-, and coumarin were also produced, although the fluorescence emission of these products was negligible compared to that of 7-hydroxycoumarin.

The Mannich reaction of substituted 4-phenylcoumarins has also been extensively studied <2000CNO485>.

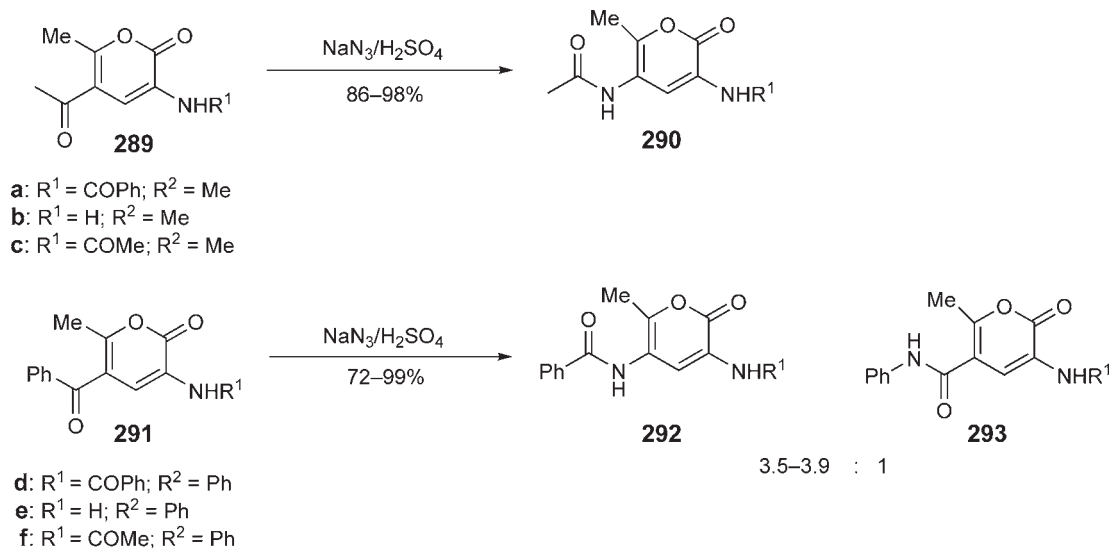
7.07.7.3.2 C-Linked substituents

Reactions of nitrogen and carbon nucleophiles have been found to proceed exclusively at an exocyclic C-1' electrophilic center rather than at C-2 or C-4 of the coumarin ring for compounds such as **285** (Scheme 36). Though the yields are somewhat low, it was reported that no other products were observed other than those from C-1' attack <2004SC3409>.



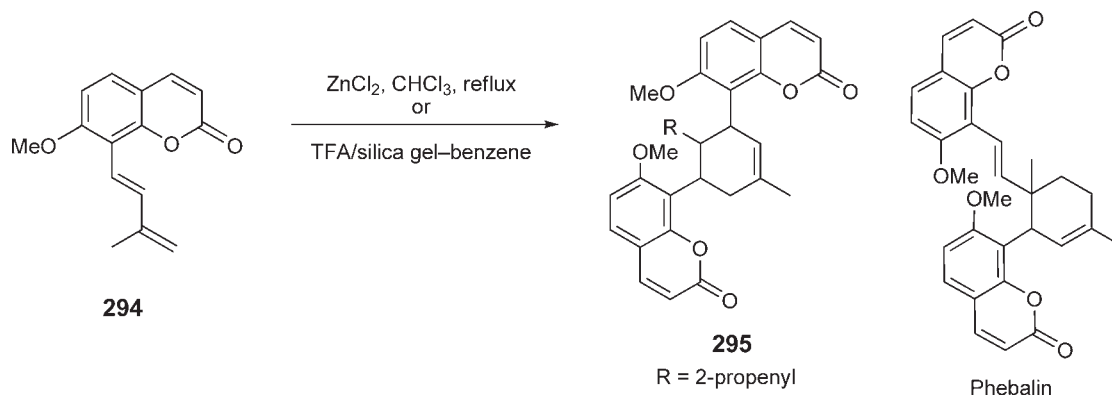
Scheme 36

The Schmidt reaction of 5-acyl-2*H*-pyran-2-ones such as **289** using sodium azide/sulfuric acid (hydrazoic acid) has been investigated (Scheme 37) <2006H(69)123>. The reaction was found to proceed with complete regioselectivity to give the corresponding 5-acetylamino derivatives via pyran-2-one migration (**289** → **290**). By contrast, when the reaction was applied to 5-benzoyl-2*H*-pyran-2-ones (e.g., **291**), formation of both regioisomers **292** and **293** was observed. The latter minor product was the result of phenyl shift rather than pyran-2-one migration.



Scheme 37

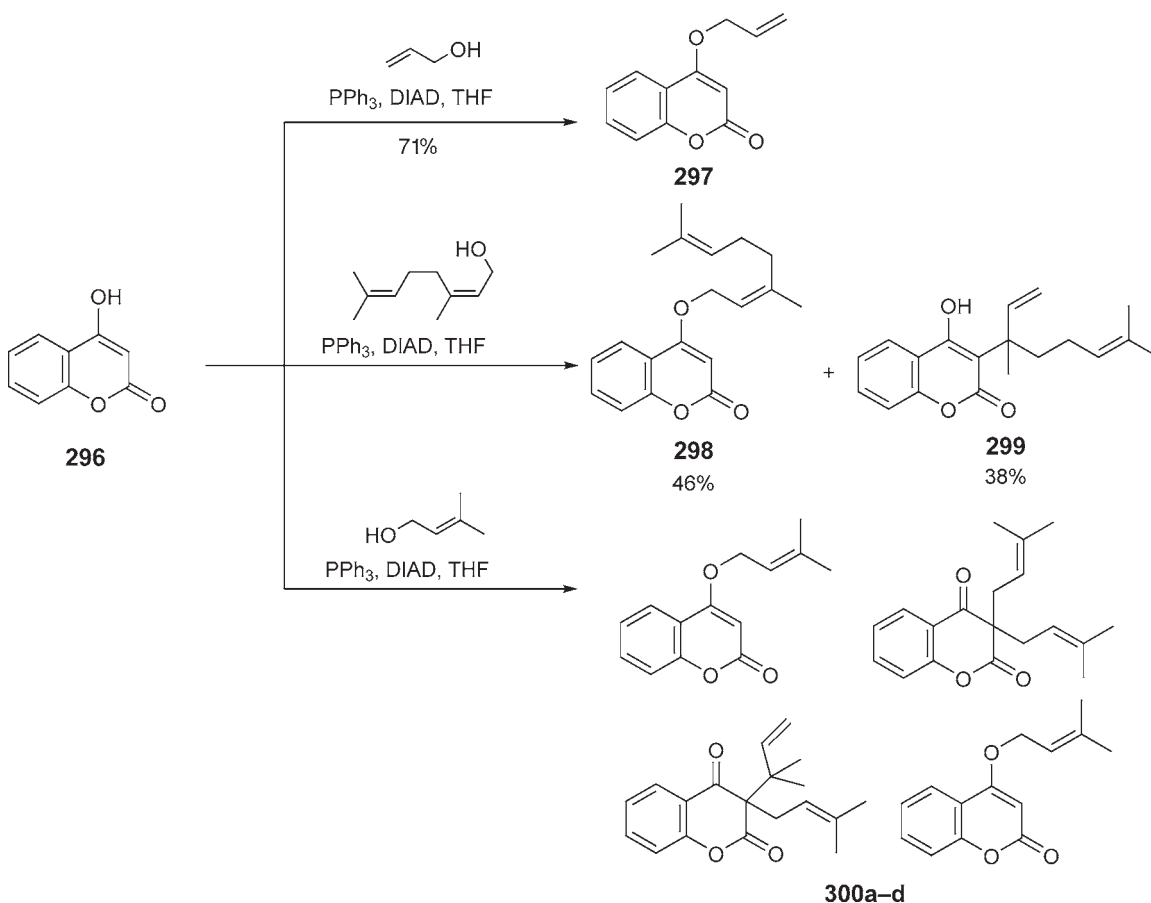
Diels–Alder homo-dimerizations of hydroxybutenyl and pentadienyl coumarins have been explored in the context of the plant-derived natural products phebalin, thamnusin, and toddasin <2000TL9909>. The Diels–Alder union of two identical coumarin units occurs under thermal, Lewis acid, or mineral acid conditions (e.g., **294** → **295**; Scheme 38).



Scheme 38

7.07.7.3.3 O-Linked substituents

The Mitsunobu alkylation of 4-hydroxycoumarins with prenyl alcohols has been studied [\[2003H\(60\)1351\]](#). Mitsunobu reactions of 1,3-carbonyls are known to be problematic due to enolate charge delocalization resulting in the formation of C- and O-alkylated product mixtures. The known reaction of 4-hydroxycoumarin **296** with allyl alcohol provided the O-alkylated product **297** exclusively (Scheme 39). The same reaction with neurol gave two products: the O-alkylated product **298** and another product **299**, which was clearly the result of a [3,3]-sigmatropic rearrangement of the O-alkylated product. Reaction of 4-hydroxycoumarin with 3-methyl-2-butenol gave four products (**300a-d**) in comparable yields.



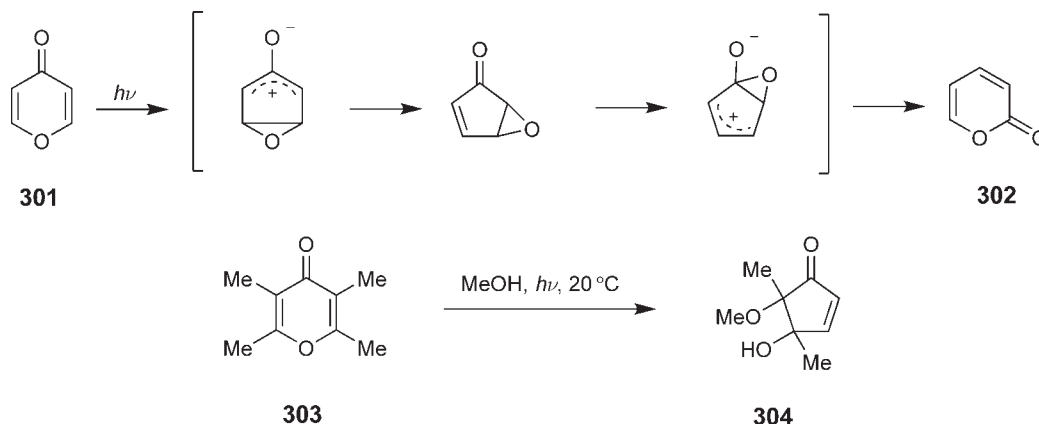
Scheme 39

7.07.8 Pyran-4-ones and Their Benzo Derivatives

7.07.8.1 Reactivity at Ring Atoms

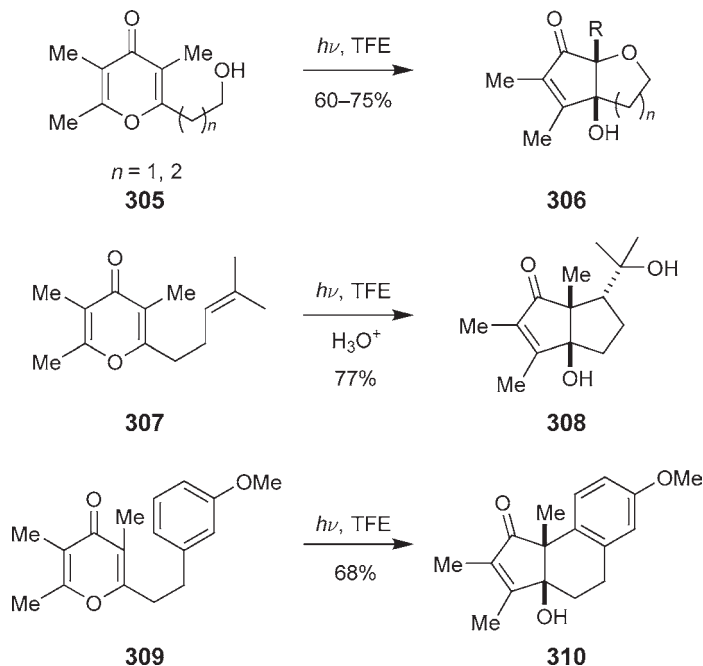
7.07.8.1.1 Photochemical reactions

Photoisomerization of pyran-4-one **301** yields pyran-2-one **302** (Scheme 40). The postulated intermediates involved in this transformation resemble those suggested in the irradiation of pyrylium salts <1984CHEC>. In a related example, irradiation of tetramethyl pyran-4-one **303** gives cyclopentenone **304** via reaction of nucleophilic solvent with the initially formed oxyallyl zwitterion intermediate.



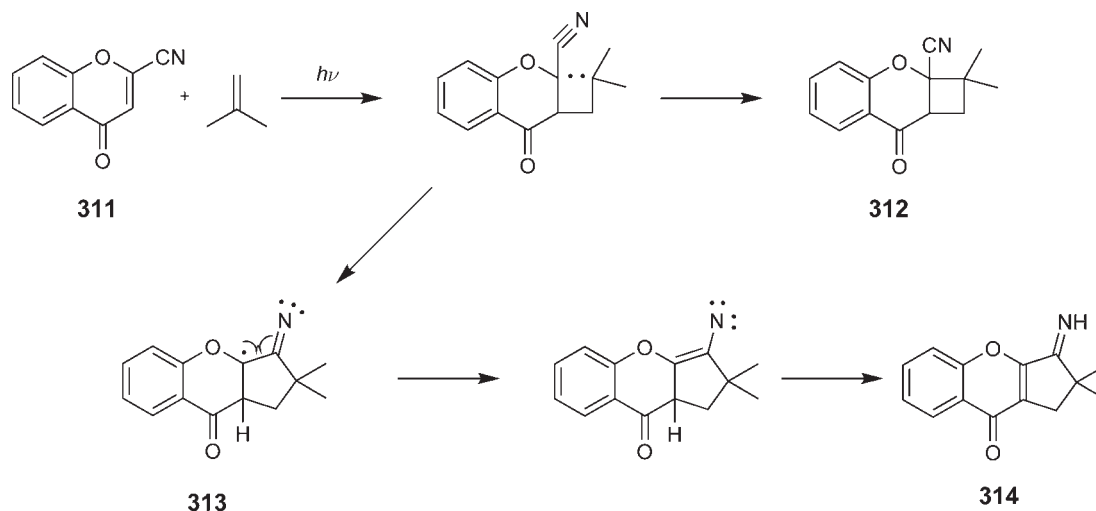
Scheme 40

4-Pyranones bearing pendant heteroatoms or π -nucleophiles undergo photochemical conversion to form diquinane, hydrindene, benzohydrindene, oxabicyclo[3.3.0]octene, and oxabicyclo[4.3.0]nonene skeletons (Scheme 41) <1998JOC2806>.



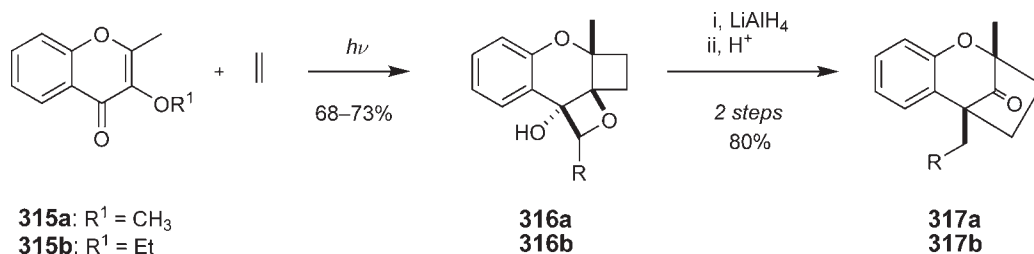
Scheme 41

Chromones are known to undergo [2+2] π - and [3+2] π -photo-cycloadditions. Irradiation of 2-cyanochromone **311** in the presence of 2-methyl-2-butene produced both [2+2] π - and [3+2] π -cycloadducts (**312** and **314**; Scheme 42). Studies of this reaction under aerobic conditions have provided proof for the existence of iminium biradical **313** <1983TL2195>.



Scheme 42

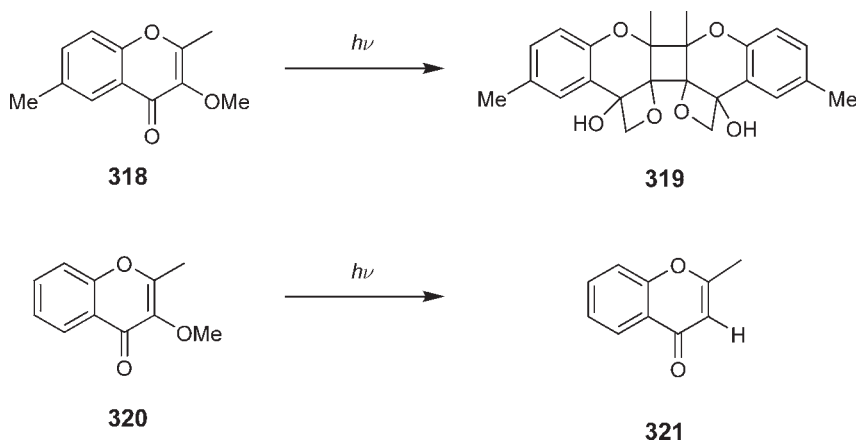
The photo-cycloaddition of ethylene to 3-alkoxy chromones such as **315** has been applied to the synthesis of marine sesquiterpene filiformin and congeners (Scheme 43) <1996JOC4391>. Tandem [2+2] π -photo-cycloaddition and γ -hydrogen abstraction provided tetracyclic intermediate **316** which was converted to terpene **317** by subsequent oxetane ring reduction and acid-catalyzed rearrangement.



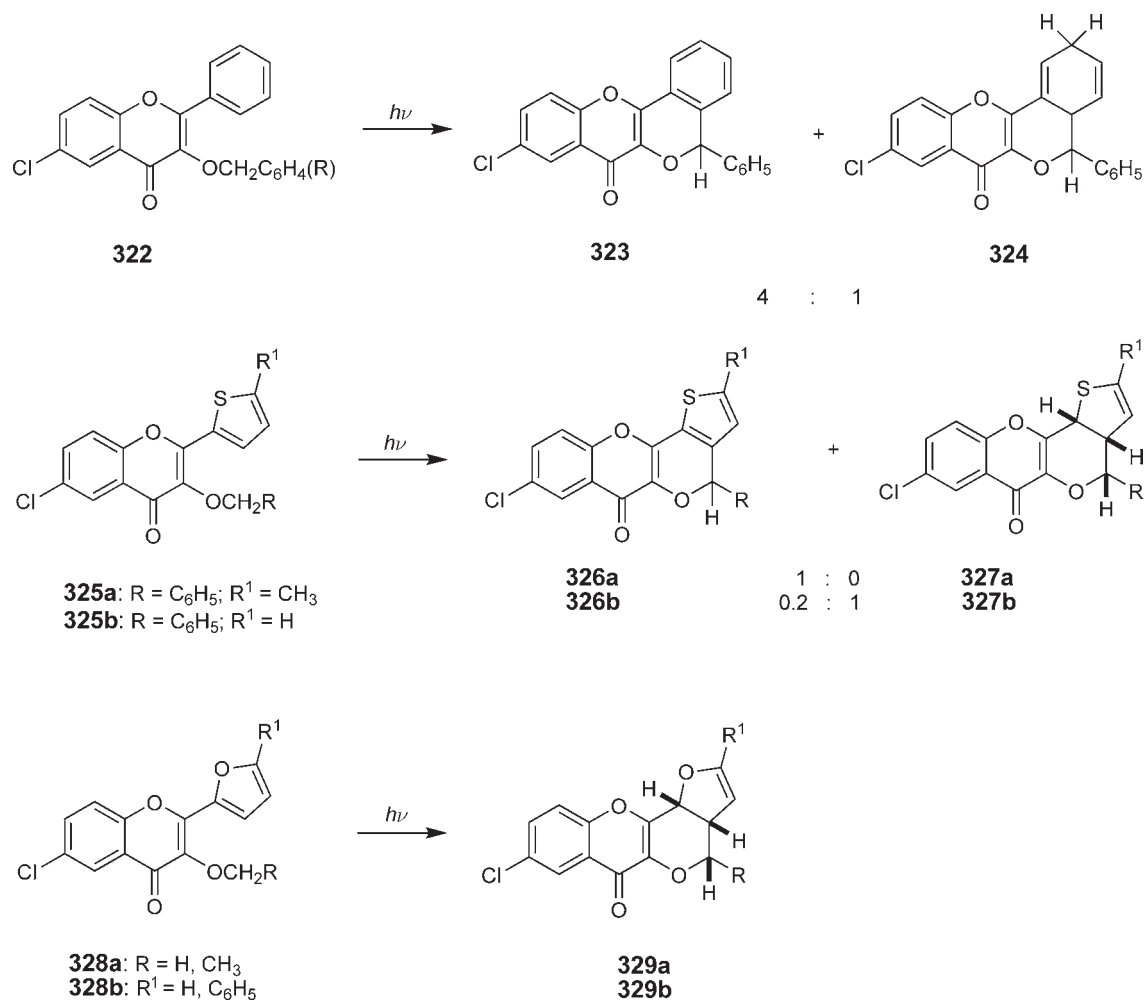
Scheme 43

The formation of dimeric oxetanol **319** was observed upon irradiation of 2,7-dimethyl-3-methoxychromone **318** (Scheme 44) <1996T7855>. Interestingly, irradiation of chromones with no substituents on the benzene ring led to the formation of demethoxylated products (e.g., **321**).

The rates of photocyclization of several 3-benzyloxy-2-phenyl chromone derivatives were found to be faster than related 3-methoxychromones <1990JIC770>. Photocyclization of 7-chloro-3-benzyloxy-2-phenyl chromone **322** yielded products **323** and **324** (Scheme 45). These results can be rationalized through initial abstraction of hydrogen from the 3-alkoxy group by the excited pyrone carbonyl followed by photodehydrogenation to produce **323** or a 1,7-hydrogen migration to furnish **324**. The photochemistry of chromones containing thiophenes and furans has also been studied <1999J(P1)2391>. In a manner similar to that described above, 3-alkoxy-2-thienyl chromones of type **325** undergo photocyclizations to form products **326** and **327**. In the phototransformation of 3-alkoxy-2-2'-furylchromones, no dehydrogenated product could be isolated and compounds of type **329** are formed <1995J(P1)177>.

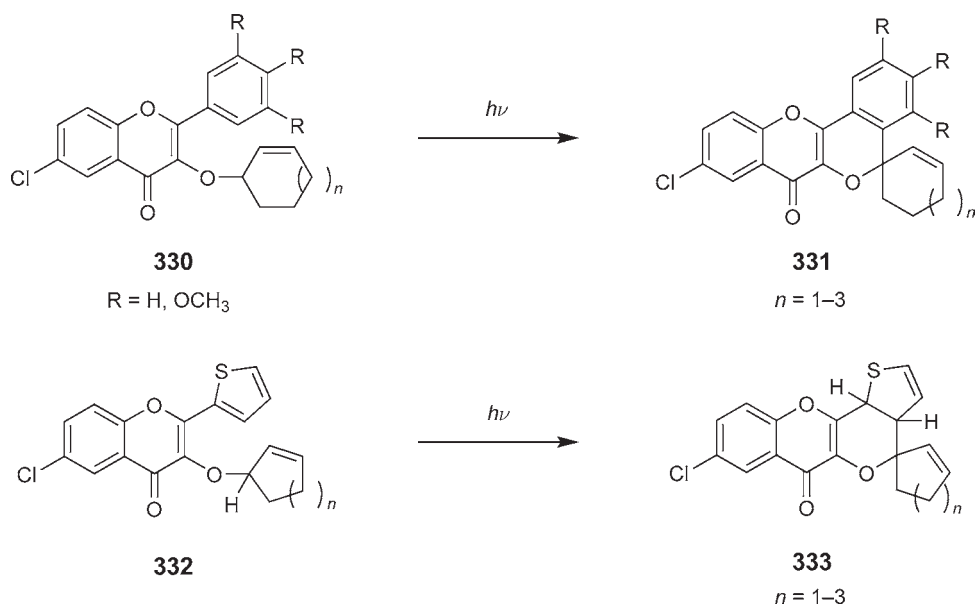


Scheme 44



Scheme 45

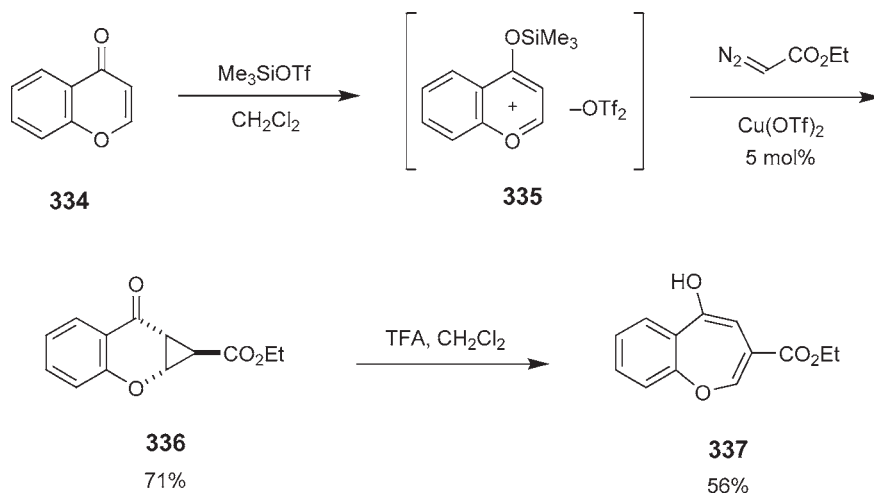
A photochemical approach to the synthesis of complex spiropyrans has been developed. A variety of spiropyrans can be synthesized by replacement of the benzylic ether moiety of previously described photocyclization substrates with allylic ethers composed of cycloalkenes of diverse size (**Scheme 46**) <1996TL8913>.



Scheme 46

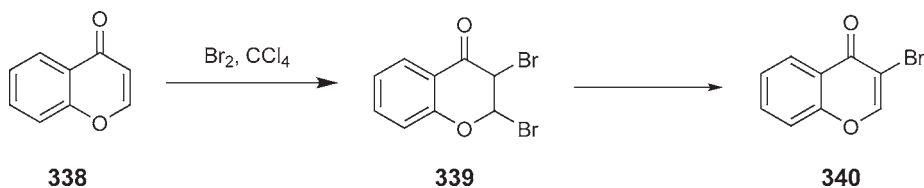
7.07.8.1.2 Reactions with electrophiles

Ring enlargement of chromone to benzoxepins has been reported (see also [Section 7.07.5](#)). The *in situ* generation of benzopyrylium triflate **335** by reaction of **334** with Me₃SiOTf followed by addition of ethyldiazoacetate and catalytic copper(II) triflate yielded cyclopropane **336** as a single diastereomer. Treatment of compound **336** with trifluoroacetic acid resulted in the formation of 2,3-benzoxepin **337** (**Scheme 47**).



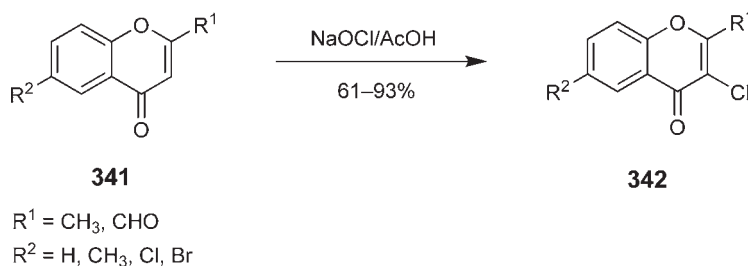
Scheme 47

The increased development of transition metal-catalyzed cross-coupling methods to form C–C bonds has served as an impetus to find methods to synthesize 3-halochromones and 3-haloisoflavones. The synthesis of 3-halochromones and flavones can be achieved with the addition of halogens across the double bond of the pyrone ring by reaction with a halogenating reagent (e.g., Br₂) followed by spontaneous, or base-induced, elimination (**Scheme 48**). Synthesis of these important compounds has been recently reviewed [<2003RCR489>](#).



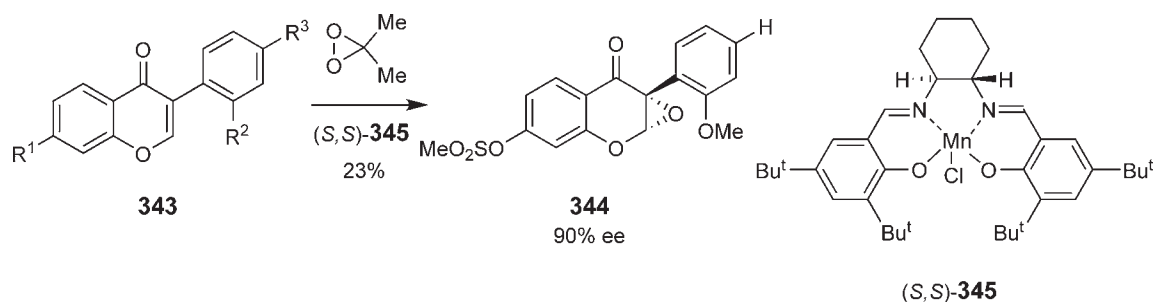
Scheme 48

2-Methylchromones and chromone-2-carbaldehyde are converted to 3-chlorochromones in good yield upon reaction with sodium hypochlorite (**Scheme 49**). The selective substitution of chlorine at C-3 is considered to involve the addition of NaO[−]Cl⁺ to the C(2)–C(3) double bond followed by elimination of NaOH [<1998SC3827>](#).



Scheme 49

The epoxidation of variously substituted flavones, isoflavones, and isoflavone glycosides has been realized using DMDO as the oxidant [<1998T13105, 2003JHC395>](#). It was found that the substitution patterns of the aromatic rings are without influence either on the course of the epoxidations or on yields of the isolated products. The enantioselective epoxidation of isoflavones has been studied employing DMDO in the presence of Jacobsen's Mn(III)salen complexes. The epoxidations were achieved in moderate yields and enantioselectivities varied from 20% to 90% ee with results depending on the substituents and substitution patterns of the isoflavone aromatic rings [<1998TA1121>](#). For example, isoflavone **343** is epoxidized to give **344** in 23% yield and 90% ee with (S,S)-**345** (**Scheme 50**).



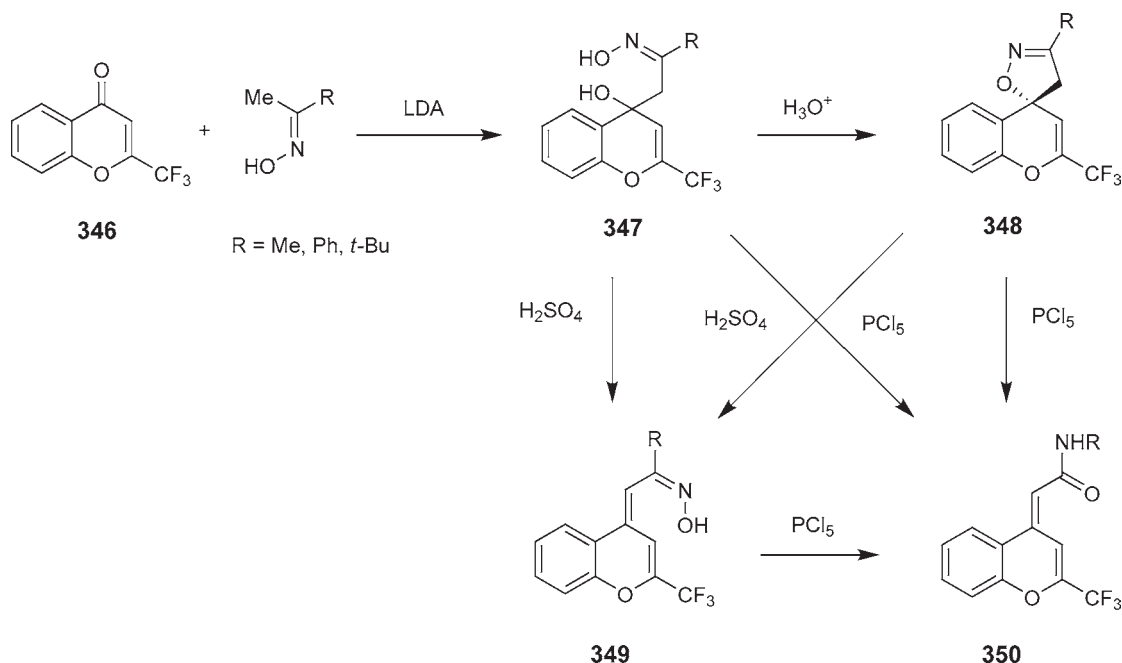
Scheme 50

7.07.8.1.3 Reactions with nucleophiles

Pyrans-4-ones and their monobenzo derivatives are easily attacked by nucleophiles via 1,4-conjugate additions which result in subsequent ring opening. Reactivity of this type makes it difficult to convert the carbonyl groups to acetals, oximes, and hydrazones by conventional methods. Since their reactivity toward nucleophiles provides a useful route for the preparation of a variety of rearranged products and new heterocyclic systems, their versatility as reactive intermediates is well documented.

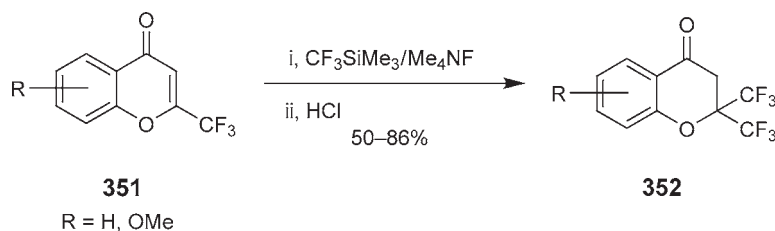
7.07.8.1.3(i) Carbon nucleophiles

The nucleophilic 1,2-addition of dilithiooximes to chromones gives, on acidification, 4*H*-chromene-4-spiro-5'-isoxazoline derivatives in high yields (**Scheme 51**). On treatment with concentrated H₂SO₄, these compounds open to give α,β -unsaturated oximes (e.g., **349**) which readily undergo the Beckmann rearrangement to the α,β -unsaturated amides such as **350**. It was found that these Beckmann rearrangement products can also be accessed directly from the 4*H*-chromene-4-spiro-5'-isoxazoline upon treatment with PCl₅ <2004TL7351>.



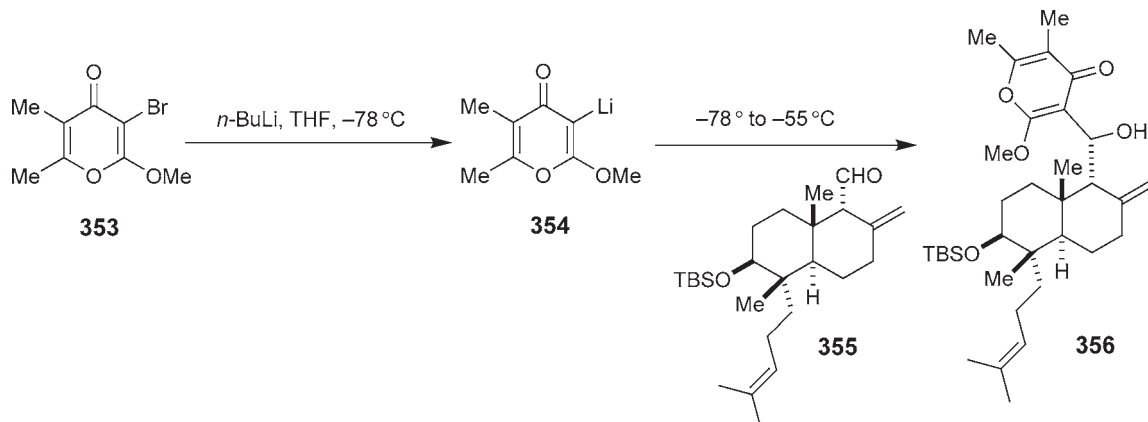
Scheme 51

Reactions of polyfluoroalkylchromones with (perfluoroalkyl)trimethylsilanes proceed as a 1,4-nucleophilic perfluoroalkylation to give 2,2-bis(polyfluoroalkyl)chroman-4-ones with high regioselectivity and good yield after acid hydrolysis of trimethylsilyl (TMS) ethers (e.g., see **Scheme 52** <2003JOC7747>).



Scheme 52

In the total synthesis of nalanthalide, the crucial coupling of the γ -pyrone moiety with the diterpenoid core was achieved by lithium halogen exchange of 3-bromo-2-methoxy-5,6-dimethyl-4*H*-pyran-4-one **353** and addition of the resulting 3-lithio- γ -pyrone **354** to aldehyde **355** to produce **356** in an impressive 87% yield (Scheme 53) <2005OL3745, 2006TL3251>.

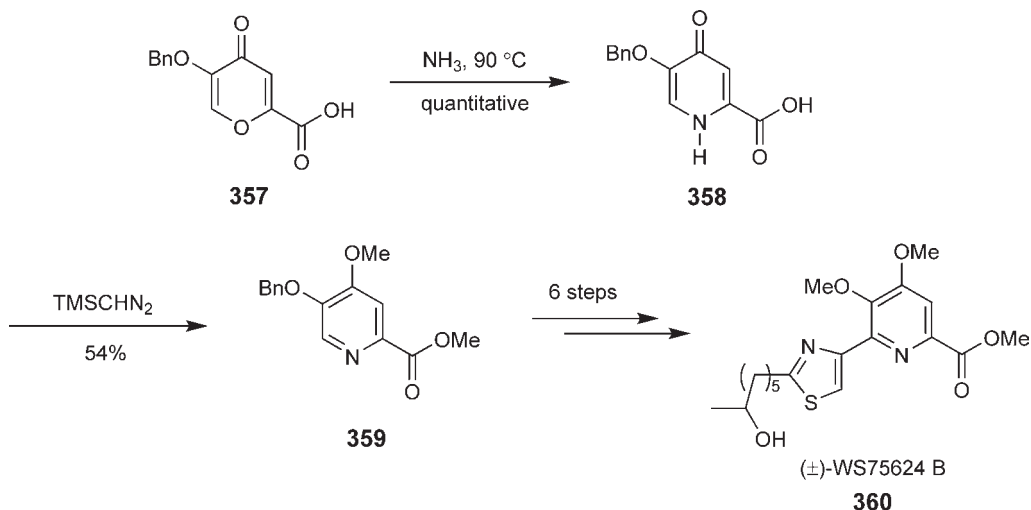


Scheme 53

7.07.8.1.3(ii) N-Nucleophiles

A large number of publications have been devoted to the reaction of flavones, isoflavones, and 2- and 3-hetarylchromones with hydroxylamine. The reactions of hydroxylamine with these 4*H*-pyrone derivatives are summarized in a recent review <2002CHE883>.

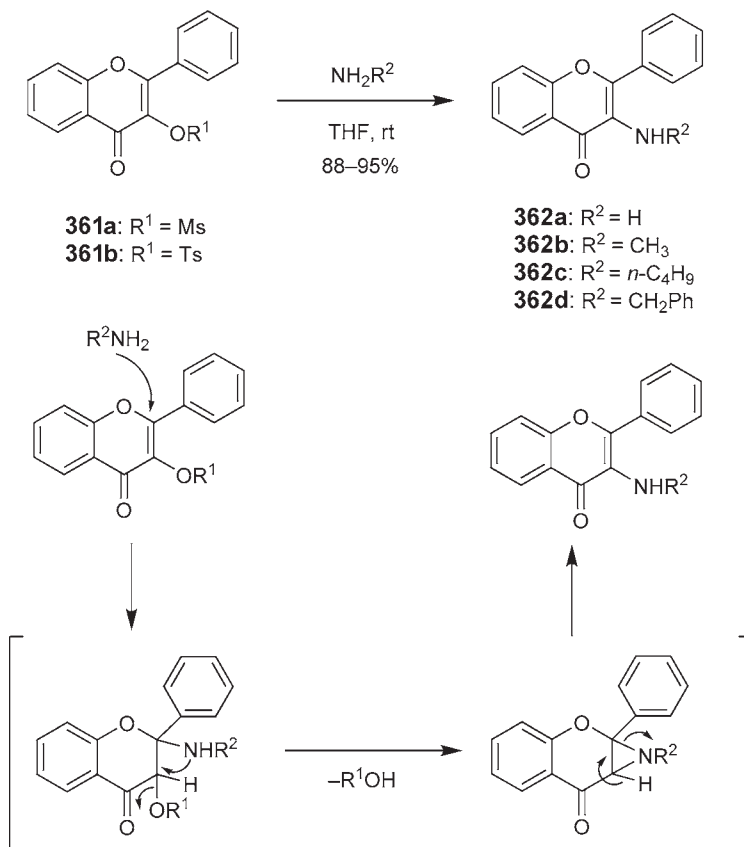
In the total synthesis of ($\pm$)-WS75644B **360**, a biaryl endothelin converting enzyme inhibitor, pyrone **357** derived from kojic acid was converted to pyridone **358** by reaction with concentrated ammonium hydroxide in a sealed flask at 90 °C. The resulting pyridine was subsequently converted to 2,4,5-trisubstituted pyridine **359** and ultimately elaborated to complete the total synthesis (Scheme 54) <1997TL1297>.



Scheme 54

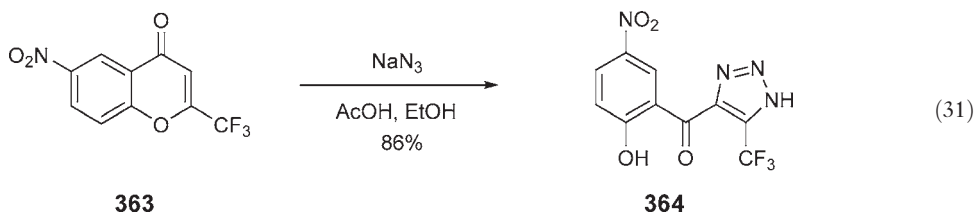
The reaction of 3-tosyloxy or 3-mesyloxy flavones (e.g., **361**) with ammonia or primary amines has been shown to yield the corresponding 3-amino flavones (e.g., **362**) in high yields (Scheme 55). The results can be rationalized through a hetero-Michael addition of the ammonia or primary amine followed by cyclization to form the aziridine

with loss of toluenesulfonic or methanesulfonic acid. The aziridine may then open by elimination to furnish the 3-aminoflavones. The formation of the aziridine cannot proceed with the addition of secondary amines which is consistent with the observed results <2006CL128>.



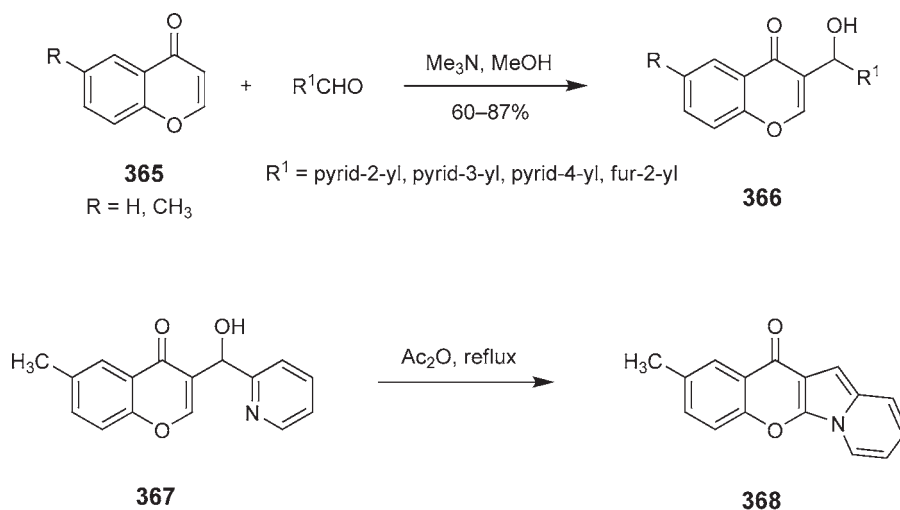
Scheme 55

Trifluoromethyl chromones react with a variety of reagents <1999MC204, 2001TL5117, 1999RCB812, 2001RCB1430> including NaN_3/AcOH (Equation 31). These conditions give salicyloyltriazoles in good to excellent yields (50–86%), but the reaction does not proceed in the absence of the trifluoromethyl group or activating groups on the aromatic ring <2002MC1>.

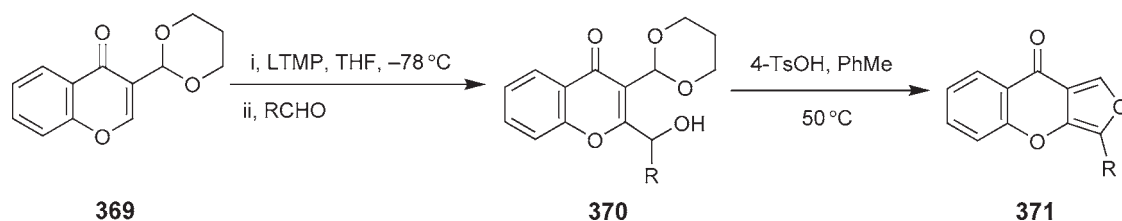


1-Benzopyran-4(4*H*)-one derivatives have been successfully employed as activated alkenes in the Baylis–Hillman coupling with heteroaromatic aldehydes, nitrobenzaldehydes, and isatin derivatives (Scheme 56). The Baylis–Hillman adduct derived from 1-benzopyran-4(4*H*)-one and pyridine-2-carboxaldehyde 367 was converted into a novel tetracyclic framework 368 <2003TL4365>.

Deprotonation of chromone 369 with lithium 2,2,6,6-tetramethylpiperidide followed by addition to aldehydes provided substrates which were converted directly to furo[3,4-*b*][1]benzopyran-9-ones (e.g., 371) upon acetal deprotection (Scheme 57) <2002S2341>.



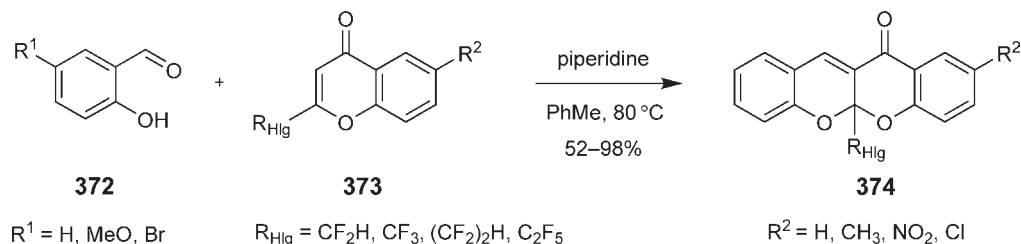
Scheme 56



Scheme 57

7.07.8.1.3(iii) O-Nucleophiles

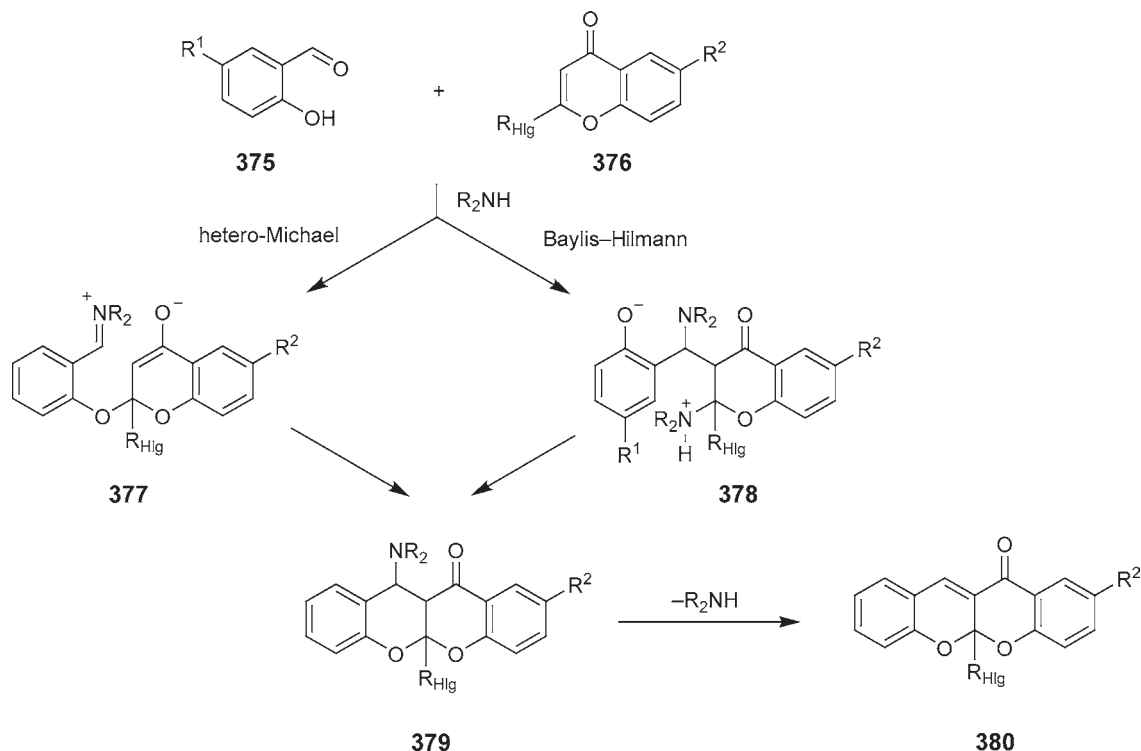
Polyhaloalkyl-substituted chromones and γ -pyrones react with salicylaldehydes in the presence of piperidine to give a variety of fused $2H$ -chromenes in good yields (Scheme 58) <2006JOC4538>. Although it is conceivable that this reaction could proceed through a Baylis–Hillman reaction pathway, studies of this reaction point to the mechanism being a tandem intramolecular oxa-Michael addition and subsequent Mannich condensation.



Scheme 58

As noted in the previous section, 2-unsubstituted chromones react with aromatic aldehydes in the presence of Me_3N to provide Baylis–Hillman products. The authors of the current study were unable to obtain analogous results with 2- CF_3 -chromones and *m*-nitrobenzaldehyde in the presence of Et_3N or 1,4-diazabicyclo[2.2.2]octane (DABCO), presumably due to steric repulsions between the CF_3 group and tertiary amine resulting from the initial conjugate addition intermediate in the Baylis–Hillman pathway. The reaction therefore likely proceeds through an oxa-Michael addition of phenolate anion to the activated double bond of the chromone, followed by intramolecular Mannich condensation between enolate anion and iminium cation arising from the formyl group and piperidine *in situ*.

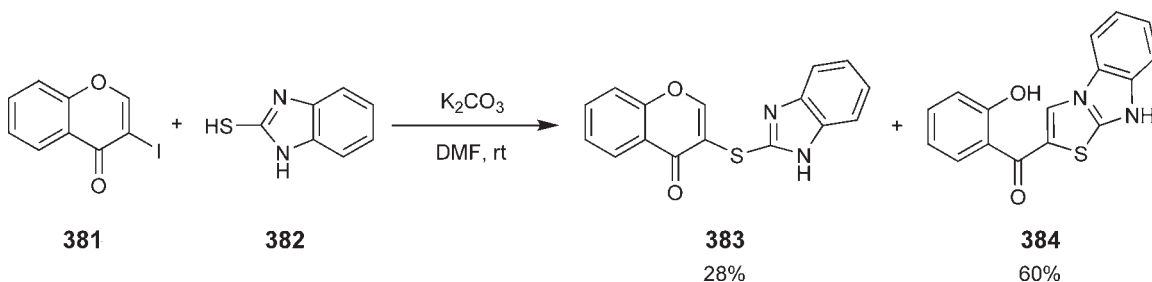
(Scheme 59). Efforts to effect an analogous reaction between salicylaldehydes and nonhalogenated chromones were unsuccessful, emphasizing the importance of the electron-withdrawing R_{Hlg} group which activates the substrate and encourages the initial conjugate addition.



Scheme 59

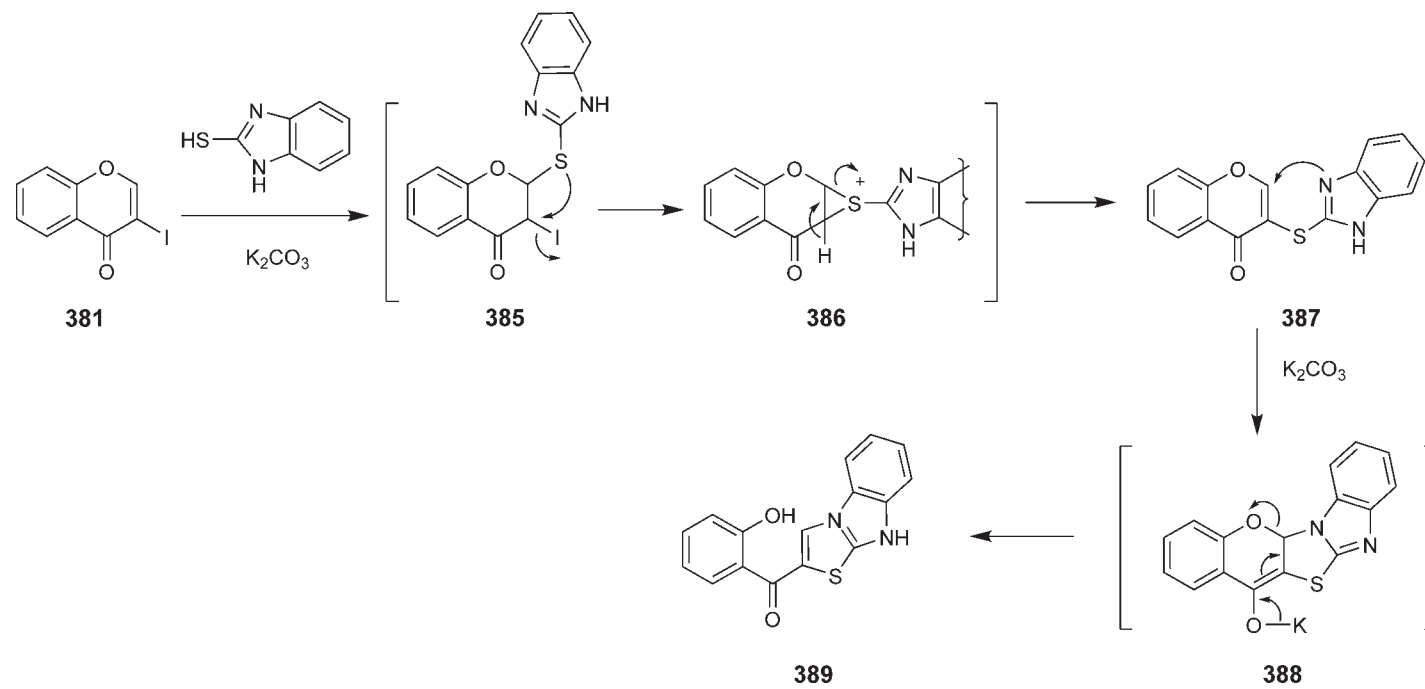
7.07.8.1.3(iv) S-Nucleophiles

Treatment of 3-iodochromone with 2-mercaptobenzimidazole in the presence of potassium carbonate in DMF at room temperature gave 3-(1*H*-benzimidazol-2-ylthio)chromone **383** and the benzimidazo[2,1-*b*]thiazole derivative **384** in 28% and 60% yields, respectively (Scheme 60) <2000H(53)2191>.



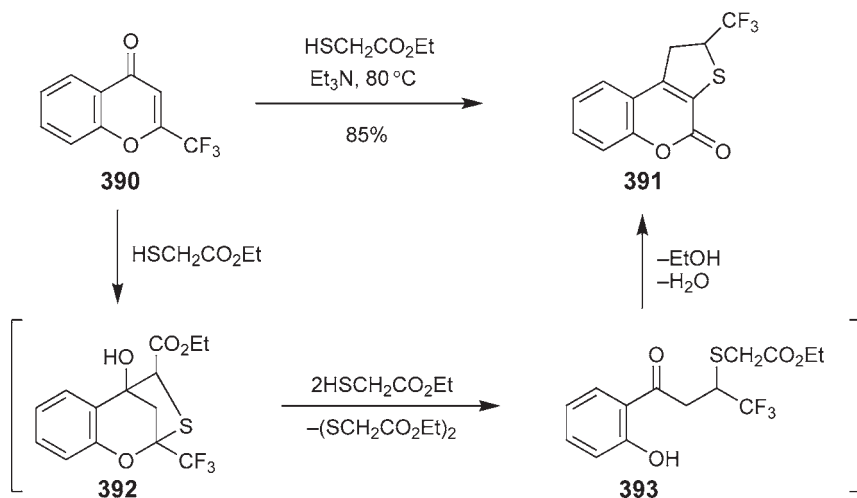
Scheme 60

A plausible mechanism for the reaction of 3-iodochromone with 2-mercaptobenzimidazole involves the conjugate addition of the thiol to the activated 2-position of the chromone ring followed by displacement of iodine by sulfur to generate an episulfonium ion (Scheme 61). Subsequent deprotonation would promote cleavage of the episulfonium ion to give 3-azolythiochromone. Formation of the benzimidazo[2,1-*b*]thiazole derivative possibly involves the intramolecular nucleophilic attack of theazole moiety on the enone of the chromone ring followed by cleavage of the carbon-oxygen bond.



Scheme 61

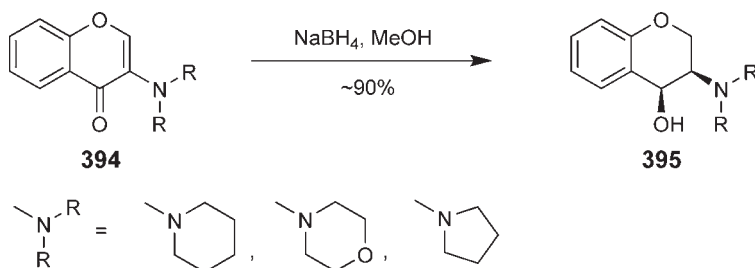
The redox reaction of 2-trifluoromethylchromones with ethyl mercaptoacetate in the presence of triethylamine results in the formation of 1,2-dihydrothieno[2,3-*c*]chromene-4-ones in high yields. Although the mechanism is not obvious, it is proposed that an initial hetero-Michael addition and subsequent cyclization gives the benzo derivative of 2-oxa-7-thiabicyclo[3.2.1]octane **392**, which undergoes reductive ring opening to ester **393** under the action of ethyl mercaptoacetate. The latter compound is oxidized to diethyl 3,4-dithiadipate, and two further intramolecular cyclizations of the intermediate ester **393** provide the product (**Scheme 62**) <2003T2625>.



Scheme 62

7.07.8.1.4 Reductions

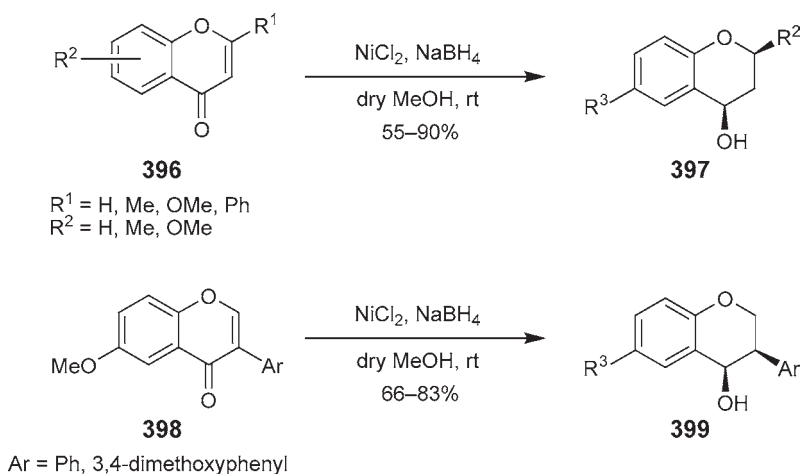
In the synthesis of some biologically active 3-substituted chroman-4-ols, for example, **395**, it was found that reductions of 3-piperidino-, morpholino-, and pyrrolidino-4*H*-chromones could be efficiently achieved by sodium borohydride in methanol (**Scheme 63**) <2002SC2227>.



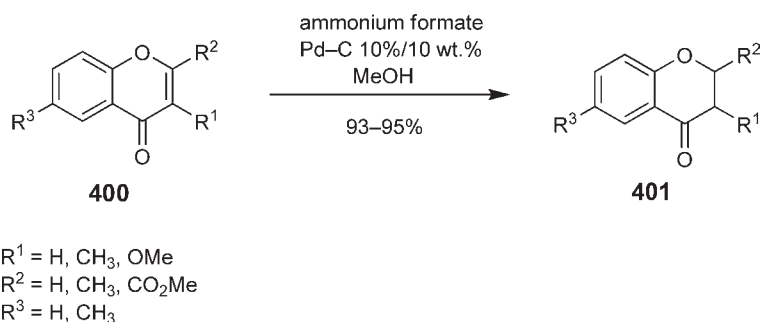
Scheme 63

Chromones, flavones, and isoflavones of general types **396** and **398** have been reported to undergo reduction with nickel borohydride in dry methanol at ambient temperatures to give the corresponding 2*H*-1-benzopyran-4-ols in good yields. In all cases studied, the products obtained were found to be the *cis*-stereoisomers, for example, **397** and **399** (**Scheme 64**) <2002JCM201>.

A method for the facile transfer hydrogenation of simple chromones using ammonium formate as the hydrogen source has been reported (**Scheme 65**). A variety of substituted chromans were synthesized with high efficiency, whereas the reduction of flavones resulted in a ring-opened product. Although aryl ketones have been reported to be reduced to the alcohols by a combination of ammonium formate and Raney nickel in methanol, under the present conditions the carbonyl group remained intact <2002JCM428>.

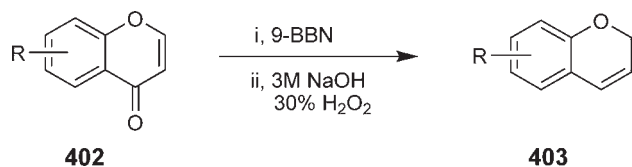


Scheme 64



Scheme 65

The reduction of substituted chromones **402** with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeds in a regioselective fashion to give 2*H*-chromenes **403** (Scheme 66). Other boranes resulted in reduction to give chromanones <2001BCJ967>.

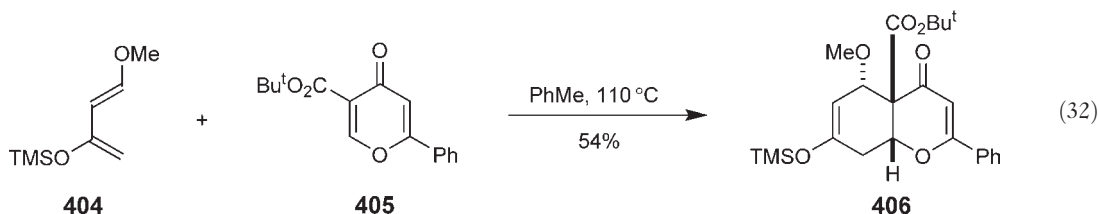


Scheme 66

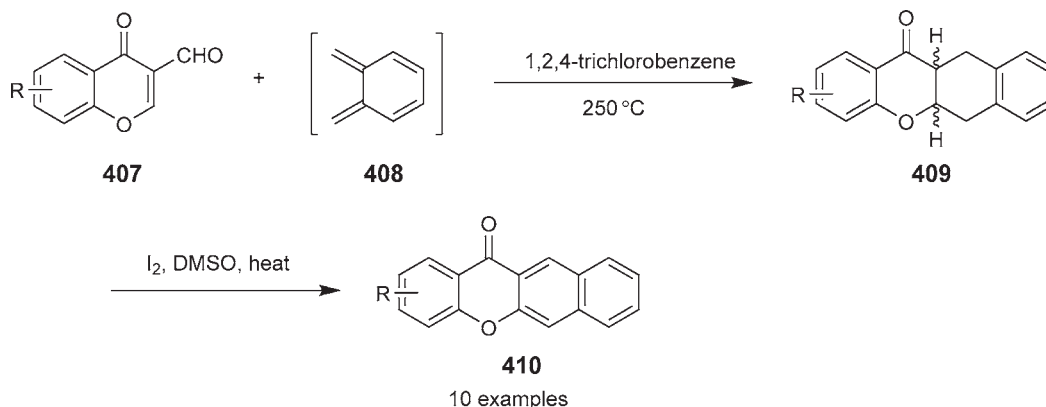
7.07.8.1.5 Other reactions

7.07.8.1.5(i) Cycloadditions

The reactivity of 4*H*-benzopyran-4-ones in Diels–Alder reactions is well documented <1987T3075>, and recently high asymmetric induction has been achieved in the reaction of 3-alkoxycarbonyl-substituted chromones with chiral auxiliaries and Danishefsky's diene <1991JOC2058>. It should be noted that 3-formylchromones can react as heterodienes in the stereoselective inverse electron Diels–Alder reaction with enol ethers <1994T11755> to provide a route to pyrano[4,3-*b*][1]benzopyrans a heterocyclic nucleus which occurs naturally in the fungal metabolite fulvic acid <1984CC1565>. The thermal Diels–Alder reaction of 4*H*-pyran-4-one **405** in the presence of an excess of Danishefsky's diene **404** provided cycloadduct **406** (Equation 32) <1996H(43)745>.

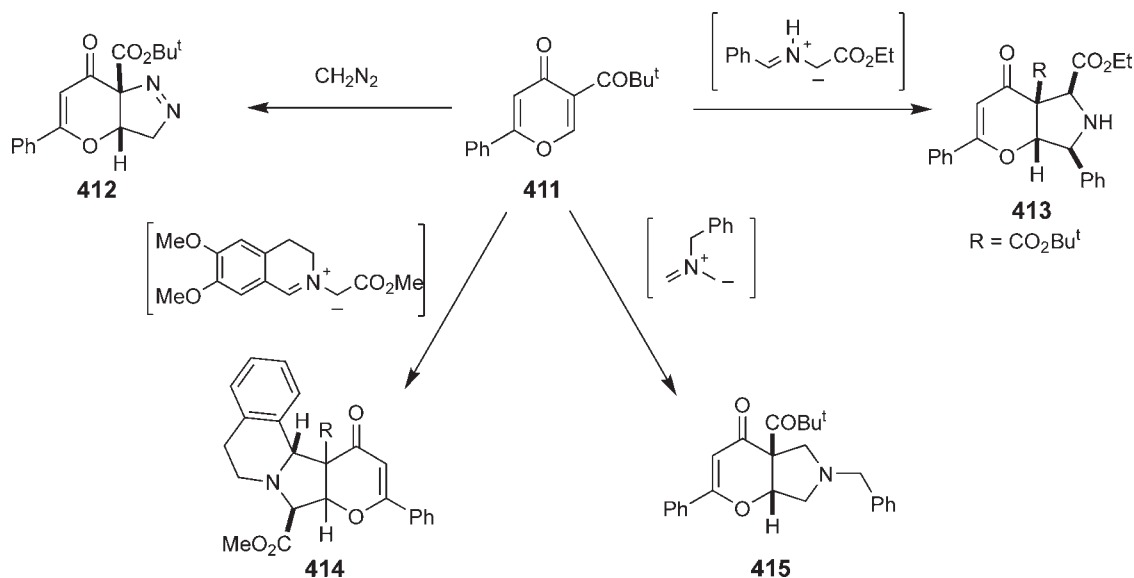


Chromone carbaldehyde **407** reacts with *o*-benzoquinodimethane **408** in a Diels–Alder reaction and concomitant deformylation to give a diastereomeric mixture of tetrahydrobenzo[*b*]xanthenes **409**. Subsequent oxidation provides benzo[*b*]xanthenes **410** in good yields (Scheme 67) <2002T997>.



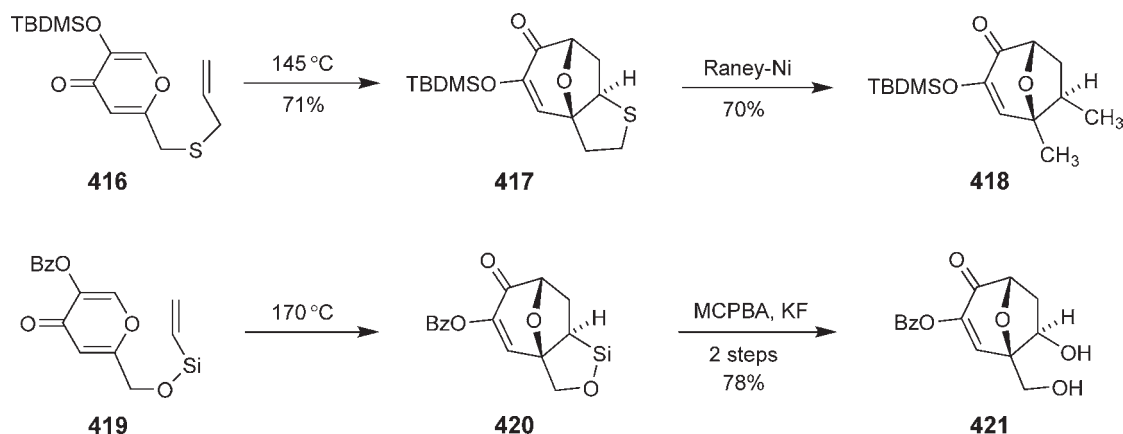
Scheme 67

The 1,3-dipolar cycloaddition of diazomethane with *tert*-butyl 4-oxo-6-phenyl-4*H*-pyran-3-carboxylate **411** has been reported to give **412** (Scheme 68) <1991JOC4963>. Further development of simple γ -pyrones as the 2π -component in 1,3-dipolar cycloadditions of stabilized and nonstabilized azomethine ylides has provided some interesting polycyclic heterocycles such as **413–415** (Scheme 68) <1999J(P1)1167>.



Scheme 68

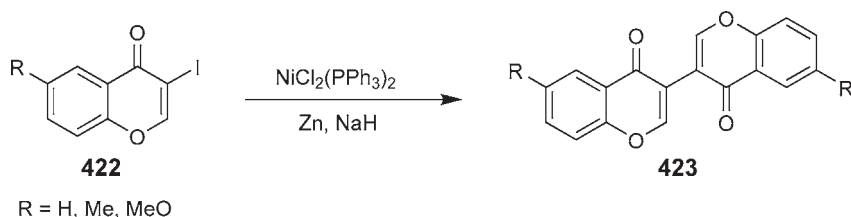
The intramolecular thermal [5+2] cycloaddition of 3-alkoxy-4-pyrones with sulfur- (e.g., **416**) or silicon- (e.g., **419**) tethered alkenes has been shown to occur with complete regio- and stereochemical control to give adducts **417** and **421**, respectively. The adducts can be converted by reduction and oxidation, respectively, to the bicyclic products **418** and **421** (Scheme 69) <1993JOC5585>. It should be noted that this thermal [5+2] cycloaddition has not been realized in a bimolecular mode <1977JOC3976>. This methodology serves as an alternative to the reaction of electron-deficient alkenes with pyrone-derived 4-methoxy-3-oxidopyrylium ylides <1992TL2115>.



Scheme 69

7.07.8.1.5(ii) Cross-coupling

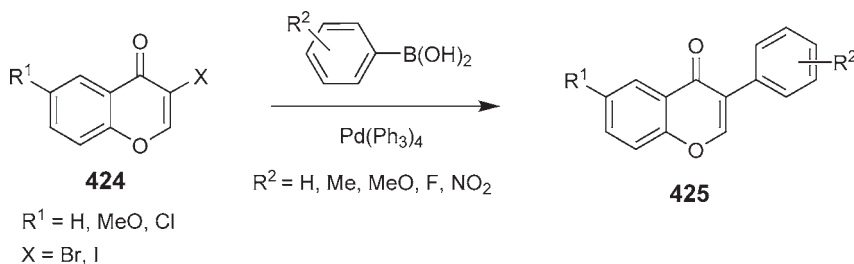
In recent years, there has been increased use of transition metal-catalyzed cross-coupling in the synthesis of 3-substituted chromones, flavones, and their derivatives. These compounds are of considerable interest because of their widespread occurrence in nature <2001PHA661> and diverse biological activities <1991JME2169>. These reactions also provide new methods for the incorporation of chromones into complex targets. The homo-coupling of 3-iodochromones **422** has been achieved in high yields using $\text{NiCl}_2(\text{PPh}_3)_2$, Zn, and sodium hydride in toluene to furnish bischromones **423**, that are of interest in the synthesis of naturally occurring biflavonoids (Scheme 70) <2001JOC2877, 2001T8685>.



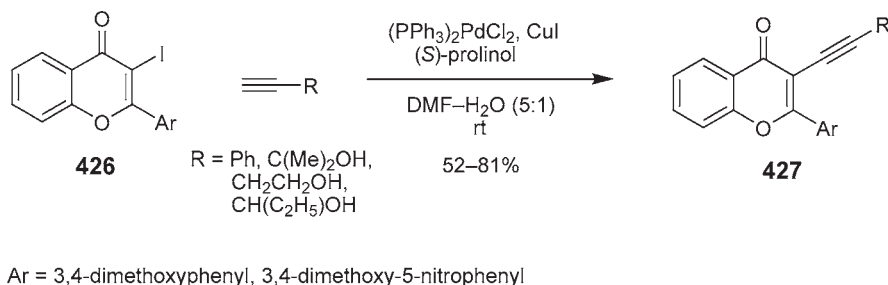
Scheme 70

Ullman reaction conditions have also been used in the synthesis of biflavonoids. Heating of 3-haloflavones in the presence of copper powder provided biflavones in good yield <1993SC1075>. Isoflavone and derivatives, for example **425**, can be prepared efficiently by the Suzuki cross-coupling of 3-bromo and 3-iodochromones **424** with arylboronic acids (Scheme 71) <1988BCJ3008, 1989CPB529>.

The (*S*)-prolinol-facilitated coupling of terminal alkynes with 3-iodoflavones **426** under palladium–copper catalysis (Sonogashira coupling) in aqueous DMF has been shown to be a mild and convenient method for the synthesis of 3-alkynyl-substituted flavones **427** of potential biological interest (Scheme 72) <2003T9563>. The coupling method tolerates a variety of functional groups and does not require the use of phase transfer catalyst (PTC)/water-soluble phosphine ligands.

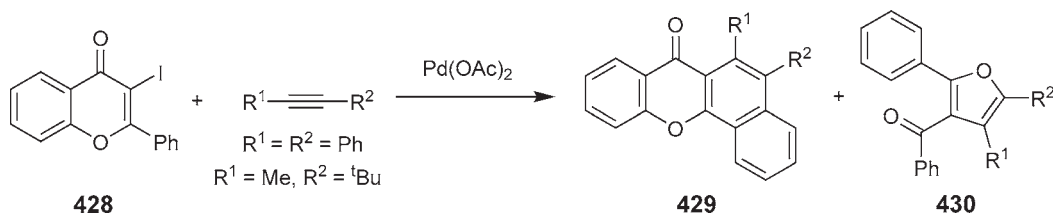


Scheme 71



Scheme 72

Attempted annulation of 3-iodoflavones, for example **428**, by internal alkynes catalyzed by Pd(OAc)_2 in the presence of NaOAc and LiCl yielded a mixture of two compounds (Scheme 73) <1998JOC2002>. While the expected benzoxanthenes (e.g., **429**) were isolated as the minor compound, tetrasubstituted furans (e.g., **430**) resulting from the electrophilic attack on the carbonyl oxygen atom by the vinylpalladium intermediate followed by pyrone ring opening were the major product.

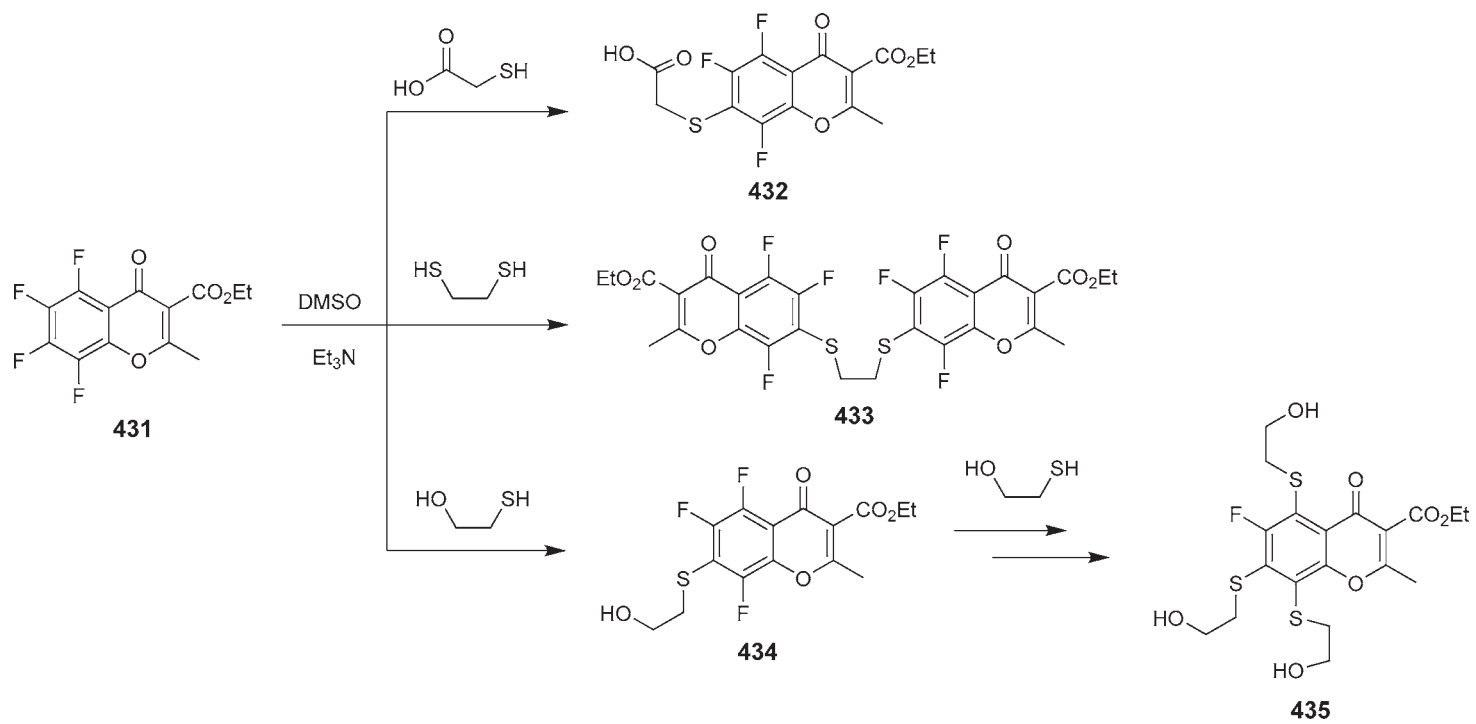


Scheme 73

7.07.8.2 Reactivity of Substituents

7.07.8.2.1 Fused benzene rings

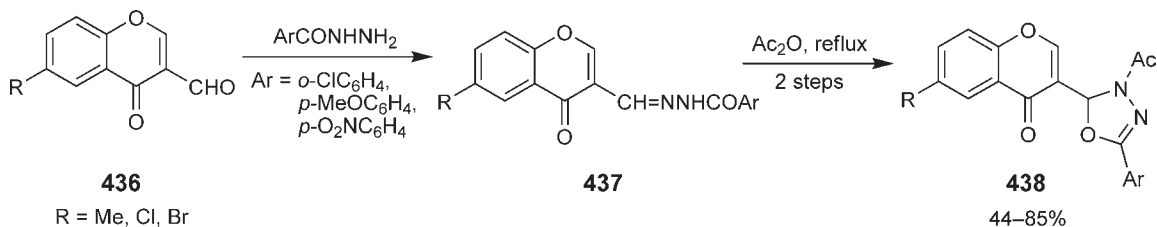
In a study of the nitration of 2-polyfluoroalkyl chromones it was found that despite the presence of the electron-withdrawing trifluoromethyl group geminal to the benzylic oxygen, nitration by the action of nitric acid and sulfuric acid followed the same trends as those of 2-alkyl- and 2-alkoxycarbonylchromones <2000RCB2074>. The reaction of 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone with methylamine for 2 h at ambient temperature yields 2-ethoxycarbonyl-5,6,7,8-trifluoro-7-methylaminochromone in good yields (75–86%) through an $\text{S}_{\text{N}}\text{Ar}$ reaction. Prolonged reaction time resulted in attack of methylamine at the C-2 and/or C-9, while in ethanol the reaction involves only attack at C-2 with opening of the pyrone ring <2005RCB2157>. The reactions of ethyl 5,6,7,8-tetrafluoro-2-methylchromone **431** with mercaptoacetic acid and 1,2-ethanedithiol afforded C-7 $\text{S}_{\text{N}}\text{Ar}$ products **432** and **433**, respectively. The above-mentioned chromone **431** reacted with 2-mercaptoethanol to yield 7-mono- or 5,7,8-trisubstituted products, **434** or **435**, depending on reaction conditions (Scheme 74) <1999RCB1537>.



Scheme 74

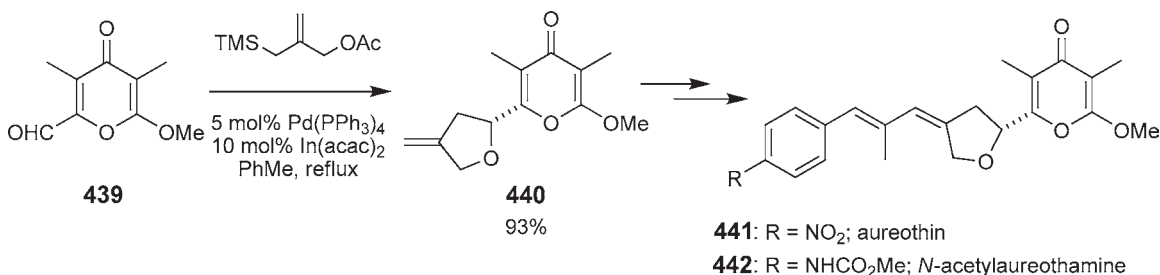
7.07.8.2.2 C-linked substituents

Treatment of 3-formyl chromones **436** with arylhydrazides gave the corresponding hydrazones (e.g., **437**, **Scheme 75**). In the presence of acetic anhydride the aroylhydrazones undergo heterocyclizations to give chromones such as **438** <2004CHE214>.



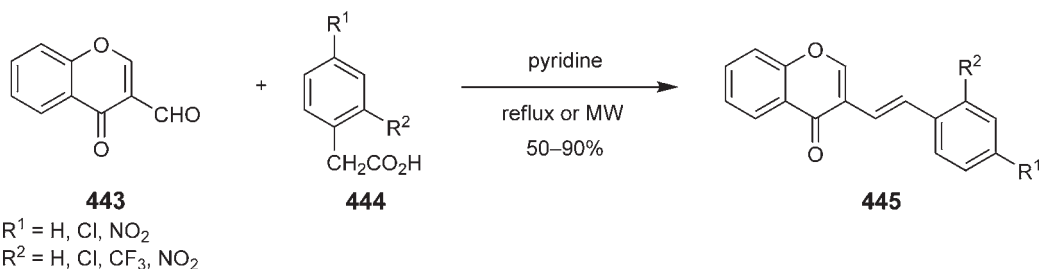
Scheme 75

A key step in the total synthesis of the nitrophenylpyrones, (±)-aureothin **441** and (±)-*N*-acetylaureothamine **442**, involved construction of the THP motif of **440** using a [3+2] cycloaddition of 2-formylpyranone **439** and a palladium trimethylmethane complex (**Scheme 76**) <2005OL641>.

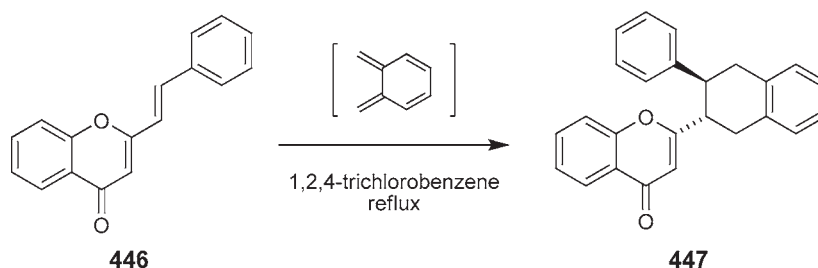


Scheme 76

An efficient and diastereoselective method for preparing (*E*)-3-styrylchromones **445** has been reported by the reaction of chromone-3-carbaldehyde **448** with phenylacetic acids **444** in the presence of potassium *tert*-butoxide under heating or microwave conditions (**Scheme 77**) <2004SL2717>. Diels–Alder reactions of 2-styrylchromones **446** with *ortho*-benzoquinodimethane afforded cycloadducts that can be converted into benzoflavone derivatives such as **447** (**Scheme 78**) <1999EJO135>.



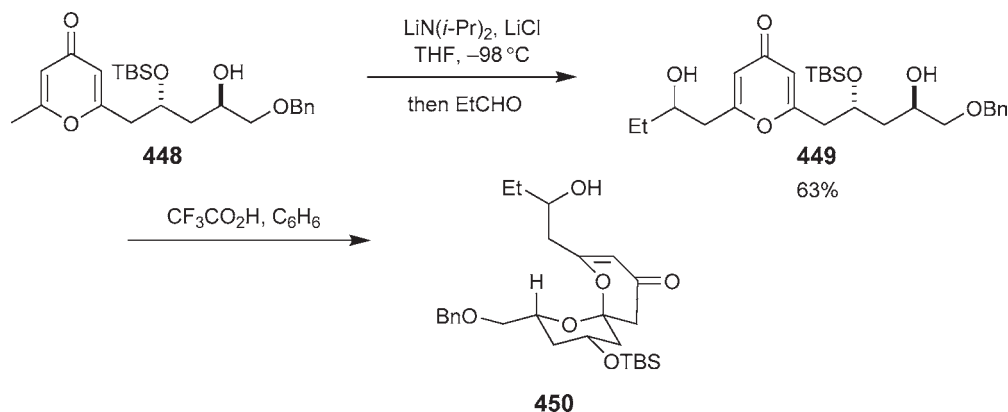
Scheme 77



Scheme 78

A study concerning the decarbonylation of aromatic aldehydes in methanol in the presence of catalytic amounts of scandium(III) triflate revealed that the decarbonylation of 3-formylchromone was observed when the reaction was heated to 60 °C <1996T11045>. The hydrolysis of ethyl chromone-2-carboxylate to chromone-2-carboxylic acid was achieved in good yield (86%) using polyphosphoric acid without ring-opening products. As expected, the use of aqueous hydrochloric acid, sodium hydroxide, or sodium carbonate for this hydrolysis resulted in only ring-opened products <2002SC709>.

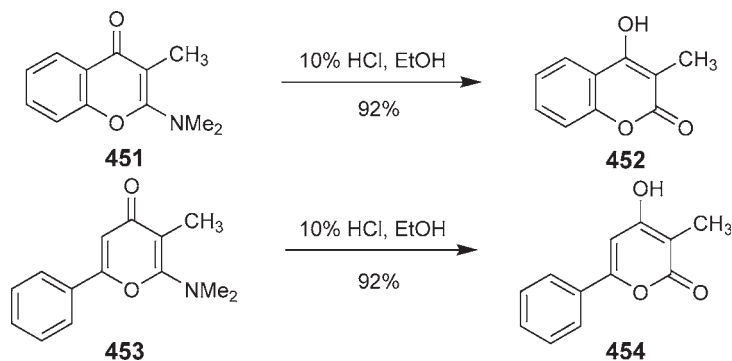
The synthesis of a spiroketal fragment **450** of spongistatin 1 has been accomplished utilizing the addition of a metalated pyrone derived from **448** to propionaldehyde to give adduct **449** followed by acid-catalyzed spirocyclization (Scheme 79) <2000OL957>.



Scheme 79

7.07.8.2.3 N-Linked substituents

Hydrolysis of 3-methyl-2-aminochromones (e.g., **451**) and aminopyrones (e.g., **453**) with 10% aqueous hydrochloric acid/ethanol afforded 4-hydroxycoumarins **452** and 4-hydroxy-2-pyrones **454**, respectively (Scheme 80) <1996JOC3218>.



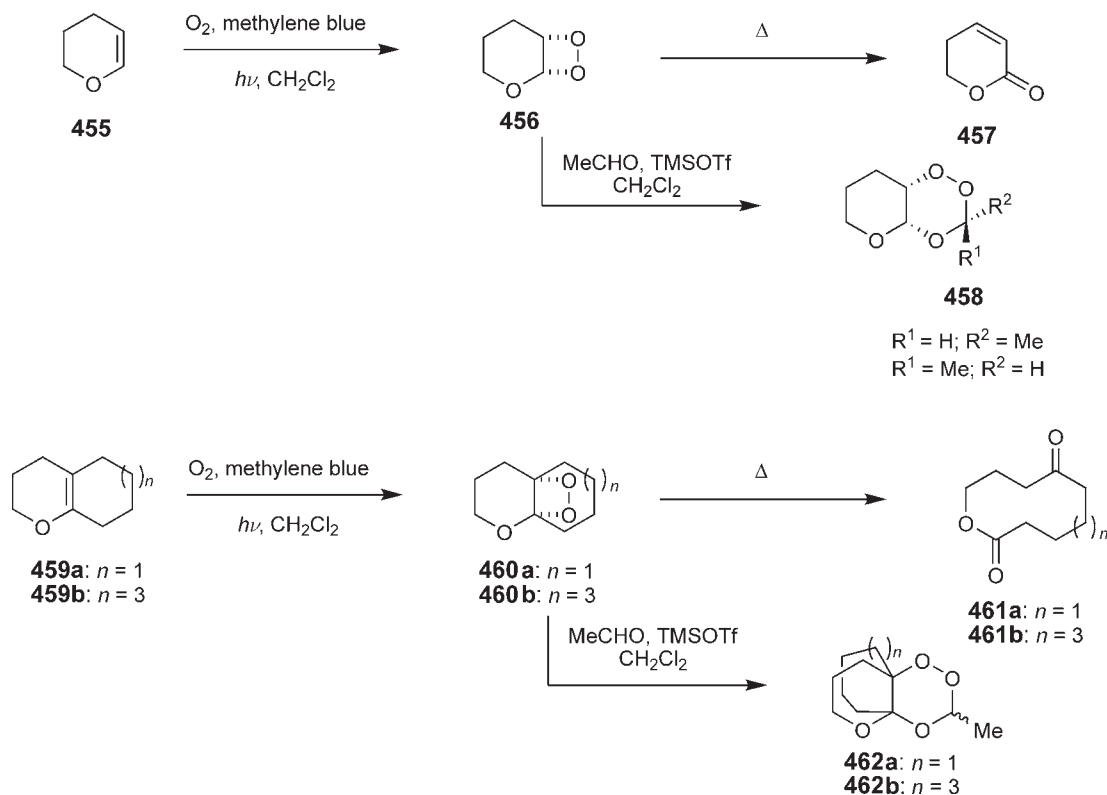
Scheme 80

7.07.9 Reduced Pyrans and Pyrones and Their Benzo Derivatives

7.07.9.1 Reactivity at Ring Atoms

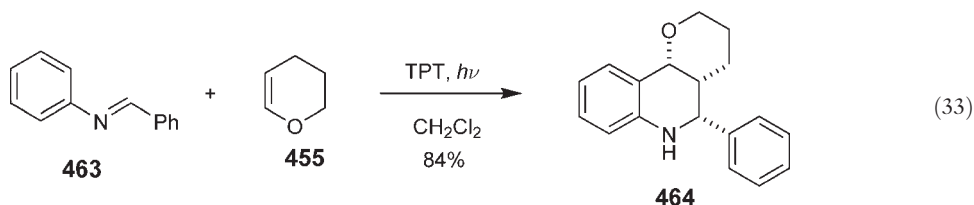
7.07.9.1.1 Photochemical reactions

The dye-sensitized photooxygenation of 3,4-dihydro-2*H*-pyran **455**, 5,6,7,8-tetrahydrochroman **459a**, and 2-oxabicyclo[4.6.0]dodec-1(6)-ene **459b** gives the corresponding 1,2-dioxetanes, for example, **456** and **460** (Scheme 81), in low to moderate yields (35–53%). Treatment of these photoadducts with acetaldehyde in the presence of catalytic TMSOTf affords the corresponding 1,2,4-trioxanes **458** and **462**, whereas thermolysis breaks the dioxetane ring to produce the monocyclic keto-lactones **457** and **461** <1997H(46)451>.



Scheme 81

Photochemically promoted Diels–Alder reactions between *N*-arylimines **463** and 3,4-dihydro-2*H*-pyran **455** were achieved by using 2,4,6-triphenylpyrylium as a photocatalyst to produce pyranoquinolines **464** in high yield (Equation 33) <2004JCM418>.

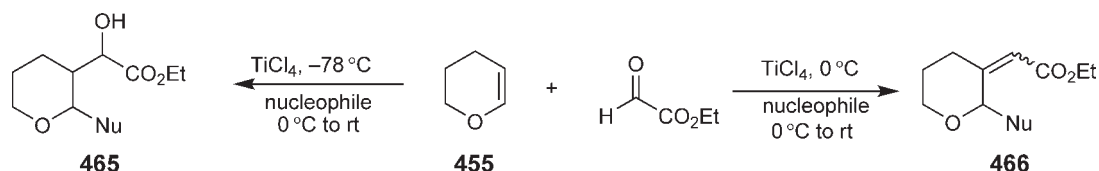


2-Alkoxy-3,4-dihydro-2*H*-pyrans are converted to 4,5-*cis*-disubstituted tetrahydrofuranones upon epoxidation and subsequent oxidation <2006TL1617, 2006MOL959>.

7.07.9.1.2 Reactions with electrophiles

7.07.9.1.2(i) Addition and substitution

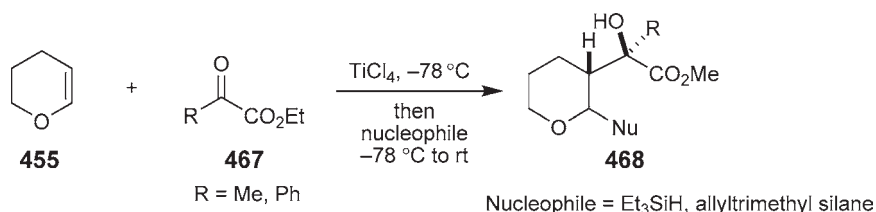
The synthesis of substituted tetrahydropyranlydene acetates such as **465** and **466** can be accomplished by TiCl_4 -promoted carbon–carbon bond-forming reactions of ethyl glyoxylate, 3,4-dihydro-2*H*-pyran **455**, and oxygen or sulfur nucleophiles (**Scheme 82**). The reaction is an efficient three-component coupling process and the overall outcome of the reaction is dependent upon reaction temperature <1999TL4751>.



Nucleophile = Et_3SiH , allyltrimethyl silane, Me_3SiCN , MeOH

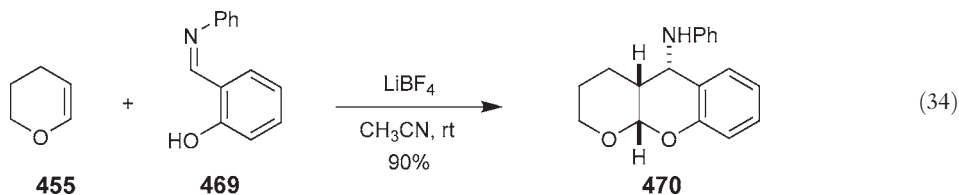
Scheme 82

Similar TiCl_4 -promoted coupling reactions of pyruvates **467** with 3,4-dihydro-2*H*-pyran **455** provided quaternary carbon stereocenters stereoselectively (**Scheme 83**) <2000TL8425>. The use of (2-trimethylsilyl)ethyl pyruvate in this transformation results in a one-pot addition sequence to deliver functionalized [2,3-*b*]pyran derivatives, for example **468**, in good yields <2003SL1491>.

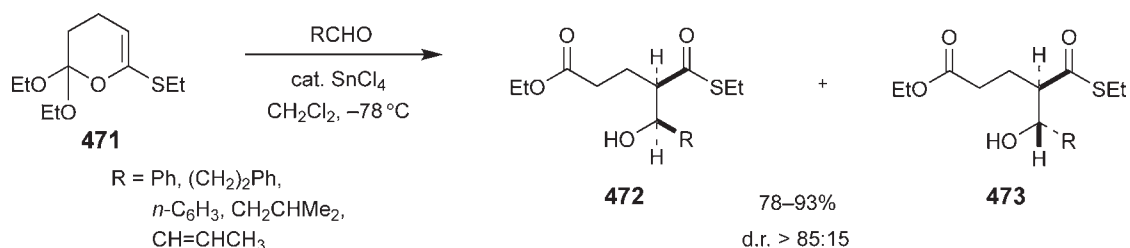


Scheme 83

Lithium tetrafluoroborate efficiently catalyzes the cyclization of *o*-hydroxybenzaldimines **469** with 3,4-dihydro-2*H*-pyran **455** at ambient temperature to afford a class of pyrano derivatives represented by **470** in excellent yields with high diastereoselectivity (**Equation 34**) <2001TL6381>. The use of catalytic indium trichloride and phosphonium perchlorate has been found to efficiently effect the same transformation <2002T10301>.

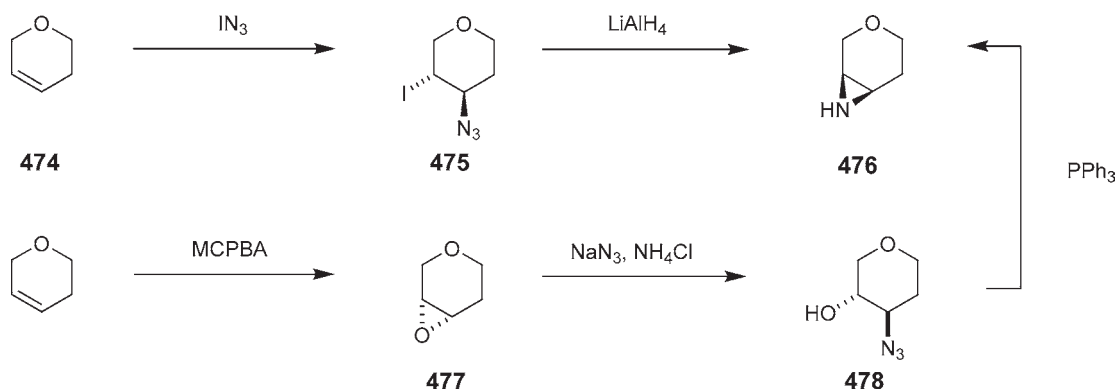


Aldol products **472** and **473** of glutarates can be formed from the reaction of 2,2-diethoxy-6-(ethylthio)-3,4-dihydro-2*H*-pyran **471** with aldehydes in the presence of catalytic tin(IV) chloride (**Scheme 84**). This unique and highly stereocontrolled transformation involves the diastereoselective generation of a carbon–carbon bond and introduction of an ester functionality from hydrolysis of the orthoester intermediate <1997JOC6687>.



Scheme 84

The reaction of 5,6-dihydro-2*H*-pyran with IN_3 results in the formation of an iodo azide **475**, which can be transformed into aziridine **476** upon reduction with lithium aluminium hydride <1963JCS4986>. Alternatively, 5,6-dihydro-2*H*-pyrans can be transformed into epoxides by treatment with *m*-chloroperbenzoic acid (MCPBA) (e.g., **477**), opened with sodium azide in aqueous methanol in the presence of ammonium chloride, and then treated with triphenylphosphine to facilitate the conversion of the azido alcohol **478** into the aziridine (Scheme 85) <1993JOC385>. Regiocontrol in the opening of 5,6-dihydro-2*H*-pyran-derived aziridines and epoxides with a variety of nucleophiles has been extensively studied <1997T1417, 1997G79, 2002T6069, 2001JCO125>.

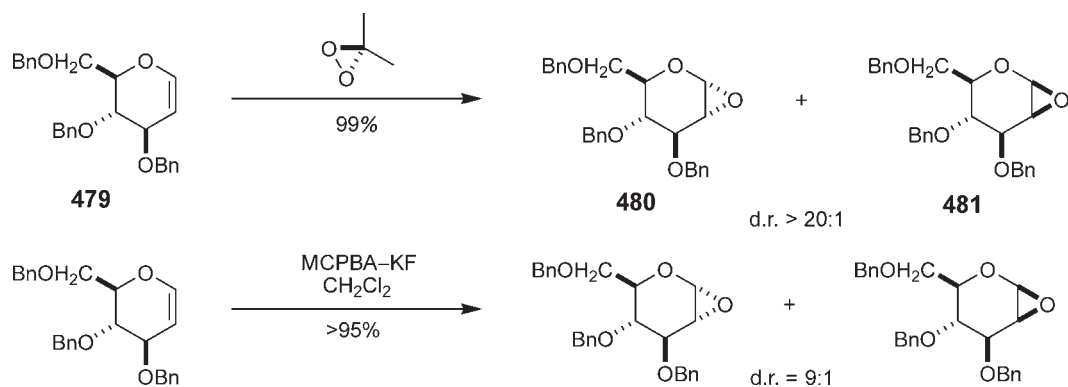


Scheme 85

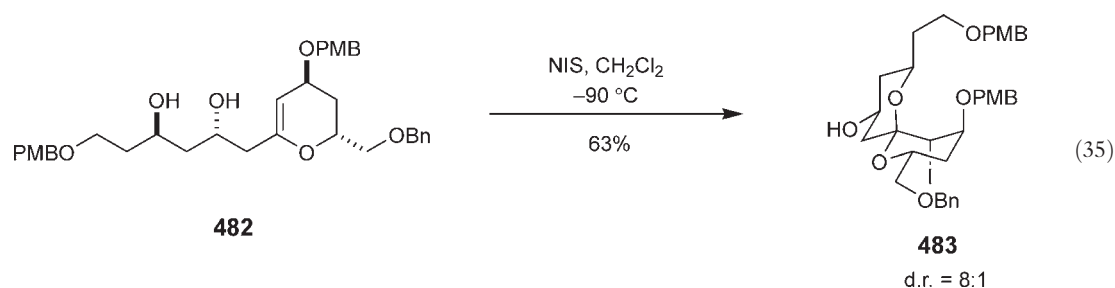
Epoxides of glycols are important intermediates in the synthesis of carbohydrates. Peroxyacids are not useful in the epoxidations of glycols, since the oxirane products are opened by the acid formed during the course of the epoxidation. The use of MCPBA–KF complex in anhydrous dichloromethane has been reported as a method for the diastereoselective epoxidation of glycols <1994TL8433>; however, direct epoxidation of glycols, for example, **479**, is most commonly achieved through the use of DMDO to give, for example, **480** and **481** (Scheme 86) <1989JA6661, 1991JOC3713>. Indirect epoxidation methods involving the cyclizations of halohydrins or of 2-tosyl derivatives have also been proposed <1982JOC5402>.

The intermolecular addition of electrophilic reagents and alcohols to activated glycols is well preceded in carbohydrate chemistry <1990TCC285, 1996AGE1380>.

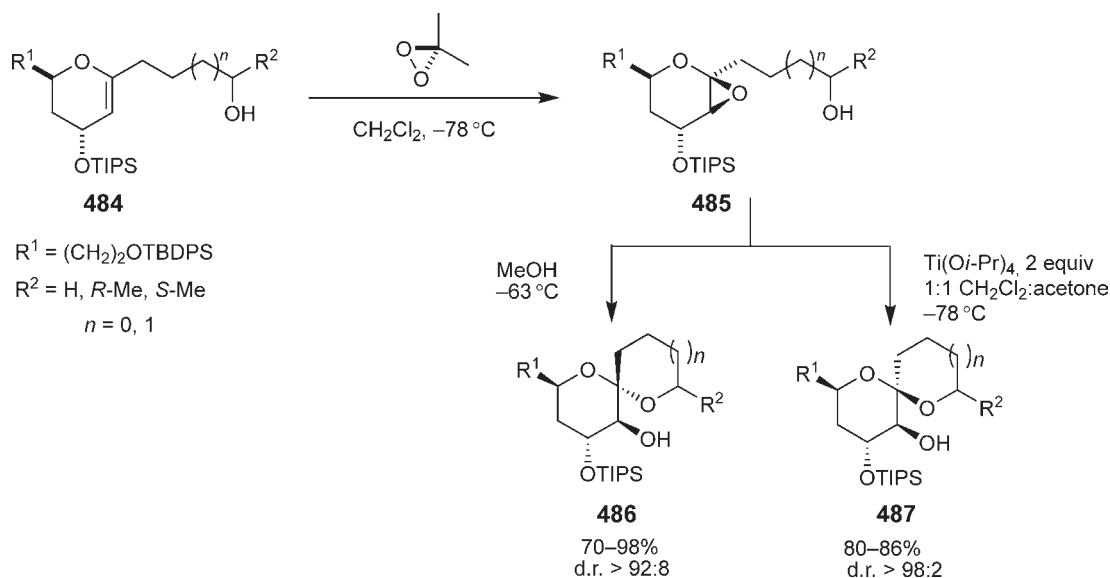
Intramolecular spiroketalization of glycols with tethered alcohols has been used in the synthesis of complex spiroketal-containing natural products <1982TL4625, 1986TL5277, 1990TL3445, 2001TL1931>. A kinetically controlled intramolecular iodo-spiroketalization of complex glycol **482** was used in the synthesis of the C–D ring fragment of spongistatin 1 **483** (Equation 35) <2002OL3719>. Activation of glycol **482** with *N*-iodosuccinimide followed by intramolecular *trans*-diaxial addition of the δ -hydroxyl group provided the spiroketal center with the configuration found in the natural product.



Scheme 86



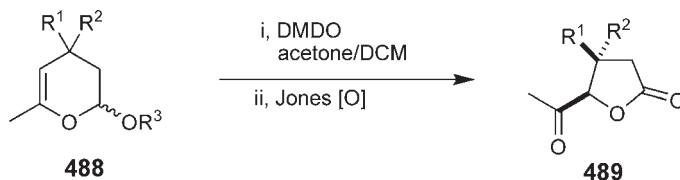
A $\text{Ti}(\text{O}i\text{-Pr})_4$ -mediated kinetic spirocyclization (with C-1 retention) for the stereocontrolled synthesis of spiroketals from glycal epoxides such as **485** has been reported (Scheme 87) <2006JA1792>. A complementary methanol-induced kinetic cyclization (with C-1 inversion) allows for a synthetically systematic approach for accessing stereo-diversified spiroketals, for example, **486** and **487** from glycals (e.g., **484**) <2005JA13796>.



Scheme 87

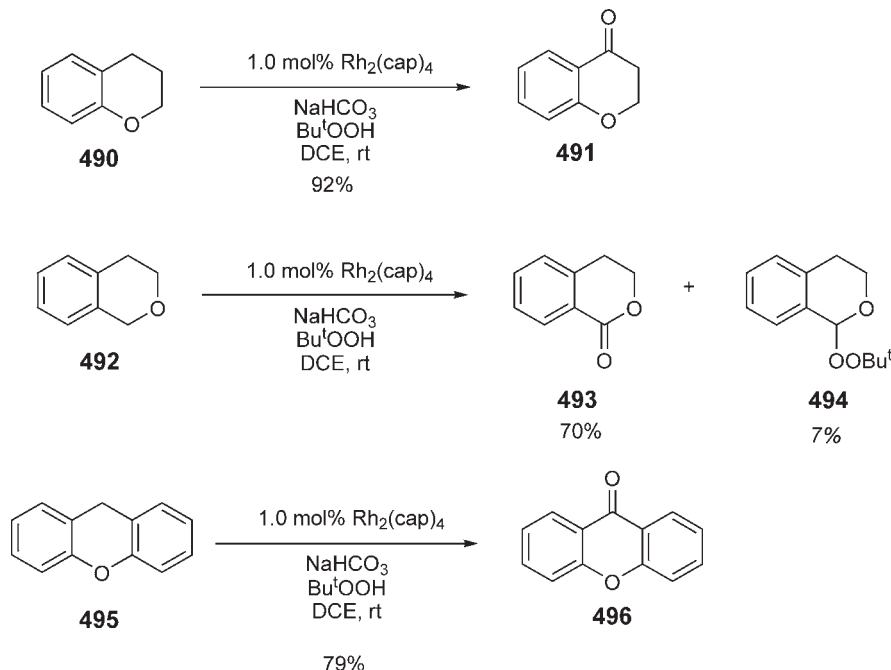
7.07.9.1.2(ii) Oxidation

2-Alkoxy-3,4-dihydro-2*H*-pyrans of general type **488** are converted to 4,5-*cis*-disubstituted tetrahydrofuranones such as **489** upon epoxidation and subsequent oxidation (Scheme 88) <2006TL1617, 2006MOL959>.



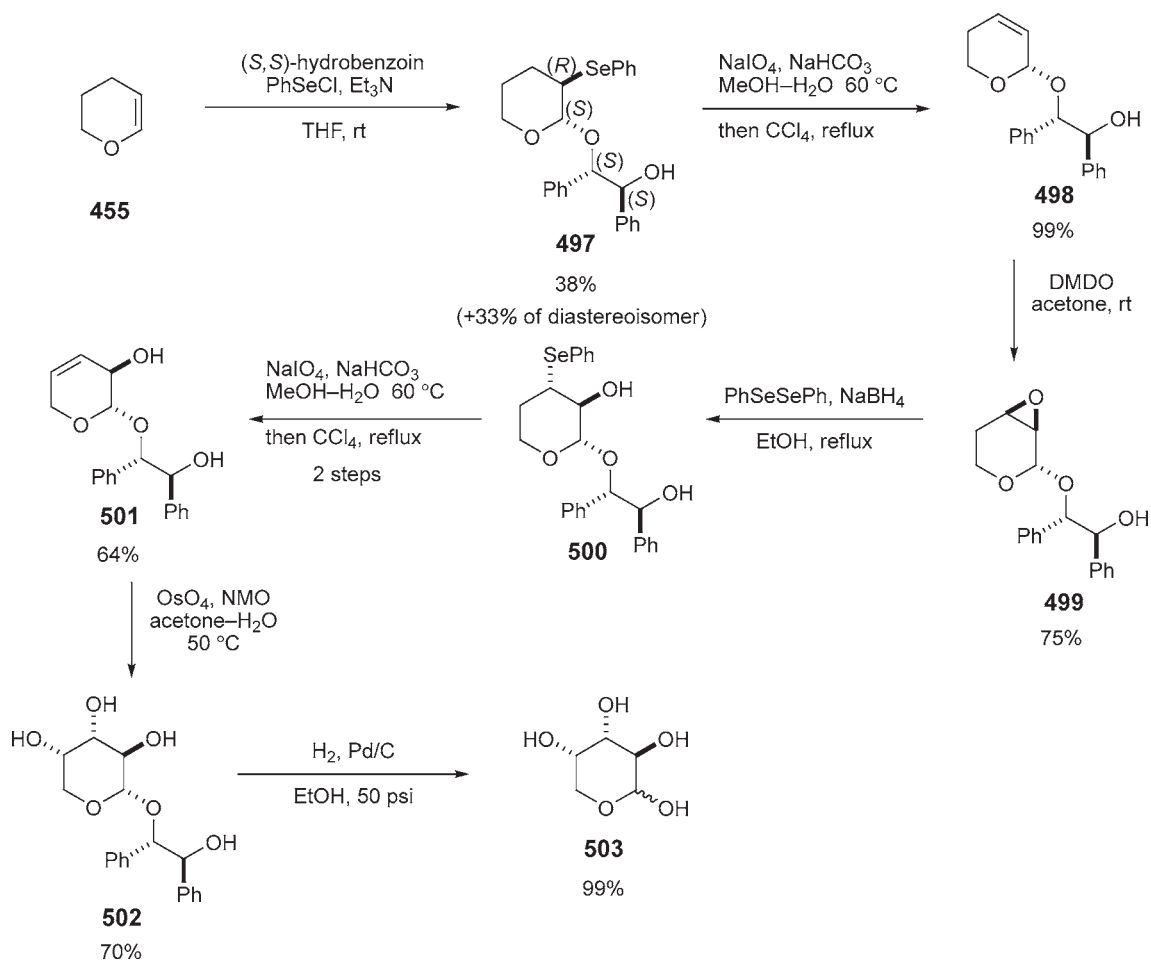
Scheme 88

Dirhodium caprolactamate [Rh₂(cap)₄] is reported to be an effective catalyst with *tert*-butyl hydrogen peroxide for benzylic oxidation of chromans, for example, **490**, **492**, and **495** under mild conditions to give lactones **491**, **493**, and **496**, along with peroxide **494** (Scheme 89). This method has been applied to a synthesis of Palmarumycin CP₂ <2005OL5167>.



Scheme 89

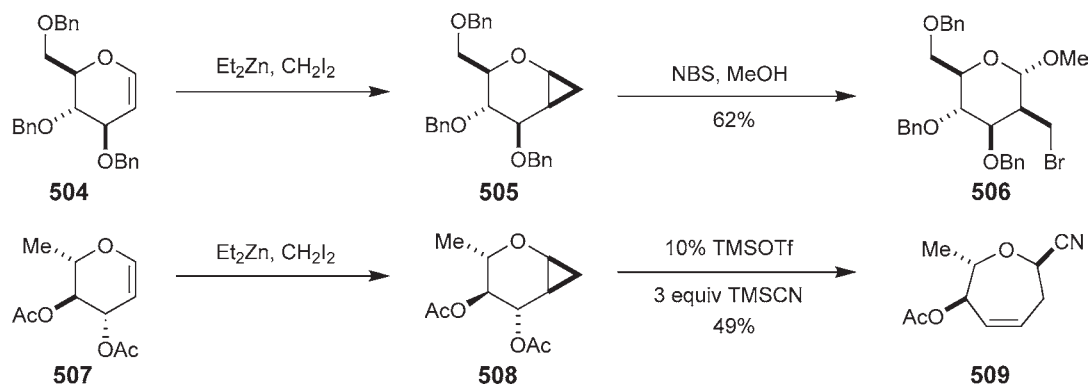
The synthesis of L- and D-arabinose via the oxyselemination of 3,4-dihydro-2*H*-pyran **455** followed by several other stereoselective transformations has been achieved, as shown in Scheme 90 <2000J(P1)1341>. Initial oxyselemination of **455** with phenylselenenylchloride and (*S,S*)-hydrobenzoin gave **497** (along with 33% of the diastereomer where the pyran stereochemistry is (2*R*,3*S*)). Subsequent oxidation and selenoxide elimination provided functionalized 3,4-dihydropyran **498**. Diastereoselective DMDO oxidation produced epoxide **499**, which was opened with NaSePh to give selenide **500**. Another round of oxidation and selenoxide elimination gave olefin **501**, which was subjected to dihydroxylation using OsO₄ and NMO to produce triol **502**. Reductive removal of the (*S,S*)-hydrobenzoin moiety gave **503**.



Scheme 90

7.07.9.1.2(iii) Reaction with carbenes

Carbenes add to the double bond of dihydropyrans as they do to benzopyrans, to form cyclopropyl pyrans. For example, the Simmons–Smith-type cyclopropanation of dihydropyrans such as **504** and **507** with diiodomethane and Et_2Zn provides 1,2-*C*-methylene carbohydrates such as **505** and **508**, respectively, in good to excellent yields (Scheme 91) <1996TL2533>. Ring-opening reactions of the cyclopropane has been achieved providing oxepanes such as **509** <1995TL6831> as well as C-2-branched sugars such as **506** of defined stereochemistry <1995TL6831>.

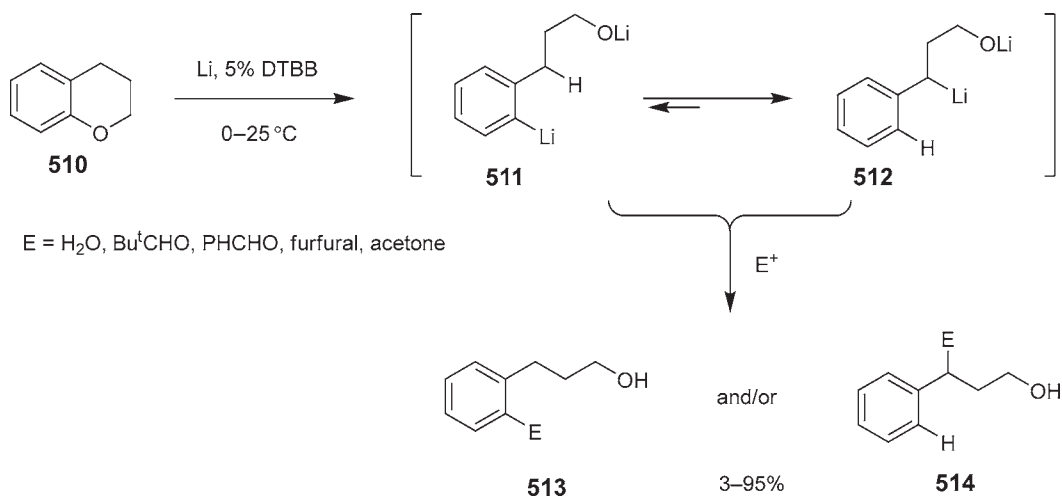


Scheme 91

Studies involving cyclopropanation of glycols with ethyl diazoacetate in the presence of catalytic rhodium acetate or copper powder have also been reported <1995TL8901, 1996TL2533, 2001OL2563>.

7.07.9.1.2(iv) Lithiation and functionalization

The reductive lithiation of cyclic benzofused ethers, for example, **510**, with 4,4'-di-*tert*-butylbiphenyl (DTBB) and lithium gives intermediate organolithiums, for example, **511** and **512**, that can be quenched with a variety of electrophiles to give general products **513** and **514** (Scheme 92). The process is not synthetically useful for 4*H*-chromene as carbon–oxygen bond cleavage occurs in both directions <2002TL4907>.

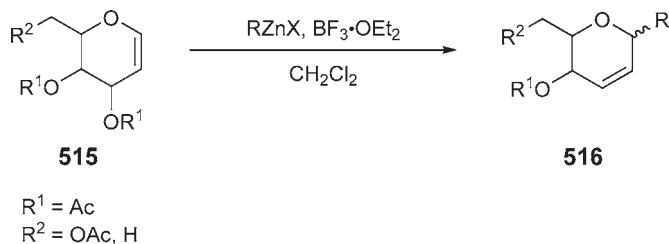


Scheme 92

7.07.9.1.3 Reactions with nucleophiles

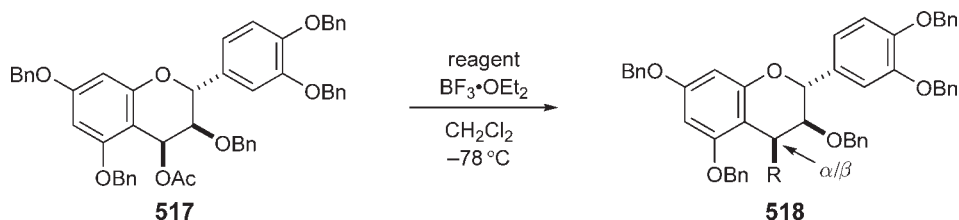
7.07.9.1.3(i) C-Nucleophiles

Organozinc reagents have been used in the nucleophilic C-glycosylation of glycols, for example, the conversion of glycols such as **515** to 3,4-dihydropyrans such as **516** (Scheme 93) <1996SL185>. This transformation occurs via the carbon–Ferrier reaction and is successful for a variety of glycols as well as structurally varied zinc reagents. Good to excellent yields and anomeric selectivities are reported for most of the substrates examined.



Scheme 93

The reaction of C-4-acetoxyated catechin **517** and epicatechin with nucleophiles under Lewis acid conditions to yield C-4-elaborated flavan-3-ols **518** has been described. The C-4 acetoxy group is activated by a Lewis acid, such as $BF_3 \cdot OEt_2$ or TMSOTf, allowing delivery of a variety of carbon-, nitrogen-, and sulfur-based nucleophiles in stereoselective fashion to this position (Scheme 94) <2002TL7753>. An S_N1 mechanism was invoked for the process. Table 4 displays the results for catechins.

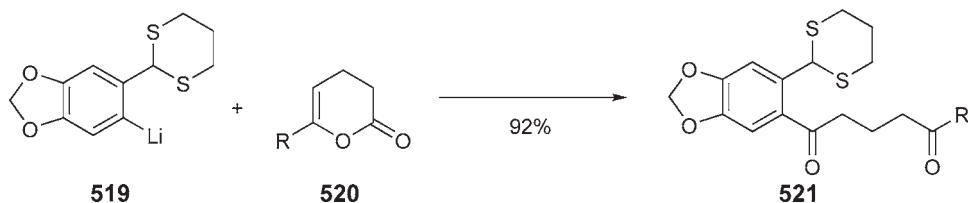


Scheme 94

Table 4 Lewis acid-catalyzed nucleophilic substitutions on catechins

Entry	Reagent	R	Yield (%)	α/β
1		$-\text{C}(\text{Me})_2\text{CO}_2i\text{-Pr}$	87	β
2		$-\text{CH}_2\text{C}(\text{O})\text{Ph}$	88	12/88
3		$-\text{CH}_2\text{CH}_2=\text{CH}_2$	7	8/92
4		$-\text{CH}_2\text{CH}_2=\text{CH}_2$	22	β
5	PhSH	$-\text{SPh}$	92	β
6	Me_3SiN_3	$-\text{N}_3$	81	β

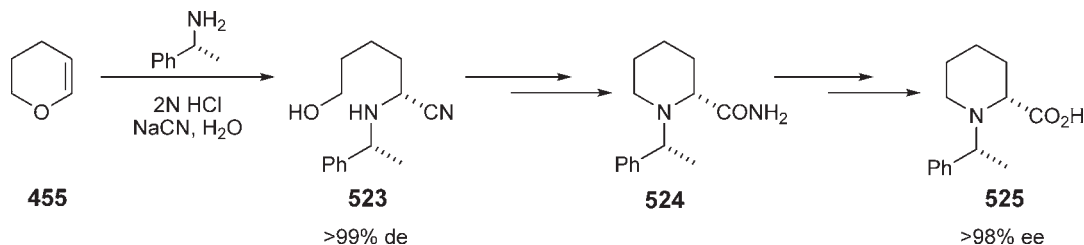
The synthesis of 1,5-diketones **521** from 3,4-dihydropyranones **519** has been reported and is shown in [Scheme 95](#) <1999T9333>. Organolithium reagents were used to open the lactone reagents, and best results were achieved when the reactions were quenched with trimethylsilyl chloride prior to hydrolytic workup.



Scheme 95

7.07.9.1.3(ii) N-Nucleophiles

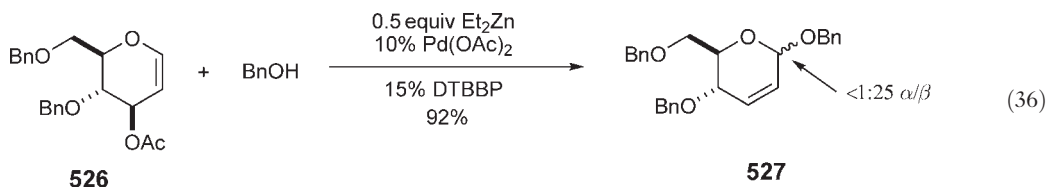
Dihydropyran **455** has been opened by (*R*)- α -methylbenzylamine and NaCN under acidic conditions to give a saturated amino alcohol **523**. Reclosure of the ring provided access to piperidines **524**, including (*R*)-pipecolic acid derivative **525** with greater than 98% ee ([Scheme 96](#)) <2007JOC1780>.



Scheme 96

7.07.9.1.3(iii) O-Nucleophiles

A stereoselective palladium-catalyzed O-glycosylation using has been reported which allows for the direct use of readily available glycal derivatives as donors <2004JA1336>. This transformation escapes the limitations of the Ferrier process in that the reagent rather than anomeric or neighboring group effects of the substrate control the anomeric configuration of the product. A representative transformation of glycal **526** to pyran **527** is shown in Equation (36).

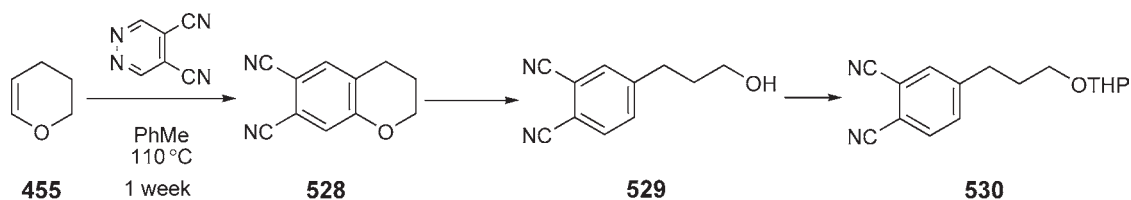


The Ferrier reaction of glycal derivatives has been extensively studied and recently reviewed <2001TCC153>. Additionally, the transformation of glycals into 2,3-unsaturated glycosyl derivatives has also been reviewed <2003OR571>.

7.07.9.1.4 Other reactions

7.07.9.1.4(i) Cycloadditions

3,4-Dihydro-2H-pyran **455** was found to undergo a Diels–Alder reaction with 4,5-dicyanopyridazine in refluxing toluene <2003JOC3340>. Subsequent expulsion of N₂ provided phthalonitrile **528**, which could be converted to **529** and **530** (Scheme 97).



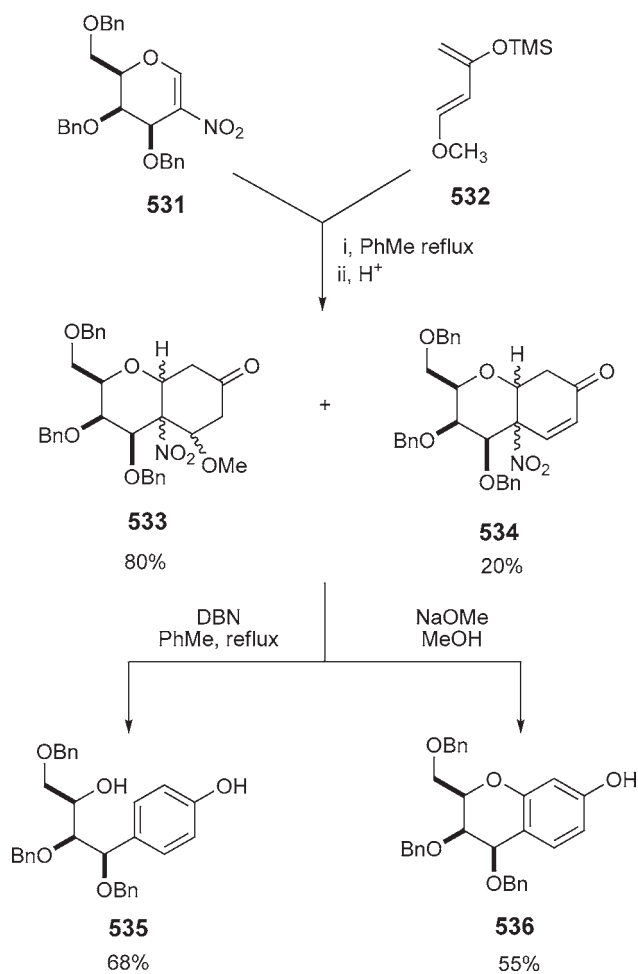
Scheme 97

The Diels–Alder reaction between 2-nitro glycols (e.g., **531**) and Danishefsky's diene **532** has been described (Scheme 98) <2003SL1355>. After subsequent elimination of the nitro and methoxy groups, benzopyrans are afforded, which are prevalent in nature and often possess interesting biological activity.

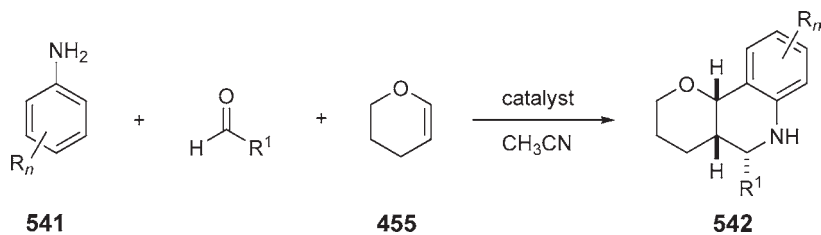
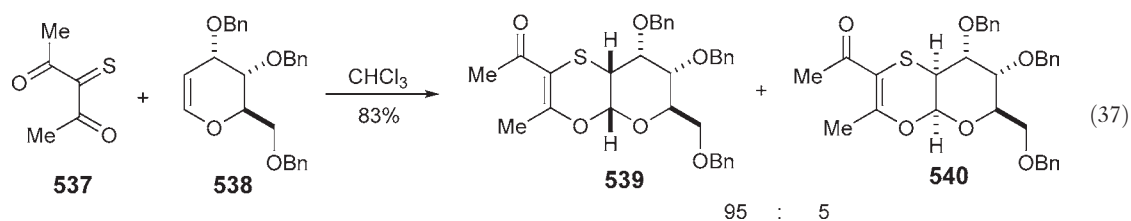
A novel reverse electron demand hetero-cycloaddition of glycals **538** with diacylthione **537** has been reported, an example of which is shown in Equation (37) giving products **539** and **540** <1998JOC6673>. It is suggested that this [4+2] cycloaddition may occur in stepwise fashion.

The three-component imino-Diels–Alder reaction between electron-rich alkenes such as **455** and 2-azadienes (derived from aromatic primary amines, e.g., **541** and aldehydes) to form pyranoquinolines, for example, **542**, has been studied extensively and is shown generally in Scheme 99 <1995T6115>. Many different catalysts have been examined for this reaction, including CAN <2003CL222>, iron trichloride/sodium iodide <2004TL3507>, lithium perchlorate/diethyl ether <2001SL240>, Fe³⁺-K-10 montmorillonite clay <2004SL1715>, indium trichloride <2000S661, 1998TL3225, 2002JOC3969>, lithium tetrafluoroborate <2001S1065>, trifluoroacetic acid <2006T11200>, zirconium tetrachloride <2004SC4089>, triphenylphosphonium perchlorate <2006TL9291>, BF₃OEt₂ <1998TL5765>, and Yb(OTf)₃ <1998TL5765>. A chiral Brønsted acid-catalyzed version of this reaction has also been reported and produces pyranoquinolines with up to 97% ee <2006JA13070>.

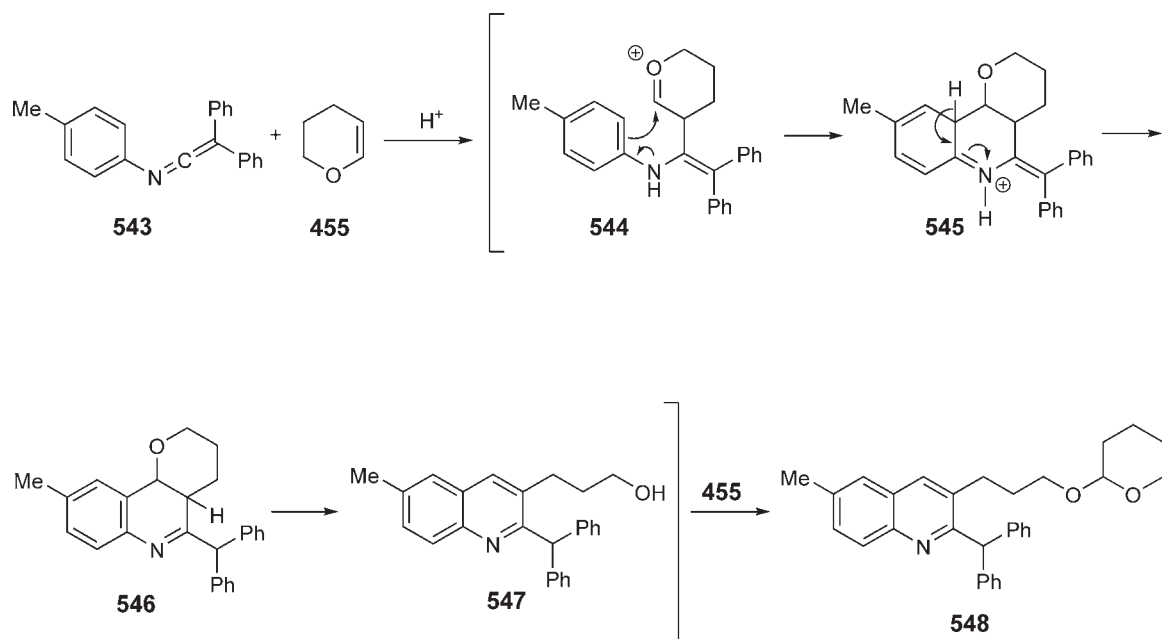
In a manifestation of the reaction shown above, quinoline rings have also been formed by the cycloaddition of *N*-arylketenimines **543** with 3,4-dihydro-2H-pyran **455** under high-pressure conditions (Scheme 100) <2001H(55)1971>. The reaction is proposed to proceed via the initial formation of **544** by attack of the enol ether on the protonated ketenimine; subsequent electrophilic aromatic substitution gives **545**. Protonation of the enamine to give **546** is followed by elimination to produce **547**. Protection of the alcohol with **455** gives **548**.



Scheme 98

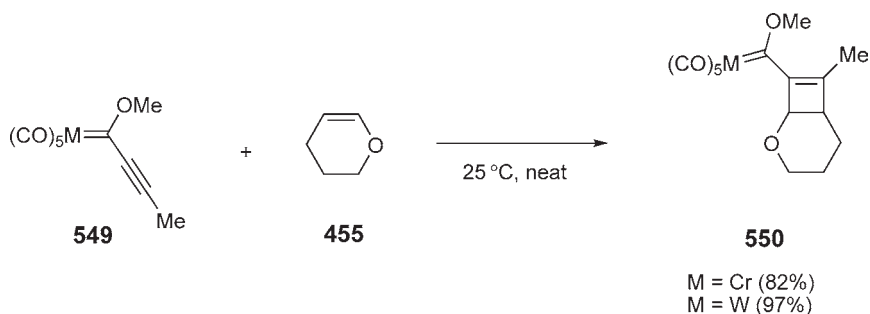


Scheme 99



Scheme 100

The [2+2] cycloaddition of alkynyl Fischer carbene complexes (e.g., **549**) with 3,4-dihydro-2H-pyran **455** to form cyclobut-1-enyl esters **550** has been described (Scheme 101) <1999J(P1)197>.

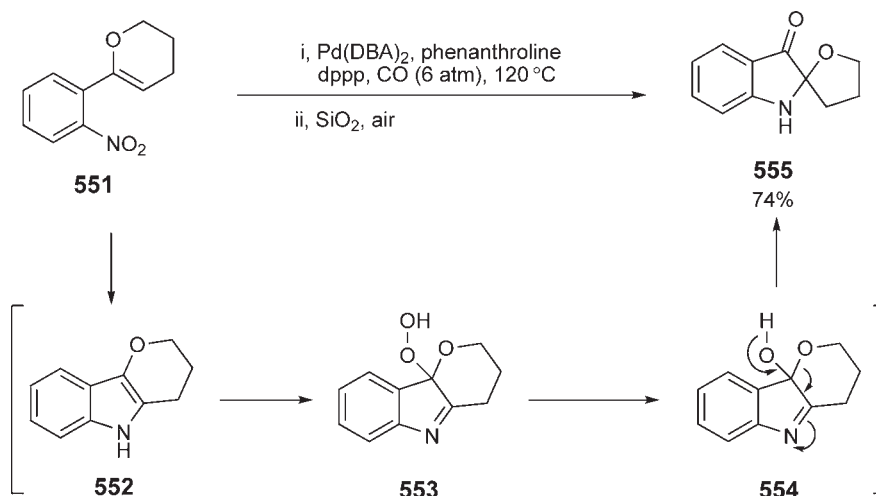


Scheme 101

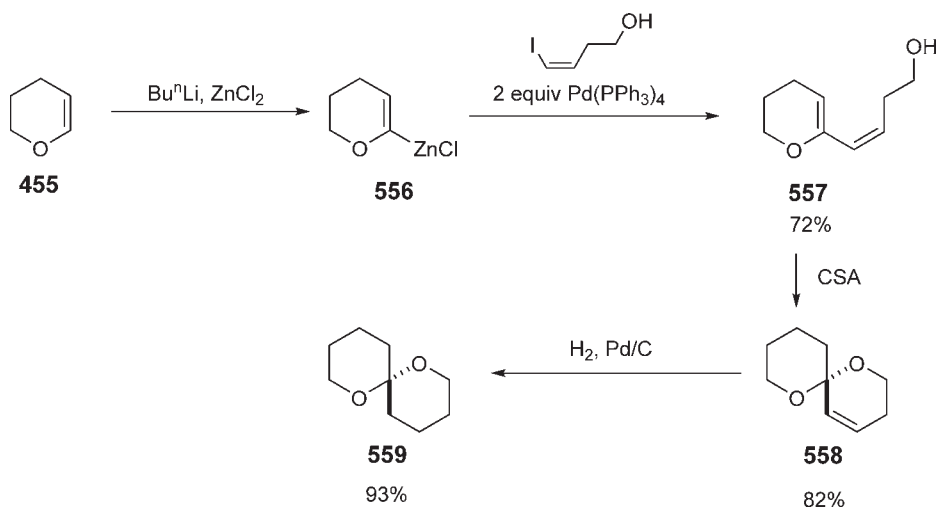
7.07.9.1.4(ii) Palladium-catalyzed reactions

The palladium-catalyzed reductive N-heteroannulation using carbon monoxide has been reported (Scheme 102). As part of this study, substrate **551** was examined in an attempt to synthesize **552**. However, **552** was found to be unstable and underwent further oxidative rearrangement in air to form spiro compound **555** via intermediates **553** and **554** <2006T10829>.

In a separate study, a stereospecific Negishi coupling and subsequent cyclization was found to provide access to the 1,7-dioxaspiro[5.5]undecane family of spiroketals that are commonly found in pheromones and other biologically active compounds (Scheme 103) <2005T11910>. For example, lithiation of dihydropyran **455** and *in situ*, transmetalation to the zinc reagent **556** followed by Pd(PPh₃)₄-catalyzed coupling with (3*Z*)-4-iodobutenol gave **557** in 72% yield. Camphorsulfonic acid-mediated spirocyclization gave spiroacetal **558**. Final reduction with H₂ and Pd/C gave **559**.



Scheme 102



Scheme 103

References

- 1963JCS4986 A. W. Burgstahler, L. K. Gibbons, and I. C. Nordin, *J. Chem. Soc.*, 1963, 4986.
 1967JCB1203 G. Gatti, A. Segre, and C. Morandi, *J. Chem. Soc. B.*, 1967, 1203.
 1968JA6543 E. W. Garbisch and M. G. Griffith, *J. Am. Chem. Soc.*, 1968, **90**, 6543.
 1969CJC1289 V. M. Rao and R. Kewley, *Can. J. Chem.*, 1969, **47**(8), 1289.
 1970KGS1308 G. N. Dorofeenko, E. I. Sadekova, and V. M. Goncharova, *Khim. Geterotsikl. Soedin.*, 1970, **6**, 1308.
 1971CC1240 J. M. Brown, B. T. Golding, and M. J. Smith, *J. Chem. Soc., Chem. Commun.*, 1971, 1240.
 1973CC410 J. A. Barltrop, K. Dawes, A. C. Day, S. J. Nuttall, and A. J. H. Summers, *J. Chem. Soc. Chem. Commun.*, 1973, 410.
 1973JA4634 B. Lambert, C. E. Mixan, and D. H. Johnson, *J. Am. Chem. Soc.*, 1973, **95**, 4634.
 1976JOC1380 L. Canuel and M. St.-Jacques, *J. Org. Chem.*, 1976, **41**, 1380.
 1977HC31 'Chemistry of Heterocyclic Compounds 1977', Volume 31 (Chromenes, Chromanones, and Chromones).
 1977JOC3976 R. A. Volkmann, P. D. Weeks, D. E. Kuhla, E. B. Whipple, and G. N. Chmurny, *J. Org. Chem.*, 1977, **42**, 3976.
 1979ACS(A)225 H. E. Breed, G. Gundersen, and R. Seip, *Acta Chem. Scand., Series A*, 1979, **A33**(3), 225.
 1979H(12)421 M. Afzal and J. M. Alhassan, *Heterocycles*, 1979, **12**, 421.
 1980S589 J. Becher, *Synthesis*, 1980, 589.
 1981HC36 'Chemistry of Heterocyclic Compounds 1981', Volume 36 (Chromans and Tocopherols).
 1981KGS1351 V. I. Dulenko, S. V. Tolkunov, and N. N. Alekseev, *Khim. Geterotsikl. Soedin.*, 1981, **17**, 1351.
 1982AHC(32)128 L. H. Klemm, in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Elsevier, Amsterdam, 1982, vol. 32, p. 127.

- 1982AHC(32)233 M. P. Sammes and A. R. Katritzky; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Elsevier, Amsterdam, 1982, vol. 32, p. 233.
- 1982AHC(suppl 2)1 A. T. Balaban, A. Dinulescu, G. N. Dorofeenko, G. W. Fischer, A. V. Koblik, V. V. Mezheritskii, and W. Schroth, *Adv. Heterocycl. Chem.* 1982, suppl. 2, p. 1.
- 1982JA3635 E. L. Eliel, K. D. Hargrave, K. M. Pietrusiewicz, and M. Manoharan, *J. Am. Chem. Soc.*, 1982, **104**, 3635.
- 1982JHC385 A. O. Obaseki, W. R. Porter, and W. F. Trager, *J. Heterocycl. Chem.*, 1982, **19**, 385.
- 1982JHC475 W. R. Porter and W. F. Trager, *J. Heterocycl. Chem.*, 1982, **19**, 475.
- 1982JOC5402 F. Camps, J. Coll, A. Messegue, and F. Pujol, *J. Org. Chem.*, 1982, **47**, 5402.
- 1982OMR55 H. Duddeck and M. Kaiser, *Org. Magn. Reson.*, 1982, **20**, 55.
- 1982TL4625 S. V. Ley and B. Lygo, *Tetrahedron Lett.*, 1982, **23**, 4625.
- 1983TL2195 I. Saito, K. Shimozono, and T. Matsuura, *Tetrahedron Lett.*, 1983, **24**, 2195.
- 1984CC1565 M. Yamuchi, S. Katayama, T. Todoroki, and T. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1984, 1565.
- 1984CHEC A. R. Katritzky and C. W. Rees, Eds.; 'Comprehensive Heterocyclic Chemistry I', Pergamon, Oxford, 1984.
- 1986TL5277 C. Greck, P. Grice, S. V. Ley, and A. Wonnacott, *Tetrahedron Lett.*, 1986, **27**, 5277.
- 1987KGS889 V. I. Dulenko and S. V. Tolkunov, *Khim. Geterotsikl. Soedin.*, 1987, **23**, 889.
- 1987T3075 P. J. Cremins, S. T. Saengchantara, and T. W. Wallace, *Tetrahedron*, 1987, **43**, 3075.
- 1988BCJ3008 Y. Hoshino, N. Miyaura, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3008.
- 1989CPB529 I. Yokoe, Y. Sugita, and Y. Shirataki, *Chem. Pharm. Bull.*, 1989, **37**, 529.
- 1989H(29)301 D. W. Boykin, D. W. Sullins, and E. J. Eisenbraun, *Heterocycles*, 1989, **29**, 301.
- 1989JA6661 R. L. Halcomb and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1989, **111**, 6661.
- 1989J(P1)683 M. Furber, J. M. Herbert, and R. J. K. Taylor, *J. Chem. Soc. Perkin Trans. 1*, 1989, 683.
- B-1989MI1 P. K. Agrawal, Ed.; Studies in Organic Chemistry, Vol. 39: Carbon-MR of Flavonoids', Elsevier, Amsterdam, 1989.
- 1990CHE980 S. V. Verin, *Chem. Heterocycl. Compd.*, 1990, **26**, 980.
- 1990JCM162 B. C. Borer and R. J. K. Taylor, *J. Chem. Res. (S)*, 1990, 162.
- 1990JIC770 N. S. Yadav, S. N. Dhawan, and S. C. Gupta, *J. Indian Chem. Soc.*, 1990, **67**, 770.
- 1990PHC(2)229 J. D. Hepworth; in 'Progress in Heterocyclic Chemistry', H. Suschitsky and E. F. V. Scriven, Eds., Elsevier, Amsterdam, 1990, vol. 2, p. 229.
- 1990TCC285 J. Thiem and W. Klaffke, *Top. Curr. Chem.*, 1990, **154**, 285.
- 1990TL3445 D. Diez-Martin, P. Grice, H. C. Kolb, S. V. Ley, and A. Madin, *Tetrahedron Lett.*, 1990, **31**, 3445.
- 1991JA7063 E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, and L. Deng, *J. Am. Chem. Soc.*, 1991, **113**, 7063.
- 1991JCR(S)6 I. Tvaroska and J. P. J. Carver, *Chem. Res. (S)*, 1991, 6.
- 1991JME2169 T. Horie, H. Tominaga, Y. Kawamura, T. Hada, N. Ueda, Y. Amano, and S. Yamamoto, *J. Med. Chem.*, 1991, **34**, 2169.
- 1991JOC2058 Y. G. Lee, K. Ishimaru, H. Iwasaki, K. Ohkata, and K. Akiba, *J. Org. Chem.*, 1991, **56**, 2058.
- 1991JOC3713 D. M. Gordon and S. J. Danishefsky, *J. Org. Chem.*, 1991, **56**, 3713.
- 1991JOC4963 S. W. McCombie, W. A. Metz, D. Nazareno, B. B. Shankar, and J. Tagat, *J. Org. Chem.*, 1991, **56**, 4963.
- 1991J(P1)2725 E. F. De Medeiros, J. M. Herbert, and R. J. K. Taylor, *J. Chem. Soc. Perkin Trans. 1*, 1991, 2725.
- 1991LA1229 V. J. Ram, M. Verma, F. A. Hussaini, and A. Shoen, *Liebigs Ann.*, 1991, 1229.
- 1991S320 Y. Y. Belosludtsev, B. C. Borer, and R. J. K. Taylor, *Synthesis*, 1991, 320.
- 1991TL7063 T. Sugai and H. Ohta, *Tetrahedron Lett.*, 1991, **32**, 7063.
- 1992C457 V. Kvita and W. Fischer, *Chimia*, 1992, **46**, 457.
- 1992CHE1219 N. P. Solovava, *Chem. Heterocycl. Compd.*, 1992, **28**, 1219.
- 1992JA859 R. J. Woods, C. W. Andrews, and J. P. Bowen, *J. Am. Chem. Soc.*, 1992, **114**, 859.
- 1992SL117 B. C. Borer and R. J. K. Taylor, *Synlett*, 1992, 117.
- 1992SL407 A. Hatayama, N. Hosoya, R. Irie, Y. Ito, and T. Katsuki, *Synlett*, 1992, 407.
- 1992TL2115 P. A. Wender and J. L. Mascarenas, *Tetrahedron Lett.*, 1992, **33**, 2115.
- 1993CC1409 K. Hemming and R. J. K. Taylor, *J. Chem. Soc. Chem. Commun.*, 1993, 1409.
- 1993CPB211 K. Nagasawa, Y. Higuchi, K. Ito, M. Imanari, and N. Fujii, *Chem. Pharm. Bull.*, 1993, **41**, 211.
- 1993JCM110 V. J. Ram, F. A. Hussaini, S. K. Singh, and A. Shoen, *J. Chem. Res. (S)*, 1993, 110.
- 1993JOC385 R. S. Coleman and J. R. Fraser, *J. Org. Chem.*, 1993, **58**, 385.
- 1993JOC1367 B. W. Gung, Z. Zhu, and D. A. Mareska, *J. Org. Chem.*, 1993, **58**, 1367.
- 1993JOC5585 A. Rumbo, L. Castedo, A. Mourino, and J. L. Mascarenas, *J. Org. Chem.*, 1993, **58**, 5585.
- 1993SC1075 Y. Li and F. Zhang, *Syn. Commun.*, 1993, **23**, 1075.
- 1994AXC1938 A. J. Blake, R. O. Gould, S. G. Harris, H. McNab, and S. Parsons, *Acta Crystallogr. Sect. C*, 1994, **50**, 1938.
- 1994JCM86 F. A. Hussaini, V. J. Pragma, Ram, S. K. Singh, M. Nath, A. Shoen, and A. P. Bhaduri, *J. Chem. Res. (S)*, 1994, 86.
- 1994JCM354 V. J. Ram, S. Mumtazuddin, N. Pragma, Haque, F. A. Hussaini, A. Shoen, and A. P. Bhaduri, *J. Chem. Res. (S)*, 1994, 354.
- 1994JCS(P2)2587 O. Dangles, M. Elhabiri, and R. Brouillard, *J. Chem. Soc., Perkin Trans. 2*, 1994, **12**, 2587.
- 1994JOC2138 U. Salzner and P. v. R. Schleyer, *J. Org. Chem.*, 1994, **59**, 2138.
- 1994JOC4895 B. W. Gung, M. A. Wolf, D. A. Mareska, and C. A. Brockway, *J. Org. Chem.*, 1994, **59**(17), 4895.
- 1994JOC4899 B. W. Gung, M. A. Wolf, A. Karipides, and D. A. Mareska, *J. Org. Chem.*, 1994, **59**(17), 4899.
- 1994RCM163 P. Hadjieva, T. Deligeorgiev, S. Fontana, S. Catinella, and P. Traldi, *Rapid Commun. Mass. Spectrom.*, 1994, **8**, 163.
- 1994SPL1431 H. Tak, F. R. Fronczek, and N. H. Fischer, *Spectrosc. Lett.*, 1994, **27**, 1431.
- 1994T11755 S. J. Coutts and T. W. Wallace, *Tetrahedron*, 1994, **50**, 11755.
- 1994TL8433 G. Bellucci, G. Catelani, C. Chiappe, and F. D'Andrea, *Tetrahedron Lett.*, 1994, **35**, 8433.
- 1995AXC1180 R. Anulewicz, B. Swirski, and P. Milart, *Acta Crystallogr., Sect. C*, 1995, **51**, 1180.
- 1995JA12649 S. D. Burke, C. J. O'Donnell, W. J. Porter, and Y. Song, *J. Am. Chem. Soc.*, 1995, **117**, 12649.
- 1995JAM132 A. Cappiello, G. Famigliini, F. Mangani, and B. Tirillini, *J. Am. Soc. Mass. Spectrom.*, 1995, **6**, 132.
- 1995JNP1455 S. Kuwahara, N. Arai, O. Kodama, R. A. Howie, and R. H. Thomson, *J. Nat. Prod.*, 1995, **58**, 1455.
- 1995JNP1776 S. De Rosa, A. Crispino, A. De Giulio, C. Iodice, R. Pronzato, and N. Zavadnik, *J. Nat. Prod.*, 1995, **58**, 1776.
- 1995JOC5380 S. L. Vander Velde and E. N. Jacobsen, *J. Org. Chem.*, 1995, **60**, 5380.

- 1995J(P1)177 S. C. Gupta, A. Saini, D. Kumar, N. S. Yadav, K. Chand, S. Mor, and S. N. Dhawan, *J. Chem. Soc. Perkin Trans. 1*, 1995, 177.
- 1995J(P1)2385 R. J. K. Taylor, K. Hemming, and E. Faria de Medeiros, *J. Chem. Soc. Perkin Trans. 1*, 1995, 2385.
- 1995LA685 D. Schummer, K. Gerth, H. Reichenbach, and G. Hoeffle, *Liebigs Ann.*, 1995, 685.
- 1995MC99 A. I. Pyshev, L. I. Butenko, and S. V. Verin, *Mendeleev Commun.*, 1995, 5, 99.
- 1995T6115 J. M. Mellor and G. D. Merriman, *Tetrahedron*, 1995, 51, 6115.
- 1995T13277 C. D. Gabbutt, J. D. Hepworth, and B. M. Heron, *Tetrahedron*, 1995, 51, 13277.
- 1995TL6831 J. O. Hoberg and J. J. Bozell, *Tetrahedron Lett.*, 1995, 36, 6831.
- 1995TL8901 K. L. Henry Jr., and B. Fraser-Reid, *Tetrahedron Lett.*, 1995, 36, 8901.
- 1996AGE1380 S. J. Danishefsky and M. T. Bilodeau, *Angew. Chem. Int. Ed. Engl.*, 1996, 35, 1380.
- 1996AHC(65)283 K. Ohkata and K. Y. Akiba, *Adv. Heterocycl. Chem.*, 1996, 65, 283.
- 1996AXC2917 J. Burgess, J. Fawcett, D. R. Russell, R. C. Hider, M. B. Hossain, C. R. Stoner, and D. van der Helm, *Acta Crystallogr., Sect. C*, 1996, 52, 2917.
- 1996AXC2633 D. Bilodeau and A. L. Beauchamp, *Acta Crystallogr., Sect. C*, 1996, 52, 2633.
- 1996CHEC-II(5)301 J. D. Hepworth, C. D. Gabbutt, and B. M. Heron, in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 301.
- 1996H(42)789 Y. Azuma, A. Sato, and M. Morone, *Heterocycles*, 1996, 42, 789.
- 1996H(43)745 P. W. Groundwater, D. E. Hibbs, M. B. Hursthouse, and M. Nyerges, *Heterocycles*, 1996, 43, 745.
- 1996IJB588 J. Mitra and K. Mitra, *J. Indian J. Chem. B*, 1996, 35, 588.
- 1996JA7946 W. Zheng, J. A. DeMattei, J.-P. Wu, J. J.-W. Duan, L. R. Cook, H. Oinuma, and Y. Kishi, *J. Am. Chem. Soc.*, 1996, 118, 7946.
- 1996JMT(370)221 L. Golender, H. Senderowitz, and B. Fuchs, *Theochem.*, 1996, 370(2-3), 221.
- 1996JOC3218 J. Morris, G. P. Luke, and D. G. Wishka, *J. Org. Chem.*, 1996, 61, 3218.
- 1996JOC4391 A. Nath, J. Mal, and R. V. Venkateswaran, *J. Org. Chem.*, 1996, 61, 4391.
- B-1996MI(18)971 B. Mikhova and H. Duddeck; 'Studies in Natural Products Chemistry', Elsevier, Amsterdam, 1996; vol. 18, p. 971.
- 1996SC3359 G. Appendino, G. Gravotto, G. Palmisano, and R. Annunziata, *Synth. Commun.*, 1996, 26, 3359.
- 1996SL185 S. N. Thorn and T. Gallagher, *Synlett*, 1996, 185.
- 1996SPL631 M. A. P. Martins, *Spectrosc. Lett.*, 1996, 29, 631.
- 1996T11045 C. Bisi Castellani, O. Carugo, M. Giusti, C. Leopizzi, A. Perotti, A. Invernizzi Gamba, and G. Vidari, *Tetrahedron*, 1996, 52, 11045.
- 1996T14081 W. E. Bauta, J. Booth, M. E. Bos, M. DeLuca, L. Diorazio, T. J. Donohoe, C. Frost, N. Magnus, P. Magnus, J. Mendoza, P. Pye, J. G. Tarrant, S. Thorn, and F. Ujjainwalla, *Tetrahedron*, 1996, 52, 14081.
- 1996T7855 P. Mandal, A. Nath, and R. V. Venkateswaran, *Tetrahedron*, 1996, 52, 7855.
- 1996TL93 V. J. Ram and A. Goel, *Tetrahedron Lett.*, 1996, 37, 93.
- 1996TL343 S. D. Burke, C. R. Heap, W. J. Porter, and Y. Song, *Tetrahedron Lett.*, 1996, 37, 343.
- 1996TL1913 P. Charoenying, D. H. Davies, D. McKerrecher, and R. J. K. Taylor, *Tetrahedron Lett.*, 1996, 37, 1913.
- 1996TL2533 J. O. Hoberg and D. J. Claffey, *Tetrahedron Lett.*, 1996, 37, 2533.
- 1996TL8913 S. C. Gupta, A. Saini, S. Sharma, M. Kapoor, and S. N. Dhawan, *Tetrahedron Lett.*, 1996, 37, 8913.
- 1997CHR197 M. Ganzer, S. Sturm, and H. Stuppner, *Chromatographia*, 1997, 46, 197.
- 1997CJC365 V. F. Traven, L. I. Vorobjeva, T. A. Chibisova, E. A. Carberry, and N. J. Beyer, *Can. J. Chem.*, 1997, 75, 365.
- 1997CJC377 V. F. Traven, V. V. Negrebetsky, L. I. Vorobjeva, and E. A. Carberry, *Can. J. Chem.*, 1997, 75, 377.
- 1997CL1021 V. J. Ram and A. Goel, *Chem. Lett.*, 1997, 1021.
- 1997DMD1318 S. L. Born, P. A. Rodriguez, C. L. Eddy, and L. D. Lehman-McKeeman, *Drug Metab. Dispos.*, 1997, 25, 1318.
- 1997G79 P. Crotti, V. Di Bussolo, L. Favero, N. Jannitti, M. Pineschi, and M. Pasero, *Gazz. Chim. Ital.*, 1997, 127, 79.
- 1997H(46)451 C. W. Jefford, M. F. Deheza, and J. B. Wang, *Heterocycles*, 1997, 46, 451.
- 1997JCM460 V. J. Ram and A. Goel, *J. Chem. Res. (S)*, 1997, 460.
- 1997JHC1821 M. Hamdi, S. Corter, C. Tedeschi, and V. Speciale, *J. Heterocycl. Chem.*, 1997, 34, 1821.
- 1997JOC6687 C.-M. Yu, H.-S. Choi, J.-K. Lee, and S.-K. Yoon, *J. Org. Chem.*, 1997, 62, 6687.
- 1997JOC7597 M. Miljković, D. Yeagley, P. Deslongchamps, and Y. L. Dory, *J. Org. Chem.*, 1997, 62, 7597.
- 1997JOC8198 A. R. Katritzky, P. Czerney, and J. R. Levell, *J. Org. Chem.*, 1997, 62, 8198.
- 1997J(P2)1279 R. J. Abraham, A. Ghersi, G. Petrillo, and J. F. Sancassan, *J. Chem. Soc. Perkin Trans. 2*, 1997, 1279.
- 1997LA1143 R. W. Hoffmann, W. Reinhard, and I. Munster, *Liebigs Annalen/Recueil*, 1997, 6, 1143.
- 1997MC204 D. E. Tosunyan, S. V. Verin, and E. V. Kuznetsov, *Mendeleev Commun.*, 1997, 7, 204.
- 1997OPP223 I. Tabakovic, K. Tabakovic, and I. Gaon, *Org. Prep. Proced. Int.*, 1997, 29, 223.
- 1997PCA2471 S. P. Lay, T. Yamada, P.-L. Tsai, and J. W. Bozzelli, *J. Phys. Chem. A*, 1997, 101, 2471.
- 1997SC1123 T. Dubuffet, B. Cimetiere, and G. lavielle, *Synth. Commun.*, 1997, 27, 1123.
- 1997T1417 P. Crotti, V. Di Bussolo, L. Favero, and M. Pineschi, *Tetrahedron*, 1997, 53, 1417.
- 1997TL1297 W. C. Patt and M. A. Massa, *Tetrahedron Lett.*, 1997, 38, 1297.
- 1997ZNB485 T. S. Balaban and N. G. Furmanova, *Z. fuer Naturforsch., B*, 1997, 52, 485.
- 1998CEJ1974 U. Spoerel, W. Stahl, W. Caminati, and P. G. Favero, *Chem. Eur. J.*, 1998, 4, 1974.
- 1998CHE159 S. V. Tolkunov and V. I. Dulencko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, 34, 159.
- 1998CHE983 S. V. Tolkunov, S. Y. Suikov, M. Y. Zubritskii, and V. I. Dulencko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, 34, 983.
- 1998CHE1234 M. P. Nemeryuk, V. D. Dimitrova, A. L. Sedov, and V. F. Traven, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, 33, 1234.
- 1998CPL543 D. Consalvo and U. Spoerel, *Chem. Phys. Lett.*, 1998, 297, 543.
- 1998EJO237 M. Christl and S. Drinkuth, *Eur. J. Org. Chem.*, 1998, 237.
- 1998EJO2083 M. Nath, P. Srivastava, A. Goel, and V. J. Ram, *Eur. J. Org. Chem.*, 1998, 2083.
- 1998EJO2623 A. R. Katritzky, P. Czerney, J. R. Levell, and W. Du, *Eur. J. Org. Chem.*, 1998, 2623.
- 1998JOC2002 R. C. Larock and Q. Tian, *J. Org. Chem.*, 1998, 63, 2002.
- 1998JOC2806 C. M. Amann, P. V. Fisher, M. L. Pugh, and F. G. West, *J. Org. Chem.*, 1998, 63, 2806.
- 1998JOC6673 A. Dios, A. Geer, C. H. Marzabadi, and R. W. Franck, *J. Org. Chem.*, 1998, 63, 6673.
- 1998JOC8748 H. Oikawa, T. Kobayashi, K. Katayama, Y. Suzuki, and A. Ichihara, *J. Org. Chem.*, 1998, 63, 8748.

- 1998J(P2)1751 R. J. Abraham, M. A. Warne, and L. Griffiths, *J. Chem. Soc. Perkin Trans. 2.*, 1998, 1751.
1998S167 A. Goel, P. Srivastava, M. Nath, and V. J. Ram, *Synthesis*, 1998, 167.
1998SC3827 S. G. Jagadeesh, G. L. D. Krupadanam, and G. Srimannarayana, *Synth. Commun.*, 1998, **28**, 3827.
1998T9747 C. Uncuta, M. T. Caproiu, V. Campeanu, A. Petride, M. G. Danila, M. Plaveti, and A. T. Balaban, *Tetrahedron*, 1998, **54**, 9747.
1998T13105 A. Levai, W. Adam, R. T. Fell, R. Gessner, T. Patonay, A. Simon, and G. Toth, *Tetrahedron*, 1998, **54**, 13105.
1998TA1121 W. Adam, R. T. Fell, A. Levai, T. Patonay, K. Peters, A. Simon, and G. Toth, *Tetrahedron Asymmetry*, 1998, **9**, 1121.
1998TL557 B. Caro, P. Le Poul, F. Robin-Le Guen, M.-C. Senéchal-Tocquer, and J. Vaisserman, *Tetrahedron Lett.*, 1998, **39**, 557.
1998TL3225 G. Babu and P. T. Perumal, *Tetrahedron Lett.*, 1998, **39**, 3225.
1998TL5765 B. Crousse, J.-P. Begue, and D. Bonnet-Delpon, *Tetrahedron Lett.*, 1998, **39**, 5765.
1999AGE1772 S. Antolinez, J. C. Lopez, and J. L. Alonso, *Angew. Chem. Int. Ed.*, 1999, **38**, 1772.
1999CHE653 A. I. Fomenko, V. N. Storozhenko, S. G. Storozhenko, A. O. Manyashin, N. T. Berberova, and O. Y. Okhlobystin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 653.
1999EJO135 A. M. S. Silva, A. M. G. Silva, A. C. Tome, and J. A. S. Cavaleiro, *Eur. J. Org. Chem.*, 1999, 135.
1999JMT(487)87 F. Freeman, M. L. Kasner, and W. J. Hehre, *Theochem.*, 1999, **487**(1–2), 87.
1999JMT(574)19 F. Freeman, M. L. Kasner, and W. J. Hehre, *Theochem.*, 2001, **574**, 19.
1999JOC2387 V. J. Ram and A. Goel, *J. Org. Chem.*, 1999, **64**, 2387.
1999JOC5768 M. J. Fehr, G. Consiglio, M. Scalone, and R. Schmid, *J. Org. Chem.*, 1999, **64**, 5768.
1999J(P1)197 W. D. Wulff, K. L. Faron, J. Su, J. P. Springer, and A. L. Rheingold, *J. Chem. Soc. Perkin Trans. 1*, 1999, 197.
1999J(P1)1167 M. Rudas, I. Fejes, M. Nyerges, A. Szollosy, L. Toke, and P. W. Groundwater, *J. Chem. Soc. Perkin Trans. 1*, 1999, 1167.
1999J(P1)2391 S. C. Gupta, S. Sharma, A. Saini, and S. N. Dhawan, *J. Chem. Soc. Perkin Trans 1*, 1999, 2391.
1999JPR152 A. R. Katritzky, W. Du, S. N. Denisenko, P. Czerney, and P. J. Steel, *J. Prakt. Chem.*, 1999, **341**, 152.
1999MC204 V. Y. Sosnovskikh, V. A. Kutsenko, and D. S. Yachevskii, *Mendeleev Commun.*, 1999, **9**, 204.
1999PCJ480 E. T. Oganessian, A. V. Pyshchev, and L. I. Butenko, *Pharm. Chem. J. USSR.*, 2000, **33**, 480.
1999RCB812 V. Y. Sosnovskikh and V. A. Kutsenko, *Russ. Chem. Bull.*, 1999, **48**, 812.
1999RCB1537 I. T. Bazyl, S. P. Kisil, S. N. Frolov, Y. V. Burgart, and V. I. Saloutin, *Russ. Chem. Bull.*, 1999, **48**, 1537.
1999S467 V. J. Ram and A. Goel, *Synthesis*, 1999, 467.
1999S1209 P. R. Blakemore, P. J. Kocienski, S. Marzcek, and J. Wicha, *Synthesis*, 1999, 1209.
1999S1884 V. J. Ram, P. Srivastava, M. Nath, and A. S. Saxena, *Synthesis*, 1999, 1884.
1999SL477 G. J. Bodwell, Z. Pi, and I. R. Pottie, *Synlett*, 1999, 477.
1999T3553 P. Magnus and L. Shen, *Tetrahedron*, 1999, **55**, 3553.
1999T9333 D. C. Harrowen and J. C. Hannam, *Tetrahedron*, 1999, **55**, 9333.
1999T15011 C. Uncuta, A. Tudose, M. T. Caproiu, M. Plaveti, and R. Kakou-Yao, *Tetrahedron*, 1999, **55**, 15011.
1999TL3293 M. A. McGuire, S. C. Shilcrat, and E. Sorenson, *Tetrahedron Lett.*, 1999, **40**, 3293.
1999TL4751 A. K. Ghosh and R. Kawahama, *Tetrahedron Lett.*, 1999, **40**, 4751.
2000AGE4364 M. Christmann, U. Bhatt, M. Quitschalle, E. Claus, and M. Kalesse, *Angew. Chem. Intl. Ed.*, 2000, **39**, 4364.
2000CNO485 M. M. Garazd, Y. L. Garazd, S. V. Shilin, and V. P. Khilya, *Chem. Nat. Compd.*, 2001, **36**, 485.
2000H(53)2191 Y. Sugita, S. Yin, and I. Yokoe, *Heterocycles*, 2000, **53**, 2191.
2000JA287 B. Engels, J. C. Schoeneboom, A. F. Muenster, S. Groetsch, and M. Christl, *J. Am. Chem. Soc.*, 2000, **124**, 287.
2000J(P1)1341 K. S. Kim, C. W. Moon, J. I. Park, and S.-H. Han, *J. Chem. Soc. Perkin Trans. 1*, 2000, 1341.
2000JMT(504)77 A. Mantas, E. Deretey, F. H. Ferretti, M. Estrada, and I. G. Csizmadia, *J. Mol. Struct. Theochem*, 2000, **504**, 77.
2000JST(554)225 M. Z. Chalaça and J. D. Figueroa-Villar, *J. Mol. Struct.*, 2000, **554**, 225.
2000OL3145 H. Suga, A. Kakehi, S. Ito, K. Inoue, H. Ishida, and T. Ibata, *Org. Lett.*, 2000, **2**, 3145.
2000OL957 M. T. Crimmins and J. D. Katz, *Org. Lett.*, 2000, **2**, 957.
2000PCA8577 A. Samanta and R. W. Fessenden, *J. Phys. Chem. A.*, 2000, **104**, 8577.
2000PCJ95 E. T. Oganessian, A. V. Pyshchev, and L. I. Butenko, *Pharm. Chem. J.*, 2000, **34**, 95.
2000RCB2074 V. Y. Sosnovskikh and B. I. Usachev, *Russ. Chem. Bull.*, 2000, **49**, 2074.
2000RJC793 V. F. Traven, O. B. Safronova, L. I. Vorob'eva, T. A. Chibisova, and I. N. Senchenya, *Russ. J. Gen. Chem.*, 2000, **70**, 793.
2000RJO793 V. F. Traven, O. B. Safronova, L. I. Vorob'eva, T. A. Chibisova, and I. N. Senchenya, *Russ. J. Gen. Chem. (Translation of Zh. Obshch. Khim.)*, 2000, **70**(5), 793.
2000S661 G. Babu, R. Nagarajan, R. Natarajan, and P. T. Perumal, *Synthesis*, 2000, 661.
2000SL254 S. Kafka, P. Trebse, S. Polanc, and M. Kocevar, *Synlett*, 2000, 254.
2000T5205 D. Passarella, G. Lesma, M. Martinelli, A. Silvani, M. Canto, and J. Hidalgo, *Tetrahedron*, 2000, **56**, 5205.
2000TL5199 D. Saleur, J. P. Bouillon, C. Portella, and N. Hoffmann, *Tetrahedron Lett.*, 2000, **41**, 5199.
2000TL5979 R. Doodeman, F. P. J. T. Rutjes, and H. Hiemstra, *Tetrahedron Lett.*, 2000, **41**, 5979.
2000TL8425 A. K. Ghosh, R. Kawahama, and D. Wink, *Tetrahedron Lett.*, 2000, **41**, 8425.
2000TL9909 S. M. Concannon, V. N. Ramachandran, and W. Franklin Smyth, *Tetrahedron Lett.*, 2000, **41**, 9909.
2001AGE568 U. Beifuss, K. Goldenstein, F. Doring, C. Lehmann, and M. Noltemeyer, *Angew. Chem. Int. Ed.*, 2001, **40**, 568.
2001BCJ967 T. Eguchi and Y. Hoshino, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 967.
2001CHE797 R. V. Seller, P. V. Reshetov, and A. P. Kriven'ko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2001, **37**, 797.
2001COR571 V. J. Ram and P. Srivastava, *Curr. Org. Chem.*, 2001, **5**, 571.
2001EJO4451 C. Fichtner, G. Remennikov, and H. Mayr, *Eur. J. Org. Chem.*, 2001, 4451.
2001H(55)1971 M. Shimizu, A. Oishi, Y. Taguchi, T. Sano, Y. Gama, and I. Shibuya, *Heterocycles*, 2001, **55**, 1971.
2001JA10425 M. A. Clark, R. C. Schoenfeld, and B. Ganem, *J. Am. Chem. Soc.*, 2001, **123**, 10425.
2001JCP6702 G. B. Dutt and S. Raman, *J. Chem. Phys.*, 2001, **114**, 6702.
2001JCO125 D. G. Hall, S. Manku, and F. Wang, *J. Comb. Chem.*, 2001, **3**, 125.
2001JOC2877 G.-q. Lin and R. Hong, *J. Org. Chem.*, 2001, **66**, 2877.
B-2001MI(1)3 T. Bruce Grindley, in 'Glycoscience', B. O. Fraser-Reid, K. Tatsuta, and J. Thiem, Eds.; Springer-Verlag, Berlin, 2001, vol. 1, p. 3.

- 2001OL2563 M. Yu, V. Lynch, and B. L. Pagenkopf, *Org. Lett.*, 2001, **3**, 2563.
- 2001PCA10123 F. Freeman, M. L. Kasner, and W. J. Hehre, *J. Phys. Chem. A*, 2001, **105**, 10123.
- 2001PCA8216 M. Mohr, R. A. Bryce, and I. H. Hillier, *J. Phys. Chem. A*, 2001, **105**, 8216.
- 2001PHA661 A. M. Khattab, M. H. Grace, and E. A. El-Khrisy, *Pharmazie*, 2001, **56**, 661.
- 2001RCB1430 V. Y. Sosnovskikh, I. I. Vorontsov, and V. A. Kutsenko, *Russ. Chem. Bull.*, 2001, **50**, 1430.
- 2001S1065 J. S. Yadav, B. V. S. Reddy, C. R. Madhuri, and G. Sabitha, *Synthesis*, 2001, 1065.
- 2001S1111 D. Schwebel, M. Soltan, and P. Margaretha, *Synthesis*, 2001, 1111.
- 2001SL240 J. S. Yadav, B. V. S. Reddy, R. Srinivas, C. Madhuri, and T. Ramalingam, *Synlett*, 2001, 240.
- 2001T6809 C. Cimarrelli, G. Palmieri, and E. Volpini, *Tetrahedron*, 2001, **57**, 6809.
- 2001T8685 R. Hong, J. Feng, R. Hoen, and G. Q. Lin, *Tetrahedron*, 2001, **57**, 8685.
- 2001TCC153 R. J. Ferrier, *Top. Curr. Chem.*, 2001, **215**, 153 (Glycoscience).
- 2001TL1931 M. Uchiyama, M. Oka, S. Harai, and A. Ohta, *Tetrahedron Lett.*, 2001, **42**, 1931.
- 2001TL4947 P. Magnus, M. J. Waring, C. Ollivier, and V. Lynch, *Tetrahedron Lett.*, 2001, **42**, 4947.
- 2001TL5117 V. Y. Sosnovskikh, B. I. Usachev, D. V. Sevenard, E. Lork, and G. V. Roschenthaler, *Tetrahedron Lett.*, 2001, **42**, 5117.
- 2001TL6381 J. S. Yadav, B. V. S. Reddy, C. Madhuri, G. Sabitha, B. Jagannadh, S. K. Kumar, and A. C. Kunwar, *Tetrahedron Lett.*, 2001, **42**, 6381.
- 2002ANS613 T. Shimo, M. Yasutake, T. Shinmyozu, and K. Somekawa, *Anal. Sci.*, 2002, **8**, 613.
- 2002CC168 P. Langer, N. R. Saleh Nehad, and I. Freifeld, *Chem. Commun.*, 2002, 168.
- 2002CHE741 S. L. Bogza, O. V. Rozhkov, N. M. Bogdan, K. I. Kobrakov, and V. I. Dulenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2002, **38**, 741.
- 2002CHE743 S. L. Bogza, A. A. Malienko, S. Y. Suikov, K. I. Suikov, K. I. Kobrakov, and V. I. Dulenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2002, **38**, 743.
- 2002CHE883 V. P. Khilya and V. V. Ishchenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2002, **38**, 883.
- 2002CHE1136 Golikov, P. V. Reshetov, and A. P. Kriven'ko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2002, **38**, 1136.
- 2002JA11584 A. K. Cheung and M. L. Snapper, *J. Am. Chem. Soc.*, 2002, **124**, 11584.
- 2002JA14836 H. Suga, K. Inoue, S. Inoue, and A. Kakehi, *J. Am. Chem. Soc.*, 2002, **124**, 14836.
- 2002JCM201 J. M. Khurana and S. Chauhan, *J. Chem. Res. (S)*, 2002, 201.
- 2002JCM428 S. K. Sabui, P. Mondal, and R. V. Venkateswaran, *J. Chem. Res. (S)*, 2002, 428.
- 2002JC3969 J. Zhang and C.-J. Li, *J. Org. Chem.*, 2002, **67**, 3969.
- 2002JPH19 N. A. Nemkovich, W. Baumann, and V. G. Pivovarenko, *J. Photochem. Photobiol. A*, 2002, **153**, 19.
- 2002JPH61 H. Wunscher, G. Hauke, and P. Czerney, *J. Photochem. Photobiol. A*, 2002, **152**, 61.
- 2002JPO689 D. Heyes, R. S. Menon, C. Ian, F. Watt, J. Wiseman, and P. Kubinski, *J. Phys. Org. Chem.*, 2002, **15**, 689.
- 2002MC1 V. A. Miluykov, O. G. Sinyashin, O. Scherer, and E. Hey-Hawkins, *Mendeleev Commun.*, 2002, **12**, 1.
- 2002OL3719 E. B. Holson and W. R. Roush, *Org. Lett.*, 2002, **4**, 3719.
- 2002S2341 V. Y. Sosnovskikh and B. I. Usachev, *Synthesis*, 2002, 2341.
- 2002SC709 X. He, Z. Li, and Q. You, *Synth. Commun.*, 2002, **32**, 709.
- 2002SC2227 M. Venkati and G. L. D. Krupadanam, *Synth. Commun.*, 2002, **32**, 2227.
- 2002T997 M. Shanmugasundaram, S. Manikandan, and R. Raghunathan, *Tetrahedron*, 2002, **58**, 997.
- 2002T6069 P. Crotti, V. Di Bussolo, L. Favero, F. Macchia, and M. Pineschi, *Tetrahedron*, 2002, **58**, 6069.
- 2002T7519 B. Caro, P. Le Poul, F. Robin-Le Guen, J.-Y. Saillard, S. Kahlal, C. Moinet, N. Le Poul, and J. Vaissermann, *Tetrahedron*, 2002, **58**, 7519.
- 2002T10301 M. Anniyappan, D. Muralidharan, and P. T. Perumal, *Tetrahedron*, 2002, **58**, 10301.
- 2002TL4395 J. Wu, L. Wang, R. Fathi, and Z. Yang, *Tetrahedron Lett.*, 2002, **43**, 4395.
- 2002TL4907 A. Voituriez, J.-C. Fiaud, and E. Schulz, *Tetrahedron Lett.*, 2002, **43**, 4907.
- 2002TL5161 H. Kawata, S. Ichikawa, T. Kumagai, and S. Niizuma, *Tetrahedron Lett.*, 2002, **43**, 5161.
- 2002TL7753 K. Ohmori, N. Ushimaru, and K. Suzuki, *Tetrahedron Lett.*, 2002, **43**, 7753.
- 2003AGE4955 N. Halland, T. Hansen, and K. A. Jorgensen, *Angew. Chem. Intl. Ed.*, 2003, **42**, 4955.
- 2003ARK132 K. Martinez, F. Cortes, I. Leal, V. Reyna, D. Quintana, S. Antúnez, and G. Cuevas, *Arkivoc*, 2003, xi, 132.
- 2003CHE386 A. V. Kibal'ny, A. A. Afonin, and V. I. Dulenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 386.
- 2003CL222 N. Ravindranath, C. Ramesh, M. R. Reddy, and B. Das, *Chem. Lett.*, 2003, 222.
- 2003H(60)1351 G. Cravotto, G. M. Nano, G. Palmisano, and S. Tagliapietra, *Heterocycles*, 2003, **60**, 1351.
- 2003JA14288 W.-S. Kim, H.-J. Kim, and C.-G. Cho, *J. Am. Chem. Soc.*, 2003, **125**, 14288.
- 2003JHC395 A. Levai, *J. Heterocycl. Chem.*, 2003, **40**, 395.
- 2003JNP1144 C. A. Gray, P. T. Kaye, and A. T. Nchinda, *J. Nat. Prod.*, 2003, **66**, 1144.
- 2003JOC3340 D. Giomi and M. Cecchi, *J. Org. Chem.*, 2003, **68**, 3340.
- 2003JOC7158 K. Afarinkia, M. J. Bearpark, and A. Ndibwami, *J. Org. Chem.*, 2003, **68**, 7158.
- 2003JOC7747 V. Y. Sosnovskikh, B. I. Usachev, D. V. Sevenard, and G.-V. Roeschenthaler, *J. Org. Chem.*, 2003, **68**, 7747.
- 2003JMT(639)87 K. Zborowski, R. Grybox, and L. M. Prionewicz, *J. Mol. Struct. Theochem*, 2003, **639**, 87.
- 2003ORS69 R. J. Ferrier and O. A. Zubkov, *Org. React. (New York)*, 2003, **62**, 569.
- 2003PHC(15)360 J. D. Hepworth and B. M. Heron, in 'Progress in Heterocyclic Chemistry', G. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2003, vol. 15, p. 360.
- 2003RCR489 V. Y. Sosnovskikh, *Russ. Chem. Rev.*, 2003, **72**, 489.
- 2003RJO663 V. A. Danilova and L. B. Krivdin, *Russ. J. Org. Chem.*, 2003, **39**, 663.
- 2003RJO1194 V. A. Danilova, N. V. Istomina, and L. B. Krivdin, *Russ. J. Org. Chem.*, 2004, **40**, 1194.
- 2003S1413 K. Inoue, H. Suga, S. Inoue, H. Sato, and A. Kakehi, *Synthesis*, 2003, 1413.
- 2003S2564 I. J. S. Fairlamb, F. J. Lu, and J. P. Schmidt, *Synthesis*, 2003, 2564.
- 2003SL1355 K. Pachamuthu and R. R. Schmidt, *Synlett*, 2003, 1355.
- 2003SL1491 M. C. Willis and S. E. Flower, *Synlett*, 2003, 1491.
- 2003T2625 V. Y. Sosnovskikh, B. I. Usachev, D. V. Sevenard, and G.-V. Roschenthaler, *Tetrahedron*, 2003, **59**, 2625.

- 2003T9563 M. Pal, V. Subramanian, K. Parasuraman, and K. R. Yeleswarapu, *Tetrahedron*, 2003, **59**, 9563.
- 2003TL4365 D. Basavaiah and A. J. Rao, *Tetrahedron Lett.*, 2003, **44**, 4365.
- 2003TL4439 S.-H. Min, S.-J. Pang, and C.-G. Cho, *Tetrahedron Lett.*, 2003, **44**, 4439.
- 2003TL4535 R. Aggarwal, A. A. Birkbeck, C. B. de Koning, R. G. F. Giles, I. R. Green, S.-H. Li, and F. J. Oosthuizen, *Tetrahedron Lett.*, 2003, **44**, 4535.
- 2003TL7921 P. Langer and B. Appel, *Tetrahedron Lett.*, 2003, **44**, 7921.
- 2004AXEo1515 L. B. Din, A. Abdullah, S. L. Tan, I. M. Said, and B. M. Yamin, *Acta Crystallogr., Sect. E*, 2004, **60**, o1515.
- 2004CHE214 L. Cao, L. Zhang, and J. J. Liu, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 214.
- 2004CHE1131 A. V. Kibalny, A. A. Afonin, and V. I. Dulenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1131.
- 2004CHE1300 S. L. Bogza, S. Y. Suikov, N. M. Bogdan, V. I. Dulenko, and K. I. Kobrakov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1300.
- 2004CHE1421 S. L. Bogza, S. Y. Suikov, N. M. Bogdan, Y. A. Nikolyukin, and V. I. Dulenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1421.
- 2004EJS523 L. Lerman, A. C. Klonkay, A. Filipovic, and I. Elenkov, *Eur. J. Mass Spectrom.*, 2004, **10**, 523.
- 2004JA1336 H. Kim, H. Men, and C. Lee, *J. Am. Chem. Soc.*, 2004, **126**, 1336.
- 2004JCM418 W. Zhang, Y. Guo, L. Yang, and Z.-L. Liu, *J. Chem. Res.*, 2004, 418.
- 2004JST(678)55 A. Kumar, S. K. Jain, and R. C. Rastogi, *J. Mol. Struct.*, 2004, **678**, 55.
- 2004SC985 L. Lei, D. Yang, Z. Liu, and L. Wu, *Synth. Commun.*, 2004, **34**, 985.
- 2004SC3409 P. T. Kaye and M. A. Musa, *Synth. Commun.*, 2004, **34**, 3409.
- 2004SC4089 M. Mahesh, C. V. Reddy, K. S. Reddy, P. Raju, and V. V. N. Reddy, *Synth. Commun.*, 2004, **34**, 4089.
- 2004SL1715 K. V. N. S. Srinivas and B. Das, *Synlett*, 2004, 1715.
- 2004SL2717 V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, and T. Patonay, *Synlett*, 2004, 2717.
- 2004SAA187 R. Ghazy, S. A. Azim, M. Shaheen, and F. El-Mekawey, *Spectrochim. Acta, Part A*, 2004, **60**, 187.
- 2004T10899 Z. Yan and J. F. Sebastian, *Tetrahedron*, 2004, **60**, 10899.
- 2004TL3507 A. Kamal, B. R. Prasad, A. V. Ramana, A. H. Babu, and K. S. Reddy, *Tetrahedron Lett.*, 2004, **45**, 3507.
- 2004TL6151 C. D. Gabbutt, B. M. Heron, D. A. Thomas, M. E. Light, and M. B. Hursthouse, *Tetrahedron Lett.*, 2004, **45**, 6151.
- 2004TL7351 V. Y. Sosnovskikh, B. I. Usachev, A. Y. Sizov, and M. I. Kodess, *Tetrahedron Lett.*, 2004, **45**, 7351.
- 2005CAR1287 R. Sagar, P. Singh, R. Kumar, P. R. Maulik, and A. K. Shaw, *Carbohydr. Res.*, 2005, **340**, 1287.
- 2005CHE515 V. S. Tolkunov, Y. B. Vysotsky, O. A. Gorban, S. V. Shishkina, O. V. Shishkin, and V. I. Dulenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2005, **41**, 515.
- 2005CPH(313)279 A. Navarro, J. J. L. González, A. G. Fernández, I. Laczik, and G. Pongor, *Chem. Phys.*, 2005, **313**, 279.
- 2005CPL(410)182 J. N. Woodford, *Chem. Phys. Lett.*, 2005, **410**, 182.
- 2005CPL(415)20 J. Preat, D. Jacquemin, and E. A. Perpète, *Chem. Phys. Lett.*, 2005, **415**, 20.
- 2005CME2481 A. M. S. Silva and D. C. G. A. Pinto, *Curr. Med. Chem.*, 2005, **12**, 2481.
- 2005COR1287 C. Cismas, A. Terec, S. Mager, and I. Grosu, *Curr. Org. Chem.*, 2005, **9**, 1287.
- 2005JA5322 S. Chamberland, J. W. Ziller, and K. A. Woerpel, *J. Am. Chem. Soc.*, 2005, **127**, 5322.
- 2005JA13796 J. S. Potuzak, S. B. Moilanen, and D. S. Tan, *J. Am. Chem. Soc.*, 2005, **127**, 13796.
- 2005JOC47 H. Suga, K. Inoue, S. Inoue, A. Kakehi, and M. Shiro, *J. Org. Chem.*, 2005, **70**, 47.
- 2005JOC1122 K. Afarinkia, M. J. Bearpark, and A. Ndibwami, *J. Org. Chem.*, 2005, **70**, 1122.
- 2005OL641 M. F. Jacobsen, J. E. Moses, R. M. Adlington, and J. E. Baldwin, *Org. Lett.*, 2005, **7**, 641.
- 2005JOP250 K. Zborowski, R. Grybos, and L. M. Proniewicz, *J. Phys. Org. Chem.*, 2005, **18**, 250.
- 2005OL1501 K. Tanaka and T. Fujiwara, *Org. Lett.*, 2005, **7**, 1501.
- 2005OL2285 G. Chen, N. Tokunaga, and T. Hayashi, *Org. Lett.*, 2005, **7**, 2285.
- 2005OL3705 S. J. Eade, R. M. Adlington, A. R. Cowley, M. W. Walter, and J. E. Baldwin, *Org. Lett.*, 2005, **7**, 3705.
- 2005OL3745 K. Watanabe, K. Iwasaki, T. Abe, M. Inoue, K. Ohkubo, T. Suzuki, and T. Katoh, *Org. Lett.*, 2005, **7**, 3745.
- 2005OL5159 M. Soltan, M. Goewert, and P. Margaretha, *Org. Lett.*, 2005, **7**, 5159.
- 2005OL5167 A. J. Catino, J. M. Nichols, H. Choi, S. Gottipamula, and M. P. Doyle, *Org. Lett.*, 2005, **7**, 5167.
- 2005PCA8684 A. Migani, P. L. Gentili, F. Negri, M. Olivucci, A. Romani, G. Favaro, and R. S. Becker, *J. Phys. Chem. A*, 2005, **109**, 8692.
- 2005RCB2157 K. V. Shcherbakov, Y. V. Burgart, and V. I. Saloutin, *Russ. Chem. Bull.*, 2005, **54**, 2157.
- 2005RJO527 V. V. Shchepin, P. S. Silaichev, R. V. Shchepin, M. A. Ezhikova, and M. I. Kodess, *Russ. J. Org. Chem.*, 2005, **41**, 527.
- 2005RPC119 G. Louit, S. Foley, J. Cabillic, H. Coffigny, F. Taran, A. Valleix, J. P. Renault, and S. Pin, *Radiat. Phys. Chem.*, 2004, **72**, 119.
- 2005T8177 R. Carrillo, V. S. Martin, M. Lopez, and T. Martin, *Tetrahedron*, 2005, **61**, 8177.
- 2005T11910 J. C. Conway, P. Quayle, A. C. Regan, and C. J. Urch, *Tetrahedron*, 2005, **61**, 11910.
- 2005TL4057 S. Rotzoll, B. Appel, and P. Langer, *Tetrahedron Lett.*, 2005, **46**, 4057.
- 2005VSP233 K. Zborowski, R. Grybos, and L. M. Proniewicz, *Vibrational Spectros.*, 2005, **35**, 233.
- 2006AGE7199 H. M. Sheldrake, C. Jamieson, and J. W. Burton, *Angew. Chem. Int. Ed.*, 2006, **45**, 7199.
- 2006AHG(91)1 P. Stanovnik, M. Tisler, A. R. Katritzky, and O. V. Denisko, *Adv. Heterocycl. Chem.*, 2006, **91**, 1.
- 2006ANA201 W. F. Smyth, V. N. Ramachandran, C. J. Hack, C. Joyce, and E. O'Kane, *Anal. Chim. Acta.*, 2006, **564**, 201.
- 2006CEJ2221 B. Appel, N. N. R. Saleh, and P. Langer, *Chem. Eur. J.*, 2006, **12**, 1221.
- 2006CL128 A. Takechi, H. Takikawa, H. Miyake, and M. Sasaki, *Chem. Lett.*, 2006, 128.
- 2006CL1082 H. Kusama and N. Iwasawa, *Chem. Lett.*, 2006, 1082.
- 2006EJO3638 B. Appel, S. Rotzoll, R. Kranich, H. Reinke, and P. Langer, *Eur. J. Org. Chem.*, 2006, 3638.
- 2006H(69)123 F. Pozgan, M. Krejan, S. Polanc, and M. Kocevar, *Heterocycles*, 2006, **69**, 123.
- 2006JA1792 S. B. Moilanen, J. S. Potuzak, and D. S. Tan, *J. Am. Chem. Soc.*, 2006, **128**, 1792.
- 2006JA3908 P. S. Baran and N. Z. Burns, *J. Am. Chem. Soc.*, 2006, **128**, 3908.
- 2006JA7742 J. Hao, F. Matsuura, Y. Kishi, M. Kita, D. Uemura, N. Asai, and T. Iwashita, *J. Am. Chem. Soc.*, 2006, **128**, 7742.
- 2006JA11044 M. Rawat, V. Prutyantov, and W. D. Wulff, *J. Am. Chem. Soc.*, 2006, **128**, 11044.
- 2006JA13070 T. Akiyama, H. Morita, and K. Fuchibe, *J. Am. Chem. Soc.*, 2006, **128**, 13070.
- 2006JOC70 R. Girotti, A. Marrocchi, L. Minuti, O. Piermatti, F. Pizzo, and L. Vaccaro, *J. Org. Chem.*, 2006, **71**, 70.

- 2006JOC804 A. Goel, D. Verma, M. Dixit, R. Raghunandan, and P. R. Maulik, *J. Org. Chem.*, 2006, **71**, 804.
- 2006JOC4538 V. Y. Sosnovskikh, V. Y. Korotaev, D. L. Chizhov, I. B. Kutyshev, D. S. Yachevskii, O. N. Kazheva, O. A. Dyachenko, and V. N. Charushin, *J. Org. Chem.*, 2006, **71**, 4538.
- 2006JMT(760)59 R. L. T. Parreira and S. E. Galembeck, *J. Mol. Struct. Theochem*, 2006, **760**, 59.
- B-2006MI37 T. Fossen and O. M. Andersen; in 'Flavonoids', O. M. Andersen and K. R. Markham, Eds.; CRC Press LLC, Boca Raton, 2006, p. 37.
- B-2006MI125 V. Exarchou and I. P. Gerothanassis; in 'Natural Antioxidant Phenols', D. Boskou, I. P. Gerothanassis, and P. Kafelas, Eds.; Research Signpost, Thiruvananthapuram, India, 2006, p. 125.
- 2006MOL959 D. Díez, M. G. Nuñez, R. F. Moro, N. M. Garrido, I. S. Marcos, P. Basabe, and J. G. Urones, *Molecules*, 2006, **11**, 959.
- 2006PCA11338 N. Manoj, G. Ajayakumar, K. R. Gopidas, and C. H. Suresh, *J. Phys. Chem. A.*, 2006, **110**, 11338.
- 2006RJO969 V. V. Plemenkov, R. V. Ashirov, O. A. Lodochnikova, I. A. Litvinov, and R. N. Zagidullin, *Russ. J. Org. Chem.*, 2006, **42**, 969.
- 2006STC323 E. Taskinen, T. Alanko, and J. F. Liebman, *Struct. Chem.*, 2006, **17**, 323.
- 2006T7674 V. T. H. Nguyen, B. Appel, and P. Langer, *Tetrahedron*, 2006, **62**, 7674.
- 2006T9218 H. Suga, T. Suzuki, K. Inoue, and A. Kakehi, *Tetrahedron*, 2006, **62**, 9218.
- 2006T9694 E. Ullah, B. Appel, C. Fischer, and P. Langer, *Tetrahedron*, 2006, **62**, 9694.
- 2006T10829 R. W. Clawson, R. E. Deavers, N. G. Akhmedov, and B. C. G. Soederberg, *Tetrahedron*, 2006, **62**, 10829.
- 2006T11200 X. Xing, J. Wu, and W.-M. Dai, *Tetrahedron*, 2006, **62**, 11200.
- 2006TL1525 J. Wu, L. Zhang, and H.-G. Xia, *Tetrahedron Lett.*, 2006, **47**, 1525.
- 2006TL1617 A. Armstrong and H. Chung, *Tetrahedron Lett.*, 2006, **47**, 1617.
- 2006TL3251 T. Abe, K. Iwasaki, M. Inoue, T. Suzuki, K. Watanabe, and T. Katoh, *Tetrahedron Lett.*, 2006, **47**, 3251.
- 2006TL9291 V. Gaddam, D. K. Sreenivas, and R. Nagarajan, *Tetrahedron Lett.*, 2006, **47**, 9291.
- 2007JOC1780 A. Fadel and N. Lahrache, *J. Org. Chem.*, 2007, **72**, 1780.

Biographical Sketch



Andrew Phillips obtained his B.Sc. (Hons, 1st class) and Ph.D. degrees from the University of Canterbury in Christchurch, New Zealand. After a postdoctoral appointment with Professor Peter Wipf at the University of Pittsburgh, he joined the faculty at the University of Colorado in 2001, where he is currently an Associate Professor of Chemistry. His research interests are broadly defined by the development of new methods and strategies for the synthesis of complex natural products.



James A. Henderson received his B.Sc. in Biochemistry from Tennessee Technological University. After completing a M.S. degree in Chemistry at the same institution with Professor Jeffrey O. Boles, he moved to the University of Colorado at Boulder where he received his Ph.D. degree under the direction of Professor Andrew Phillips. In 2008, he moved to Harvard University where he is currently a postdoctoral researcher in the lab of Professor Yoshito Kishi. His research interests include the development of new methods for the synthesis of biologically active natural products.



Katrina L. Jackson obtained her B.S. degree in biochemistry from Boston College in 2002, where she performed undergraduate research with Professor Shana O. Kelley. In 2007, she obtained her Ph.D. from the University of Colorado-Boulder under the direction of Professor Andrew J. Phillips. Currently, she is a postdoctoral researcher at Harvard University with Professor Yoshito Kishi. Her research interests are focused on the total synthesis of biologically active natural products.

7.08

Pyrans and their Benzo Derivatives: Synthesis

M. A. Brimble, J. S. Gibson, and J. Sperry

The University of Auckland, Auckland, New Zealand

© 2008 Elsevier Ltd. All rights reserved.

7.08.1 Introduction	425
7.08.2 Pyrans and Fused Pyrans: 2H-Pyrans	425
7.08.2.1 Formation of One Bond	425
7.08.2.1.1 Adjacent to the heteroatom	425
7.08.2.2 Formation of More than One Bond	429
7.08.2.3 From a Preformed Heterocyclic Ring	429
7.08.2.3.1 From dihydropyrans	429
7.08.2.3.2 From pyranones	429
7.08.3 2H-Chromenes (2H-1-Benzopyrans)	431
7.08.3.1 Formation of One Bond	431
7.08.3.1.1 Adjacent to the heteroatom	431
7.08.3.1.2 γ to the heteroatom	434
7.08.3.1.3 δ to the heteroatom	435
7.08.3.2 Formation of More than One Bond	439
7.08.3.3 From Other Heterocycles	444
7.08.3.3.1 From benzofurans	444
7.08.3.4 From a Preformed Heterocyclic Ring	444
7.08.3.4.1 From chromones	444
7.08.3.4.2 From chromanols	445
7.08.3.4.3 From chroman-4-ones	445
7.08.4 4H-Pyrans and Fused 4H-Pyrans	446
7.08.4.1 Formation of One Bond	446
7.08.4.1.1 Adjacent to the heteroatom	446
7.08.4.2 Formation of More than One Bond	447
7.08.4.3 From a Preformed Heterocyclic Ring	452
7.08.4.3.1 From pyrylium salts	452
7.08.4.3.2 From pyranones	452
7.08.5 4H-Chromenes (4H-1-Benzopyrans)	452
7.08.5.1 Formation of One Bond	452
7.08.5.1.1 Adjacent to the heteroatom	452
7.08.5.1.2 β to the heteroatom	452
7.08.5.2 Formation of More than One Bond	453
7.08.5.3 From a Preformed Heterocyclic Ring	458
7.08.5.3.1 From pyrylium salts	458
7.08.5.3.2 From chromans	458
7.08.5.3.3 From chromones	458
7.08.5.3.4 From chroman-2-ones	458
7.08.6 1H-Isochromenes (1H-2-Benzopyrans)	459
7.08.6.1 Formation of One Bond	459
7.08.6.1.1 Adjacent to the heteroatom	459
7.08.6.1.2 β to the heteroatom	462

7.08.6.1.3 γ to the heteroatom	464
7.08.6.2 Formation of More than One Bond	465
7.08.6.3 From Other Heterocycles	466
7.08.6.3.1 From furans	466
7.08.6.4 From a Preformed Heterocyclic Ring	466
7.08.6.4.1 From isochromans	466
7.08.6.4.2 From isochromanones	466
7.08.7 Xanthenes (9H-Dibenzo[b,e]pyrans)	467
7.08.7.1 Formation of One Bond	467
7.08.7.1.1 Adjacent to the heteroatom	467
7.08.7.1.2 γ to the heteroatom	467
7.08.7.2 Formation of More than One Bond	468
7.08.7.3 From Other Heterocycles	470
7.08.7.3.1 From dihydrodibenzo[b,f]oxepines	470
7.08.7.4 From a Preformed Heterocyclic Ring	470
7.08.7.4.1 From xanthenes	470
7.08.8 Reduced Pyrans	470
7.08.9 Dihydropyrans	470
7.08.9.1 3,4-Dihydro-2H-pyrans	470
7.08.9.1.1 Formation of one bond	470
7.08.9.1.2 Formation of more than one bond	473
7.08.9.1.3 From a preformed heterocyclic ring	478
7.08.9.2 3,6-Dihydropyrans	479
7.08.9.2.1 Formation of one bond	479
7.08.9.2.2 Formation of more than one bond	483
7.08.9.2.3 From other heterocycles	489
7.08.9.2.4 From a preformed heterocyclic ring	489
7.08.10 Tetrahydropyrans	490
7.08.10.1 Formation of One Bond	490
7.08.10.1.1 Adjacent to the heteroatom	490
7.08.10.1.2 β to the heteroatom	494
7.08.10.1.3 γ to the heteroatom	498
7.08.10.2 Formation of More than One Bond	500
7.08.10.3 From Other Heterocycles	504
7.08.10.3.1 From 1,3-dioxanes	504
7.08.10.3.2 From dioxepanes	505
7.08.10.3.3 From tetrahydrofurans	505
7.08.10.4 From a Preformed Heterocyclic Ring	506
7.08.10.4.1 From tetrahydropyranones	506
7.08.10.4.2 From dihydropyrans	506
7.08.11 Chromans (3,4-Dihydro-2H-1-benzopyrans)	507
7.08.11.1 Formation of One Bond	507
7.08.11.1.1 Adjacent to the heteroatom	507
7.08.11.1.2 β to the heteroatom	511
7.08.11.1.3 γ to the heteroatom	513
7.08.11.1.4 δ to the heteroatom	515
7.08.11.2 Formation of More than One Bond	519
7.08.11.3 From Other Heterocycles	524
7.08.11.3.1 From tetrahydrofurans	524

7.08.11.3.2	From benzo-1,3-dioxans	524
7.08.11.3.3	From oxapalladacycles	524
7.08.11.4	From a Preformed Heterocyclic Ring	525
7.08.11.4.1	From dihydropyrans	525
7.08.11.4.2	From tetrahydropyrans	527
7.08.11.4.3	From chromenes	527
7.08.11.4.4	From chromanones	528
7.08.11.4.5	From chromones	528
7.08.11.4.6	From coumarins	529
7.08.12	Isochromans (3,4-Dihydro-1<i>H</i>-2-benzopyrans)	529
7.08.12.1	Formation of One Bond	530
7.08.12.1.1	Adjacent to the heteroatom	530
7.08.12.1.2	β to the heteroatom	532
7.08.12.1.3	γ to the heteroatom	532
7.08.12.2	Formation of More than One Bond	538
7.08.12.3	From Other Heterocycles	542
7.08.12.3.1	From isobenzofurans (phthalanes)	542
7.08.12.3.2	From naphthofurans	543
7.08.12.4	From a Preformed Heterocyclic Ring	543
7.08.12.4.1	From dihydropyrans	543
7.08.12.4.2	From isochromenes	543
7.08.13	Pyrones and Fused Pyrones: 2<i>H</i>-Pyran-2-Ones (2 Pyrones)	544
7.08.13.1	Formation of One Bond	544
7.08.13.1.1	Adjacent to the heteroatom	544
7.08.13.2	Formation of More than One Bond	545
7.08.13.3	From Other Heterocycles	555
7.08.13.3.1	From furans	555
7.08.13.4	From a Preformed Heterocyclic Ring	556
7.08.13.4.1	From pyran-4-ones	556
7.08.13.4.2	From tetrahydropyranones	556
7.08.14	Coumarins (2<i>H</i>-Benzopyran-2-ones)	557
7.08.14.1	Formation of One Bond	557
7.08.14.1.1	Adjacent to the heteroatom	557
7.08.14.1.2	γ to the heteroatom	558
7.08.14.1.3	δ to the heteroatom	560
7.08.14.2	Formation of More than One Bond	560
7.08.14.3	From Other Heterocycles	569
7.08.14.3.1	From furans	569
7.08.14.4	From a Preformed Heterocyclic Ring	569
7.08.14.4.1	From chromones	569
7.08.14.4.2	From chroman-2,4-diones	569
7.08.14.4.3	From chroman-4-ones	571
7.08.15	Pyran-4-ones and Fused Pyran-4-ones (4-Pyrones)	572
7.08.15.1	Formation of One Bond	572
7.08.15.1.1	Adjacent to the heteroatom	572
7.08.15.2	Formation of More than One Bond	572
7.08.15.3	From Other Heterocycles	575
7.08.15.3.1	From furans	575
7.08.15.3.2	From isoxazoles	575

7.08.15.4 From a Preformed Heterocyclic Ring	575
7.08.15.4.1 From pyran-2-ones	575
7.08.16 Chromones (4<i>H</i>-1-Benzopyran-4-ones)	576
7.08.16.1 Formation of One Bond	576
7.08.16.1.1 Adjacent to the heteroatom	576
7.08.16.1.2 γ to the heteroatom	579
7.08.16.1.3 δ to the heteroatom	579
7.08.16.2 Formation of More than One Bond	580
7.08.16.3 From Other Heterocycles	586
7.08.16.3.1 From benzofurans	586
7.08.16.4 From a Preformed Heterocyclic Ring	586
7.08.16.4.1 From chromanones	586
7.08.16.4.2 From coumarins	588
7.08.16.4.3 From 3-diazochroman-2,4-diones	588
7.08.16.4.4 From chromenes	589
7.08.17 Isocoumarins (1<i>H</i>-2-Benzopyran-1-ones)	589
7.08.17.1 Formation of One Bond	589
7.08.17.1.1 Adjacent to the heteroatom	589
7.08.17.1.2 γ to the heteroatom	592
7.08.17.2 Formation of More than One Bond	592
7.08.17.3 From Other Heterocycles	598
7.08.17.3.1 From phthalides	598
7.08.17.3.2 From indenone epoxides	598
7.08.17.4 From a Preformed Heterocyclic Ring	599
7.08.17.4.1 From pyran-2-ones	599
7.08.18 3<i>H</i>-2-Benzopyran-3-ones	599
7.08.18.1 Formation of One Bond	599
7.08.18.1.1 Adjacent to the heteroatom	599
7.08.19 Xanthenes (9<i>H</i>-Dibenzo [<i>b,e</i>]pyran-9-ones)	600
7.08.19.1 Formation of One Bond	600
7.08.19.1.1 Adjacent to the heteroatom	600
7.08.19.1.2 γ to the heteroatom	600
7.08.19.2 Formation of More than One Bond	601
7.08.19.3 From a Preformed Heterocyclic Ring	603
7.08.19.3.1 From xanthenes	603
7.08.19.3.2 From chromones	603
7.08.20 Reduced Pyranones	606
7.08.21 Dihydropyran-2-ones	606
7.08.21.1 3,4-Dihydropyran-2-ones	607
7.08.21.1.1 Formation of one bond	607
7.08.21.1.2 Formation of more than one bond	607
7.08.21.2 3,6-Dihydropyran-2-ones	610
7.08.21.2.1 Formation of one bond	610
7.08.21.2.2 Formation of More than One Bond	612
7.08.21.3 5,6-Dihydropyran-2-ones	613
7.08.21.3.1 Formation of one bond	613
7.08.21.3.2 Formation of more than one bond	617
7.08.21.3.3 From other heterocycles	620

7.08.21.3.4 From a Preformed Heterocyclic Ring	622
7.08.22 Dihydropyran-3-ones	623
7.08.22.1 2,4-Dihydropyran-3-ones	623
7.08.22.1.1 Formation of one bond	623
7.08.22.1.2 From other heterocycles	624
7.08.22.2 2,6-Dihydropyran-3-ones	624
7.08.22.2.1 Formation of more than one bond	624
7.08.22.2.2 From other heterocycles	624
7.08.23 Dihydropyran-4-ones	625
7.08.23.1 Formation of One Bond	625
7.08.23.1.1 Adjacent to the heteroatom	625
7.08.23.2 Formation of More than One Bond	626
7.08.23.3 From Other Heterocycles	628
7.08.23.3.1 From isoxazoles	628
7.08.23.3.2 From oxetanones	629
7.08.23.4 From a Preformed Heterocyclic Ring	629
7.08.23.4.1 From dihydropyrans	629
7.08.23.4.2 From dihydropyran-2-ones	629
7.08.24 Tetrahydropyranones	630
7.08.24.1 Tetrahydropyran-2-ones	630
7.08.24.1.1 Formation of One Bond	630
7.08.24.1.2 Formation of more than one bond	633
7.08.24.1.3 From other heterocycles	636
7.08.24.1.4 From a preformed heterocyclic ring	637
7.08.24.2 Tetrahydropyran-3-ones	638
7.08.24.2.1 Formation of one bond	638
7.08.24.2.2 From other heterocycles	639
7.08.24.2.3 From a preformed heterocyclic ring	640
7.08.24.3 Tetrahydropyran-4-ones	640
7.08.24.3.1 Formation of one bond	640
7.08.24.3.2 Formation of more than one bond	640
7.08.24.3.3 From other heterocycles	642
7.08.24.3.4 From a preformed heterocyclic ring	644
7.08.25 Dihydrocoumarins (Chroman-2-ones; 3,4-Dihydrobenzopyran-2-ones)	645
7.08.25.1 Formation of One Bond	645
7.08.25.1.1 Adjacent to the heteroatom	645
7.08.25.1.2 γ to the heteroatom	646
7.08.25.1.3 δ to the heteroatom	646
7.08.25.2 Formation of More than One Bond	646
7.08.25.3 From Other Heterocycles	648
7.08.25.3.1 From dihydrobenzo[1,3]oxazin-2-ones	648
7.08.25.4 From a Preformed Heterocyclic Ring	648
7.08.25.4.1 From coumarins	648
7.08.25.4.2 From chromans	649
7.08.25.4.3 From 4H-chromenes	649
7.08.26 Chroman-3-ones (2,4-Dihydrobenzopyran-3-ones)	649
7.08.26.1 Formation of One Bond	649
7.08.26.1.1 γ to the heteroatom	649
7.08.26.2 From a Preformed Heterocyclic Ring	649

7.08.26.2.1	From chromans	649
7.08.26.2.2	From 2H-chromenes	650
7.08.27	Chroman-4-ones (2,3-Dihydrobenzopyran-4-ones)	651
7.08.27.1	Formation of One Bond	651
7.08.27.1.1	Adjacent to the heteroatom	651
7.08.27.1.2	γ to the heteroatom	652
7.08.27.1.3	δ to the heteroatom	653
7.08.27.2	Formation of More than One Bond	654
7.08.27.3	From a Preformed Heterocyclic Ring	656
7.08.27.3.1	From chromanes	656
7.08.27.3.2	From chromones	656
7.08.27.3.3	From 2H-chromenes	656
7.08.27.3.4	From 4H-chromenes	656
7.08.28	Dihydroisocoumarins (Isochroman-1-ones)	657
7.08.28.1	Formation of One Bond	657
7.08.28.1.1	Adjacent to the heteroatom	657
7.08.28.2	Formation of More than One Bond	659
7.08.28.3	From Other Heterocycles	663
7.08.28.3.1	From isobenzofuranones	663
7.08.28.4	From a Preformed Heterocyclic Ring	664
7.08.28.4.1	From isochromans	664
7.08.28.4.2	From isochroman-1,3-diones (homophthalic anhydrides)	664
7.08.28.4.3	From dihydropyran-2-ones	664
7.08.29	Isochroman-3-ones	665
7.08.29.1	Formation of One Bond	665
7.08.29.1.1	Adjacent to the heteroatom	665
7.08.29.1.2	β to the heteroatom	665
7.08.29.1.3	γ to the heteroatom	666
7.08.29.2	Formation of More than One Bond	666
7.08.29.3	From Other Heterocycles	667
7.08.29.3.1	From dihydroisobenzofurans (phthalans)	667
7.08.29.3.2	From vinylnorcaradienes	668
7.08.29.3.3	From palladacycles	668
7.08.30	Isochroman-4-ones	669
7.08.30.1	Formation of One Bond	669
7.08.30.1.1	Adjacent to the heteroatom	669
7.08.30.2	Formation of More than One Bond	671
7.08.30.3	From Other Heterocycles	671
7.08.30.3.1	From dihydroisobenzofurans (phthalans)	671
7.08.30.4	From a Preformed Heterocyclic Ring	672
7.08.30.4.1	From isochromans	672
7.08.30.4.2	From dihydropyranones	672
7.08.30.4.3	From 3,3a,5,9b-tetrahydrofuro[3,2-c]isochromenes	672
7.08.31	Pyrylium Salts and Their Benzo Derivatives	673
7.08.31.1	Formation of One Bond	673
7.08.31.1.1	Adjacent to the heteroatom	673
7.08.31.2	Formation of More than One Bond	673
References		675

7.08.1 Introduction

The abundance of six-membered oxygen containing heterocycles in bioactive natural products continues to encourage the development of new and improved syntheses. There is a vast amount of new literature dedicated to the synthesis of pyrans and their benzo derivatives; however, many traditional approaches are still of great value and this chapter should be read in conjunction with the corresponding chapters in the first and second editions of *Comprehensive Heterocyclic Chemistry* <1984CHEC, 1996CHEC-II>.

The syntheses of six-membered oxygen heterocycles and their benzo derivatives is subject to annual review <1996PHC(8)277, 1997PHC(9)289, 1998PHC(10)292, 1999PHC(11)299, 2000PHC(12)317, 2001PHC(13)317, 2002PHC(14)332, 2003PHC(15)360, 2004PHC(16)405, 2005PHC(17)362>. Synthetic advances for the synthesis of saturated oxygen heterocycles are also regularly collated <1996CTC229, 1997CTC238, 1998J(P1)4175, 1999J(P1)1377, 2000J(P1)1291, 2001J(P1)2303, 2002J(P1)2301>.

The largest known nonpolymeric natural product, maitotoxin, which consists of four polyether ladders, each ladder being comprised of fused-tetrahydropyran ring systems, has been isolated from *Gambierdiscus toxicus* <2006AGE4406>. Numerous total syntheses of complex pyran containing natural products are available in the literature; specific examples include syntheses of the spiroketal macrolide spongistatin 1 <2001AGE4055>, (+)- and (-)-ratjadone <2000AGE4364, 2001JOC1885, 2001OL1383, 2004JA12216>, (-)-lailimalide <2000JA11027, 2001AGE3842, 2001JOC8973, 2001OL3149, 2002TL3381, 2002JA4956>, phorbaxazole A <2003AGE1255, 2003AGE1258, 2003AGE2711, 2003OBC4173>, (+)- and (-)-clavosolide A <2006OL661, 2006OL3315, 2006OL3319> and everninomicin 13,384-1 <1999AGE3334, 1999AGE3340, 1999AGE3345>.

The total synthesis of pyran and pyranone natural products has been reviewed <2004MOL498>. Reviews concerning the total synthesis of biologically active compounds <2004NJC771>, bioactive macrolides <2002AGE4632, 2005CRV4237>, new antimalarial drugs <2003AGE5274>, HIV-1 active *Calophyllum* coumarins <2000H(53)453>, leptomycins <2002S981>, pyranonaphthoquinone antibiotics <2000T1937>, anthocyanins and flavanoids <2001NPR310> and the cyclopenta[*c*]pyran skeleton of iridoid lactones <1997T14507> are also available. Accounts of syntheses of polycyclic ethers <1997CEJ849, 2002CEJ4346, 2004BCJ2129, 2004SL1851, 2005ACR423, 2005CRV4314, 2005CRV4379, 2006CC3571>, oxacyclic macrodiolide natural products <2005CRV4348> and natural products that feature a bis-spiroacetal moiety <2003COR1461> may also be of interest to readers.

7.08.2 Pyrans and Fused Pyrans: 2*H*-Pyrans

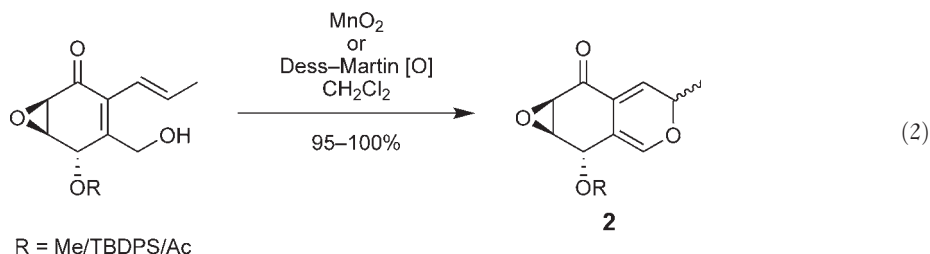
The 2*H*-pyran system can undergo relatively facile electrocyclic ring opening to form *cis*-2,4-dienones **1**, and as a consequence, simple 2*H*-pyrans are commonly present as a mixture of their cyclic and acyclic isomers (Equation 1) <1984CHEC, 1996CHEC-II>.



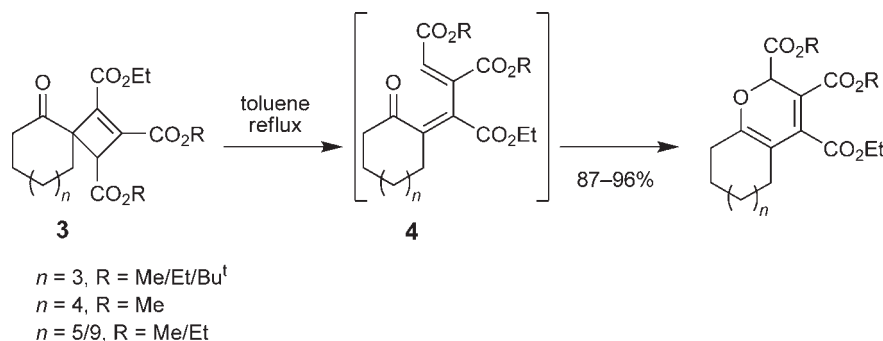
7.08.2.1 Formation of One Bond

7.08.2.1.1 Adjacent to the heteroatom

Numerous syntheses of 2*H*-pyrans feature the preparation of an acyclic dienone precursor that readily undergoes electrocyclic ring closure. In this manner, 2*H*-pyrans can be prepared directly from *cis*-2,4-dienols using a variety of oxidizing reagents. The epoxyquinoid-fused 2*H*-pyrans **2** are formed in high yield upon oxidation of their corresponding *cis*-2,4-dienols (Equation 2) <2003TL7205, 2004JA1310>.

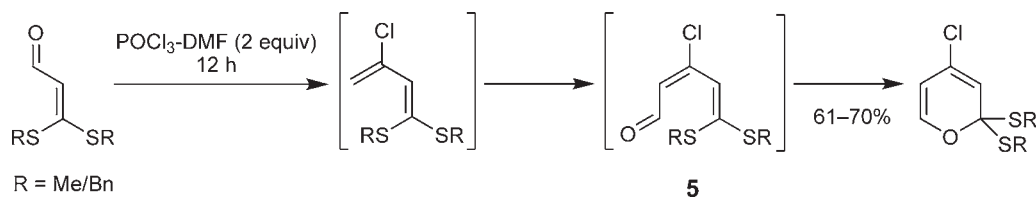


Spirocyclobutene systems **3** undergo electrocyclic ring opening in toluene under reflux to form *cis*-2,4-dienones **4**, which spontaneously recyclize to afford highly functionalized 2*H*-pyrans (**Scheme 1**) <2003T2001>.



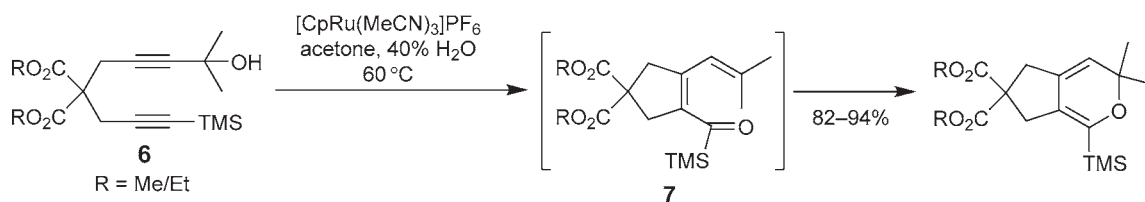
Scheme 1

α -Oxo ketenedithioacetals react with two equivalents of the Vilsmeier reagent to afford 4-chloro-2-dithioacetal-2*H*-pyrans via formation and electrocyclic ring closure of the intermediate dienal **5** (**Scheme 2**) <2004OBC28>.



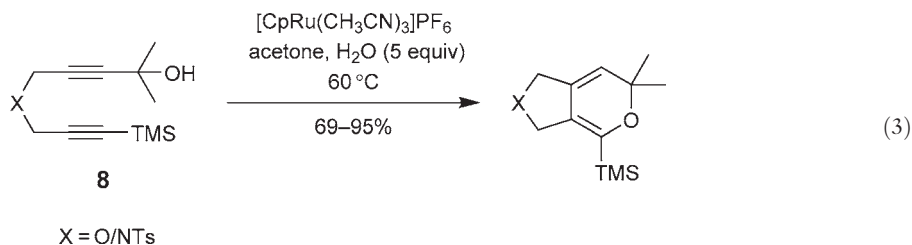
Scheme 2

Diyne **6**, which consist of a trimethylsilyl alkyne tethered to a tertiary propargyl alcohol, undergo ruthenium catalyzed cycloisomerization in aqueous acetone to form the dienone intermediate **7**. Concomitant electrocyclization affords 2-trimethylsilyl-2*H*-pyrans in high yield (**Scheme 3**) <2004OL4235>.

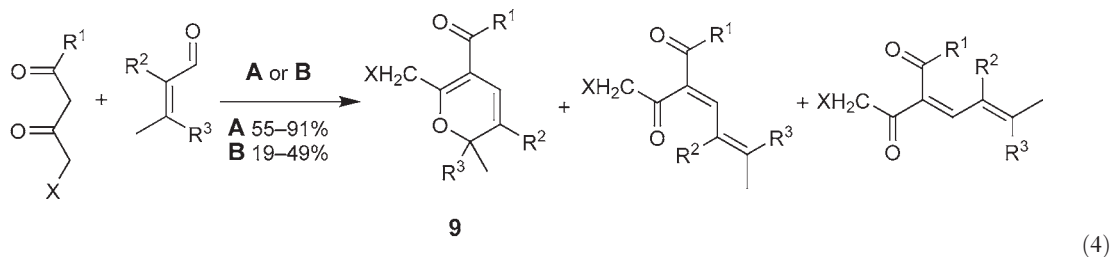


Scheme 3

Diyne **8** that contain a heteroatom in the tether can undergo ruthenium catalyzed cycloisomerization, in the presence of only five equivalents of water, to afford 2-silyl 2*H*-pyrans (**Equation 3**) <2004OL4235>.



Knoevenagel methodology can be used to synthesize *2H*-pyrans from 1,3-dicarbonyl compounds and α,β -unsaturated aldehydes. The choice of base, catalyst, and solvent are important to avoid unwanted side reactions. A mixture of alkyl-*2H*-pyran 5-carboxylates **9** and their corresponding dienones are formed in good yield, using sodium benzoate in the presence of triethylbenzylammonium chloride (TEBAC) under reflux in benzene (Equation 4) <1997S685>. Catalytic amounts of hydroquinone can be added to prevent the formation of undesired polymerization products. 6-Halomethyl-*2H*-pyran-5-carboxylates are similarly prepared from 4-halo-3-oxobutanoates using lithium carbonate in methanol (Equation 4). 6-Halomethyl-*2H*-pyran-5-carboxylates are accessed in lower overall yield than their non-halogenated counterparts, however, 6-halomethyl substitution of the product favours the *2H*-pyran conformer over the acyclic dienone <1997S685>.



A PhCO₂Na, TEBAC, benzene, reflux, hydroquinone (cat.)

X = H, R¹ = OMe/SEt/SBu^t, R² = H, R³ = Me

X = H, R¹ = OMe, R² = R³ = H

B Li₂CO₃, 18-C-6, MeOH

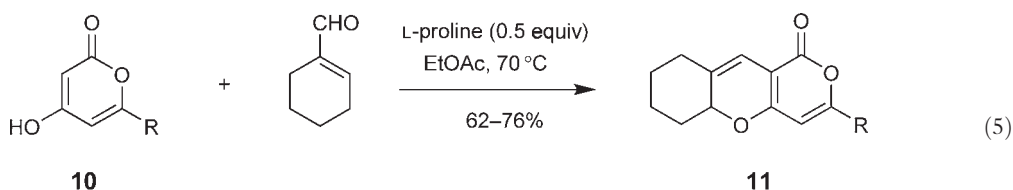
X = Cl, R¹ = SBu^t, R² = H, R³ = Me

X = Cl, R¹ = OMe, R² = H/Me, R³ = H

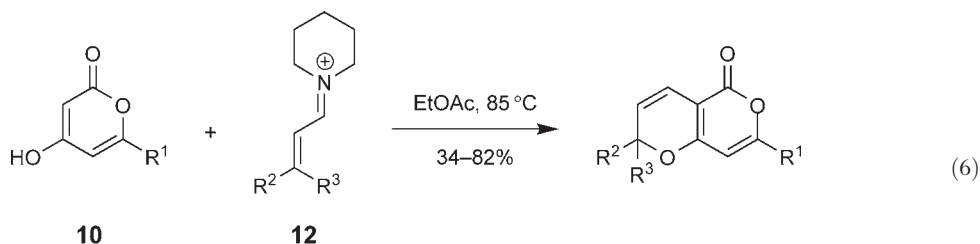
X = Br, R¹ = OMe, R² = H, R³ = H/Me

X = Br, R¹ = OPrⁱ, R² = H, R³ = Me

L-Proline can effectively catalyze the Knoevenagel condensation of cyclic enals with 4-hydroxy-2-pyrone derivatives **10** to afford pyran-2-one fused *2H*-pyrans **11** in good yield (Equation 5) <1997JOC6888, 1996T1473>. However, the reaction of 4-hydroxy-2-pyrones **10** with acyclic enones and enals, generally affords undesired 1,4-addition products rather than *2H*-pyrans. Acyclic α,β -unsaturated iminium salts **12** can react with 4-hydroxy-2-pyrone derivatives **10** to afford the corresponding *2H*-pyrans in high yield (Equation 6) <1999JOC690>. This strategy has been successfully exploited for the total synthesis of the pyranoquinoline alkaloids simulenoline, huajiaoosimuline and 7-demethoxyzanthodioline <2001JOC1049>. Likewise, the condensation of cycloalkylidene α,β -unsaturated iminium salts with 4-hydroxy-2-pyrone derivatives **10** leads to spiro-fused *2H*-pyrans **13** (Equation 7) <1999JOC690>. Modest stereocinduction at the spirocentre of the resulting *2H*-pyrans **13** can be obtained using chiral cycloalkylidene α,β -unsaturated iminium salts <2001TL609>.

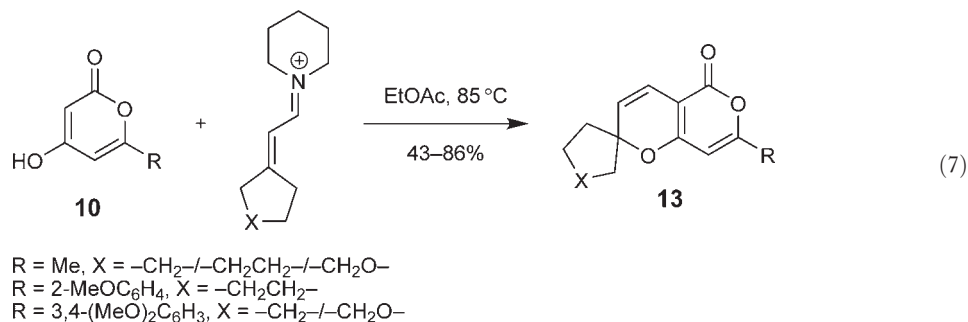


R = 3,4-(MeO)₂C₆H₃/3-pyridyl/Me

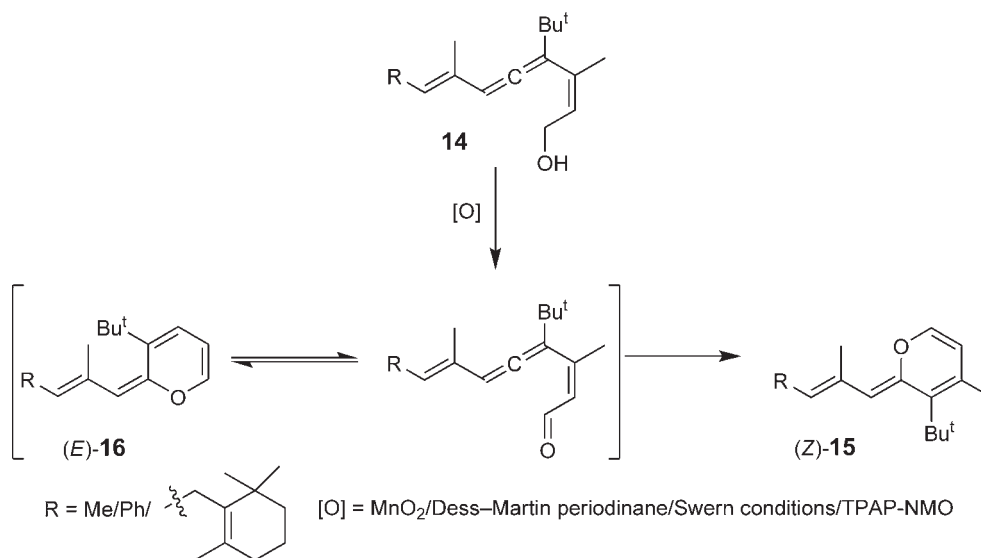


R¹ = Me/3-MeOC₆H₄/2-MeOC₆H₄/3,4-(MeO)₂C₆H₃/3,5-(MeO)₂C₆H₃, R² = R³ = Me

R¹ = Me, R² = Me/Prⁿ/Ph, R³ = H

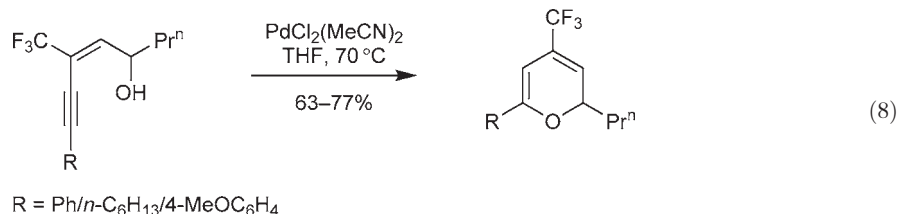


(Z)-Divinylallenols **14** are oxidized to (2Z)-divinylallenals, which undergo electrocyclic ring closure to form (Z)-alkylidene-2*H*-pyrans **15** <1997TL7421>. The kinetic product of the electrocyclization is the (*E*)-alkylidene-2*H*-pyran **16**, which can undergo electrocyclic ring opening back to the intermediate (2Z)-divinylallenal. The competing electrocyclic ring closure to form the (Z)-alkylidene-2*H*-pyran **15** is irreversible (**Scheme 4**) <1997TL7421>.

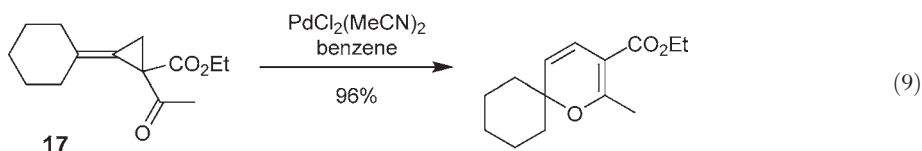


Scheme 4

The palladium-catalyzed cyclization of (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohols proceeds via a favourable 6-*endo*-dig cyclization due to the electron withdrawing properties of the trifluoromethyl group to afford 4-trifluoromethyl-2*H*-pyrans (Equation 8) <2000TL7727>.

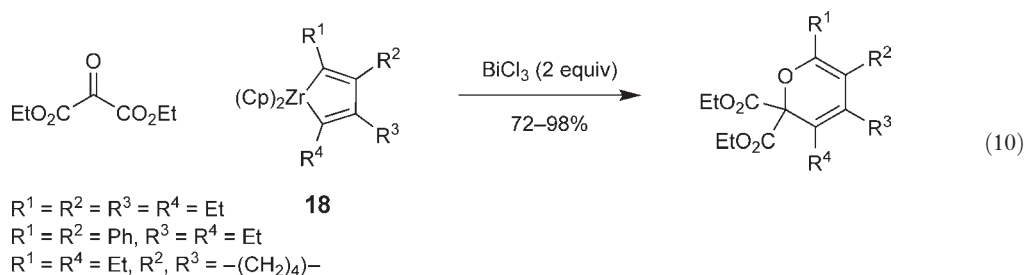


1-(Ethoxycarbonyl)-2,2'-(cyclohexylidene)cyclopropyl methyl ketone **17** undergoes a palladium-catalyzed cycloisomerization to form a spiro-fused 2*H*-pyran in excellent yield (Equation 9) <2004JA9645>.

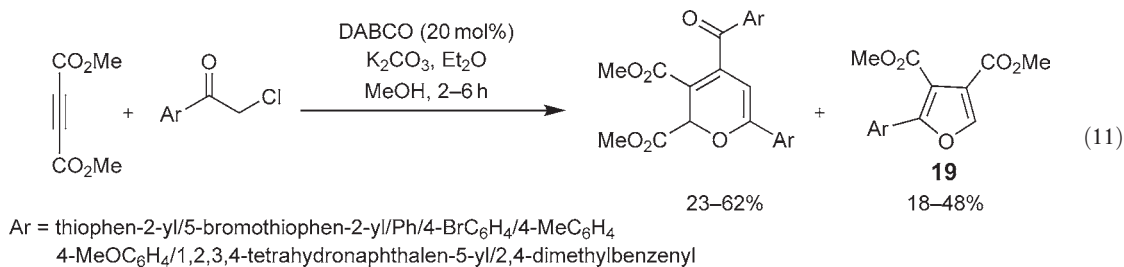


7.08.2.2 Formation of More than One Bond

Zirconacyclopentadienes **18** react with diethyl ketomalonate in the presence of BiCl_3 to afford fully substituted 2*H*-pyrans in excellent yield (Equation 10) <2002JA1144>.



Dimethyl acetylenedicarboxylate (DMAD) reacts with α -chloro carbonyl compounds to form 2*H*-pyrans as the major products and furans **19** as minor components (Equation 11) <2005JOC8204>. Under the same reaction conditions the equivalent α -bromo carbonyl compounds and DMAD react to form only the furans **19** <2005JOC8204>.



A three-component one-pot coupling of 2,6-dimethylphenyl isocyanide, methyl 2,4-dioxopentanoate and alkynoic esters leads to the isatin-like compounds (or fused pyrans) **20** (Scheme 5). The reaction proceeds by initial formation of the zwitterionic intermediate **21**, which is protonated by methyl 2,4-dioxopentanoate. Attack of the newly generated nucleophile then forms the intermediate **22**. The pyrrolidinone ring is formed upon loss of methanol and electrocyclization then occurs to afford the desired 2*H*-pyrans (Scheme 5) <2005S1049>.

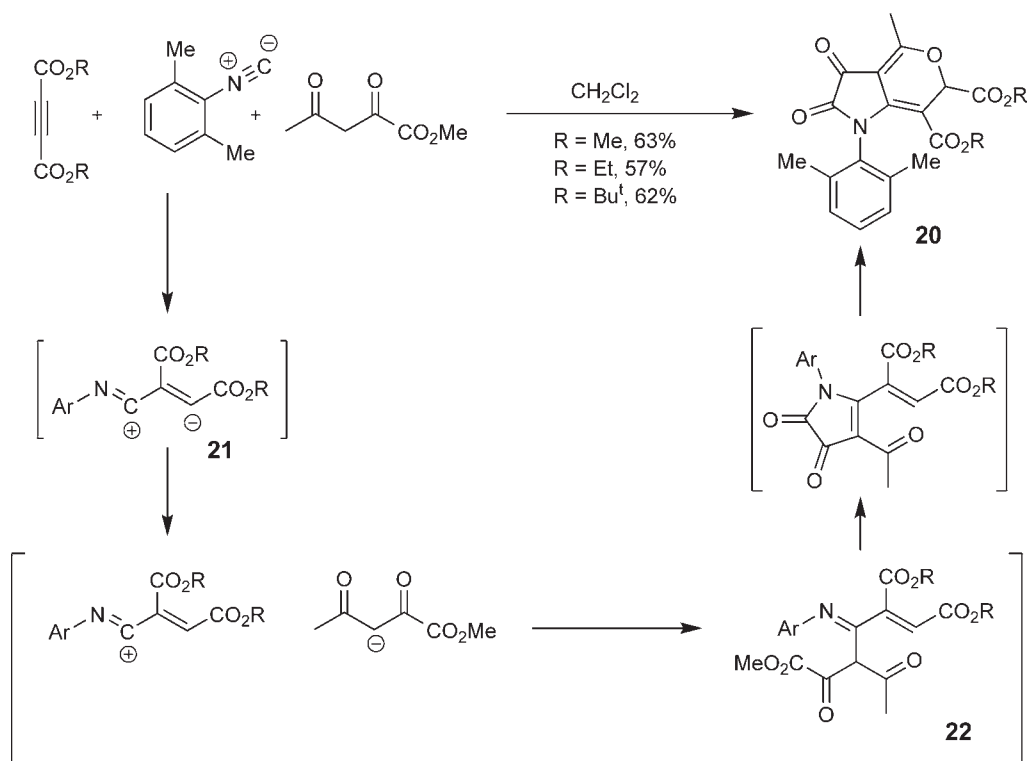
7.08.2.3 From a Preformed Heterocyclic Ring

7.08.2.3.1 From dihydropyrans

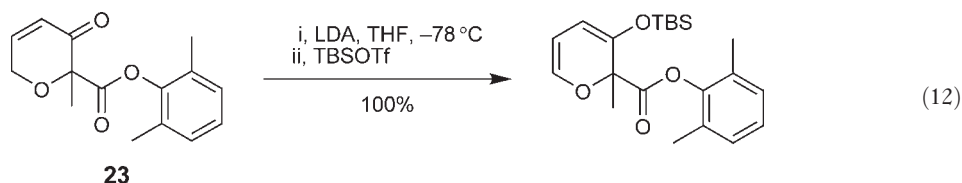
Hydroxy derivatives of dihydropyrans can be dehydrated to the corresponding 2*H*-pyrans <1984CHEC, 1996CHEC-II>.

7.08.2.3.2 From pyranones

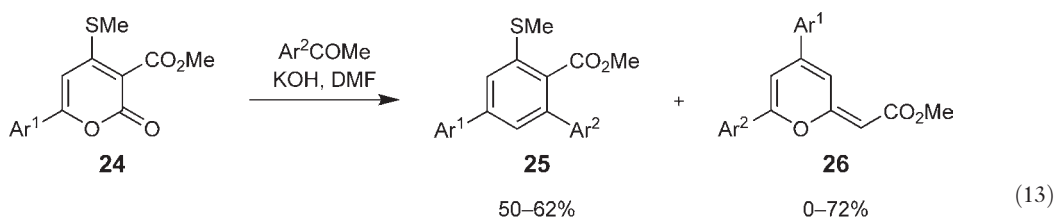
The extended enolate of the dihydropyran-3-one **23**, formed using LDA, can be trapped as its silyl ether to afford the corresponding 2*H*-pyran (Equation 12) <2002OL3059>.



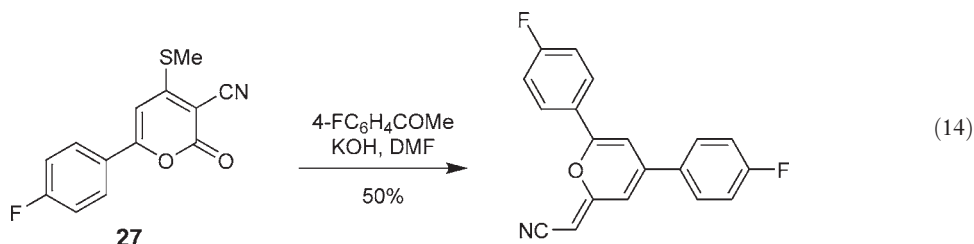
Scheme 5



The reaction of 2*H*-pyran-2-ones **24** with aryl methyl ketones in the presence of KOH provides a mixture of 1,3-teraryls **25** and alkylidene-2*H*-pyrans **26** (Equation 13) <1998S167>. Likewise, 6-(4-fluorophenyl)-3-cyano-4-(methylthio)-2*H*-pyran-2-one **27** reacts to afford the corresponding alkylidene 2*H*-pyran as the sole product (Equation 14) <2001J(P1)1953>.



$\text{Ar}^1 = \text{Ar}^2 = 3\text{-MeC}_6\text{H}_4/4\text{-BrC}_6\text{H}_4$
 $\text{Ar}^1 = 4\text{-ClC}_6\text{H}_4, \text{Ar}^2 = 3,4\text{-(Cl)}_2\text{C}_6\text{H}_3/4\text{-FC}_6\text{H}_4/4\text{-BrC}_6\text{H}_4$
 $\text{Ar}^1 = 4\text{-ClC}_6\text{H}_4, \text{Ar}^2 = 4\text{-O}_2\text{NC}_6\text{H}_4/3\text{-O}_2\text{NC}_6\text{H}_4/2\text{-O}_2\text{NC}_6\text{H}_4$
 $\text{Ar}^1 = 4\text{-FC}_6\text{H}_4, \text{Ar}^2 = 3,4\text{-(Cl)}_2\text{C}_6\text{H}_3$
 $\text{Ar}^1 = 4\text{-BrC}_6\text{H}_4, \text{Ar}^2 = 2\text{-O}_2\text{NC}_6\text{H}_4$



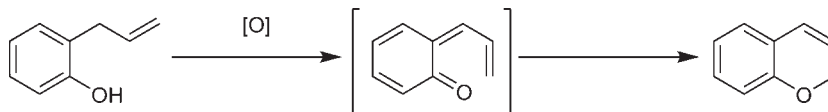
7.08.3 2H-Chromenes (2H-1-Benzopyrans)

The photochromic properties of 2H-chromene derivatives has generated much interest in recent years. Under UV irradiation these molecules can undergo reversible electrocyclic opening of the pyran ring to afford colored *ortho*-quinone methides [<2005T11730, 2005T1681>](#).

7.08.3.1 Formation of One Bond

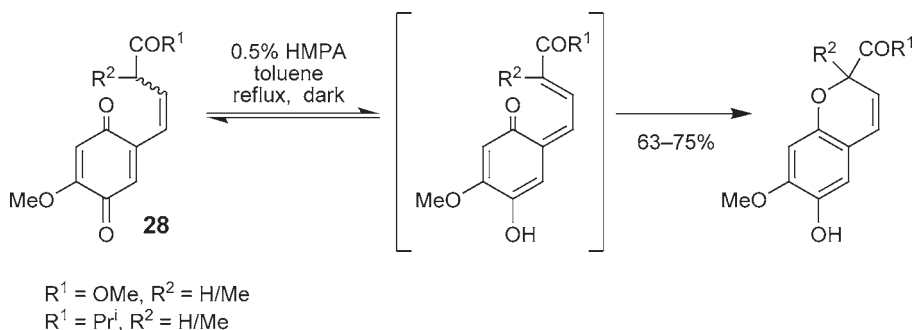
7.08.3.1.1 Adjacent to the heteroatom

The facile electrocyclic ring closure of *ortho*-quinone methides provides a convenient strategy for the synthesis of 2H-chromenes. Oxidation of *ortho*-allylic phenols using DDQ or potassium dichromate is a popular method for the formation of 2H-chromenes, via *ortho*-quinone methide intermediates, and is discussed in detail in the preceding volumes ([Scheme 6](#) [<1984CHEC, 1996CHEC-II>](#)).



Scheme 6

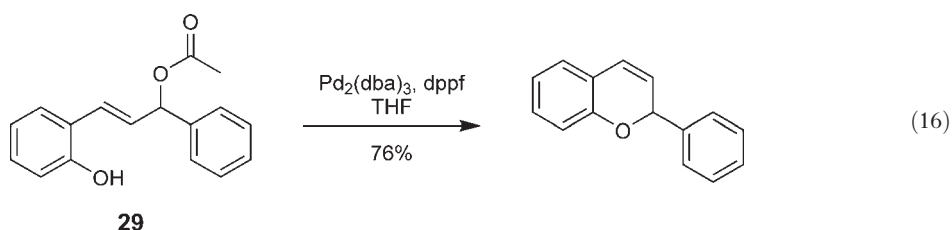
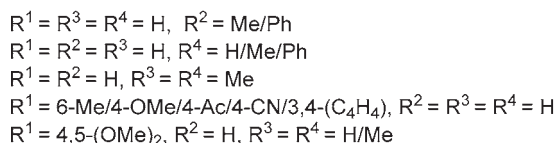
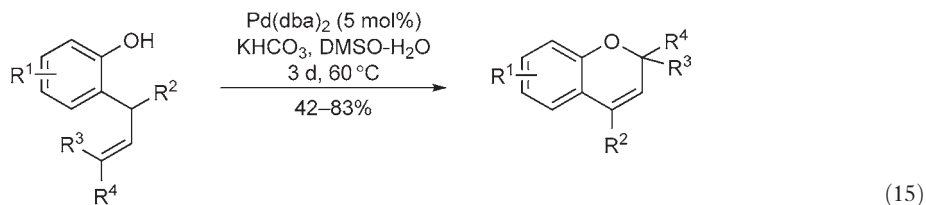
Enolization of the *para*-quinones **28** in the presence of hexamethylphosphoric acid (HMPA) forms the corresponding *ortho*-quinone methide intermediates, which undergo electrocyclic ring closure to afford 2-acyl-2H-chromenes ([Scheme 7](#) [<2001OL3875>](#)).



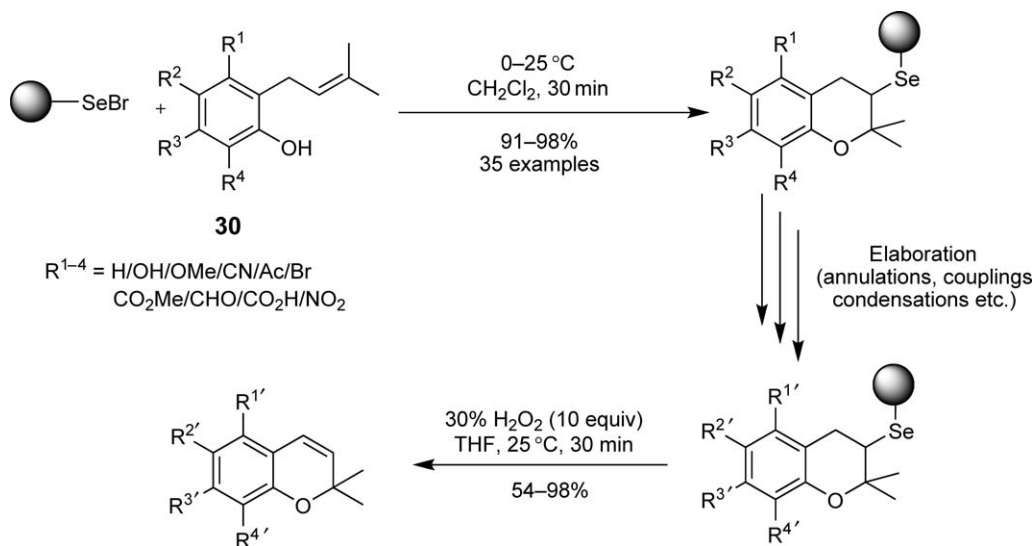
Scheme 7

The palladium(II) catalyzed cyclization of *ortho*-allylic phenols can lead to a mixture of benzopyran and benzofuran products. The palladium(II) catalyzed cyclization of *ortho*-allylic phenols, which bear a variety of substituents on both the aryl ring and the allyl group, in the presence of KHCO_3 in DMSO–water (9:1) affords 2H-chromenes exclusively ([Equation 15](#) [<1998SL522>](#)). Lower yields of 2H-chromenes are obtained when electron-withdrawing groups are

present *para*- to the hydroxy functionality (Equation 15) <1998SL522>. 2-Phenyl-2*H*-chromene is accessible via the palladium(II) catalyzed cyclization of (*E*)-3-(2-hydroxyphenyl)-1-phenylallyl acetate **29** in good yield (Equation 16) <2002SC3667>.

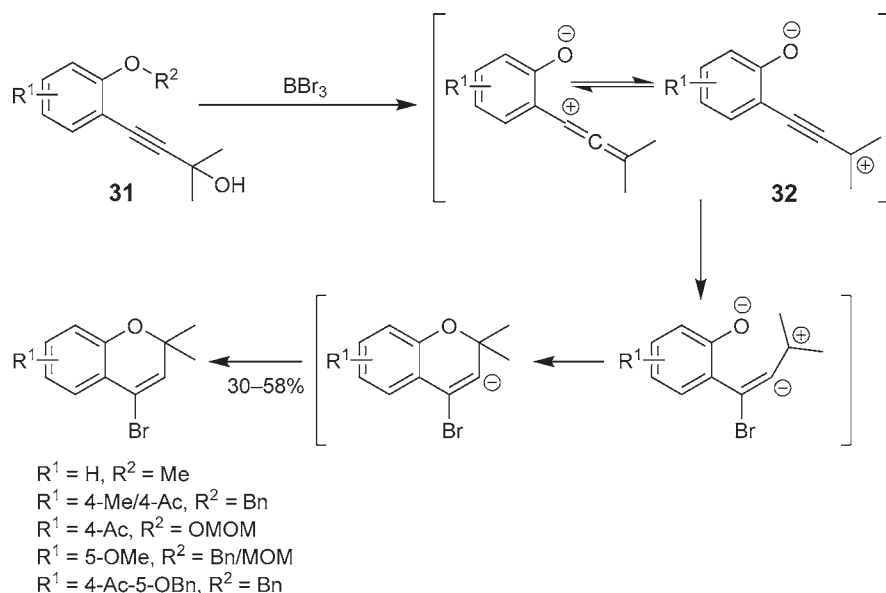


A wide variety of substituted *ortho*-prenylated phenols **30** can be loaded onto selenium functionalized resins with high efficiency. The resulting resin-bound benzopyrans can be elaborated in a number of ways to afford a variety of resin-bound natural products and analogs. Oxidation of the resin-bound selenides results in *syn*-elimination of the corresponding selenoxides releasing 2,2-dimethyl-2*H*-chromenes (Scheme 8) <2000AGE734>. This strategy can be used to prepare combinatorial libraries of 2,2-dimethyl-2*H*-chromenes <2000AGE734, 2000AGE739>.



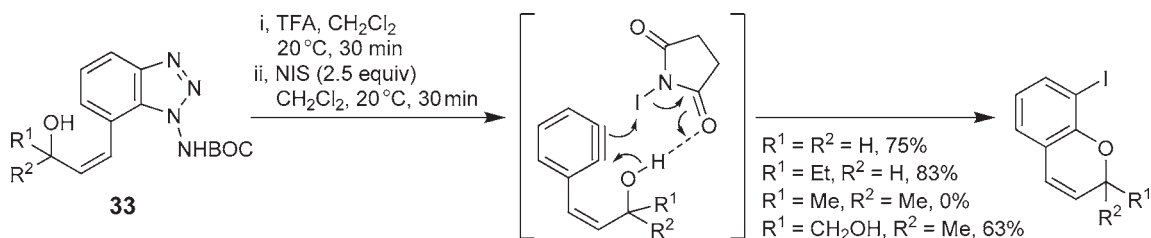
Scheme 8

2,2-Dimethyl-4-bromo-2*H*-chromenes are accessible via a boron tribromide induced cyclization of phenol derivatives **31** (Scheme 9). The reaction is proposed to proceed via *O*-deprotection and subsequent elimination of hydroxide to form the intermediate zwitterionic species **32**. Addition of bromide, pyran ring closure and protonation provides 4-bromo-2*H*-chromenes in moderate yield (Scheme 9) <1997H(45)1131>.



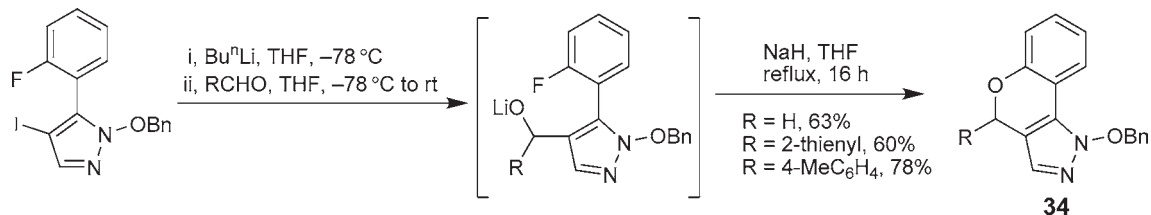
Scheme 9

N-Deprotection of benzotriazole derivatives **33** produces a benzyne intermediate that upon interaction with *N*-iodosuccinimide (NIS) undergoes intramolecular trapping by the hydroxyl group with concomitant incorporation of iodine to afford 8-iodo-2*H*-chromenes (**Scheme 10**). However, the dimethyl derivative ($\text{R}^1 = \text{R}^2 = \text{Me}$), when treated with TFA, undergoes dehydration of the allylic alcohol group rather than N-deprotection <2000J(P1)2343>.



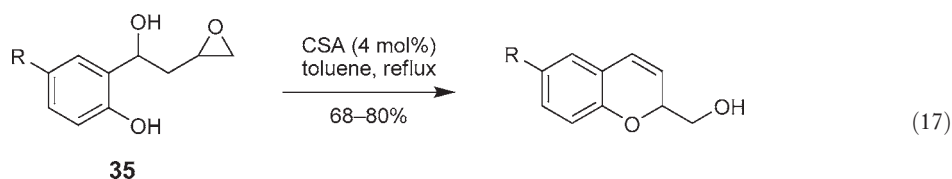
Scheme 10

Chromene[4,3-*c*]pyrazoles **34** are synthesized from 1-(benzyloxy)-5-(2-fluorophenyl)-4-iodo-1*H*-pyrazole by iodine–lithium exchange using *n*-BuLi, followed by addition of an aldehyde. Ring closure of the resulting lithium alkoxides, via an $\text{S}_{\text{N}}\text{Ar}$ reaction, is effected using sodium hydride in THF under reflux (**Scheme 11**) <2001JOC4214>.

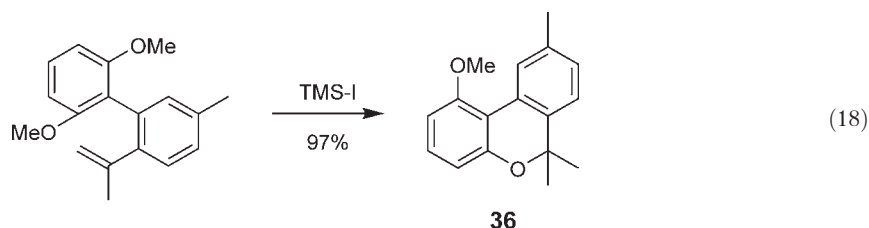


Scheme 11

Treatment of the epoxides **35** with a catalytic quantity of camphorsulfonic acid (CSA) furnishes 2*H*-chromenes in good yield (Equation 17) <2004T4037, 2002SL322>.

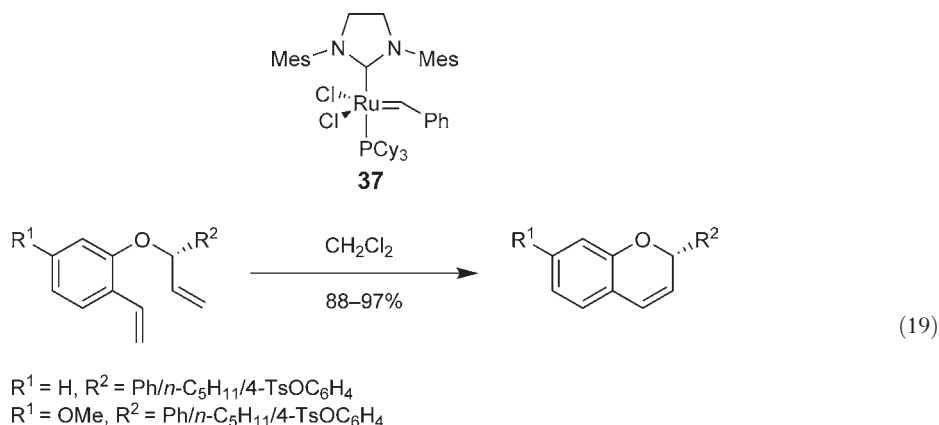


1-Methoxy-9-methyl-6*H*-benzo[*c*]chromene **36** can be synthesized in high yield upon treatment of 2',6'-dimethoxy-5-methyl-2-(prop-1-en-2-yl)biphenyl with trimethylsilyl iodide (Equation 18) <2003AGE2795>.

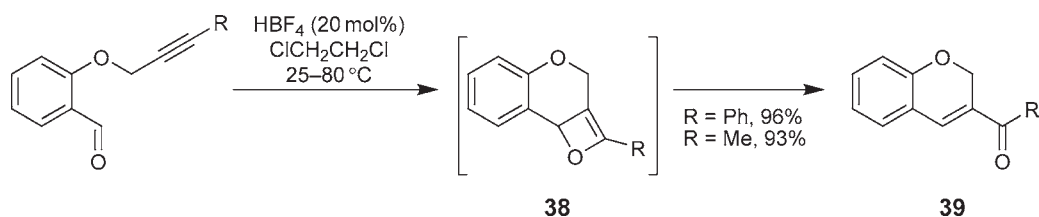


7.08.3.1.2 γ to the heteroatom

A variety of substituted *ortho*-allyloxystyrenes undergo facile ruthenium or molybdenum catalyzed RCM to form 2*H*-chromenes in high yield <1998JOC864, 2000TL5979, 1998JA2343, 1997JA1488, 1998JA8340>. RCM of chiral *ortho*-allyloxystyrenes using Grubbs' second-generation catalyst **37** furnishes 2*H*-chromenes in excellent yield with no epimerization of the C-2 stereocentre (Equation 19) <2003TL435>. The use of ruthenium-catalyzed RCM for the synthesis of 2*H*-chromenes has been recently reviewed <2004CRV2199>.



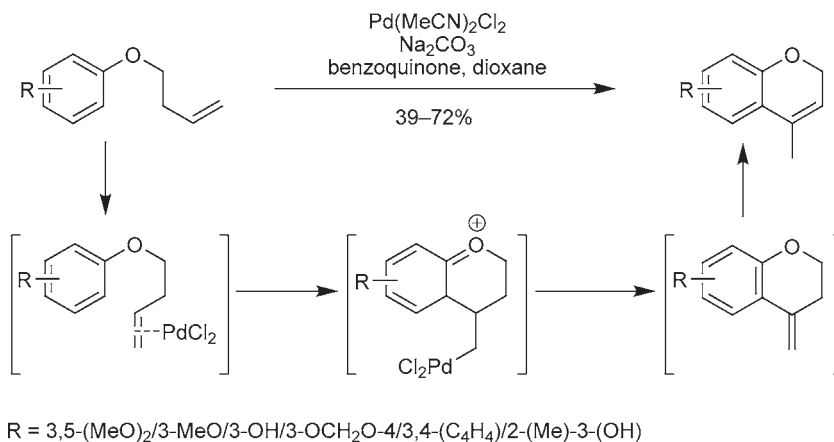
3-Acyl-2*H*-chromenes can be synthesized from *O*-propargylic salicylaldehydes in the presence of a Brønsted acid (HBF₄). The reaction proceeds via a formal [2+2]-cycloaddition of the alkyne and carbonyl group to form intermediate oxete **38**, which undergoes cycloreversion to afford 3-acyl-2*H*-chromenes in excellent yield (Scheme 12) <2005OL2493>.



Scheme 12

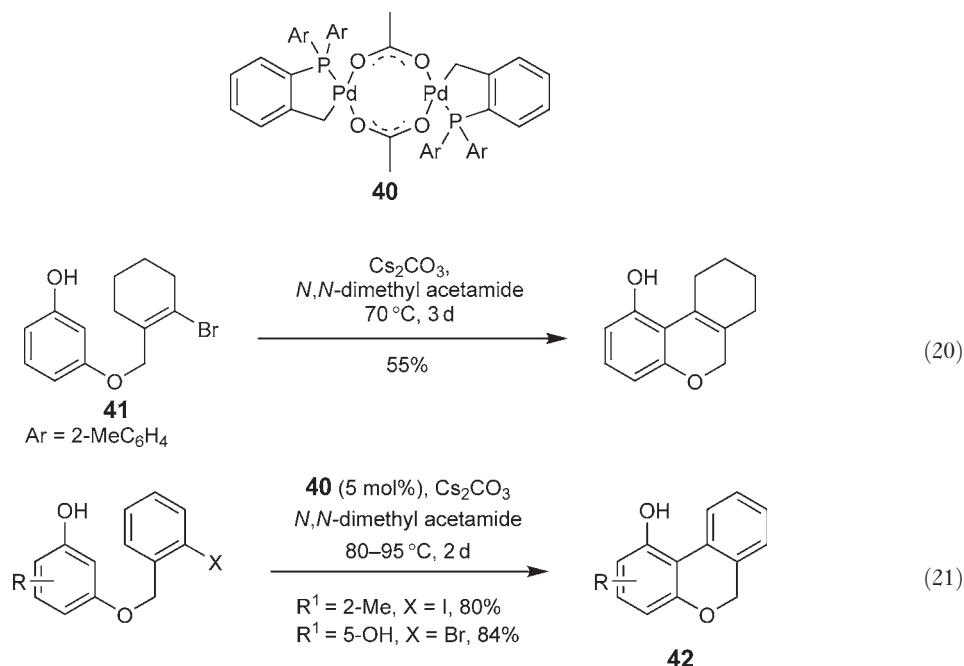
7.08.3.1.3 δ to the heteroatom

Palladium-catalyzed oxidative cyclization of aryl homoallyl ethers affords 4-methyl-2*H*-chromenes in moderate yield. The reaction is proposed to proceed via activation of the alkene by coordination to Pd(II) followed by intramolecular nucleophilic attack by the arene. Subsequent β -hydride elimination and isomerization then affords 4-methyl-2*H*-chromenes (**Scheme 13**). Electron-rich aryl homoallyl ethers give the best yield and good regio-selectivity is observed for the reaction of unsymmetrical arenes <2005OL3355>.

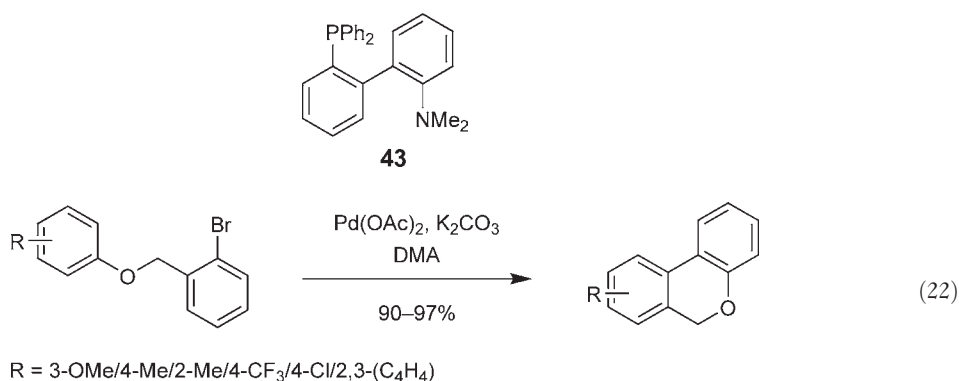


Scheme 13

Herrmann's catalyst **40** can effect the intramolecular *ortho*-cyclization of the vinyl bromide **41** to give the corresponding cyclohexyl-fused 2*H*-chromene (**Equation 20**). The same catalyst is also effective during the intramolecular coupling of phenols with aryl halides to afford 6*H*-benzo[*c*]chromen-1-ols **42** (**Equation 21**) <1997TL6379, 1997JOC2>.



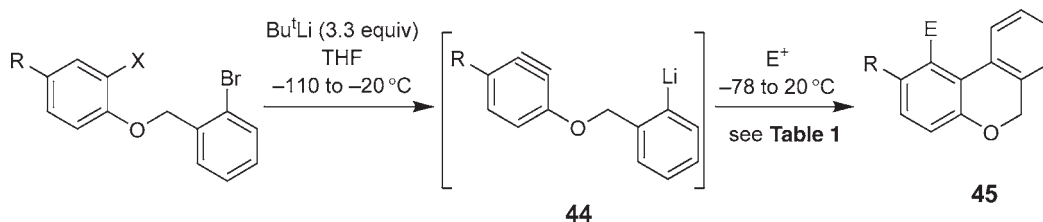
1-Bromo-2-(phenoxy)methylbenzene derivatives undergo facile palladium-catalyzed intramolecular cyclization in the presence of the ligand **43** to form 6*H*-benzo[*c*]chromenes (**Equation 22**) <2004JA9186>.



Treatment of 1-bromo-2-((2-halophenoxy)methyl)benzene derivatives with *t*-BuLi produces a benzyne intermediate tethered to an aryllithium species **44**, which can react with various electrophiles to afford 6*H*-benzo[*c*]chromenes **45** in high yield (Table 1, Scheme 14) <2002CEJ2034>.

Table 1 Formation of 6*H*-benzo[*c*]chromenes **45** by formation and reaction of the benzyne **44** with various electrophiles (Scheme 14)

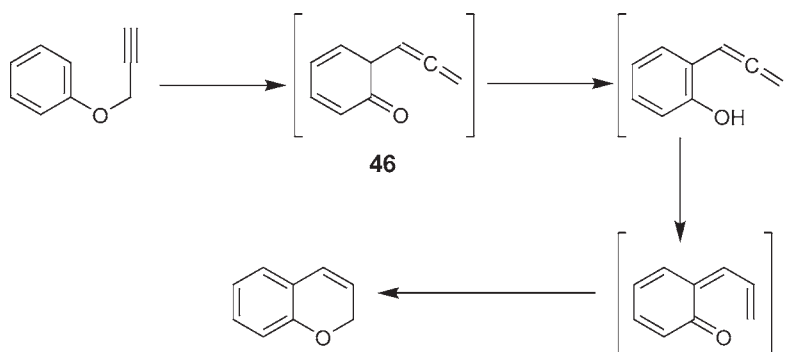
<i>R</i>	<i>X</i>	<i>E</i> ⁺	<i>E</i>	Yield 45 (%)
H	F	BrCH ₂ CH ₂ Br	Br	61
H	F	ClCO ₂ Et	CO ₂ Et	68
H	F	PhCHO	PhCH(OH)	56
H	F	Bu ₃ SnCl	Bu ₃ Sn	60
OMe	Cl	H ₂ O	H	81
OMe	Cl	ClCO ₂ Et	CO ₂ Et	75
OMe	Cl	4-MeC ₆ H ₄ CHO	4-MeC ₆ H ₄ CH(OH)	79
OMe	Cl	Ph ₂ S ₂	SPh	73



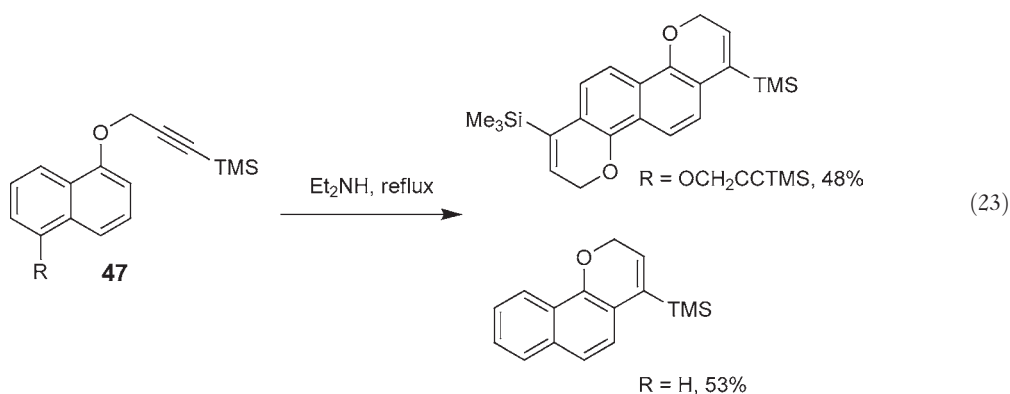
Scheme 14

The thermal cyclization of aryl propargyl ethers is a well-documented procedure for the preparation of 2*H*-chromenes and is discussed in the preceding volumes <1984CHEC, 1996CHEC-II>. The reaction proceeds via a [3,3]-sigmatropic Claisen rearrangement to form the allene **46**, which is easily rearomatized to the corresponding allenic phenol. A subsequent [1,5]-hydrogen shift forms an *ortho*-quinone methide which undergoes electrocyclization to close the pyran ring (Scheme 15).

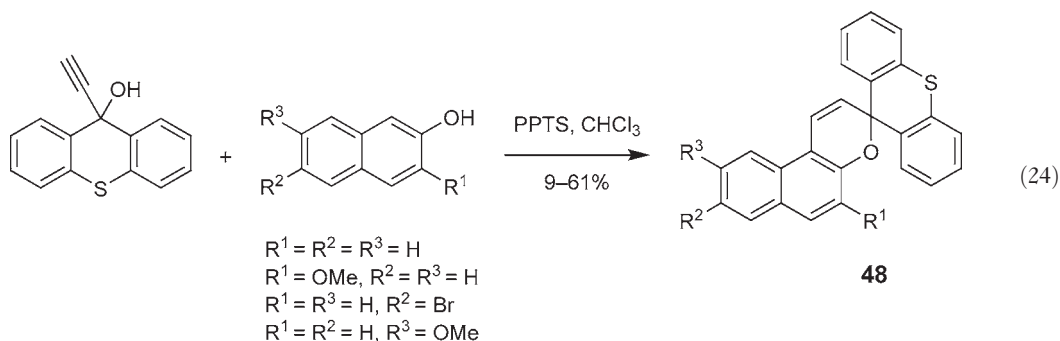
Yields for this reaction are generally higher for aryl propargyl ethers substituted at the propargylic position, most likely due to stabilization of the allene intermediates. However, bulky alkyl substituents at the propargylic position can lead to formation of benzofurans rather than the desired benzo-2*H*-pyrans <2004SC4507>. Thermal cyclization of *meta*-acylaryl-1,1-dimethylpropargyl ethers affords the corresponding 5-acyl-2,2-dimethyl-2*H*-chromenes in high yield. The inductive effect of the *meta*-acyl group both facilitates the thermal cyclization and induces high *ortho*-selectivity in the reaction <2001TL1091>. Naphthyl trimethylsilylpropargyl ethers **47** undergo thermal cyclization under reflux in *N,N*-diethylamine furnishing 4-trimethylsilyl substituted naphthopyrans in moderate yield (Equation 23) <1996H(43)751>.



Scheme 15

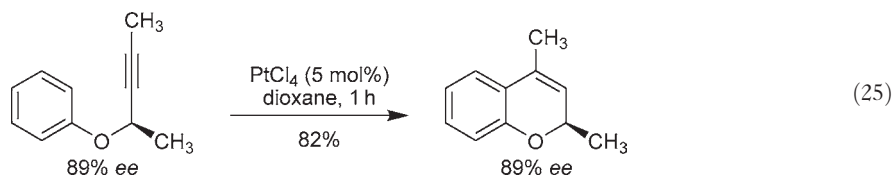


In the presence of an acidic catalyst, phenols and propargylic alcohols can combine to form the corresponding aryl propargyl ethers, which then undergo thermal cyclization to afford *2H*-chromenes [<1984CHEC, 1996CHEC-II>](#). This method has been used to give moderate yields of spiro[thioxanthene-naphthopyrans] **48** that display excellent photochromic properties (Equation 24) [<2002T9505>](#).

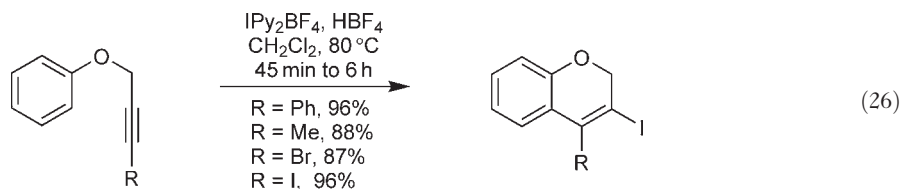


Photochromic *2H*-benzopyran derivatives can be prepared by the reaction of phenols or naphthols with diaryl propargylic alcohols, in the presence of pyridinium *p*-toluenesulfonate and trimethyl orthoformate as a dehydrating agent, in high yield (85–100%) [<2003OL4153>](#). Zeolite HSZ-360 and silica gel are also effective dehydrating agents that can promote this reaction [<1997JOC7024, 2000OL2133>](#).

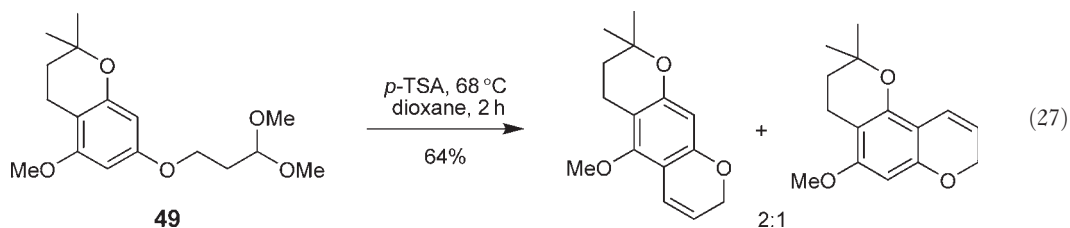
Platinum tetrachloride ($PtCl_4$) is a good catalyst for the formation of *2H*-chromenes from aryl propargyl ethers. The $PtCl_4$ -catalyzed cyclization of aryl propargyl ethers is proposed to proceed via electrophilic hydroarylation rather than a Claisen type rearrangement. The reaction is compatible with alkyne substitution and various functionalities on the arene, including bromine, ketones, and amines. Furthermore, stereogenic centers at the propargyl position are not compromised during the reaction (Equation 25) [<2003T8859>](#).



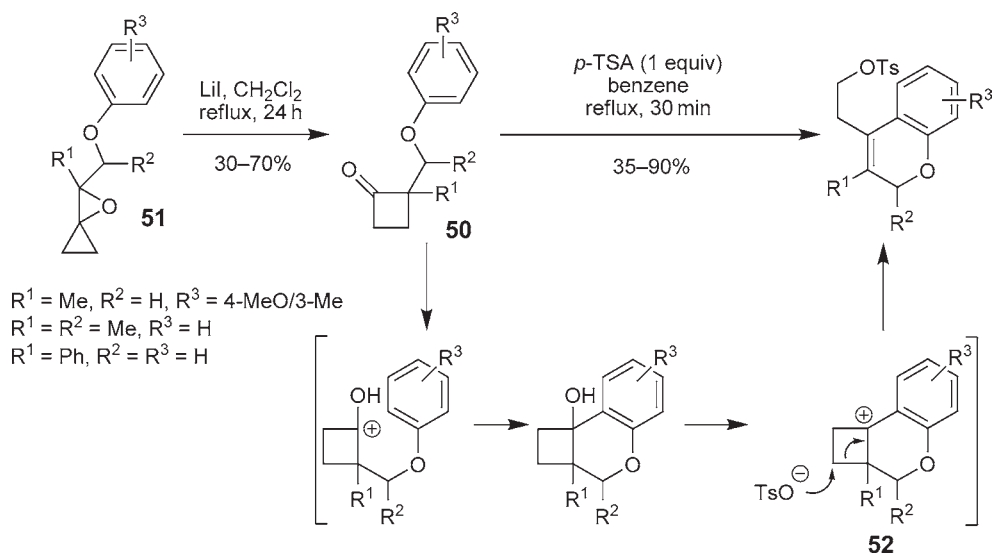
Aryl propargyl ethers can undergo intramolecular iodoarylation in high yield to afford 3-iodo-2*H*-chromenes (Equation 26). The reaction is believed to proceed by initial formation of a vinylidonium species, with subsequent trapping by the aryl group. Although the reaction works well for internal alkynes, terminal alkynes fail to give the desired 2*H*-chromenes <2005CC2008>. Iodoarylation of aryl propargyl ethers can also be carried out in water using NaI or I₂ as the source of electrophilic iodine with comparable yields <2005CC2008>.



The acetal **49** undergoes acid promoted cyclization to form a mixture of linear- and angular-fused 2*H*-chromenes (Equation 27) <1997J(P1)1875>.



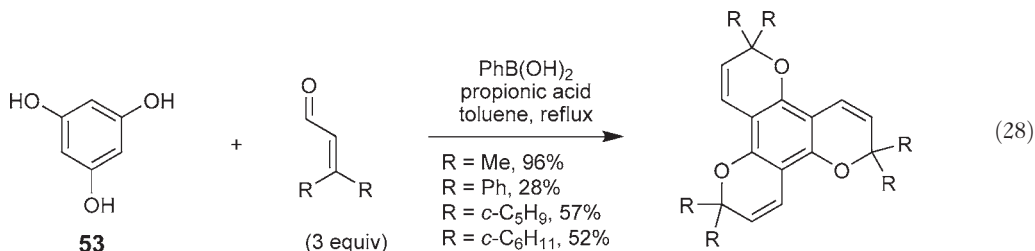
Cyclobutanones **50** can be synthesized by a lithium iodide induced ring expansion of oxaspiropentanes **51**. Treatment of the cyclobutanones **50** with *p*-toluenesulfonic acid (*p*-TSA) in benzene under reflux affords 2*H*-chromenes via a tosylate induced ring fission of the intermediate cyclobutyl cation **52** (Scheme 16). The oxaspiropentane **51** (R¹ = Me, R² = H, R³ = 4-OMe/3-Me) can be directly transformed into the corresponding 2*H*-chromene upon treatment with *p*-TSA in 55% yield <2004T449>.



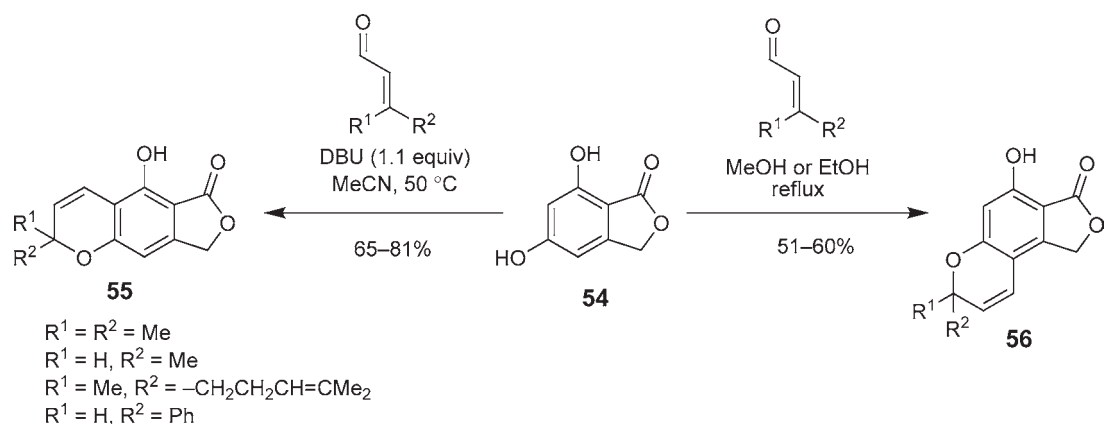
Scheme 16

7.08.3.2 Formation of More than One Bond

The condensation of α,β -unsaturated carbonyl compounds with phenols is a well-established method for the preparation of 2*H*-chromenes and is reviewed in the preceding volumes <1984CHEC, 1996CHEC-II>. Phenylboronic acid can effectively mediate this condensation <1998S279>. C(3)-Symmetrical 2*H*-chromenes are synthesized using a phenylboronic acid-mediated triple condensation of phloroglucinol **53** with three equivalents of an α,β -unsaturated carbonyl compound (Equation 28) <2005OL467>.

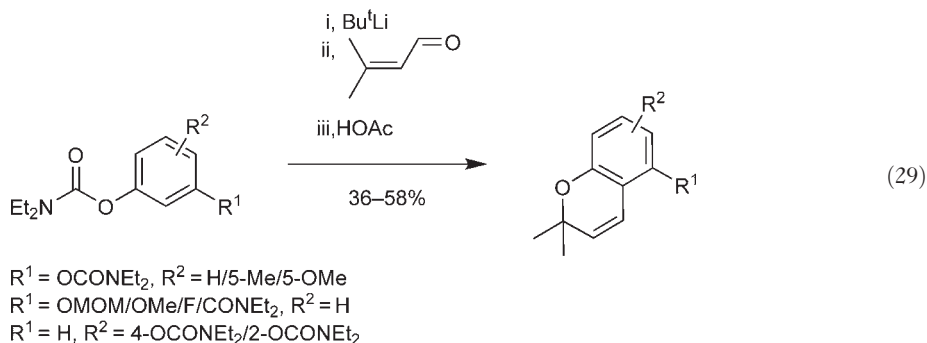


A 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed condensation of 3,5-dihydroxyphthalide **54** with α,β -unsaturated carbonyl compounds leads exclusively to linear fused 5-hydroxy-2,2-dialkyl-2*H*-furo[3,4-*g*]chromen-6(8*H*)-ones **55**. Under neutral conditions angular fused 4-hydroxy-7,7-dialkyl-1*H*-furo[3,4-*f*]chromen-3(7*H*)-ones **56** are formed in good yield (Scheme 17) <2004SL1243>.



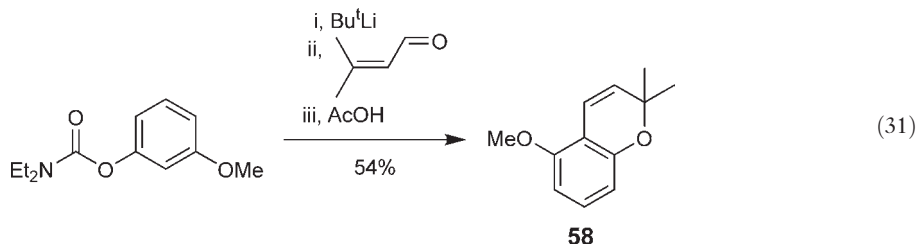
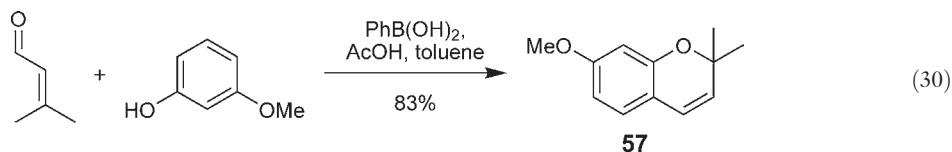
Scheme 17

Directed *ortho*-metallation of aryl *O*-carbamates and subsequent reaction with α,β -unsaturated carbonyl compounds affords 2*H*-chromenes (Equation 29) <2001S140>.

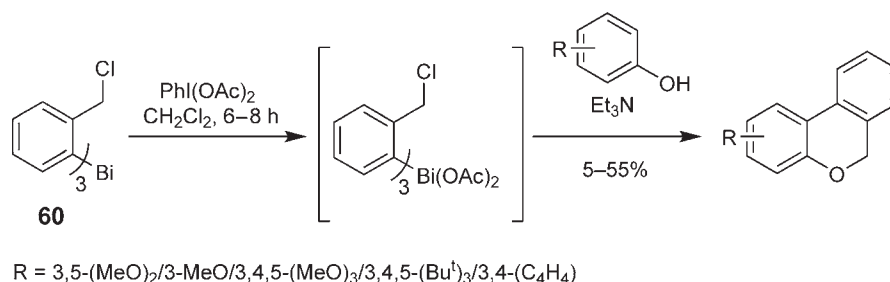
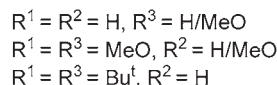
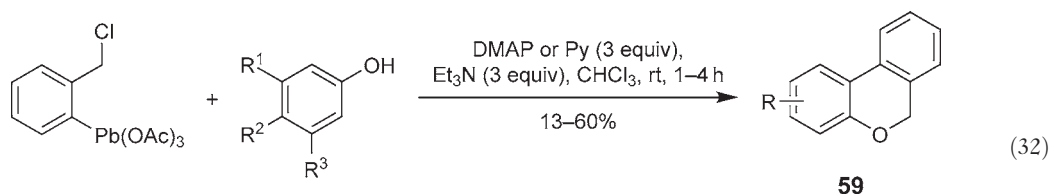


Although the yields are moderate, a directed *ortho*-metallation approach can be used to access 2*H*-chromenes that are difficult to prepare by the condensation of phenols with α,β -unsaturated carbonyl compounds <2001S140>. For

example, while the condensation of *meta*-hydroxyanisole with 3-methylbut-2-enal can be mediated by phenylboronic acid to afford 7-methoxy-2,2-dimethyl-2*H*-chromene **57** in good yield (Equation 30) <1998S279>. The regioisomer, 5-methoxy-2,2-dimethyl-2*H*-chromene **58**, is accessed using a directed *ortho*-metallation approach, albeit in moderate yield (Equation 31) <2001S140>.

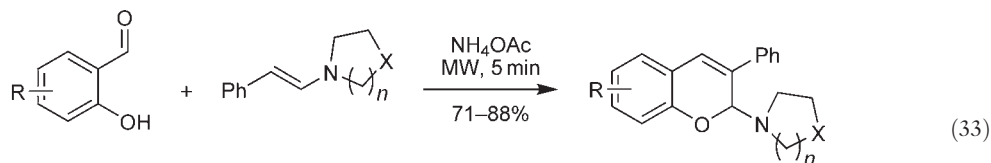


ortho-Chloromethyl-phenyllead triacetates react with phenols to afford dibenzo[*b,d*]-6*H*-pyrans **59** in moderate yield (Equation 32) <2001TL5875>. In a related procedure, tris[*ortho*-chloromethylphenyl]bismuth diacetate, formed *in situ* by oxidation of the organobismuth(III) derivative **60**, can react with phenols to yield dibenzo[*b,d*]-6*H*-pyrans (Scheme 18) <2002TL8245>.



Scheme 18

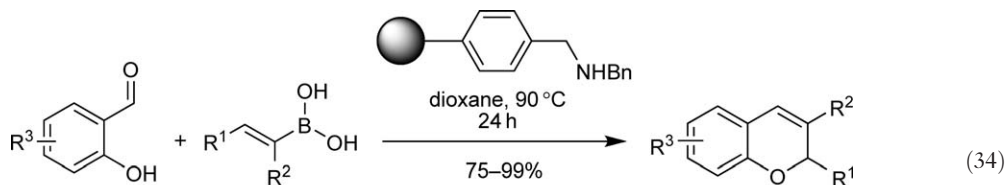
ortho-Hydroxybenzaldehydes react with *N*-styryl amines in the presence of ammonium acetate under microwave irradiation to afford 2-amino-3-phenyl-2*H*-chromenes (Equation 33) <1998JOC8038>. In the presence of a resin bound amine, *ortho*-hydroxybenzaldehydes and vinyl boronic acids undergo a Petasis-type condensation to give 2*H*-chromenes in high yield (Equation 34) <2000OL4063>. This reaction can also be performed in ionic liquids catalyzed by dibenzylamine with a comparable yield <2004SL2194>.



X = O, $n = 2$, R = H/4-NO₂/4-Cl/6-OMe/5-OMe/3-OMe

X = CH₂, $n = 2$, R = H/4-NO₂/4-Cl

X = O, $n = 1$, R = H/4-NO₂/4-Cl

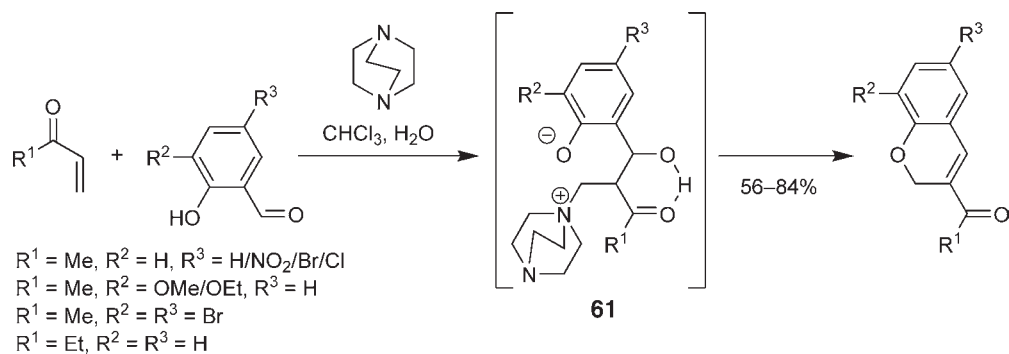


R¹ = *n*-C₄H₉, R² = H, R³ = H/6-OH/6-MeO/4-Br/4,6-(Cl)₂/4,6-(Bu^t)₂/3,4-(C₄H₄)

R¹ = Ph/Bu^t/*n*-C₆H₁₂CCH/*n*-C₆H₁₂CHCHB(OH)₂, R² = R³ = H

R¹ = Ph, R² = Me, R³ = H

2-Hydroxybenzaldehydes react with alkyl vinyl ketones in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to yield 3-acyl-2*H*-chromenes (Scheme 19) <2000J(P1)1331>. The reaction proceeds via a Baylis–Hillman type pathway to form the zwitterionic intermediate **61** with subsequent cyclization and dehydration to afford 2-acyl-2*H*-chromenes (Scheme 19) <2003OBC1133>.



R¹ = Me, R² = H, R³ = H/NO₂/Br/Cl

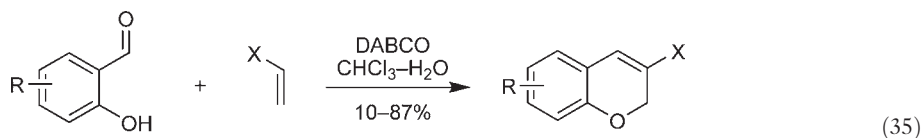
R¹ = Me, R² = OMe/OEt, R³ = H

R¹ = Me, R² = R³ = Br

R¹ = Et, R² = R³ = H

Scheme 19

2-Hydroxybenzaldehydes and 2-hydroxy-1-naphthaldehydes react under Baylis–Hillman conditions with various activated alkenes to yield 3-substituted 2*H*-chromene derivatives (Equation 35) <2002J(P1)1318>. 2-Hydroxybenzaldehyde also reacts with acrylic acid and acrylic esters under Baylis–Hillman conditions to afford 3-carboxylate-2*H*-chromenes in high yield <2001SC1233>.

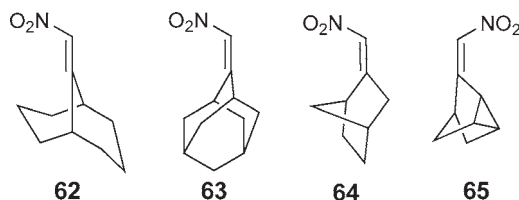
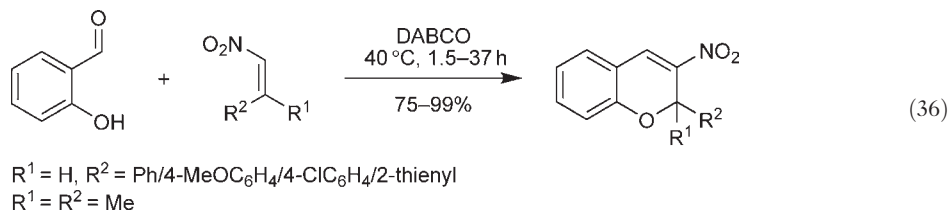


R = H, X = COMe/COEt/CHO/SO₂Ph/SO₃Ph/CN/COPh

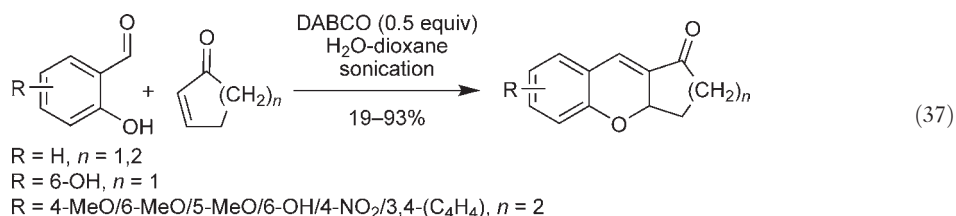
R = 6-OMe/6-OEt/3-NO₂/3-Cl/3-Br/3,6-(Br)₂, X = COMe

R = 3,4-(C₄H₄), X = COMe/COEt/CHO/SO₂Ph/SO₃Ph/CN

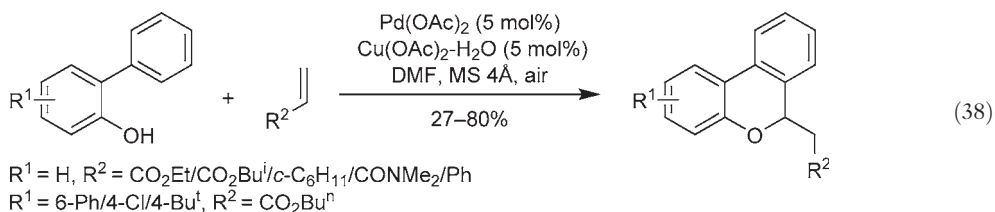
Nitroethenes react with 2-hydroxybenzaldehyde under Baylis–Hillman conditions to afford 3-nitro-2*H*-chromenes in high yield (Equation 36) <2001TL2717>. Likewise, the polycyclic nitroethenes **62–65** react with 2-hydroxybenzaldehyde to form the corresponding 2-spirocyclic-3-nitro-2*H*-chromenes in good yield (49–99%) <2001TL2717>.



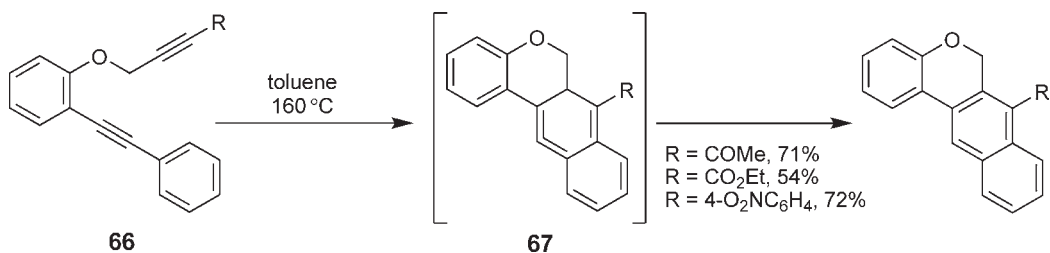
Cyclopentenones and cyclohexenones react with 2-hydroxybenzaldehydes in presence of DABCO to afford cyclopentanone- and cyclohexanone-fused 2*H*-chromenes (Equation 37) <2004AGE115>.



Oxidative coupling of 2-phenylphenol derivatives with alkenes in the presence of a palladium(II)–copper(II) catalytic system affords 6*H*-benzo[*c*]chromenes in moderate yield (Equation 38) <1997CL1103>.

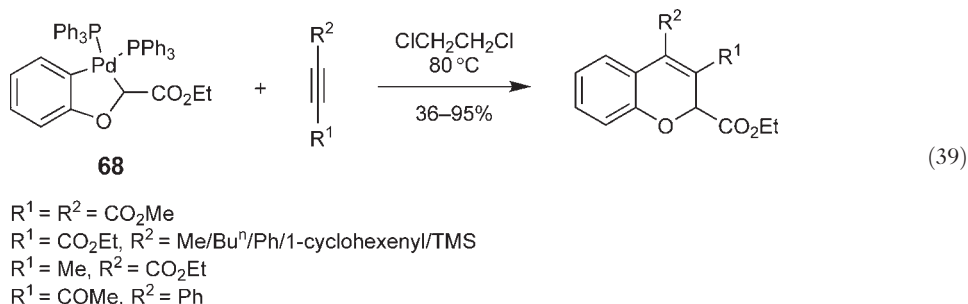


The diyne **66** undergoes an intramolecular dehydro Diels–Alder reaction in toluene under reflux to afford naphtho[2,3-*c*]chromene derivatives in reasonable yield (Scheme 20). The reaction is presumed to proceed via a [4+2]-cycloaddition of the alkyne to the aryl alkyne group to form the cyclic allene intermediate **67**, which then isomerizes to the aromatic product <2003SL1524>.

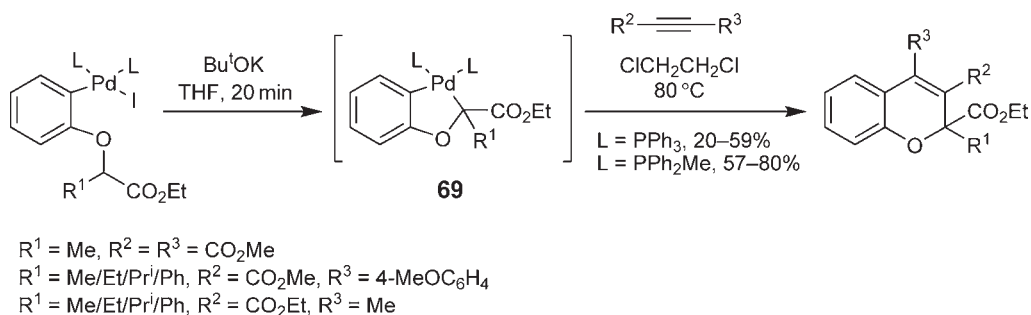


Scheme 20

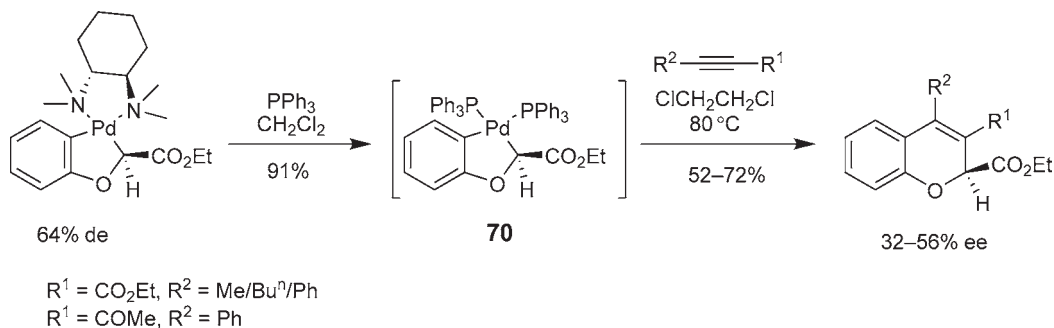
Oxapalladacycle **68** can react with activated internal alkynes to afford 2,3,4-trisubstituted-2*H*-chromenes in good yield (Equation 39) <2002OL3679>.



Similarly, 2,2,3,4-tetrasubstituted-2*H*-chromenes are prepared by the *in situ* formation of the oxapalladacycles **69** and subsequent reaction with activated internal alkynes. Oxapalladacycles that feature diphenylmethylphosphine ligands give consistently higher yields of 2*H*-chromenes, than their counterparts containing triphenylphosphine ligands (Scheme 21) <2005OM945>. The asymmetric synthesis of 2*H*-chromenes from the (–)-oxapalladacycle **70** (64% de) furnishes 2*H*-chromenes with average enantioselectivity (32–56% ee) (Scheme 22) <2004JOC4701>.

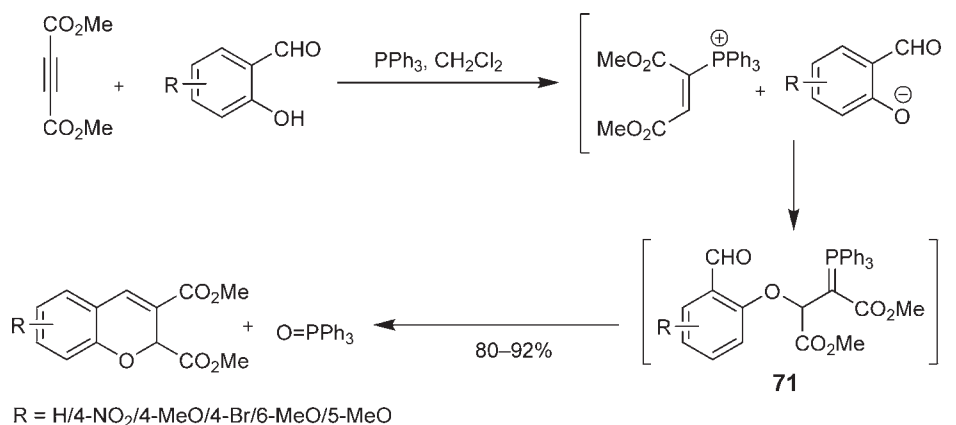


Scheme 21



Scheme 22

Salicylaldehyde derivatives react with dimethyl acetylenedicarboxylate in the presence of triphenylphosphine (PPh_3) to afford dimethyl-2*H*-chromene-2,3-dicarboxylates in high yield. The reaction proceeds via an intramolecular Wittig reaction of the ylide intermediate **71** (Scheme 23) <2003PS1457>.

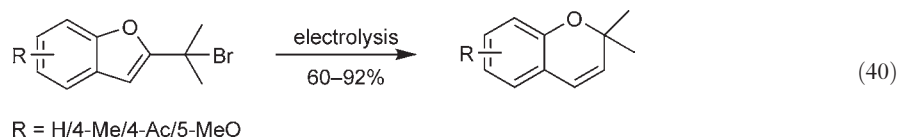


Scheme 23

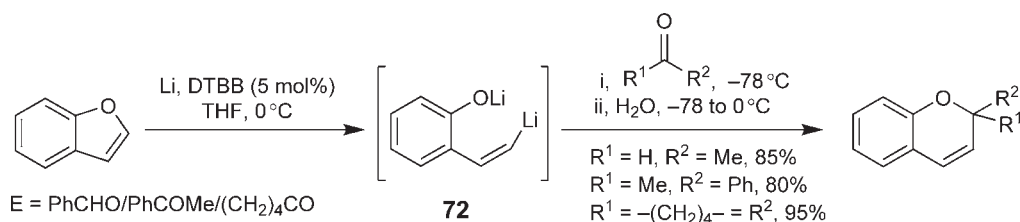
7.08.3.3 From Other Heterocycles

7.08.3.3.1 From benzofurans

The electrochemical reduction of 2-(1-bromo-1-methylethyl)benzofurans leads directly to 2,2-dimethyl-2H-chromenes via cleavage of the C–Br bond and subsequent ring expansion (Equation 40) <1995CC615>.



Selective ring opening of benzofuran with lithium, in the presence of a catalytic amount of 4,4'-di(*tert*-butyl)diphenyl (DTBB), forms the (*Z*)-dilithiated species **72**, which upon addition of a ketone or aldehyde forms 2H-chromenes (Scheme 24) <2001EJO2809>.



Scheme 24

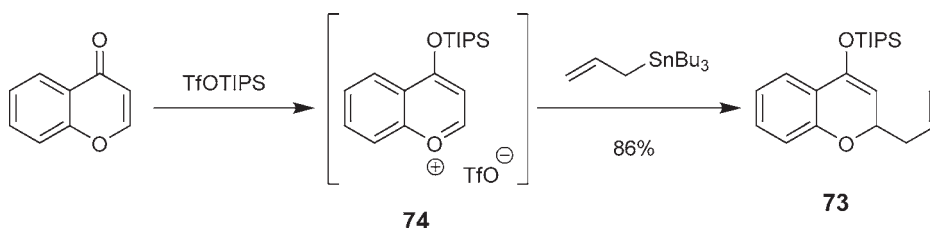
7.08.3.4 From a Preformed Heterocyclic Ring

7.08.3.4.1 From chromones

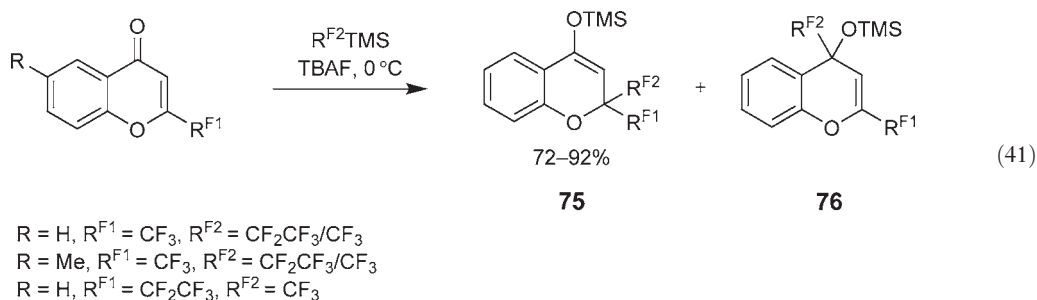
Chroman-4-ones can be selectively reduced to 2H-chromenes via 1,2-addition of 9-borabicyclo[3.3.1]nonane (9-BBN) <2001BCJ967>.

The 2-allyl-2H-chromene derivative **73** is synthesized from 4H-chromen-4-one by *in situ* formation of the 4-silyloxy-benzopyrylium salt **74** followed by reaction with allyltri-*n*-butyltin (Scheme 25) <2001T1005>.

2-Perfluoroalkyl-chroman-4-ones react with (perfluoroalkyl)trimethylsilane in the presence of a catalytic amount of tetra-*n*-butyl ammonium fluoride (TBAF) to give 2-bis(perfluoroalkyl)-2H-chromenes **75** as the major products along with trace amounts of the corresponding 4H-chromenes **76** (Equation 41) <2003TL2097>.

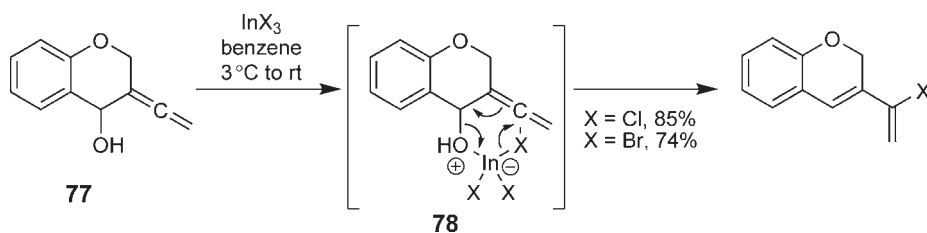


Scheme 25



7.08.3.4.2 From chromanols

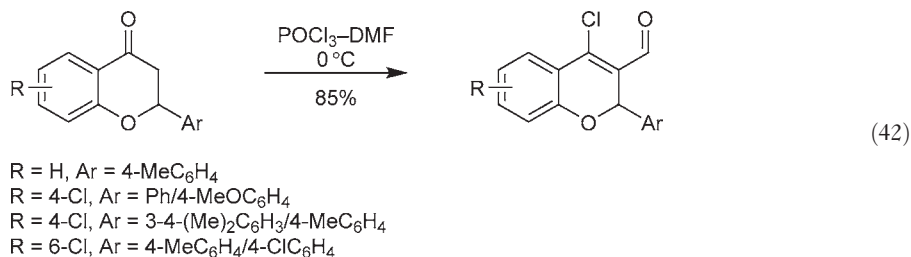
Various dehydrating reagents can effect the formation of 2*H*-chromenes from chroman-4-ols <1996CHEC-II>. Treatment of 3-vinylidenechroman-4-ol **77** with indium(III) halide affords 3-(1-halovinyl)-2*H*-chromenes in high yield, most likely via a pseudo [3,3]-sigmatropic rearrangement of the coordinated species **78** (Scheme 26) <2004S2620>.



Scheme 26

7.08.3.4.3 From chroman-4-ones

Flavan-4-ones react under Vilsmeier–Haack conditions providing 2-aryl-3-formyl-4-chloro-2*H*-chromenes in high yield (Equation 42) <2001SC2589>.

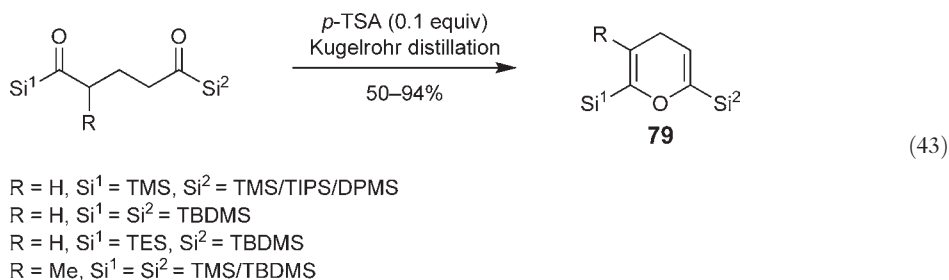


7.08.4 4*H*-Pyrans and Fused 4*H*-Pyrans

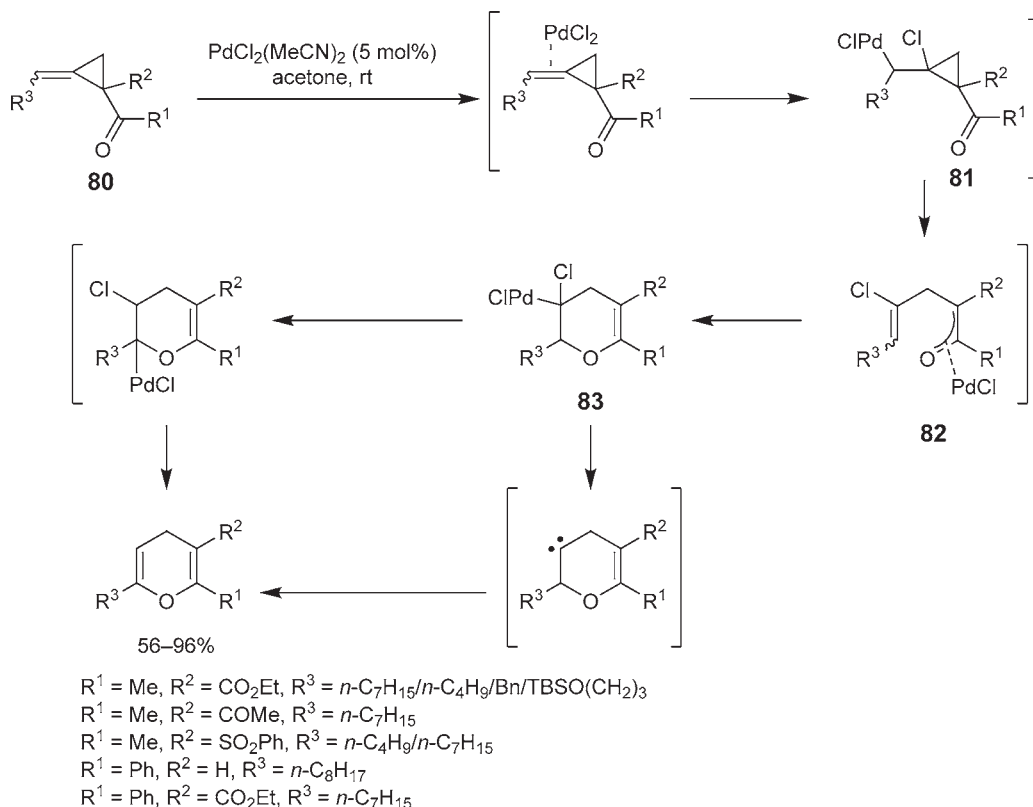
7.08.4.1 Formation of One Bond

7.08.4.1.1 Adjacent to the heteroatom

The majority of syntheses of 4*H*-pyrans derive from the ring closure of 1,5-dicarbonyl compounds or their equivalents, which is discussed in detail in the previous volumes <1984CHEC, 1996CHEC-II> and is also the subject of a recent review <2000CHE1007>. In this manner, 2,6-bis(silyl)-4*H*-pyrans **79** are synthesized by the cyclodehydration of their corresponding 1,5-bis(silyl)pentane-1,5-diones in good yield (Equation 43) <2000S843>.



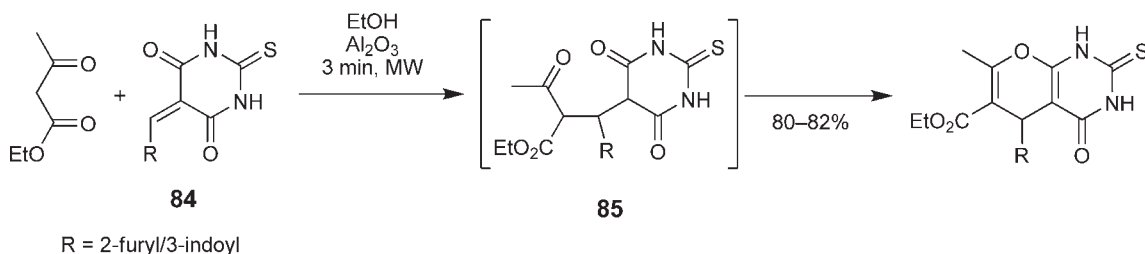
Alkylidenecyclopropyl ketones **80** can undergo palladium-catalyzed cycloisomerization to afford 4*H*-pyrans (Scheme 26) <2004JA9645, 2003AGE183>. The reaction is proposed to proceed via regioselective chloropalladation of the C=C bond of the alkylidene cyclopropyl ketone **80** to form the intermediate **81**, which then undergoes β -decarbopalladation to afford the delocalized intermediate **82**. Intramolecular insertion of the C=C bond into the oxygen–palladium bond leads to the cyclic intermediate **83**, which can either undergo β -hydride elimination–hydropalladation followed by β -halide elimination to furnish 4*H*-pyrans. Alternatively, the cyclic intermediate **83** could undergo α -halide elimination to form the carbene intermediate followed by intramolecular 1,2-migration of hydrogen to afford 4*H*-pyrans (Scheme 27) <2004JA9645, 2003AGE183>.



Scheme 27

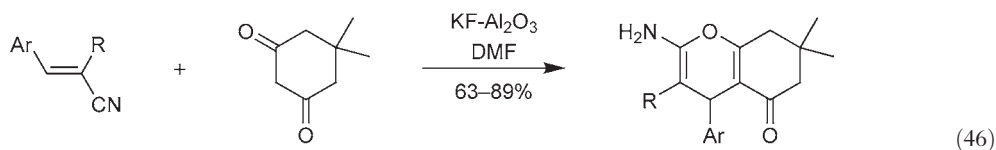
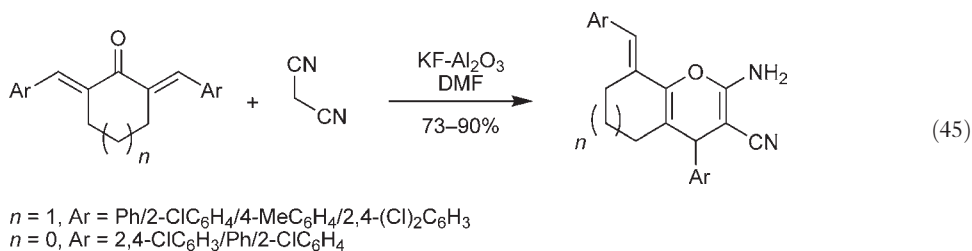
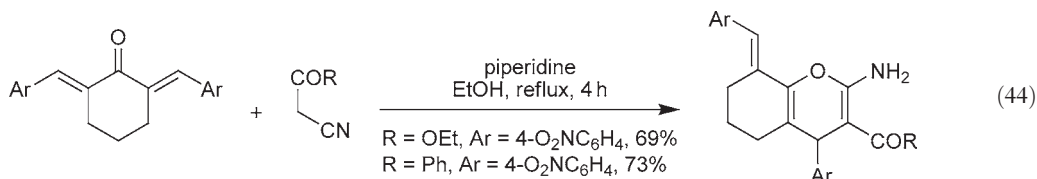
7.08.4.2 Formation of More than One Bond

The prerequisite 1,5-dicarbonyl compounds and their equivalents can be formed *in situ* by a Michael addition of activated methylene groups onto α,β -unsaturated systems <1996CHEC-II>. In this manner, 5-alkylidene-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **84** reacts with ethyl 3-oxobutanoate under microwave irradiation to form the intermediate 1,5-dicarbonyl compound **85**, which spontaneously cyclize to afford the corresponding 4*H*-pyrans in high yield (Scheme 28) <2003SC3747>.



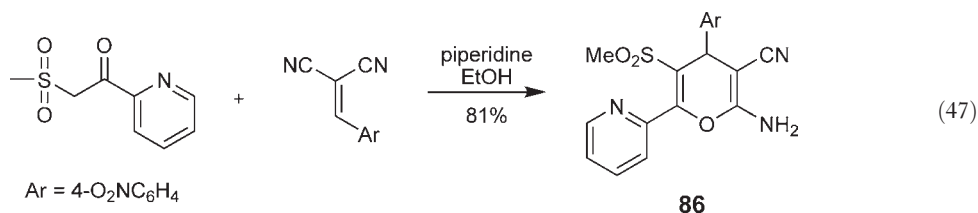
Scheme 28

When methylene activation is provided by a nitrile group, 2-amino-4*H*-pyrans are formed (Equation 44) <2001T10163>. Likewise, malononitrile reacts with α,β -unsaturated carbonyl systems to provide 2-amino-3-cyano-4*H*-pyrans (Equation 45) <2004SC1425>. Acrylonitrile derivatives also react with carbonyl activated methylene groups to afford 2-amino-4*H*-pyrans (Equation 46) <2003SC119>.

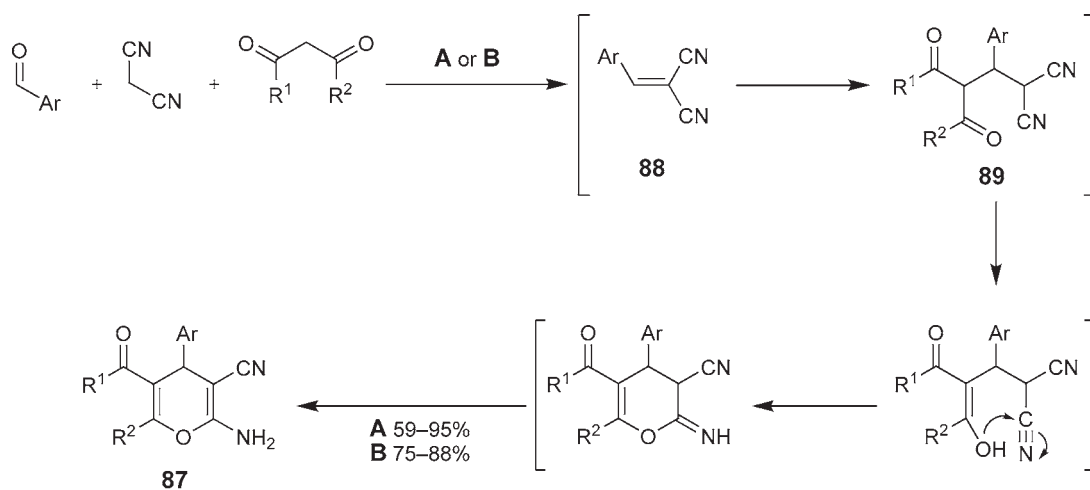


$\text{R} = \text{CN}$, Ar = Ph/4-MeC₆H₄/3,3-OCH₂OC₆H₃/3,4-(MeO)₂C₆H₃
 $\text{R} = \text{CN}$, Ar = 4-ClC₆H₄/4-O₂NC₆H₄/2-furyl
 $\text{R} = \text{CO}_2\text{Me}$, Ar = Ph/4-MeC₆H₄/4-ClC₆H₄/2-ClC₆H₄
 $\text{R} = \text{CO}_2\text{Et}$, Ar = Ph/4-MeC₆H₄/4-ClC₆H₄/2-ClC₆H₄/3,4-(OCH₂O)₂C₆H₃

β -Keto-sulfones, which contain a 2-pyridyl ketone moiety, react with alkylidenemalononitriles to afford 2-amino-5-sulfonyl-4-aryl-6-(pyridin-2-yl)-4*H*-pyran-3-carbonitriles **86** (Equation 47) <1997JOC6575>. Likewise, β -keto-sulfoxides featuring a 2-pyridyl ketone moiety react with alkylidenemalononitriles to form 2-amino-5-sulfinyl-4-aryl-6-(pyridin-2-yl)-4*H*-pyran-3-carbonitriles. Additionally, chiral β -keto-sulfoxides that contain a 2-pyridyl ketone moiety can add to alkylidenemalononitriles with high stereoselectivity <1997JOC6575>.



In a one-pot three-component reaction, aromatic aldehydes, malononitrile and 1,3-dicarbonyl compounds react to form 2-amino-5-carboxy-4-aryl-4*H*-pyran-3-carbonitriles **87**. The reaction proceeds by an initial Knoevenagel condensation of malononitrile with the aromatic aldehyde to afford the 2-benzylidenemalononitrile intermediate **88**. Michael addition of the activated methylene group forms the 1,5-dicarbonyl equivalent **89**, which upon ring closure affords 4*H*-pyrans (Scheme 29) <2004SL871, 1999H(51)1101>.



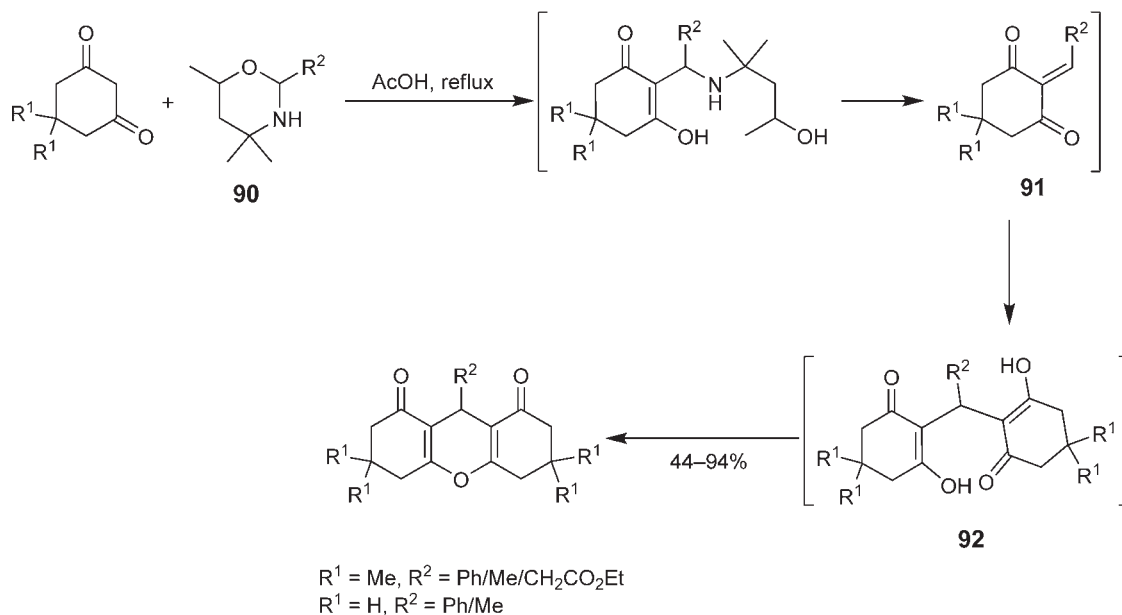
A HTMAB (10 mol%), H₂O
 R¹ = –CH₂C(Me)₂CH₂– = R²
 Ar = Ph, 2-ClC₆H₄/3-ClC₆H₄/4-ClC₆H₄/2-O₂NC₆H₄/4-O₂NC₆H₄/3-O₂NC₆H₄
 Ar = 3-HO-4-MeOC₆H₃/4-Me₂NC₆H₃/4-HOC₆H₄/4-MeOC₆H₄/3,4-(MeO)₂C₆H₃/4-MeC₆H₄
B electrolysis, MeCN, TBAB
 R¹ = OEt, R² = Me
 Ar = Ph/4-ClC₆H₄/3-O₂NC₆H₄/2-thienyl/4-pyridyl

HTMAB = hexadecyltrimethyl ammonium bromide
 TMBAB = tetrabutyl ammonium bromide

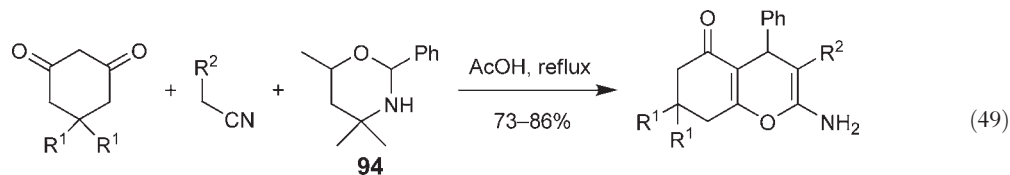
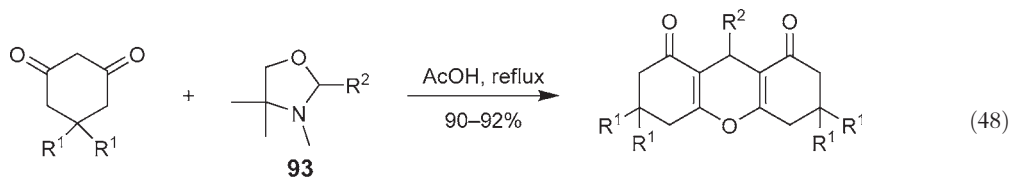
Scheme 29

Oxazinanes **90** react with 1,3-cyclohexanediones, in acetic acid under reflux, to afford the alkylidene 1,3-diketone intermediate **91**. Michael addition of a second equivalent of 1,3-cyclohexanedione then occurs to form the 1,5-dicarbonyl equivalent **92**, which upon cyclodehydration furnishes tricyclic 4*H*-pyrans (Scheme 30) <1996T14273>.

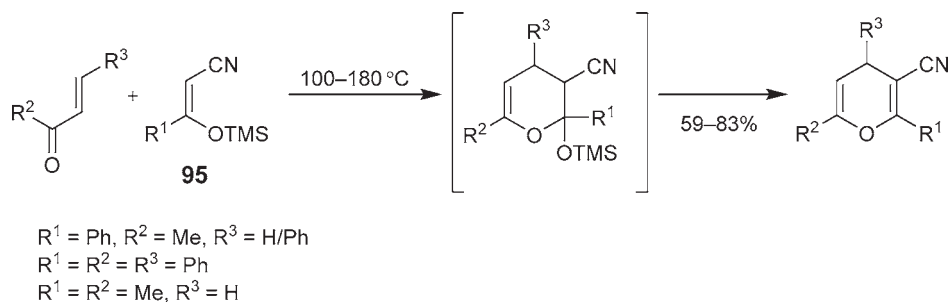
Likewise, 1,3-cyclohexanediones react with 3-methyloxazolidines **93** to afford tricyclic 4*H*-pyrans (Equation 48) <1996T14273>. In the presence of malononitrile or ethyl 2-cyanoacetate, 1,3-cyclohexanediones react with oxazinanes **94** to afford bicyclic 2-amino-4*H*-pyrans (Equation 49) <1996T14273>.



Scheme 30

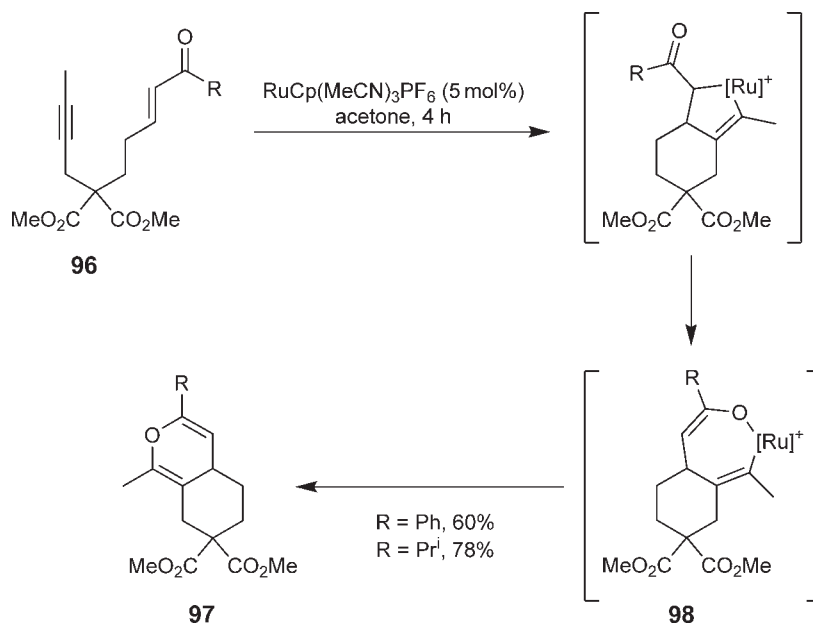


(*Z*)- β -Silyloxyacrylonitriles **95** undergo cycloaddition reactions with α,β -unsaturated ketones to form a dihydropyran intermediate, which eliminates trimethylsilanol to furnish 3-cyano-4*H*-pyrans (Scheme 31) <1997S628>.

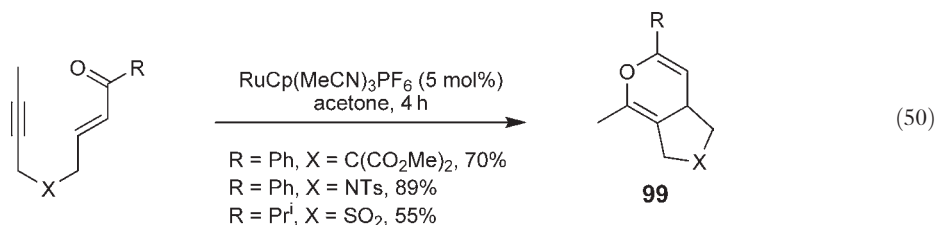


Scheme 31

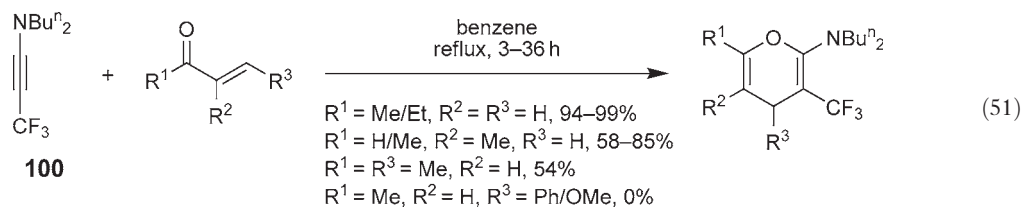
(*E*)-Dimethyl 2-(but-2-ynyl)-2-(5-oxopent-3-enyl)malonates **96** undergo ruthenium-catalyzed intramolecular cyclizations to yield cyclohexyl fused 4*H*-pyrans **97**, most likely via formation of and reductive elimination from the ruthenacycle intermediate **98** (Scheme 32). Likewise, internal alkynes tethered to an α,β -unsaturated ketone via a three-component chain undergo ruthenium-catalyzed cyclizations furnishing 4*H*-pyrans that are fused to five-membered rings **99** (Equation 50) <2000JA5877>.



Scheme 32

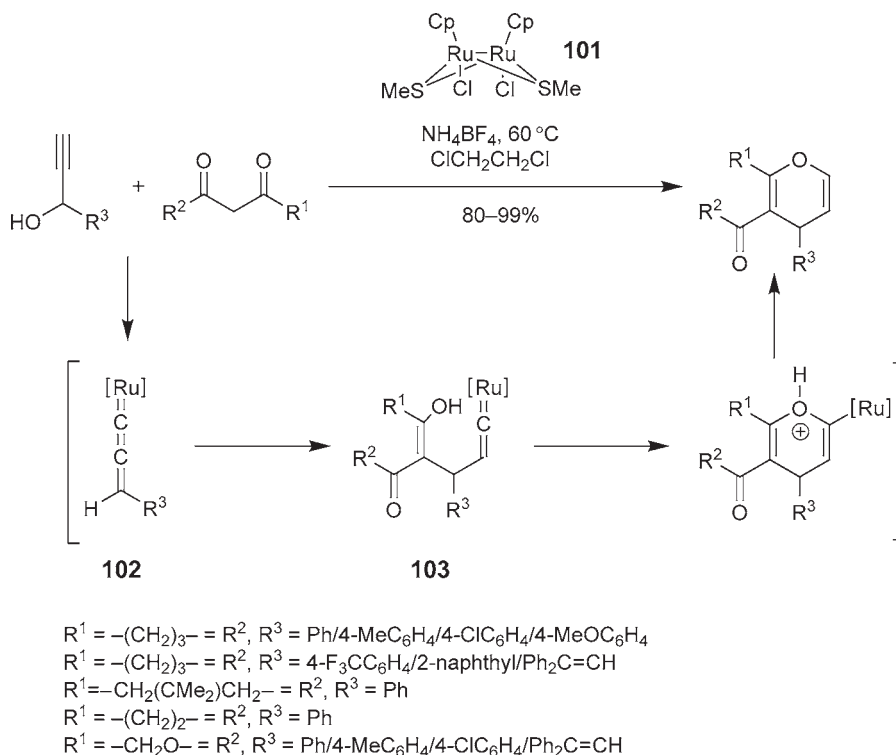


A hetero Diels–Alder reaction of α,β -unsaturated ketones or aldehydes with *N,N*-dibutyl(3,3,3-trifluoro-1-propynyl)-amine **100** affords 2-(dibutylamino)-3-(trifluoromethyl)-4*H*-pyrans in good yield (Equation 51). However, β -methoxy and β -phenyl- α,β -unsaturated ketones fail to react under these conditions (Equation 51) <2000CL666>.

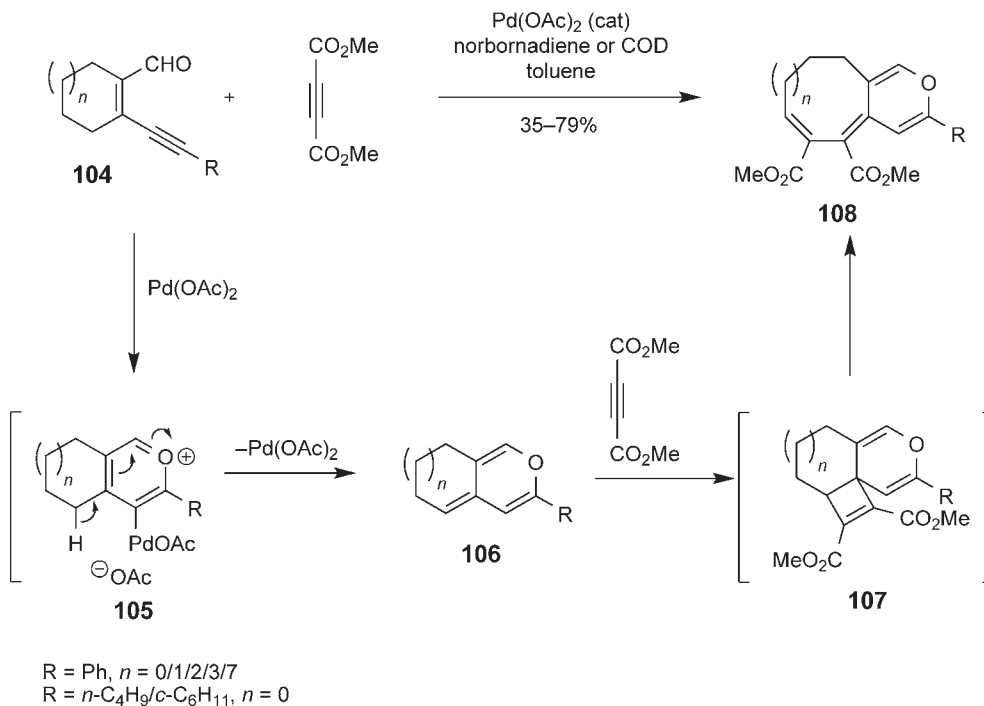


The thiolate-bridged diruthenium complex **101** can promote a cycloaddition reaction between propargylic alcohols and 1,3-dicarbonyl compounds to provide 3-acyl-4*H*-pyrans in excellent yield (Scheme 33). The reaction proceeds via formation and alkylation of the allenylidene complex **102** to form the vinylidene intermediate **103**, which upon cyclization furnishes 4*H*-pyrans (Scheme 33) <2004JOC3408>.

Enynals **104** can undergo a palladium-catalyzed cyclization to form the pyrylium intermediate **105**, which upon deprotonation affords the triene **106**. In the presence of DMAD, a [2+2]-cycloaddition then occurs to form the tricyclic 4*H*-pyran intermediate **107**, which undergoes expansion of the cyclobutene ring to afford the bicyclic 4*H*-pyrans **108** (Scheme 34) <2004SI1409>.



Scheme 33

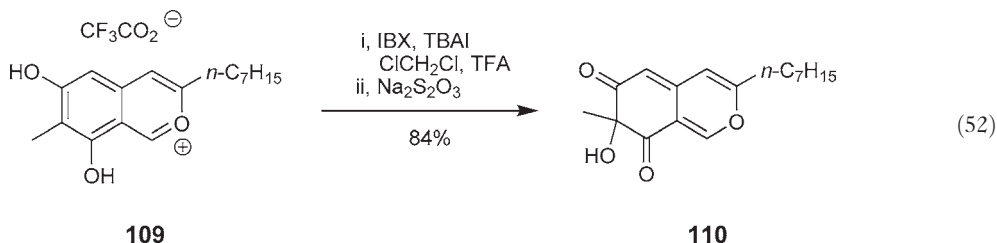


Scheme 34

7.08.4.3 From a Preformed Heterocyclic Ring

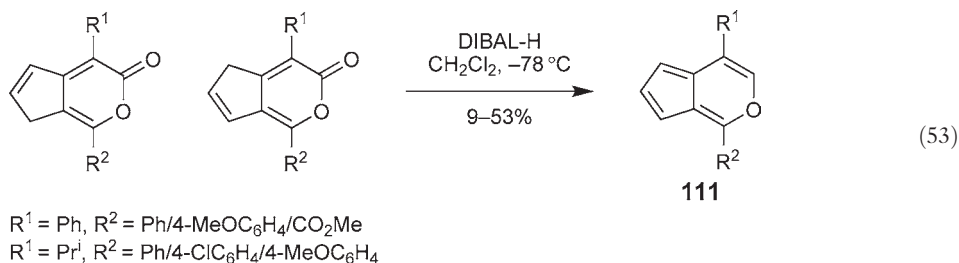
7.08.4.3.1 From pyrylium salts

3-Heptyl-6,8-dihydroxy-7-methylisochromenylium 2,2,2-trifluoroacetate **109** can be oxidized using *ortho*-iodobenzoic acid (IBX) to afford the azaphilone nucleus **110** in high yield (Equation 52) <2004AGE1239>.



7.08.4.3.2 From pyranones

Cyclopenta[*c*]pyrans **111** are formed upon treatment of a regioisomeric mixture of cyclopenta[*c*]pyran-3(7*H*)-ones and cyclopenta[*c*]pyran-3(5*H*)-ones with DIBAL-H (Equation 53) <1998CC2387>.



7.08.5 4*H*-Chromenes (4*H*-1-Benzopyrans)

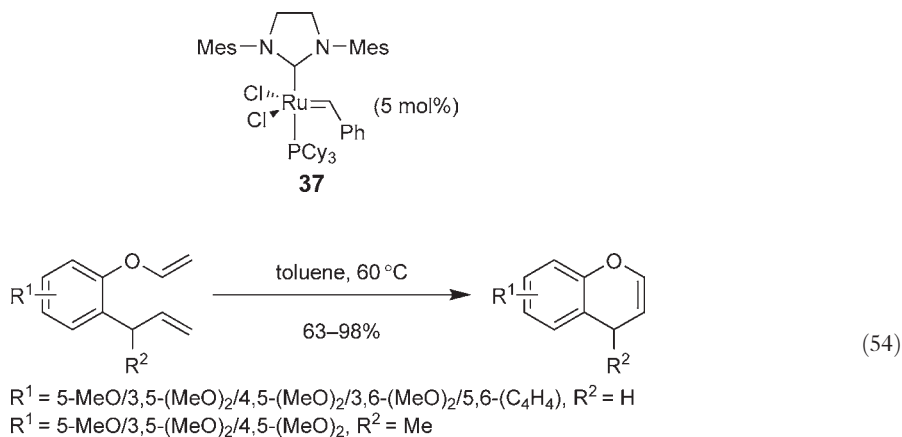
7.08.5.1 Formation of One Bond

7.08.5.1.1 Adjacent to the heteroatom

The acid-catalyzed cyclization of 2-hydroxyphenylpropan-3-ones affords 4*H*-chromenes and is discussed in detail in the preceding volumes <1984CHEC, 1996CHEC-II>.

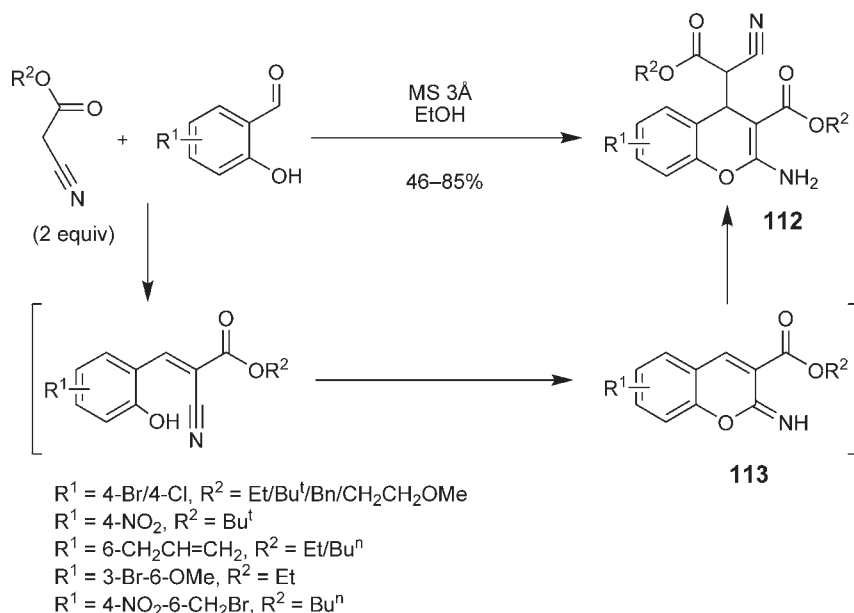
7.08.5.1.2 β to the heteroatom

RCM of 1-allyl-2-(vinylloxy)benzenes using Grubbs' second generation catalyst **37** provides 4*H*-chromenes in excellent yield (Equation 54) <2003TL311, 2005T9996>.



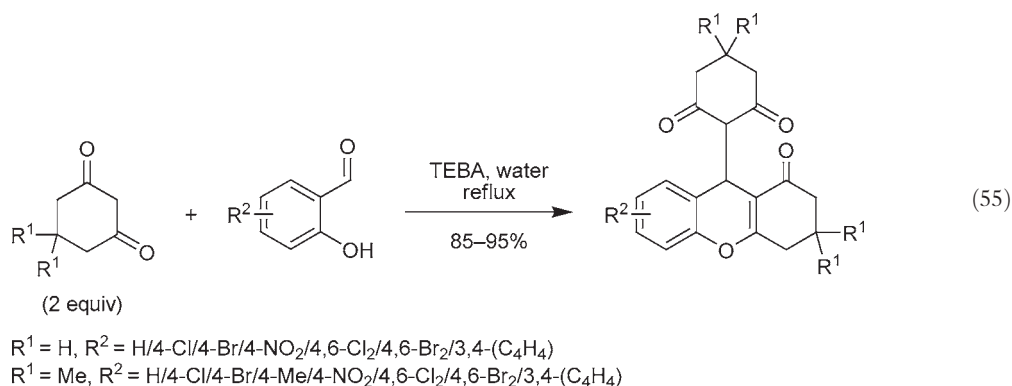
7.08.5.2 Formation of More than One Bond

Salicylaldehydes usually react with activated methylene groups to afford coumarins; however, when activation of the methylene group is brought about by a nitrile group, 2-amino-4*H*-chromenes are formed. In this manner, salicylaldehydes react with two equivalents of ethyl 2-cyanoacetate in the presence of 3 Å molecular sieves to form 2-amino-4*H*-chromenes **112** in moderate yield (Scheme 35) <2000TL6993>. The reaction proceeds via an initial Knoevenagel condensation of the aromatic aldehyde with the activated methylene group, followed by cyclization to form the 2-imino-2*H*-chromene-3-carboxylate intermediate **113**. Michael addition of a second molecule of ethyl 2-cyanoacetate then affords 4*H*-chromenes **112** (Scheme 35) <2000TL6993>.

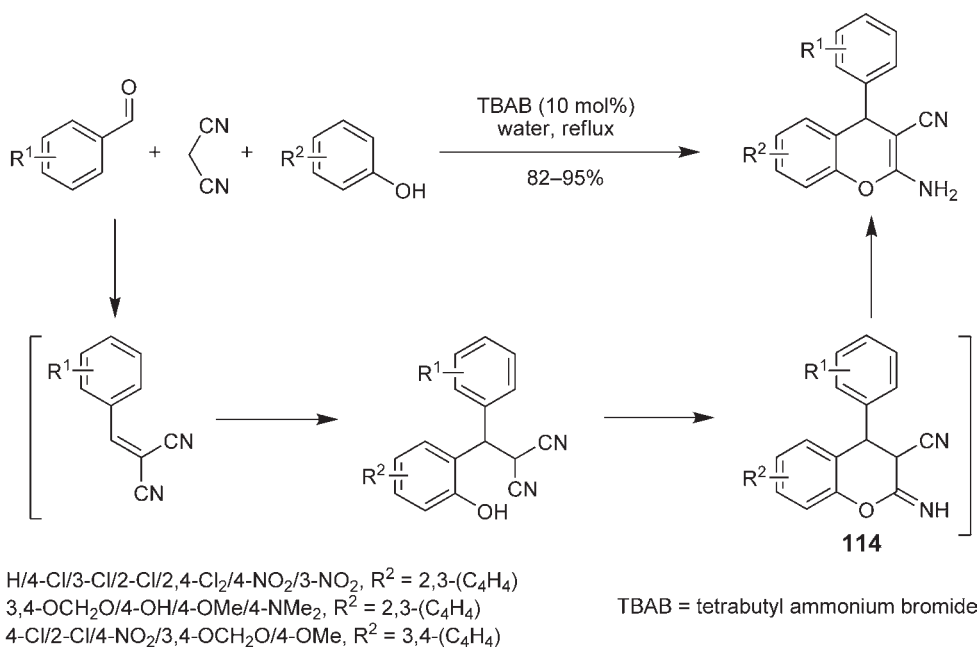


Scheme 35

Likewise, 1,3-hexanediones react with salicylaldehydes in the presence of a catalytic amount of triethylbenzylammonium chloride (TEBA) to afford cyclohexanone fused 4*H*-chromenes in excellent yield (Equation 55) <2005SC97>.

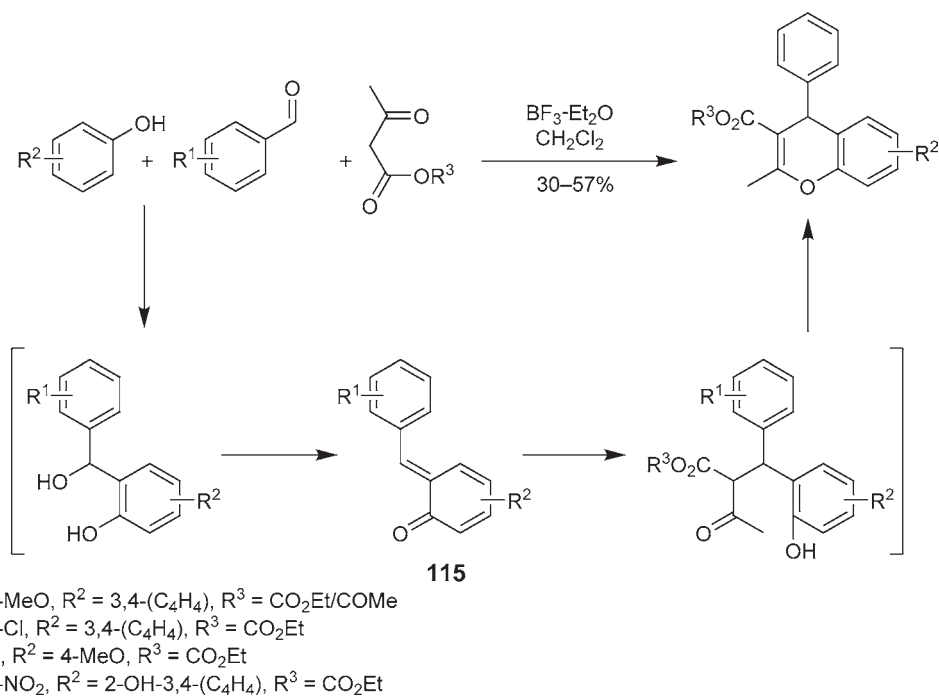


A three-component reaction of aromatic aldehydes, malononitrile and phenols leads to 4-aryl-2-amino-3-cyano-4*H*-chromenes; this reaction can be carried out in aqueous media with improvements in yield and obvious environmental advantages (Scheme 35). The aromatic aldehyde undergoes a Knoevenagel condensation with malononitrile, followed by *ortho*-alkylation of the phenol and cyclization to form the iminopyran intermediate **114**, which isomerizes to the 4*H*-chromenes (Scheme 36) <2003SL2001>. High yields for this three-component reaction can also be achieved in aqueous media when mediated by γ -alumina <2004TL2297> or cetyltrimethylammonium chloride <2001T1395>.



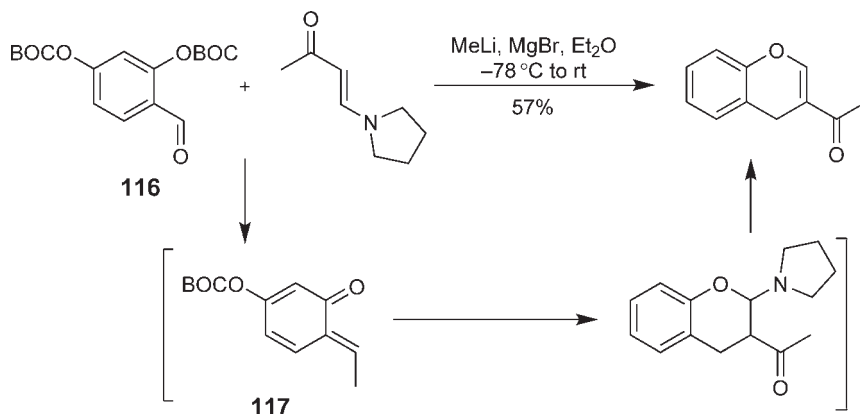
Scheme 36

Benzaldehydes react with phenols and 3-oxobutanoates in the presence of a Lewis acid to afford 4-aryl-3-carboxylate-4*H*-chromenes. The reaction proceeds via formation and reaction of the *ortho*-quinone methide intermediate **115** with 3-oxobutanoates (Scheme 37) <2004CL1058>.



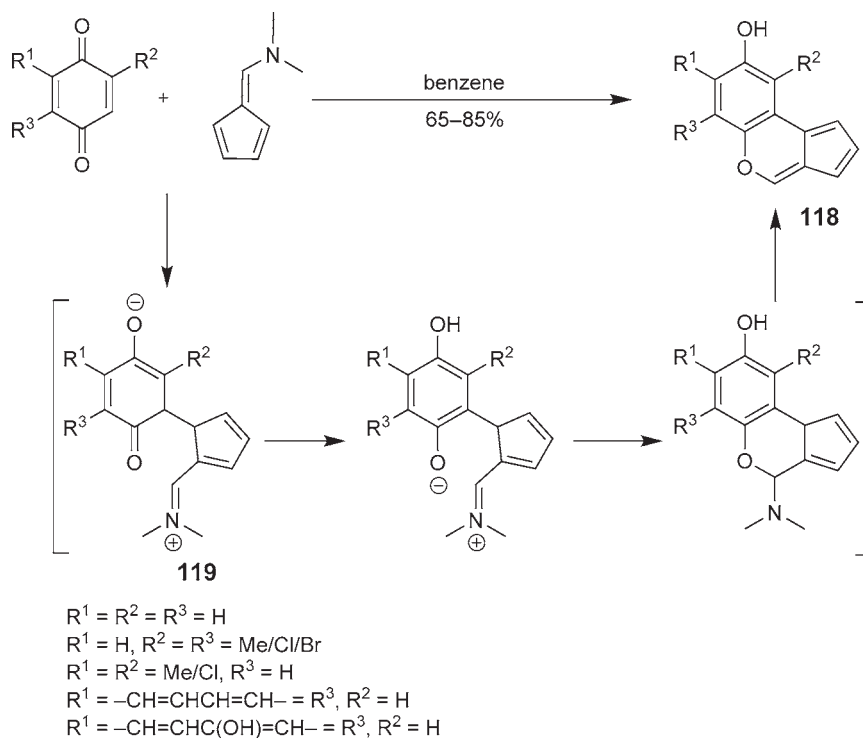
Scheme 37

Treatment of *tert*-butyl 4-formyl-1,3-phenylene dicarbonate **116** with methyl magnesium bromide forms the *ortho*-quinone methide **117**, which undergoes a [4+2]-cycloaddition with (*E*)-4-(pyrrolidin-1-yl)but-3-en-2-one. Elimination of pyrrolidine from the resulting benzopyran then provides 1-(4*H*-chromen-3-yl)ethanone in moderate yield (Scheme 38) <2002JOC6911>.



Scheme 38

Cyclopenta[*c*]-4*H*-chromen-8-ols **118** are formed in high yield by a formal hetero [6+3]-cycloaddition of 6-dimethylaminofulvene with benzoquinones (Scheme 39). The reaction proceeds via a 1,4-addition of 6-dimethylaminofulvene onto the benzoquinone to yield the zwitterionic intermediate **119**. Tautomerization, cyclization and elimination of dimethylamine then affords cyclopenta[*c*]chromenes **118** (Scheme 39) <1999CC2125>. However, a regioisomeric mixture of cyclopenta[*c*]chromenes results from the formal hetero [6+3]-cycloaddition of 6-dimethylaminofulvene with 2-methyl- or 2-chloro-benzoquinone (Equation 56, Table 2) <1999CC2125>. Likewise, a solid phase synthesis of cyclopenta[*c*]-4*H*-chromen-8-ols can be effected by the reaction of resin-bound aminofulvenes with benzoquinones <2000OL2647>.



Scheme 39

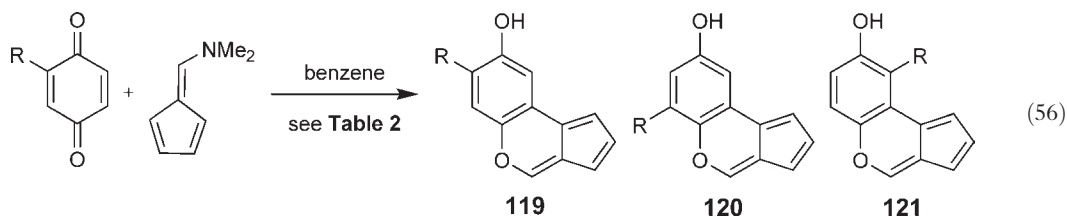
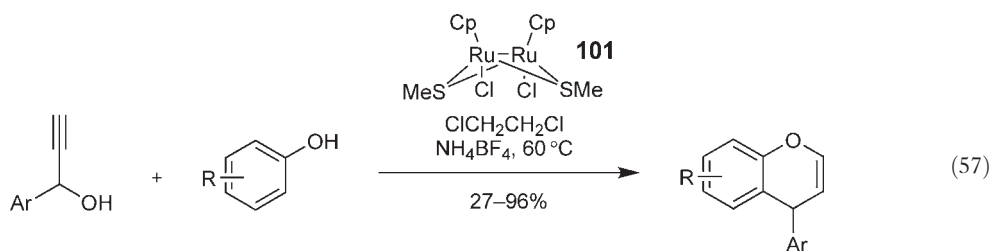


Table 2 Products formed by the reaction of 6-dimethylaminofulvene with 2-methyl and 2-chlorobenzoquinone (Equation 56)

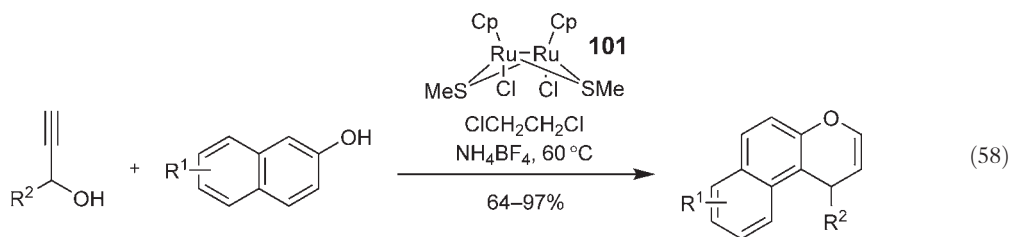
<i>R</i>	Ratio of products 119 : 120 : 121	Total yield (%)
Me	2.1:1:0	82
Cl	2.2:1:3.8	86

The acid catalyzed cycloaddition of propargylic alcohols with phenols gives a mixture of 2*H*- and 4*H*-chromenes <2001SC439>. The thiolate-bridged diruthenium complex **101** can effectively mediate the cycloaddition of aryl propargylic alcohols with phenols or naphthols to afford 4-aryl-4*H*-chromenes (Equations 57 and 58) <2002JA7900>.



Ar = Ph, R = 3,5-(MeO)₂/3,4,5-(MeO)₃/4-NMe₂/4-NEt₂/3,4,5-(Me)₃

Cp = cyclopentadiene

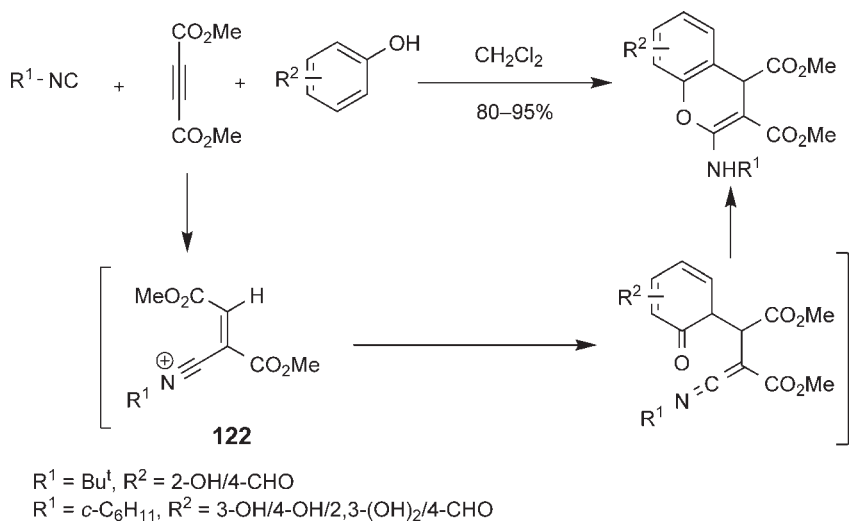


R¹ = H/6-Br/7-OMe, R² = Ph

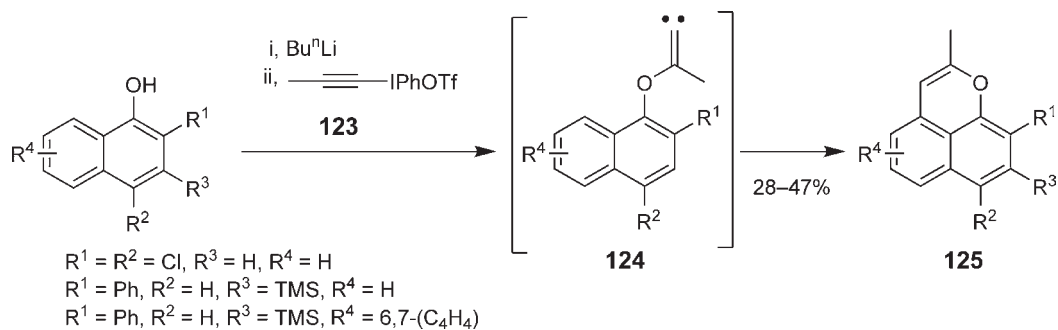
R¹ = H, R² = 2-MeC₆H₄/4-FC₆H₄/Ph₂C=CH

Alkylisocyanates react with dimethyl acetylenedicarboxylate to form the reactive intermediate **122**, which can be trapped by phenols to afford dimethyl 2-amino-4*H*-chromene-3,4-dicarboxylates in high yield (Scheme 40) <2003T9409>. Likewise, alkylisocyanates react with dibenzoyl acetylene and naphthols to yield the corresponding 2-amino-3,4-dibenzoyl-4*H*-chromenes <2003T1289>.

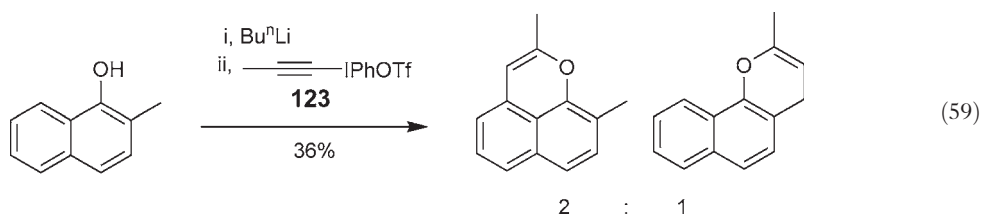
Alkylidenecarbenes **124**, formed from alkynylidonium salts **123** and 1-naphthol derivatives, undergo 1,6-C-H insertion at the *peri*-position to yield benzo[*de*]chromenes **125** (Scheme 41) <2001TL6031>. The alkylidenecarbene formed from alkynylidonium salt **123** and 2-methylnaphthalen-1-ol, can undergo 1,6-C-H insertion at both the *peri*-position and at the 2-methyl substituent, resulting in a 2:1 mixture of 2,9-dimethylbenzo[*de*]chromene and 2-methyl-4*H*-benzo[*h*]chromene (Equation 59) <2001TL6031>.



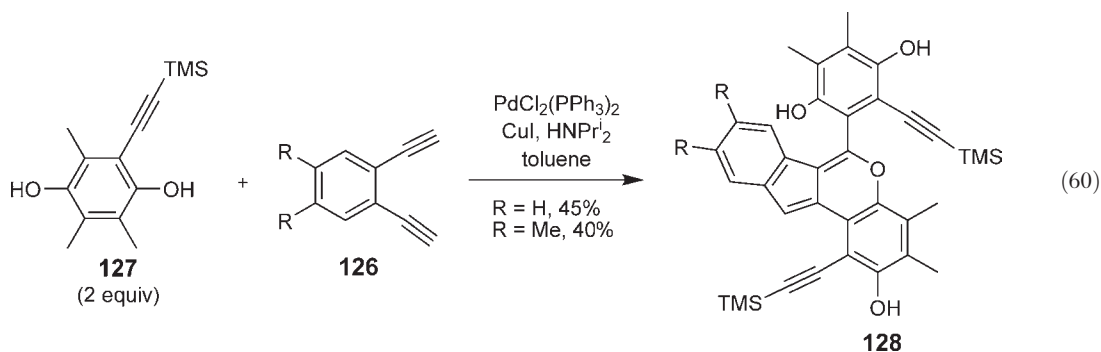
Scheme 40



Scheme 41



1,2-Diethynylbenzenes **126** react with two equivalents of 2-((trimethylsilyl)ethynyl)benzene-1,4-diol **127** via an alkyne-zipper type bicyclization to afford the complex indenopyran ring systems **128** (Equation 60) <1998TL8237>.



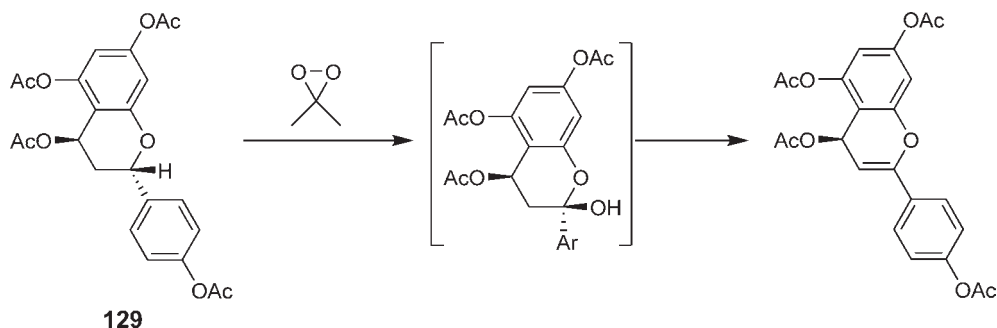
7.08.5.3 From a Preformed Heterocyclic Ring

7.08.5.3.1 From pyrylium salts

Nucleophiles attack at C-4 of flavylium salts to afford 4*H*-chromenes <2001EJO4451, 1997JOC8198>.

7.08.5.3.2 From chromans

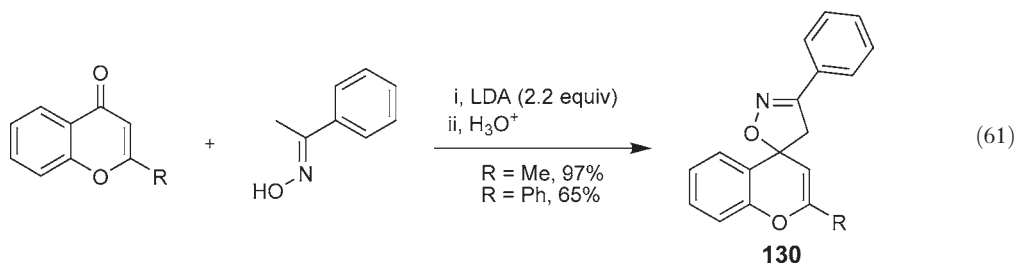
Elimination of water from chroman-2-ols using oxalic acid under benzene reflux <2002T2163> or POCl₃ <1997TL4651> affords 4*H*-chromenes. Treatment of the chroman **129** with dimethyldioxirane affords the corresponding 4*H*-chromene via dehydration of the chroman-2-ol intermediate (Scheme 42) <1997TL4651>.



Scheme 42

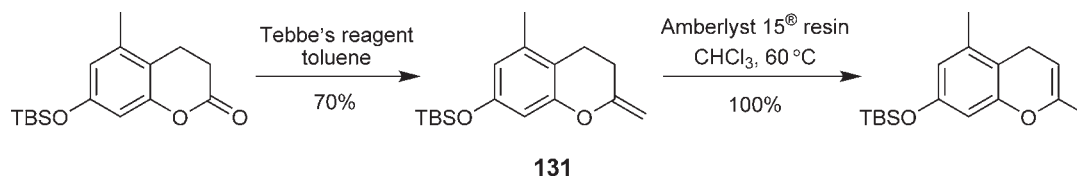
7.08.5.3.3 From chromones

Nucleophiles usually react with 4*H*-benzopyran-4-ones at C-2, which results in pyran ring opening. The condensation of dilithiooximes onto 4*H*-chroman-4-ones occurs by a 1,2-addition process to afford 4*H*-chromene-4-spiro-5'-isoxazolines **130** in good yield (Equation 61) <2004TL7351>.



7.08.5.3.4 From chroman-2-ones

7-(*tert*-Butyldimethylsilyloxy)-5-methylchroman-2-one can be converted into *tert*-butyldimethyl(5-methyl-2-methylenechroman-7-yloxy)silane **131** upon treatment with Tebbe's reagent. Isomerization of **131** occurs in the presence of Amberlyst-15® resin affording *tert*-butyl(2,5-dimethyl-4*H*-chromen-7-yloxy)dimethylsilane in quantitative yield (Scheme 43) <1999J(P1)3071>.



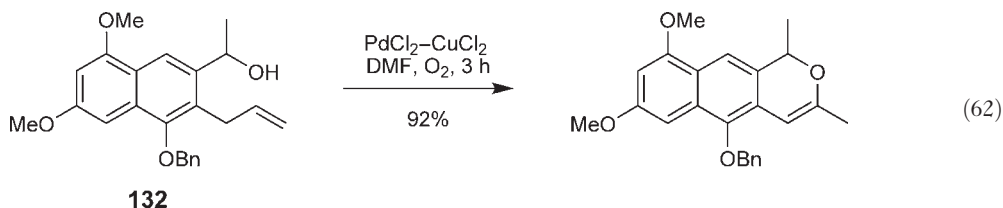
Scheme 43

7.08.6 1*H*-Isochromenes (1*H*-2-Benzopyrans)

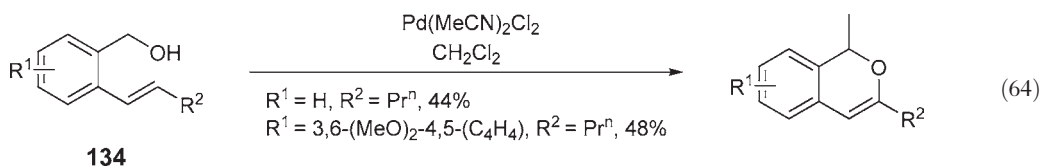
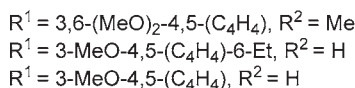
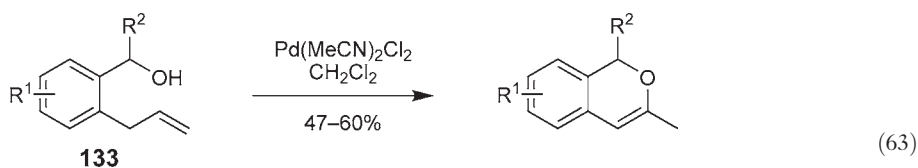
7.08.6.1 Formation of One Bond

7.08.6.1.1 Adjacent to the heteroatom

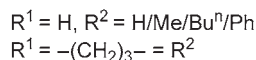
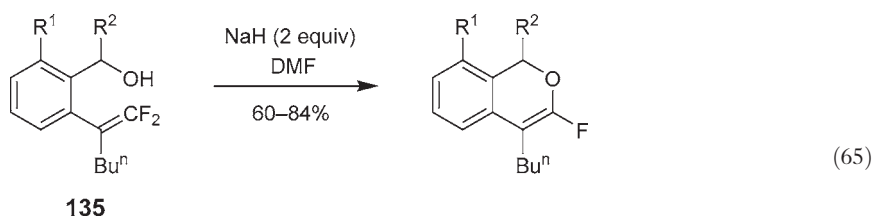
Oxidation of 1-(3-allylnaphthalen-2-yl)ethanol derivative **132** under Wacker oxidation conditions gives 5-(benzyloxy)-7,9-dimethoxy-1,3-dimethyl-1*H*-benzo[*g*]isochromene in excellent yield (Equation 62) <2004OBC2461>.



2-Allylbenzyl alcohols **133** can cyclize to their corresponding isochromenes under palladium(II) catalysis in moderate yield (Equation 63) <1999TL4871>. Similarly, (*E*)-(2-hydroxymethyl)styrene derivatives **134** undergo intramolecular cyclization under palladium(II) catalysis to afford isochromenes (Equation 64) <1999TL4871>.



Treatment of *ortho*-hydroxymethyl- β,β -difluorostyrenes **135** with sodium hydride effects an intramolecular nucleophilic substitution of a vinylic fluorine by the hydroxyl group to furnish 3-fluoro-1*H*-isochromenes (Equation 65) <2001BCJ971>.



Under palladium(II) catalysis 2-alkynylbenzyl alcohols **136** can cyclize by either a 5-*exo-dig* process to form (*Z*)-1-alkylidene-1,3-dihydrobenzofurans **138** or a 6-*endo-dig* process to afford 1*H*-isochromenes **137** (Equation 66). Lower solvent polarity and alkyl, rather than aryl substitution of the alkyne favour a 6-*endo-dig* cyclization (Table 3) <2003T6251>.

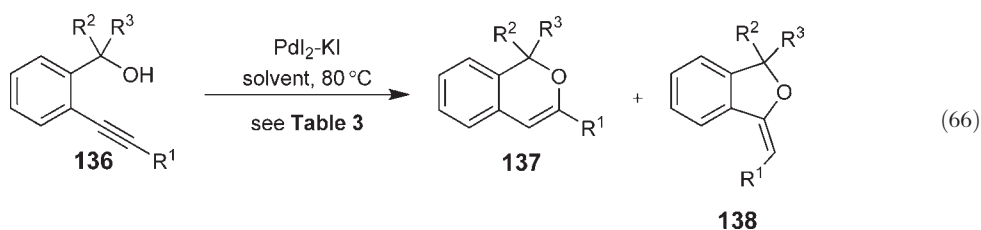
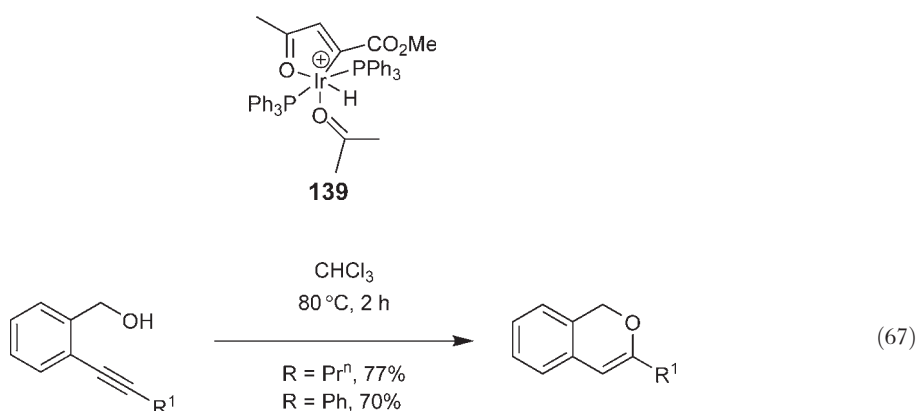


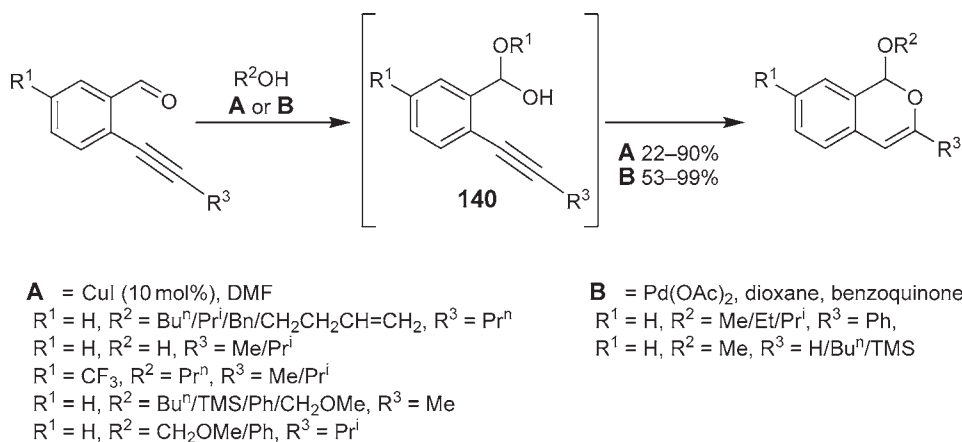
Table 3 Product yields for the Pd(II)-catalyzed cyclizations of 2-alkynylbenzyl alcohols **136** (Equation 67)

R^1	R^2	R^3	<i>Solvent</i>	<i>Yield 137 (%)</i>	<i>Yield 138 (%)</i>
Bu ⁿ	H	H	Dioxane	63	0
Bu ⁿ	Bu ⁿ	H	Dioxane	74	0
Bu ⁿ	Et	Et	Dioxane	73	15
Bu ⁿ	Et	Et	MeOH	0	77
Ph	H	H	Dioxane	40	15
Ph	H	H	DMA	9	49
Ph	Bu ⁿ	H	Dioxane	40	27
Ph	Bu ⁿ	H	DMA	4	70
Ph	Et	Et	MeOH	0	89

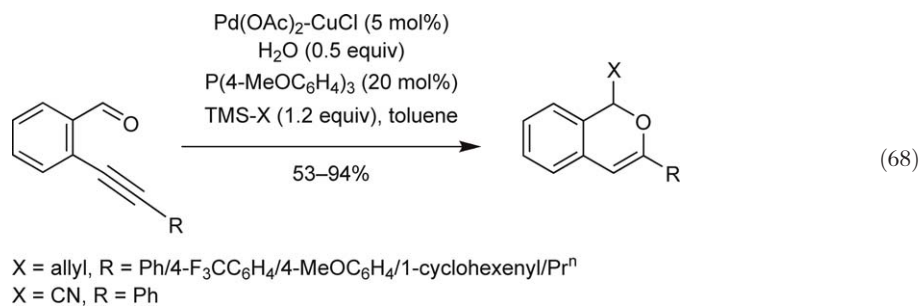
Alkyl and aryl substitution of the alkyne is tolerated for the iridium(III) hydride **139** mediated 6-*endo-dig* cyclization of 2-alkynylbenzyl alcohols to form 1*H*-isochromenes (Equation 67) <2005OL5437>.



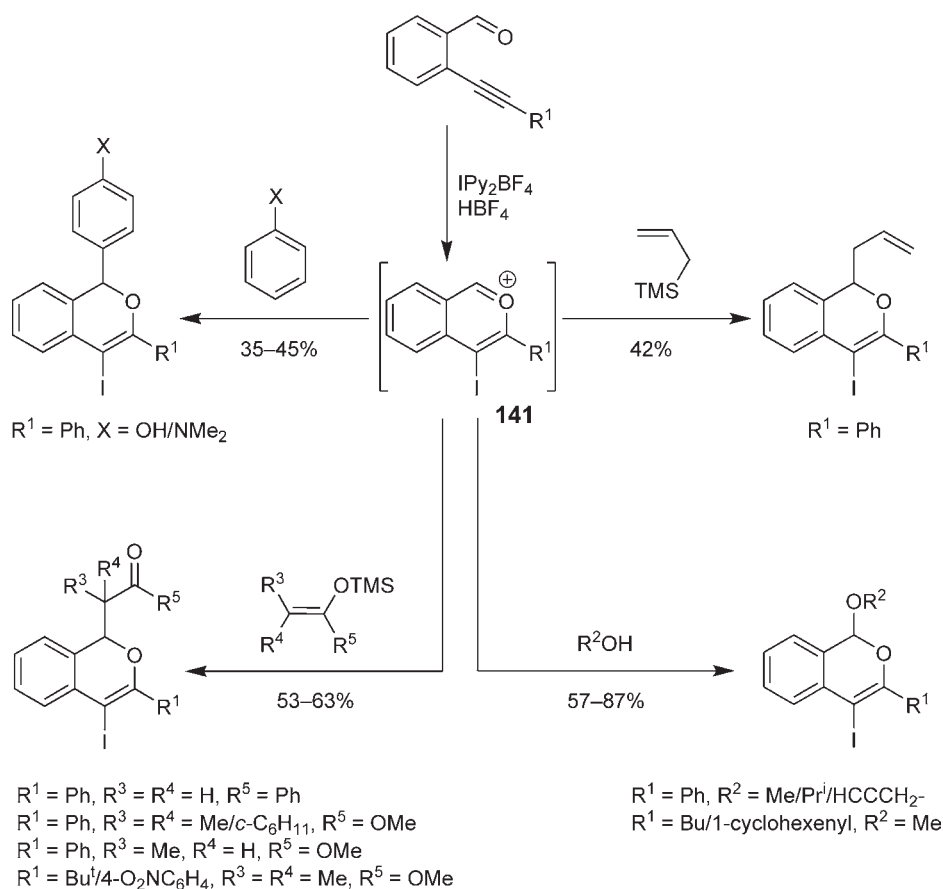
2-Alkynylbenzaldehydes react with alcohols in the presence of a palladium(II) catalyst or CuI to afford 1-alkoxy-1*H*-isochromenes (Scheme 44) <2002JA764, 2004JOC5139>. The reaction proceeds by initial formation of the hemiacetal **140** followed by 6-*endo-dig* cyclization to afford 1*H*-isochromenes (Scheme 44) <2002JA764, 2004JOC5139>.

**Scheme 44**

Allylation of 2-alkynylbenzaldehydes followed by 6-*endo-dig* cyclization can be mediated by a palladium(II)-copper(I) bimetallic system to afford 1-allyl-1*H*-isochromenes. In a similar fashion, cyanation and 6-*endo-dig* cyclization of 2-alkynylbenzaldehydes furnishes 1-cyano-1*H*-isochromenes (Equation 68) <2005T11322>.

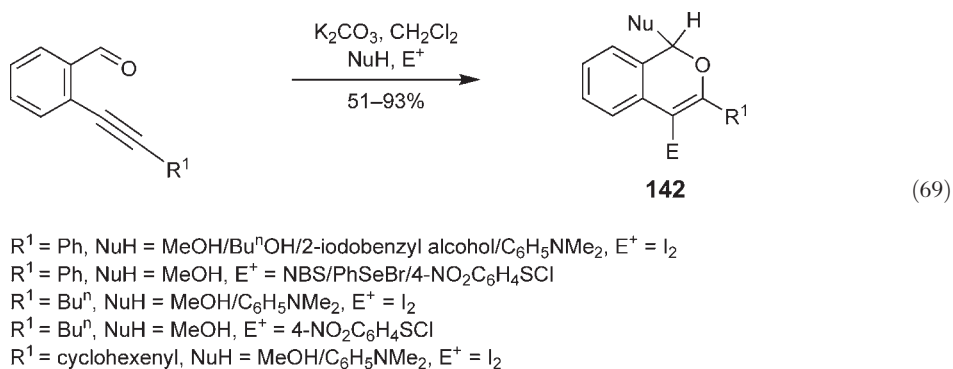


2-Alkynylbenzaldehydes cyclize in the presence of bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4) to form the intermediate 4-iodoisochromenylium species **141**, which can be trapped by various nucleophiles to afford 4-iodo-1*H*-isochromene derivatives (**Scheme 45**) <2003JA9028>.

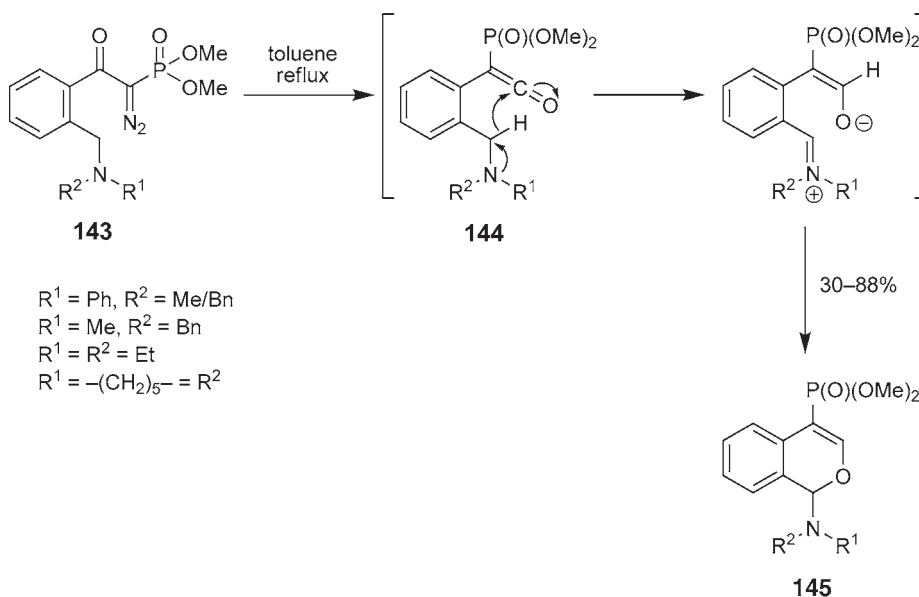


Scheme 45

A range of electrophiles can promote the cyclization of 2-alkynylbenzaldehydes with the subsequent trapping of various nucleophiles to afford 1,3,4-trisubstituted-1*H*-isochromenes **142** in good yield (**Equation 69**) <2004OL1581>.



A thermal Wolff rearrangement of diazophosphonates **143** forms the intermediate ketenes **144**, which undergo [1,5]-hydrogen shift and ring closure to afford 1-amino-4-phosphonate-1*H*-isochromenes (**Scheme 46**) <1998T6457, 1995TL7859>.

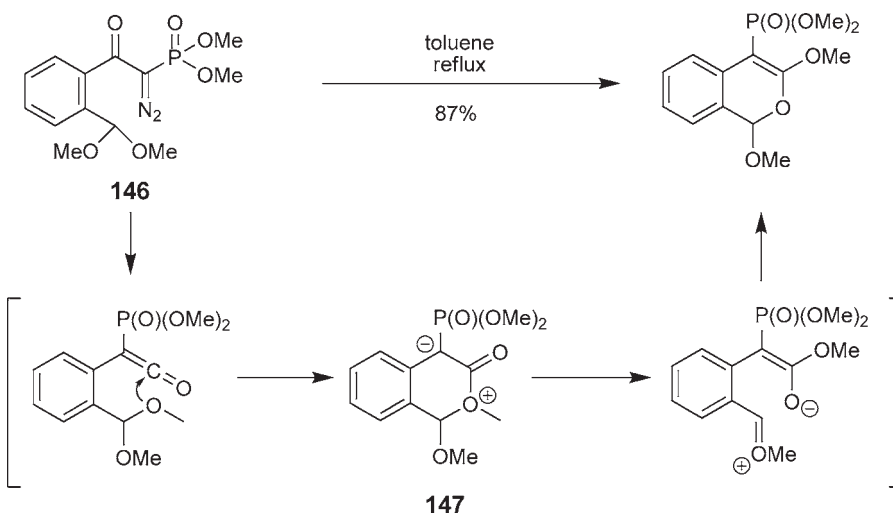


Scheme 46

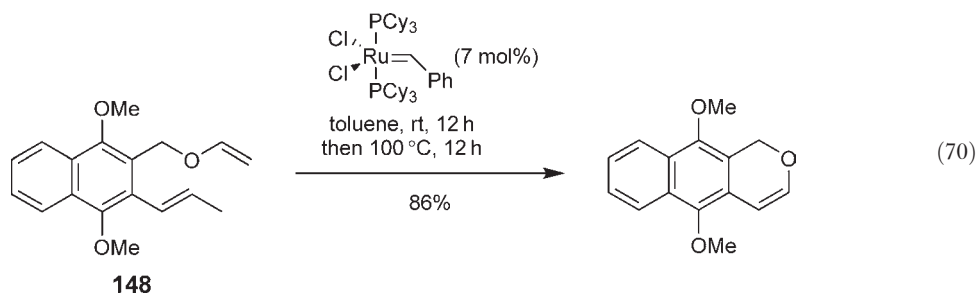
Similarly, the acetal **146** can undergo a thermal Wolff rearrangement to afford the intermediate ketene. Intramolecular nucleophilic attack of the acetal oxygen onto the ketene forms the zwitterion **147**. Subsequent C–O⁺ bond cleavage and cyclization then furnishes dimethyl 1,3-dimethoxy-1*H*-isochromen-4-yl phosphonate in excellent yield (**Scheme 47**) <1998T6457>.

7.08.6.1.2 β to the heteroatom

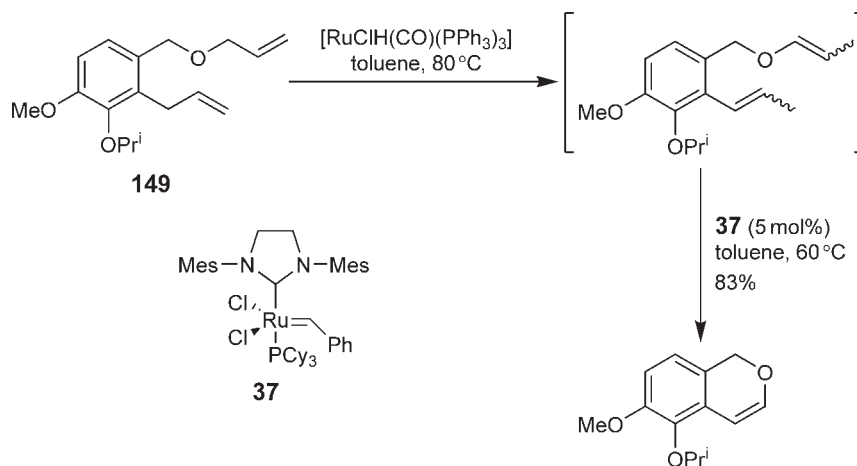
RCM of (*E*)-1,4-dimethoxy-2-(prop-1-enyl)-3-(vinylloxymethyl)naphthalene **148** using Grubbs' first generation catalyst affords 5,10-dimethoxy-1*H*-benzo[*g*]isochromene in high yield (**Equation 70**) <2004TL3443>.



Scheme 47



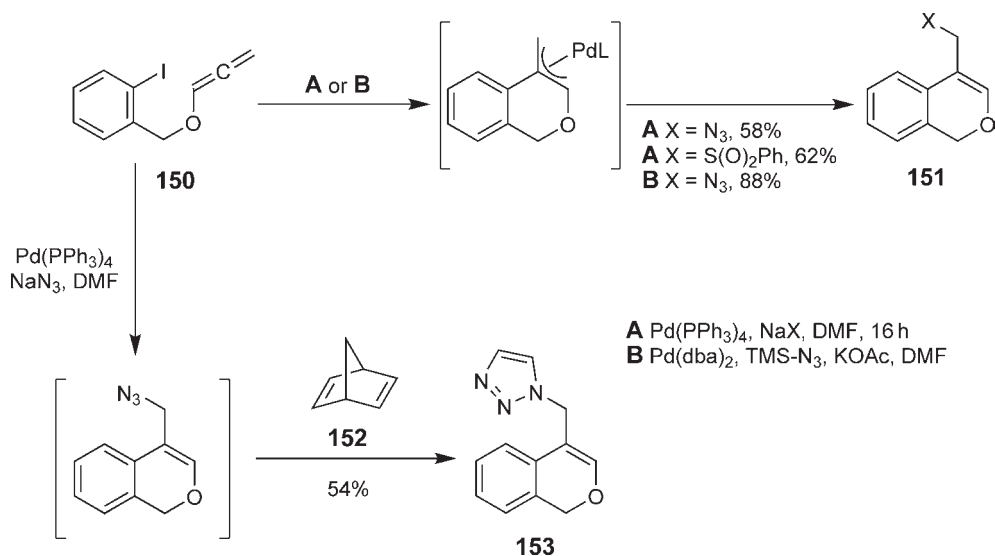
2-Allyl-1-(allyloxymethyl)-3-isopropoxy-4-methoxybenzene **149** can undergo a one-pot ruthenium catalyzed isomerization followed by RCM in the presence of Grubbs' second generation catalyst **37** to afford 5-isopropoxy-6-methoxy-1*H*-isochromene (Scheme 48) <2003SL1859>.



Scheme 48

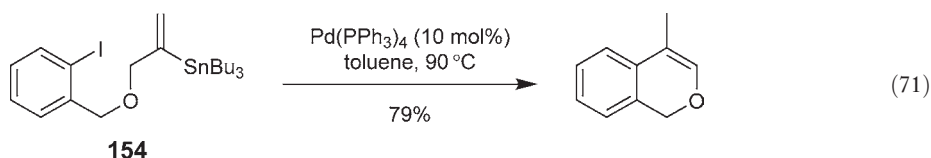
7.08.6.1.3 γ to the heteroatom

Palladium catalyzed cyclization of 1-iodo-2-((propa-1,2-dienyloxy)methyl)benzene **150** occurs with concomitant anion incorporation to furnish 4-substituted-1*H*-isochromenes **151** (Scheme 49) <1998TL435, 2000J(P1)3799>. In the presence of norbornadiene **152**, the initially formed azide can undergo a further 1,3-dipolar cycloaddition reaction and fragmentation to give 1-((1*H*-isochromen-4-yl)methyl)-1*H*-1,2,3-triazole **153** (Scheme 49) <1998TL435, 2001T7729>.

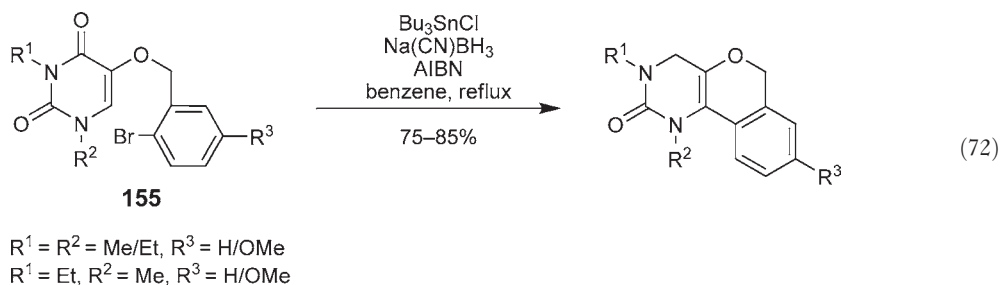


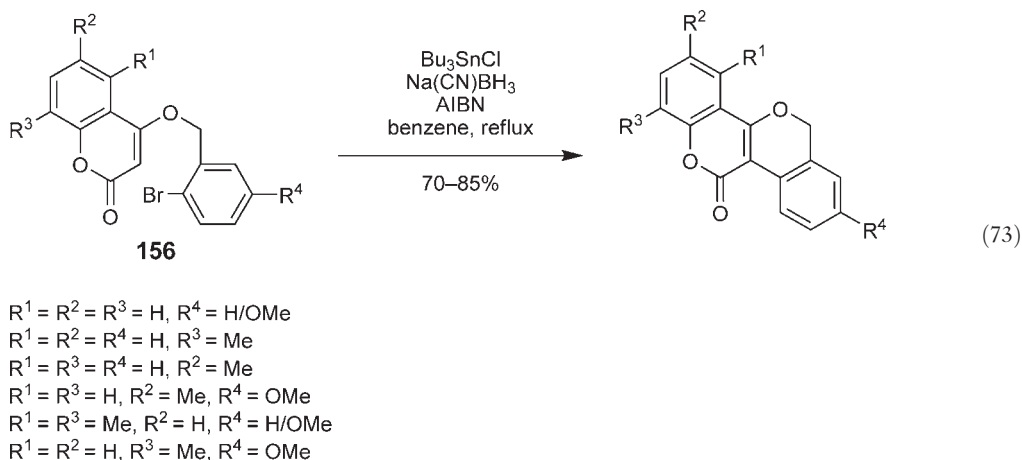
Scheme 49

An intramolecular Stille coupling of tributyl(3-(2-iodobenzyloxy)prop-1-en-2-yl)stannane **154** at 90 °C affords 4-methyl-1*H*-isochromene in good yield (Equation 71) <2004JOC468>.



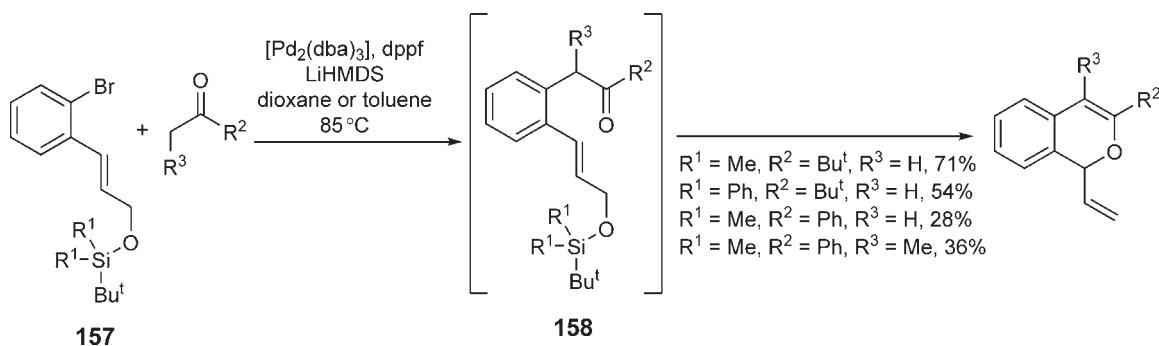
5-(2'-Bromobenzyloxy)pyrimidine-2,4-diones **155** undergo a radical induced cyclization to furnish 1*H*-isochromeno-[4,3-*d*]pyrimidin-2(6*H*)-ones (Equation 72). In a similar fashion, 4-(2'-bromobenzyloxy)benzopyran-7-ones **156** cyclize to afford 1*H*-isochromeno[4,3-*c*]chromen-11(6*H*)-ones in high yield (Equation 73) <2003T2151>.





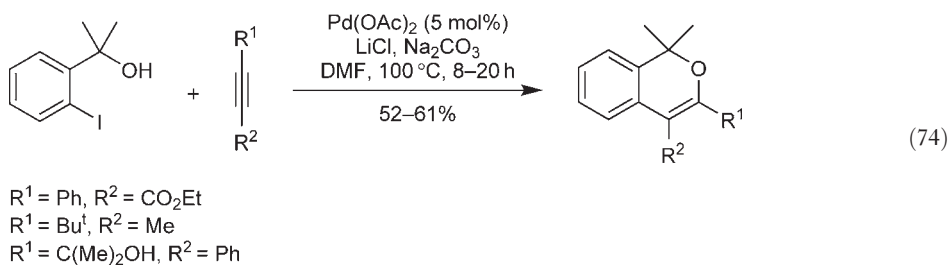
7.08.6.2 Formation of More than One Bond

1-Vinyl-1*H*-isochromenes can be prepared in moderate yield by a palladium-catalyzed coupling of (*E*)-(3-(2-bromophenyl)allyloxy)(*tert*-butyl)silyl derivatives **157** with ketones. The reaction proceeds via initial ketone arylation to furnish the intermediate **158** followed by intramolecular cyclization of the ketone enolate onto the tethered allylic system (Scheme 50) <2000CC1675>.



Scheme 50

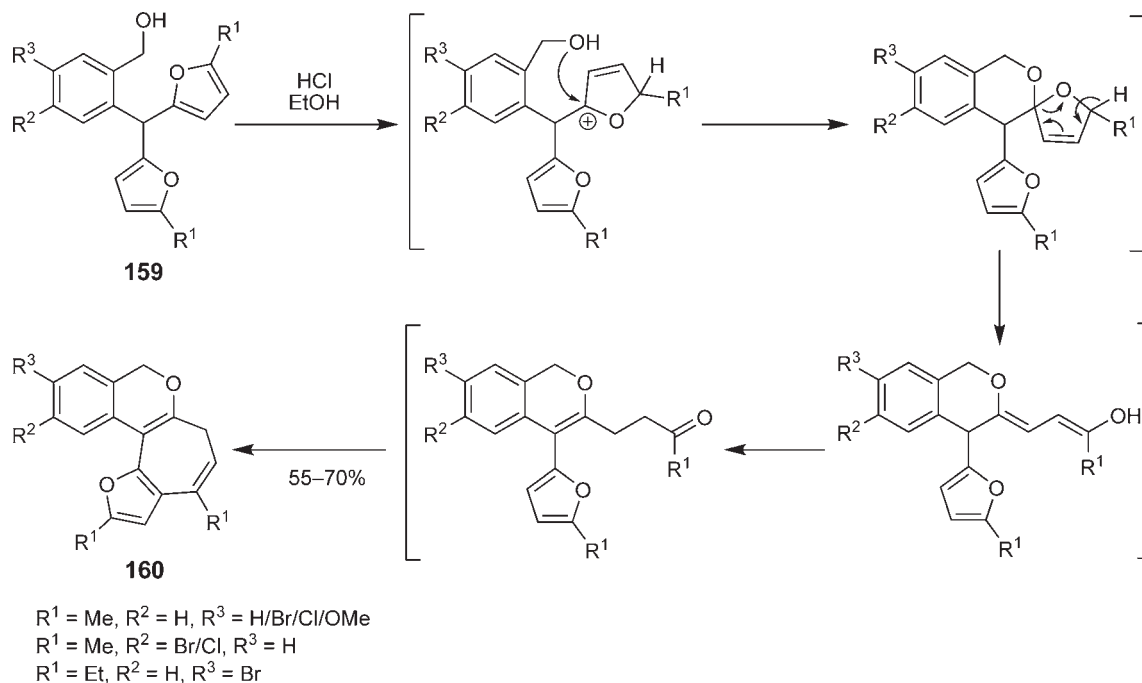
A palladium(II)-mediated cycloaddition of 2-(2-iodophenyl)propan-2-ol with unsymmetrically substituted internal alkynes yields 1,1-dimethyl-1*H*-isochromenes with high regioselectivity (Equation 74) <1995JOC3270>.



7.08.6.3 From Other Heterocycles

7.08.6.3.1 From furans

ortho-Hydroxymethylbenzylfurans **159** undergo acid-catalyzed furan ring opening and recyclization to form cycloheptyl-fused 1*H*-isochromenes **160** (Scheme 51) <2005TL8439>.

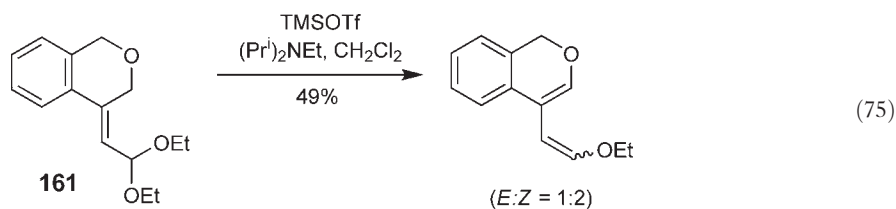


Scheme 51

7.08.6.4 From a Preformed Heterocyclic Ring

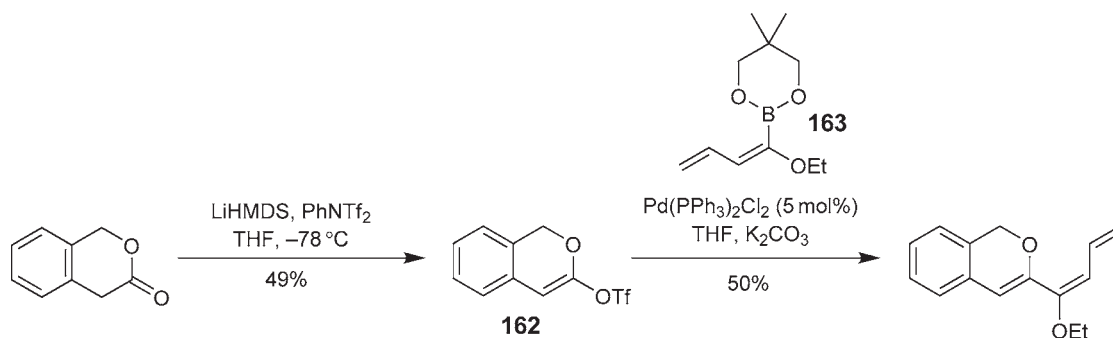
7.08.6.4.1 From isochromans

(*Z*)-4-(2,2-Diethoxyethylidene)isochroman **161** can undergo δ -elimination, in the presence of TMSOTf, to afford 4-(2-ethoxyvinyl)-1*H*-isochromene in moderate yield (Equation 75) <2005JOC489>.



7.08.6.4.2 From isochromanones

1*H*-Isochromen-3-yl trifluoromethanesulfonate **162**, formed from isochroman-3-one, can undergo a palladium-catalyzed cross-coupling reaction with the boronate **163** to afford (*E*)-3-(1-ethoxybuta-1,3-dienyl)-1*H*-isochromene in moderate yield (Scheme 52) <2005T3429>.



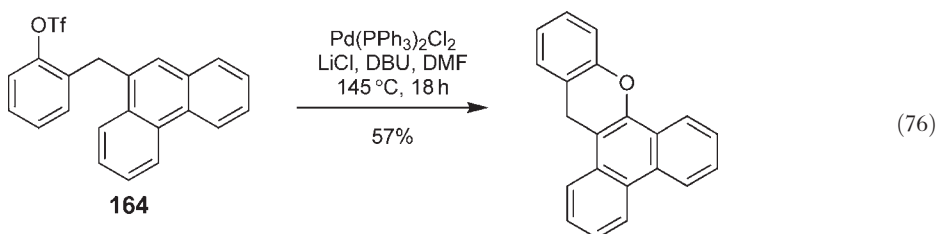
Scheme 52

7.08.7 Xanthenes (9H-Dibenzo[b,e]pyrans)

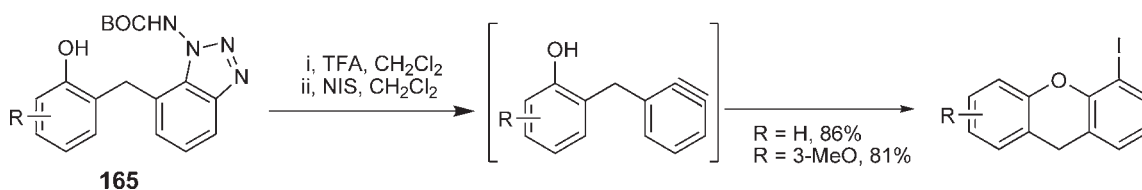
7.08.7.1 Formation of One Bond

7.08.7.1.1 Adjacent to the heteroatom

2-(Phenanthren-9-ylmethyl)phenyl trifluoromethanesulfonate **164** undergoes a palladium-catalyzed cyclization via *S*-*O* bond cleavage to afford 14*H*-dibenzo[*a,c*]xanthene in moderate yield (Equation 76) <2002T5927>.



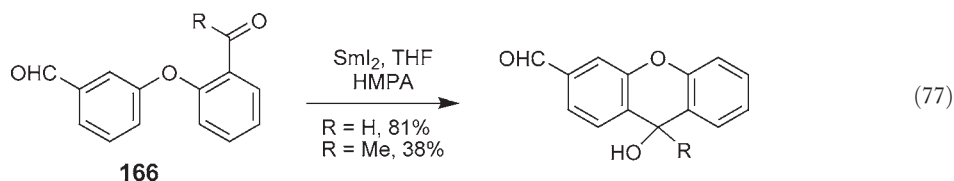
N-Deprotection of 1-(tert-butoxycarbonylamino)benzotriazoles **165** generates a benzyne intermediate which upon treatment with *N*-iodosuccinimide (NIS), undergoes intramolecular trapping by the tethered phenol group with concomitant incorporation of iodine to afford 4-iodo-9*H*-xanthenes in high yield (Scheme 53) <1998SL1141, 2001J(P1)1771>.



Scheme 53

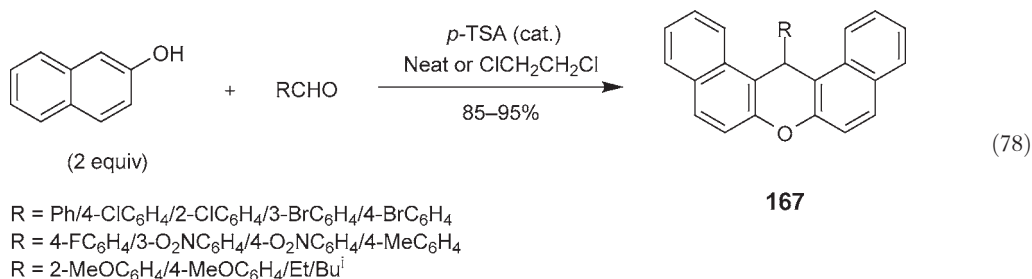
7.08.7.1.2 γ to the heteroatom

Diaryl ethers **166** undergo a samarium(II) iodide promoted intramolecular phenyl-carbonyl coupling to afford 3-formyl-9-hydroxy-9*H*-xanthenes in moderate yield (Equation 77) <2001SC877>.

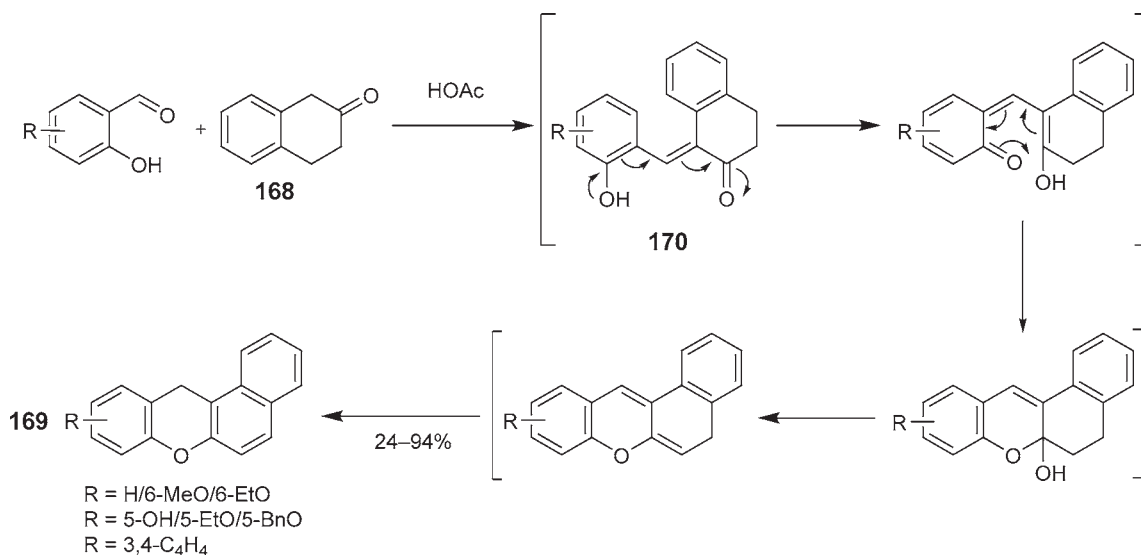


7.08.7.2 Formation of More than One Bond

The acid-mediated condensation of 2-naphthol with aliphatic or aromatic aldehydes can proceed under solvent-free conditions or in dichloroethane to give 14-alkyl/aryl-14*H*-dibenzo[*a,j*]xanthenes **167** in excellent yield (Equation 78) <2005SL955>. Sulfamic acid can also effectively catalyze the condensation of 2-naphthol with aromatic aldehydes either at 125 °C or under microwave irradiation to yield 14-aryl-14*H*-dibenzo[*a,j*]xanthenes in high yield (92–96%) <2005TL8691>.



The acid-catalyzed reaction of salicylaldehydes with 2-tetralone **168** affords 12*H*-benzo[*a*]xanthenes **169**. The reaction proceeds via an initial condensation of the aromatic aldehyde with the activated methylene group to form the intermediate **170**. The extended enolate of the intermediate **170** undergoes electrocyclization, dehydration, and rearomatization to afford 12*H*-benzo[*a*]xanthenes (Scheme 54) <2004TL8999>.

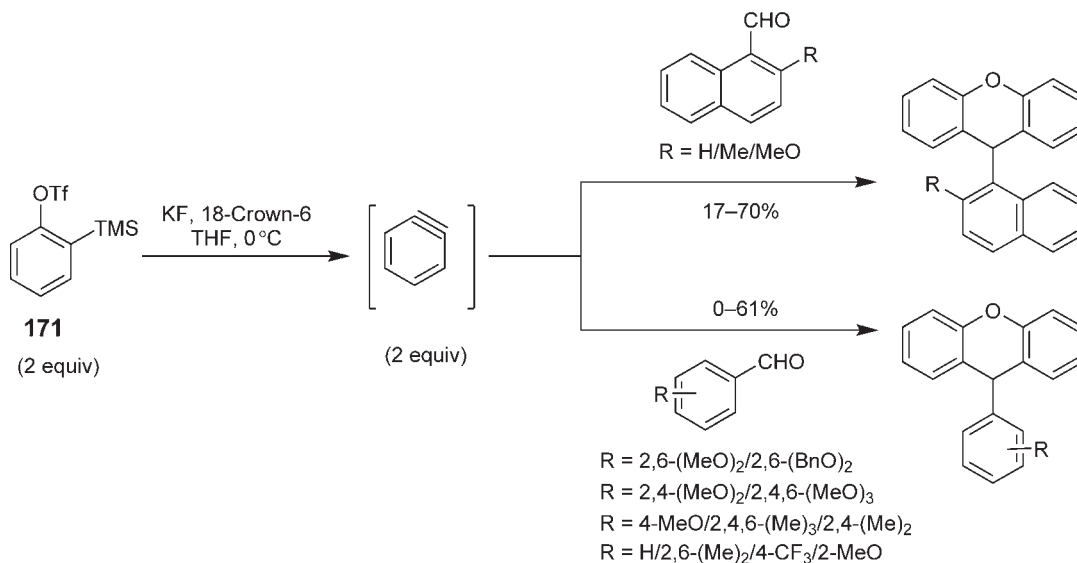


Scheme 54

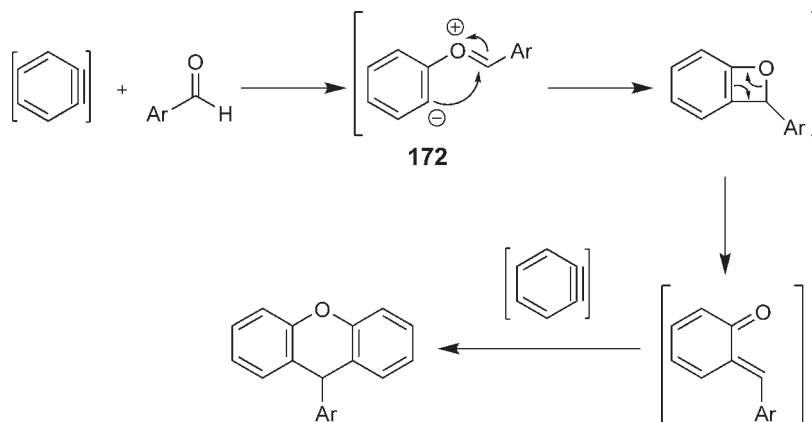
Treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **171** with KF generates benzyne, which can then react with aromatic aldehydes to furnish 9-aryl-9*H*-xanthenes in moderate yield (Scheme 55). Electron-rich aromatic aldehydes are necessary to obtain high yields of the desired xanthenes <2004OL4049>.

The reaction of benzyne with aromatic aldehydes proceeds via nucleophilic attack of the carbonyl oxygen onto the benzyne to give the zwitterionic intermediate **172** followed by cyclization to the benzoxete intermediate. Cycloreversion then forms an *ortho*-quinone methide, which undergoes a [4+2] cycloaddition with a second molecule of the benzyne to form the xanthene (Scheme 56) <2004OL4049>.

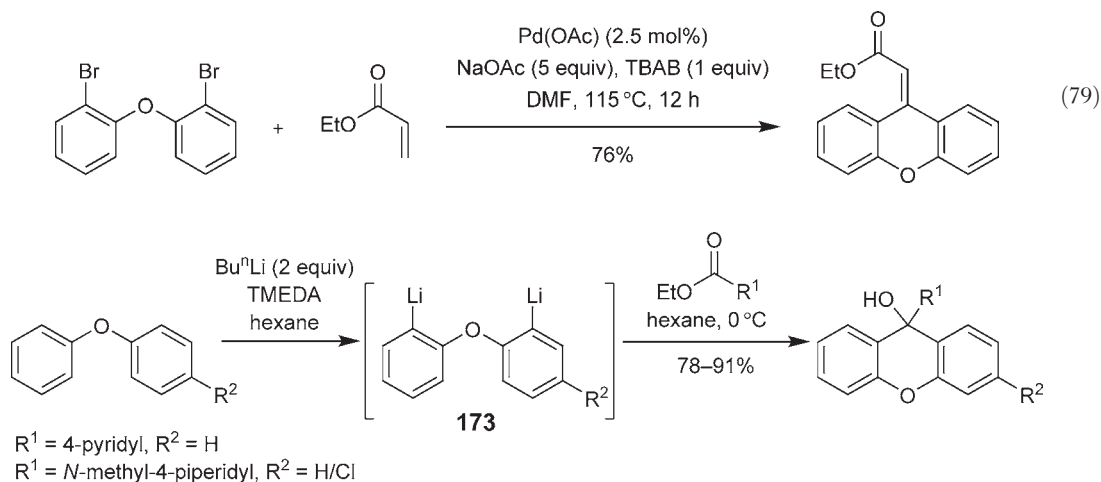
2,2'-Dibromo-diphenyl ether can undergo two consecutive Heck reactions with ethyl acrylate to afford 9-(ethoxycarbonylmethylene)-9*H*-xanthene (Equation 79) <2002TL8559>. 2,2'-Dilithio-diphenyl ether **173**, formed upon treatment of the corresponding diphenyl ethers with *n*-butyllithium, reacts with esters to provide 9-hydroxy-9*H*-xanthenes in good yield (Scheme 57) <1996TL5073>. A palladium-catalyzed coupling of 1,2-dibromobenzene with 1-naphthol derivatives yields benzo[*k,l*]xanthenes **174** (Equation 80) <1999BCJ2345>.



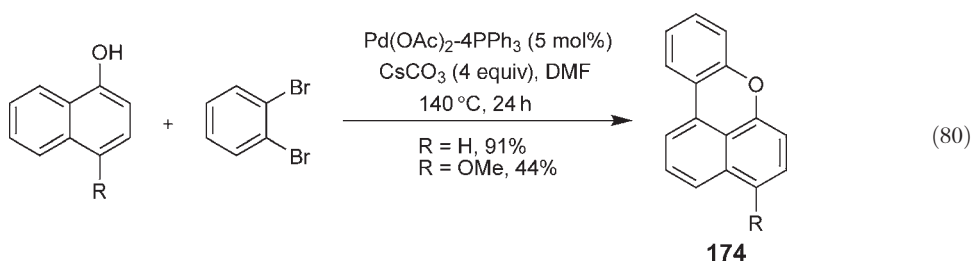
Scheme 55



Scheme 56



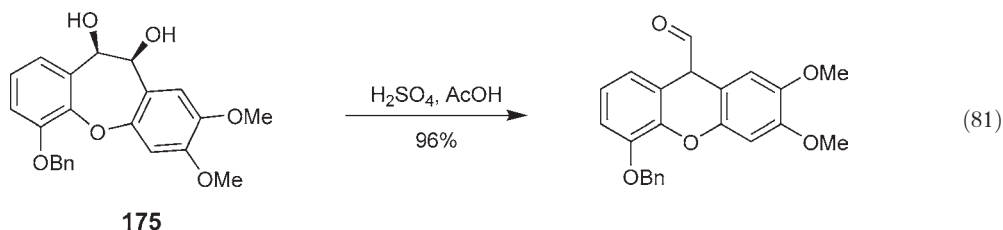
Scheme 57



7.08.7.3 From Other Heterocycles

7.08.7.3.1 From dihydrodibenzo[*b,f*]oxepines

An acid-induced pinacol rearrangement of (10*R*,11*S*)-10,11-dihydrodibenzo[*b,f*]oxepine-10,11-diol **175** affords 5-(benzyloxy)-2,3-dimethoxy-9*H*-xanthene-9-carbaldehyde in excellent yield (Equation 81) <1996JOC5818>.



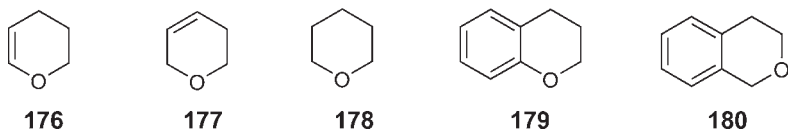
7.08.7.4 From a Preformed Heterocyclic Ring

7.08.7.4.1 From xanthenes

The reduction of xanthenes to 9*H*-xanthen-9-ols can be achieved upon treatment with zinc powder in alkaline ethanol <2001TL5219>. Complete reduction of the carbonyl group of xanthenes is achieved using LAH <2001HCA117> or BH₃-Me₂S <2002OL3139>. Xanthenes can also react with aryl-Grignard or aryllithium reagents to yield 9-aryl-9*H*-xanthen-9-ols in good yield <2002BCJ1325>.

7.08.8 Reduced Pyrans

Dihydropyrans **176**, **177**, tetrahydropyran **178** and their benzo analogues chroman **179** and isochroman **180** are discussed in this section.



7.08.9 Dihydropyrans

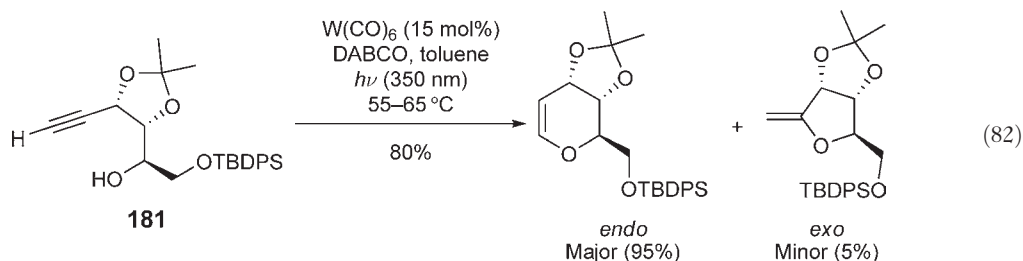
7.08.9.1 3,4-Dihydro-2*H*-pyrans

7.08.9.1.1 Formation of one bond

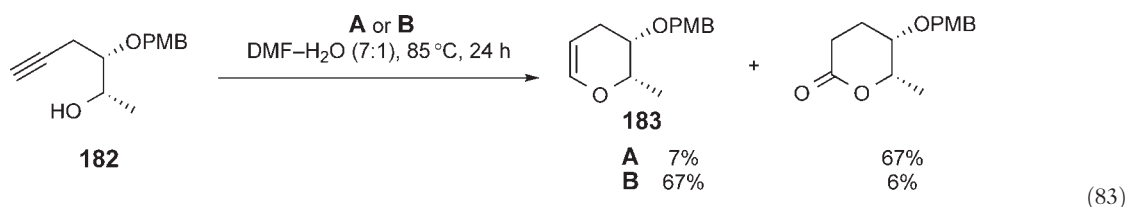
7.08.9.1.1(i) Adjacent to the heteroatom

A tungsten-catalyzed cycloisomerization of the D-ribose-derived alkynyl alcohol **181** provides a 6-*endo-dig* cyclization route to 3,4-dihydropyrans. Excellent *endo*-mode selectivity, and hence minimal tetrahydrofuran production is

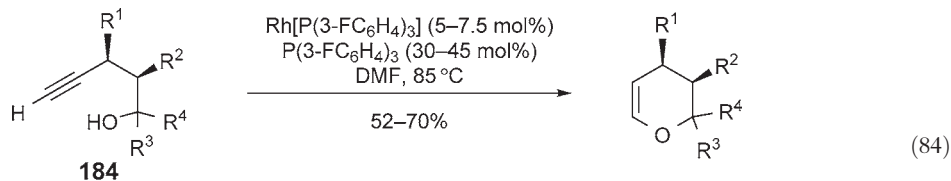
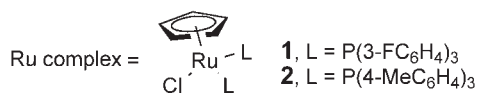
observed when 1,4-diazabicyclo[2.2.2]octane (DABCO) is present (Equation 82) <2004OL3877>. Cyclization of similar substrates reveals that the *endo*- to *exo*-product ratio is strongly dependent upon the substituents present at the propargylic position <2003JOC8798>. These 6-*endo-dig* cyclizations have been subjected to a computational study <2002JA4149>, and have been used for the synthesis of various saccharide substructures <1998JA4246, 1999CEJ3103, 2000JA4304, 2001JOM(617)444, 2001AGE3653, 2002OL749, 2002OL3979>.



A 6-*endo-dig* cyclization of the homopropargylic alcohol **182** is achieved by careful manipulation of the ruthenium catalyst and reaction conditions to afford the 3,4-dihydropyran **183** (Equation 83) <2002JA2528>. Likewise, alkynols **184** undergo rhodium(I) mediated 6-*endo*-selective cyclizations to afford 3,4-dihydropyrans in good yield (Equation 84) <2003JA7482>.

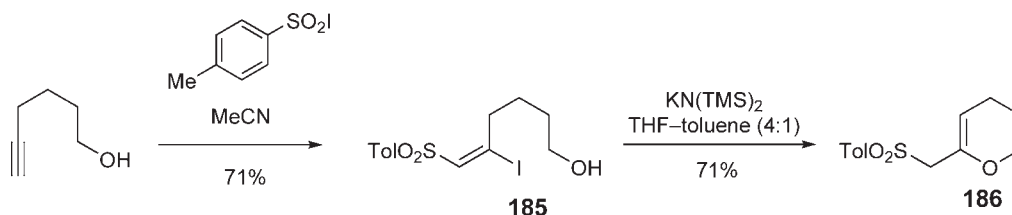


A = Ru complex **1** (15 mol%), ligand (L, 60 mol%), (C₄H₉)₄NPF₆ (45 mol%), NHS (6 equiv), NaHCO₃ (2 equiv).
B = Ru complex **2** (5 mol%), ligand (L, 60 mol%), (C₄H₉)₄NPF₆ (15 mol%), NHS (0.5 equiv).



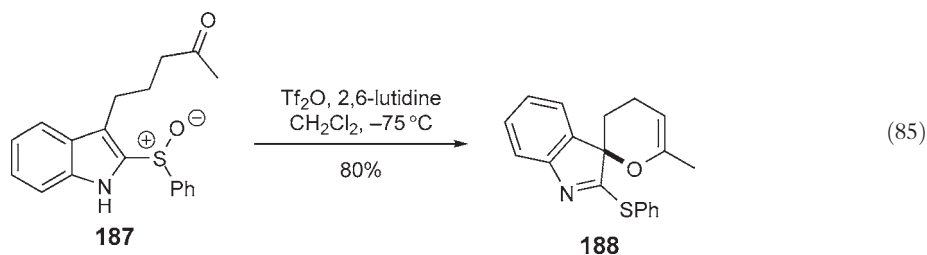
R¹ = R² = H, R³ = H/Me, R⁴ = *n*-C₇H₁₃
 R¹ = OPMB/NHTos R² = R³ = H, R⁴ = Me
 R¹ = OBn, R² = NHBoc, R³ = H, R⁴ = Me

5-Hexyn-1-ol reacts with tosyl iodide to form the (*E*)-iodovinyl sulfone **185**, which can undergo 6-*exo-dig* cyclization upon treatment with KN(TMS)₂ followed by elimination of HI to afford the 3,4-dihydropyran **186** (Scheme 58) <1996T7779, 2005S3613>.



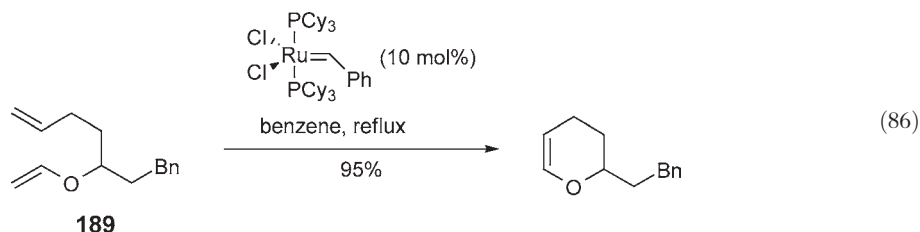
Scheme 58

2-(Phenylsulfinyl)indole **187** bearing a pendant nucleophile at C3 undergoes a Pummerer-like rearrangement upon treatment with TiF_2O to furnish 3,3-spirocyclic-2-(phenylthio)indolenine **188** in high yield (Equation 85) <2004OL1869>.



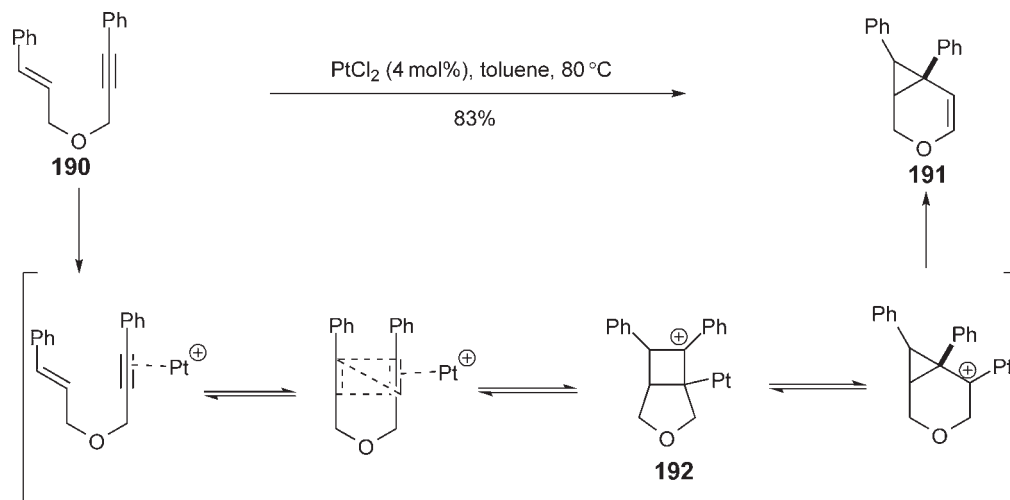
7.08.9.1.1(ii) β to the heteroatom

Construction of 3,4-dihydropyrans by RCM is far less common than for 3,6-dihydropyrans. RCM of 5-(vinylxy)pent-1-ene **189** affords 2-phenethyl-3,4-dihydro-2*H*-pyran in high yield; however, examples of high-yielding reactions of this type are limited (Equation 86) <1998TL9623>. Despite this, a review containing relevant examples and elegant efforts undertaken towards making the methodology a more attractive means of 3,4-dihydropyran synthesis is available <2004CRV2199>. 3,4-Dihydropyran synthesis by RCM mediated by molybdenum and tungsten imido alkylidene complexes has also been reviewed <2003AGE4592>.



7.08.9.1.1(iii) γ to the heteroatom

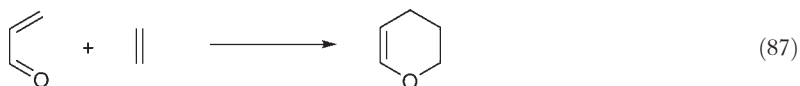
Enyne **190** undergoes platinum(II)-catalyzed ring closures to afford the cyclopropyl-fused 3,4-dihydropyran **191**. The reaction is thought to proceed via formation and rearrangement of the intermediate cyclobutyl cation **192** (Scheme 59) <2000JA6785, 2001JA11863>.



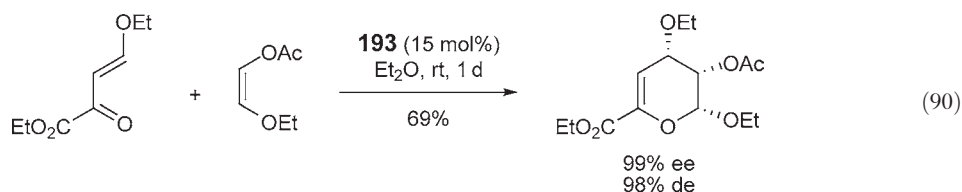
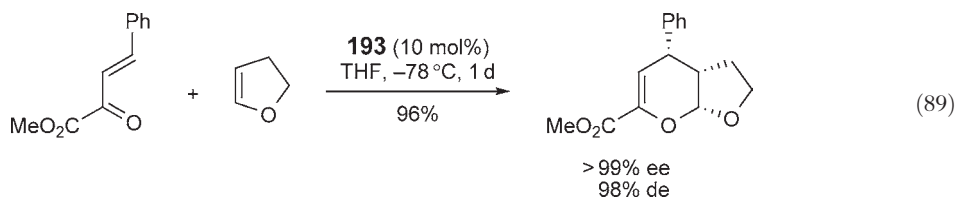
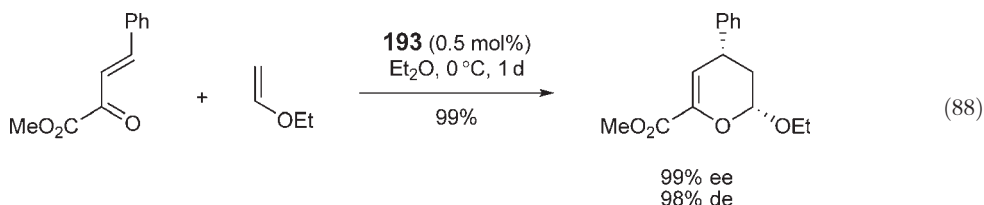
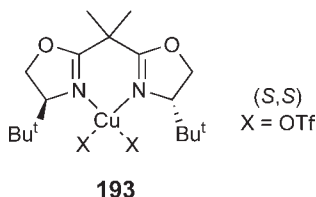
Scheme 59

7.08.9.1.2 Formation of more than one bond

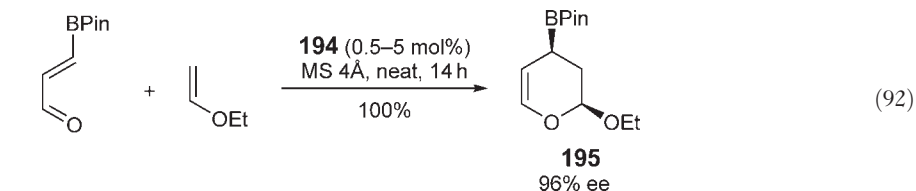
The inverse electron demand hetero Diels–Alder (hDA) reaction of α,β -unsaturated carbonyl compounds with alkenes provides a powerful tool for the synthesis 3,4-dihydropyrans and is discussed in detail in the preceding volumes (Equation 87) <1984CHEC, 1996CHEC-II>. The discovery of several new catalytic systems has led to the term asymmetric hDA reaction, which often allows for the use of unconventional starting materials such as achiral unactivated heterodienes. 3,4-Dihydropyrans formed using the asymmetric hDA reaction are often obtained in excellent yield and with high diastereo- and enantioselectivity. A review outlining the use of ketones as both a diene and a dienophile in the asymmetric hDA reaction <2004EJO2093> and a review detailing the catalytic enantioselective hDA reaction as a means of accessing both 3,4-dihydropyrans and 3,6-dihydropyrans is available <2000AGE3558>.



The bis(oxazoline)-copper(II) complex **193** can effectively catalyze an asymmetric hDA reaction between γ -substituted β,γ -unsaturated α -ketoesters and vinyl ethers leading to tri- or tetrasubstituted dihydropyrans with high diastereo- and enantioselectivity (Equations 88–90) <2000JOC4487>. These bis(oxazoline)-copper(II) complexes are also effective for the hDA reaction of α,β -unsaturated carbonyl compounds with electron-rich alkenes <2000JA1635, 2000JA7936, 2001AGE3417, 2003CAL145>. A review describing the use of chiral bis(oxazoline)-copper(II) complexes as catalysts for the asymmetric hDA reaction is available <2000ACR325>.



Another landmark development in the area of hDA chemistry is the emergence of the tridentate chromium complexes **194** that can catalyze the reaction of α,β -unsaturated aldehydes with vinyl ethers to afford dihydropyrans with high diastereo- and enantioselectivity (Equation 91) <2002AGE3059>. The same catalytic system can be used for the asymmetric synthesis of the 3,4-dihydropyran **195** from 3-boronoacrolein pinacolate and ethyl vinyl ether in quantitative yield (Equation 92) <2003JA9308, 2005JA1628>.



$\text{K}_2\text{CO}_3, 100^\circ\text{C}$
 72 h
 58%

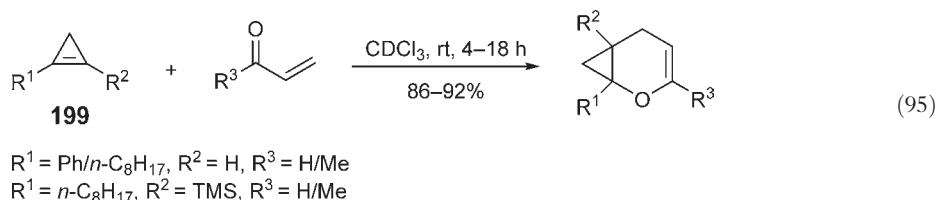
196

(93)

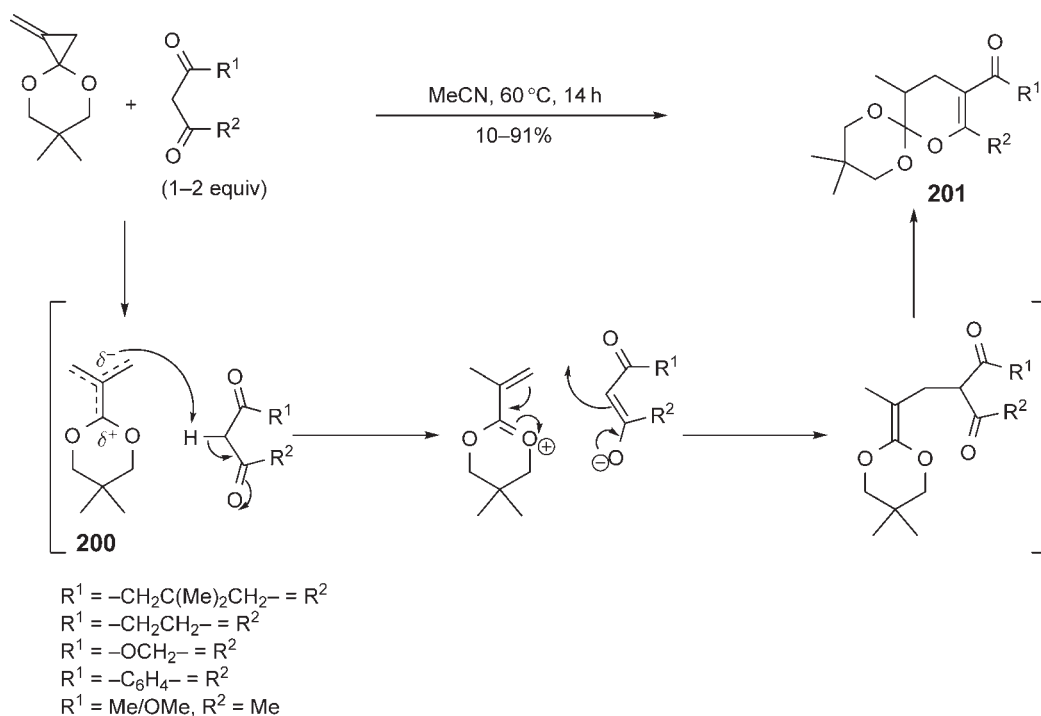
197 + $\text{CH}_2=\text{CH}-\text{C}(=\text{O})\text{R} \xrightarrow[\text{MeCN, reflux, 46-62 h}]{\text{ZnCl}_2 (10 \text{ mol}\%)}$ 198

R = H, 42%
 R = Me, 40%

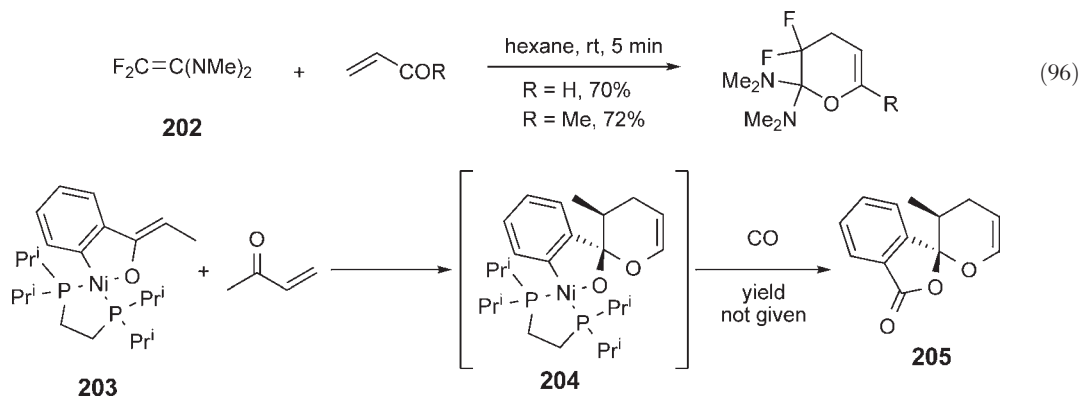
(94)



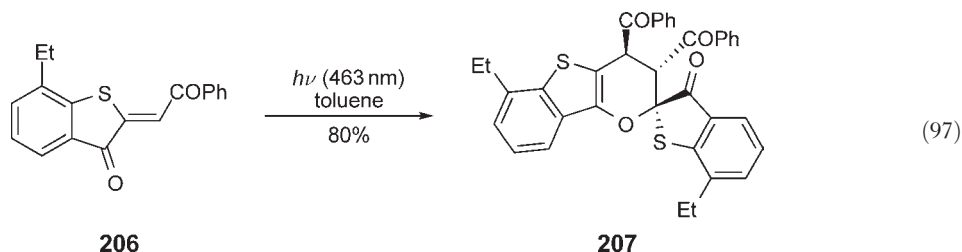
The thermally generated dipolar dialkoxy trimethylenemethane species **200** reacts with activated methylene compounds via a formal [3+3] cycloaddition to afford 3,4-dihydropyrans **201** (Scheme 60) <2001SL1030>. Difluoroketene aминаl **202** can undergo a [2+4] cycloaddition with α,β -unsaturated carbonyl compounds to afford 3,4-dihydropyrans (Equation 96) <1997JOC6503>. A cycloaddition reaction of methyl vinyl ketone and an *O*-bound nickel enolate **203** proceeds with complete stereoselectivity to furnish a [2+4] cycloadduct **204** that upon demetalation affords the spirocyclic 3,4-dihydropyran **205** (Scheme 61) <2003CCC1742>. A benzoyl substituted hemithio-indigo **206** exhibits an unexpected type of photochromic behaviour, and upon irradiation a novel [2+4] pentacyclic cycloadduct possessing a 3,4-dihydropyran moiety **207** is formed (Equation 97) <2004CL848>.



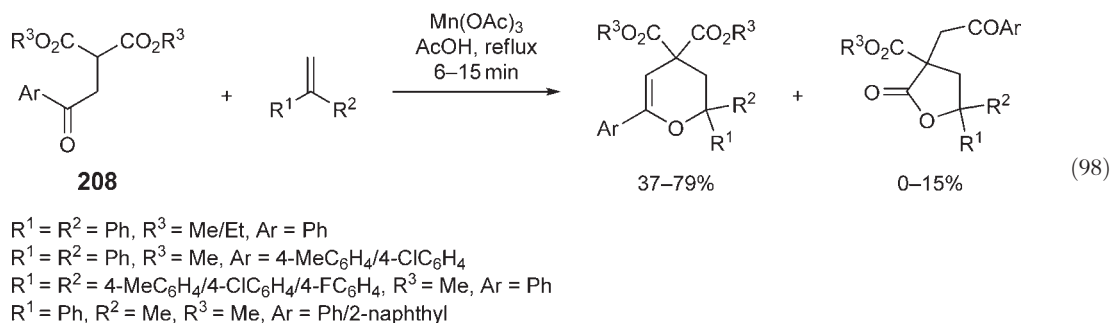
Scheme 60



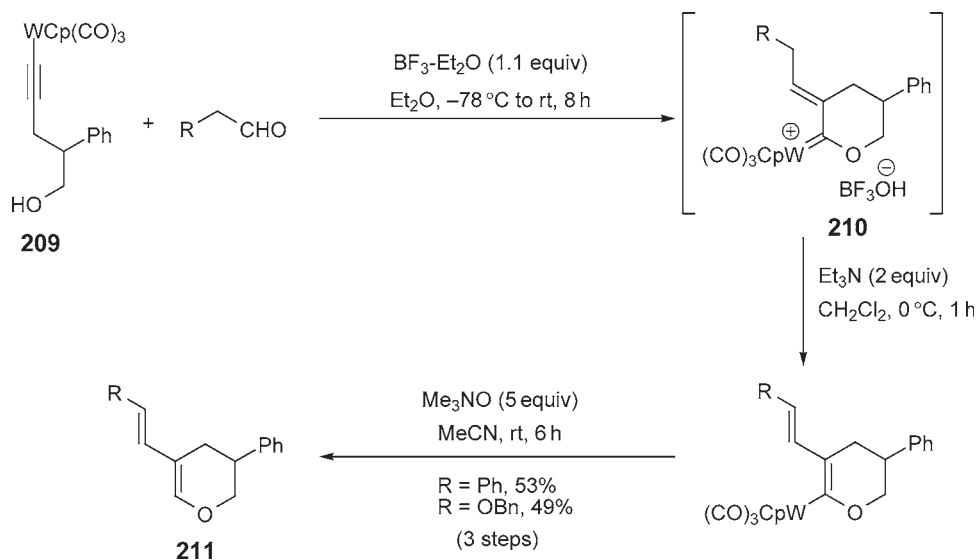
Scheme 61



1,1-Disubstituted alkenes undergo a manganese(III) catalyzed reaction with (2-aryl-2-oxoethyl)malonates **208** to afford tetrasubstituted 3,4-dihydropyrans; the formation of a γ -lactone side-product is observed in some instances (Equation 98) <2004TL3373>.

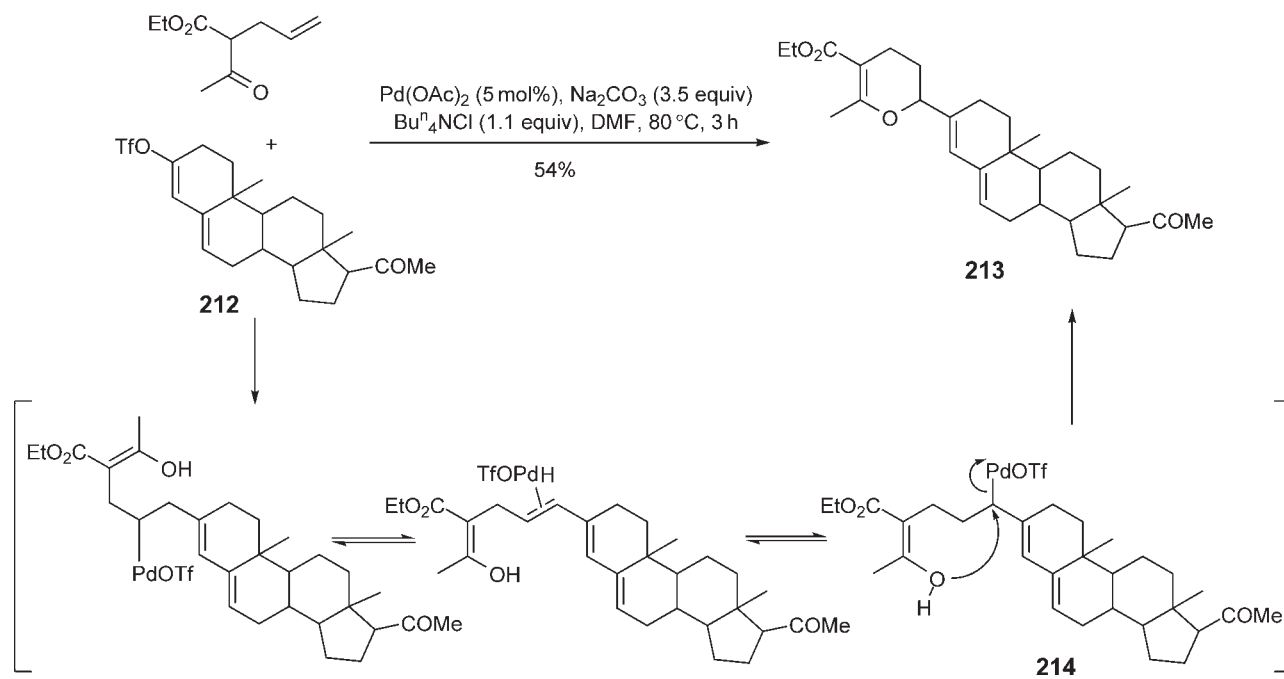


A Lewis-acid-mediated reaction of tungsten linked alkynes **209** with aldehydes forms the intermediate tungsten- η^1 -oxacarbenium salts **210**; treatment with base and subsequent demetalation affords 3,4-dihydropyrans **211** that are classed as oxacyclic dienes (Scheme 62) <1997JA4404, 1998JOC7289, 1998JA4520, 2000JOC3761>.



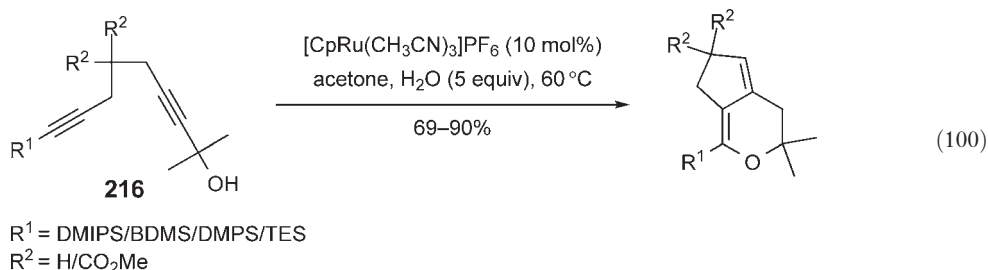
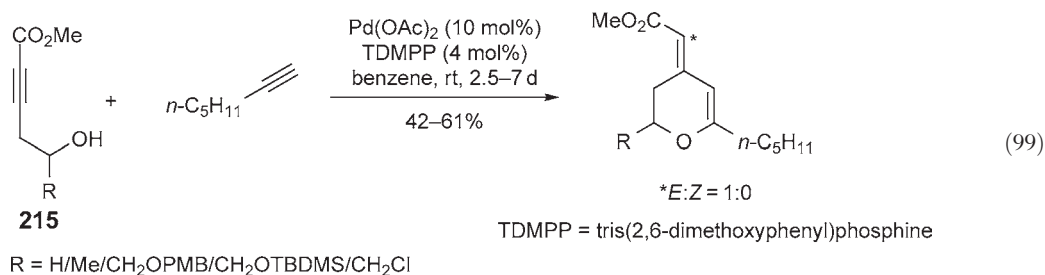
Scheme 62

Vinyl triflate **212** and ethyl 2-acetylpent-4-enoate react under palladium(II) catalysis to afford the steroidal 3,4-dihydropyran derivative **213**. The reaction proceeds via an intramolecular cyclization of the σ -allylpalladium intermediate **214** (Scheme 63) <1998SL888>.



Scheme 63

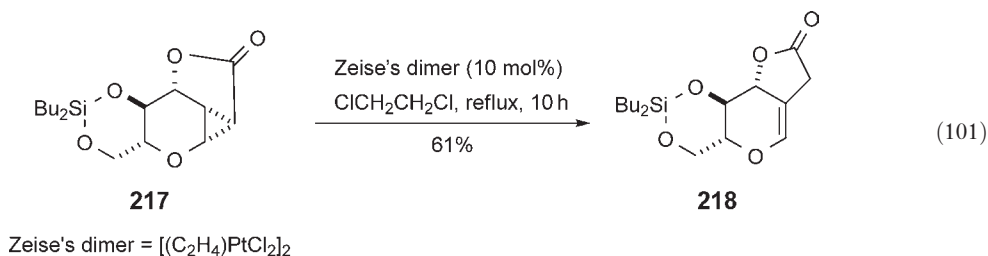
A palladium(II)-catalyzed reaction between 1-heptyne and hydroxyalkynoates **215** provides a route to 3,4-dihydropyrans that feature an (*E*)-exocyclic double bond (Equation 99) <2000JA11727>. A ruthenium-catalyzed double-ring closure of the diynols **216** furnishes fused 3,4-dihydropyrans in excellent yield (Equation 100) <2004OL4235>.



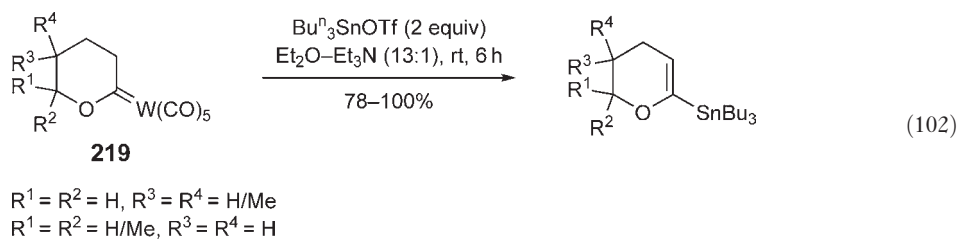
7.08.9.1.3 From a preformed heterocyclic ring

7.08.9.1.3(i) From tetrahydropyrans

Zeise's dimer can catalyze a rearrangement of the fused cyclopropane **217** to afford the 3,4-dihydropyran **218** in moderate yield (Equation 101) <2003T2765>.



Tetrahydropyranidene carbenes **219** are easily converted into α -stannyl 3,4-dihydropyrans upon reaction with tributyltin hydride (Equation 102) <1996TL4675>.

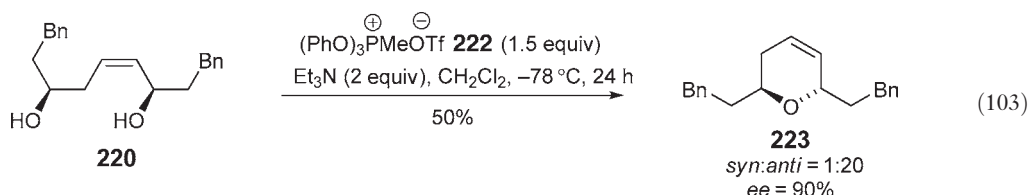


7.08.9.2 3,6-Dihydropyrans

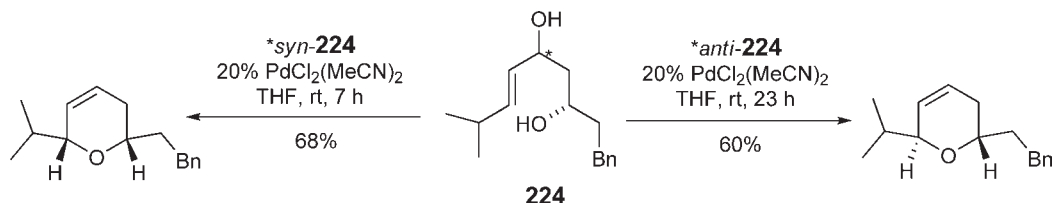
7.08.9.2.1 Formation of one bond

7.08.9.2.1(i) Adjacent to the heteroatom

The use of standard Mitsunobu conditions for the cyclization of (*Z*)-1,5-*syn*-diol **220** leads to a considerable decrease in the enantiomeric excess of the resulting 3,6-dihydropyran. Cyclization of (*Z*)-1,5-*syn*-diol **221**, using the phosphonium salt **222** as a dehydrating agent, provides an asymmetric synthesis of 2,6-*anti*-5,6-dihydropyran **223** (Equation 103) <2005MIBJO7>.

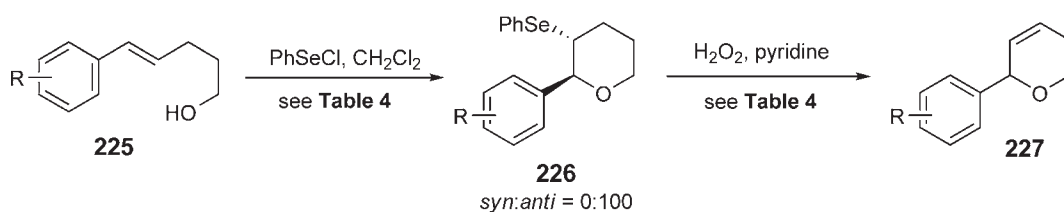


Syn- and *anti*-1,5-allylic diols **224** undergo stereospecific intramolecular palladium-catalyzed cyclizations to afford *syn*- or *anti*-2,6-disubstituted 3,6-dihydropyrans; the stereochemistry of the 3,6-dihydropyran product is defined by that of the starting diol (Scheme 64) <2005TA1299>.



Scheme 64

A 6-*endo*-trig selenoetherification of (*E*)-5-hydroxyalkenes **225** provides *anti*-2,3-selenides **226**, which undergo oxidative elimination upon treatment with H_2O_2 to afford 2-aryl-3,4-dihydropyrans **227** in high yield (Scheme 65, Table 4) <2002TL1735>.

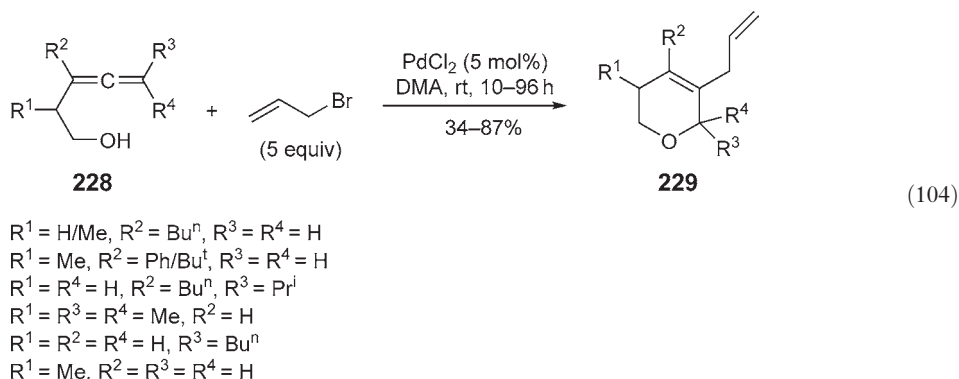


Scheme 65

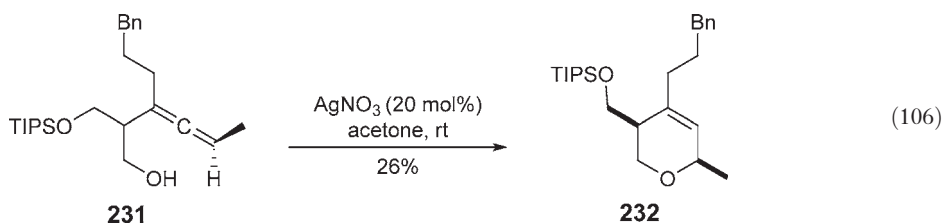
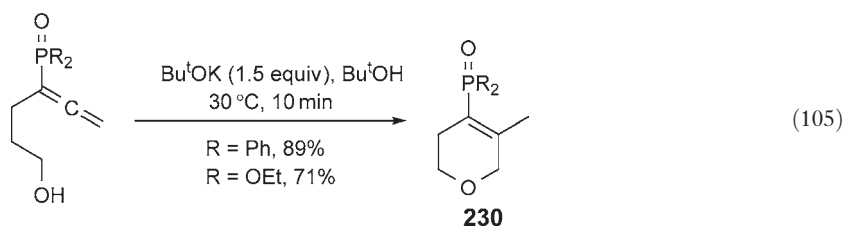
Table 4 Formation of selenides **226** and their elimination to 3,6-dihydropyrans **227** (Scheme 65)

R	Yield 226 (%)	Yield of 227 (%)
H	89	76
2-MeO	87	81
3-MeO	92	83
2,5-(MeO) ₂	81	79
3,4-(C ₄ H ₄)	86	82

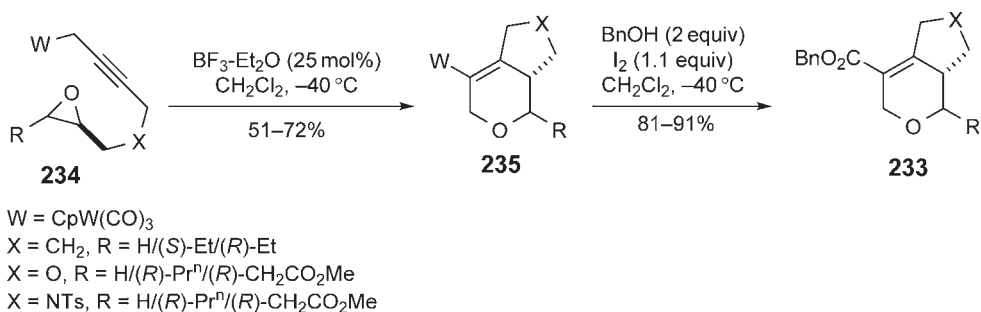
3-Substituted 3,4-allenols **228** react with allyl bromide under palladium(II) catalysis to afford polysubstituted 3,6-dihydropyrans **229** (Equation 104) <2002JOC6104>.



Allenes bearing a phosphoryl group and a suitable δ -hydroxyalkyl side chain at C1 undergo 6-*exo* ring closure upon treatment with base to afford 4-phosphoryl 3,6-dihydropyrans **230** (Equation 105) <2004JOC6867>. Similarly, a silver promoted cyclization of the allene **231** provides the 3,6-dihydropyran **232** in moderate yield (Equation 106) <2004JA15978>.

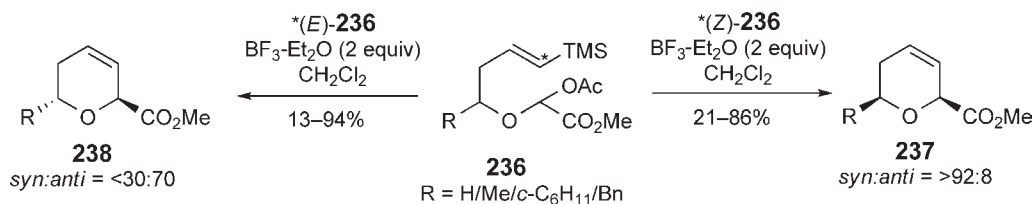


3,4-Fused-3,6-dihydropyrans **233** are accessible in high yield via a Lewis-acid-promoted intramolecular [3+3] cycloaddition of the epoxides **234** with the tethered propargyltungsten group, followed by demetallation of the intermediate tungsten complexes **235** (Scheme 66) <2001JOC8106>.



Scheme 66

Vinylsilanes **236** undergo Lewis acid-mediated stereoselective cyclizations to afford 3,6-dihydropyrans. The stereochemistry of the dihydropyran product is dictated by the geometry of the vinyl silane with (*Z*)-**236** and (*E*)-**236** providing *syn*-**237** and *anti*-3,6-dihydropyrans **238**, respectively (**Scheme 67**) <1997JOC3426>.



Scheme 67

An intramolecular Prins-type cyclization of α -acetoxy acetals **239** is catalyzed by $(i\text{-PrO})_2\text{Ti}(\text{NTf}_2)$ and provides a stereoselective route to 2,6-*anti*-substituted 3,6-dihydropyrans **240** (Equation 107, Table 5) <2004BK1625>.

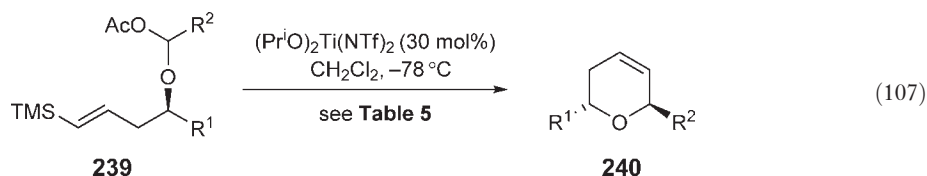
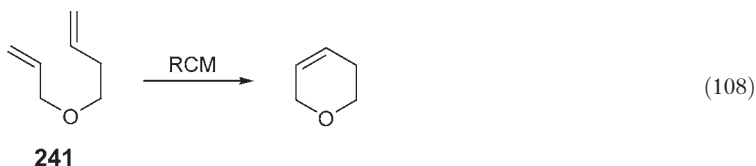


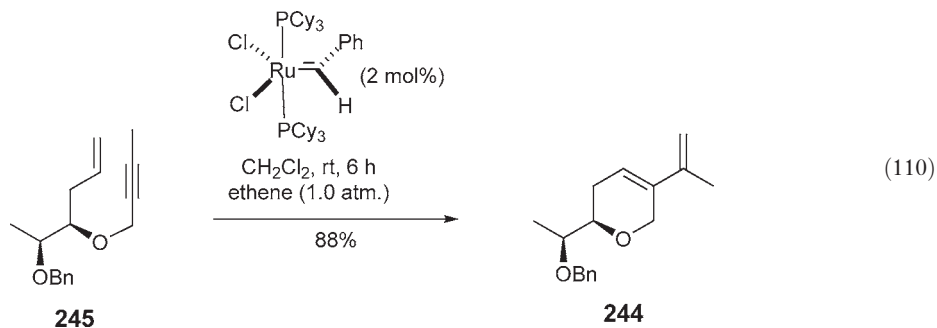
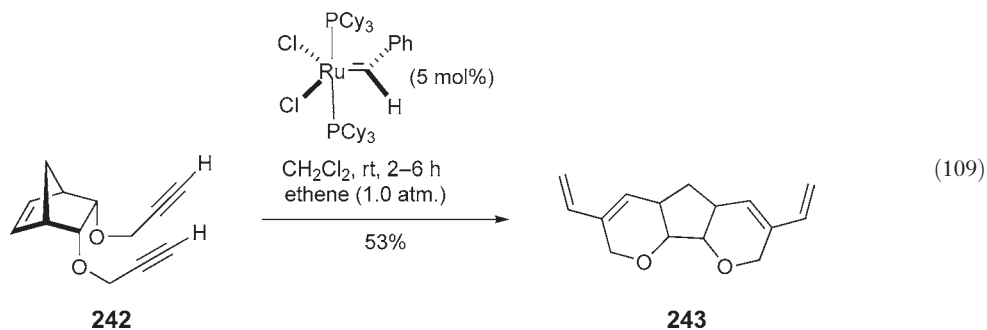
Table 5 Diastereoselective formation of 3,6-dihydropyrans **240** (Equation 107)

R^1	R^2	Yield 240 (%)	<i>syn:anti</i>
CH ₂ Bn	Me	81	9:91
H	CH ₂ Bn	78	12:88
H	CH ₂ Pr ⁱ	64	19:81
Ph	Me	77	7:93
H	CH ₂ Bn	67	14:84
H	CH ₂ Pr ⁱ	58	12:88
<i>n</i> -C ₆ H ₁₃	Me	73	9:91
H	CH ₂ Bn	81	17:83
H	CH ₂ Pr ⁱ	71	22:78

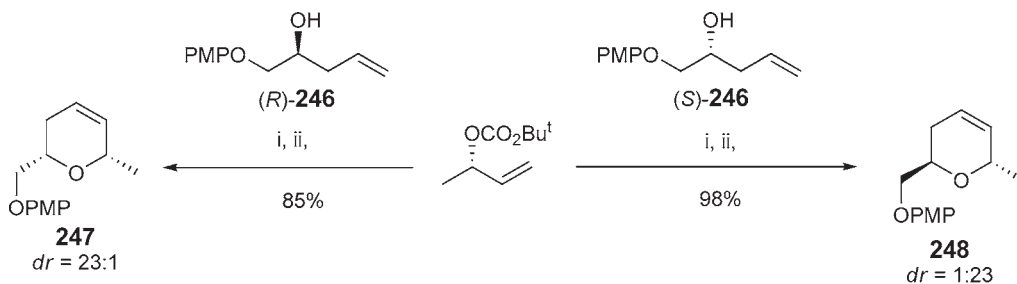
3,6-Dihydropyrans can be synthesized by RCM of 4-(allyloxy)but-1-enes **241** (Equation 108). The synthesis of 3,6-dihydropyrans via RCM is vastly more common than for 3,4-dihydropyrans, as emphasized in two recent reviews [\[2003AGE4592, 2004CRV2199\]](#).



Despite this reaction being extensively reviewed, some novel, recent examples are discussed herein. The norbornene derivative **242** that features two terminal alkynes undergoes tandem enyne RCM to afford the tricyclic product bearing two dienic 3,6-dihydropyrans **243** (Equation 109) <2002TL1561, 2004T8043>. RCM is not restricted to ruthenium catalysis; palladium catalysts <2004JOC6697> and manganese carbene complexes <2003OM3915> are also commonly used. 3,6-Dihydropyran **244** bearing a chiral oxacyclic diene can be constructed via enyne metathesis of the chiral ether **245** (Equation 110) <2002T5627>.

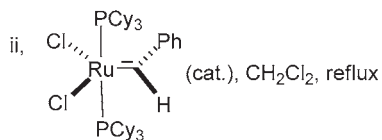


Rhodium(II)-catalyzed etherification of an allylic carbonate with enantiopure alkenyl alcohols **246** followed by RCM proceeds with excellent diastereoselectivity to afford *syn*-**247** or *anti*-3,6-dihydropyrans **248** in high yield (Scheme 68) <2004AGE4788>. This methodology can be extended to the preparation of chiral 2,3,6-trisubstituted 3,6-dihydropyrans <2004JA8642>.



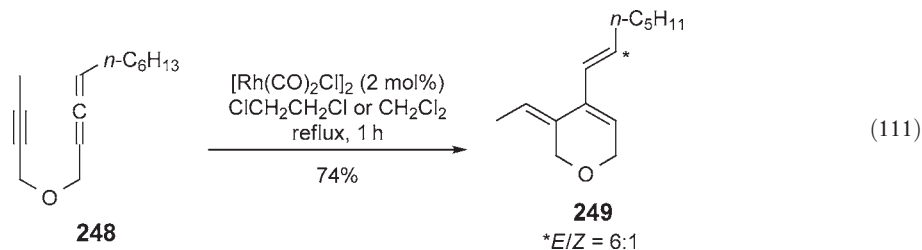
PMP = *para*-methoxyphenyl

i, LiHMDS, P(OMe)₃, CuI then
[RhCl(PPh₃)₃], THF, 0 °C to rt

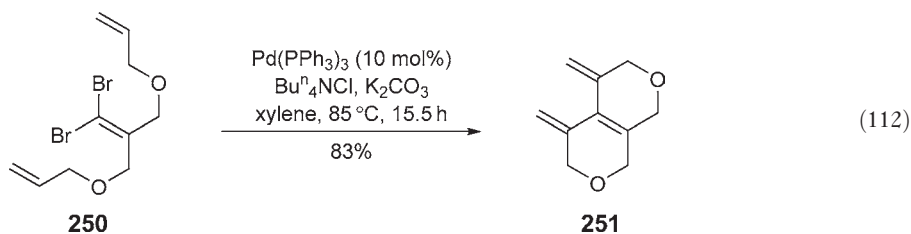


Scheme 68

The ether-tethered allenyne **248** undergoes a rhodium(I)-catalyzed intramolecular allenic Alder ene reaction to afford the (*E*)-3,6-dihydropyran **249** as the major product (Equation 111) <2002JA15186>. Likewise, ether tethered enynes can undergo rhodium(I)-catalyzed cycloisomerizations to afford 3,6-dihydropyrans <2005JA10180>.

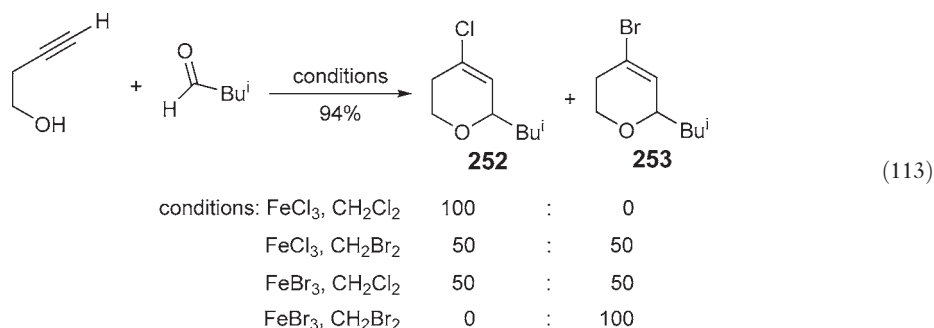


A double intramolecular carbopalladation reaction of the *gem*-dibromide **250** provides a route to the bicyclic 3,6-dihydropyran **251** in high yield (Equation 112) <1998JOC9156>.



7.08.9.2.2 Formation of more than one bond

An iron(III)-catalyzed Prins-type cyclization between a homopropargylic alcohol and an aliphatic aldehyde provides 2-alkyl-3-halo-3,6-dihydropyrans in excellent yield (Equation 113). The solvent and the catalyst equally contribute to the halogen observed in the product; therefore, a straightforward choice of catalyst and solvent provides a route to either monochlorinated **252** or monobrominated 3,6-dihydropyrans **253** (Equation 113). Indium compounds have also shown potential as catalysts for this process, with high yields also obtained <2003OL1979>.



The silyl-modified Prins reaction and the silyl-modified Sakurai reaction are common methods employed for dihydropyran (and tetrahydropyran) synthesis, and are in fact the same reaction. For the sake of clarity, the term silyl-Prins cyclization is adopted herein. A review of the use of silicon containing compounds in reactions of this type is available <1995CRV1375>.

syn-2,6-Dialkyl 3,6-dihydropyrans **254** can be accessed from aldehydes and 3-trimethylsilylallyltributylstannane via a Lewis-acid-mediated carbonyl-allylation-Prins cyclization process. Aromatic aldehydes fail to give the desired cyclized product; however, aliphatic aldehydes bearing aromatic, halogen, or alkene substituents are tolerated (Equation 114, Table 6) <1999OL993>.

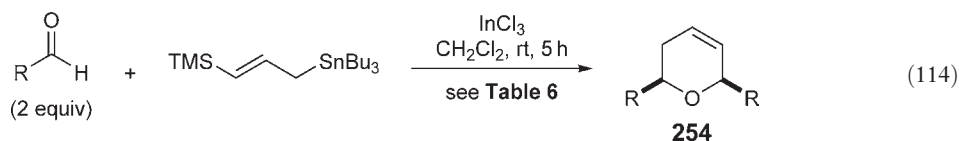
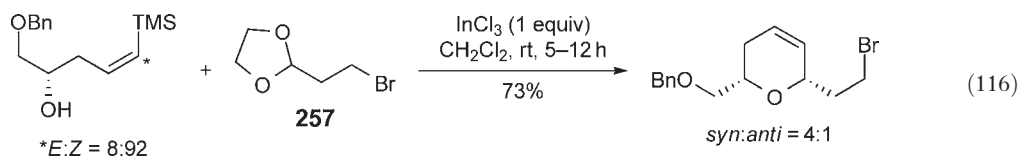
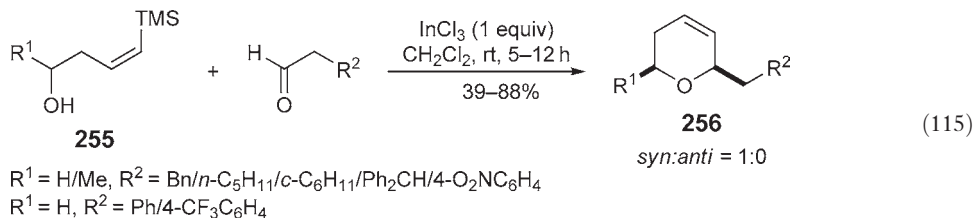


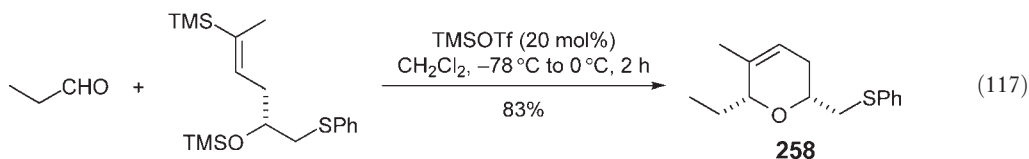
Table 6 Results of the carbonyl-allylation-Prins cyclization of aldehydes and 3-trimethylsilylallyltributylstannane (Equation 114)

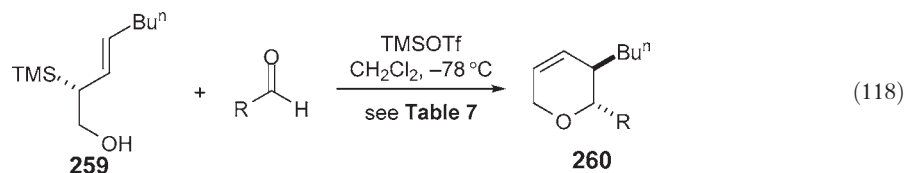
<i>R</i>	Yield 254 (%)	<i>syn:anti</i>
Ph	68	8:1
CH ₂ Bn	57	7.5:1
<i>c</i> -C ₆ H ₁₁	69	6:1
<i>n</i> -C ₉ H ₁₈ CH=CH ₂	50	7:1
<i>n</i> -C ₉ H ₁₈ OBn	50	1:0
<i>n</i> -C ₆ H ₁₃ Br	51	>20:1
<i>n</i> -C ₇ H ₁₅	55	5:1
<i>n</i> -C ₈ H ₁₇	59	8.5:1
<i>n</i> -C ₆ H ₁₉	61	5:1
<i>n</i> -C ₁₀ H ₂₁	65	>10:1

The silyl-Prins reaction between (*Z*)-4-trimethylsilyl-3-buten-1-ol **255** and aldehydes under mild Lewis acid conditions exclusively provides 2,6-*syn*-disubstituted 3,6-dihydropyrans **256** (Equation 115) <2002TL7055, 2003JOC7880>. A silyl-Prins reaction is also used to construct a 3,6-dihydropyran intermediate during a synthesis of the bis-spiroacetal moiety of the spirolics B and D; in this instance a masked bromoaldehyde **257** is used as the cyclization partner (Equation 116) <2005OL3497>.



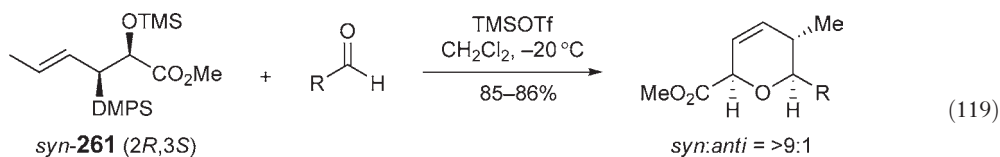
An intermolecular silyl-Prins cyclization of vinyl oxysilanes with aldehydes or simple ketones provides a stereocontrolled synthesis of 3,6-dihydropyrans, such as dihydropyran **258**, a key intermediate during the syntheses of the fully functionalized right-hand portion of ambruticin (Equation 117) <1996S297>, and the *anti*-dioxadecalin unit of okadaic acid <1997TL2899>. Enantioenriched β -hydroxyallylsilane **259** undergoes Lewis-acid-promoted intramolecular cyclizations with aldehydes to afford *anti*-3,6-dihydropyrans **260** in excellent yield and with high diastereo- and enantioselectivity (Equation 118, Table 7) <2001SL1042>. A report is available detailing the role of oxonia-Cope rearrangements in reactions of similar β -hydroxyallylsilanes with aldehydes <2001SL955>.



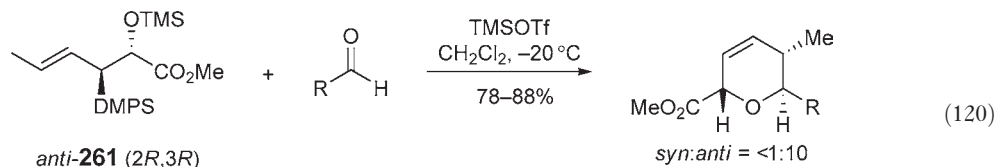
**Table 7** Reaction of hydroxyallylsilane **259** with aldehydes (Equation 118)

<i>R</i>	Yield 260 (%)	<i>syn:anti</i>	<i>ee</i> (%)
Me	94	3:97	99.7
<i>n</i> -C ₆ H ₁₁	92	4:96	99.9
Ph	94	2:98	99.8
(<i>E</i>)-Pr ⁱ CH=CH	83	5:95	>99.9

A formal [4+2] annulation of chiral crotylsilanes **261** with aldehydes provides a stereoselective synthesis of functionalized 3,6-dihydropyrans. Since both enantiomers of the starting silanes are readily available, four possible *syn*- and *anti*-2,6-dihydropyrans can be prepared (Equations 119 and 120) <2000JA9836>. This methodology has been incorporated into an asymmetric synthesis of the C19-C28 tetrahydropyran ring of the phorboxazoles <2001OL1693>, as well as the C1a-C10 fragment of kendomycin <2005OL1529>.

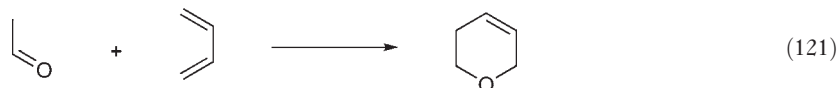


R = Prⁱ/Buⁿ/*n*-C₆H₁₁/Ph

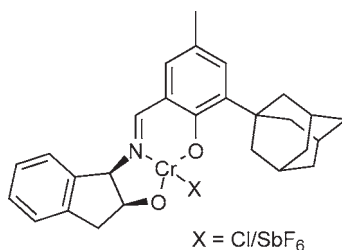
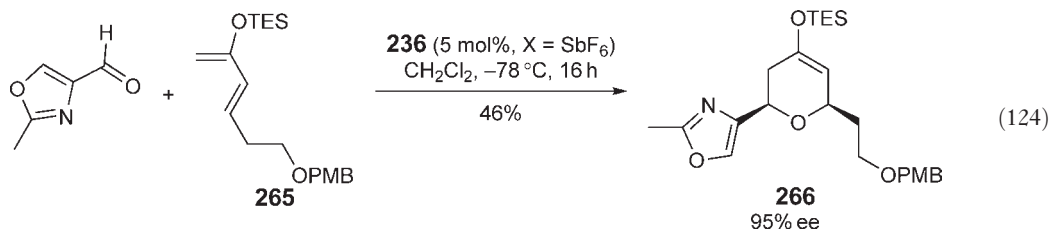
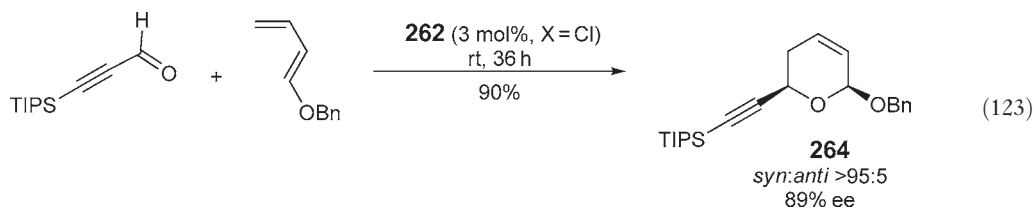
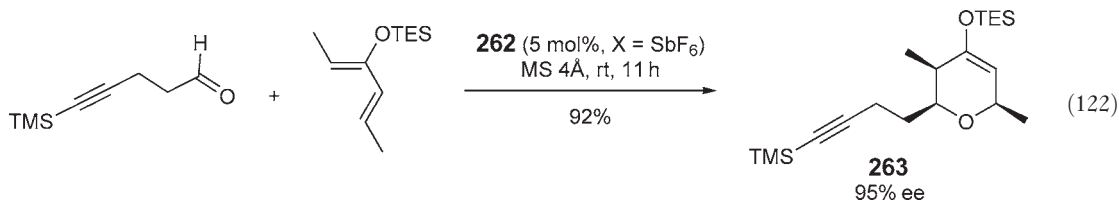


R = Prⁱ/Buⁿ/*n*-C₆H₁₁/Ph

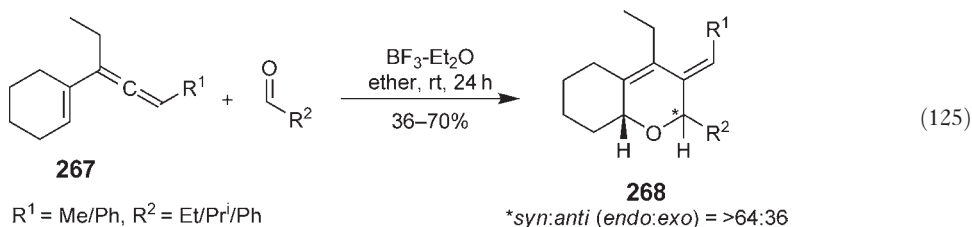
An hDA reaction of carbonyl compounds with dienes provides a powerful tool for the synthesis of 3,6-dihydropyrans (Equation 121), and has been discussed in detail in the preceding volumes <1984CHEC, 1996CHEC-II>. As with the synthesis of 3,4-dihydropyrans via the hDA reaction, the reviews mentioned previously are also relevant here <2000AGE3558, 2004EJO2093>.



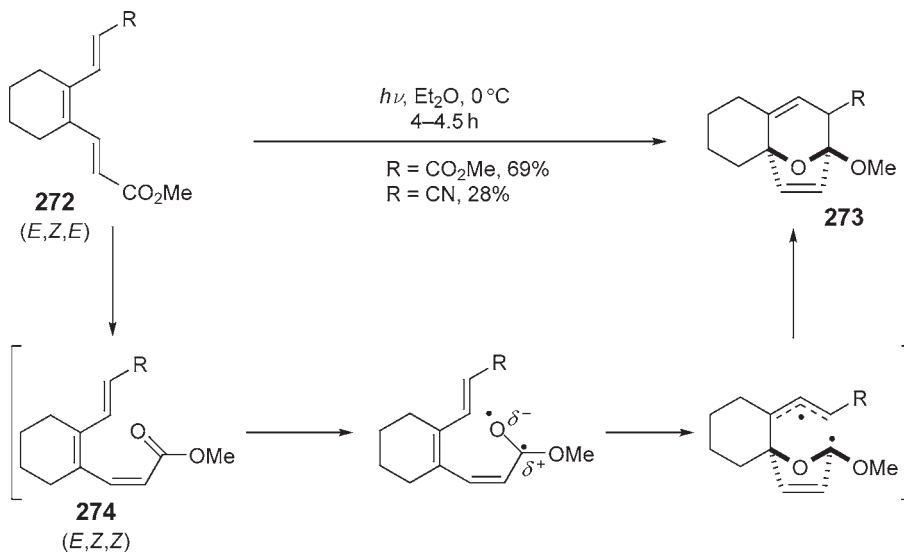
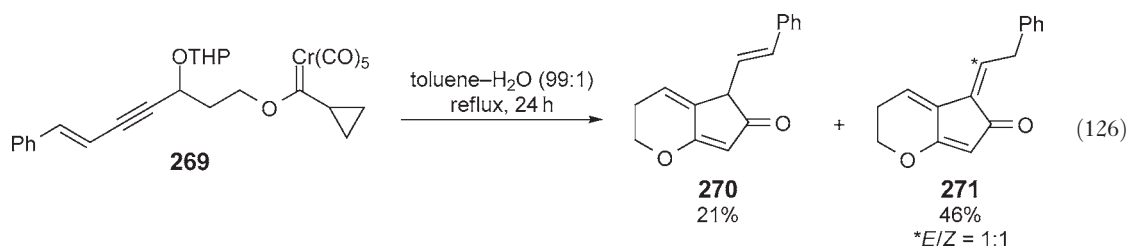
Noteworthy is Jacobsen's development of the tridentate chromium complexes **262** as catalysts for the hDA syntheses of 3,6-dihydropyrans. This methodology is used to great effect for the syntheses of dihydropyrans **263** (Equation 122) and **264** (Equation 123) that are incorporated into the total syntheses of FR901464 <2001JA9974> and fostriecin (CI-920) <2001AGE3667> respectively. Jacobsen's methodology is also evident in the asymmetric hDA reaction between a 2-methyloxazole-4-carbaldehyde and diene **265** providing 3,6-dihydropyran **266**, an intermediate in the synthesis of the C4-C32 subunit of phorboxazole A (Equation 124) <2003TL3749>. Enantiopure 3,6-dihydropyrans are accessed via hDA reactions using these tridentate chromium complexes <2004SL1755>.

**262** (1*R*, 2*S*)

Vinyl allenes **267** undergo Lewis-acid-promoted intermolecular hDA reactions with simple aldehydes to afford *syn*-2,6-disubstituted 3,6-dihydropyrans **268** (Equation 125) <2000TL6781>. An intramolecular variant of this reaction has also been reported <2003TL8471>.

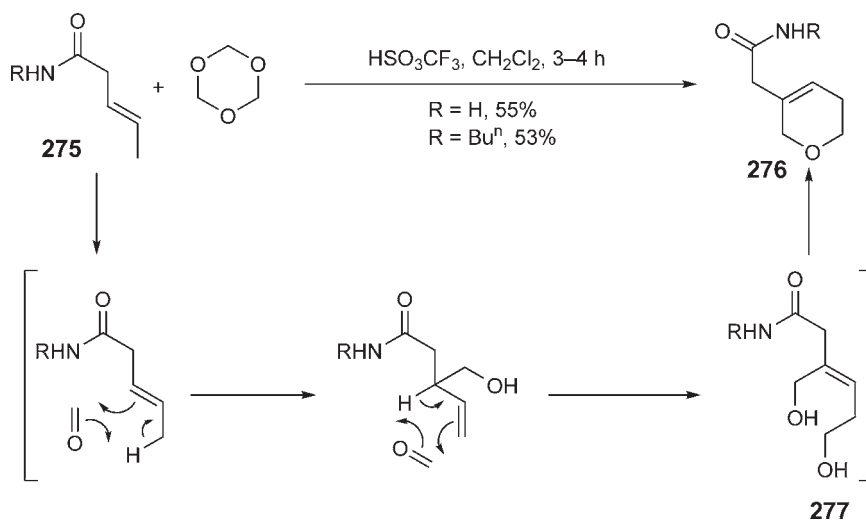


The intramolecular coupling of propargylic alcohol derivative **269** with a tethered cyclopropylcarbene–chromium complex furnishes a mixture of regioisomeric 3,6-dihydropyrans **270** and **271** bearing a fused cyclopentenone moiety (Equation 126) <1999OL15>. Phototransformation of (*E,Z,E*)-1,3,5-hexatrienes **272** provides novel bridged 3,6-dihydropyran **273**; the reaction proceeds through an intramolecular hDA triggered by inversion of an *E*-double bond to form the (*E,Z,Z*)-1,3,5-hexatriene **274** (Scheme 69) <2004CEJ4341>.

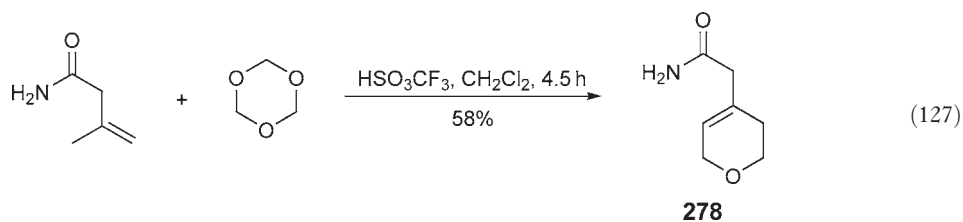


Scheme 69

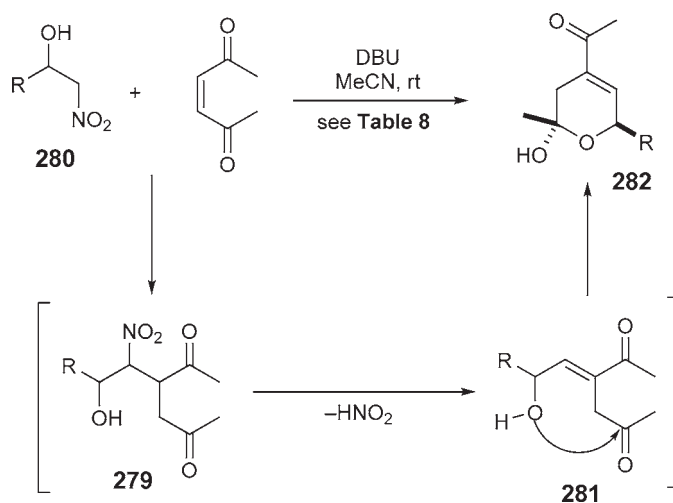
Trifluoromethanesulfonic acid can mediate the condensation of alkenamides **275** with *s*-trioxane to afford 3,6-dihydropyrans **276**. The reaction proceeds via two oxo-ene reactions to afford the intermediate diol **277**, which undergoes cyclodehydration to form the desired dihydropyrans (**Scheme 70**). This methodology can provide a route to the regioisomeric dihydropyran **278** by simple modification of the starting alkenamide (**Equation 127**) <1997TL9057>.



Scheme 70



Elimination of nitrous acid from the Michael adduct **279** arising from the reaction of *cis*-hex-3-en-2,5-dione with β -nitroalkanol **280** forms an allylic alcohol intermediate **281**, which cyclizes with high diastereoselectivity to afford *anti*-dihydropyran-6-ols **282** (Scheme 71, Table 8) <2004SL2618>.

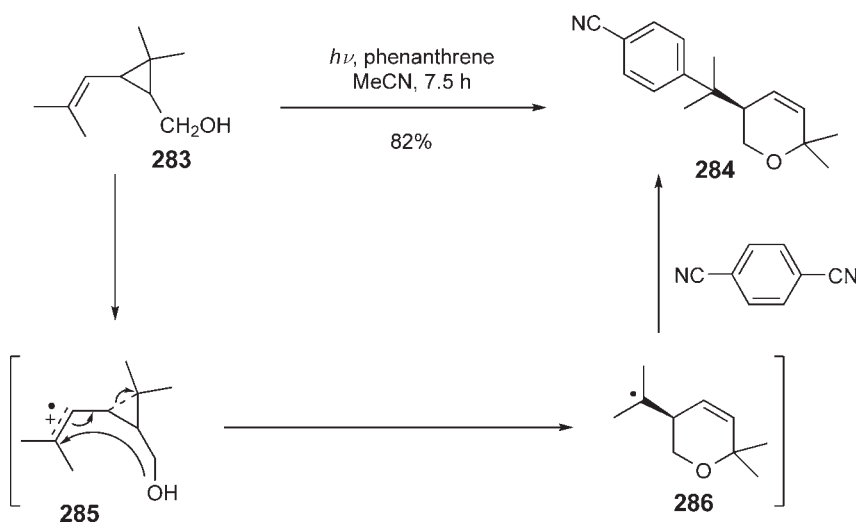


Scheme 71

Table 8 Formation of dihydropyran-6-ols **282** from *cis*-hex-3-en-2,5-dione and β -nitroalkanol **280** (Scheme 71)

<i>R</i>	Yield 282 (%)	<i>syn:anti</i>
H	77	18:82
Me	60	16:84
Et	61	20:80
Pr ⁿ	54	15:85
<i>n</i> -C ₆ H ₁₃	55	19:81
<i>n</i> -C ₁₃ H ₂₇	58	19:81
Pr ⁱ	56	16:84
(<i>E</i>)-EtCH=CH <i>n</i> -C ₅ H ₁₀	60	15:85
BnCH ₂	68	17:83
MeOCOPr ⁿ	53	18:82

Irradiation of a solution of (1*R*,3*S*)-chrysanthemol **283** in the presence of phenanthrene and dicyanobenzene leads to formation of 3,6-dihydropyran **284**. The reaction proceeds via formation and cyclization of the radical cation **285** followed by reaction of the radical intermediate **286** with dicyanobenzene (Scheme 72) <1996JA10954>.

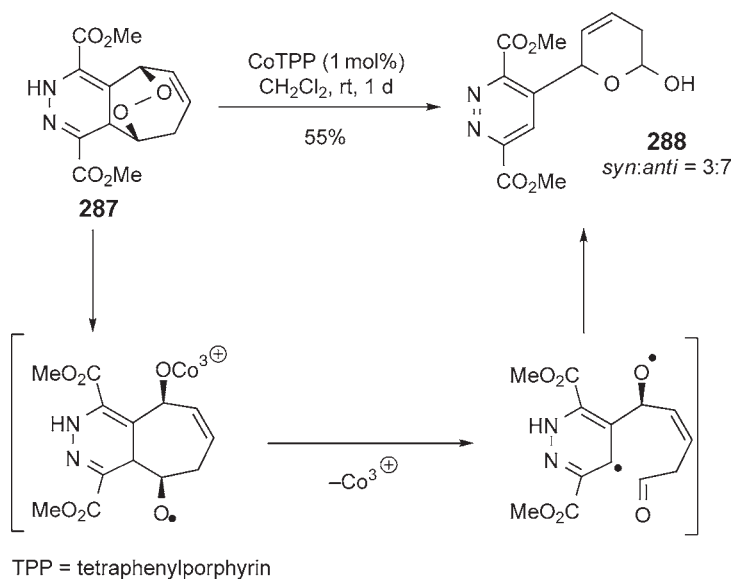


Scheme 72

7.08.9.2.3 From other heterocycles

7.08.9.2.3(i) From dioxabicyclo[3.2.2]nonanes

A cobalt-mediated reaction of dioxabicyclo[3.2.2]nonane **287** furnishes the dihydropyranyl pyridazine derivative **288** in moderate yield (Scheme 73) <2003JOC7009>.

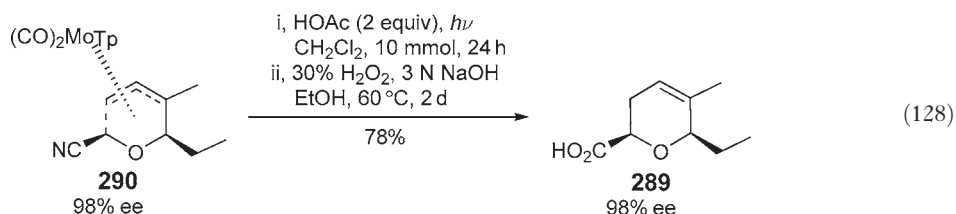


Scheme 73

7.08.9.2.4 From a preformed heterocyclic ring

7.08.9.2.4(i) From pyranymolybdenum complexes

Synthesis of 2,3,6-trisubstituted 3,6-dihydropyran **289** can be achieved in excellent yield and with high enantioselectivity upon demetallation and hydrolysis of the hydropyranyl molybdenum complex **290** (Equation 128) <2000JA10458>.

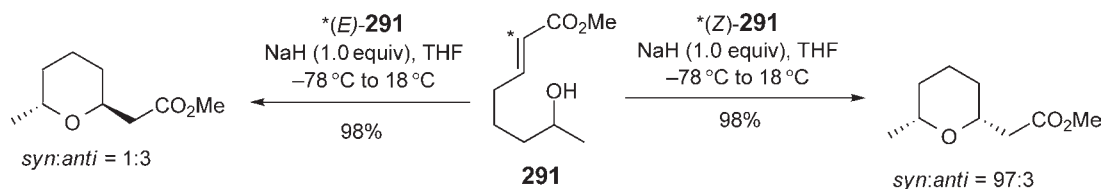


7.08.10 Tetrahydropyrans

7.08.10.1 Formation of One Bond

7.08.10.1.1 Adjacent to the heteroatom

A base-mediated 6-*exo-trig* cyclization of alkenols **291** affords 2,6-disubstituted tetrahydropyrans (**Scheme 74**). The geometry about the C–C double bond of the starting α,β -unsaturated ester has a significant impact upon the diastereoselectivity of the cyclization (**Scheme 74**) <1996J(P1)967>. A computational study of the stereocontrolled Michael cyclization of (*E*)- and (*Z*)-7-hydroxy-4-substituted-2,3-unsaturated esters leading to 2,3-disubstituted tetrahydropyrans is available <1997JOC4584>. 7-Hydroxy-2-enimides **292** undergo oxa-conjugate additions in the presence of base to afford the kinetic product, *anti*-2,4-disubstituted tetrahydropyran **293** (Equation 129, **Table 9**). When 7-hydroxy-2-enoates **294** are employed the reaction proceeds under thermodynamic control and the stereochemical outcome of the cyclization is reversed providing *syn*-2,4-disubstituted tetrahydropyrans **293** (Equation 129, **Table 9**) <2000EJO73>.



Scheme 74

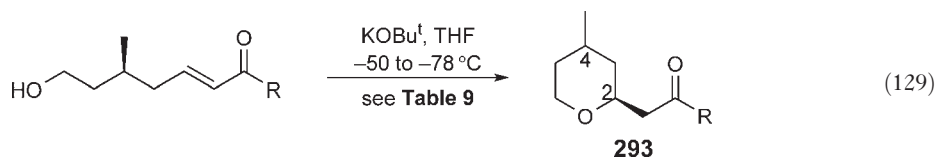
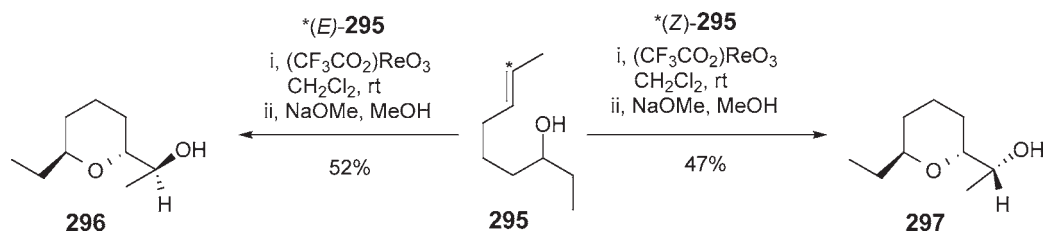


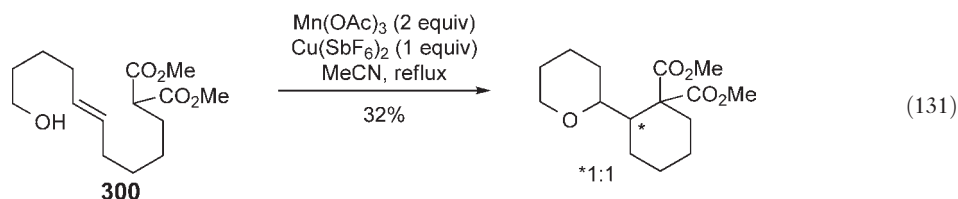
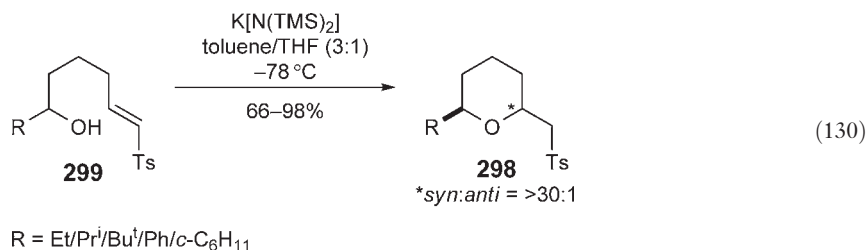
Table 9 The affect of enamide **292** vs. enoate **294** upon diastereoselectivity of the tetrahydropyran **293** (Equation 129)

Compound	R	Yield (%) 293	C2-C4 <i>syn:anti</i>
292		79%	1:4
294	OEt	83%	1:0

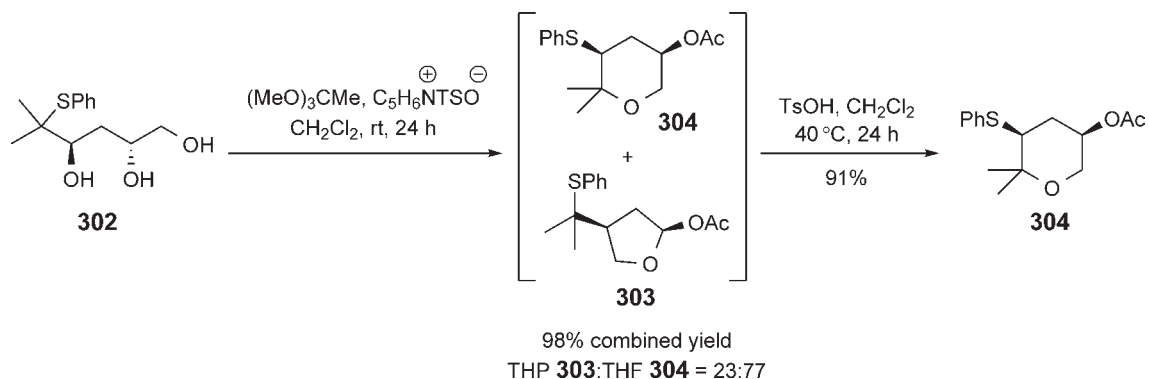
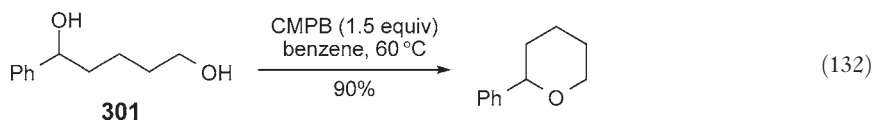
Racemic 5-hexen-1-ols **295** cyclize in the presence of trifluoroacetylperhenate, providing a highly efficient synthesis of *anti*-2,6-disubstituted tetrahydropyrans **296**, **297**. The stereochemistry of the alcohol side chain of the tetrahydropyrans **296** and **297** is controlled by defining the geometry of the double bond of the starting 5-hexen-1-ols **295** (Scheme 75) <1997TL7683>. *Syn*-2,6-disubstituted tetrahydropyrans **298** can be formed by a highly stereoselective 6-*exo-trig* cyclization of 5-hexen-1-ols **299** in the presence of K[N(TMS)₂] (Equation 130) <1997SL1318>. A diastereomeric mixture of 2-cyclohexyl tetrahydropyrans is formed upon cyclization of the unsaturated malonate **300** (Equation 131) <2004OBC965>.



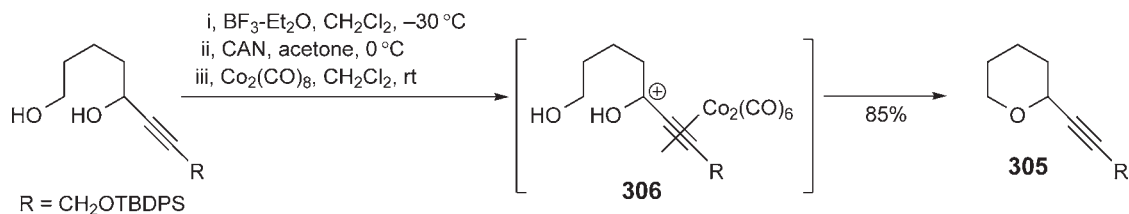
Scheme 75



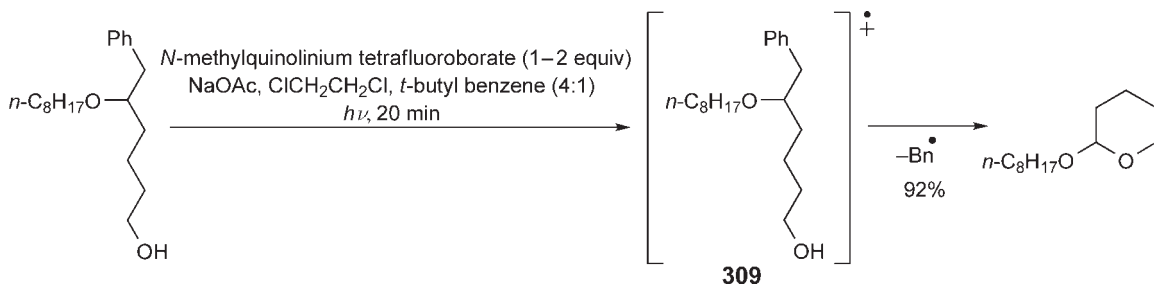
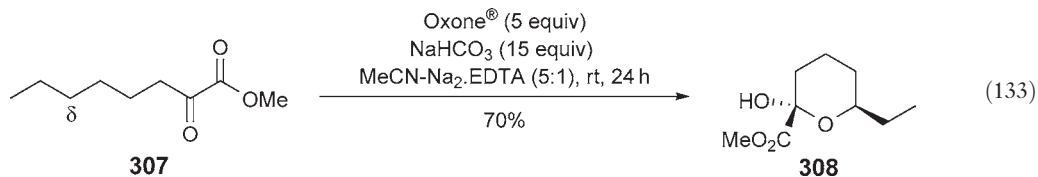
Racemic 2-phenyl tetrahydropyran can be accessed via an intramolecular Mitsunobu condensation of the 1,5-diol **301** with cyanomethylenetriphenylphosphorane (CMPB) proving to be an effective reagent for this transformation (Equation 132) <1996TL2463>. The enantiopure triol **302** undergoes a trimethyl orthoacetate mediated cyclization in the presence of pyridinium *p*-toluene sulfonate to furnish a mixture of tetrahydrofuran **303** and tetrahydropyran **304** arising from a [1,2]-phenylsulfanyl migration. Treatment of this mixture with toluene *p*-sulfonic acid affords the tetrahydropyran **304** as the sole product (Scheme 76) <2000CC1781>. This methodology has been extended to triols that feature three stereogenic centers <2002J(P1)2646, 2002J(P1)2652>. 2-Alkynyl-tetrahydropyrans **305** can be accessed by intramolecular trapping of the dicobalt hexacarbonyl-stabilized propargylic cations by the terminal hydroxy group of the intermediate **306** (Scheme 77) <2003JOC3216>. This methodology can be used to synthesize tricyclic ethers <2004OL4949>. An elegant δ -selective Oxone[®] mediated C–H bond oxidation of the linear ketone **307** results in concomitant cyclization to afford the *anti*-tetrahydropyranol **308** (Equation 133) <1998JA6611>. Tetrahydropyran construction can also be achieved using an elegant electron transfer initiated cyclization (ETIC) based upon activation of a carbon–carbon σ -bond by a single electron transfer. The benzylic carbon–carbon bond in the highly reactive radical cation intermediate **309** is significantly weakened; therefore, benzyl radical displacement can be achieved by even poor nucleophiles and cyclization of the radical cation **309** to 2-(octyloxy)tetrahydropyran is observed in excellent yield (Scheme 78) <2001JA3842>.



Scheme 76

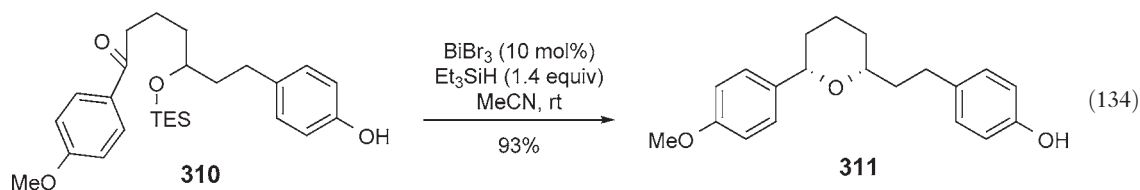


Scheme 77

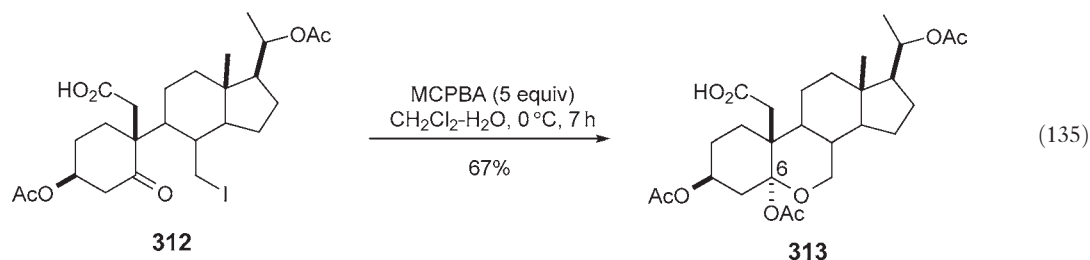


Scheme 78

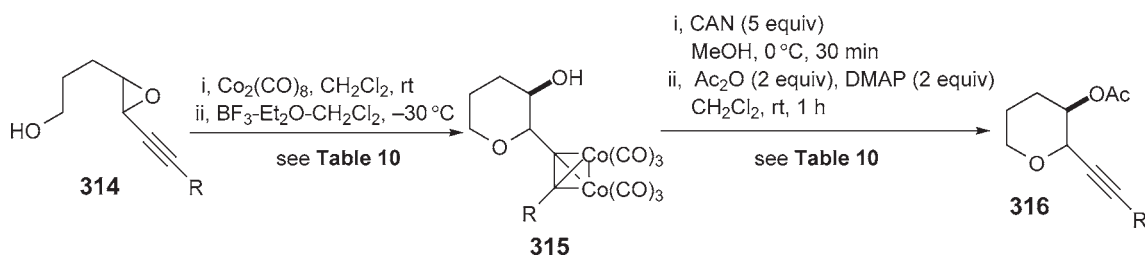
A high-yielding stereoselective intramolecular reductive etherification of the δ -silyloxy substituted ketone **310** provides the final step in a total synthesis of the antibiotic (–)-centrolbine **311** (Equation 134) <2003OL3883>.



The oxidative cyclization of the δ -iodoketone **312** is achieved with high stereoselectivity during the synthesis of 6-oxa-5 α -pregnane **313** (Equation 135) <1996JOC6673>.



Treatment of epoxy-alkyne derivatives **314** with dicobalthexacarbonyl [$\text{Co}_2(\text{CO})_6$] and a catalytic quantity of Lewis acid, followed by oxidative demetallation of the intermediate cobalt complex **315** affords 2-alkynyl-3-acetoxy tetrahydropyrans **316** in excellent yield. *Syn*- or *anti*-tetrahydropyrans are obtained by selection of either the *anti*- or *syn*- starting epoxides **314** respectively (Scheme 79, Table 10) <1998T823, 2000JOC6761>.

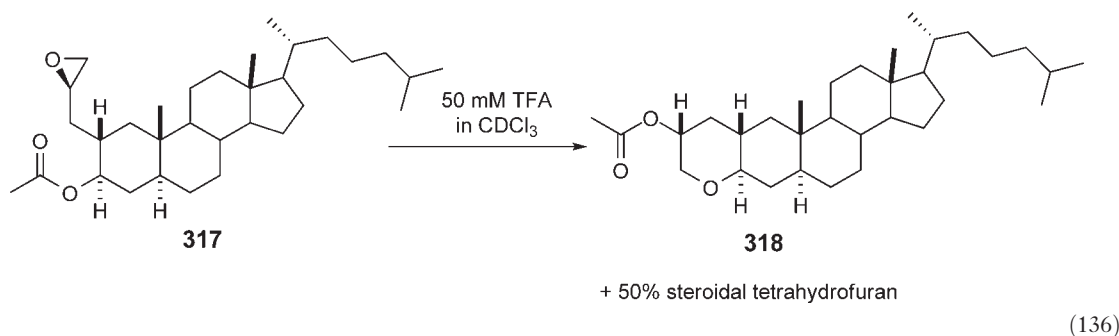


Scheme 79

Table 10 Formation of tetrahydropyrans **315** and **316** (Scheme 79)

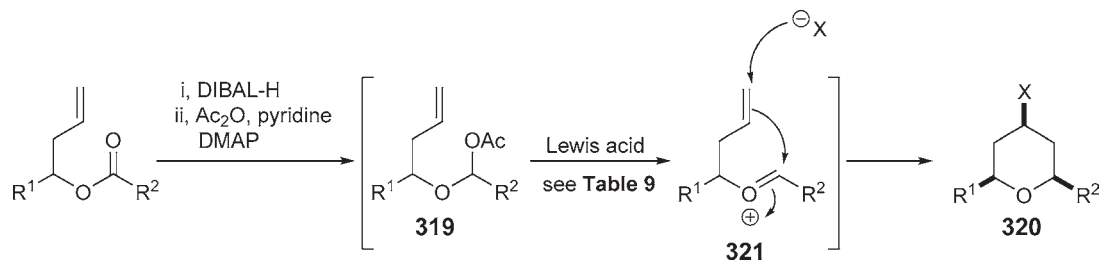
Epoxide 314	R	Yield 315 (%)	Yield 316 (%)	<i>anti:syn</i> 316
<i>anti</i>	H	65	95	4:96
<i>anti</i>	TMS	86	93	9:91
<i>anti</i>	Bu ⁿ	97	96	3:97
<i>anti</i>	Ph	96	100	1:99
<i>anti</i>	4-MeC ₆ H ₄	98	93	2:98
<i>anti</i>	COPh	90	98	2:98
<i>syn</i>	H	92	98	99:1
<i>syn</i>	TMS	88	93	100:0
<i>syn</i>	Bu ⁿ	92	96	99:1
<i>syn</i>	Ph	93	94	99:1
<i>syn</i>	4-MeC ₆ H ₄	95	93	97:3
<i>syn</i>	COPh	89	94	97:3

Rearrangement of the epoxy ester **317** affords a 1:1 mixture of the tetrahydropyran **318** and a steroidal tetrahydrofuran by-product. This methodology offers a new hypothesis regarding the biosynthesis of polyether natural products (Equation 136) <2005JOC721>.



7.08.10.1.2 β to the heteroatom

The Lewis-acid-mediated Prins cyclization of α -acetoxyethers **319** provides a route to *syn*-2,4,6-trisubstituted tetrahydropyrans **320** (Scheme 80, Table 11). The substituent incorporated at C-4 during the reaction is dependent on the choice of Lewis acid that participates in trapping of the intermediate cations **321**. A model for the bis-tetrahydropyran moiety of phorboxazole is successfully assembled using this approach <1998TL7271>, as is the C(22)–C(26) tetrahydropyran segment of phorboxazole B <2000OL1217> and (–)-centrolobine <2002OL3919>. A report regarding the scope of this type of Prins cyclization is available. Particular emphasis is placed upon the stereochemical and regiochemical outcome of the reaction when regioisomeric alkenes and alkynes are substrates <2001JOC4679>. A study regarding the role of the 2-oxonia Cope rearrangement during Prins cyclization is also available <2001OL3815>.



Scheme 80

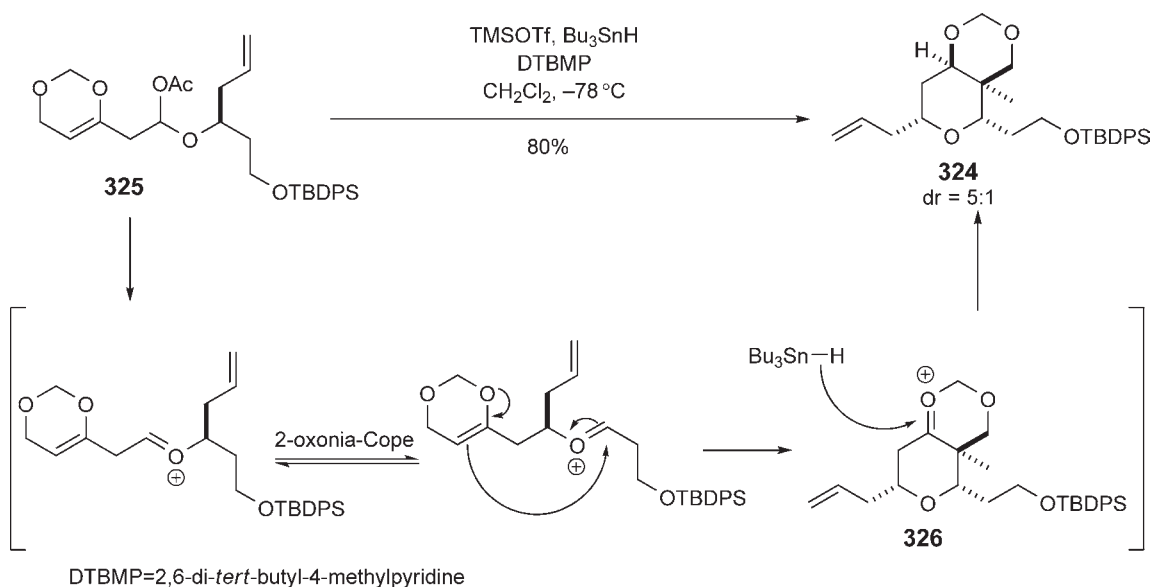
Table 11 Formation of tetrahydropyrans **320** (Scheme 80)

Lewis acid	R ¹	R ²	X	Yield 320 (%)	dr
TiCl ₄	<i>n</i> -C ₆ H ₁₃	Me	Cl	80	1:0
TFAA	<i>n</i> -C ₆ H ₁₃	Me	OH	79	1:0
TiCl ₄	<i>n</i> -C ₆ H ₁₃	CH ₂ Cl	Cl	95	7:1
TFAA	<i>n</i> -C ₆ H ₁₃	CH ₂ Cl	OH	80	8:1
TiCl ₄	CH ₂ Bn	CF ₃	Cl	65	1:1.5
TiCl ₄	CH ₂ Bn	CH ₂ I	Cl	91	5:1

Treatment of the α -acetoxy ether **322** with trimethylsilyl bromide affords the axial 4-bromotetrahydropyran **323** (Equation 137). This axial selective Prins cyclization can also be conducted in the presence of acetyl bromide, but use of SnBr₄ affords equatorial 4-bromotetrahydropyrans and hence the all *syn*-product <2004JA9904>.

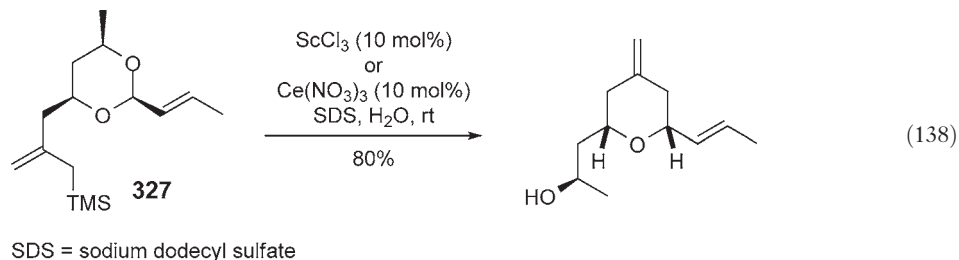


The enantioselective synthesis of the C(18)–C(25) segment of lasanolid A **324** can be achieved via an oxonia–Cope–Prins cascade cyclization of α -acetoxy ether **325**. The *in situ* reduction of the oxocarbenium ion intermediate **326** with Bu_3SnH prevents the formation of a tetrahydropyran-4-one side product (Scheme 81) <2005OL1589>.

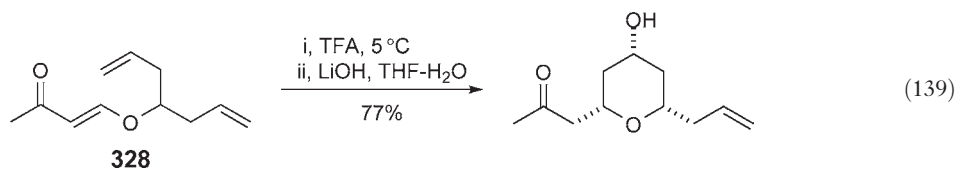


Scheme 81

Prins cyclization of the acetal **327** can be conducted in the presence of a Lewis acid surfactant catalyst in water to afford 2,4,6-trisubstituted tetrahydropyrans. The reaction proceeds via ionization of the α,β -unsaturated acetal and subsequent reaction with the tethered electron-rich alkene, proving that the interior of micelles are sufficiently anhydrous to protect Prins cyclization intermediates (Equation 138) <2003OL4521>.



An acid-mediated Prins type cyclization of enol ether **328** followed by basic hydrolysis of the intermediate trifluoroacetate provides a key step during synthetic studies toward leucascandrolide A (Equation 139) <2001OL755>. The acid-promoted Prins cyclization of enol ethers attracts much attention <2003OL1499, 2004HCA2750, 2005OL2683>.



Aldehydes undergo a Mukaiyama-aldol reaction followed by a Prins cyclization with the highly reactive allylsilane **329** to afford *syn*-2,6-tetrahydropyrans **330** that feature an *exo*-methylene group at C-4 (Equation 140, Table 12). This Mukaiyama-aldol–Prins (MAP) cascade cyclization has been used to form a key bis-tetrahydropyran intermediate during the total synthesis of leucascandrolide A <2001JA8420>. Similarly, titanium tetrabromide mediated MAP reactions afford 4-bromo tetrahydropyrans <2003OL3163>.

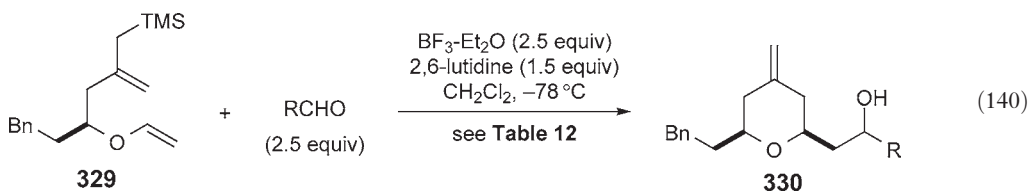


Table 12 Formation of 4-*exo*-methylene tetrahydropyrans **330** (Equation 140)

<i>R</i>	Yield 330 (%)	<i>dr</i>
Pr ⁱ	98	1:1
Ph	84	1.2:1
(<i>E</i>)-PhCH=CH	87	1.4:1
CH ₂ CH ₂ OTBS	87	1.8:1
<i>n</i> -C ₆ H ₁₁	72	1.7:1

A stereocontrolled synthesis of 2,4,5-trisubstituted tetrahydropyrans **331** can be achieved via a Lewis-acid-catalyzed intramolecular Prins cyclization of homoallylic acetals **332**. Incorporation of a variety of substituents at C-4 of the resulting tetrahydropyrans is possible by simple variation of the reaction conditions (Equation 141, Table 13) <2001CC835>.

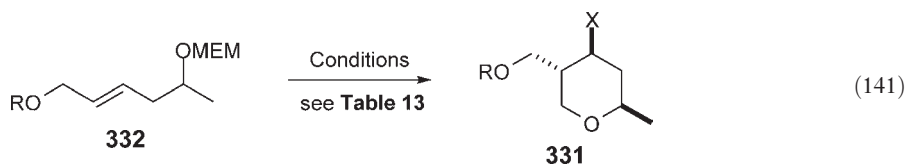
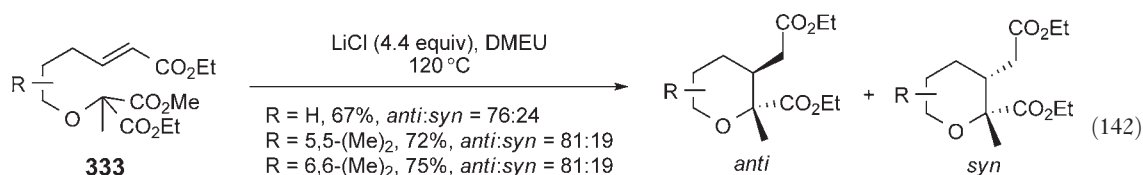


Table 13 Formation of 2,3,5-trisubstituted tetrahydropyrans **331** (Equation 141)

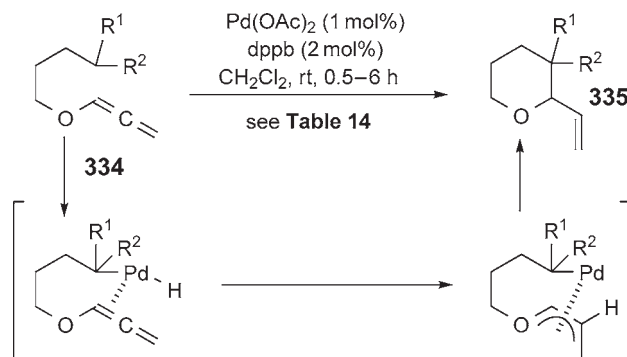
<i>X</i>	<i>R</i>	Conditions	Yield 331 (%)
Cl	H	TiCl ₄ , CH ₂ Cl ₂	63
Cl	TBDPS	TiCl ₄ , CH ₂ Cl ₂	74
Br	TBDPS	TiBr ₄ , CH ₂ Cl ₂	85
F	H	BF ₃ -Et ₂ O, CH ₂ Cl ₂	55
OH	H	i, TFA; ii, K ₂ CO ₃	72
OMe	H	BF ₃ -Et ₂ O, AcOH TMSOAc	53
NHAc	TBDPS	CF ₃ SO ₃ H, MeCN	>95

Methyl esters **333** that are activated toward decarboxylation by a C-2-ethoxycarbonyl group and tethered by an alkyl chain to an acrylate Michael-acceptor undergo chemoselective S_N2-dealkylation of the methyl ester, decarboxylation and cyclization upon exposure to lithium chloride in DMEU, affording tetrahydropyrans in excellent yield and diastereoselectivity (Equation 142) <1998JOC144>.



DMEU = 1,3-dimethyl-2-imidazolinone

A palladium(II)-catalyzed intramolecular hydrocarbonation of alkoxyallenes **334** affords tetrahydropyrans **335** in excellent yield with high diastereoselectivity (Scheme 82, Table 14) <1999TL1747>.

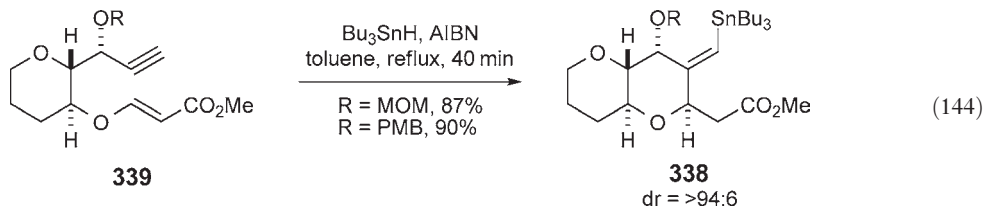
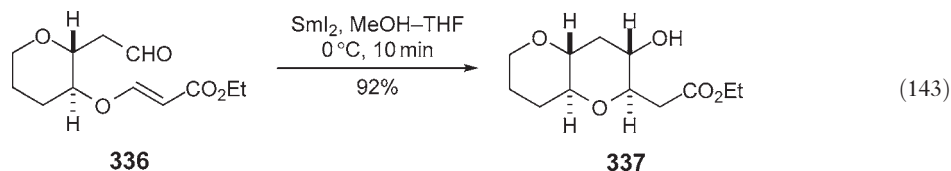


Scheme 82

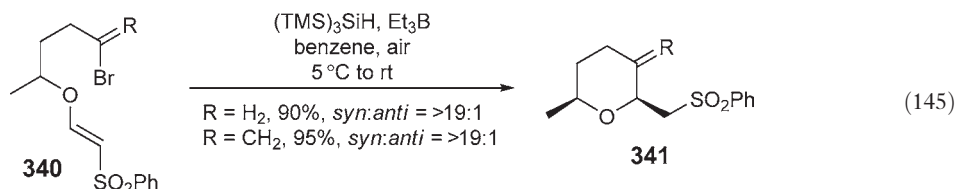
Table 14 Formation of the tetrahydropyrans **335** (Scheme 82)

R^1	R^2	Yield 335 (%)	<i>dr</i>
CN	CN	86	
CN	SO ₂ Ph	88	94:6
SO ₂ Ph	SO ₂ Ph	92	
CN	CO ₂ Me	77	80:20
SO ₂ Ph	CO ₂ Me	70	81:19

The first samarium diiodide induced cyclization of the β -alkoxy acrylate **336** furnishes the desired 2,6-*syn*-2,3-*anti*-tetrahydropyran **337** in excellent yield (Equation 143). The selectivity of the cyclization can be altered upon addition of HMPA <1999TL2811, 2002T1853>. This methodology was used to construct a tetrahydropyran intermediate during the total synthesis of a proposed structure of pyragonicin <2005OL2783>. A stereoselective route to multi-substituted tetrahydropyrans **338** features a vinyl radical cyclization as the key step, in which the vinyl radical is generated from acetylenic β -alkoxy acrylate **339** (Equation 144) <2005T8589>.

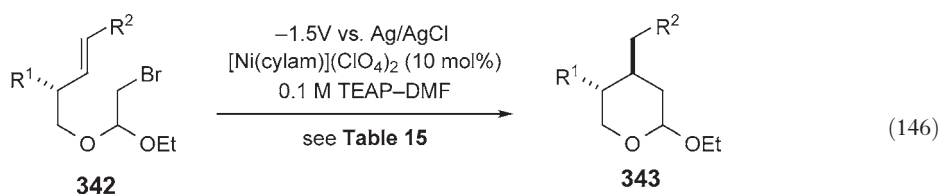


Treatment of *E*-vinyl sulfonates **340** with tris(trimethylsilyl)silane and triethylborane provides a diastereoselective route to *syn*-2,6-tetrahydropyrans **341** in high yield (Equation 145) <2000JOC4523>.



7.08.10.1.3 γ to the heteroatom

A [Ni(cylam)](ClO₄)₂-catalyzed electrolytic reduction of alkenyl bromides **342** allows for an environmentally friendly entry to 4,5-*anti*-tetrahydropyrans **343**. Either (*E*)- or (*Z*)-alkenes can be used as substrates, but diastereoselectivity is not observed if an isomeric mixture of alkenes is subjected to the cyclization conditions (Equation 146, Table 15) <1996JOC677>.



cylam = 1,4,8,11-tetraazacyclotetradecane

Table 15 Formation of tetrahydropyrans **343** (Equation 146)

<i>R</i> ¹	<i>R</i> ²	Yield 343 (%)	<i>anti:syn</i> ratio
Ph	H	16	>99:1
Ph	(<i>Z</i>)-Me	29	>99:1
Ph	(<i>E</i>)-CO ₂ Me	75	>99:1
H	(<i>E/Z</i>)-SPh	27	1:1
Et	(<i>E</i>)-CO ₂ Me	83	>4:1
Et	(<i>Z</i>)-CO ₂ Me	88	>99:1

A Lewis-acid-mediated intramolecular cyclization of allenyl stannane **344** furnishes 2,6-*anti*-tetrahydropyran as the major product, the stereochemistry of which can be switched to *syn* with moderate effect if a propargylstannane **345** is used as a substrate (Equation 147, Table 16) <1996TL3059>. The stereoselectivity observed in an analogous system, the intramolecular cyclization of γ -alkoxyallyl stannanes **346** with a tethered aldehyde, can be controlled by changing the geometry of the alkene (Scheme 83) <1997JOC7439>. γ -Alkoxyallyl stannanes are also known to cyclize both diastereoselectively and enantioselectively, by incorporation of both a chiral auxiliary and a chiral catalyst respectively into the reaction <1999JOC4901>.

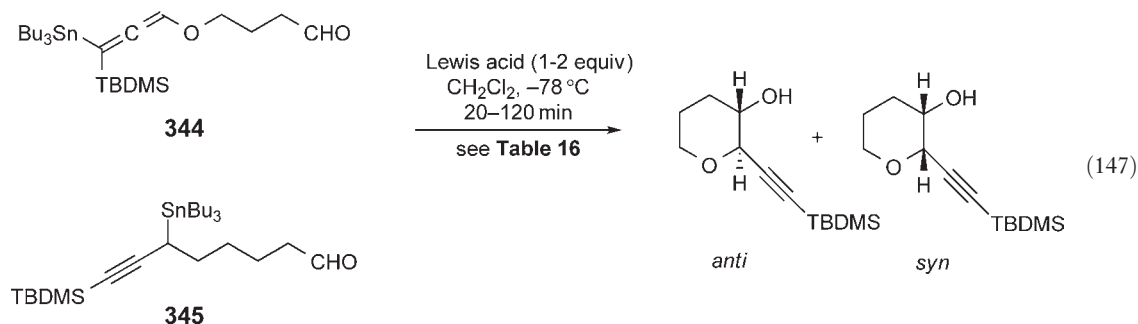
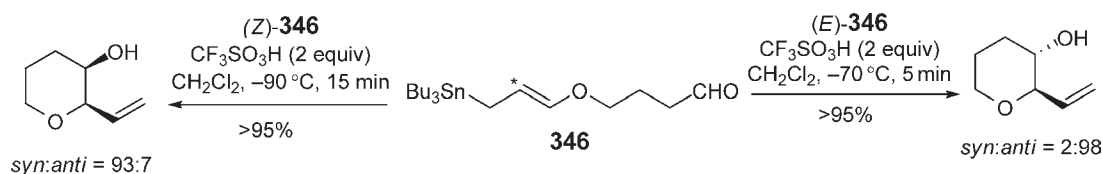
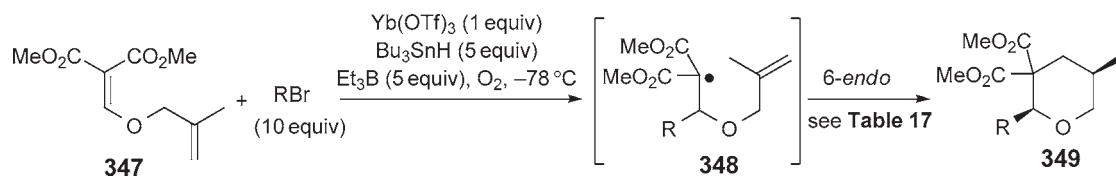


Table 16 Synthesis of tetrahydropyrans from substrates **344** and **345** (Equation 147)

<i>Lewis acid</i>	<i>Substrate 344 anti:syn Yield (%)</i>	<i>Substrate 345 anti:syn Yield (%)</i>
BF ₃ ·Et ₂ O	91:9 87	
TiCl ₄	89:11 70	
SnCl ₄	90:10 44	67:33 52
BuSnCl ₃		52:48 53
ZnCl ₂ ·OEt ₂	94:6 77	26:74 61

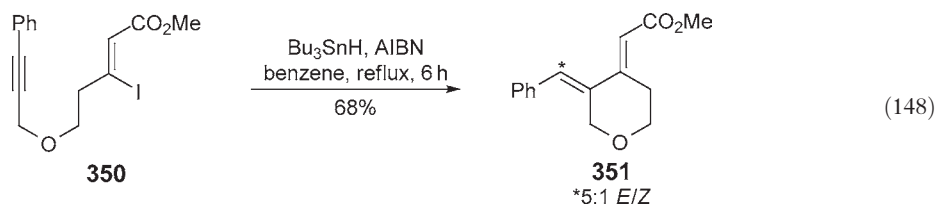
**Scheme 83**

Radical addition to β -alkoxyalkylidenemalonate **347** provides highly electrophilic malonyl radical intermediates **348** that undergo 6-*endo* cyclization onto tethered unactivated alkenes to afford tetrahydropyrans **349**. The diastereoselectivity in the product can be improved by using bulky radicals (**Scheme 84**, **Table 17**) <2004EJO372>.

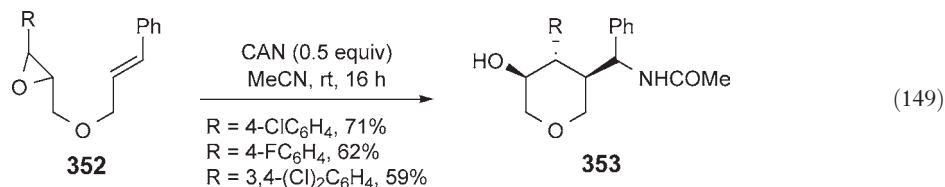
**Scheme 84****Table 17** Effect of increasing radical size on diastereoselectivity observed in tetrahydropyrans **349** (**Scheme 84**)

<i>R</i>	<i>Yield 349 (%)</i>	<i>dr</i>
CH ₂ OMe	85	1.5:1
Et	70	1.2:1
Pr ⁱ	68	2.5:1
<i>n</i> -C ₆ H ₁₁	78	6:1
MeC(O)	72	2:1
Adamantyl	88	14:1

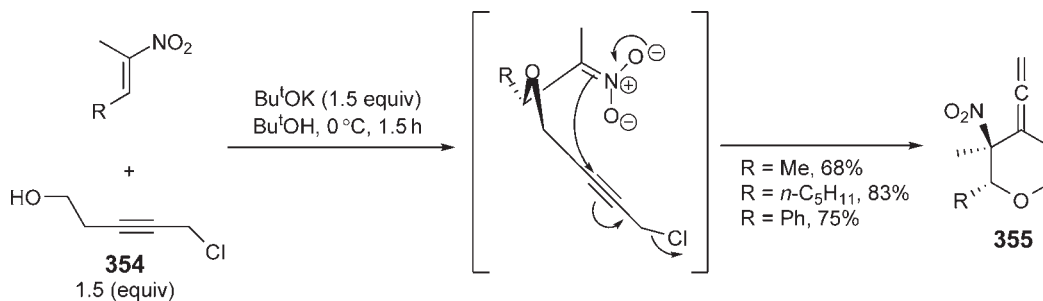
Radical cyclization of alkenyl iodide **350** provides a route to a tetrahydropyran **351** bearing an exocyclic moiety (Equation 148) <2000OL2011>.



A ceric ammonium nitrate (CAN) mediated stereoselective cyclization of epoxypropyl cinnamyl ethers **352** provides a facile route to 3,4,5-trisubstituted tetrahydropyran derivatives **353** (Equation 149) <2004TL2413>.



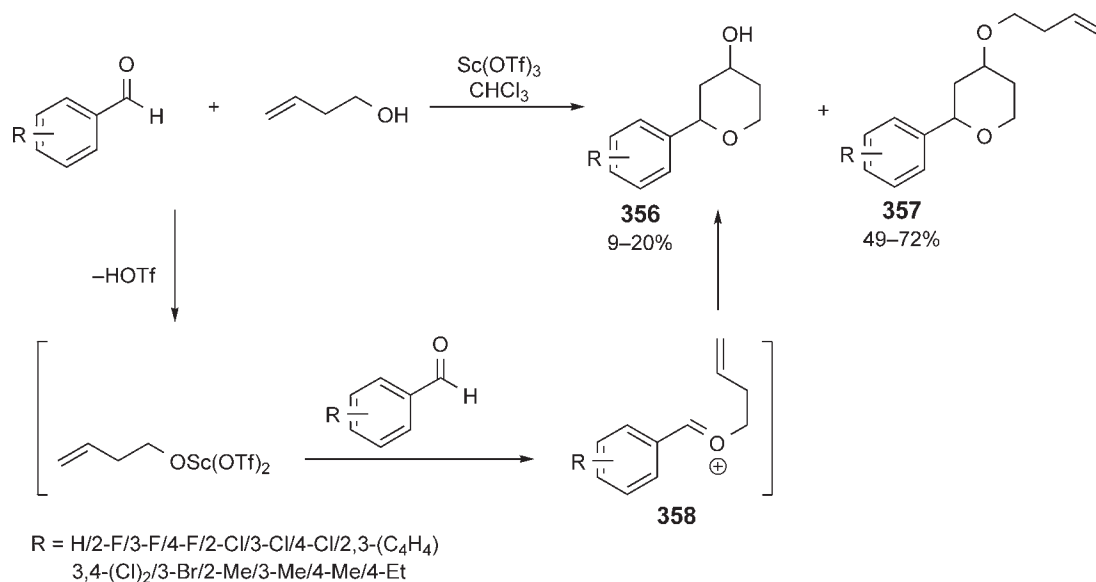
A tandem oxa-Michael addition-S_N2' substitution of 5-chlorobut-2-yn-1-ol **354** with nitroalkenes affords 3-allenyl-4-nitro tetrahydropyrans **355** in good yield (Scheme 85) <2001EJO2577>.



Scheme 85

7.08.10.2 Formation of More than One Bond

Scandium triflate can catalyze a Prins reaction between aromatic aldehydes and homoallylic alcohol to provide a mixture of tetrahydropyran-4-ols **356** and homoallyl ethers **357** in good yield. Nucleophilic trapping of the intermediate cation **358** by both homoallylic alcohol and trifluoromethanesulfonic acid (TfOH) explains the product mixture (Scheme 86) <1999CC291, 2000T2403>. Montmorillonite clay is also an effective catalyst for this process <2001TL89>, as is In(OTf)₃ <2001OL2669, 2002TL7193, 2005OL4491>.

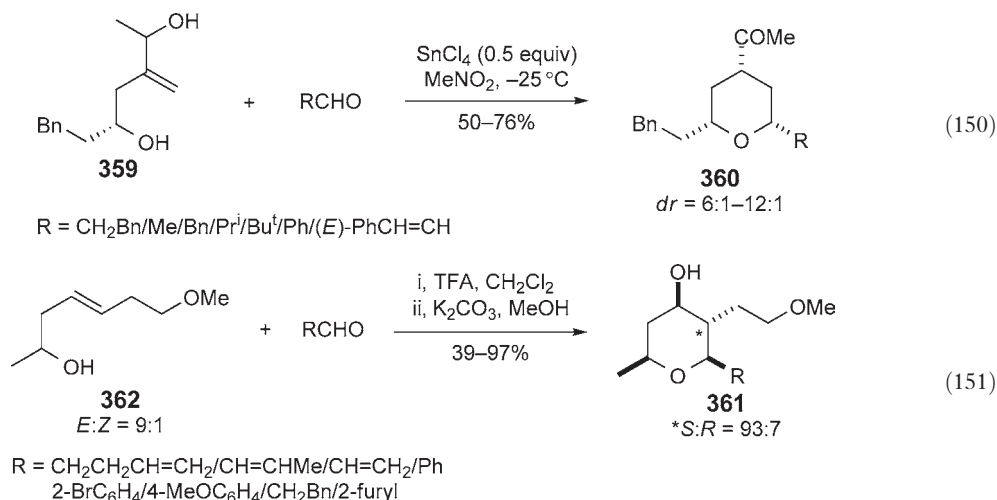


Scheme 86

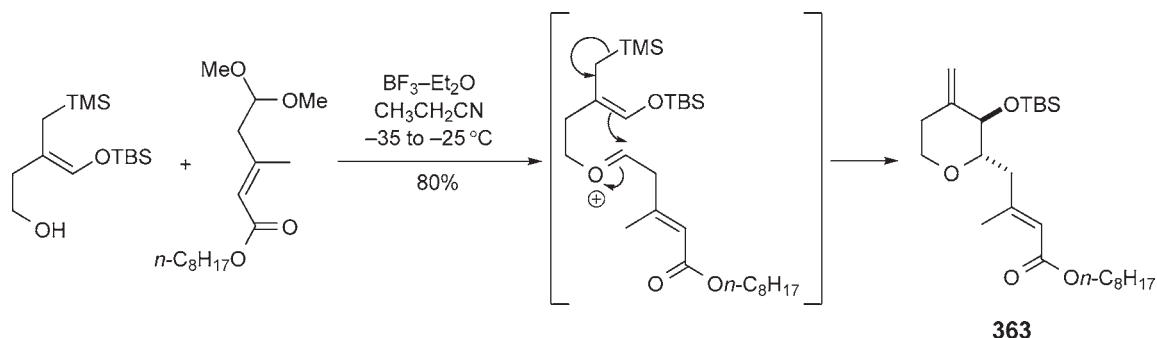
The intermolecular Prins cyclization between aldehydes and homoallylic bromides can be catalyzed by indium trichloride, giving 4-chlorotetrahydropyrans in high yield and stereoselectivity <1999TL1627>. Indium trichloride is also an effective Lewis acid catalyst for the reaction of aldehydes with chloro homoallylic alcohols, a Prins type cyclization that furnishes *syn*-2,6-disubstituted 4,4-dichlorotetrahydropyrans <1999SL717>. Indium trichloride is also effective for the reaction of aldehydes and allylsilanes <2004TL8387>, and is the Lewis acid catalyst of choice during the intermolecular Prins cyclization of epoxides and homoallylic alcohols, furnishing 2,4-disubstituted and 2,3,4-trisubstituted tetrahydropyrans in high yield and diastereoselectivity <2001TL793>, 2001JOC739>; bismuth trichloride is also effective <2005SL1945>.

The intermolecular Prins cyclization between ketones and homoallylic alcohols can be catalyzed by mercuric triflate <1999TL1153>. TMSNTf₂ is an effective catalyst for the reaction between aldehydes and homoallylic alcohols <2002AGE161>.

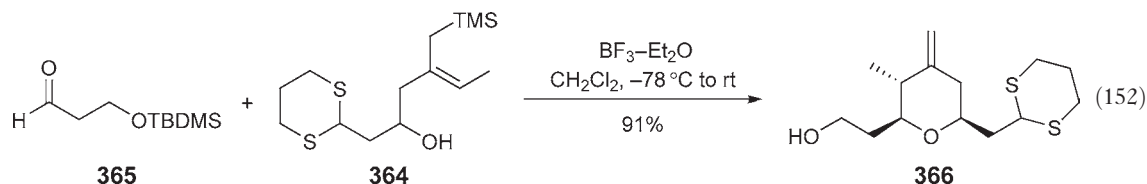
Reaction of 2-methylene-1,4-diol **359** with aldehydes affords all *syn*-2,4,6-trisubstituted tetrahydropyrans **360** with excellent diastereoselectivity (Equation 150, Table 18) <1999JA1092>. Varying the diastereomeric mixture of the starting allylic alcohol has no effect upon the diastereomeric excess of the product, indicating that the configuration of the allylic alcohol does not effect the stereochemical outcome of the reaction <1999JA1092>. Similarly, the stereoselective synthesis of 2,3,6-trisubstituted tetrahydropyran-4-ols **361** can be achieved by reaction of homoallylic alcohol **362** and aldehydes. In this instance, four new stereocentres are generated during the cyclization, and by varying the aldehyde component a variety of functionalized side chains can be installed at C2 (Equation 151) <2003OL2429>.



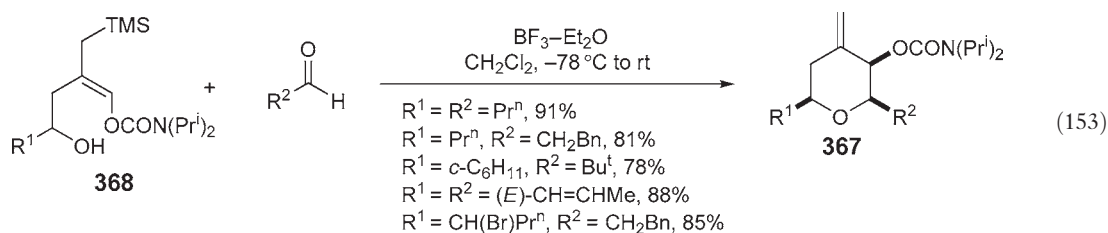
The synthesis of tetrahydropyrans by a silyl-modified Prins cyclization, notably in the synthesis of a pseudomonic acid C analogue **363**, illustrates the versatility of this methodology (Scheme 87) <1999TL5259>. The (*Z*)-allylsilane **364** also undergoes smooth cyclization with aldehyde **365** in the presence of a Lewis acid providing a novel connective approach toward the tetrahydropyran subunit of polycavernoside A **366** (Equation 152) <2005TL4887, 2006T2331>. This methodology can also be used to construct complex bis-tetrahydropyran targets <2002OL1189>.



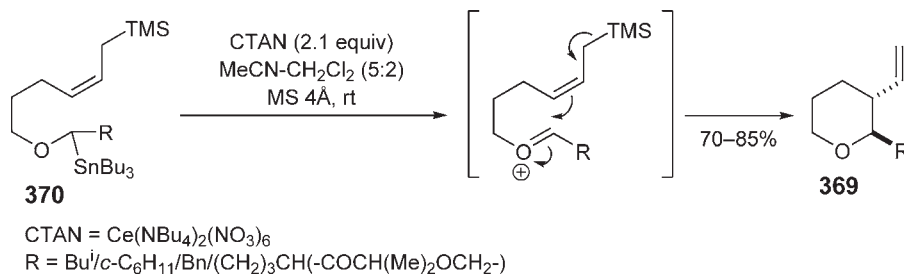
Scheme 87



All *syn*-2,3,6, 4-*exo*-methylene tetrahydropyrans **367** can be readily assembled using a Lewis acid promoted Prins reaction between enol carbamates **368** and aldehydes (Equation 153). The presence of an *exo*-methylene group and the labile carbamate in the product allows for simple transformation into tetrahydropyranones and tetrahydropyransols <2000TL7225, 2001TL8685, 2002JOC8744>.



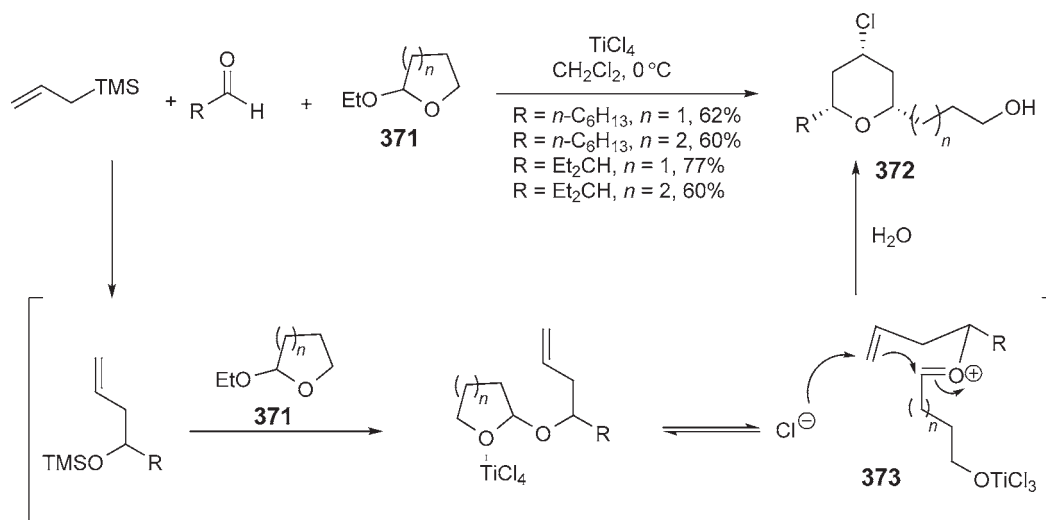
2,3-*anti*-Tetrahydropyrans **369** can be accessed via a mild cerium-mediated oxidation of α -stannyl ethers **370**, especially attractive for Prins cyclization substrates that possess Lewis-acid-sensitive functionality. The reaction proceeds smoothly due to the ease at which α -stannyl ethers are transformed to oxonium ions by metal based oxidizing agents (Scheme 88) <2000JOC3252>.



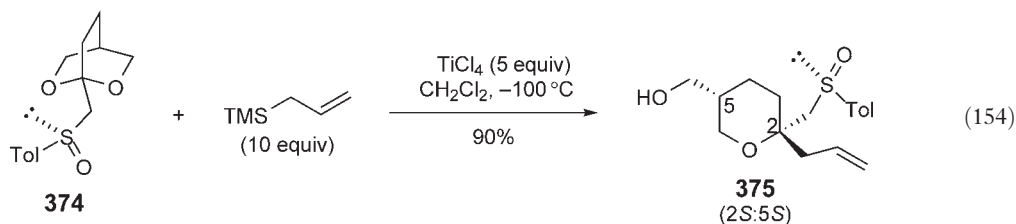
Scheme 88

Tetrahydropyrans bearing halides at C4 can be accessed by a modified Taddei-Ricci reaction. The reaction involves condensation of allyltrimethylsilane, aldehydes and a cyclic acetal **371** in the presence of a Lewis acid to afford all *syn*-tetrahydropyrans **372** as a single diastereomer. The reaction proceeds via anion mediated ring closure of oxonium ion intermediate **373** (Scheme 89). This methodology was successfully applied to the synthesis of a model compound bearing all the structural motifs present in the eastern subunit of okadaic acid <1997TL2895>.

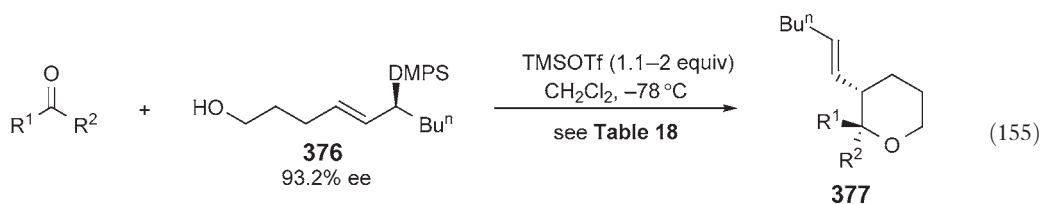
Cleavage of the bicyclic acetal **374** with Lewis acid in the presence of allyltrimethylsilane occurs with 1,3- and 1,6-asymmetric induction effected by the chiral sulfinyl group, furnishing 2,2,5-trisubstituted tetrahydropyran **375** (Equation 154). Removal/conversion of the *p*-tolylsulfinyl group is straightforward, and this methodology was successfully used during the total synthesis of (–)-malyngolide <1997CC1755>.



Scheme 89



Enantioenriched (*E*)-allyl silane **376** is a highly useful building block for the synthesis of optically active tetrahydropyrans **377**, reacting with aldehydes and simple ketones with very effective chirality transfer in the presence of a Lewis acid (Equation 155, Table 18) <1998JOC6096>.

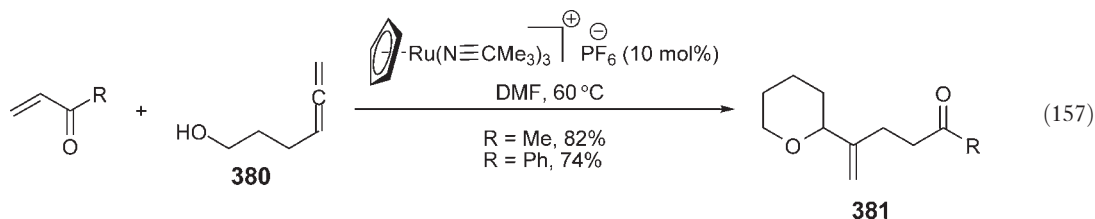
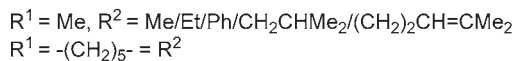
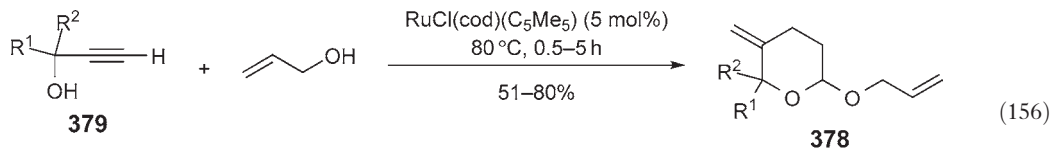


DMPS = dimethylphenylsilane

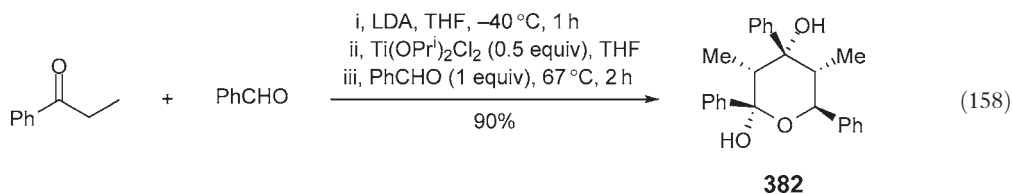
Table 18 Yield, diastereo- and enantioselectivity of tetrahydropyrans **377** (Equation 155)

R^1	R^2	Yield 377 (%)	<i>anti:syn</i>	<i>ee</i> (%)
Me	H	89	>10:1	93.4
<i>n</i> -C ₆ H ₁₃	H	92	>10:1	92.1
Pr ⁱ	H	98	99:1	92.8
<i>c</i> -C ₆ H ₁₁	H	99	99:1	92.3
Bu ^t	H	88	9:1	93.6
Me	Me	95		91.5
CH=CMc ₂	H	72	12:1	92.0

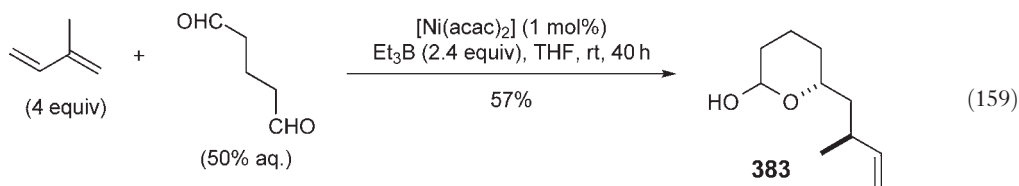
The synthesis of 5-*exo*-methylene tetrahydropyrans **378** can be accomplished by a regioselective ruthenium catalyzed C–C coupling reaction of prop-2-yn-1-ols **379** and allylic alcohol (Equation 156) <1999JOC3524>. A ruthenium catalyzed alkylative cycloetherification reaction between allene **380** and vinyl ketones furnishes 2-substituted tetrahydropyrans **381** in high yield (Equation 157) <1999JA10842>.



A metal-directed domino aldol-aldol hemiacetal reaction allows for a highly stereoselective synthesis of tetrahydropyran-2,4-diols containing up to five stereogenic centres (Equation 158). Propiophenone is deprotonated with LDA, and subsequent treatment with $\text{Ti}(\text{O}i\text{-Pr})_2\text{Cl}_2$ followed by benzaldehyde gives the tetrahydropyran **382** as a single diastereomer in good yield, with all the large substituents occupying equatorial positions and both hydroxyl groups axial (Equation 158) <1999EJO2007>.



An intermolecular homoallylation of glutaraldehyde with isoprene occurs regioselectively at C-1 when promoted by $[\text{Ni}(\text{acac})_2]/\text{triethylborane}$ to afford the tetrahydropyran **383** as a single isomer, the methyl group being 1,3-*anti* with respect to the tetrahydropyranyl oxygen (Equation 159) <2001AGE3600>.



7.08.10.3 From Other Heterocycles

7.08.10.3.1 From 1,3-dioxanes

Treatment of the vinyl acetals **384** with triisobutylaluminium results in the transposition of an O-atom with a C-atom on the ring, providing tetrahydropyrans **385** in excellent yield (Equation 160, Table 19) <1996TL141>.

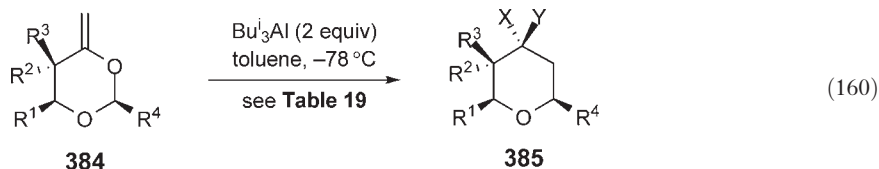
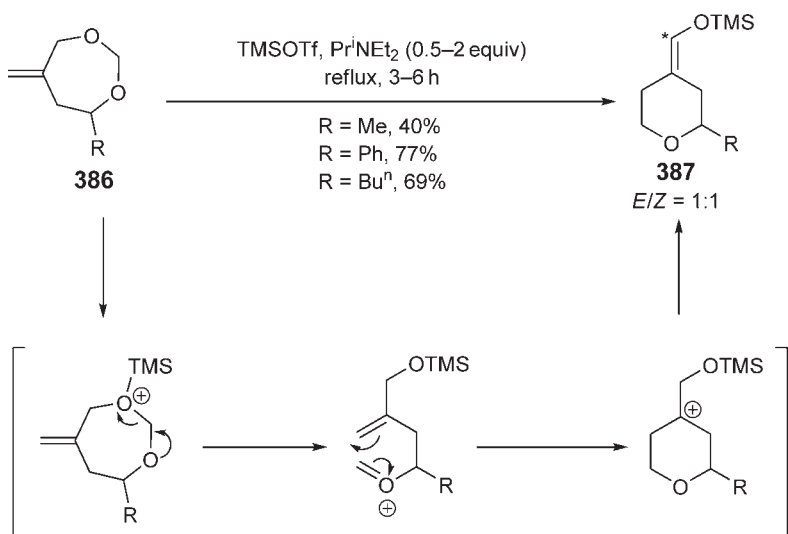


Table 19 Formation of tetrahydropyrans **385** (Equation 160)

R^1	R^2	R^3	R^4	Yield 385 (%)	$X=H, Y=OH$: $X=OH, Y=H$ ratio
H	H	Me	Ph	91	1:1
Me	H	H	Bu ^t	81	1:1.5
Me	H	H	CH ₂ Bn	96	1:0
Me	H	H	<i>n</i> -C ₁₀ H ₂₁	93	1:0
Me	H	H	Ph	90	1:0
H	Ph	H	Pr ⁱ	88	1:8
H	H	Ph	Pr ⁱ	90	1:0
H	Bn	H	Bu ^t	92	1:8

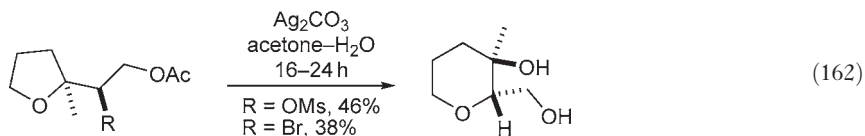
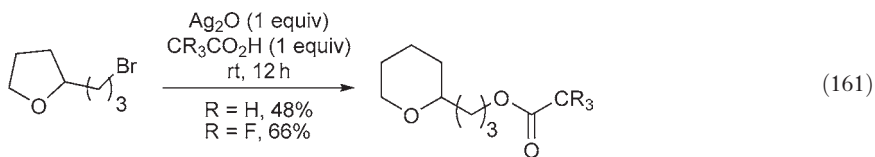
7.08.10.3.2 From dioxepanes

The reaction of 5-methylene-1,3-dioxepanes **386** with trimethylsilyl trifluoromethanesulfonate in the presence of base forms cyclic silyl enol ethers **387** (Scheme 90) <2000TL2171>.

**Scheme 90**

7.08.10.3.3 From tetrahydrofurans

Oxidative ring expansion of tetrahydrofurans can be promoted by silver(I) salts to afford tetrahydropyrans in moderate yield (Equations 161 and 162) <1996J(P1)413, 1996TL213>. Zinc salts can also effect this transformation <1999TL2145>.



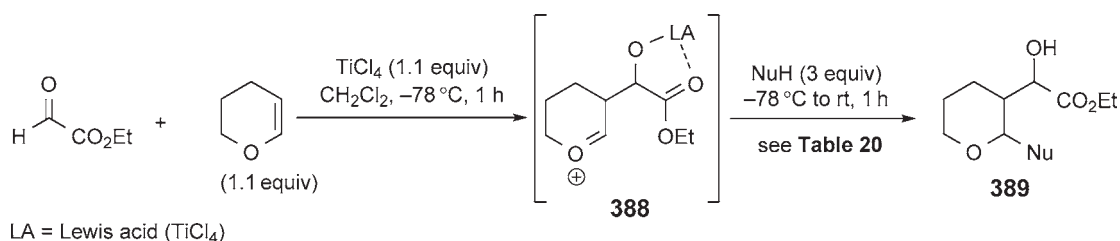
7.08.10.4 From a Preformed Heterocyclic Ring

7.08.10.4.1 From tetrahydropyranones

A convenient two-step method for tetrahydropyran synthesis from tetrahydropyran-2-ones can be achieved by using a titanocene complex in the presence of a stoichiometric reducing agent, followed by treatment with Amberlyst 15[®] and triethylsilane <1998JOC2360>.

7.08.10.4.2 From dihydropyrans

A titanium(IV)-promoted coupling of ethyl glyoxylate and dihydropyran provides an oxonium ion intermediate **388** which can be trapped with nucleophiles (NuH) providing access to 2,3-disubstituted tetrahydropyrans **389** (Scheme 91, Table 20) <1999TL1083>. This methodology is incorporated into the total synthesis of the antitumor agent mucocin <2002AGE4751>.



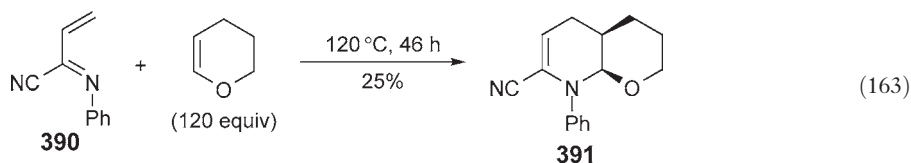
Scheme 91

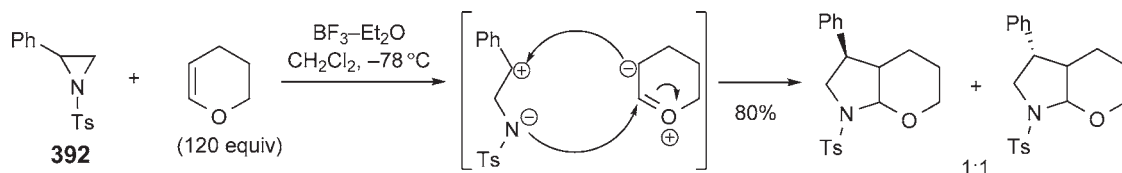
Table 20 Nucleophile addition to cation **388** furnishing tetrahydropyrans **389** (Scheme 91)

NuH	Nu	Yield 389 (%)	dr ^a
Et ₃ SiH	H	95	1:1
TMS-CH=CH ₂	CH=CH ₂	85	1:1
MeOH	OMe	65	2:1

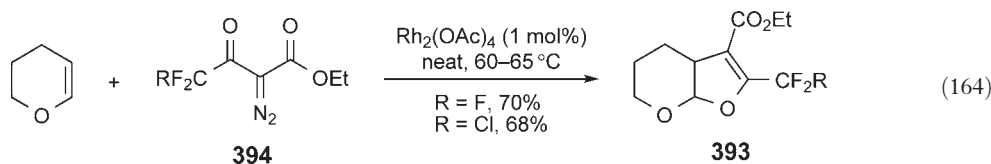
^aValues determined after oxidation of alcohol.

3,4-Dihydropyran undergoes an hDA reaction when present in vast excess with respect to an azadiene **390** producing a bicyclic *syn*-tetrahydropyran **391** (Equation 163) <1996JOC3715>. 3,4-Dihydropyran can also undergo a tetrabutylammonium peroxydisulfate-mediated oxidative cycloaddition with 1,3-dicarbonyl compounds furnishing fused tetrahydropyran derivatives <2000S1091>. Several other examples of a 3,4-dihydropyran participating in an hDA reaction are available <2001SL240> 3,4-Dihydropyran participates in a Lewis-acid-promoted cyclocondensation reaction with phenylaziridine **392** to afford a diastereomeric mixture of bicyclic tetrahydropyrans (Scheme 92) <1999TL5315, 2000AGE4615, 2001TL9089>. 3,4-Dihydropyran also participates in a Lewis-acid-mediated spiroannulation reaction with benzo- and naphthoquinones <1996TL5221>. Bis-dihydropyrans can be converted to polyspiroketal through a thermodynamically driven acid-catalyzed process <2000OL3453>. Fluoroalkyl substituted tetrahydropyrans **393** are accessible via a rhodium(II) catalyzed 1,3-dipolar reaction of 3,4-dihydropyran with 2-diazo-1,3-dicarbonyl compounds **394** (Equation 164) <2001T3383>.



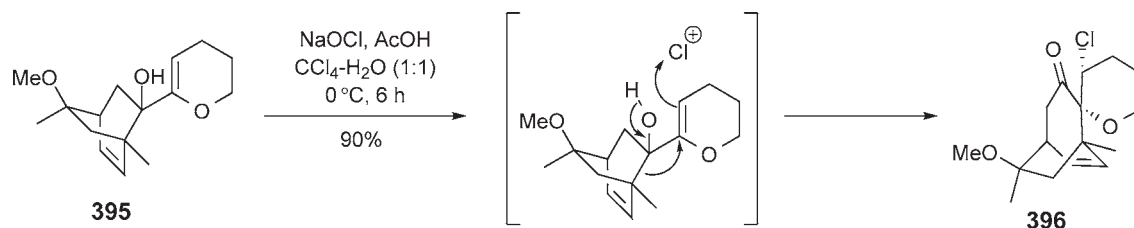


Scheme 92



3,4-Dihydropyran undergoes several reactions that result in a tetrahydropyran product, including a TiCl_4 -mediated addition/cyclization reaction with pyruvate esters [<2003SL1491>](#), a three-component coupling with anilines and benzaldehydes [<2003TL2117, 2004SL1175, 2004SL1715, 2005S2357>](#), a zirconocene-induced cocyclization/elimination reaction as a 1,6-diene [<2005S2061>](#), Nazarov reactions [<2005OL4345>](#), hydroaminations [<2005AGE4914>](#), Stille couplings with (Z)-vinyl iodoalcohols [<2005T11910>](#), and cyclopropanations-catalyzed by copper(i)- or rhodium(ii)-salts [<2005SL1397, 2005HCA1010, 2005CC5109>](#).

Dihydropyran **395** can undergo a hypochlorite–acetic acid promoted chlorination–ring expansion process to afford the tetrahydropyran **396** in high yield (**Scheme 93**) [<2002OL3899>](#).



Scheme 93

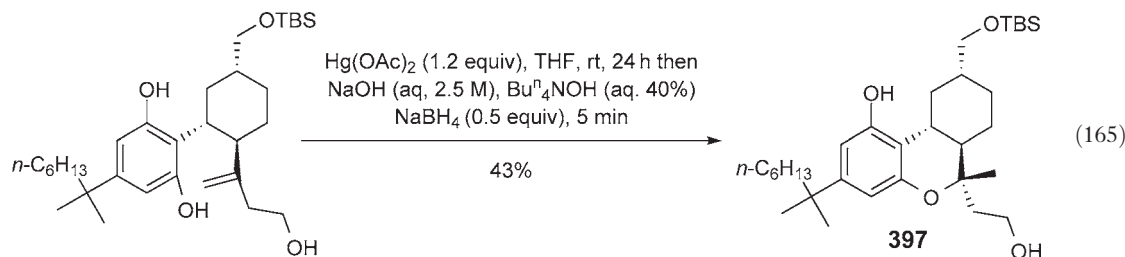
7.08.11 Chromans (3,4-Dihydro-2H-1-benzopyrans)

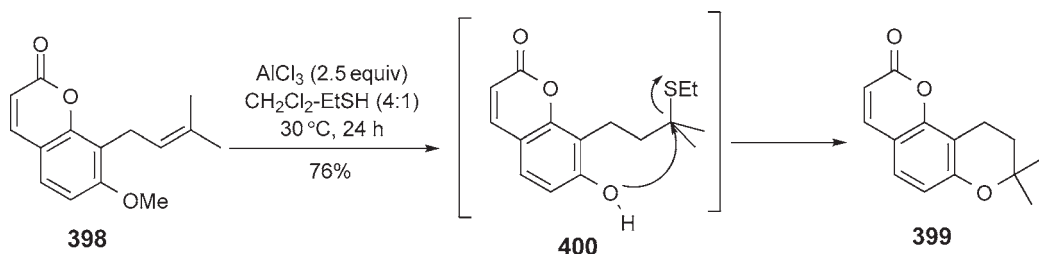
Reviews are available on natural products that contain the chroman ring system [<2000NPR193, 2001NPR310>](#), and the synthesis of compounds that modulate potassium channels, many of which feature a chroman moiety [<1996S307>](#).

7.08.11.1 Formation of One Bond

7.08.11.1.1 Adjacent to the heteroatom

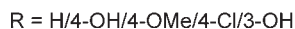
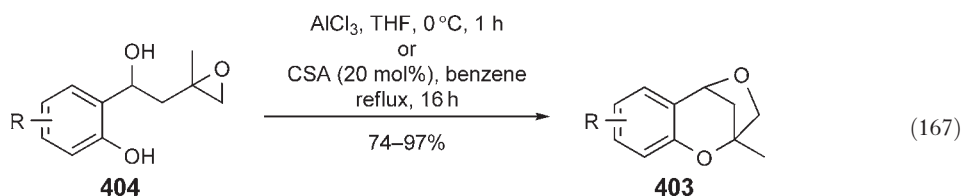
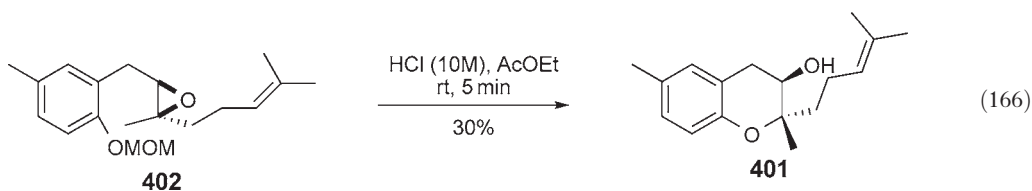
The mercury(II)-promoted cyclization of alkenols to afford chromans continues to attract attention and is seen during the synthesis of a cannabinoid analogue **397** (Equation 165) [<1998JME3596>](#). Intramolecular cyclization of the methyl ester **398** to form the 2,2-disubstituted chroman **399** can be achieved by a tandem demethylation/cyclization sequence using $\text{AlCl}_3/\text{EtSH}$ via the intermediate **400** (**Scheme 94**) [<2000MOL880>](#). Cyclizations of this type can also be effected by $\text{SnCl}_4\text{--I}_2$ [<1997S23>](#).



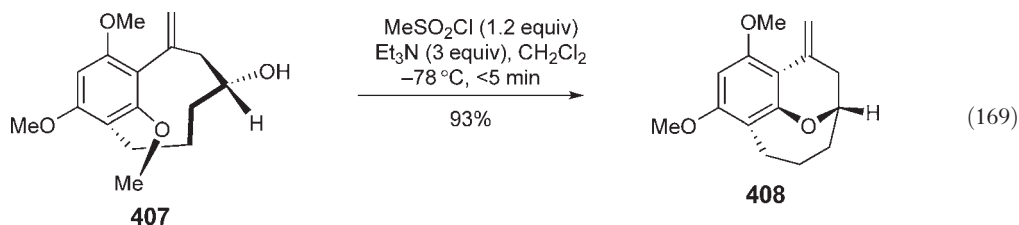
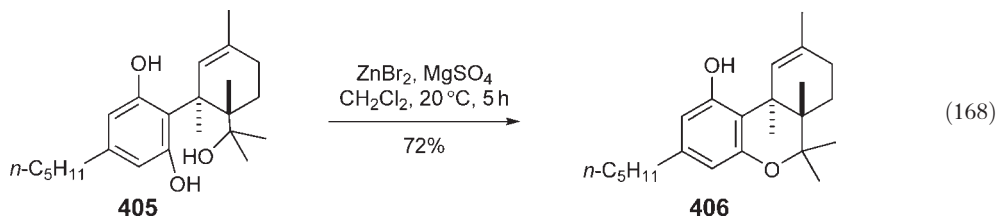


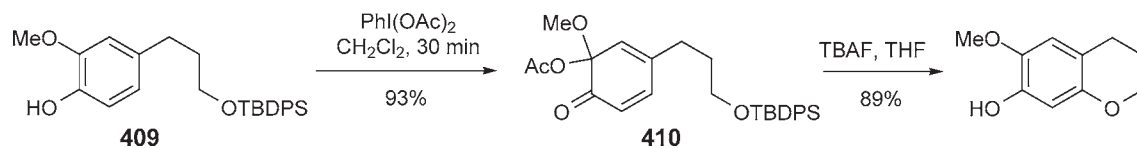
Scheme 94

A diastereoselective synthesis of 2,6-dimethyl-2-homoprenylchroman-3-ol **401** can be achieved by an acid-mediated stereoselective intramolecular epoxide ring opening of *ortho*-(2,3-epoxyalkyl)phenol **402** (Equation 166) <1998SL679>. A similar cyclization is a key step in the first total synthesis of (–)-heliannuol <2001JOC309> and inhibitors of neutral sphingomyelinase (N-SMase) <2002T4559>. Bridged chromans **403** arise from the Brønsted or Lewis-acid-catalyzed intramolecular cyclization of epoxides **404** (Equation 167) <2002SL322>.



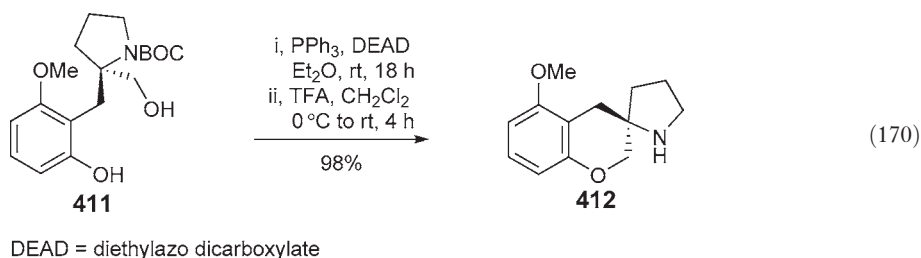
Known cyclization conditions applied to diol **405** affords chroman **406** thus providing the first asymmetric synthesis of *ent*- Δ^1 -tetrahydrocannabinol (THC) (Equation 168) <1991SL553, 1997TL3193> and the tetrahydrocannabinols <2002JOC8771>. Metacyclophanol **407** undergoes a fast intramolecular $\text{S}_{\text{N}}2$ reaction when exposed to MeSO_2Cl to afford the strained chroman **408** in excellent yield (Equation 169) <1997TL3267>. Hypervalent iodine oxidation of phenol **409** provides orthoquinone monoketal **410**, which upon deprotection of the alcohol regioselectively cyclizes to afford 6-methoxychroman-7-ol (Scheme 95) <1998JOC9597>.



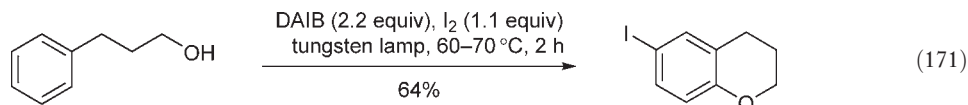


Scheme 95

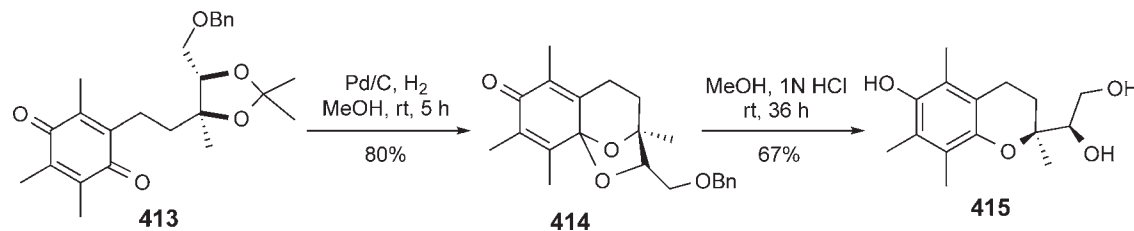
An intramolecular Mitsunobu reaction of the L-proline-derived phenol **411** followed by deprotection provides the first enantioselective synthesis of a 3-aminochroman subunit **412** seen in the potent 5-HT_{1A} agonist (+)-*S* 21552 (Equation 170) <2000JOC914>. This methodology is extended to the synthesis of (*R*)- and (*S*)-3-aminochromans from serine derived precursors <2001TA1689> and enantiopure spirocyclic aminochromans <2003JOC1401>, and in general, the use of the Mitsunobu reaction to generate chromans is widespread <1998TL7759, 2000TL8655, 2001OL1503, 2001JME4704, 2002TA715, 2005CC2689>. Phosphoric acid can also promote this cyclization <2002T4907>. A novel cyclodehydration of 3-(2-hydroxyphenyl)propanols via their imidate esters gives chromans as the product, a viable alternative to the Mitsunobu reaction <1996J(P1)2249>.



3-Phenylpropan-1-ols undergo photolytic cyclization and 6-iodination in the presence of iodine and the hypervalent iodine oxidant diacetoxyiodobenzene (DAIB) to furnish 6-iodochroman (Equation 171) <1996TL2441, 1997J(P1)787, 1998JOC5193>. Treatment of 3-arylpropan-1-ols with phenyliodine(III) bistrifluoroacetate (PIFA) leads to substituted chromans <2004TL2293>.



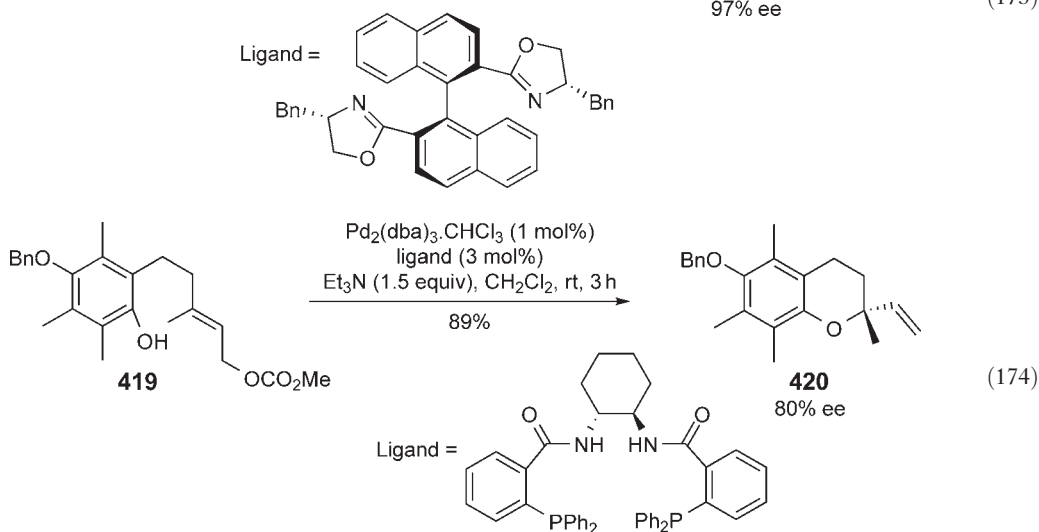
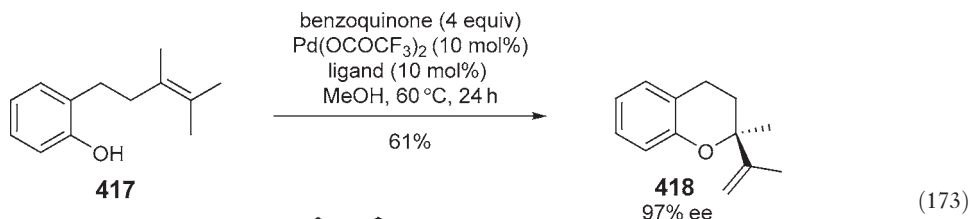
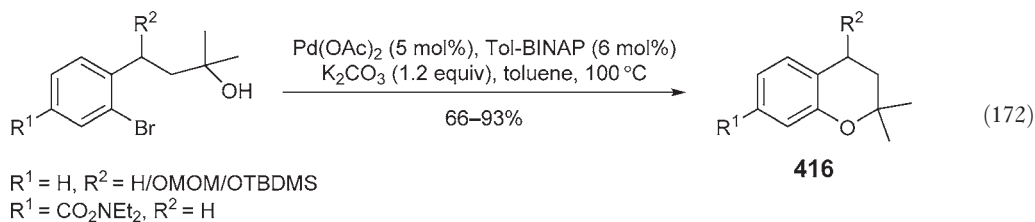
Quinone **413** undergoes an intramolecular cyclization to give the tricyclic acetal **414**, aromatization of which is achieved upon hydrogenation affording the enantiopure chroman **415** (Scheme 96) <1997S877>. This methodology has been applied to the cyclization of both quinones and hydroquinones <1997TL5959, 1999TL6339, 2000T3339, 2001SL989, 2000EJO3223, 2002J(P1)496>.



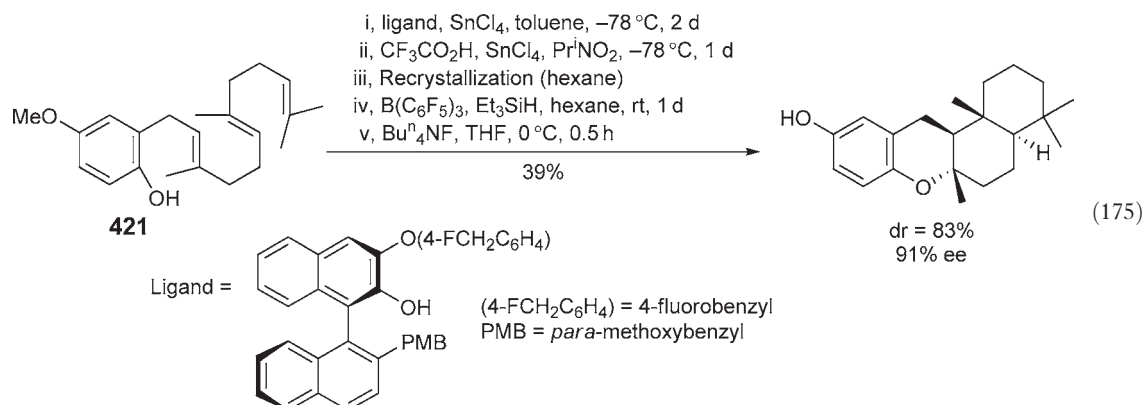
Scheme 96

The first reported intramolecular palladium-catalyzed synthesis of chromans **416** from tertiary alcohols and aryl halides proceeds in high yield (Equation 172) <1996JA10333, 1997JA6787, 2000JA10718>. This methodology has

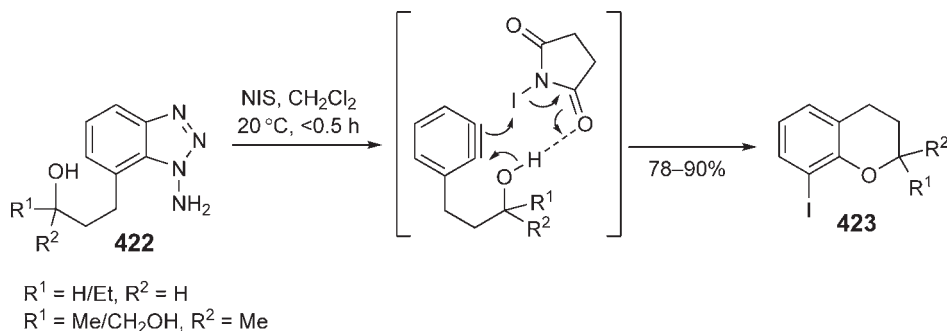
been extended to the cyclization of primary and secondary alcohols <2000JA5043, 2000JA12907, 2001JA12202, 2002JOC5553, 2005TL987> as seen during a total synthesis of (–)-heliannuol E <2003SL2395>. A catalytic asymmetric Wacker type cyclization of a pentenylphenol **417** into the corresponding chroman **418** occurs with high enantioselectivity in the presence of a Pd–BINAP catalytic system (Equation 173) <1997JA5063>. This methodology can be seen during the enantioselective synthesis of vitamin E <2005AGE257>. Similar cyclizations can be conducted asymmetrically by incorporation of an excess of (–)-sparteine into the reaction <2003AGE2892>. The palladium-catalyzed asymmetric allylic alkylation (AAA) of an allylic carbonate **419** can be seen during a stereoselective synthesis of the vitamin E core (Equation 174). Discrimination between the enantiotopic alkene faces, thus constructing a quaternary centre with the desired configuration in the chroman **420**, is achieved by optimizing the catalyst and ligand loadings as well as studying the effect of various amine additives (Equation 174) <1999S1491>. This methodology is used during the first total synthesis of (+)-clusifolol <2003JA9276>, a biomimetic synthesis of (–)-siccanin <2003AGE3943, 2004JA12565>, an asymmetric synthesis of 2-vinylchroman <1999TA1069>, and can be catalyzed by iridium complexes <2005OL1239>. The use of AAA methodology for the synthesis of 2,2-disubstituted chromans has been well studied <2004JOC5813, 2004JA11966>.



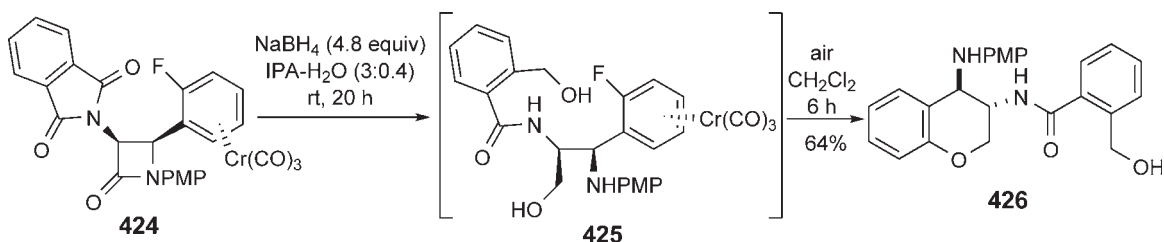
An enantioselective polycyclization of the triene **421** can be promoted by a chiral tin complex to afford (–)-chromazonarol in excellent yield with high diastereo- and enantioselectivity (Equation 175). This methodology can also be seen during the synthesis of (+)-8-*epi*-puupehedione and (–)-11'-deoxytaondiol methyl ether <2004JA11122>. A carbocation intermediate is thought to be involved during palladium(II) promoted cyclizations of this type <2004AGE3459, 2004T7405>. The intramolecular conjugate addition of a phenolic nucleophile to an α,β -unsaturated ester can be catalyzed by Cinchona alkaloids, providing asymmetric syntheses of 2-substituted chromans <2004TL4697>.



Treatment of 7-substituted-1-aminobenzotriazole derivatives **422** with *N*-iodosuccinimide (NIS) leads to a benzyne intermediate that upon further interaction with NIS undergoes intramolecular trapping by the hydroxyl group to afford 7-iodochromans **423** (Scheme 97) <1998TL5105, 2000J(P1)2343>. *N*-Bromosuccinimide can similarly effect the synthesis of chromans from 7-substituted-1-aminobenzotriazole derivatives <2000T1013>. Treatment of an enantiomerically pure tricarbonyl(η^6 -arene) chromium(0)-complexed β -lactam **424** with sodium borohydride results in stereoselective ring-opening to form intermediate **425**, which undergoes facile cyclization and demetalation upon exposure to air affording the chroman **426** (Scheme 98) <2005TA971>.



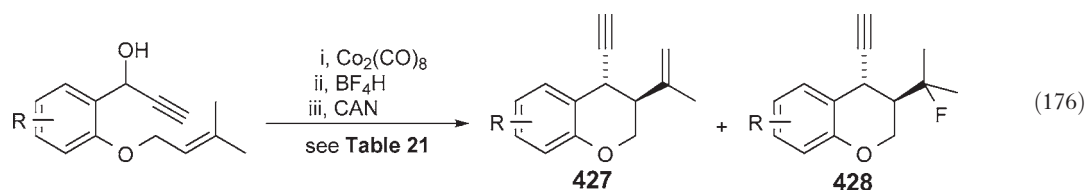
Scheme 97



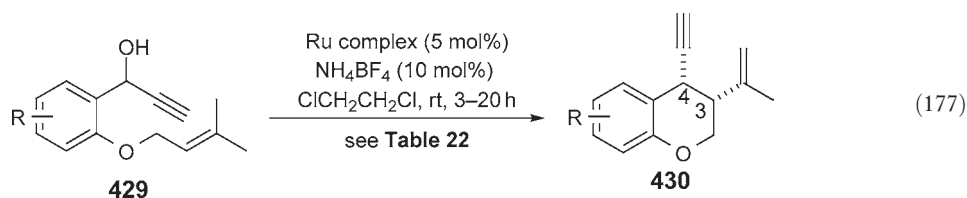
Scheme 98

7.08.11.1.2 β to the heteroatom

Intramolecular cyclization of a cobalt-stabilized cation onto a trisubstituted alkene leads to a mixture of *anti*-substituted chromans **427** and **428** depending upon the substitution pattern on the aromatic ring (Equation 176, Table 21) <1997TL685, 1998J(P1)1427>. Similarly, ruthenium-mediated intramolecular cyclization of propargylic alcohols **429** proceeds via an allenylidene-ene pathway to afford 3,4-*syn*-substituted chromans **430** (Equation 177, Table 22) <2003JA6060>. Fused polycyclic compounds possessing the chroman moiety can be accessed using this methodology <2004JA16066>.

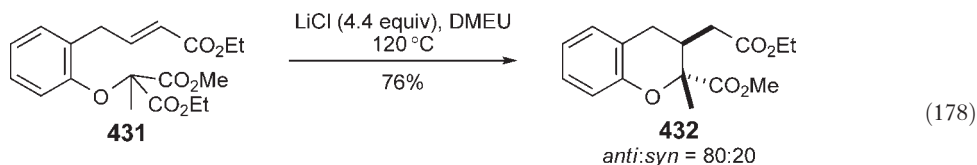
**Table 21** Formation of tetrahydropyrans **427** and **428** (Equation 176)

<i>R</i>	Ratio 427 : 428	Combined yield (%)
H	1:1	35%
2,4-(NO ₂) ₂	0:1	65%
2,4-Cl ₂	0:1	55%

**Table 22** *syn*-Selective formation of tetrahydropyrans **430** (Equation 177)

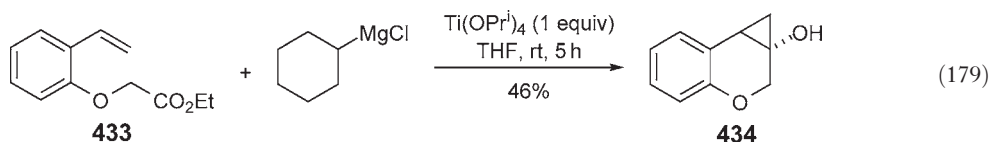
<i>R</i>	Yield 430 (%)	<i>C</i> -3: <i>C</i> -4 <i>syn:anti</i>
H	74	19:1
4-Me	75	16:1
4-MeO	79	16:1
4-Br	82	19:1
4-Cl	74	20:1
6-Me	81	25:1
6-MeO	80	25:1

Methyl ester **431** is tethered by an alkyl chain to an acrylate Michael-acceptor and activated toward decarboxylation by a C-2-ethoxycarbonyl group. As a result of this, chemoselective S_N2-dealkylation of the methyl ester, decarboxylation and cyclization of the enolate by Michael addition occurs upon exposure to lithium chloride in DMEU, affording chroman **432** in excellent yield and diastereoselectivity (Equation 178) <1998JOC144>.

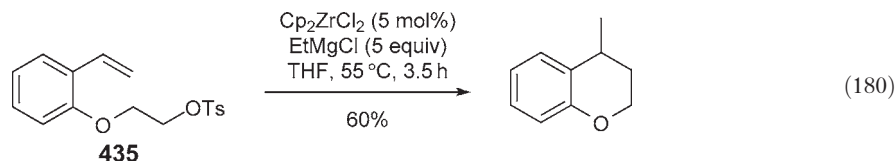


DMEU = 1,3-dimethyl-2-imidazolinone

An intramolecular Kulinkovich cyclopropanation of an oxa- ω -alkenoic ester **433** occurs upon treatment with cyclohexyl magnesium chloride to furnish the cyclopropanochroman-3-ol **434** in moderate yield (Equation 179) <2003OBC3600>.

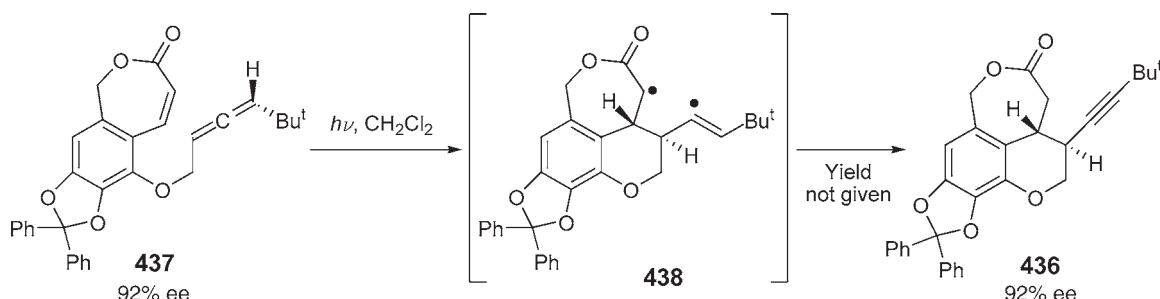


The synthesis of 4-methylchroman can be achieved in good yield by a zirconium-catalyzed intramolecular alkylation of the unsaturated tosylate **435** (Equation 180) <2002OL395>. 3-Methylchromans can be prepared via the photodecarboxylation of 2-allylaryloxyacetic acids in moderate to excellent yield <1997T16817>.



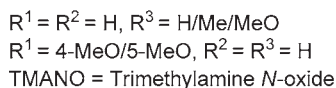
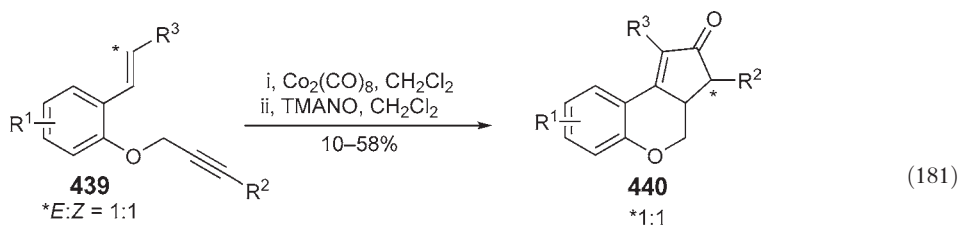
7.08.11.1.3 γ to the heteroatom

The highly functionalized chroman **436** is formed with complete asymmetric induction upon irradiation of the allene **437**. Labeling experiments implicate an intermediate biradical **438** that undergoes a stereospecific 1,5-hydrogen shift to furnish the alkynic moiety seen in the product (Scheme 99) <1997TL8789>.

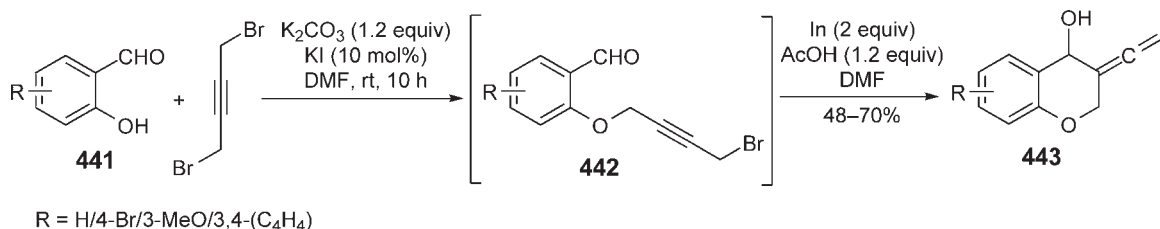


Scheme 99

Aromatic enynes **439** can undergo a Pauson–Khand reaction to afford the chroman **440** that features a 3,4-fused pentenone moiety (Equation 181) <1999TL2817>. The addition of molecular sieves can increase the yield of the chroman <1999OL1187, 2000JOC3513>. Further reports detailing the use of this methodology for chroman synthesis are available <2001OL2607, 2003AGE2409>.

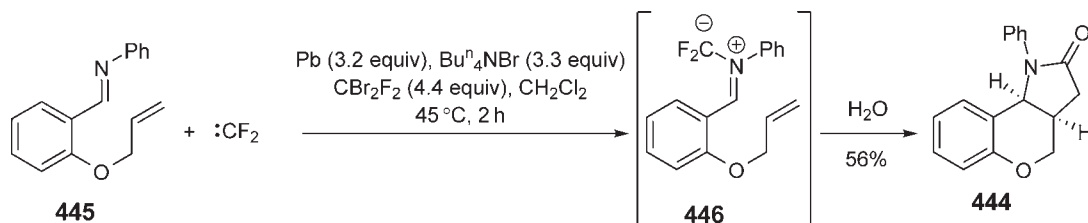


A one-pot reaction between salicylaldehydes **441** and 1,4-dibromobut-2-yne followed by an indium-mediated cyclization of the intermediate 2-(4-bromobut-2-ynoxy)benzaldehydes **442** furnishes 3-allenylchroman-4-ols **443** (Scheme 100). This reaction can also be conducted in aqueous media <2004SL45>.

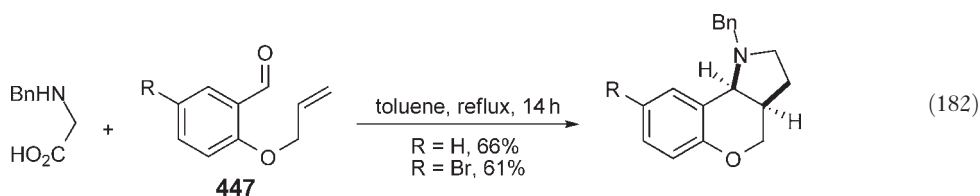


Scheme 100

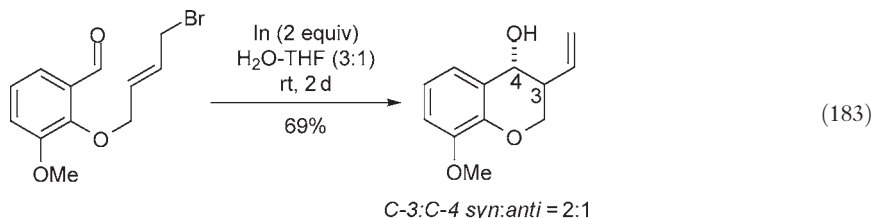
Chroman[3,4-*b*]pyrrolidines **444** are available by reaction of difluorocarbene with imine **445**. The reaction proceeds via a 1,3-dipolar cycloaddition of the intermediate iminodifluoromethanide **446** (Scheme 101) <2001TL533>. A chromano[3,4-*b*]pyrrole ring system is the product of a condensation of *N*-benzylglycine with 2-allyloxybenzaldehydes **447** (Equation 182). This methodology is used during the synthesis of the hindered *N,N,N'*-trisubstituted guanidine moiety present in the alkaloids martinelline and martinellie acid <2001TL2455>.



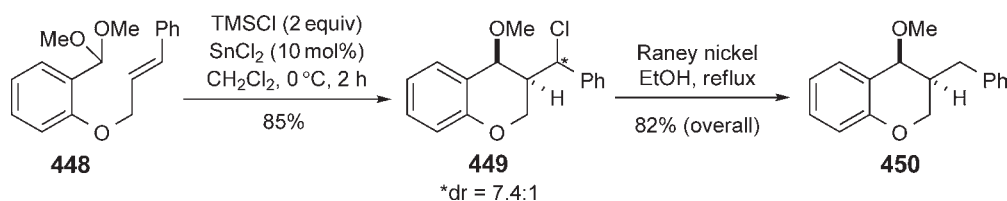
Scheme 101



(4*R*)-8-Methoxy-3-vinylchroman-4-ol is accessed via an indium-mediated intramolecular allylation of (*E*)-2-(4-bromobut-2-enyloxy)-3-methoxybenzaldehyde; formation of the *syn*-disubstituted chroman is favoured (Equation 183) <2004BKC1123>. Imines can be successfully used in this process, leading to 4-aminochromans <2004BKC1627>. This reaction is also successfully promoted by InCl_3 with allylic acetates or chlorides as cyclization precursors <2005BKC711>.



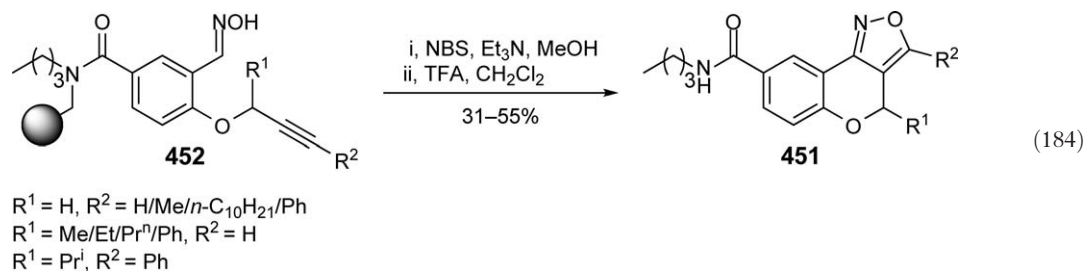
Phenyl 3-phenyl-2-propenyl ethers **448**, which feature a latent oxonium ion functionality, cyclize upon treatment with acid to afford the chroman **449** as a mixture of diastereomers. Reduction of the chroman **449** with Raney nickel affords a single diastereomeric product **450** (Scheme 102) <2005TL3719>.



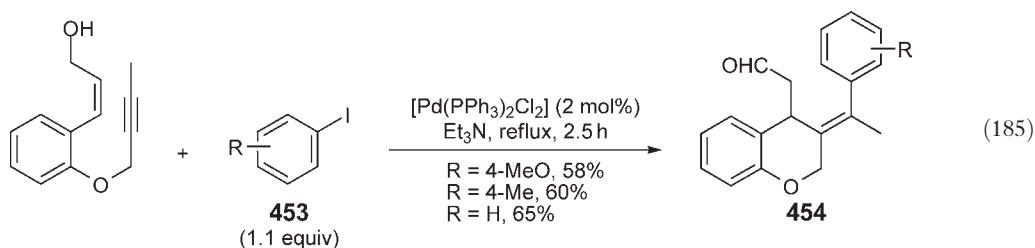
Scheme 102

Oximes of salicyclic 1-allyloxybenzenes undergo intramolecular 1,3-dipolar cycloadditions to afford chromans that feature a fused isoxazolidine or isoxazoline moiety. The process can be accelerated by the introduction of *ortho*-substituents onto the aromatic ring <1995J(P1)2551, 1995T10923, 1996TA797> or by employing mild oxidants in the reaction <2003TL3697, 2005S1572, 2005ARK27>. Diastereoselectivities of up to 22:1 can be achieved during an intramolecular 1,3-dipolar nitron cycloaddition by careful choice of Lewis acid and chiral auxiliary on the nitron partner <2002JOC3317>. A solid phase

synthesis of substituted chromans **451** bearing a fused isoxazole unit can be achieved via a 1,3-dipolar cycloaddition of a nitrile oxide generated from the oxime **452** with a tethered alkyne (Equation 184) <2002OL323>.

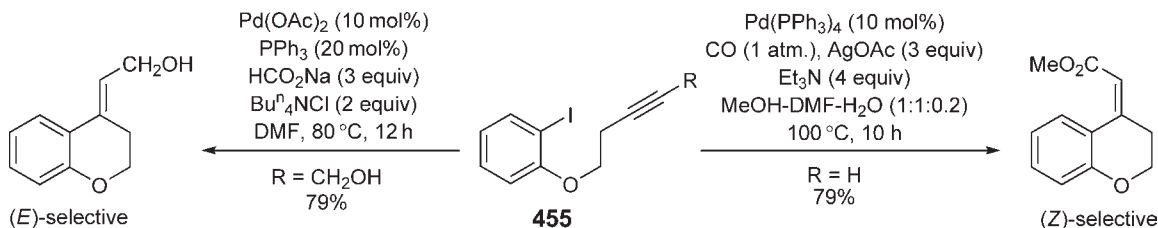


A domino Heck carbopalladation/cyclization reaction of (Z)-3-(2-(but-2-ynyloxy)phenyl)prop-2-en-1-ol **453** with aryl iodides furnishes chroman derivatives **454** in good yield (Equation 185) <2004AGE5997>.



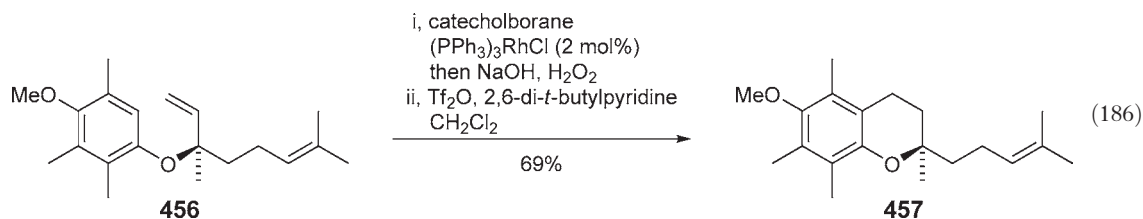
7.08.11.1.4 δ to the heteroatom

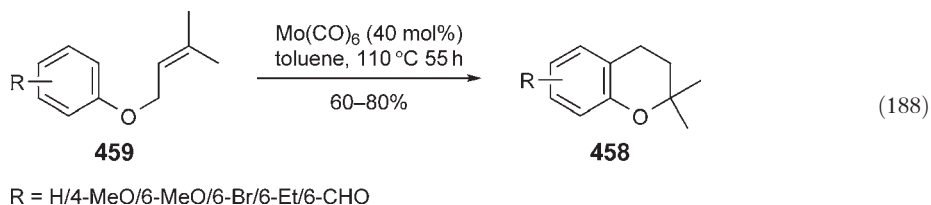
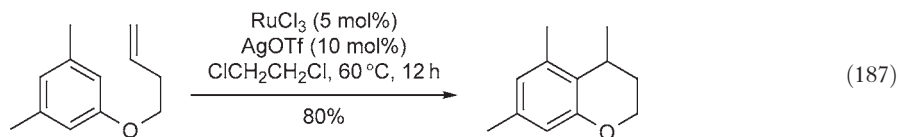
4-Methylene chromans can be prepared by a palladium-catalyzed intramolecular cyclization of 2-iodophenyl alkynyl ethers **455**. Simple modifications to the reaction conditions lead to either (*E*)- or (*Z*)-4-methylene chromans (Scheme 103) <2001TL2657>. 2-Iodophenyl alkynyl acetals are also viable substrates for this reaction <2005JOC489>. Addition of tris(2,6-diphenylbenzyl)tin hydride (TDTH) to a triethylborane-mediated intramolecular cyclization of 2-iodophenyl alkynyl ethers ensures complete (*E*)-selectivity is observed in the resulting 4-methylene chroman <2001AGE411>.



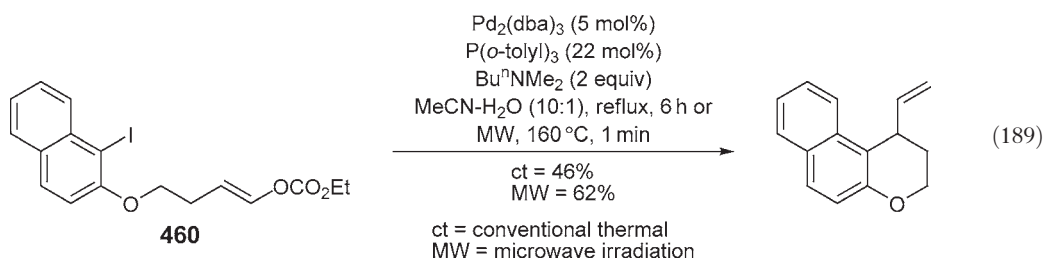
Scheme 103

The palladium-catalyzed hydroboration of allyl phenyl ether **456** is followed by cyclization of the corresponding triflate to afford the chroman core of the tocopheryls **457** (Equation 186) <1998JA9074>. The intramolecular hydroarylation of 1-(but-3-enyloxy)-3,5-dimethylbenzene to afford 4,5,7-trimethylchroman can be accomplished using a $\text{RuCl}_3/\text{AgOTf}$ catalytic system (Equation 187) <2004OL581>. 2,2-Dimethylchromans **458** are formed by a $\text{Mo}(\text{CO})_6$ catalyzed intramolecular cyclization of aryl prenyl ethers **459** (Equation 188) <1998S256>.

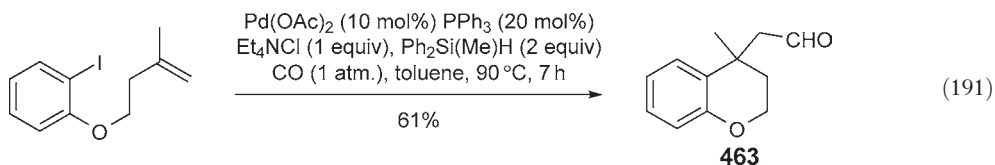
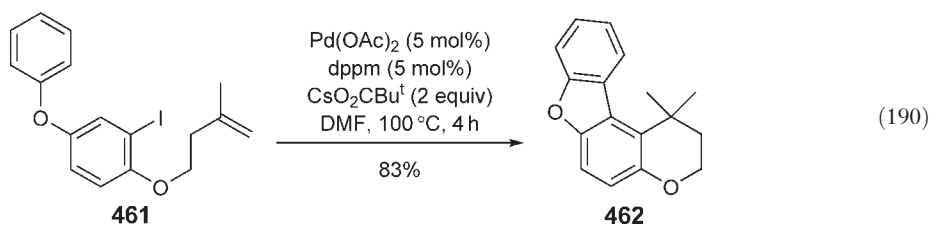




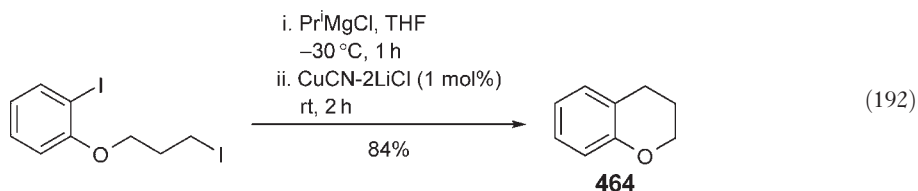
The palladium-catalyzed intramolecular coupling between an aryl iodide and an allyl moiety **460** proceeds under thermal heating or microwave irradiation, with improved yields of the 1-vinyl-benzo[*f*]chroman obtained with the latter (Equation 189) <2005JA72>.



2-Iodo-1-(3-methylbut-3-enyloxy)-4-phenoxybenzene **461** undergoes palladium(II)-mediated ring closure via a 1,4-shift of palladium from alkyl to aryl followed by intramolecular arylation to afford the fused chroman **462** (Equation 190) <2004JA7460>. Similarly, 1-iodo-2-(3-methylbut-3-enyloxy)benzene can undergo a palladium(II)-mediated cyclocarboformylation to afford the chroman **463** (Equation 191) <2001T1347>.



1-Iodo-2-(3-iodopropoxy)benzene undergoes iodine magnesium exchange with *i*-PrMgCl leading to an arylmagnesium intermediate, which upon exposure to catalytic quantities of a copper(II)-salt, cyclizes to chroman **464** in excellent yield (Equation 192) <2002TL4875>.



Ortho-substituted cyclohexadienyl aryl iodide **465** undergoes palladium-catalyzed cross-couplings with C-, N- and O- nucleophiles affording tricyclic chromans **466** with good levels of diastereoselectivity (Equation 193, Table 23) <1998SL748, 1999JOC1875>.

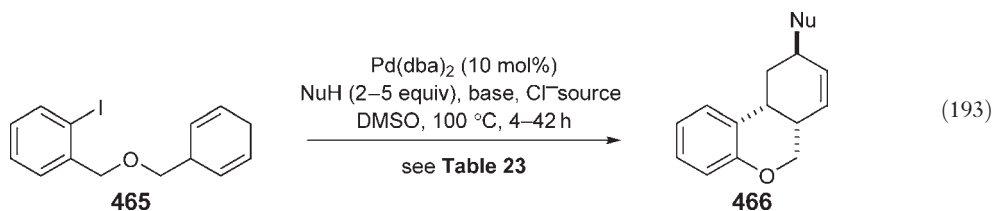
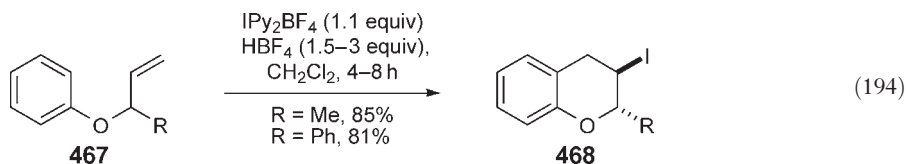


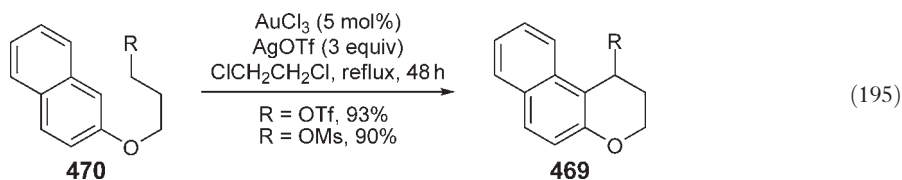
Table 23 Nucleophilic cross-coupling with cyclohexadienyl aryl iodide **465** furnishing tetrahydropyrans **466** (Equation 193)

NuH	Nu	Base, Cl [−] source	Yield 466 (%)
EtO ₂ CCH ₂ CO ₂ Et	CH(CO ₂ Et) ₂	K ₂ CO ₃ (2.5 equiv) TBAC (2 equiv)	72
		Na ₂ CO ₃ (2 equiv) TBAC (2 equiv)	91
TsNHBn	N(Ts)Bn	Na ₂ CO ₃ (2 equiv) TBAC (2 equiv)	60
Bu ^t O ₂ CNHCO ₂ Bu ^t	N(CO ₂ Bu ^t) ₂	Na ₂ CO ₃ (2 equiv) TBAC (1 equiv)	52
NaO ₂ SPh	O ₂ SPh	LiCl (1.5 equiv) TBAC (1 equiv)	62

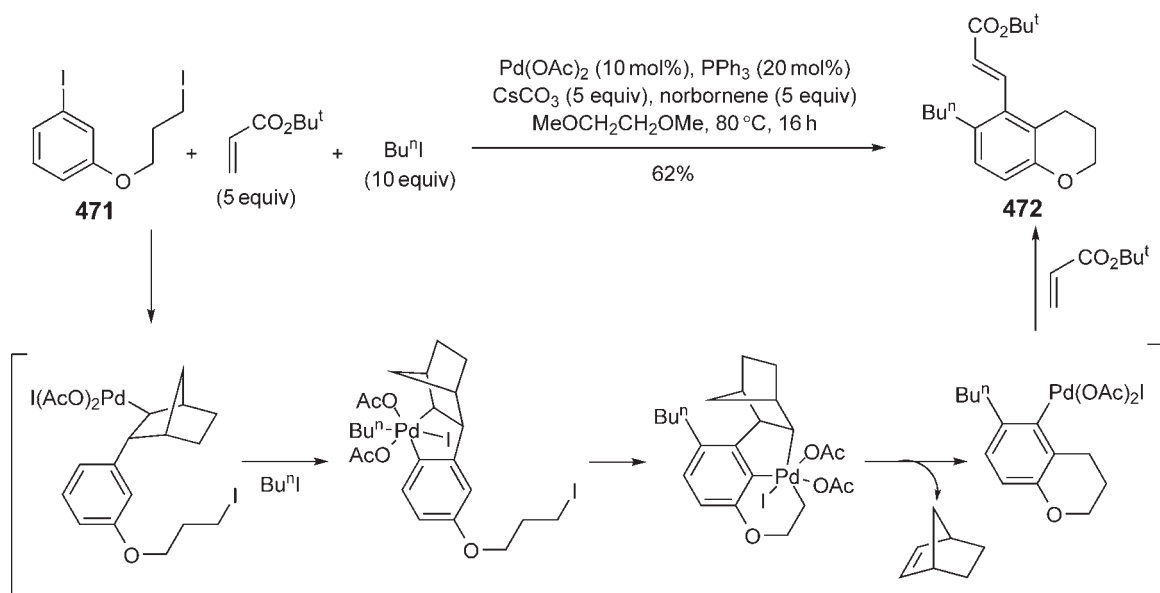
Iodonium-ion-promoted intramolecular arylation of allyloxybenzenes **467** provides a metal-free approach to *anti*-substituted 3-iodochromans **468** (Equation 194) <2004JA3416>.



4-Substituted chromans **469** can be synthesized in good yield by a gold(III)-catalyzed intramolecular cyclization of aryl ethers **470** (Equation 195) <2004JA13596>. Gold(III)-catalysis is also effective during the cycloalkylation of electron-rich arenes with epoxides affording chroman-4-ols <2004JA5964>.

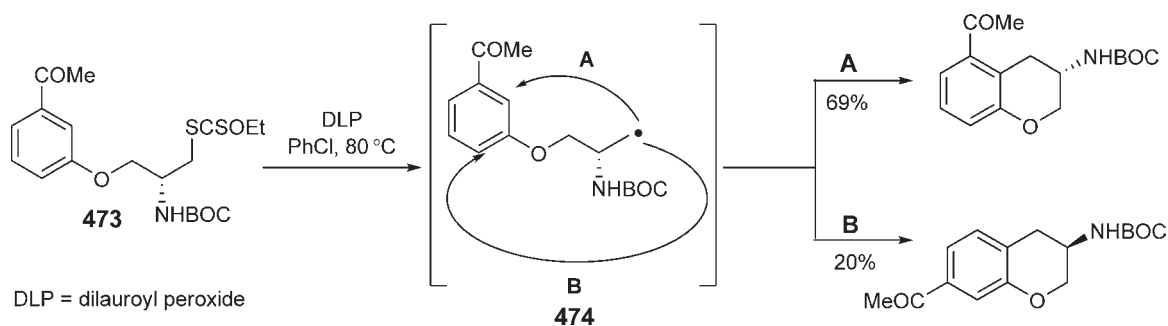


A three-component palladium(II)-catalyzed reaction of ((2-iodoethoxy)methyl)benzene **471** with an excess of both alkyl halide and Heck acceptor leads to the formation of three new C–C bonds to afford the chroman **472** (Scheme 104) <2003OL4827>.



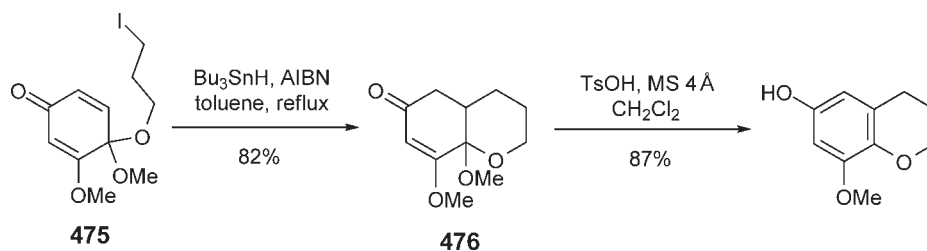
Scheme 104

An intramolecular radical cyclization provides the basis for an asymmetric synthesis of 3-aminochromans. The chirality of the cyclization precursor **473** is derived from either L- or D-serine, and the separable regioisomeric chromans, (*S*)-*tert*-butyl 5-acetylchroman-3-ylcarbamate and (*R*)-*tert*-butyl 7-acetylchroman-3-ylcarbamate arise due to two possible cyclization modes **A** or **B** of the radical intermediate **474** (Scheme 105) <2003OL4253>.



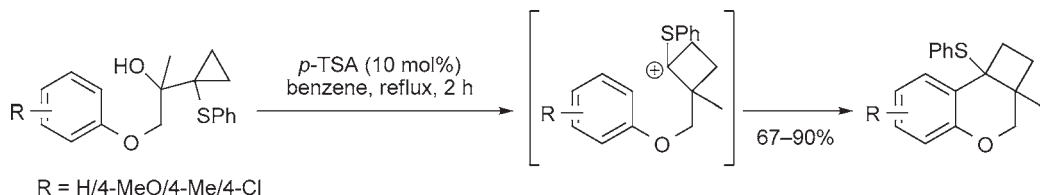
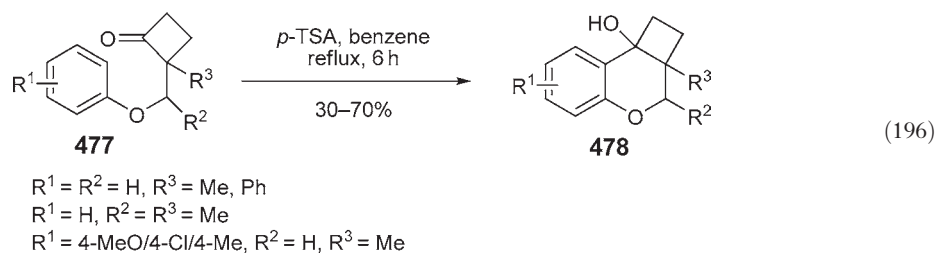
Scheme 105

Dienone **475** undergoes an intramolecular radical cyclization to afford the bicyclic enone **476**, which is readily aromatized to 8-methoxychroman-6-ol in excellent yield (Scheme 106). Various alkylations and/or halogenations can also be carried out prior to aromatization allowing entry to highly functionalized isochromans <2004JOC3282>.



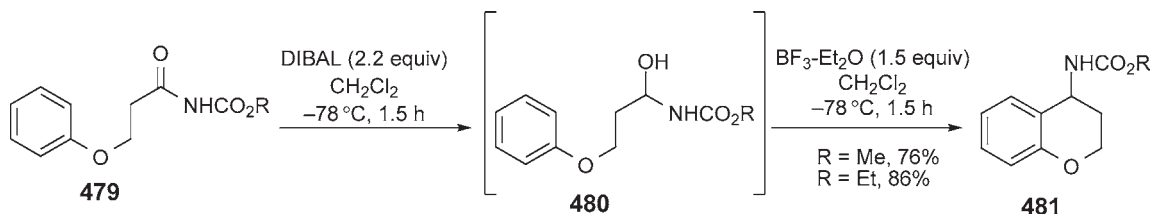
Scheme 106

2-(Phenoxymethyl)cyclobutanones **477** undergo intramolecular alkylation of the aromatic ring to afford cyclobuta[*c*]chroman-4-ols **478** (Equation 196) <2002SL796, 2004T449>. A similar procedure allows entry to 4-thiophenyl cyclobuta[*c*]chromans (Scheme 107) <2002OL2565>.



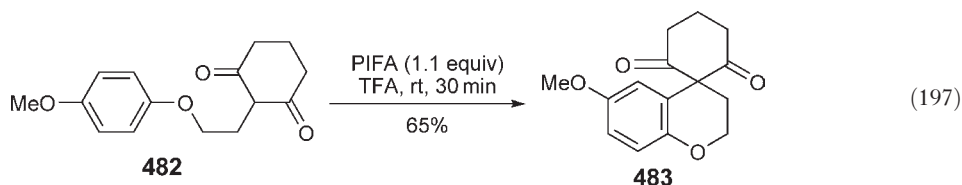
Scheme 107

Acyclic *N*-acylcarbamates **479** can be reduced to their corresponding *N*-acylhemiaminals **480** which, upon treatment with Lewis acid, undergo intramolecular nucleophilic substitution to furnish racemic 4-aminochromans **481** (Scheme 108) <2001JOC6988>.



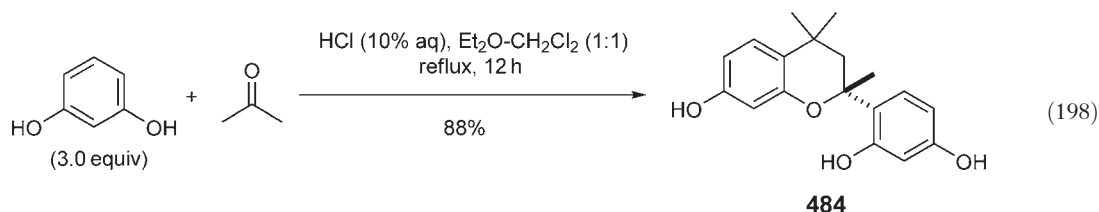
Scheme 108

A hypervalent iodine-induced intramolecular cyclization of the α -(aryl)alkyl- β -dicarbonyl compound **482** furnishes the spirobenzannulated chroman **483** in good yield (Equation 197) <2001JOC59>.

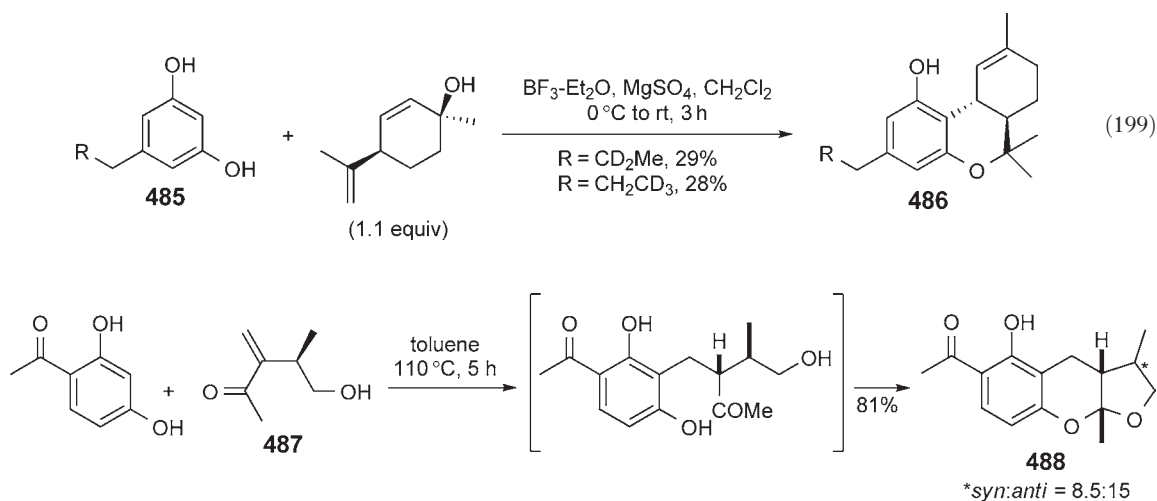


7.08.11.2 Formation of More than One Bond

First isolated in 1892 and after several incorrectly proposed structures, the product obtained from the reaction of resorcinol and acetone is finally confirmed unequivocally from X-ray crystallographic studies as chroman **484** (Equation 198) <1997JOC737>. A study concerning the reaction of resorcinol with a variety of α,β -unsaturated ketones is available <1998JOC636>.

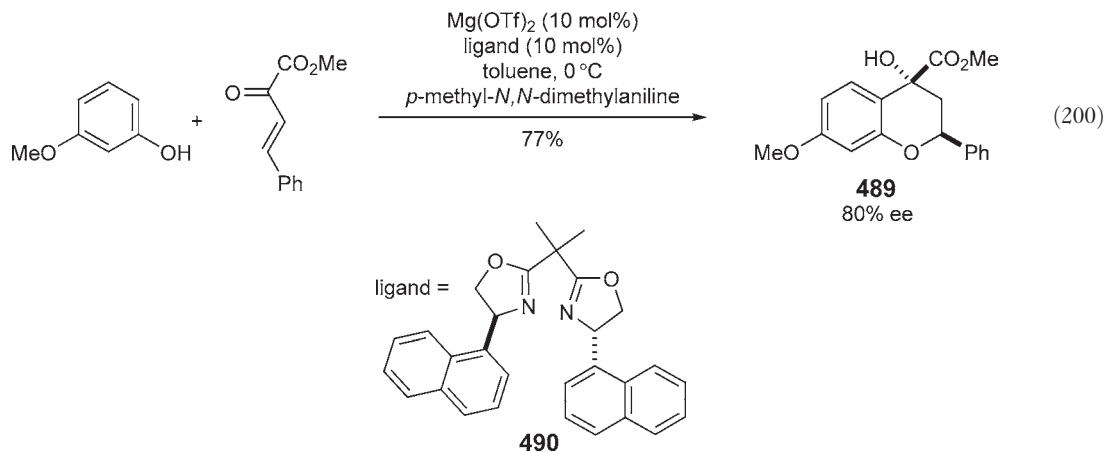


A Lewis-acid-mediated condensation of deuterated resorcinols **485** and (+)-*anti*-*p*-mentha-2,8-dien-1-ol affords tricyclic chromans **486**, intermediates during the synthesis of deuterated (–)- Δ^9 -tetrahydrocannabinarins (Equation 199) <2002J(P1)2544>. The condensation of trimethylhydroquinone and isophytol is catalyzed by the super Lewis acid {trimethylsilyl pentafluorophenylbis(trifluoromethanesulfonyl)methide}, $\text{Me}_3\text{Si}[\text{C}_6\text{F}_5\text{CTf}_2]$, furnishing (±)- α -tocopherol (vitamin E) <2003AGE5731>. The total synthesis of (+)-xyloketal D features a one-pot multistep reaction involving Michael addition and intramolecular condensation of 2,4-dihydroxyacetophenone and (*R*)-5-hydroxy-4-methyl-3-methylenepentan-2-one **487** to afford the chroman **489** (Scheme 109) <2004TL293>. This methodology can also be used to synthesize other tocopherols <2001BMC1337, 2003EJO2840> and xyloketal natural products <2004EJO1261>.

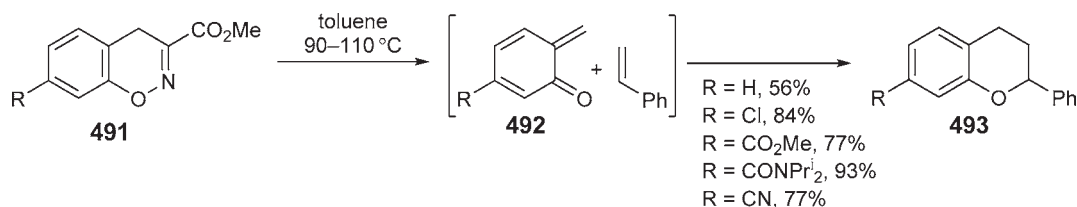


Scheme 109

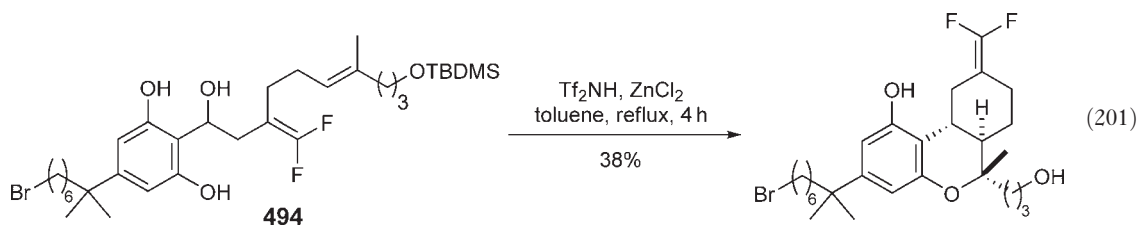
The synthesis of the optically active chroman **489** can be achieved by use of a catalytic asymmetric tandem oxa-Michael addition Friedel–Crafts alkylation sequence between 3-methoxyphenol and (*E*)-methyl 2-oxo-4-phenylbut-3-enoate. The chiral C_2 -symmetric box manganese(II)- complex **490** exerts excellent stereocontrol upon the reaction (Equation 200) <2003OBC1953>, whereas only moderate enantioselectivity is observed in the presence of a chiral C_2 -symmetric 2,2'-bipyridyl copper(II)- complex (42% = ee) <2005OL901>.



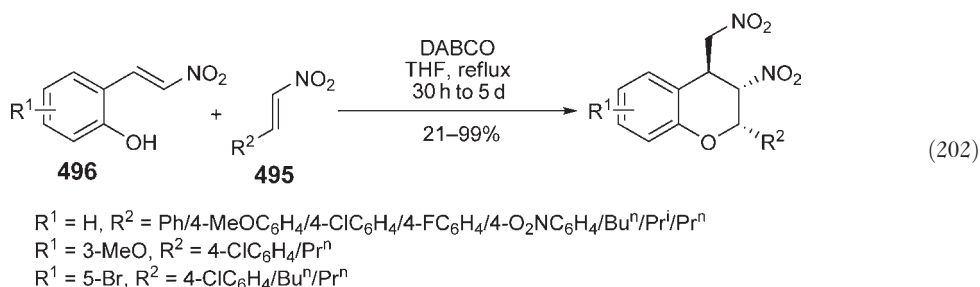
The use of *ortho*-quinone methides as the diene component in an hDA reaction continues to attract widespread interest as a means of constructing the chroman ring system and is discussed in depth in the previous issues <1984CHEC, 1996CHEC-II>. Despite this, noteworthy progress is seen in this area, namely incorporation into the synthesis of several ring systems and natural products <1996J(P1)1435, 1999TL1925, 2000TL2643, 2004S949, 2004SL1101, 2004S1783, 2004T4223, 2004TL7727, 2004JOC9196>. The emergence of novel, often mild conditions to generate *ortho*-quinone methides allows for the synthesis of increasingly complex targets <1997TL5005, 1998TL9035, 1999BCJ73, 1999CC691, 1996CL889, 1999JOC9507, 2002JOC6911, 2003OM4170, 2005OL3617, 2005OBC3488, 2005T8419>, with the use of new catalysts in these hDA reactions increasing their scope even further <2002J(P1)1401, 2002J(P1)165, 2002TL2999>. The introduction of electron-withdrawing groups onto the aromatic ring of 4*H*-1,2-benzoxazines **491**, known *ortho*-quinone methide **492** precursors, leads to a significant increase in yield of the 2-phenylchroman products **493** (Scheme 110) <2003JA5282>. A quinone methide is proposed as an intermediate in the intramolecular hDA reaction observed for **494**, a key step during the synthesis of a bifunctional cannabinoid (Equation 201) <1997CC1867>.



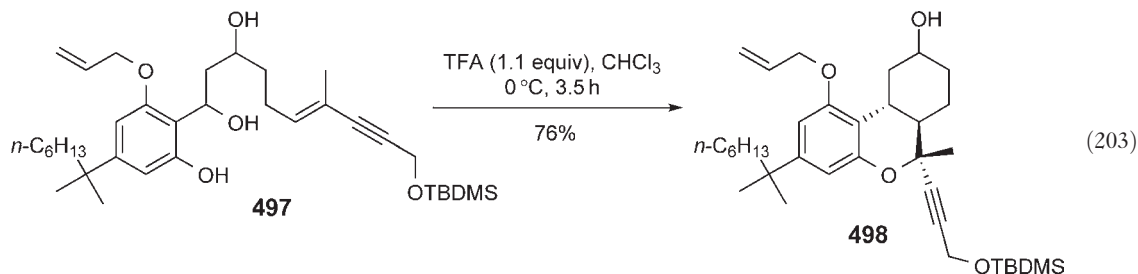
Scheme 110



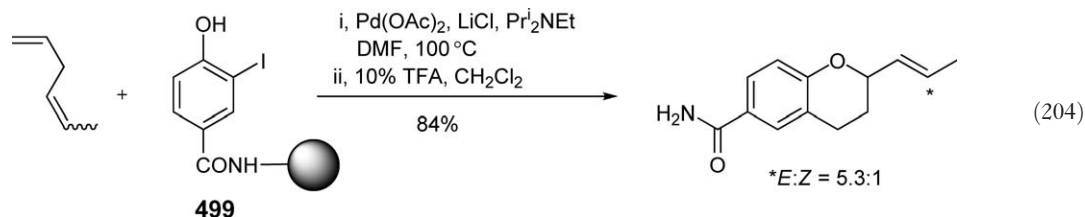
The DABCO-mediated reaction of nitroalkenes **495** with 2-(2-hydroxyaryl)-1-nitroethene derivatives **496** affords 3-nitro-4-nitromethylchromans with high levels of stereoselectivity (Equation 202) <2003TL3813>. Similarly, DABCO is also the base of choice when forming 3-nitrochroman-4-ols from salicylaldehyde and β-disubstituted nitrostyrenes <2001TL2717>.



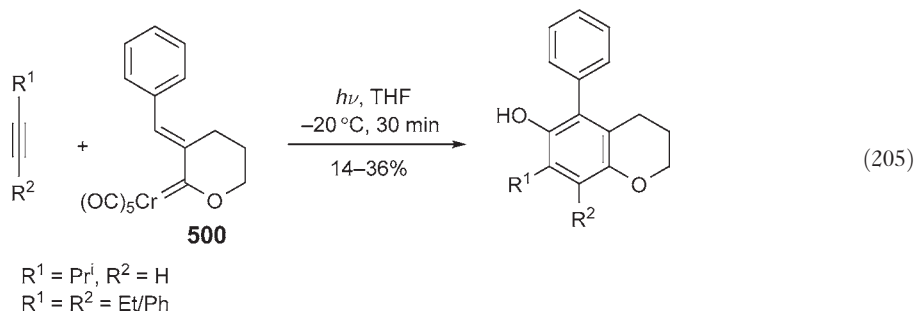
Exposure of the diastereomeric mixture of alcohols **497** to TFA leads to the construction two nonaromatic rings via a cation–alkene cyclization process. The chroman **498** is isolated as a 1:1 mixture of epimeric alcohols and is a key intermediate during cannabinoid synthesis (Equation 203) <2000JOC6576>.



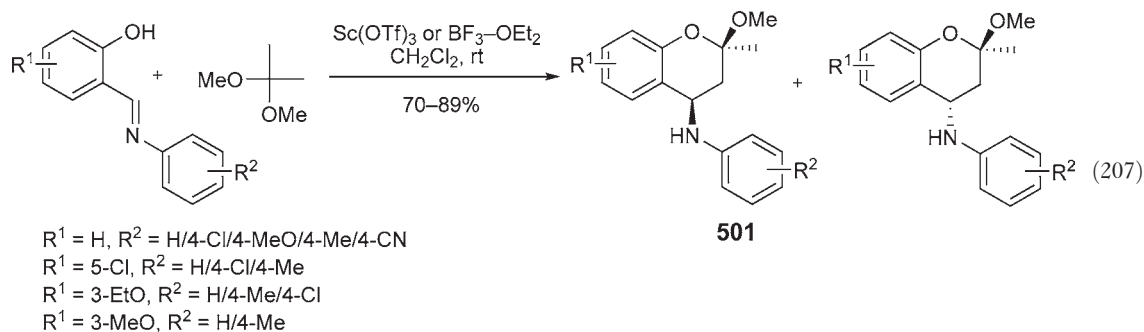
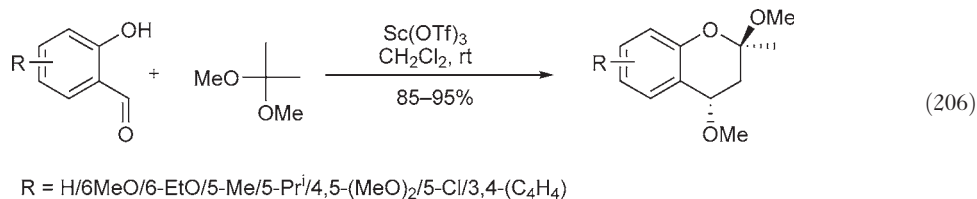
Palladium-catalyzed cross-coupling of *ortho*-allylphenol with vinylic halides or triflates provides a route to 2-substituted chromans <1998TL237>. A resin bound *ortho*-iodophenol **499** undergoes a palladium(II)-catalyzed annulation with 1,4-hexadiene to afford *trans*-2-prop-2-enylchroman as the major product (Equation 204) <1998TL9605>.



A novel approach to chroman-6-ols involves a poor yielding photochemical benzannulation of the α -*exo*-benzylidene-2-oxacyclohexylidene chromium complex **500** with alkynes (Equation 205) <1999SL231>.



Scandium triflate can catalyze the cyclocondensation of salicylaldehydes with 2,2-dimethoxypropane to afford 2,4-dimethoxy-2-methylchromans in high yield and diastereoselectivity (Equation 206) <2000TL7943>. Iodine and bismuth triflates can also mediate the cyclocondensation of salicylaldehydes with 2,2-dimethoxypropane to afford 2,4-dimethoxy-2-methylchromans <2000J(P1)3082, 2004TL9369>. Salicylaldimines can also undergo cyclocondensation with 2,2-dimethoxypropane to afford 2-methoxy-2-methyl-4-aminochromans in high yield; chroman **501** is the major isomer formed (Equation 207) <2001TL4405>.



Salicylaldehyde reacts with trimethylsilylketene dithioacetal in the presence of a Lewis acid to form the chroman **502**, the product of a deoxygenative divinylolation (Equation 208) <2001JOC3924>. This reaction can also be applied to salicylaldimines <2003JOC4947>. Treatment of 3,5-dibromosalicylaldehyde with methyl vinyl ketone (MVK) in the presence of DABCO leads to a chroman-4-ol as the major product <2002J(P1)1318>. A stereoselective one-pot synthesis of *syn*-fused chromans from salicylaldehydes, aromatic amines and cyclic enol ethers is carried out in the

presence of an ionic liquid catalyst <2004CL1436>. A DBU-mediated reaction of salicylaldehydes with allene **503** provides chroman derivatives **504** in excellent yield and diastereoselectivity (Equation 209, Table 24) <2005OL4527>. The DBU-catalyzed reaction of salicylaldehydes with α,β -unsaturated aldehydes leads to bicyclic chromans <2005ASC555>.

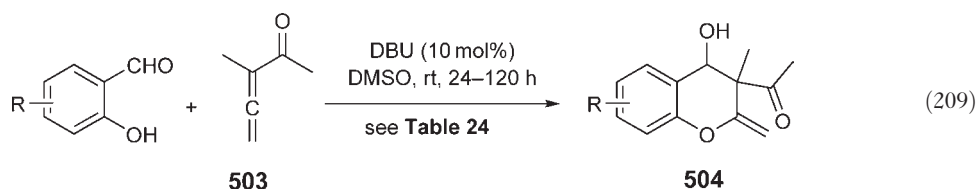
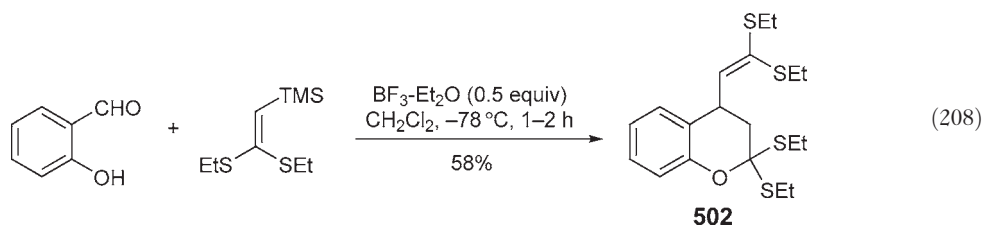
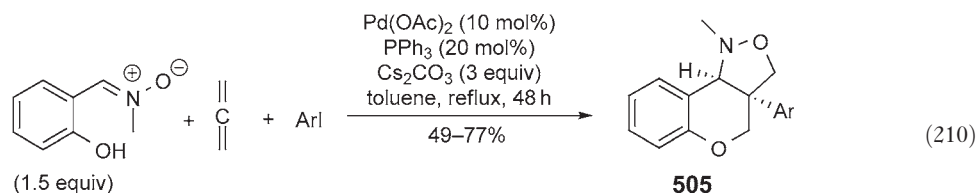


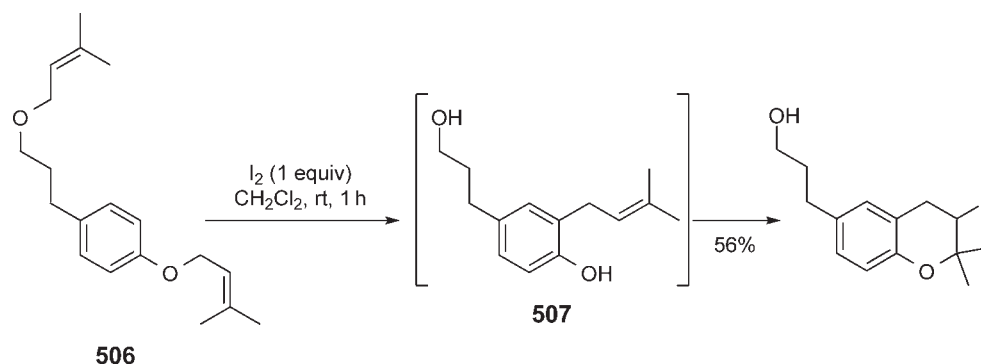
Table 24 Formation of chromans **504** (Equation 209)

<i>R</i>	Yield 504 (%)	<i>C3:C4 anti:syn</i>
5-Me	>99	70:30
3-MeO	>99	81:19
4-MeO	>99	88:12
5-MeO	>99	70:30
3-OH	92	68:32
3,5-Cl ₂	>99	76:24
5-Br	93	64:29
3,4-(C ₄ H ₄)	>99	80:20

Chromans possessing a fused isoxazolidine moiety **505** can be accessed via a palladium-catalyzed allene insertion-intramolecular 1,3-dipolar cycloaddition cascade reaction between (*E*)-*N*-(2-hydroxybenzylidene)methanamine oxide, allene, and aryl iodides. This process creates two rings, two stereocentres and a quaternary carbon centre in one-pot (Equation 210) <2002CC1754>.

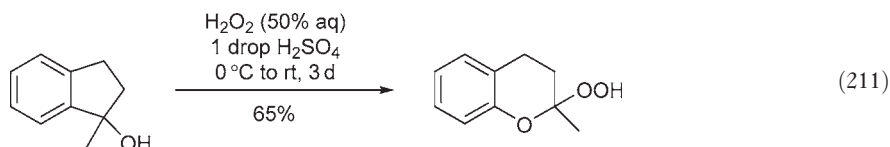


Iodine-mediated removal of both prenyl protecting groups from aryl ether **506** leads to the unexpected formation of 3-(3-iodo-2,2-dimethylchroman-6-yl)propan-1-ol. The reaction proceeds via formation of the *ortho*-allylic phenol intermediate **507** by electrophilic removal of a prenyl species, followed by an iodine promoted electrophilic cyclization (Scheme 111) <2001SL1989, 2002T5689>.



Scheme 111

2-Hydroperoxy-2-methylchroman results from a hydrogen peroxide mediated rearrangement of 1-methyl-2,3-dihydroinden-1-ol (Equation 211) <2000JOC1873>. Further reports regarding this rearrangement are available <2001SL96>.



Heating a variety of phenols with isoprene under pressure in the presence of a zeolite catalyst affords chromans in good yield <1998S301>. Likewise, the synthesis of 2,2-dimethylchromans can be achieved via Montmorillonite K10 clay catalyzed condensation of substituted phenols with prenyl bromide <2004SL2028>.

7.08.11.3 From Other Heterocycles

7.08.11.3.1 From tetrahydrofurans

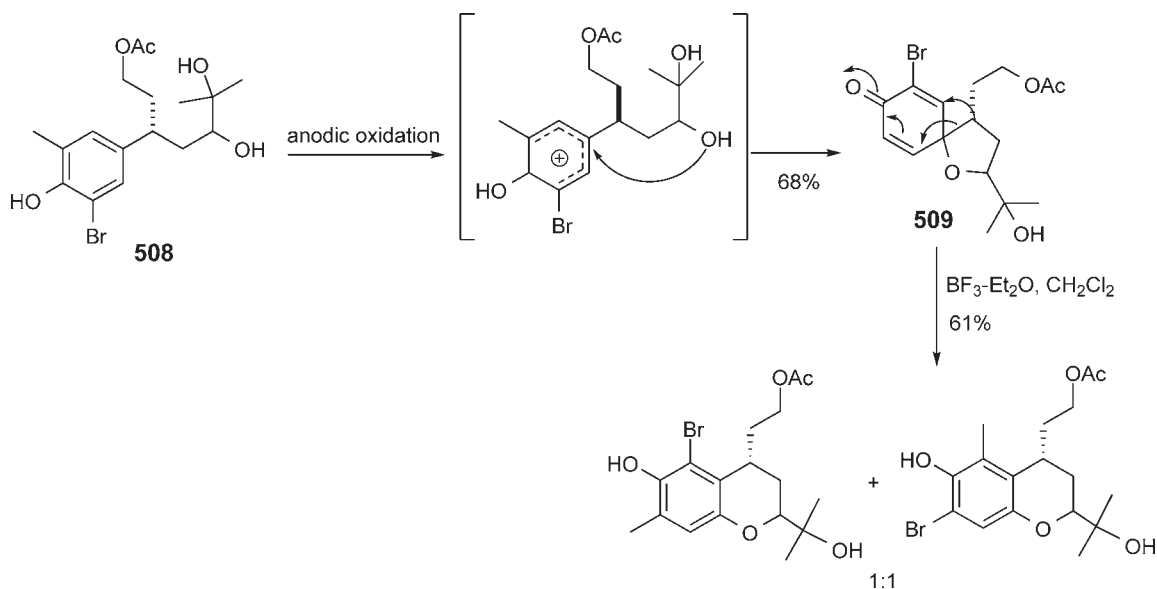
Anodic oxidation of *para*-substituted-2-bromophenol **508** leads to a tetrahydrofuran based spirodienone **509**, which undergoes a Lewis-acid-catalyzed rearrangement furnishing a diastereomeric mixture of chroman products. The regiochemistry of the product is dependent upon the substitution pattern of the spirodienone (Scheme 112) <2001T5533>. This ring expansion methodology is used during an enantioselective total synthesis of heliannuol E, whereby two regioisomeric chromans are formed, separable at a later stage in the synthesis <2003SL411>, as well as during another synthesis which assigned the correct absolute stereochemistry for the natural product <2003TL4877>. Chromans tested for their plant growth inhibitory effects are also synthesized in this manner <2004BCJ2257>.

7.08.11.3.2 From benzo-1,3-dioxans

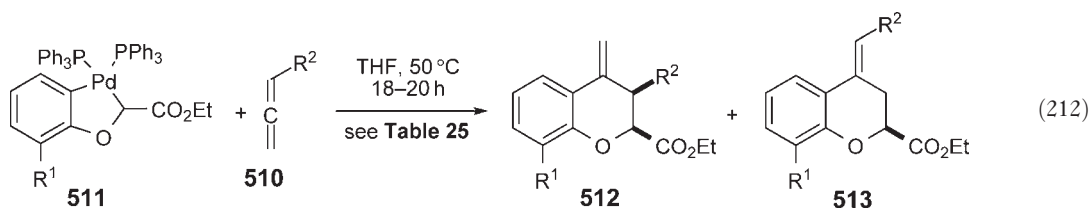
Thermolysis of a benzodioxan leads to a cycloadduct processing the chroman ring system, a key intermediate during synthetic studies on communesin B <2003OL3169>.

7.08.11.3.3 From oxapalladacycles

Monosubstituted allenes **510** can be successfully inserted into the oxapalladacycles **511** to afford regioisomeric chromans **512** and **513**. Oxapalladacycles **511** bearing no substitution on the aromatic ring give a mixture of regioisomeric products, but *exo*-methylene chromans **512** are exclusively formed upon introduction of a substituent at C7 (Equation 212, Table 25) <2004JOC8266>.



Scheme 112

Table 25 Formation of chromans **512** and **513** (Equation 212)

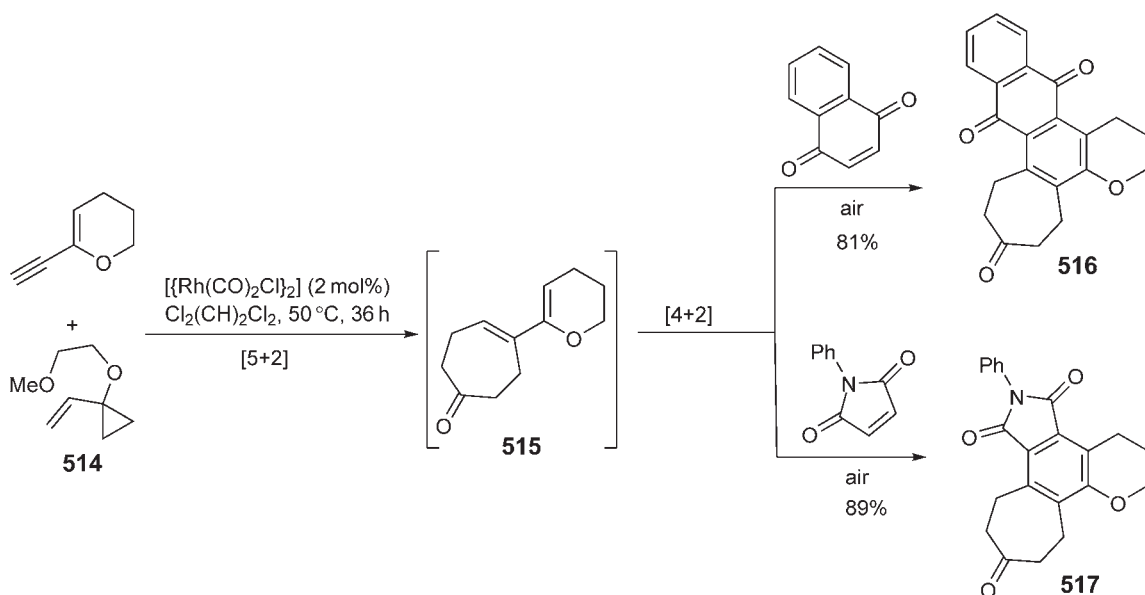
R ¹	R ²	Yield (%)	Ratio 512:513
H	–(CH ₂) ₅ Me	84	91:9
CF ₃	–(CH ₂) ₅ Me	56	100:0
OMe	–(CH ₂) ₅ Me	78	100:0
H	–(CH ₂) ₂ CHMe ₂	84	92:8
CF ₃	–(CH ₂) ₂ CHMe ₂	49	100:0
OMe	–(CH ₂) ₂ CHMe ₂	72	100:0
H	–CH ₂ CH(Et)(CH ₂) ₃ Me	64	90:10
CF ₃	–CH ₂ CH(Et)(CH ₂) ₃ Me	52	100:0
OMe	–CH ₂ CH(Et)(CH ₂) ₃ Me	81	100:0
H	–CH ₂ C(Me) ₂ Ph	68	45:23

7.08.11.4 From a Preformed Heterocyclic Ring

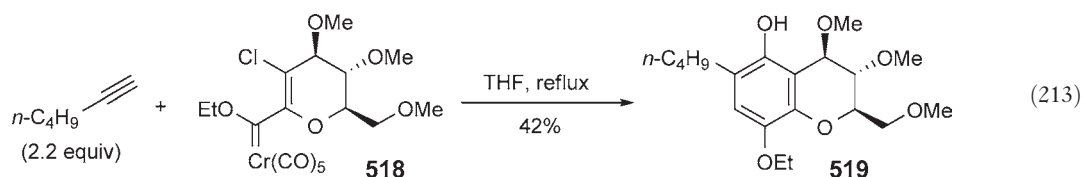
7.08.11.4.1 From dihydropyrans

Vinylcyclopropane **514** undergoes a rhodium catalyzed [5+2] cycloaddition reaction with 6-ethynyl-3,4-dihydropyran to furnish intermediate diene **515** that then undergoes an hDA reaction with dienophiles to afford complex pentacyclic chromans **516**, **517** (Scheme 113) <2001AGE3895>.

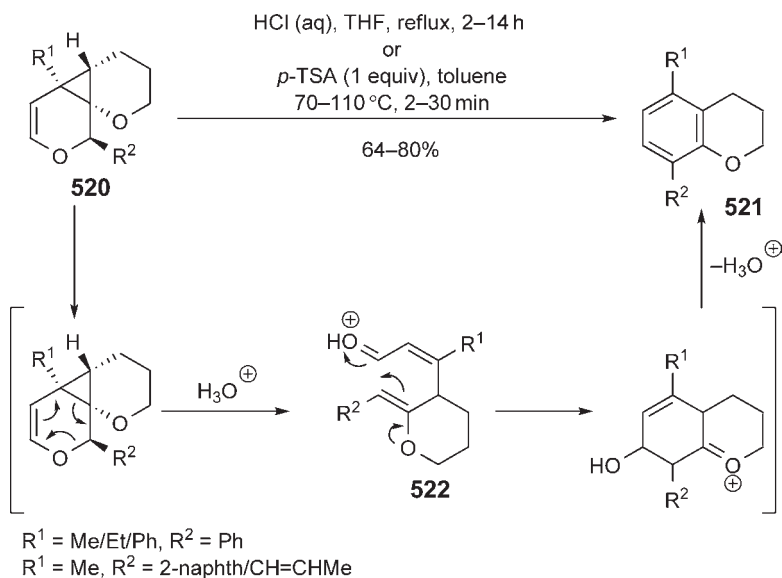
The Fischer carbene complex **518** undergoes a benzannulation reaction with 1-hexyne to furnish the highly substituted chroman **519** (Equation 213) <1998TL2851>. Treatment of the same complex with various functionalized alkynes provides tricyclic chromans <1998SL61>.



Scheme 113



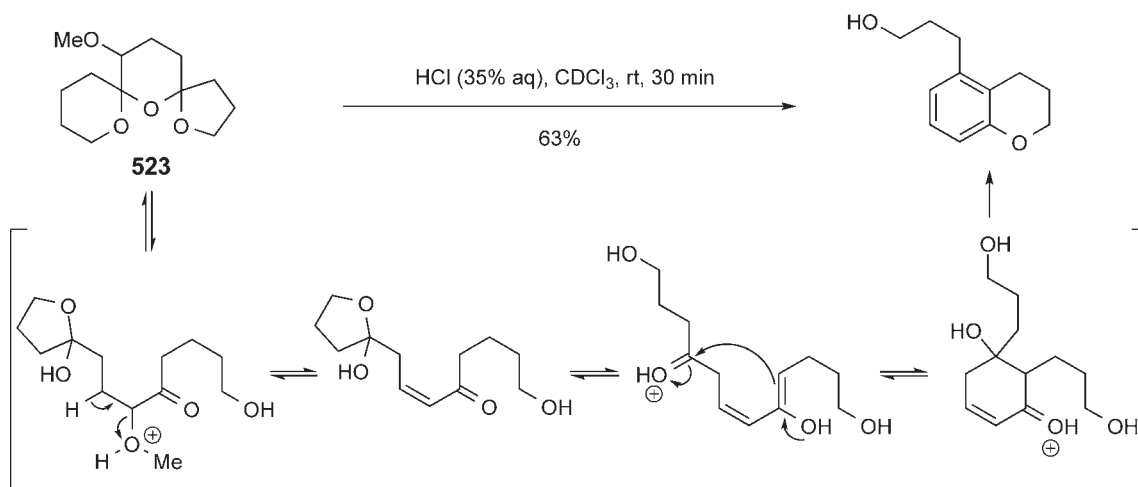
Treatment of cycloprop[c]pyrans **520** with acid leads to chromans **521** with a 5,8-substitution pattern, which is difficult to obtain by other synthetic methods (Scheme 114). This novel reaction is believed to proceed via a retro-hDA opening of the dihydropyran ring to afford **522** followed by an acid-catalyzed aldol-type cyclization and dehydration (Scheme 114) <2004OL3191>.



Scheme 114

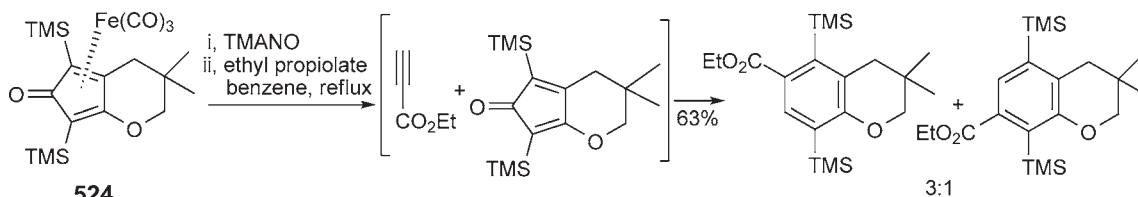
7.08.11.4.2 From tetrahydropyrans

An acid-catalyzed rearrangement of the trioxadispiroacetal **523** provides a route to 5-(3-hydroxypropyl)chroman (**Scheme 115**) <1997JOC2273>.



Scheme 115

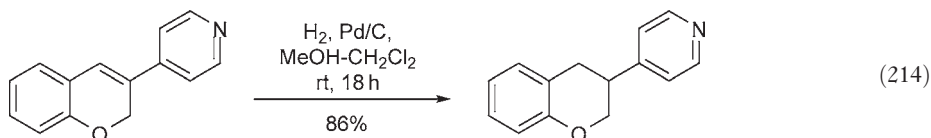
The tetrahydropyran-based iron complex **524** can undergo demetallation followed by a cycloaddition reaction with ethyl propiolate to afford a regioisomeric mixture of polysubstituted chromans (**Scheme 116**) <2001TL6987>.



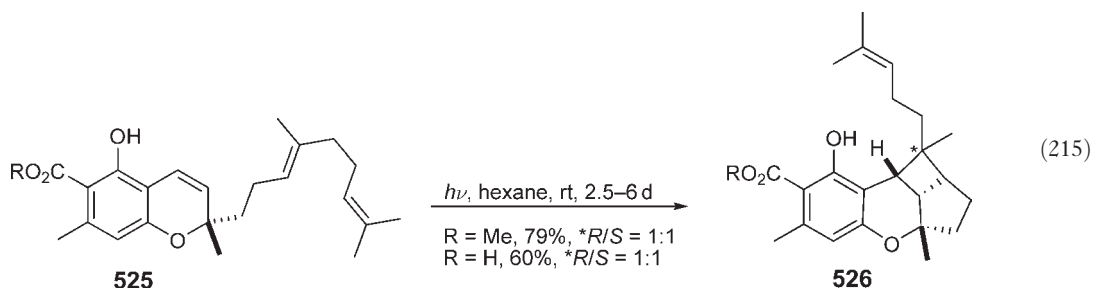
Scheme 116

7.08.11.4.3 From chromenes

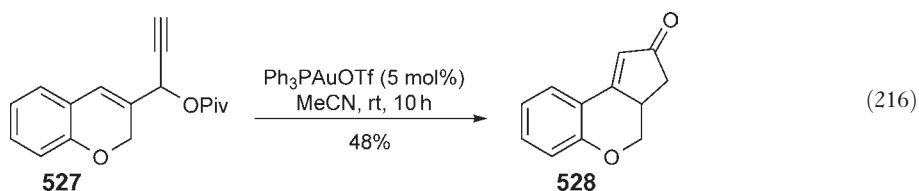
The reductive hydrogenation of chromenes continues to provide an attractive route to the chroman ring system and is discussed in depth in the previous volumes <1984CHEC, 1996CHEC-II>. An example is the preparation of 4-(chroman-3-yl)pyridine by hydrogenation of the double bond in 4-(2*H*-chromen-3-yl)pyridine (**Equation 214**) <1997TL5501>. The synthesis of optically pure 3-aminochromans can be achieved by ruthenium-catalyzed asymmetric hydrogenation of chromenes bearing an enamide <1999SL1832> or carbamate <1999TA3467>. Optically pure 3-aminochromans are available from chromenes via an asymmetric hydroboration–amination sequence <1997CC173>.



Jacobsen epoxidation of a chromene is used during the first asymmetric syntheses of several *syn*-3,4-dihydroxy-2,2-dimethylchromans <2004TA29>. An intramolecular photochemical [2+2] cycloaddition of the chromene **525** (R = Me) furnishes the cycloadduct **526**, the methyl ester of rhododaurichroman acids A and B, as a 1:1 mixture of diastereomers (Equation 215) <2003OL3935>. Optically pure daurichromenic acid **525** (R=H) can undergo the same photochemical reaction without the need for protecting groups <2003OL3935, 2003OL4481>.



A gold(III)-catalyzed Rautenstrauch rearrangement of the chromene **527** provides a chroman that features a 3,4-fused cyclopentenone moiety **528**, a reaction that is a viable alternative to Pauson-Khand type methodology (Equation 216) <2005JA5802>.



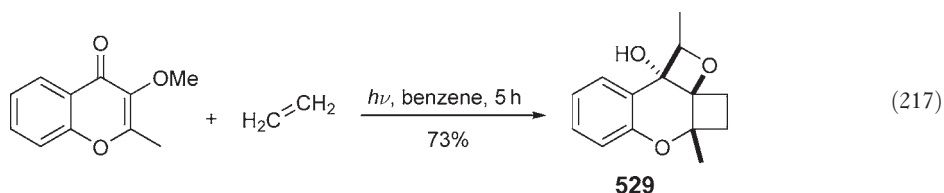
7.08.11.4.4 From chromanones

The reduction of chromanones to chromanols and chromans is used extensively, and is covered in detail in the preceding volumes <1984CHEC, 1996CHEC-II>. Deracemization of (±)-3-hydroxy-4-chromanone by the yeast *Trichosporon cutaneum* provides a stereoselective route to (3*R*, 4*S*)-3,4-chromandiol <2005TA2125>. The synthesis of heliannuol as its *syn*-epimer involves the indium-mediated allylation of a chroman-4-one followed by one carbon degradation to a vinyl group <2003T8375>. A Lewis-acid-catalyzed allylation of chroman-4-one can also be achieved in the presence of tetra-allylstannane <2001TL7525>. A convenient two-step method for chroman synthesis via deoxygenation of a chroman-2-one can be achieved by use of a titanocene complex in the presence of a stoichiometric amount of reducing agent, followed by exposure to Amberlyst 15® and triethylsilane <1998JOC2360>.

7.08.11.4.5 From chromones

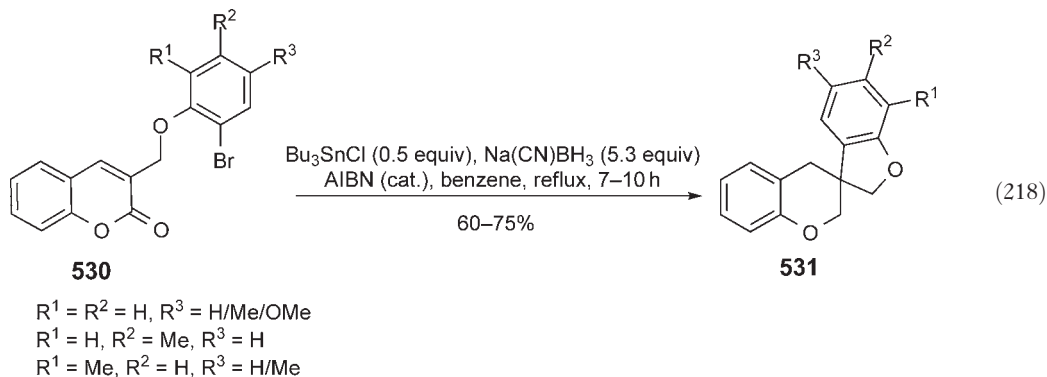
The total reduction of the enone system present in chromone to the corresponding chroman is effected by hydrogenation and is a key step during the synthesis of 2-(aminomethyl)chromans (2-AMCs) for evaluation of their affinity for the dopamine (DA) D₂ receptor <1997JME4235>. Luche reduction of a chroman-4-one is used during the synthesis of antagonists of leukotrine D₄ <1998BML1791>.

The reaction of ethylene and 3-methoxy-2-methylchromen-4-one proceeds via a cycloaddition followed by γ-hydrogen abstraction to afford the chroman **529** (Equation 217). The product can undergo further reduction and rearrangement providing a route to the benzooxabicyclo[3.2.1]octane ring system seen in the natural product filiformin and its numerous congeners <1996JOC4391, 1996JOC9164>. This methodology is also used for the synthesis of tetrasubstituted chromans <1996CC1965>.



7.08.11.4.6 From coumarins

A Bu_3SnCl and $\text{Na}(\text{CN})\text{BH}_3$ mediated radical cyclization of 3-(*o*-bromophenoxymethyl)coumarins **530** furnishes 3*H*-spirobenzofuran-2,3'-chromans **531** (Equation 218) <2004TL6871>.



The [4+2] cycloaddition of 3-nitrocoumarins with electron rich dienophiles proceeds with high *endo*-selectivity to afford nitronates, hydrolysis of which gives a mixture of chroman-2-ols <2002JOC7238>.

7.08.12 Isochromans (3,4-Dihydro-1*H*-2-benzopyrans)

A recent review of the oxa-Pictet–Spengler cyclization reaction as a method for preparation of isochromans is available <2006S187>. An intermolecular oxa-Pictet–Spengler cyclization is used during the total synthesis of deoxyfrenolicin (Equation 219) <1999OL1599>. Unmasking of the chiral 1,3-dioxolanes **532** followed by *in situ* oxa-Pictet–Spengler cyclization provides an elegant stereoselective route to isochromans (Equation 220) <1996J(P1)2241>. An extensive review of synthetic strategies towards the pyranonaphthoquinones antibiotics that feature the naphtho[2,3-*c*]pyran-5,10-dione ring system (Figure 1) is available <2000T1937>.

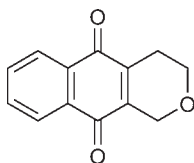
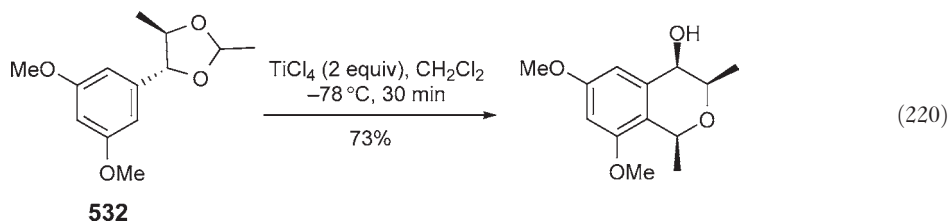
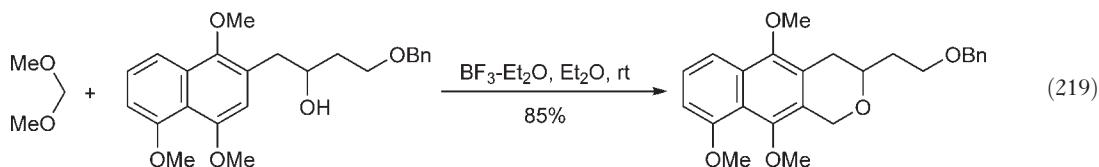
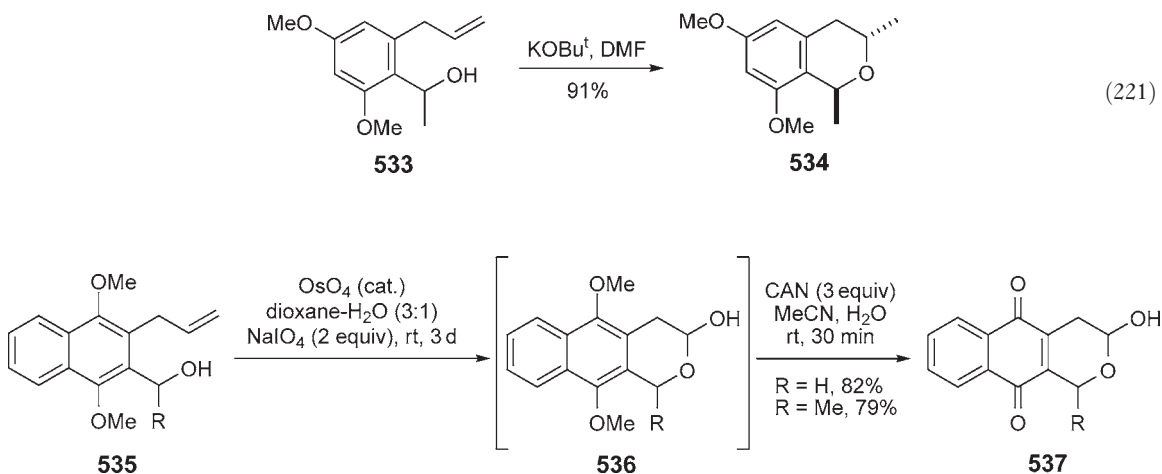


Figure 1

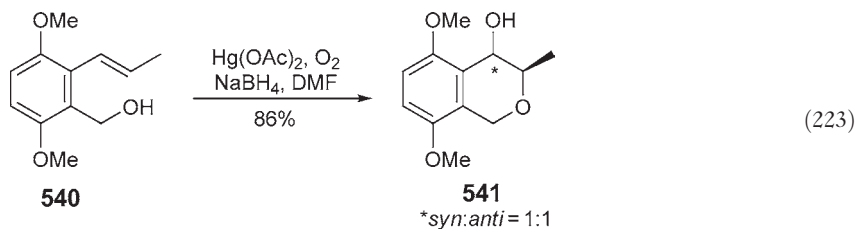
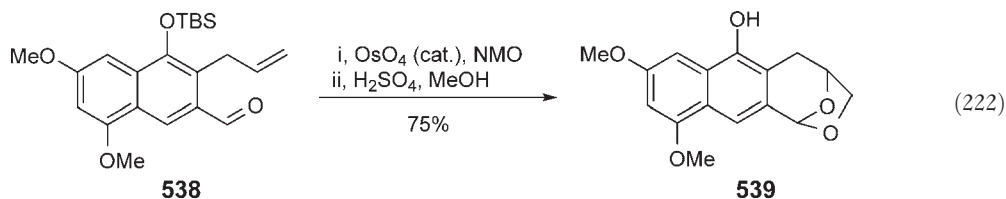
7.08.12.1 Formation of One Bond

7.08.12.1.1 Adjacent to the heteroatom

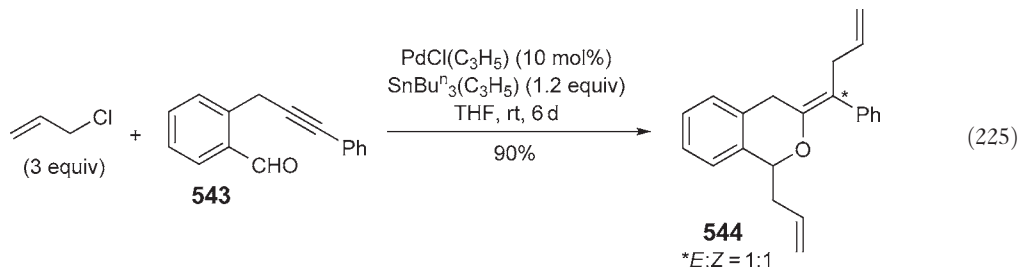
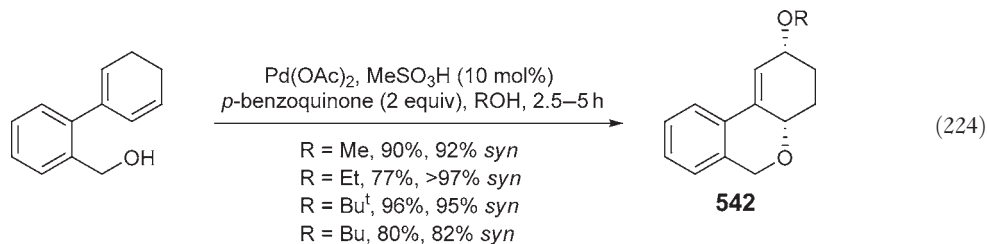
The base mediated cyclization of (2-allylphenyl)methanol derivatives continues to attract interest as a method to construct the isochroman ring system. During a synthesis of an isochroman analogue of the michellamines the (2-allylphenyl)methanol derivative **533** cyclizes in the presence of potassium-*tert*-butoxide leading to the *anti*-1,3-isochroman **534** in excellent yield (Equation 221) <1999TL3037>. Similar cyclizations can be seen during the synthesis of (±)-puraquinonic acid <2001JOC954>, ventiloquinone L <2004OBC2461>, models for benzo[*g*]isochromanols <2001T9623> and a (±)-pyranonaphthoquinone inhibitor of phosphatase <2004TL939, 2004BCJ1925>. Related methodology, the so called Lemieux–Johnson oxidation, proceeds from the (2-allylphenyl)methanol derivatives **535** to form isochromans **536**, which are not isolated but immediately treated with CAN to afford the corresponding pyranonaphthoquinones **537** in good yield (Scheme 117) <1999JOC1173>. Similarly, the osmium tetroxide mediated cyclization of the 2-allylbenzaldehyde derivative **538** to afford the isochroman **539** is used during the synthesis of an analogue of thysanone (Equation 222) <2002T7391>. The isochroman ring system can also be accessed via an oxidative mercury(II)-mediated ring closure of 2-vinyl(phenyl) methanol **540**. In this instance, a separable diastereomeric mixture of chromans **541** is obtained (Equation 223) <1997TL5055>. This mercury-mediated cyclization is a pivotal step during the synthesis of ventiloquinones J and F <2004S1601, 2004EJO4416> and a variety of enantiopure 4-hydroxyisochromanoquinones <2004T2629>.



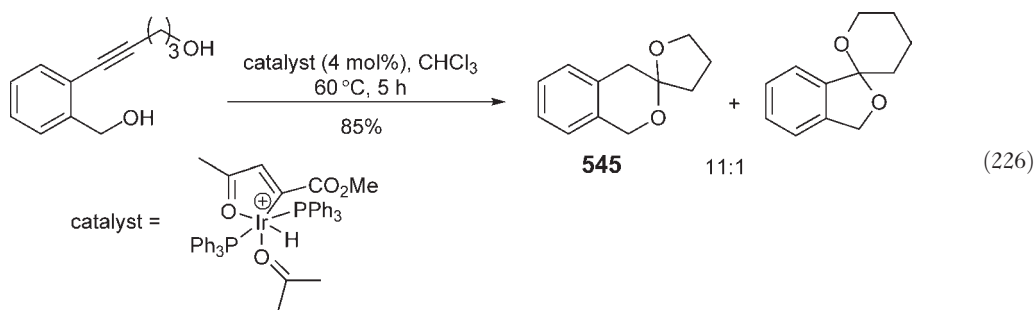
Scheme 117



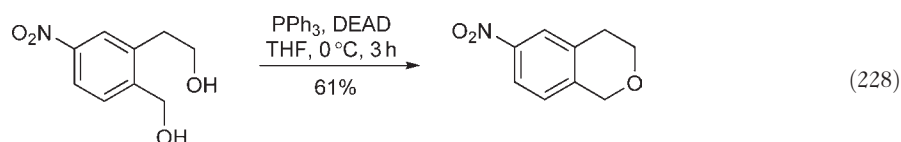
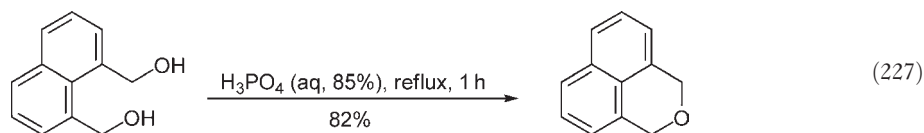
A palladium-catalyzed intramolecular 1,4-dialkoxylation of (2-(cyclohexa-1,5-dienyl)phenyl)methanol provides a stereocontrolled route to isochromans **542** (Equation 224) <1998TL1223>. A tandem nucleophilic allylation-alkoxyallylation reaction of an *ortho*-alkynylbenzaldehyde **543**, allyl chloride and allyltributylstannane in the presence of allylpalladium chloride furnishes the isochroman **544** via a 6-*endo-dig* cyclization process (Equation 225) <2002TL7631>.

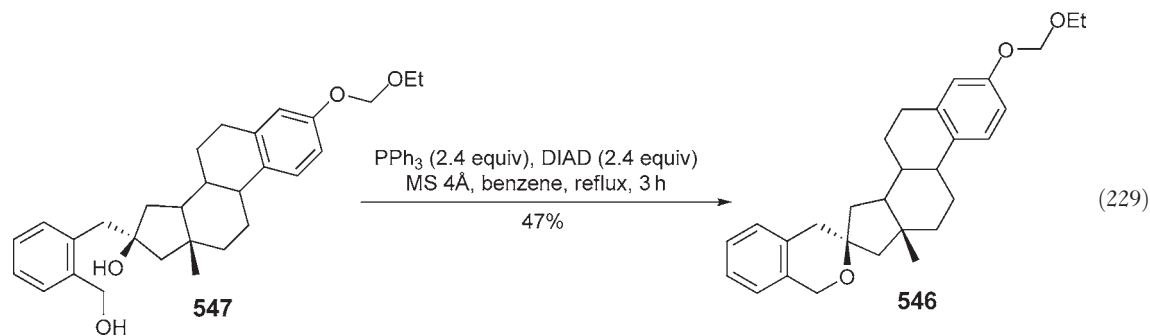


An iridium(III) hydride catalyzed intramolecular alkyne hydroalkoxylation can be used to construct isochromans **545** bearing a C(3)-spiroacetal moiety (Equation 226) <2005OL5437>. Novel isochromans bearing an array of C(3)-spiroacetal moieties are accessible via the hydroboration of alkynediols with disiamylborane followed by treatment of the resulting alkenylboron compounds with alkaline hydrogen peroxide <1998CL81>.



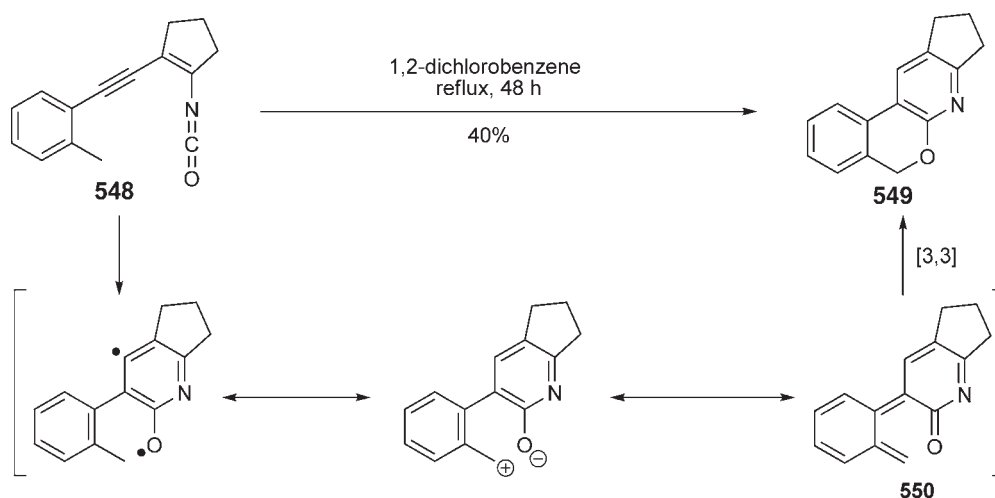
The cyclodehydration of 2,2'-hydroxymethyl-1,1'-diphenyl can be achieved in aqueous phosphoric acid under reflux (Equation 227) <2000T8375>. A similar cyclization is used during the synthesis of other isochromans <2004OL4563>. The ring closure of 1-substituted 2-(hydroxymethyl)phenylethanols using *p*-TSA supported on silica gel leads to 3-substituted isochromans in good yield <1998TL6751>. The synthesis of 6-nitroisochroman can be achieved via an intramolecular Mitsunobu reaction of 2-(2-(hydroxymethyl)-5-nitrophenyl)ethanol (Equation 228) <1998JOC4116>. Mitsunobu conditions are successfully employed during the synthesis of a steroid analogue **546** from the diol precursor **547** (Equation 229) <2001TA801>.





DIAD = diisopropyl azodicarboxylate

Thermolysis of the enyne-isocyanate **548** affords the isochroman **549** via generation and electrocyclic ring closure of the intermediate *cis*-2,4-dienone **550** (Scheme 118) <2004JOC4500>.



Scheme 118

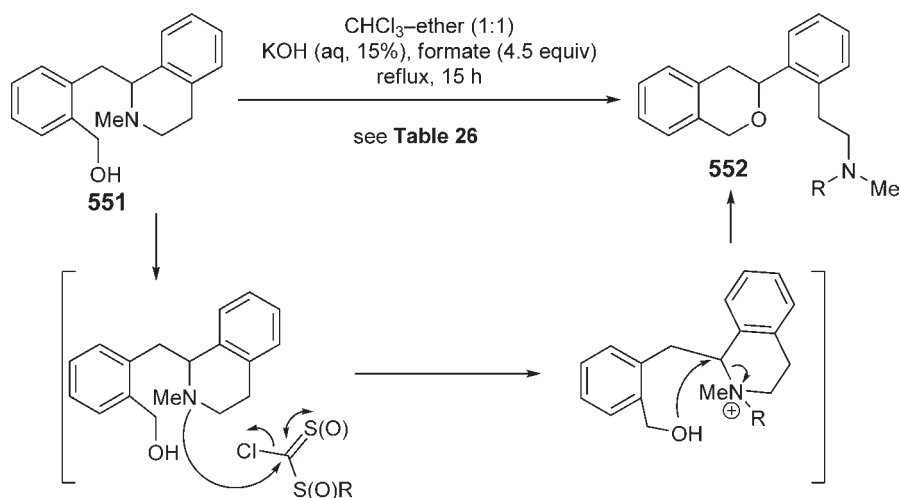
Ring cleavage of hydroxyalkyl-substituted tetrahydroisoquinoline **551** followed by ring closure to their corresponding isochromans **552** is affected by chlorothiono-, chlorothiol-, and chlorodithiolformates in moderate yield (Scheme 119, Table 26) <2003BKC256>.

7.08.12.1.2 β to the heteroatom

The first total synthesis of isagarin **553** (R=Me) involves the reaction and intramolecular condensation of 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone with pyridinium ylides **554** as the key step (Scheme 120) <1999JOC438>.

7.08.12.1.3 γ to the heteroatom

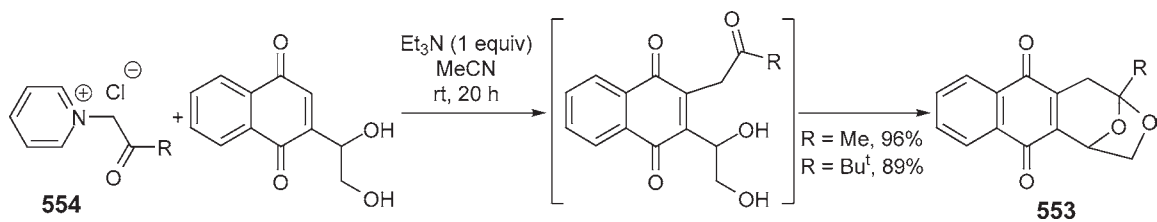
1-(Allyloxymethyl)-2-iodobenzene derivatives bearing (*E*)- or (*Z*)-alkene moieties undergo palladium-catalyzed intramolecular Heck reactions to give *anti*-3-alkyl-4-vinyl <1997LA887>. An intramolecular Heck reaction of the aryl iodides **555**, **556** can be used to afford tri- or tetracyclic isochromans with excellent *syn*-selectivity (Equations 230 and 231) <1998TL4139>. A one-pot triple intramolecular Heck reaction of the *tris*-allyl ether **557** provides a route to 3,7,11-trioxa-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrotriphenylene **558**, where the chirality of the starting material is upheld in the triannulated product (Equation 232) <2002JOC8280>. The Heck cyclization of electron rich chromium tricarbonylchloroarene allyl ether complexes **559** followed by *in situ* demetalation provides a route to poly-substituted 1-methylene isochroman **560** (Scheme 121) <1999TL6757>. Rhodium(i) dichloride or triethylsilane can be added to Heck catalytic conditions to increase the yield of the isochromans <1999JOC3461, 2003TL3785>.



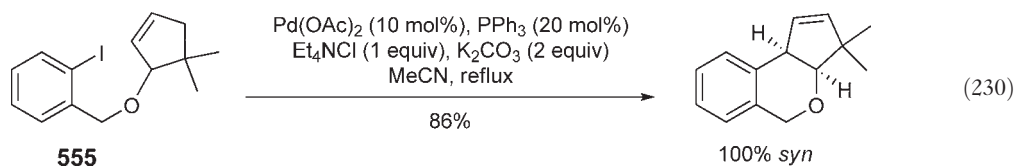
Scheme 119

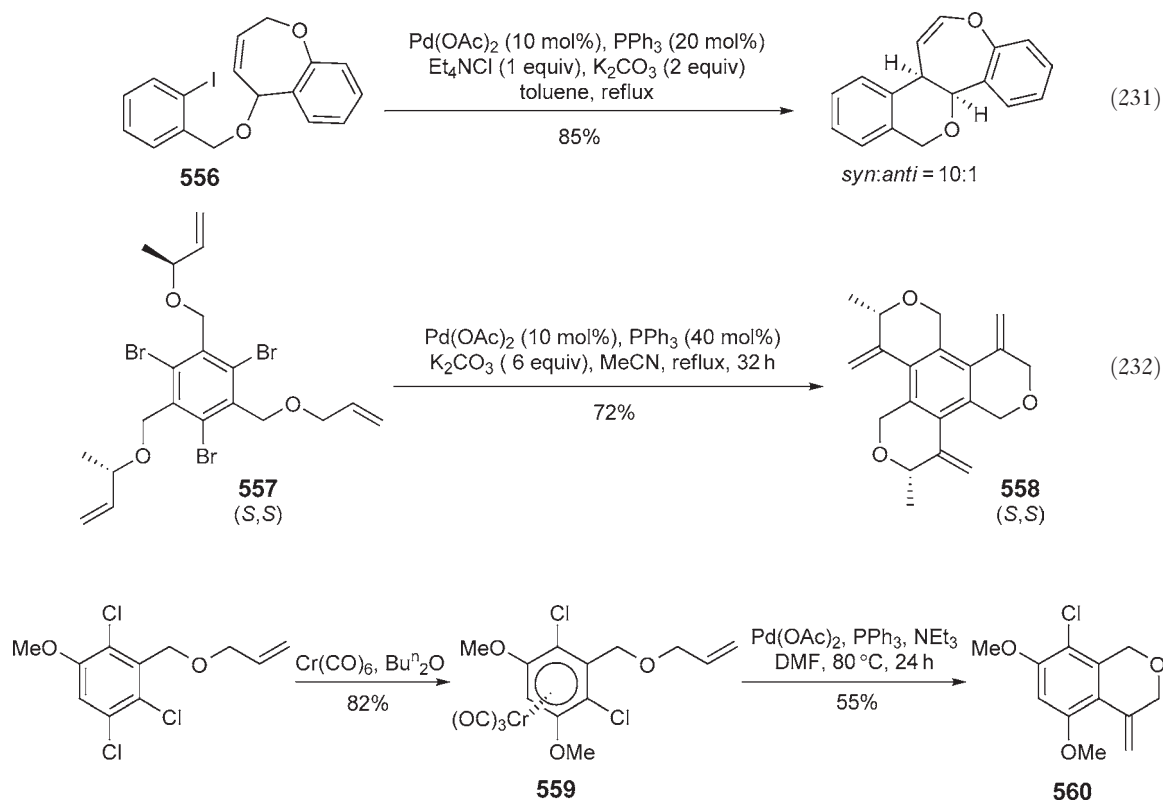
Table 26 Addition of various formates to laudanoline **551** furnishing iso-chromans **552** (Scheme 119)

Formate	R	Yield 552 (%)
	CSOPh	30
	CSO-4-ClC ₆ H ₄	31
	COSEt	42
	CSSEt	29



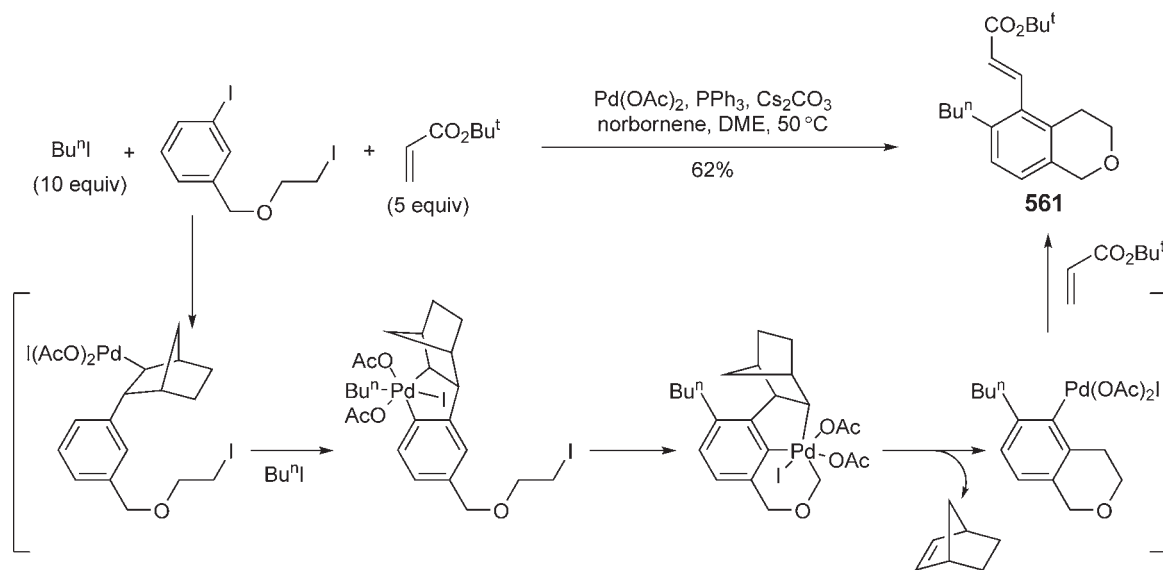
Scheme 120





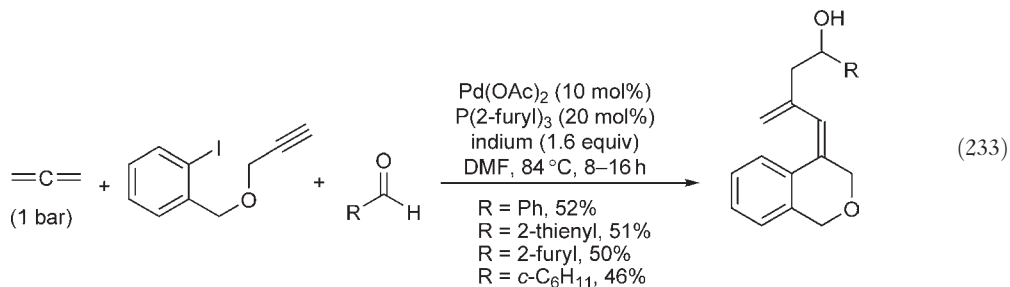
Scheme 121

1-Iodo-3-((2-iodoethoxy)methyl)benzene reacts under palladium catalysis with an excess of both alkyl halide and Heck acceptor to afford the isochroman **561** (Scheme 122) <2003OL4827>. A palladium(II)-mediated queuing process involving cyclization of aryl halides onto 1-iodo-2-((prop-2-ynyloxy)methyl)benzene, allene insertion,

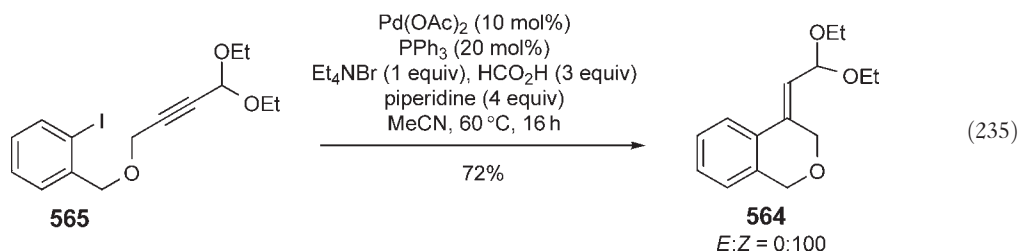
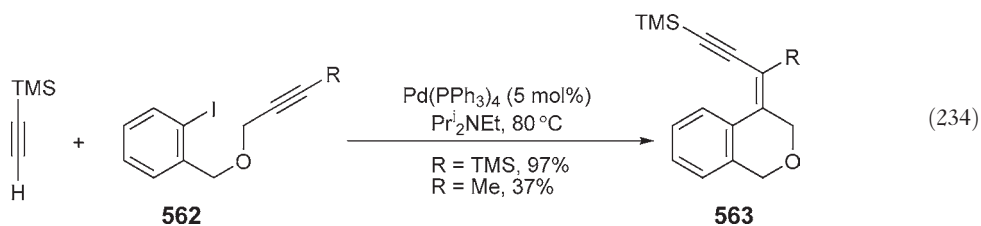


Scheme 122

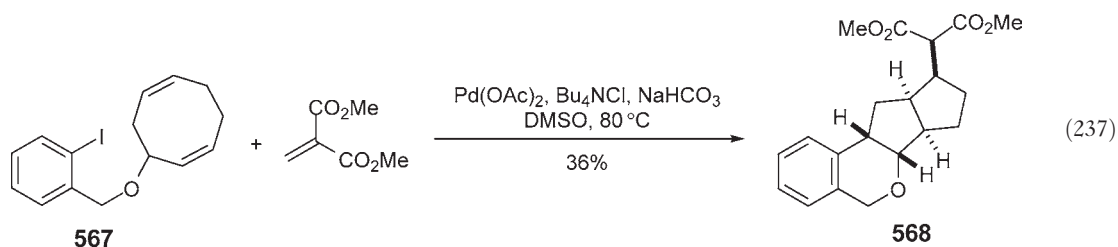
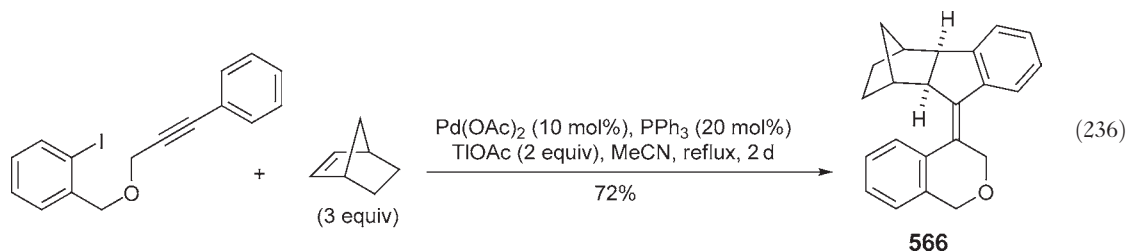
transmetallation of the resulting π -allylpalladium(II) species with indium and addition to an aldehyde allows entry into complex C4-substituted isochromans in moderate yield (Equation 233) <2000CC933>.



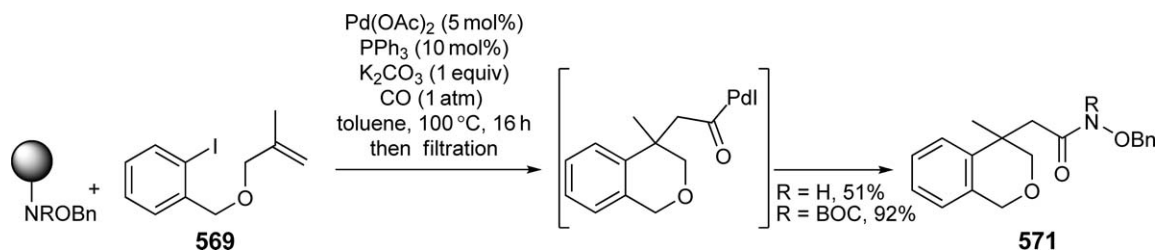
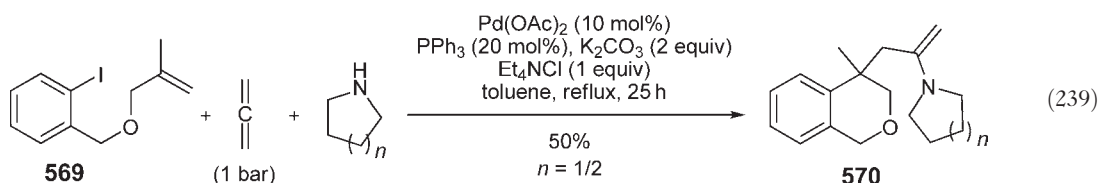
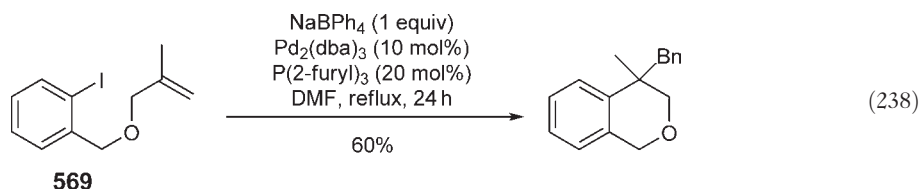
A palladium-catalyzed cyclization of 2-iodobenzyl 2-butynyl ethers **562** with ethynyltrimethylsilane leads to 4-substituted isochromans **563** (Equation 234) <2002T9007>. Isochromans **564** can be accessed using a similar palladium-catalyzed cyclization of a propargylic acetal **565** with (Z)-selectivity observed in the exocyclic double bond (Equation 235) <2005JOC489>.



1-Iodo-2-((3-phenylprop-2-ynyl)oxy)methylbenzene undergoes palladium-catalyzed cyclization and Friedel–Crafts alkylation with norbornene producing the pentacyclic isochroman **566** (Equation 236) <1998T2595>. Reaction of the cyclooctadiene (COD) tethered aryl iodide **567** with dimethyl 2-methylenemalonate under palladium(II) catalysis leads to the formation of the functionalized bicyclopentanoid **568** that features an isochroman ring (Equation 237) <2004OL4343>.

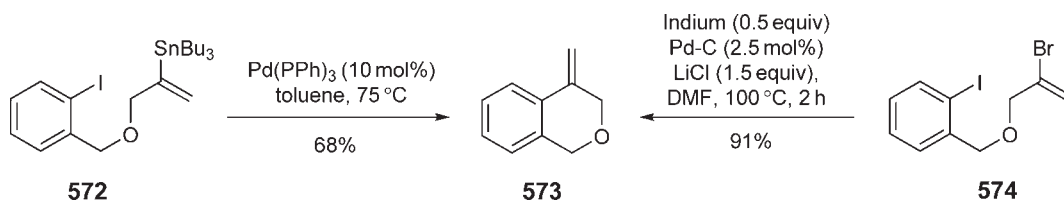


1-Iodo-2-((2-methylallyloxy)methyl)benzene **569** reacts with sodium tetraphenylboronate under palladium-catalysis to afford 4-benzyl-4-methylisochroman with good regio-, and stereoselectivity, via a 6-*exo-trig* cyclization-anion capture process (Equation 238) <1997T11803>. 1-Iodo-2-((2-methylallyloxy)methyl)benzene **569** can also undergo a palladium(II)-mediated 6-*exo-trig* cyclization/allenylation/amination cascade to afford isochromans **570** (Equation 239) <2002T8613> and a 6-*exo-trig* cyclization/carbonylation process to form an acylpalladium intermediate, which upon trapping with resin bound O-benzylhydroxylamines to affords isochromans **571** (Scheme 123) <1999TL7709>.



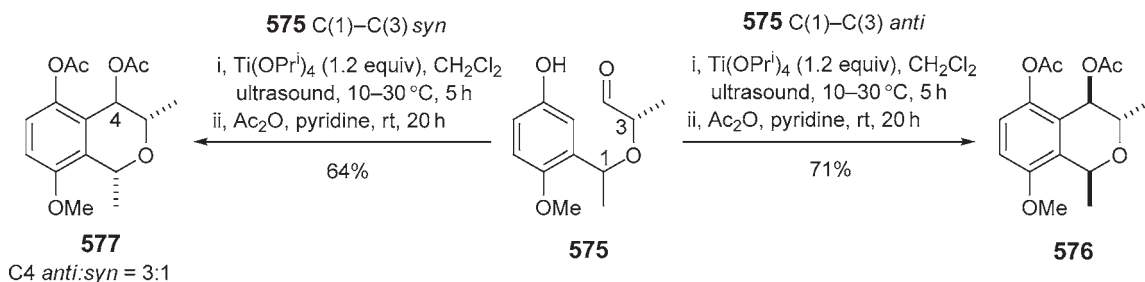
Scheme 123

The intramolecular Stille coupling of tributyl(3-(2-iodobenzyloxy)prop-1-en-2-yl)stannane **572** provides 4-methyleneisochroman **573** in good yield, with careful control of the reaction temperature necessary to prevent isomerization of the double bond to form 4-methylisochromene (Scheme 124) <2004JOC468>. 4-Methyleneisochroman **573** can also be synthesized via an indium-mediated intramolecular cyclization of 2-bromoallyloxymethyl iodobenzene **574** in excellent yield (Scheme 124) <2005OL343>.



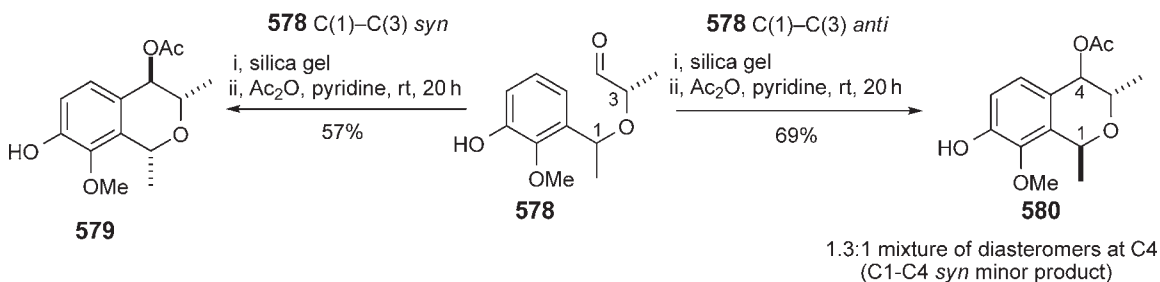
Scheme 124

A $\text{Ti}(\text{O}-i\text{-Pr})_4$ -mediated intramolecular cyclization of the C(1)-C(3)-*anti* phenolic aldehyde **575** occurs with total diastereocontrol to afford *anti*-1,3-dimethyl isochroman **576**. Cyclization of the C(1)-C(3)-*syn* phenolic aldehyde **575** does not occur with the same level of diastereoselectivity and *syn*-1,3-dimethyl isochroman **577** is formed as an inseparable mixture of diastereomers (Scheme 125) <1999J(P1)3039>.

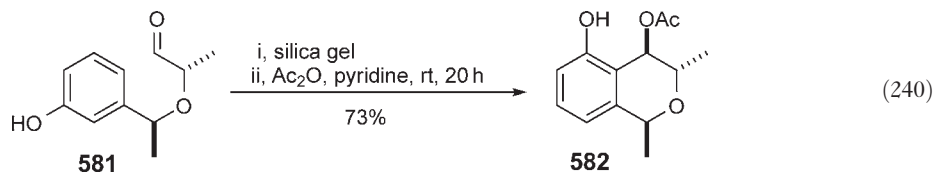


Scheme 125

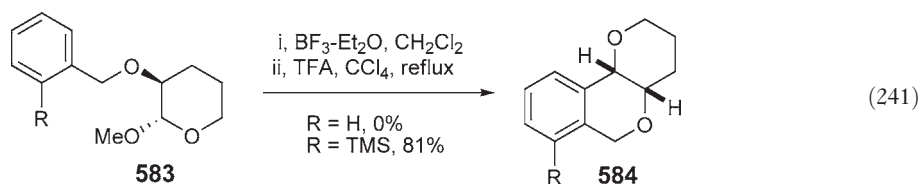
Ortho-methoxyphenols **578** cyclize upon exposure to silica gel, with the stereoselectivity of the reaction switching with *syn*-substrates cyclizing to afford one diastereomer **579**, whereas *anti*-substrates epimerize at C-4, leading to an inseparable mixture of diastereomeric products **580** (Scheme 126) <2000AJC341>. The use of the *meta*-hydroxyphenol **581** results in cyclization occurring exclusively *ortho* to the phenolic hydroxyl group with good levels of diastereoselectivity observed in the isochroman product **582** (Equation 240). The reasoning behind the excellent regioselectivity during this reaction can be explained through conformational studies <2003AJC489>. This cyclization methodology has been incorporated into syntheses of several aphid pigment derivatives containing the pyranonaphthoquinone ring system <2001TL5753, 2005OBC263>.



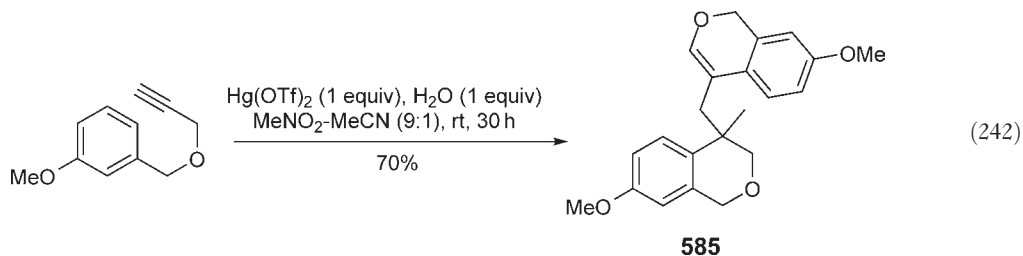
Scheme 126



A Lewis-acid-promoted Friedel–Crafts intramolecular cyclization of 2-*O*-benzyl ethers **583** provides fused isochromans **584**. The reaction unexpectedly fails in the absence of a TMS substituent on the aromatic ring, but this can be easily removed upon treatment of the cyclized product with TFA. The silyl group is proposed to promote the cyclization by stabilization of a carbocationic intermediate (Equation 241) <2002OL3797>.

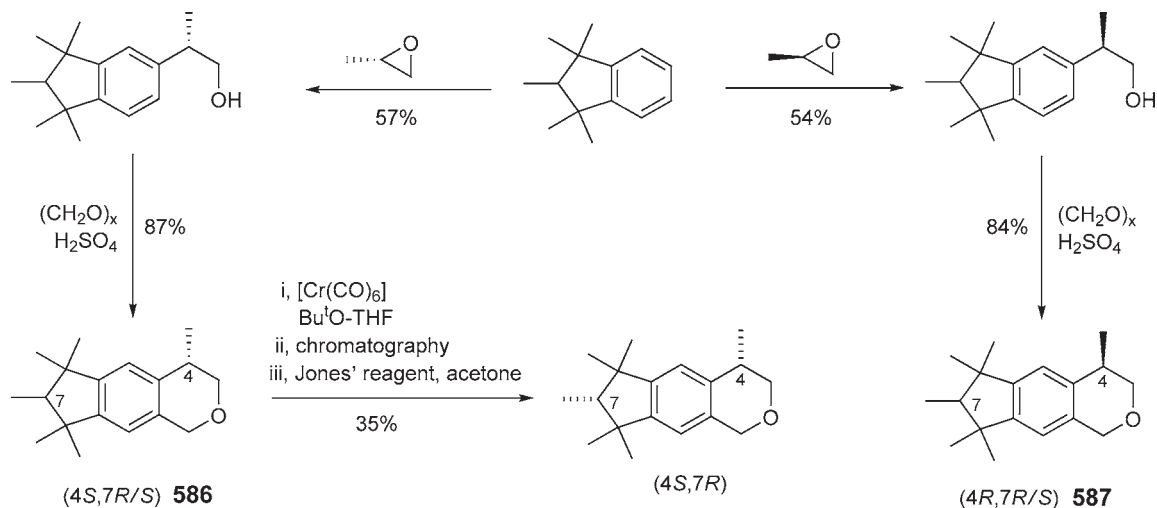


A mercury(II)-catalyzed hydroxylation carbocyclization of 1-methoxy-3-((prop-2-yn-1-yloxy)methyl)benzene affords the dimerized product **585** (Equation 242) <2003OL1609>.



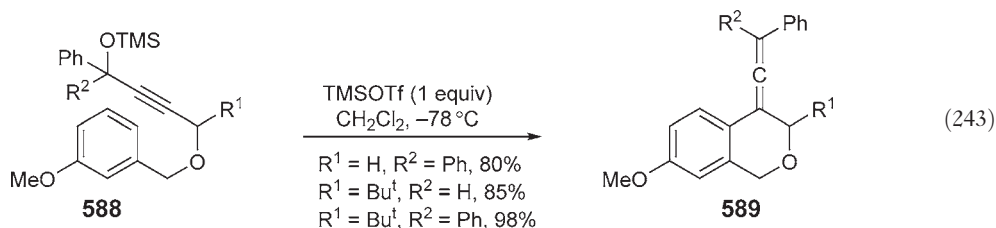
7.08.12.2 Formation of More than One Bond

A Friedel–Crafts type alkylation of 1,1,2,3,3-pentamethylindane with (*R*)- or (*S*)-methylepoxyde followed by acid-catalyzed condensation of the resulting alcohols with paraformaldehyde affords two diastereomeric pairs of isochromans **586**, **587** (Scheme 127) <1999HCA1656>. Separation of the enantiomers of (4*S*,7*R*/*S*)-isochromans **586** is achieved by flash chromatography of their corresponding tricarbonylchromium complexes and subsequent oxidative demetallation; the result of this synthetic work establishes that (4*S*,7*R*)-isochroman is found to be responsible for the intense musk odour of the perfume galaxolide® (Scheme 127) <1999HCA1656>.

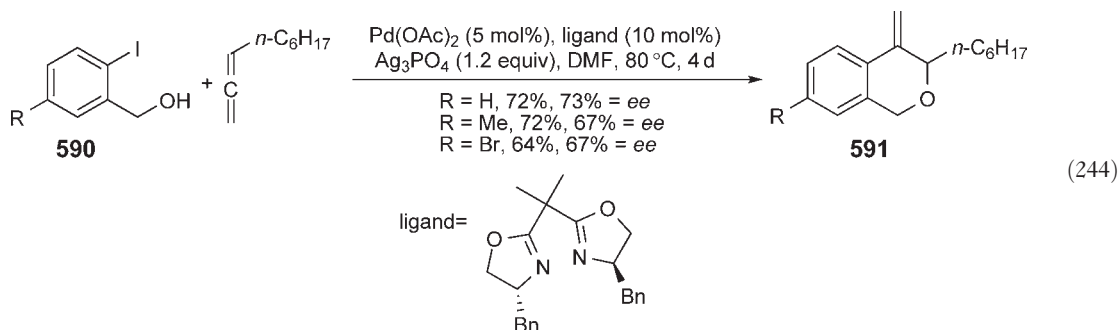


Scheme 127

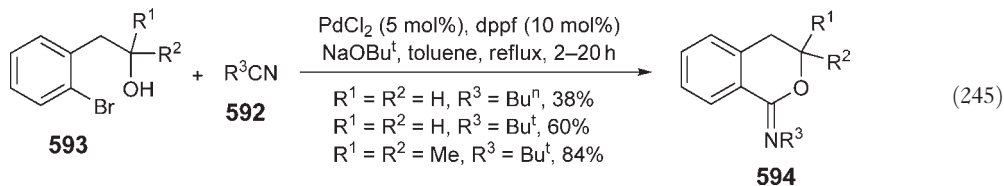
Propargylic silyl ethers **588** undergo intramolecular Friedel–Crafts alkylation to afford 4-allenyl isochromans **589** in excellent yield (Equation 243) <2001JOC4635>.



Aryl iodides **590** react with nona-1,2-diene in the presence of a palladium catalyst and a chiral bisoxazoline ligand to afford isochromans **591** in good yield with moderate enantioselectivity (Equation 244) <1999JOC7312>.



Isonitriles **592** undergo a palladium mediated insertion into aryl bromides **593** followed by intramolecular cyclization upon reaction with the pendant alcohol to afford isochromans that feature a C-1 imidate moiety **594** (Equation 245) <2004TL6995>.



Trifluoromethyl benzocyclobutenol derivatives **595** undergo ring opening upon treatment with LiTMP followed by reaction with aromatic aldehydes to furnish highly substituted isochroman-1-ols **596** via a laterally-lithiated trifluoromethylketone intermediate (Equation 246, Table 27) <1996SL57>.

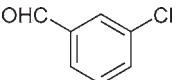
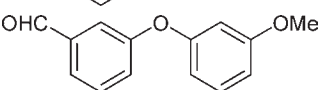
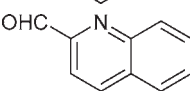
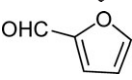
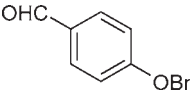
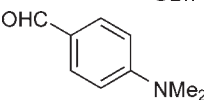
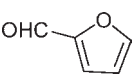
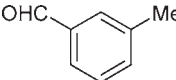


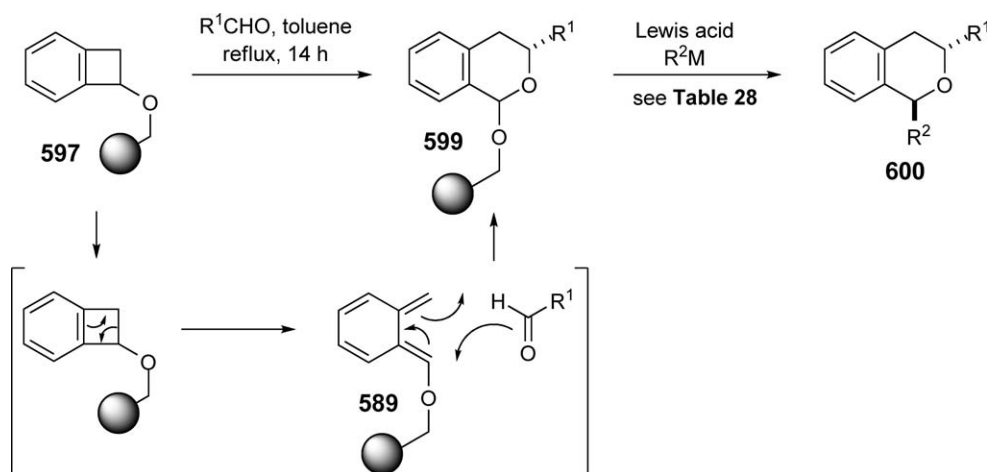
Resin-supported benzocyclobutenol **597** provides a solid phase source of *ortho*-quinonedimethide **598**, which undergoes hDA reactions with aldehydes to afford 1,3-disubstituted isochromans **599**, treatment of which with a Lewis acid liberates isochromans **600** with excellent 1,3-*anti* selectivity (Scheme 128, Table 28) <1998SL1381>.

The *anti*-substituted benzocyclobutenes **601** undergo bond reorganization under mild conditions to form *ortho*-quinone dimethide intermediates **602**, which function as dienes in an hDA reaction with aldehydes to afford all *syn*-substituted isochromans **603** in excellent yield (Scheme 129) <2000AGE1937>.

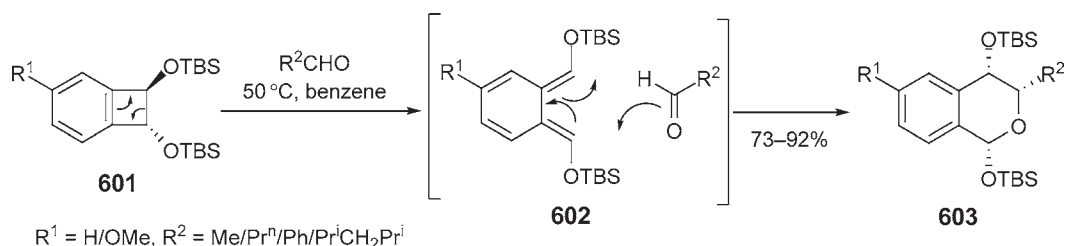
The isochroman **604** is capable of DNA cleavage and can be accessed via a poor yielding cycloaromatization of the 10-membered cyclic diyne **605** (Equation 247) <1996TL2433>. A rhodium- or ruthenium-catalyzed [2+2+2] cyclization of the triyne **606** can be used to construct the tricyclic isochroman **607** in excellent yield (Equation 248) <2003JA7784, 2003JA12143>.

Table 27 Aryl aldehyde addition to benzocyclobutenols **595** furnishing isochromans **596** (Equation 246)

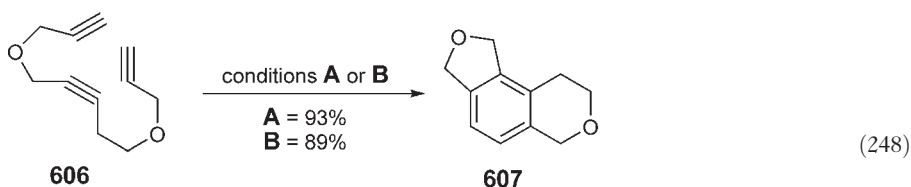
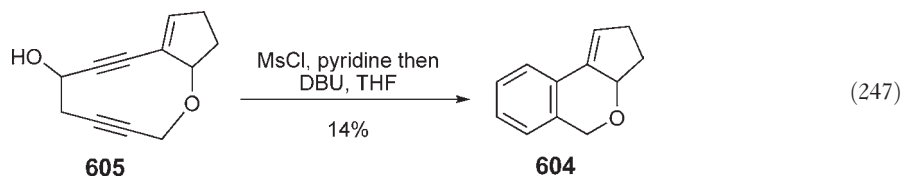
<i>R</i>	<i>ArCHO</i>	Yield 596 (%)
F		73
F		73
F		5
F		27
Cl		57
Cl		9
Cl		24
OMe		51

**Scheme 128****Table 28** Formation of tetrahydropyrans **600** by Lewis-acid-mediated nucleophilic addition to resin bound isochromans **599**

<i>R</i> ¹	<i>R</i> ²	<i>Lewis acid</i>	Yield 600 (%)
4-O ₂ NC ₆ H ₄	H	TFA, Et ₃ SiH	41
4-O ₂ NC ₆ H ₄	Me	Me ₃ Al	26
4-O ₂ NC ₆ H ₄	CH ₂ =CHCH ₂	SnCl ₄	24
4-O ₂ NC ₆ H ₄	CH ₂ COBu ^t	TMS-CH=CH ₂	33
CO ₂ Me	H	SnCl ₄ TBDMSOCCH ₂ Bu ^t	10
4-BrC ₆ H ₄	Me	TFA, Et ₃ SiH	18
		Me ₃ Al	



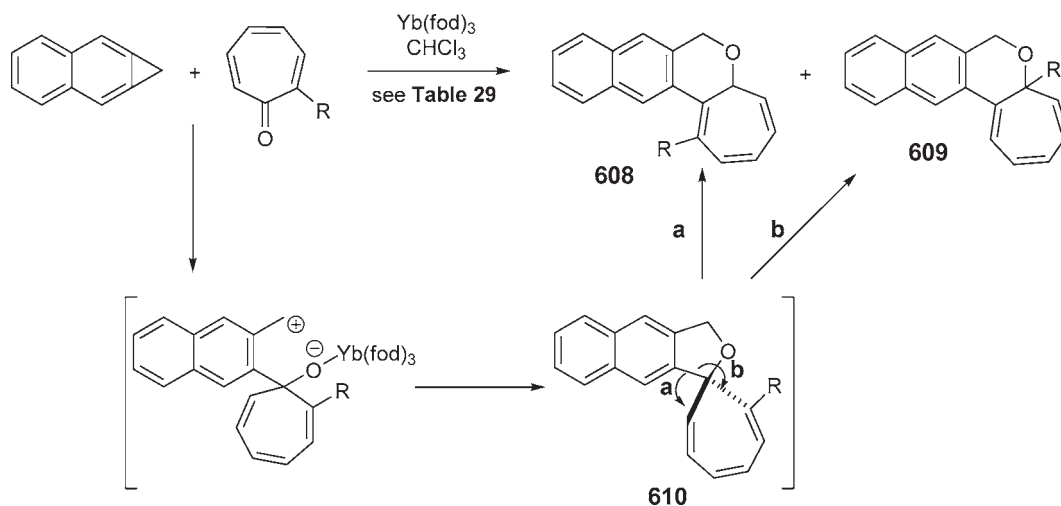
Scheme 129



A: $[\text{RhCl}(\text{cod})]_2$ (2.5 mol%), tppts (16 mol%), H_2O -ether (5:1), rt, 10 h

B: $\text{CpRu}(\text{cod})\text{Cl}$ (5 mol%), $\text{ClCH}_2\text{CH}_2\text{Cl}$, rt, 18 h

1*H*-Cyclopropa[*b*]naphthalene undergoes an [8+2]-cycloaddition with a tropone in the presence of a ytterbium-complex producing regioisomeric fused isochromans **608**, **609**. The reaction proceeds through two possible ring expansion pathways of dihydroisobenzofuran **610** (Scheme 130, Table 29) <2000H(53)2601>.

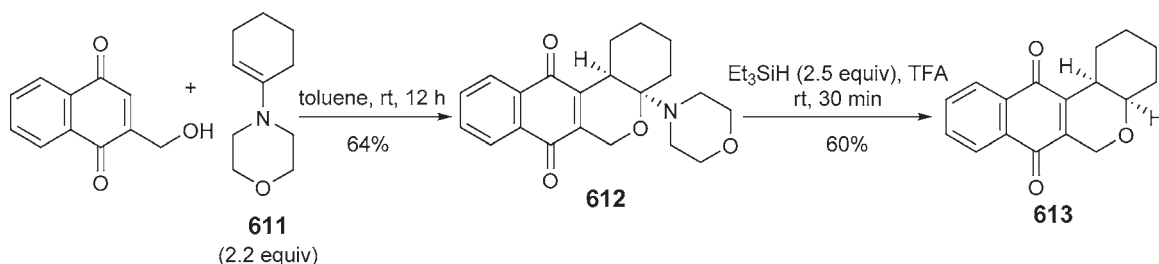


Scheme 130

2-(1-Hydroxyalkyl)-1,4-naphthoquinone reacts with morpholine enamine **611** via a tandem conjugate addition–cyclization sequence. Elimination of morpholine from the isolable adduct **612** allows entry to the 1*H*-naphtho[2,3-*c*]pyran-5,10-dione ring system **613** (Scheme 131) <2001J(P1)2977>. Pyrrolidine enamines and imines can also be effectively used in this reaction <2003S673>.

Table 29 Affect of R on ratio of products **608** and **609** (Scheme 130)

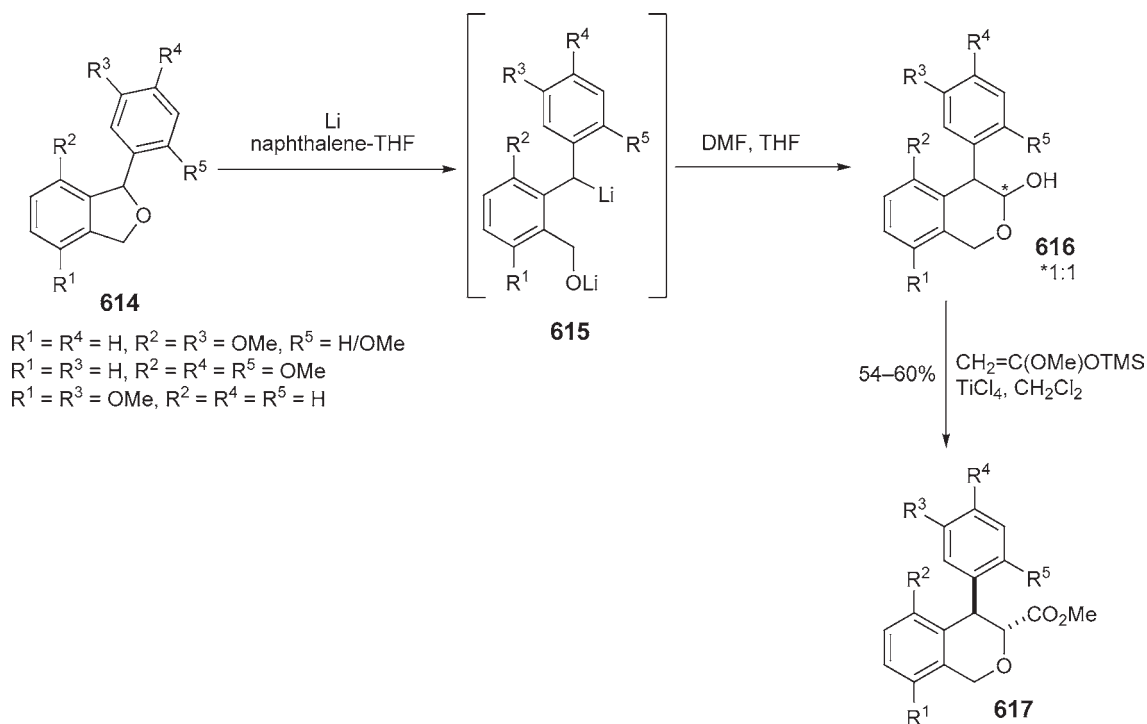
R	Yield 608 (%)	Yield 609 (%)
H	48	8
Me	56	13
Ph	0	25

**Scheme 131**

7.08.12.3 From Other Heterocycles

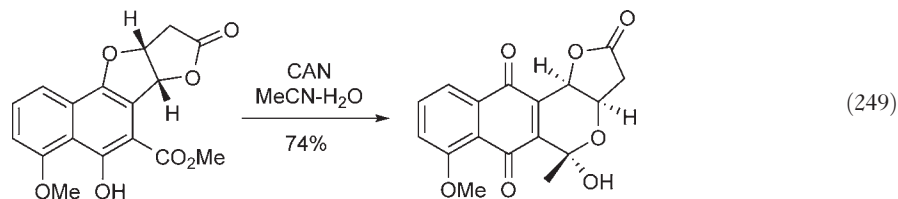
7.08.12.3.1 From isobenzofurans (phthalanes)

Ring opening of phthalanes **614** to form the bis-lithiated species **615** via reductive lithiation, followed by treatment with DMF furnishes anomeric 3-hydroxy-4-arylisochromans **616**. The mixture of anomers obtained can be converted to *anti*-3-carboxymethyl-4-aryl isochromans **617** using Mukaiyama's procedure (Scheme 132) <2001TL9293>. Similar bis-lithiated species can react with (–)-menthone, with the subsequent dehydration leading to C(3)-spirocyclic isochromans <2004S1115>.

**Scheme 132**

7.08.12.3.2 From naphthofurans

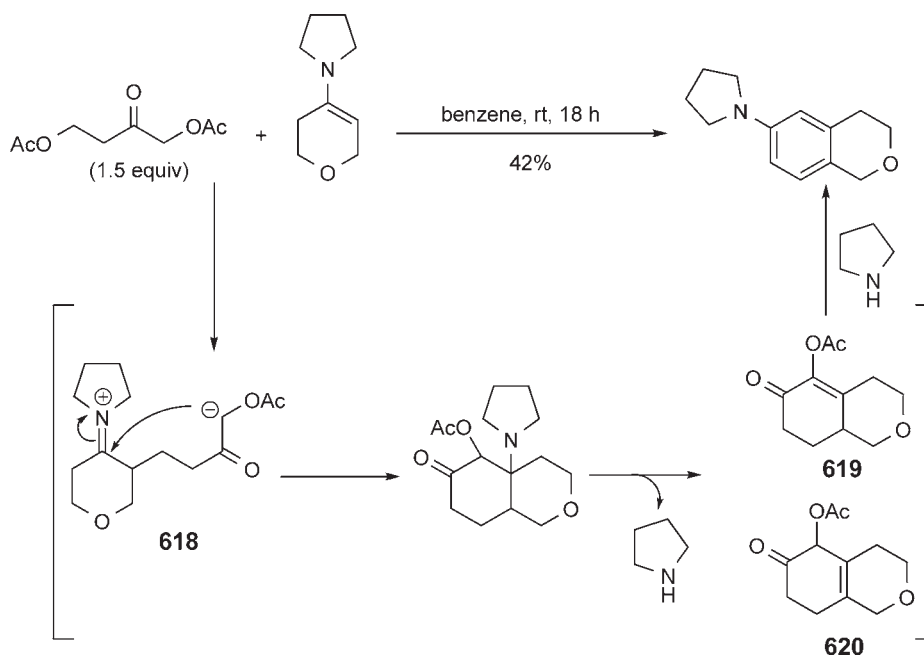
An oxidative rearrangement of naphthofurans provides the naphtho[2,3-*c*]pyran-5,10-dione ring system seen in the pyranonaphthoquinone family of antibiotics, a key step during a synthesis of kalafungin (Equation 249) <2000PAC1635>. This step is pivotal during syntheses of several natural products and their analogues <1999OL1459, 2000AJC571, 2000ARK909, 2000J(P1)697, 2001J(P1)1624, 2002TL4777, 2002SL1318, 2003OBC1690, 2003OBC4227, 2004T5751>.



7.08.12.4 From a Preformed Heterocyclic Ring

7.08.12.4.1 From dihydropyrans

Condensation of 1-(3,6-dihydropyran-4-yl)pyrrolidine with 1,4-diacetoxy-2-butanone affords 1-(isochroman-6-yl)pyrrolidine in moderate yield. The reaction proceeds via intramolecular cyclization and elimination of pyrrolidine from the zwitterion **618** to form the ketones **619** and **620**, which yield the desired isochroman upon aromatization (Scheme 133) <2000OL1773>.

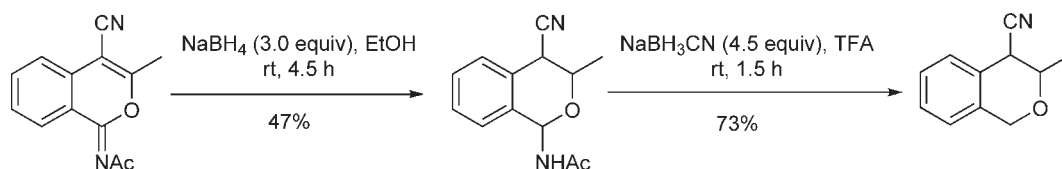


Scheme 133

7.08.12.4.2 From isochromenes

The reduction of 1-acetylamino-3-methylisochromene-4-carbonitrile with sodium borohydride affords *N*-(4-cyano-3-methylisochroman-1-yl)acetamide, which can be further reduced with sodium cyanoborohydride to furnish 3-methylisochroman-4-carbonitrile (Scheme 134) <2001AJC135>.

3-Phenylisochromene undergoes a photochemically induced addition of methanol across the C(3)–C(4) double bond to afford 3-methoxy-3-phenyl isochroman <1997JOC1183>.



Scheme 134

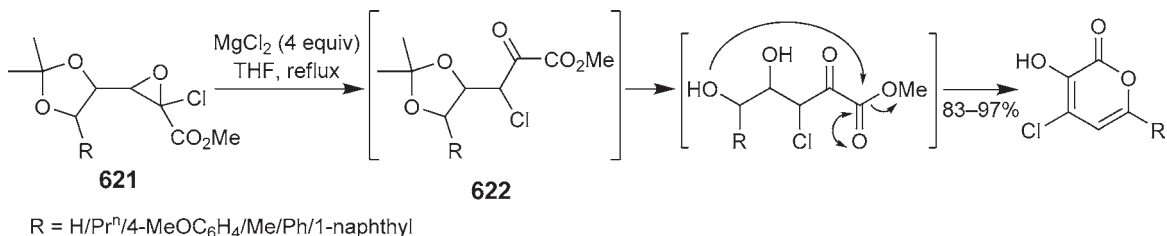
7.08.13 Pyrones and Fused Pyrones: 2*H*-Pyran-2-Ones (2 Pyrones)

2*H*-Pyran-2-ones are useful synthons in organic chemistry and also occur as structural subunits in a number of biologically active natural compounds <2001COR571>. Consequently, there is a vast amount of literature dedicated to the synthesis of this class of pyran.

7.08.13.1 Formation of One Bond

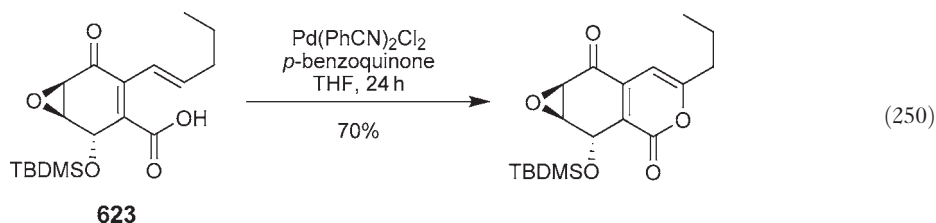
7.08.13.1.1 Adjacent to the heteroatom

Treatment of 2-chloroglycidic esters **621** with magnesium chloride in THF under reflux forms the intermediate 3-chloro-2-keto ester **622**. Cyclization occurs upon deprotection of the acetonide group, followed by elimination of water and tautomerization to afford 4-chloro-3-hydroxy-2*H*-pyran-2-ones in good yield (Scheme 135) <2004TL6299, 2005T2541>.

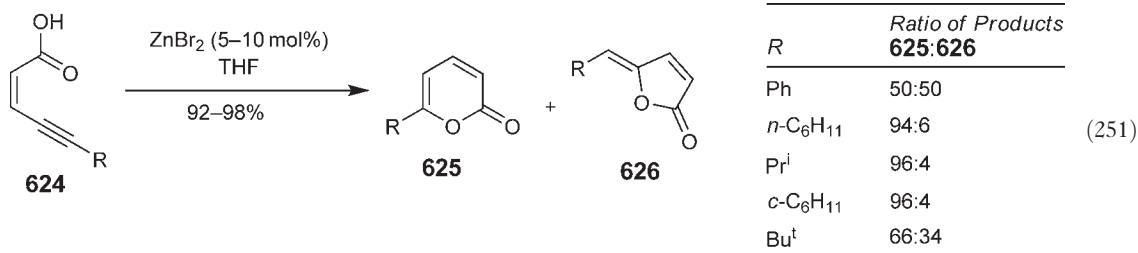


Scheme 135

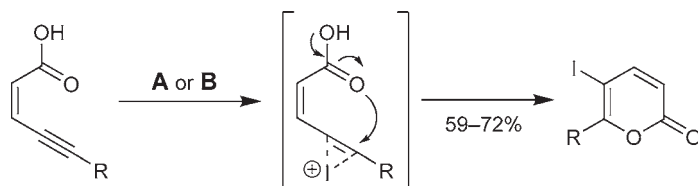
2,4-Dienoic acid **623** can undergo palladium(II)-catalyzed carboxypalladation followed by β -hydride elimination to form the corresponding 2*H*-pyran-2-one in high yield (Equation 250) <2004OL4535>.



(*Z*)-2-En-4-ynoic acids **624** undergo ZnBr_2 promoted 6-*endo-dig* lactonizations to afford 2*H*-pyran-2-ones **625** as the major product along with the alternate 5-*exo-dig* lactonization product **626** (Equation 251) <2002TL5673>.



Iodolactonization of (*Z*)-2-en-4-ynoic acids with iodine or *N*-iodosuccinimide (NIS) affords 5-iodo-2*H*-pyran-2-ones via activation of the triple bond via an iodonium ion intermediate followed by nucleophilic attack of the carbonyl oxygen (Scheme 136) <2001T2857>. Similarly, (*Z*)-2-en-4-ynoates can be converted into 5-iodo-2*H*-pyran-2-ones upon treatment with ICl (Equation 252) <2002T5023>.

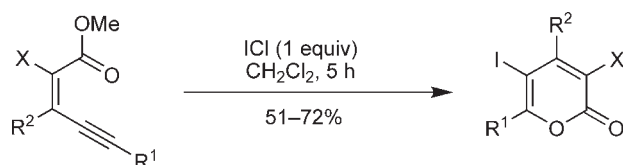


A, I₂ (3 equiv), NaHCO₃ (3 equiv), MeCN

B, NIS (1.1 equiv), KHCO₃ (1 equiv), MeCN

R = Me/Ph/Buⁿ/*n*-C₅H₁₁/*n*-C₆H₁₃/(*E*)-CH = CHC₃H₇

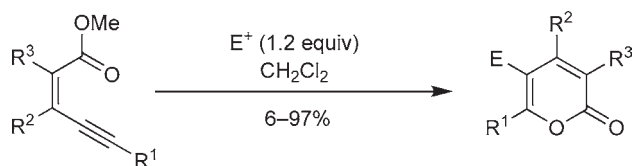
Scheme 136



(252)

R¹ = *n*-C₅H₁₁, R² = H, X = H/Br
 R¹ = (*Z*)-MeCH = CMe₂, R² = H, X = Br
 R¹ = R² = *n*-C₅H₁₁, X = H

A variety of electrophilic reagents can induce a 6-*endo-dig* lactonization of (*Z*)-2-en-4-ynoates to afford 2*H*-pyran-2-ones with concomitant incorporation of the electrophile onto C-5 (Equation 253) <2003JOC5936>. However, formation of 5-methylenefuran-2(5*H*)-ones, via an alternate 5-*exo-dig* lactonization, lowers the yield of the desired 2*H*-pyran-2-ones <2003JOC5936>.



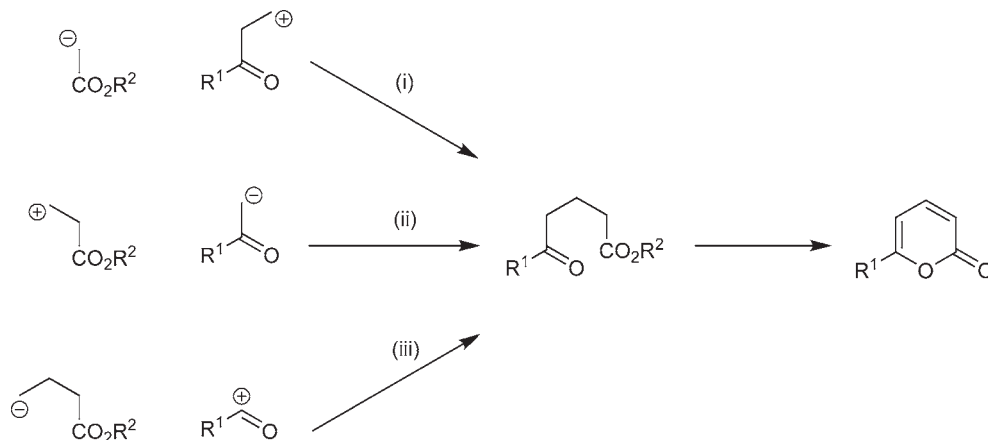
(253)

R¹ = Ph, R² = R³ = H, E⁺ = ICl/4-O₂NC₆H₄SeCl/PhSeCl
 R¹ = Buⁿ, R² = R³ = H, E⁺ = ICl
 R¹ = Ph, R² = H, R³ = Me, E⁺ = ICl
 R¹ = R² = Ph, R³ = H, E⁺ = ICl
 R¹ = R² = Ph, R³ = Me, E⁺ = I₂
 R¹ = R² = Ph, R³ = Ph, E⁺ = I₂/ICl/PhSeCl
 R¹ = Ph, R² = -(CH₂)₄-, R³ = R³, E⁺ = ICl/PhSeCl
 R¹ = Ph, R² = -(CH₂)₃-, R³ = R³, E⁺ = I₂

7.08.13.2 Formation of More than One Bond

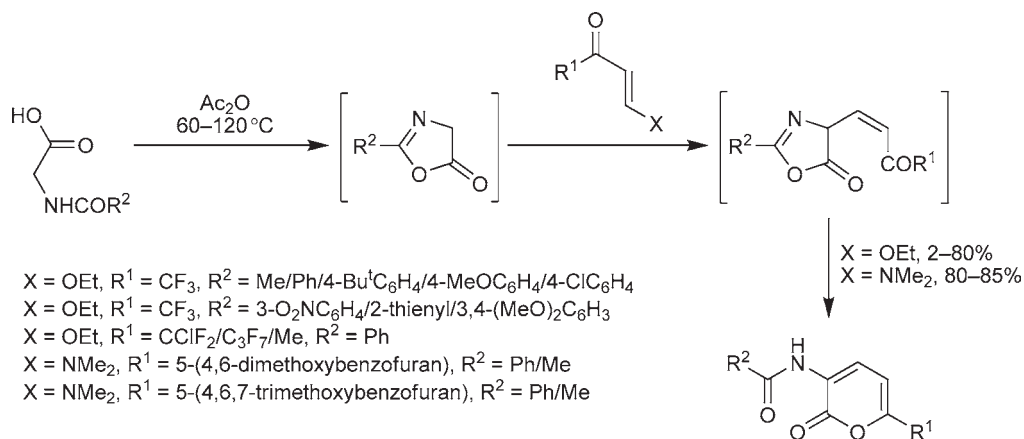
The ring closure of 1,5-keto-acids and their derivatives is a widely used strategy for the synthesis of 2*H*-pyran-2-ones <1984CHEC, 1996CHEC-II>. The 1,5-keto acid derivatives are typically formed *in situ* with concomitant ring closure to form 2*H*-pyran-2-ones. There are three main approaches to access the prerequisite 1,5-keto acid derivatives, namely; (i) reaction of an ester enolate with a 2-acyl vinyl cation equivalent, (ii) the reaction of a ketone enolate

with a 2-carboxyl vinyl cation equivalent, and (iii) 4-acylation of an ester dienolate equivalent (**Scheme 137**). These approaches are discussed in detail in the previous volumes <1984CHEC, 1996CHEC-II>.



Scheme 137

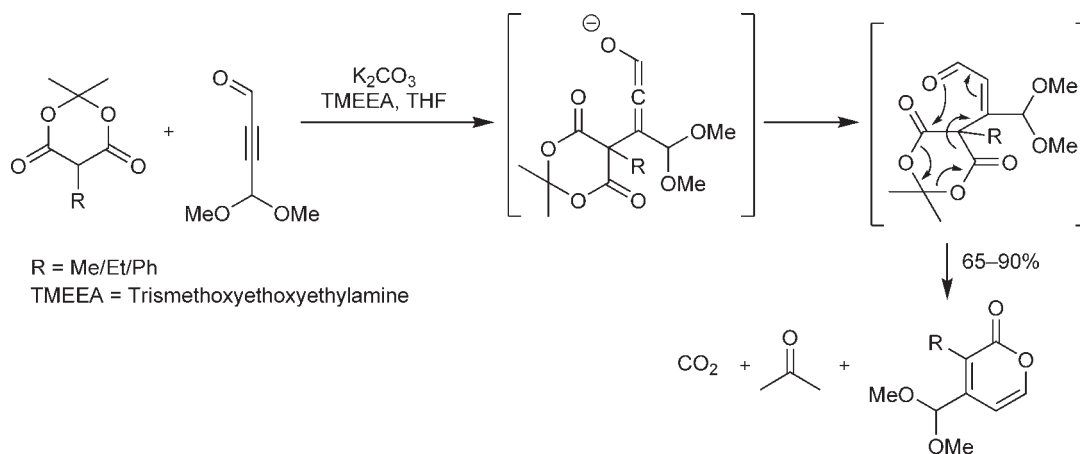
Approaches of type (i) include the Michael type addition of ester activated methylene groups to α,β -unsaturated carbonyls with subsequent cyclization to afford 2*H*-pyran-2-ones <1984CHEC, 1996CHEC-II>. In this manner, 3-acylamino-2*H*-pyran-2-ones are prepared by the reaction of β -ethoxyvinyl ketones or β -(dimethylamino)vinyl ketones with *N*-acylglycines (**Scheme 138**) <2005S1269, 2004HAC85>.



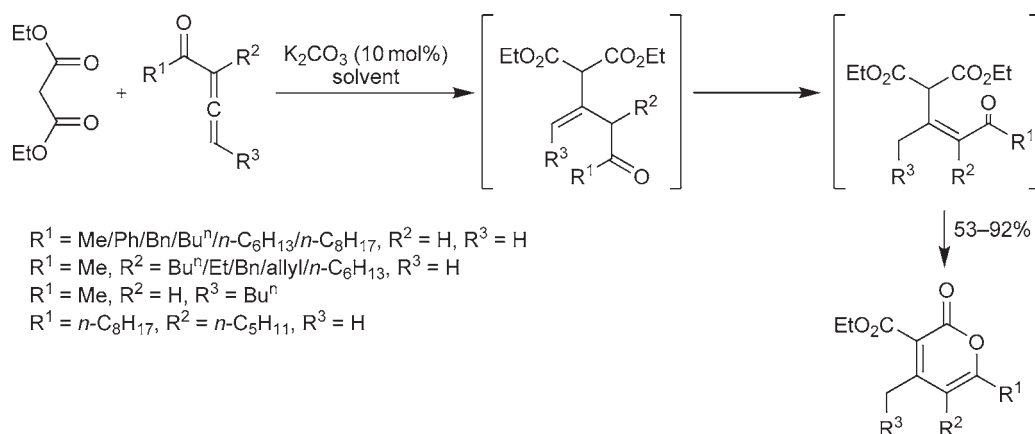
Scheme 138

Similarly, ester-activated methylene groups react with propiolaldehydes (**Scheme 139**) <2004TL9197> and 1,2-allenic ketones (**Scheme 140**) <2002OL505, 2003JOC8996> to afford 2*H*-pyran-2-ones.

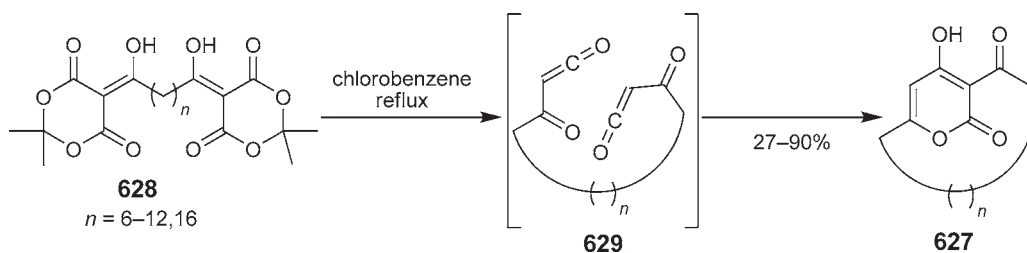
The self condensation of α -carbonyl ketenes also constitutes a type (i) synthesis of 2*H*-pyran-2-ones. Cyclophanes **627** are synthesized by the thermal decomposition of bis(4,6-dioxo-1,3-dioxanes) **628** and dimerization of the resulting bis(α -carbonyl ketenes) **629** (**Scheme 141**) <1999JA8270>. Similarly, thermal decomposition of 4,5-diarylfuran-2,3-diones **630** forms the intermediate α -carbonyl ketenes, which dimerize to afford 3,4,5-aryl-2*H*-pyran-2-ones (**Scheme 142**) <2003RJO103>.



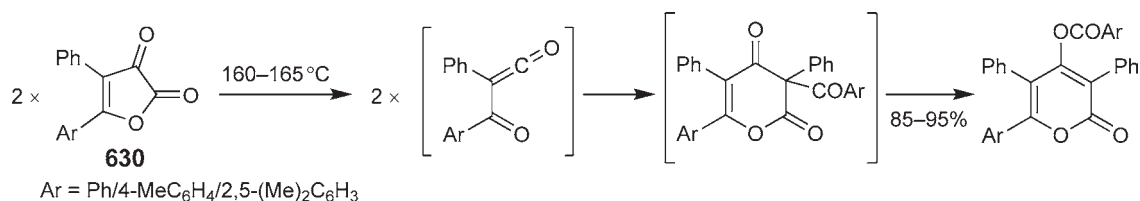
Scheme 139



Scheme 140

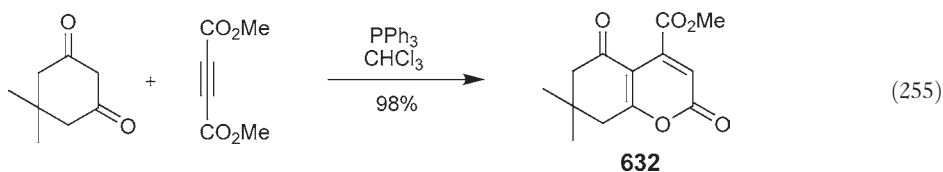
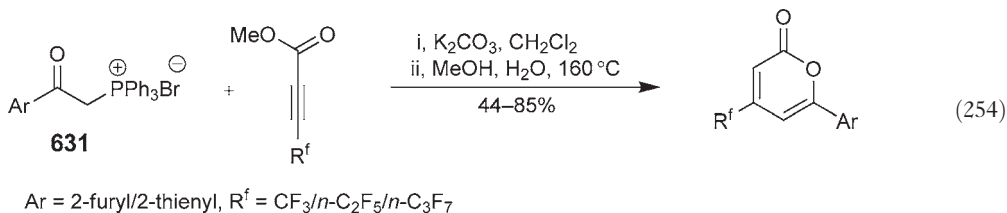


Scheme 141

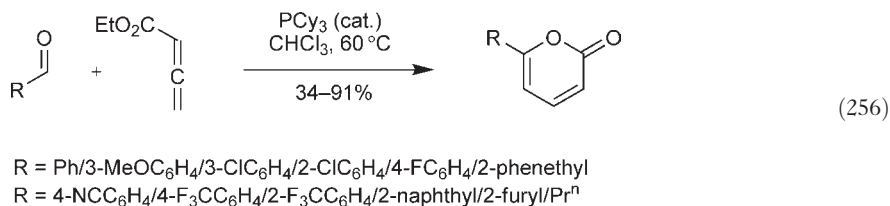


Scheme 142

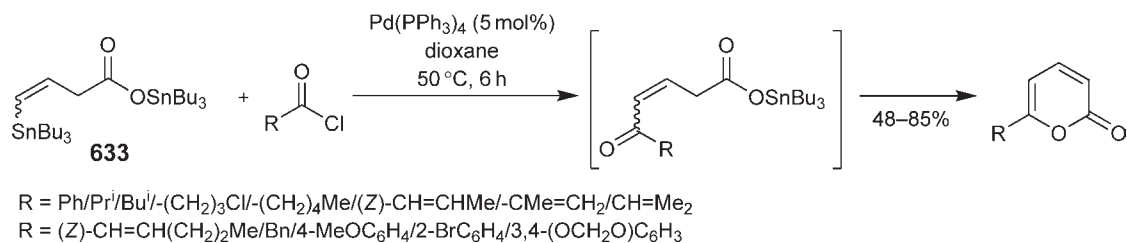
Approaches that represent a type (ii) synthesis of 2*H*-pyran-2-ones include the self-condensation of 1,3-dicarbonyl compounds, the reaction of cyclopropanones with pyridinium enolbetaines and the reaction of activated methylene groups with acetylenic esters <1984CHEC, 1996CHEC-II>. 4-Perfluoroalkyl-6-aryl-pyran-2-ones are formed by the reaction of the phosphonium salts **631** with 2-perfluoroalkynoates (Equation 254) <1999JFC(95)135, 1998JFC(91)99>. Dimedone reacts with dimethyl acetylenedicarboxylate to afford the pyran-2-one **632** in excellent yield (Equation 255) <2003PS2627>.



Tricyclohexylphosphine can catalyze the reaction of ethyl allenolate with aldehydes to afford 6-substituted 2*H*-pyran-2-ones, which represents a type (iii) synthesis of 2*H*-pyran-2-ones (Equation 256) <2005OL2977>.

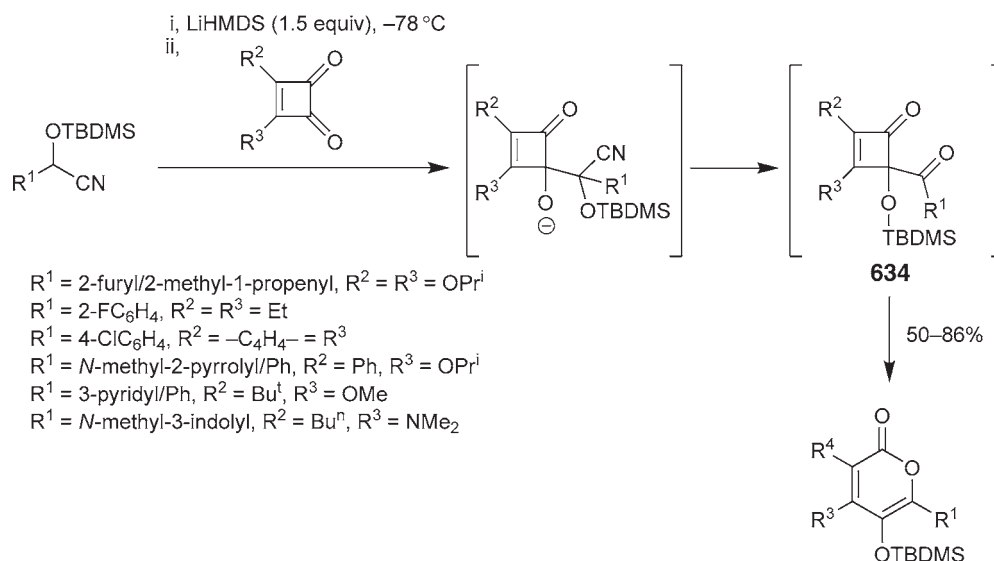


A Stille coupling of the vinyl tin reagents **633** with acyl chlorides followed by cyclization of the resulting 1,5-keto carboxylate gives 2*H*-pyran-2-ones in good yield (Scheme 143) <2002JOC3941>.



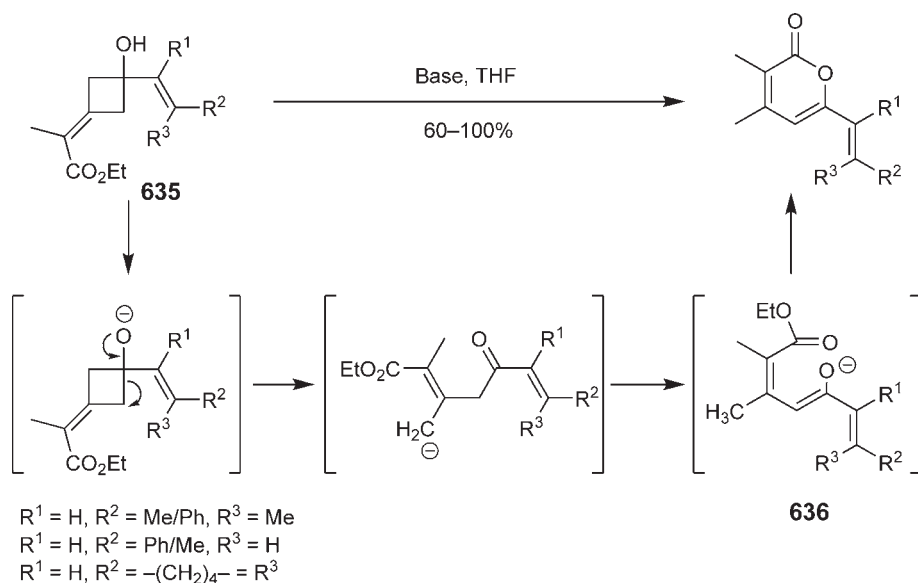
Scheme 143

Lithiated *O*-silyl cyanohydrins add to cyclobutenediones to form acyl cyclobutenone intermediates **634**, which can undergo ring expansion to provide 2*H*-pyran-2-ones (Scheme 144) <1999JOC2145>.



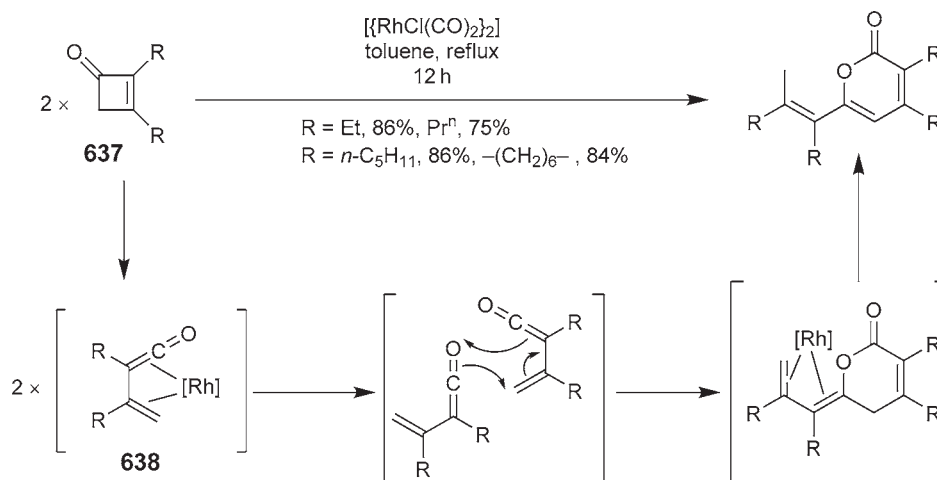
Scheme 144

2-Hydroxy cyclobutylidenes **635** undergo base promoted rearrangements to afford 2*H*-pyran-2-ones via formation and ring closure of the intermediate 1,5-keto ester **636** (Scheme 145) <2005TL8237>.

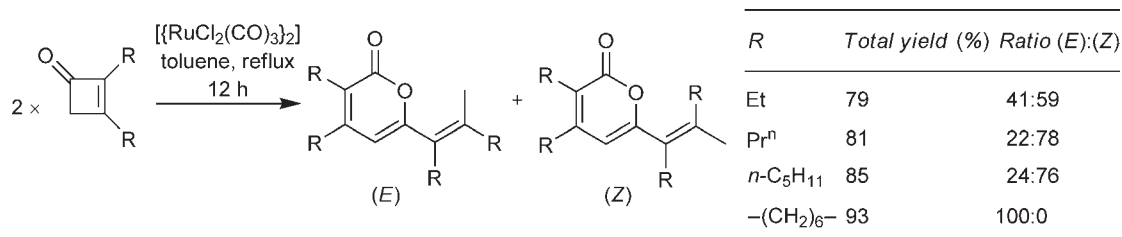


Scheme 145

A rhodium-catalyzed ring opening of the cyclobutenones **637** forms the η^4 -vinylketene intermediates **638**, which can dimerize to afford (*E*)-6-vinyl-2*H*-pyran-2-ones in excellent yield (Scheme 146) <2004AGE5369>. A ruthenium-mediated ring opening and dimerization of cyclobutenones forms a mixture of (*E*)- and (*Z*)-6-vinyl-2*H*-pyran-2-ones in high yield (Equation 257) <2004AGE5369>.

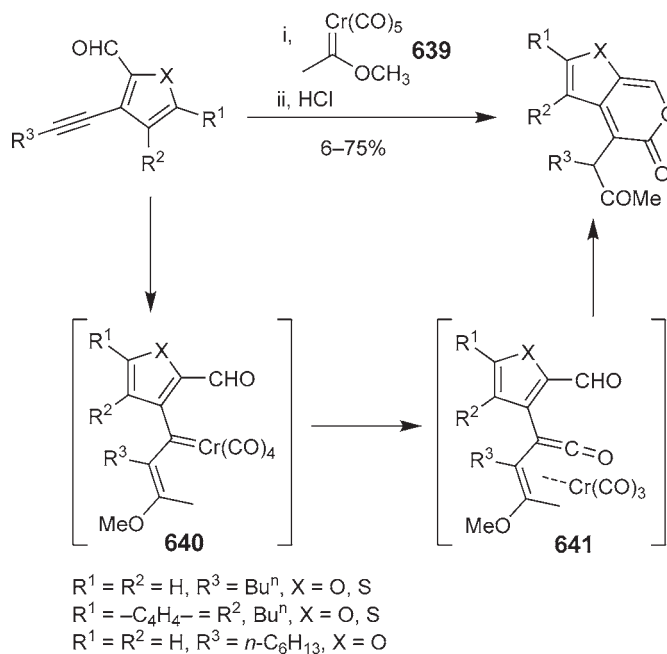


Scheme 146

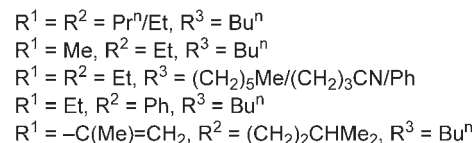


(257)

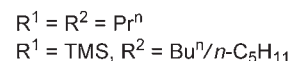
Fischer carbene complexes **639** can be coupled with 3-alkynyl-2-heteroaromatic carbaldehydes to form initially the alkenylcarbene complexes **640**, which undergo CO insertion to give the ketene intermediates **641**, which upon ring closure affords heteroaryl-fused 2*H*-pyran-2-ones (Scheme 147) <2001TL777, 2002JOC4177>.



Scheme 147



Scheme 148



reaction are unclear [<2003TL7633>](#).

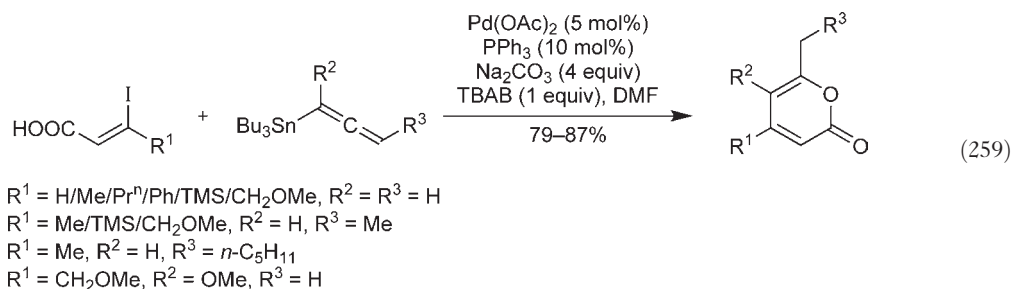


Scheme 149

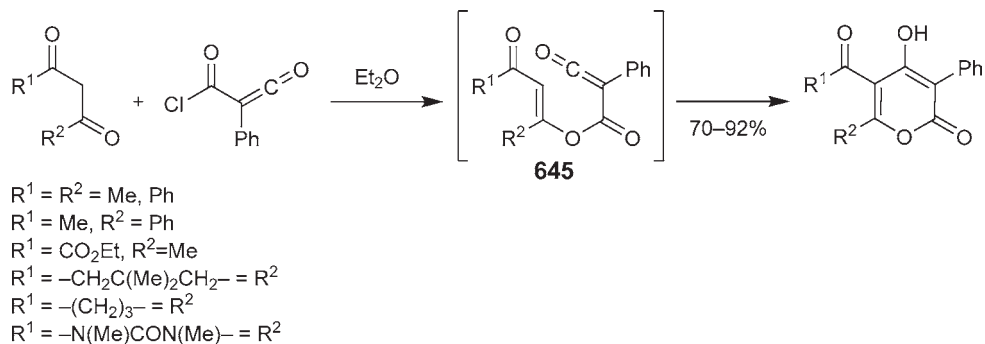
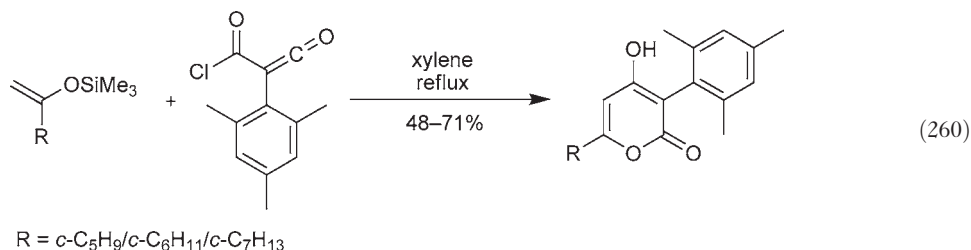
Table 30 Products of the Stille coupling of (*Z*)-tributylstannyl 3-iodoacrylates and alkynyltin reagents (Scheme 149)

	Yield (%) 644	Yield (%) 643
$R^1 = \text{H}, R^2 = \text{Ph}$	0	72
$R^1 = \text{Me}, R^2 = \text{Ph}$	0	68
$R^1 = \text{Me}, R^2 = \text{CH}_2\text{OMe}$	0	52
$R^1 = \text{Me}, R^2 = (\text{CH}_2)\text{OTMS}$	62	0
$R^1 = \text{Me}, R^2 = n\text{-C}_5\text{H}_{11}$	50	0
$R^1 = \text{Me}, R^2 = n\text{-C}_6\text{H}_{13}$	49	0

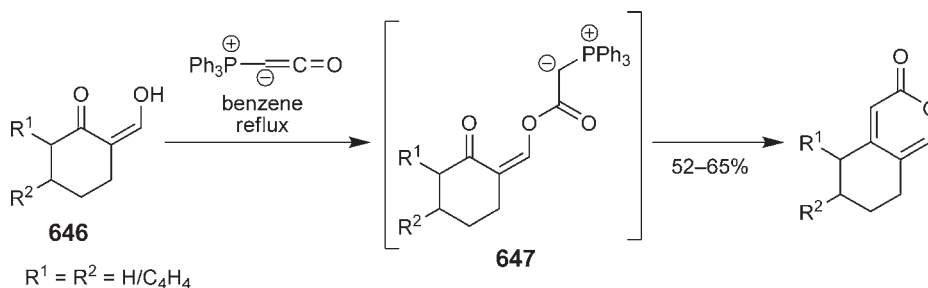
Tributylstannyl allenes react with (*Z*)- β -iodoacrylic acids in the presence of a palladium catalyst to yield 2*H*-pyran-2-ones (Equation 259) <2000CC1987, 2005JOC6669>.



1,3-Diketones and α -(chlorocarbonyl)phenyl ketene react to provide the intermediate ketene **645**, which can cyclize to afford 2*H*-pyran-2-ones in high yield (Scheme 150) <2004T5931>. Similarly, silyl enol ethers react with α -(chlorocarbonyl)mesitylketene to afford 2*H*-pyran-2-ones (Equation 260) <2001T4133>.

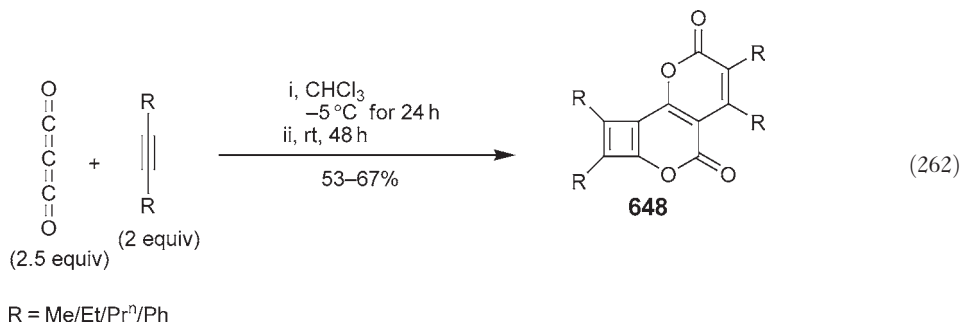
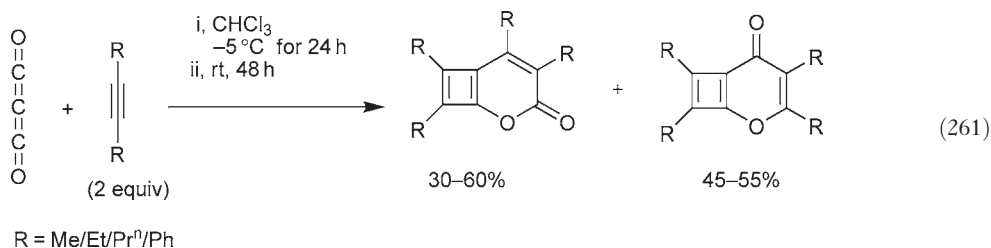
**Scheme 150**

Treatment of α -hydroxymethylene ketones **646** with (triphenylphosphoranylidene)ethenone forms the intermediate ylide **647**, which can undergo an intramolecular Wittig reaction to afford 2*H*-pyran-2-ones (Scheme 151) <1998T2161>.

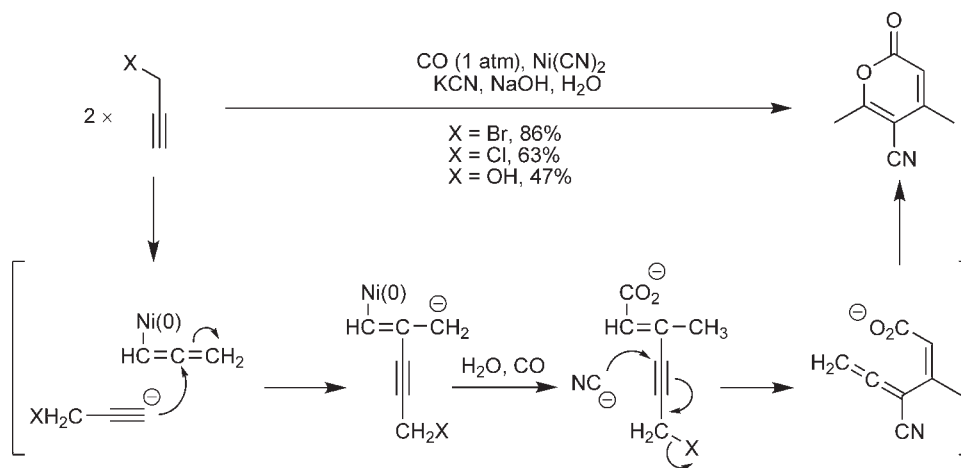


Scheme 151

The reaction of carbonsuboxide with 2 equiv of an internal alkyne affords a mixture of pyran-2-ones and pyran-4-ones (Equation 261). 3,3,7,8-Tetraalkyl-2*H*-cyclobuta[*b*]pyrano[2,3-*d*]pyran-2,5-diones **648** can be obtained from the reaction of internal alkynes with an excess of carbonsuboxide (Equation 262) <2003JHC321>.

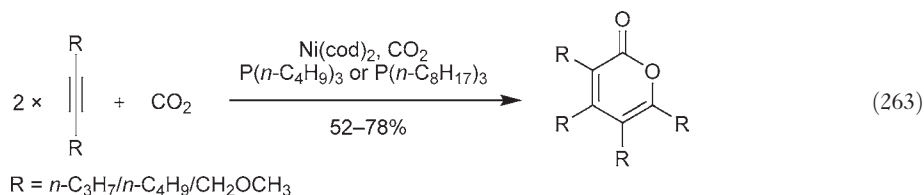


The reaction of propargylic halides or alcohols with carbon monoxide in the presence of $\text{Ni}(\text{CN})_2$ affords 4,6-dimethyl-5-cyano-pyran-2-ones in good yield (Scheme 152) <2000J(P1)1493>.

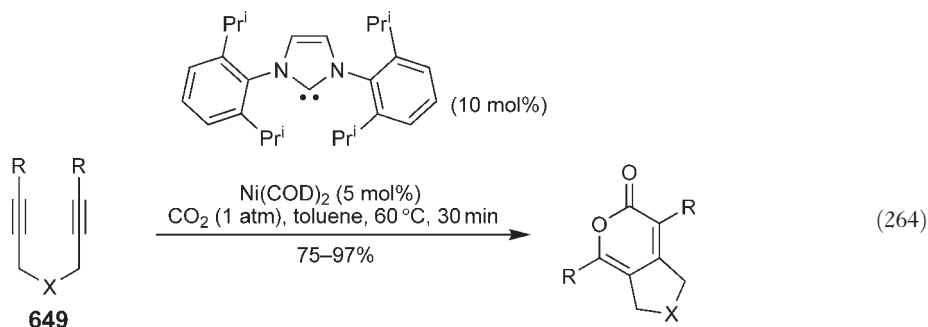


Scheme 152

2*H*-Pyrans-2-ones are accessed in good yield by a nickel-catalyzed reaction of internal alkynes with carbon dioxide under solvent free conditions (Equation 263) <2005SL2141>.



A nickel(0)-catalyzed cycloaddition of carbon dioxide and symmetrical tethered diynes **649** affords cycloalkyl-fused 2*H*-pyran-2-ones in high yield (Equation 264) <2002JA15188>. The nickel(0)-catalyzed cycloaddition of carbon dioxide and unsymmetrical tethered diynes **650** leads to the formation of two regioisomeric 2*H*-pyran-2-ones **651**, **652**; the major regioisomeric product **651** features the larger alkyne group at C-3 (Equation 265, Table 31) <2004T7431>.



$\text{X} = \text{C}(\text{CO}_2\text{Me})_2$, $\text{R} = \text{Me}/\text{Et}/\text{Pr}^i$

$\text{X} = \text{C}(\text{CH}_2\text{OBn})_2/\text{C}(\text{CH}_2\text{OTBS})_2/\text{CHCO}_2\text{Me}$, $\text{R} = \text{Me}$

$\text{X} = -\text{CH}_2\text{CH}_2-/-\text{C}(\text{CO}_2\text{Et})_2\text{C}(\text{CO}_2\text{Et})_2-$, $\text{R} = \text{Me}$

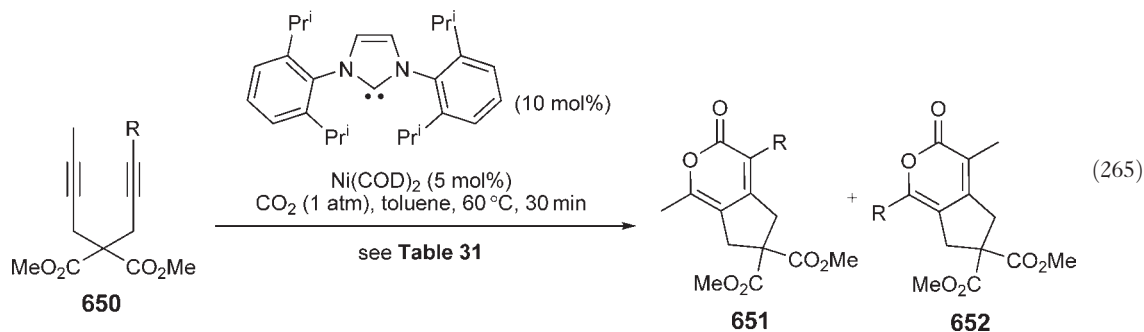
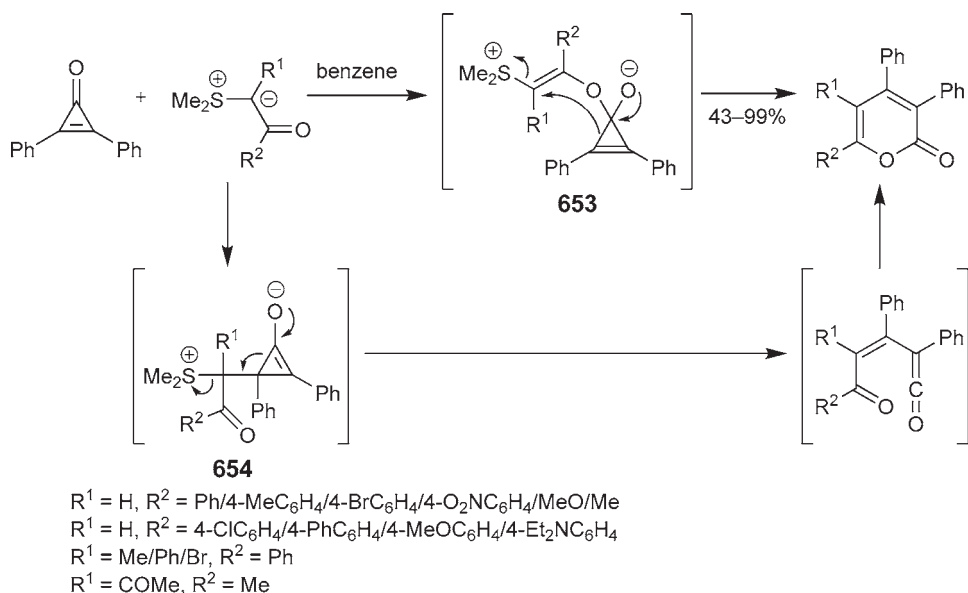


Table 31 Ratio of products **651:652** formed during the nickel(0)-catalyzed cycloaddition of carbon dioxide and unsymmetrical tethered diynes **650** (Equation 265)

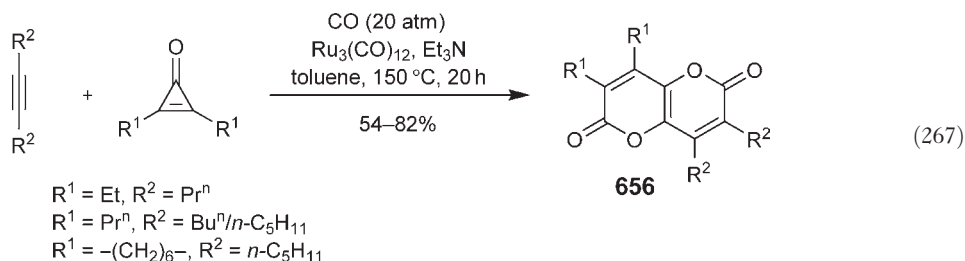
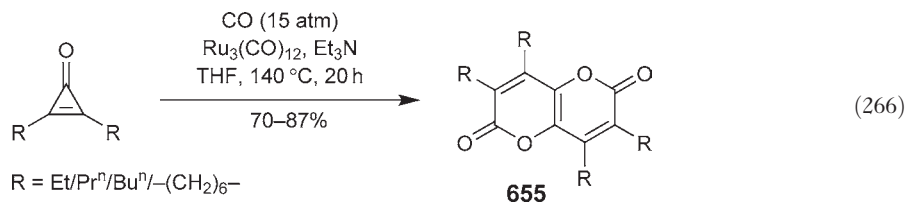
Ratio of products 651:652	
$\text{R} = \text{Et}$	62:38
$\text{R} = \text{Pr}^i$	80:20
$\text{R} = \text{Bu}^t$	100:0

Diphenylcyclopropanone reacts with a sulfonium ylide via either intermediate **653** or **654** to form 2*H*-pyran-2-ones in high yield (Scheme 153) <1971T3085, 2001BCJ1567>.



Scheme 153

Cyclopropenones and carbon monoxide react in the presence of $Ru_3(CO)_{12}$ to form tetrasubstituted pyranopyr-andiones **655** in high yield (Equation 266) <2002JA6824>. Unsymmetrical tetrasubstituted pyranopyr-andiones **656** can be accessed by the cross-carbonylation of cyclopropenones and internal alkynes in the presence of a ruthenium catalyst (Equation 267) <2002JA6824>.

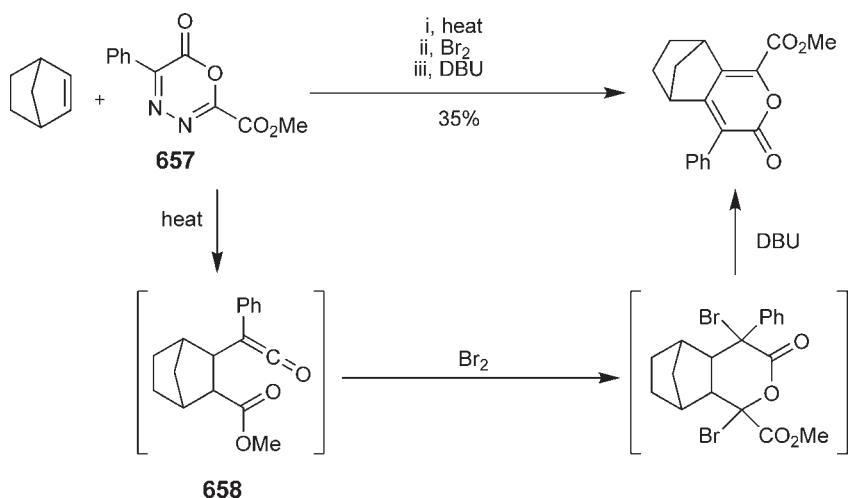


Methyl 6-oxo-5-phenyl-6*H*-1,3,4-oxadiazine-2-carboxylate **657** reacts with alkenes to yield 2*H*-pyran-2-ones. The reaction proceeds *via* cycloaddition of **657** to the alkene to form the γ -oxoketene intermediate **658**; addition of bromine and bis-elimination of HBr then affords 2*H*-pyran-2-ones (Scheme 154 and 155) <1998J(P1)2031>.

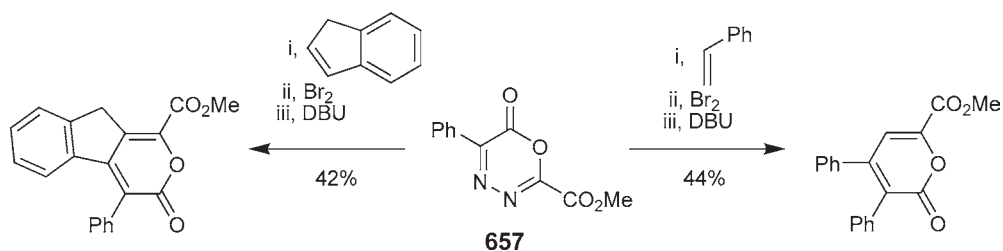
7.08.13.3 From Other Heterocycles

7.08.13.3.1 From furans

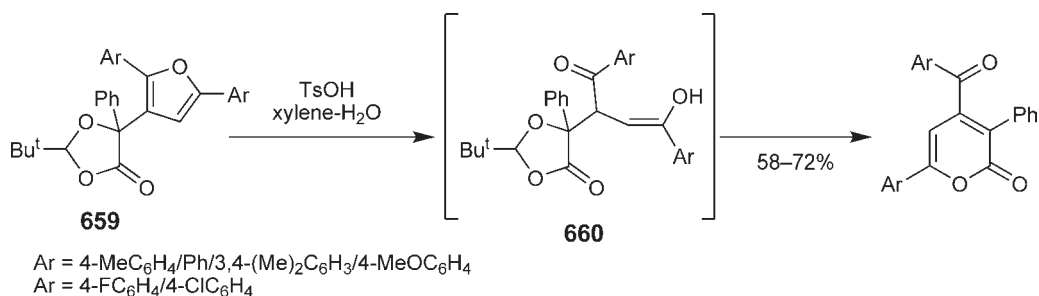
Acid-catalyzed ring opening of the furans **659** forms the intermediate **660**, which recyclize to afford 4-aryyl-2*H*-pyran-2-ones in good yield (Scheme 156) <2004TL8583>.



Scheme 154



Scheme 155



Scheme 156

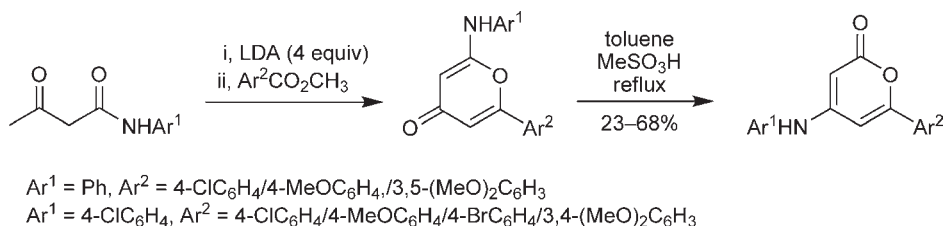
7.08.13.4 From a Preformed Heterocyclic Ring

7.08.13.4.1 From pyran-4-ones

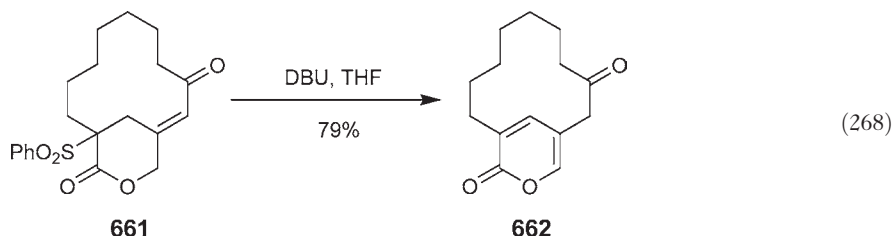
Trilithiated acetoacetanilides can undergo a Claisen-type condensation with benzoate esters to form initially pyran-4-ones, which can then undergo complex acid promoted rearrangements to afford 2H-pyran-2-ones (Scheme 157) <2004CJC659>.

7.08.13.4.2 From tetrahydropyranones

Elimination of the sulfone from the tetrahydropyran-2-one **661** occurs with a concomitant shift of the exocyclic methylene bond to afford the *meta*-bridged 2H-pyran-2-one **662** (Equation 268) <1999JOC8281>. The addition of bromine to dihydropyranones and elimination of 2 equiv of HBr yields 2H-pyran-2-ones <1984CHEC, 1996CHEC-II>.



Scheme 157



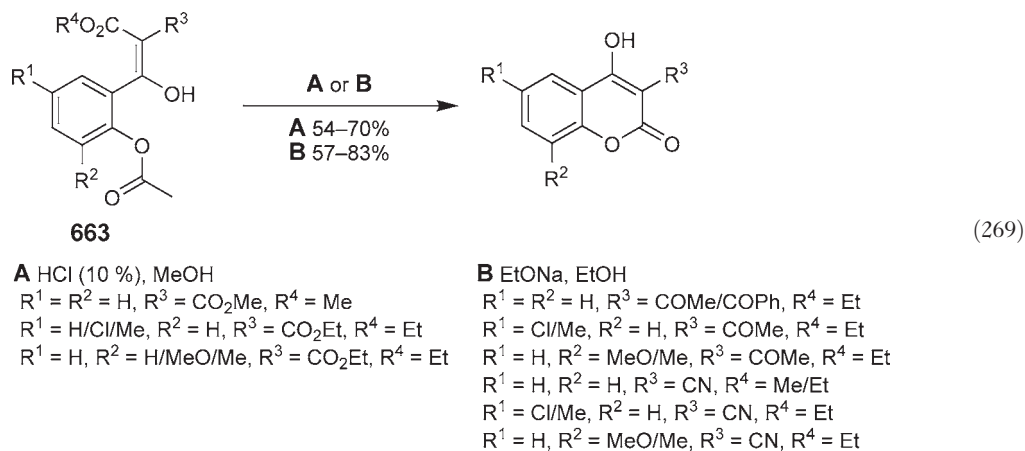
7.08.14 Coumarins (2*H*-Benzopyran-2-ones)

A review detailing the structures and isolation of naturally occurring coumarins is available [<1997NPR465>](#).

7.08.14.1 Formation of One Bond

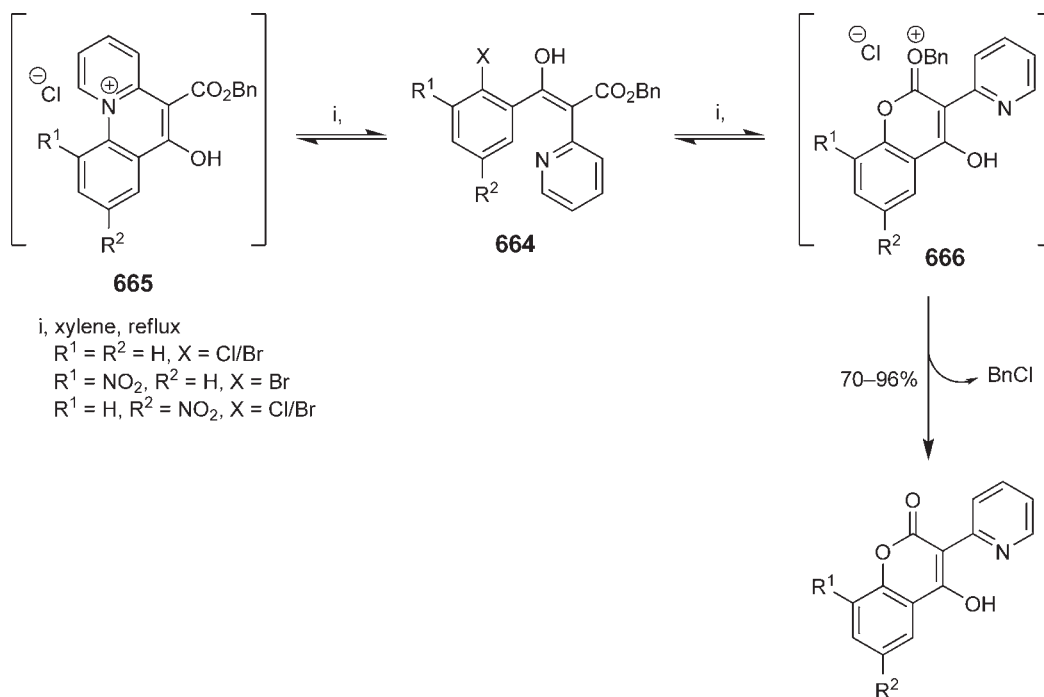
7.08.14.1.1 Adjacent to the heteroatom

The intramolecular lactonization of 3-(2-acetoxyphenyl)-3-hydroxyacrylic acid derivatives **663** to afford 4-hydroxy-coumarins can be achieved under either acidic or basic conditions in good yield (Equation 269) [<2004S1775>](#).

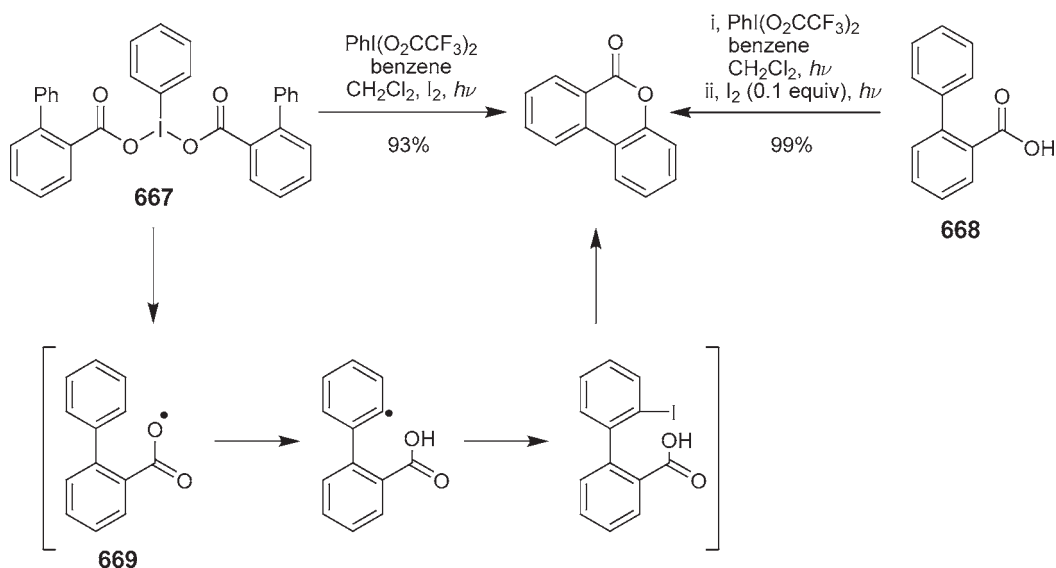


(*Z*)-Benzyl-3-(2-halophenyl)-3-hydroxy-2-(pyridin-2-yl)acrylates **664** can undergo competitive intramolecular *ipso*-substitutions to form the intermediates **665** and **666**. The irreversible elimination of benzyl chloride from intermediate **666** affords 4-hydroxy-3-(2'-pyridyl)coumarins in high yield (Scheme 158) [<2001CC639>](#).

[Bis(*ortho*-phenylphenylcarbonyloxy)iodo]benzene **667** and biphenyl-2-carboxylic acid **668** can be converted into 6*H*-benzo[*c*]chromen-6-one in excellent yield via generation and cyclization of their corresponding carbonyloxy radicals **669** (Scheme 159) [<1997J\(P1\)787, 1999J\(P1\)1713>](#).



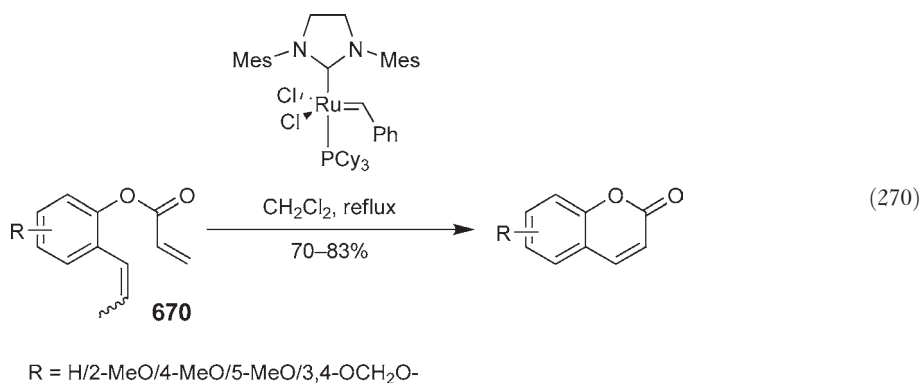
Scheme 158



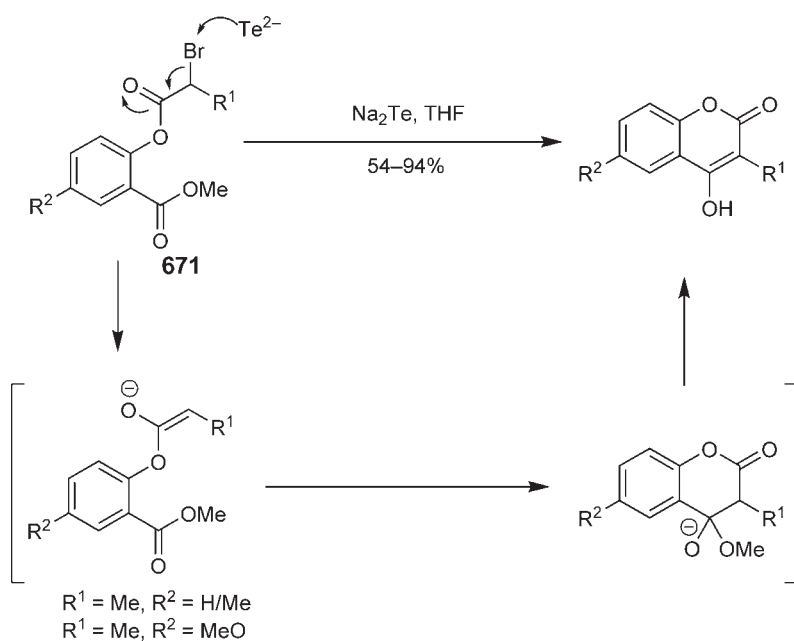
Scheme 159

7.08.14.1.2 γ to the heteroatom

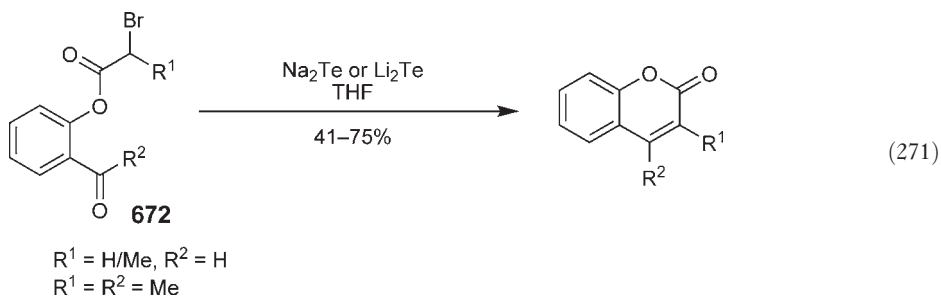
Grubbs' second generation catalyst can effectively catalyze the RCM of 2-vinylphenyl acrylates **670** to afford coumarins in high yields (Equation 270) <2003TL4199>.



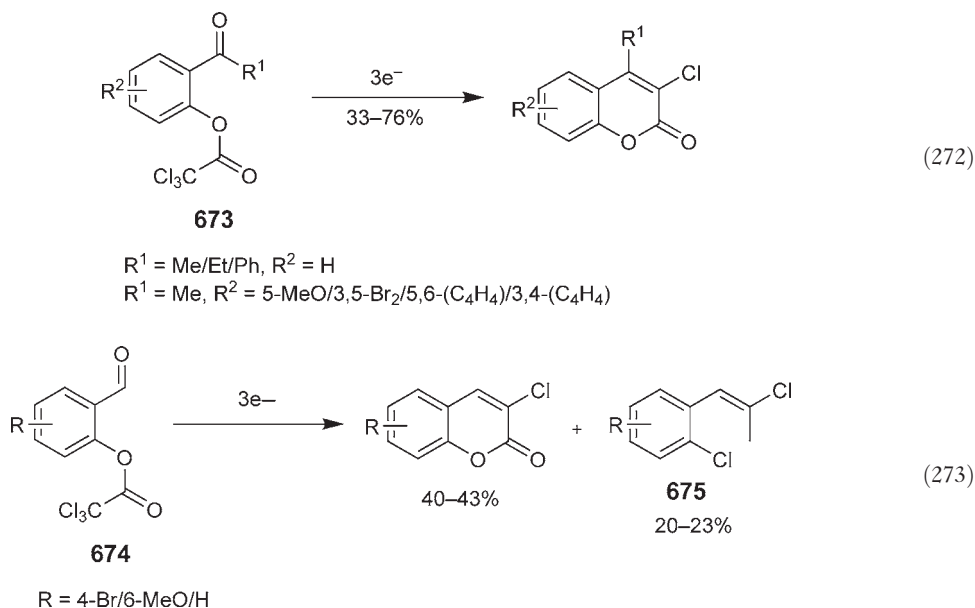
A tellurium-triggered cyclization of methyl 2-(2-bromoacetoxy)benzoates **671** affords 4-hydroxy coumarins in good yield (Scheme 160) <2005JOC4682>. Similarly, the tellurium-triggered cyclization of 2-formyl and 2-acetyl-phenyl 2-bromoacetates **672** provides coumarins (Equation 271) <2005JOC4682>.



Scheme 160

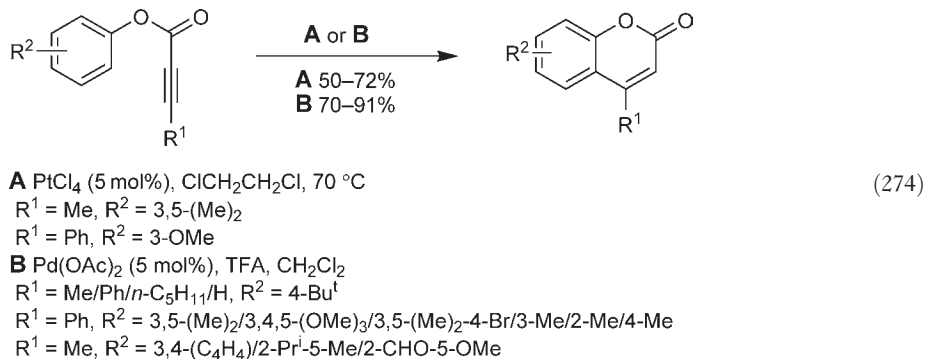


Cathodic reduction of the trichloroacetates **673** affords 3-chloro-coumarins in moderate yield (Equation 272). When salicylaldehyde derivatives **674** are reduced a mixture of 3-chloro-coumarins and (*E*)-1-chloro-2-(2-chloroprop-1-enyl)benzenes **675** are formed (Equation 273) <2003T9161, 1999JEC201>.



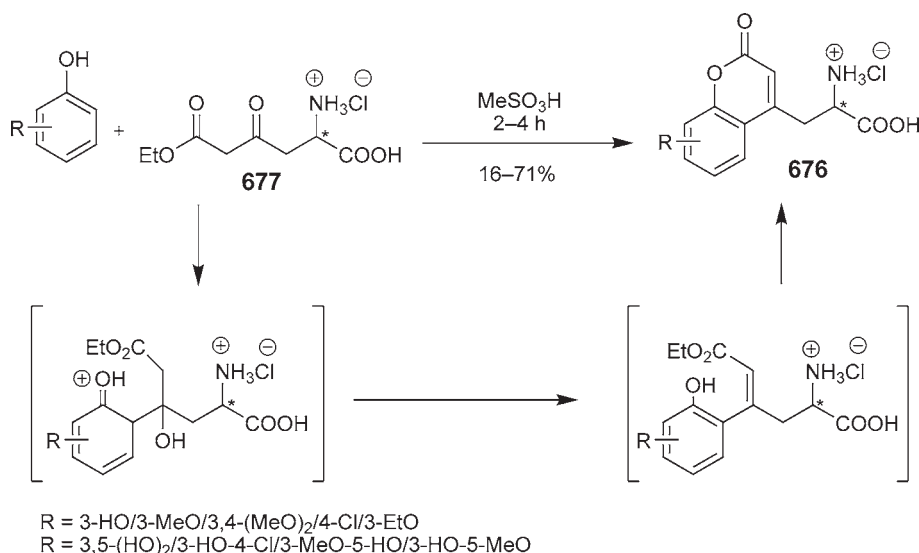
7.08.14.1.3 δ to the heteroatom

The intramolecular hydroarylation of aryl alkynoates to yield 4-substituted coumarins can be catalyzed by palladium(II) or platinum(IV) (Equation 274) <2000JOC7516, 2003T8859>. The intramolecular hydroarylation of aryl alkynoates can also be carried out in ionic liquids catalyzed by $\text{Hf}(\text{OTf})_4$ <2004AGE6183> and under solvent free conditions catalyzed by $\text{AuCl}_3\text{-3AgOTf}$ <2004JOC3669>.



7.08.14.2 Formation of More than One Bond

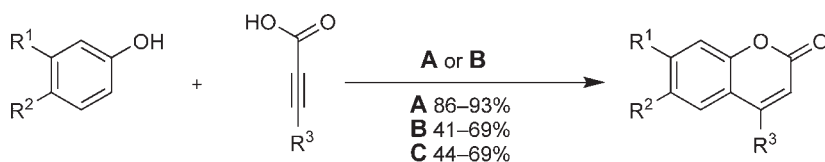
Coumarins are readily accessed via the Pechmann condensation of phenols and 1,3-dicarbonyl compounds, which proceeds via electrophilic aromatic substitution of the phenol followed by dehydration and lactonization <1984CHEC, 1996CHEC-II>. In this manner, the amino acid bearing coumarins **676** are formed by a Pechmann condensation of phenols and 2-amino-6-ethoxy-4,6-dioxohexanoic acid **677** (Scheme 161) <2004AGE3432>. The popularity of this approach results from the wide range of readily available substrates (phenols and 1,3-dicarbonyl compounds). However, a major drawback is that electron withdrawing groups on the phenolic component dramatically reduces the yield of a Pechmann reaction.



Scheme 161

In recent years there has been an abundance of improved and environmentally benign procedures reported for the formation of coumarins using the Pechmann reaction, which can be carried out in refluxing toluene catalyzed by zinc and iodine <2002TL8583> or W/ZrO₂ <2001SC3603>. Solvent-free conditions for the Pechmann reaction can be catalyzed by *p*-TsOH <2001CL110>, titanium(IV) chloride <2005TL3501>, bismuth(III) chloride <2005S1231>, Wells–Dawson heteropolyacid (H₆P₂W₁₈O₆₂·24H₂O) <2004TL8935>, indium(III) chloride <2002TL9195>, samarium(III) nitrate hexahydrate <2004TL7999>, sulfamic acid (H₂NSO₃H) <2004SL1909>, zirconium(IV) chloride <2004SC3997> chloroaluminate acidic ionic liquids <2001TL9285> and nonchloroaluminate acidic ionic liquids <2005ASC512>. The Pechmann reaction can also be carried out under microwave irradiation catalyzed by P₂O₅/3 Å molecular sieves <2002PS2835>, ZnCl₂/Al₂O₃ <2003PS143>, cation-exchange resins <1999SL608> and graphite/montmorillonite K10 clay <2001TL2791>.

A popular variant of the Pechmann reaction involves the use of propynoic acids as a 1,3-dicarbonyl equivalent. Cation-exchange resins under microwave irradiation <1999SL608>, PtCl₂–AgOTf <2005TL3823> and Pd(OAc)₂ <2000JOC7516, 2004S1466> can effectively promote the reaction of phenols with propynoic acids to afford coumarins (Equation 275).



A PtCl₂ (0.05 mol%), AgOTf (0.10 mol%), TFA

R¹ = OMe, R² = R³ = H

R¹ = –C₄H₄–, R², R³ = *n*-C₅H₁₁

B Dowex 50X2-200, 15 min, MW, 120 °C

R¹ = OH, H, R² = R³ = H

C Pd(OAc)₂ (1 mol%), TFA, CH₂Cl₂

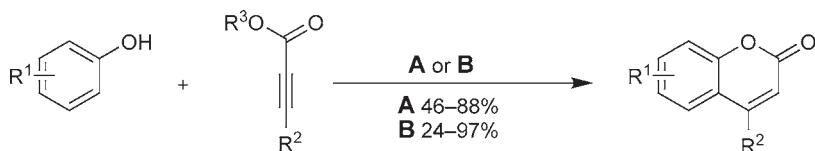
R¹ = H, R² = Bu^t, R³ = Ph/Me

R¹ = OMe, R² = H, R³ = Ph

R¹ = R² = Me/C₄H₄/–OCH₂O–, R³ = Ph

(275)

Similarly, propynoic esters react with phenols in the presence of a palladium catalyst to afford coumarins in moderate to high yield (Equation 276) <1996JA6305, 2000JOC7516, 2002CL380, 2003BCJ1889, 2003JA4518>.



A $\text{Pd}_2(\text{dba})_3\text{-CHCl}_3$ (2.5 mol%), NaOAc (10 mol%), HCO_2H

$\text{R}^1 = 3,5\text{-(MeO)}_2$, $\text{R}^2 = \text{H/Ph/Me}$, $\text{R}^3 = \text{Et}$

$\text{R}^1 = 3\text{-MeO/3-MeO-5-Me/3,4,5-(MeO)}_3/3\text{-OCH}_2\text{O-4/3,4-(C}_4\text{H}_4\text{)}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Et}$

$\text{R}^1 = 3,5\text{-(HO)}_2$, $\text{R}^2 = \text{H/Me}$, $\text{R}^3 = \text{Et}$

$\text{R}^1 = 3,5\text{-(MeO)}_2$, $\text{R}^2 = (\text{CH}_2)_2\text{OCO}_2\text{Et}/(\text{CH}_2)_3\text{CN/DPMS/CH}_2\text{OH}/(\text{CH}_2)_2\text{CO}_2\text{Bu}^t$, $\text{R}^3 = \text{Et}$

B $\text{Pd}(\text{OAc})_2$ (1 mol%), TFA, CH_2Cl_2

$\text{R}^1 = 4\text{-Bu}^t/4\text{-MeO/3-MeO}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Et}$

$\text{R}^1 = 4\text{-Bu}^t/3\text{-OCH}_2\text{O-4/3-MeO/3,5-(MeO)}_2/3,4\text{-(C}_4\text{H}_4\text{)}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{Et}$

$\text{R}^1 = 3,4\text{-(Me)}_2/3,5\text{-(Me)}_2/2\text{-MeO}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{Et}$

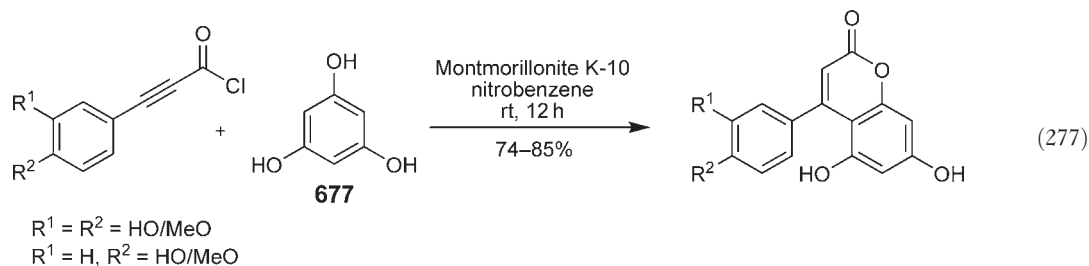
$\text{R}^1 = 3,5\text{-(MeO)}_2$, $\text{R}^2 = \text{H/Me/CO}_2\text{Et}$, $\text{R}^3 = \text{Et}$

$\text{R}^1 = 3,5\text{-(MeO)}_2$, $\text{R}^2 = n\text{-C}_5\text{H}_{11}$, $\text{R}^3 = \text{Me}$

(276)

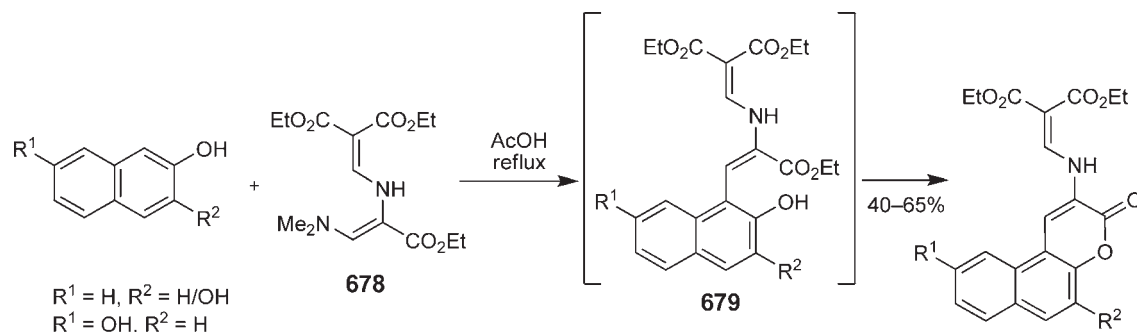
Silver(I) tetrafluoroborate and indium(III) chloride can also promote the reaction of propynoic esters with phenols to afford coumarins. However, substitution of the alkyne is not tolerated for the silver(I) promoted reaction <2003JA4518, 2004SC1909>.

The reaction of aryl propynoic acid chlorides and phloroglucinol **677** to form 4-aryl-coumarins can be catalyzed by montmorillonite-K10 clay in high yield (Equation 277) <2001S2247>.

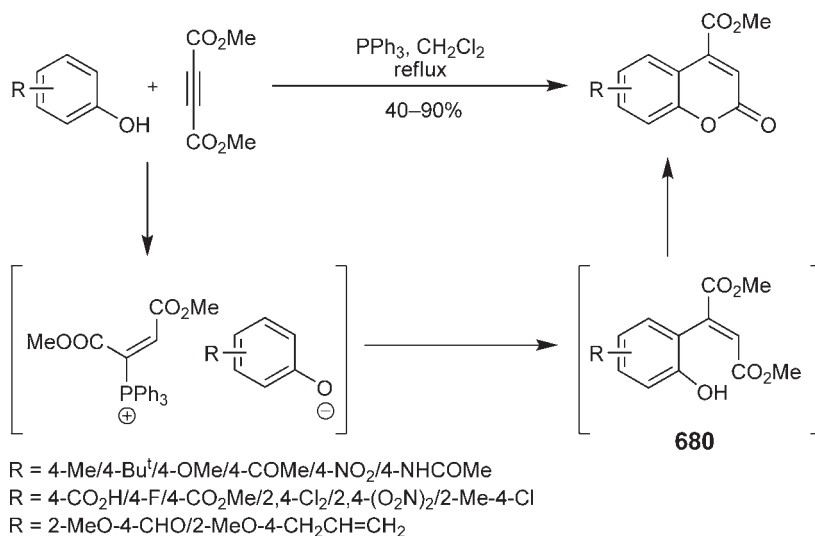


(277)

(*E*)-Ethyl 3-(dimethylamino)acrylate derivatives **678** can act as 1,3-dicarbonyl equivalents in a Pechmann reaction. (*E*)-Ethyl 3-(dimethylamino)acrylate derivatives **678** react with naphthols via electrophilic aromatic substitution and elimination of dimethylamine to form the cinnamate intermediates **679**, which can cyclize to afford coumarins (Scheme 162) <1997H(45)555>. A related approach is the triphenylphosphine mediated reaction of dimethyl acetylenedicarboxylate with phenols to afford 4-carboxycoumarins. The reaction proceeds via electrophilic attack of the vinyl triphenyl phosphonium intermediate onto the aromatic ring followed by elimination of triphenylphosphine to form the cinnamate intermediate **680**. Intramolecular lactonization then affords 4-carboxy-coumarins (Scheme 163) <1998TL2391, 2004PS2163, 2002PS1147>. This reaction can be carried out under microwave irradiation in good yield <2002PS2827, 2004PS529>.

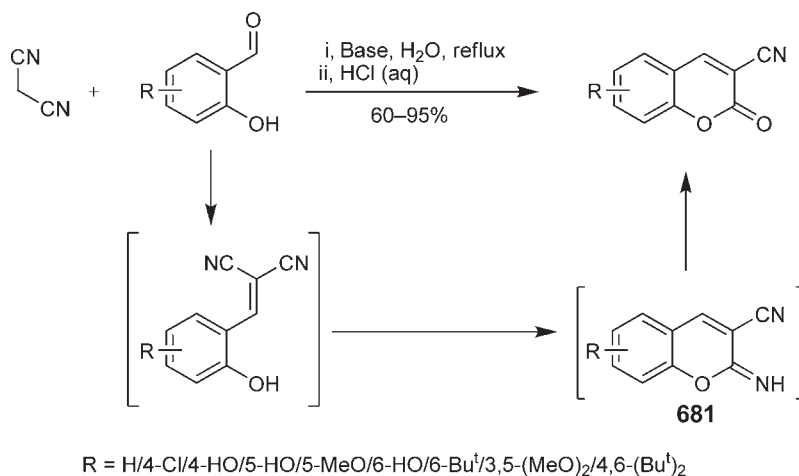


Scheme 162



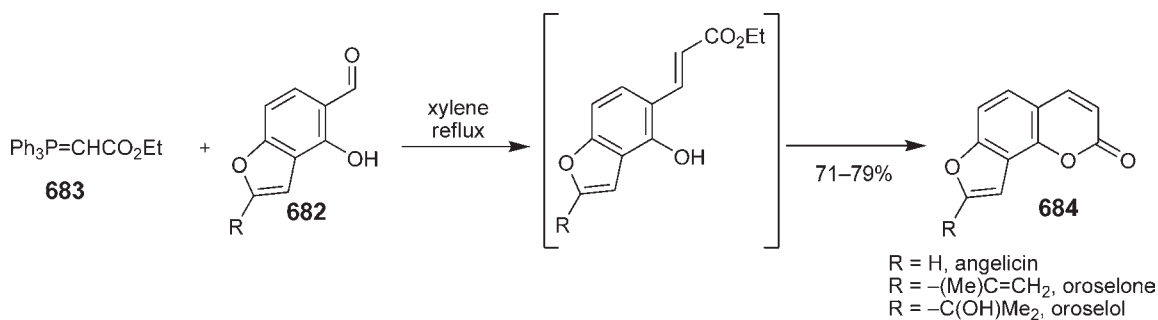
Scheme 163

Knoevenagel methodology is also extensively used for the synthesis of coumarins, from salicylaldehydes and activated methylene groups [<1984CHEC, 1996CHEC-II>](#). Improved and environmentally benign procedures for this reaction are reported, and include an adaptation to work in aqueous media [<2003SC3299, 2001GC173, 2000GC245, 1999JOC1033>](#) and the reaction of polymer bound ethyl malonate [<1998TL6087>](#). Calcined Mg–Al hydrotalcite [<1999GC163>](#) and Lewis acidic ionic liquids [<2002TL1127>](#) can promote the Knoevenagel condensation to afford coumarins in high yield. Under solvent free conditions, piperidine [<2001CL110>](#), MgO/piperidine [<2002PS2555>](#) and neutral kaolinitic clays under microwave irradiation [<1999GC243>](#) can catalyze the synthesis of coumarins from salicylaldehydes and 1,3-dicarbonyl compounds. Generally, the Knoevenagel condensation of salicylaldehydes with nitrile-activated methylene groups results in the formation of 2-amino-4*H*-chromenes. Salicylaldehydes react with malononitrile to form the intermediate iminocoumarin **681**, which can be hydrolyzed to afford 3-cyanocoumarins in excellent yield ([Scheme 164](#)) [<2003S2331>](#).



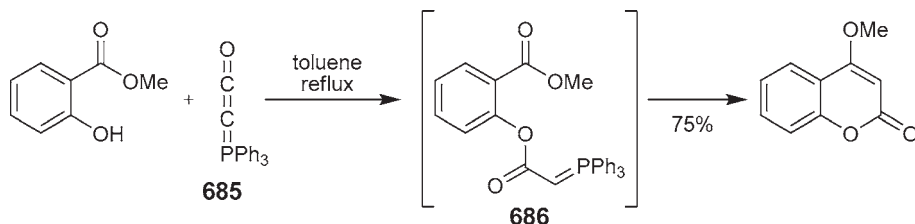
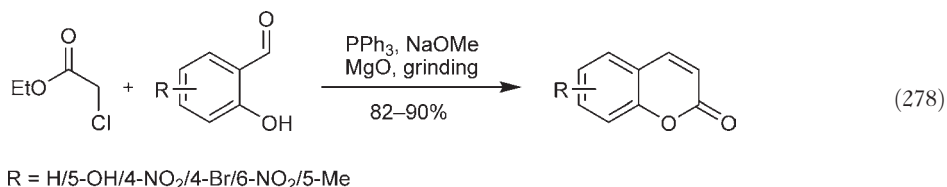
Scheme 164

4-Hydroxybenzofuran-5-carbaldehydes **682** can react with carbethoxymethylenetriphenyl-phosphorane **683** to afford biologically active furanocoumarins **684** in high yield. The reaction proceeds via Wittig reaction of the phosphorane **683** with the aromatic aldehyde to form the intermediate cinnamate, which then undergoes isomerization of the double bond and lactonization to furnish the desired furanocoumarins **684** ([Scheme 165](#)) [<1995T3087>](#).



Scheme 165

Wittig reagents, which are formed *in situ* from ethyl 2-chloroacetate and triphenylphosphine, react with salicylaldehydes under solvent-free conditions to afford coumarins in high yield (Equation 278) <2003PS501>. Methyl 2-hydroxybenzoate reacts with ketenylidene(triphenyl)phosphorane **685** to yield 4-methoxy coumarin, via formation of the ylide intermediate **686** (Scheme 166) <1996J(P1)2799>.



Scheme 166

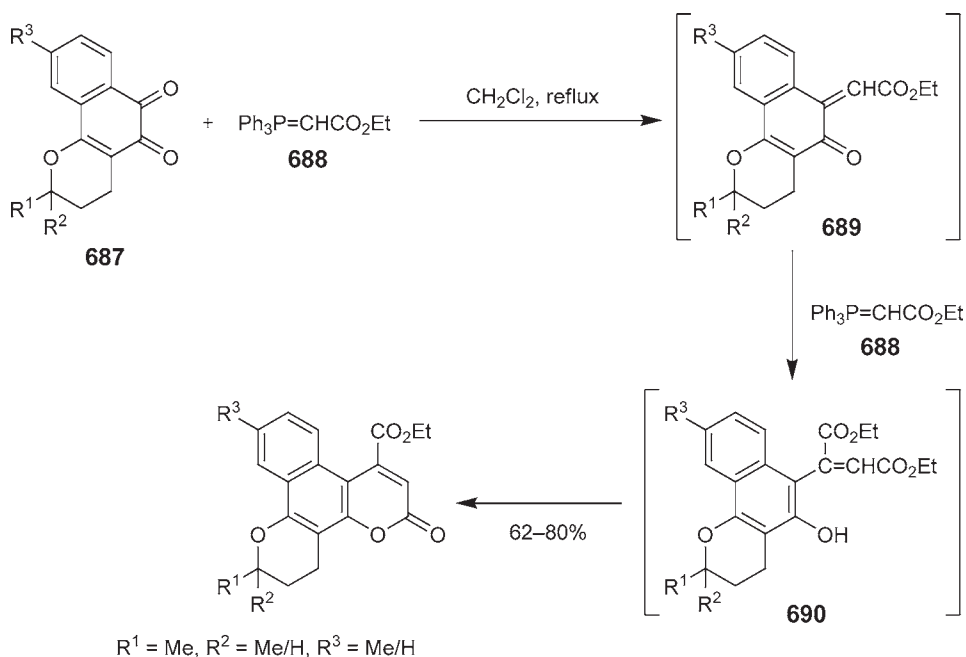
Treatment of the *ortho*-quinones **687** with 2 equiv of carbethoxymethylenetriphenylphosphorane **688** affords coumarins in good yield. The reaction proceeds via Wittig olefination of the C-6 carbonyl to form the intermediate *ortho*-quinone methanides **689**. Michael addition of a second equivalent of the phosphorane **688** followed by a Hoffmann type elimination of triphenylphosphine affords the intermediate **690**. Intramolecular lactonization then forms the desired coumarins (Scheme 167) <2002J(P1)1455>.

Esterification of salicylaldehydes with acetic acid derivatives forms 2-formylphenyl acetate intermediates, which cyclize in high yield to afford 3-substituted coumarins (Scheme 168) <2004SC3129>.

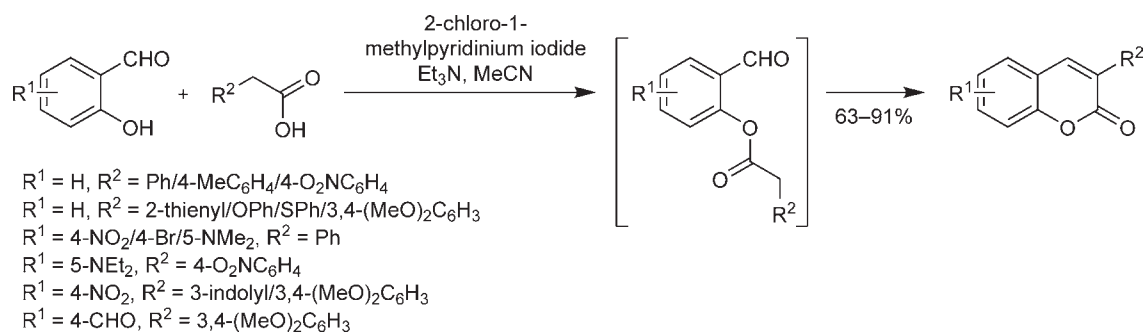
In a three component one-pot reaction, *tert*-butyl isocyanide, dialkyl acetylenedicarboxylates and salicylaldehydes react to afford 3-carboxycoumarins in high yield (Scheme 169) <2004S679>.

Cinnamic esters **691** react with aryl halides via a domino Heck reaction–lactonization process in molten *n*-Bu₄NOAc/*n*-Bu₄NBr to yield 4-arylcoumarins (Scheme 170) <2005ASC308>. Likewise, the palladium(II)-catalyzed reaction of cinnamic esters with vinyl triflates yields 4-vinyl coumarins <1996SL568>.

Coumarins are also formed by the palladium(II) catalyzed reaction of phenols with propenoates. This reaction requires an oxidant ($\text{K}_2\text{S}_2\text{O}_8$) to regenerate the palladium(II) species after β -elimination of palladium hydride from the intermediate **692** (Scheme 171) <2005BCJ468>. The more electron rich phenols give lower yields of the desired coumarins due to competing oxidative coupling reactions <2005BCJ468>.



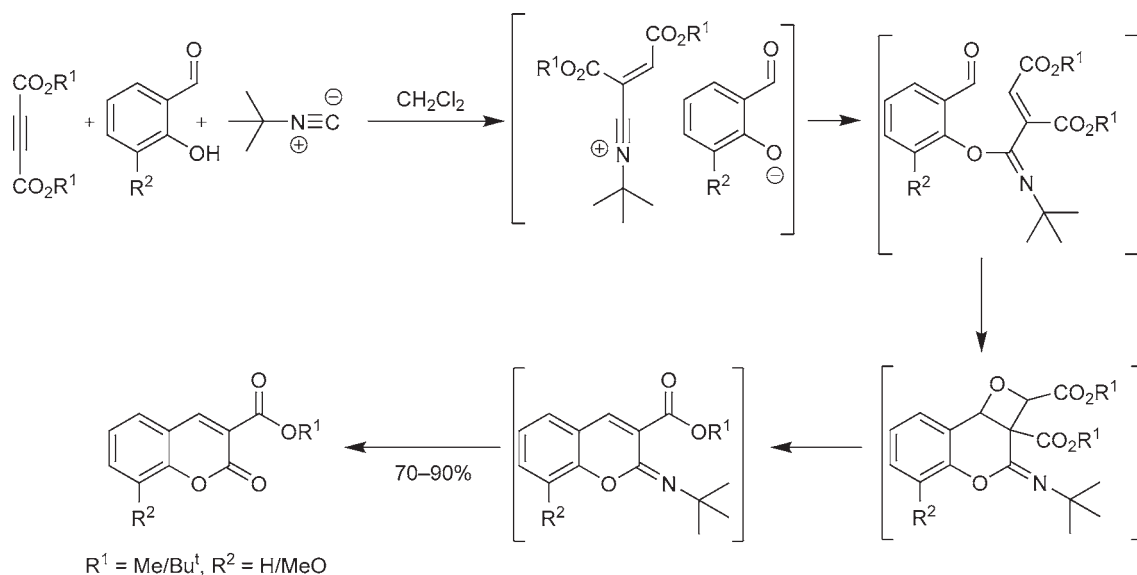
Scheme 167



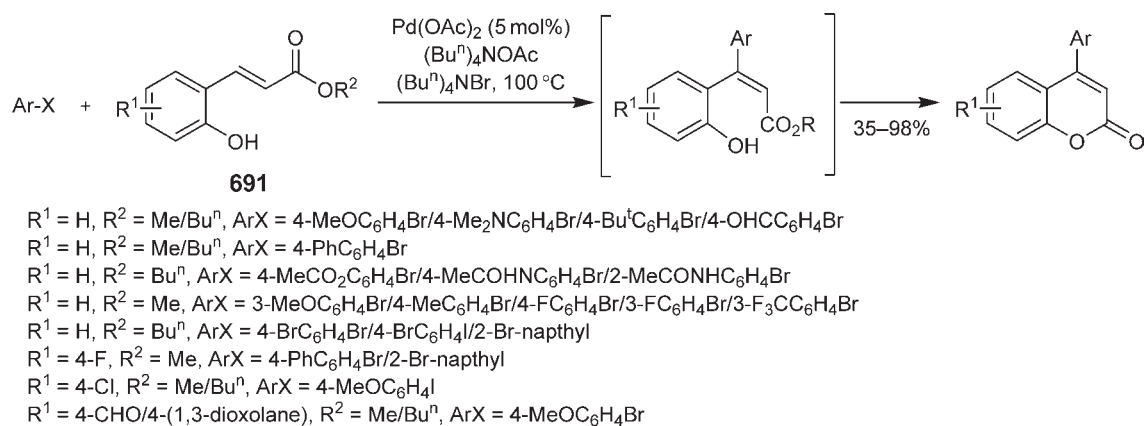
Scheme 168

In the presence of $\text{Ni}(\text{dppe})\text{Br}_2$ the oxabicyclic alkenes **693** react with propynoic esters to yield 2H-benzo[h]coumarins **696** (Scheme 172) <2001AGE1286>. The reaction mechanism involves cyclometallation of the propynoic ester and oxabicyclic alkene **693** to form the nickelacyclopentene intermediate **694**. β -Oxy elimination then forms the intermediate **695**, which undergoes protonation and isomerization of the double bond followed by intramolecular lactonization to afford the desired 2H-benzo[h]coumarins **696** (Scheme 172) <2001AGE1286>.

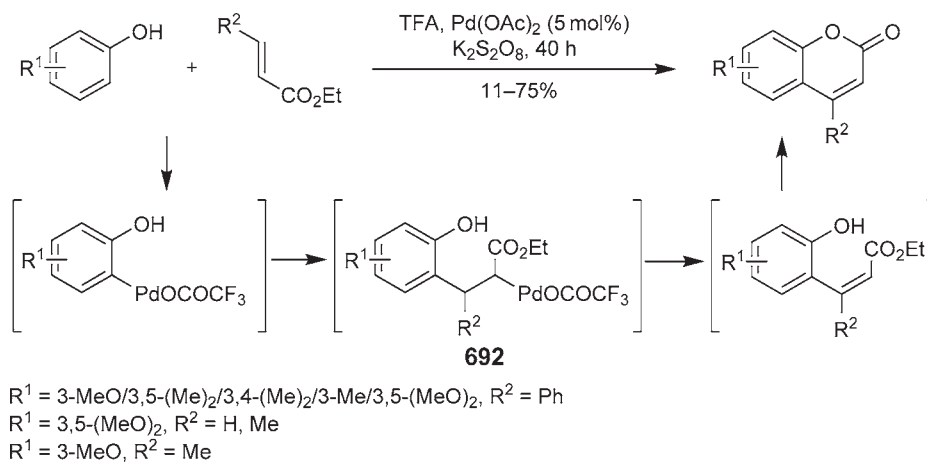
Similarly, $\text{Ni}(\text{dppe})\text{Br}_2$ catalyzes the reaction of β -iodo-(Z)-propenoates and 2-iodobenzoates **697** with oxabicyclic alkenes **698** to afford 2H-benzo[h]coumarins (Equation 279) <2003OL4903>.



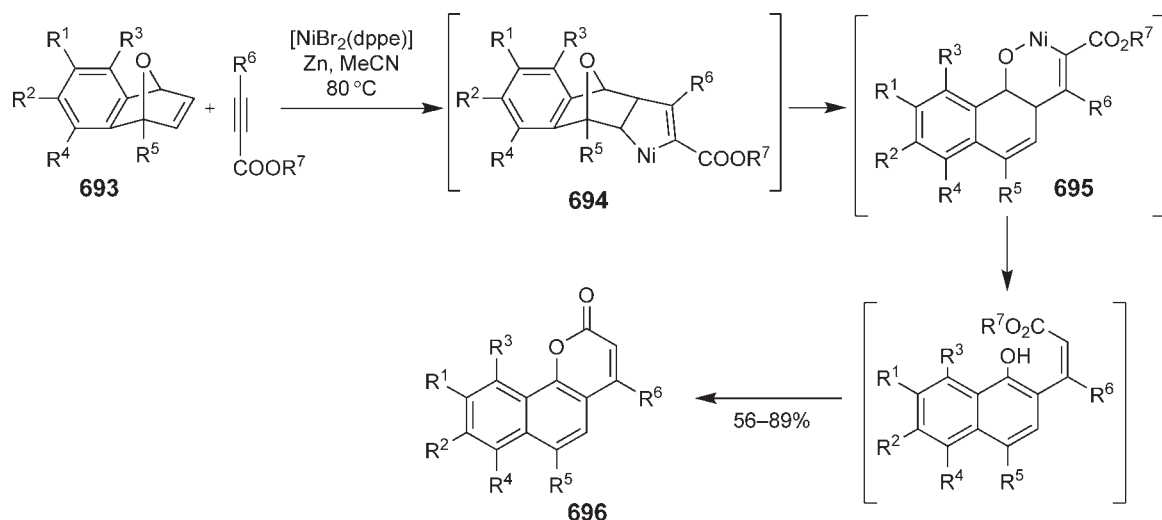
Scheme 169



Scheme 170



Scheme 171



$\text{R}^{1-5} = \text{H}$, $\text{R}^6 = \text{Me}/\text{Bu}^n/(\text{CH}_2)_4\text{CH}_3/\text{CH}=\text{CHCO}_2\text{Me}$, $\text{R}^7 = \text{Me}$

$\text{R}^{1-5} = \text{H}$, $\text{R}^6 = \text{Ph}/\text{TMS}/\text{H}$, $\text{R}^7 = \text{Et}$

$\text{R}^{1-5} = \text{H}$, $\text{R}^6 = \text{Ph}/\text{TMS}/\text{H}$, $\text{R}^7 = \text{Et}$

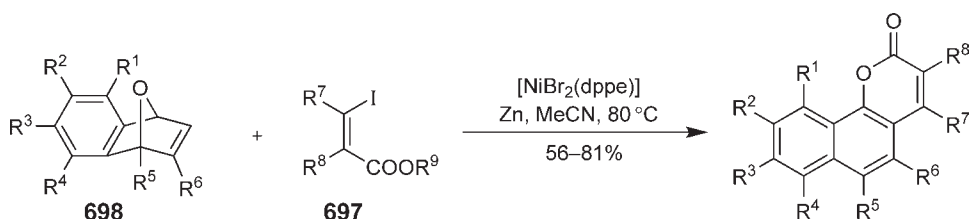
$\text{R}^{1-4} = \text{H}$, $\text{R}^5 = \text{Me}$, $\text{R}^6 = \text{Me}/(\text{CH}_2)_4\text{CH}_3$, $\text{R}^7 = \text{Me}$

$\text{R}^{1-2} = \text{OMe}$, $\text{R}^{3-5} = \text{H}$, $\text{R}^6 = \text{Me}/\text{Bu}^n$, $\text{R}^7 = \text{Me}$

$\text{R}^1\text{--OCH}_2\text{O--R}^2$, $\text{R}^{3-5} = \text{H}$, $\text{R}^6 = \text{Me}/(\text{CH}_2)_4\text{CH}_3$, $\text{R}^7 = \text{Me}$

$\text{R}^{1,3} = \text{C}_6\text{H}_4$, $\text{R}^{2,4} = \text{C}_6\text{H}_4$, $\text{R}^5 = \text{H}$, $\text{R}^6 = \text{R}^7 = \text{Me}$

Scheme 172



$\text{R}^{1-2} = \text{H}$, $\text{R}^3 = \text{H}/\text{MeO}$, $\text{R}^{4-6} = \text{H}$, $\text{R}^{7-8} = \text{H}$, $\text{R}^9 = \text{Et}$

$\text{R}^{1-2} = \text{H}$, $\text{R}^3 = \text{H}/\text{MeO}$, $\text{R}^{4-6} = \text{H}$, $\text{R}^7 = \text{Me}$, $\text{R}^8 = \text{H}$, $\text{R}^9 = \text{Et}$

$\text{R}^{1,2} = \text{C}_6\text{H}_4$, $\text{R}^{3,4} = \text{C}_6\text{H}_4$, $\text{R}^{5-6} = \text{H}$, $\text{R}^7 = \text{Me}$, $\text{R}^8 = \text{H}$, $\text{R}^9 = \text{Et}$

$\text{R}^{1-2} = \text{H}$, $\text{R}^3 = \text{H}/\text{MeO}$, $\text{R}^{4-6} = \text{H}$, $\text{R}^{7,8} = \text{C}_6\text{H}_4$, $\text{R}^9 = \text{Me}$

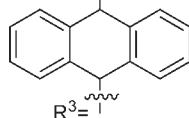
$\text{R}^{1-4} = \text{H}$, $\text{R}^5 = \text{Me}$, $\text{R}^6 = \text{H}/\text{CO}_2\text{Me}$, $\text{R}^{7,8} = \text{C}_6\text{H}_4$, $\text{R}^9 = \text{Me}$

$\text{R}^1 = \text{H}$, $\text{R}^{2,3} = \text{C}_6\text{H}_4$, $\text{R}^{4-6} = \text{H}$, $\text{R}^{7,8} = \text{C}_6\text{H}_4$, $\text{R}^9 = \text{Me}$

$\text{R}^{1,2} = \text{C}_6\text{H}_4$, $\text{R}^{3,4} = \text{C}_6\text{H}_4$, $\text{R}^{5-6} = \text{H}$, $\text{R}^{7,8} = \text{C}_6\text{H}_4$, $\text{R}^9 = \text{Me}$

$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{C}_6\text{H}_4$, $\text{R}^{3-6} = \text{H}$, $\text{R}^7 = \text{Me}$, $\text{R}^8 = \text{H}$, $\text{R}^9 = \text{Et}$

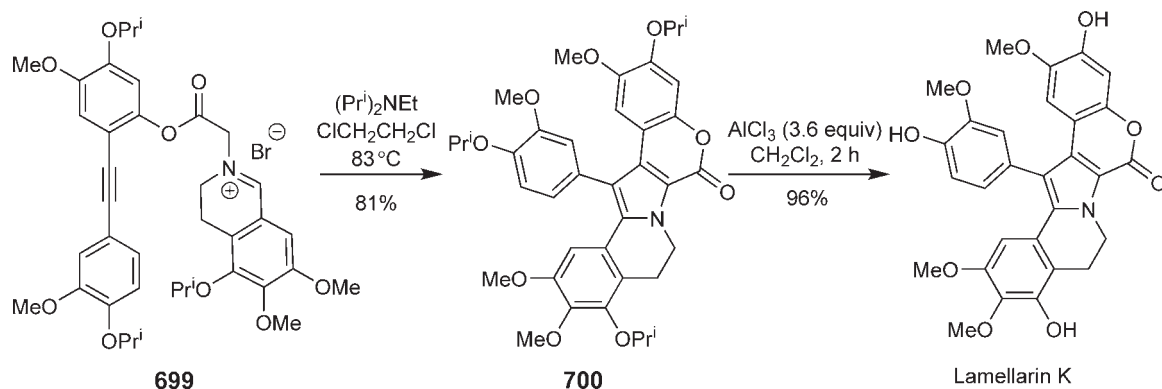
$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{C}_6\text{H}_4$, $\text{R}^{3-6} = \text{H}$, $\text{R}^7 = \text{Me}$, $\text{R}^8 = \text{H}$, $\text{R}^9 = \text{Et}$



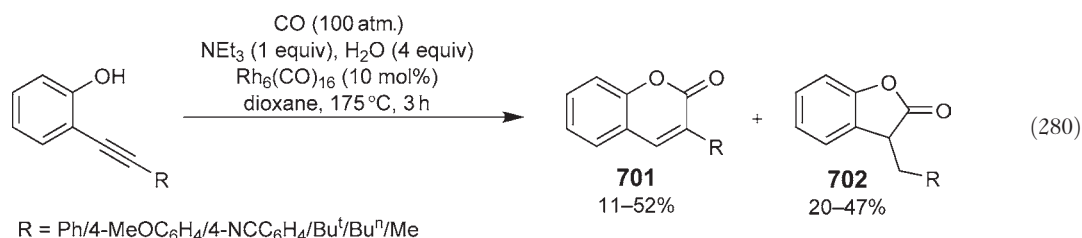
(279)

Treatment of the dihydroisoquinolinium salt **699** with Hünig's base (*i*-Pr₂NEt) produces the corresponding azomethine ylide, which can undergo intramolecular cycloaddition with the tethered alkyne to afford the chromeno[3,4-*b*]pyrrol-4(3*H*)-one **700** in high yield. Subsequent deprotection of the isopropyl protecting groups affords the marine natural product lamellarin K (**Scheme 173**) <1997CC2259>.

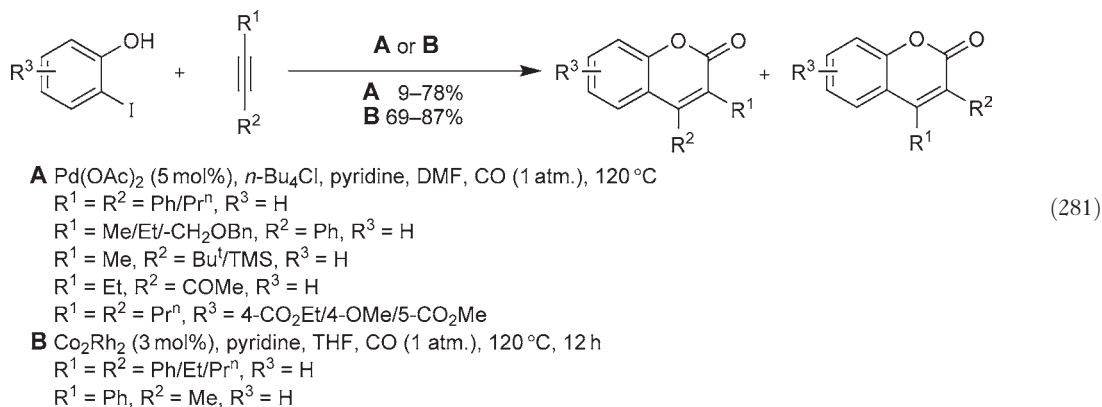
ortho-Alkynylphenols can undergo rhodium-catalyzed carbonylation and lactonization under water–gas shift reaction conditions to yield a mixture of coumarins **701** and benzofuranones **702** (Equation 280) <1998J(P1)477>.



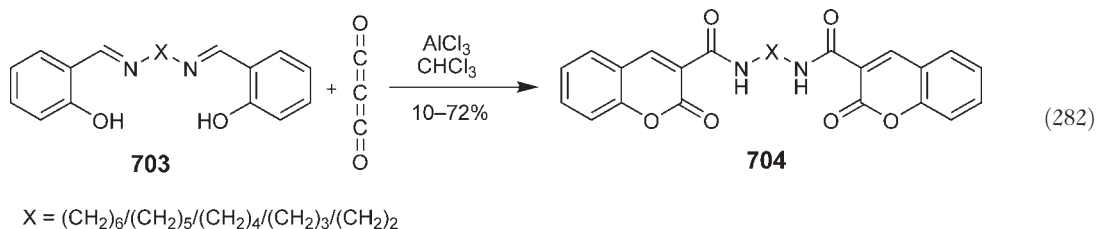
Scheme 173



Palladium(II) and cobalt–rhodium heterobimetallic nanoparticles can catalyze the reaction of *ortho*-iodophenols with internal alkynes and carbon monoxide to furnish 3,4-disubstituted coumarins (Equation 281) <2000OL3643, 2003JOC9423, 2004SL2541>. Unsymmetrical alkynes react to form two regioisomeric coumarins; the major product usually features the more bulky alkyne substituent at C-3 (Equation 281) <2000OL3643, 2003JOC9423, 2004SL2541>.



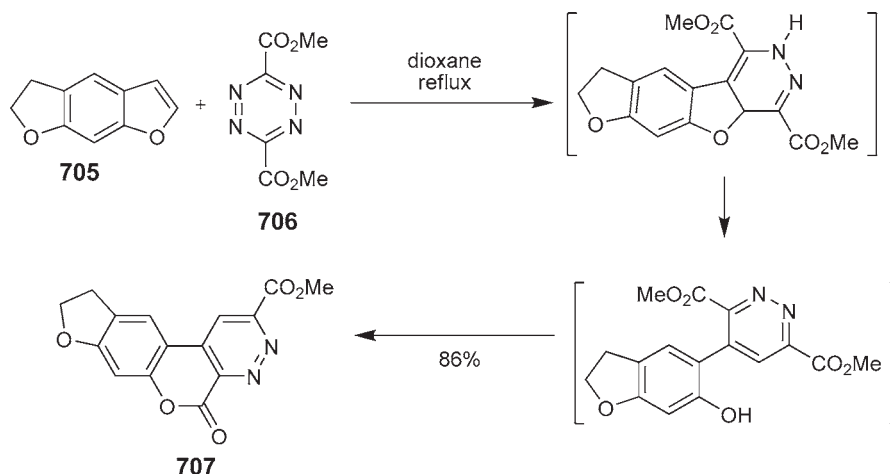
N,N'-Bis(salicylidene)diamines **703** react with carbonsuboxide to afford dicoumarinoyl diamines **704** (Equation 282) <2005SC769>.



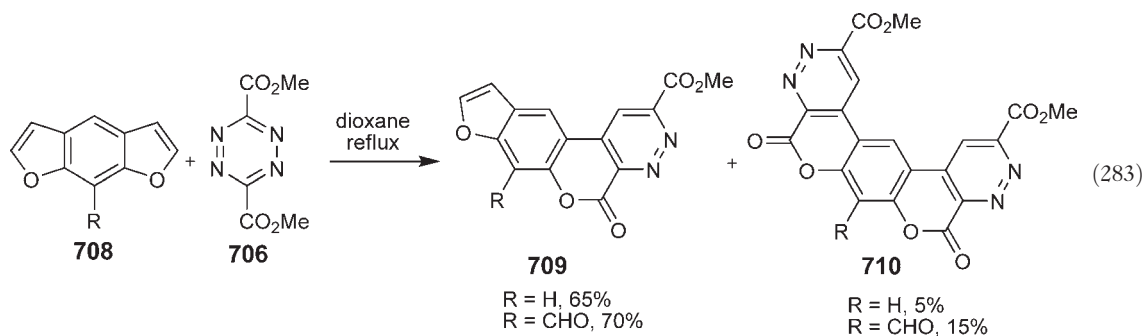
7.08.14.3 From Other Heterocycles

7.08.14.3.1 From furans

The 2,3-dihydrobenzo[1,2-*b*:5,4-*b'*]difuran **705** can undergo a cycloaddition reaction with tetrazine **706** followed by furan ring opening and lactonization to afford the pyridazino-fused coumarin **707** (Scheme 174) <2005T4805>. Similarly, benzo[1,2-*b*:5,4-*b'*]difurans **708** react with tetrazine **706** to form the pyridazino-fused coumarins **709** and **710** (Equation 283) <2005T4805>.



Scheme 174



7.08.14.4 From a Preformed Heterocyclic Ring

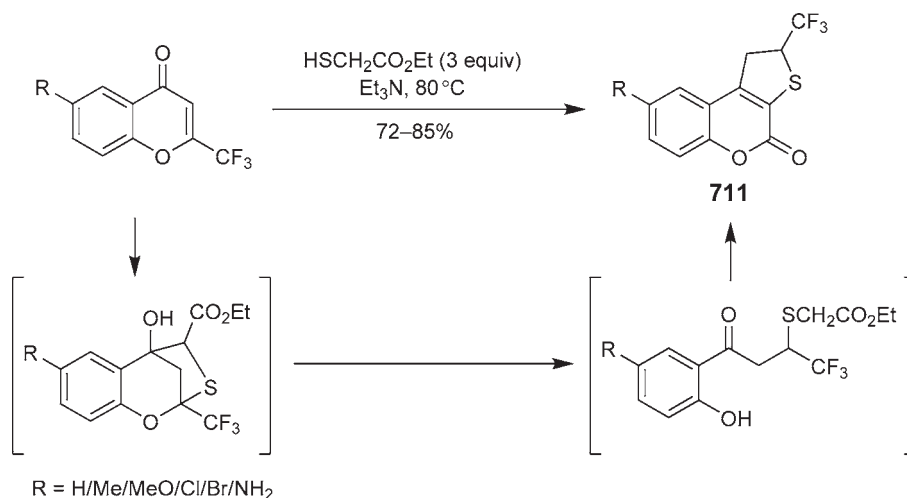
7.08.14.4.1 From chromones

Treatment of 2-trifluoromethyl-chromones with mercaptoacetate in the presence of triethylamine affords dihydro-thienocoumarins **711** in high yield (Scheme 175) <2001TL5117, 2003T2625>.

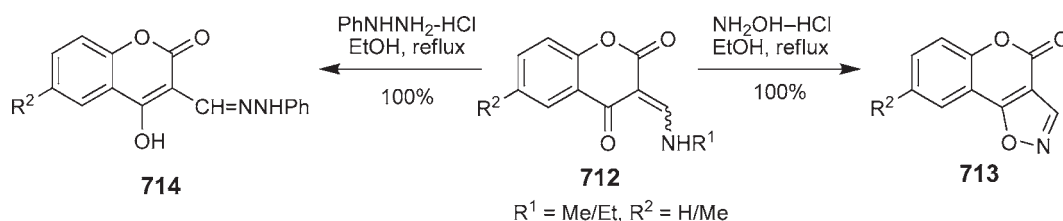
7.08.14.4.2 From chroman-2,4-diones

Treatment of 3-(alkylaminomethylene)chroman-2,4-dione **712** with hydroxylamine hydrochloride yields coumarino[3,4-*d*]isoxazoles **713** (Scheme 176) <2004TL6169>. Similarly, treatment with phenylhydrazine hydrochloride yields the hydrazone derivative **714** (Scheme 176) <2004TL6169>.

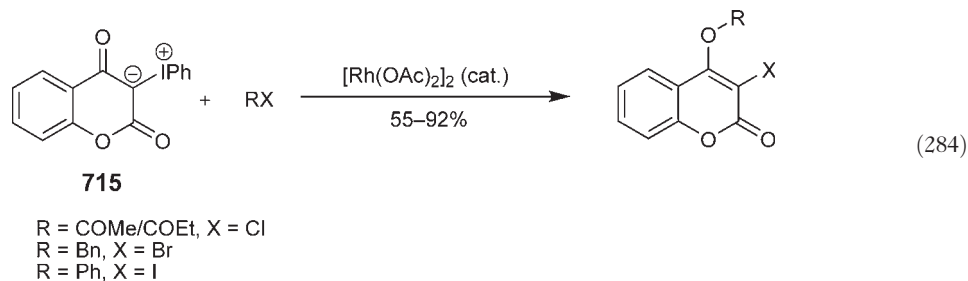
Iodonium ylides **715** undergo rhodium-catalyzed reactions with acyl, phenyl, or benzyl halides to form 3-halo-coumarins in good yield (Equation 284) <2002J(P1)1309>.



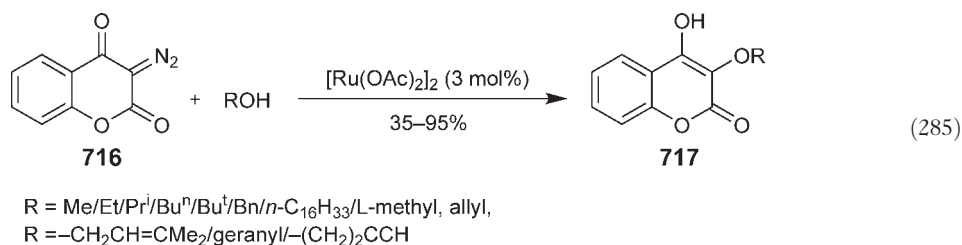
Scheme 175

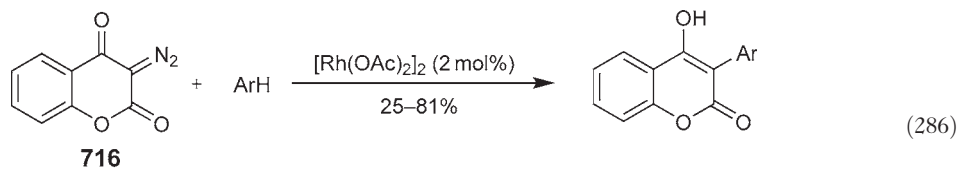


Scheme 176



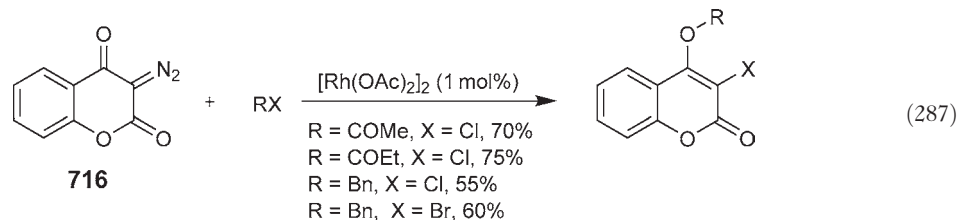
In the presence of a ruthenium catalyst, 3-diazochroman-2,4-dione **716** undergoes insertion into the O–H bond of alcohols to yield 3-alkoxy-4-hydroxycoumarins **717** (Equation 285) <2002TL3637>. In the presence of a rhodium catalyst, 3-diazochroman-2,4-dione **716** can undergo insertion into the C–H bond of arenes to yield 3-aryl-4-hydroxycoumarins (Equation 286) <2005SL927>. In the presence of $[\text{Rh}(\text{OAc})_2]_2$, 3-diazochroman-2,4-dione **716** can react with acyl or benzyl halides to afford to 3-halo-4-substituted coumarins (Equation 287) <2003T9333> and also with terminal alkynes to give a mixture of 4*H*-furo[3,2-*c*]chromen-4-ones and 4*H*-furo[2,3-*b*]chromen-4-ones (Equation 288) <2001S735>.





ArH = PhH/PhMe/1,4-(Me)₂C₆H₄/PhBu^t/PhOMe

ArH = 1,2-(MeO)₂C₆H₄/1,2(OCH₂O)C₆H₄

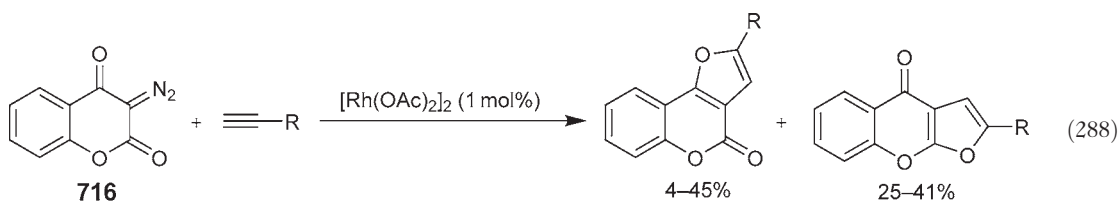


R = COMe, X = Cl, 70%

R = COEt, X = Cl, 75%

R = Bn, X = Cl, 55%

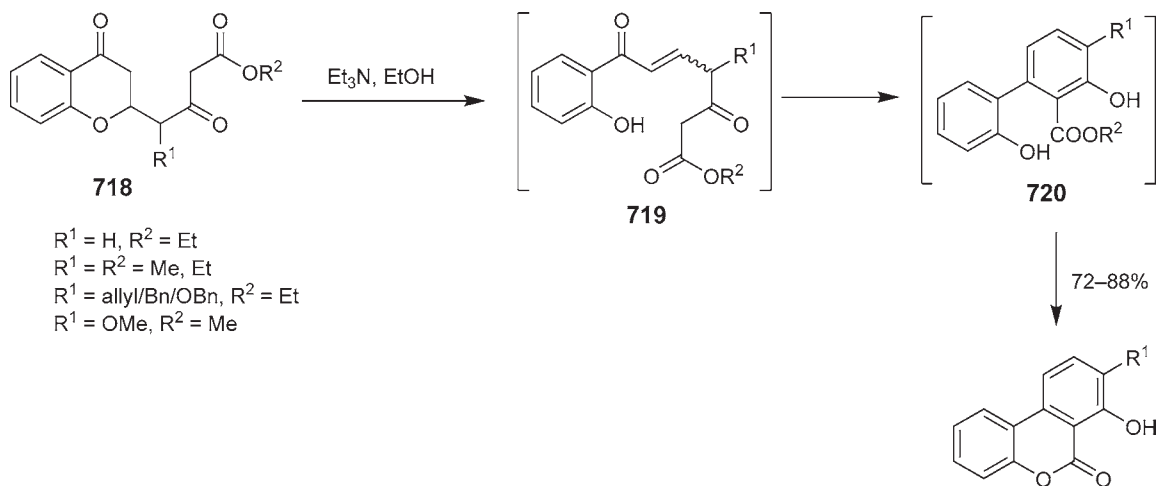
R = Bn, X = Br, 60%



R = Ph/CH₂Br/—(CH₂)₅CH₃/—(CH₂)₄CCH/—C(Me)₂OH/TMS

7.08.14.4.3 From chroman-4-ones

Treatment of 2,3-dihydrobenzopyran-4-ones **718** with base results in a retro-Michael reaction leading to the open-chain intermediate **719**. An intramolecular aldol reaction followed by dehydration affords the biaryl intermediate **720**, which cyclizes to form 7-hydroxy-6H-benzo[c]chromen-6-ones (Scheme 177) <2002CC168>.



R¹ = H, R² = Et

R¹ = R² = Me, Et

R¹ = allyl/Bn/Obn, R² = Et

R¹ = OMe, R² = Me

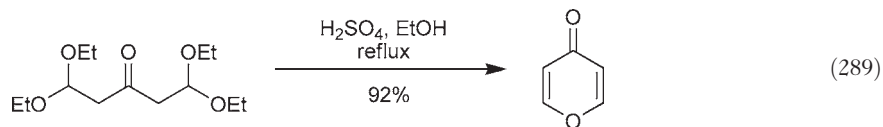
Scheme 177

7.08.15 Pyran-4-ones and Fused Pyran-4-ones (4-Pyrones)

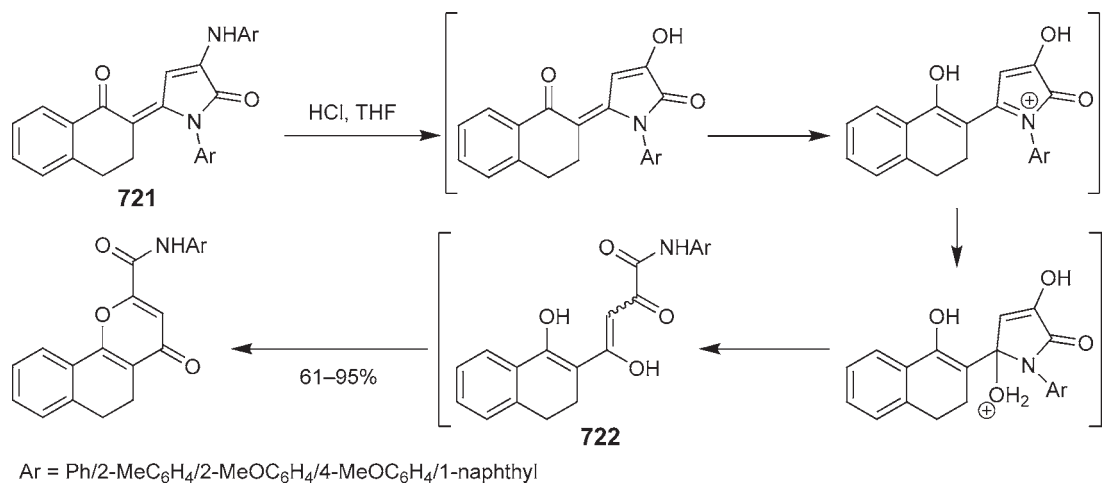
7.08.15.1 Formation of One Bond

7.08.15.1.1 Adjacent to the heteroatom

Pyran-4-ones can be accessed via a reliable cyclization of 1,3,5-triketetoacids and their derivatives [<1984CHEC, 1996CHEC-II>](#). In this manner, γ -pyrone can be prepared on a multi-gram scale by the acid catalyzed cyclization of 1,1,5,5-tetraethoxy-3-pentanone ([Equation 289](#)) [<2005SL123>](#).



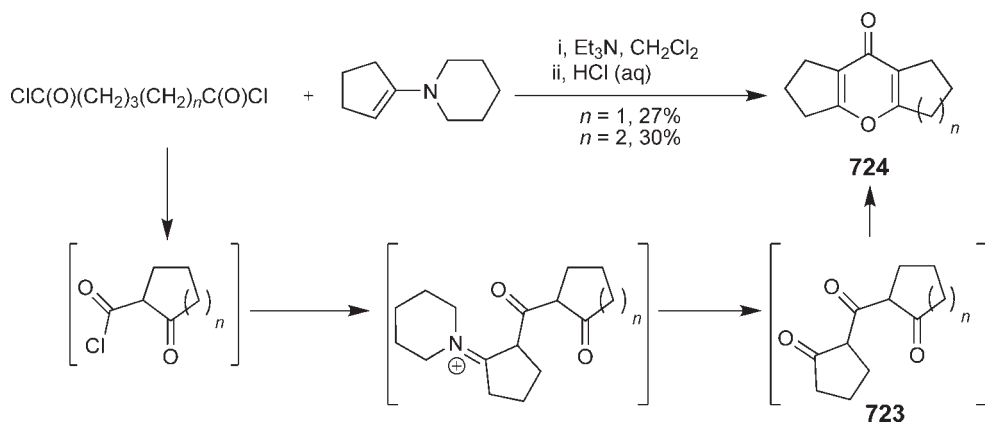
5-Alkylidene-3-arylamino-2,5-dihydropyrrol-2-ones **721** can rearrange under acidic conditions to form the intermediate 1,3,5-triketetoacid equivalent **722**, which cyclizes to afford 5,6-fused 2-carbamoylpyran-4-ones ([Scheme 178](#)) [<2004SL2779>](#).



Scheme 178

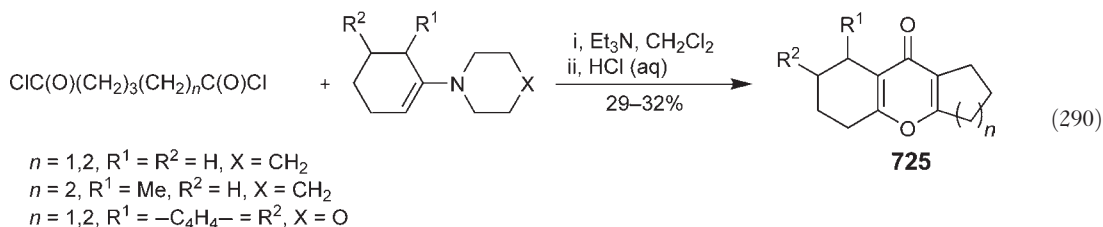
7.08.15.2 Formation of More than One Bond

2,3-Cyclopenteno-5,6-cycloalkeno-4*H*-pyran-4-ones **724** are prepared by the reaction of 1-cyclopentenylpiperidine with diacyl chlorides via formation and ring closure of the 1,3,5-triketone intermediate **723** ([Scheme 179](#))

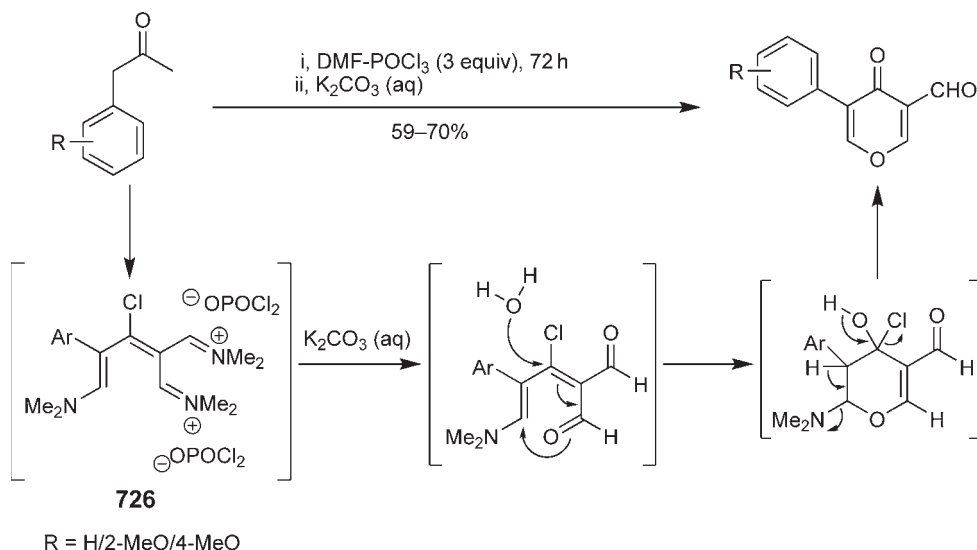


Scheme 179

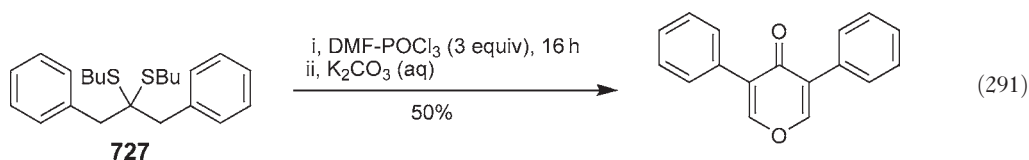
<2000TL10257>. Likewise, 1-cyclohexenylpiperidine reacts with diacylchlorides to afford 2,3-cyclohexeno-5,6-cycloalkeno-4*H*-pyran-4-ones **725** (Equation 290) <2000TL10257>.



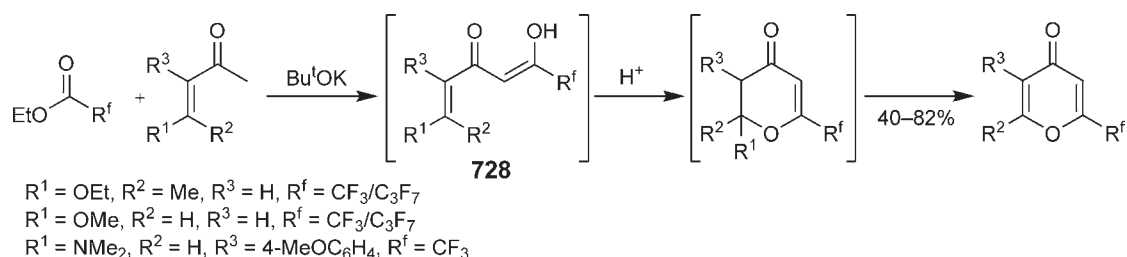
Aryl acetones react with the Vilsmeier–Haack reagent to form conjugated iminium salts **726**, which spontaneously cyclize upon basic aqueous work-up to afford 3-formyl-pyran-4-ones (Scheme 180) <2004T5069>. (1,3-Diphenylpropane-2,2-diyl)bis(butylsulfane) **727** also reacts with the Vilsmeier–Haack reagent to afford 3,5-diphenyl-4*H*-pyran-4-one upon basic aqueous workup (Equation 291) <2004T5069>.



Scheme 180

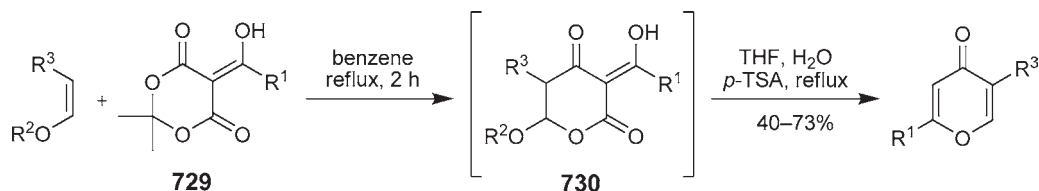


(*E*)-4-Ethoxybut-3-en-2-ones and (*E*)-4-(dimethylamino)but-3-en-2-ones react with ethyl perfluoroalkanoates to form intermediate **728**. Acid promoted cyclization of the intermediate **728** and subsequent elimination of HR^1 affords 2-perfluoroalkyl-pyran-4-ones (Scheme 181) <1998T2819, 2000T7313>.

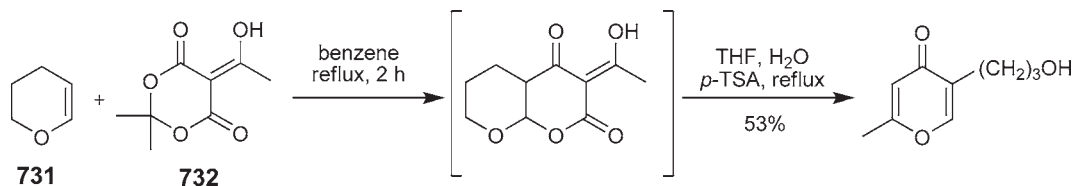


Scheme 181

Enol ethers add to acylated Meldrum's acid derivatives **729** to form the intermediate 3-methylenedihydro-2*H*-pyran-2,4(3*H*)-diones **730**, which are converted into pyran-4-ones upon treatment with *p*-TSA (Scheme 182) <1996TL6499>. Likewise, 3,4-dihydro-2*H*-pyran **731** reacts with the Meldrum's acid derivative **732** to afford 5-(3-hydroxypropyl)-2-methyl-4*H*-pyran-4-one (Scheme 183) <1996TL6499>.

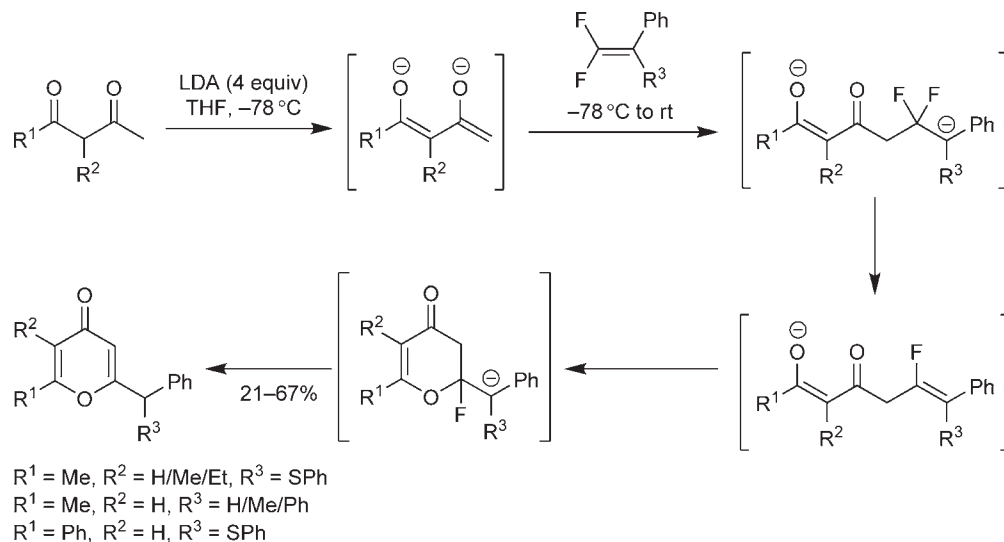


Scheme 182



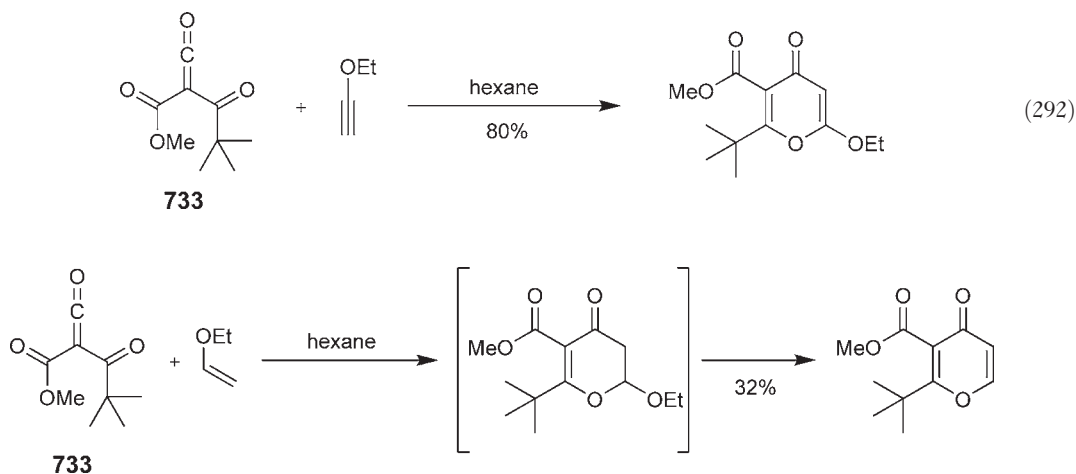
Scheme 183

The dianions of 1,3-diketones react with β,β -difluorostyrenes to afford pyran-4-ones in moderate yield (Scheme 184) <1997H(45)37>.



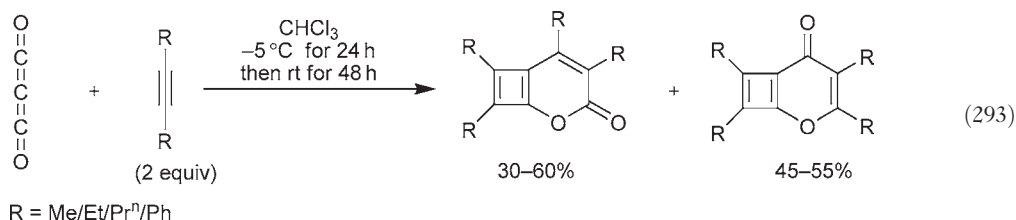
Scheme 184

Carbomethoxypivaloylketene **733** can undergo a hetero-Diels–Alder reaction with ethoxyalkyne to yield methyl 2-*tert*-butyl-6-ethoxy-4-oxo-4*H*-pyran-3-carboxylate (Equation 292). Likewise, carbomethoxypivaloylketene **733** undergoes a hetero-Diels–Alder reaction with ethoxyethene to afford the intermediate dihydropyran-4-one, which upon elimination of ethanol affords methyl 2-*tert*-butyl-4-oxo-4*H*-pyran-3-carboxylate (Scheme 185) <2001T6757>.



Scheme 185

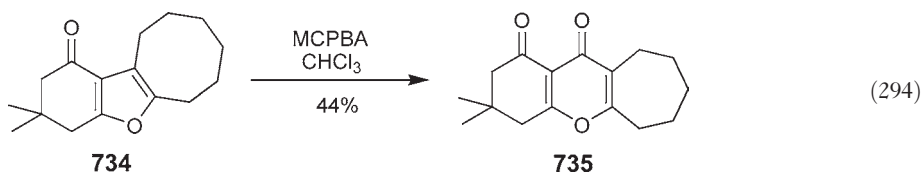
The reaction of carbon suboxide with two equivalents of an internal alkyne affords a mixture of pyran-2-ones and pyran-4-ones (Equation 293) <2003JHC321>.



7.08.15.3 From Other Heterocycles

7.08.15.3.1 From furans

The cyclooctyl-fused furan **734** undergoes oxidation and expansion of the furan ring upon treatment with *m*-CPBA to afford cycloheptyl-fused 4*H*-pyran-4-one **735** in moderate yield (Equation 294) <2000OL1387>.



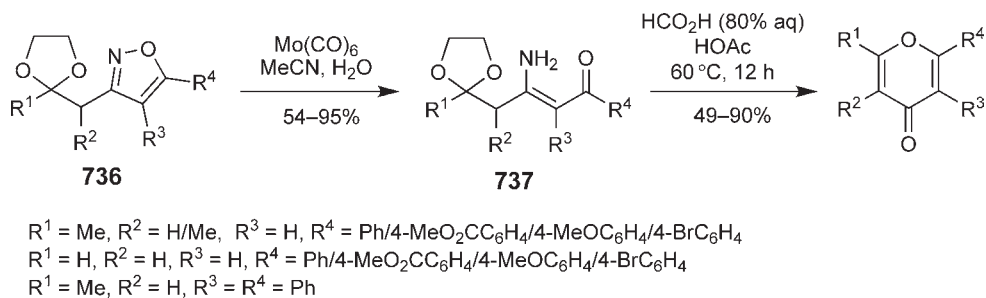
7.08.15.3.2 From isoxazoles

Reduction of the isoxazoles **736** with Mo(CO)₆ affords the corresponding enamino ketone intermediates **737**, which can be isolated or treated directly with aqueous acid to afford pyran-4-ones (Scheme 186) <2002TL3565>.

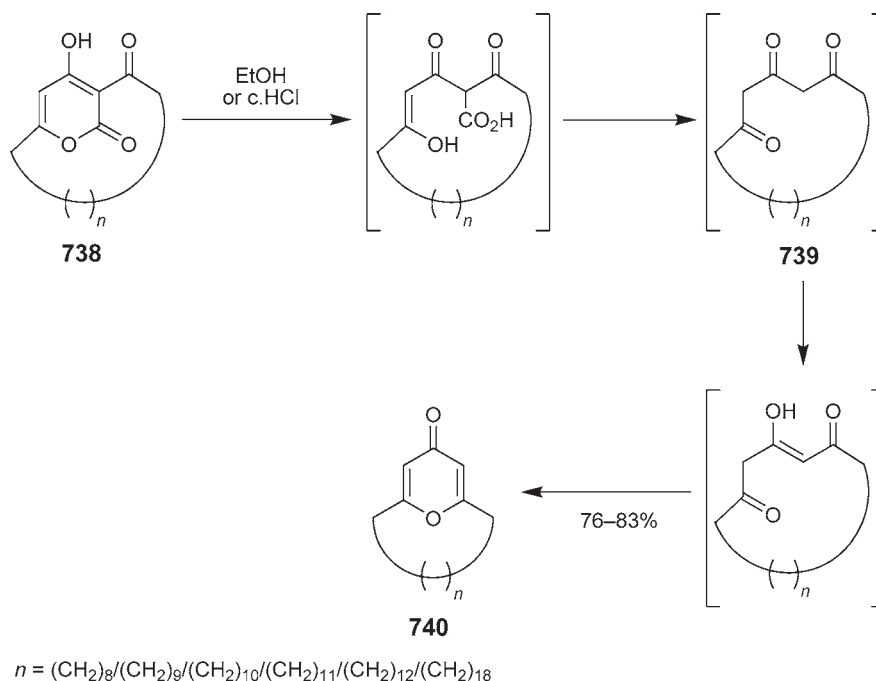
7.08.15.4 From a Preformed Heterocyclic Ring

7.08.15.4.1 From pyran-2-ones

Metacyclophanes **740** are synthesized from 4-hydroxy-3-acyl-pyran-2-ones **738** in high yield. The reaction proceeds via hydrolysis of the pyran-2-one ring, followed by decarboxylation to afford the intermediate 1,3,5-triketone **739**, which recycles to afford 2,6-bridged pyran-4-ones **740** (Scheme 187) <2003T2651>.



Scheme 186



Scheme 187

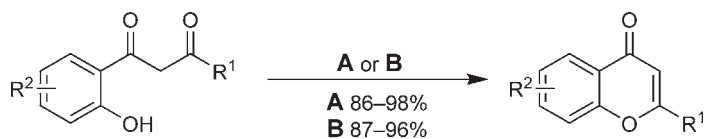
7.08.16 Chromones (4*H*-1-Benzopyran-4-ones)

The chromone motif features in a number of natural products: especially abundant are the flavones (2-arylchromones) and isoflavones (3-arylchromones). A range of biological activities are exhibited by both synthetic and naturally occurring chromones; the antimicrobial activity <2005JAA343>, biochemistry <2005CJB433> and recent advances in flavonoid research have been reviewed <2000P481, 2005BTL365, 2005CME713>.

7.08.16.1 Formation of One Bond

7.08.16.1.1 Adjacent to the heteroatom

The cyclodehydration of 2-hydroxyacetophenones can be promoted by Fe(III) or carried out under microwave irradiation promoted by copper(II) chloride to afford chromones in high yield (Equation 295) <2005TL6315, 2005HCO97>.



A CuCl_2 , EtOH, MW, 5 min

$\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}/4\text{-Me}/4\text{-Me-5-Cl}/5\text{-Br}/5\text{-Cl}/4\text{-OH}/3,5\text{-(OH)}_2$

$\text{R}^1 = 4\text{-O}_2\text{NC}_6\text{H}_4$, $\text{R}^2 = \text{H}$

$\text{R}^1 = \text{Me}/\text{CF}_3$, $\text{R}^2 = \text{H}$

$\text{R}^1 = \text{Me}$, $\text{R}^2 = 5\text{-Br}/5\text{-Cl}$

B FeCl_3 , CH_2Cl_2 , 1 h, rt

$\text{R}^1 = 2\text{-ClC}_6\text{H}_4/3\text{-MeOC}_6\text{H}_4/4\text{-BnOC}_6\text{H}_4/3,4,5\text{-(MeO)}_3\text{C}_6\text{H}_2$, $\text{R}^2 = \text{H}$

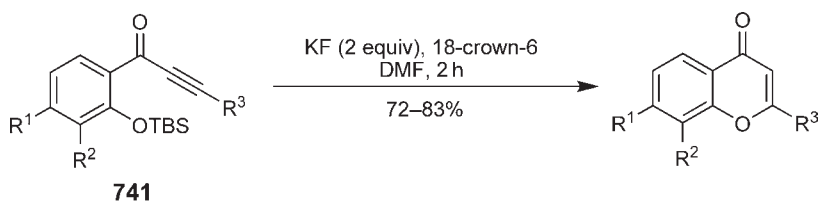
$\text{R}^1 = 4\text{-ClC}_6\text{H}_4/3,4\text{-(MeO)}_2\text{C}_6\text{H}_3/4\text{-MeOC}_6\text{H}_4/4\text{-O}_2\text{NC}_6\text{H}_4/\text{Ph}$, $\text{R}^2 = \text{H}$

$\text{R}^1 = \text{Ph}$, $\text{R}^2 = 5\text{-OH}$

$\text{R}^1 = 4\text{-O}_2\text{NC}_6\text{H}_4$, $\text{R}^2 = 5\text{-Me}$

(295)

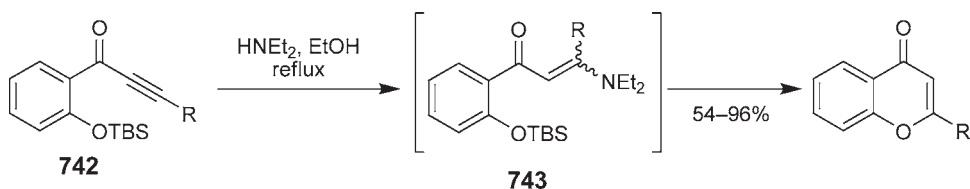
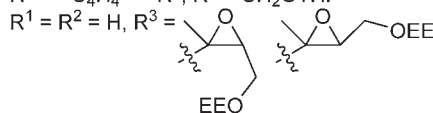
The cyclization of *ortho*-hydroxyphenyl ethynyl ketones under basic conditions can proceed via a 6-*endo-dig* process to afford chromones or a 5-*exo-dig* process to form benzofuranones; the product ratio is highly dependent upon the reaction conditions <1996T9427, 1996CHEC-II>. *ortho*-Silyloxyphenyl ethynyl ketones **741** undergo fluoride promoted 6-*endo-dig* cyclizations to afford chromones in high yield (Equation 296) <1996T9427>. Likewise, in the presence of a secondary amine, *ortho*-silyloxyphenyl ethynyl ketones **742** cyclize to afford chromones via the enamino ketone intermediate **743** (Scheme 188) <1999TL2469>.



(296)

$\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = (Z)\text{-C(Me)=CHCH}_2\text{OTHP}/(E)\text{-C(Me)=CHCH}_2\text{OTHP}/\text{CH}_2\text{OTHP}$

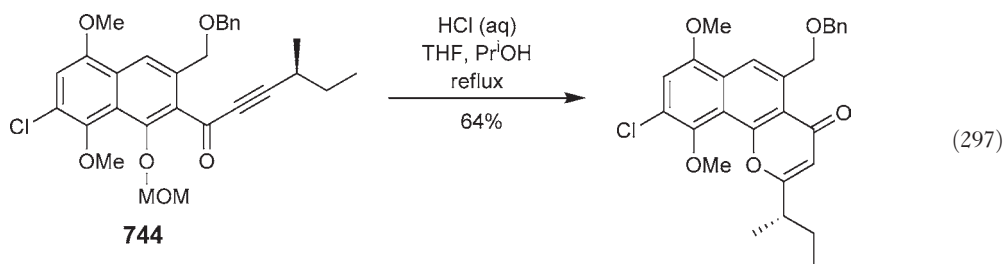
$\text{R}^1 = \text{-C}_4\text{H}_4\text{-}$, $\text{R}^2 = \text{R}^3 = \text{CH}_2\text{OTHP}$



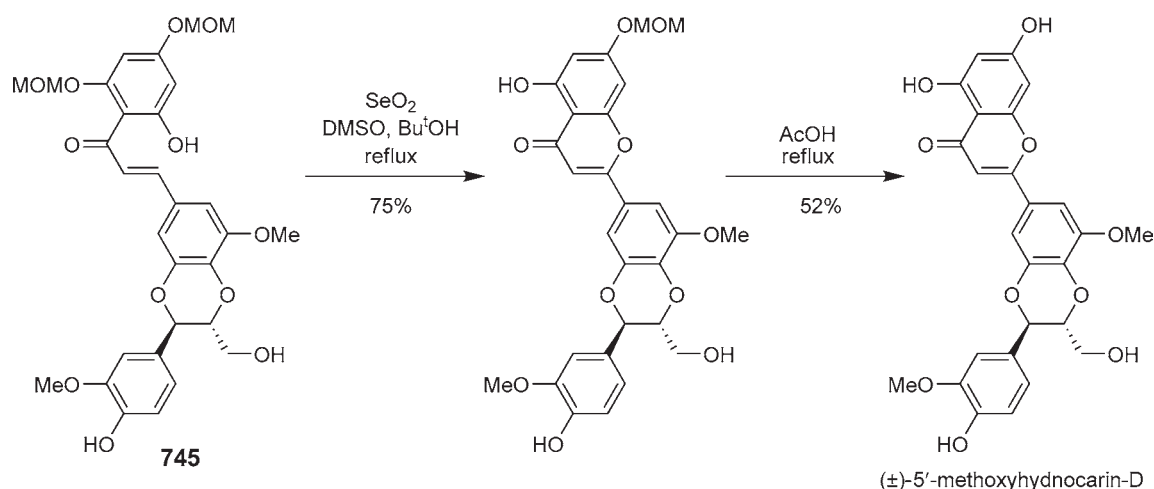
$\text{R} = \text{Ph}/4\text{-MeC}_6\text{H}_4/\text{-(CH}_2\text{)}_3\text{Cl}/\text{CH}_2\text{OMe}$
 $\text{R} = \text{-C(OH)Me}_2/\text{cyclohexenyl}/\text{-CH(OEt)}_2$

Scheme 188

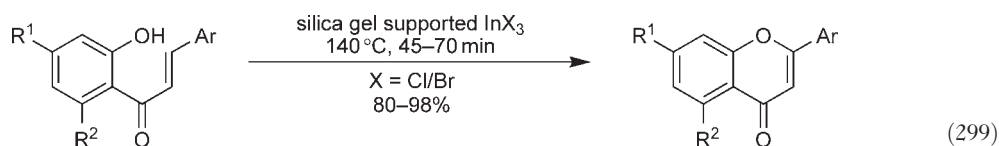
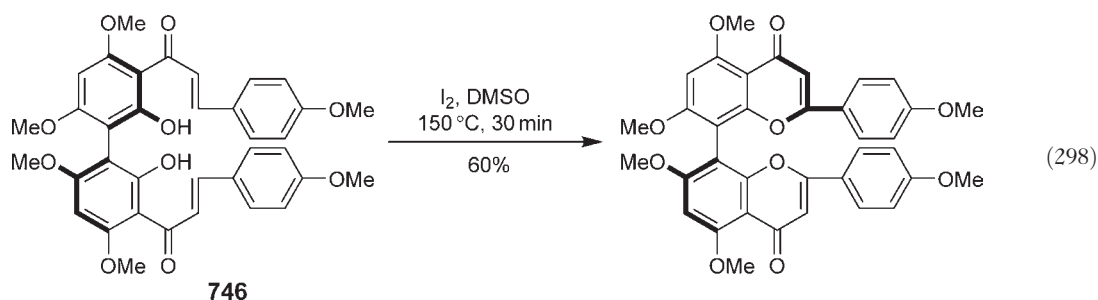
The acid promoted 6-*endo-dig* ring closure of the ynone **744** features in the total synthesis of (*S*)-espicufolin (Equation 297) <1999CC1005>.



A selenium dioxide induced oxidative cyclization of the 2'-hydroxychalcone **745** is a key step in the total synthesis of (±)-5'-methoxyhydrinocarin-D (**Scheme 189**) <2005T4149>. DMSO containing catalytic amounts of iodine also effectively promotes the oxidative cyclization of 2'-hydroxychalcones to afford flavones <1996CHEC-II>. The DMSO-iodine mediated cyclization of the bis(2'-hydroxychalcone) **746** is a key step in the synthesis of the natural atropisomer 4'4'',7,7''-tetra-*O*-methylcupressuflavone (**Equation 298**) <1997TL1087>. Likewise, silica gel supported indium(III) halides catalyze the oxidative cyclization of 2'-hydroxychalcones to afford flavones in excellent yield (**Equation 299**) <2005TL253>.



Scheme 189

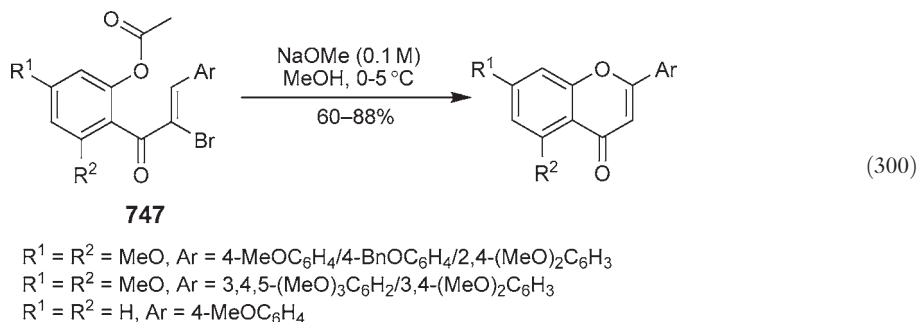


$R^1 = R^2 = \text{H}$, $\text{Ar} = \text{Ph}/2,6\text{-(Cl)}_2\text{C}_6\text{H}_3/2,4\text{-(MeO)}_2\text{C}_6\text{H}_3/4\text{-Me}_2\text{NC}_6\text{H}_4/4\text{-HOC}_6\text{H}_4$

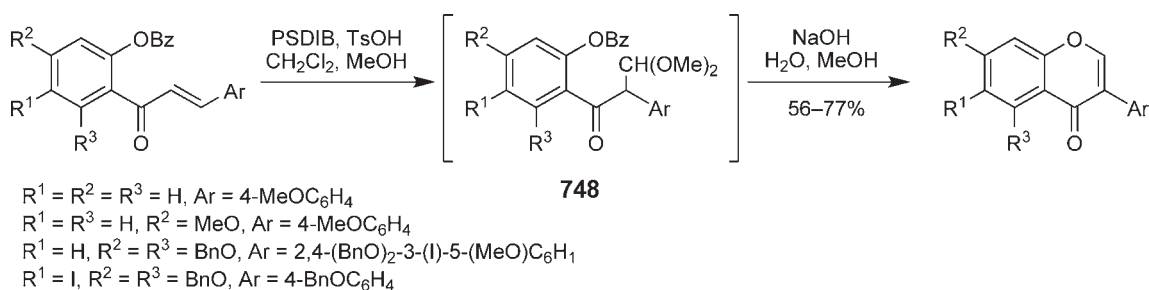
$R^1 = R^2 = \text{MeO}$, $\text{Ar} = 4\text{-FC}_6\text{H}_4/4\text{-BrC}_6\text{H}_4/2,6\text{-(MeO)}_2\text{C}_6\text{H}_3/4\text{-MeOC}_6\text{H}_4$

$R^1 = R^2 = \text{HO}$, $\text{Ar} = \text{Ph}$

Flavones can also be accessed from α -bromo-2'-acetoxychalcones **747** in good yield upon treatment with base (Equation 300) <2001TL8907>.



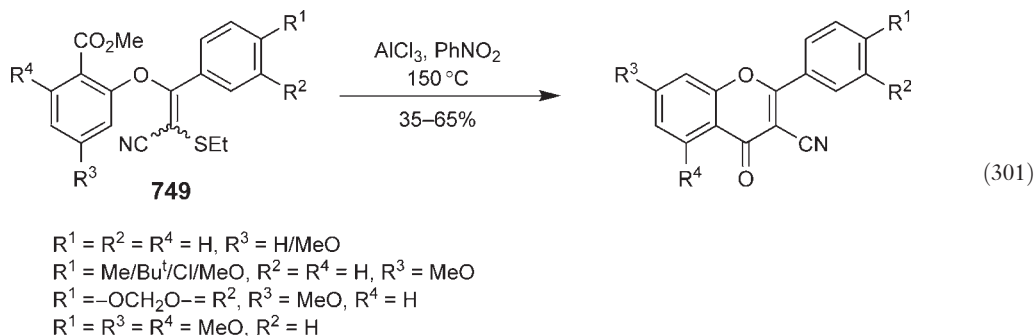
Polymer-supported (diacetoxyiodo)benzene (PSDIB) can promote an oxidative rearrangement of 2'-benzyloxychalcones to form the intermediate acetal **748**, which can be isolated or directly treated with aqueous base to afford isoflavones (Scheme 190) <2002S2490>.



Scheme 190

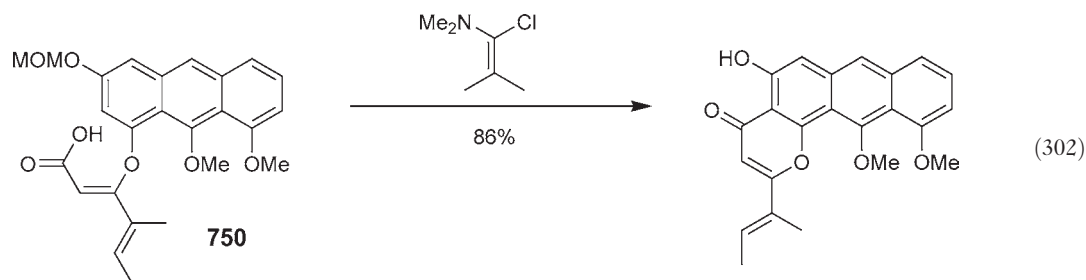
7.08.16.1.2 γ to the heteroatom

Treatment of methyl 2-(2-cyano-2-(ethylthio)-1-phenylvinyl)oxy)benzoate derivatives **749** with AlCl_3 in nitrobenzene affords 3-cyanoflavones in moderate yield (Equation 301) <2003TL9283>.



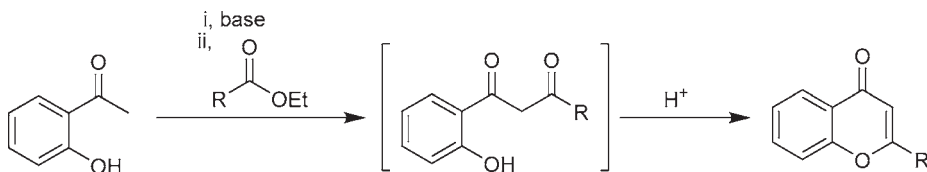
7.08.16.1.3 δ to the heteroatom

A key step in the synthesis of the aglycone structures of the altromycins and kidamycin involves activation of the acid **750** with 1-chloro-*N,N*-2-trimethyl-1-propenylamine, which results in spontaneous cyclization to form the corresponding chromone in high yield (Equation 302) <2005OL3617>.

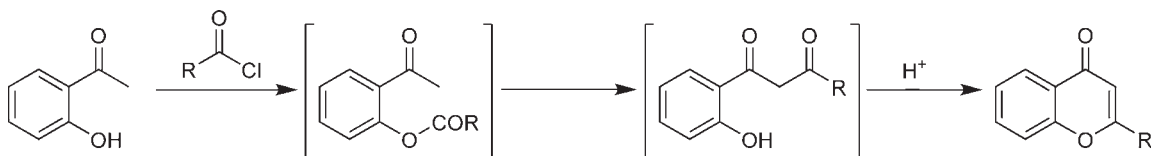


7.08.16.2 Formation of More than One Bond

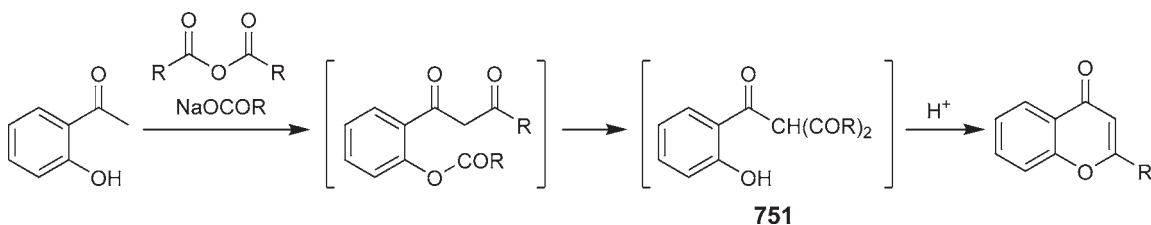
Extension of the acyl group of *ortho*-hydroxyacetophenones and subsequent cyclization is a well-documented strategy for the synthesis of chromones <1982CHEC, 1996CHEC-II>. This can be achieved by the direct C-acylation of *ortho*-hydroxyacetophenones via a Claisen condensation to form 1,3-diketone intermediates, which afford chromones upon cyclization (Scheme 191). Alternatively, a Baker–Venkataraman approach proceeds by initial O-acylation of *ortho*-hydroxyacetophenones, which then rearrange to afford the prerequisite 1,3-diketones (Scheme 192). A Kotstanecki–Robinson synthesis of chromones features both O- and C-acylation of the *ortho*-hydroxyacetophenone, followed by a Baker–Venkataraman-type rearrangement to form the intermediate **751**, which can undergo cyclization and subsequent C-3 acyl cleavage to afford chromones (Scheme 193). These approaches are well documented and are discussed in detail in the previous volumes <1982CHEC, 1996CHEC-II>.



Scheme 191

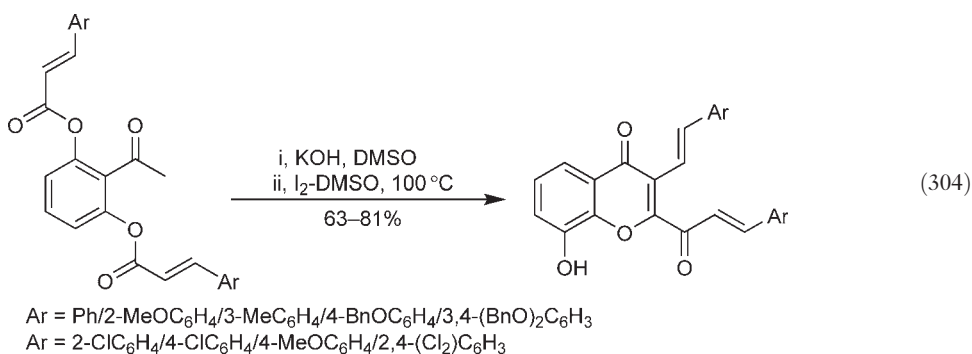
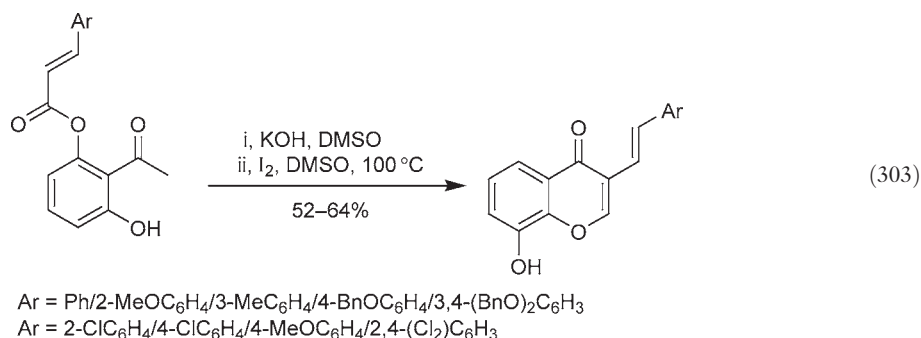


Scheme 192

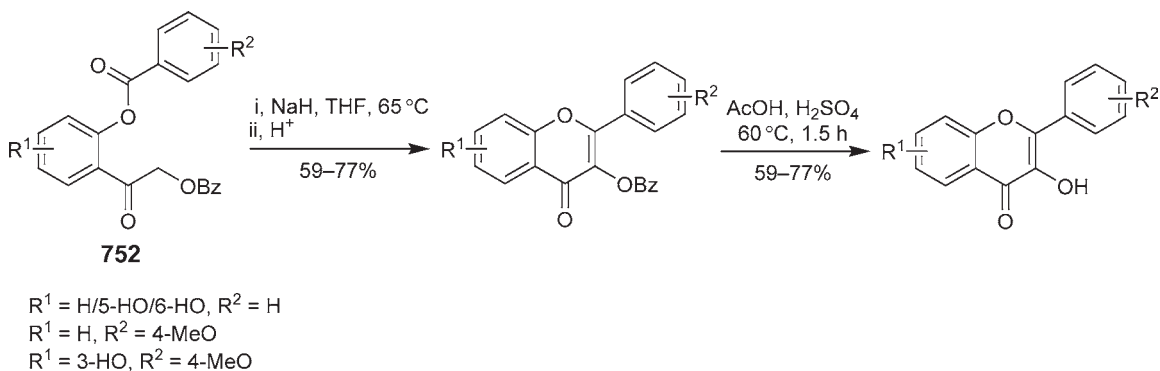


Scheme 193

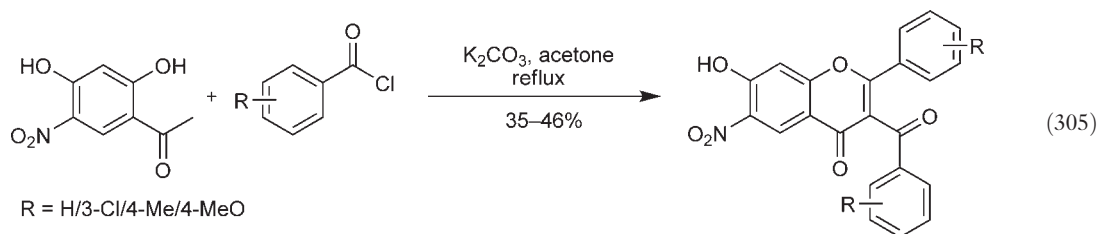
A Baker–Venkataraman reaction of 2-hydroxyphenyl ketone derivatives with acyl chlorides or propioloyl chlorides can be mediated by DBU to give 2,3-disubstituted chromones in high yield [<1997S195>](#). TMS-Cl can also effectively mediate a Baker–Venkataraman rearrangement of 2-(2-phenylacetyl)phenyl acetate derivatives to form isoflavones [<1998S1793>](#). 3-Styrylchromones and 2-cinnamoyl-3-styrylchromones are accessed using a Baker–Venkataraman rearrangement followed by iodine promoted cyclodehydration (Equations 303 and 304) [<2000NJC85>](#).



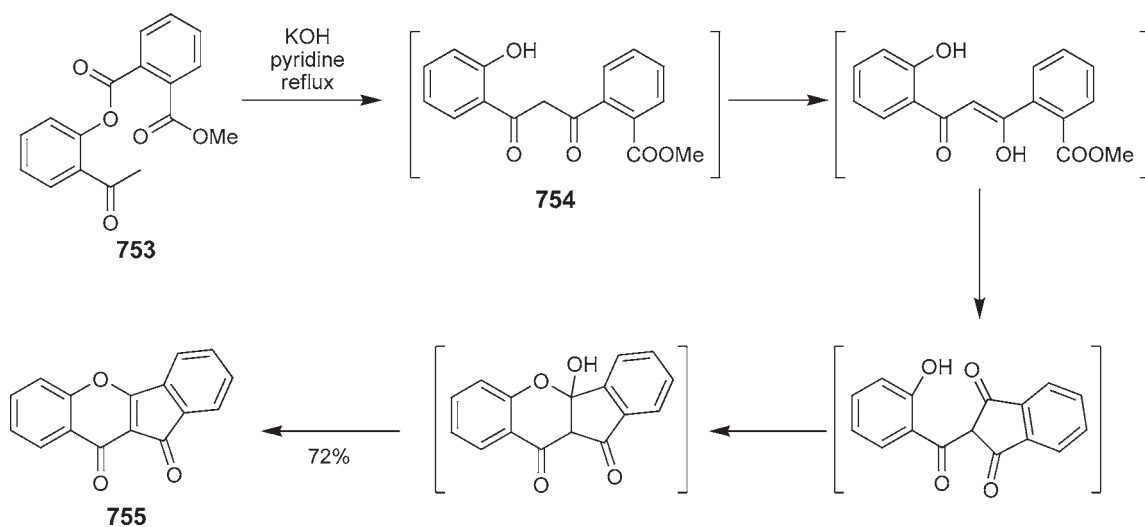
Flavanols are similarly accessed from 2-(2-(benzoyloxy)acetyl)phenyl benzoates **752** via a Baker–Venkataraman rearrangement to form 3-benzoyloxy flavones followed by deprotection of the hydroxyl group (Scheme 194) [<2000JOC583>](#). 3-Aroyl flavones are prepared from *ortho*-hydroxyacetophenones and aroyl chlorides in modest yield, using a Kostanecki–Robinson approach (Equation 305) [<2005SC315>](#).



Scheme 194

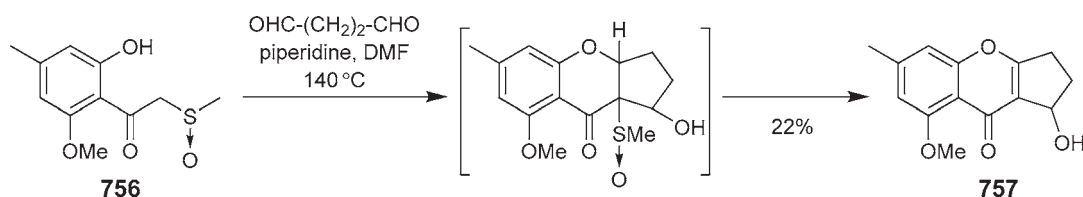


A Baker–Venkataraman rearrangement of 2-acetylphenyl methyl phthalate **753** forms the β -diketone intermediate **754**, which undergoes successive ring closures leading to the formation of benzo[*b*]indeno[2.1-*e*]pyran-1,11-dione **755** in high yield (Scheme 195) <2002TL4515>.



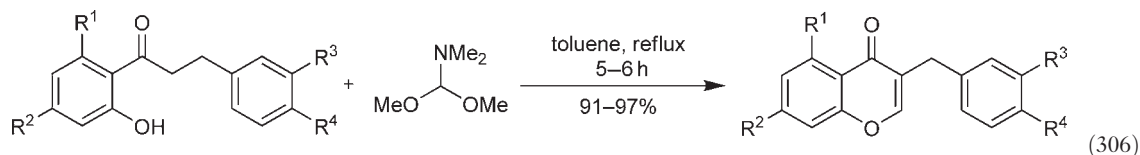
Scheme 195

Total syntheses of coniochaetones A and ($\pm$)-B feature the reaction of β -ketosulfoxide **756** with succindialdehyde to form the cyclopentane-fused chromone **757** in modest yield (Scheme 196) <1998SL259>.



Scheme 196

Formyl equivalents, such as DMF and triethyl *ortho*-formate, are used to extend the acyl group of *ortho*-hydroxyacetophenones by one carbonyl unit, which upon cyclization form chromones that are unsubstituted at C-2 <1984CHEC, 1996CHEC-II>. Dimethylaminodimethoxymethane can react with 1-(2-hydroxyphenyl)-3-phenylpropan-1-ones to afford homoisoflavones that are unsubstituted at C-2 (Equation 306) <2005SC563>.



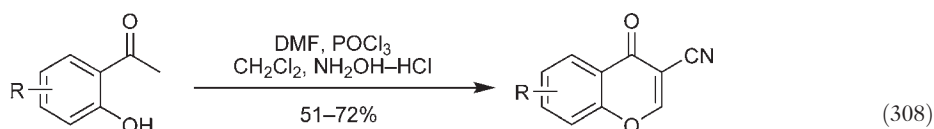
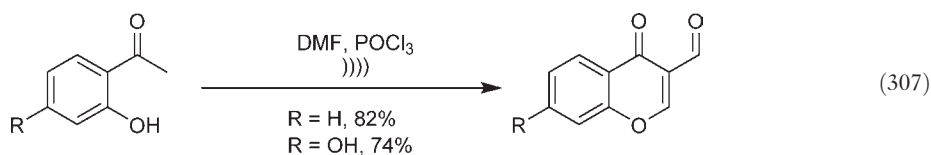
$R^1 = R^2 = R^3 = H, R^4 = H/MeO/Cl$

$R^1 = H, R^2 = MeO, R^3 = R^4 = H$

$R^1 = R^2 = H, R^3 = -OCH_2O- = R^4$

$R^1 = R^2 = H, R^3 = H/MeO, R^4 = MeO$

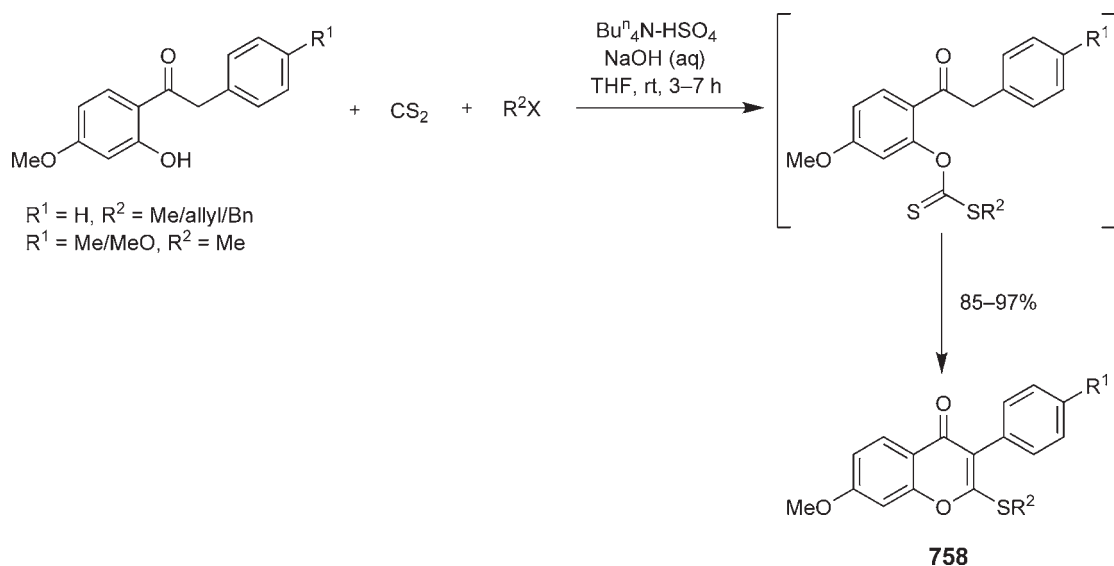
ortho-Hydroxyacetophenones react with Vilsmeier–Haack reagent under ultrasound irradiation to form 3-formylchromones in high yield (Equation 307) <2002SC1351>. A modified Vilsmeier–Haack reaction affords 3-cyanochromones directly from *ortho*-hydroxyacetophenones in good yield (Equation 308) <2004TL847>.



$R = H/5\text{-Me}/5\text{-Et}/5\text{-Pr}^i/5\text{-Br}/5\text{-Cl}$

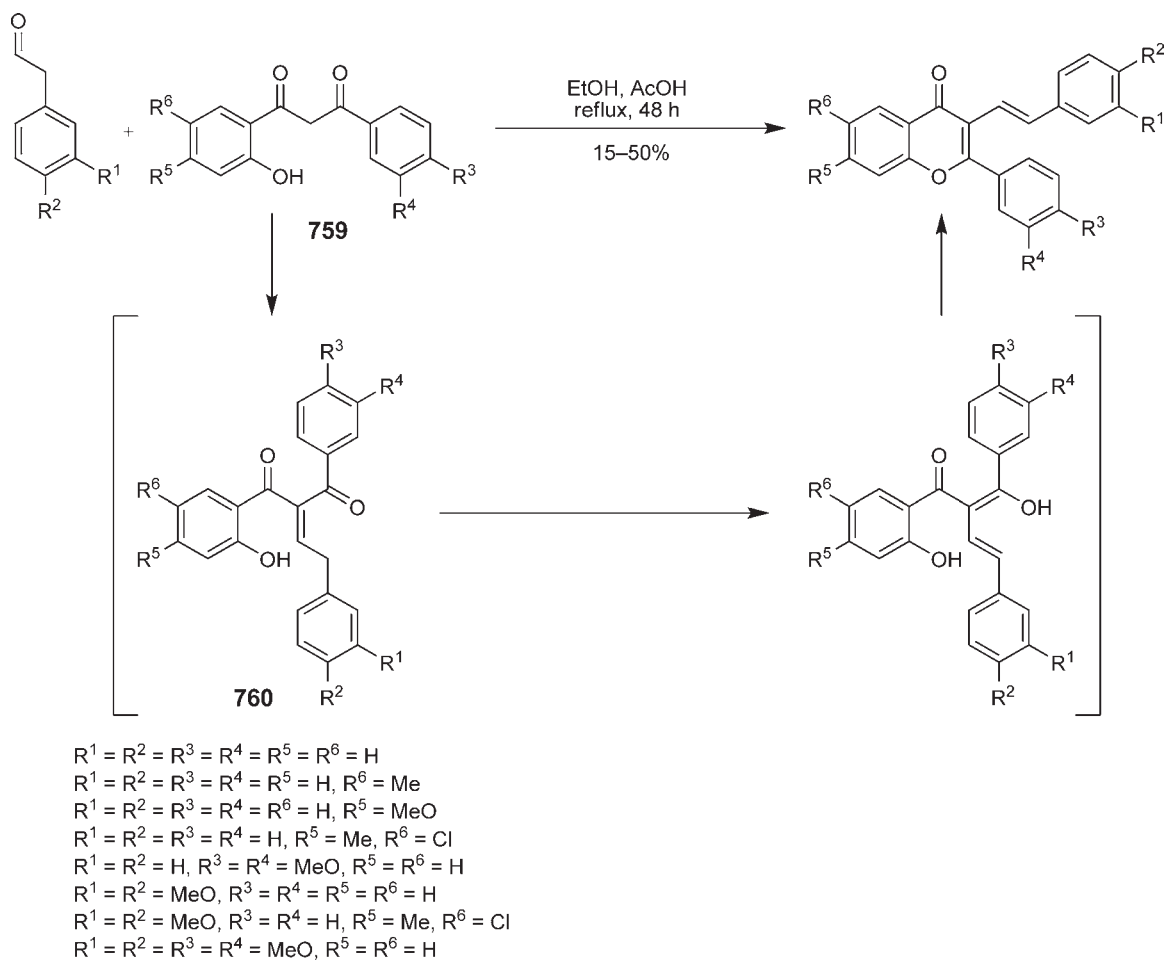
$R = 5\text{-F}/3\text{-5-Cl}_2/4,5\text{-Me}_2/5\text{-Cl-4-Me}$

2-(Alkylthio)isoflavones **758** can be prepared by the reaction of deoxybenzoins with carbon disulfide and alkyl halides under phase transfer catalysis in excellent yield (Scheme 197) <2002TL6113>.



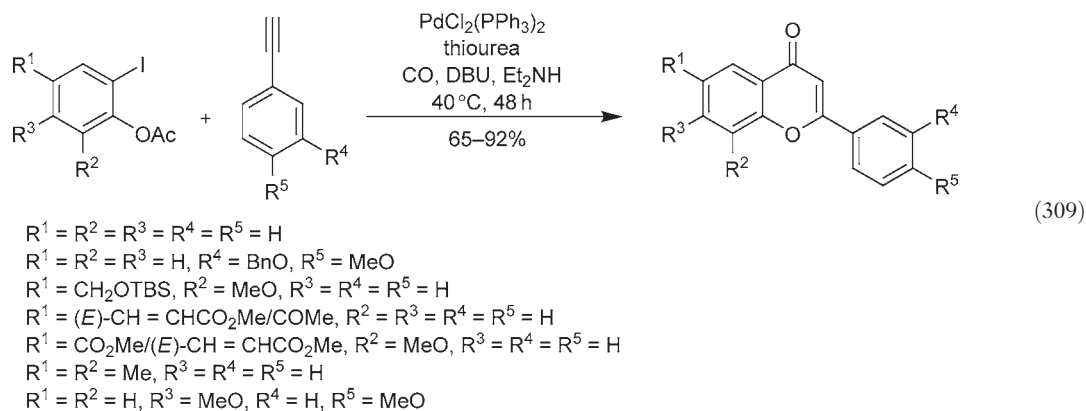
Scheme 197

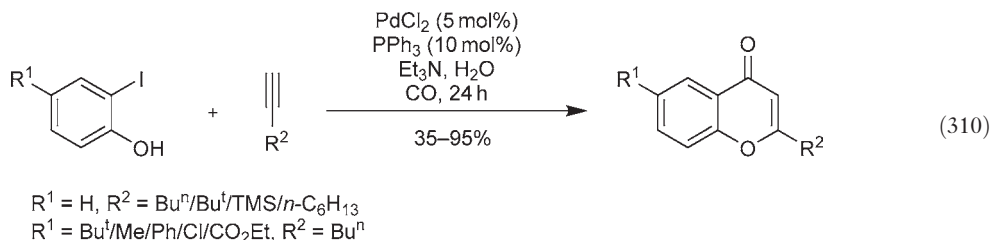
3-Styrylflavones can be accessed in modest yield by the reaction of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones **759** with 2-phenylacetaldehydes. The reaction proceeds via an initial Knoevenagel condensation to form intermediate **760**, which undergoes extended enolization and cyclization to afford 3-styrylflavones (Scheme 198) <1999TL6761>.



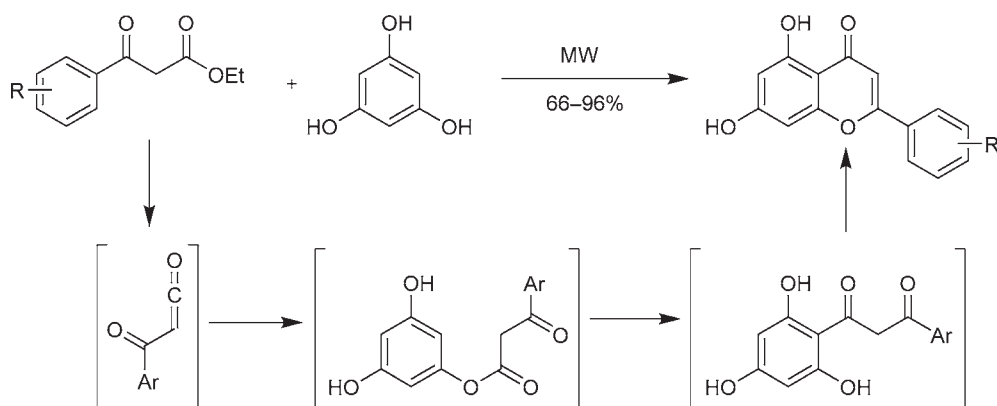
Scheme 198

2-Iodophenyl acetates undergo palladium-catalyzed carbonylation in the presence of aryl alkynes to yield flavones (Equation 309) <2000OL1765>. 2-Iodophenols can similarly undergo a palladium-catalyzed carbonylation in the presence of terminal alkynes to afford chromones (Equation 310) <2005JOC6097>.

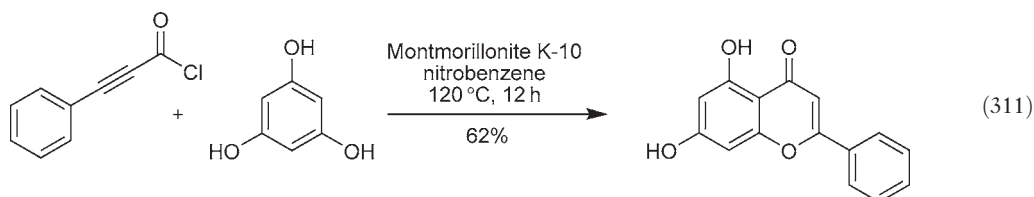




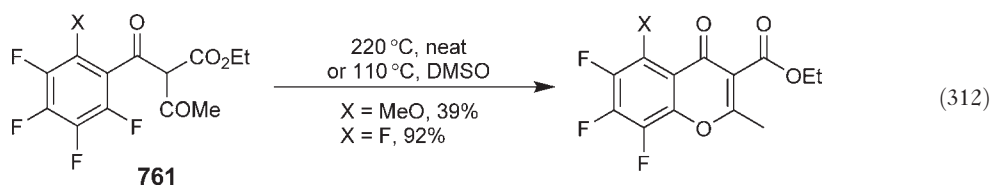
The condensation of phenols with β -keto esters to form chromones is known as the Simonis reaction and is closely related to the Pechmann synthesis of coumarins, and as a consequence, mixtures of both coumarins and chromones are usually obtained [\(<1984CHEC, 1996CHEC-II>\)](#). Microwave irradiation is effective for promoting the reaction of phloroglucinol with β -keto esters to exclusively form flavones [\(Scheme 199\) <2005JOC2855>](#). In a related procedure, the reaction of aryl propynoyl chloride with phloroglucinol can be promoted by montmorillonite-K10 clay at 120 °C to afford 5,7-dihydroxy-2-phenyl-chromone [\(Equation 311\) <2001S2247>](#).

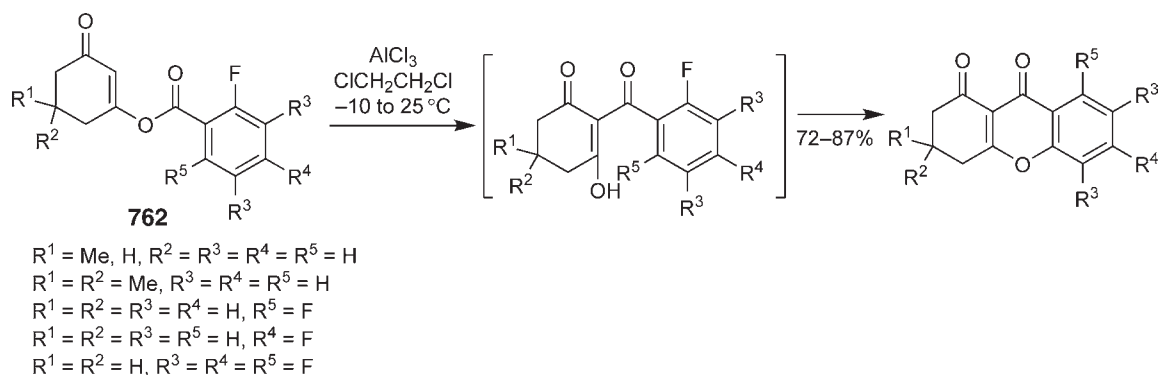


Scheme 199



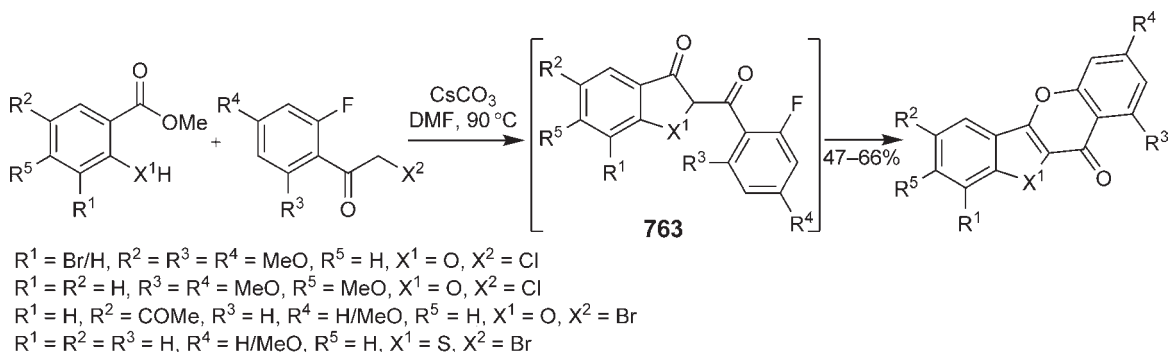
$\beta\beta'$ -Dioxoesters **761** readily undergo cyclization via *ipso*-fluorine substitution to give the fluorinated chromones in moderate to high yield [\(Equation 312\) <2001JFC\(108\)125, 2001RJO1455>](#). *ortho*-Fluorobenzoates **762** can undergo a Fries rearrangement followed by cyclization via *ipso*-fluorine substitution to afford cyclohexanone-fused chromones [\(Scheme 200\) <1997J\(P1\)1819>](#).





Scheme 200

The reaction of salicylates with *ortho*-fluoro- α -haloacetophenones in the presence of cesium carbonate forms the intermediates **763**, which can undergo ring closure via *ispo*-fluorine substitution to afford 5,11-dioxabenzob[*b*]fluoren-10-ones ($X^1 = \text{O}$) and 5-oxa-11-thiabenzob[*b*]fluoren-10-ones ($X^1 = \text{S}$) (Scheme 201) <2001TL8429>.



Scheme 201

2-Substituted chromones can be synthesized in good yield from the corresponding silyl esters **764** via formation of the ylide intermediate **765**, followed by an intramolecular Wittig reaction (Scheme 202) <2000OL3821>.

7.08.16.3 From Other Heterocycles

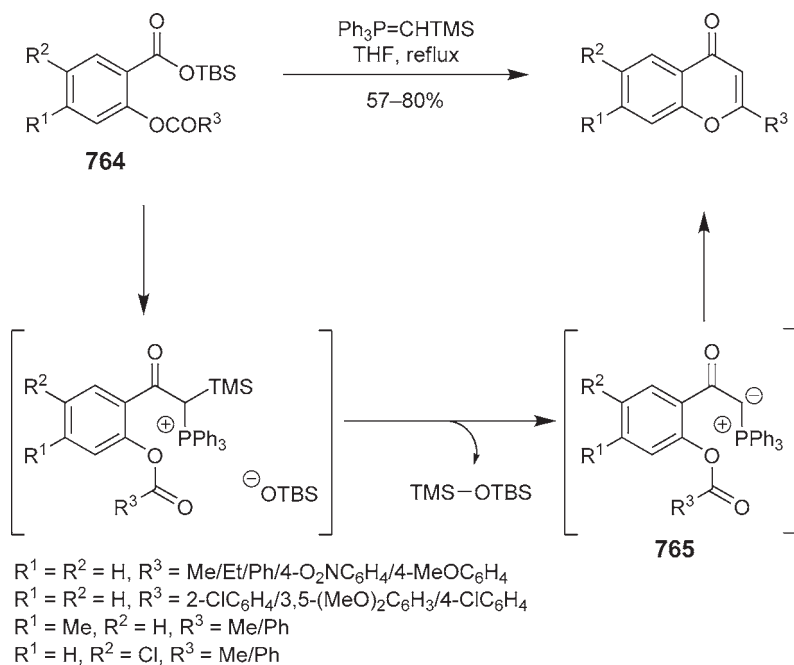
7.08.16.3.1 From benzofurans

Ring expansion of methyl 2-(bromomethyl)-7-methoxybenzofuran-5-carboxylate **766** to form the corresponding 3-hydroxychromone can be achieved, in modest yield, upon treatment with OsO_4 followed by aqueous Na_2SO_3 (Scheme 203) <1997H(45)2273>.

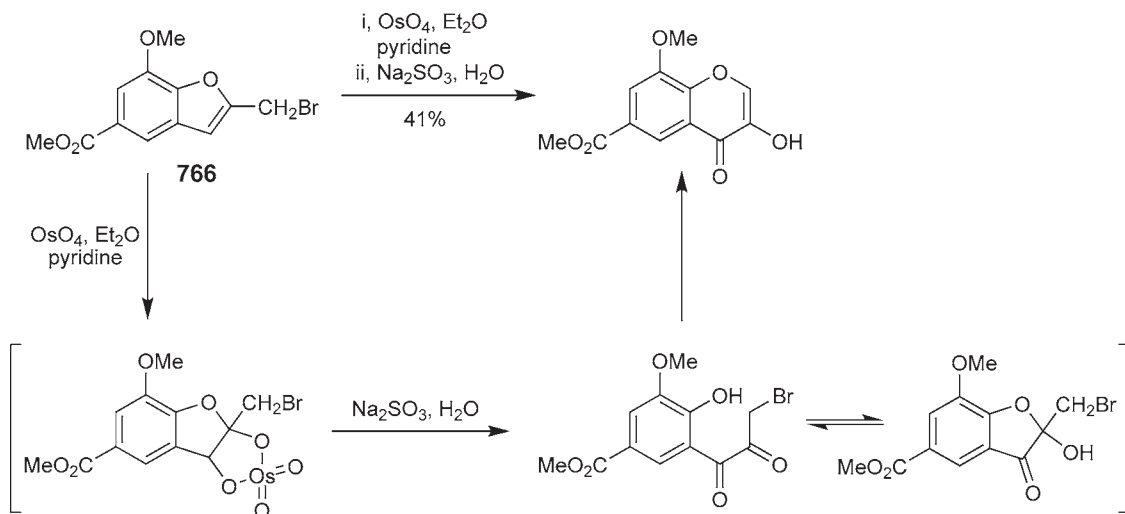
7.08.16.4 From a Preformed Heterocyclic Ring

7.08.16.4.1 From chromanones

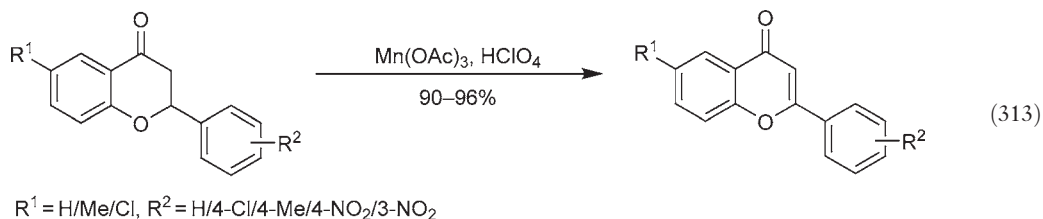
Oxidation of flavanones with manganese(III) acetate affords the corresponding flavones in high yield (Equation 313) <2005SC2723>.



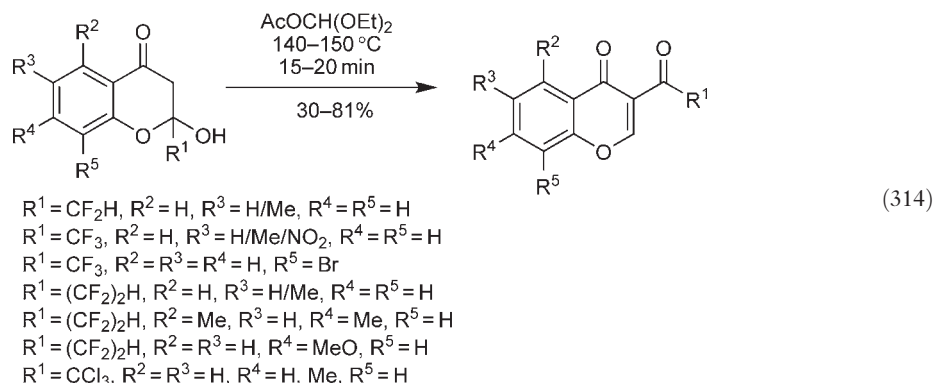
Scheme 202



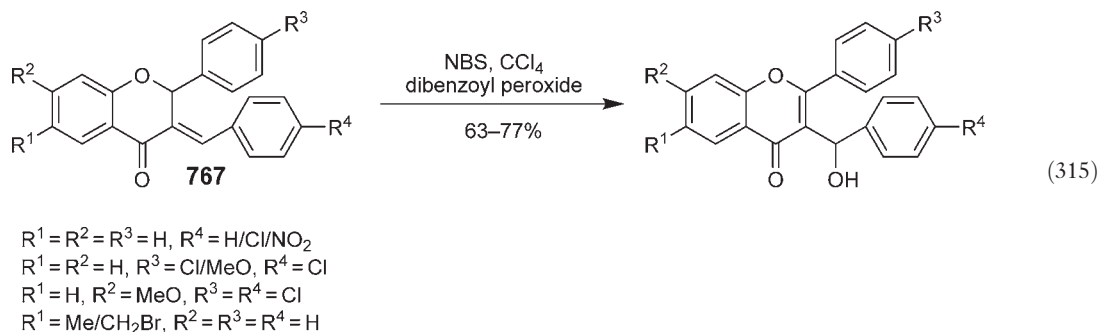
Scheme 203



Treatment of 2-hydroxy-2-(polyhaloalkyl)chroman-4-ones with diethoxymethyl acetate affords 3-(polyhaloacyl)-chromones in modest to high yield (Equation 314) <2005SL1164>.

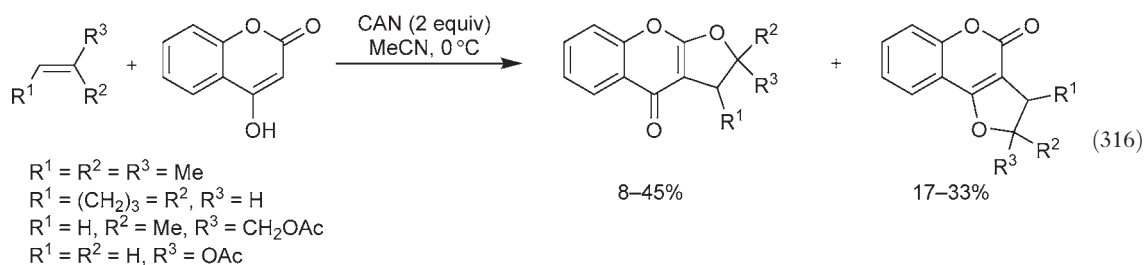


(*E*)-3-Benzylidene flavanones **767** can be transformed into 3-(α -hydroxybenzyl)flavones upon treatment with NBS and dibenzoyl peroxide (Equation 315) <1996TL8001>.



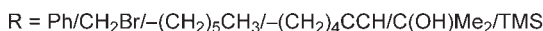
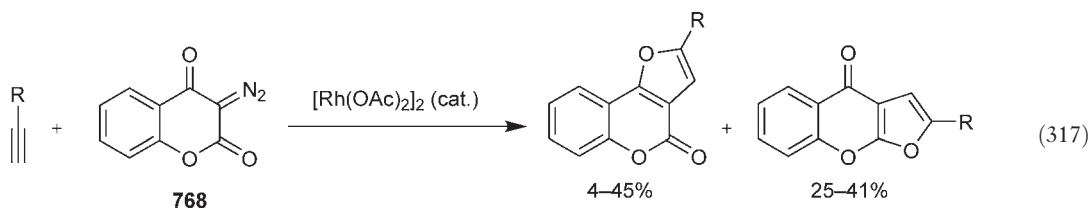
7.08.16.4.2 From coumarins

4-Hydroxycoumarin can react with alkenes in the presence of cerium(IV) ammonium nitrate (CAN) to form a mixture of furochromones and furocoumarins in modest yield (Equation 316) <1999H(51)2881>.



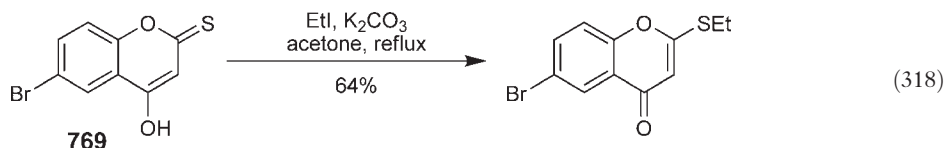
7.08.16.4.3 From 3-diazochroman-2,4-diones

3-Diazochroman-2,4-dione **768** reacts with terminal alkynes in the presence of $[Rh(OAc)_2]_2$ to provide a mixture of 4*H*-furo[3,2-*c*]chromen-4-ones and 4*H*-furo[2,3-*b*]chromen-4-ones (Equation 317) <2001S735>.



7.08.16.4.4 From chromenes

6-Bromo-4-hydroxy-2*H*-chromene-2-thione **769** can be converted to the corresponding 2-(ethylthio)chromone upon treatment with ethyl iodide in the presence of K₂CO₃ (Equation 318) <2004BML6083>.



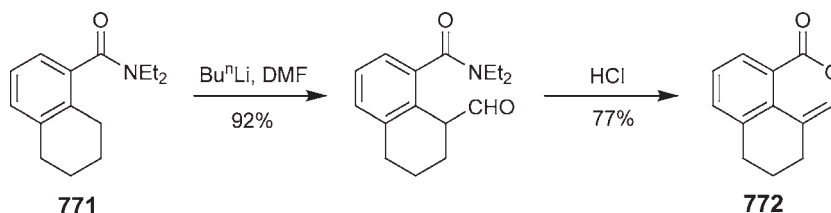
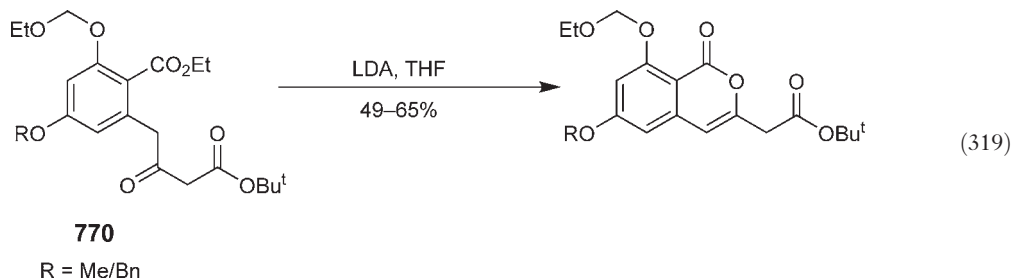
7.08.17 Isocoumarins (1*H*-2-Benzopyran-1-ones)

A review detailing synthetic approaches towards isocoumarins is available <1997OPP631>.

7.08.17.1 Formation of One Bond

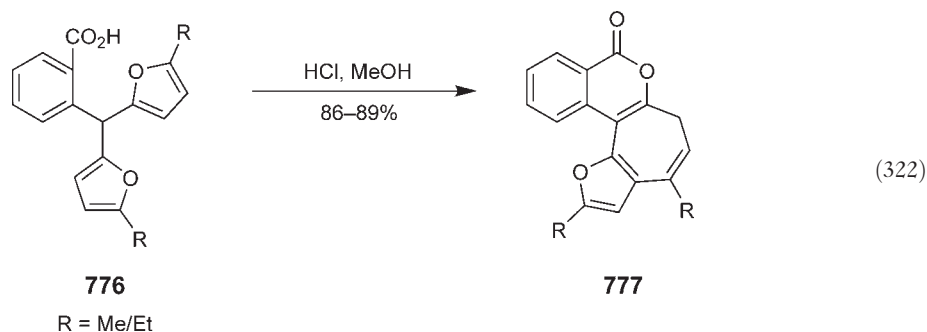
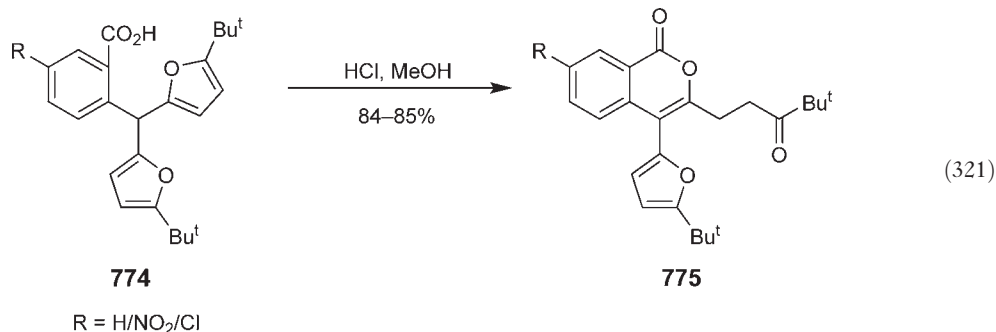
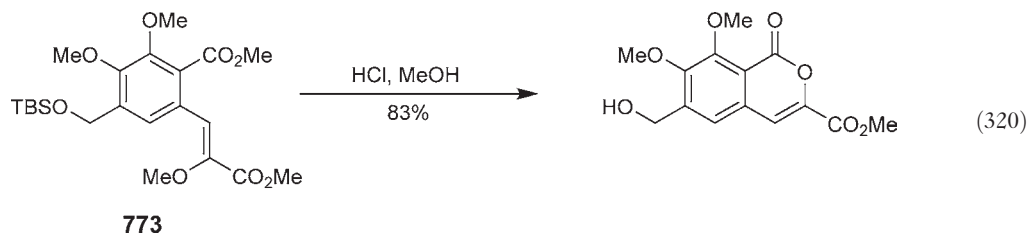
7.08.17.1.1 Adjacent to the heteroatom

The cyclization of 2-carboxybenzyl ketones and their derivatives affords isocoumarins <1984CHEC, 1996CHEC-II>. The LDA promoted cyclization of the 2-carboxybenzyl ketones **770** features in the synthesis of anti-angiogenic isocoumarins (Equation 319) <2004COR>. Similarly, the diethyl amide **771** undergoes formylation via lateral lithiation followed by acid-promoted cyclization to afford 5,6-dihydrobenzo[*de*]isochromen-1(4*H*)-one **772** in high yield (Scheme 204) <2000S1113>.

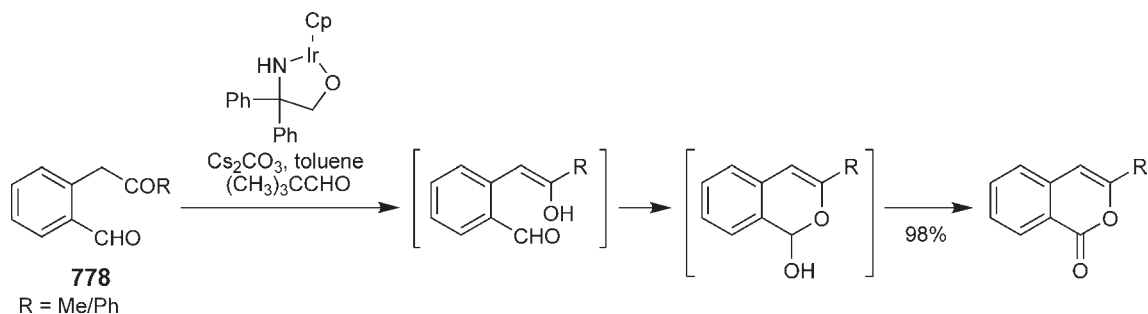


Scheme 204

Furans and enol ethers can provide latent carbonyl groups for heterocyclization. In this manner, acid promoted lactonization of the enol ether **773** is used to synthesize the isocoumarin portion of the rubromycins (Equation 320) <2001TL3567>. The acid-promoted furan ring opening and recyclization of bis(2-furyl)(2-carboxyphenyl) methanes **774** affords 4-(5-*tert*-butylfuran-2-yl)-3-(4,4-dimethyl-3-oxopentyl)-isocoumarins **775** in high yield (Equation 321) <2001JOC8685, 2005CHE1194>. In addition, the bis(2-furyl)(2-carboxyphenyl) methanes **776** can undergo further furan ring opening and recyclization to afford tetracyclic isocoumarins **777** in high yield (Equation 322) <2001JOC8685, 2005CHE1194>.

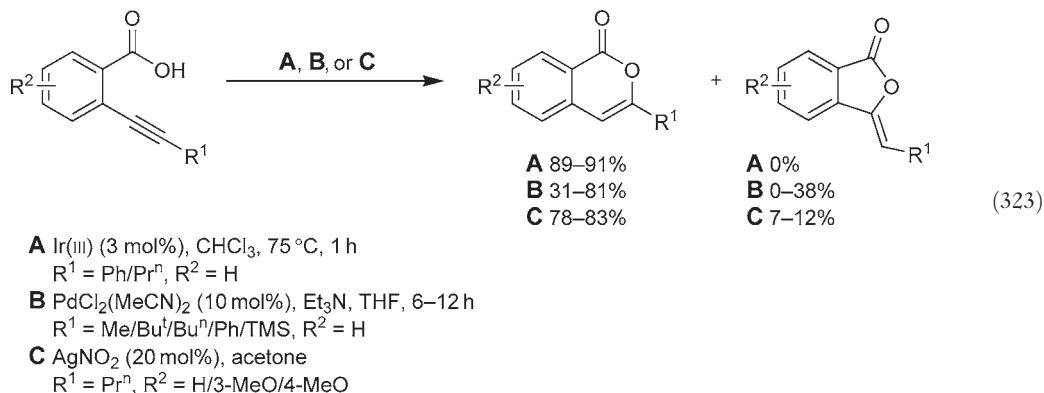


The iridium-catalyzed oxidative lactonization of 2-carbaldehyde benzylketones **778** forms isocoumarins in high yield (Scheme 205) <2005BML2583>.

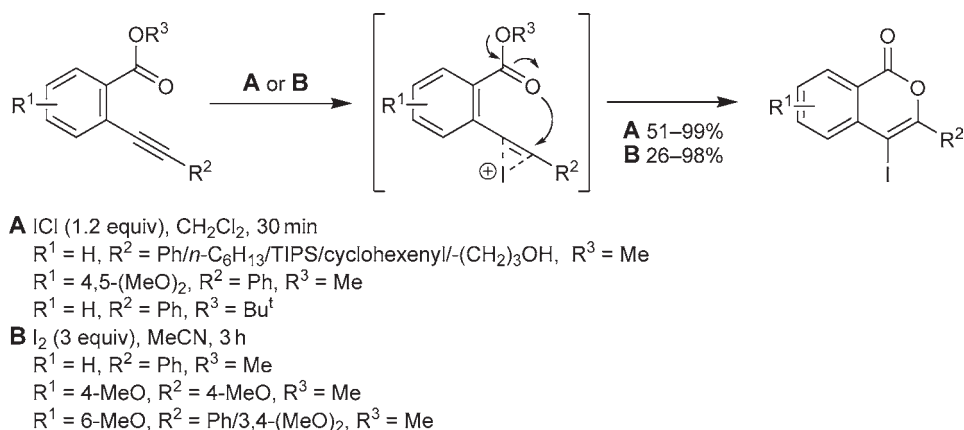


Scheme 205

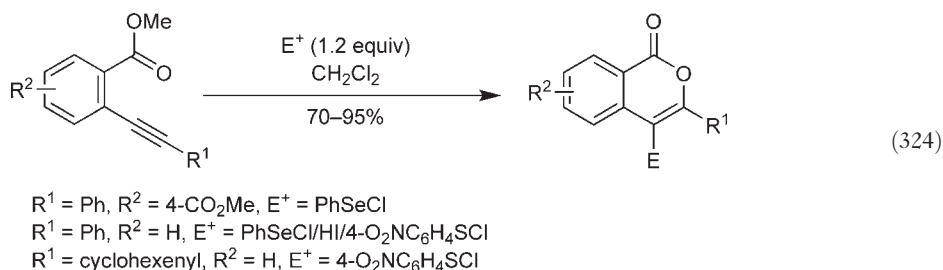
Iridium(III) hydrides catalyze a 6-*endo-dig* cyclization of *ortho*-alkynyl benzoic acids to afford isocoumarins (Equation 323) <2005OL5437>. Likewise, the intramolecular cyclization of *ortho*-alkynyl benzoic acids can be catalyzed by palladium(II) and silver(II) to afford isocoumarins as the major product along with formation of the 5-*endo-dig* cyclization product (Equation 323) <1999S1145, 2000T2533>.



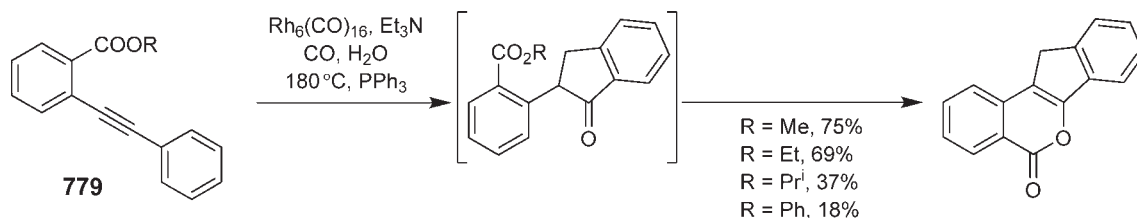
Electrophilic cyclization of *ortho*-alkynyl benzoates using iodine or ICl affords 4-iodocoumarins in good yield (Scheme 206) <2002TL7401, 2002T5023, 2003JOC5936>. Electrophiles other than iodine can effectively mediate the electrophilic cyclization of *ortho*-alkynyl benzoates with concomitant incorporation of the electrophile into C-4 of the resulting isocoumarin (Equation 324) <2003JOC5936>.



Scheme 206

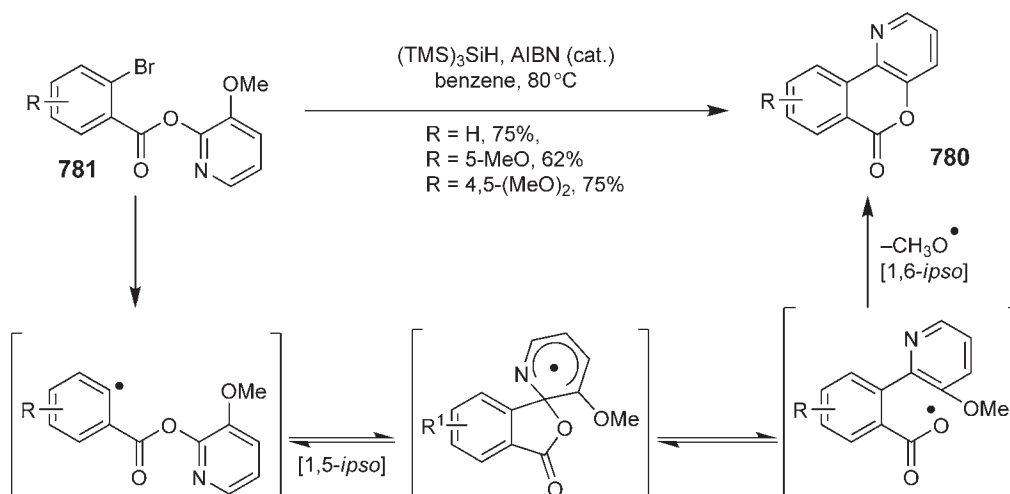


Alkyl 2-phenylethynylbenzoates **779** can undergo rhodium-catalyzed carbonylation and cyclizations under water–gas shift reaction conditions to form indeno[1,2-*c*]isocoumarins (Scheme 207) <1997TL4989, 1999JMO211>.



Scheme 207

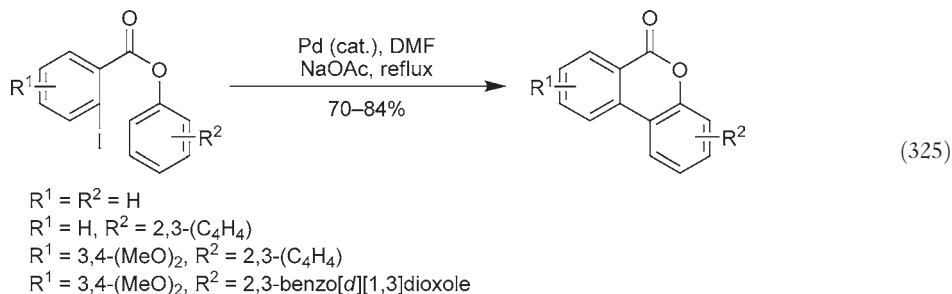
Azabenzisocoumarins **780** are prepared from 3-methoxyphenyl 2-bromobenzoates **781** by a double radical *ipso*-substitution process (Scheme 208) <2003T3009>.



Scheme 208

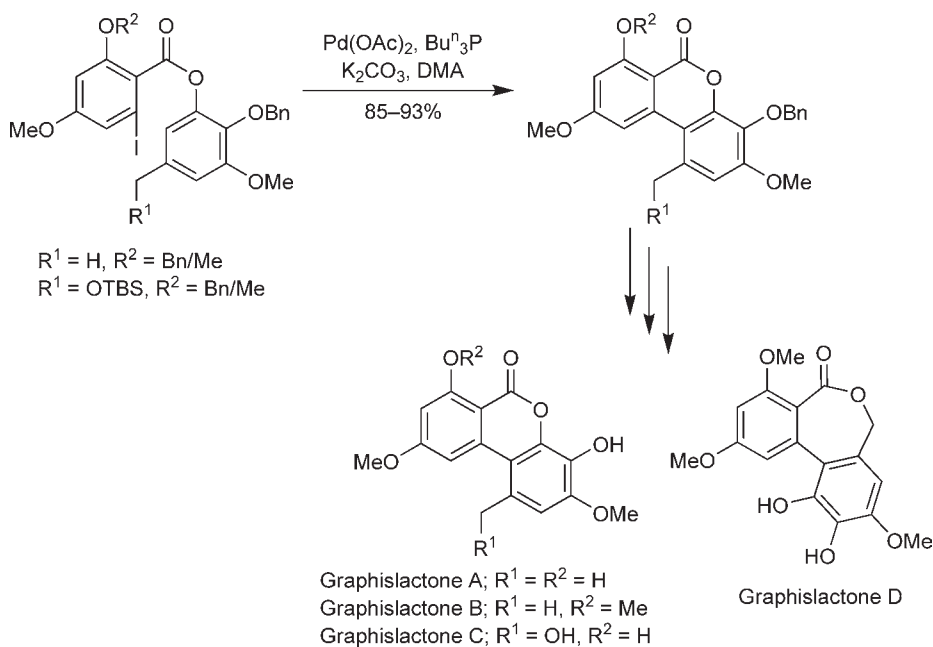
7.08.17.1.2 γ to the heteroatom

Phenyl 2-iodobenzoates can undergo palladium mediated intramolecular biaryl coupling reactions to afford benzo[*c*]-coumarins in good yield (Equation 325) <1997H(46)61>. This high-yielding intramolecular biaryl coupling features in the total syntheses of graphislacones A–D (Scheme 209) <2005TL3197>.

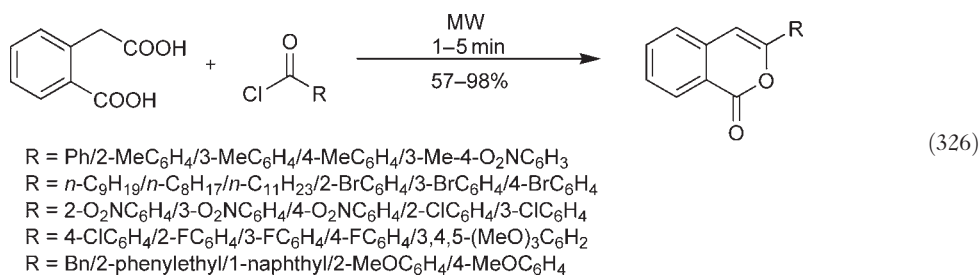


7.08.17.2 Formation of More than One Bond

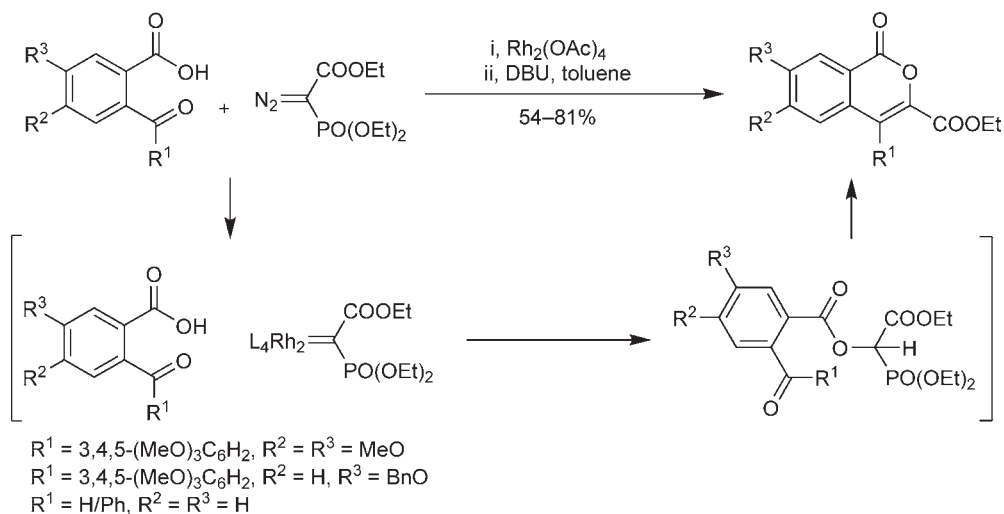
3-Substituted isocoumarins can easily be accessed via the condensation of acyl chlorides with homophthalic acid, which proceeds in short reaction times under microwave irradiation in high yield (Equation 326) <2005MI532>.



Scheme 209

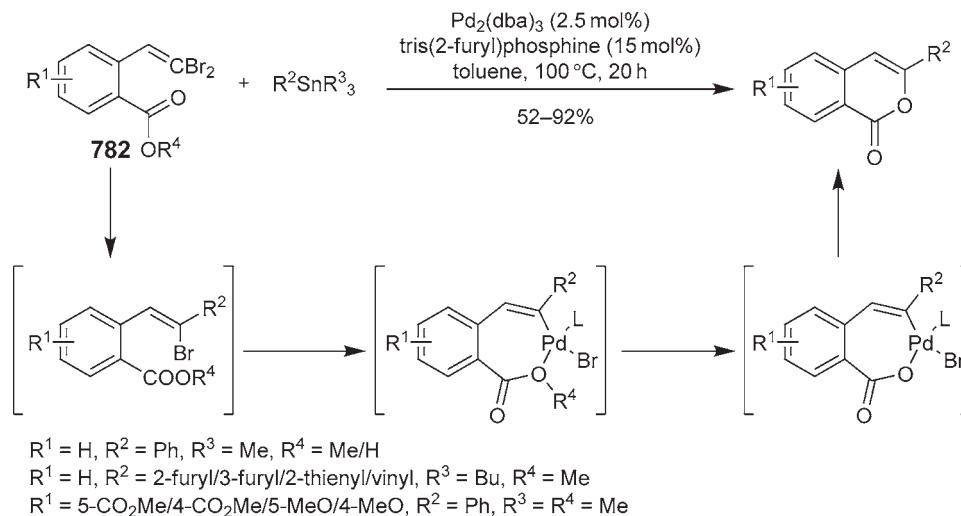


3,4-Disubstituted isocoumarins are prepared from *ortho*-carboxy benzoic acids and α -diazophosphonates via a dirhodium(II)-mediated O–H insertion followed by a Horner–Wadsworth–Emmons intramolecular cyclization (Scheme 210) <2002OL2317>.

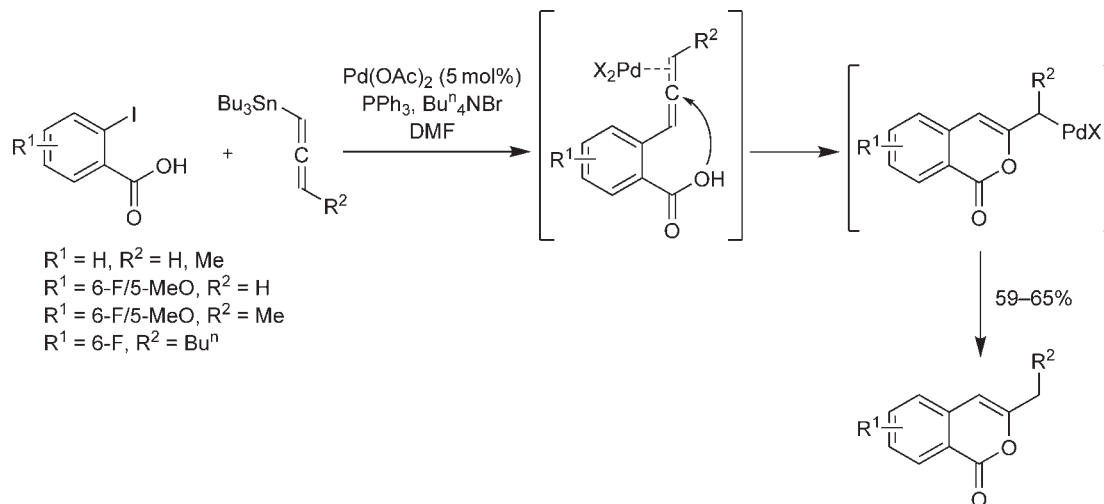


Scheme 210

Methyl 2-(2,2-dibromovinyl)benzoates **782** can undergo a Stille coupling, followed by palladium-catalyzed lactonization to form 3-substituted isocoumarins in good yield (**Scheme 211**) <1998TL7625>. Similarly, the reaction of *ortho*-iodobenzoic acids with allenyltributyltin reagents proceeds via a Stille coupling followed by a palladium-induced lactonization (**Scheme 212**) <2005JOC6669>.



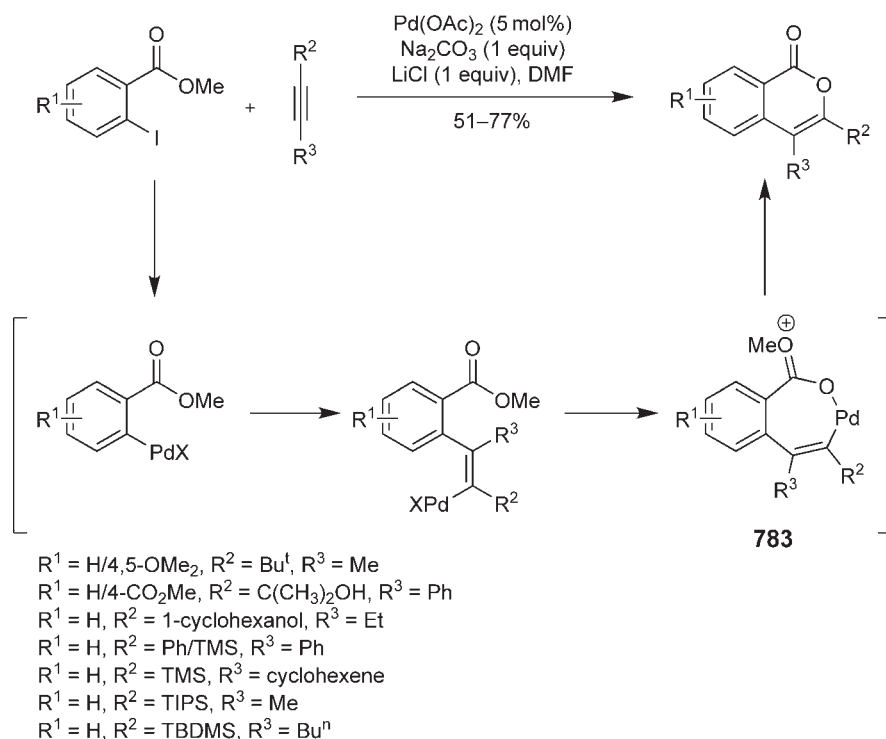
Scheme 211



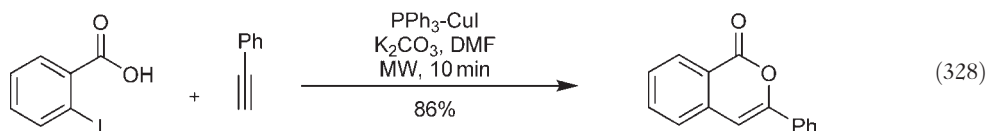
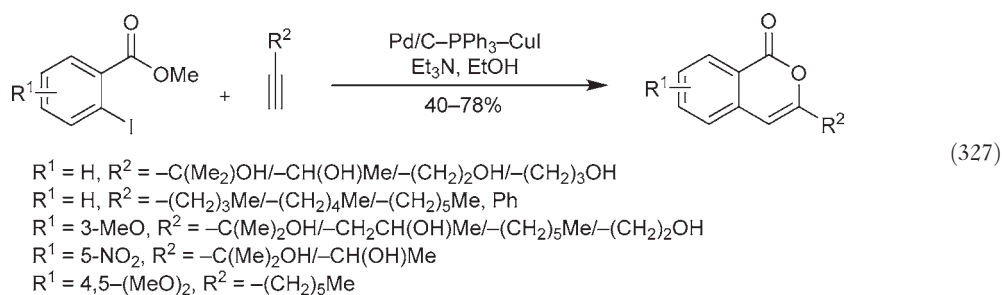
Scheme 212

ortho-Iodobenzoates react with internal alkynes to give isocoumarins via formation of the seven-membered palladacycle intermediate **783** (**Scheme 213**) <1999JOC8770>. This process displays high regioselectivity with unsymmetrically substituted alkynes, whereby the less sterically demanding group becomes the C-4 substituent of the resulting isocoumarin (**Scheme 213**) <1999JOC8770>.

Terminal alkynes can be coupled with *ortho*-iodobenzoic acids, using a $Pd/C-PPh_3-CuI$ catalytic system to afford 3-substituted isocoumarins (Equation 327) <2005JOC4778>. Likewise, the copper(I) mediated coupling of *ortho*-iodobenzoic acid with ethynylbenzene under microwave irradiation forms 3-phenyl-isocoumarin in excellent yield (Equation 328) <2002SC1937>.



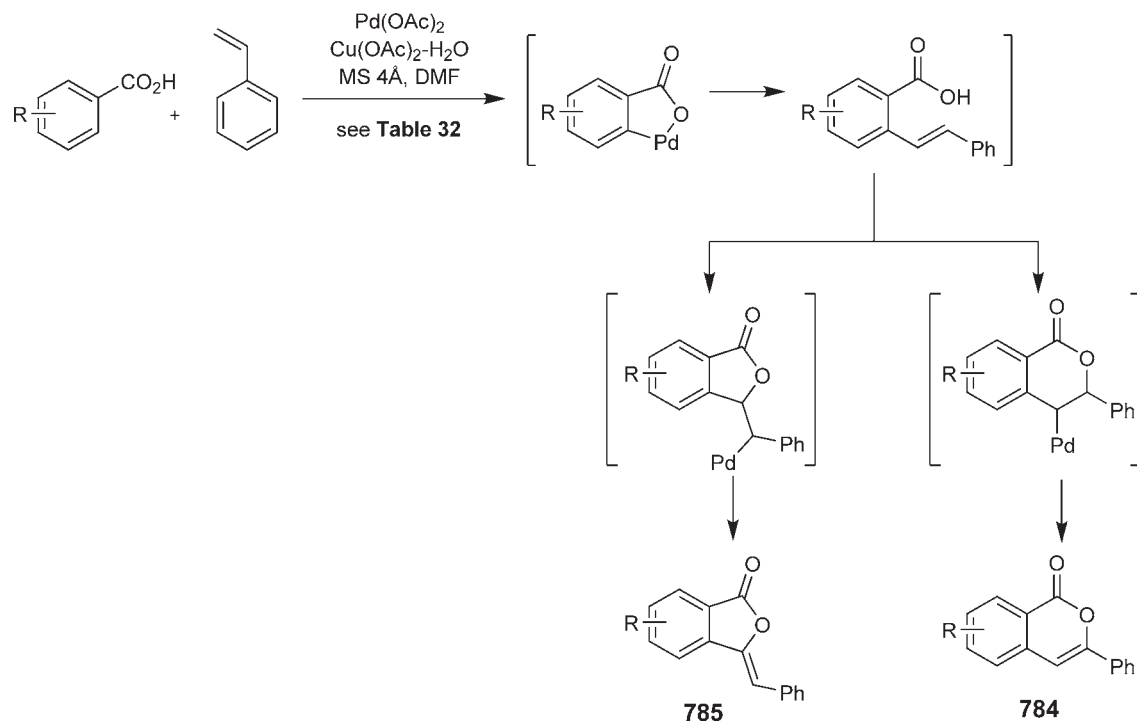
Scheme 213



Mediated by a palladium(II)–copper(II) catalytic system benzoic and naphthoic acids react with styrene to yield a mixture of isocoumarins **784** and alkylidene phthalides **785** (Scheme 214, Table 32) <1998JOC5211>.

2-Formylbenzoic acid, potassium cyanide and anilines react in the presence of acetic acid to afford 3-amino-4-arylamino-isocoumarins (Scheme 215). The reaction proceeds via an initial Strecker reaction to form intermediate **786** followed by intramolecular attack of the carboxyl group onto the nitrile (Scheme 215) <2005EJO817>.

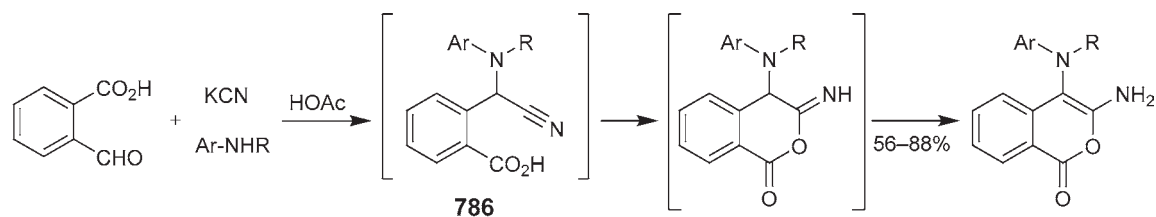
(*Z*)-2-(But-3-en-1-ynyl)phenyl 3-bromoacrylates **787** react with terminal alkynes via a Sonogashira coupling–benzannulation process to afford 10-vinyl-6*H*-benzo[*c*]chromen-6-ones **788** (Scheme 216) <2002JOC5138>. An intramolecular aldol condensation of 2-(3-(2-formylphenyl)-2-oxopropyl)benzoic acid **789** forms the intermediate **790**, which undergoes spontaneous lactonization to afford 5*H*-dibenzo[*c,g*]chromen-5-one (Scheme 217) <2005T1353>. Boroxarenes **791** undergo palladium(II)-catalyzed carbonylation leading to benzo[*c*]isocoumarins in excellent yield (Equation 329) <2004JOC5147>.



Scheme 214

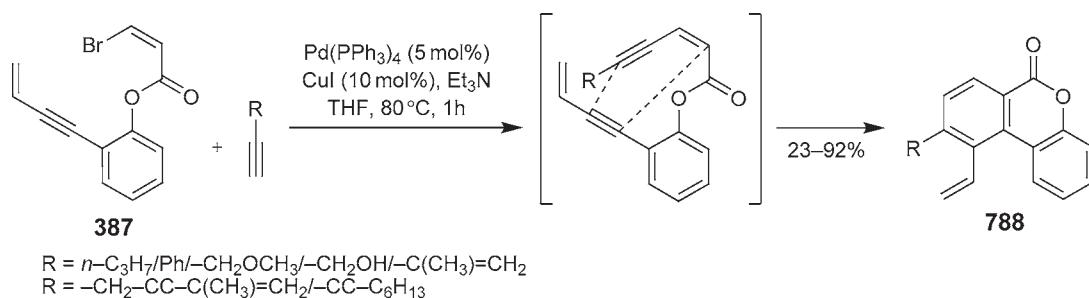
Table 32 Yields of **784** and **785** for the Pd(II)–Cu(II) coupling of aryl carboxylic acids with styrene

R	Yield (%)	
	784	785
H	56	0
4-MeO	26	14
2-Me	0	55
2,3-(C ₄ H ₄)	0	34
3,4-(C ₄ H ₄)	59	0

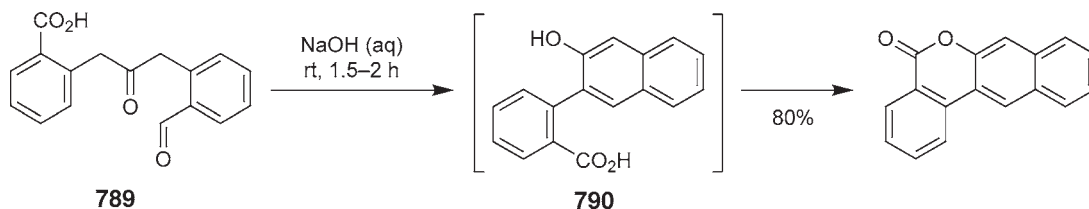


R = H, Ar = Ph/2-MeC₆H₄/3-MeC₆H₄/4-MeC₆H₄/3-MeOC₆H₄
 R = H, Ar = 4-MeOC₆H₄/4-CF₃C₆H₄/4-BrC₆H₄/4-ClC₆H₄/2,4-(Me)₂C₆H₃
 R = Me, Ar = Ph

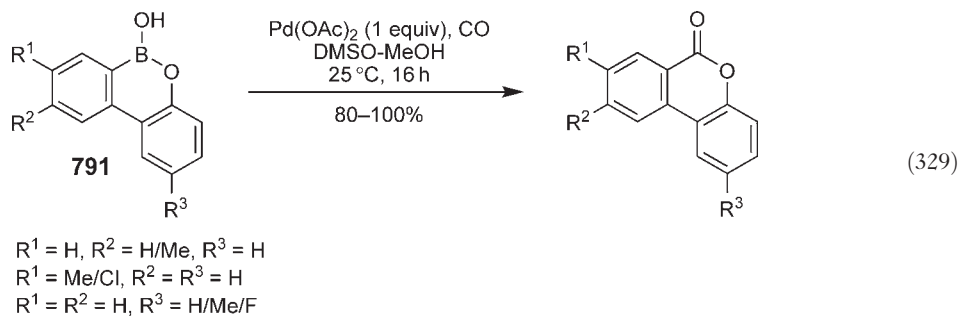
Scheme 215



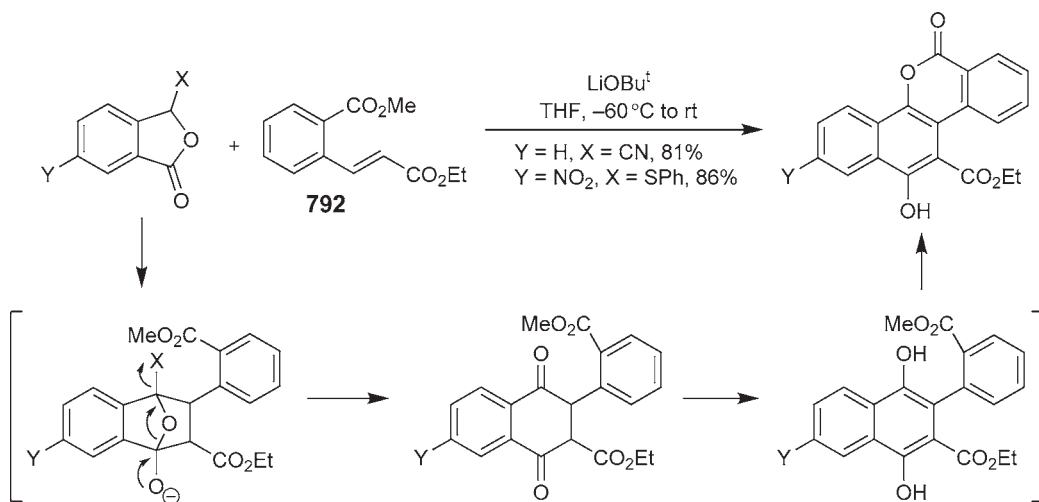
Scheme 216



Scheme 217

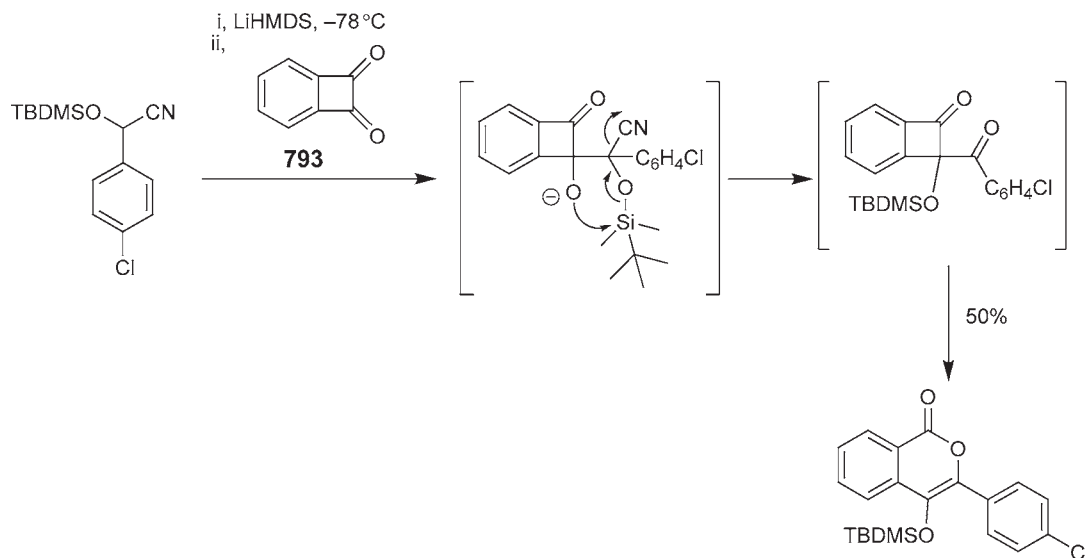


A Hauser-Kraus annulation of the *ortho*-acetyl cinnamate **792** with phthalides affords naphtho[*c*]-isocoumarins in high yield (Scheme 218) <2004TL7895>.



Scheme 218

The addition of lithiated *tert*-butyldimethylsilyloxy(4-chlorophenyl)acetonitrile to the cyclobutenedione **793** affords 4-silyloxy-3-aryl-isocoumarin in moderate yield (Scheme 219) <1999JOC2145>.

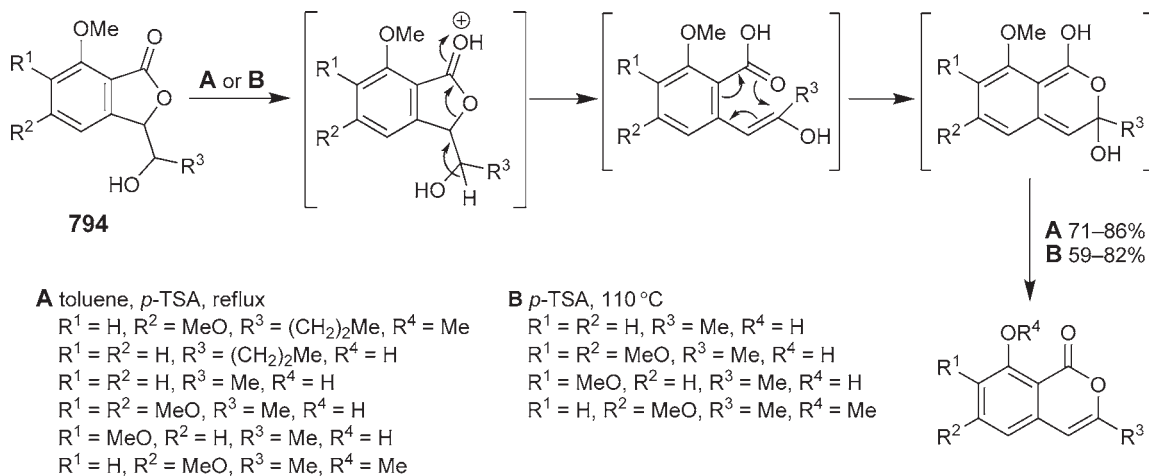


Scheme 219

7.08.17.3 From Other Heterocycles

7.08.17.3.1 From phthalides

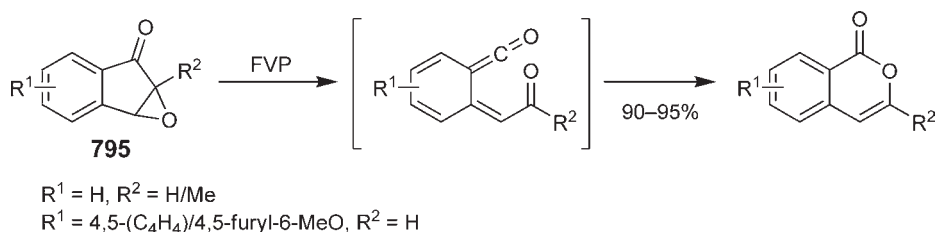
The acid-catalyzed rearrangement of 7-methoxy-3-(1-hydroxyalkyl)phthalides **794** affords 3-alkylisocoumarins in good yield (Scheme 220) <1998JOC2488>.



Scheme 220

7.08.17.3.2 From indenone epoxides

Flash vacuum pyrolysis (FVP) of the indenone epoxides **795** results in a thermal rearrangement to form the intermediate ketene, which can undergo electrocyclicization to afford isocoumarins in high yield (Scheme 221) <2000TL3677>.

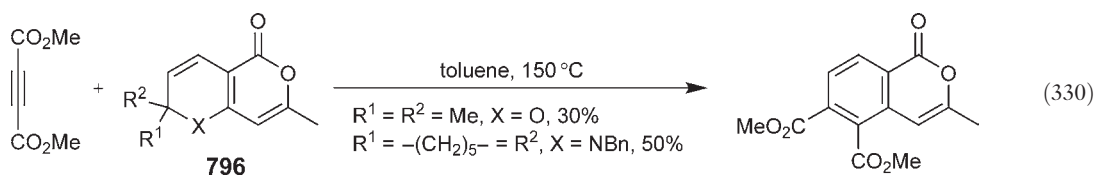


Scheme 221

7.08.17.4 From a Preformed Heterocyclic Ring

7.08.17.4.1 From pyran-2-ones

2*H*-Pyran-2-ones **796** can undergo Diels–Alder reaction with dimethyl acetylene dicarboxylate to afford dimethyl 3-methyl-isocoumarin-5,6-dicarboxylate in modest yield (Equation 330) <2003JOC1729>.

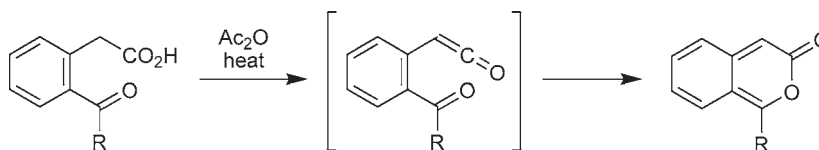


7.08.18 3*H*-2-Benzopyran-3-ones

7.08.18.1 Formation of One Bond

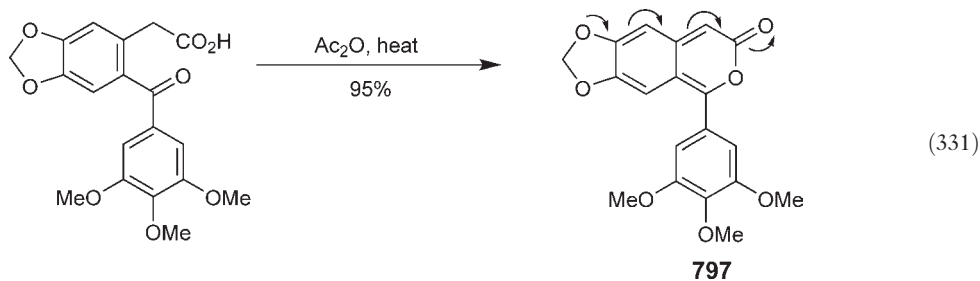
7.08.18.1.1 Adjacent to the heteroatom

3*H*-2-Benzopyran-3-ones are not generally isolated, but they are useful as reactive intermediates and especially as reactive Diels–Alder dienes. The generation of 3*H*-2-benzopyran-3-ones is usually achieved by the cyclodehydration of *ortho*-acylphenylacetic acids carried out in the presence of acetic anhydride (Scheme 222) <1996CHEC-II>.



Scheme 222

6,7-Methylenedioxy-1-(3,4,5-trimethoxyphenyl)-2-benzopyran-3-one **797** can be isolated in high yield due to stabilization by conjugation of the C-6 oxygen onto the pyrone carbonyl group (Equation 331) <1993J(P1)2533>. A key step in the asymmetric synthesis of (–)-podophyllotoxin is the Diels–Alder reaction of 3*H*-2-benzopyran-3-one **797** with the chiral dienophile **798** (Figure 2) <1996J(P1)151>.



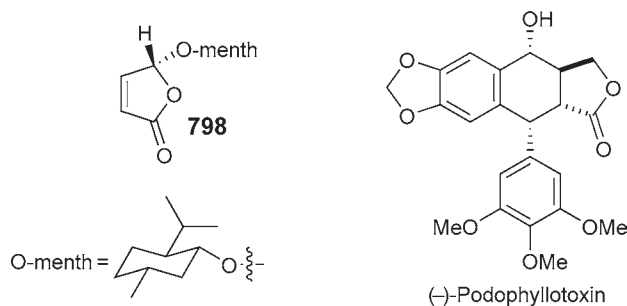


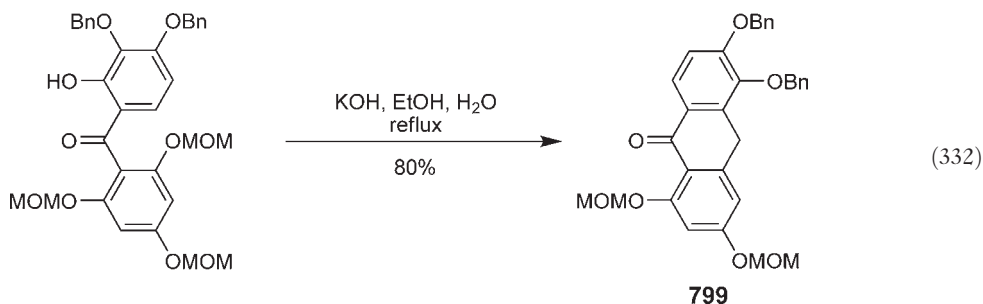
Figure 2

7.08.19 Xanthenes (9*H*-Dibenzo [*b,e*]pyran-9-ones)

7.08.19.1 Formation of One Bond

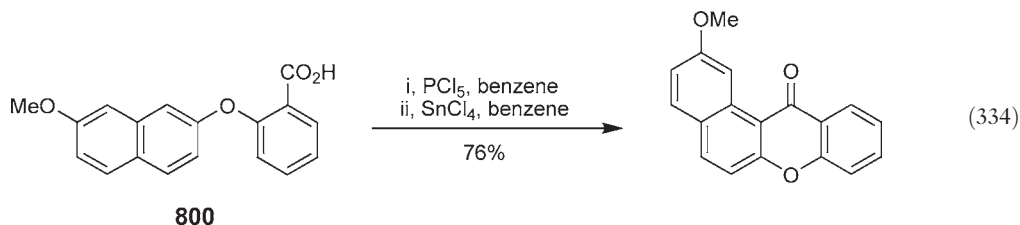
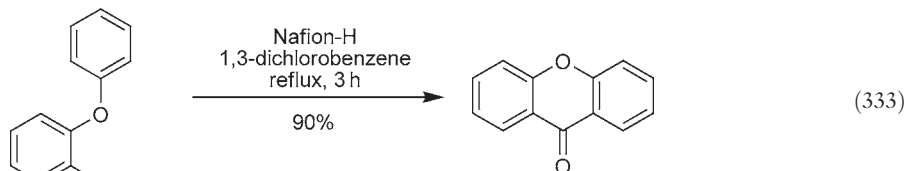
7.08.19.1.1 Adjacent to the heteroatom

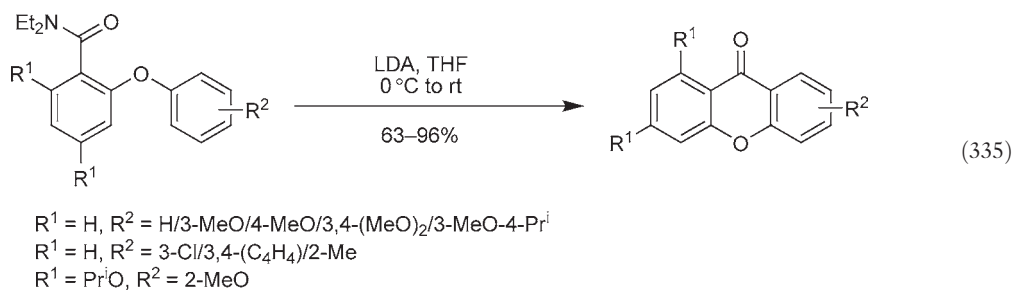
The cyclization of 2-hydroxybenzophenones is a well-documented procedure for the synthesis of xanthenes <1984CHEC, 1996CHEC-II>. Xanthone **799** is a key intermediate during the synthesis of gambogin and can be accessed in high yield via cyclization of the corresponding 2-hydroxybenzophenone derivative (Equation 332) <2005AGE756>.



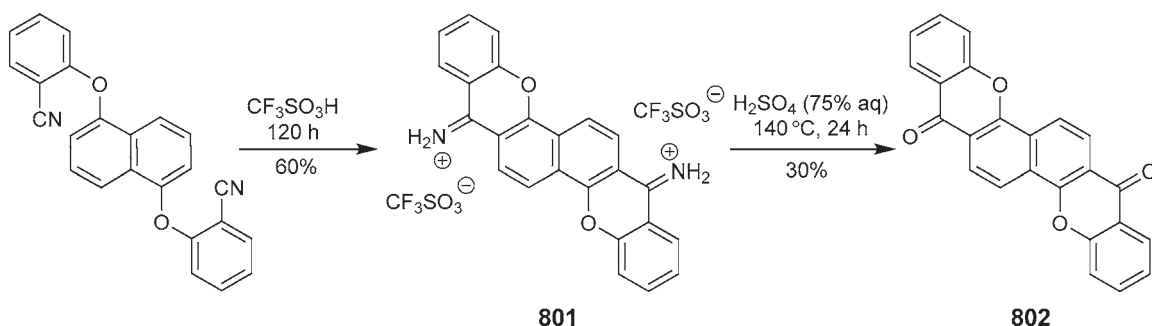
7.08.19.1.2 γ to the heteroatom

The cyclodehydration of *ortho*-phenoxybenzoic acid derivatives is a well-established route to xanthenes <1996CHEC-II>. Nafion-H can effectively mediate the intramolecular benzoylation of *ortho*-phenoxybenzoic acid to afford xanthone in an excellent yield (Equation 333) <1999SL1067>. Transformation of the *ortho*-naphthoxybenzoic acid **800** into the corresponding acyl chloride followed by treatment with SnCl_4 affords the corresponding xanthone in high yield (Equation 334) <2002OL1067>. Similarly, diaryl ether 2-carboxamides undergo LDA mediated intramolecular benzoylations to afford xanthenes (Equation 335) <1997SL1081>.





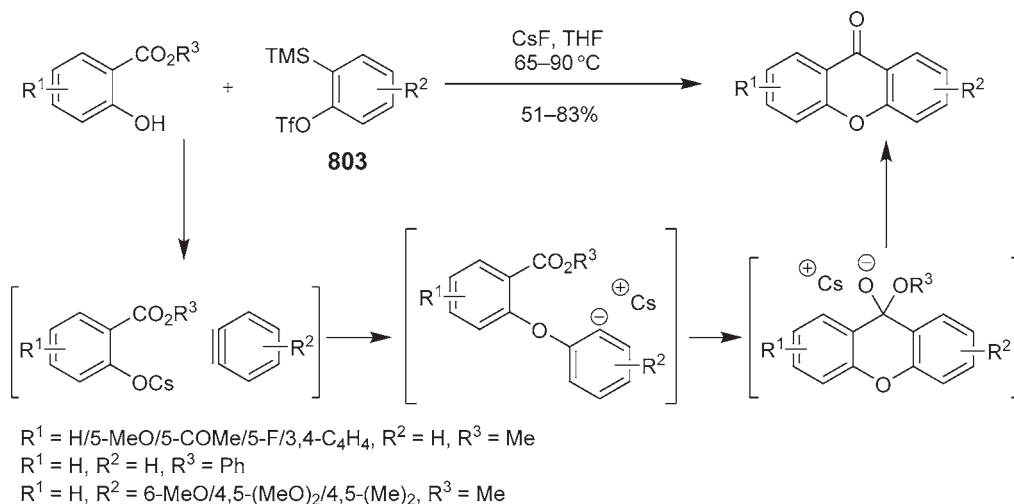
Cyclization of 2,2'-(naphthalene-1,5-diylbis(oxy))dibenzonitrile to form the dioxanthone-iminium triflate **801** occurs upon treatment with trifluoromethanesulfonic acid in good yield. Vigorous conditions are required for the hydrolysis of the dioxanthone-iminium triflate **801** and the corresponding xantheno[4,3-*c*]xanthene-8,16-dione **802** is accessed in modest yield (Scheme 223) <2001OL2337>. This approach can also be used to synthesize polymeric dioxanthenes in moderate yield <2001OL2337>.



Scheme 223

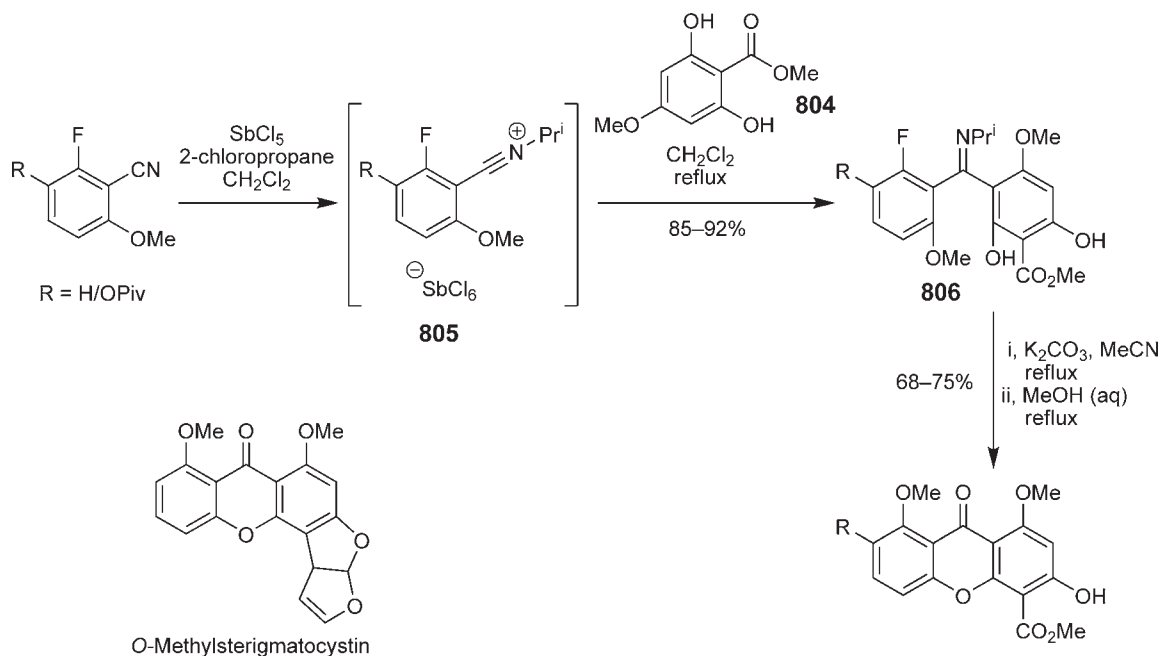
7.08.19.2 Formation of More than One Bond

Benzyne generated from silylaryl triflates **803** react with *ortho*-hydroxy benzoates via a tandem nucleophilic coupling–electrophilic cyclization process to afford xanthenes in good yield (Scheme 224) <2005OL4273>.



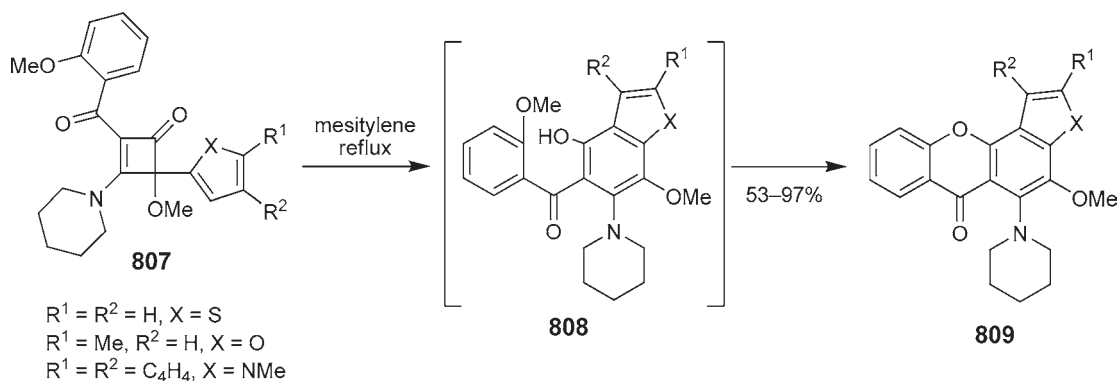
Scheme 224

The total synthesis of *O*-methylsterigmatocystin features the intermolecular imino-acylation of methyl 2,6-dihydroxy-4-methoxybenzoate **804** with *N*-alkylnitrilium salts **805** to form the benzophenone ketoimines **806**. Treatment of the benzophenone ketoimines **806** with K_2CO_3 under reflux in acetonitrile forms the corresponding imine xanthone, which is hydrolyzed to afford the xanthone (Scheme 225) <1999JOC4050>.

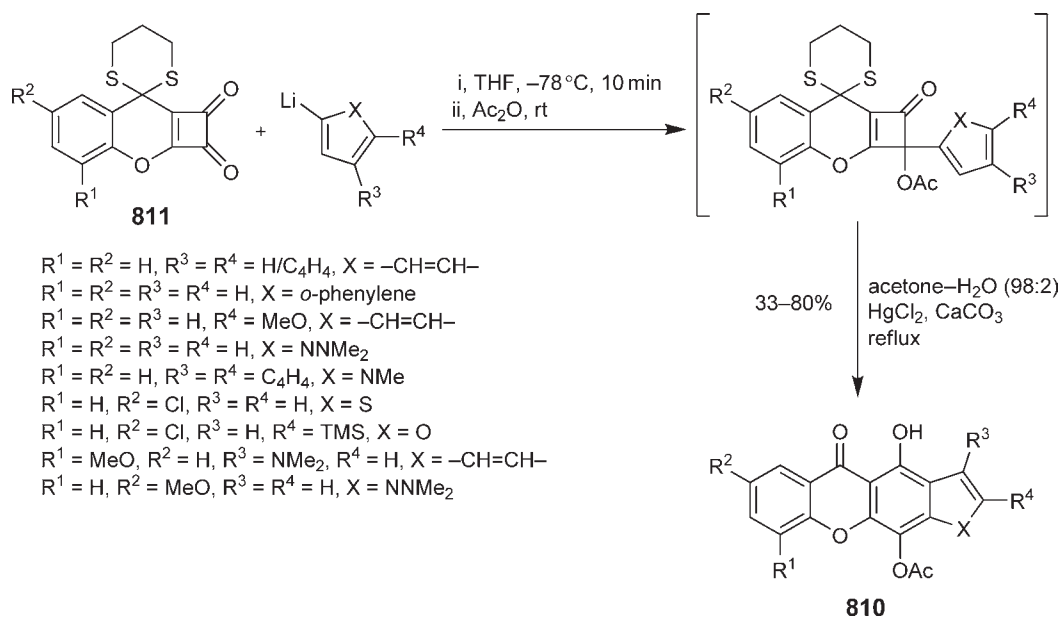


Scheme 225

Thermolysis of 3-(*ortho*-anisoyl)-1-(1-piperidiny)-3-cyclobutenes **807** in the presence of mesitylene affords angular-fused xanthenes **809** via formation and ring closure of the intermediate **808** (Scheme 226) <1997TL3663>. Linear-fused xanthenes **810** are prepared by nucleophilic addition of aryl and heteroaryl lithiates to dithiane protected benzopyrone-fused cyclobutenediones **811** followed by hydrolysis of the dithiane protecting group (Scheme 227) <1996JA12473>.



Scheme 226

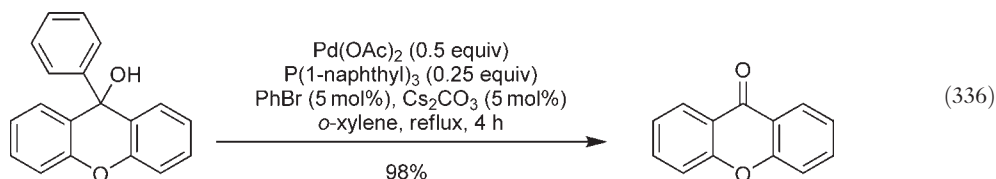


Scheme 227

7.08.19.3 From a Preformed Heterocyclic Ring

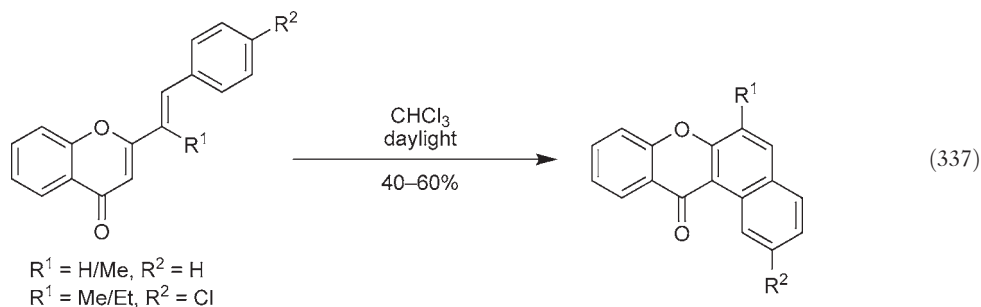
7.08.19.3.1 From xanthenes

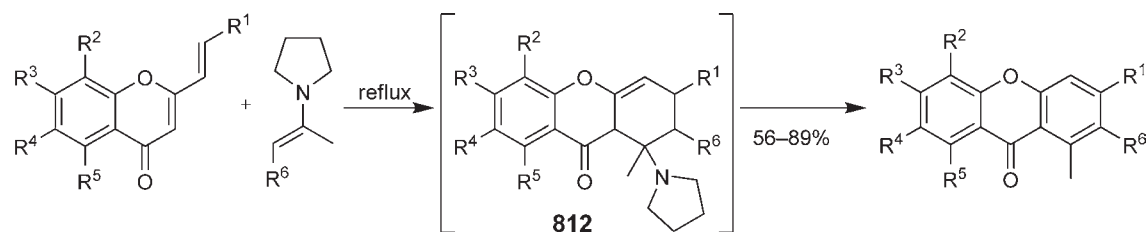
A variety of oxidizing reagents can effect the oxidation of xanthenes to xanthenes <1984CHEC, 1996CHEC-II, 1997CC447, 2004CC1500, 2002BCJ1905, 2004T11415>. The palladium-catalyzed dehydroarylation of 9-phenyl-9H-xanthen-9-ol affords xanthone in excellent yield (Equation 336) <2004JOC6942>.



7.08.19.3.2 From chromones

(*E*)-2-Styrylchromones undergo photooxidative cyclization to afford 12*H*-benzo[*a*]xanthen-12-ones in moderate yield (Equation 337) <1998EJO2031, 1996HCO251>. 2-Vinyl chromones undergo [4+2]-cycloaddition reactions with enamines to form the intermediates **812**, which afford xanthenes upon elimination of pyrrolidine (Scheme 228) <2000J(P1)3732>.





R¹ = H/2-thienyl/2-furyl/Ph, R² = R³ = R⁴ = R⁵ = R⁶ = H

R¹ = Ph, R² = H, R³ = R⁴ = Me, R⁵ = R⁶ = H

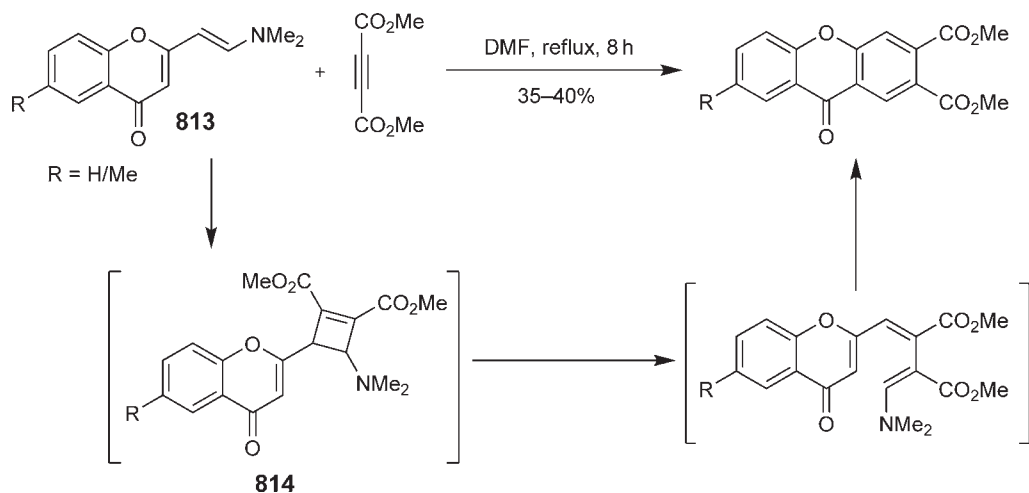
R¹ = 2,4-Cl₂C₆H₄/Ph, R² = R³ = H, R⁴ = Cl, R⁵ = R⁶ = H

R¹ = Ph, R² = R³ = R⁴ = H, R⁵ = MeO, R⁶ = H

R¹ = Ph, R² = R³ = R⁴ = R⁵ = H, R⁶ = Me

Scheme 228

(*E*)-2-(2-(Dimethylamino)vinyl)chromones **813** undergo a [2+2] cycloaddition reaction with DMAD to form the intermediate **814**, which rearrange to afford xanthenes in modest yield (**Scheme 229**) <1997J(P1)2167, 1999J(P1)3005>. (*E*)-2-(2-(Dimethylamino)vinyl)chromones **813** can also react with *N*-phenylmaleimide **815** and chromone-3-carboxylic acid **816** to afford xanthenes in modest yield (**Scheme 230**) <1997J(P1)2167, 1999J(P1)3005>.

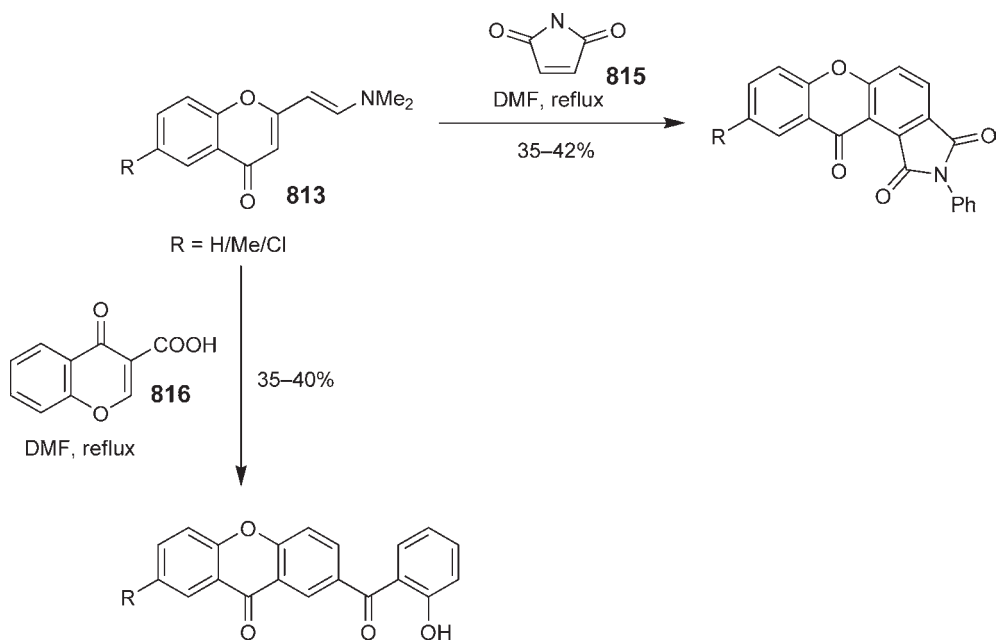


Scheme 229

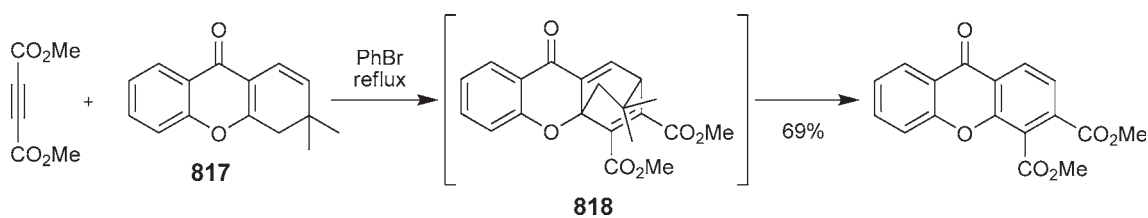
3,3-Dimethyl-3*H*-xanthen-9(4*H*)-one **817** undergoes a [4+2] cycloaddition with DMAD to form the intermediate **818**. Expulsion of isobutene from the initial adduct **818** affords xanthone-3,4-dicarboxylate in good yield (**Scheme 231**) <1998J(P1)1547>.

Chromone-3-carbaldehydes undergo Diels–Alder reactions with *ortho*-benzoquinodimethane **819** and deformylation to yield initially benzo[*b*]-1,6,6a,12a-tetrahydroxanthenes **820**, which are easily transformed into their corresponding benzo[*b*]xanthenes upon treatment with I₂-DMSO (**Scheme 232**) <2002T105>.

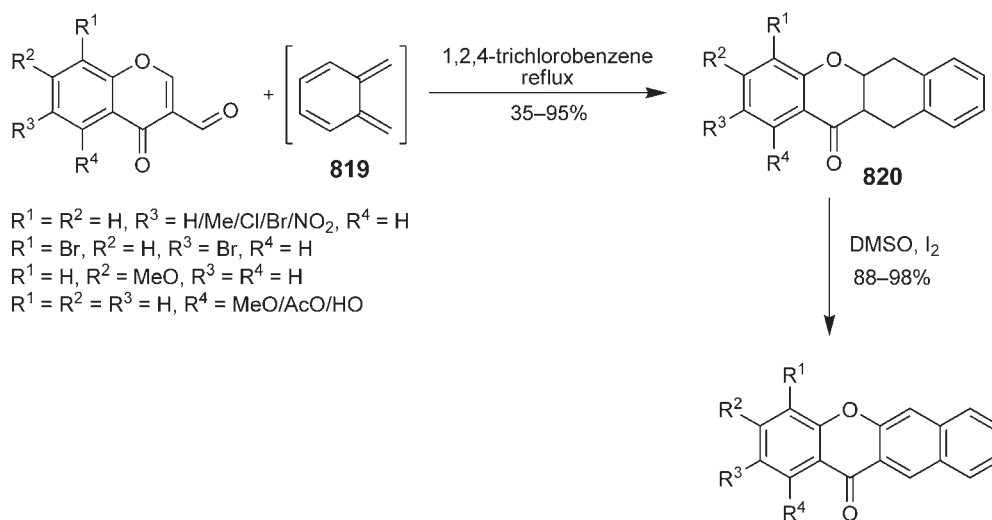
Benzopyranone phthalide **821** reacts with enones to afford xanthenes in excellent yield (Equation 338, **Table 33**) <2003OL3753>.



Scheme 230



Scheme 231



Scheme 232

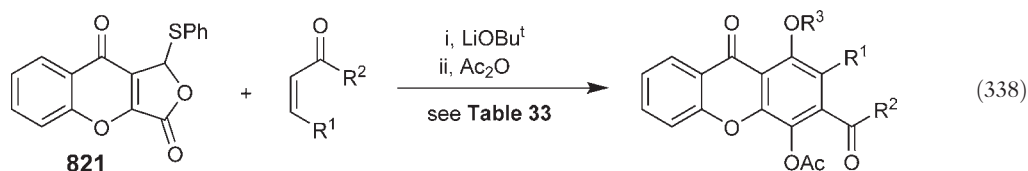


Table 33 The reaction of enones with the phthalide **821** (Equation 338)

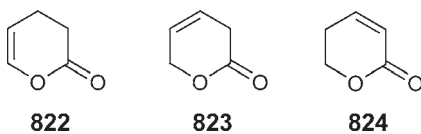
Enone	Product	Yield (%)
		88
		82 ^a
		67
		78

^aNot quenched with Ac₂O.

7.08.20 Reduced Pyranones

7.08.21 Dihydropyran-2-ones

The three regioisomeric dihydropyran-2-ones are discussed in this section: 3,4-dihydropyran-2-one **822**, 3,6-dihydropyran-2-one **823** and 5,6-dihydropyran-2-one **824**.

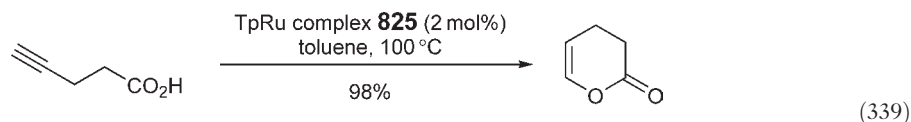


7.08.21.1 3,4-Dihydropyran-2-ones

7.08.21.1.1 Formation of one bond

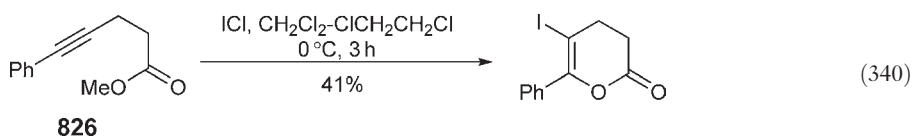
7.08.21.1.1(i) Adjacent to the heteroatom

A regioselective cyclization of pent-4-ynoic acid is catalyzed by a TpRu complex **825**. The *anti*-Markovnikov 3,4-dihydropyran-2-one product is exclusively formed in excellent yield (Equation 339) <2001CC2324>. Similarly, alkynoic esters **826** undergo ICl-promoted iodolactonizations to afford 5-iodo-3,4-dihydropyran-2-ones in moderate yield (Equation 340) <2003JOC10175>.

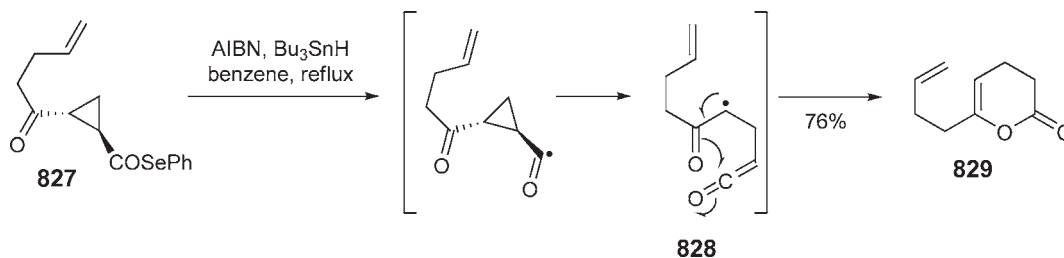


TpRu complex = [TpRu{C(Ph)=C(Ph)C≡CPh}(P-MePrⁱ₂)] **825**

Tp = hydrotris(pyrazolyl)borate



Radical induced ring opening of the cyclopropyl ketone **827** affords the radical intermediate **828**, 6-*exo*-trig cyclization of which furnishes 3,4-dihydropyran-2-one **829** in good yield (Scheme 233) <1998TL6971, 2005OBC316>.



Scheme 233

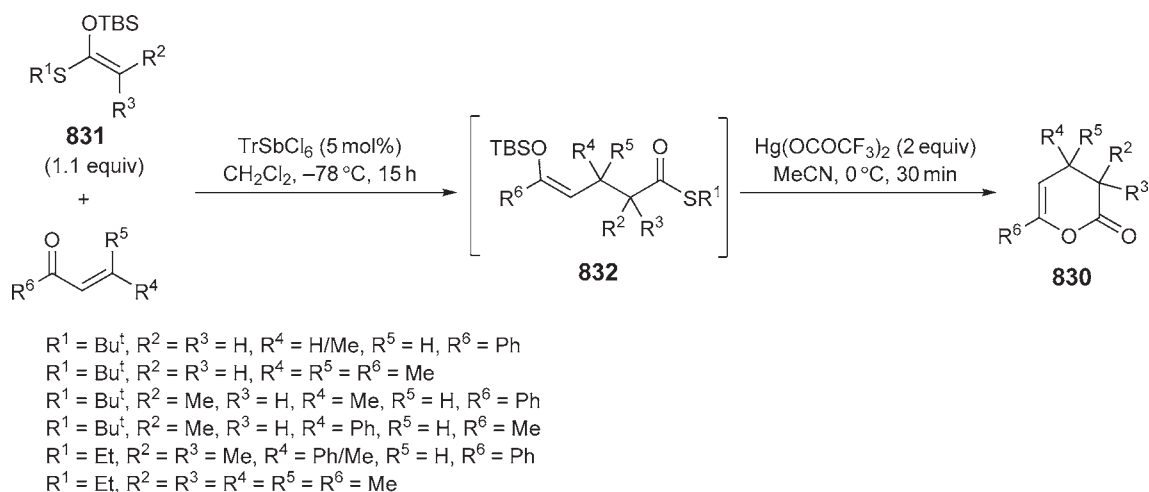
7.08.21.1.2 Formation of more than one bond

A common strategy for the synthesis of 3,4-dihydropyran-2-ones is the ring closure of 1,5-keto esters and their derivatives. The 1,5-keto esters are usually formed *in situ* with concomitant ring closure. In this manner, 3,4-dihydropyran-2-ones **830** are prepared in excellent yield via a trityl hexachloroantimonate-catalyzed Michael addition of the enol ether **831** onto α,β -unsaturated ketones to afford the intermediate **832**, which undergoes a mercury salt promoted lactonization (Scheme 234) <1997SL551>. Similar methodology, involving a Lewis-base-catalyzed Michael addition of silyl enolates with α,β -unsaturated ketones followed by *in situ* cyclization of the resulting adducts also provides a route to 3,4-dihydropyran-2-ones <2004CL1454, 2005CL514>.

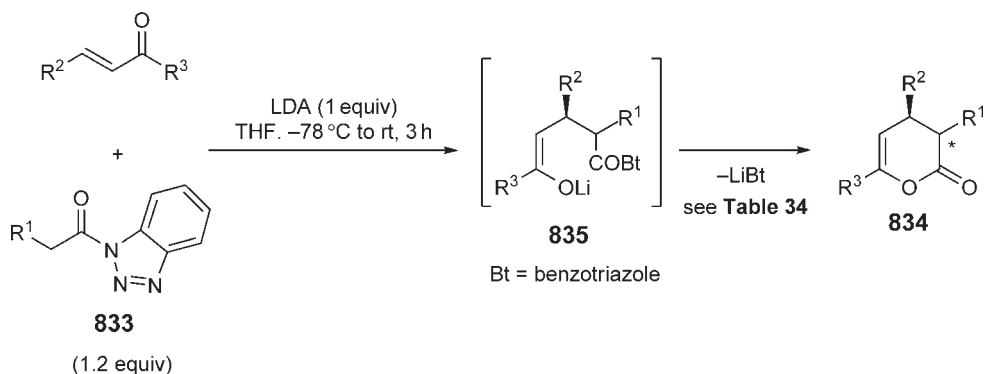
Lithiation of aliphatic 1-acylbenzotriazoles **833** followed by 1,4-addition onto α,β -unsaturated ketones affords *anti*-3-alkyl-4,6-diaryl-3,4-dihydropyran-2-ones **834** via ring closure of the enolate intermediate **835** (Scheme 235, Table 34) <2002JOC3104>.

Addition of β -ketoesters to unsaturated *N*-acylthiazolidinethiones **836** is catalyzed by the Ni(II) Tol-BINAP Lewis acid complex **837**. The initial addition products **838** cyclize upon treatment with base to afford enantiopure 3,4-dihydropyran-2-ones **839** in excellent yield (Scheme 236, Table 35) <2005JA10816>.

The reaction of lithium 2-(trimethylsilyl)ethynolate **840** with (*E*)-ethyl 2-benzylidene-3-oxobutanoate proceeds via 1,4-addition to form the intermediate ketene **841**, concomitant cyclization and tautomerization of which affords 3,4-dihydropyran-2-one **842** as a single diastereomer in excellent yield (Scheme 237) <1996JA7634>.



Scheme 234



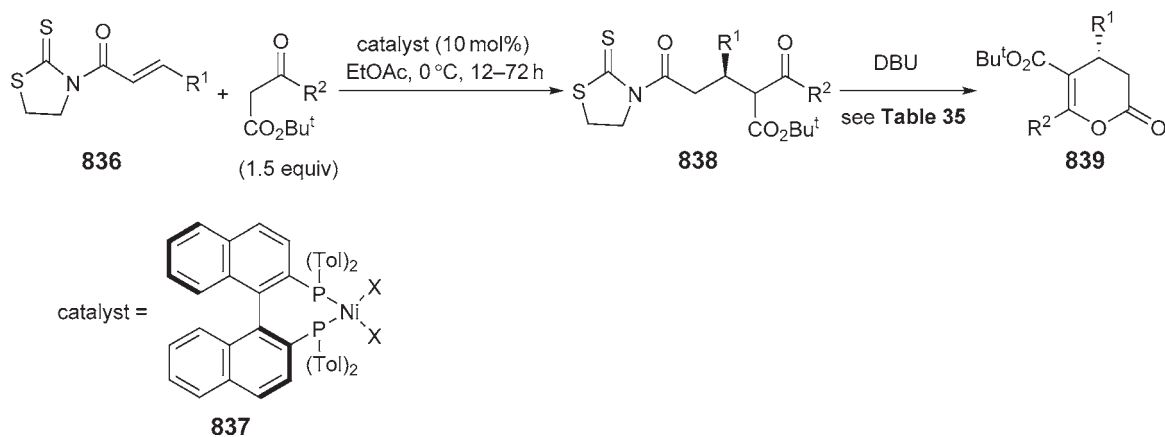
Scheme 235

Table 34 Formation of 3,4-dihydropyran-2-ones **834** (Scheme 235)

R^1	R^2	R^3	Yield 834 (%)	834 ^a <i>anti:syn</i>
Et	Ph	Ph	70	4:1
Et	4-ClC ₆ H ₄	Ph	74	4:1
Et	4-O ₂ NC ₆ H ₄	Ph	81	20:1
Et	PhCO	Ph	72	1:0
Et	Ph	PhCH=CH	53	12:1
<i>n</i> -C ₆ H ₁₃	Ph	Ph	79	1:0
Me ₂ CH	Ph	Ph	24	15:1

The (2*S*)-pyrrolidine derivative **843** can catalyze a hetero Diels–Alder (hDA) reaction between aldehydes and enones **844** to form dihydropyrans **845**, PCC oxidation of which affords *anti*-3,4-dihydropyran-2-ones **846** in good yield and enantioselectivity (Scheme 238) <2003AGE1498>.

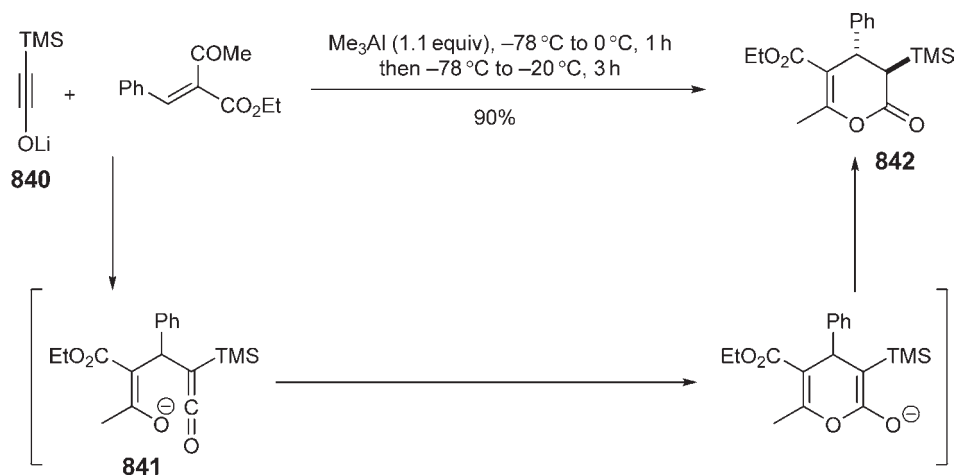
The cyclopenten-2-one **847** undergoes Baeyer–Villiger oxidation to afford 3,4-dihydropyran-2-one **848** in good yield (Equation 341) <2000JOC635>.



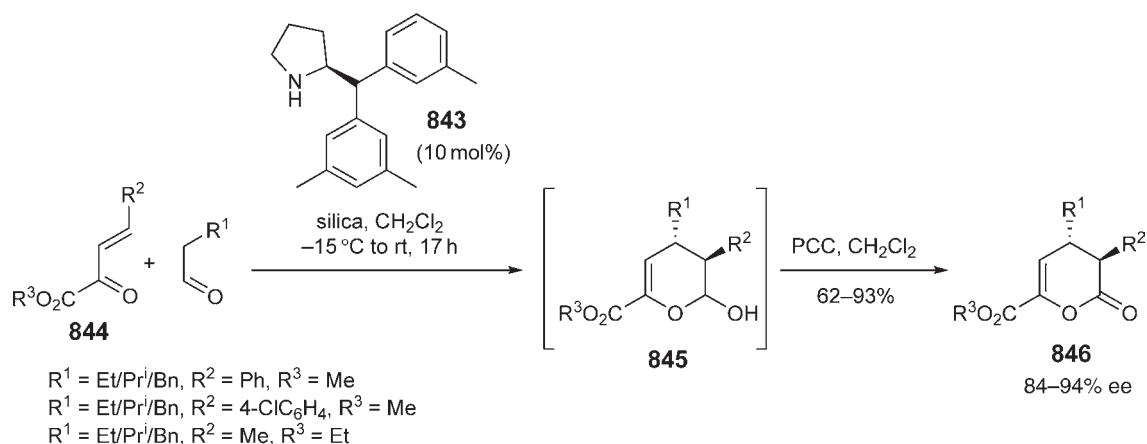
Scheme 236

Table 35 Formation of addition products **838** and their cyclization to 3,4-dihydropyran-2-ones **839** (Scheme 236)

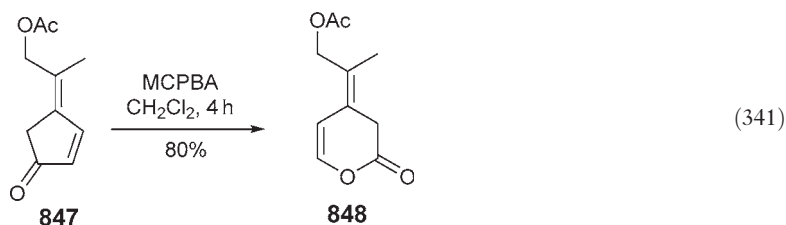
R^1	R^2	Catalyst 837 $X=$	Yield 838 (%)	Yield 839 (%)	ee 839 (%)
Me	Me	OTf	89	84	93
Me	Et	OTf	92	80	94
Me	Pr ⁿ	OTf	86	85	93
Me	Bu ⁱ	OTf	78	72	91
Me	<i>n</i> -C ₆ H ₁₁	OTf	97	94	90
Me	Ph	OTf	85	94	83
Me	Ph	OTf	95	94	91
Me	Me	BF ₄	95	84	93
Et	Me	BF ₄	88	89	95
Pr ⁿ	Me	BF ₄	91	75	95
Bu ⁱ	Me	BF ₄	67	72	84
CO ₂ Et	Me	BF ₄	87	97	97



Scheme 237



Scheme 238

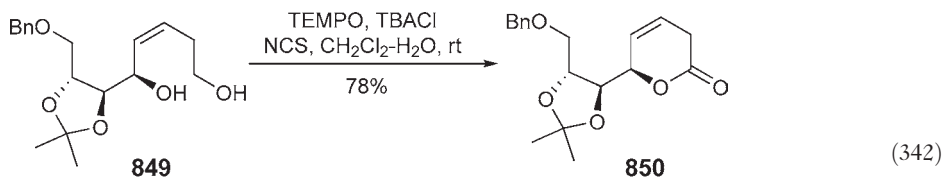


7.08.21.2 3,6-Dihydropyran-2-ones

7.08.21.2.1 Formation of one bond

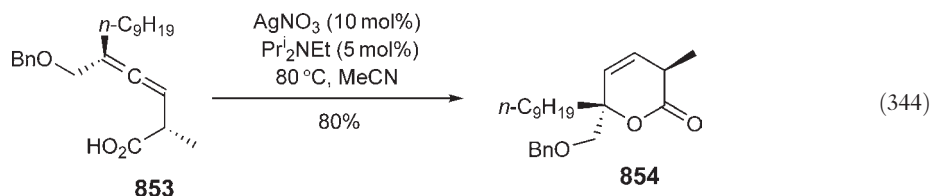
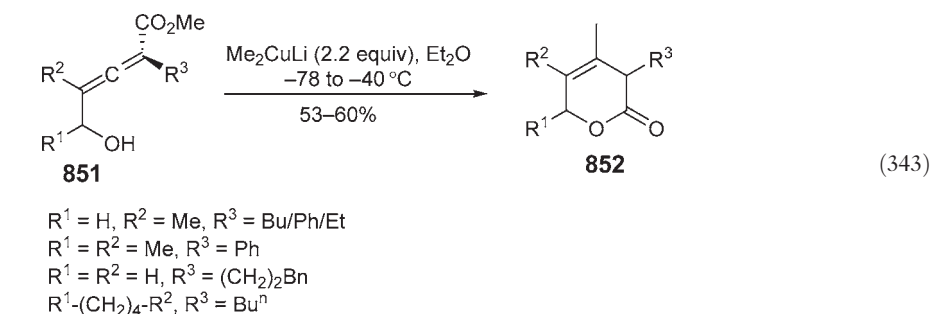
7.08.21.2.1(i) Adjacent to the heteroatom

Chemoselective primary alcohol oxidation of the 1,5-diol **849** followed by *in situ* cyclization and lactol oxidation to afford 3,6-dihydropyran-2-one **850** is achieved using catalytic TEMPO in the presence of NCS (Equation 342) <2005OL1853>.



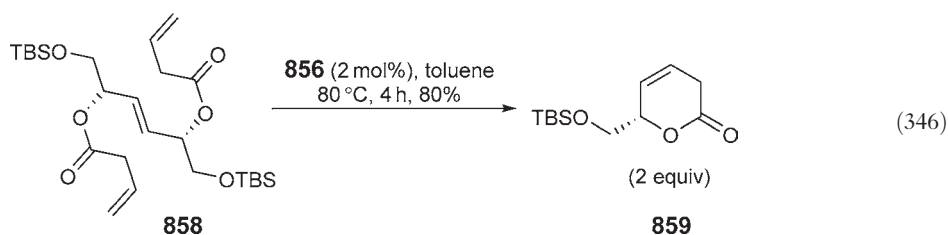
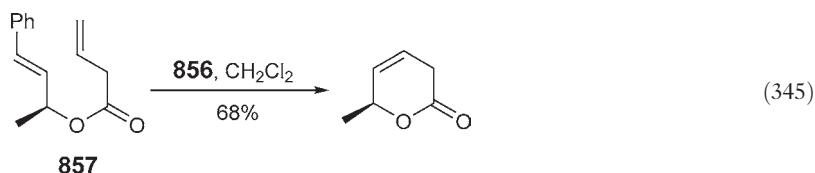
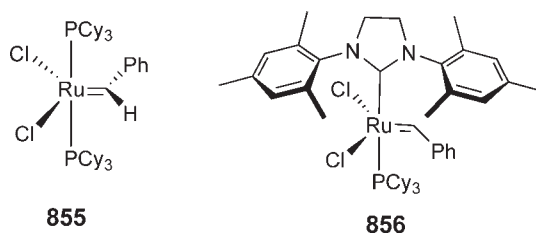
TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl
 TBACl = tetrabutyl ammonium chloride
 NCS = *N*-chlorosuccinimide

Stereocontrolled conjugate addition of lithium dimethylcuprate to the electron deficient 2,3-double bond of allenes **851** leads to 5,6-dihydropyran-4-ones **852** in moderate yield (Equation 343) <2000J(P1)3188>. Similarly, the Ag(I)-catalyzed intramolecular cyclization of the allenic acid **853** is accelerated upon addition of diisopropylethylamine to afford the 3,6-dihydropyran-2-one **854**, an intermediate during the total synthesis of (–)-malyngolide (Equation 344) <2000JA10470>.



7.08.21.2.1(ii) γ to the heteroatom

Grubbs' first **855** and second **856** generation catalysts can be used to synthesize 3,6-dihydropyran-2-ones via RCM methodology, with many relevant examples contained within a recent review [<2004CRV2199>](#). RCM of the enantiopure diene **857** proceeds with no epimerization of the stereocentre to furnish (*S*)-6-methyl-3,6-dihydropyran-2-one (Equation 345) [<2005TL811>](#). An elegant use of a domino RCM involves the symmetric cleavage of the D-mannitol derived triene **858** to form two equivalents of the enantiopure 3,6-dihydropyran-4-one **859** (Equation 346) [<2005TL3867>](#). Synthesis of methyl substituted 3,6-dihydropyran-2-ones **860** can also be achieved by RCM using both Grubbs' first **855** and second **856** generation catalysts, with the latter providing superior yields (Equation 347, Table 36) [<2002OL3875>](#).



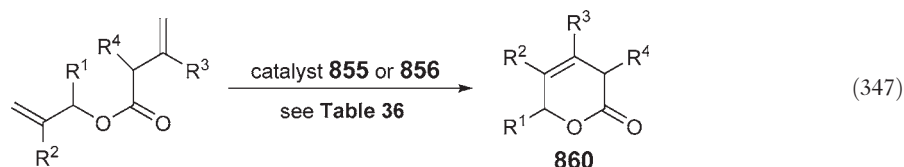
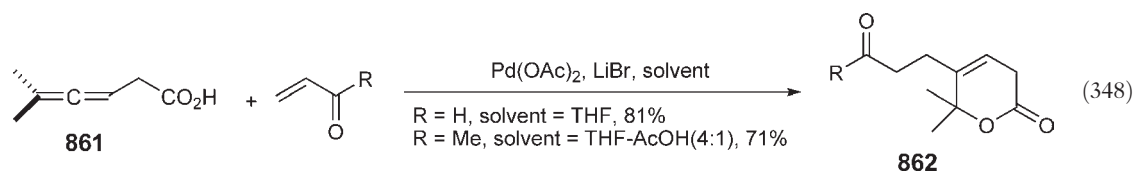


Table 36 Formation of 3,6-dihydropyran-2-ones **860** using both Grubbs' first **855** and second **856** generation catalysts (Equation 347)

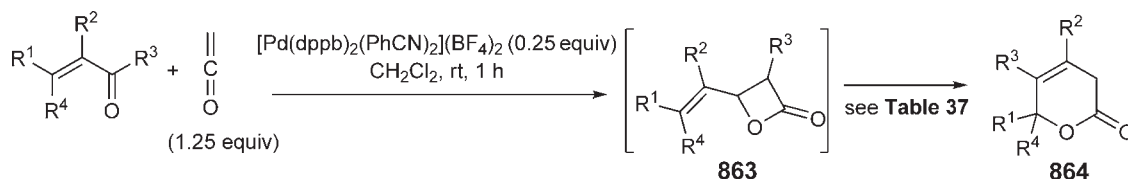
R^1	R^2	R^3	R^4	855 yield (%)	856 yield (%)
H	H	H	H	82	97
H	H	H	Me		83
H	H	Me	H	81	97
H	Me	H	H	83	96
Me	H	H	Me		75
H	Me	Me	H		52
(<i>S</i>)-Me	H	H	H	87	93
(<i>S</i>)-Me	H	Me	H	95	97
(<i>R</i>)-Me	H	H	H	87	93
(<i>R</i>)-Me	H	Me	H	95	97

7.08.21.2.2 Formation of More than One Bond

5-Methylhexa-3,4-dienoic acid **861** can undergo a palladium(II)-mediated cyclization with concomitant Michael addition to α,β -unsaturated carbonyl compounds occurring at C-5 to afford 3,6-dihydropyran-2-ones **862** (Equation 348) <2003TL127>.



The reaction of ketene with α,β -unsaturated carbonyl compounds in the presence of a cationic palladium(II) complex leads to the formation of 4-vinyloxetan-2-one intermediates **863**, which rearrange under the reaction conditions to give 3,6-dihydropyran-2-ones **864**. α,β -Unsaturated aldehydes provide higher yields of the desired 3,6-dihydropyran-2-ones than their corresponding ketones (Scheme 239, Table 37) <2000CC73, 2002T5215>.



Scheme 239

Table 37 Formation of 3,6-dihydropyran-2-ones **864** (Scheme 239)

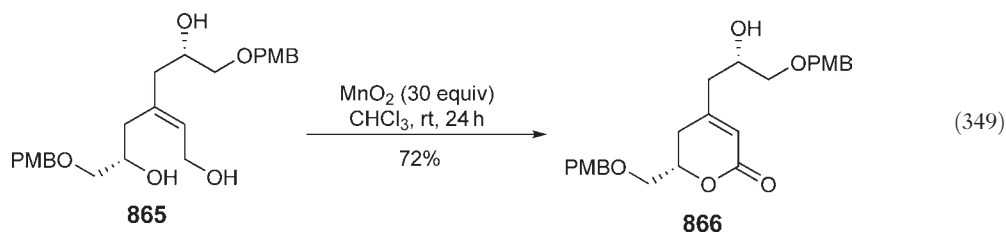
R^1	R^2	R^3	R^4	Yield 864 (%)
Ph	H	H	H	77
4-O ₂ NC ₆ H ₄	H	H	H	36
<i>n</i> -C ₃ H ₇	H	H	H	58
<i>n</i> -C ₅ H ₁₁	H	H	H	58
Me	H	H	Me	31
<i>n</i> -C ₃ H ₇	Et	H	H	66
H	H	Me	H	7
Me	H	Me	H	19
Ph	H	Me	H	18

7.08.21.3 5,6-Dihydropyran-2-ones

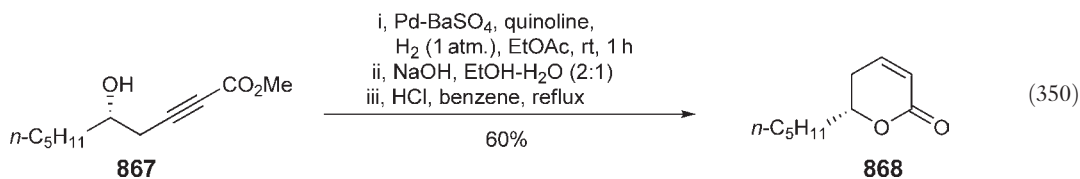
7.08.21.3.1 Formation of one bond

7.08.21.3.1(i) Adjacent to the heteroatom

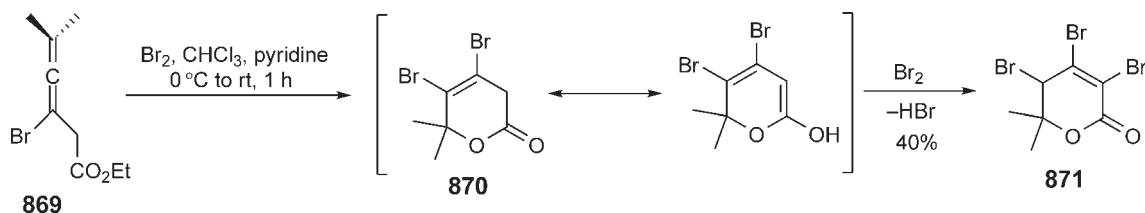
Chemoselective oxidation of the allylic alcohol in triol **865** with manganese dioxide followed by *in situ* cyclization and oxidation of the resulting 5,6-dihydropyran-2-ol provides the 5,6-dihydropyran-2-one subunit **866** of bryostatin (Equation 349) <2000OL2189>.



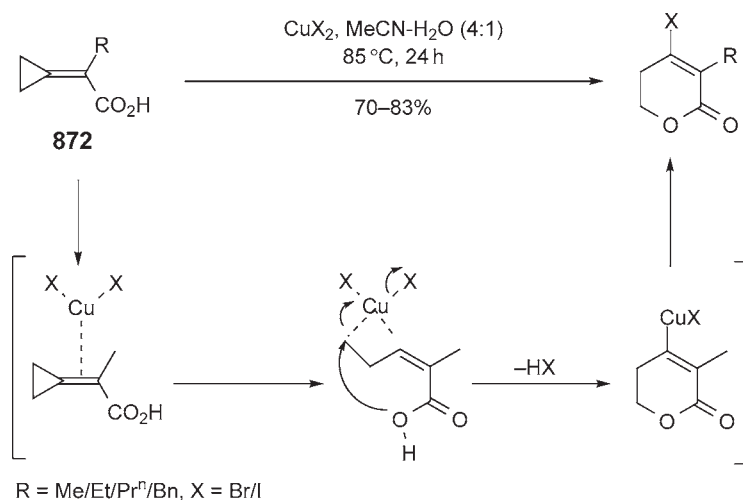
Partial hydrogenation of the alkyne **867** to the (*Z*)-alkene occurs with concomitant lactonization to provide the final step in an asymmetric synthesis of (+)-massoialactone **868** (Equation 350) <1999T13445>.



Treatment of 1-bromoallenyl ethyl ester **869** with bromine leads to 3,4,5-tribromo-6,6-dimethyl-3,6-dihydropyran-2-one **871**. The reaction proceeds through initial electrophilic addition of bromine to the central allene carbon atom and cyclization of the resulting carbenium bromide furnishing the intermediate **870**. Further reaction with bromine followed by loss of HBr affords the 3,6-dihydropyran-2-one **871** (Scheme 240) <1996LA171>.

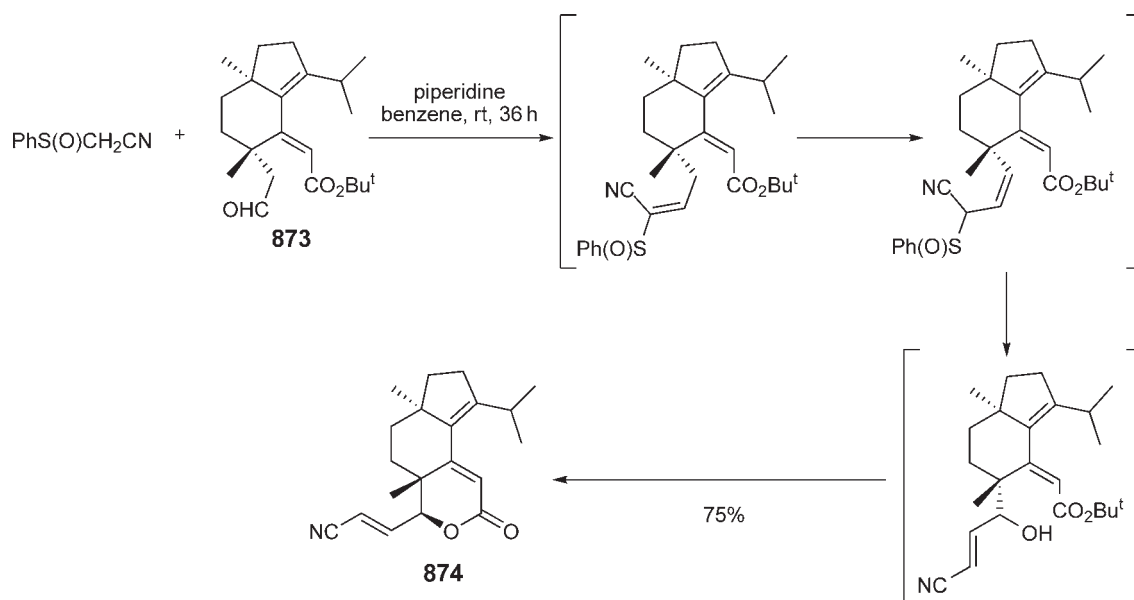
**Scheme 240**

A copper(II)-mediated ring cleavage and recyclization of cyclopropylideneacetic acids **872** provides a facile route to 4-halo-5,6-dihydropyran-2-ones (Scheme 241) <2002OL4419, 2004JOC839>.



Scheme 241

A hydroxylation Knoevenagel reaction of the aldehyde **873** proceeds in the presence of phenylsulfinyl acetonitrile to afford the 5,6-dihydropyran-2-one **874**, an intermediate during the enantioselective total synthesis of (+)-allo-cyathin B₂ (Scheme 242) <2005JA10259>.

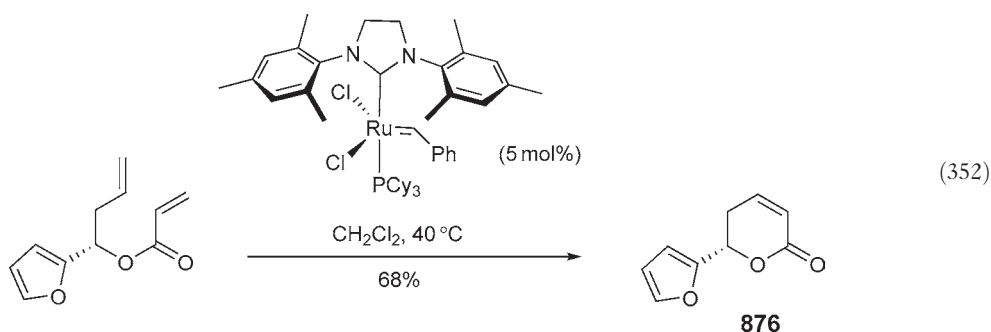
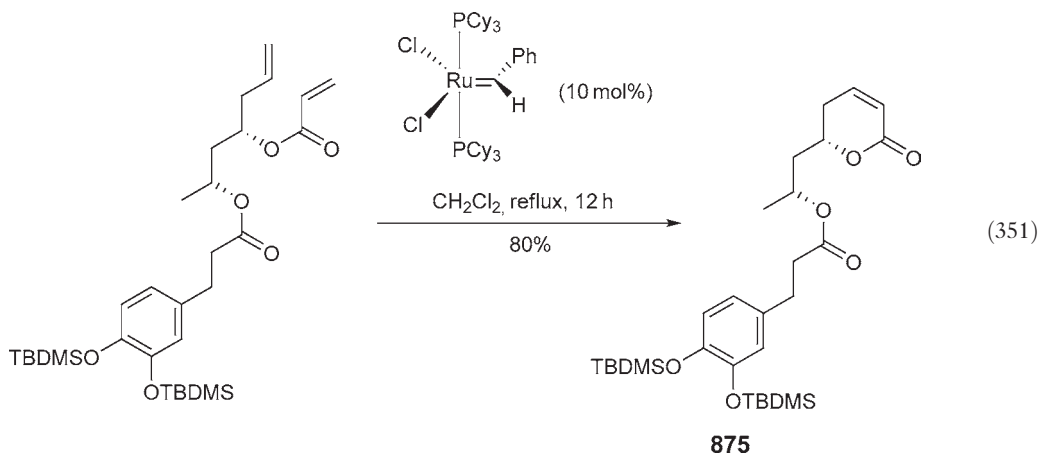


Scheme 242

7.08.21.3.1(ii) γ to the heteroatom

One of the most attractive and dependable methods for synthesizing the 5,6-dihydropyran-2-one ring system is via the RCM of but-3-enyl acrylates. A review contains many relevant examples <2004CRV2199>. Many other noteworthy examples include the use of a pivotal RCM step during the construction of the 5,6-dihydropyran-2-one subunit **875** of tarchonanthuslactone (Equation 351) <2001JOC2512>, and an intermediate **876** during the total synthesis of ricciocarpins A and B (Equation 352) <2001AGE1058>. The RCM of similar acrylate esters can be seen during the synthesis of (–)-tetrahydrolipstatin <1999CC1743>, the C(1)–C(7) fragment of methymycin

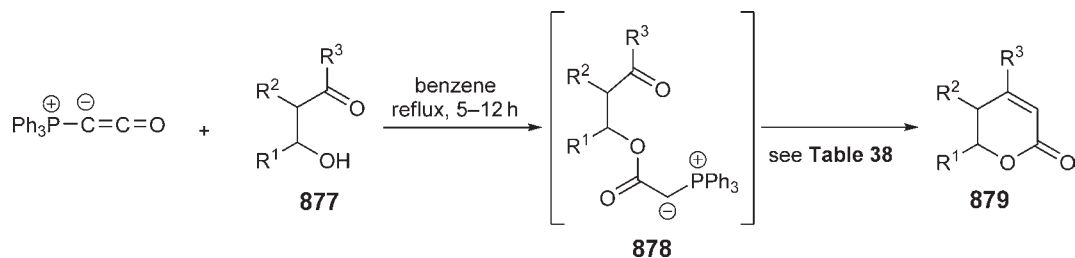
<1999TL4187>, the C(15)–C(27) <2000TL6323> and C(2)–C(16) segment <2000TL2319> of laulimalide, the C(3)–C(15) segment of phorbaxazole <2000TL3801, 2002T6009>, the lactone moiety of compactin and mevinolin <2000JOC4779>, parasorbic acid and related natural products <2000TL583>, the C(1)–C(12) fragment of fostriecin <2001OL2233>, cryptocarya diacetate <2001OL2777>, (–)-laulimalide <2001JOC8973>, terpenoid derivatives <2001TL6069>, seleno compounds <2001CC605>, analogues of farnesyl pyrophosphate <2002JOC5701>, (+)-boronolide <2002JOC6560>, the C(1)–C(21) fragment of SCH 351448 <2002OL481>, the C(9)–C(19) subunit of dictostatin-1 <2004TL4253>, (+)-methynolide <2002T5909>, (+)-tankolide and (–)-malyngolide <2002T8929>, precursors for SmI₂ couplings <2002JOC3861>, di- and tetrahydropyrans with orthogonally protected hydroxymethyl side chains <2002T7951>, enantiopure 5-hydroxydihydropyran-2-ones <2003JOC799>, (*R*)-goniothalamine <2003TL8721, 2003ARK118, 2005BMC2927>, (+)-goniothalamine <2004TL83, 2004T521>, constanolactones A and B <2003SL1698>, the C(1)–C(11) subunit of 8-*epi*-fostriecin <2003OL3755>, natural (5′-oxoheptene-1′(*E*),3′(*E*)-dienyl)-5,6-dihydro-2*H*-pyran-2-one <2004TL2615>, (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one <2004TL9299>, passifloricin A <2003TL4471, 2003OL1447>, (+)-strictiflone <2003OL1995>, the C(1)–C(9) <2003TL3697>, C(1)–C(11) <2004TL387> and C(10)–C(24) <2003TL7659> fragments of peloruside, peloruside itself <2003AGE1648>, apratoxin A <2003JA8734>, (±)-massoilactone and (±)-prelactone B <2003SL107>, 1,3-polyol/α-pyrones <2003OL495, 2004CEJ1527>, the C(1)–C(8) subunit of (+)-discodermolide <2004JOC6294>, (–)-callystatin <2004OL3203>, (–)-centrolobine <2005TL2021>, 10-*epi*-anamarine <2005OL1069>, cicosanoid <2005ARK144>, massoilactone and analogues <2004TL849, 2004TL9479>, a formal total synthesis of fostriecin <2002OL4615>, the glycosyl nucleoside amino acid core of complex peptidyl antibiotics <2004JOC8594> and enantiopure spirocyclic β-lactams <2004TL6429>.



6-Methyl-5,6-dihydropyran-2-one is accessible via a RCM reaction catalyzed by an *in situ* prepared Grubbs' second generation catalyst and its subsequent activation with ethereal HCl <2000OL3253>. The syntheses of 3- and 4-substituted 5,6-dihydropyran-2-ones by RCM is notable due to the formation of a trisubstituted double bond in the product <2000JA3783, 2002JOC4284, 2002AGE4038, 2002TL3513, 2002TL9055>.

Treatment of keto alcohols **877** with (triphenylphosphonylidene)ethanone forms the intermediate ylide **878**, which cyclizes via an intramolecular Wittig reaction to afford 5,6-dihydropyran-2-ones **879** (Scheme 243, Table 38). A slight improvement in yield can be observed by using keto alcohols masked as their 1,3-acetals <1998T2161>.

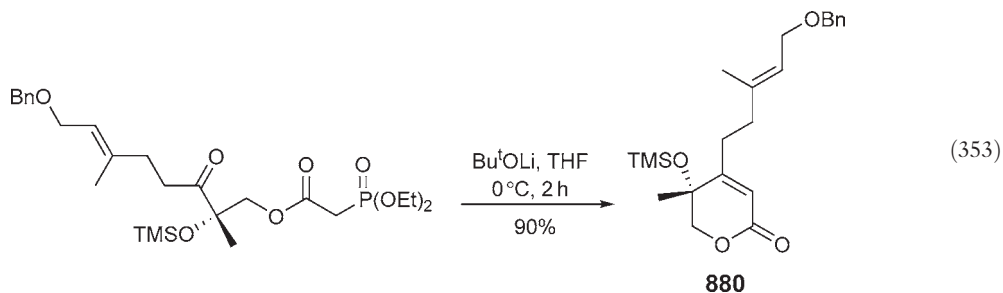
A similar intramolecular Wittig–Horner reaction provides a key 5,6-dihydropyran-2-one **880** intermediate during synthetic studies towards leinamycin. The choice of base, lithium *tert*-butylate (*t*-BuOLi), is vital for the high yield observed due to the importance of the lithium cation for smooth deprotonation of the phosphonoacetate, the first time this base is documented during a Wittig–Horner olefination (Equation 353) <2005T7481>.



Scheme 243

Table 38 Cyclization of keto alcohols **877** to 5,6-dihydropyran-2-ones **879** (Scheme 243)

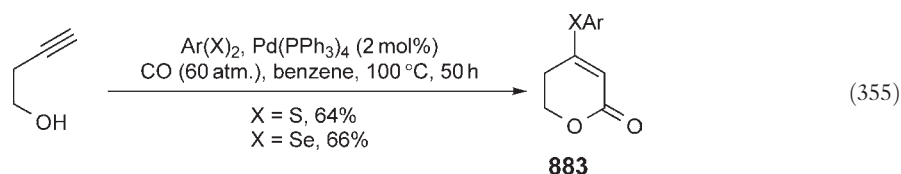
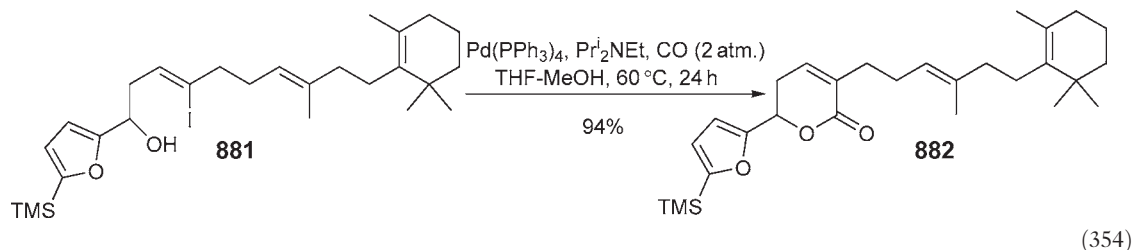
Keto alcohol 877	Product 879	Yield 879 (%)
		47
		36
		52
		65
		70



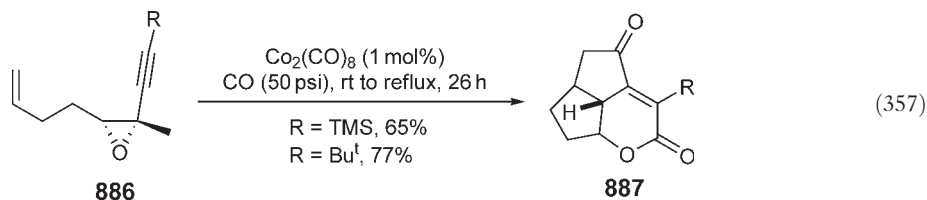
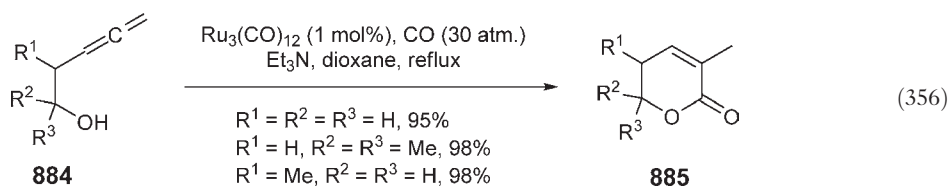
7.08.21.3.2 Formation of more than one bond

The dianion of methyl acetoacetate combines with ketoamides and undergoes cyclization via an intramolecular aldol condensation to afford 4-hydroxy-5,6-dihydropyran-2-ones, common substrates for testing as anti-HIV agents <1996BML719, 1997JME3707, 1999BML2019, 1999BMC2775, 2000JME843, 2001JME2319, 2005BML3257, 2005BMC4078>. The lithium anions of vinylogous urethanes react with carbonyl compounds to afford 5,6-dihydropyran-2-ones <1996TL1331, 1996JA3301, 1998TL4983, 1998JOC9089, 1999TL1257>. Condensation of dimethyl 3-methylglutaconate with aldehydes leads diastereoselectively to 6-substituted 5,6-dihydropyran-2-ones via an aldolization–cyclization cascade <1999T7847>. Reaction of the lithium enolate of methyl acetate with β -acetoxyaldehydes also provides a route to 5,6-dihydropyran-2-ones <1999OL411>.

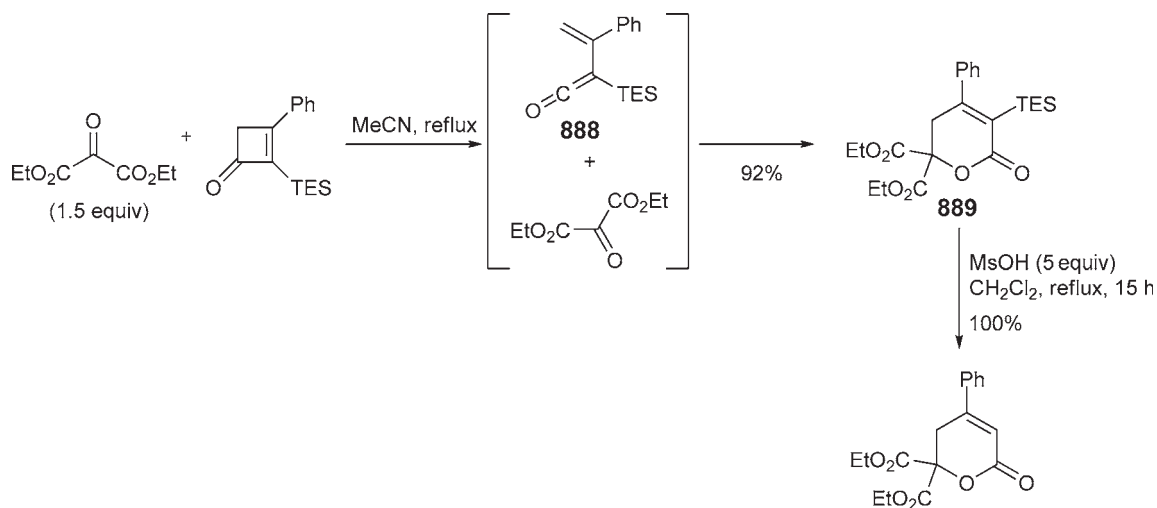
An intramolecular Heck-carbonylation/cyclization of the vinyl iodide **881** provides the 5,6-dihydropyran-2-one **882** during a total synthesis of manoalide (Equation 354) <1997CC1139>. The reaction of but-3-yn-1-ol with diaryl sulfides and carbon monoxide in the presence of a palladium(0) catalyst leads to a novel thiolactonization and hence arylthiosubstituted 5,6-dihydropyran-2-one **883** (Equation 355). Similar results are obtained with diaryl diselenides (Equation 355) <1997JOC8361>. Hydrazirconation of *O*-protected homopropargylic alcohols followed by carbonylation and quenching with iodine provides a simple route to 5,6-dihydropyran-2-ones <1998TA949>.



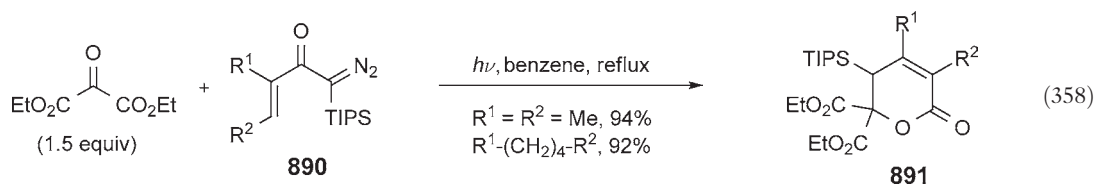
A ruthenium-promoted carbonylation of allenyl alcohols **884** is a powerful method for the synthesis of 5,6-dihydropyran-2-ones **885** (Equation 356) <2000OL441, 2003JOC8571>. $\text{Co}_2(\text{CO})_8$ -mediated tandem [5+1]/[2+2+1] cycloaddition reactions of the epoxide **886** with carbon monoxide provide a one-pot synthesis of tricyclic 5,6-dihydropyran-2-ones **887** in good yield (Equation 357) <2003JA9610>.



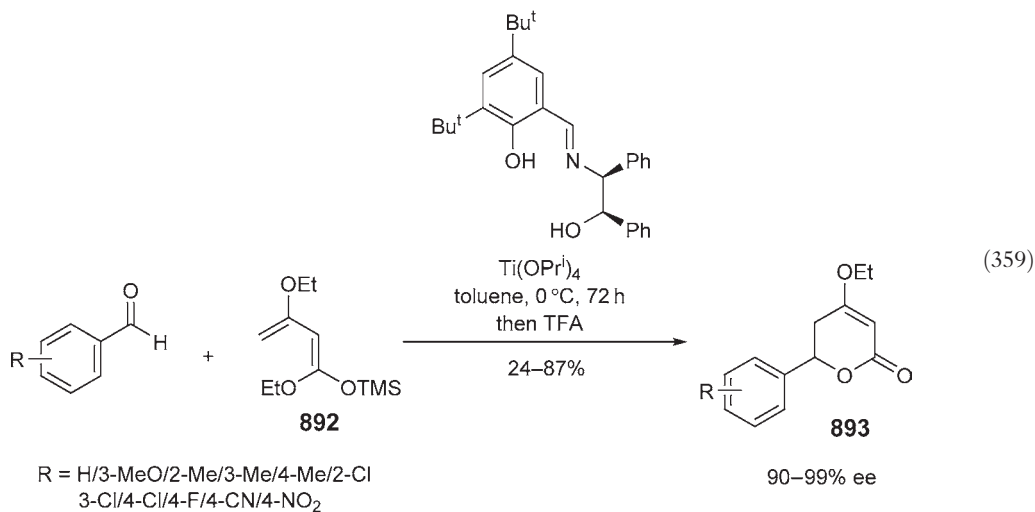
An hDA reaction of the thermally generated (trialkylsilyl)vinylketene **888** with diethyl ketomalonate furnishes the 5,6-dihydropyran-2-one **889** in excellent yield. Protodesilylation of the cycloadduct **889** is achieved in quantitative yield upon its exposure to methanesulfonic acid (Scheme 244). A photochemical Wolff rearrangement of the silyl diazo compound **890** can also be used to generate an intermediate diene for reaction with diethyl ketomalonate to afford the 5,6-dihydropyran-2-ones **891** (Equation 358) <1999OL641>.

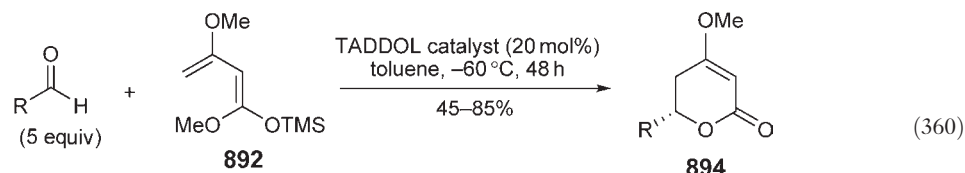


Scheme 244

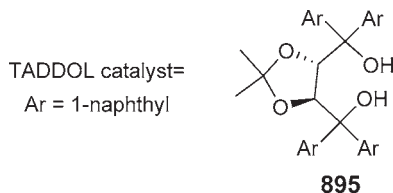


A highly enantioselective hDA reaction between Brassard's diene **892** and benzaldehydes in the presence of a titanium(IV) tridentate Schiff base complex affords dihydropyran-2-ones **893** (Equation 359) <2004OL2185, 2005EJO3542>. The hDA reaction between Brassard's diene **892** and aldehydes bearing proline esters as a chiral auxiliary proceeds with high diastereoselectivity to the corresponding 5,6-dihydropyran-2-ones <1999EJO329>. Several 6,6-disubstituted-5,6-dihydropyran-2-ones are accessible via a Lewis-acid-catalyzed hDA reaction between a polymer bound Danishefsky-type diene with aldehydes or ketones <2003TL3645>. The enantioselective hDA reaction between Brassard's diene **892** and aldehydes provides 5,6-dihydropyran-2-ones **894**. The reaction is driven by hydrogen-bonding activation from the TADDOL catalyst **895** (Equation 360). This methodology was used in a one-step synthesis of (*S*)-(+)-dihydrokawain <2004CEJ5964>.

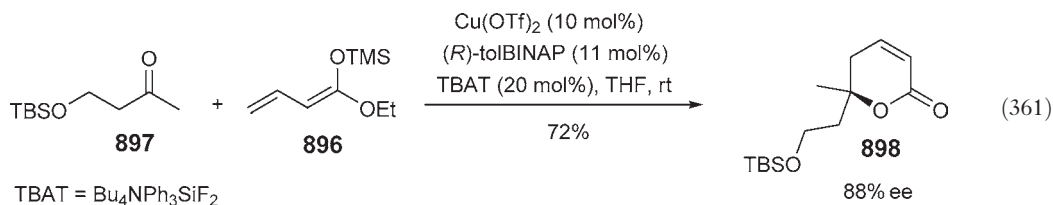




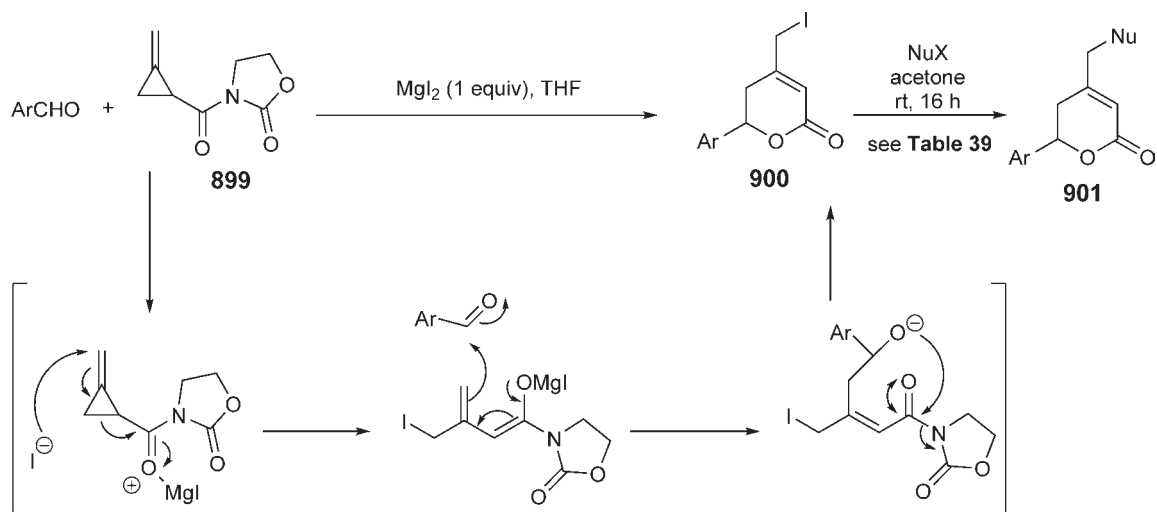
R = Ph/2-furyl/2-MeC₆H₄/3-MeC₆H₄/2-BrC₆H₄
4-ClC₆H₄/4-BrC₆H₄/3-BrC₆H₄/3-BrC₆H₄/CH₂Bn



A catalytic asymmetric vinylogous Mukaiyama reaction between silyl dienolate **896** and aliphatic ketone **897** provides the 5,6-dihydropyran-2-one **898**, a key intermediate during a formal synthesis of enantiopure taurospongins A (Equation 361) <2005JA7288>.



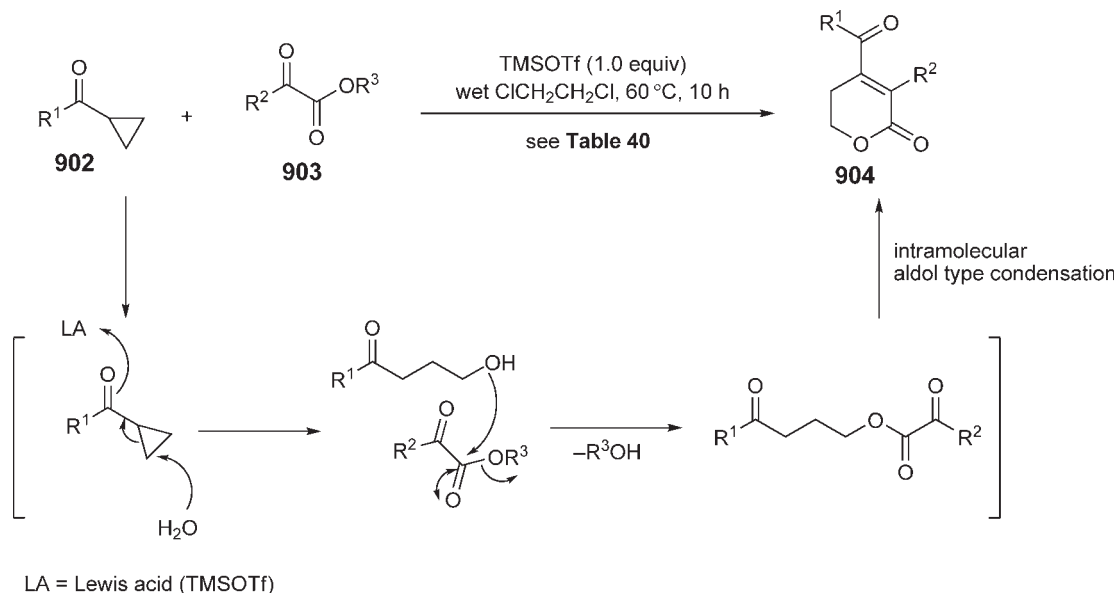
Iodide-mediated ring expansion of activated methylenecyclopropane **899** and subsequent reaction with aryl aldehydes occurs in the presence of MgI₂ affording 5,6-dihydropyran-2-ones **900**. Due to their instability, conversion to the stable 5,6-dihydropyran-2-ones **901** is necessary and can be achieved by facile nucleophilic displacement of iodide ion (Scheme 245, Table 39) <2002JA6312>. Nucleophilic ring opening of an activated cyclopropane **902** by ambient H₂O followed by Lewis-acid-mediated transesterification with α -ketoesters **903** and an aldol-type reaction provides a facile route to 3,4-disubstituted-5,6-dihydropyran-2-ones **904** (Scheme 246, Table 40) <2005JOC10082>.



Scheme 245

Table 39 Formation of 5,6-dihydropyran-2-ones **901** (Scheme 245)

<i>Ar</i>	<i>NuX</i>	Yield 901 (%)
Ph	XN ₃	88
2-BrC ₆ H ₄	XSPH	61
4-O ₂ NC ₆ H ₄	XOAc	75
3,4-(OCH ₂ O)-C ₆ H ₃	XTs	65
2,4-Cl ₂ C ₆ H ₃	XN ₃	74

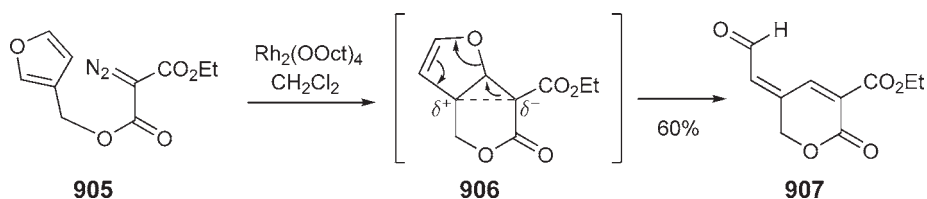
**Scheme 246****Table 40** Formation of 5,6-dihydropyran-2-ones **904** (Scheme 246)

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	Yield 904 (%)
Ph	Ph	Me	89
Ph	4-MeC ₆ H ₄	Me	60
Ph	4-MeOC ₆ H ₄	Et	50
Ph	4-ClC ₆ H ₄	Et	87
Ph	H	Et	94
Ph	Me	Et	97
Ph	<i>n</i> -C ₆ H ₁₃	Et	40
Ph	<i>c</i> -C ₆ H ₁₁	Et	35
4-MeC ₆ H ₄	Me	Et	97
2,6-(Me) ₂ C ₆ H ₃	Me	Et	92
4-MeOC ₆ H ₄	Me	Et	72
2-thienyl	Me	Et	80

7.08.21.3.3 From other heterocycles

7.08.21.3.3(i) From furans

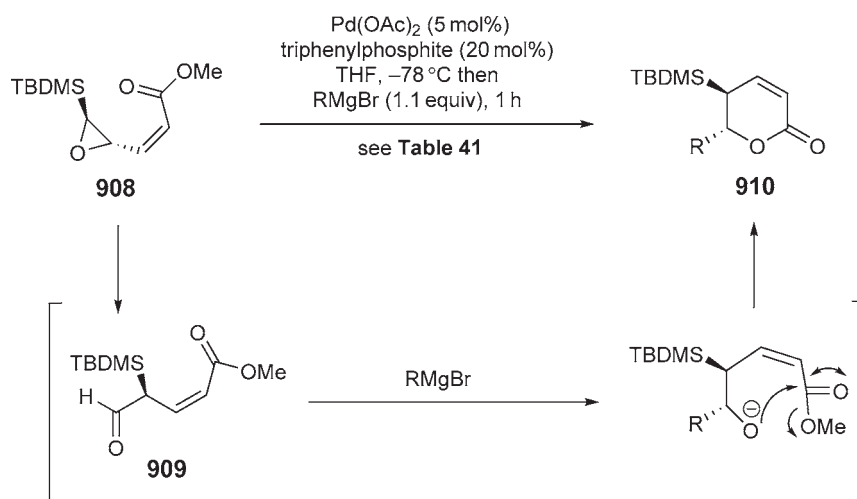
Treatment of the diazofuran **905** with dirhodium tetraoctanoate leads to decomposition affording 5,6-dihydropyran-2-one **907**. The reaction proceeds via ring opening of a zwitterionic cyclopropane intermediate **906** (Scheme 247) <1997TL5623, 2000JOC4261>.



Scheme 247

7.08.21.3.3(ii) From epoxides

Silylated vinyloxyepoxide **908** rearranges under Pd(0) catalysis to furnish the α -silylated- β,γ -unsaturated aldehyde **909**, which cyclizes upon treatment with Grignard reagents affording enantiomerically pure 5,6-dihydropyran-2-ones **910**. This methodology is used for the syntheses of the pheromones 6-*n*-undecyltetrahydropyran-2-one and massoilactone (Scheme 248, Table 41) <2001SL138, 2006EJO453>.



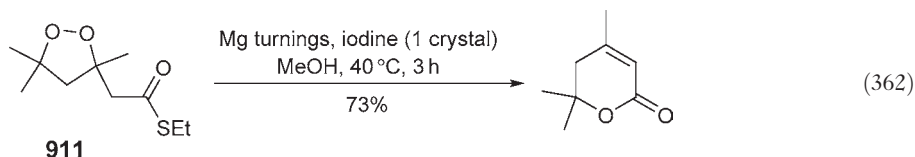
Scheme 248

Table 41 Formation of 5,6-dihydropyran-2-ones **910** (Scheme 248)

<i>R</i>	Yield 910 (%)	<i>de</i> (%)
Me	78	74
Pr ⁱ	79	>96
Bu ^t	90	>96
<i>n</i> -C ₁₁ H ₂₃	73	>96
<i>n</i> -C ₅ H ₁₁	70	>96
-C $\equiv$ CH	70	>96
CH=CH ₂	60	>96

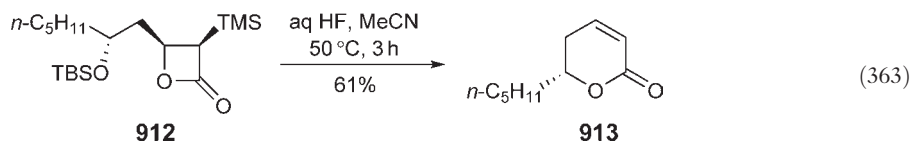
7.08.21.3.3(iii) From peroxides

Magnesium in methanol effects the reductive ring opening of the cyclic peroxide **911**, recyclization of which affords 4,6,6-trimethyl-5,6-dihydropyran-2-one in good yield (Equation 362) <2004JOC2851>.



7.08.21.3.3(iv) From oxetan-2-ones

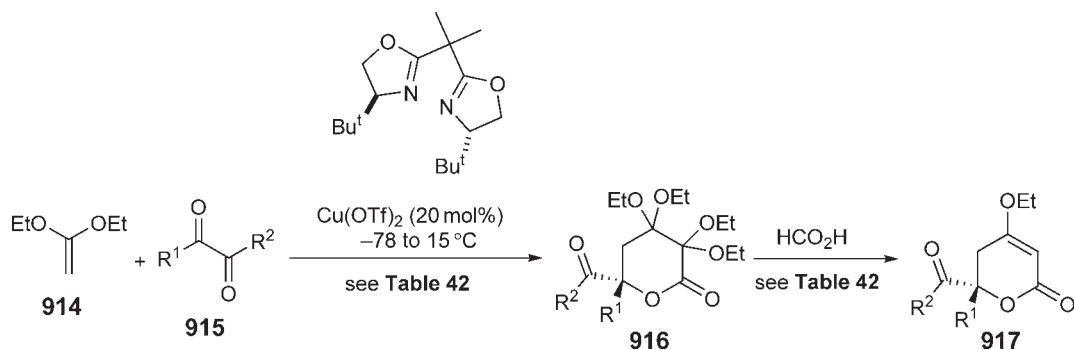
A HF-induced translaconization of the 2'-silyloxy-3-trimethylsilyloctan-2-one **912** is applied as the final step in the total synthesis of (–)-massoialactone **913** (Equation 363) <2004T1659>.



7.08.21.3.4 From a Preformed Heterocyclic Ring

7.08.21.3.4(i) From tetrahydropyranones

Functionalized enantiopure 5,6-dihydropyran-2-ones **917** are accessible from a Cu(II)- (BOX) catalyzed reaction of ketene diethylacetal **914** and α -dicarbonyl compounds **915** followed by hydrolysis of intermediate **916** with formic acid (**Scheme 249**, **Table 42**) <2000JA11543>.

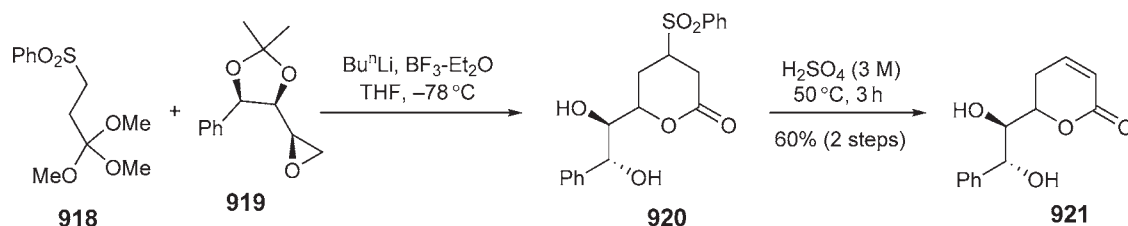


Scheme 249

Table 42 Formation of tetrahydropyran-2-ones **916** and their elimination to 5,6-dihydropyran-2-ones **917** (Scheme 249)

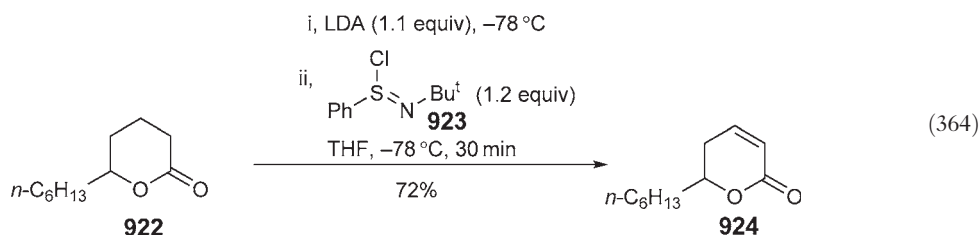
R^1	R^2	Yield 916 (%)	Yield 917 (%)	ee 917 (%)
Me	OMe	74	63	83
Et	OMe	70	72	77
Pr ⁱ	OEt	58	67	80
CH ₂ Br	OEt	55	50	53

During a total synthesis of (+)-goniodiol the 5,6-dihydropyran-2-one **921** is constructed from the epoxide **919** and the sulfonyl ester **918** using Ghosez's methodology to form the tetrahydropyran-2-one **920** followed by acid mediated elimination (**Scheme 250**) <1996TL371>.



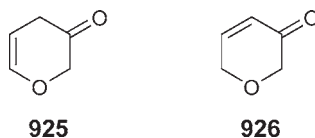
Scheme 250

A one-pot dehydrogenation of tetrahydropyran-2-one **922** can be achieved upon treatment of the lithium enolate of **922** with *N*-*tert*-butylbenzenesulfinimidoyl chloride **923** to furnish the corresponding 5,6-dihydropyran-2-one **924** in good yield (Equation 364) <2005TL407>.



7.08.22 Dihydropyran-3-ones

The two regioisomeric dihydropyran-3-ones, 2,4-dihydropyran-3-one **925** and 2,6-dihydropyran-3-one **926**.

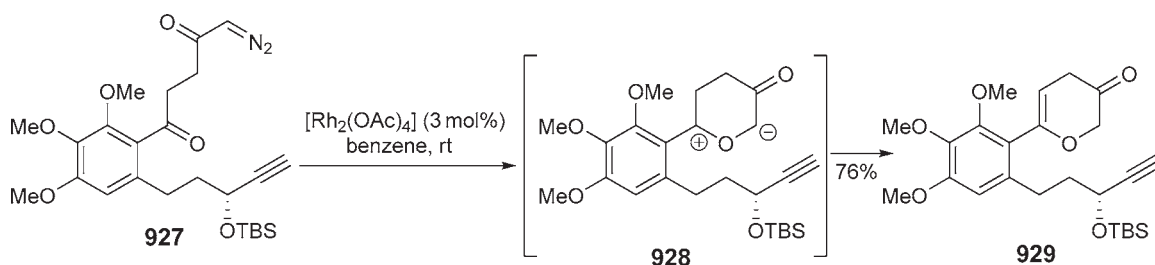


7.08.22.1 2,4-Dihydropyran-3-ones

7.08.22.1.1 Formation of one bond

7.08.22.1.1(i) Adjacent to the heteroatom

Treatment of the diazo ketone **927** with a rhodium(II)-catalyst furnishes the 6-substituted 2,4-dihydropyran-3-one **929** arising from a proton transfer (1,4-shift) within the carbonyl ylide intermediate **928** (Scheme 251) <2002AGE1524>.



Scheme 251

7.08.22.1.2 From other heterocycles

7.08.22.1.2(i) From η^2 -furan complexes

Lewis acid treatment of a 2-furanylmethanol complexed to the π -base pentaamine osmium(II) in the presence of carbonyl compounds provides a route to 4-substituted dihydropyran-3-ones. However, the design of a protocol for efficient removal of the osmium from the products is in its early stages <2000T2313>.

7.08.22.2 2,6-Dihydropyran-3-ones

7.08.22.2.1 Formation of more than one bond

Mo(CO)_6 catalyzes the cyclization of both (*E*)- and (*Z*)-enediones **930** to dihydropyran-3-ones **931** in the presence of the oxygen donor *t*-butyl hydroperoxide (TBHP) (Equation 365, Table 43) <2003TL835>.

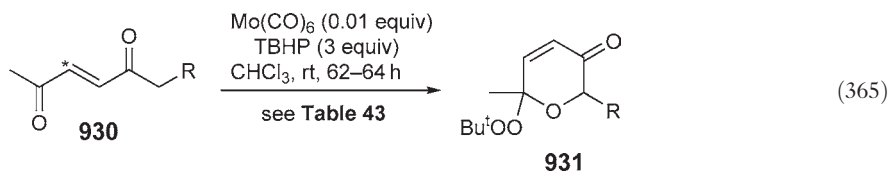


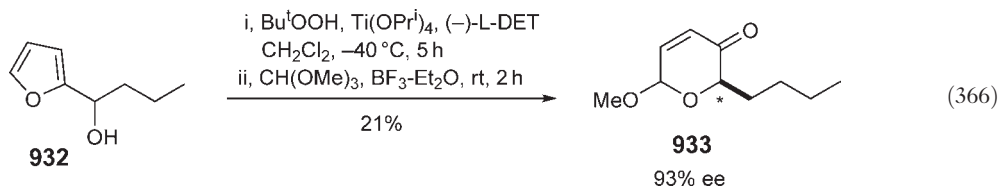
Table 43 Geometry of alkenes **930** and their oxidative cyclization to 2,6-dihydropyran-3-ones **931** (Equation 365)

<i>R</i>	* 930 geometry	Yield 931 (%)
<i>n</i> -C ₇ H ₁₅	<i>Z</i>	58
<i>n</i> -C ₇ H ₁₅	<i>E</i>	57
<i>n</i> -C ₉ H ₁₉	<i>E</i>	59
H	<i>E</i>	63

7.08.22.2.2 From other heterocycles

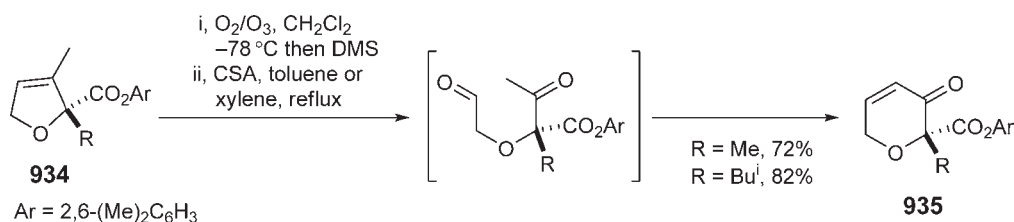
7.08.22.2.2(i) From furans

The oxidative ring expansion of furfuryl alcohols continues to be the most popular method for construction of the 2,6-dihydropyran-3-one ring system. This step can be seen during the first asymmetric synthesis of phorbol <1997JA7897>, the syntheses of allixin and related compounds <1998TL2339, D-, L-mannose, gulose, talose <1999JOC2982>, (–)-calicheamicinone <2000CC1341>, (*R*)-(–)-argentilactone <2001TL7401>, (+)-ambruticin S <2003T6819>, isoaltholactone, 3-epi-altholactone 5-hydroxyginiothahalamin <2000OL2983>, spiro compounds <2000OL863, 2003TL5015> and in other synthetic studies <1999J(P1)1983, 1999EJO1449, 2000T8953, 2003EJO82, 2003TL8227, 2004TL1005, 2004JA3428, 2005TL823, 2005T3025, 2005SL1547, 2005OL3921, 2006OL293>. Sharpless kinetic resolution of a furfuryl alcohol **932** followed by acetylation furnishes the optically active 2,6-dihydropyran-3-one **933** (Equation 366) <2002J(P1)1444>.



7.08.22.2.2(ii) From dihydrofurans

Dihydrofuran **934** undergoes an oxidative cleavage/aldol ring closure sequence without epimerization at the stereo-centre providing a route to enantiopure 2,6-dihydropyran-3-ones **935** (Scheme 252) <2002OL3059>.



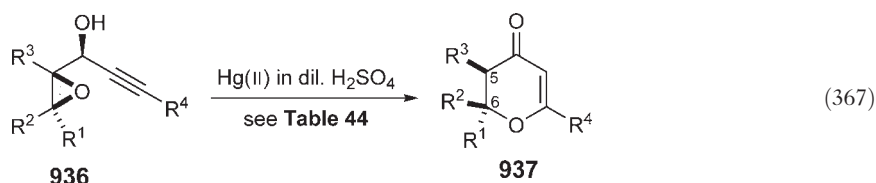
Scheme 252

7.08.23 Dihydropyran-4-ones

7.08.23.1 Formation of One Bond

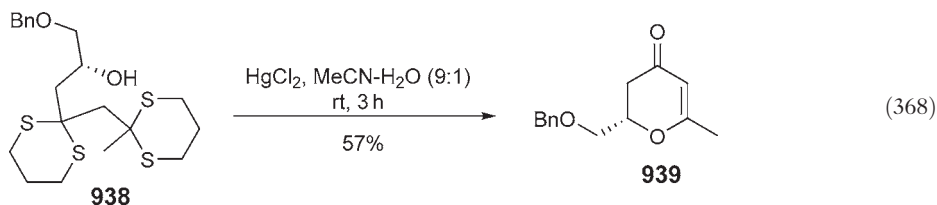
7.08.23.1.1 Adjacent to the heteroatom

A stereospecific synthesis of dihydropyran-4-ones **937** can be achieved by a mercury(II)-catalyzed rearrangement of 1-alkynyl-2,3-epoxy alcohols **936**. The configuration of the epoxide is transferred unchanged to the product (Equation 367, Table 44) <1998JOC3798>.

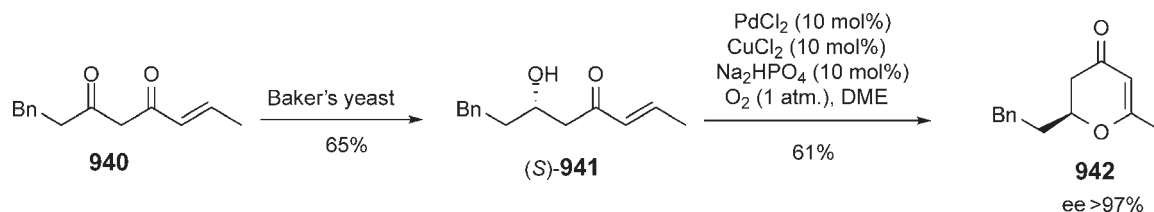
Table 44 Formation of dihydropyran-4-ones **937** (Equation 367)

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	Yield 937 (%)	<i>C5:C6</i>
H	H	Me	<i>n</i> -C ₅ H ₁₁	74	
H	H	Me	Ph	80	
H	H	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₅ H ₁₁	67	
H	Et	Me	<i>n</i> -C ₅ H ₁₁	56	100% <i>syn</i>
H	Et	Me	CH ₂ OH	57	100% <i>syn</i>
H	Et	Ph	<i>n</i> -C ₅ H ₁₁	53	100% <i>syn</i>
Pr ⁱ	H	Me	<i>n</i> -C ₅ H ₁₁	50	100% <i>anti</i>

Mercury(II)-mediated removal of both dithianes from alcohol **938** followed by *in situ* cyclization of the unmasked diketone provides the dihydropyran-4-one **939** during a synthetic approach to thysiferol (Equation 368) <2005JOC5249>.



Palladium(II)-mediated oxidative cyclization of enantiopure β-hydroxyenone **941** provides a route to dihydropyran-4-one **942** with complete stereocontrol. The chirality in the starting material is introduced via a baker's yeast-mediated reduction of **940** (Scheme 253) <2004OL91>. Obtaining chiral cyclization precursors for the same cyclization can also be achieved via an antibody mediated resolution, with this methodology applicable to tetrahydropyran-4-one synthesis <2005JA1481> and retention of configuration is achieved if substrates bearing multiple stereocentres are used <2005JOC8478>.

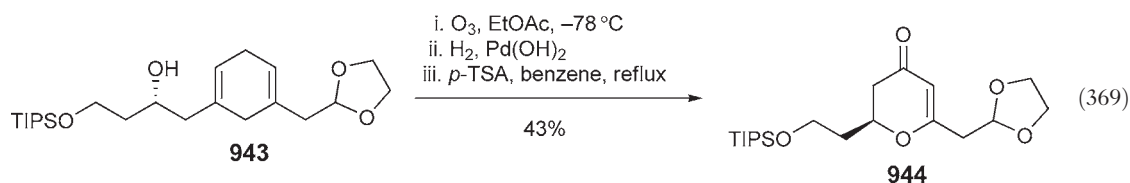


Scheme 253

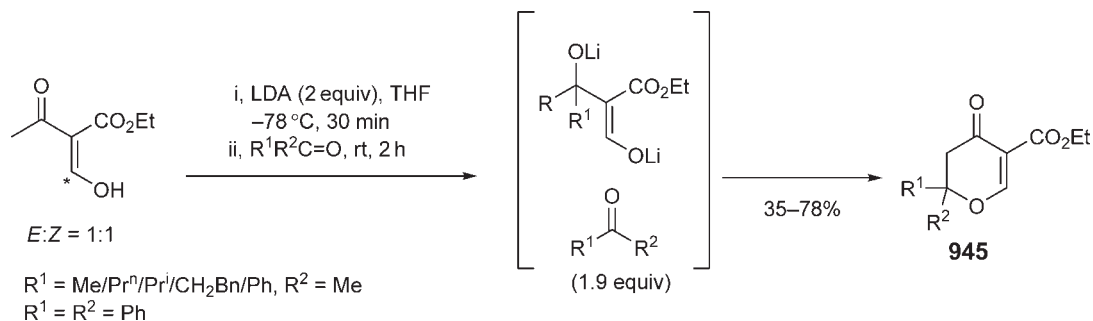
Trifluoroacetic acid-promoted cyclization/dehydration is used to construct a dihydropyran-4-one ring during the total synthesis of (–)-maurenone, establishing the relative stereochemistry of the natural product [<2006JOC117>](#). A double aldol reaction forms two dihydropyran-4-one rings during the total syntheses of (–)- and (+)-membrenone C [<2003OL1729>](#).

7.08.23.2 Formation of More than One Bond

Ozonolysis of the double bond in 1,4-cyclohexadiene **943** followed by reductive work-up and dehydration provides the dihydropyran-4-one **944**, an intermediate during a formal synthesis of leucascandrolide (Equation 369) [<2002CC2066>](#).



Condensation of (*E/Z*)-ethyl 2-formyl-3-oxobutanoate with ketones provides a route to 3-carbonylethoxydihydropyran-4-ones **945** (Scheme 254) [<1998TL213>](#).



Scheme 254

The use of hDA methodology as a means of constructing the dihydropyran-4-one ring system continues to attract much interest. A review concerning the enantioselective hDA reaction covers the synthesis of dihydropyran-4-ones using this cycloaddition approach [<2000AGE3558>](#).

An hDA reaction between Danishefsky's diene and nitrosubstituted aromatic aldehydes is catalyzed by dirhodium(II) complexes in up to 95% ee [<2001JA5366, 2003JMO93>](#). Similar dirhodium(II) complexes are also reported to be effective catalysts for this reaction [<2004SL2425, 2004AGE2665, 2005JOC5291>](#).

The asymmetric hDA reaction between activated dienes and aldehydes is catalyzed by titanium(IV) [<2000CC1605, 2001JA10942, 2002SL931, 2002SL2122, 2002JA10, 2002CEJ5033, 2002JA14866, 2003CEJ5989, 2003JA6042, 2003JOC6466, 2004SL1772, 2004JA11326, 2005JOC8533>](#), cerium(III)-BNP [<2003CL608>](#), chromium

<2000TL8069, 2001CEJ2873, 2001OL2919, 2002HCA913, 2002JA4956, 2002OL1795, 2004OBC3026>, zirconium <2002OL1221> and 3-oxobutylideneaminatocobalt complexes <2001BCJ1333> giving dihydropyran-4-ones with good to excellent diastereo- and enantioselectivity. Similar cycloadditions can also be catalyzed by LiClO_4 <2003OL1163> or $\text{BF}_3\cdot\text{Et}_2\text{O}$ <2004JA1843>.

The use of the zinc complex of the BINOL ligand **946** in the hDA reaction between Danishefsky's diene **947** and aldehydes proceeds in excellent yield and enantioselectivity to afford dihydropyran-4-ones **948** (Equation 370, Table 45) <2002OL4349>. An asymmetric diethyl zinc addition can occur in tandem with the cycloaddition reaction between Danishefsky's diene **947** and isophthalaldehyde using a related catalyst **949** (Equation 371) <2003OL1091, 2005T9465>.

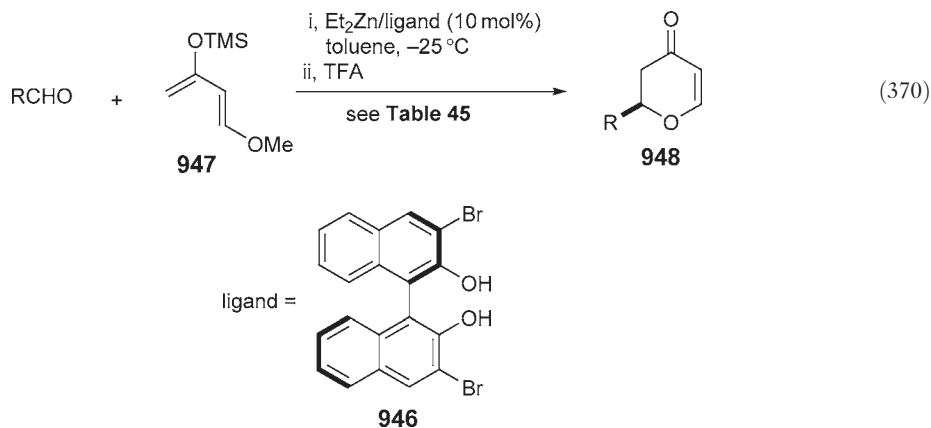
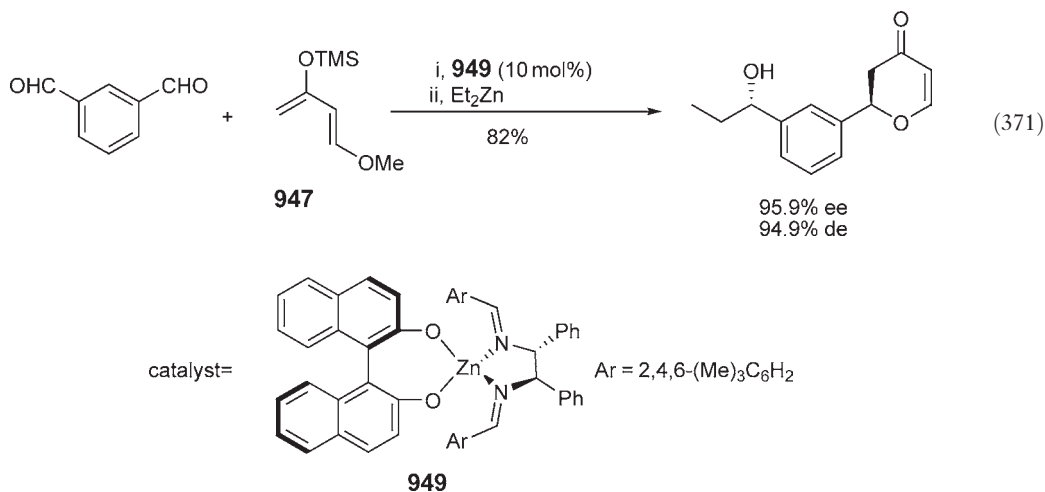


Table 45 Formation of dihydropyran-4-ones **948** (Equation 370)

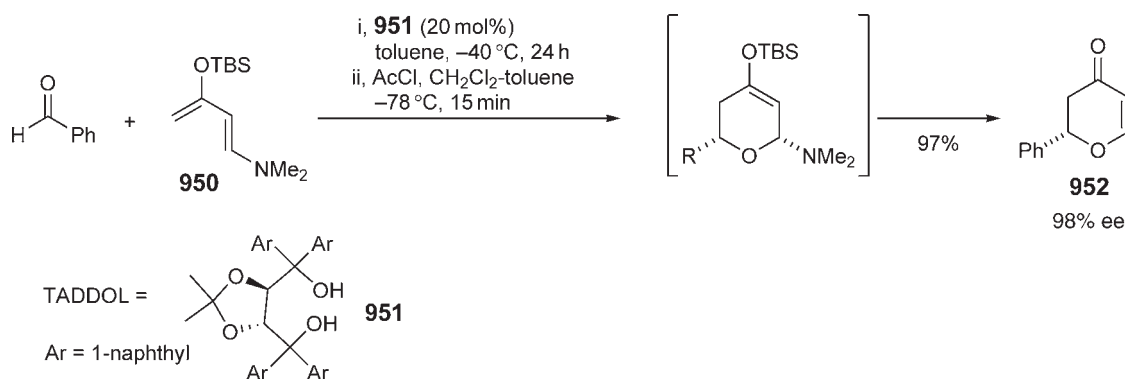
<i>R</i>	Yield 948 (%)	<i>ee</i> 948 (%)
Ph	>99	97
4-MeOC ₆ H ₄	>99	98
(<i>E</i>)-styryl	34	86
2-furfuryl	>99	96
3-MeC ₆ H ₄	>99	96
4-CNC ₆ H ₄	>99	96
3-BrC ₆ H ₄	>99	94
3-ClC ₆ H ₄	92	98
4-BrC ₆ H ₄	>99	94
4-ClC ₆ H ₄	>99	95
2,6-(Cl) ₂ C ₆ H ₃	82	89



An hDA reaction between Danishefsky's diene and benzaldehyde is catalyzed by hypervalent chromium <2000CEJ123>, titanium(IV) <2000TL5043, 2002JOC2175>, zirconium <2003CC2016, 2003JA3793>, trivalent rare earth-chiral phosphate <2003TL6129, 2003T10509>, metallosalen <2001T845> and chiral aluminium complexes <2001T907> with excellent enantioselectivity. Lewis bases can also catalyze this process <2006CL328>.

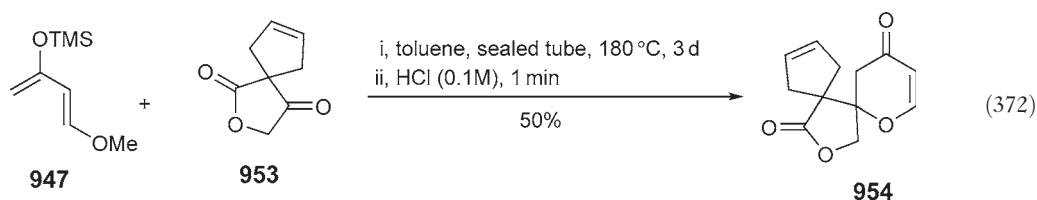
An hDA reaction between Danishefsky's diene and glyoxylate esters proceeds in the presence of bisoxazoline-lanthanide complexes with moderate levels of enantioselectivity <2000TL2203>. A similar reaction between Danishefsky's diene and α -keto esters proceeds with excellent enantioselectivity in the presence of bisoxazoline-copper <2001TL6231, 2003EJO317, 2004TA1987> or Cr(III), Co(II and III)-salen complexes <2004TA3189>.

An hDA reaction between a 1-amino-3-siloxy-1,3-butadiene with methylpyruvate proceeds in the absence of Lewis acid catalysis. Dihydropyran-4-ones are formed upon treatment of the dihydropyran products with acetyl chloride <2000OL3321>. Unactivated ketones are also viable dienophiles for this reaction <2002JA9662>. The asymmetric hDA reaction between the 1-amino-3-silyloxy-1,3-butadiene **950** and benzaldehyde is controlled by hydrogen bonding to the TADDOL catalyst **951** to afford the dihydropyran-4-one **952** (Scheme 255) <2003NAT146, 2006JOC2862>. The same reaction can be catalyzed by oxazoline <2005OL5473> and BAMOL catalysts with comparable enantioselectivities <2005JA1336>.



Scheme 255

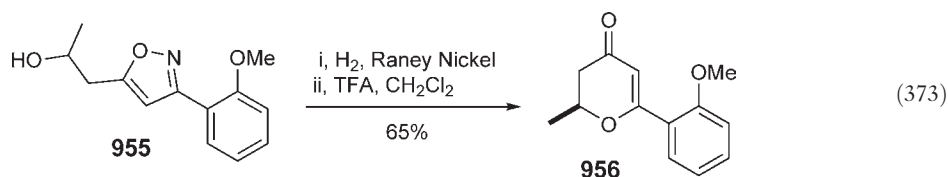
Heating 3,3-spirocyclopentenylidihydrofuran-2,4-dione **953** with Danishefsky's diene **947** in a sealed tube affords the 3,4-dispiro hDA adduct **954** in moderate yield (Equation 372) <2005TL3657>.



7.08.23.3 From Other Heterocycles

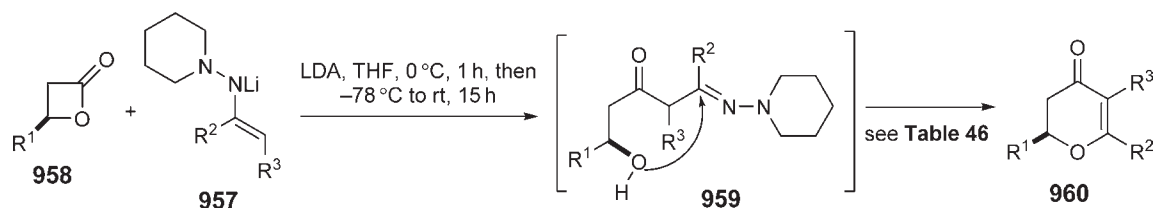
7.08.23.3.1 From isoxazoles

Hydrogenolysis of the racemic isoxazolyl alcohol **955** followed by an acid-mediated cyclization of the resulting diketone provides the dihydropyran-4-one **956**, an intermediate during a synthesis of C-aryl glycosides (Equation 373) <2002OL977>.



7.08.23.3.2 From oxetanones

Hydrazone anion **957** induced ring opening of the enantiopure 4-substituted oxetan-2-ones **958** followed by cyclization/dehydroamination of the resulting β -ketohydrazones **959** affords dihydropyran-4-ones **960** in good to excellent yield and enantioselectivity (Scheme 256, Table 46) <2002OL1823>.



Scheme 256

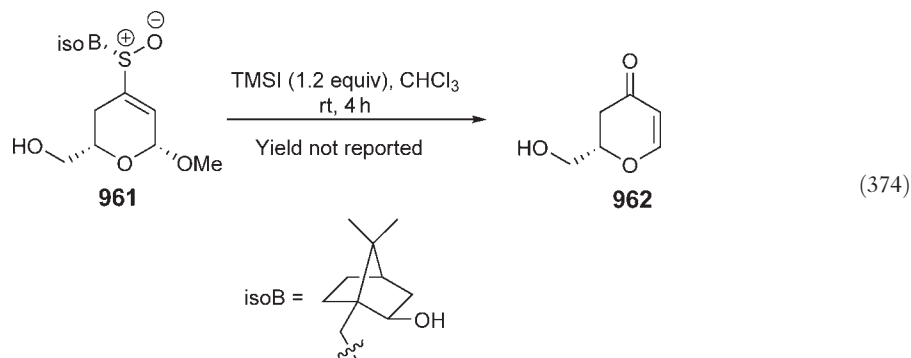
Table 46 Formation of dihydropyran-4-ones **960** (Scheme 256)

R^1	R^2	R^3	Yield 960 (%)	ee 960 (%)
CH_2Bn	H	Me	78	91
$-\text{C}\equiv\text{C}-\text{TMS}$	H	Me	72	90
CH_2OBn	H	Me	75	91
CH_2Bn	H	Et	74	91
CH_2Bn	Et	Me	78	91
$-\text{C}\equiv\text{C}-\text{TMS}$	Et	Me	68	90
CH_2Bn	Et	Me	76	91

7.08.23.4 From a Preformed Heterocyclic Ring

7.08.23.4.1 From dihydropyrans

Treatment of the chiral α,β -unsaturated sulfoxide **961** with TMSI results in formation of the unstable dihydropyran-4-one **962** (Equation 374) <2002T10145>.

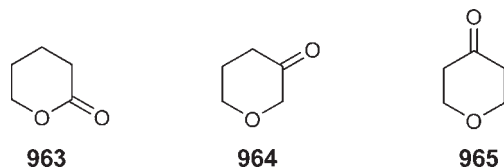


7.08.23.4.2 From dihydropyran-2-ones

Dihydropyran-4-ones can be prepared by addition of various nucleophiles to 3-ethoxy-5,6-dihydropyran-2-ones prepared from the hDA reaction between Brassard's diene and aldehydes <2005OL2421>.

7.08.24 Tetrahydropyranones

Three regioisomeric tetrahydropyranones are discussed in this section: tetrahydropyran-2-one **963**, tetrahydropyran-3-one **964** and tetrahydropyran-4-one **965**.

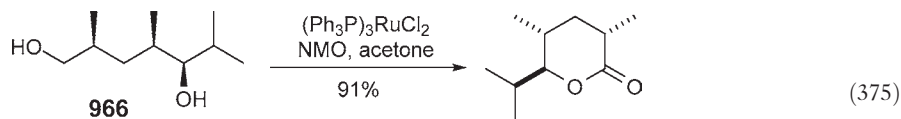


7.08.24.1 Tetrahydropyran-2-ones

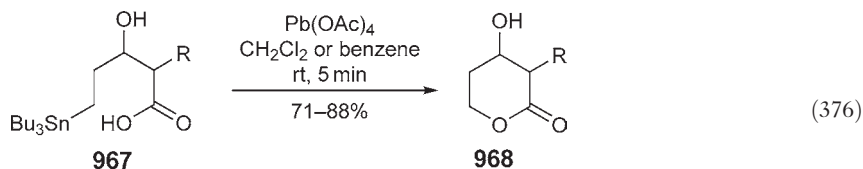
7.08.24.1.1 Formation of One Bond

7.08.24.1.1(i) Adjacent to the heteroatom

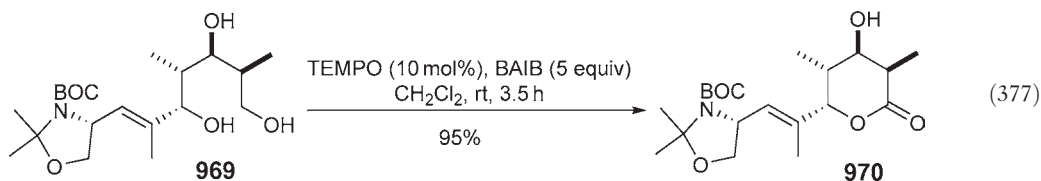
Ruthenium(II)-catalyzed oxidative lactonization of the 1,5-diol **966** provides the final step in a stereoselective synthesis of the pheromone (3*S*,5*R*,6*S*)-3,5-dimethyl-6-isopropyltetrahydropyran-2-one (Equation 375) <1996T5907>. The conversion of 5-hydroxyhexanenitrile to 6-methyltetrahydropyran-2-one proceeds in poor yield in the presence of the microorganism *Rhodococcus rhodochroms* <1996JOC9084>. 2-Substituted-3-hydroxy-5-tributylstannylpentanoic acids **967** cyclize to 3-substituted-4-hydroxytetrahydropyran-2-ones **968** upon exposure to lead tetraacetate (Equation 376) <1997S937>. A highly chemoselective oxidation of the 1,5-diol **969** to the tetrahydropyran-2-one **970** can be achieved upon treatment with bis-acetoxyiodobenzene (BAIB) and catalytic amounts of TEMPO (Equation 377) <2003TL57>. A novel amino alcohol-based iridium bifunctional complex **971** is an efficient catalyst for the formation of tetrahydropyran-2-ones **973** from 1,5-diols **972** (Equation 378) <2002OL2361>. An asymmetric lactonization of 1,5-diols leading to tetrahydropyran-2-ones can be conducted electrochemically <2003CC114>. Aryl substituted silene **974** can undergo reductive ring opening followed by oxidative cyclization of the resulting 1,5-diol **975** to afford the tetrahydropyran-2-one **976** with good *anti*-selectivity (Scheme 257) <2003TL9135>. A tandem OsO₄-mediated oxidative cleavage/oxidative lactonization of hex-5-en-1-ol affords tetrahydropyran-2-one in good yield (Equation 379) <2003OL3089>.

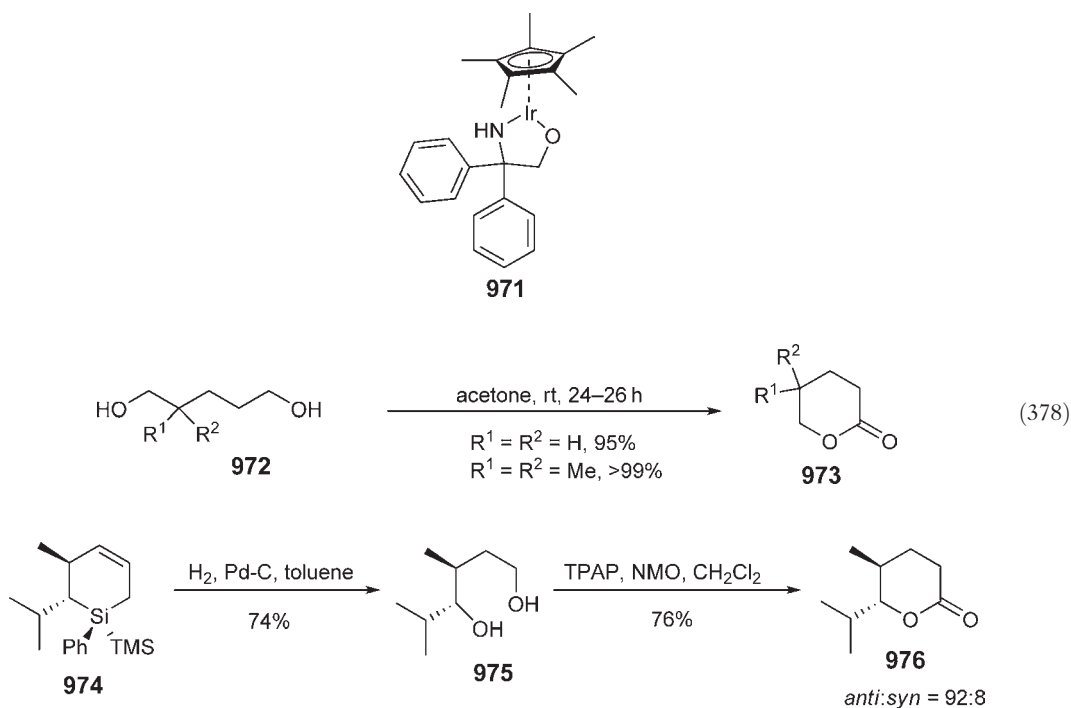


NMO = *N*-methylmorpholine-*N*-oxide

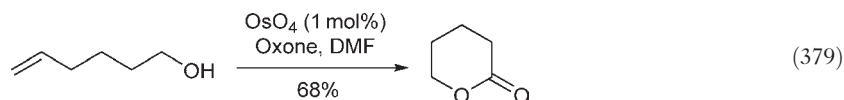


R = H/*n*-C₆H₁₃/Bn/cinnamyl/allyl

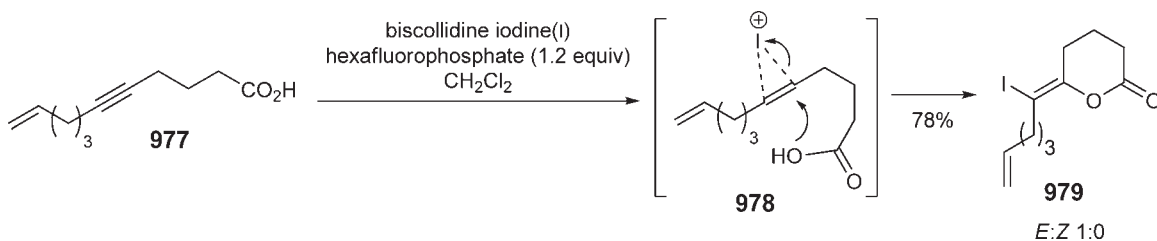




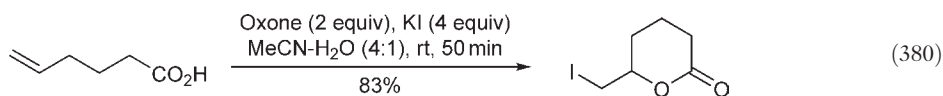
Scheme 257

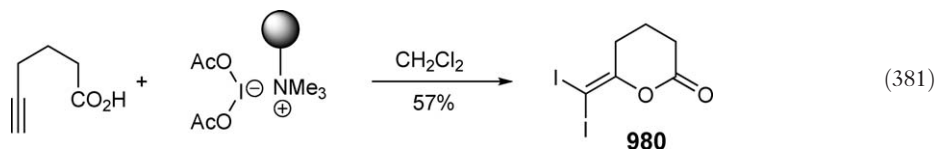


Reaction of the ω -ene-5-yne carboxylic acid **977** with biscollidine iodine(i) hexafluorophosphate leads to exclusive formation of the C(6)-(E)-iodovinyl tetrahydropyran-2-one **979**. The product arises via attack of the acid onto the iodonium ion intermediate **978** (Scheme 258) <2004TL4503>. A similar iodolactonization of hex-5-enoic acid can be induced by Oxone[®]-potassium iodide to furnish 6-(iodomethyl)tetrahydropyran-2-one in excellent yield (Equation 380) <2004SL368>. Similarly, treatment of 5-hexynoic acid with a polymer bound source of electrophilic iodide affords the tetrahydropyran-2-one **980** bearing a diiodo-substituted exocyclic double bond (Equation 381) <1999OL2101>.

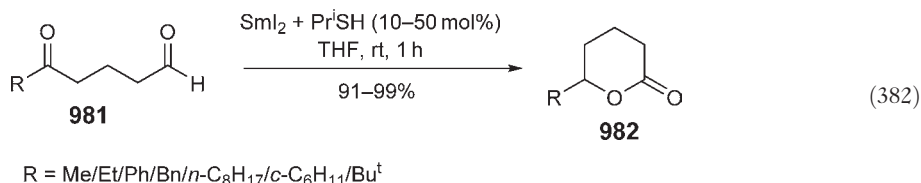


Scheme 258

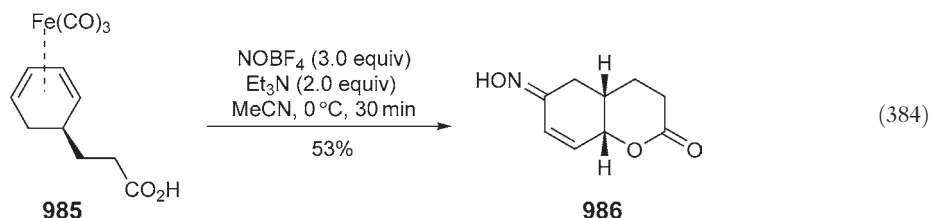
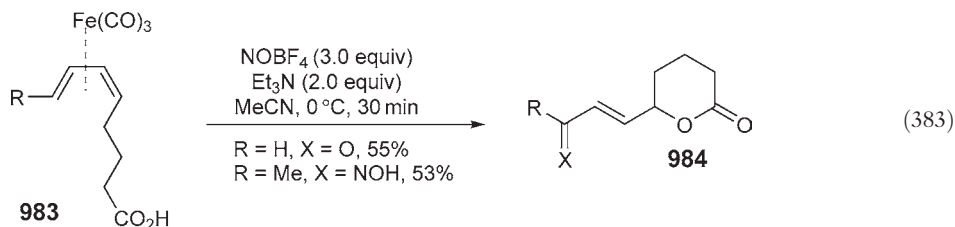




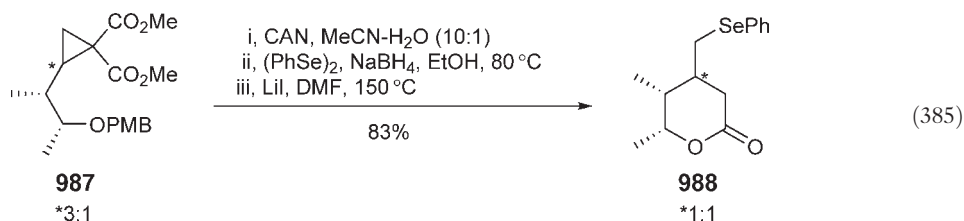
Transformation of the 5-oxopentanal **981** to 6-substituted tetrahydropyran-2-ones **982** can be achieved by synergistic catalysis using samarium diiodide and 2-propanethiol in excellent yield (Equation 382) <1999OL1989>.



Treatment of carboxylic acid functionalized cyclic (η^4 -diene)- $\text{Fe}(\text{CO})_3$ complexes **983** with an excess of NOBF_4 in the presence of base generates tetrahydropyran-2-ones **984**. When the acyclic diene possesses $R = \text{Me}$, the product is an α,β -unsaturated oxime but when $R = \text{H}$, the α,β -unsaturated aldehyde is formed (Equation 383). Similar treatment of the cyclic complex **985** affords the bicyclic tetrahydropyran-2-one **986** (Equation 384) <1999CC805>.

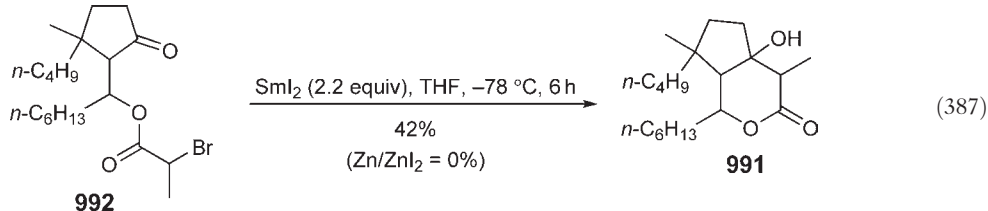
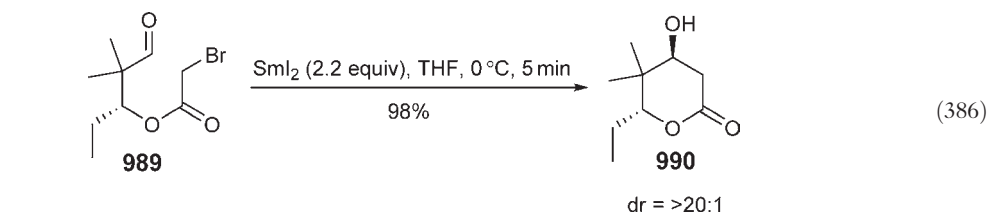


Oxidative removal of the PMB group of the cyclopropane **987** followed by δ -lactonization and Krapcho reaction furnishes tetrahydropyran-2-one **988**, a key intermediate during the total synthesis of (+)-mycalamide A (Equation 385) <2006OL875>.

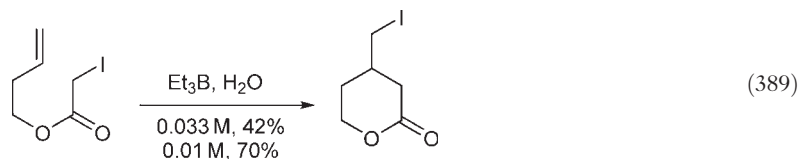
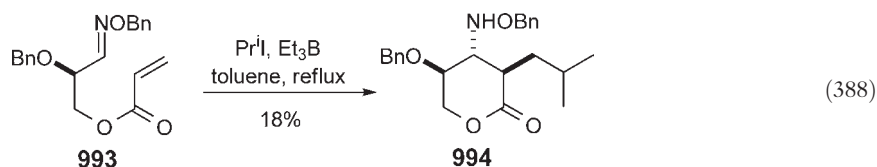


7.08.24.1.1(ii) γ to the heteroatom

An intramolecular Reformatsky reaction of the α -haloester **989** can be conducted in the presence of samarium diiodide leading to the tetrahydropyran-2-one **990** in excellent yield and diastereoselectivity (Equation 386) <1998JOC9580>. This choice of reagent is superior compared to the traditional Reformatsky reagent (Zn/ZnI_2), as emphasized by the synthesis of the tetrahydropyran-2-one **991** from the α -haloester **992** during a total synthesis of clavulactone (Equation 387) <2001JOC2692>.

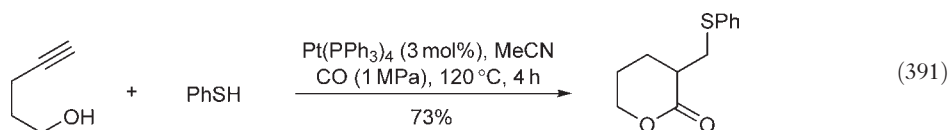
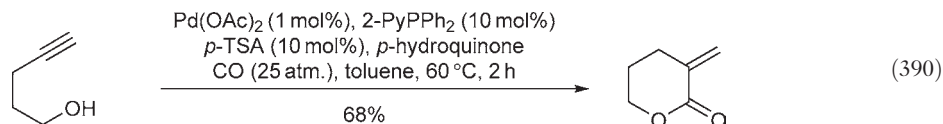


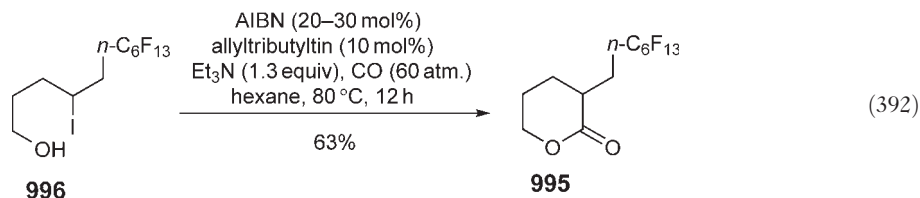
Intramolecular cyclization of the chiral oxime ether **993** in the presence of isopropyl iodide and triethylborane affords the 3,4,5-trisubstituted tetrahydropyran-2-one **994** in poor yield but with good diastereoselectivity (Equation 388) <2003JOC5618>. Similarly, a triethylborane-induced atom transfer radical cyclization of 3-butenyl 2-iodoacetate leads to 4-(iodomethyl)tetrahydropyran-2-one. Higher yields are achieved when conducting the reaction at lower concentrations (Equation 389) <2000JA11041>.



7.08.24.1.2 Formation of more than one bond

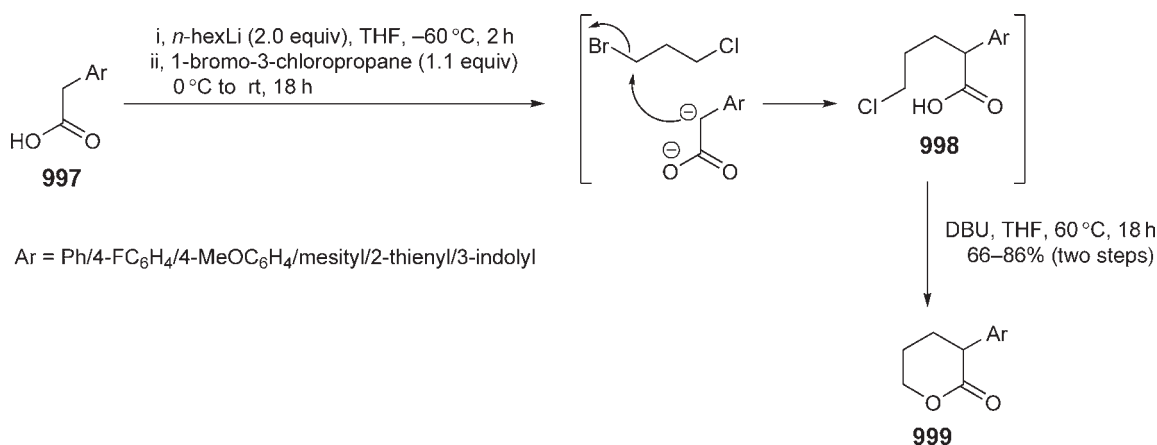
A review regarding the use of transition metal catalyzed cyclocarbonylation reactions for the synthesis of tetrahydropyran-2-ones and their benzo derivatives is available <2000SL161>. The Pd(II)/2-PyPPH₂ catalyzed carbonylation and cyclization of 1-alkyn-4-ol affords 3-methylenetetrahydropyran-2-one in good yield (Equation 390) <2002TL753>. A platinum-catalyzed cyclocarbonylation and addition of benzenethiol to 1-alkyn-4-ol provides 3-(phenylthiomethyl)tetrahydropyran-2-one in good yield (Equation 391) <2003T3521>. Polyfluorinated tetrahydropyran-2-one **995** can be prepared from ω -hydroxyalkyl iodide **996** and CO by an atom transfer carbonylation reaction in the absence of a transition metal catalysis (Equation 392) <2000OL389>.





Tetrahydropyran-2-ones can be accessed via a Baeyer–Villiger (BV) oxidation of cyclohexanones that bear a 6-hydroxymethyl substituent [<2001JOC6803>](#) and via BV oxidations of cyclopentanones [<1996TL4555, 1998JOC1390, 1998T10329, 2000OL2861, 2000TL3631, 2000SL1052, 2001S1356, 2001JOC2429, 2001JA7162, 2002CC1588, 2002T3977, 2002TL4175, 2003SL2092, 2003TL8991, 2003EJO2243, 2003JOC6222, 2003TL2893, 2005TA1305, 2005TL3505, 2005T8390, 2005JOC10879>](#).

The dianions of arylacetic acids **997** undergo alkylation reactions with 1-bromo-3-chloropropane, with the resulting 5-chloropentanoic acids **998** cyclizing upon treatment with DBU providing a one-pot preparation of 3-aryltetrahydropyran-2-ones **999** (Scheme 259) [<2003TL365>](#).



Scheme 259

A one-pot cross-metathesis/hydrogenation/cyclization protocol allows for the synthesis of 6-disubstituted tetrahydropyran-2-ones **1001** from homoallylic alcohols **1000** and acrylic acid (Equation 393, Table 47) [<2003OL459>](#). This methodology is invaluable during the total synthesis of (–)-centrolobine [<2004TL6603>](#).

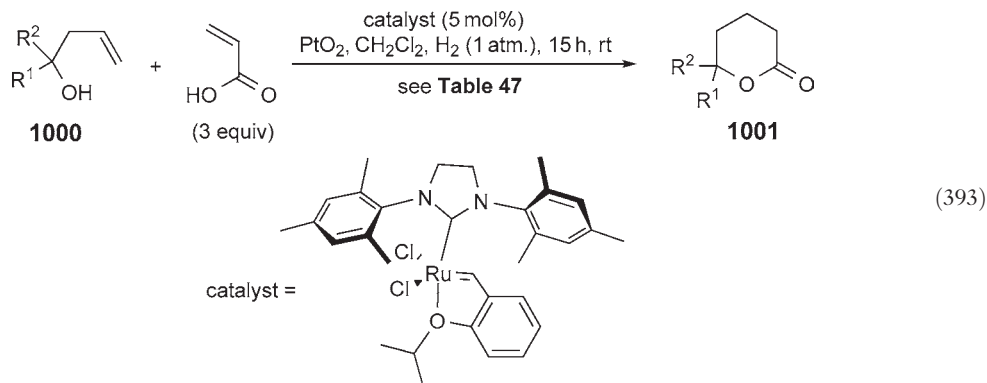
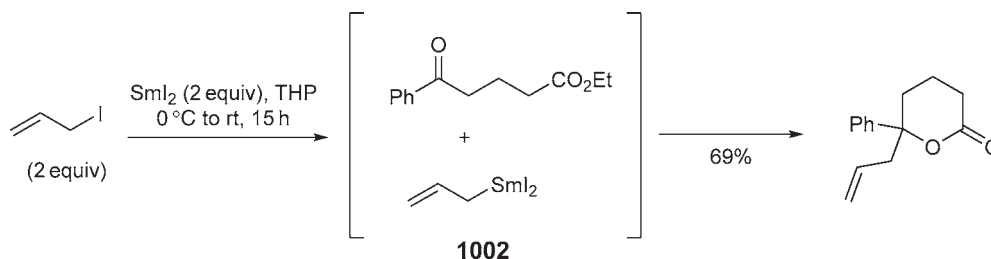


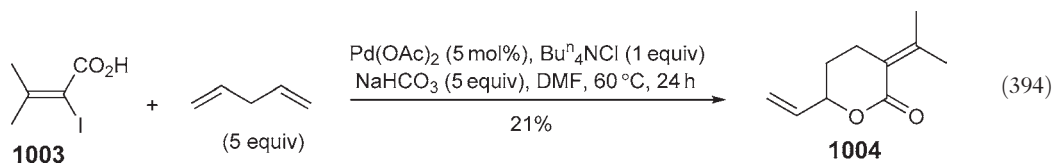
Table 47 Formation of tetrahydropyran-2-ones **1001** from homoalcohols **1000** (Equation 393)

Alcohol 1000	Product 1001	Yield 1001 (%)
		66
		50
		10
		42
		50
		35

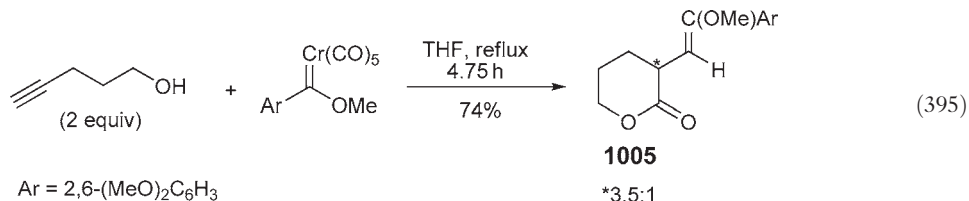
Samarium diiodide reduces allyl iodide at low temperature forming a stable organosamarium compound **1002** which reacts with ethyl-5-oxo-5-phenylpentenoate to afford 6-allyl-6-phenyltetrahydropyran-2-one in good yield (**Scheme 260**) <1997TL6585>.

**Scheme 260**

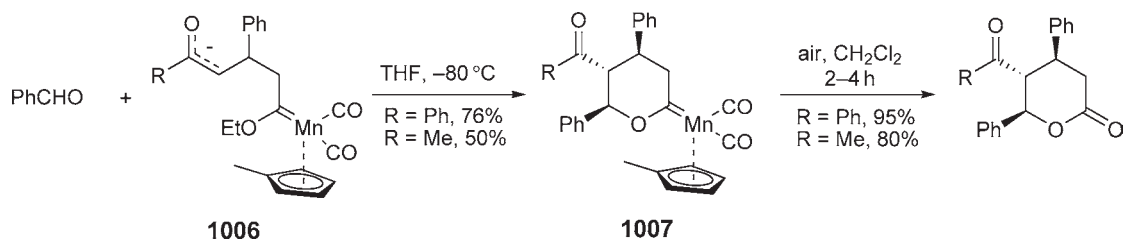
1-Iodocarboxylic acid **1003** and 1,4-pentadiene undergo a palladium-catalyzed heteroannulation reaction producing the tetrahydropyran-2-one **1004** in poor yield (Equation 394) <2000JOC1525>.



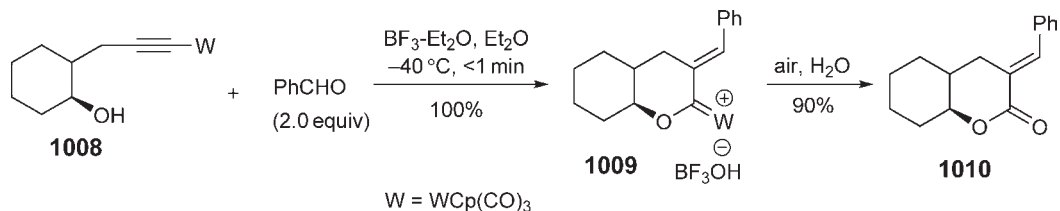
A reaction between pentacarbonyl[methoxy(2,6-dimethoxyphenyl) methylene]chromium(0) and pent-4-yn-1-ol provides direct access to the functionalized tetrahydropyran-2-one **1005**; the best yield is obtained *via* thermal heating of the two starting materials in THF (Equation 395) <2000TL9323>.



Carbon enolate complexes **1006** react with benzaldehyde to form the oxacyclocarbene complexes **1007**, which undergo demetallation upon exposure to air to afford tetrahydropyran-2-ones (Scheme 261) <2000TL7341>. The tungsten- η^1 -alkynyl compound **1008** react with benzaldehyde in the presence of a Lewis acid to form the tungsten- η^1 -pyridine salt **1009**, which undergoes demetallation upon exposure to air furnishing the bicyclic tetrahydropyran-2-one **1010** in high yield (Scheme 262) <1997JA4404>.



Scheme 261



Scheme 262

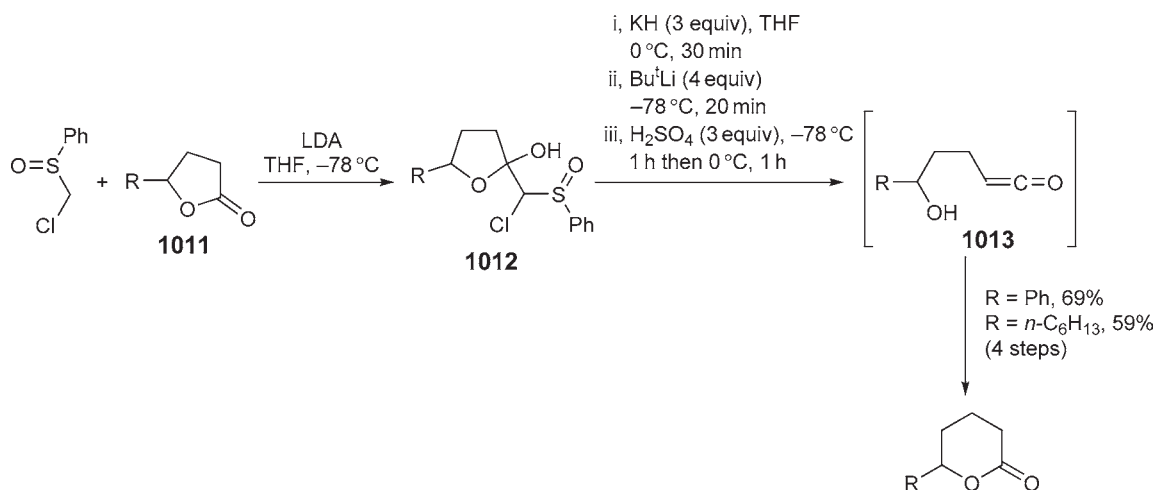
7.08.24.1.3 From other heterocycles

7.08.24.1.3(i) From tetrahydrofuranones

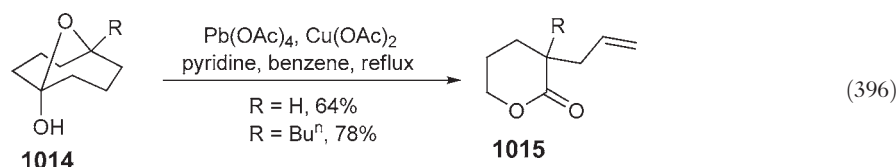
The lithium anion of chloromethyl phenyl sulfoxide reacts with tetrahydrofuran-2-ones **1011** to afford a diastereomeric mixture of hemiacetal adducts **1012**, the potassium enolate of which is treated with *t*-BuLi followed by addition of a proton source leading to ω -hydroxyalkyl ketenes **1013**, which themselves cyclize to 6-substituted tetrahydropyran-2-ones in excellent overall yield (Scheme 263) <1998TL9215>.

7.08.24.1.3(ii) From 9-oxabicyclo[3.2.1]nonanes

Treatment of 9-oxabicyclo[3.3.1]nonan-1-ols **1014** with a combination of lead tetraacetate and copper diacetate affords 3-allenyl tetrahydropyran-2-ones **1015** via an alkoxy radical accelerated β -fragmentation pathway (Equation 396) <2001TL2047>.



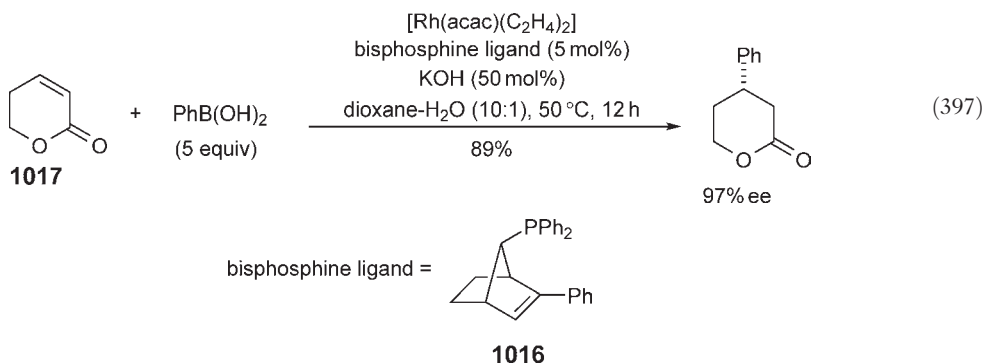
Scheme 263



7.08.24.1.4 From a preformed heterocyclic ring

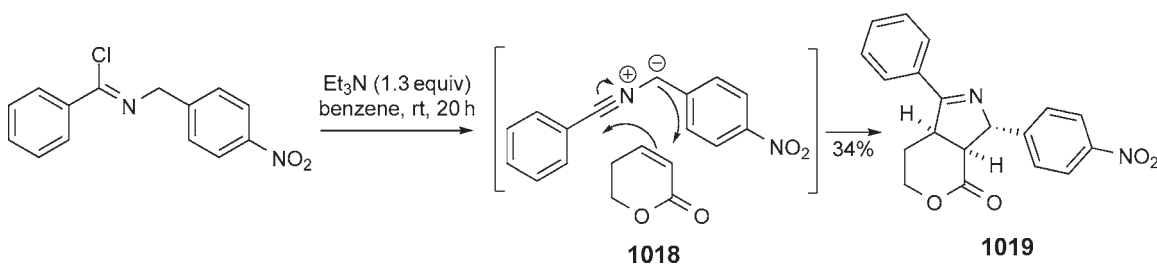
7.08.24.1.4(i) From dihydropyranones

Much attention is paid to the asymmetric 1,4-addition reaction of 5,6-dihydropyran-2-ones leading to tetrahydropyran-2-ones. Treatment of *N*-BOC-*N*-(*p*-methoxyphenyl)cinnamylamine with *n*-BuLi and (–)-sparteine followed by a 5,6-dihydropyran-2-one gives the Michael adduct tetrahydropyran-2-one with excellent diastereoselectivity <1997JA10537, 2002OL2657>. Michael addition of (*S*)-formaldehyde SAMP-hydrazone to 5,6-dihydropyran-2-one with Lewis acid activation proceeds in good yield and diastereoselectivity to give tetrahydropyran-2-ones (SAMP=(*S*)-1-amino-2-methoxymethylpyrrolidine) <1999CC701, 1999SL629, 2000EJO893>. The conjugate addition of a (*Z*)-2-ethoxyvinyl anion to 5,6-dihydropyran-2-one is best conducted using Noyori-type organocopper reagents <2000TL8873>. A rhodium(II)-catalyzed conjugate addition of boronic acids to 5,6-dihydropyran-2-one in the presence of monodentate phosphoramidite ligands proceeds with moderate enantioselectivity (62%) <2003OL681>, improved somewhat by the addition of base <2003SL1040, 2003JOC9481>. The use of the bisphosphine ligand **1016** during the addition of phenylboronic acid to 5,6-dihydropyran-2-one **1017** furnishes (*S*)-4-phenyltetrahydropyran-2-one in excellent yield and enantioselectivity (Equation 397) <2005AGE4611>. Rhodium(II)-catalyzed conjugate addition of arylboron reagents to 5,6-dihydropyran-2-ones proceeds in excellent enantioselectivity in the presence of BINAP ligands <1999TA4047>. The asymmetric addition of organotrifluoroborates can also be conducted in this manner <2004JOC8045>.



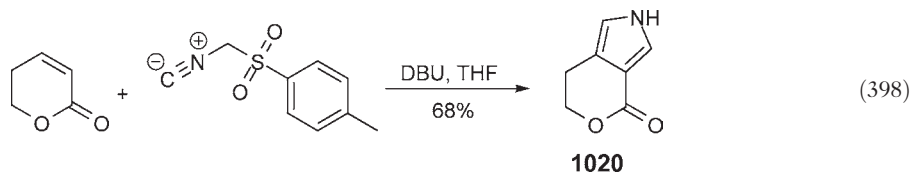
1,1'-Bi-2-naphthol (BINOL) based diphosphonites <2001OL4083>, C(2)-symmetric bicyclo[2.2.2]octa-2,5-dienes <2005JOC2503>, 1,5-diphenyl-1,5-cyclooctadienes <2005OL5889> and planar cyrhetrenes, novel rhenium complexes <2005JOC9925> are ligands that can be used successfully for the asymmetric rhodium(II)-catalyzed 1,4-addition of arylboronic acids and phenylzinc chloride to 5,6-dihydropyran-2-ones. A highly enantioselective conjugate addition of dialkylzinc reagents to 5,6-dihydropyran-2-one is possible using a chiral diphosphite-copper(I) catalyst <2000CC115, 2002TL1189, 2003TL7217, 2004TA2575>, copper(I)-peptide complexes <2005AGE5306> and alkoxy-*N*-heterocyclic carbenes (NHC's) in the presence of copper(I) salts <2005TA921>. Similar asymmetric 1,4-additions to 5,6-dihydropyran-2-one can be conducted using chiral phosphoramidate anions <2000JOC5623>. Copper(I) catalysts are also used for the asymmetric addition of Grignard reagents to 5,6-dihydropyran-2-ones <1999T3843>, and the asymmetric reduction of 4-substituted 5,6-dihydropyran-2-ones <2003JA11253>.

Treatment of (*Z*)-*N*-(4-nitrobenzyl)benzimidoyl chloride with base generates the nitrile ylide **1018**, which undergoes a 1,3-dipolar cycloaddition with 5,6-dihydropyran-2-one to afford the *exo*-adduct tetrahydropyran-2-one **1019** as the exclusive product (Scheme 264) <1998T11613>. A 1,3-dipolar cycloaddition of a chiral cyclic nitron with 5,6-dihydropyran-2-one proceeds with high stereoselectivity to the *exo*-tetrahydropyran-2-one <2000TA2015, 2001TA3163>.



Scheme 264

Treatment of dihydropyran-2-one with tosylmethyl isocyanide in the presence of DBU provides the tetrahydropyran-2-one **1020**, an intermediate during the synthesis of cyclin-dependant kinase 2 inhibitors (Equation 398) <2003BML1939>.



7.08.24.1.4(ii) From pyran-2-ones

Complete reduction of a pyran-2-one to the corresponding tetrahydropyran-2-one can be achieved under an atmospheric pressure of hydrogen in the presence of catalytic quantities of rhodium on alumina in excellent yield <2003SL253>.

7.08.24.1.4(iii) From tetrahydropyrans

Tetrahydropyran can be oxidized to tetrahydropyran-2-one in moderate yield using a trimethylsilylnitrate-chromium trioxide (TMSONO₂-CrO₃) system <1999JOC4509>.

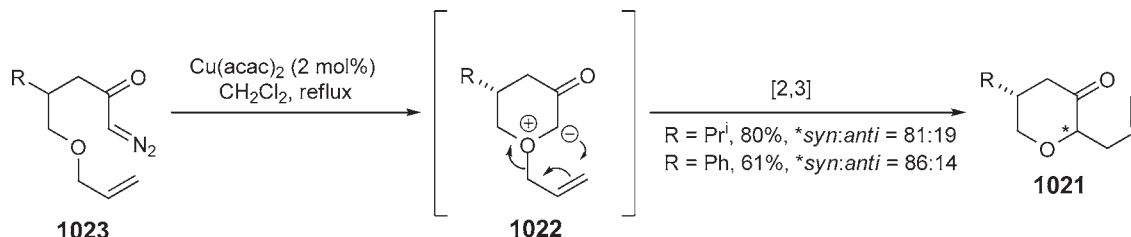
7.08.24.2 Tetrahydropyran-3-ones

7.08.24.2.1 Formation of one bond

7.08.24.2.1(i) Adjacent to the heteroatom

A diastereoselective synthesis of tetrahydropyran-3-ones **1021** can be achieved via [2,3]-sigmatropic rearrangement of the ylides **1022**, generated from the achiral diazoketone **1023** via formation of a copper carbenoid followed by an

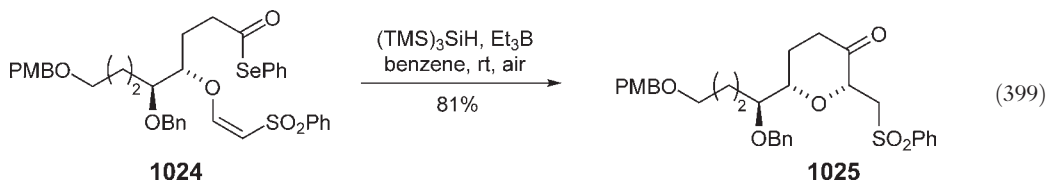
intramolecular reaction with the oxygen atom of the pendant allylic ether (**Scheme 265**) <2003CC2578>. This rearrangement is pivotal during the synthesis of the C(3)–C(12) portion of laulimalide <2005CPB989>. Chiral rhodium(II) catalysts can also promote this rearrangement with moderate enantioselectivity <1997TL4705>. Related benzylic oxonium ylide [1,2]- and [2,3]-sigmatropic rearrangements feature prominently during studies towards the synthesis of polycyclic ethers <2001JA5144, 2002T2027>.



Scheme 265

7.08.24.2.1(ii) β to the heteroatom

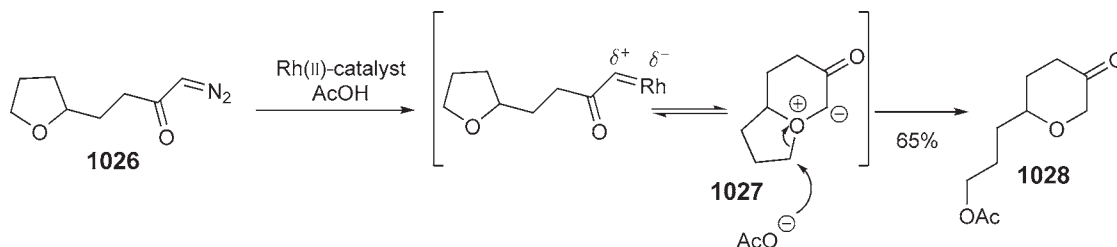
An intramolecular acyl radical cyclization of acyl selenide **1024** uses a (*Z*)-vinylogous sulfonate to control rotamer population, affording *syn*-2,6-disubstituted tetrahydropyran-4-one **1025**, a key intermediate during synthesis of the tetrahydropyran unit of mucocin (**Equation 399**) <1997TL5249>. This methodology is also applicable to the synthesis of polycyclic ethers <1996JOC4880>.



7.08.24.2.2 From other heterocycles

7.08.24.2.2(i) From tetrahydrofurans

A rhodium(II)-catalyzed ring expansion of the diazoacetyl-substituted tetrahydrofuran **1026** affords the acetylated tetrahydropyran-3-one **1028** in good yield. The reaction proceeds via ring opening of the bicyclic ethereal oxonium ylide intermediate **1027** (**Scheme 266**) <1996CC1077>.

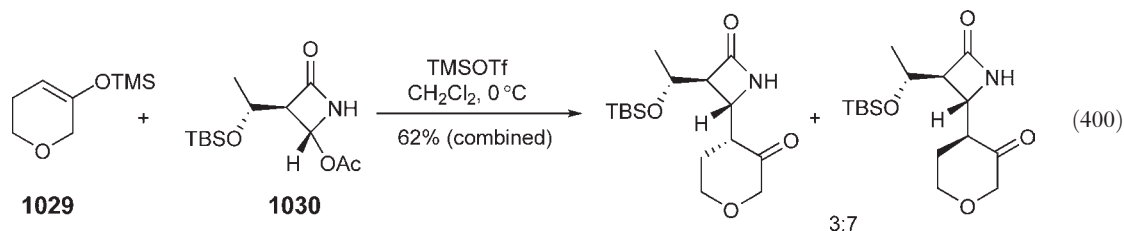


Scheme 266

7.08.24.2.3 From a preformed heterocyclic ring

7.08.24.2.3(i) From dihydropyrans

Silyl enol ether **1029** and β -lactam **1030** react in the presence of a Lewis acid to afford an inseparable diastereomeric mixture of tetrahydropyran-3-ones, key intermediates during the synthesis of tricyclic β -lactam antibiotics (trinems) that possess enhanced antibacterial activity (Equation 400) <1996BML2589>.



7.08.24.2.3(ii) From dihydropyran-3-ones

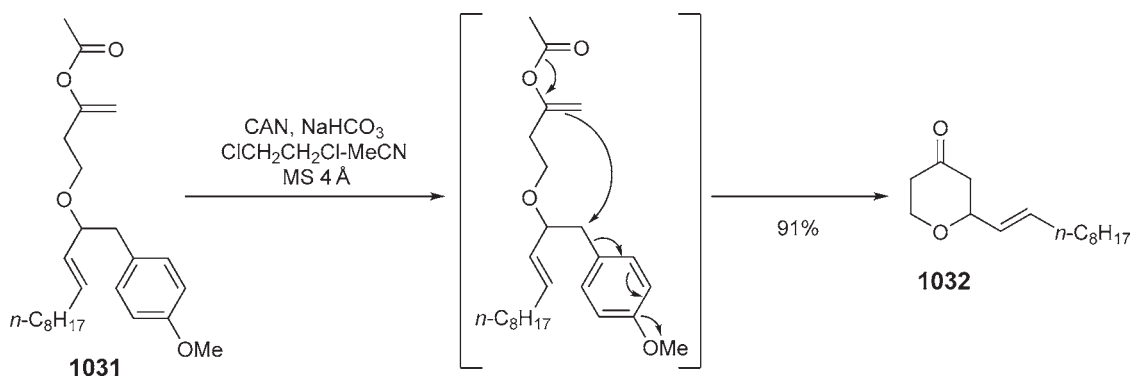
Sugar derived dihydropyran-3-ones are active dienophiles that undergo highly *endo*- and facial-diastereoselective [4+2] cycloadditions with butadienes and cyclic dienes affording tetrahydropyran-3-ones <2001JOC8859, 2002JOC7839, 2003TL4023, 2004TA3023>.

7.08.24.3 Tetrahydropyran-4-ones

7.08.24.3.1 Formation of one bond

7.08.24.3.1(i) β to the heteroatom

An intramolecular cerium(IV)-mediated electron transfer initiated cyclization (ETIC) provides an elegant route to tetrahydropyran-4-one **1032**. The reaction proceeds on the basis that the arene radical cation produced upon exposure of **1031** to a cerium oxidant weakens the carbon–carbon bond therefore permitting cleavage and hence cyclization (Scheme 267) <2003JA2406>. This methodology can be applied to stereoselective synthesis of 2,6-disubstituted tetrahydropyran-4-ones <2004JA12596> and can be conducted on polymer bound substrates <2005JOC3814>.



Scheme 267

7.08.24.3.2 Formation of more than one bond

A highly enantio- and diastereoselective hDA reaction between substituted hexadiene **1033** and aldehydes is catalyzed by Jacobsen's chiral tridentate chromium(III)-catalyst **1034** furnishing tetrahydropyran-4-ones **1035** (Equation 401, Table 48) <1999AGE2398>. This methodology is incorporated into a stereocontrolled total synthesis of (+)-leucascandrolide A <2003AGE343> and the synthesis of the C(20)–C(32) segment of the phorbaxazoles

<2005JOC3757>. Dirhodium(II) carboxamidate complexes <2004AGE2665> and dendritic titanium(IV) complexes <2003CEJ5989> are also excellent catalysts for the hDA reaction between Danishefsky's diene and aldehydes leading to enantioenriched tetrahydropyran-4-ones.

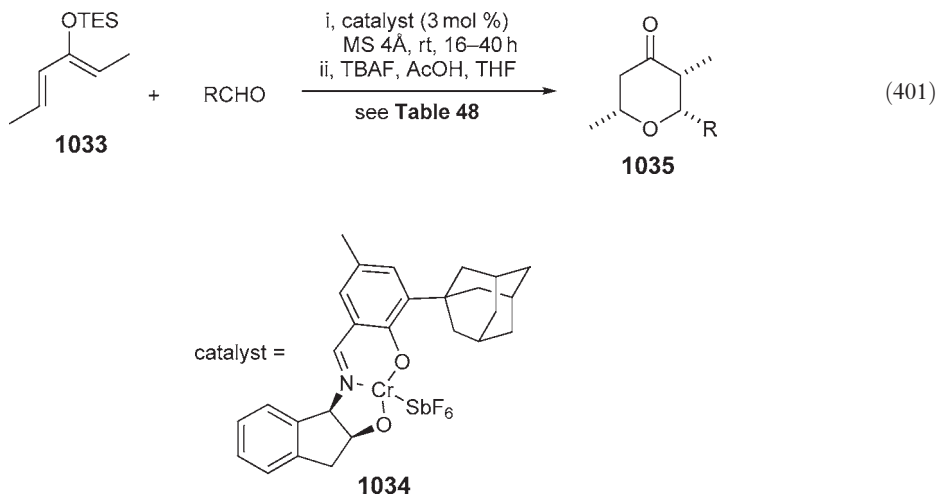
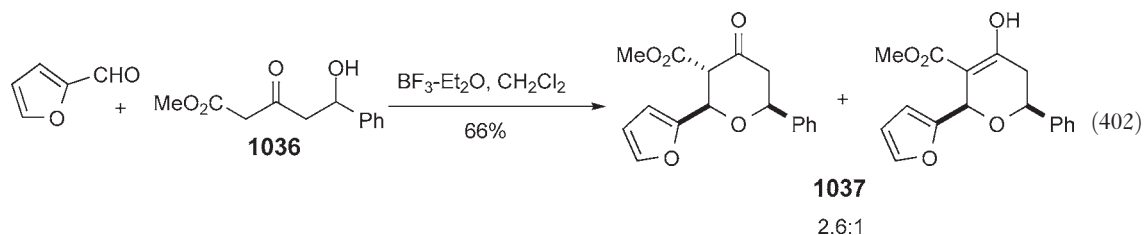


Table 48 hDA formation of tetrahydropyran-4-ones **1035** (Equation 401)

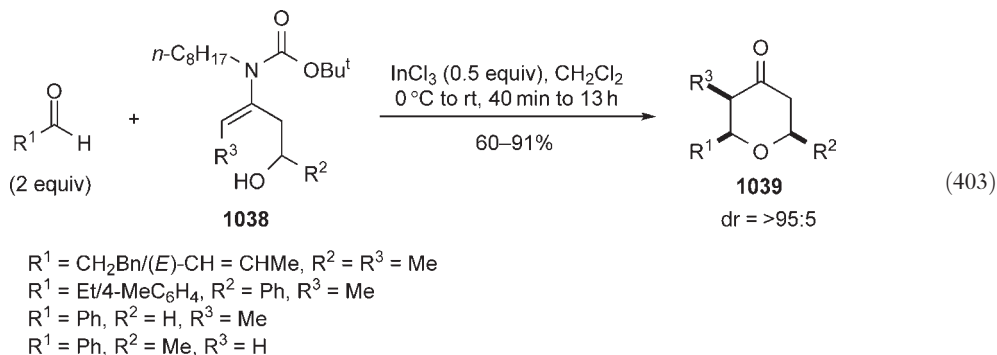
<i>R</i>	Yield (%) 1035	<i>ee</i> (%) 1035
CH ₂ OTBS	93	98
Ph	n.d	81
CH ₂ OBn	89	94
<i>n</i> -C ₅ H ₁₁	85	98
(CH ₂) ₄ CH=CH ₂	78	98
CH ₂ Bn	78	98
CH ₂ CH ₂ NHBOC	28	96
2-furyl	77	95

A reaction between α -diazo ketones and α,β -unsaturated aldehydes under rhodium(II)-catalysis provides a route to epoxy-bridged tetrahydropyran-4-ones <2002JOC8019>. This methodology allows entry to functionalized spiro-dioxo-bridged polycyclic frameworks <2002TL3931, 2003T8117>.

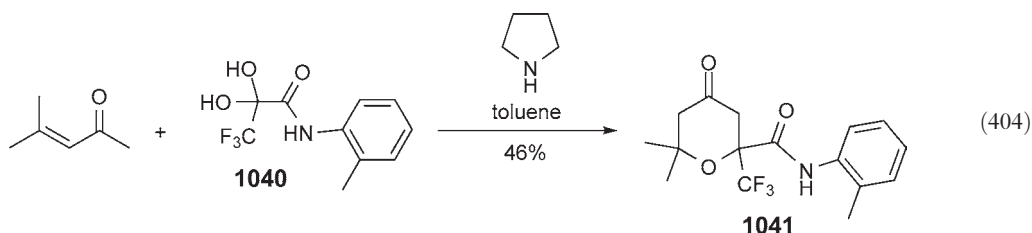
In a process that follows Maitland–Japp-type methodology, the β -ketoester **1036** undergoes a Lewis-acid-catalyzed diastereoselective tandem Knoevenagel–Michael reaction with furfuraldehyde to afford the tetrahydropyran-4-one **1037** as a mixture of keto/enol tautomers in good yield (Equation 402) <2002OL4257>. This methodology is used as a key step during the synthesis of ($\pm$)-centrolobine <2004TL9061, 2005T5433> and the preparation of enantiopure *syn*-2,6-disubstituted tetrahydropyran-4-ones <2005CC1061, 2005OBC3551>. This process can also be catalyzed by iodotrimethylsilane <2003TL7455>.



A diastereoselective synthesis of all *syn*-2,3,6-trisubstituted tetrahydropyran-4-ones **1039** via an intramolecular Prins cyclization of enecarbamates **1038** with aldehydes is used during a formal synthesis of (+)-ratjadone (Equation 403) <2004JA12216>. Similarly, tetrahydropyran-4-ones bearing quaternary centres α -to the carbonyl are accessible via a Lewis acid-mediated Prins cyclization of silyl enol ether substrates <2004JA15662>.



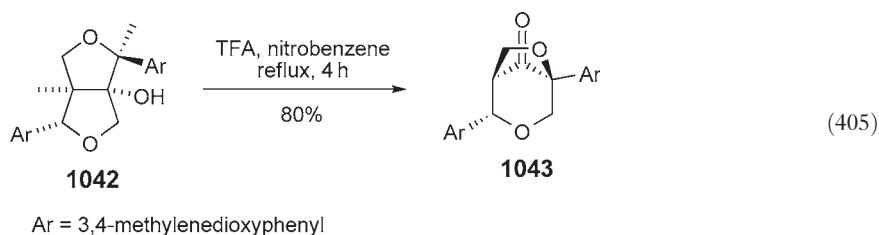
Trifluoropyruvamide **1040** can react with 4-methylpent-3-en-2-one to afford the tetrahydropyran-4-one **1041** in moderate yield (Equation 404) <2004TL5611>.



7.08.24.3.3 From other heterocycles

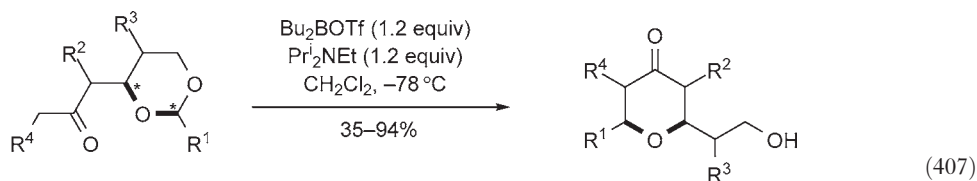
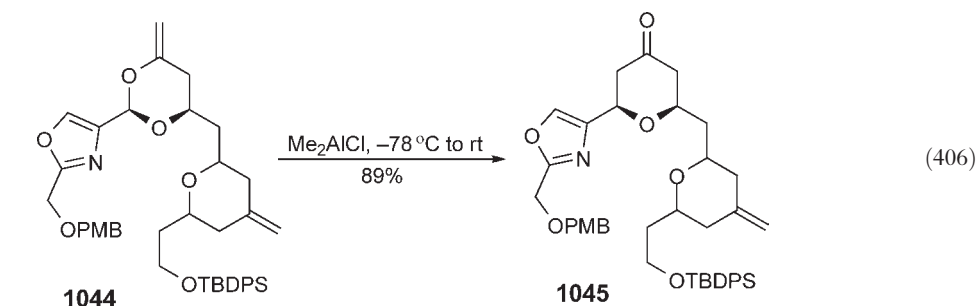
7.08.24.3.3(i) From tetrahydrofurans

A TFA-mediated pinacol-type rearrangement of arboreal **1042** leads to gmelanone **1043**, confirming the biogenesis and relative absolute configuration of the latter natural product (Equation 405) <2005T8956>.



7.08.24.3.3(ii) From 1,3-dioxanes

Lewis acid-treatment of the vinyl acetal **1044** brings about a Petasis–Ferrier rearrangement providing *syn*-2,6-disubstituted tetrahydropyran-4-one **1045** in excellent yield and enantioselectivity (Equation 406) <1999OL909>. This method for the synthesis of tetrahydropyran-4-ones is a key step during the syntheses of the C(20)–C(28) subunit of the phorbaxozoles <1999OL913>, the C(1)–C(15) and C(16)–C(29) subunits of (+)-sorangicin <2005OL3099> as well as the total syntheses of (+)-phorbaxazole A <2001JA4834, 2001JA10942>, (+)-zampanolide <2001JA12426> and (–)-kendomycin <2005JA6948>. A dibutylboron triflate/diisopropylethylamine mediated aldol-type cyclization provides a route for the stereoselective synthesis of tetrahydropyran-4-ones from 1,3-dioxanes in a single step (Equation 407) <2004OL123>.



*both *syn*-diastereomers used

R¹ = Ph/PMP/CH=CHPh/CH₂Bn/CH₂CH₂OBn/Et/CH₂CH=CH₂/(CH₂)₅–

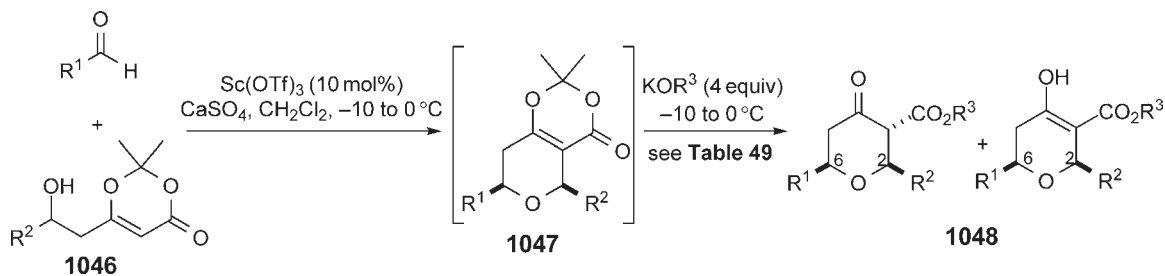
R² = H/(*S*)-Me/(*R*)-Me/(Me)₂

R³ = H/(*S*)-Me/(*R*)-Me

R⁴ = H/Me

7.08.24.3.3(iii) From dioxinones

An intramolecular [2+2] photocycloaddition of allyl ethers with dioxinones followed by a base-induced fragmentation leads to substituted tetrahydropyran-4-ones [<1997TL5579>](#). A one-pot scandium triflate catalyzed diastereoselective cyclization between aldehydes and β-hydroxy dioxinones **1046** followed by alkoxide addition to the resulting bicycles **1047** leads to 3-carboxy-substituted tetrahydropyran-4-ones **1048** with high levels of diastereoselectivity as a mixture of keto/enol tautomers ([Scheme 268](#), [Table 49](#)) [<2005OL1113>](#).



Scheme 268

Table 49 Addition of nucleophiles to intermediates **1047** producing a tautomeric mixture of tetrahydropyran-4-ones **1048** ([Scheme 268](#))

R ¹	R ²	nucleophile (KOR ³)	Yield 1048 (%)	C2:C6 <i>syn:anti</i>	<i>keto:enol</i>
CH ₂ Bn	CH ₂ Bn	KOEt	78	95:5	4:1
CH ₂ Bn	<i>c</i> -C ₆ H ₁₁	KOEt	72	95:5	4:1
CH ₂ Bn	Ph	KOEt	60	95:5	6:1
Ph	CH ₂ Bn	KOEt	67	93:7	2:1
CH ₂ Bn	CH ₂ Bn	KOBn	82	94:6	4:1
CH ₂ Bn	CH ₂ Bn	KO(CH ₂) ₂ TMS	72	95:5	3:1

7.08.24.3.3(iv) From oxabicyclo[3.2.1]octenes

A ruthenium-catalyzed ring opening cross-metathesis of 8-oxabicyclo[3.2.1]oct-6-en-3-one **1049** with alkenes provides an efficient method for the preparation of substituted tetrahydropyran-4-ones **1050** (Equation 408, Table 50) <1999T8169, 2001OL4275>. Similarly, ozone can be used to cleave the same ring system during the synthesis of chiral tetrahydropyran-4-ones <2006T257>.

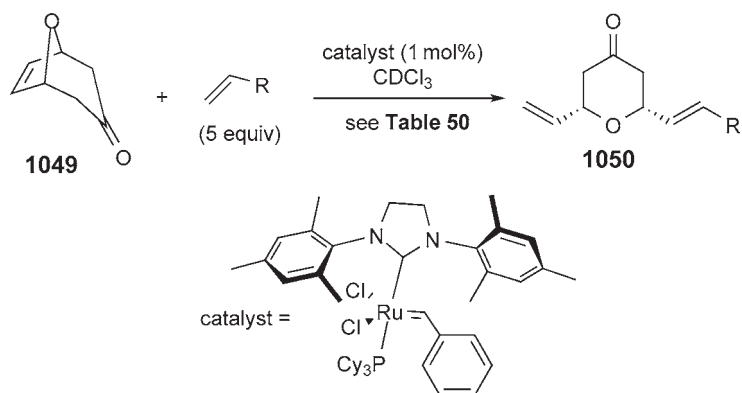


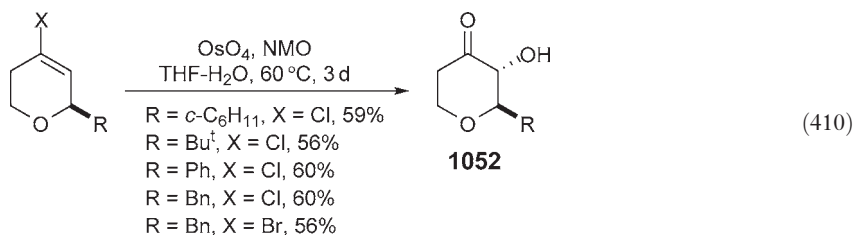
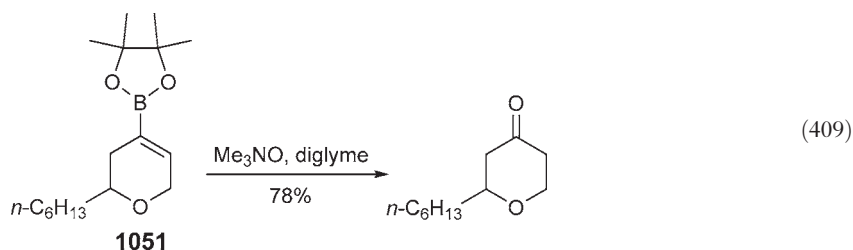
Table 50 Formation of tetrahydropyran-4-ones **1050** (Equation 408)

<i>R</i>	Yield (%) 1050	<i>E/Z</i> 1050
Ph	83	>95:5
2-BrC ₆ H ₄	65	>95:5
(CH ₂) ₃ Me	89	>95:5
CH ₂ Br	71	>95:5
CH ₂ CH ₂ Br	72	>95:5
CO ₂ Me	33	>95:5
CN	10	>95:5

7.08.24.3.4 From a preformed heterocyclic ring

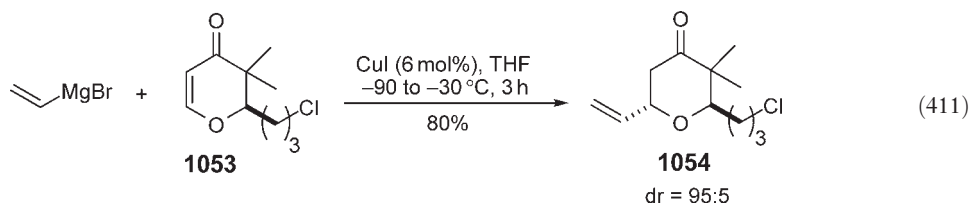
7.08.24.3.4(i) From dihydropyrans

Oxidation of the dihydropyran **1051** bearing a vinyl borane moiety affords 6-hexyltetrahydropyran-4-one in good yield (Equation 409) <2001JA4601>. *cis*-Hydroxylation of 2-alkyl-4-halo-dihydropyrans affords *anti*-2-alkyl-3-hydroxytetrahydropyran-4-ones **1052** as a single stereoisomer (Equation 410) <2003OL1979>.



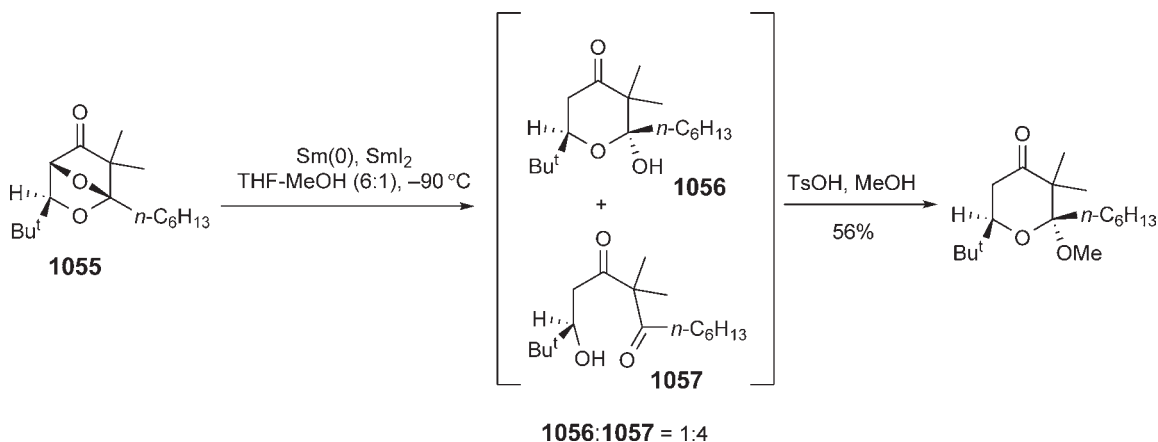
7.08.24.3.4(ii) From dihydropyranones

A copper(I)-catalyzed 1,4-addition of vinylmagnesium bromide to dihydropyran-4-one **1053** proceeds in good yield and with high diastereoselectivity to afford the tetrahydropyran-4-one **1054**, a key intermediate during synthetic studies towards the pederin family of antitumour agents (Equation 411) <2000J(P1)2357>.



7.08.24.3.4(iii) From dioxanobornanes

Exposure of the dioxanobornane **1055** to samarium diiodide in the presence of samarium metal at low temperature leads to the formation of a mixture of the tetrahydropyran-4-one **1056** and the ring opened product **1057**. Treatment of this mixture with tosic acid leads to a single tetrahydropyran-4-one product (Scheme 269) <2004OL3735>.



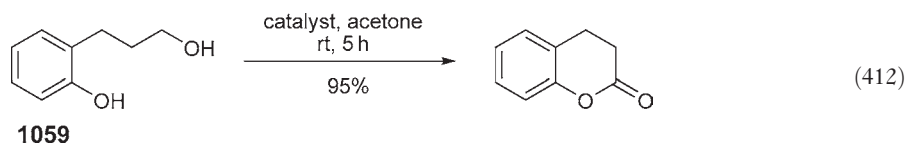
Scheme 269

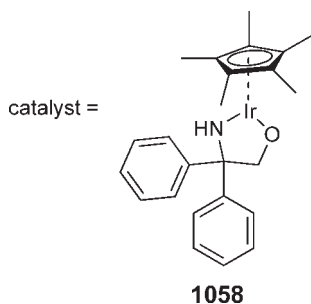
7.08.25 Dihydrocoumarins (Chroman-2-ones; 3,4-Dihydrobenzopyran-2-ones)

7.08.25.1 Formation of One Bond

7.08.25.1.1 Adjacent to the heteroatom

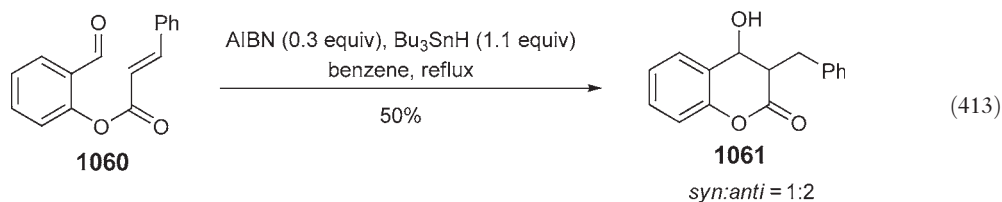
An amino alcohol-based iridium bifunctional complex **1058** is an efficient catalyst for the formation of dihydrocoumarin from the 1,5-diol **1059** (Equation 412) <2002OL2361>.





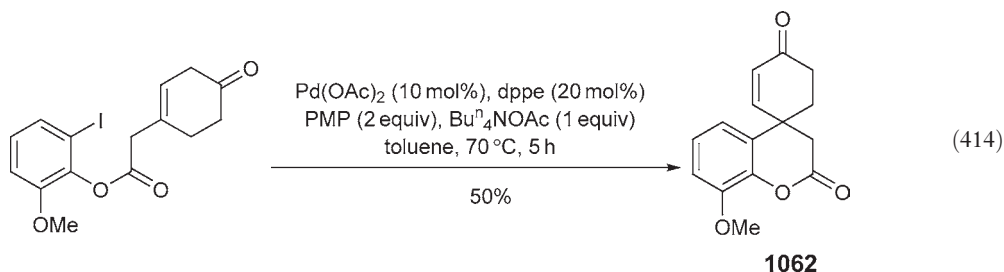
7.08.25.1.2 γ to the heteroatom

A tributyltin hydride-mediated intramolecular cyclization of the α,β -unsaturated ester **1060** proceeds to form dihydrocoumarin **1061** as an inseparable mixture of diastereomers (Equation 413) <2002J(P1)1461>.

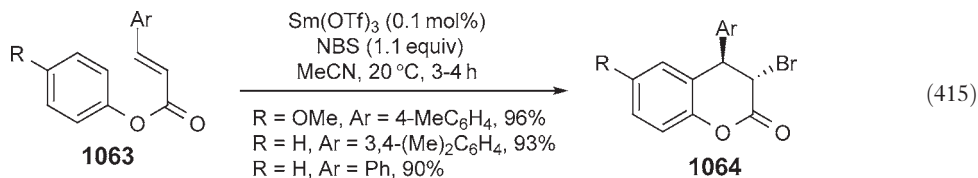


7.08.25.1.3 δ to the heteroatom

An intramolecular Heck reaction is used to construct the dihydrocoumarin **1062** during a formal synthesis of ($\pm$)-lycoramine (Equation 414) <1999TL9243>. Similar Heck methodology is used during a total synthesis of ($\pm$)-galanthamine <2001AGE4745>, the syntheses of herbertenediol and mastigophorenes A and B <2000JA9127>, and the construction of the biaryl moiety of stegane <2004TL2327>.



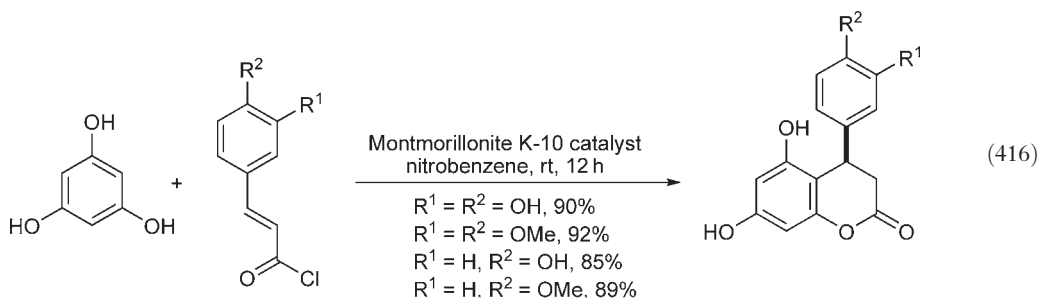
A Sm(OTf)₃-catalyzed intramolecular haloarylation of the alkenes **1063** in the presence of *N*-bromosuccinimide provides a route to *anti*-4-aryl-3-bromodihydrocoumarins **1064** (Equation 415) <2005TL8599>.



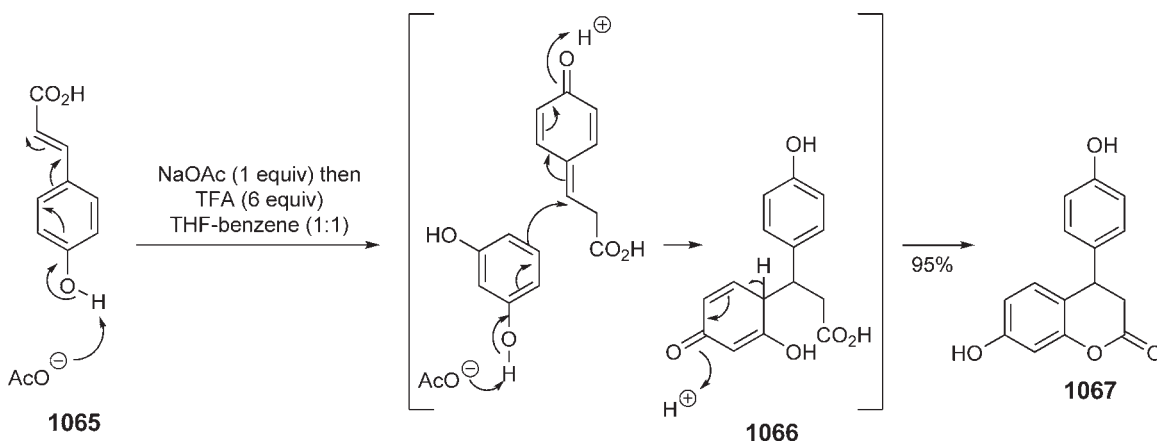
7.08.25.2 Formation of More than One Bond

Dihydrocoumarins can be accessed via a Bi(OTf)₃-catalyzed Baeyer–Villiger oxidation of dihydroinden-1-one with MCPBA <2003SC3035>, or with silica gel-supported 4-aminoperoxybenzoic acid <2004M1409>.

Phenols react with cinnamyl compounds via an intermolecular condensation/cyclization providing a reliable method for the construction of dihydrocoumarins. Montmorillonite K-10 clay can catalyze the condensation/cyclization reaction of phloroglucinol and cinnamoyl chlorides to provide a high-yielding route to dihydrocoumarins (Equation 416) <2001S2247>.

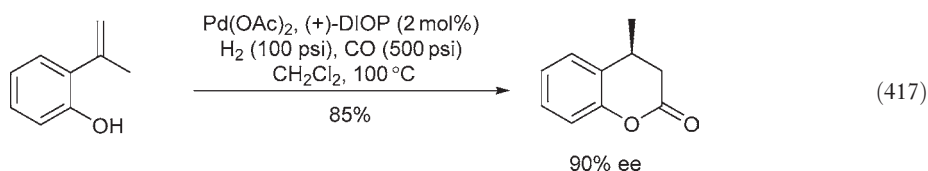


An efficient one-pot regioselective synthesis of phenylpropanoid-substituted flavan-3-ols is achieved upon reaction of catechin with cinammic acids <2002OL1707>. The condensation of substituted cinnamic acids with phenols leads to dihydrocoumarins for biocatalytic studies <2003BMC529>. The reaction pathway is emphasized by interaction of the carboxylic acid **1065** with base followed by Michael addition of resorcinol and a dienone–phenol rearrangement/cyclization of the intermediate **1066** to furnish the dihydrocoumarin **1067** (Scheme 270) <2004ARK138>. This methodology continues to receive widespread attention <1997JBS229, 1997S931, 2000S123, 2005T9291, 2005JOC2881, 2005EJM1042>.

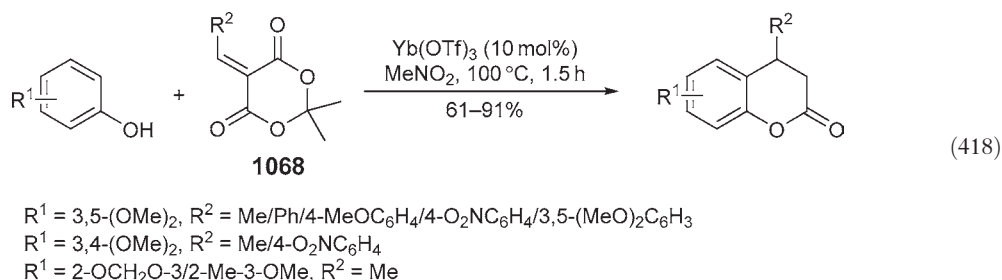


Scheme 270

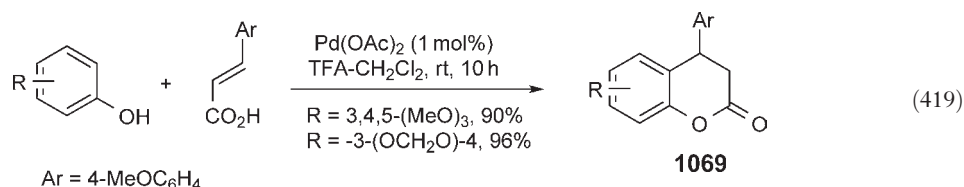
A catalytic asymmetric cyclocarbonylation of 2-(prop-1-en-2-yl)phenol provides a route to (*S*)-4-methyldihydrocoumarin in excellent yield and with high enantioselectivity (Equation 417) <2004JOC5011>.



A $\text{Yb}(\text{OTf})_3$ -catalyzed reaction between 5-alkylidene Meldrum's acid derivatives **1068** and phenols provides a route to 4-substituted dihydrocoumarins (Equation 418) <2006JOC409>.



A palladium(II)-catalyzed intramolecular hydroarylation of α,β -unsaturated carboxylic acids with electron rich phenols provides straightforward entry to 4-aryldihydrocoumarins **1069** (Equation 419) <2000JOC7516>.

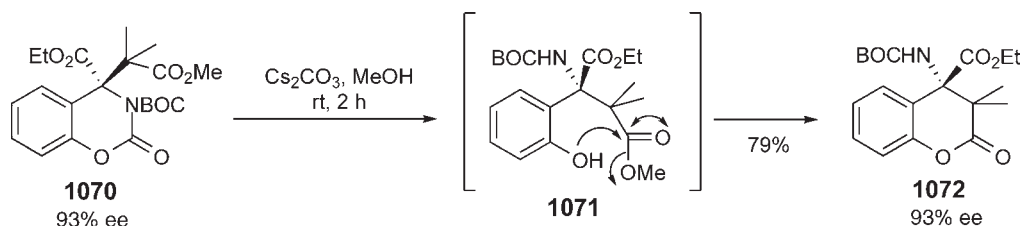


A modified Pechmann cyclization reaction of resorcinol and acrylic acid is catalyzed by silica nanocomposites to afford 7-hydroxydihydrocoumarin in good yield <2003JMO315>. A study concerning the biosynthesis of 7-hydroxydihydrocoumarin from a catechol precursor is available <2005CC666>.

7.08.25.3 From Other Heterocycles

7.08.25.3.1 From dihydrobenzo[1,3]oxazin-2-ones

Basic hydrolysis of phenoxyl carbamate **1070** proceeds without loss of optical purity via spontaneous cyclization of the liberated phenol **1071** to afford the dihydrocoumarin **1072** (Scheme 271) <2003CEJ6145>.



Scheme 271

7.08.25.4 From a Preformed Heterocyclic Ring

7.08.25.4.1 From coumarins

Catalytic asymmetric hydrogenation of 4-aryl coumarins provides a key step in the synthesis of a class of endothelin receptor antagonists <1999TL3293>. Raney Nickel can be used to achieve the chemoselective hydrogenation of coumarins to dihydrocoumarins in excellent yield <1999SL1663>.

3-Methylenedihydrocoumarins are accessible via Michael addition of nucleophiles to 3-diethoxyphosphorylcoumarins followed by a Horner–Wadsworth–Emmons reaction of the resulting adducts with formaldehyde <2004T1049>. The conjugate addition of (*Z*)-2-ethoxyvinyl anion to coumarin is best effected via the use of Noyori-type organocopper reagents <2000TL8873>. The Michael addition of *N,N*-dialkylhydrazones to coumarins can be achieved in good yield in the presence of MgI_2 <2005T4115>. The synthesis of spirolactones is achieved by an intramolecular free radical Michael addition of enol esters onto the coumarin C–C double bond <2000TL2523>. The Lewis acid-promoted

conjugate addition of functionalized organolithium compounds to coumarins leads mainly to 1,4-addition products <2001T5799>. A [4+2] cycloaddition reaction of 3-nitrocoumarins with a range of simple dienes can be conducted under aqueous conditions to afford dihydrocoumarins <2003JOC9263>. The rhodium catalyzed 1,4-addition of arylboronic acids to coumarin proceeds with excellent enantioselectivity, and this methodology has been used in the asymmetric synthesis of (*R*)-tolterodine <2005OL2285>.

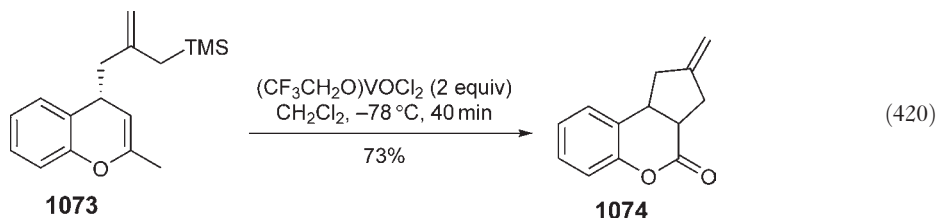
Coumarin can be cyclopropanated via an electroreductive coupling with *gem*-dichloro compounds <2002S533>. When the coumarins possess an electron-withdrawing group in the 3-position, successful cyclopropanation can be achieved with dimethylsulfoxonium methylide giving dihydrocoumarins, which easily rearrange to the cyclopenta[*b*]benzofuran-3-ol ring system <2002T1497>. A significant rate acceleration of the RuO₄-catalyzed dihydroxylation of coumarin can be achieved by addition of Brønsted acids <2004OBC1116> and a RuCl₃/CeCl₃/NaIO₄ oxidation system can also be used to conduct this transformation <2005JOC2402>.

7.08.25.4.2 From chromans

6-Methyldihydroisocoumarin can be obtained via IBX oxidation of the corresponding chroman-2-ol, albeit in poor yield <2004TL309>.

7.08.25.4.3 From 4H-chromenes

Dichloro(2,2,2-trifluoroethoxy)oxovanadium(v) is an effective reagent for promoting a one-electron oxidative cyclization of the silyl enol ether **1073**, providing the cyclopentane fused dihydrocoumarin **1074** (Equation 420) <1998JA2658>.

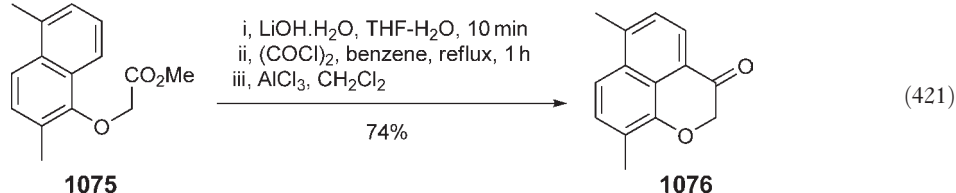


7.08.26 Chroman-3-ones (2,4-Dihydrobenzopyran-3-ones)

7.08.26.1 Formation of One Bond

7.08.26.1.1 γ to the heteroatom

A facile *peri*-ring closure of dimethylnaphthol ether **1075** proceeds via ester hydrolysis and conversion to the corresponding acid halide followed by an intramolecular Friedel–Crafts acylation to afford the tricyclic chroman-3-one **1076**, an intermediate during a formal synthesis of mansonone F (Equation 421) <2000CC1203>.



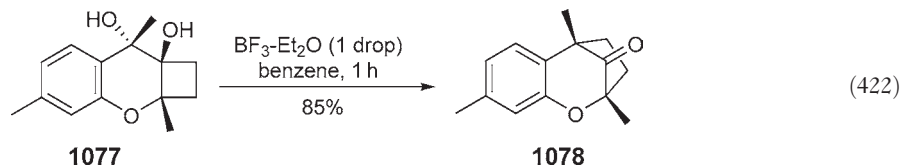
7.08.26.2 From a Preformed Heterocyclic Ring

7.08.26.2.1 From chromans

Oxidation of a chroman-3-ol with Dess–Martin periodinane provides a chroman-3-one, an intermediate in the synthesis of a 3,4,5-trimethoxybenzoyl ester analogue of epigallocatechin-3-gallate (EGCG) <2001OL843> and related compounds <2004BMC3521, 2005BMC2177, 2005BML2633>. DMP can also be used to construct

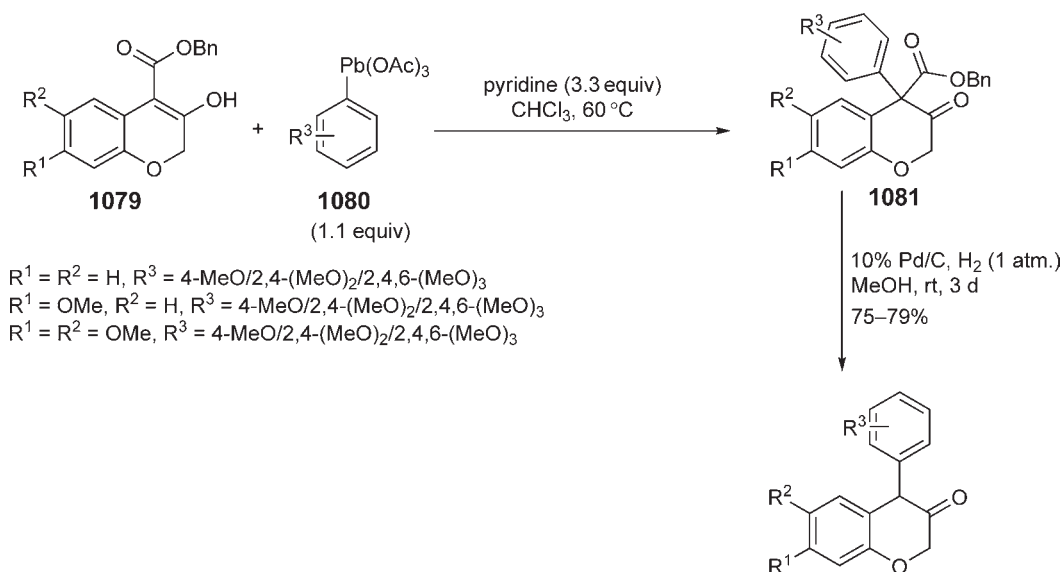
chroman-3-ones from the corresponding chroman-3-ols during enantioselective syntheses of afzelechin, *epi*-afzelechin <2004T8207> and synthetic building blocks for (+)-catechin <1999JA12073>.

An acid-mediated cyclobutyl carbinol rearrangement of the chroman **1077** favors primary external bond migration providing the bridged chroman-3-one **1078**, an intermediate during a novel synthetic approach to the benzoxabicyclo[3.2.1]octane ring system (Equation 422) <1996JOC4391>. This rearrangement is used during the synthesis of an A-ring aromatic trichothecene analogue <1998JOC3855> and heliannuol D <2004TL983>.



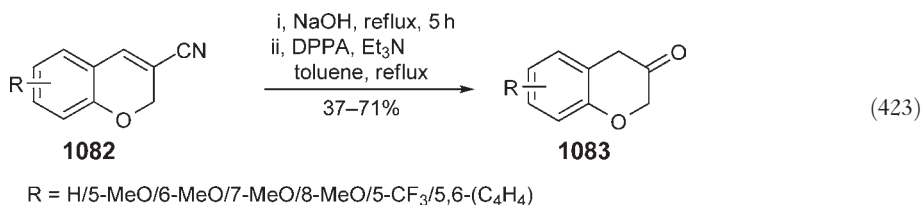
7.08.26.2.2 From 2H-chromenes

2H-Chromenes **1079** react with aryllead(IV) triacetates **1080** to afford chroman-3-ones **1081** which upon hydrogenation furnish 4-arylchroman-3-ones, key intermediates for the synthesis of neoflavenes (Scheme 272) <2001T413>.



Scheme 272

Basic hydrolysis of 3-cyano-2H-chromenes **1082** followed by a diphenylphosphoryl azide (DPPA) mediated Curtius rearrangement affords chroman-3-ones **1083**, important precursors for the synthesis of spirocyclic benzopyrans (Equation 423) <2004S121>. This methodology is also used during the synthesis of 3-aminochroman derivatives for testing as potential serotonin 5-HT₇-receptor agonists and antagonists <2004JME3927>.



7.08.27 Chroman-4-ones (2,3-Dihydrobenzopyran-4-ones)

7.08.27.1 Formation of One Bond

7.08.27.1.1 Adjacent to the heteroatom

An asymmetric synthesis of *anti*-2-aryl-3-hydroxychroman-4-ones (dihydroflavanols) **1085** is achieved by use of a thiophilic Lewis acid to mediate the cyclization of enantiopure dihydrochalcones **1084** in good yield (Equation 424, Table 51) <1996CC2747>. Other dihydroflavanols can also be accessed using this methodology <1997T14141>.

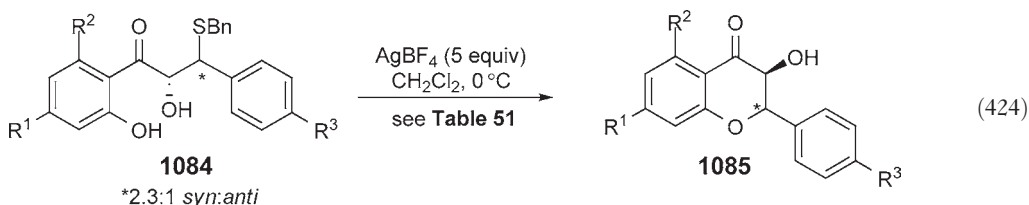
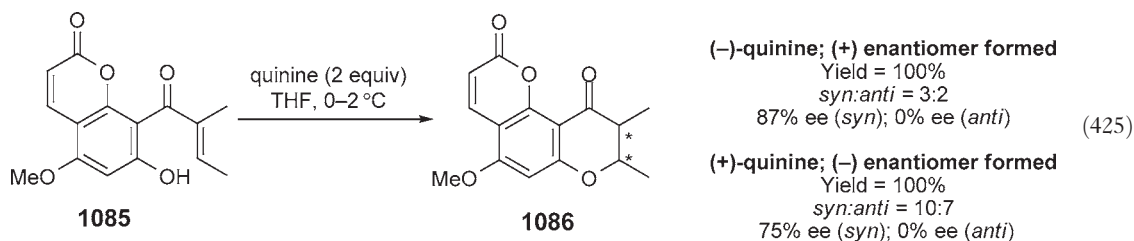


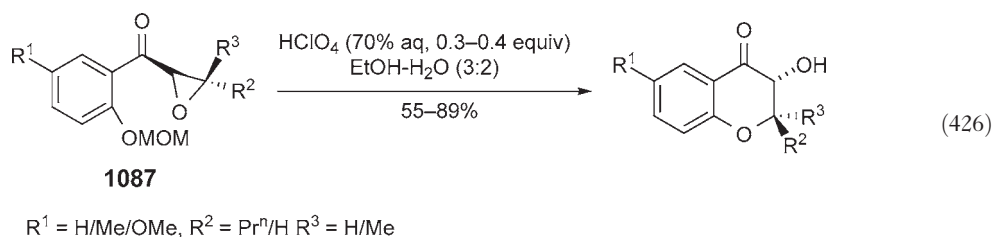
Table 51 Formation of chroman-4-ones **1085** (Equation 424)

R^1	R^2	R^3	Yield 1085 (%)	<i>ee</i> (%)	* <i>anti:syn</i>
H	H	OMe	86	83	93:7
OMe	H	OMe	71	84	79:21
OMe	OMe	OMe	65	69	78:22

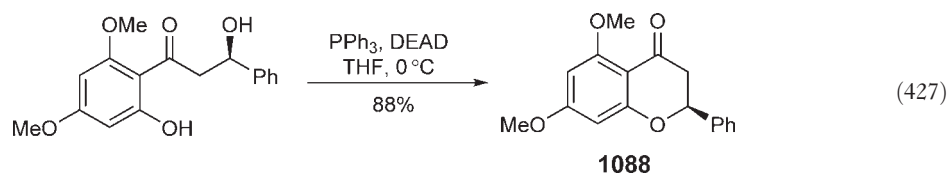
An intramolecular Michael addition (IMA) between a phenol and a suitable α,β -unsaturated acceptor continues to provide a reliable synthetic route to the chroman-4-one ring system, with several reports detailing stereoselective products being isolated upon subjecting this IMA reaction to various additives. Diastereoselective construction of *anti*-2,3-dimethylchroman-4-ones can be achieved via a cesium fluoride-induced IMA <1996JOC6484, 1997T14915>. An IMA is a key step during the synthesis of the aglycone of actinoflavoside <2004SL116> and 6-hydroxy-7-methoxychroman-4-one, a potential antioxidant <2005BML2745>. *Syn*-2,3-dialkyl/diarylchroman-4-ones obtained using this IMA methodology can be equilibrated to the *anti*-product upon treatment with DBU <2000T1811>. An enantioselective synthesis of *syn*-2,3-dimethylchroman-4-one **1086** via the IMA of alkenol **1085** is possible upon the addition of quinine, with the *anti*-products exhibiting no enantioselectivity (Equation 425) <1999TL3777>. A study into the remarkable effect of solvent on the stereochemical outcome of this reaction is available, recommending the use of chlorobenzene to significantly increase enantio- and diastereoselectivities <2000TA4633>. The enantioselective total synthesis of the anti HIV-1 agent (+)-calanolide A incorporates this quinine-catalyzed IMA methodology <2000TL10229, 2004JOC2760>. Use of DMSO- I_2 as a means of *O*-allyl protecting group removal can be followed by an *in situ* IMA and hence a synthesis of flavones <2005TL1573>.



Acidic hydrolysis of benzoylperoxides **1087** provides an asymmetric route to 2-alkylchroman-4-ones (Equation 426) <1999JOC3489>. During treatment of (*E*)-2'-hydroxy-4-methoxychalcone with DMDO in a reaction medium buffered to pH 4.4, a chalcone epoxide is implicated as the 6-*exo-trig* cyclization precursor that leads to an *anti*-2,3-dihydroflavanol <1997T8491>.

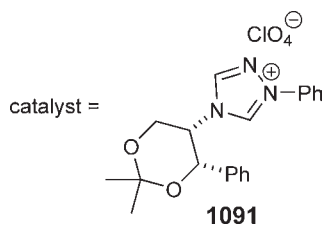
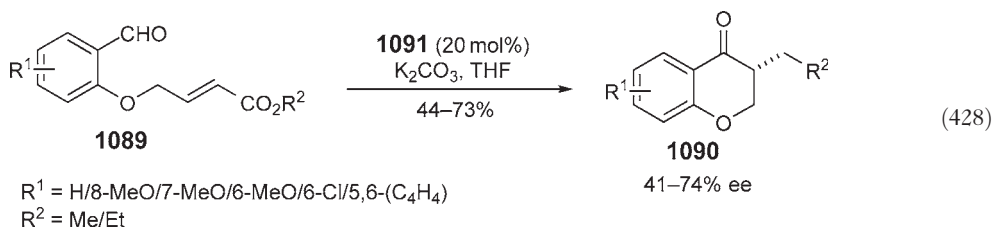


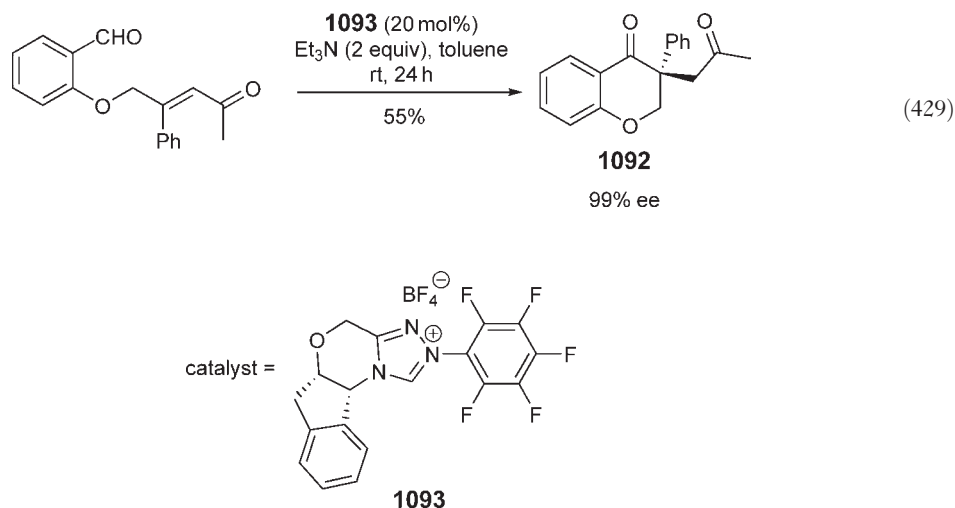
An intramolecular Mitsunobu reaction can be used for the synthesis of the optically active 2-substituted chroman-4-one **1088**, an advanced intermediate during the total synthesis of (–)-pinostrobin (Equation 427) <2001TL3763>. This methodology has been incorporated into the syntheses of several other synthetic and biologically active chroman-4-ones <2005T6860>. A simple protocol involving an intramolecular Mitsunobu reaction followed by dithiane cleavage is used in the synthesis of both enantiomers of flavanone and 2-methylchroman-4-one <2002HCA3473> and the synthesis of 3-hydroxyflavanones <2000TL7925>.



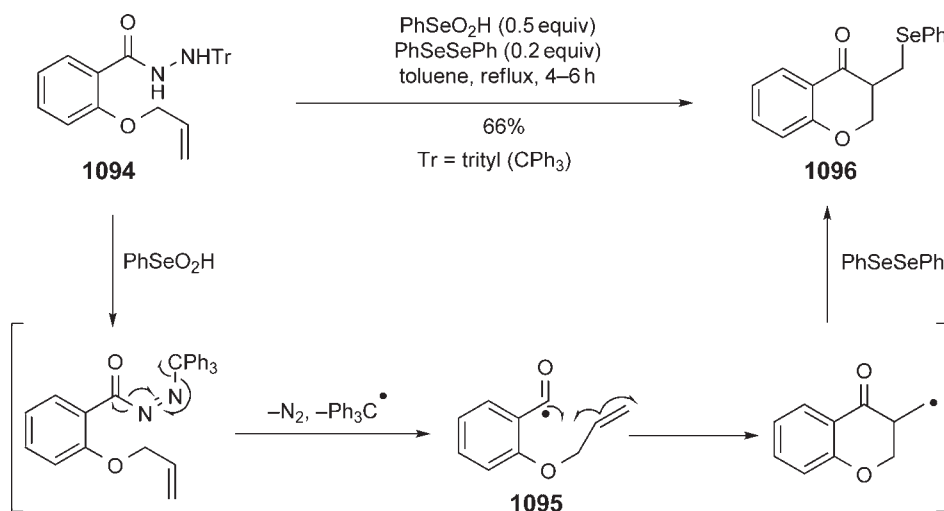
7.08.27.1.2 γ to the heteroatom

The first report of an enantioselective intramolecular Stetter reaction describes a preparation of 3-substituted chroman-4-ones **1090** in moderate enantioselectivity from 4-(2-formylphenoxy)but-2-enoates **1089** in the presence of a chiral triazolium salt **1091** (Equation 428) <1996HCA1899>. Modifications of the catalytic process allow for both (*S*)- or (*R*)-C3-substituted chromans to be obtained with excellent enantioselectivity <2002JA10298, 2005JA6284, 2005CC195>, with the reactivity of substrates bearing electron deficient double bonds varying significantly <2003SL1934>. Chroman-4-one **1092** bearing a C-3 quaternary centre is also accessible via this methodology catalyzed by the triazolium salt **1093** (Equation 429) <2004JA8876>. Thiazolium salts are also effective catalysts for this process <2005SL955>.





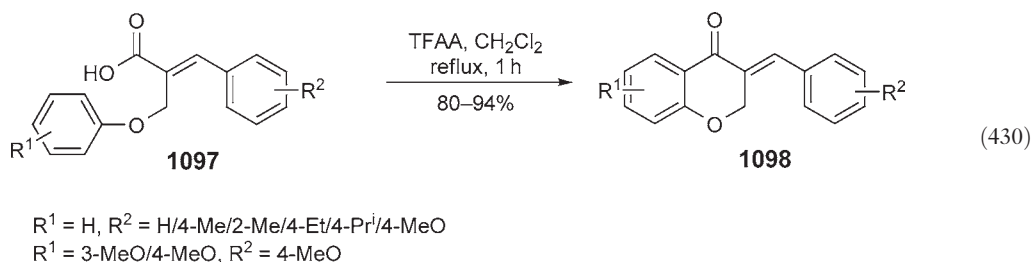
Acyl radical **1095** generated from the hydrazide **1094** can undergo cyclization and reaction with diphenyldiselenide to afford the chroman-4-one **1096** in good yield (Scheme 273) <2003CC204>.



Scheme 273

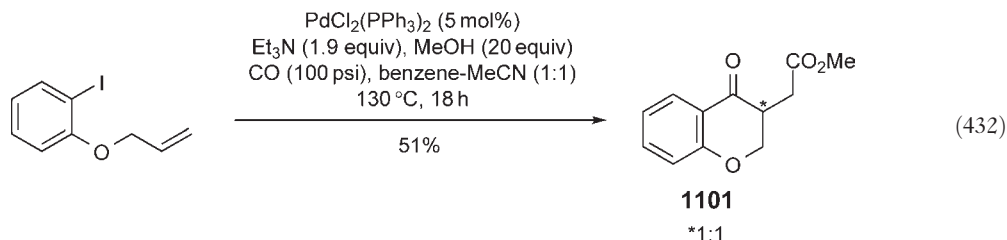
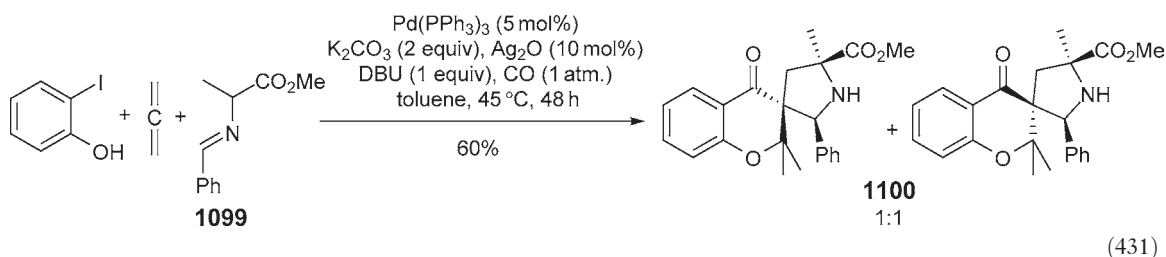
7.08.27.1.3 δ to the heteroatom

Synthesis of (*E*)-3-benzylidenechroman-4-ones **1098** is achieved via a TFAA-mediated cyclization of (2*E*)-2-phenoxy-methyl-3-phenylprop-2-enoic acids **1097**. Synthesis of the methyl ether of bonducillin **1098** ($\text{R}^1 = 3\text{-MeO}$, $\text{R}^2 = 4\text{-MeO}$) and an antifungal agent **1098** ($\text{R}^1 = 4\text{-MeO}$, $\text{R}^2 = 4\text{-MeO}$) incorporates this cyclization (Equation 430) <1998CC1639>. Similar substrates undergo cyclization in the presence of aluminium trichloride <1999T5567, 2001T8743, 2003TA489>. Enantiopure precursors cyclize under the same reaction conditions providing an asymmetric route to 2-substituted chroman-4-ones <2003TA1529, 2006H(68)483>, and homoisoflavanone <2005H(65)761>. Facile resolution of racemic 2-substituted chroman-4-ones obtained using this methodology can be achieved in up to ee 75% in the presence of hydrogen and catalytic amounts of both palladium and (*endo*, *endo*)-aminoborneol via a deprotection/decarboxylation/protonation cascade <2003T9641>.

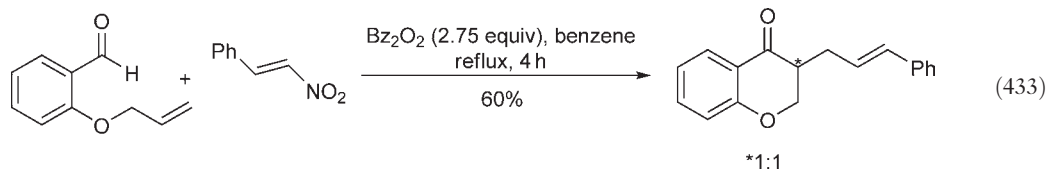


7.08.27.2 Formation of More than One Bond

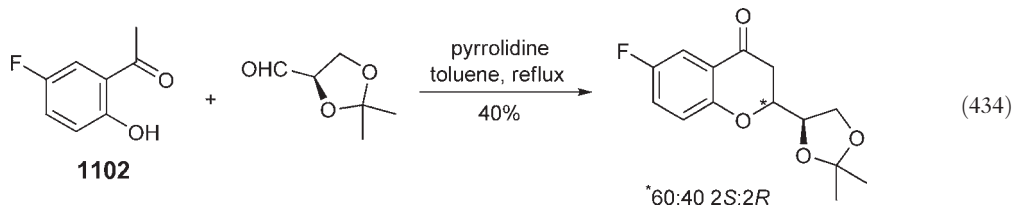
A one-pot chroman-4-one synthesis-azomethine ylide cycloaddition can be performed using 2-iodophenol, carbon monoxide, allene and imine **1099** to furnish a mixture of *exo*- and *endo*-cycloadducts **1100** (Equation 431) <2000TL7129>. Other nucleophiles are viable alternatives for this process <2000TL7125>. Synthesis of chroman-4-one **1101** is possible using a palladium catalyzed carbonylative cyclization of *o*-allyloxyiodobenzene (Equation 432) <2001JOC2175>.



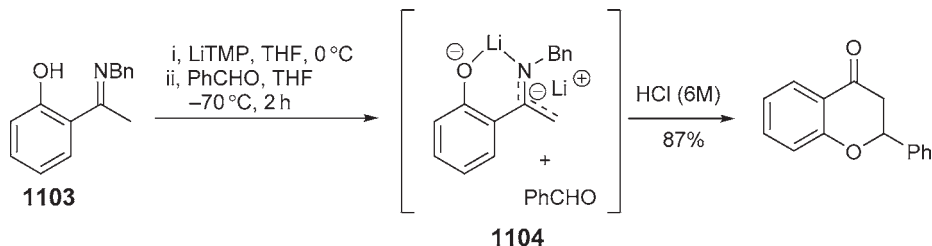
Moderate yields of 3-cinnamylchroman-4-one are achieved upon heating a mixture of 2-allyloxybenzaldehyde and (*E*)- β -nitrostyrene in the presence of benzoyl peroxide. This radical induced addition–elimination reaction proceeds in a regioselective manner (Equation 433) <2004JOC3961>.



A one-pot Kebbe reaction of *p*-fluorophenol **1102** and (*R*)-2,3-isopropylideneglyceraldehyde affords a separable diastereomeric mixture of chroman-4-ones (Equation 434) <2005SL1465>.

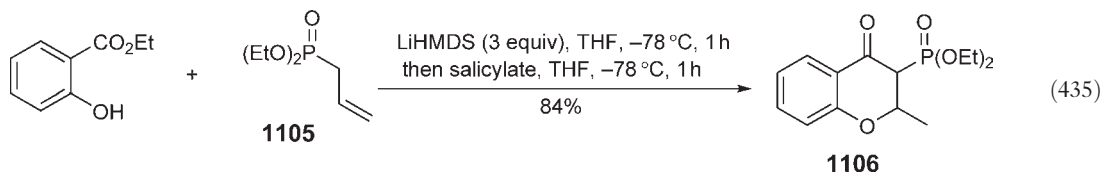


Reaction of the imido phenol **1103** with benzaldehyde proceeds via the lithium dianion **1104** to furnish 2-phenylchroman-4-one in good yield (Scheme 274) <2001T6809>.

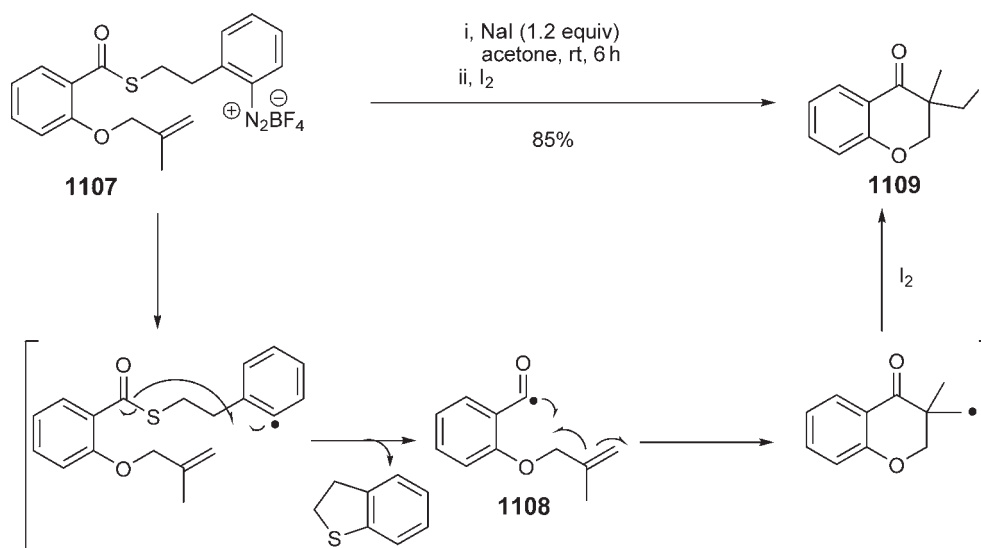


Scheme 274

2-Methyl-3-phosphorylchroman-4-one **1106** is accessible via a tandem allyl–vinyl migration and cyclization reaction of the allylic phosphonate **1105** and ethyl salicylate (Equation 435) <2001SC2613>.



Exposure of the diazonium salt **1107** to iodide ion generates an aryl radical, which undergoes intramolecular homolytic substitution at sulfur to liberate the acyl radical intermediate **1108**. An *exo*-mode cyclization with concomitant incorporation of iodide then occurs to afford the 3-disubstituted-chroman-4-one **1109** in excellent yield (Scheme 275) <1997JOC5982>.



Scheme 275

7.08.27.3 From a Preformed Heterocyclic Ring

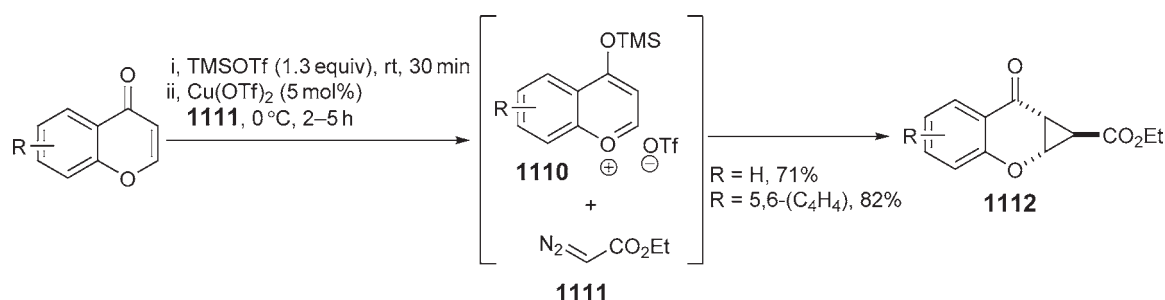
7.08.27.3.1 From chromanes

The conversion of chroman-4-oxime to chroman-4-one occurs upon treatment with Fe-HCl <2005SC913>.

7.08.27.3.2 From chromones

An iodotrimethylsilane-promoted 1,4-addition of copper acetylides to chromones provides 2-alkynylchroman-4-ones in excellent yield <1997JOC182>. Lithium dialkynyl cuprates undergo conjugate addition to activated chromones giving 2-alkynylchroman-4-ones <2003TL1461>. The conjugate addition to 3-arylsulfinylchromones provides a route to homo-chiral 2-substituted chroman-4-ones <2001T6793> and is used as a key step in the synthesis of the biologically active natural product (+)-(*R*)-5-hydroxy-6-hydroxymethyl-7-methoxy-8-methylflavone <1999TA2739>. The first example of a preparative 1,4-perfluoroalkylation shows that 2-perfluoroalkylchromones react with (perfluoroalkyl)trimethylsilanes via 1,4-addition to give 2,2-bis(perfluoroalkyl)chroman-4-ones <2003TL2097, 2003JOC7747>. Regioselective anodic mono-fluorination of a chromone provides the corresponding 2-fluorochroman-4-one <2001JOC7691>. The high regioselectivity observed in the nucleophilic 1,4-trifluoromethylation of chromone using (trifluoromethyl)trimethylsilane can be attributed to blocking of the carbonyl group with a bulky aluminium-centered Lewis acid <2003TL7623>. The Lewis acid catalyzed conjugate addition of vinylmagnesium bromide to chromone provides 2-vinylchroman-4-one, a key intermediate in the synthesis of potent antibiotic agents <2005BMC1531>. Converting 4*H*-chromenes to chroman-4-ones can be achieved using calcium metal in liquid ammonia <1996JOC1493> and with nickel(II)-boride in methanol-water <2004BCJ549>. Irradiation of 2,7-dimethyl chromone in the presence of ethylene provides the corresponding cyclobutachroman-4-one in good yield <1996JOC9164>.

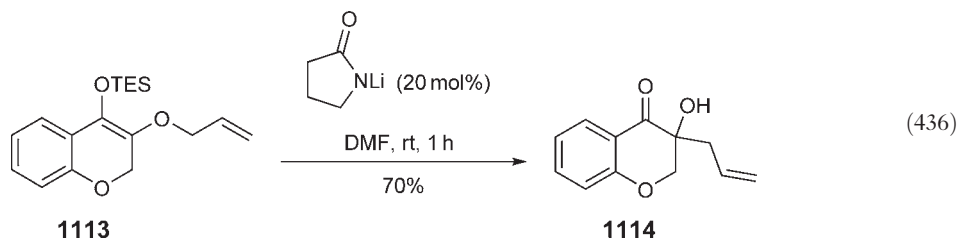
A copper(II)-catalyzed cyclopropanation of the chromone derived benzylum triflates **1110** with the diazoester **1111** affords 2,3-cyclopropyl chroman-4-ones **1112** in good yield (Scheme 276) <2005TL4057>.



Scheme 276

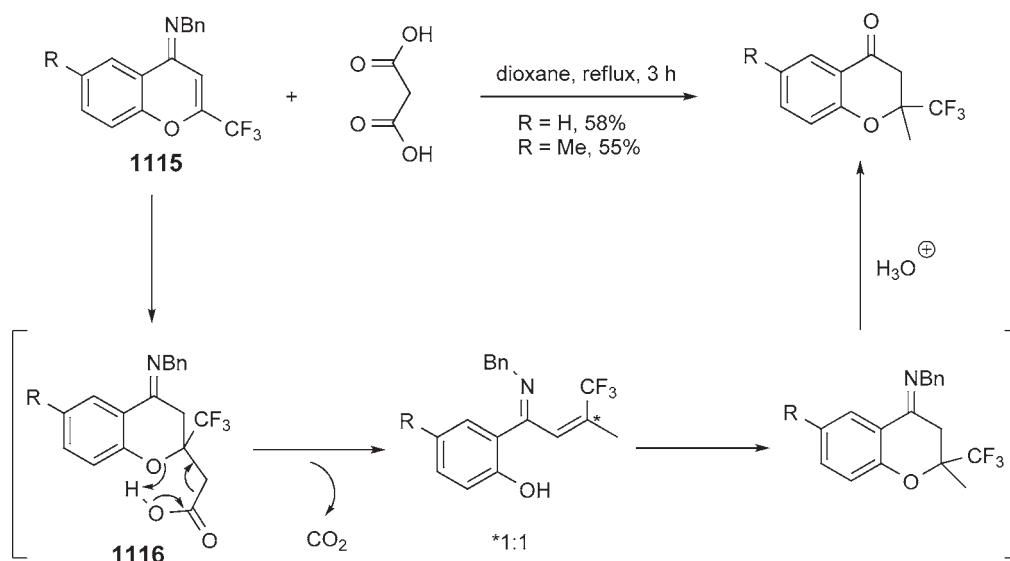
7.08.27.3.3 From 2*H*-chromenes

A Lewis-base-catalyzed [2,3]-Wittig rearrangement of the silyl enolate **1113** exclusively affords the chroman-4-one **1114** (Equation 436) <2005CL588>.



7.08.27.3.4 From 4*H*-chromenes

A simple synthesis of 2-methyl-2-trifluoromethylchroman-4-ones is possible upon heating *N*-benzyl-2-trifluoromethyl-4*H*-chromen-4-imines **1115** in the presence of malonic acid. The reaction proceeds through ring opening and recyclization of the intermediate **1116** (Scheme 277) <2002S2341>.



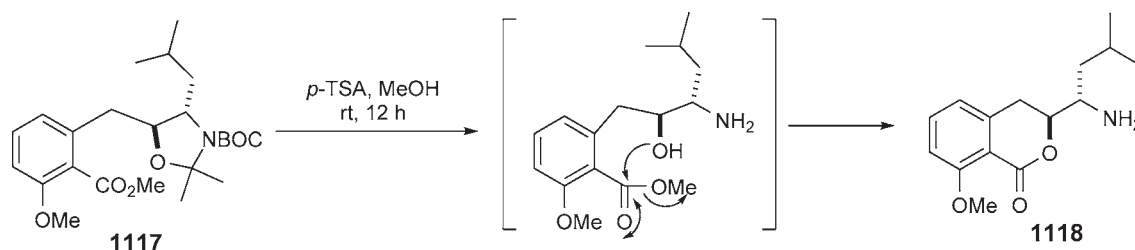
Scheme 277

7.08.28 Dihydroisocoumarins (Isochroman-1-ones)

7.08.28.1 Formation of One Bond

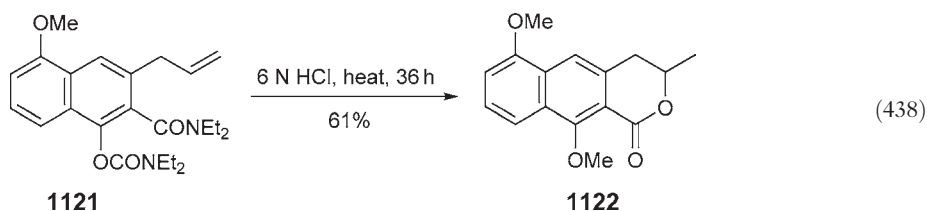
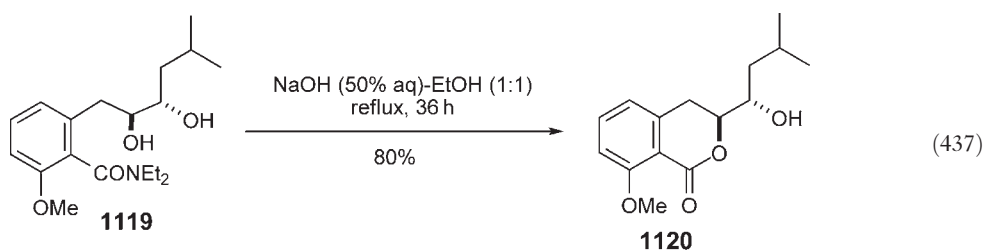
7.08.28.1.1 Adjacent to the heteroatom

Protecting group removal from trisubstituted benzene **1117** followed by *in situ* cyclization of the resulting alcohol occurs during the stereoselective synthesis of the dihydroisocoumarin moiety **1118** of AI-77-B (Scheme 278) <1998TL8803>. Cyclizations of this type can be seen during three asymmetric total syntheses of AI-77-B <1999OL499, 2001OL2677, 2003EJO821>, the synthesis of both enantiomers of mullein <1997TL2153>, both enantiomers of hiburipyranone <1998T8975>, the synthesis of metabolites from *Ononis natrix* possessing a dihydroisocoumarin ring system <2003HCA377> and during the first total synthesis of (*R*)-7-butyl-6,8-dihydroxy-3-pentyl-dihydroisocoumarin <2005TA2231>.

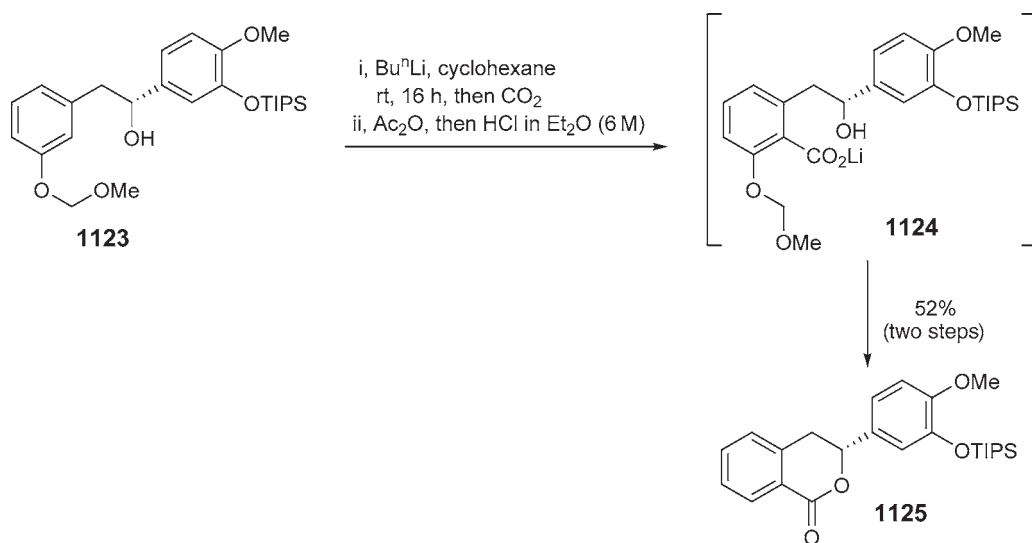


Scheme 278

Base-mediated cyclization of the diol **1119**, obtained via Sharpless asymmetric dihydroxylation methodology, provides the dihydroisocoumarin subunit **1120** during the asymmetric synthesis of a portion of AI-77-B (Equation 437) <1996JOC3183>. Acid mediated cyclization of *o*-allylbenzamide **1121** provides the dihydroisocoumarin **1122** during the synthesis of semivioxanthin analogues (Equation 438) <2001TL5955>. The cyclization of these substrates can also be effected by iodine <2001SL1019, 2002T6455>.

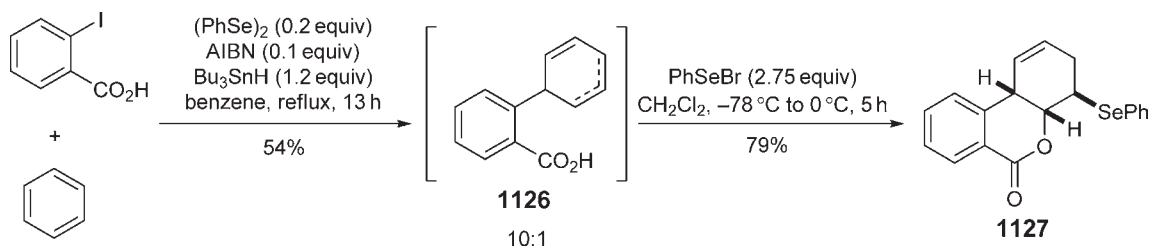


(*R*)-1-[4-Methoxy-3-[(triisopropylsilyl)oxyphenyl]-2-[3-(methoxymethoxy)phenyl]ethanol **1123** undergoes selective hydrogen metal exchange followed by carbonylation to form the lithiated intermediate **1124**, which undergoes cyclization in acid conditions to provide the dihydroisocoumarin **1125**, a key intermediate during an enantioselective synthesis of phyllodulcin (Scheme 279) <1996JOC5371>.



Scheme 279

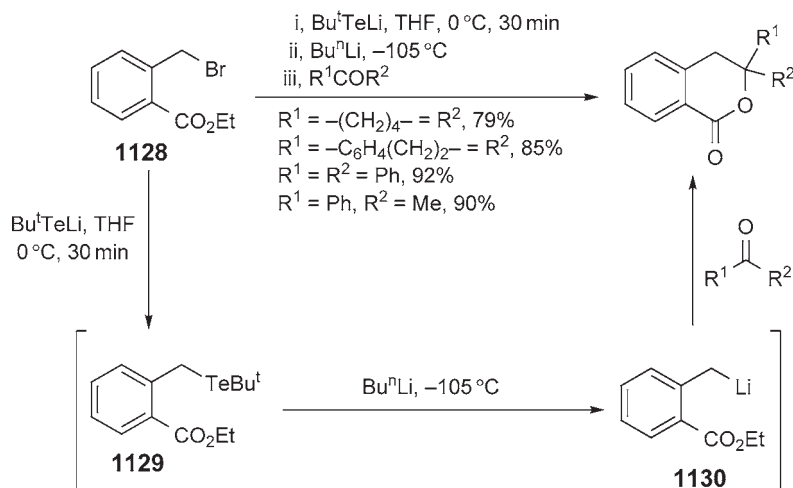
Radical reaction of 2-iodobenzoic acid with benzene affords the cyclohexadiene intermediate **1126** as a mixture of regioisomers, which cyclize in the presence of phenylselenium bromide to afford the dihydroisocoumarin **1127** in good yield (Scheme 280) <2002T3319>.



Scheme 280

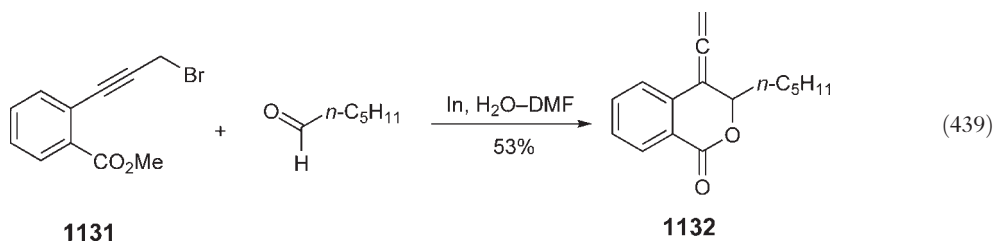
7.08.28.2 Formation of More than One Bond

Tellurides **1129** prepared from α -bromo-*o*-toluylesters **1128** undergo lithium–tellurium exchange to give the corresponding benzylic anions **1130**, which react with aldehydes or ketones to afford dihydroisocoumarins in high yield (Scheme 281) <1997SL1047>.

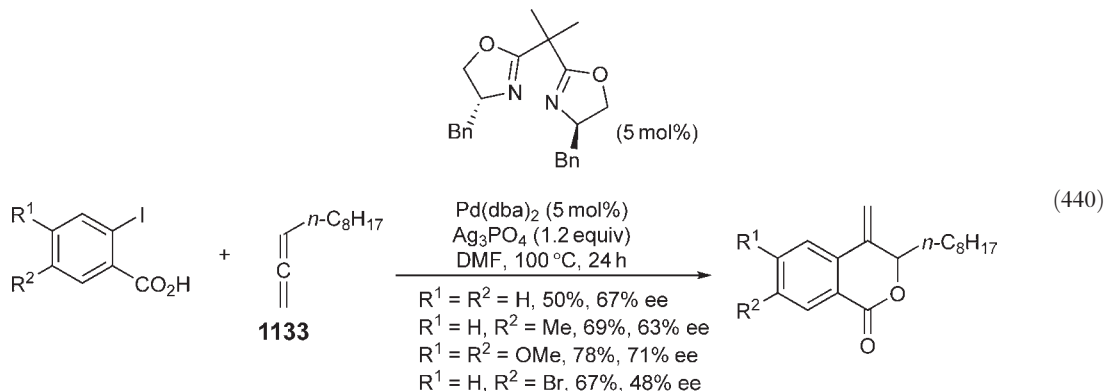


Scheme 281

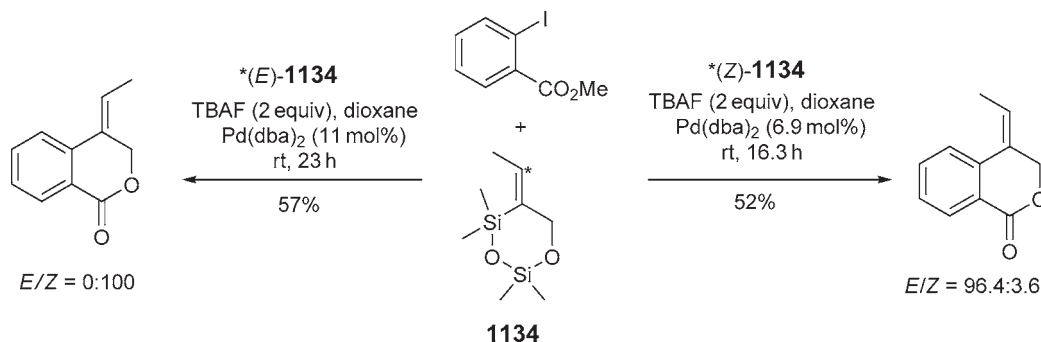
An indium mediated reaction of *o*-carboxyarylpropargyl bromide **1131** with hexanal in aqueous media provides a route to the 4-allenyldihydroisocoumarin **1132** (Equation 439) <1998TL6837>.



A palladium-catalyzed asymmetric annulation of the allene **1133** with 2-iodobenzoic acids proceeds in the presence of a chiral bisoxazoline ligand to afford 4-methylenedihydroisocoumarins in good yield and enantiomeric excess (Equation 440) <1999JOC7312>.

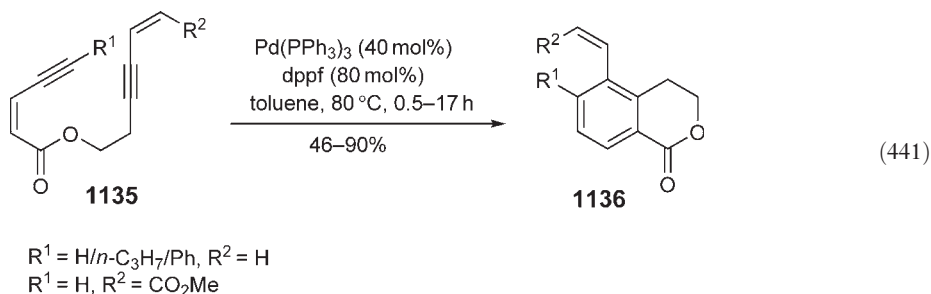


The (*E*)- and (*Z*)-regioisomers of 6-ethylidenedioxadisilacyclohexane **1134** undergo palladium catalyzed-cross coupling with methyl-2-iodobenzoate to furnish dihydroisocoumarins with excellent (*E*)- or (*Z*)- selectivity (Scheme 282) <2003OL1119>.

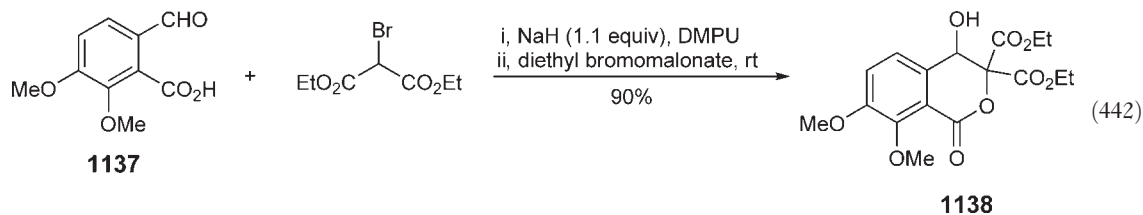


Scheme 282

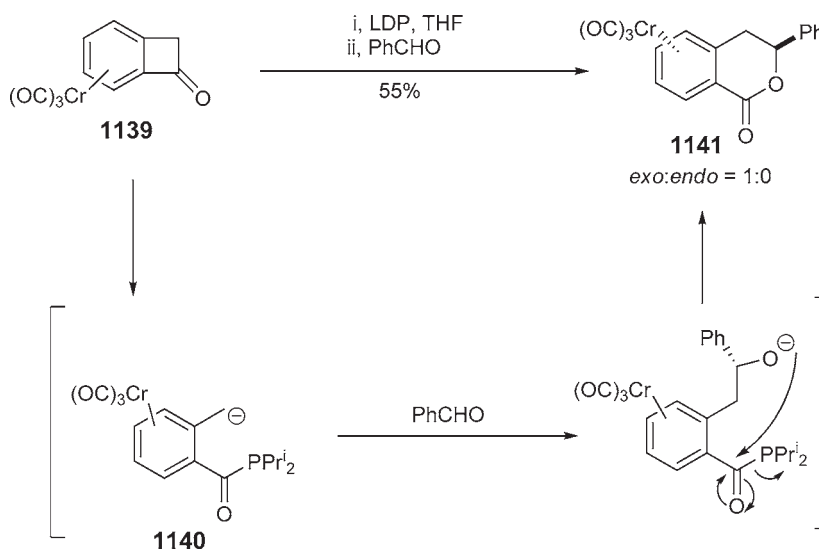
A palladium-catalyzed intramolecular benzannulation of bis-enynes **1135** proceeds chemoselectively to afford dihydroisocoumarins **1136** (Equation 441) <2002JOC2653>. A reaction sequence involving ruthenium-catalyzed yne-ene cross-metathesis of a polystyrene supported undecynoic acid ester followed by a Diels-Alder cycloaddition reaction with DMAD provides the basis for a combinatorial approach to dihydroisocoumarins featuring a variety of side chains at C-6 and C-8 <1999SL1879>.



During the synthesis of the isocoumarin moiety of heliquinomycin, diethyl bromomalonate and phthalaldehydic acid **1137** condense to form the dihydroisocoumarin **1138** in excellent yield (Equation 442) <2000TL29>.

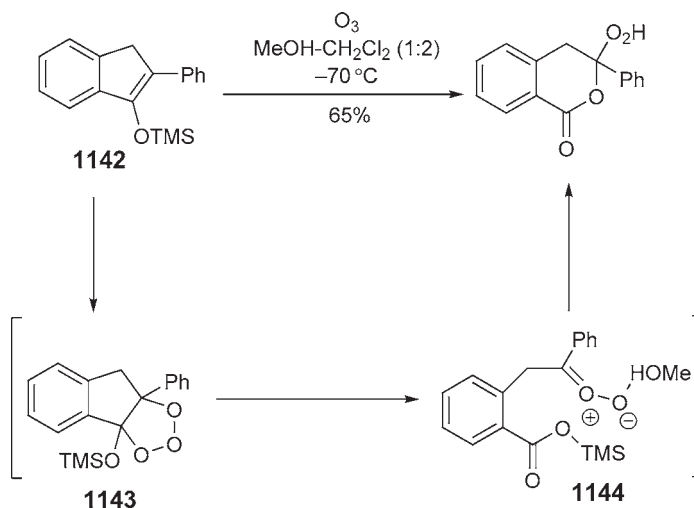


Lithium diisopropylphosphide (LDP) mediated distal ring opening of *rac*-(benzocyclobutenone)tricarbonylchromium **1139** forms the acylphosphane intermediate **1140**, which reacts diastereoselectively with benzaldehyde to furnish the 3-phenyl-isochroman-1-one chromium complex **1141** in moderate yield (Scheme 283) <2003EJO4363>.



Scheme 283

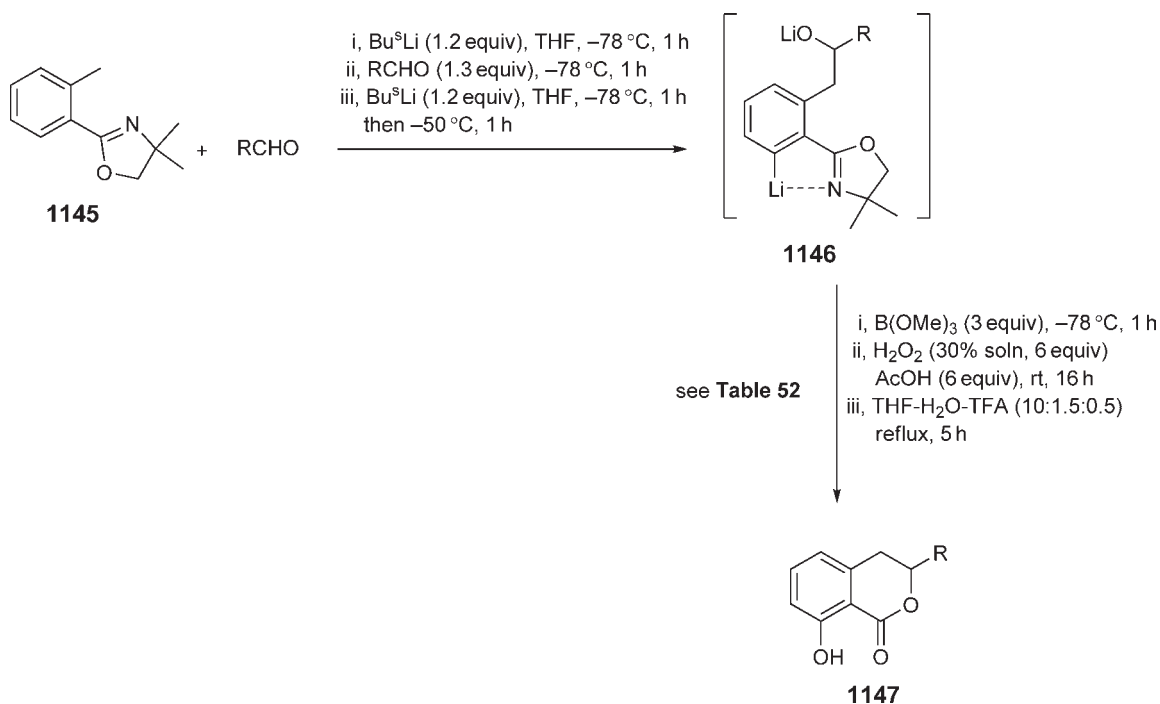
Ozonolysis of 3-trimethylsilyloxyindene **1142** in the presence of methanol affords 3-hydroperoxy-3-phenyldihydroisocoumarin via selective cleavage of the ozonide **1143** followed by an intramolecular nucleophilic attack onto the solvated carbonyl in the intermediate **1144** (Scheme 284) <1999JOC2137>.



Scheme 284

Sequential treatment of 4,4-dimethyl-2-(*o*-tolyl)oxazoline **1145** with *s*-BuLi, aromatic or aliphatic aldehydes and *s*-BuLi leads to intermediate oxazolines **1146**, treatment of which with B(OMe)₃ and H₂O₂ followed by TFA provides a one-pot process for the synthesis of 3-substituted 8-hydroxyisochroman-1-ones **1147** in moderate to good overall yield (Scheme 285, Table 52) <2004TL5117>.

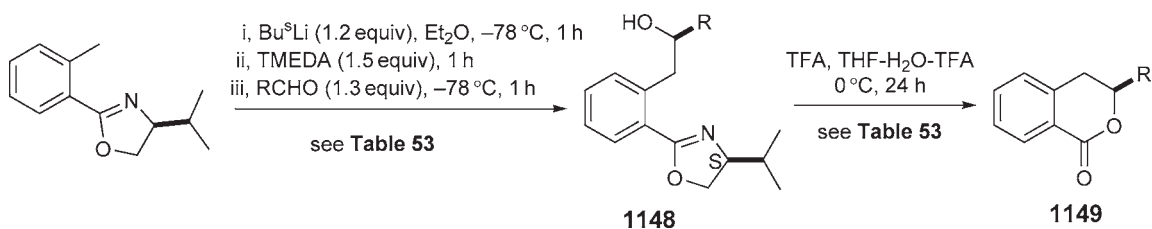
Lateral lithiation of (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline and reaction with aldehydes provides the addition products **1148** with moderate to good diastereoselectivity. The addition of TMEDA is vital for any diastereoselectivity to be observed. The major (*S,S*)-products lactonize faster under acidic conditions providing dihydroisocoumarins **1149** in up to ee 97% (Scheme 286, Table 53) <2005T3289>. Similarly, the addition of laterally metallated *o*-toluates to chiral aldehydes provides a key dihydroisocoumarin during a total synthesis of AI-77-B <1999J(P1)1083>.



Scheme 285

Table 52 Formation of dihydroisocoumarins **1147**
(Scheme 285)

<i>R</i>	Yield 1147 (%)
Ph	71
4-MeC ₆ H ₄	75
4-MeOC ₆ H ₄	67
3-Pr ^t O,4-MeOC ₆ H ₄	56
3,4,5-(Me) ₃ C ₆ H ₄	57
(<i>E</i>)-styryl	60
Pr ⁿ	44
4-TBDMSOC ₆ H ₄	59
3-OMe, 4-TBDMSOC ₆ H ₄	53

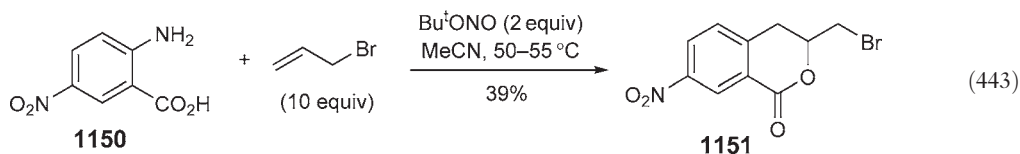


Scheme 286

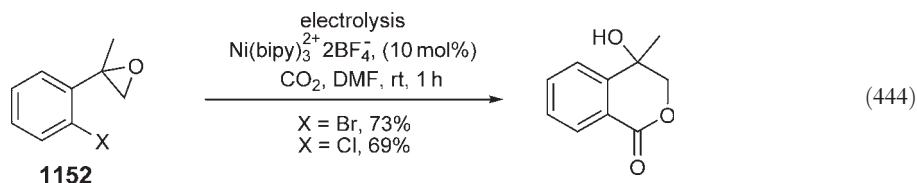
Table 53 Formation of addition products **1148** and their conversion to dihydroisocoumarins **1149** (Scheme 286)

<i>R</i>	Yield 1148 (%)	<i>dr</i> 1148 (<i>S,S,S,S,R</i>)	Yield 1149 (%)	<i>ee</i> 1149 (%)
Ph	94	8.2:1	84	89
4-MeC ₆ H ₄	99	7.6:1	77	91
4-MeOC ₆ H ₄	95	6.2:1	72	86
4-ClC ₆ H ₄	97	3.2:1	83	73
3,4-(Me) ₂ C ₆ H ₃	97	5.7:1	57	82
1-naphthyl	95	5.7:1	72	92
(<i>E</i>)-styryl	87	7.1:1	67	88
Bu ^t	91	11.8:1	56	97
<i>n</i> -C ₇ H ₁₅	75	1:2.1	43	79

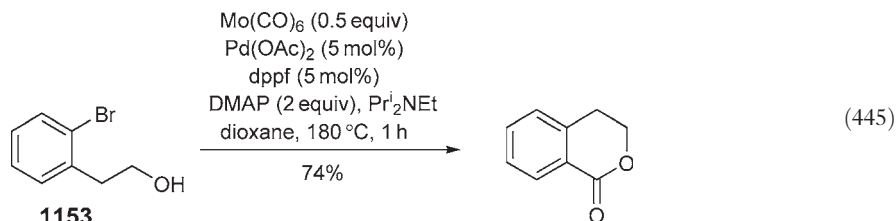
The nitroanthranilic acid **1150** reacts with allyl bromide in the presence of *tert*-butyl nitrite to furnish the dihydroisocoumarin **1151** in poor yield (Equation 443) <2003JOC1911>.



An electrochemical, nickel-catalyzed incorporation of carbon dioxide into 2-haloaryl epoxides **1152** affords 4-hydroxy-4-methyldihydroisocoumarin (Equation 444) <2000SL245>.



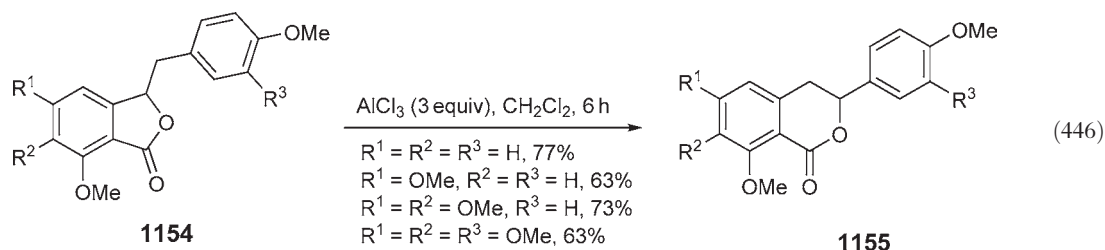
Dihydroisocoumarin is accessible from a microwave promoted palladium-catalyzed reaction of the aryl bromide **1153** with Mo(CO)₆ as a source of carbon monoxide (Equation 445) <2004TL4635>.



7.08.28.3 From Other Heterocycles

7.08.28.3.1 From isobenzofuranones

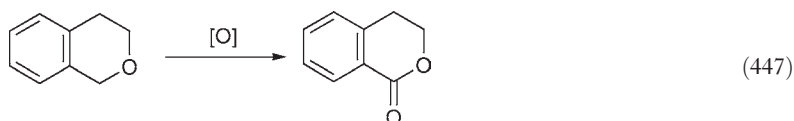
A Lewis-acid-mediated ring expansion of isobenzofuranones **1154** provides the final step during the total synthesis of naturally occurring (±)-3-aryl-8-hydroxydihydroisocoumarins **1155** (Equation 446) <2001J(P1)3017>.



7.08.28.4 From a Preformed Heterocyclic Ring

7.08.28.4.1 From isochromans

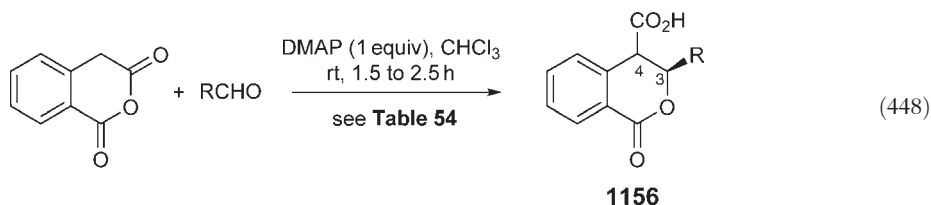
A variety of oxidative conditions can be used to effect the transformation of isochromans to dihydroisocoumarins (Equation 447).



These include photoirradiation with benzil and O_2 <1996TL4179>, with I_2 <2001CL686> and mesoporous silica (FSM-16) <2001OL2653>. Ultrasound assisted heterogeneous potassium permanganate <2000T8561>, montmorillonite K10 clay supported potassium permanganate <2002TL5165>, MnO_2 - supported potassium permanganate <2004T11415>, copper sulfate pentahydrate and moist alumina-supported potassium permanganate <1997JOC8767, 2004SL481> and potassium permanganate without a solid support if acetonitrile is employed as the solvent <2005SC571>. Gif chemistry <2002BKC937>, O_2 promoted by lactase <2003NJC329>, nitric acid in CH_2Cl_2 <2003EJO526>, dirhodium caprolactamate $[\text{Rh}_2(\text{cap})_4]$ <2005OL5167>, $\text{Mn}(\text{III})$ -salen complexes <1998TL1385, 2005BKC454>, chromium(VI) oxide-catalyzed with periodic acid <1999OL2129>, *N*-hydroxyphthalimides <1999TL2165, 2004CC1500, 2005TL4647>, dimethyldiepoxy (DMDO) <1997T9755>, 2-nitrobenzenesulfonylperoxyl intermediates <1998J(P1)633>, polyoxomolybdate-mediated oxygen transfer from sulfoxides <2002JA4198>, magnetic field accelerated radical oxidation with hypervalent (*tert*-butylperoxy)iodane <2004CL716> and ruthenium/periodate <2000TA409> are also all effective catalytic conditions for the above oxidation.

7.08.28.4.2 From isochroman-1,3-diones (homophthalic anhydrides)

Isochroman-1,3-dione reacts with benzaldehyde in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give the cycloadduct 3-phenyldihydroisocoumarin-4-carboxylic acid in good yield as a mixture of *syn*- and *anti*-isomers <1999T13735>. Changing the catalyst to DMAP provides high yields of *syn*- and *anti*-3-substituted dihydroisocoumarin-4-carboxylic acids **1156**, with the *anti*-product predominating (Equation 448, Table 54) <2004T2525>.

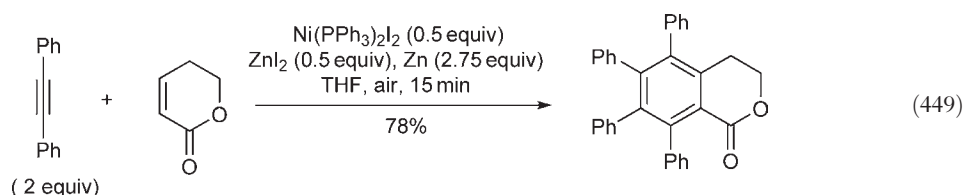


7.08.28.4.3 From dihydropyran-2-ones

1,2-Diphenylethyne reacts with 5,6-dihydropyran-2-one in the presence of $\text{Ni}(\text{PPh}_3)_3\text{I}_2$, ZnI_2 and Zn powder to give 5,6,7,8-tetraphenyldihydroisocoumarin, the product of a [2+2+2] cycloaddition–dehydrogenation sequence (Equation 449) <1999JOC3663>.

Table 54 Formation of dihydroisocoumarins **1156** (Equation 448)

<i>R</i>	Yield 1156 (%)	<i>anti:syn</i> (C3:C4)
Ph	100	70:30
4-O ₂ NPh	98	77:23
4-MeOPh	98	80:16
	100	79:16
2-thienyl	100	82:9
2-furyl	100	62:8
	80	91:9

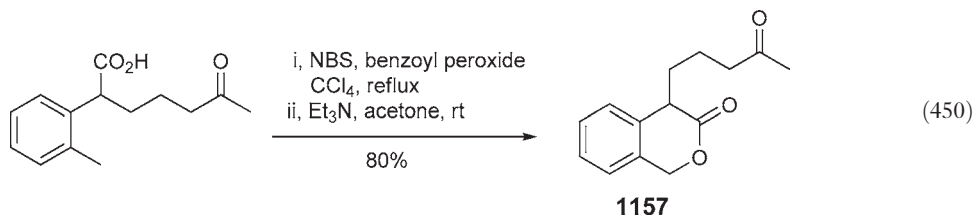


7.08.29 Isochroman-3-ones

7.08.29.1 Formation of One Bond

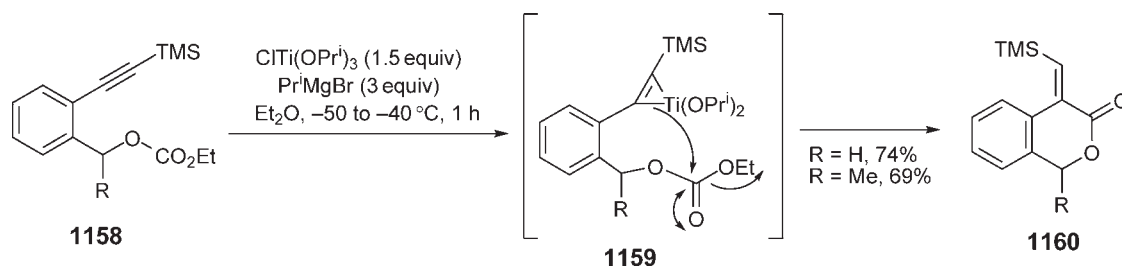
7.08.29.1.1 Adjacent to the heteroatom

Conversion of 2-(2-methyl)-phenyl-6-oxoheptanoic acid to 4-alkylisochroman-3-one **1157** can be achieved by a radical bromination followed by a base induced cyclization (Equation 450) <2001TL6737>.



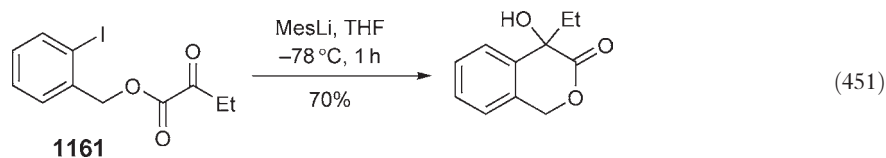
7.08.29.1.2 β to the heteroatom

The reaction between ClTi(*Oi*-Pr)₃ and *i*-PrMgBr generates a low-valent titanium reagent, diisopropoxy(η²-propene)titanium, which mediates the cyclization of the alkynic carbonates **1158** to isochroman-3-ones **1160** via the intermediate **1159** (Scheme 287) <1995TL6075, 1996JA2208>.

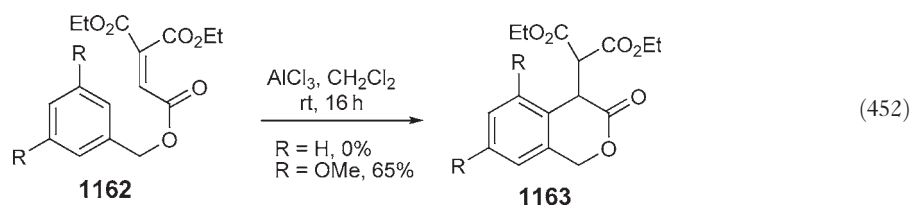
**Scheme 287**

7.08.29.1.3 γ to the heteroatom

Iodobenzyl ketoester **1161** undergoes halogen–lithium exchange with mesityllithium followed by 1,2-addition to the ketone to give 4-hydroxy-4-ethylisochroman-3-one in good yield. An intermediate during the synthesis of camptothecin is synthesized using this methodology (Equation 451) <2001OL13>.



A Lewis-acid-promoted cyclization of ethene tricarboxylate derivatived aromatic compounds **1162** provides a route to isochroman-3-ones **1163** via a Friedel–Crafts intramolecular Michael addition protocol. The substrate must possess two *meta*-positioned electron donating groups in order for the reaction to proceed (Equation 452) <2004OBC3134>.



7.08.29.2 Formation of More than One Bond

Isochroman-3-one can be accessed via an MCPBA mediated Baeyer–Villiger oxidation of indan-2-one <2003OBC2120>.

Benzocyclobutenones **1164** undergo heterolytic C(1)–C(4) bond fission and reaction with aldehydes to provide a route to isochroman-3-ones **1165** (Equation 453, Table 55) <1997TL8985>.

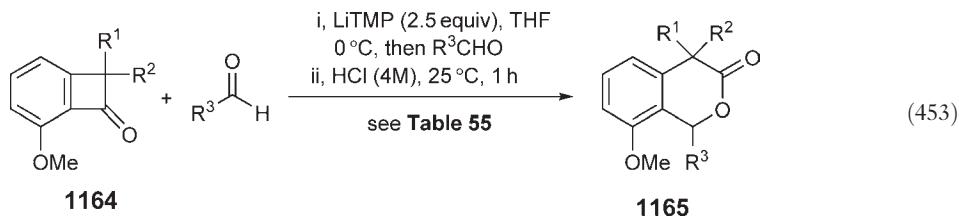


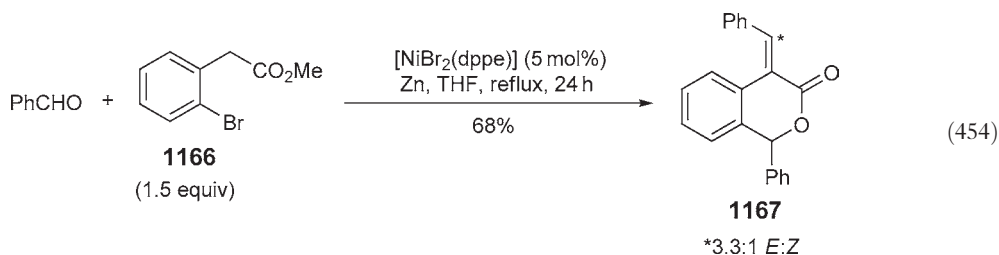
Table 55 Formation of isochroman-3-ones **1165** (Equation 453)

R^1	R^2	R^3	Yield (%)
H	H	Ph	70
H	H	4-MeOC ₆ H ₄	87
H	H	4-MeC ₆ H ₄	73
H	H	4-ClC ₆ H ₄	64
H	H	3,4-(MeO) ₂ C ₆ H ₃	78
H	H	cinnamyl	54
H	OMe	4-MeOC ₆ H ₄	83 ^a
H	Me	4-MeOC ₆ H ₄	81 ^b
Me	Me	4-MeOC ₆ H ₄	40

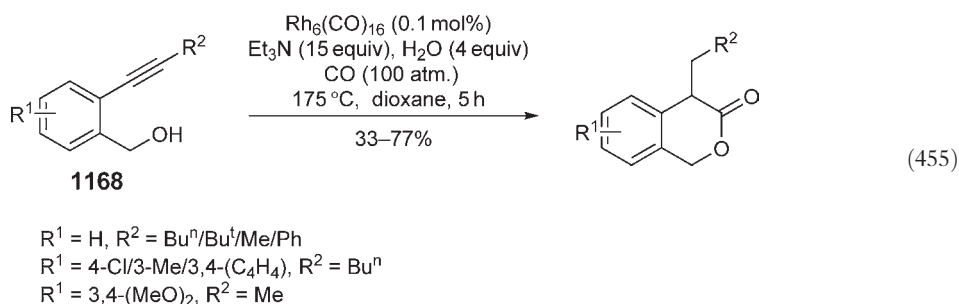
^a*anti:syn* = 14:1.

^b*anti:syn* = 3.4:1.

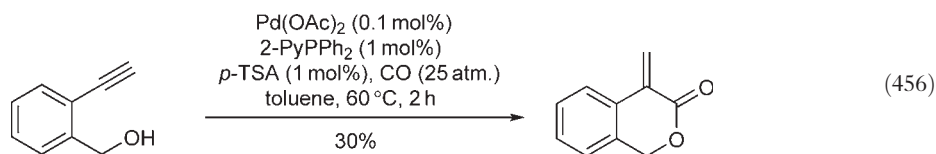
Synthesis of the isochroman-3-one **1167** can be achieved by a nickel-catalyzed intermolecular cyclization of the *ortho*-haloester **1166** and benzaldehyde, with the (*E*)-isomer predominating in the product (Equation 454) <2004CEJ2991>.



Rhodium-catalyzed cyclization and carbonylation of 2-ethynylbenzylalcohols **1168** under water–gas shift reaction conditions leads to isochroman-3-ones (Equation 455) <1998TL5061>.



The carbonylation of (2-ethynylphenyl)methanol is catalyzed by $\text{Pd}(\text{OAc})_2$ in the presence of 2-(diphenylphosphino)pyridine (2-PyPPh₂) to provide 4-methyleneisochroman-3-one, isolated in poor yield due to its instability (Equation 456) <2002TL753>. The synthesis of isochroman-3-one can be achieved by a palladium and HI-mediated carbonylation of 1,2-bis(hydroxymethyl)benzene <1998BCJ723>.

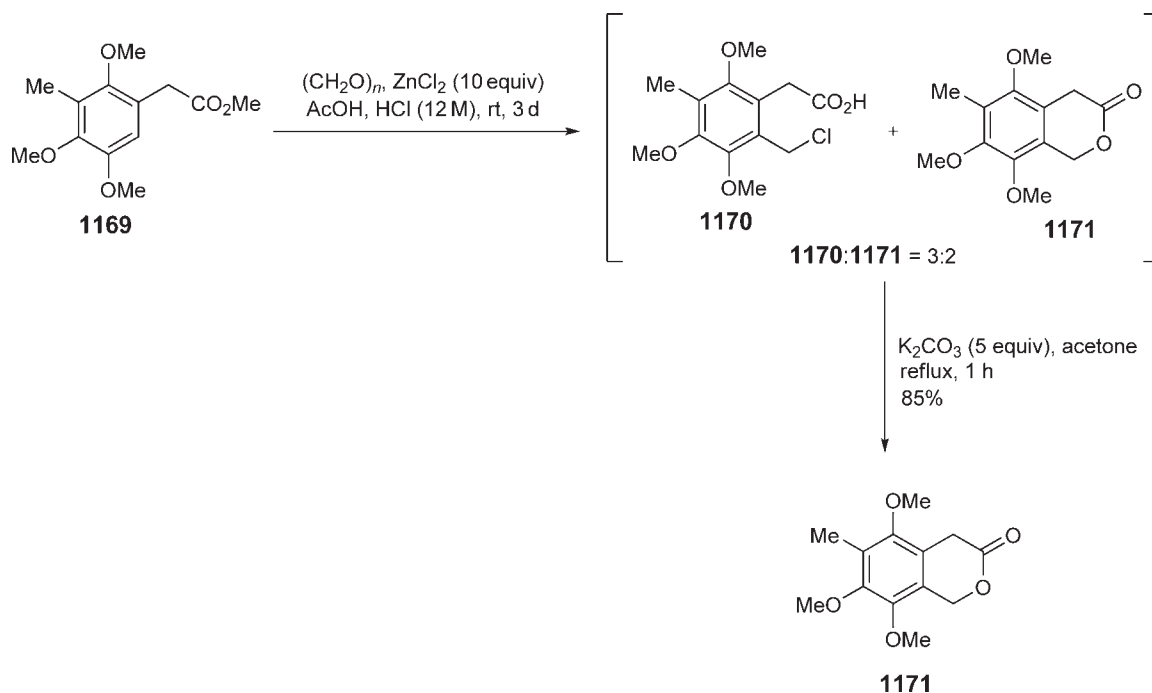


Treatment of pentasubstituted benzene **1169** with an excess of paraformaldehyde in the presence of ZnCl_2 under acidic conditions successfully installs a chloromethyl group *ortho*- to the acetic acid substituent, furnishing a mixture of **1170** and the cyclized isochroman-3-one **1171**. As these acidic conditions are not themselves enough to totally finish the cyclization, basic hydrolysis is conducted to complete the cyclization to the isochroman-3-one **1171**, a key intermediate during a synthesis of mimosamycin (Scheme 288) <2000JOC635>.

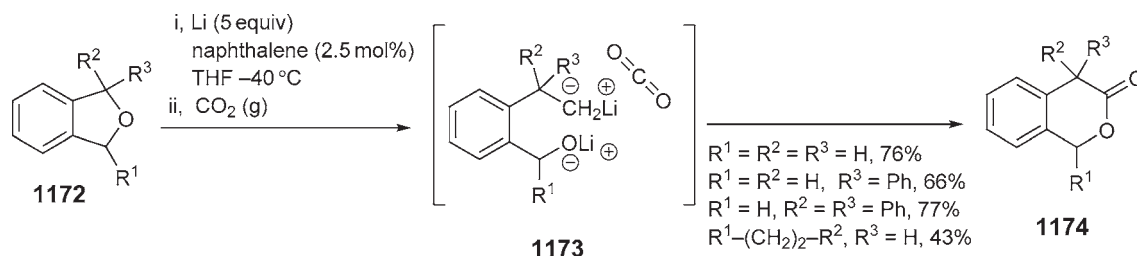
7.08.29.3 From Other Heterocycles

7.08.29.3.1 From dihydroisobenzofurans (phthalans)

Treatment of substituted phthalans **1172** with lithium metal in the presence of catalytic quantities of naphthalene leads to reductive cleavage of the arylmethyl carbon–oxygen bond to form a stable dilithium compound **1173**, which upon trapping with carbon dioxide furnishes isochroman-3-ones **1174** (Scheme 289) <1996JOC4913>.



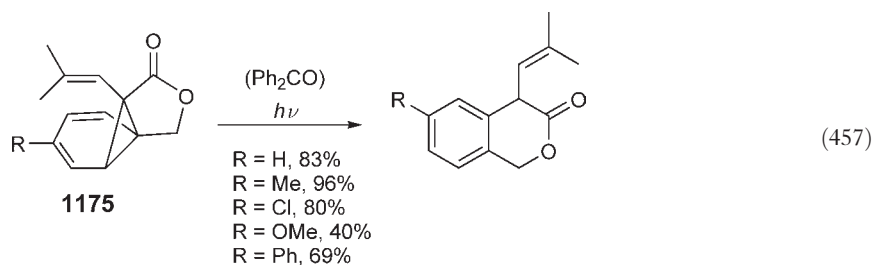
Scheme 288



Scheme 289

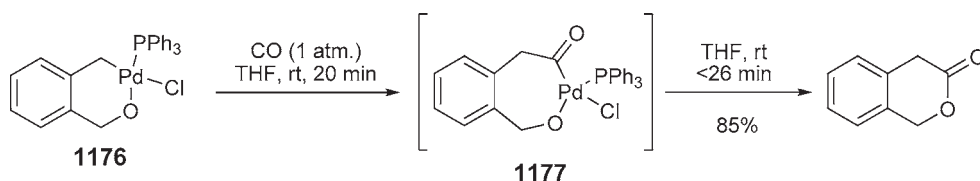
7.08.29.3.2 From vinylnorcaradienes

Vinylnorcaradiene derivatives **1175** undergo a photochemical reaction resulting in the regioselective cleavage of one of the cyclopropyl σ -bonds and the formation of isochroman-3-ones (Equation 457) <1997CC1973>.



7.08.29.3.3 From palladacycles

Carbon monoxide reacts with the palladacycle **1176** to form the intermediate **1177**, which undergoes reductive elimination to afford isochroman-3-one (Scheme 290) <2005OM1119>.



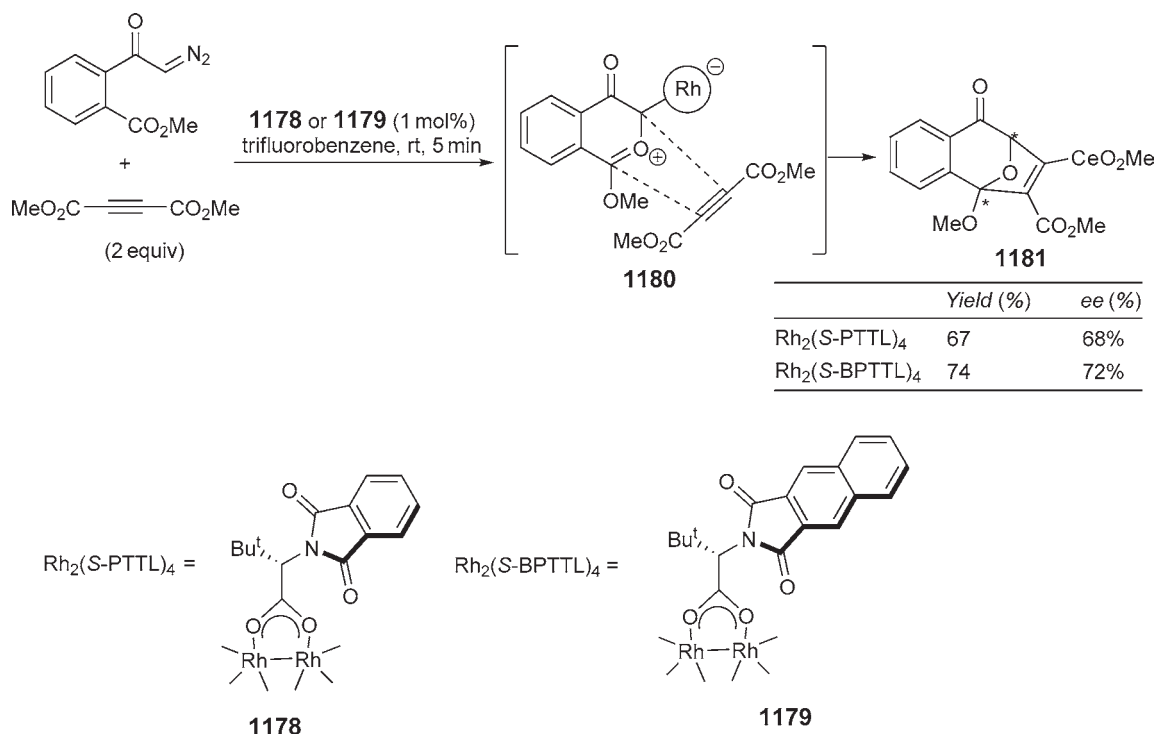
Scheme 290

7.08.30 Isochroman-4-ones

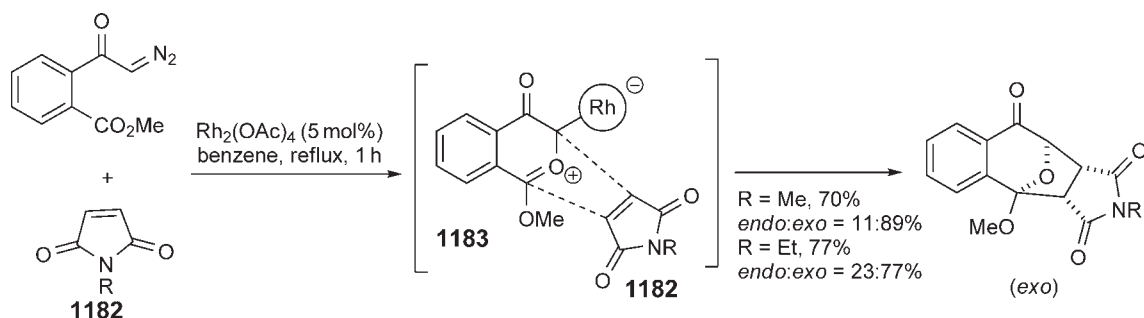
7.08.30.1 Formation of One Bond

7.08.30.1.1 Adjacent to the heteroatom

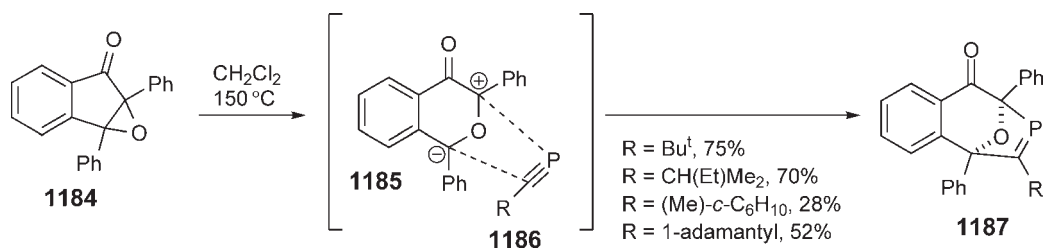
A $\text{Rh}_2(\text{S-PTTL})_4$ **1178** or $\text{Rh}_2(\text{S-BPTTL})_4$ **1179** catalyzed intermolecular 1,3-dipolar cycloaddition of the ester-derived carbonyl ylide **1180** and DMAD proceeds with moderate enantioselectivity to form bridged isochroman-4-ones **1181** (Scheme 291) <2000TL5931>. Ruthenium(II)-porphyrins can also catalyze this process <2002OL3235>. The $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of the carbonyl ylide **1183** with *N*-methylmaleimides **1182** provides the corresponding bridged isochroman-4-one cycloadducts with excellent levels of *exo*-selectivity (Scheme 292) <1998TL3165>. Adding $\text{Yb}(\text{OTf})_3$ to the reaction switches the stereochemical outcome to *exo*-selective <1998TL3165, 2001BCJ1115>. The addition of other rare-earth triflates and pybox ligands to the reaction between carbonyl ylide and a variety of dipolarophiles furnishes isochroman-4-one adducts with excellent levels of enantioselectivity <2002JA14836, 2003SI413, 2005JOC47>. Thermal ring opening of epoxide **1184** followed by a 1,3-dipolar cycloaddition of the resulting carbonyl ylide **1185** with phosphalkynes **1186** provides a route to polycyclic phosphalkenes **1187** (Scheme 293) <2000T6259>.



Scheme 291

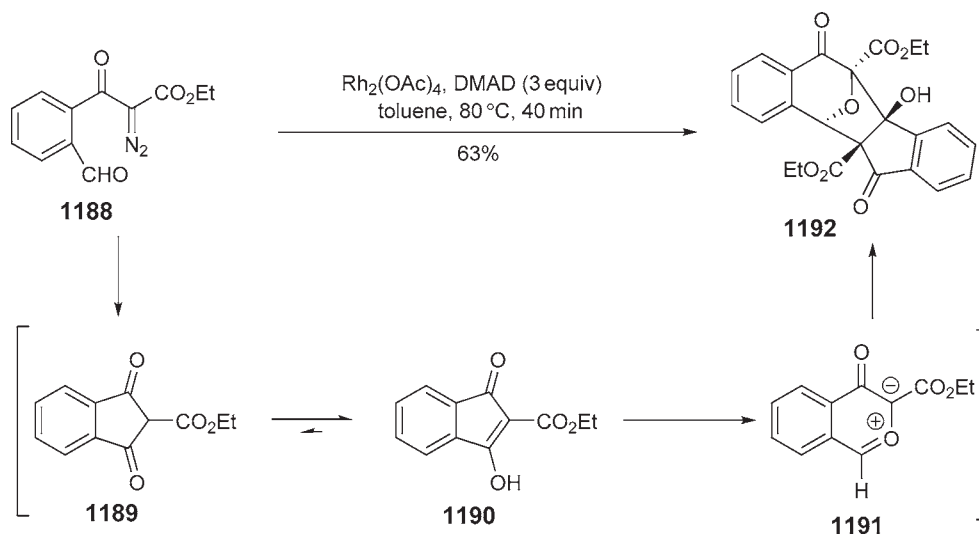


Scheme 292



Scheme 293

The rhodium-catalyzed CH insertion reaction of the diazo compound **1188** affords 1,3-indandione **1189**, the enol tautomer **1190** of which undergoes ring expansion furnishing the six-membered ring dipole **1191** which dimerizes, even in the presence of excess DMAD to produce an unusual isochroman-4-one **1192** (Scheme 294) <1999JOC4079>.



Scheme 294

The rhodium-catalyzed formation of the above six membered 1,3-dipoles is involved in the construction of various other complex ring systems, including the oxatricyclo[6.3.1.0^{0,0}]dodecane core of komaroviquinone <2005OL3725>, the synthesis of tropolone natural products <1999OL1933> and the cyclization of *o*-(1,6-enynyl)benzaldehydes, which leads to polycyclic ring systems seen in many natural products <2005CC4429>.

7.08.30.2 Formation of More than One Bond

Photolysis of chromium alkoxycarbene complexes **1193** leads to isochroman-4-ones **1194** via an intramolecular Friedel–Crafts acylation of the arene. The reaction yield is highly dependent upon the amount of ZnCl_2 present, which varies considerably for specific substrates (Equation 458, Table 56) <1998JOC1462>.

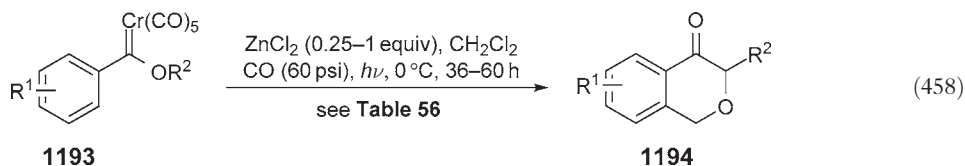
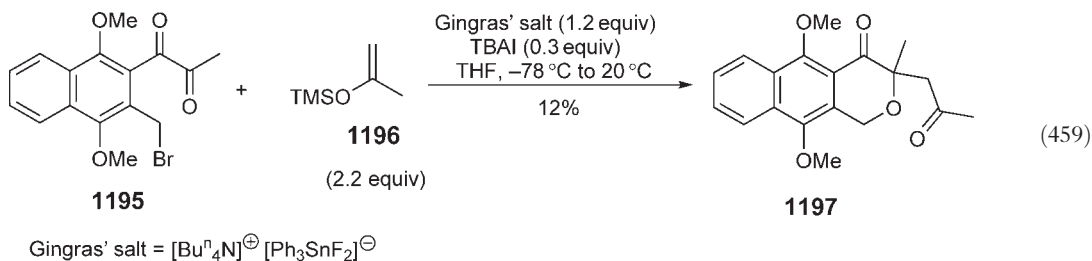


Table 56 Formation of isochroman-4-ones **1194** (Equation 458)

ZnCl_2 (eq.)	R^1	R^2	Yield 1194 (%)
1	3-MeO	Me	69
1	3-MeO		43
1	3-MeO	Ph	15
0.25	3-OH	Me	59
0.1	3,4-(Me) ₂	Me	38

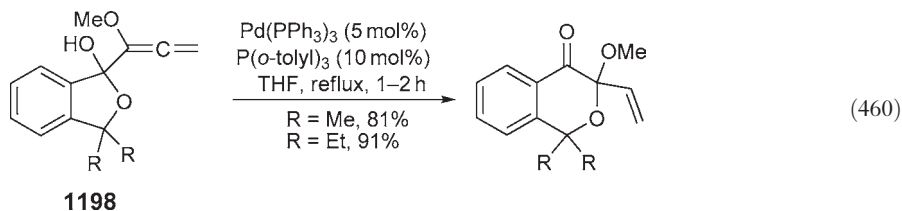
Reaction of the benzylic bromide **1195** with silylenol ether **1196** in the presence of TBAI and Gingras' salt ($[\text{n-Bu}_4\text{N}][\text{Ph}_3\text{SnF}_2]$) affords the isochroman-4-one **1197** in poor yield. The product can be explained by the 1,2-addition of the enolate to the top side chain, followed by nucleophilic substitution of the benzylic bromide (Equation 459) <2000CEJ3887>.



7.08.30.3 From Other Heterocycles

7.08.30.3.1 From dihydroisobenzofurans (phthalans)

Palladium(0)-catalyzed ring expansion of hydroxyl methoxyallenylphthalans **1198** provides a route to highly substituted isochroman-4-ones (Equation 460) <2000H(52)85, 2002OL455>.



7.08.30.4 From a Preformed Heterocyclic Ring

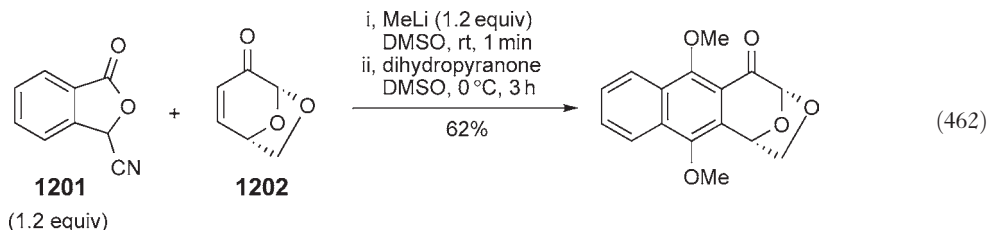
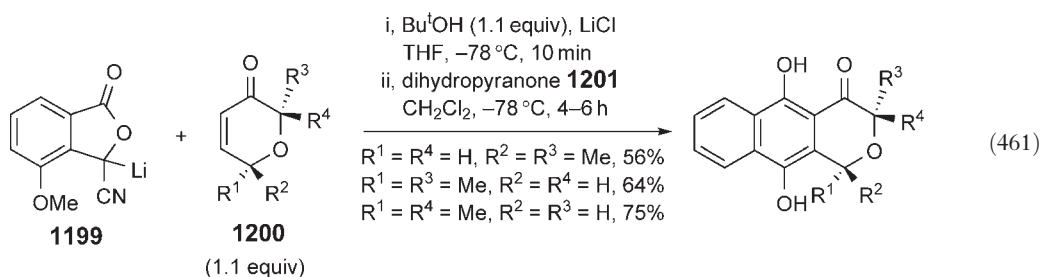
7.08.30.4.1 From isochromans

Oxidation of isochroman-4-ols to the corresponding isochroman-4-ones is observed during the syntheses of 4-hydroxybenzo[*c*]pyran quinones <1997TL5055>, benzo[*g*]isochromanols <2001T9623>, and model studies towards the stephaxocanes <2003EJO4731>.

The first synthesis of the tetracyclic integrastatin nucleus involves a benzylic oxidation of a bridged isochroman using PDC in the presence of *t*-butylhydroperoxide (TBHP) <2003OL4441, 2005OBC756>.

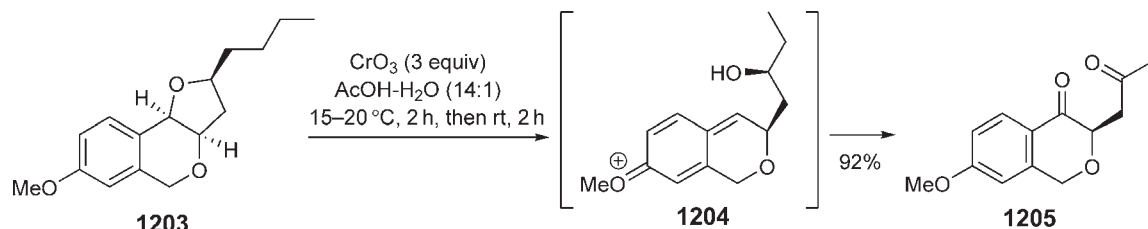
7.08.30.4.2 From dihydropyranones

Total syntheses of hongconin describe Hauser annulation reactions of cyanophthalides **1199** and **1201** with 2,6-dihydropyran-3-ones **1200** and **1202** respectively as key steps in constructing the isochroman-4-one backbone during the synthesis of hongconin (Equations 461 and 462) <1996JOC455, 1996JOC459>. Modifications of polymer bound 2,6-dihydropyran-3-ones leads to several pharmacophoric structures, including those containing a isochroman-4-one moiety <2002AGE3677>.



7.08.30.4.3 From 3,3a,5,9b-tetrahydrofuro[3,2-*c*]isochromenes

Oxidation of the chroman **1203** bearing a fused tetrahydrofuran moiety leads to the isochroman-4-one **1205** via oxidation of the quinoid-like intermediate **1204**. This diketone is observed as an unwanted side-product during enantiospecific syntheses of monocerin analogues (Scheme 295) <1996T8535>.



Scheme 295

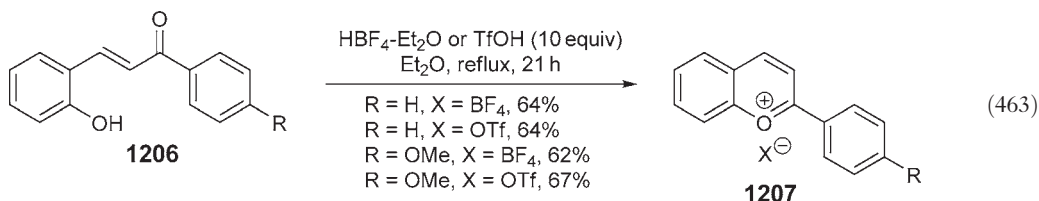
7.08.31 Pyrylium Salts and Their Benzo Derivatives

7.08.31.1 Formation of One Bond

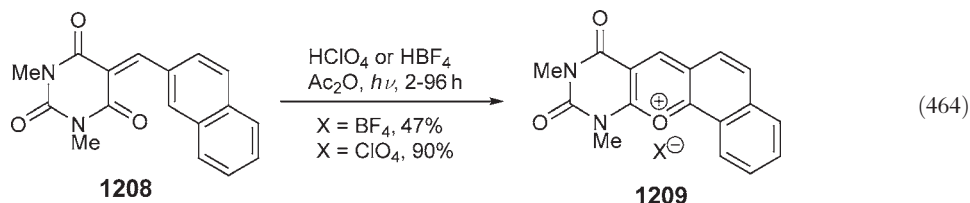
7.08.31.1.1 Adjacent to the heteroatom

Cyclodehydration of 1,5-diones continues to provide an attractive synthetic route to pyrylium salts [<2003OL2587, 2005S245>](#).

Two different 2-arylchromenylium salts **1207** are accessed by heating salicylideneacetophenones **1206** in the presence of the appropriate acid (Equation 463) [<2001EJO4451>](#).



The synthesis of areno[*b*]pyrimido[5,4-*e*]pyran-2,4(1,3*H*)-dionylium ions **1209** can be accomplished via a novel photoinduced oxidative cyclization of the enone **1208** (Equation 464) [<2005T4919>](#).



7.08.31.2 Formation of More than One Bond

Formation of pyrylium salts by a Brønsted- or Lewis-acid-mediated condensation of acetophenones with chalcones or benzaldehydes continues to receive widespread interest [<1996J\(P2\)307, 1997J\(P2\)1055, 2001CEJ3106, 2001EJO2343, 2002OL4269, 2002JOC2065, 2003S1878, 2005CC2790>](#). Replacing benzaldehydes ($\text{R}^2 = \text{H}$) with benzoic acids/esters ($\text{R}^2 = \text{OH}$, OMe) in the Lewis-acid-mediated condensation reaction with *p*-bromoacetophenone leads to increased yields of the corresponding pyrylium salts **1210** (Equation 465, Table 57) [<2003TL9271>](#).

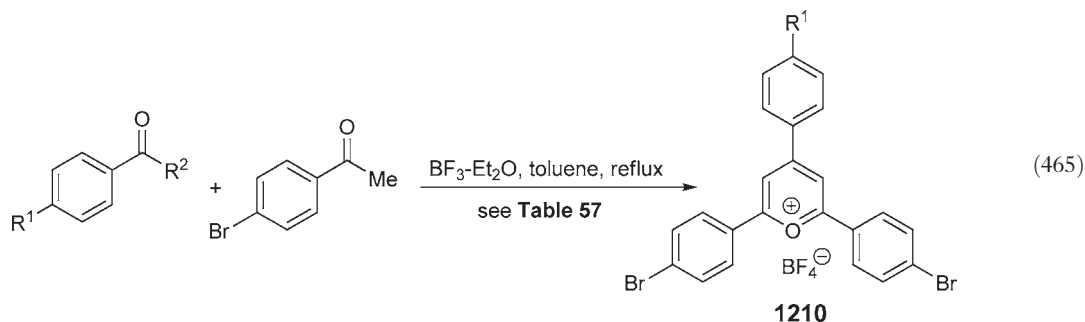
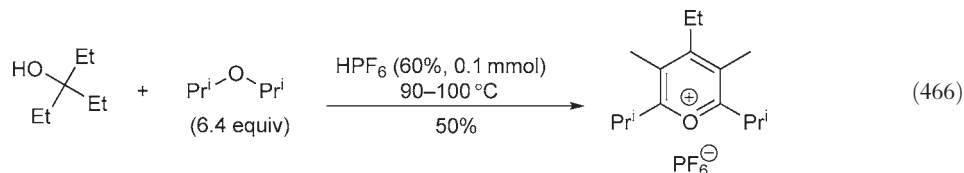


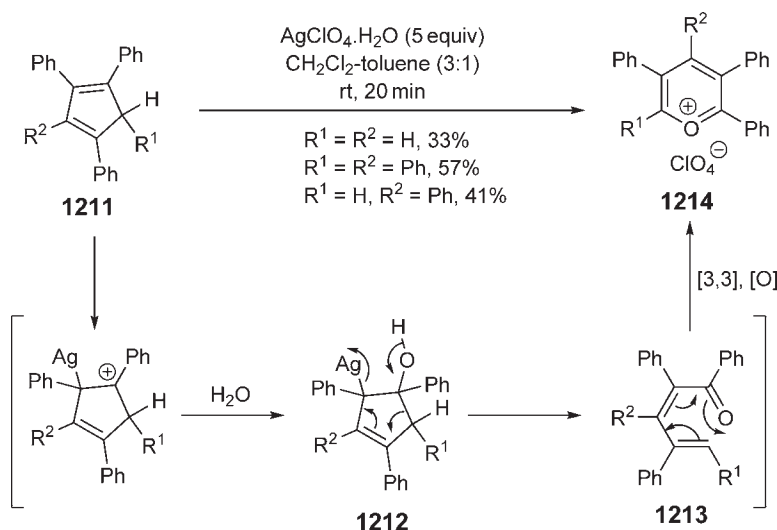
Table 57 Formation of pyrylium salts **1210** (Equation 465)

R^1	R^2 yield (%)		
	<i>H</i>	<i>OH</i>	<i>OMe</i>
H	42	37	55
Br	22	28	31
OMe	42	51	61
NO_2	45	53	65

Addition of concentrated hexafluorophosphoric acid to a mixture of isobutyric anhydride and 3-ethyl-3-pentanol leads to 4-ethyl-2,6-diisopropyl-3,5-dimethylpyrylium hexafluorophosphate, a reaction that proceeds via a rapid exothermal diacylation (Equation 466) <2004JOC536>.

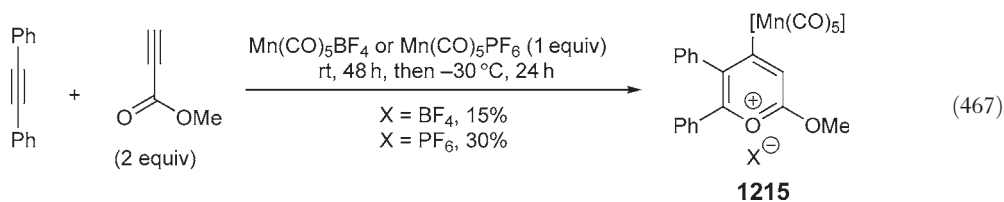


Phenyl-substituted cyclopentadienes **1211** are converted to pyrylium salts **1214** in the presence of silver(I) perchlorate via insertion of an oxygen atom into the cyclopentadiene ring. The reaction proceeds via ring opening of cyclopentene **1212** followed by electrocyclic ring closure and oxidation of the resulting 2,4-dienone **1213** (Scheme 296) <2004JOC1432>.

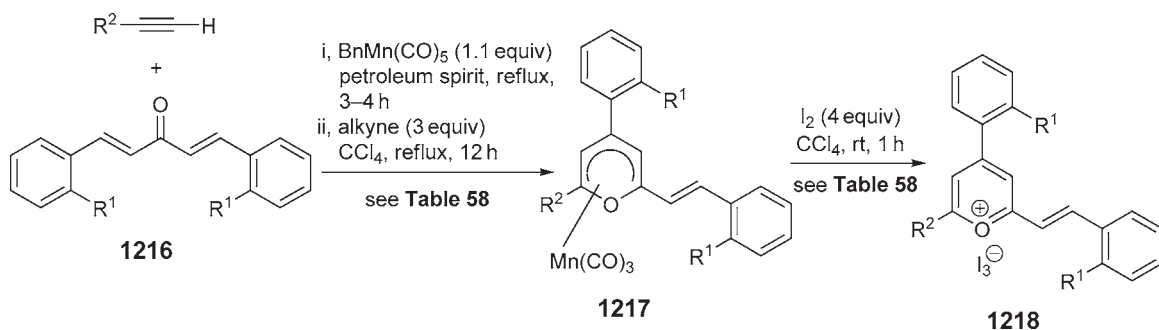


Scheme 296

A [Mn(CO)₅] mediated condensation of methyl propiolate and 1,2-diphenylethyne affords the organometallic pyrylium ion complex **1215** in poor yield (Equation 467) <2002OM3434>.



1,5-Diphenylpenta-1,4-dien-3-ones **1216** undergo cyclometalation with benzylpentacarbonylmanganese and the resulting manganese complexes are coupled with terminal alkynes to form [4-phenyl-2-(2-phenylethenyl)pyranyl-η⁵]tricarbonylmanganese complexes **1217**. Demetallation occurs upon treatment with iodine to afford the pyrylium ions **1218** as their triiodide salts in high yield (Scheme 297, Table 58) <2001JOM(633)162>.



Scheme 297

Table 58 Formation of complexes **1217** and their demetalation to afford pyrylium salts **1218** (Scheme 297)

R^1	R^2	Yield 1217 (%)	Yield 1218 (%)
H	TMS	79	78
CF_3	TMS	96	69
CF_3	Ph	70	85

References

- 1971T3085 Y. Hayasi and H. Nozaki, *Tetrahedron*, 1971, **27**, 3085.
 1984CHEC A. R. Katritzky and C. W. Rees; in 'Comprehensive Heterocyclic Chemistry I', Pergamon, Oxford, 1984.
 1991SL553 P. Stoss and P. Merrath, *Synlett*, 1991, 553.
 1993J(P1)2533 D. W. Jones and A. M. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2533.
 1995CC615 M. Tsukayama, H. Utsumi, and A. Kunugi, *J. Chem. Soc., Chem. Commun.*, 1995, 615.
 1995SCR1375 E. Langkopf and D. Schinzer, *Chem. Rev.*, 1995, **95**, 1375.
 1995JOC3270 R. C. Larock, E. K. Yum, M. J. Doty, and K. K. C. Sham, *J. Org. Chem.*, 1995, **60**, 3270.
 1995JOC3397 J. T. North, D. R. Kronenthal, A. J. Pullockaran, S. D. Real, and H. Y. Chen, *J. Org. Chem.*, 1995, **60**, 3397.
 1995J(P1)2551 J. E. Bishop, K. A. Flaxman, B. S. Orlek, P. G. Sammes, and D. J. Weller, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2551.
 1995T3087 Y. R. Lee, *Tetrahedron*, 1995, **51**, 3087.
 1995T10923 A. Kella-Bennani, M. Soufiaoui, A. Kerbal, S. Fkih-Tetouani, and N. Bitit, *Tetrahedron*, 1995, **51**, 10923.
 1995TL6075 A. Kasatkin, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, 1995, **36**, 6075.
 1995TL7859 B. Chantegrel, C. Deshayes, and R. Faure, *Tetrahedron Lett.*, 1995, **36**, 7859.
 1996BML719 H. W. Hamilton, B. D. Tait, C. Gajda, S. E. Hagen, D. Ferguson, E. A. Lunney, A. Pavlovsky, and P. J. Tummino, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 719.
 1996BML2589 D. Andreotti, T. Rossi, and C. Marchioro, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2589.
 1996CC1077 A. Oku, S. Ohki, T. Yoshida, and K. Kimura, *J. Chem. Soc., Chem. Commun.*, 1996, 1077.
 1996CC1965 B. C. Ranu, S. Bhar, A. Patra, N. P. Nayak, and M. Mukherjee, *J. Chem. Soc., Chem. Commun.*, 1996, 1965.
 1996CC2747 H. Van Rensburg, P. S. Van Heerden, B. C. B. Bezuidenhoudt, and D. Ferreira, *J. Chem. Soc., Chem. Commun.*, 1996, 2747.
 1996CHEC-II A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds; In 'Comprehensive Heterocyclic Chemistry II' Pergamon, Oxford, 1996.
 1996CL889 S. Inoue, M. Asami, K. Honda, and H. Miyazaki, *Chem. Lett.*, 1996, 889.
 1996CTC229 C. J. Burns and D. S. Middleton, *Contemp. Org. Synth.*, 1996, **3**, 229.
 1996H(43)751 M. R. Saidi, R. Zadmand, and T. Saberi, *Heterocycles*, 1996, **43**, 751.
 1996HCA1899 D. Enders, K. Breuer, J. Runsink, and J. H. Teles, *Helv. Chim. Acta*, 1996, **79**, 1899.
 1996HCO251 A. M. S. Silva, H. R. Tavares, and J. A. S. Cavaleiro, *Heterocycl. Commun.*, 1996, **2**, 251.
 1996JA2208 S. Okamoto, A. Kasatkin, P. K. Zubaidha, and F. Sato, *J. Am. Chem. Soc.*, 1996, **118**, 2208.
 1996JA3301 R. H. Schlessinger and Y.-J. Li, *J. Am. Chem. Soc.*, 1996, **118**, 3301.
 1996JA6305 B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 1996, **118**, 6305.
 1996JA7634 H. Kai, K. Iwamoto, N. Chatani, and S. Murai, *J. Am. Chem. Soc.*, 1996, **118**, 7634.
 1996JA10333 M. Palucki, J. P. Wolfe, and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 10333.
 1996JA10954 T. Herberich and H. D. Roth, *J. Am. Chem. Soc.*, 1996, **118**, 10954.
 1996JA12473 L. Sun and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1996, **118**, 12473.
 1996JOC455 P. P. Deshpande, K. N. Price, and D. C. Baker, *J. Org. Chem.*, 1996, **61**, 455.
 1996JOC459 J. S. Swenton, J. N. Freskos, P. Dalidowicz, and M. L. Kerns, *J. Org. Chem.*, 1996, **61**, 459.
 1996JOC677 M. Ihara, A. Katsumata, F. Setsu, Y. Tokunaga, and K. Fukumoto, *J. Org. Chem.*, 1996, **61**, 677.
 1996JOC1493 J. R. Hwu, Y. S. Wein, and Y.-J. Leu, *J. Org. Chem.*, 1996, **61**, 1493.

- 1996JOC3183 S. Superchi, F. Minutolo, P. Filippo, and P. Salvadori, *J. Org. Chem.*, 1996, **61**, 3183.
1996JOC3715 N. J. Sisti, I. A. Motorina, M.-E. T. H. Dau, C. Riche, F. W. Fowler, and D. S. Grierson, *J. Org. Chem.*, 1996, **61**, 3715.
1996JOC4391 A. Nath, J. Mal, and R. V. Venkateswaran, *J. Org. Chem.*, 1996, **61**, 4391.
1996JOC4880 P. A. Evans, J. D. Roseman, and L. T. Garber, *J. Org. Chem.*, 1996, **61**, 4880.
1996JOC4913 U. Azzena, S. Demartis, and G. Melloni, *J. Org. Chem.*, 1996, **61**, 4913.
1996JOC5818 M. C. de la Fuente, L. Castedo, and D. Domínguez, *J. Org. Chem.*, 1996, **61**, 5818.
1996JOC6484 T. Ishikawa, Y. Oku, K.-I. Kotake, and H. Ishii, *J. Org. Chem.*, 1996, **61**, 6484.
1996JOC6673 D. Nicoletti, A. A. Ghini, and G. Burton, *J. Org. Chem.*, 1996, **61**, 6673.
1996JOC9084 S. K. Taylor, N. H. Chmiel, L. J. Simons, and J. R. Vyvyan, *J. Org. Chem.*, 1996, **61**, 9084.
1996JOC9164 J. Mal, A. Nath, and R. V. Venkateswaran, *J. Org. Chem.*, 1996, **61**, 9164.
1996J(P1)151 E. J. Bush and D. W. Jones, *J. Chem. Soc., Perkin Trans. 1.*, 1996, 151.
1996J(P1)413 T. Kamada, Ge-Qing, M. Abe, and A. Oku, *J. Chem. Soc., Perkin Trans. 1.*, 1996, 413.
1996J(P1)967 M. G. Branwell, C. T. Bui, H. T. T. Pham, and G. W. Simpson, *J. Chem. Soc., Perkin Trans. 1.*, 1996, 967.
1996J(P1)1435 G. Impellizzeri, G. Pappalardo, E. Rizzarelli, and C. Tringali, *J. Chem. Soc., Perkin Trans. 1.*, 1996, 1435.
1996J(P1)2241 R. G. F. Giles, R. W. Rickards, and B. S. Senanayake, *J. Chem. Soc., Perkin Trans. 1.*, 1996, 2241.
1996J(P1)2249 P. A. Procopiou, A. C. Brodie, M. J. Deal, D. F. Hayman, and G. M. Smith, *J. Chem. Soc., Perkin Trans. 1.*, 1996, 2249.
1996J(P1)2799 J. Löffler and R. Schobert, *J. Chem. Soc., Perkin Trans. 1.*, 1996, 2799.
1996J(P2)307 R. Beddoes, D. Heyes, R. S. Menon, C. Ian, and F. Watt, *J. Chem. Soc., Perkin Trans. 2.*, 1996, 307.
1996LA171 R. W. Saalfrank, A. Welch, M. Haubner, and U. Bauer, *Liebigs Ann. Chem.*, 1996, 171.
1996PHC(8)277 J. D. Hepworth and B. M. Heron, in 'Progress in Heterocyclic Chemistry', H. Suschitzky and G. Gribble, Eds.; Elsevier, Amsterdam, 1996, vol. 8, p. 277.
1996S297 I. E. Marko and D. J. Bayston, *Synthesis*, 1996, 297.
1996S307 C. J. Roxburgh, *Synthesis*, 1996, 307.
1996SL57 D. P. Becker and D. L. Flynn, *Synlett*, 1996, 57.
1996SL568 A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, and P. Pace, *Synlett*, 1996, 568.
1996T1473 M. Jonassohn, O. Sterner, and H. Anke, *Tetrahedron*, 1996, **52**, 1473.
1996T5907 G.-Q. Lin and W.-C. Xu, *Tetrahedron*, 1996, **52**, 5907.
1996T7779 G. L. Edwards, C. A. Muldoon, and D. J. Sinclair, *Tetrahedron*, 1996, **52**, 7779.
1996T8535 K. Mallareddy and S. P. Rao, *Tetrahedron*, 1996, **52**, 8535.
1996T9427 K. Nakatani, A. Okamoto, and I. Saito, *Tetrahedron*, 1996, **52**, 9427.
1996T14273 K. Singh, J. Singh, and H. Singh, *Tetrahedron*, 1996, **52**, 14273.
1996TA797 G. Brogini, F. Folcio, N. Sardone, M. Sonzogni, and G. Zecchi, *Tetrahedron Asymmetry*, 1996, **7**, 797.
1996TL141 N. A. Petasis and S.-P. Lu, *Tetrahedron Lett.*, 1996, **37**, 141.
1996TL213 T. Nakata, S. Nomura, and H. Matsukura, *Tetrahedron Lett.*, 1996, **37**, 213.
1996TL371 J.-P. Surivet, J. Gore, and J.-M. Vatele, *Tetrahedron Lett.*, 1996, **37**, 371.
1996TL1331 R. H. Schlessinger and K. W. Gillman, *Tetrahedron Lett.*, 1996, **37**, 1331.
1996TL2433 T. Takahashi, H. Tanaka, A. Matsuda, H. Yamada, T. Matsumoto, and Y. Sugiura, *Tetrahedron Lett.*, 1996, **37**, 2433.
1996TL2441 T. Muraki, H. Togo, and M. Yokoyama, *Tetrahedron Lett.*, 1996, **37**, 2441.
1996TL2463 T. Tsunoda, F. Ozaki, N. Shirakata, Y. Tamaoka, H. Yamamoto, and S. Ito, *Tetrahedron Lett.*, 1996, **37**, 2463.
1996TL3059 I. Kadota, D. Hatakeyama, K. Seki, and Y. Yamamoto, *Tetrahedron Lett.*, 1996, **37**, 3059.
1996TL4179 K. Seto, K. Yoshida, S. Yoshida, T. Shimizu, H. Seki, and M. Hoshino, *Tetrahedron Lett.*, 1996, **37**, 4179.
1996TL4555 K. Kaneda and T. Yamashita, *Tetrahedron Lett.*, 1996, **37**, 4555.
1996TL4675 F. E. McDonald and J. L. Bowman, *Tetrahedron Lett.*, 1996, **37**, 4675.
1996TL5073 V. B. Birman, A. Chopra, and C. A. Ogle, *Tetrahedron Lett.*, 1996, **37**, 5073.
1996TL5221 D. Neville and W. S. Murphy, *Tetrahedron Lett.*, 1996, **37**, 5221.
1996TL6499 F. J. Zawacki and M. T. Crimmins, *Tetrahedron Lett.*, 1996, **37**, 6499.
1996TL8001 M. G. Dhara, S. K. De, and A. K. Mallik, *Tetrahedron Lett.*, 1996, **37**, 8001.
1997CC173 E. Fernandez, M. W. Hooper, F. I. Knight, and J. M. Brown, *J. Chem. Soc., Chem. Commun.*, 1997, 173.
1997CC447 C. Einhorn, J. Einhorn, C. Marcadal, and J.-L. Pierre, *J. Chem. Soc., Chem. Commun.*, 1997, 447.
1997CC1139 A. Pommier and P. J. Kocienski, *J. Chem. Soc., Chem. Commun.*, 1997, 1139.
1997CC1755 N. Maezaki, Y. Matsumori, T. Shogaki, M. Soejima, T. Tanaka, H. Ohishi, and C. Iwata, *J. Chem. Soc., Chem. Commun.*, 1997, 1755.
1997CC1867 M. A. Tius, J. Busch-Petersen, and A. R. Marris, *J. Chem. Soc., Chem. Commun.*, 1997, 1867.
1997CC1973 S. Kohmoto, H. Yajima, S. Takami, K. Kishikawa, M. Yamamoto, and K. Yamada, *J. Chem. Soc., Chem. Commun.*, 1997, 1973.
1997CC2259 M. Banwell, B. Flynn, and D. Hockless, *J. Chem. Soc., Chem. Commun.*, 1997, 2259.
1997CEJ849 Y. Mori, *Chem.-Eur. J.*, 1997, **3**, 849.
1997CL1103 M. Miura, T. Tsuda, T. Satoh, and M. Nomura, *Chem. Lett.*, 1997, 1103.
1997CTC238 M. C. Elliott, *Contemp. Org. Synth.*, 1997, **4**, 238.
1997H(45)37 T. B. Kim, N. K. Park, C. S. Chwang, S. Myong, and I. H. Jeong, *Heterocycles*, 1997, **45**(1), 37.
1997H(45)555 R. Toplak, L. Selic, G. Sorsak, and B. Stanovnik, *Heterocycles*, 1997, **45**(3), 555.
1997H(45)1131 M. Tsukayama, H. Utsumi, A. Kunugi, and H. Nozaki, *Heterocycles*, 1997, **45**(6), 1131.
1997H(45)2273 T. Ishikawa and C. Miwa, *Heterocycles*, 1997, **45**(11), 2273.
1997H(46)61 T. Harayama and H. Yasuda, *Heterocycles*, 1997, **46**, 61.
1997JA1488 J. P. A. Harrity, M. S. Visser, J. D. Gleason, and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1997, **119**, 1488.
1997JA4404 K.-W. Liang, W.-T. Li, S.-M. Peng, S.-L. Wang, and R. Shung, *J. Am. Chem. Soc.*, 1997, **119**, 4404.
1997JA5063 Y. Uozumi, K. Kato, and T. Hayashi, *J. Am. Chem. Soc.*, 1997, **119**, 5063.
1997JA6787 R. A. Widenhoefer, H. A. Zhong, and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 6787.
1997JA7897 P. A. Wender, K. D. Rice, and M. E. Schnute, *J. Am. Chem. Soc.*, 1997, **119**, 7897.
1997JA10537 Y. S. Park, G. A. Weisenburger, and P. Beak, *J. Am. Chem. Soc.*, 1997, **119**, 10537.
1997JBS229 M. Z. B. Bezerra, M. I. L. Machado, S. M. De Morais, and R. Braz-Filho, *J. Braz. Chem. Soc.*, 1997, **8**, 229-234.

- 1997JME4235 R. E. Mewshaw, J. Kavavagh, G. Stack, K. L. Marquis, X. Shi, M. Z. Kagan, M. B. Webb, A. H. Katz, A. Park, Y. H. Kang, M. Abou-Gharbia, R. Scerni, T. Wasik, L. Cortes-Burgos, T. Spanglaer, J. A. Brennan, M. Piesla, H. Mazandarani, M. I. Cockett, R. Ochalski, J. Coupet, and T. H. Andree, *J. Med. Chem.*, 1997, **40**, 4235.
- 1997JOC2 D. D. Hennings, S. Iwasa, and V. H. Rawal, *J. Org. Chem.*, 1997, **62**, 2.
- 1997JOC182 M. Eriksson, T. Iliefski, M. Nilsson, and T. Olsson, *J. Org. Chem.*, 1997, **62**, 182.
- 1997JOC737 P. Livant, T. R. Webb, and W. Xu, *J. Org. Chem.*, 1997, **62**, 737.
- 1997JOC1183 R. E. Smith and N. G. J. Richards, *J. Org. Chem.*, 1997, **62**, 1183.
- 1997JOC1196 K. J. McRae and M. A. Rizzacasa, *J. Org. Chem.*, 1997, **62**, 1196.
- 1997JOC2273 R. L. Dorta, A. Martin, E. Suarez, and C. Betancor, *J. Org. Chem.*, 1997, **62**, 2273.
- 1997JOC3426 C. Semeyn, R. H. Blaauw, H. Heimstra, and W. N. Speckamp, *J. Org. Chem.*, 1997, **62**, 3426.
- 1997JOC4584 M. A. Ramirez, J. M. Padron, J. M. Palazon, and V. S. Martin, *J. Org. Chem.*, 1997, **62**, 4584.
- 1997JOC5982 D. Crich and X. Hao, *J. Org. Chem.*, 1997, **62**, 5982.
- 1997JOC6503 Y. Xu and W. R. Dolbier, Jr., *J. Org. Chem.*, 1997, **62**, 6503.
- 1997JOC6575 J. L. Marco, *J. Org. Chem.*, 1997, **62**, 6575.
- 1997JOC6888 D. H. Hua, Y. Chen, H.-S. Sig, M. J. Maroto, P. D. Robinson, S. W. Newell, E. M. Perchellet, J. B. Ladesich, J. A. Freeman, J.-P. Perchellet, and P. K. Chiang, *J. Org. Chem.*, 1997, **62**, 6888.
- 1997JOC7024 F. Bigi, S. Carloni, R. Maggi, C. Muchetti, and G. Sartori, *J. Org. Chem.*, 1997, **62**, 7024.
- 1997JOC7439 I. Kadota, M. Kawada, V. Gevorgyan, and Y. Yamamoto, *J. Org. Chem.*, 1997, **62**, 7439.
- 1997JOC8198 A. R. Katritzky, P. Czerney, and J. R. Levell, *J. Org. Chem.*, 1997, **62**, 8198.
- 1997JOC8361 A. Ogawa, H. Kuniyasu, N. Sonoda, and T. Hirao, *J. Org. Chem.*, 1997, **62**, 8361.
- 1997JOC8767 N. A. Noureldin, D. Zhao, and D. G. Lee, *J. Org. Chem.*, 1997, **62**, 8767.
- 1997J(P1)787 H. Togo, T. Muraki, Y. Hoshina, K. Yamaguchi, and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1.*, 1997, 787.
- 1997J(P1)1819 C. D. Gabbutt, J. D. Hepworth, M. W. J. Urquhart, and L. M. Vazquez de Miguel, *J. Chem. Soc., Perkin Trans. 1.*, 1997, 1819.
- 1997J(P1)1875 K. Subburaj, M. G. Muruges, and G. K. Trivedi, *J. Chem. Soc., Perkin Trans. 1.*, 1997, 1875.
- 1997J(P1)2167 K. Ghosh, S. Bhattacharyya, and A. Patra, *J. Chem. Soc., Perkin Trans. 1.*, 1997, 2167.
- 1997J(P2)1055 C. Aliaga, J. S. Galdames, and M. C. Rezende, *J. Chem. Soc., Perkin Trans. 2.*, 1997, 1055.
- 1997JME3707 S. E. Hagen, J. V. N. V. Prasad, F. E. Boyer, J. M. Domagala, E. L. Ellsworth, C. Gajda, H. W. Hamilton, L. J. Markoski, B. A. Steinbaugh, B. D. Tait, E. A. Lunney, P. J. Tummino, D. Ferguson, D. Hupe, C. Nouhan, S. J. Gracheck, J. M. Saunders, and S. VanderRoest, *J. Med. Chem.*, 1997, **40**, 3707.
- 1997LA887 L. F. Tietze, O. Burkhardt, and M. Henrich, *Liebigs Ann. Chem.*, 1997, 887.
- 1997NPR465 A. Estevez-Braun and A. G. Gonzalez, *Nat. Prod. Rep.*, 1997, **14**, 465.
- 1997OPP631 E. Napolitano, *Org. Prep. Proced. Int.*, 1997, **29**, 631.
- 1997PHC(9)289 J. D. Hepworth and B. M. Heron, in 'Progress in Heterocyclic Chemistry', G. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 1997, vol. 9, p. 289.
- 1997S23 K. Orito, T. Hatakeyama, M. Takeo, H. Suginome, and M. Tokuda, *Synthesis*, 1997, 23.
- 1997S195 C. Riva, C. De Toma, L. Donadel, C. Boi, R. Pennini, G. Motta, and A. Leonardi, *Synthesis*, 1997, 195.
- 1997S628 A. Barbero, C. Garcia, B. Gonzalez, F. J. Pulido, and J. A. Rincon, *Synthesis*, 1997, 628.
- 1997S685 C. M. Moorhoff, *Synthesis*, 1997, 685.
- 1997S877 L. F. Tietze and J. Grlitzer, *Synthesis*, 1997, 877.
- 1997S931 G. Speranza, A. De Meo, S. Zanzola, G. Fontana, and P. Manitto, *Synthesis*, 1997, 931.
- 1997S937 M. Yamamoto, M. Hirota, K. Kishikawa, S. Kohmoto, and K. Yamada, *Synthesis*, 1997, 937.
- 1997SL551 S. Kobayashi and M. Moriwaki, *Synlett*, 1997, 551.
- 1997SL1047 L. Ollero, L. Castedo, and D. Dominguez, *Synlett*, 1997, 1047.
- 1997SL1081 O. B. Familoni, I. Ionica, J. F. Bower, and V. Snieckus, *Synlett*, 1997, 1081.
- 1997SL1318 D. C. Craig, G. L. Edwards, and C. A. Muldoon, *Synlett*, 1997, 1318.
- 1997T8491 A. J. Burke and W. I. O'Sullivan, *Tetrahedron*, 1997, **53**, 8491.
- 1997T9755 P. Bovicelli, A. Sanetti, R. Bernini, and P. Lupattelli, *Tetrahedron*, 1997, **53**, 9755-9760.
- 1997T11803 R. Grigg, J. M. Sandano, V. Santhakumar, V. Sridharan, R. Thangavelanthum, M. Thornton-Pett, and D. Wilson, *Tetrahedron*, 1997, **53**, 11803.
- 1997T14141 H. Van Rensburg, P. S. Van Heerden, B. C. B. Bezuidenhoudt, and D. Ferrera, *Tetrahedron*, 1997, **53**, 14141.
- 1997T14507 A. Nangia, G. Prasuna, and P. B. Rao, *Tetrahedron*, 1997, **53**, 14507.
- 1997T14915 T. Ishikawa, Y. Oku, and K.-I. Kotake, *Tetrahedron*, 1997, **53**, 14915.
- 1997T16817 C. S. Rajesh, T. L. Thanulingham, and S. Das, *Tetrahedron*, 1997, **53**, 16817.
- 1997TL685 J. Berge, S. Claridge, A. Mann, C. Muller, and E. Tyrrell, *Tetrahedron Lett.*, 1997, **38**, 685.
- 1997TL1087 G.-Q. Lin and M. Zhong, *Tetrahedron Lett.*, 1997, **38**, 1087.
- 1997TL2153 B. M. Adger, U. C. Dyer, I. C. Lennon, P. D. Tiffin, and S. E. Ward, *Tetrahedron Lett.*, 1997, **38**, 2153.
- 1997TL2895 I. E. Marko and F. Chelle, *Tetrahedron Lett.*, 1997, **38**, 2895.
- 1997TL2899 I. E. Marko, A. P. Dobbs, V. Scheirmann, F. Chelle, and D. J. Bayston, *Tetrahedron Lett.*, 1997, **38**, 2899.
- 1997TL3193 D. A. Evans, E. A. Shaughnessy, and D. M. Barnes, *Tetrahedron Lett.*, 1997, **38**, 3193.
- 1997TL3267 W. S. Lee and Y. Nagao, *Tetrahedron Lett.*, 1997, **38**, 3267.
- 1997TL3663 L. Sun and L. S. Leibeskind, *Tetrahedron Lett.*, 1997, **38**, 3663.
- 1997TL4651 R. Bernini, E. Minciione, and A. Sanetti, *Tetrahedron Lett.*, 1997, **38**, 4651.
- 1997TL4705 N. Pierson, C. Fernandez-Garcia, and M. A. McKerver, *Tetrahedron Lett.*, 1997, **38**, 4705.
- 1997TL4989 T. Sugioka, E. Yoneda, K. Onitsuka, S.-W. Zhang, and S. Takahashi, *Tetrahedron Lett.*, 1997, **38**, 4989.
- 1997TL5005 K. Nakatani, N. Higashida, and I. Saito, *Tetrahedron Lett.*, 1997, **38**, 5005.
- 1997TL5055 C. B. de Koning, I. R. Green, J. P. Michael, and J. R. Oliveira, *Tetrahedron Lett.*, 1997, **38**, 5055.
- 1997TL5249 P. A. Evans and J. D. Roseman, *Tetrahedron Lett.*, 1997, **38**, 5249.
- 1997TL5501 S. Usse, G. Guillaumet, and M.-C. Viaud, *Tetrahedron Lett.*, 1997, **38**, 5501.
- 1997TL5579 J. H. Dritz and E. M. Carreira, *Tetrahedron Lett.*, 1997, **38**, 5579.

- 1997TL5623 H. M. L. Davies and R. L. Calvo, *Tetrahedron Lett.*, 1997, **38**, 5623.
1997TL5959 T. Rosenau and W. D. Habicher, *Tetrahedron Lett.*, 1997, **38**, 5959.
1997TL6379 D. D. Hennings, S. Iwasa, and V. H. Rawal, *Tetrahedron Lett.*, 1997, **38**, 6379.
1997TL6585 B. Hamann-Gaudinet, J.-L. Namy, and H. B. Kagan, *Tetrahedron Lett.*, 1997, **38**, 6585.
1997TL7421 A. R. de Lera and A. Torrado, *Tetrahedron Lett.*, 1997, **38**, 7421.
1997TL7683 F. E. McDonald and A. D. Singhi, *Tetrahedron Lett.*, 1997, **38**, 7683.
1997TL8789 C. A. Hastings, J. D. Riggensberg, and E. M. Carreira, *Tetrahedron Lett.*, 1997, **38**, 8789.
1997TL8985 T. Matsumoto, T. Hamura, Y. Toshiyuki, and K. Suzuki, *Tetrahedron Lett.*, 1997, **38**, 8985.
1997TL9057 C. M. Marson and A. Fallah, *Tetrahedron Lett.*, 1997, **38**, 9057.
1998BCJ723 Y.-S. Lin and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 723.
1998BML1791 R. J. Chambers, G. W. Antognoli, J. B. Cheng, A. Marfat, J. S. Pillar, J. T. Shirley, and J. W. Watson, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1791.
1998CC1639 D. Basavaiah and M. Bakthadoss, *J. Chem. Soc., Chem. Commun.*, 1998, 1639.
1998CC2387 M. Christl, N. Bien, G. Bodedschatz, E. Feineis, J. Hegmann, C. Hofmann, S. Mertelmeyer, J. Ostheimer, F. Samtleben, S. Wehner, E.-M. Peters, K. Peters, M. Pfeiffer, and D. Stalke, *J. Chem. Soc., Chem. Commun.*, 1998, 2387.
1998CL81 K. Fugami, N. Hagiwara, T. Okeda, and M. Kosugi, *Chem. Lett.*, 1998, 81.
1998EJO2031 A. M. S. Silva, D. C. G. A. Pinto, H. R. Tavares, J. A. S. Cavaleiro, M. L. Jimeno, and J. Elguero, *Eur. J. Org. Chem.*, 1998, 2031.
1998JA2343 J. P. A. Harrity, D. S. La, D. R. Cefalo, M. S. Visser, and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1998, **120**, 2343.
1998JA2658 K. Ryter and T. Livinghouse, *J. Am. Chem. Soc.*, 1998, **120**, 2658.
1998JA4246 F. E. McDonald and H. Y. H. Zhu, *J. Am. Chem. Soc.*, 1998, **120**, 4246.
1998JA6611 D. Yang, M.-K. Wong, X.-C. Wang, and Y.-C. Tang, *J. Am. Chem. Soc.*, 1998, **120**, 6611.
1998JA8340 C. W. Johannes, M. S. Visser, G. S. Weatherhead, and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1998, **120**, 8340.
1998JA9074 B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 1998, **120**, 9074.
1998JFC(91)99 W. Cao, W. Ding, T. Huang, H. Huang, and C. Wei, *J. Fluorine Chem.*, 1998, **91**, 99.
1998JME3596 D. J. Drake, R. S. Jensen, J. Busch-Petersen, J. K. Kawakami, M. C. Fernandez-Garcia, A. Makriyannis, and M. A. Tius, *J. Med. Chem.*, 1998, **41**, 3596.
1998JOC144 R. A. Bunce, E. D. Dowdy, R. S. Childress, and P. B. Jones, *J. Org. Chem.*, 1998, **63**, 144.
1998JOC636 P. Livant and W. Xu, *J. Org. Chem.*, 1998, **63**, 636.
1998JOC864 S. Chang and R. H. Grubbs, *J. Org. Chem.*, 1998, **63**, 864.
1998JOC1390 K. B. Wiberg and J. R. Snoonian, *J. Org. Chem.*, 1998, **63**, 1390.
1998JOC1462 A. B. Bueno, W. H. Moser, and L. S. Hegedus, *J. Org. Chem.*, 1998, **63**, 1462-1466.
1998JOC2360 M. C. Hansen, X. Verdager, and S. L. Buchwald, *J. Org. Chem.*, 1998, **63**, 2360.
1998JOC2488 R. S. Mali and K. N. Babu, *J. Org. Chem.*, 1998, **63**, 2488.
1998JOC3798 C. M. Marson, S. Harper, C. A. Oare, and T. Walsgrove, *J. Org. Chem.*, 1998, **63**, 3798.
1998JOC3855 J. Mal and R. V. Venkateswaran, *J. Org. Chem.*, 1998, **63**, 3855.
1998JOC4116 G. J. Quallich, T. W. Makowski, A. F. Sanders, F. J. Urban, and E. Vazquez, *J. Org. Chem.*, 1998, **63**, 4116.
1998JOC5193 H. Togo, Y. Hoshina, T. Muraki, H. Nakayama, and M. Yokoyama, *J. Org. Chem.*, 1998, **63**, 5193.
1998JOC5211 M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art, and M. Nomura, *J. Org. Chem.*, 1998, **63**, 5211.
1998JOC6096 M. Suginome, T. Iwanami, and Y. Ito, *J. Org. Chem.*, 1998, **63**, 6096.
1998JOC7289 K.-W. Liang, M. Chandrasekharan, C.-L. Li, and R. Shung, *J. Org. Chem.*, 1998, **63**, 7289.
1998JOC8038 R. S. Varma and R. Dahiya, *J. Org. Chem.*, 1998, **63**, 8038.
1998JOC9089 R. H. Schlessinger and L. H. Pettus, *J. Org. Chem.*, 1998, **63**, 9089.
1998JOC9156 S. Ma and B. Xu, *J. Org. Chem.*, 1998, **63**, 9156.
1998JOC9580 R. E. Taylor, G. M. Galvin, K. A. Hilfiker, and Y. Chen, *J. Org. Chem.*, 1998, **63**, 9580.
1998JOC9597 S. Quideau, L. Pouysegue, and M. A. Looney, *J. Org. Chem.*, 1998, **63**, 9597.
1998J(P1)477 E. Yoneda, T. Sugioka, K. Hirao, S.-W. Zhang, and S. Takahashi, *J. Chem. Soc., Perkin Trans. 1*, 1998, 477.
1998J(P1)633 Y. H. Kim, Y. Kim, and J. Y. Kim, *J. Chem. Soc., Perkin Trans. 1*, 1998, 633.
1998J(P1)1427 A. Mann, C. Muller, and E. Tyrrell, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1427.
1998J(P1)1547 C. D. Gabbutt, J. D. Hepworth, M. W. J. Urquhart, and L. M. Vazquez de Miguel, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1547.
1998J(P1)2031 T. T. Tidwell, F. Samtleben, and M. Christl, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2031.
1998J(P1)4175 M. C. Elliott, *J. Chem. Soc., Perkin Trans. 1*, 1998, 4175.
1998PHC(10)292 J. D. Hepworth and B. M. Heron, in 'Progress in Heterocyclic Chemistry', G. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 1998, vol. 10, p. 292.
1998S167 A. Goel, P. Srivastava, M. Nath, and V. Ram, *Synthesis*, 1998, 167.
1998S256 A. M. Bernard, M. T. Cocco, V. Onnis, and P. P. Piras, *Synthesis*, 1998, 256.
1998S279 B. A. Chauder, C. C. Lopes, R. S. C. Lopes, A. J. M. da Silva, and V. Sneckus, *Synthesis*, 1998, 279.
1998S301 F. Bigi, S. Carloni, R. Maggi, C. Muchetti, M. Rastelli, and G. Sartori, *Synthesis*, 1998, 301.
1998S1793 A. Pelter, R. S. Ward, and J. L. Whalley, *Synthesis*, 1998, 1793.
1998SL61 S. A. Eastham, J. Herbert, J. E. Painter, P. Patel, and P. Quayle, *Synlett*, 1998, 61.
1998SL259 K. Mori, G. Audran, and H. Monti, *Synlett*, 1998, 259.
1998SL522 R. C. Larock, L. Wei, and T. R. Hightower, *Synlett*, 1998, 522.
1998SL679 S. Inoue, M. Asami, K. Honda, K. S. Shrestha, M. Takahashi, and T. Yoshino, *Synlett*, 1998, 679.
1998SL748 X. Han and R. C. Larock, *Synlett*, 1998, 748.
1998SL888 S. Cacchi, G. Fabrizzi, R. C. Larock, P. Pace, and V. Reddy, *Synlett*, 1998, 888.
1998SL1141 D. W. Knight and P. B. Little, *Synlett*, 1998, 1141.
1998SL1381 D. Craig, M. J. Robson, and S. J. Shaw, *Synlett*, 1998, 1381.
1998T823 C. Mukai, Y. Sugimoto, Y. Ikeda, and M. Hanaoka, *Tetrahedron*, 1998, **54**, 823.
1998T2161 P. Kumar and K. Saravanan, *Tetrahedron*, 1998, **54**, 2161.
1998T2595 D. Brown, R. Grigg, V. Sridharan, V. Tambyrajah, and M. Thornton-Pett, *Tetrahedron*, 1998, **54**, 2595.

- 1998T2819 V. I. Tyvorskii, D. N. Bobrov, O. G. Kulinkovich, N. De Kimpe, and K. A. Tehrani, *Tetrahedron*, 1998, **54**, 2819.
1998T6457 F. Léost, B. Chantegrel, and C. Deshayes, *Tetrahedron*, 1998, **54**, 6457.
1998T8975 K. Uchida, H. Watanabe, and T. Kitahara, *Tetrahedron*, 1998, **54**, 8975.
1998T10329 E. Winter and D. Hoppe, *Tetrahedron*, 1998, **54**, 10329.
1998T11613 P. De March, M. El Arrad, M. Figueredo, and J. Font, *Tetrahedron*, 1998, **54**, 11613.
1998TA949 J. Dupont and A. J. Donato, *Tetrahedron Asymmetry*, 1998, **9**, 949.
1998TL213 N. I. Totah and D. Chen, *Tetrahedron Lett.*, 1998, **39**, 213.
1998TL237 R. C. Larock, H. Yang, P. Pace, S. Cacchi, and G. Fabrizi, *Tetrahedron Lett.*, 1998, **39**, 237.
1998TL435 M. Gardiner, R. Grigg, V. Sridharan, and N. Vicker, *Tetrahedron Lett.*, 1998, **39**, 435.
1998TL1223 K. Itami, A. Palmgren, and J.-E. Backvall, *Tetrahedron Lett.*, 1998, **39**, 1223.
1998TL1385 N. H. Lee, C.-S. Lee, and D.-S. Jung, *Tetrahedron Lett.*, 1998, **39**, 1385.
1998TL2339 Y. Matsumura, K. Shirai, T. Maki, Y. Itakura, and Y. Kodera, *Tetrahedron Lett.*, 1998, **39**, 2339.
1998TL2391 I. Yavari, R. Heckmat-Shoar, and A. Zonouzi, *Tetrahedron Lett.*, 1998, **39**, 2391.
1998TL2851 M. R. Hallett, J. E. Painter, P. Quayle, and D. Ricketts, *Tetrahedron Lett.*, 1998, **39**, 2851.
1998TL3165 H. Suga, H. Ishida, and T. Ibata, *Tetrahedron Lett.*, 1998, **39**, 3165.
1998TL4139 R. Grigg, V. Sridharan, and M. York, *Tetrahedron Lett.*, 1998, **39**, 4139.
1998TL4983 J. W. Dankwardt, S. M. Dankwardt, and R. H. Sclessinger, *Tetrahedron Lett.*, 1998, **39**, 4983.
1998TL5105 D. W. Knight and P. B. Little, *Tetrahedron Lett.*, 1998, **39**, 5105.
1998TL5061 E. Yoneda, T. Kaneko, S.-W. Zhang, and S. Takahashi, *Tetrahedron Lett.*, 1998, **39**, 5061.
1998TL5713 R. C. Larock, X. Han, and M. J. Doty, *Tetrahedron Lett.*, 1998, **39**, 5713.
1998TL6087 B. T. Watson and G. E. Christiansen, *Tetrahedron Lett.*, 1998, **39**, 6087.
1998TL6751 R. Antonioletti, P. Bovicelli, B. Crescenzi, and P. Lupattelli, *Tetrahedron Lett.*, 1998, **39**, 6751.
1998TL6837 X.-G. Hua, J. T. Mague, and C.-J. Li, *Tetrahedron Lett.*, 1998, **39**, 6837.
1998TL6971 B. De Boeck, N. Herbert, and G. Pattenden, *Tetrahedron Lett.*, 1998, **39**, 6971.
1998TL7271 S. D. Rychnovsky, Y. Hu, and B. Ellsworth, *Tetrahedron Lett.*, 1998, **39**, 7271.
1998TL7625 L. Wang and W. Shen, *Tetrahedron Lett.*, 1998, **39**, 7625.
1998TL7759 A. Bachki, F. Foubelo, and M. Yus, *Tetrahedron Lett.*, 1998, **39**, 7759.
1998TL8237 M. Chakraborty, D. B. McConville, T. Saito, H. Meng, P. L. Rinaldi, C. A. Tessier, and W. J. Youngs, *Tetrahedron Lett.*, 1998, **39**, 8237.
1998TL8803 A. K. Ghosh and J. Cappiello, *Tetrahedron Lett.*, 1998, **39**, 8803.
1998TL9035 K. Chiba, Y. Yamaguchi, and M. Tada, *Tetrahedron Lett.*, 1998, **39**, 9035.
1998TL9215 T. Satoh and T. Kurihara, *Tetrahedron Lett.*, 1998, **39**, 9215.
1998TL9605 Y. Wang and T.-N. Huang, *Tetrahedron Lett.*, 1998, **39**, 9605.
1998TL9623 C. F. Sturino and J. C. Y. Wong, *Tetrahedron Lett.*, 1998, **39**, 9623.
1999AGE2398 A. G. Dossetter, T. F. Jamison, and E. N. Jacobsen, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 2398.
1999AGE3334 K. C. Nicolaou, H. J. Mitchell, H. Suzuki, R. M. Rodríguez, O. Baudoin, and K. C. Fylaktakidou, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 3334.
1999AGE3340 K. C. Nicolaou, R. M. Rodríguez, K. C. Fylaktakidou, H. Suzuki, and H. J. Mitchell, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 3340.
1999AGE3345 K. C. Nicolaou, R. M. Rodríguez, K. C. Fylaktakidou, H. Suzuki, and H. J. Mitchell, *Angew. Chem., Int. Ed. Engl.*, 1999, **38**, 3345.
1999BCJ73 K. S. Shrestha, K. Honda, M. Asami, and S. Inoue, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 73.
1999BCJ2345 Y. Terao, T. Satoh, M. Miura, and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 2345.
1999BMC2775 J. V. N. V. Prasad, F. E. Boyer, J. M. Domagala, E. L. Ellsworth, C. Gajda, H. W. Hamilton, S. E. Hagen, L. J. Markoski, B. A. Steinbaugh, B. D. Tait, C. Humblet, E. A. Lunney, A. Pavlovsky, J. R. Rubin, D. Ferguson, N. Graham, T. Holler, D. Hupe, C. Nouhan, P. J. Tummino, A. Urumov, E. Zeikus, G. Zeikus, S. J. Gracheck, J. M. Saunders, S. VanderRoest, J. Brodfuehrer, K. Iyer, M. Sinz, S. V. Gulnik, and J. W. Erickson, *Bioorg. Med. Chem.*, 1999, **7**, 2775.
1999BML2019 E. L. Ellsworth, J. Domagala, J. V. N. V. Prasad, S. Hagen, D. Ferguson, T. Holler, D. Hupe, N. Graham, C. Nouhan, P. J. Tummino, G. Zeikus, and E. A. Lunney, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2019.
1999CC291 W.-C. Zhang, G. S. Viswanathan, and C.-J. Li, *J. Chem. Soc., Chem. Commun.*, 1999, 291.
1999CC691 K. Chiba, T. Hirano, Y. Kitano, and M. Tada, *J. Chem. Soc., Chem. Commun.*, 1999, 691.
1999CC701 D. Enders, J. Vazquez, and G. Raabe, *J. Chem. Soc., Chem. Commun.*, 1999, 701.
1999CC805 M.-C. P. Yeh, L.-W. Chuang, Y.-S. Hsieh, and M.-S. Tsai, *J. Chem. Soc., Chem. Commun.*, 1999, 805.
1999CC1005 H. Uno, K. Sakamoto, E. Honda, and N. Ono, *J. Chem. Soc., Chem. Commun.*, 1999, 1005.
1999CC1743 A. K. Ghosh and C. Liu, *J. Chem. Soc., Chem. Commun.*, 1999, 1743.
1999CC2125 B.-C. Hong, H.-I. Sun, and Z.-Y. Chen, *J. Chem. Soc., Chem. Commun.*, 1999, 2125.
1999CEJ3103 F. E. McDonald, *Chem. Eur. J.*, 1999, **5**, 3103.
1999EJO329 E. Blaeser, P. Kolar, D. Fenske, H. Goesmann, and H. Waldmann, *Eur. J. Org. Chem.*, 1999, 329.
1999EJO1449 S. D. Koulouchei, S. A. Haroutounian, C. D. Apostolopoulos, R. K. Chada, and E. A. Couladouros, *Eur. J. Org. Chem.*, 1999, 1449.
1999EJO2007 M. Schmittle, M. K. Ghorai, A. Haeseler, W. Henn, T. Koy, and R. Sollner, *Eur. J. Org. Chem.*, 1999, 2007.
1999GC163 A. Ramani, B. M. Chanda, S. Velu, and S. Sivasanker, *Green Chem.*, 1999, **1**, 163–165.
1999GC243 B. P. Bandgar, L. S. Uppalla, and D. S. Kurule, *Green Chem.*, 1999, **1**, 243.
1999H(51)1101 A. M. Shestopalov, Z. I. Niazimbetova, I. Zukhra, D. H. Evans, and M. E. Niyazymbetov, *Heterocycles*, 1999, **51**(5), 1101.
1999H(51)2881 K. Kobayashi, K. Sakashita, H. Akamatsu, K. Tanaka, M. Uchida, T. Uneda, T. Kitamura, O. Morikawa, and H. Konishi, *Heterocycles*, 1999, **51**(12), 2881.
1999HCA1656 G. Frater, U. Muller, and P. Kraft, *Helv. Chim. Acta*, 1999, **82**, 1656.
1999JA8270 M. Sato, F. Uehara, K. Sato, M. Yamaguchi, and C. Kabuto, *J. Am. Chem. Soc.*, 1999, **121**, 8270.
1999JA1092 M. J. Cloninger and L. E. Overman, *J. Am. Chem. Soc.*, 1999, **121**, 1092.
1999JA10842 B. M. Trost and A. B. Pinkerton, *J. Am. Chem. Soc.*, 1999, **121**, 10842.
1999JA12073 W. Tueckmantel, A. P. Kozikowski, and L. J. Romanczyk, *J. Am. Chem. Soc.*, 1999, **121**, 12073.
1999JEC201 B. Batanero, M. J. Pérez, and F. Barba, *J. Electroanal. Chem.*, 1999, **469**, 201.

- 1999JFC(95)135 W. Cao, W. Ding, R. Liu, T. Huang, and J. Cao, *J. Fluorine Chem.*, 1999, **95**, 135.
- 1999JMO211 S.-W. Zhang, T. Sugioka, and S. Takahashi, *J. Mol. Catal. A.*, 1999, **143**, 211.
- 1999JOC438 B. Kesteleyn, L. Van Puyvelde, and N. De Kimpe, *J. Org. Chem.*, 1999, **64**, 438.
- 1999JOC690 R. P. Hsung, H. C. Shen, C. J. Douglas, C. D. Morgan, S. J. Degen, and L. J. Yao, *J. Org. Chem.*, 1999, **64**, 690.
- 1999JOC1033 F. Bigi, L. Chesini, R. Maggi, and G. Sartori, *J. Org. Chem.*, 1999, **64**, 1033.
- 1999JOC1173 B. Kesteleyn, N. De Kimpe, and L. Van Puyvelde, *J. Org. Chem.*, 1999, **64**, 1173.
- 1999JOC1875 R. C. Larock and X. Han, *J. Org. Chem.*, 1999, **64**, 1875.
- 1999JOC2137 K. J. McCullough, R. Takeuchi, A. Masuyama, and M. Nojima, *J. Org. Chem.*, 1999, **64**, 2137.
- 1999JOC2145 P. Mingo, S. Zhang, and L. S. Liebeskind, *J. Org. Chem.*, 1999, **64**, 2145.
- 1999JOC2982 J. M. Harris, M. D. Keranen, and G. A. O'Doherty, *J. Org. Chem.*, 1999, **64**, 2982.
- 1999JOC3461 D. Bankston, F. Fang, E. Huie, and S. Xie, *J. Org. Chem.*, 1999, **64**, 3461.
- 1999JOC3489 K. Woydowski, B. Ziemer, and J. Liebscher, *J. Org. Chem.*, 1999, **64**, 3489.
- 1999JOC3524 S. Derien, L. Ropartz, J. Le Paih, and P. H. Dixneuf, *J. Org. Chem.*, 1999, **64**, 3524.
- 1999JOC3663 T. Sambaiah, L.-P. Li, D.-J. Huang, C.-H. Lin, D. K. Rayabarapu, and C.-H. Cheng, *J. Org. Chem.*, 1999, **64**, 3663.
- 1999JOC4050 L. K. Casillas and C. A. Townsend, *J. Org. Chem.*, 1999, **64**, 4050.
- 1999JOC4079 A. Padwa, L. Precedo, and M. A. Semones, *J. Org. Chem.*, 1999, **64**, 4079.
- 1999JOC4509 S. P. Shahi, A. Gupta, S. V. Pitre, M. V. R. Reddy, R. Kumareswaran, and Y. D. Vankar, *J. Org. Chem.*, 1999, **64**, 4509.
- 1999JOC4901 J.-Y. Park, I. Kadota, and Y. Yamamoto, *J. Org. Chem.*, 1999, **64**, 4901.
- 1999JOC7312 J. M. Zenner and R. C. Larock, *J. Org. Chem.*, 1999, **64**, 7312.
- 1999JOC8281 A. Fürstner and H. Krause, *J. Org. Chem.*, 1999, **64**, 8281.
- 1999JOC8770 R. C. Larock, M. J. Doty, and X. Han, *J. Org. Chem.*, 1999, **64**, 8770.
- 1999JOC9507 H. Miyazaki, K. Honda, M. Asami, and S. Inoue, *J. Org. Chem.*, 1999, **64**, 9507.
- 1999J(P1)1083 S. D. Broady, J. E. Rexhausen, and E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1083.
- 1999J(P1)1377 I. Collins, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1377.
- 1999J(P1)1713 T. Muraki, H. Togo, and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1713.
- 1999J(P1)1983 A. Nelson and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1983.
- 1999J(P1)3005 C. K. Ghosh, S. Bhattacharyya, C. Ghosh, and A. Patra, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3005.
- 1999J(P1)3039 R. G. F. Giles and C. A. Joll, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3039.
- 1999J(P1)3071 S. R. Graham, J. A. Murphy, and A. R. Kennedy, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3071.
- 1999OL15 J. W. Herndon and J. Zhu, *Org. Lett.*, 1999, **1**, 15.
- 1999OL411 G. E. Keck, X.-Y. Li, and C. E. Knutson, *Org. Lett.*, 1999, **1**, 411.
- 1999OL499 H. Kotsuki, T. Araki, A. Miyazaki, M. Iwasaki, and P. K. Datta, *Org. Lett.*, 1999, **1**, 499.
- 1999OL641 D. M. Bennett, I. Okamoto, and R. L. Danheiser, *Org. Lett.*, 1999, **1**, 641.
- 1999OL909 A. B. Smith, P. R. Verhoest, K. P. Minbiole, and J. J. Lim, *Org. Lett.*, 1999, **1**, 909.
- 1999OL913 A. B. Smith, P. R. Verhoest, K. P. Minbiole, and T. J. Beauchamp, *Org. Lett.*, 1999, **1**, 913–916.
- 1999OL993 G. S. Viswanathan, J. Yang, and C.-J. Li, *Org. Lett.*, 1999, **1**, 993.
- 1999OL1187 L. Perez-Serrano, L. Casarubios, G. Dominguez, and J. Perez-Castells, *Org. Lett.*, 1999, **1**, 1187.
- 1999OL1459 M. A. Brimble, M. R. Nairn, and J. Park, *Org. Lett.*, 1999, **1**, 1459.
- 1999OL1599 Y.-C. Xu, D. T. Kohlman, S. X. Liang, and C. Eriksson, *Org. Lett.*, 1999, **1**, 1599.
- 1999OL1933 J. E. Baldwin, A. V. W. Mayweg, K. Neumann, and G. J. Pritchard, *Org. Lett.*, 1999, **1**, 1933.
- 1999OL1989 J.-L. Hsu, C.-T. Chen, and J.-M. Fang, *Org. Lett.*, 1999, **1**, 1989.
- 1999OL2101 H. Monenschein, G. Sourkouni-Argirusi, K. M. Schubothe, T. O'Hare, and A. Kirschning, *Org. Lett.*, 1999, **1**, 2101.
- 1999OL2129 S. Yamazaki, *Org. Lett.*, 1999, **1**, 2129.
- 1999OL2145 L.-L. Wei, R. P. Hsung, H. Xiong, J. A. Mulder, and N. T. Nkansah, *Org. Lett.*, 1999, **1**, 2145.
- 1999PHC(11)299 J. D. Hepworth and B. M. Heron, in 'Progress in Heterocyclic Chemistry', G. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 1999, vol. 11, p. 299.
- 1999S1145 H. Sashida and A. Kawamukai, *Synthesis*, 1999, 1145.
- 1999S1491 B. M. Trost and N. Asakawa, *Synthesis*, 1999, 1491.
- 1999SL231 B. Weyershausen and K.-H. Doetz, *Synlett*, 1999, 231.
- 1999SL608 A. de la Hoz, A. Moreno, and E. Vázquez, *Synlett*, 1999, 608.
- 1999SL629 D. Enders and J. Vazquez, *Synlett*, 1999, 629.
- 1999SL717 J. Yang and C.-J. Li, *Synlett*, 1999, 717.
- 1999SL1067 G. A. Olah, T. Mathew, M. Farnia, and G. K. S. Prakash, *Synlett*, 1999, 1067.
- 1999SL1663 A. F. Barrero, E. J. Alvarez-Manzaneda, R. Chahboun, and R. Meneses, *Synlett*, 1999, 1663.
- 1999SL1832 P. Dupau, P. Le Gendre, C. Bruneau, and P. H. Dixneuf, *Synlett*, 1999, 1832.
- 1999SL1879 S. C. Schurer and S. Blechert, *Synlett*, 1999, 1879.
- 1999T3843 M. Kanai, Y. Nakagawa, and K. Tomioka, *Tetrahedron*, 1999, **55**, 3843.
- 1999T4969 M. Kotora, M. Ishikawa, F.-Y. Tsai, and T. Takahashi, *Tetrahedron*, 1999, **55**, 4969.
- 1999T5567 F. Bertha, J. Fetter, M. Kajtar-Peredy, and K. Lempert, *Tetrahedron*, 1999, **55**, 5567.
- 1999T7847 P. Audin, N. Piveteau, A.-S. Dussert, and J. Paris, *Tetrahedron*, 1999, **55**, 7847.
- 1999T8169 G. D. Cuny, J. Cao, A. Sidhu, and J. R. Hauske, *Tetrahedron*, 1999, **55**, 8169.
- 1999T13445 G. C. G. Pais, R. A. Fernandes, and P. Kumar, *Tetrahedron*, 1999, **55**, 13445.
- 1999T13735 N. Yu, R. Poulain, A. Tartar, and J.-C. Gesquiere, *Tetrahedron*, 1999, **55**, 13735–13740.
- 1999TA1069 J.-R. Labrosse, C. Poncet, P. Lhoste, and D. Sinou, *Tetrahedron Asymmetry*, 1999, **10**, 1069.
- 1999TA2739 G. Solladie, N. Gehrold, and J. Maignan, *Tetrahedron Asymmetry*, 1999, **10**, 2739.
- 1999TA3467 P. Dupau, C. Bruneau, and P. H. Dixneuf, *Tetrahedron Asymmetry*, 1999, **10**, 3467.
- 1999TA4047 Y. Takaya, T. Senda, H. Kurushima, M. Ogasawara, and T. Hayashi, *Tetrahedron Asymmetry*, 1999, **10**, 4047.
- 1999TL1083 A. K. Ghosh and R. Kawahama, *Tetrahedron Lett.*, 1999, **40**, 1083.
- 1999TL1153 M. Nishizawa, T. Shigaraki, H. Takao, H. Imagawa, and T. Sugihara, *Tetrahedron Lett.*, 1999, **40**, 1153.

- 1999TL1257 R. H. Schlessinger and K. W. Gillman, *Tetrahedron Lett.*, 1999, **40**, 1257.
1999TL1747 S. Kamijo and Y. Yamamoto, *Tetrahedron Lett.*, 1999, **40**, 1747.
1999TL1627 J. Yang, G. S. Viswanathan, and C.-J. Li, *Tetrahedron Lett.*, 1999, **40**, 1627.
1999TL1925 K. Tatsuta, T. Tamura, and T. Mase, *Tetrahedron Lett.*, 1999, **40**, 1925.
1999TL2145 N. Hori, K. Nagasawa, T. Shimizu, and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 2145.
1999TL2165 K. Matsunaka, T. Iwahama, S. Sakaguchi, and Y. Ishii, *Tetrahedron Lett.*, 1999, **40**, 2165.
1999TL2469 A. S. Bhat, J. L. Whetstone, and R. W. Brueggemeier, *Tetrahedron Lett.*, 1999, **40**, 2469.
1999TL2811 N. Hori, H. Matsukura, G. Matsuo, and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 2811.
1999TL2817 J. Blanco-Urgoiti, L. Casarrubios, and J. Perez-Castells, *Tetrahedron Lett.*, 1999, **40**, 2817.
1999TL3037 G. B. De Koning, J. P. Michael, and W. A. L. Van Otterlo, *Tetrahedron Lett.*, 1999, **40**, 3037.
1999TL3293 M. A. McGuire, S. C. Shilcrat, and E. Sorenson, *Tetrahedron Lett.*, 1999, **40**, 3293.
1999TL3777 T. Ishikawa, Y. Oku, T. Tanaka, and T. Kumamoto, *Tetrahedron Lett.*, 1999, **40**, 3777.
1999TL4187 J. Cossy, D. Bauer, and V. Bellota, *Tetrahedron Lett.*, 1999, **40**, 4187.
1999TL4871 R. G. F. Giles, I. R. Green, and C. P. Taylor, *Tetrahedron Lett.*, 1999, **40**, 4871.
1999TL5259 I. E. Marko and J.-M. Plancher, *Tetrahedron Lett.*, 1999, **40**, 5259.
1999TL5315 I. Ungureanu, C. Bologa, S. Chayer, and A. Mann, *Tetrahedron Lett.*, 1999, **40**, 5315.
1999TL6339 M. E. Jung and J. M. MacDougall, *Tetrahedron Lett.*, 1999, **40**, 6339.
1999TL6757 S. Brase, *Tetrahedron Lett.*, 1999, **40**, 6757.
1999TL6761 V. Lokshin, A. Heynderickx, A. Samat, G. Pèpe, and R. Guglielmetti, *Tetrahedron Lett.*, 1999, **40**, 6761.
1999TL6903 L.-L. Wei, H. Xiong, C. J. Douglas, and R. P. Hsung, *Tetrahedron Lett.*, 1999, **40**, 6903.
1999TL7709 R. Grigg, J. P. Major, F. M. Martin, and M. Whittaker, *Tetrahedron Lett.*, 1999, **40**, 7709.
1999TL9243 E. Gras, C. Guillou, and C. Thal, *Tetrahedron Lett.*, 1999, **40**, 9243.
2000ACR325 J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, 2000, **33**, 325.
2000AGE734 K. C. Nicolaou, G.-Q. Cao, and J. A. Pfefferkorn, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 734.
2000AGE739 K. C. Nicolaou, G.-Q. Cao, and J. A. Pfefferkorn, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 739.
2000AGE1937 M. F. Hentemann, J. G. Allen, and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 1937.
2000AGE3558 K. A. Jorgensen, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 3558.
2000AGE4364 M. Christmann, U. Bhatt, M. Quitschalle, E. Claus, and M. Kalesse, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 4364.
2000AGE4615 I. Ungureanu, P. Klotz, and A. Mann, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 4615.
2000AJC341 R. G. F. Giles, I. R. Green, Y. Gruchlik, and F. J. Oosthuizen, *Aus. J. Chem.*, 2000, **53**, 341.
2000AJC571 M. A. Brimble, R. J. Elliott, and J. F. McEwan, *Aus. J. Chem.*, 2000, **53**, 571.
2000ARK909 M. A. Brimble and J. F. McEwan, *ARKIVOC*, 1(6), 909.
2000CC73 T. Hattori, Y. Suzuki, O. Uesugi, S. Oi, and S. Miyano, *J. Chem. Soc., Chem. Commun.*, 2000, 73.
2000CC115 M. Yan, Z.-Y. Zhou, and A. S. C. Chan, *J. Chem. Soc., Chem. Commun.*, 2000, 115.
2000CC933 U. Anwar, R. Grigg, and V. Sridharan, *J. Chem. Soc., Chem. Commun.*, 2000, 933.
2000CC1203 Y.-G. Suh, D.-Y. Shin, K.-H. Min, S.-S. Hyun, J.-K. Jung, and S.-Y. Seo, *J. Chem. Soc., Chem. Commun.*, 2000, 1203.
2000CC1341 D. L. J. Clive, Y. Tao, Y. Bo, Y.-Z. Hu, N. Selvakumar, S. Sun, S. Daigheault, and Y.-J. Wu, *J. Chem. Soc., Chem. Commun.*, 2000, 1341.
2000CC1605 B. Wang, X. Feng, X. Cui, H. Liu, and Y. Jiang, *J. Chem. Soc., Chem. Commun.*, 2000, 1605.
2000CC1675 R. Mutter, E. M. Martin, de la Neva, and M. Wills, *J. Chem. Soc., Chem. Commun.*, 2000, 1675.
2000CC1781 D. J. Fox, D. House, S. Warren, and F. Kerr, *J. Chem. Soc., Chem. Commun.*, 2000, 1781.
2000CC1987 S. Rousset, M. Abarbi, J. Thibonnet, A. Duchêne, and J.-L. Parrain, *J. Chem. Soc., Chem. Commun.*, 2000, 1987.
2000CHE1007 V. G. Kharchenko, N. V. Pchelintseva, L. I. Markova, and O. V. Fedotova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2000, **36**, 1007.
2000CL666 T. Mantani, T. Konno, T. Ishihara, and H. Yamanaka, *Chem. Lett.*, 2000, 666.
2000CEJ123 K. B. Simonsen, N. Svenstrup, M. Robertson, and K. A. Jorgensen, *Chem. Eur. J.*, 2000, **6**, 123.
2000CEJ3887 K. Krohn, P. Frese, and U. Florke, *Chem. Eur. J.*, 2000, **6**, 3887.
2000EJO73 C. Schneider and A. Schuffenhauer, *Eur. J. Org. Chem.*, 2000, 73.
2000EJO893 D. Enders, J. Vazquez, and G. Raabe, *Eur. J. Org. Chem.*, 2000, 893.
2000EJO3223 S. BouzBouz, J.-Y. Goujon, J. Deplanne, and B. Kirschleger, *Eur. J. Org. Chem.*, 2000, 3223.
2000GC245 J. L. Scott and C. L. Raston, *Green Chem.*, 2000, **2**, 245.
2000H(52)85 I.-Y. Jeong, M. Shiro, and Y. Nagao, *Heterocycles*, 2000, **52**(1), 85.
2000H(53)453 T. Ishikawa, *Heterocycles*, 2000, **53**(2), 453.
2000H(53)2601 K. Saito, S. Ando, and Y. Kondo, *Heterocycles*, 2000, **53**(12), 2601.
2000JA1635 D. A. Evans, J. S. Johnson, and E. J. Olhava, *J. Am. Chem. Soc.*, 2000, **122**, 1635.
2000JA3783 A. K. Chatterjee, J. P. Morgan, M. Scholl, and R. H. Grubbs, *J. Am. Chem. Soc.*, 2000, **122**, 3783.
2000JA4304 F. E. McDonald, K. S. Reddy, and Y. Diaz, *J. Am. Chem. Soc.*, 2000, **122**, 4304.
2000JA5043 P. J. Fagan, E. Hauptman, R. Shapiro, and A. Casalnuovo, *J. Am. Chem. Soc.*, 2000, **122**, 5043.
2000JA5877 B. M. Trost, R. E. Brown, and F. D. Toste, *J. Am. Chem. Soc.*, 2000, **122**, 5877.
2000JA6785 A. Fuerstner, H. Szillat, and F. Stelzer, *J. Am. Chem. Soc.*, 2000, **122**, 6785.
2000JA7936 D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, and T. Vojkovsky, *J. Am. Chem. Soc.*, 2000, **122**, 7936.
2000JA9127 G. Bringmann, T. Pabst, P. Henschel, J. Kraus, K. Peters, E.-M. Peters, D. S. Rycroft, and J. D. Connolly, *J. Am. Chem. Soc.*, 2000, **122**, 9127.
2000JA9836 H. Huang and J. S. Panek, *J. Am. Chem. Soc.*, 2000, **122**, 9836.
2000JA10458 J. Yin, I. Llorente, L. A. Villanueva, and L. S. Leibeskind, *J. Am. Chem. Soc.*, 2000, **122**, 10458.
2000JA10470 Z. Wan and S. G. Nelson, *J. Am. Chem. Soc.*, 2000, **122**, 10470.
2000JA10718 Q. Shelby, N. Kataoka, G. Mann, and J. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 10718.
2000JA11027 A. K. Ghosh and Y. Wang, *J. Am. Chem. Soc.*, 2000, **122**, 11027.
2000JA11041 H. Yorimitsu, T. Nakamura, H. Shinokubo, O. Hiroshi, K. Oshima, K. Omoto, and H. Fujimoto, *J. Am. Chem. Soc.*, 2000, **122**, 11041.
2000JA11543 H. Audrain and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2000, **122**, 11543.
2000JA11727 B. M. Trost and A. J. Frontier, *J. Am. Chem. Soc.*, 2000, **122**, 11727.

- 2000JA12907 K. E. Torrance, S.-I. Kuwabe, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 12907.
- 2000JME843 F. E. Boyer, J. V. N. V. Prasad, J. M. Domagala, E. L. Ellsworth, C. Gajda, S. E. Hagen, L. J. Markoski, B. D. Tait, E. A. Lunney, A. Palovsky, D. Ferguson, N. Graham, T. Holler, D. Hupe, C. Nouhan, P. J. Tummino, A. Urumov, E. Zeikus, G. Zeikus, S. J. Gracheck, J. M. Sanders, S. VanderRoest, J. Brodfuehrer, K. Iyer, M. Sinz, S. V. Gulnik, and J. W. Erickson, *J. Med. Chem.*, 2000, **43**, 843.
- 2000JOC583 A. Fougereuse, E. Gonzalez, and R. Brouillard, *J. Org. Chem.*, 2000, **65**, 583.
- 2000JOC635 B. Kesteleyn and N. De Kimpe, *J. Org. Chem.*, 2000, **65**, 635.
- 2000JOC914 S. Usse, G. Guillaumet, and M.-C. Viaud, *J. Org. Chem.*, 2000, **65**, 914.
- 2000JOC1525 S. V. Gagnier and R. C. Larock, *J. Org. Chem.*, 2000, **65**, 1525.
- 2000JOC1873 H.-J. Hamann and J. Leibscher, *J. Org. Chem.*, 2000, **65**, 1873.
- 2000JOC3252 C. Chen and P. S. Mariano, *J. Org. Chem.*, 2000, **65**, 3252.
- 2000JOC3513 L. Perez-Serrano, J. Blanco-Urgoiti, L. Casarrubios, G. Dominguez, and J. Perez-Castells, *J. Org. Chem.*, 2000, **65**, 3513.
- 2000JOC3761 W.-T. Li, M.-H. Pan, Y.-R. Yu, S.-L. Wang, F.-L. Liao, and R.-S. Liu, *J. Org. Chem.*, 2000, **65**, 3761.
- 2000JOC4523 P. A. Evans and T. Manangan, *J. Org. Chem.*, 2000, **65**, 4523.
- 2000JOC4261 H. M. Davies, R. L. Calvo, R. J. Townsend, P. Ren, and R. M. Churchill, *J. Org. Chem.*, 2000, **65**, 4261.
- 2000JOC4487 H. Audrain, J. Thorhauge, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, 2000, **65**, 4487.
- 2000JOC4779 A. K. Ghosh and H. Lei, *J. Org. Chem.*, 2000, **65**, 4779.
- 2000JOC5623 S. Hanessian, A. Gomtsyan, and N. Malek, *J. Org. Chem.*, 2000, **65**, 5623.
- 2000JOC6576 P. E. Harrington, I. A. Stergiades, J. Erickson, A. Makriyannis, and M. A. Tius, *J. Org. Chem.*, 2000, **65**, 6576.
- 2000JOC6761 C. Mukai, S. Yamaguchi, Y. Sugimoto, N. Miyakoshi, E. Kasamatsu, and M. Hanaoka, *J. Org. Chem.*, 2000, **65**, 6761.
- 2000JOC7516 C. Jia, D. Piao, T. Kitamura, and Y. Fujiwara, *J. Org. Chem.*, 2000, **65**, 7516.
- 2000JP1697 M. A. Brimble, M. R. Nairn, and J. S. O. Park, *J. Chem. Soc., Perkin Trans. 1*, 2000, 697.
- 2000JP11291 M. C. Elliott, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1291.
- 2000JP11331 P. T. Kaye and X. W. Nocanda, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1331.
- 2000JP11493 N. Rosas, M. Salmon, P. Sharma, C. Alvarez, R. Ramirez, J.-L. Garcia, and H. Arzoumanian, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1493.
- 2000JP12343 D. W. Knight and P. B. Little, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2343.
- 2000JP12357 P. Kocienski, R. Narquizian, P. Raubo, C. Smith, L. J. Farrugia, K. Muir, and F. T. Boyle, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2357.
- 2000JP13082 S. J. Yadav, B. V. S. Reddy, and S. R. Hashim, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3082.
- 2000JP13188 J. G. Knight, S. W. Ainge, C. A. Baxter, T. P. Eastmann, and S. J. Harwood, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3188.
- 2000JP13732 A. S. Kelkar, R. M. Letcher, K.-K. Cheung, K.-F. Chiu, and G. D. Brown, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3732.
- 2000JP13799 H.-M. Chang and C.-H. Cheng, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3799.
- 2000MOL880 G. Gopalakrishnan, K. Viswanathan, N. D. P. Singh, R. Thirumurugan, S. Raj, S. Shanmuga, and G. Shamuga, *Molecules*, 2000, **5**(6), 880.
- 2000NJC85 D. C. G. A. Pinto, A. M. S. Silva, and J. A. S. Cavaleiro, *New J. Chem.*, 2000, **24**, 85.
- 2000NPR193 D. Ferreira and X.-C. Li, *Nat. Prod. Rep.*, 2000, **17**(2), 193.
- 2000OL389 S. Kreimerman, I. Ryu, S. Minakata, and M. Komatsu, *Org. Lett.*, 2000, **2**, 389.
- 2000OL441 E. Yoneda, T. Kaneko, S.-W. Zhang, K. Onitsuka, and S. Takahashi, *Org. Lett.*, 2000, **2**, 441.
- 2000OL863 D. Balachari and G. A. O'Doherty, *Org. Lett.*, 2000, **2**, 863.
- 2000OL1217 S. D. Rychnovsky and C. R. Thomas, *Org. Lett.*, 2000, **2**, 1217.
- 2000OL1387 Y. R. Lee, J. Y. Suk, and B. S. Kim, *Org. Lett.*, 2000, **2**, 1387.
- 2000OL1765 H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 1765.
- 2000OL1773 C. Wang and H. Kohn, *Org. Lett.*, 2000, **2**, 1773.
- 2000OL2011 C.-K. Sha, Z.-P. Zhan, and F.-S. Wang, *Org. Lett.*, 2000, **2**, 2011.
- 2000OL2133 K. Tanaka, H. Aoki, H. Hosomi, and S. Ohba, *Org. Lett.*, 2000, **2**, 2133.
- 2000OL2189 K. J. Hale, M. G. Hummersone, and G. S. Bhatia, *Org. Lett.*, 2000, **2**, 2189.
- 2000OL2647 B.-C. Hong, Z.-Y. Chen, and W.-H. Chen, *Org. Lett.*, 2000, **2**, 2647.
- 2000OL2861 K. Neimann and R. Neumann, *Org. Lett.*, 2000, **2**, 2861.
- 2000OL2983 J. M. Harris and G. A. O'Doherty, *Org. Lett.*, 2000, **2**, 2983.
- 2000OL3253 J. Mendiola, J. M. Minguez, J. Alvarez-Builla, and J. J. Vaquero, *Org. Lett.*, 2000, **2**, 3253.
- 2000OL3321 Y. Huang and V. H. Rawal, *Org. Lett.*, 2000, **2**, 3321.
- 2000OL3453 G. J. McGarvey, M. W. Stepanian, A. R. Bressette, and M. Sabat, *Org. Lett.*, 2000, **2**, 3453.
- 2000OL3643 D. V. Kadnikov and R. C. Larock, *Org. Lett.*, 2000, **2**, 3643.
- 2000OL3821 P. Kumar and M. S. Bodas, *Org. Lett.*, 2000, **2**, 3821.
- 2000OL4063 Q. Wang and M. G. Finn, *Org. Lett.*, 2000, **2**, 4063.
- 2000P481 J. B. Harborne and C. A. Williams, *Phytochemistry*, 2000, **55**, 481.
- 2000PAC1635 M. A. Brimble, *Pure Appl. Chem.*, 2000, **72**, 1635.
- 2000PHC(12)317 J. D. Hepworth and B. M. Heron; in 'Progress in Heterocyclic Chemistry', G. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 2000, vol. 12, p. 317.
- 2000S123 G. Speranza, C. F. Morelli, and P. Manitti, *Synthesis*, 2000, 123.
- 2000S843 J.-P. Bouillon, D. Saleur, and C. Portella, *Synthesis*, 2000, 843.
- 2000S1091 F.-E. Chen, H. Fu, G. Meng, Y. Cheng, and Y.-L. Hu, *Synthesis*, 2000, 1091.
- 2000S1113 B. A. Kowalczyk, *Synthesis*, 2000, 1113.
- 2000SL161 B. El Ali and H. Alper, *Synlett*, 2000, 161.
- 2000SL245 P. Tascadda and E. Dunach, *Synlett*, 2000, 245.
- 2000SL1052 A. Lambert, J. A. Elings, D. J. Macquarrie, G. Carr, and J. H. Clark, *Synlett*, 2000, 1052.
- 2000T1013 M. A. Berkett, D. W. Knight, P. B. Little, and M. B. Mitchell, *Tetrahedron*, 2000, **56**, 1013.
- 2000T1811 R. W. Draper, B. Hu, R. V. Iyer, X. Li, Y. Lu, M. Rahman, and E. J. Vater, *Tetrahedron*, 2000, **56**, 1811.
- 2000T1937 M. A. Brimble, M. R. Nairn, and H. Prabakaran, *Tetrahedron*, 2000, **56**, 1937.
- 2000T2313 H. Chen, R. Caughey, R. Liu, M. McMills, M. Rupp, W. H. Myers, and W. D. Harman, *Tetrahedron*, 2000, **56**, 2313.

- 2000T2403 W.-C. Zhang and C.-J. Li, *Tetrahedron*, 2000, **56**, 2403.
- 2000T2533 F. Bellina, D. Ciucci, P. Vergamini, and R. Rossi, *Tetrahedron*, 2000, **56**, 2533.
- 2000T3339 R. A. Barrow, R. E. Moore, L.-H. Li, and M. A. Tius, *Tetrahedron*, 2000, **56**, 3339.
- 2000T6259 S. G. Ruf, J. Dietz, and M. Regitz, *Tetrahedron*, 2000, **56**, 6259.
- 2000T7313 V. I. Tyvorskii, D. N. Bobrov, O. G. Kulinkovich, W. Aelterman, and N. De Kimpe, *Tetrahedron*, 2000, **56**, 7313.
- 2000T8375 U. Azzena, S. Demartis, L. Pilo, and E. Piras, *Tetrahedron*, 2000, **56**, 8375.
- 2000T8561 M. Meciarova, S. Toma, and A. Heribanova, *Tetrahedron*, 2000, **56**, 8561.
- 2000T8953 S. Caddick, S. Khan, L. M. Frost, N. J. Smith, S. Cheung, and G. Pairaudeau, *Tetrahedron*, 2000, **56**, 8953.
- 2000TA409 C. Rousseau and O. R. Martin, *Tetrahedron Asymmetry*, 2000, **11**, 409.
- 2000TA2015 M. Jurzak, J. Rabczko, D. Socha, M. Chmielewski, F. Cardona, A. Goti, and A. Brandi, *Tetrahedron Asymmetry*, 2000, **11**, 2015.
- 2000TA4633 T. Tanaka, T. Kumamoto, and T. Ishikawa, *Tetrahedron Asymmetry*, 2000, **11**, 4633.
- 2000TL29 T. P. Thrash, T. D. Welton, and V. Behar, *Tetrahedron Lett.*, 2000, **41**, 29.
- 2000TL583 P. V. Ramachandran, M. V. R. Reddy, and H. C. Brown, *Tetrahedron Lett.*, 2000, **41**, 583.
- 2000TL2171 K. Okuma, T. Hayano, K. Shioji, and H. Matsuyama, *Tetrahedron Lett.*, 2000, **41**, 2171.
- 2000TL2203 C. Qian and L. Wang, *Tetrahedron Lett.*, 2000, **41**, 2203.
- 2000TL2319 A. K. Ghosh and Y. Wang, *Tetrahedron Lett.*, 2000, **41**, 2319.
- 2000TL2523 W. Zhang, *Tetrahedron Lett.*, 2000, **41**, 2523.
- 2000TL2643 H. Miyazaki, Y. Honda, K. Honda, and S. Inoue, *Tetrahedron Lett.*, 2000, **41**, 2643.
- 2000TL3631 R. M. Kanada, T. Taniguchi, and K. Ogasawara, *Tetrahedron Lett.*, 2000, **41**, 3631.
- 2000TL3677 D. Mal, M. Bandyopadhyay, S. K. Ghorai, and K. Datta, *Tetrahedron Lett.*, 2000, **41**, 3677.
- 2000TL3801 P. B. Greer and W. A. Donaldson, *Tetrahedron Lett.*, 2000, **41**, 3801.
- 2000TL4205 J. R. Al Dulayymi, M. S. Baird, H. H. Hussain, B. J. Alhourani, A.-M. Y. Alhabashna, S. J. Coles, and M. B. Hursthouse, *Tetrahedron Lett.*, 2000, **41**, 4205.
- 2000TL5043 L. Leveque, M. Le Blanc, and R. Pastor, *Tetrahedron Lett.*, 2000, **41**, 5043.
- 2000TL5931 S. Kitagaki, M. Yasugahira, M. Anada, M. Nakajima, and S. Hashimoto, *Tetrahedron Lett.*, 2000, **41**, 5931.
- 2000TL5979 R. Doodeman, F. P. J. T. Rutjes, and H. Heimstra, *Tetrahedron Lett.*, 2000, **41**, 5979.
- 2000TL6323 E. K. Dorling, E. Ohler, and J. Mulzer, *Tetrahedron Lett.*, 2000, **41**, 6323.
- 2000TL6781 D. Regas, M. M. Afonso, A. Galindo, and J. A. Palenzuela, *Tetrahedron Lett.*, 2000, **41**, 6781.
- 2000TL6993 N. Yu, J. M. Aramini, M. W. Germann, and Z. Huang, *Tetrahedron Lett.*, 2000, **41**, 6993.
- 2000TL7125 R. Grigg, A. Liu, D. Shaw, S. Suganthan, D. E. Woodall, and G. Yoganathan, *Tetrahedron Lett.*, 2000, **41**, 7125.
- 2000TL7129 R. Grigg, A. Liu, D. Shaw, S. Suganthan, M. L. Washington, D. E. Woodall, and G. Yoganathan, *Tetrahedron Lett.*, 2000, **41**, 7129.
- 2000TL7225 I. E. Marko and B. Leroy, *Tetrahedron Lett.*, 2000, **41**, 7225.
- 2000TL7341 C. Mongin, K. Gruet, N. Lugan, and R. Mathieu, *Tetrahedron Lett.*, 2000, **41**, 7341.
- 2000TL7727 F.-L. Qing and W.-Z. Gao, *Tetrahedron Lett.*, 2000, **41**, 7727.
- 2000TL7925 S.-S. Jew, H.-A. Kim, S.-Y. Bae, J.-H. Kim, and H.-G. Park, *Tetrahedron Lett.*, 2000, **41**, 7925.
- 2000TL7943 J. S. Yadav, B. V. S. Reddy, and T. P. Rao, *Tetrahedron Lett.*, 2000, **41**, 7943.
- 2000TL8069 A. Bhattacharjee and J. K. De Brabander, *Tetrahedron Lett.*, 2000, **41**, 8069.
- 2000TL8655 K. J. Hodgetts, *Tetrahedron Lett.*, 2000, **41**, 8655.
- 2000TL8873 S. Bennabi, K. Narkunan, L. Rousset, D. Bouchu, and M. A. Ciufolini, *Tetrahedron Lett.*, 2000, **41**, 8873.
- 2000TL9323 G. M. Good, M. I. Kemp, and W. J. Kerr, *Tetrahedron Lett.*, 2000, **41**, 9323.
- 2000TL10229 T. Tanaka, T. Kumamoto, and T. Ishikawa, *Tetrahedron Lett.*, 2000, **41**, 10229.
- 2000TL10257 F. Xu, X. Cao, Z. Cao, and L. Zou, *Tetrahedron Lett.*, 2000, **41**, 10257.
- 2001AGE411 K. Sasaki, Y. Kondo, and K. Maruoka, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 411.
- 2001AGE1058 C. Held, R. Frohlich, and P. Metz, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 1058.
- 2001AGE1286 D. K. Rayabarapu, T. Sambiah, and C.-H. Cheng, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 1286.
- 2001AGE3417 R. A. Stavenger and S. L. Schreiber, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3417.
- 2001AGE3600 M. Kimura, A. Ezoe, S. Tanaka, and Y. Tamaru, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3600.
- 2001AGE3653 F. E. Reddy and K. S. Reddy, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3653.
- 2001AGE3667 D. E. Chavez and E. N. Jacobsen, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3667.
- 2001AGE3842 J. Mulzer and E. Ohler, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3842.
- 2001AGE3895 P. A. Wender, G. G. Gamber, and M. J. C. Scano, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3895.
- 2001AGE4055 I. Paterson, D. Y.-K. Chen, M. J. Coster, J. L. Aceña, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson, and R. D. Norcross, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 4055.
- 2001AGE4745 C. Guillou, J.-L. Beunard, E. Gras, and C. Thal, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 4745.
- 2001AJC135 L. W. Deady and C. L. Smith, *Aus. J. Chem.*, 2001, **54**, 135.
- 2001BCJ967 T. Eguchi and Y. Hoshino, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 967.
- 2001BCJ971 Y. Wada, J. Ichikawa, T. Katsume, T. Nohiro, T. Okauchi, and T. Minami, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 971.
- 2001BCJ1115 H. Suga, A. Kakehi, S. Ito, K. Inoue, H. Ishida, and T. Ibata, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 1115.
- 2001BCJ1333 S. Kezuka, T. Mita, N. Ohtsuki, T. Ikeno, and T. Yamada, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 1333.
- 2001BCJ1567 K. Hirano, S. Minakata, and M. Komatsu, *Bull. Chem. Soc. Jpn.*, 2002, **74**, 1567.
- 2001BMC1337 S. A. S. Pope, G. E. Burtin, P. T. Clayton, D. J. Madge, and D. P. R. Muller, *Bioorg. Med. Chem.*, 2001, **9**, 1337.
- 2001CC605 D. L. J. Clive and H. Cheng, *J. Chem. Soc., Chem. Commun.*, 2001, 605.
- 2001CC639 C. Alonso, M. M. Olmstead, M. H. Nantz, and M. J. Kurth, *J. Chem. Soc., Chem. Commun.*, 2001, 639.
- 2001CC835 E. H. Al-Mutairi, S. R. Crosby, J. Darzi, R. A. Hughes, T. J. Simpson, R. W. Smith, C. L. Willis, J. R. Harding, and C. D. King, *J. Chem. Soc., Chem. Commun.*, 2001, 835.
- 2001CC2324 M. Jimenez-Tenorio, P. M. Carmen, P. Valerga, F. J. Moreno-Dorado, F. M. Guerra, and G. M. Massanet, *J. Chem. Soc., Chem. Commun.*, 2001, 2324.
- 2001CEJ2873 H. Sellner, J. K. Karjalainen, and D. Seebach, *Chem. Eur. J.*, 2001, **7**, 2873.

- 2001CEJ3106 B. Breit, R. Winde, T. Mackewitz, P. Paciello, and K. Harms, *Chem. Eur. J.*, 2001, **7**, 3106.
- 2001CL110 T. Sugino and K. Tanaka, *Chem. Lett.*, 2001, 110.
- 2001CL686 A. Itoh, T. Kodama, and Y. Masaki, *Chem. Lett.*, 2001, 686.
- 2001COR571 V. J. Ram and P. Srivastava, *Curr. Org. Chem.*, 2001, **5**, 571.
- 2001EJO2343 C. Reichardt, D. Che, G. Heckenkemper, and G. Schafer, *Eur. J. Org. Chem.*, 2001, 2343.
- 2001EJO2577 E. Dumez, R. Faure, and J.-P. Dulcere, *Eur. J. Org. Chem.*, 2001, 2577.
- 2001EJO2809 M. Yus, F. Foubelo, and J. V. Ferrández, *Eur. J. Org. Chem.*, 2001, 2809.
- 2001EJO4451 C. Fichtner, G. Remennikov, and H. Mayr, *Eur. J. Org. Chem.*, 2001, 4451.
- 2001GC173 R. Maggi, F. Bigi, S. Carloni, A. Mazzacani, and G. Sartori, *Green Chem.*, 2001, **3**, 173.
- 2001HCA117 P. J. Coelho, L. M. Carvalho, J. C. Silva, A. M. F. Oliveira-Campos, A. Samat, and R. Guglielmetti, *Helv. Chim. Acta.*, 2001, **84**, 117.
- 2001JA3842 V. S. Kumar and P. E. Floreancig, *J. Am. Chem. Soc.*, 2001, **123**, 3842.
- 2001JA4601 M. Suginome, Y. Ohmori, and Y. Ito, *J. Am. Chem. Soc.*, 2001, **123**, 4601.
- 2001JA5144 F. P. Marmasater and F. G. West, *J. Am. Chem. Soc.*, 2001, **123**, 5144.
- 2001JA4834 A. B. Smith, P. R. Verhoest, K. P. Minbiole, and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 4834.
- 2001JA5366 M. P. Doyle, I. M. Phillips, and W. Hu, *J. Am. Chem. Soc.*, 2001, **123**, 5366.
- 2001JA7162 B. M. Trost and T. Yasukata, *J. Am. Chem. Soc.*, 2001, **123**, 7162.
- 2001JA8420 D. R. Kopecky and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2001, **123**, 8420.
- 2001JA9974 C. F. Thompson, T. F. Jamison, and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2001, **123**, 9974.
- 2001JA10942 A. B. Smith, K. P. Minbiole, P. R. Verhoest, and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 10942.
- 2001JA11863 A. Fuertsner, F. Stelzer, and H. Szillat, *J. Am. Chem. Soc.*, 2001, **123**, 11863.
- 2001JA12202 S.-I. Kuwabe, K. E. Torrace, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 12202.
- 2001JA12426 A. B. Smith, I. G. Safonov, and R. M. Corbett, *J. Am. Chem. Soc.*, 2001, **123**, 12426.
- 2001JFC(108)125 S. P. Kisil, Y. V. Burgart, V. I. Saloutin, and O. N. Chupakhin, *J. Fluorine Chem.*, 2001, **108**, 125.
- 2001JME2319 S. E. Hagen, J. Domagala, C. Gajda, M. Lovdahl, B. D. Tait, E. Wise, T. Holler, D. Hupe, C. Nouhan, A. Urumov, G. Zeikus, E. Zeikus, E. A. Lunney, A. Pavlovsky, S. J. Gracheck, J. Saunders, S. VanderRoest, and J. Brodfuehrer, *J. Med. Chem.*, 2001, **44**, 2319.
- 2001JME4704 S. M. N. Efange, Z. Tu, K. von Hohenberg, L. Francesconi, R. C. Howell, M. V. Rampersad, L. J. Todaro, R. L. Papke, and M.-P. Kung, *J. Med. Chem.*, 2001, **44**, 4704.
- 2001JOC59 M. Arisawa, N. G. Ramesh, M. Nakajima, H. Tohma, and Y. Kita, *J. Org. Chem.*, 2001, **66**, 59.
- 2001JOC309 K. Sato, T. Yoshimura, M. Shindo, and K. Shishido, *J. Org. Chem.*, 2001, **66**, 309.
- 2001JOC739 X. F. Yang, J. T. Mague, and C. J. Li, *J. Org. Chem.*, 2001, **66**, 739.
- 2001JOC954 D. L. Clive, M. Sannigrahi, and S. Hisaindee, *J. Org. Chem.*, 2001, **66**, 954.
- 2001JOC1049 M. J. McLaughlin and R. P. Hsung, *J. Org. Chem.*, 2001, **66**, 1049.
- 2001JOC1885 U. Bhatt, M. Christmann, M. Quitschalle, E. Claus, and M. Kalesse, *J. Org. Chem.*, 2001, **66**, 1885.
- 2001JOC2175 J. A. Nieman and M. D. Ennis, *J. Org. Chem.*, 2001, **66**, 2175.
- 2001JOC2512 M. V. R. Reddy, A. J. Yucel, and P. V. Ramachandra, *J. Org. Chem.*, 2001, **66**, 2512.
- 2001JOC2429 G. J. ten Brink, J. M. Vis, I. W. Arends, and R. A. Sheldon, *J. Org. Chem.*, 2001, **66**, 2429.
- 2001JOC2692 Q. Zhu, L. Qiao, Y. Wu, and Y. L. Wu, *J. Org. Chem.*, 2001, **66**, 2692.
- 2001JOC3924 T. Okauchi, T. Tanaka, and T. Minami, *J. Org. Chem.*, 2001, **66**, 3924.
- 2001JOC4214 J. Pawlas, P. Vedso, P. Jakobsen, P. O. Huusfeldt, and M. Begtrup, *J. Org. Chem.*, 2001, **66**, 4214.
- 2001JOC4635 T. Ishikawa, M. Okano, T. Aikawa, and S. Saito, *J. Org. Chem.*, 2001, **66**, 4635.
- 2001JOC4679 J. J. Jaber, K. Mitsui, and S. D. Rychnovsky, *J. Org. Chem.*, 2001, **66**, 4679.
- 2001JOC6803 S. R. Ghorpade, U. R. Kalkote, S. P. Chavan, S. R. Bhide, T. Ravindranathan, and V. G. Puranik, *J. Org. Chem.*, 2001, **66**, 6803.
- 2001JOC6988 M. P. DeNinno, C. Eller, and J. B. Etienne, *J. Org. Chem.*, 2001, **66**, 6988.
- 2001JOC7691 K. M. Dawood and T. Fuchigami, *J. Org. Chem.*, 2001, **66**, 7691.
- 2001JOC8106 K.-H. Shen, S.-F. Lush, T.-L. Chen, and R.-S. Liu, *J. Org. Chem.*, 2001, **66**, 8106.
- 2001JOC8685 A. V. Gutnov, V. T. Abaev, A. V. Butin, and A. S. Dmitriev, *J. Org. Chem.*, 2001, **66**, 8685.
- 2001JOC8859 C. A. Cappaccio and O. Varela, *J. Org. Chem.*, 2001, **66**, 8859.
- 2001JOC8973 A. K. Ghosh, Y. Wang, and J. T. Kim, *J. Org. Chem.*, 2001, **66**, 8973.
- 2001JOM(617)444 F. E. McDonald and K. S. Reddy, *J. Organomet. Chem.*, 2001, **617–618**, 444.
- 2001JOM(633)162 W. Tully, L. Main, and B. K. Nicholson, *J. Organomet. Chem.*, 2001, **633**, 162.
- 2001JP11624 M. A. Brimble and T. J. Brenstrum, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1624.
- 2001JP11771 D. W. Knight and P. B. Little, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1771.
- 2001JP11953 V. J. Ram, P. Srivastava, N. Agarwal, A. Sharon, and P. R. Maulik, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1953.
- 2001JP12303 M. C. Elliott and E. Williams, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2303.
- 2001JP12977 K. Kobayashi, M. Uchida, T. Uneda, K. Yoneda, M. Tanmatsu, O. Morikawa, and H. Konishi, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2977.
- 2001JP13017 R. S. Mali, K. N. Babu, and P. G. Jagtap, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3017.
- 2001NJC179 R. Hua and M. Tanaka, *New J. Chem.*, 2001, **25**, 179.
- 2001NPR310 J. B. Harborne and C. A. Williams, *Nat. Prod. Rep.*, 2001, **18**, 310.
- 2001OL13 Y. Kondo, M. Asai, T. Miura, M. Uchiyama, and T. Sakamoto, *Org. Lett.*, 2001, **3**, 13.
- 2001OL755 S. A. Kozmin, *Org. Lett.*, 2001, **3**, 755.
- 2001OL843 N. T. Zaveri, *Org. Lett.*, 2001, **3**, 843.
- 2001OL1383 D. R. Williams, D. C. Ihle, and S. V. Plummer, *Org. Lett.*, 2001, **3**, 1383.
- 2001OL1503 P. Wipf and S. Ribe, *Org. Lett.*, 2001, **3**, 1503.
- 2001OL1693 H. Huang and J. S. Panek, *Org. Lett.*, 2001, **3**, 1693.
- 2001OL2233 J. Cossy, F. Pradaux, and S. BouzBouz, *Org. Lett.*, 2001, **3**, 2233.
- 2001OL2337 H. M. Colquhoun, D. F. Lewis, and D. J. Williams, *Org. Lett.*, 2001, **3**, 2337.
- 2001OL2607 C. J. Lovely, H. Seshadri, B. R. Wayland, and A. W. Cordes, *Org. Lett.*, 2001, **3**, 2607.
- 2001OL2653 A. Itoh, T. Kodama, S. Inagaki, and Y. Masaki, *Org. Lett.*, 2001, **3**, 2653.

- 2001OL2669 T. P. Loh, Q. Y. Hu, K. T. Tan, and H. S. Cheng, *Org. Lett.*, 2001, **3**, 2669.
2001OL2677 A. K. Ghosh, A. Bischoff, and J. Cappiello, *Org. Lett.*, 2001, **3**, 2677.
2001OL2777 T. J. Hunter and G. A. O'Doherty, *Org. Lett.*, 2001, **3**, 2777.
2001OL2919 J. M. Cox and J. D. Rainier, *Org. Lett.*, 2001, **3**, 2919.
2001OL3149 I. Paterson, C. De Savi, and M. Tudge, *Org. Lett.*, 2001, **3**, 3149.
2001OL3815 S. D. Rychnovsky, S. Marumoto, and J. J. Jaber, *Org. Lett.*, 2001, **3**, 3815.
2001OL3875 K. A. Parker and T. L. Mindt, *Org. Lett.*, 2001, **3**, 3875.
2001OL4083 M. T. Reetz, D. Moulin, and A. Gosberg, *Org. Lett.*, 2001, **3**, 4083.
2001OL4275 D. L. Wright, L. C. Usher, and M. Estrella-Jimenez, *Org. Lett.*, 2001, **3**, 4275.
2001PHC(13)317 J. D. Hepworth and B. M. Heron; in 'Progress in Heterocyclic Chemistry', G. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 2001, vol. 13, p. 317.
2001RJO1455 S. P. Kisil, Y. V. Burgart, and V. I. Saloutin, *Russ. J. Org. Chem. (Engl. Transl.)*, 2001, **37**, 1455.
2001SI140 B. A. Chauder, A. V. Kalinin, and V. Snieckus, *Synthesis*, 2001, 140.
2001S735 S. Tollari, G. Palmisano, S. Cenini, G. Cravotto, G. B. Giovenzana, and A. Penoni, *Synthesis*, 2001, 735.
2001SI1356 M. J. Heileman and L. S. Hegedus, *Synthesis*, 2001, 1356.
2001S2247 J.-M. Lee, T.-H. Tseng, and Y.-J. Lee, *Synthesis*, 2001, 2247.
2001SC439 Y. Ishino, M. Milhara, N. Hayakawa, T. Miyata, Y. Kaneko, and T. Miyata, *Synth. Commun.*, 2001, **31**, 439.
2001SC877 C.-W. Kuo and J.-M. Fang, *Synth. Commun.*, 2001, **31**, 877.
2001SC1233 S. Ravichandran, *Synth. Commun.*, 2001, **31**, 1233.
2001SC2589 M. Venkati and G. L. D. Krupadanam, *Synth. Commun.*, 2001, **31**, 2589.
2001SC2613 W. B. Jang, C.-W. Lee, K. Lee, J. W. Sung, and D. Y. Oh, *Synth. Commun.*, 2001, **31**, 2613.
2001SC3603 B. M. Reddy, V. R. Reddy, and D. Giridhar, *Synth. Commun.*, 2001, **31**, 3603.
2001SL96 H.-J. Hamann and J. Leibscher, *Synlett*, 2001, 96.
2001SL138 F. Marion, R. Le Fol, C. Courillon, and M. Malacria, *Synlett*, 2001, 138.
2001SL240 J. S. Yadav, B. V. S. Reddy, R. Srinivas, C. Madhuri, and T. Ramalingam, *Synlett*, 2001, 240.
2001SL955 W. R. Roush and G. J. Dilley, *Synlett*, 2001, 955.
2001SL989 H. Mikoshiba, K. Mikami, and T. Nakai, *Synlett*, 2001, 989.
2001SL1019 A. B. Smith and J. Zheng, *Synlett*, 2001, 1019.
2001SL1030 N. Nakamura, N. Yoshikai, M. Toganoh, and E. Nakamura, *Synlett*, 2001, 1030.
2001SL1042 M. Sugino, T. Iwanami, A. Yamamoto, and Y. Ito, *Synlett*, 2001, 1042.
2001SL1989 J.-M. Vatele, *Synlett*, 2001, 1989.
2001T413 D. M. X. Donnelly, J.-P. Finet, G. P. Guiry, and K. Nesbitt, *Tetrahedron*, 2001, **57**, 413.
2001T845 K. Aikawa, R. Irie, and T. Katsuki, *Tetrahedron*, 2001, **57**, 845.
2001T6793 K. J. Hodgetts, K. I. Maragkou, T. W. Wallace, and R. D. R. Wootton, *Tetrahedron*, 2001, **57**, 6793.
2001T8743 T. V. Rezanka and V. M. Dembitsky, *Tetrahedron*, 2001, **57**, 8743.
2001T1005 U. Beifuss, U. Schniske, and G. Feder, *Tetrahedron*, 2001, **57**, 1005.
2001T1347 S. Brown, S. Clarkson, R. Grigg, W. A. Thomas, V. Sridharan, and D. M. Wilson, *Tetrahedron*, 2001, **57**, 1347.
2001T1395 R. Ballini, G. Bosica, M. L. Conforti, R. Maggi, A. Mazzacani, P. Righi, and G. Sartori, *Tetrahedron*, 2001, **57**, 1395.
2001T2857 F. Bellina, M. Biagetti, A. Carpita, and R. Rossi, *Tetrahedron*, 2001, **57**, 2857.
2001T3383 Y. Wang and S. Zhu, *Tetrahedron*, 2001, **57**, 3383.
2001T4133 F. Lieb, J. Benet-Buchholz, T. Fäcke, R. Fischer, A. Graff, I. M. Lefebvre, and J. Stetter, *Tetrahedron*, 2001, **57**, 4133.
2001T5533 K. Mori, S. Yamamura, and S. Nishiyama, *Tetrahedron*, 2001, **57**, 5533.
2001T5799 M. Yus, I. M. Pastor, and J. Gomis, *Tetrahedron*, 2001, **57**, 5799.
2001T6757 A. Stadler, K. Zangger, F. Belaj, and G. Kollenz, *Tetrahedron*, 2001, **57**, 6757.
2001T6809 C. Cimarelli, G. Palmieri, and E. Volpini, *Tetrahedron*, 2001, **57**, 6809.
2001T7729 M. Gardiner, R. Grigg, M. Kordes, V. Sridharan, and N. Vicker, *Tetrahedron*, 2001, **57**, 7729.
2001T9623 C. B. de Koning, I. R. Green, J. P. Michael, and J. R. Oliveira, *Tetrahedron*, 2001, **57**, 9623.
2001T10163 F. Al-Omran, A.-Z. A. Elassar, and A. A. El-Khair, *Tetrahedron*, 2001, **57**, 10163.
2001TA801 M. Yus, T. Soler, and F. Foubelo, *Tetrahedron Asymmetry*, 2001, **12**, 801.
2001TA1689 S. Usse, G. Pave, G. Guillaumet, and M.-C. Viaud-Massuard, *Tetrahedron Asymmetry*, 2001, **12**, 1689.
2001TA3163 D. Socha, M. Jurczak, J. Frelek, A. Klimek, J. Rabczko, Z. Urbanczyk-Lipkowska, K. Suwinska, M. Chmielewski, F. Cardona, A. Goti, and A. Brandi, *Tetrahedron Asymmetry*, 2001, **12**, 3163.
2001TL89 J. S. Yadav, B. V. Subba-Reddy, G. Mahesh-Kumar, and C. V. S. R. Murthy, *Tetrahedron Lett.*, 2001, **42**, 89.
2001TL533 M. S. Novikov, A. F. Klebnikov, O. V. Besedina, and R. R. Kostikov, *Tetrahedron Lett.*, 2001, **42**, 533.
2001TL609 M. J. McLaughlin, H. C. Shen, and R. P. Hsung, *Tetrahedron Lett.*, 2001, **42**, 609.
2001TL777 Y. Zhang and J. W. Herndon, *Tetrahedron Lett.*, 2001, **42**, 777.
2001TL793 J. Li and C.-J. Li, *Tetrahedron Lett.*, 2001, **42**, 793.
2001TL1091 S. Yamaguchi, M. Ishibashi, K. Akasaka, H. Yokoyama, M. Miyazawa, and Y. Hirai, *Tetrahedron Lett.*, 2001, **42**, 1091.
2001TL2047 J. H. Rigby, A. Payen, and N. Warshakoon, *Tetrahedron Lett.*, 2001, **42**, 2047.
2001TL2455 B. B. Snider and S. M. O'Hare, *Tetrahedron Lett.*, 2001, **42**, 2455.
2001TL2657 O. Barberan, M. Alami, and J.-D. Brion, *Tetrahedron Lett.*, 2001, **42**, 2657.
2001TL2717 M.-C. Yan, Y.-J. Jang, and C.-F. Yao, *Tetrahedron Lett.*, 2001, **42**, 2717.
2001TL2791 S. Frère, V. Thiéry, and T. Besson, *Tetrahedron Lett.*, 2001, **42**, 2791.
2001TL3567 S. P. Waters and M. C. Kozlowski, *Tetrahedron Lett.*, 2001, **42**, 3567.
2001TL3763 K. J. Hodgetts, *Tetrahedron Lett.*, 2001, **42**, 3763.
2001TL4405 J. S. Yadav, B. V. S. Reddy, K. C. Sekhar, and V. Geetha, *Tetrahedron Lett.*, 2001, **42**, 4405.
2001TL5117 V. Y. Sosnovskikh, B. I. Usachev, D. V. Sevenard, E. Lork, and G.-V. Röschenthaler, *Tetrahedron Lett.*, 2001, **42**, 5117.
2001TL5219 A. García and D. Domínguez, *Tetrahedron Lett.*, 2001, **42**, 5219.
2001TL5753 R. G. F. Giles, I. R. Green, F. J. Oosthuizen, and C. P. Taylor, *Tetrahedron Lett.*, 2001, **42**, 5753.

- 2001TL5875 A. Y. Fedorov, F. Carrara, and J.-P. Finet, *Tetrahedron Lett.*, 2001, **42**, 5875.
2001TL5955 S. Kamila, C. Mukherjee, and A. De, *Tetrahedron Lett.*, 2001, **42**, 5955.
2001TL6031 K. S. Feldman and A. L. Perkins, *Tetrahedron Lett.*, 2001, **42**, 6031.
2001TL6069 Y. Du and D. F. Wiemer, *Tetrahedron Lett.*, 2001, **42**, 6069.
2001TL6231 A. K. Ghosh and M. Shirai, *Tetrahedron Lett.*, 2001, **42**, 6231.
2001TL6737 J.-M. Wu and Y. Li, *Tetrahedron Lett.*, 2001, **42**, 6737.
2001TL6987 J. E. Imbriglio and J. D. Rainier, *Tetrahedron Lett.*, 2001, **42**, 6987.
2001TL7401 M. Saeed, T. Ilg, M. Schick, M. Abbas, and W. Voelter, *Tetrahedron Lett.*, 2001, **42**, 7401.
2001TL7525 R. M. Kamble and V. K. Singh, *Tetrahedron Lett.*, 2001, **42**, 7525.
2001TL8429 M. D. Collini and C. P. Miller, *Tetrahedron Lett.*, 2001, **42**, 8429.
2001TL8685 B. Leroy and I. E. Marko, *Tetrahedron Lett.*, 2001, **42**, 8685.
2001TL8907 G. Bose, E. Mondal, A. T. Khan, and M. J. Bordoloi, *Tetrahedron Lett.*, 2001, **42**, 8907.
2001TL9089 J. S. Yadav, B. V. S. Reddy, P. Kumar, S. P. Sushil, and I. Prathap, *Tetrahedron Lett.*, 2001, **42**, 9089.
2001TL9285 M. K. Potdar, S. S. Mohile, and M. M. Salunkhe, *Tetrahedron Lett.*, 2001, **42**, 9285.
2001TL9293 A. Bieniek, J. Epszajn, J. A. Kowalska, and Z. Malinowski, *Tetrahedron Lett.*, 2001, **42**, 9293.
2002AGE161 C.-M. Yu, J.-Y. Lee, B. So, and J. Hong, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 161.
2002AGE1524 T. Graening, W. Friedrichsen, J. Lex, and H.-G. Schmalz, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 1524.
2002AGE3059 K. Gademann, D. E. Chavez, and E. N. Jacobsen, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 3059.
2002AGE3677 E. A. Couladouros and A. T. Strongilos, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 3677.
2002AGE4038 K. Grela, S. Harutyunyan, and A. Michrowska, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 4038–4040.
2002AGE4632 K.-S. Yeung and I. Paterson, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 4623.
2002AGE4751 S. Takahashi, A. Kubota, and T. Nakata, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 4751.
2002BCJ1325 T. Erabi, M. Asahara, M. Miyamoto, K. Goto, and M. Wada, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1325.
2002BCJ1905 H. Tanaka, K. Hashimoto, K. Suzuki, Y. Kitaichi, M. Sato, K. Ikeno, and T. Yamada, *Bull. Chem. Soc. Jpn.*, 2002, **77**, 1905.
2002BKE937 S. S. Kim, S. K. Sar, and P. Tamrakar, *Bull. Korean Chem. Soc.*, 2002, **23**, 937.
2002CC168 P. Langer, N. N. R. Saleh, and I. Freifeld, *J. Chem. Soc., Chem. Commun.*, 2002, 168.
2002CC1588 C. Bolm, C. Palazzi, G. Francio, and W. Leitner, *J. Chem. Soc., Chem. Commun.*, 2002, 1588.
2002CC1754 T. Aftab, R. Grigg, M. Ladlow, V. Sridharan, and M. Thornton-Pett, *J. Chem. Soc., Chem. Commun.*, 2002, 1754.
2002CC2066 P. Wipf and J. T. Reeves, *J. Chem. Soc., Chem. Commun.*, 2002, 2066.
2002CEJ2034 J. Barluenga, F. J. Fañanás, R. Sanz, and Y. Fernández, *Chem. Eur. J.*, 2002, **8**, 2034.
2002CEJ4346 F. P. Marmasäter and F. G. West, *Chem. Eur. J.*, 2002, **8**, 4346.
2002CEJ5033 Y. Yuan, J. Long, J. Sun, and K. Ding, *Chem. Eur. J.*, 2002, **8**, 5033.
2002CL380 J. Oyamada, C. Jia, Y. Fujiwara, and T. Kitamura, *Chem. Lett.*, 2002, 380.
2002HCA913 A. Heckel and D. Seebach, *Helv. Chim. Acta*, 2002, **85**, 913.
2002HCA3473 Y. Noda and M. Watanabe, *Helv. Chim. Acta*, 2002, **85**, 3473.
2002JA10 J. Long, J. Hu, X. Shen, B. Ji, and K. Ding, *J. Am. Chem. Soc.*, 2002, **124**, 10.
2002JA764 N. Asao, T. Nogami, K. Takahashi, and Y. Yamamoto, *J. Am. Chem. Soc.*, 2002, **124**, 764.
2002JA1144 T. Takahashi, Y. Li, T. Ito, F. Xu, K. Nakajima, and Y. Liu, *J. Am. Chem. Soc.*, 2002, **124**, 1144.
2002JA2528 B. M. Trost and Y. H. Rhee, *J. Am. Chem. Soc.*, 2002, **124**, 2528.
2002JA4149 Y. Sheng, D. G. Musaev, K. S. Reddy, F. E. McDonald, and K. Morokuma, *J. Am. Chem. Soc.*, 2002, **124**, 4149.
2002JA4198 A. M. Khenkin and R. Neumann, *J. Am. Chem. Soc.*, 2002, **124**, 4198.
2002JA4956 P. A. Wender, S. G. Hegde, R. D. Hubbard, and L. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 4956.
2002JA6312 M. Lautens and W. Han, *J. Am. Chem. Soc.*, 2002, **124**, 6312.
2002JA6824 T. Kondo, Y. Kaneko, Y. Taguchi, A. Nakamura, T. Okada, M. Shiotsuki, Y. Ura, K. Wada, and T. Mitsudo, *J. Am. Chem. Soc.*, 2002, **124**, 6824.
2002JA7900 Y. Nishibatashi, Y. Inada, M. Hidai, and S. Uemura, *J. Am. Chem. Soc.*, 2002, **124**, 7900.
2002JA9662 Y. Huang and V. H. Rawal, *J. Am. Chem. Soc.*, 2002, **124**, 9662.
2002JA10298 M. S. Kerr, J. Read de Alaniz, and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 10298.
2002JA14836 H. Suga, K. Inoue, S. Inoue, and A. Kakehi, *J. Am. Chem. Soc.*, 2002, **124**, 14836.
2002JA14866 Y. Yuan, X. Li, J. Sun, and K. Ding, *J. Am. Chem. Soc.*, 2002, **124**, 14866.
2002JA15186 K. M. Brummond, H. Chen, P. Sill, and L. You, *J. Am. Chem. Soc.*, 2002, **124**, 15186.
2002JA15188 J. Louie, J. E. Gibby, M. V. Farnworth, and T. N. Tekavec, *J. Am. Chem. Soc.*, 2002, **124**, 15188.
2002JOC2065 A. Moghimi, M. F. Rastegar, M. Ghandi, M. Taghizadeh, A. Yari, M. Shamsipur, G. P. A. Yap, and H. Rahbarnoohi, *J. Org. Chem.*, 2002, **67**, 2065.
2002JOC2175 B. Wang, X. Feng, Y. Huang, H. Liu, X. Cui, and Y. Jiang, *J. Org. Chem.*, 2002, **67**, 2175.
2002JOC2653 T. Kawasaki, S. Saito, and Y. Yamamoto, *J. Org. Chem.*, 2002, **67**, 2653.
2002JOC3104 A. R. Katritzky and O. V. Denisko, *J. Org. Chem.*, 2002, **67**, 3104.
2002JOC3317 Q. Zhao, F. Han, and D. L. Romero, *J. Org. Chem.*, 2002, **67**, 3317.
2002JOC3861 G. A. Molander and D. J. St Jean, Jr., *J. Org. Chem.*, 2002, **67**, 3861.
2002JOC3941 J. Thibonnet, M. Abarbri, J.-L. Parrain, and A. Duchêne, *J. Org. Chem.*, 2002, **67**, 3941.
2002JOC4177 Y. Zhang and J. W. Herndon, *J. Org. Chem.*, 2002, **67**, 4177.
2002JOC4284 W. R. Roush, T. D. Bannister, M. D. Wendt, M. S. Van Nieuwenhze, D. J. Gustin, G. J. Dilley, G. C. Lane, K. A. Scheidt, and W. J. Smith, III, *J. Org. Chem.*, 2002, **67**, 4284.
2002JOC5138 T. Kawasaki and Y. Yamamoto, *J. Org. Chem.*, 2002, **67**, 5138.
2002JOC5553 N. Kotaoka, Q. Shelby, J. P. Stambuli, and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 5553.
2002JOC5701 Y. Du and D. F. Wiemer, *J. Org. Chem.*, 2002, **67**, 5701.
2002JOC6104 S. Ma and W. Gao, *J. Org. Chem.*, 2002, **67**, 6104.
2002JOC6560 M. Carda, S. Rodríguez, B. Segovia, and J. A. Marco, *J. Org. Chem.*, 2002, **67**, 6560.
2002JOC6911 R. M. Jones, C. Selenski, and T. R. R. Pettus, *J. Org. Chem.*, 2002, **67**, 6911.

- 2002JOC7238 D. Amantini, F. Friguelli, and F. Pizzo, *J. Org. Chem.*, 2002, **67**, 7238.
2002JOC7839 C. A. I. Capaccio and O. Varela, *J. Org. Chem.*, 2002, **67**, 7839.
2002JOC8019 S. Muthusamy, S. A. Babu, C. Gunanathan, B. Ganguly, E. Suresh, and P. Dastidar, *J. Org. Chem.*, 2002, **67**, 8019.
2002JOC8280 S. Ma and B. Ni, *J. Org. Chem.*, 2002, **67**, 8280.
2002JOC8744 B. Leroy and I. E. Marko, *J. Org. Chem.*, 2002, **67**, 8744.
2002JOC8771 A. D. Williams and Y. Kobayashi, *J. Org. Chem.*, 2002, **67**, 8771.
2002J(P1)165 J. S. Yadav, B. V. S. Reddy, M. Aruna, C. Venugopal, T. Ramalingam, S. K. Kumar, and A. C. Kunwar, *J. Chem. Soc., Perkin Trans. 1*, 2002, 165.
2002J(P1)496 J.-Y. Goujon, A. Duval, and B. Kirschleger, *J. Chem. Soc., Perkin Trans. 1*, 2002, 496.
2002J(P1)1309 Y. R. Lee and Y. U. Jung, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1309.
2002J(P1)1318 P. T. Kaye and X. W. Nocanda, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1318.
2002J(P1)1401 J. S. Yadav, B. V. S. Reddy, C. V. Rao, and K. V. Rao, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1401.
2002J(P1)1444 R. Hodgson, T. Majid, and A. Nelson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1444.
2002J(P1)1455 D. N. Nicolaides, D. R. Gautam, K. E. Litinas, and T. Papamehael, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1455.
2002J(P1)1461 J. Bentley, P. A. Nilsson, and A. F. Parsons, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1461.
2002J(P1)2301 M. C. Elliott, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2301.
2002J(P1)2544 S. P. Nikas, G. A. Thakur, and A. Makriyannis, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2544.
2002J(P1)2646 L. Caggiano, D. J. Fox, D. House, Z. A. Jones, F. Kerr, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2646.
2002J(P1)2652 D. House, F. Kerr, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2652.
2002OL323 E. Y. Chao, D. J. Minick, D. D. Sternbach, B. G. Shearer, and J. L. Collins, *Org. Lett.*, 2002, **4**, 323.
2002OL395 R. R. Cesati, J. de Armas, and A. H. Hoveyda, *Org. Lett.*, 2002, **4**, 395.
2002OL455 Y. Nagao, A. Ueki, K. Asano, S. Tanaka, S. Sano, and M. Shiro, *Org. Lett.*, 2002, **4**, 455.
2002OL481 A. Bhattacharjee, O. Soltani, and J. K. De Brabander, *Org. Lett.*, 2002, **4**, 481.
2002OL505 S. Ma, S. Yin, L. Li, and F. Tao, *Org. Lett.*, 2002, **4**, 505.
2002OL749 W. W. Cutchins and F. E. McDonald, *Org. Lett.*, 2002, **4**, 749.
2002OL977 F. M. Hauser and X. Hu, *Org. Lett.*, 2002, **4**, 977.
2002OL1067 M. Querol, H. Stoekli-Evans, and P. Belser, *Org. Lett.*, 2002, **4**, 1067.
2002OL1189 G. E. Keck, J. A. Covel, T. Schiff, and T. Yu, *Org. Lett.*, 2002, **4**, 1189.
2002OL1221 Y. Yamashita, S. Saito, H. Ishiani, and S. Kobayashi, *Org. Lett.*, 2002, **4**, 1221.
2002OL1707 S. Awale, Y. Tezuka, S. Wang, and S. Kadota, *Org. Lett.*, 2002, **4**, 1707.
2002OL1795 G. D. Joly and E. N. Jacobsen, *Org. Lett.*, 2002, **4**, 1795.
2002OL1823 G. G. Zipp, M. A. Hilfiker, and S. G. Nelson, *Org. Lett.*, 2002, **4**, 1823.
2002OL2317 Y. Nakamura and T. Ukita, *Org. Lett.*, 2002, **4**, 2317.
2002OL2361 T. Suzuki, K. Morita, M. Tsuchida, and K. Hiroi, *Org. Lett.*, 2002, **4**, 2361.
2002OL2565 A. M. Bernard, E. Cadoni, A. Frongia, P. P. Piras, and F. Secci, *Org. Lett.*, 2002, **4**, 2565.
2002OL2657 S. H. Lim and P. Beak, *Org. Lett.*, 2002, **4**, 2657.
2002OL3059 T. J. Donohoe, A. Raoof, G. C. Freestone, I. D. Linney, A. Cowley, and M. Helliwell, *Org. Lett.*, 2002, **4**, 3059.
2002OL3139 A. Piettre, E. Chevenier, C. Massardier, Y. Gimbert, and A. E. Green, *Org. Lett.*, 2002, **4**, 3139.
2002OL3235 C.-Y. Zhou, W.-Y. Yu, and C.-M. Che, *Org. Lett.*, 2002, **4**, 3235.
2002OL3679 J. L. Portscheller and H. C. Malinakova, *Org. Lett.*, 2002, **4**, 3679.
2002OL3797 S. P. Fearnley and M. W. Tidwell, *Org. Lett.*, 2002, **4**, 3797.
2002OL3875 P. R. Andreana, J. S. McLellan, Y. Chen, and P. G. Wang, *Org. Lett.*, 2002, **4**, 3875.
2002OL3899 E. L. Ruggles and R. E. Maleczka, *Org. Lett.*, 2002, **4**, 3899.
2002OL3919 S. Marumoto, J. J. Jaber, J. P. Vitale, and S. D. Rychnovsky, *Org. Lett.*, 2002, **4**, 3919.
2002OL3979 F. E. McDonald and M. Wu, *Org. Lett.*, 2002, **4**, 3979.
2002OL4257 L. Chabaud, Y. Landais, and P. Renaud, *Org. Lett.*, 2002, **4**, 4257.
2002OL4269 S. Hoger, S. Rosselli, A.-D. Ramminger, and V. Enkelmann, *Org. Lett.*, 2002, **4**, 4269.
2002OL4349 H. Du, J. Long, J. Hu, X. Li, and K. Ding, *Org. Lett.*, 2002, **4**, 4349.
2002OL4419 X. Huang and H. Zhou, *Org. Lett.*, 2002, **4**, 4419.
2002OL4615 Y.-G. Wang and Y. Kobayashi, *Org. Lett.*, 2002, **4**, 4615.
2002OM3434 M. J. Shaw and J. Mertz, *Organometallics*, 2002, **21**, 3434.
2002PHC(14)332 J. D. Hepworth and B. M. Heron; in 'Progress in Heterocyclic Chemistry', G. Gribble and T. L. Gilchrist, Eds.; Elsevier, Amsterdam, 2002, vol. 14, p. 332.
2002PS1147 I. Yavari, F. Nourmohammadian, and H. R. Bijanzadeh, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 1147.
2002PS2555 A. Shockvari, H. Shargi, H. Valizadeh, and M. M. Heravi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 2555.
2002PS2827 R. Hekmatshoar, S. Soury, M. Rahimifard, and F. Faridbod, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 2827.
2002PS2835 A. Shockvari, H. Valizadeh, and M. M. Heravi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 2835.
2002S533 S. Sengmany, E. Leonel, J. P. Paugam, and J.-Y. Nedelec, *Synthesis*, 2002, 533.
2002S981 M. Kalesse and M. Christmann, *Synthesis*, 2002, 981.
2002S2341 V. Y. Sosnovskikh and B. I. Usachev, *Synthesis*, 2002, 2341.
2002S2490 Y. Kawamura, M. Maruyama, T. Tokuoka, and M. Tsukayama, *Synthesis*, 2002, 2490.
2002SC1351 M. M. Ali, S. Sana, Tasneem, K. C. Rajanna, and P. K. Saiprakash, *Synth. Commun.*, 2002, **32**, 1351.
2002SC1937 J.-X. Wang, Z. Liu, Y. Hu, B. Wei, and L. Kang, *Synth. Commun.*, 2002, **32**, 1937.
2002SC3667 J.-R. Labrosse, P. Lhoste, and D. Sinou, *Synth. Commun.*, 2002, **32**, 3667.
2002SL322 J.-Y. Goujon, F. Zammattio, S. Pagnoncelli, Y. Boursereau, and B. Kirschleger, *Synlett*, 2002, 322.
2002SL796 A. M. Bernard, C. Floris, A. Frongia, and P. P. Piras, *Synlett*, 2002, 796.
2002SL931 S. Kii, T. Hashimoto, and K. Maruoka, *Synlett*, 2002, 931.
2002SL1318 M. A. Brimble, R. M. Davey, and M. D. McLeod, *Synlett*, 2002, 1318.
2002SL2122 Y. Huang, X. Feng, B. Wang, G. Zhang, and Y. Jiang, *Synlett*, 2002, 2122.

- 2002T105 A. Sandulache, A. M. S. Silva, and J. A. S. Cavaleiro, *Tetrahedron*, 2002, **58**, 105.
- 2002T1497 M. Yamashita, K. Okuyama, T. Kawajiri, A. Takada, Y. Inagaki, H. Nakano, M. Tomiyama, A. Ohnaka, I. Terayama, I. Kawasaki, and S. Ohta, *Tetrahedron*, 2002, **58**, 1497.
- 2002T1853 N. Hori, H. Matsukura, G. Hiroko, and T. Nakata, *Tetrahedron*, 2002, **58**, 1853.
- 2002T2027 F. P. Marmsater, J. A. Vanecko, and F. G. West, *Tetrahedron*, 2002, **58**, 2027.
- 2002T2163 J. Demyttenaere, K. V. Syngel, A. P. Markusse, S. Vervisch, S. Debenedetti, and N. De Kimpe, *Tetrahedron*, 2002, **58**, 2163.
- 2002T3319 D. Crich and M. Sannigrahi, *Tetrahedron*, 2002, **58**, 3319.
- 2002T3977 G.-J. ten Brink, J. M. Vis, I. W. C. E. Arends, and R. A. Sheldon, *Tetrahedron*, 2002, **58**, 3977.
- 2002T4559 C. C. Lindsey, C. Gomez-Diaz, J. M. Villalba, and R. R. Thomas, *Tetrahedron*, 2002, **58**, 4559.
- 2002T4907 M. Yus, F. Foubelo, J. V. Ferrandez, and A. Bachki, *Tetrahedron*, 2002, **58**, 4907.
- 2002T5023 M. Biagetti, F. Bellina, A. Carpita, P. Stabile, and R. Rossi, *Tetrahedron*, 2002, **58**, 5023.
- 2002T5215 T. Hattori, Y. Suzuki, Y. Ito, D. Hotta, and S. Miyano, *Tetrahedron*, 2002, **58**, 5215.
- 2002T5627 H. Guo, R. J. Madhushaw, F.-M. Shen, and R.-S. Liu, *Tetrahedron*, 2002, **58**, 5627.
- 2002T5689 J.-M. Vatele, *Tetrahedron*, 2002, **58**, 5689.
- 2002T5909 J. Cossy, D. Bauer, and V. Bellosta, *Tetrahedron*, 2002, **58**, 5909.
- 2002T5927 J.-Q. Wang and R. G. Harvey, *Tetrahedron*, 2002, **58**, 5927.
- 2002T6009 P. B. Greer and W. A. Donaldson, *Tetrahedron*, 2002, **58**, 6009.
- 2002T6455 A. B. Smith and J. Zheng, *Tetrahedron*, 2002, **58**, 6455.
- 2002T7391 G. A. Kraus and H. Ogutu, *Tetrahedron*, 2002, **58**, 7391.
- 2002T7951 B. Schmidt, M. Pohler, and B. Costisella, *Tetrahedron*, 2002, **58**, 7951.
- 2002T8613 R. Grigg, V. Savic, V. Sridharan, and C. Terrier, *Tetrahedron*, 2002, **58**, 8613.
- 2002T8929 H. Mizutani, M. Watanabe, and T. Honda, *Tetrahedron*, 2002, **58**, 8929.
- 2002T9007 F. Tepy, I. G. Stara, I. Stary, A. Kollarovic, D. Saman, and P. Fiedler, *Tetrahedron*, 2002, **58**, 9007.
- 2002T9505 P. J. Coelho, L. M. Carvalho, S. Abrantes, M. M. Oliveira, A. M. F. Oliveira-Campos, A. Samat, and R. Guglielmetti, *Tetrahedron*, 2002, **58**, 9505.
- 2002T10145 M. C. Aversa, A. Barattucci, P. Bonaccorsi, and P. Giannetto, *Tetrahedron*, 2002, **58**, 10145.
- 2002TA715 S.-S. Jew, D.-Y. Lim, S.-Y. Bae, H.-A. Kim, J.-H. Kim, J. Lee, and H. G. Park, *Tetrahedron Asymmetry*, 2002, **13**, 715.
- 2002TL753 C. S. Consorti, G. Ebeling, and J. Dupont, *Tetrahedron Lett.*, 2002, **43**, 753.
- 2002TL1127 J. R. Harjani, S. J. Nara, and M. M. Salunkhe, *Tetrahedron Lett.*, 2002, **43**, 1127.
- 2002TL1189 M. T. Reetz, A. Gosberg, and D. Moulin, *Tetrahedron Lett.*, 2002, **43**, 1189.
- 2002TL1561 D. Banti and M. North, *Tetrahedron Lett.*, 2002, **43**, 1561.
- 2002TL1735 M. A. Brimble, G. S. Pavia, and R. J. Stevenson, *Tetrahedron Lett.*, 2002, **43**, 1735.
- 2002TL2999 J. S. Yadav, B. V. S. Reddy, C. Parisse, P. Carvalho, and T. P. Rao, *Tetrahedron Lett.*, 2002, **43**, 2999.
- 2002TL3381 J. Mulzer and M. Hanbauer, *Tetrahedron Lett.*, 2002, **43**, 3381.
- 2002TL3513 M. Schuman and V. Gouverneur, *Tetrahedron Lett.*, 2002, **43**, 3513.
- 2002TL3565 C.-S. Li and E. Lacasse, *Tetrahedron Lett.*, 2002, **43**, 3565.
- 2002TL3637 S. Cennini, G. Cravotto, G. B. Giovenzana, G. Palmisano, A. Penoni, and S. Tollari, *Tetrahedron Lett.*, 2002, **43**, 3637.
- 2002TL3931 S. Muthusamy, S. A. Babu, and C. Gunanathan, *Tetrahedron Lett.*, 2002, **43**, 3931.
- 2002TL4175 H. Tanaka, Y. Kozuki, and K. Ogasawara, *Tetrahedron Lett.*, 2002, **43**, 4175.
- 2002TL4515 N. Thasana and S. Ruchirawat, *Tetrahedron Lett.*, 2002, **43**, 4515.
- 2002TL4777 M. A. Brimble, R. Halim, and M. Petersson, *Tetrahedron Lett.*, 2002, **43**, 4777.
- 2002TL4875 F. F. Kneisel, Y. Monguchi, K. M. Knapp, H. Zipse, and P. Knochel, *Tetrahedron Lett.*, 2002, **43**, 4875.
- 2002TL5165 A. Shaabani, A. Bazgir, F. Teimouri, and D. G. Lee, *Tetrahedron Lett.*, 2002, **43**, 5165.
- 2002TL5673 L. Anastasia, C. Xu, and E. Negishi, *Tetrahedron Lett.*, 2002, **43**, 5673.
- 2002TL6113 Y.-W. Kim and R. Brueggemeier, *Tetrahedron Lett.*, 2002, **43**, 6113.
- 2002TL7055 A. P. Dobbs and S. Martinovic, *Tetrahedron Lett.*, 2002, **43**, 7055.
- 2002TL7193 T.-P. Loh, J.-Y. Yang, L.-C. Feng, and Y. Zhou, *Tetrahedron Lett.*, 2002, **43**, 7193.
- 2002TL7401 T. Yao and R. C. Larock, *Tetrahedron Lett.*, 2002, **43**, 7401.
- 2002TL7631 H. Nakamura, M. Ohtaka, and Y. Yamamoto, *Tetrahedron Lett.*, 2002, **43**, 7631.
- 2002TL8245 A. V. Bolshakov, O. G. Ganina, A. S. Shavirin, Y. A. Kurskii, J.-P. Finet, and A. Y. Fedorov, *Tetrahedron Lett.*, 2002, **43**, 8245.
- 2002TL8559 M. Prasad, Y. Liu, X. Y. Mak, D. Har, O. Repić, and T. J. Blacklock, *Tetrahedron Lett.*, 2002, **43**, 8559.
- 2002TL8583 S. P. Chavan, K. Shivasankar, R. Sivappa, and R. Kale, *Tetrahedron Lett.*, 2002, **43**, 8583.
- 2002TL9055 K. Grela, M. Tryznowski, and M. Bieniek, *Tetrahedron Lett.*, 2002, **43**, 9055.
- 2002TL9195 D. S. Bose, A. P. Rudradas, and M. H. Babu, *Tetrahedron Lett.*, 2002, **43**, 9195.
- 2003AGE183 S. Ma and J. Zhang, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 183.
- 2003AGE343 I. Paterson and M. Tudge, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 343.
- 2003AGE1255 M. A. González and G. Pattenden, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 1255.
- 2003AGE1258 D. R. Williams, A. K. Kiryanov, U. Emde, M. P. Clark, M. A. Berliner, and J. T. Reeves, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 1258.
- 2003AGE1498 K. Juhl and K. A. Jorgensen, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 1498.
- 2003AGE1648 X. Liao, Y. Wu, and J. K. De Brabander, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 1648.
- 2003AGE2409 K. Fujii, T. Morimoto, K. Tsutsumi, and K. Kakiuchi, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 2409.
- 2003AGE2711 L. O. Haustedt, I. V. Hartung, and H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 2711.
- 2003AGE2795 G. Hilt and K. I. Smolko, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 2795.
- 2003AGE2892 R. M. Trend, Y. K. Ramtohl, E. M. Ferreira, and B. M. Stoltz, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 2892.
- 2003AGE3943 B. M. Trost, H. C. Shen, and J.-P. Surivet, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 3943.
- 2003AGE4592 R. R. Schrock and A. H. Hoveyda, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 4592.
- 2003AGE5274 J. Wiesner, R. Ortmann, H. Jomaa, and M. Schlitzer, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 5274.
- 2003AGE5731 A. Hasegawa, K. Ishihara, and H. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 5731.
- 2003AJC489 R. Aggarwal, A. A. Birkbeck, R. G. F. Giles, I. R. Green, Y. Gruchlik, and F. J. Oosthuizen, *Aus. J. Chem.*, 2003, **56**, 489.

- 2003ARK118 A. De Fatima and R. A. Pilli, *ARKIVOC*, 2003, **10**, 118.
2003BCJ1889 T. Kitamura, K. Yamamoto, M. Kotani, J. Oyamada, C. Jia, and Y. Fujiwara, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 1889.
2003BKC256 D. U. Lee, *Bull. Korean. Chem. Soc.*, 2003, **24**, 256.
2003BMC529 I. Singh, A. K. Prasad, A. K. Sharma, R. K. Saxena, C. E. Olsen, A. L. Cholli, L. A. Samuelson, J. Kumar, A. C. Watterson, and V. S. Parmar, *Bioorg. Med. Chem.*, 2003, **11**, 529.
2003BML1939 X. Li, P. Huang, J. J. Cui, J. Zhang, and C. Tang, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1939.
2003CC114 Y. Kashiwagi, F. Kurashima, S. Chiba, J. Anzai, T. Osa, and J. B. Bobbitt, *J. Chem. Soc., Chem. Commun.*, 2003, 114.
2003CAL145 Y. Wan, P. McMorn, F. E. Hancock, and G. J. Hutchings, *Catal. Lett.*, 2003, **91**, 145.
2003CC204 S. Bath, N. M. Laso, H. Lopez-Ruiz, B. Quicler-Sire, and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 2003, 204.
2003CC1742 J. Campora, C. M. Maya, P. Palma, E. Carmona, C. Graiff, and A. Tiripicchio, *J. Chem. Soc., Chem. Commun.*, 2003, 1742.
2003CC2016 S. Kobayashi, S. Saito, M. Ueno, and Y. Yamashita, *J. Chem. Soc., Chem. Commun.*, 2003, 2016.
2003CC2578 J. S. Clark, G. Whitlock, S. Jiang, and N. Onyia, *J. Chem. Soc., Chem. Commun.*, 2003, 2578.
2003CEJ5989 B. Ji, Y. Yuan, K. Ding, and J. Meng, *Chem. Eur. J.*, 2003, **9**, 5989.
2003CEJ6145 S. Saaby, K. Nakama, M. A. Lie, R. G. Hazell, and K. A. Jorgensen, *Chem. Eur. J.*, 2003, **9**, 6145.
2003CL608 T. Hayano, T. Sakaguchi, H. Furuno, M. Ohba, H. Okawa, and J. Inanaga, *Chem. Lett.*, 2003, **32**, 608.
2003COR1461 M. A. Brimble and D. P. Furkert, *Curr. Org. Chem.*, 2003, **7**, 1461.
2003EJO82 K.-F. Chan and H. N. C. Wong, *Eur. J. Org. Chem.*, 2003, 82.
2003EJO317 H. L. Van Lingen, J. K. W. Van de Mortel, K. F. W. Hekking, F. L. Van Delft, T. Sonke, and F. P. J. T. Rutjes, *Eur. J. Org. Chem.*, 2003, 317.
2003EJO526 P. Strazzolini and A. Runcio, *Eur. J. Org. Chem.*, 2003, 526.
2003EJO821 A. K. Ghosh, A. Bischoff, and J. Cappiello, *Eur. J. Org. Chem.*, 2003, 821.
2003EJO2243 P. Gros, S. Choppin, and Y. Fort, *Eur. J. Org. Chem.*, 2003, 2243.
2003EJO2840 F. Mazzini, E. Alpi, P. Salvadori, and T. Netscher, *Eur. J. Org. Chem.*, 2003, 2840.
2003EJO4363 M. Schnebel, I. Weidner, R. Wartchow, and B. Butenschoten, *Eur. J. Org. Chem.*, 2003, 4363.
2003EJO4731 D. A. Bianchi, M. A. Cipulli, and T. S. Kaufman, *Eur. J. Org. Chem.*, 2003, 4731.
2003HCA377 A. Saeed, *Helv. Chim. Acta*, 2003, **86**, 377.
2003JHC321 L. Casu, L. Bonsignore, F. Cottiglia, G. Loy, and E. Maccioni, *J. Heterocycl. Chem.*, 2003, **40**, 321.
2003JA2406 J. R. Seiders, L. Wang, and P. E. Floreancig, *J. Am. Chem. Soc.*, 2003, **125**, 2406.
2003JA3793 Y. Yamashita, S. Saito, H. Ishitani, and S. Kobayashi, *J. Am. Chem. Soc.*, 2003, **125**, 3793.
2003JA4518 B. M. Trost, F. D. Toste, and K. Greenman, *J. Am. Chem. Soc.*, 2003, **125**, 4518.
2003JA5282 S. Nakamura, M. Uchiyama, and T. Ohwada, *J. Am. Chem. Soc.*, 2003, **125**, 5282.
2003JA6042 C. Gaul, J. T. Njardarson, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2003, **125**, 6042.
2003JA6060 Y. Nishibayashi, Y. Inada, M. Hidai, and S. Uemura, *J. Am. Chem. Soc.*, 2003, **125**, 6060.
2003JA7482 B. M. Trost and Y. H. Rhee, *J. Am. Chem. Soc.*, 2003, **125**, 7482.
2003JA7784 H. Kinoshita, H. Shinokubo, and K. Oshima, *J. Am. Chem. Soc.*, 2003, **125**, 7784.
2003JA8734 J. Chen and C. J. Forsyth, *J. Am. Chem. Soc.*, 2003, **125**, 8734.
2003JA9028 J. Barluenga, H. Vázquez-Villa, A. Ballesteros, and J. M. González, *J. Am. Chem. Soc.*, 2003, **125**, 9028.
2003JA9276 B. M. Trost, H. C. Shen, L. Dong, and J.-P. Surivet, *J. Am. Chem. Soc.*, 2003, **125**, 9276.
2003JA9308 X. Gao and D. G. Hall, *J. Am. Chem. Soc.*, 2003, **125**, 9308.
2003JA9610 A. Odedra, C.-J. Wu, R. J. Madhushaw, S.-L. Wang, and R.-S. Liu, *J. Am. Chem. Soc.*, 2003, **125**, 9610.
2003JA11253 G. Hughes, M. Kimura, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11253.
2003JA12143 Y. Yamamoto, T. Arakawa, R. Ogawa, and K. Itoh, *J. Am. Chem. Soc.*, 2003, **125**, 12143.
2003JMO93 M. P. Doyle and J. Colyer, *J. Mol. Catal.*, 2003, **196**, 93.
2003JMO315 T. Osawa, E. Mieno, T. Harada, and O. Takayasu, *J. Mol. Catal.*, 2003, **200**, 315.
2003JOC799 H. Wildemann, P. Dunkelmann, M. Muller, and B. Schmidt, *J. Org. Chem.*, 2003, **68**, 799.
2003JOC1401 G. Pave, J.-M. Leger, C. Jarry, M.-C. Viaud-Massuard, and G. Guillaumet, *J. Org. Chem.*, 2003, **68**, 1401.
2003JOC1729 H. C. Shen, J. Wang, K. P. Cole, M. J. McLaughlin, C. D. Morgan, C. J. Douglas, R. P. Hsung, H. A. Coverdale, A. I. Gerasyuto, J. M. Hahn, J. Liu, H. M. Sklenicka, L.-L. Wei, L. R. Zehnder, and C. A. Zifcsak, *J. Org. Chem.*, 2003, **68**, 1729.
2003JOC1911 F. Ek, L.-G. Wistrand, and T. Frejd, *J. Org. Chem.*, 2003, **68**, 1911.
2003JOC3216 J. M. Betancort, T. Martin, J. M. Palazon, and V. S. Martin, *J. Org. Chem.*, 2003, **68**, 3216.
2003JOC4947 S. Yahiro, K. Shibata, T. Saito, T. Okauchi, and T. Minami, *J. Org. Chem.*, 2003, **68**, 4947.
2003JOC5618 H. Miyabe, M. Ueda, K. Fujii, A. Nishimura, and T. Naito, *J. Org. Chem.*, 2003, **68**, 5618.
2003JOC5936 T. Yao and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 5936.
2003JOC6222 S. Wang, M. M. Kayser, and V. Jurkauskas, *J. Org. Chem.*, 2003, **68**, 6222.
2003JOC6354 T. Hanamoto and T. Kobayashi, *J. Org. Chem.*, 2003, **68**, 6354.
2003JOC6466 V. N. Kourafalos, P. Marakos, N. Pouli, and L. B. Townsend, *J. Org. Chem.*, 2003, **68**, 6466.
2003JOC7009 G. Oezer, N. Saracoglu, and M. Balci, *J. Org. Chem.*, 2003, **68**, 7009.
2003JOC7747 V. Y. Sosnovskikh, B. I. Usachev, D. V. Sevenard, and G.-V. Roeschenthaler, *J. Org. Chem.*, 2003, **68**, 7747.
2003JOC7880 A. P. Dobbs, S. J. J. Guesne, S. Martinovic, S. J. Coles, and M. B. Hursthouse, *J. Org. Chem.*, 2003, **68**, 7880.
2003JOC8571 E. Yoneda, S.-W. Zhang, D.-Y. Zhou, K. Onitsuka, and S. Takahashi, *J. Org. Chem.*, 2003, **68**, 8571.
2003JOC8798 P. Wipf and T. H. Graham, *J. Org. Chem.*, 2003, **68**, 8798.
2003JOC8996 S. Ma, S. Yu, and S. Yin, *J. Org. Chem.*, 2003, **68**, 8996.
2003JOC9263 D. Amantini, F. Fringuelli, O. Piermatti, F. Pizzo, and L. Vaccaro, *J. Org. Chem.*, 2003, **68**, 9263.
2003JOC9423 D. V. Kadnikov and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 9423.
2003JOC9481 J.-G. Boiteau, A. J. Minnaard, and B. L. Feringa, *J. Org. Chem.*, 2003, **68**, 9481.
2003JOC10175 F. Bellina, F. Colzi, L. Mannina, R. Rossi, and S. Viel, *J. Org. Chem.*, 2003, **68**, 10175.
2003NAT146 Y. Huang, A. K. Unni, A. N. Thadani, and V. H. Rawal, *Nature*, 2003, **424**, 146.
2003NJC329 F. d'Acunzo, P. Baiocco, and C. Galli, *New J. Chem.*, 2003, **27**, 329.
2003OBC1133 P. T. Kaye, M. A. Musa, X. W. Nocanda, and R. S. Robinson, *Org. Biomol. Chem.*, 2003, **1**, 1133.

- 2003OBC1690 M. A. Brimble, R. M. Davey, M. D. McLeod, and M. Murphy, *Org. Biomol. Chem.*, 2003, **1**, 1690.
- 2003OBC1953 H. L. van Lingen, W. Zhuang, T. Hansen, F. P. J. T. Rutjes, and K. A. Jorgensen, *Org. Biomol. Chem.*, 2003, **1**, 1953.
- 2003OBC2120 M. E. Kuehne, W. G. Bornmann, I. Marko, Y. Qin, K. L. LeBoulluec, D. A. Frasier, F. Xu, T. Mulamba, C. L. Ensinger, L. S. Borman, A. E. Huot, C. Exon, F. T. Bizzarro, J. B. Cheung, and S. L. Bane, *Org. Biomol. Chem.*, 2003, **1**, 2120.
- 2003OBC3600 F. Lecornue and J. Olivier, *Org. Biomol. Chem.*, 2003, **1**, 3600.
- 2003OBC4173 G. Pattenden, M. A. Gonzalez, P. B. Little, D. S. Millan, A. T. Plowright, J. A. Tornos, and T. Ye, *Org. Biomol. Chem.*, 2003, **1**, 4173.
- 2003OBC4227 M. A. Brimble and M. Y. H. Lai, *Org. Biomol. Chem.*, 2003, **1**, 4227.
- 2003OL459 J. Cossy, F. Bargiggia, and S. Bouzbouz, *Org. Lett.*, 2003, **5**, 459.
- 2003OL495 S. Tosaki, T. Nemoto, T. Ohshima, and M. Shibasaki, *Org. Lett.*, 2003, **5**, 495.
- 2003OL681 J.-G. Boiteau, R. Imbos, A. J. Minnaard, and B. L. Feringa, *Org. Lett.*, 2003, **5**, 681.
- 2003OL1091 H. Du and K. Ding, *Org. Lett.*, 2003, **5**, 1091.
- 2003OL1119 S. E. Denmark and W. Pan, *Org. Lett.*, 2003, **5**, 1119.
- 2003OL1163 A. Kulesza, F. H. Ebetino, R. K. Mishra, D. Cross-Doersen, and A. W. Mazur, *Org. Lett.*, 2003, **5**, 1163.
- 2003OL1447 J. Garcia-Fortanet, J. Murga, M. Carda, and J. A. Marco, *Org. Lett.*, 2003, **5**, 1447.
- 2003OL1499 D. J. Hart and C. E. Bennett, *Org. Lett.*, 2003, **5**, 1499.
- 2003OL1609 M. Nishizawa, V. K. Yadav, M. Skwarczynski, H. Takao, H. Imagawa, and T. Sugihara, *Org. Lett.*, 2003, **5**, 1609.
- 2003OL1729 J. A. Marshall and K. C. Ellis, *Org. Lett.*, 2003, **5**, 1729.
- 2003OL1979 P. O. Miranda, D. D. Diaz, J. I. Padron, J. Bermejo, and V. S. Martin, *Org. Lett.*, 2003, **5**, 1979.
- 2003OL1995 S. Bouzbouz and J. Cossy, *Org. Lett.*, 2003, **5**, 1995.
- 2003OL2429 C. J. Barry, S. R. Crosby, J. R. Harding, R. A. Hughes, C. D. King, G. D. Parker, and C. L. Willis, *Org. Lett.*, 2003, **5**, 2429.
- 2003OL2587 X. H. Cheng, S. Hoeger, and D. Fenske, *Org. Lett.*, 2003, **5**, 2587.
- 2003OL3089 J. M. Schomaker, B. R. Travis, and B. Borhan, *Org. Lett.*, 2003, **5**, 3089.
- 2003OL3163 B. Patterson, S. Marumoto, and S. D. Rychnovsky, *Org. Lett.*, 2003, **5**, 3163.
- 2003OL3169 S. L. Crawley and R. L. Funk, *Org. Lett.*, 2003, **5**, 3169.
- 2003OL3753 F. M. Hauser and W. A. Dorsch, *Org. Lett.*, 2003, **5**, 3753.
- 2003OL3755 P. V. Ramachandran, H. Liu, M. V. R. Reddy, and H. C. Brown, *Org. Lett.*, 2003, **5**, 3755.
- 2003OL3883 P. A. Evans, J. Cui, and S. J. Gharpure, *Org. Lett.*, 2003, **5**, 3883.
- 2003OL3935 A. V. Kurduumov, R. P. Hsung, K. Ihlen, and J. Wang, *Org. Lett.*, 2003, **5**, 3935.
- 2003OL4153 W. Zhao and E. Carreira, *Org. Lett.*, 2003, **5**, 4153.
- 2003OL4253 G. Pave, S. Usse-Versluys, M.-C. Viaud-Massuard, and G. Guillaumet, *Org. Lett.*, 2003, **5**, 4253.
- 2003OL4441 J. S. Foot, G. M. P. Giblin, and R. J. K. Taylor, *Org. Lett.*, 2003, **5**, 4441.
- 2003OL4481 Y. Kang, Y. Mei, Y. Du, and Z. Jin, *Org. Lett.*, 2003, **5**, 4481.
- 2003OL4521 D. L. Aubele, C. A. Lee, and P. E. Floreancig, *Org. Lett.*, 2003, **5**, 4521.
- 2003OL4827 S. Pache and M. Lautens, *Org. Lett.*, 2003, **5**, 4827.
- 2003OL4903 D. K. Rayabarapu, P. Shukla, and C.-H. Cheng, *Org. Lett.*, 2003, **5**, 4903.
- 2003OM3915 C. P. Casey, T. L. Dzwiniel, S. Kraft, and I. A. Guzei, *Organometallics*, 2003, **22**, 3915.
- 2003OM4170 S. M. Stokes, F. Ding, P. L. Smith, J. M. Keane, M. E. Kopach, R. Jervis, M. Sabat, and W. D. Harman, *Organometallics*, 2003, **22**, 4170.
- 2003PHC(15)360 J. D. Hepworth and B. M. Heron, in 'Progress in Heterocyclic Chemistry', G. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2003, vol. 15, p. 360.
- 2003PS143 A. Shochravi, M. M. Heravi, and H. Valizadeh, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 143.
- 2003PS501 A. Shochravi, H. Valizadeh, and M. M. Heravi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 501.
- 2003PS1457 R. Hekmat-Shoar, S. Sour, and F. Faridbod, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 1457.
- 2003PS2627 I. Yavari, F. Nasiri, and H. Djahaniani, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 2627.
- 2003RJO103 E. S. Vostrov, E. V. Leont'eva, O. P. Tarasova, and A. N. Maslivets, *Russ. J. Org. Chem.*, 2003, **39**, 103.
- 2003S673 K. Kobayashi, K. Nomura, T. Ogata, M. Tanmatsu, O. Morikawa, and H. Konishi, *Synthesis*, 2003, 673.
- 2003SL1413 K. Inoue, H. Suga, S. Inoue, H. Sato, and A. Kakehi, *Synthesis*, 2003, 1413.
- 2003SL1878 T. Mas, *Synthesis*, 2003, 1878.
- 2003SL2331 F. Fringuelli, O. Piermatti, and F. Pizzo, *Synthesis*, 2003, 2331.
- 2003SC119 X.-S. Wang, D.-Q. Shi, S.-J. Tu, and C.-S. Yao, *Synth. Commun.*, 2003, **33**, 119.
- 2003SC3299 M. N. Deshmukh, R. Burud, C. Baldino, P. C. M. Chan, and J. Liu, *Synth. Commun.*, 2003, **33**, 3299.
- 2003SC3035 M. M. Alam, R. Varala, and S. R. Adapa, *Synth. Commun.*, 2003, **33**, 3035.
- 2003SC3747 M. Kidwai, R. Mohan, and S. Rastogi, *Synth. Commun.*, 2003, **33**, 3747.
- 2003SL107 L. Fournier, A. GaudeL-Siri, P. J. Kochienski, and J.-M. Pons, *Synlett*, 2003, 107.
- 2003SL253 E. C. Gravett, P. J. Hilton, K. Jones, and J.-M. Peron, *Synlett*, 2003, 253.
- 2003SL411 F. Doi, T. Ogami, T. Sugai, and S. Nishiyama, *Synlett*, 2003, 411.
- 2003SL1040 Y. Iguchi, R. Itooka, and N. Miya, *Synlett*, 2003, 1040.
- 2003SL1491 M. C. Willis and S. E. Flower, *Synlett*, 2003, 1491.
- 2003SL1524 D. Rodríguez, M. F. Martínez-Esperon, L. Castedo, D. Domínguez, and C. Saá, *Synlett*, 2003, 1524.
- 2003SL1698 J. Pietruszka and T. Wilhelm, *Synlett*, 2003, 1698.
- 2003SL1859 W. A. L. van Otterlo, R. Pathak, and C. B. de Koning, *Synlett*, 2003, 1859.
- 2003SL1934 M. S. Kerr and T. Rovis, *Synlett*, 2003, 1934.
- 2003SL2001 T.-S. Jin, J.-C. Xiao, S.-J. Wang, T.-S. Li, and X.-R. Song, *Synlett*, 2003, 2001.
- 2003SL2092 A. G. Csaky, M. Mba, and J. Plumet, *Synlett*, 2003, 2092.
- 2003SL2395 T. Kamei, M. Shindo, and K. Shishido, *Synlett*, 2003, 2395.
- 2003T1289 I. Yavari, M. Anary-Abbasinejad, A. Alizadeh, and Z. Hossaini, *Tetrahedron*, 2003, **59**, 1289.
- 2003T2001 I. Yavari and M. Bayat, *Tetrahedron*, 2003, **59**, 2001.
- 2003T2151 K. C. Majumdar, P. K. Basu, P. P. Mukhopadhyay, S. K. Ghosh, and P. Biswas, *Tetrahedron*, 2003, **59**, 2151.
- 2003T2625 V. Y. Sosnovskikh, B. I. Usachev, D. V. Sevenard, and G.-V. Röschenthaler, *Tetrahedron*, 2003, **59**, 2625.

- 2003T2651 M. Sato, T. Oda, K.-I. Iwamoto, and E. Murakami, *Tetrahedron*, 2003, **59**, 2651.
2003T2765 M. Yu and B. L. Pagenkopf, *Tetrahedron*, 2003, **59**, 2765.
2003T3009 W. Zhang and G. Pugh, *Tetrahedron*, 2003, **59**, 3009.
2003T3521 J. Kawakami, M. Mihara, I. Kamiya, M. Takeba, A. Ogawa, and N. Sonoda, *Tetrahedron*, 2003, **59**, 3521.
2003T6251 B. Gabriele, G. Salerno, A. Fazio, and R. Pittelli, *Tetrahedron*, 2003, **59**, 6251.
2003T6819 S. M. Berberich, R. J. Cherney, J. Colucci, C. Courillon, L. S. Geraci, T. A. Kirkland, M. A. Marx, M. F. Schneider, and S. F. Martin, *Tetrahedron*, 2003, **59**, 6819.
2003T8117 S. Muthusamy, S. Babu, S. Arulananda, and M. Nethaji, *Tetrahedron*, 2003, **59**, 8117.
2003T8375 S. K. Sabui and R. V. Venkateswaran, *Tetrahedron*, 2003, **59**, 8375.
2003T8859 S. J. Pastine, S. W. Youn, and D. Sames, *Tetrahedron*, 2003, **59**, 8859.
2003T9161 D. B. Batanero and F. Barba, *Tetrahedron*, 2003, **59**, 9161.
2003T9333 Y. R. Lee, B. S. Cho, and H. J. Kwon, *Tetrahedron*, 2003, **59**, 9333.
2003T9409 I. Yavari, H. Djahaniani, and F. Nasiri, *Tetrahedron*, 2003, **59**, 9409.
2003T9641 O. Roy, F. Loiseau, A. Riahi, F. Henin, and J. Muzart, *Tetrahedron*, 2003, **59**, 9641.
2003T10509 H. Furuno, T. Hayano, T. Kambara, Y. Sugimoto, T. Hanamoto, Y. Tanaka, Y. Z. Jin, T. Kagawa, and J. Inanaga, *Tetrahedron*, 2003, **59**, 10509.
2003TA489 J. L. Vicario, D. Badia, and L. Carrillo, *Tetrahedron Asymmetry*, 2003, **14**, 489.
2003TA1529 M. Kawasaki, H. Kakuda, M. Goto, S. Kawabata, and T. Kmetani, *Tetrahedron Asymmetry*, 2003, **14**, 1529.
2003TL57 T. M. Hansen, G. J. Florence, P. Lugo-Mas, J. Chen, J. N. Abrams, and C. J. Forsyth, *Tetrahedron Lett.*, 2003, **44**, 57.
2003TL127 G. Liu and X. Lu, *Tetrahedron Lett.*, 2003, **44**, 127.
2003TL311 W. A. L. van Otterlo, E. L. Ngidi, E. M. Cayanis, and C. B. de Koning, *Tetrahedron Lett.*, 2003, **44**, 311.
2003TL365 J. D. Rosen, T. D. Nelson, M. A. Huffman, and J. M. McNamara, *Tetrahedron Lett.*, 2003, **44**, 365.
2003TL435 C. Hardouin, L. Burgaud, A. Valleix, and E. Doris, *Tetrahedron Lett.*, 2003, **44**, 435.
2003TL835 A. Massa, M. R. Acocella, M. De Rosa, A. Soriente, R. Villano, and A. Scettri, *Tetrahedron Lett.*, 2003, **44**, 835.
2003TL1461 D. E. Daia, C. D. Gabbutt, B. M. Heron, J. D. Hepworth, M. B. Hursthouse, and K. M. A. Malik, *Tetrahedron Lett.*, 2003, **44**, 1461.
2003TL2061 I. Hachiya, H. Shibuya, and M. Shimizu, *Tetrahedron Lett.*, 2003, **44**, 2061.
2003TL2097 V. Y. Sosnovskikh, D. V. Sevenard, B. I. Usachev, and G.-V. Röschenthaler, *Tetrahedron Lett.*, 2003, **44**, 2097.
2003TL2117 T. R. Sharp, J. F. Lambert, and S. W. Walinsky, *Tetrahedron Lett.*, 2003, **44**, 2117.
2003TL2893 H. Zhai, Q. Chen, J. Zhao, S. Luo, and X. Jia, *Tetrahedron Lett.*, 2003, **44**, 2893.
2003TL3645 C. Pierres, P. George, L. Van Hijfte, J.-B. Ducep, M. Hibert, and A. Mann, *Tetrahedron Lett.*, 2003, **44**, 3645.
2003TL3697 J. S. Yadav, B. V. S. Reddy, D. Narsimhaswamy, K. Narsimulu, and A. C. Kunwar, *Tetrahedron Lett.*, 2003, **44**, 3697.
2003TL3749 I. Paterson and C. A. Luckhurst, *Tetrahedron Lett.*, 2003, **44**, 3749.
2003TL3785 C. H. Oh and S. J. Park, *Tetrahedron Lett.*, 2003, **44**, 3785.
2003TL3813 C.-F. Yao, Y.-J. Jang, and M.-C. Yan, *Tetrahedron Lett.*, 2003, **44**, 3813.
2003TL4023 C. A. I. Capaccio and O. Varela, *Tetrahedron Lett.*, 2003, **44**, 4023.
2003TL4199 T. N. Van, S. Debenedetti, and N. De Kimpe, *Tetrahedron Lett.*, 2003, **44**, 4199.
2003TL4471 S. BouzBouz and J. Cossy, *Tetrahedron Lett.*, 2003, **44**, 4471.
2003TL4877 F. Doi, T. Ogami, T. Sugai, and S. Nishiyama, *Tetrahedron Lett.*, 2003, **44**, 4877.
2003TL5015 S. V. Kandula, V. G. Puranik, and P. Kumar, *Tetrahedron Lett.*, 2003, **44**, 5015.
2003TL6129 H. Furuno, T. Kambara, Y. Tanaka, T. Hanamoto, T. Kagawa, and J. Inanaga, *Tetrahedron Lett.*, 2003, **44**, 6129.
2003TL7205 M. Shoji, S. Kishida, Y. Kadera, I. Shiina, H. Kadeya, H. Osada, and Y. Hayashi, *Tetrahedron Lett.*, 2003, **44**, 7205.
2003TL7217 L. Liang, L. Su, X. Li, and A. S. C. Chan, *Tetrahedron Lett.*, 2003, **44**, 7217.
2003TL7455 G. Sabitha, G. S. K. K. Reddy, M. Rajkumar, J. S. Yadav, K. V. S. Ramakrishna, and A. C. Kunwar, *Tetrahedron Lett.*, 2003, **44**, 7455.
2003TL7623 D. V. Sevenard, V. Y. Sosnovskikh, A. A. Kolomeitsev, M. H. Königsmann, and G.-V. Roschenthaler, *Tetrahedron Lett.*, 2003, **44**, 7623.
2003TL7633 S. Rousset, M. Abarbri, J. Thibonnet, J.-L. Parrain, and A. Duchêne, *Tetrahedron Lett.*, 2003, **44**, 7633.
2003TL7659 A. K. Ghosh and J.-H. Kim, *Tetrahedron Lett.*, 2003, **44**, 7659.
2003TL8227 U. Murali-Krishna, G. S. C. Srikanth, and G. K. Trivedi, *Tetrahedron Lett.*, 2003, **44**, 8227.
2003TL8471 D. Regas, J. M. Ruiz, M. M. Alfonso, A. Galindo, and J. A. Palenzuela, *Tetrahedron Lett.*, 2003, **44**, 8471.
2003TL8721 A. De Fatima and R. A. Pilli, *Tetrahedron Lett.*, 2003, **44**, 8721.
2003TL8991 R. Bernini, A. Coratti, G. Fabrizi, and A. Goggiamani, *Tetrahedron Lett.*, 2003, **44**, 8991.
2003TL9135 M. B. Berry, R. J. Griffiths, M. J. Sangane, G. Patrick, and D. K. Wheligan, *Tetrahedron Lett.*, 2003, **44**, 9135.
2003TL9271 A. M. Bello and L. P. Kotra, *Tetrahedron Lett.*, 2003, **44**, 9271.
2003TL9283 F. Lassagne and F. Pochat, *Tetrahedron Lett.*, 2003, **44**, 9283.
2004AGE115 B. Lesch and S. Bräse, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 115.
2004AGE1239 J. Zhu, A. R. Germain, and J. A. Porco, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 1239.
2004AGE2665 M. Anada, T. Washio, N. Shimada, S. Kitagaki, M. Nakajima, M. Shiro, and S. Hashimoto, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 2665.
2004AGE3432 M.-P. Brun, L. Bischoff, and C. Garbay, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 3432.
2004AGE3459 J. H. Koh and M. R. Gagne, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 3459.
2004AGE4788 P. A. Evans, D. K. Leahy, W. J. Andrews, and D. Uruguchi, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 4788.
2004AGE5369 T. Kondo, Y. Taguchi, Y. Kaneko, M. Niimi, and T. Mitsudo, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 5369.
2004AGE5997 C. J. Kressierer and T. J. J. Mueller, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 5997.
2004AGE6183 C. E. Song, D. Jung, S. Y. Choung, E. J. Roh, and S. Lee, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 6183.
2004ARK138 R. Suthunuru and E. Biehl, *ARKIVOC*, 2004, **1**, 138.
2004BCJ549 J. M. Khurana and P. Sharma, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 549.
2004BCJ1925 A. Shimabashi, A. Tsuchiya, M. Imoto, and S. Nishiyama, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1925.
2004BCJ2129 K. Fujiwara and A. Murai, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 2129.
2004BCJ2257 F. Doi, T. Ohara, T. Ogami, K. Higashinakasu, K. Hasegawa, and S. Nishiyama, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 2257.

- 2004BKC1123 J. H. Cha, Y. S. Cho, H. Y. Koh, E. Lee, Y.-T. Kim, H.-H. Yang, and H.-Y. Kang, *Bull. Korean Chem. Soc.*, 2004, **25**, 1123.
- 2004BKC1625 C.-M. Yu, M.-S. Shin, and E.-Y. Cho, *Bull. Korean Chem. Soc.*, 2004, **25**, 1625.
- 2004BKC1627 H.-Y. Kang and Y.-K. Yu, *Bull. Korean Chem. Soc.*, 2004, **25**, 1627.
- 2004BMC3521 S. B. Wan, D. Chen, Q. P. Dou, and T. H. Chan, *Bioorg. Med. Chem.*, 2004, **12**, 3521.
- 2004BML6083 J. J. J. Leahy, B. T. Golding, R. J. Griffin, I. R. Harcastle, C. Richardson, L. Rigoreau, and G. C. M. Smith, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 6083.
- 2004CC1500 M. Nechab, C. Einhorn, and J. Einhorn, *J. Chem. Soc., Chem. Commun.*, 2004, 1500.
- 2004CEJ1527 S.-Y. Tosaki, Y. Horiuchi, T. Nemoto, T. Ohshima, and M. Shibasaki, *Chem. Eur. J.*, 2004, **10**, 1527.
- 2004CEJ2991 D. K. Rayabarapu, H.-T. Chang, and C.-H. Cheng, *Chem. Eur. J.*, 2004, **10**, 2991.
- 2004CEJ4341 R. von Essen, P. von Zezschwitz, D. Vidovic, and A. de Meijere, *Chem. Eur. J.*, 2004, **10**, 4341.
- 2004CEJ5964 H. Du, D. Zhao, and K. Ding, *Chem. Eur. J.*, 2004, **10**, 5964.
- 2004CJC659 J. R. Downs, S. P. Grant, J. D. Townsend, D. A. Schady, S. J. Pastine, M. C. Embree, C. R. Metz, W. T. Pennington, R. D. Bailey-Walsch, and C. F. Beam, *Can. J. Chem.*, 2004, **82**, 659.
- 2004CL716 K. Iba, S. Fukuyoshi, and T. Kusumi, *Chem. Lett.*, 2004, **33**, 716.
- 2004CL848 K. Tanaka, K. Taguchi, S. Iwata, and T. Irie, *Chem. Lett.*, 2004, **33**, 848.
- 2004CL1058 S. H. Mashraqui, M. B. Patil, H. D. Mistry, S. Ghadigaonkar, and A. Meetsma, *Chem. Lett.*, 2004, **33**, 1058.
- 2004CL1436 J. S. Yadav, B. V. S. Reddy, and P. N. Reddy, *Chem. Lett.*, 2004, **33**, 1436.
- 2004CL1454 T. Tozawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, 2004, **33**, 1454.
- 2004COR1 H. Yuan, B. Junker, P. Helquist, and R. E. Taylor, *Curr. Org. Synth.*, 2004, **1**, 1.
- 2004CRV2199 A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199.
- 2004EJO372 M. P. Sibi, K. Patil, and T. R. Rheault, *Eur. J. Org. Chem.*, 2004, 372.
- 2004EJO1261 K. Krohn, M. Riaz, and U. Floerke, *Eur. J. Org. Chem.*, 2004, 1261.
- 2004EJO2093 K. A. Jorgensen, *Eur. J. Org. Chem.*, 2004, 2093.
- 2004EJO4416 R. G. F. Giles, I. R. Green, and N. van Eeden, *Eur. J. Org. Chem.*, 2004, 4416.
- 2004HAC85 E. M. Keshk, *Heteroatom Chem.*, 2004, **15**, 85.
- 2004HCA2750 G. Frateer, U. Mueller, and P. Kraft, *Helv. Chim. Acta*, 2004, **87**, 2750.
- 2004JA1310 C. Li and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 1310.
- 2004JA1843 R. Astala and S. M. Auerbach, *J. Am. Chem. Soc.*, 2004, **126**, 1843.
- 2004JA3416 J. Barluenga, M. Trincado, E. Rubio, and J. M. Gonzalez, *J. Am. Chem. Soc.*, 2004, **126**, 3416.
- 2004JA3428 R. S. Babu, M. Zhou, and G. A. O'Doherty, *J. Am. Chem. Soc.*, 2004, **126**, 3428.
- 2004JA5964 Z. Shi and C. He, *J. Am. Chem. Soc.*, 2004, **126**, 5964.
- 2004JA7460 Q. Huang, A. Fazio, G. Dai, M. A. Campo, and R. C. Larock, *J. Am. Chem. Soc.*, 2004, **126**, 7460.
- 2004JA8642 A. P. Evans and M. J. Lawler, *J. Am. Chem. Soc.*, 2004, **126**, 8642.
- 2004JA8876 M. S. Kerr and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 8876.
- 2004JA9186 L.-C. Campeau, M. Parisien, M. Leblanc, and K. Fagnou, *J. Am. Chem. Soc.*, 2004, **126**, 9186.
- 2004JA9645 S. Ma, L. Lu, and J. Zhang, *J. Am. Chem. Soc.*, 2004, **126**, 9645.
- 2004JA9904 R. Jasti, J. Vitale, and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2004, **126**, 9904.
- 2004JA11122 H. Ishibashi, K. Ishihara, and H. Kazuaki, *J. Am. Chem. Soc.*, 2004, **126**, 11122.
- 2004JA11326 C. Gaul, J. T. Njardarson, D. Shan, D. C. Dorn, K.-D. Wu, W. P. Tong, X.-Y. Huang, M. A. S. Moore, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2004, **126**, 11326.
- 2004JA11966 B. M. Trost, H. C. Shen, Li. Dong, J.-P. Surivet, and C. Sylvain, *J. Am. Chem. Soc.*, 2004, **126**, 11966.
- 2004JA12216 K. M. Cossey and R. L. Funk, *J. Am. Chem. Soc.*, 2004, **126**, 12216.
- 2004JA12565 B. M. Trost, H. C. Shen, and J.-P. Surivet, *J. Am. Chem. Soc.*, 2004, **126**, 12565.
- 2004JA12596 L. Wang, J. R. Seiders, and P. E. Floreancig, *J. Am. Chem. Soc.*, 2004, **126**, 12596.
- 2004JA13596 Z. Shi and C. He, *J. Am. Chem. Soc.*, 2004, **126**, 13596.
- 2004JA15662 J. E. Dalgard and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2004, **126**, 15662.
- 2004JA15978 B. D. Sherry and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 15978.
- 2004JA16066 Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, and S. Uemura, *J. Am. Chem. Soc.*, 2004, **126**, 16066.
- 2004JME3927 P. Holmberg, D. Sohn, R. Leideborg, P. Caldirola, P. Zlatoidsky, S. Hanson, N. Mohell, S. Rosqvist, G. Nordvall, A. M. Johansson, and R. Johansson, *J. Med. Chem.*, 2004, **47**, 3927.
- 2004JOC468 S. Braune, M. Pohlman, and U. Kazmaier, *J. Org. Chem.*, 2004, **69**, 468.
- 2004JOC536 A. T. Balaban, I. Ghiviriga, E. M. Czerwinski, P. De, and R. Faust, *J. Org. Chem.*, 2004, **69**, 536.
- 2004JOC839 X. Huang, H. Zhou, and W. Chen, *J. Org. Chem.*, 2004, **69**, 839.
- 2004JOC1432 G. L. Ning, X. C. Li, M. Munakata, W. Y. Gong, M. Maekawa, and T. Kamikawa, *J. Org. Chem.*, 2004, **69**, 1432.
- 2004JOC2760 E. Sekino, T. Kumamoto, T. Tanaka, T. Ikeda, and T. Ishikawa, *J. Org. Chem.*, 2004, **69**, 2760.
- 2004JOC3282 D. L. J. Clive, S. P. Fletcher, and D. Liu, *J. Org. Chem.*, 2004, **69**, 3282.
- 2004JOC3408 Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, and S. Uemura, *J. Org. Chem.*, 2004, **69**, 3408.
- 2004JOC3669 Z. Shi and C. He, *J. Org. Chem.*, 2004, **69**, 3669.
- 2004JOC3961 Y.-J. Jang, M.-C. Yan, Y.-F. Lin, and C.-F. Yao, *J. Org. Chem.*, 2004, **69**, 3961.
- 2004JOC4500 H. Li, H. Yang, J. L. Petersen, and K. K. Wang, *J. Org. Chem.*, 2004, **69**, 4500.
- 2004JOC4701 G. Lu and H. C. Malinakova, *J. Org. Chem.*, 2004, **69**, 4701.
- 2004JOC5011 C. Dong and H. Alper, *J. Org. Chem.*, 2004, **69**, 5011.
- 2004JOC5139 N. T. Patil and Y. Yamamoto, *J. Org. Chem.*, 2004, **69**, 5139.
- 2004JOC5147 Q. J. Zhou, K. Worm, and R. E. Dolle, *J. Org. Chem.*, 2004, **69**, 5147.
- 2004JOC5813 B. M. Trost, *J. Org. Chem.*, 2004, **69**, 5813.
- 2004JOC6294 P. V. Ramachandran, B. Prabhudas, J. S. Chandra, and M. V. R. Reddy, *J. Org. Chem.*, 2004, **69**, 6294.
- 2004JOC6697 Y. Yamamoto, S. Kuwabara, Y. Ando, H. Nagata, H. Nishiyama, and K. Itoh, *J. Org. Chem.*, 2004, **69**, 6697.
- 2004JOC6867 C. Mukai, M. Ohta, H. Yamashita, and S. Kitagaki, *J. Org. Chem.*, 2004, **69**, 6867.
- 2004JOC6942 Y. Terao, M. Nomoto, T. Satoh, M. Miura, and M. Nomura, *J. Org. Chem.*, 2004, **69**, 6942.

- 2004JOC8266 G. Lu and H. C. Malinakova, *J. Org. Chem.*, 2004, **69**, 8266.
- 2004JOC8045 A. Duursma, J.-G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. Minnaars, and B. L. Feringa, *J. Org. Chem.*, 2004, **69**, 8045.
- 2004JOC8594 P. Bhaket, C. S. Stauffer, and A. Datta, *J. Org. Chem.*, 2004, **69**, 8594.
- 2004JOC9196 C. Selenski and T. R. R. Pettus, *J. Org. Chem.*, 2004, **69**, 9196.
- 2004M1409 D. Ghazanfari, F. Najafizadeh, and F. Khosravi, *Monatsh. Chem.*, 2004, **135**, 1409.
- 2004MOL498 C. D. Donner, M. Gill, and L. M. Tewierik, *Molecules*, 2004, **9**, 498.
- 2004NJC771 A. Nelson, *New J. Chem.*, 2004, **28**, 771.
- 2004OBC28 Y. Liu, D. Dong, Q. Liu, Y. Qi, and Z. Wang, *Org. Biomol. Chem.*, 2004, **2**, 28.
- 2004OBC965 D. G. Hulcoop, H. M. Sheldrake, and J. W. Burton, *Org. Biomol. Chem.*, 2004, **2**, 965.
- 2004OBC1116 B. Plietker, M. Niggemann, and A. Pollrich, *Org. Biomol. Chem.*, 2004, **2**, 1116.
- 2004OBC2461 E. M. Mutlane, J. P. Michael, I. R. Green, and C. B. De Koning, *Org. Biomol. Chem.*, 2004, **2**, 2461.
- 2004OBC3026 I. Paterson, A. Steven, and C. A. Luckhurst, *Org. Biomol. Chem.*, 2004, **2**, 3026.
- 2004OBC3134 S. Yamazaki, S. Morikawa, Y. Iwata, M. Yamamoto, and K. Kuramoto, *Org. Biomol. Chem.*, 2004, **2**, 3134.
- 2004OL91 M. Reiter, S. Ropp, and V. Gouverneur, *Org. Lett.*, 2004, **6**, 91.
- 2004OL123 S. Das, L.-S. Li, and S. C. Sinha, *Org. Lett.*, 2004, **6**, 123.
- 2004OL581 S. W. Youn, S. J. Pastine, and D. Sames, *Org. Lett.*, 2004, **6**, 581.
- 2004OL1581 D. Yue, N. D. Cà, and R. C. Larock, *Org. Lett.*, 2004, **6**, 1581.
- 2004OL1869 K. S. Feldman and D. B. Vidulova, *Org. Lett.*, 2004, **6**, 1869.
- 2004OL2185 Q. Fan, L. Lin, J. Liu, Y. Huang, X. Feng, and G. Zhang, *Org. Lett.*, 2004, **6**, 2185.
- 2004OL3191 C. Nevado, C. Ferrer, and A. M. Echavarren, *Org. Lett.*, 2004, **6**, 3191.
- 2004OL3203 N. F. Langille and J. S. Panek, *Org. Lett.*, 2004, **6**, 3203.
- 2004OL3735 J. D. Winkler and P. J. Mikochik, *Org. Lett.*, 2004, **6**, 3735.
- 2004OL3877 E. Alcazar, J. M. Pletcher, and F. E. McDonald, *Org. Lett.*, 2004, **6**, 3877.
- 2004OL4049 H. Yoshida, M. Watanabe, H. Fukushima, J. Oshita, and A. Kunai, *Org. Lett.*, 2004, **6**, 4049.
- 2004OL4235 B. M. Trost, M. T. Rudd, M. G. Costa, P. I. Lee, and A. E. Pomerantz, *Org. Lett.*, 2004, **6**, 4235.
- 2004OL4343 B. Hulin, L. S. Newton, S. Cabral, A. J. Walker, and J. Bordner, *Org. Lett.*, 2004, **6**, 4343.
- 2004OL4535 M. Shoji, T. Uno, and Y. Hayashi, *Org. Lett.*, 2004, **6**, 4535.
- 2004OL4563 T. Saitoh, S. Yoshida, and J. Ichikawa, *Org. Lett.*, 2004, **6**, 4563.
- 2004OL4949 M. M. Quintal, K. D. Closser, and K. M. Shea, *Org. Lett.*, 2004, **6**, 4949.
- 2004PHC(16)405 J. D. Hepworth and B. M. Heron, in 'Progress in Heterocyclic Chemistry', G. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2004, vol. 16, p. 405.
- 2004PS529 A. Ramazani and A. Souldozi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 529.
- 2004PS2163 I. Yavari, R. Amiri, and M. Haghdadi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 2163.
- 2004S121 G. Pave, P. Chalard, M.-C. Viaud-Massuard, Y. Troin, and G. Guillaumet, *Synthesis*, 2004, 121.
- 2004S679 I. Yavari, H. Djahaniani, and F. Nasiri, *Synthesis*, 2004, 679.
- 2004S949 R. S. Kumar, R. Nagarajan, and P. T. Perumal, *Synthesis*, 2004, 949.
- 2004S1115 M. Yus, B. Moreno, and F. Foubelo, *Synthesis*, 2004, 1115.
- 2004S1409 K. Sato, S. Yudha, N. Asao, and Y. Yamamoto, *Synthesis*, 2004, 1409.
- 2004S1466 M. Kotani, K. Yamamoto, J. Oyamada, Y. Fujiwara, and T. Kitamura, *Synthesis*, 2004, 1466.
- 2004S1601 R. G. F. Giles, I. R. Green, and N. van Eeden, *Synthesis*, 2004, 1601.
- 2004S1775 G. Athanasellis, G. Melagraki, H. Chatzidakis, A. Afantitis, A. Detsi, O. Igglessi-Markopoulou, and J. Markopoulos, *Synthesis*, 2004, 1775.
- 2004S1783 J. S. Yadav, B. V. S. Reddy, V. Naveenkumar, R. S. Rao, and K. Nagaiah, *Synthesis*, 2004, 1783.
- 2004S2620 Y. S. Cho, B. K. Jun, A. N. Pae, J. H. Cha, H. Y. Koh, M. H. Chang, and S.-Y. Han, *Synthesis*, 2004, 2620.
- 2004SC1425 X.-S. Wang, D.-Q. Shi, Y. Du, Y. Zhou, and S.-J. Tu, *Synth. Commun.*, 2004, **34**, 1425.
- 2004SC1909 N. Kalyanam, A. Nagarajan, and M. Majeed, *Synth. Commun.*, 2004, **34**, 1909.
- 2004SC3129 S. H. Mashraqui, D. Vashi, and H. D. Mistry, *Synth. Commun.*, 2004, **34**, 3129.
- 2004SC3997 G. Smitha and C. S. Reddy, *Synth. Commun.*, 2004, **34**, 3997.
- 2004SC4507 Q. Zhang, Y. Chen, Y. Xia, Z. Yang, and P. Xia, *Synth. Commun.*, 2004, **34**, 4507.
- 2004SL45 H.-Y. Kang, T.-T. Kim, Y.-K. Yu, J. H. Cha, Y. S. Cho, and H. Y. Koh, *Synlett*, 2004, 45.
- 2004SL116 K. Suzuki, T. Tsuruga, K. Hiranuma, and M. Yamaura, *Synlett*, 2004, 116.
- 2004SL368 M. Curini, F. Epifano, M. C. Marcotullio, and F. Montanari, *Synlett*, 2004, 368.
- 2004SL481 Y. Nagao, S. Tanaka, K. Hayashi, S. Sano, and M. Shiro, *Synlett*, 2004, 481.
- 2004SL871 T.-S. Jin, A.-Q. Wang, X. Wang, J. S. Zhang, and T.-S. Li, *Synlett*, 2004, 871.
- 2004SL1101 C. Selenski, L. H. Mejorado, and T. R. R. Pettus, *Synlett*, 2004, 1101.
- 2004SL1175 Y.-G. Wang, X.-F. Lin, and S.-L. Cui, *Synlett*, 2004, 1175.
- 2004SL1243 M. Mondal and N. P. Argade, *Synlett*, 2004, 1243.
- 2004SL1715 K. V. N. S. Srinivas and B. Das, *Synlett*, 2004, 1715.
- 2004SL1755 P. Kwiatkowski, M. Asztemborska, and J. Jurczak, *Synlett*, 2004, 1755.
- 2004SL1772 Z. Fu, B. Gao, Z. Yu, L. Yu, Y. Huang, X. Feng, and G. Zhang, *Synlett*, 2004, 1772.
- 2004SL1851 M. Sasaki and H. Fuwa, *Synlett*, 2004, 1851.
- 2004SL1909 P. R. Singh, D. U. Singh, and S. D. Samant, *Synlett*, 2004, 1909.
- 2004SL2028 M. R. Dintzner, K. M. McClelland, K. M. Morse, and M. H. Akroush, *Synlett*, 2004, 2028.
- 2004SL2194 G. W. Kabalka, B. Venkataiah, and B. C. Das, *Synlett*, 2004, 2194.
- 2004SL2425 M. Valenzuela, M. P. Doyle, C. Hedberg, W. Hu, and A. Holmstrom, *Synlett*, 2004, 2425.
- 2004SL2541 K. H. Park, I. G. Jung, and Y. K. Chung, *Synlett*, 2004, 2541.
- 2004SL2618 R. Ballini, L. Barboni, D. Fiorni, and A. Palmieri, *Synlett*, 2004, 2618.
- 2004SL2779 J. T. Anders, V. T. H. Nguyen, and P. Langer, *Synlett*, 2004, 2779.

- 2004T449 A. M. Bernard, C. Floris, A. Frongia, P. P. Piras, and F. Secci, *Tetrahedron*, 2004, **60**, 449.
- 2004T521 E. Sundby, L. Perk, T. Anthonsen, A. J. Aasen, and T. V. Hansen, *Tetrahedron*, 2004, **60**, 521.
- 2004T1049 T. Janeczek and T. Wasek, *Tetrahedron*, 2004, **60**, 1049.
- 2004T1659 L. Fournier, P. Kocienski, and J.-M. Pons, *Tetrahedron*, 2004, **60**, 1659.
- 2004T2525 M. G. Bogdanov and M. D. Palamareva, *Tetrahedron*, 2004, **60**, 2525.
- 2004T2629 C. B. de Koning, R. G. F. Giles, I. R. Green, and N. M. Jahed, *Tetrahedron*, 2004, **60**, 2629.
- 2004T4037 J.-Y. Goujon, F. Zammattio, J.-M. Chrétien, and I. Beaudet, *Tetrahedron*, 2004, **60**, 4037.
- 2004T4223 G. A. Kraus, T. Nguyen, J. Bae, J. Hostetter, and E. Steadham, *Tetrahedron*, 2004, **60**, 4223.
- 2004T5069 A. D. Thomas, J. Asokan, and C. V. Asokan, *Tetrahedron*, 2004, **60**, 5069.
- 2004T5751 M. A. Brimble, C. Burgess, R. Halim, M. Petersson, and J. Ray, *Tetrahedron*, 2004, **60**, 5751.
- 2004T5931 H. Sheibani, M. R. Islami, H. Khabazzadeh, and K. Saidi, *Tetrahedron*, 2004, **60**, 5931.
- 2004T7405 J. H. Koh, C. Mascarenhas, and M. R. Gagne, *Tetrahedron*, 2004, **60**, 7405.
- 2004T7431 T. N. Tekavec, A. M. Arif, and J. Louie, *Tetrahedron*, 2004, **60**, 7431.
- 2004T8043 D. Banti, E. Groaz, and M. North, *Tetrahedron*, 2004, **60**, 8043.
- 2004T8207 S. B. Wan and T. H. Chan, *Tetrahedron*, 2004, **60**, 8207.
- 2004T11415 A. Shaabani, P. Mirzaei, S. Naderi, and D. G. Lee, *Tetrahedron*, 2004, **60**, 11415.
- 2004TA29 Q. Wang, X. She, X. Ren, J. Ma, and X. Pan, *Tetrahedron Asymmetry*, 2004, **15**, 29.
- 2004TA1987 C. Wolf, Z. Fadul, P. A. Hawes, and E. C. Volpe, *Tetrahedron Asymmetry*, 2004, **15**, 1987.
- 2004TA2575 L. Liang, M. Yan, Y.-M. Li, and A. S. C. Chan, *Tetrahedron Asymmetry*, 2004, **15**, 2575.
- 2004TA3023 C. A. I. Capaccio and O. Varela, *Tetrahedron Asymmetry*, 2004, **15**, 3023.
- 2004TA3189 P. Kwiatowski, M. Asztomborska, and J. Jurczak, *Tetrahedron Asymmetry*, 2004, **15**, 3189.
- 2004TL83 M. Gruttadauria, P. Lo Meo, and R. Noto, *Tetrahedron Lett.*, 2004, **45**, 83.
- 2004TL293 K. Krohn and M. Riaz, *Tetrahedron Lett.*, 2004, **45**, 293.
- 2004TL309 J. N. Moorthy, N. Singhal, and P. Mal, *Tetrahedron Lett.*, 2004, **45**, 309.
- 2004TL387 K. M. Gurjar, Y. Pedduri, C. V. Ramana, V. G. Puranik, and R. G. Gonnade, *Tetrahedron Lett.*, 2004, **45**, 387.
- 2004TL847 G. J. Reddy, D. Latha, C. Thirupathiah, and K. S. Rao, *Tetrahedron Lett.*, 2004, **45**, 847.
- 2004TL849 P. Gupta, N. S. Vasudeva, and P. Kumar, *Tetrahedron Lett.*, 2004, **45**, 849.
- 2004TL939 A. Shimbashi, Y. Ishikawa, and S. Nishiyama, *Tetrahedron Lett.*, 2004, **45**, 939.
- 2004TL983 S. K. Sabui and R. V. Venkatswaran, *Tetrahedron Lett.*, 2004, **45**, 983.
- 2004TL1005 M. Li, J. Scott, and G. A. O'Doherty, *Tetrahedron Lett.*, 2004, **45**, 1005.
- 2004TL2293 H. Hamamoto, K. Hata, H. Nambu, Y. Shiozaki, H. Tohma, and Y. Kita, *Tetrahedron Lett.*, 2004, **45**, 2293.
- 2004TL2297 R. Maggi, R. Ballini, G. Sartori, and R. Sartorio, *Tetrahedron Lett.*, 2004, **45**, 2297.
- 2004TL2327 H. Abe, S. Takeda, T. Fujita, K. Nishioka, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett.*, 2004, **45**, 2327.
- 2004TL2413 V. Nair, L. Balagopal, R. Rajan, A. Deepthi, K. Mohanan, and N. P. Rath, *Tetrahedron Lett.*, 2004, **45**, 2413.
- 2004TL2615 S. BouzBouz, E. De Lemos, J. Cossy, J. Saez, X. Franck, and B. Figadere, *Tetrahedron Lett.*, 2004, **45**, 2615.
- 2004TL3373 V.-H. Nguyen and H. Nishino, *Tetrahedron Lett.*, 2004, **45**, 3373.
- 2004TL3443 T. N. Van and N. De Kimpe, *Tetrahedron Lett.*, 2004, **45**, 3443.
- 2004TL4253 G. W. O'Neil and A. J. Phillips, *Tetrahedron Lett.*, 2004, **45**, 4253.
- 2004TL4503 G. Rousseau, T. Strzalko, and M.-C. Roux, *Tetrahedron Lett.*, 2004, **45**, 4503.
- 2004TL4635 X. Wu, A. K. Mahalingam, Y. Wan, and M. Alterman, *Tetrahedron Lett.*, 2004, **45**, 4635.
- 2004TL4697 A. Merschaeft, P. Delbeke, D. Daloz, and G. Dive, *Tetrahedron Lett.*, 2004, **45**, 4697.
- 2004TL5117 N. Tahara, T. Fukuda, and M. Iwao, *Tetrahedron Lett.*, 2004, **45**, 5117.
- 2004TL5611 T. Colin, L. El Kaim, L. Gaultier, L. Grimaud, L. Gatay, and V. Michaut, *Tetrahedron Lett.*, 2004, **45**, 5611.
- 2004TL6169 T. Ghosh and C. Bandyopadhyay, *Tetrahedron Lett.*, 2004, **45**, 6169.
- 2004TL6299 T. Komiya, Y. Takaguchi, and S. Tsuboi, *Tetrahedron Lett.*, 2004, **45**, 6299.
- 2004TL6429 B. Alcaide, P. Almendros, T. Martinez-del Campo, and R. Rodriguez-Acebes, *Tetrahedron Lett.*, 2004, **45**, 6429.
- 2004TL6603 L. Boulard, S. BouzBouz, J. Cossy, X. Franck, and B. Figadere, *Tetrahedron Lett.*, 2004, **45**, 6603.
- 2004TL6871 K. C. Majumdar and S. K. Chattopadhyay, *Tetrahedron Lett.*, 2004, **45**, 6871.
- 2004TL6995 C. G. Saluste, S. Crumpler, M. Furber, and R. J. Whitby, *Tetrahedron Lett.*, 2004, **45**, 6995.
- 2004TL7351 V. Y. Sosnovskikh, B. I. Usachev, A. Y. Sizov, and M. I. Kodess, *Tetrahedron Lett.*, 2004, **45**, 7351.
- 2004TL7727 I. Devi and P. J. Bhuyan, *Tetrahedron Lett.*, 2004, **45**, 7727.
- 2004TL7895 D. Mal, A. Patra, and H. Roy, *Tetrahedron Lett.*, 2004, **45**, 7895.
- 2004TL7999 S. S. Bahekar and D. B. Shinde, *Tetrahedron Lett.*, 2004, **45**, 7999.
- 2004TL8387 K.-P. Chan and T.-P. Loh, *Tetrahedron Lett.*, 2004, **45**, 8387.
- 2004TL8583 S. Barroso, G. Blay, I. Fernández, and J. R. Pedro, *Tetrahedron Lett.*, 2004, **45**, 8583.
- 2004TL8935 G. P. Romanelli, D. Bennardi, D. M. Ruiz, G. Baronetti, H. J. Thomas, and J. C. Autino, *Tetrahedron Lett.*, 2004, **45**, 8935.
- 2004TL8999 A. Jha and J. Beal, *Tetrahedron Lett.*, 2004, **45**, 8999.
- 2004TL9061 P. A. Clarke and W. H. C. Martin, *Tetrahedron Lett.*, 2004, **45**, 9061.
- 2004TL9197 R. Akué-Gédu, J.-P. Hénichart, D. Couturier, and B. Rigo, *Tetrahedron Lett.*, 2004, **45**, 9197.
- 2004TL9299 S. Chandrasekhar, C. Narsimulu, S. S. Sultana, and M. S. Reddy, *Tetrahedron Lett.*, 2004, **45**, 9299.
- 2004TL9369 M. P. Nguyen, J. N. Arnold, K. E. Peterson, and R. S. Mohan, *Tetrahedron Lett.*, 2004, **45**, 9369.
- 2004TL9479 Z.-W. You, Y.-Y. Wu, and F.-L. Qing, *Tetrahedron Lett.*, 2004, **45**, 9479.
- 2005ACR423 I. Kadota and Y. Yamamoto, *Acc. Chem. Res.*, 2005, **38**, 423.
- 2005AGE257 L. F. Tietze, K. M. Sommer, J. Zinngrabe, and F. Stecker, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 257.
- 2005AGE756 K. C. Nicolaou, H. Xu, and M. Wartmann, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 756.
- 2005AGE4611 R. Shintani, W.-L. Duan, T. Nagano, A. Okada, and T. Hayashi, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 4611.
- 2005AGE4914 J. Kemper and A. Studer, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 4914.
- 2005AGE5306 M. K. Brown, S. J. Degrado, and A. H. Hoveyda, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 5306.
- 2005ARK27 B. Das, G. Mahender, H. Holla, and J. Banerjee, *ARKIVOC*, 2005, **3**, 27.

- 2005ARK144 D. K. Mohapatra and G. S. Yellol, *ARKIVOC*, 2005, **3**, 144.
- 2005ASC308 G. Battistuzzi, S. Cacchi, I. De Salve, G. Fabrizi, and L. M. Parisi, *Adv. Synth. Catal.*, 2005, **347**, 308.
- 2005ASC512 Y. Gu, J. Zhang, Z. Duan, and Y. Deng, *Adv. Synth. Catal.*, 2005, **347**, 512.
- 2005ASC555 B. Lesch, J. Toraeng, S. Vanderheiden, and S. Braese, *Adv. Synth. Catal.*, 2005, **347**, 555.
- 2005BCJ468 S. Aoki, J. Oyamada, and T. Kitamura, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 468.
- 2005BJO7 E. M. Flamme and W. R. Roush, *Beilstein J. Org. Chem.*, 2005, **1**, 7.
- 2005BK454 N. H. Lee, J. C. Byun, and T.-H. Oh, *Bull. Korean Chem. Soc.*, 2005, **26**, 454.
- 2005BK711 V. C. Nguyen, Y.-T. Kim, Y.-K. Yu, and H.-Y. Kang, *Bull. Korean Chem. Soc.*, 2005, **26**, 711.
- 2005BML1531 U. Albrecht, M. Lalk, and P. Langer, *Bioorg. Med. Chem.*, 2005, **13**, 1531.
- 2005BMC2177 S. B. Wan, K. R. Landis-Piwowar, D. J. Kuhn, D. Chen, Q. P. Dou, and T. H. Chan, *Bioorg. Med. Chem.*, 2005, **13**, 2177.
- 2005BMC2927 A. De Fatima, L. K. Kohn, M. A. Antonio, J. E. De Carvalho, and R. A. Pilli, *Bioorg. Med. Chem.*, 2005, **13**, 2927.
- 2005BMC4078 B. Bhattacharai and R. Garg, *Bioorg. Med. Chem.*, 2005, **13**, 4078.
- 2005BML2583 T. Suzuki, T. Yamada, K. Watanabe, and T. Katoh, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2583.
- 2005BML2633 J. C. Anderson, C. Headley, P. D. Stapleton, and P. W. Taylor, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2633.
- 2005BML2745 H. Lee, K. Lee, J.-K. Jung, J. Cho, and E. A. Theodorakis, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2745.
- 2005BML3257 C.-L. Sun, R.-F. Pang, H. Zhang, and M. Yang, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3257.
- 2005BTL365 H.-H. Woo, B. R. Jeong, and M. C. Hawes, *Biotechnol. Lett.*, 2007, **27**, 365.
- 2005CC195 S. M. Mennen, J. T. Blank, M. B. Tran-Dube, J. E. Imbriglio, and S. J. Miller, *J. Chem. Soc., Chem. Commun.*, 2005, 195.
- 2005CC666 S. Mendel, A. Arndt, and T. D. H. Bugg, *J. Chem. Soc., Chem. Commun.*, 2005, 666.
- 2005CC1061 P. A. Clarke, W. H. C. Martin, J. M. Hargreaves, C. Wilson, and A. J. Blake, *J. Chem. Soc., Chem. Commun.*, 2005, 1061.
- 2005CC2008 J. Barluenga, M. Trincado, M. Marco-Arias, A. Ballesteros, E. Rubio, and J. M. González, *J. Chem. Soc., Chem. Commun.*, 2005, 2008.
- 2005CC2689 L. Jimenez-Gonzalez, M. Alvarez-Corral, M. Munoz-Dorado, and I. Rodriguez-Garcia, *J. Chem. Soc., Chem. Commun.*, 2005, 2689.
- 2005CC2790 F. Garcia, J. M. Garcia, B. Garcia-Acosta, R. Martinez-Manez, F. Sancenon, and J. Soto, *J. Chem. Soc., Chem. Commun.*, 2005, 2790.
- 2005CC4429 S. Shin, A. K. Gupta, C. Y. Rhima, and C. H. Oh, *J. Chem. Soc., Chem. Commun.*, 2005, 4429.
- 2005CC5109 R. E. Gawley and S. Narayan, *J. Chem. Soc., Chem. Commun.*, 2005, 5109.
- 2005CHE1194 A. S. Dmitriev, S. A. Podelyakin, V. T. Abaev, and A. V. Butin, *Chem. Heterocycl. Comp. (Engl. Transl.)*, 2005, **41**, 1194.
- 2005CJB433 R. K. Ibrahim, *Can. J. Bot.*, 2005, **83**, 433.
- 2005CL514 T. Tozawa, Y. Yamane, and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 514.
- 2005CL588 Y. Sato, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 588.
- 2005CME713 B. Botta, A. Vitali, P. Menendez, D. Misiti, and G. D. Monache, *Curr. Med. Chem.*, 2005, **12**, 713–739.
- 2005CRV4237 K.-S. Yeung and I. Paterson, *Chem. Rev.*, 2005, **105**, 4237.
- 2005CRV4314 T. Nakata, *Chem. Rev.*, 2005, **105**, 4314.
- 2005CRV4348 E. J. Kang and E. Lee, *Chem. Rev.*, 2005, **105**, 4348.
- 2005CRV4379 M. Inoue, *Chem. Rev.*, 2005, **105**, 4379.
- 2005EJM1042 F. Roelens, K. Huvaere, W. Dhooe, M. Van Cleemput, F. Comhaire, and D. De Keukeleire, *Eur. J. Med. Chem.*, 2005, **40**, 1042.
- 2005EJO817 T. Opatz and D. Ferenc, *Eur. J. Org. Chem.*, 2005, 817.
- 2005EJO3542 Q. Fan, L. Lin, J. Liu, Y. Huang, and X. Feng, *Eur. J. Org. Chem.*, 2005, 3542.
- 2005H(65)761 M. Kawasaki, N. Toyooka, Y. Matsui, A. Tanaka, M. Goto, H. Kakuda, S. Kawabata, and T. Kometani, *Heterocycles*, 2005, **65**, 761.
- 2005HCA1010 P. Mueller and S. Chappolet, *Helv. Chim. Acta*, 2005, **88**, 1010.
- 2005HCO97 P. K. Zubaidha, A. M. Hashmi, and R. S. Bhosale, *Heterocycl. Commun.*, 2005, **11**, 97.
- 2005JA72 H. Lautens, E. Tayama, and C. Herse, *J. Am. Chem. Soc.*, 2005, **127**, 72.
- 2005JA1336 A. K. Unni, N. Takenaka, H. Yamamoto, and V. H. Rawal, *J. Am. Chem. Soc.*, 2005, **127**, 1336.
- 2005JA1481 C. Baker-Glenn, N. Hodnett, M. Reiter, S. Ropp, R. Ancliff, and V. Gouverneur, *J. Am. Chem. Soc.*, 2005, **127**, 1481.
- 2005JA1628 X. Gao and D. G. Hall, *J. Am. Chem. Soc.*, 2005, **127**, 1628.
- 2005JA5802 X. Shi, D. J. Gorin, and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 5802.
- 2005JA6284 J. Read de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2005, **127**, 6284.
- 2005JA6948 A. B. Smith, E. F. Mesaros, and E. A. Meyer, *J. Am. Chem. Soc.*, 2005, **127**, 6948.
- 2005JA7288 X. Moreau, B. Bazan-Tejeda, and J.-M. Campagne, *J. Am. Chem. Soc.*, 2005, **127**, 7288.
- 2005JA10180 H. Kim and C. Lee, *J. Am. Chem. Soc.*, 2005, **127**, 10180.
- 2005JA10259 B. M. Trost, L. Dong, and G. M. Schroeder, *J. Am. Chem. Soc.*, 2005, **127**, 10259.
- 2005JA10816 D. A. Evans, R. J. Thomson, and F. Franco, *J. Am. Chem. Soc.*, 2005, **127**, 10816.
- 2005JAA343 T. P. T. Cushnie and A. J. Lamb, *Int. J. Antimicrob. Agents*, 2005, **26**, 343.
- 2005JOC47 H. Suga, K. Inoue, S. Inoue, A. Kakehi, and M. Shiro, *J. Org. Chem.*, 2005, **70**, 47.
- 2005JOC489 F. Le Strat, D. C. Harrowven, and J. Maddaluno, *J. Org. Chem.*, 2005, **70**, 489.
- 2005JOC721 J.-L. Giner, *J. Org. Chem.*, 2005, **70**, 721.
- 2005JOC2402 B. Plietker and M. Niggemann, *J. Org. Chem.*, 2005, **70**, 2402.
- 2005JOC2503 Y. Otomaru, K. Okamoto, R. Shintani, and T. Hayashi, *J. Org. Chem.*, 2005, **70**, 2503.
- 2005JOC2855 J. A. Seijas and M. P. Vázquez-Tato, *J. Org. Chem.*, 2005, **70**, 2855.
- 2005JOC2881 K. Li, L. N. Lindsay, and J. A. Tunge, *J. Org. Chem.*, 2005, **70**, 2881.
- 2005JOC3757 B. S. Lucas, L. M. Luther, and S. D. Burke, *J. Org. Chem.*, 2005, **70**, 3757.
- 2005JOC3814 H. Liu, S. Wan, and P. E. Floreancig, *J. Org. Chem.*, 2005, **70**, 3814.
- 2005JOC4682 D. C. Dittmer, Q. Li, and D. V. Avilov, *J. Org. Chem.*, 2005, **70**, 4682.
- 2005JOC4778 V. Subramanian, V. R. Batchu, D. Barange, and M. Pal, *J. Org. Chem.*, 2005, **70**, 4778.
- 2005JOC5249 G. A. Nishiguchi and R. D. Little, *J. Org. Chem.*, 2005, **70**, 5249.
- 2005JOC5291 M. P. Doyle, J. P. Morgan, J. C. Fetters, P. Y. Zavali, J. T. Colyer, D. J. Timmons, and M. D. Carducci, *J. Org. Chem.*, 2005, **70**, 5291.
- 2005JOC6097 B. Liang, M. Huang, Z. You, Z. Xiong, K. Lu, R. Fathi, J. Chen, and Z. Yang, *J. Org. Chem.*, 2005, **70**, 6097.
- 2005JOC6669 K. Cherry, J.-L. Parrain, J. Thibonnet, A. Duchêne, and M. Abarbri, *J. Org. Chem.*, 2005, **70**, 6669.
- 2005JOC8204 M. Fan, Z. Yan, W. Liu, and Y. Liang, *J. Org. Chem.*, 2005, **70**, 8204.

- 2005JOC8478 M. Reiter, H. Turner, R. Mills-Webb, and V. Gouverneur, *J. Org. Chem.*, 2005, **70**, 8478.
2005JOC8533 W. Yang, D. Shang, Y. Liu, Y. Du, and X. Feng, *J. Org. Chem.*, 2005, **70**, 8533.
2005JOC9925 R. T. Stemmler and C. Bolm, *J. Org. Chem.*, 2005, **70**, 9925.
2005JOC10082 Y.-H. Yang and M. Shi, *J. Org. Chem.*, 2005, **70**, 10082.
2005JOC10879 M. E. Gonzalez-Nunez, R. Mello, A. Olmos, and G. Asensio, *J. Org. Chem.*, 2005, **70**, 10879.
2005MI532 K. M. Khan, S. Ahmed, Z. A. Khan, M. Rani, S. Perveen, M. I. Choudhary, and A. Rahman, *Lett. Org. Chem.*, 2005, **2**, 532.
2005OBC263 R. Aggarwal, R. G. F. Giles, I. R. Green, F. J. Oosthuizen, and C. P. Taylor, *Org. Biomol. Chem.*, 2005, **3**, 263.
2005OBC316 C. J. Hayes, N. M. A. Herbert, N. M. Harrington-Frostr, and G. Pattenden, *Org. Biomol. Chem.*, 2005, **3**, 316.
2005OBC756 J. S. Foot, G. M. P. Giblin, A. C. Whitwood, and R. J. K. Taylor, *Org. Biomol. Chem.*, 2005, **3**, 756.
2005OBC3488 R. Rodriguez, J. E. Moses, R. M. Adlington, and J. E. Baldwin, *Org. Biomol. Chem.*, 2005, **3**, 3488.
2005OBC3551 P. A. Clarke, W. H. C. Martin, J. M. Hargreaves, C. Wilson, and A. J. Blake, *Org. Biomol. Chem.*, 2005, **3**, 3551.
2005OL343 P. H. Lee, D. Seomoon, and K. Lee, *Org. Lett.*, 2005, **7**, 343.
2005OL467 J. D. Pettigrew, J. A. Cadieux, S. S. So, and P. D. Wilson, *Org. Lett.*, 2005, **7**, 467.
2005OL901 M. P. A. Lyle, N. D. Draper, and P. D. Wilson, *Org. Lett.*, 2005, **7**, 901.
2005OL1069 D. Gao and G. A. O'Doherty, *Org. Lett.*, 2005, **7**, 1069.
2005OL1113 W. J. Morris, D. W. Custar, and K. A. Scheidt, *Org. Lett.*, 2005, **7**, 1113.
2005OL1239 C. Welter, A. Dahnz, B. Brunner, S. Streiff, P. Duebon, and G. Helmchen, *Org. Lett.*, 2005, **7**, 1239.
2005OL1529 J. T. Lowe and J. S. Panek, *Org. Lett.*, 2005, **7**, 1529.
2005OL1589 J. E. Dalgard and S. D. Rychnovsky, *Org. Lett.*, 2005, **7**, 1589.
2005OL1853 J. Da Vicente, B. Betzemeier, and S. D. Rychnovsky, *Org. Lett.*, 2005, **7**, 1853.
2005OL2285 G. Chen, N. Tokunaga, and T. Hayashi, *Org. Lett.*, 2005, **7**, 2285.
2005OL2421 J. D. Winkler and K. Oh, *Org. Lett.*, 2005, **7**, 2421.
2005OL2493 J. U. Rhee and M. J. Krische, *Org. Lett.*, 2005, **7**, 2493.
2005OL2683 C. S. Barry, N. Bushby, J. R. Harding, and C. L. Willis, *Org. Lett.*, 2005, **7**, 2683.
2005OL2783 S. Takahashi, N. Ogawa, H. Koshino, and T. Nakata, *Org. Lett.*, 2005, **7**, 2783.
2005OL2977 X.-F. Zhu, A.-P. Schaffner, R. C. Li, and O. Kwon, *Org. Lett.*, 2005, **7**, 2977.
2005OL3099 A. B. Smith, R. J. Fox, and J. A. Vanecko, *Org. Lett.*, 2005, **7**, 3099.
2005OL3355 S. W. Youn and J. I. Eom, *Org. Lett.*, 2005, **7**, 3355.
2005OL3497 K. Meilert and M. A. Brimble, *Org. Lett.*, 2005, **7**, 3497.
2005OL3617 Z. Fei and F. E. McDonald, *Org. Lett.*, 2005, **7**, 3617.
2005OL3725 A. Padwa, J. Boonsombat, P. Rashatasakhon, and J. Willis, *Org. Lett.*, 2005, **7**, 3725.
2005OL3921 H. Guo and G. A. O'Doherty, *Org. Lett.*, 2005, **7**, 3921.
2005OL4273 J. Zhao and R. C. Larock, *Org. Lett.*, 2005, **7**, 4273.
2005OL4345 C. Prandi, A. Deagostino, P. Venturello, and E. G. Occhiato, *Org. Lett.*, 2005, **7**, 4345.
2005OL4491 K.-P. Chan and T.-P. Loh, *Org. Lett.*, 2005, **7**, 4491.
2005OL4527 G.-L. Zhao, Y.-L. Shi, and M. Shi, *Org. Lett.*, 2005, **7**, 4527.
2005OL5167 A. J. Catino, J. M. Nichols, H. Choi, S. Gottipamula, and M. P. Doyle, *Org. Lett.*, 2005, **7**, 5167.
2005OL5437 X. Li, A. R. Chianese, T. Vogel, and R. H. Crabtree, *Org. Lett.*, 2005, **7**, 5437.
2005OL5473 S. Rajaram and M. S. Sigman, *Org. Lett.*, 2005, **7**, 5473.
2005OL5889 A. Kina, K. Ueyama, and T. Hayashi, *Org. Lett.*, 2005, **7**, 5889.
2005OM945 G. Lu, J. L. Porscheller, and H. C. Malinakova, *Organometallics*, 2005, **24**, 945.
2005OM1119 W. E. Lindsell, D. D. Palmer, P. N. Preston, G. M. Rosair, R. V. H. Jones, and A. J. Whitton, *Organometallics*, 2005, **24**, 1119.
2005PHC(17)362 J. D. Hepworth and B. M. Heron, in 'Progress in Heterocyclic Chemistry', G. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2005, vol. 17, p. 362.
2005S245 A. A. Abdel-Fattah, *Synthesis*, 2005, 245.
2005S1049 I. Yavari and M. Esnaashari, *Synthesis*, 2005, 1049.
2005S1231 S. K. De and R. A. Gibbs, *Synthesis*, 2005, 1231.
2005S1269 I. I. Gerus, N. A. Tolmachova, S. I. Vdovenko, R. Fröhlich, and G. Haufe, *Synthesis*, 2005, 1269.
2005S1572 B. Das, H. Holla, G. Mahender, K. Venkateswarlu, and B. P. Bandgar, *Synthesis*, 2005, 1572.
2005S2061 D. R. Owen and R. J. Whitby, *Synthesis*, 2005, 2061.
2005S2357 D. Weber, H. Eberhard, C. Hoenke, S. Hoerer, P. Baeuerle, and V. Austel, *Synthesis*, 2005, 2357.
2005S3613 G. L. Edwards and D. J. Sinclair, *Synthesis*, 2005, 3613.
2005SC97 X.-S. Wang, *Synth. Commun.*, 2005, **35**, 97.
2005SC315 L. Tang, *Synth. Commun.*, 2005, **35**, 315.
2005SC563 B. S. Kirkiacharian and M. Gomis, *Synth. Commun.*, 2005, **35**, 563.
2005SC571 A. Shaabani, F. Tavasoli-Rad, and D. G. Lee, *Synth. Commun.*, 2005, **35**, 571.
2005SC769 F. Chimenti, D. Secci, A. Bolasco, P. Chimenti, and A. Granese, *Synth. Commun.*, 2005, **35**, 769.
2005SC913 P. K. Pradhan, S. Dey, P. Jaisankar, and V. S. Giri, *Synth. Commun.*, 2005, **35**, 913.
2005SC2723 O. V. Singh, M. Muthukrishnan, and G. Raj, *Synth. Commun.*, 2005, **35**, 2723.
2005SL123 D. Hobuß, S. Laschat, and A. Baro, *Synlett*, 2005, 123.
2005SL927 L. Goldoni, G. Cravotto, A. Penoni, S. Tollari, and G. Palmisano, *Synlett*, 2005, 927.
2005SL955 A. R. Khosropour, M. M. Khodaei, and H. Moghannian, *Synlett*, 2005, 955.
2005SL1164 V. Y. Sosnovskikh and R. A. Irgashev, *Synlett*, 2005, 1164.
2005SL1397 P. Mueller, G. Bernardinelli, Y. F. Allenbach, M. Ferri, and S. Grass, *Synlett*, 2005, 1397.
2005SL1465 A.-G. Yu, N.-X. Wang, Y.-L. Xing, J.-P. Zhang, Y.-X. Yang, W.-W. Wang, and R.-L. Sheng, *Synlett*, 2005, 1465.
2005SL1547 L. Zhu, A. Talukdar, G. Zhang, J. P. Kedenburg, and P. G. Wang, *Synlett*, 2005, 1547.
2005SL1945 J. S. Yadav, K. Rajasekhar, and M. S. R. Murty, *Synlett*, 2005, 1945.
2005SL2141 Y. Kishimoto and I. Mitani, *Synlett*, 2005, 2141.
2005T1353 A. Martínez, M. Fernández, J. C. Estévez, R. J. Estévez, and L. Castedo, *Tetrahedron*, 2005, **61**, 1353.

- 2005T1681 M. M. Oliveira, M. A. Salvador, P. J. Coelho, and L. M. Carvalho, *Tetrahedron*, 2005, **61**, 1681.
- 2005T2541 T. Komiyama, Y. Takaguchi, A. T. Gubaidullin, V. A. Mamedov, I. A. Litinov, and S. Tsuboi, *Tetrahedron*, 2005, **61**, 2541.
- 2005T3025 S. Celanire, F. Marlin, J. E. Baldwin, and R. M. Adlington, *Tetrahedron*, 2005, **61**, 3025.
- 2005T3289 Y. Kurosaki, T. Fukuda, and M. Iwao, *Tetrahedron*, 2005, **61**, 3289.
- 2005T3429 A. Deagostino, M. Migliardi, E. G. Occhiato, C. Prandi, C. Zavattaro, and P. Venturello, *Tetrahedron*, 2005, **61**, 3429.
- 2005T4115 J. Vasquez, E. Cristea, E. Diez, J. M. Lassaletta, A. Prieto, and R. Fernandez, *Tetrahedron*, 2005, **61**, 4115.
- 2005T4805 J. C. González-Gómez, L. Santana, and E. Uriarte, *Tetrahedron*, 2005, **61**, 4805.
- 2005T4919 S.-I. Naya, M. Miyagawa, and M. Nitta, *Tetrahedron*, 2005, **61**, 4919.
- 2005T5433 P. A. Clarke and W. H. C. Martin, *Tetrahedron*, 2005, **61**, 5433.
- 2005T6860 K. J. Hodgetts, *Tetrahedron*, 2005, **61**, 6860.
- 2005T7481 M. Nahmany and A. Melman, *Tetrahedron*, 2005, **61**, 7481.
- 2005T8390 Q. Chen, H. Deng, J. Zhao, Y. Lu, M. He, and H. Zhai, *Tetrahedron*, 2005, **61**, 8390.
- 2005T8419 K. Wojciechowski and K. Dolatowska, *Tetrahedron*, 2005, **61**, 8419.
- 2005T8589 N. Hiramatsu, N. Takahashi, R. Noyori, and Y. Mori, *Tetrahedron*, 2005, **61**, 8589.
- 2005T8956 R. Venkateswarlu, C. Kamakshi, P. V. Subhash, S. G. A. Moinuddin, M. P. Gowri, R. S. Ward, A. Pelter, M. B. Hursthouse, S. J. Coles, and M. E. Light, *Tetrahedron*, 2005, **61**, 8956.
- 2005T9291 S. Aoki, C. Amamoto, J. Oyamada, and T. Kitamura, *Tetrahedron*, 2005, **61**, 9291.
- 2005T9465 H. Du, X. Zhang, Z. Wang, and K. Ding, *Tetrahedron*, 2005, **61**, 9465.
- 2005T9996 W. L. A. van Otterlo, E. L. Ngidi, S. Kuzvidza, G. L. Morgans, S. S. Moleele, and C. B. de Koning, *Tetrahedron*, 2005, **61**, 9996.
- 2005T11322 N. Asao, C. S. Chan, K. Takahashi, and Y. Yamamoto, *Tetrahedron*, 2005, **61**, 11322.
- 2005T11730 P. J. Coelho, M. A. Salvador, B. M. Heron, and L. M. Carvalho, *Tetrahedron*, 2005, **61**, 11730.
- 2005T11910 J. C. Conway, P. Quayle, A. C. Regan, and C. J. Urch, *Tetrahedron*, 2005, **61**, 11910.
- 2005TA921 H. Clavier, L. Coutable, J.-C. Guillemin, and M. Mauduit, *Tetrahedron Asymmetry*, 2005, **16**, 921–924.
- 2005TA971 P. Del Buttero, G. Molteni, A. Papagni, and T. Pilati, *Tetrahedron Asymmetry*, 2005, **16**, 971.
- 2005TA1299 T. Uenishi, M. Ohmi, and A. Ueda, *Tetrahedron Asymmetry*, 2005, **16**, 1299.
- 2005TA1305 B. Sun, L. Peng, X. Chen, Y. Li, Y. Li, and K. Yamasaki, *Tetrahedron Asymmetry*, 2005, **16**, 1305.
- 2005TA2125 U. Koehn, M. Schulz, H. Goerls, and E. Anders, *Tetrahedron Asymmetry*, 2005, **16**, 2125.
- 2005TA2231 W. Quan, J. Ma, X. Peng, T. Wu, X. She, and X. Pan, *Tetrahedron Asymmetry*, 2005, **16**, 2231.
- 2005TL253 N. Ahmed, H. Ali, and J. E. van Lier, *Tetrahedron Lett.*, 2005, **46**, 253.
- 2005TL407 J.-I. Matsuo and Y. Aizawa, *Tetrahedron Lett.*, 2005, **46**, 407.
- 2005TL811 L. Zhu, J. P. Kedenburg, M. Xian, and P. G. Wang, *Tetrahedron Lett.*, 2005, **46**, 811.
- 2005TL823 B. B. Snider and J. F. Grabowski, *Tetrahedron Lett.*, 2005, **46**, 823.
- 2005TL987 M. Palucki and N. Yasuda, *Tetrahedron Lett.*, 2005, **46**, 987.
- 2005TL1573 P. D. Lokhande, S. S. Sakate, K. N. Taksande, and B. Navghare, *Tetrahedron Lett.*, 2005, **46**, 1573.
- 2005TL2021 M. P. Jennings and R. T. Clemens, *Tetrahedron Lett.*, 2005, **46**, 2021.
- 2005TL3197 H. Abe, K. Nishioka, S. Takeda, M. Arai, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett.*, 2005, **46**, 3197.
- 2005TL3501 H. Valizadeh and A. Shokravi, *Tetrahedron Lett.*, 2005, **46**, 3501.
- 2005TL3505 Z. Lei, Q. Zhang, J. Luo, and X. He, *Tetrahedron Lett.*, 2005, **46**, 3505.
- 2005TL3657 R. Schobert and J.-M. Urbina-Gonzalez, *Tetrahedron Lett.*, 2005, **46**, 3657.
- 2005TL3719 J.-F. Bonfanti and D. Craig, *Tetrahedron Lett.*, 2005, **46**, 3719.
- 2005TL3823 J. Oyamada and T. Kitamura, *Tetrahedron Lett.*, 2005, **46**, 3823.
- 2005TL3867 B. Nay, N. Gaboriaud-Kolar, and B. Bodo, *Tetrahedron Lett.*, 2005, **46**, 3867–3870.
- 2005TL4057 S. Rotzoll, B. Appel, and P. Langer, *Tetrahedron Lett.*, 2005, **46**, 4057.
- 2005TL4119 A. K. Ganguly, S. Kaur, P. K. Mahata, D. Biswas, B. N. Pramanik, and T. M. Chan, *Tetrahedron Lett.*, 2005, **46**, 4119.
- 2005TL4647 J.-R. Wang, L. Liu, Y.-F. Wang, Y. Zhang, W. Deng, and Q.-X. Guo, *Tetrahedron Lett.*, 2005, **46**, 4647.
- 2005TL4887 C. Perez-Balado and I. E. Marko, *Tetrahedron Lett.*, 2005, **46**, 4887.
- 2005TL6315 G. W. Kabalka and A. R. Mereddy, *Tetrahedron Lett.*, 2005, **46**, 6315.
- 2005TL8237 M. E. Jung and A. R. Novack, *Tetrahedron Lett.*, 2005, **46**, 8237.
- 2005TL8439 A. V. Butin, V. T. Abaev, V. V. Mel'chin, and A. S. Dmitriev, *Tetrahedron Lett.*, 2005, **46**, 8439.
- 2005TL8599 S. Hajra, B. Maji, and A. Karmakar, *Tetrahedron Lett.*, 2005, **46**, 8599.
- 2005TL8691 B. Rajitha, B. S. Kumar, Y. T. Reddy, P. N. Reddy, and N. Sreenivasulu, *Tetrahedron Lett.*, 2005, **46**, 8691.
- 2006AGE4406 A. R. Gallimore and J. B. Spencer, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**, 4406.
- 2006CC3571 J. S. Clark, *J. Chem. Soc., Chem. Commun.*, 2006, 3571.
- 2006CL328 T. Mukaiyama, T. Kitazawa, and H. Takayuki, *Chem. Lett.*, 2006, **35**, 328.
- 2006EJO453 F. Marion and D. B. Shinde, *Eur. J. Org. Chem.*, 2006, 453.
- 2006H(68)483 M. Kawasaki, H. Yoshikai, H. Kakuda, N. Toyooka, A. Tanaka, M. Goto, and T. Kometani, *Heterocycles*, 2006, **68**, 483.
- 2006JOC117 J. S. Crossman and M. V. Perkins, *J. Org. Chem.*, 2006, **71**, 117.
- 2006JOC409 E. Fillion, A. M. Dumas, B. A. Kuropatwa, N. R. Malhotra, and T. C. Sitler, *J. Org. Chem.*, 2006, **71**, 409.
- 2006JOC2862 X. Zhang, H. Du, Z. Wang, Y.-D. Wu, and K. Ding, *J. Org. Chem.*, 2006, **71**, 2862.
- 2006OL661 J. B. Son, S. N. Kim, N. Y. Kim, and D. H. Lee, *Org. Lett.*, 2006, **8**, 661.
- 2006OL3315 A. B. Smith, III, and V. Simov, *Org. Lett.*, 2006, **8**, 3315.
- 2006OL3319 C. S. Barry, J. D. Elsworth, P. T. Seden, N. Bushby, J. R. Harding, R. W. Alder, and C. L. Willis, *Org. Lett.*, 2006, **8**, 3319.
- 2006S187 V. Tararov, A. Korostylev, G. Koenig, and A. Boerner, *Synthesis*, 2006, 187.
- 2006T257 A. Armstrong and T. Tsuchiya, *Tetrahedron*, 2006, **62**, 257.
- 2006T2331 C. Perez-Balado and I. E. Marko, *Tetrahedron*, 2006, **62**, 2331.

Biographical Sketch



Jennifer Gibson was born in Oldham, UK and received her BSc (Hons) in 2001 from Sheffield Hallam University, UK. She obtained her PhD from the University of Bristol, UK under the supervision of Russell J. Cox and in 2005 was awarded a Royal Society (UK) postdoctoral fellowship to work for Professor Margaret Brimble at the University of Auckland, NZ. She is currently working for Professor Margaret Brimble at the University of Auckland involving the synthesis of pyranonaphthoquinone antibiotics.



Jonathan Sperry was born in Ascot, UK and received his BSc (Hons) in 2002 from the University of Exeter, UK and obtained his PhD from the same institution under the supervision of Christopher J. Moody in 2006. He is currently conducting postdoctoral research with Professor Margaret Brimble at the University of Auckland, NZ involving the synthesis of pyranonaphthoquinone antibiotics.



Margaret Brimble was born in Auckland, New Zealand where she was educated and graduated from the University of Auckland with an MSc (first class) in chemistry. She was then awarded a UK Commonwealth Scholarship to undertake her PhD studies at Southampton University. In 1986 she was appointed as a lecturer at Massey University, NZ. After a brief stint as a visiting Professor at the University of California, Berkeley she moved to the University of Sydney. In 2000, she returned to New Zealand to take up the Chair in Organic and Medicinal Chemistry at the University of Auckland where her research program continues to focus on the synthesis of spiroacetal-containing natural products (especially shellfish toxins), the synthesis of pyranonaphthoquinone antibiotics, the synthesis of alkaloids and peptidomimetics for the treatment of neurodegenerative disorders, and the synthesis of glycopeptides as components for cancer vaccines. She is currently President of the International Society of Heterocyclic Chemistry.

7.09

Pyrans and their Benzo Derivatives: Applications

B. W. Fravel

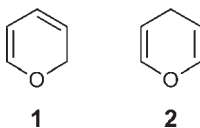
Butler University, Indianapolis, IN, USA

© 2008 Elsevier Ltd. All rights reserved.

7.09.1	Introduction	701
7.09.2	Reagents in Synthesis	702
7.09.3	Reagents in Qualitative and Quantitative Analysis	705
7.09.4	Pharmaceuticals	707
7.09.4.1	Anti-Infective Therapy	707
7.09.4.1.1	Antibacterials	707
7.09.4.1.2	Antivirals	708
7.09.4.1.3	Antifungal agents	708
7.09.4.1.4	Anti-infective agents	709
7.09.4.2	Antitumor Agents	710
7.09.4.3	Cardiovascular Agents	713
7.09.4.4	Anti-Inflammatory Agents	714
7.09.4.5	Antidiabetic Agents	714
7.09.4.6	Healthcare	714
7.09.4.7	Miscellaneous	715
7.09.5	Polymers	716
7.09.5.1	Natural Polymers	716
7.09.5.2	Hydrogels	717
7.09.5.3	Photoactive Polymers	717
7.09.6	Cyclodextrins	718
7.09.7	Additives and Dyes	719
7.09.7.1	Photosensitizers and Photoinitiators	719
7.09.7.2	Surfactants	720
7.09.7.3	Flavors and Food Products	720
7.09.7.4	Laser Dyes	721
7.09.8	Miscellaneous Natural Products	722
7.09.8.1	Marine Natural Products	722
7.09.8.2	Terrestrial Natural Products	723
	References	724

7.09.1 Introduction

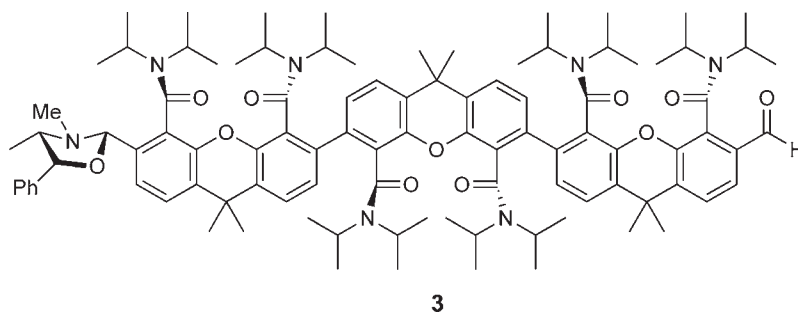
Although the instability of the simple, unsaturated pyran ring systems seen in *2H*-pyran **1** and *4H*-pyran **2** prevents their production via biosynthetic pathways, six-membered oxygen heterocyclic ring derivatives are found in an abundant range of naturally occurring compounds.



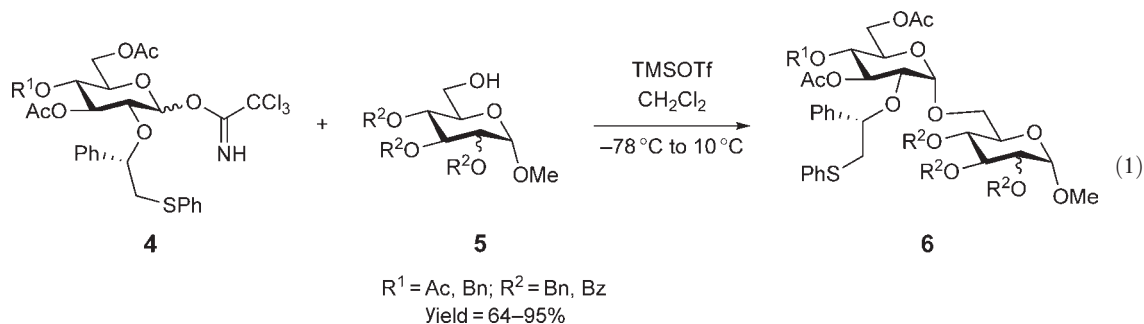
Fusion of aromatic rings to the basic pyran structure results in a substantially more stable heterocyclic system. Consequently, benzopyrans are widely distributed in nature and have quite an extensive chemistry, both in synthesis and applications. Almost every category of pyran and benzopyran derivatives provides examples of secondary metabolites, and their biosynthesis is discussed in CHEC(1984) <1984CHEC874>. These natural products together with a wide-ranging variety of synthetic analogs have been used in an array of diverse applications that include synthetic and analytical reagents, polymers, additives, dyes, pharmaceuticals, veterinary products, and agrochemicals. The applications of pyran and its benzo derivatives were reviewed in CHEC(1984) and then more exhaustively treated in CHEC-II(1996) <1984CHEC874, 1996CHEC-II469>.

7.09.2 Reagents in Synthesis

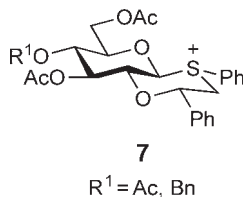
Clayden *et al.* have effected remote intramolecular stereocontrol by transmission of conformational information from the controlling center to a reaction site up to 22 bonds away <2004NAT966>. Usually the need for direct communication between the two parts of the molecule limits the control of stereoselectivity to about five bond lengths or short absolute distances <2001T2917>. Remote stereocontrol exceeding these limits has been reported, but the (1,23)-asymmetric induction achieved by the trisxanthene **3** represents a significant advance over prior asymmetric inductions. The stereochemistry of the oxazolidine group induces the pendant amide groups to all adopt *anti*-conformations with respect to one another. Information about the asymmetry of the oxazolidine group is relayed over 2.5 nm through the molecule to influence the aldehyde group's conversion to the (*S*)-alcohol with greater than 95% diastereoselectivity. Influencing remote active sites through induced conformational changes provides a chemical model for comparable information transfer in biochemical systems and molecular devices.



A method for the stereoselective introduction of 1,2-*cis*-glycosidic linkages, a principal challenge in the synthesis of biologically important oligosaccharides, has been developed. The conventional approach for stereoselective glycosylations is based on neighboring group participation of acyl functionality adjacent to the reactive anomeric carbon leading to pure 1,2-*trans*-glycosides <2003SL1225>. However, induction of exclusively 1,2-*cis*-glycosidic linkages was achieved by changing the directing group to an (*S*)-phenylthiomethylbenzyl moiety <2005JA12090>. Glycosyl donors **4** were coupled with glycosyl acceptors **5** using a catalytic amount of trimethylsilyl triflate in dichloromethane to give only disaccharides **6** with only α -anomeric selectivity (Equation 1).

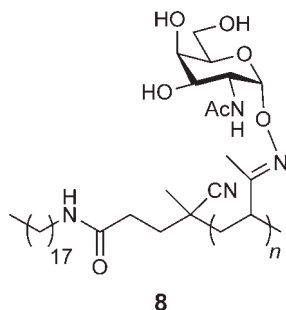


The presence of an equatorially substituted cyclic sulfonium intermediate **7** that controls the stereoselectivity of glycosylation was confirmed by nuclear magnetic resonance (NMR) spectroscopy. Combined use of this methodology to introduce α -glycosides and traditional β -glycoside protocols provides a potential route to one-pot multistep glycosylations and automated syntheses for a wide variety of oligosaccharides.



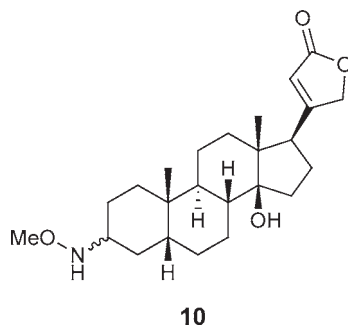
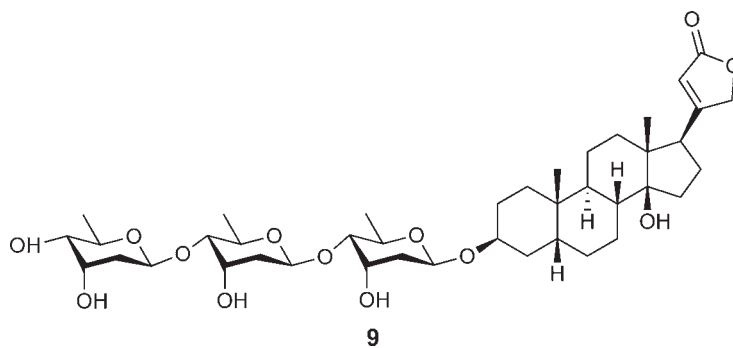
Because of their scale and unique physical properties, carbon nanotubes have attracted considerable attention for studying physiology at the level of single cells. Bertozzi and co-workers have taken advantage of cellular surface recognition of external carbohydrate molecules to interface carbon nanotubes with living cells <2006JA6292>. In the past, the inherent cytotoxicity of carbon nanotubes coupled with a lack of specificity in their interactions with cell surfaces has imposed substantial limitations on their use in biological systems; however, carbohydrate-coated carbon nanotubes were found to be nontoxic and were able to be interfaced with living cells using a highly specific cell-surface protein.

The carbon nanotubes were coated with a biomimetic poly(methylvinylketone) glycopolymer adorned with α -*N*-acetylgalactosamine residues. Glycopolymer **8** was designed to mimic cell-surface mucin glycoproteins. The hydrophobic lipid tail provided a hydrophobic anchor for carbon nanotube surface assembly by the polymer chains. The sugar residues are similar to those that decorate natural mucins. Agglutinin, a α -*N*-acetylgalactosamine-specific binding protein from the snail *Helix pomatia*, was used to cross-link cells with the glycoproteins coating the surface of the carbon nanotubes. Biocompatibility was demonstrated using several important cell lines, which have exhibited either inhibited cell growth or induced cell death when exposed to unfunctionalized carbon nanotubes. Experimental and theoretical studies have indicated that carbon nanotubes' surroundings can influence their electrical, mechanical, and optical properties; therefore, carbon nanotubes bound to living cell surfaces using carbohydrate-coating techniques hold tremendous promise as biosensors for monitoring small variations in targeted cells' composition and the cellular environment.

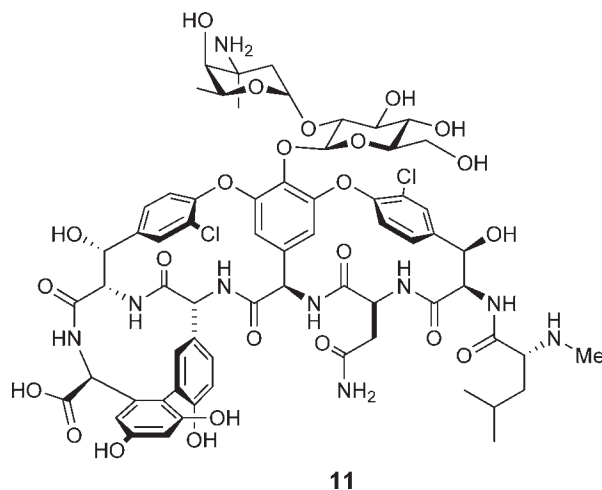


Chemical and biocatalytic approaches to glycosylations of proteins and natural products speed up the process of creating diverse libraries of carbohydrate-bearing molecules. Neoglycorandomization and chemoenzymatic glycorandomization are two such methods developed by Thorson and co-workers to generate libraries of analogs of important biomolecules <2005JNP1696>. Sugars are often essential to the functions of biomolecules and the ability to modify and control the types and locations of bound sugars enables changes to the properties and functions of these compounds.

Neoglycorandomization has been used to synthesize 78 derivatives of digitoxin **9**, an important cardiac drug <2005PNA12305>. During library screening, one analog was found to have potent cytotoxic activity against six cancer cell lines and another was highly selective for a very drug-resistant cancer cell line. The technique forms N-glycosidic bonds between reducing sugar donors and secondary alkoxyamine groups added to aglycons <1998T12269>. Both α - and β -isomers of the aglycon **10** were used for generating the library of digitoxin derivatives. One major advantage of neoglycorandomization is that it accomplishes glycosylation chemically without enzymes or prior sugar protection and activation schemes.



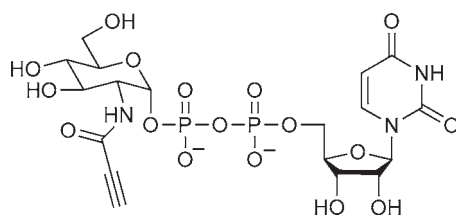
Chemoenzymatic glycorandomization utilizes enzymes to ligate activated sugars to natural product-based scaffolds. This rapid method of introducing glycodiversity employs the substrate promiscuity of anomeric kinases and nucleotidyltransferases to provide activated diphosphosugar donors to natural product glycotransferases [<2004BMC1577>](#). Vancomycin **11**, a potent antibiotic bearing a 1,2-D-glucosyl disaccharide moiety on a heptapeptide, has been subjected to glycorandomization [<2003MI1467>](#).



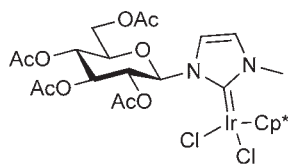
Vancomycin has received considerable attention as the scaffold for this process because the final step in its biosynthesis is a glycotransferase-mediated assembly of the disaccharide group. Additionally, novel antibiotics with activity against vancomycin-resistant enterococci have been developed by modification of the sugar substituents [<2001CEJ3798>](#). A primary advantage of this chemoenzymatic approach is its amenability to *in vivo* applications that should enable further development of the process, especially in scaling production of drug candidates.

Another enzymatic method uses oligosaccharide oxazolines as carbohydrate donor reagents in a protein glycosylation catalyzed by endoglycosidase. Covalently attached oligosaccharides can affect the glycoprotein's structure and *in vivo* activity, and participate in several important cellular recognition processes such as adhesion and immune response <1996CRV683>. This chemoenzymatic technique facilitates the synthesis of large, complex glycopeptides like HIV-1 glycopeptides, which are HIV vaccine candidates and recent efforts by Wang and co-workers have extended the method with increased efficiency and product homogeneity <2006OL3081>.

Many glycosyltransferases have been demonstrated to accept non-natural nucleotide diphosphate sugars, but the synthesis of these unusual sugar donors has been challenging. The enzymes relied upon to synthesize normal nucleotide diphosphate sugars have proved to be limited in their ability to install non-natural sugar analogs on proteins and natural products. Pohl and co-workers, however, have reported that recombinant sugar nucleotidyltransferases recently isolated from the archaebacterium, *Pyrococcus furiosus*, readily synthesized an alkyne-tagged uridine diphosphate-*N*-acetylglucosamine **12** <2005JA836>. *P. furiosus* is a hyperthermophile and its thermostable enzymes enable chemical steps that are slow or do not occur at normal reaction temperatures to be carried out at temperatures that would inactivate other enzymes.

**12**

Saccharide groups have recently been incorporated into transition-metal complexes to improve their water solubility and molecular recognition properties <B-2000MI7>, which are useful in catalysis <2002TA2155>, drug delivery <2004BMCL2533>, and sensor applications <2006CC4392>. Nishioka and co-workers have reported the first synthesis of an iridium-based, N-heterocyclic carbene complex **13** containing a glucopyranoside substituent <2007OM1126>. The glucopyranosyl group was added to 1-methylimidazole and the resulting intermediate was reacted with silver(I) oxide to form a silver N-heterocyclic carbene complex, which is a carbene transfer agent. Transmetalation using this silver complex afforded the iridium complex **13**.

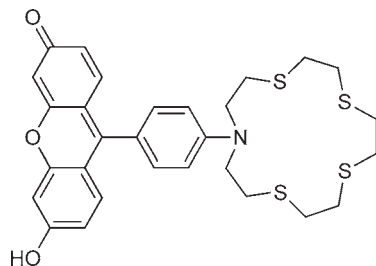
**13**

Cp* = C₅(CH₃)₅

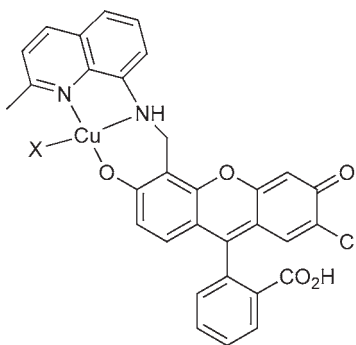
7.09.3 Reagents in Qualitative and Quantitative Analysis

Current techniques for monitoring aqueous mercury(II) cation concentrations from biological and environmental samples involve expensive and sophisticated instrumentation. A novel, fluorescent chemosensor has been developed that detects mercury ions at 60 nM concentrations with high selectivity over competing metal ions in aqueous solution, including copper and lead <2005JA16030>. Chemosensor **14** combines an azathiocrown ether that favors selective and stable binding of soft mercury ions and a water-soluble fluorescein indicator with desirable optical properties for mercury ion screening. Fluorescence screening with mercury-responsive chemosensors has been limited by several factors including interference from competing metal ions, incompatibility with aqueous media,

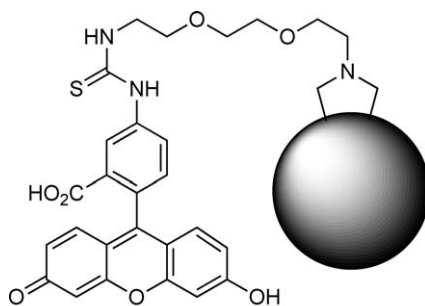
and poor mercury response kinetics. Chemosensor **14** reliably detected 0.1–8 part-per-million (ppm) mercury levels in fish during field trials with the largest fluorescence enhancement to date for sensing aqueous mercury ions providing a simple and rapid tracking approach for biological, toxicological, and environmental monitoring.

**14**

A new copper-based fluorescent probe detects intracellular levels of nitric oxide, a key messenger in the signaling networks of living cells. Unlike other fluorescent nitric oxide sensors, the cell-permeable fluorescein-based copper(II) chemosensor **15** detects nitric oxide directly rather than oxidized nitric oxide derivatives <2006MI375>. Nitric oxide produced by the living cells reduced the fluorescent complex to copper(I) triggering the irreversible nitrosation and release of the fluorescein ligand. The ensuing bright visible-light emissions were detectable by microscopy and enabled nitric oxide-producing cells to be distinguishable in mixed cell cultures over a wide range of concentrations.

**15**

Carbon nanotubes have also been functionalized with fluorescent probes to track and image the nanotubes when they penetrate the cell membrane of living cells. Fluorescein isothiocyanate pendant groups **16** were covalently grafted onto solubilized single- and multiwalled carbon nanotubes <2007MI108>. Cellular uptake experiments showed that the functionalized carbon nanotubes penetrated the plasma membranes and translocated directly into the cytoplasm without causing significant cell damage or death. Movement through the cells occurred as individual nanotubes and as small bundles, even under conditions that inhibit endocytosis, establishing the potential for carbon nanotubes for biomedical and biotechnological applications.

**16**

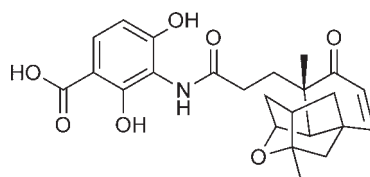
7.09.4 Pharmaceuticals

A tremendous number of commercial pharmaceutical agents and promising new drug candidates containing the pyran unit have been encountered in a survey of the recent literature and therefore, a narrow selection of the more pertinent has been included into this chapter. The pharmaceutical compounds of interest exhibit exceptional qualities in one or more areas such as selectivity, efficacy, mode of action, etc., and are arranged by therapeutic area.

7.09.4.1 Anti-Infective Therapy

7.09.4.1.1 Antibacterials

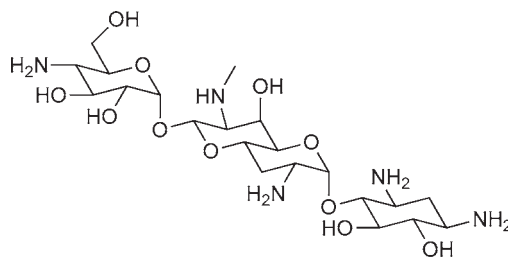
Bacterial infection remains a serious threat to human lives because of the alarming increase in resistance to existing antibiotic drugs. The antibiotics currently used kill bacteria by one of four established mechanisms; however, platensimycin **17** uses a unique mechanism of action – inhibition of cellular lipid biosynthesis <2006NAT358>. This is the first new mechanism of antibiotic action discovered in over 40 years. Platensimycin **17**, a previously unknown class of antibiotics produced by *Streptomyces platensis* isolated from South African soil, exhibits strong, broad-spectrum Gram-positive antibacterial activity by selectively targeting β -ketoacyl-acyl-carrier-protein synthase I/II in the synthetic pathway of fatty acids. Because of its unique mode of action, **17** showed no cross-resistance to other key antibiotic-resistant strains tested including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.



17

A mere 4 months after the discovery of platensimycin **17**, Nicolaou *et al.* achieved the first total synthesis of the molecule in racemic form <2006AGE7086>. Although the racemic platensimycin obtained would have to be resolved to render the active version of the natural product, the synthesis established an approach for synthesizing nonnatural analogs to be used in structure–activity relationship studies in search of characteristics better than the native compound.

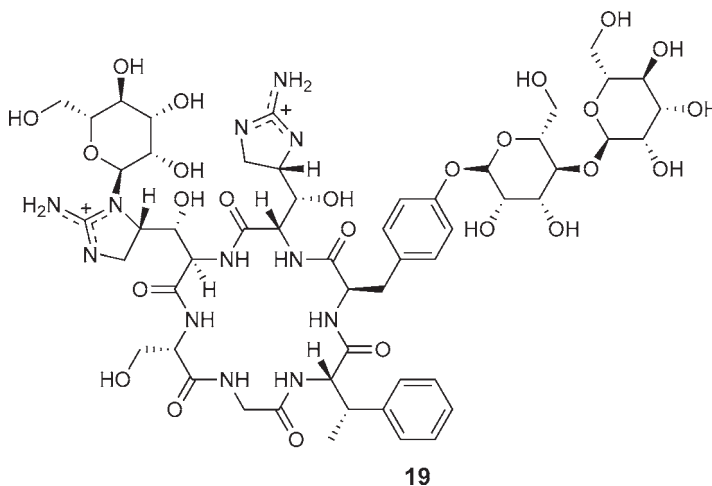
Methicillin-resistant *S. aureus*, vancomycin-resistant enterococci and other common drug-resistant pathogens typically gain the ability to survive antibiotics from the uptake of plasmids, strands of DNA that take up residence in bacteria <2003SCI1488>. These plasmids encode enzymes that confer resistance to antibiotics by either destroying or eliminating the particular drug from the bacterial cells. Plasmids, which exist apart from the bacteria's own DNA, can be transferred readily between diverse types of bacteria. Hergenrother and co-workers have shown that a small aminoglycoside molecule, apramycin **18**, can cause antibiotic-resistant bacteria to eliminate their resistance-conferring plasmids making them susceptible to the antibacterial drug once more <2004JA15402>. Apramycin takes advantage of a natural phenomenon known as plasmid incompatibility.



18

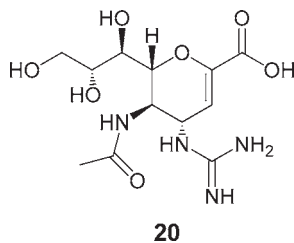
Plasmid incompatibility is a situation where plasmids that replicate themselves in similar ways cannot coexist in the same bacterial cell because of forced competition for replication proteins and RNA. Apramycin **18** mimics the function of a small piece of RNA that dictates incompatibility with an ampicillin-resistance plasmid and triggers the eviction of those plasmids from the bacterial cells rendering them susceptible to ampicillin treatment.

Scientists first discovered the mannopeptimycins, which are produced by a strain of *Streptomyces hygroscopicus*, in the late 1950s. Despite showing bioactivity against Gram-positive bacteria, the mixture of compounds was put into cold storage for 40 years. Resurrected in the search for new antibiotics to use in the war on bacterial resistance, the mannopeptimycins have shown remarkable activity against strains of bacteria that powerful broad-spectrum antibiotics like vancomycin cannot kill <2004JME3487>. Mannopectimycin α **19** is a representative member of the mannopeptimycin family, which are glycosylated cyclic hexapeptides that contain both D and L stereoisomers of the unusual amino acid β -hydroxyenduracididine. Mannopectimycin α exerts its antibacterial effects like many glycopeptides by binding to precursors of the bacterial cell wall, inhibiting transglycosylation and ultimately disrupting cell wall biosynthesis <2004AAC728>.



7.09.4.1.2 Antivirals

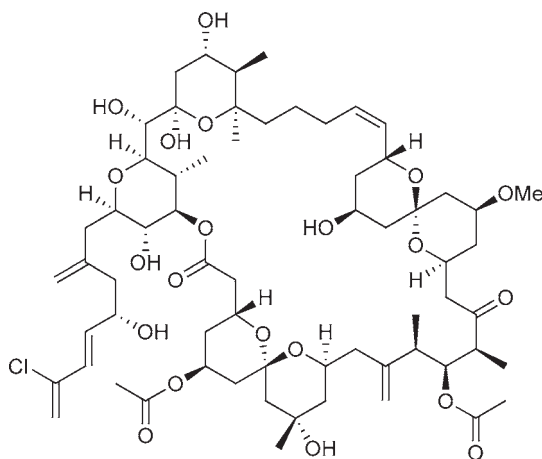
The avian flu virus, also known as H5N1, is still evolving and has not yet developed into a strain that can be transmitted from human to human. However, if an avian flu pandemic breaks out before an influenza vaccination has been created, the influenza antiviral agents oseltamivir (Tamiflu) and zanamivir **20** (Relenza) will provide the first line of defense. These agents are viral neuraminidase inhibitors and impede the ability of influenza viruses to infect respiratory epithelial cells <2003MI49>. Neuraminidase is a viral enzyme that allows newly replicated virus particles to easily release from the host cell membrane and to disperse without clumping, enhancing their ability to infect other cells. Zanamivir **20**, which unlike oseltamivir is inhaled instead of ingested, has been shown to be effective in treating both influenza A and influenza B. It typically lessens the severity of the illness and reduces the duration by approximately 2 days <1999MI254>.



7.09.4.1.3 Antifungal agents

(+)-Spongistatin **1** **21** is a bis-spiroketal macrolide isolated from the marine sponge *Hyrtios altum* that has exhibited potent antifungal bioactivity, as well as its more well-known anticancer properties. Pettit and co-workers evaluated the *in vitro* and *in vivo* antifungal efficacies and mechanism of **21** <2005MI453>. (+)-Spongistatin **1** was fungicidal

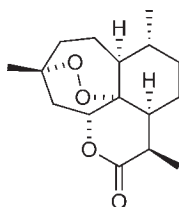
for the majority of the 74 reference strains tested including those resistant to flucytosine, ketoconazole, or fluconazole. Additionally, it retained activity in the presence of human serum and at lowered pH. When pulmonary cryptococcal microtubules were visualized by fluorescence microscopy and iterative deconvolution, **21** was shown to first disrupt cytoplasmic and then spindle microtubules in a time- and concentration-dependent manner.



21

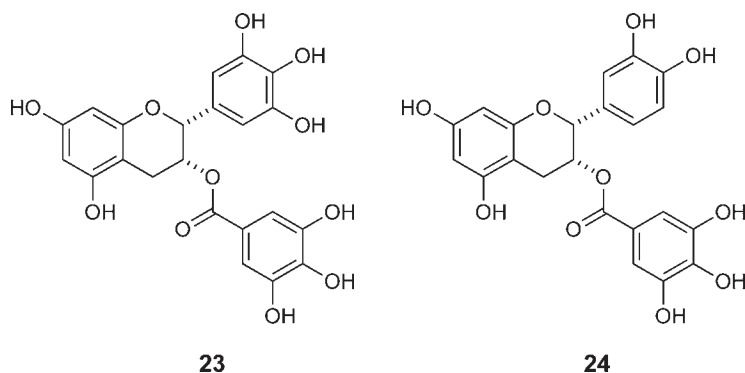
7.09.4.1.4 Anti-infective agents

The evergreen plant *Artemisia annua* contains artemisinin **22**, a potent natural antimalarial, but efforts to cultivate the plant and extract the compound for large-scale production have proved difficult and expensive. Recently, Keasling and co-workers have engineered a yeast to produce **22** in quantities comparable to the evergreen plant but in much less time <2006NAT940>. The yeast farnesyl pyrophosphate biosynthetic pathway was manipulated to increase production and prevent an alternative sterol synthesis pathway from competing. A gene for amorphaadiene synthetase from *A. annua* was inserted into the modified yeast that converts farnesyl pyrophosphate into amorphaadiene, an important artemisinin intermediate. Finally, a novel cytochrome P450 that oxidizes amorphaadiene to artemisinic acid over the course of three steps was introduced. The artemisinic acid produced was easily transported out of the yeast in high yield and transformed to **22** via established chemistry <1992JOC3610, 1994USP5310946>.



22

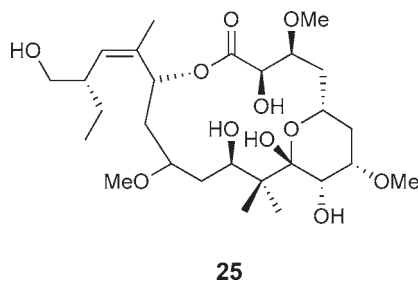
Another natural product that has exhibited antimalarial activity is the polyphenol (–)-epigallocatechin-3-gallate **23**. This particular polyphenol, which is extracted from green tea leaves, has been launched as a key ingredient for a variety of health-enhancing applications in the food industry. Catechin **23** and a structural cousin, (–)-epicatechin-3-gallate **24**, both demonstrate strong effects against *Plasmodium falciparum*, the mosquito-borne organism responsible for malaria <2007BBR177>. A particularly noteworthy finding was the effectiveness of these agents for strains of *Plasmodium* that are resistant to the common antimalarial drug chloroquine. Additionally, pharmacological interactions between the two catechins and artemisinin showed enhancement of the antiplasmodial effects of **22** when the latter was administered in sublethal doses.



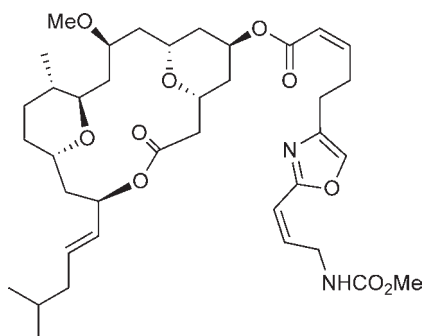
7.09.4.2 Antitumor Agents

Marine organisms, particularly sponges and associated bacteria, have yielded a tremendous variety of structurally diverse secondary metabolites that possess sufficiently potent biological activities to enter advanced preclinical and clinical development as chemotherapeutic agents [\[2004JNP1216\]](#). Marine macrolides like (+)-spongistatin 1 **21** are among the most potent cancer cell growth inhibitory compounds tested against the US National Cancer Institute's panel of 60 human carcinoma cell lines including highly chemoresistant tumor types [\[2005CRV4237\]](#). Despite highly promising biological profiles, development of **21** and other high-profile marine natural products has been impeded by the vanishingly small natural supply from the sponge sources. For instance, **21** requires 13 tons of wet sponge to isolate just 35 mg of the natural product. The chronic supply problems are being addressed by numerous academic and industrial natural product synthesis groups working on scalable routes to (+)-spongistatin 1 and similarly important target molecules [\[2004OL3637\]](#).

The macrolide peloruside A **25**, isolated from the marine sponge *Mycale hentscheli* that grows in the coastal waters of New Zealand [\[2000JOC445\]](#), exhibits pronounced cytotoxicity against a range of cancer cell lines and multidrug-resistant cells. This novel compound arrests the cell cycle in the G2/M phase, leading to apoptosis, by promoting tubulin polymerization in a manner similar to paclitaxel (Taxol) but with a different binding site [\[2004MI5063\]](#). De Brabander *et al.* reported the first total synthesis of **25** using a Mitsunobu macrolactonization step [\[2003AGE1648\]](#).

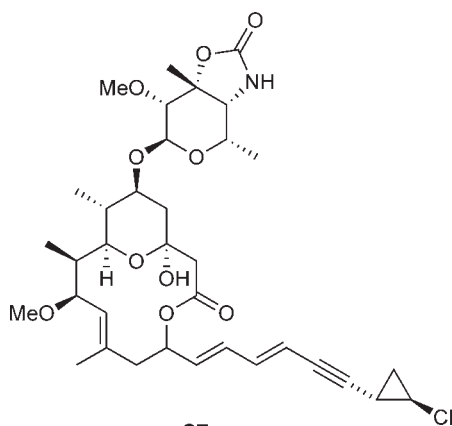


The structurally novel macrolide leucascandrolide A **26**, isolated from bacteria colonizing the New Caledonian calcareous sponge *Leucascandra caveolata* [\[1999HCA347\]](#), exhibits *in vitro* cytotoxicity against KB throat epithelial carcinoma and P388 murine leukemia cell lines, as well as strongly inhibits the growth of the pathogenic yeast *Candida albicans* [\[1996HCA51\]](#). Leighton *et al.* reported the first total synthesis of **26** using a Yamaguchi macrolactonization [\[2000JA12894\]](#).



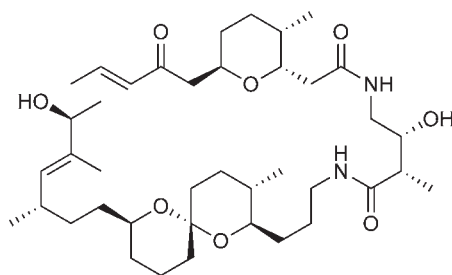
26

The highly unusual glycosylated marine macrolide callipeltoside A **27** was isolated from the shallow-water lithistid sponge *Callipelta* sp. Although it shows only moderate *in vitro* cytotoxicity against human bronchopulmonary non-small-cell lung carcinoma and P388 murine leukemia cell lines, preliminary studies indicated its bioactivity to be cell-cycle dependent, blocking proliferation in the G1 phase [\[1996JA11085\]](#). Paterson *et al.* developed an expedient synthesis of the aglycon of **27** [\[2001AGE603\]](#) and, subsequently, accomplished the first total synthesis of natural callipeltoside A utilizing a similar synthetic sequence [\[2003OL4477\]](#).



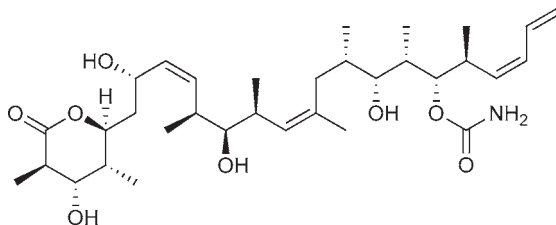
27

Bistramide A **28** is a macrolide metabolite isolated along with several analogous compounds from the ascidian *Lissoclinum bistratum* Sluiter, a marine organism found in the waters of New Caledonia and Australia [\[1994JNP1336\]](#). The family of bistramides exhibits numerous biological activities including antiproliferative [\[2005MI383\]](#), immunomodulating [\[1996MI1\]](#), and neurotoxic [\[1993MI465\]](#) properties. Compound **28** is a very potent suppressor of cell proliferation with its activity attributed to a high and specific affinity for actin. The total synthesis of bistramide A by Kozmin and co-workers enabled the binding studies by supplying sufficient quantities of the natural product [\[2004JA9546\]](#). Compound **28** disrupts the equilibrium between monomeric and polymeric actin, which makes up the cytoskeleton and plays a key role in cell division. Bistramide A forms a tightly bound complex with actin with the solvent-accessible surface area of **28** sequestered by the interaction with the receptor, providing the physical basis for the high binding affinity observed [\[2006JA3882\]](#).

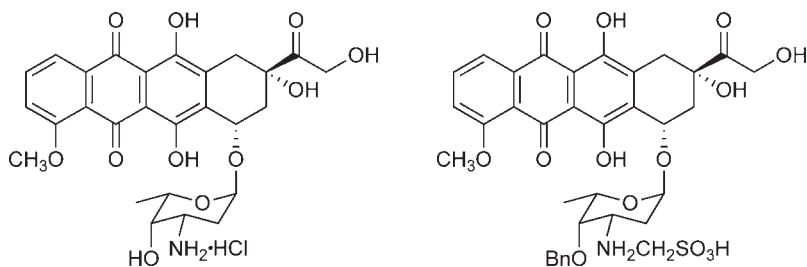


28

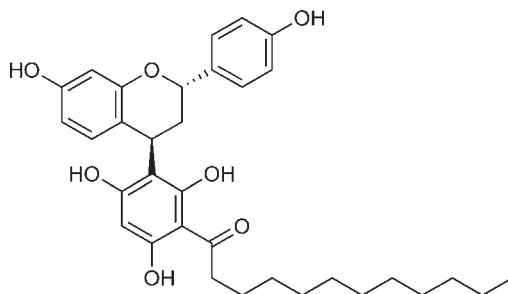
Mickel and colleagues developed the first industrial-scale total synthesis of the promising anticancer agent (+)-discodermolide **29**, which has a mechanism of action similar to that of paclitaxel <2004OPD92>. Previously, **29** had to be harvested from the Caribbean sponge *Discoderma dissolute* in extremely small amounts <1991JOC1346>. (+)-Discodermolide is a particularly attractive drug candidate because its antimitotic activity resulting from binding to microtubules is maintained against multidrug-resistant cells <1997MPH613> and because of its demonstrated synergism with paclitaxel <2006MI298>.

**29**

Doxorubicin **30**, an anthracycline antibiotic, is widely used in the treatment of a variety of cancers <1999BP727>. Anthracyclines mediate their anticancer effect by targeting topoisomerase II, an enzyme overexpressed in cancerous tissues including brain tumors. Brain tumors however have proved extraordinarily difficult to clinically treat since most active drugs cannot gain access to the brain because they cannot cross the blood–brain barrier. Priebe and colleagues have synthesized and evaluated a derivative of doxorubicin, the anthracycline **31**, that is capable of crossing the blood–brain barrier and inhibiting topoisomerase II leading to DNA damage in the cancer cells <2004BP353>. In addition, **31** was shown to be at least 50 times more active than native doxorubicin for cytotoxicity against a number of cancer cell lines.

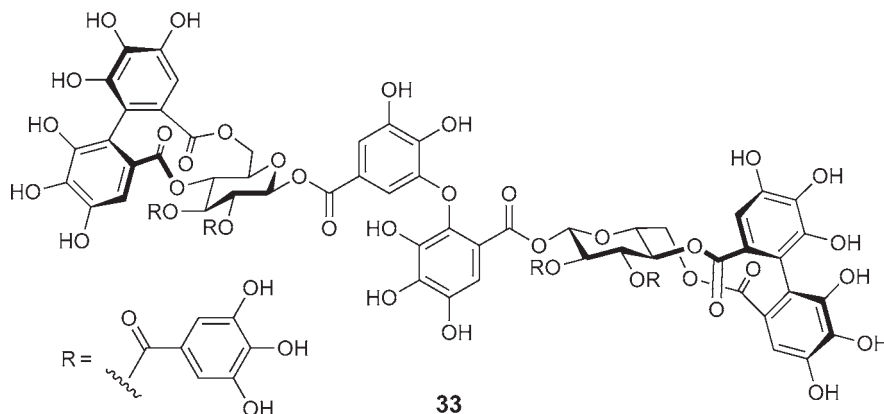
**30****31**

One goal of cancer therapy based on DNA damage is to keep the damage from being repaired. A number of DNA polymerase β -inhibitors that have been isolated from *Myristica cinnamomea* are capable of blocking the repair of DNA damage inflicted by clinically used pharmaceuticals boosting their overall efficacy <2003MI68>. Remarkably, the flavanoid (+)-myristinin A **32** both cleaves DNA and prevents polymerase β , the DNA repair enzyme, from functioning properly. This unusual bioactivity was confirmed along with its structure and absolute stereochemistry after the stereoselective total synthesis of **32** was achieved by Hecht and co-workers <2005JA4140>.

**32**

Continuing studies on the total synthesis of ellagitannin plant metabolites have led to the preparation of the antitumor compound coriariin A **33** and other structural analogs <2005P1984>. Companion studies designed to assay

the immunostimulation and immunosuppression properties of these molecules have concluded that tumor necrosis factor α serves as a mediator of coriariin A's tumor remissive activity. Dimeric ellagitannins like **33** elicit secretion of tumor necrosis factor α from human peripheral blood monocytes.

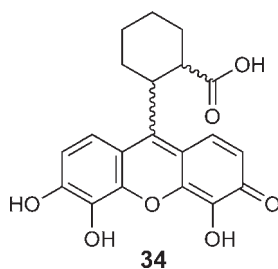


Traditional Chinese medicinal plants associated with anticancer bioactivity contain a variety of natural phenolic compounds with numerous structural features and possessing widely different antioxidant activity. Cai *et al.* characterized the antioxidant activity and phenolic compounds from 112 species selected from more than 400 species of anticancer-related traditional Chinese medicinal plants <2004LS2157>. Total antioxidant activity and phenolic content of the 112 plant extracts showed a positive and highly statistically significant linear correlation. The tested medicinal plants contained substantially higher levels of phenolic compounds and exhibited far greater antioxidant behavior than common fruits and vegetables. Among the representative compounds identified in the extracts were flavonoids, tannins, and coumarins. A subsequent study elucidated the structure-radical scavenging activity relationships of the representative compounds <2006LS2872>. Tannins demonstrated the strongest mean radical scavenging activity, and the significant mean differences in activity between categories of examined compounds were attributed to structural differences in hydroxylation, methoxylation, and glycosylation.

7.09.4.3 Cardiovascular Agents

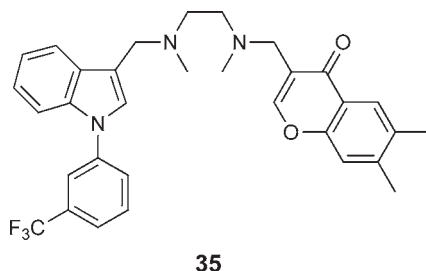
A therapeutic strategy to combat a number of diseases such as heart failure and vascular disease is to target the $\beta\gamma$ -subunit of heterotrimeric guanine nucleotide binding proteins (G proteins). The $\beta\gamma$ -subunit is released upon ligand activation of G protein-coupled receptors. Free $\beta\gamma$ -subunits regulate multiple target proteins within the cell and mediate physiological processes such as neutrophil chemotaxis, vascular cell proliferation, and cardiac chronotropy <2003MI765>. Small molecule binders of the G protein $\beta\gamma$ -subunit could differentially modulate downstream cellular functions through their interactions with subunits and their protein targets.

Smrcka and co-workers have developed a computer-based screening methodology that finds small molecules which have a high affinity for binding with specific amino acids on the surface of the $\beta\gamma$ -subunit of G proteins <2006SCI443>. The amino acids involved are primarily responsible for binding the target proteins that are regulated by the $\beta\gamma$ -subunit. One of the identified compounds, M119 **34**, was tested in mouse cell cultures and was found to increase the potency of morphine over 10-fold. Extensive screening for additional small-molecule modulators is underway and could yield therapeutically useful agents that enhance the efficacy, potency, or selectivity of existing medications.



7.09.4.4 Anti-Inflammatory Agents

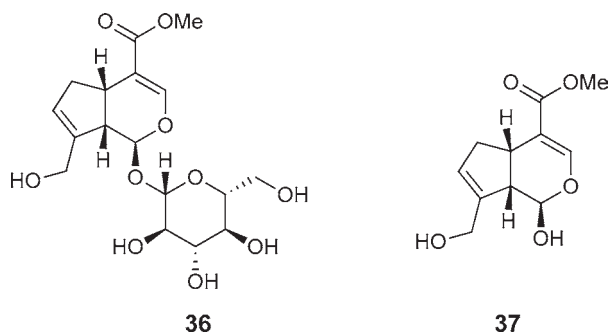
A small-molecule inhibitor of tumor necrosis factor α , a protein involved in inflammatory diseases such as rheumatoid arthritis, has been identified <2005SCI1022>. Direct inhibition by the commercial biological agents Enbrel and Remicade has produced major advances in rheumatoid arthritis treatment and validated extracellular inhibition of this proinflammatory cytokine as an effective therapy. The new inhibitor **35** is composed of trifluoromethylphenyl indole and dimethylchromone moieties linked by a dimethylethylenediamine spacer.



An X-ray crystal structure of **35** with tumor necrosis factor α revealed that the inhibitor binds with the intact biologically active trimer and accelerates subunit disassociation of one of the three subunits in the protein, rapidly inactivating the cytokine. Interestingly, **35** is able to access the normally buried interior of the tumor necrosis factor α trimer to form a complex with two of the subunits. The surprising results should help with the identification of other small-molecule inhibitors that inactivate multimeric proteins via a rapid predissociation-independent subunit dissociation process.

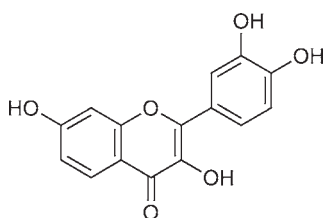
7.09.4.5 Antidiabetic Agents

The fruit of gardenia, *Gardenia jasminoides* Ellis, is a traditional Chinese folk medicine used in the treatment of an array of illnesses including jaundice, headaches, fever, inflammation, hepatic disorders, and hypertension. Genioposide **36**, one of the major glycosides in gardenia fruit extract, is hydrolyzed to the aglycone genipin **37** by β -D-glucosidases in the human liver and intestines. The pharmacological action of **37** has been recently shown to include the rapid inhibition of uncoupling protein 2, a negative regulator of insulin secretion in pancreatic tissues <2006MI417>. Uncoupling protein 2 deficiency increases obesity- and high glucose-induced pancreatic β -cell dysfunction and consequently increases type 2 diabetes in mice. Acute addition of **37** to isolated pancreatic islets reversed the β -cell dysfunction. Genipin stimulates insulin secretion by inhibiting uncoupling protein 2-mediated proton leak in the islets.

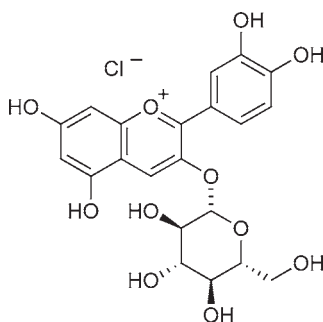


7.09.4.6 Healthcare

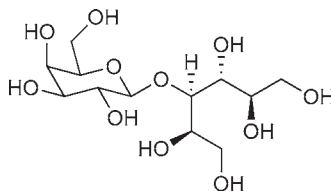
Neurotrophic factors are polypeptides that promote the health of nerve cells, but their difficulty crossing the blood-brain barrier has limited their clinical use. Maher and co-workers have recently identified the flavonoid fisetin **38** as a small molecule that strongly exhibits several properties of a neurotrophic factor and can be taken orally <2006PNA16568>. Fisetin, which is found in strawberries and other natural foods, enhanced memory in mice by increasing activation of a specific transcription factor, the cAMP response element-binding protein. This transcription factor is involved in the physical changes in the brain associated with sustaining long-term memory.

**38**

Anthocyanins, a group of natural flavonoids found in dark-colored foods such as berries and red grapes, possess a remarkable spectrum of biological activities including anti-inflammatory, antioxidant, antimutagenic, and anti-carcinogenic properties <2003P923>. Cyanidin-3-*O*-glucoside **39**, an anthocyanin prevalent in the human diet, has been demonstrated to protect skin cells exposed to UV-B radiation from the sun, which is one of the most significant risk factors associated with the development of skin cancer <2006JFA4041>. Human skin cells pretreated with **39** showed reduced adverse oxidative stress responses that occur with UVB radiation exposure. This result suggests that commercially available sunscreens could be made more effective by the addition of this photoprotective agent to their formulation.

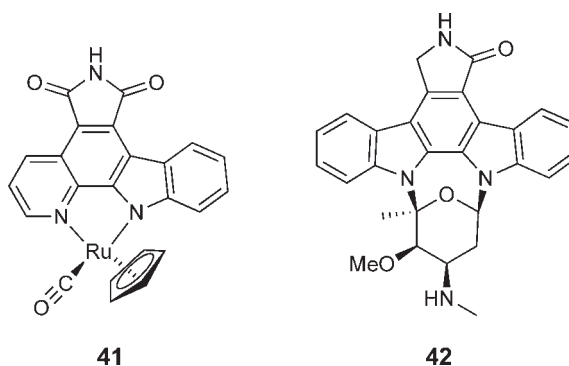
**39**

Lactitol **40** is a disaccharide that has been used in the management of hepatic encephalopathy, a major neuropsychiatric complication of both acute and chronic liver failure. It has mild laxative properties and is used to reduce the production and absorption of gut-derived neurotoxic substances symptomatic of hepatic encephalopathy. Although long considered a first-line pharmacological treatment, there is a lack of sufficient evidence to support lactitol's efficacy and continued use when weighed against other suitable therapeutic alternatives such as oral antibiotics <2006MI94>.

**40**

7.09.4.7 Miscellaneous

A natural product's bioactivity is often due to a defined shape that complements the binding site of a protein. Meggers and co-workers have demonstrated that simple organometallic scaffolds can be substituted for structurally more complicated natural products in binding at a target protein's active site <2006AGE1580>. A ruthenium complex **41** was synthesized to mimic the shape of the alkaloid staurosporine **42**, a potent inhibitor of protein kinase Pim-1.

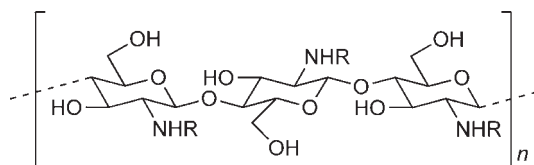


Staurosporine **42** has attracted much attention due to its broad spectrum antitumor activity. It is one of the strongest known inhibitors of protein kinases as it has nanomolar affinity for the ATP binding pocket of these enzymes [<1986BBR397>](#). Because this activity is shared by its bis-linked sugar-indolocarbazole analogs, the presence of the carbohydrate moiety was long considered important for recognition by these cellular targets. However, mimicking staurosporine's rigid, planar shape with an organometallic half-sandwich complex not only replicated the alkaloid's unique protein-binding activity, but **41** exhibits both higher affinity and greater selectivity. Ruthenium complex **41** binds protein kinase Pim-1 with picomolar affinity and does not bind to any other protein kinase, even though the active sites are very similar.

7.09.5 Polymers

7.09.5.1 Natural Polymers

Two of the more important natural biomaterials are chitin **43** ($R = \text{Ac}$), which consists predominantly of unbranched polymeric chains of β -(1,4)-linked *N*-acetylglucosamines, and chitosan **44** ($R = \text{H}$), chitin's more soluble derivative. Chitosan **44** is soluble in aqueous acidic media and forms solutions that can be used to produce functional beads, membrane coatings, fibers, and sponges [<B-1998MI96>](#). The amino and hydroxyl groups are suitable for facile chemical modification. The set of characteristics that make chitosan special as a functional biomaterial safe for human use are biocompatibility, biodegradability, stability *in vivo*, and antibacterial properties [<1998MI595>](#). These characteristics make chitosan-based materials suitable for biomedical applications including artificial skin [<2000RFP1>](#), tissue regeneration [<2001MI147>](#), and drug delivery systems [<1998MI979>](#).



43: $R = \text{Ac}$

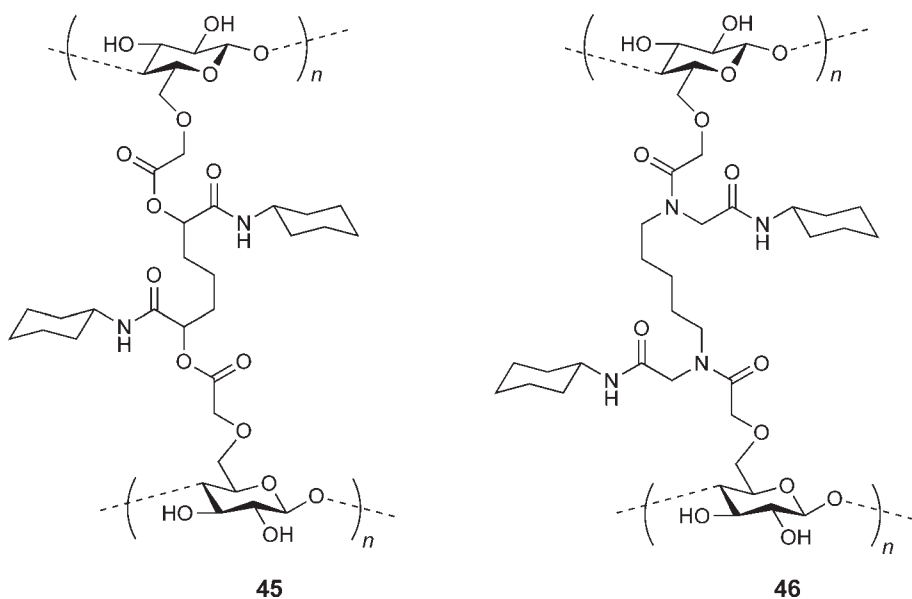
44: $R = \text{H}$

Chitosan **44** for tissue engineering and similar medical applications must have sufficient mechanical strength and other physical properties to perform satisfactorily. Hourston and co-workers have prepared novel chitosan-based films using genipin **37** as a cross-linking agent that exhibited improved stability and better mechanical properties than typical chitosan films [<2004BMM162>](#). The use of genipin, a naturally occurring and nontoxic cross-linking agent, overcomes the problem of physiological toxicity inherent in the use of common synthetic chemicals as polymer cross-linkers.

7.09.5.2 Hydrogels

Hydrogels are lightly cross-linked, biocompatible polymeric materials that absorb large amounts of water and other polar solvents. Cross-linked hydrogels cannot dissolve in water because of their size; instead, they absorb the water and swell. They find biomedical application as drug delivery matrices, contact lens materials, the functional components of permselective membranes and in tissue engineering <1996CHEC-II489>.

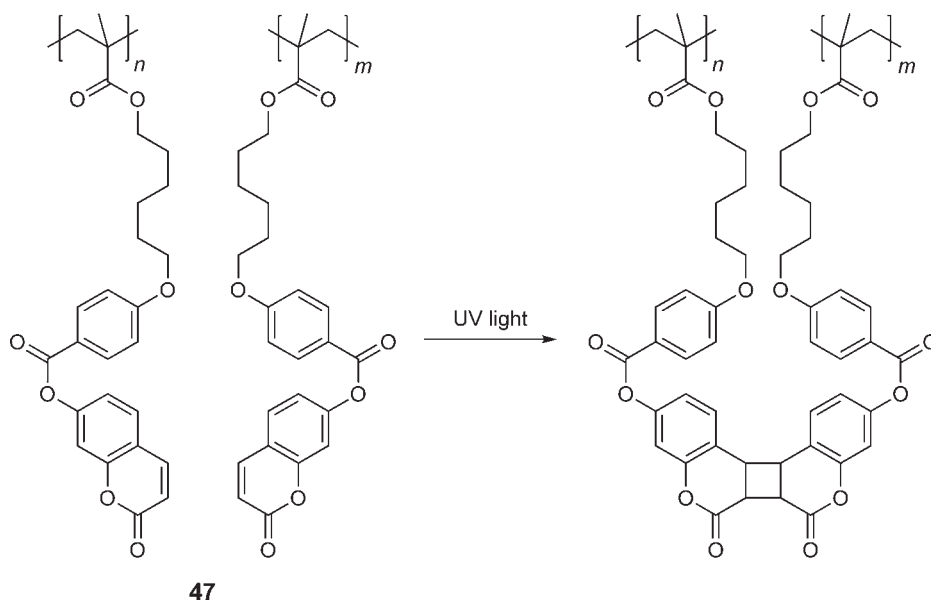
Crescenzi and co-workers have proved that Passerini and Ugi multicomponent condensations are versatile and simple methods for the synthesis of carboxylated polysaccharide hydrogels with tunable properties such as transparency, swelling behavior, and elastic modulus <2000BMM259>. Both reactions are rapid and efficient in water when compared to an organic solvent <1998TL5957>. The primary difference between a Passerini gel **45** and a Ugi gel **46** is that the ester linkage in the former can be readily hydrolyzed at only slightly alkaline pH, whereas the amide linkage in the latter is completely stable at this pH. The obtained Ugi gels reached an equilibrium weight when swelled in water that did not change over the course of several months, which is an important consideration in specific types of tissue engineering such as lip and breast augmentations.



7.09.5.3 Photoactive Polymers

Coumarin groups are commonly incorporated into photoactive polymers because of their favorable photochemical characteristics and the ease of integration into the polymer matrix. The addition of the appropriate coumarin moiety into the monomers themselves or as an additive in the polymerization process can result in the polymeric product possessing beneficial visible and ultraviolet light absorption properties.

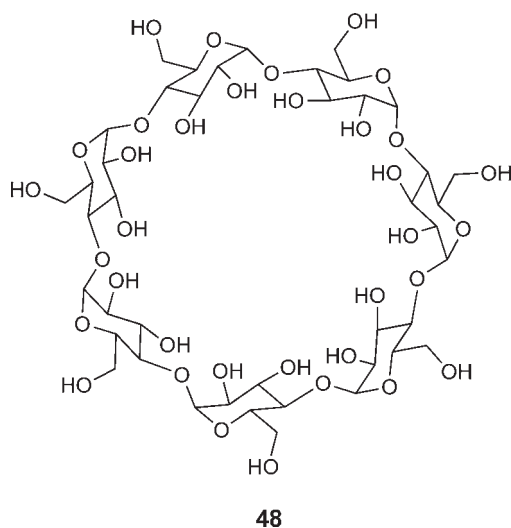
Liquid crystal photoalignment involves the development of an optical anisotropy in a polymer thin film by irradiation with polarized ultraviolet light. The layer is subsequently used in a process to uniformly align the liquid crystals in a display through surface interactions between the layer and the liquid crystal. Polymers with pendant groups capable of photochemical dimerization are an important class of photoaligning materials <1992MI2155>. Coumarin side-chain polymers **47**, such as the one derived from 7-hydroxycoumarin, can be anisotropically cross-linked by a [2+2] cycloaddition reaction under ultraviolet irradiation creating an anisotropic thin film (Scheme 1) <2002SM(127)95>.



Scheme 1

7.09.6 Cyclodextrins

Cyclodextrins are a thoroughly reviewed class of supramolecular ring compounds composed of various numbers of D-glucopyranosyl units connected by α -(1,4)-glycosidic linkages. The three naturally occurring members of this class of molecules are the α -, β -, and γ -cyclodextrins, consisting of 6-, 7-, and 8-glucopyranose units respectively with β -cyclodextrin **48** being the most widely studied of the three and of the class as a whole. The natural cyclodextrins are produced during the degradation of starch in the enantiomerically pure dextrorotatory state by the action of cyclodextrin glycosyltransferase, an enzyme produced by several microbial organisms such as *Bacillus macerans*. The most stable three-dimensional configuration for these nonreducing cyclic oligosaccharides takes the form of a toroid with the larger and smaller openings presenting secondary and primary hydroxyl groups, respectively, to the solvent environment. The interior of the cyclodextrin molecule is a chiral, nonpolar, hydrophobic cavity that readily forms stable inclusion complexes with a wide range of chemical substances. Complexes with drugs, essential oils, and other compounds usually form quite rapidly, providing an attractive way to enhance the water solubility of these entities.



Chemical modification of both the primary and secondary hydroxyl substituents has been used to further improve their toxicity, water solubility, and biodegradability. Since the hydroxyl groups differ in chemical reactivity, chemical modification typically produces thousands of regio- and stereoisomers resulting in a substantially less crystalline molecule. The amorphous character of chemically modified cyclodextrins has beneficial effects on aqueous solubility and toxicity. Variation of the degree of substitution provides a means for optimizing physical and chemical parameters of the molecules in specific applications.

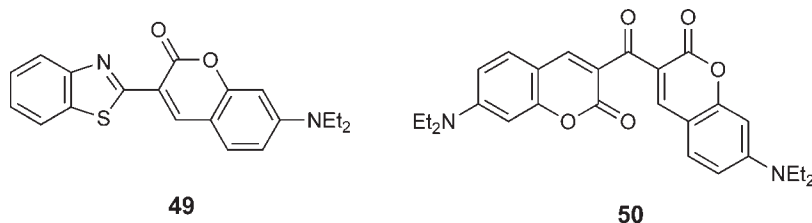
Cyclodextrins are integral parts of products in a range of industries. Applications in the areas of pharmaceuticals including drug delivery systems <2007MI1> and biotechnology including biocatalysis <2002MI341> have recently been reviewed. The technological advantages of their use in food processing and as food additives have also been reviewed <2006MI343, B-2004MI271>. A systematic review of fragrance and cosmetic microencapsulation contains numerous examples of incorporation of cyclodextrins for their improved physical and chemical characteristics in formulations <2003MI157>. Cyclodextrins have been extensively employed in enantiomeric resolution of chiral molecules and other advance separation techniques <2000JCH(875)89>. Polymeric cyclodextrins are an important class of new materials that exhibit potential for immediate or future use in all of the aforementioned applications <2001MI315>.

7.09.7 Additives and Dyes

7.09.7.1 Photosensitizers and Photoinitiators

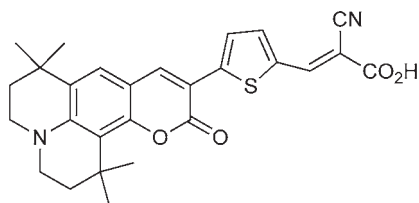
Compounds capable of generating free radicals on exposure to light and thereby inducing free radical polymerization are known as photoinitiators. However, the utility of many of these compounds is limited to activation by ultraviolet light only. The addition of a compound that absorbs incident light more efficiently may activate the photoinitiator to produce free radicals using visible light. Such compounds are known as photosensitizers.

Coumarin **49** and ketocoumarin **50** were recently examined for suitability in the radical polymerization reactions applicable to laser imaging and determined to be fitting for this application <2000MI237>. The interactions of the excited states of **49** or **50** photosensitizers with bisimidazole derivatives, mercaptobenzoxazole photoinitiators, and titanocene were studied by laser absorption spectroscopy to elucidate the specific photochemical mechanisms responsible. Coumarin **49** forms radicals through an electron transfer reaction, whereas the ketocoumarin **50** undergoes either an energy transfer reaction or a hydrogen abstraction reaction depending upon the initiator present.

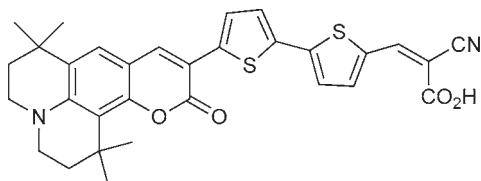


In nanostructured dye-sensitized solar cells, a promising type of organic photovoltaic cell, the photochemical properties of the photosensitizer are critically important to the overall performance of the solar cells <2000ACR269>. The light absorption characteristics of the photosensitizer directly determine the photoresponse range of the cell and the molecular structure must be strategically designed to match the iodine electrolyte's redox potential and the TiO₂ electrode conduction band edge level for the dye-sensitized solar cell to useable. Organic dyes have several advantages over the ruthenium–bipyridyl complexes that are typically used in these solar cells including lower cost than the noble metal complexes and large absorption coefficients due to intramolecular π – π^* transitions.

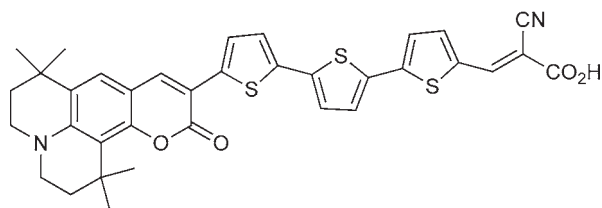
Coumarin derivatives have been used successfully as organic dye photosensitizers in dye-sensitized solar cells, but they produced solar energy-to-electricity conversion efficiencies well below those achieved by ruthenium complexes <2003NJC783>. Hara *et al.* have expanded the π -conjugation system of these coumarin derivatives by introducing thiophene moieties <2005PCB15476>. The resulting thiophene-modified coumarin dyes **51**, **52**, and **53** yielded markedly improved performance in conversion efficiency relative to the previous coumarin dyes when incorporated into the photovoltaic device. While the efficiencies remained below those of ruthenium complexes in these solar cells, the performance improvements indicated that organic dye photosensitizers have a promising potential in nanostructured dye-sensitized solar cell applications.



51



52

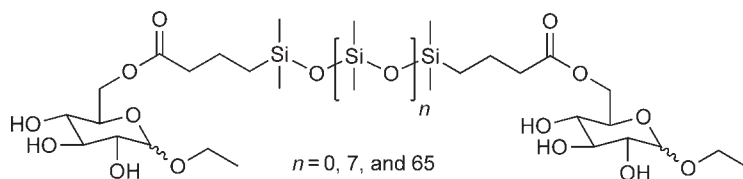


53

7.09.7.2 Surfactants

Amphiphilic organosilicon–carbohydrate conjugates have the ability to self-assemble giving rise to unusual physical properties in solution or as neat materials <1995MM17>. Depending upon the structure of the attached carbohydrate, these silicones can be used as surfactants, adhesion promoters, and chiral templates. Typically, their synthesis requires long reaction times at high temperature with an acid or base catalyst <1986MI49>. Under these conditions a number of uncontrolled side reactions compete with the condensation, and poor regioselectivity impedes the ability to control the structure of the resulting material. Gross and co-workers circumvented these problems using an enzymatic catalysis protocol <2005OL3857>.

Immobilized lipase B from *Candida antarctica* catalyzed the regioselective condensation of dimethylsiloxane oligomers containing carboxylic acid end groups with ethyl glucoside. The neutral pH, solvent-free reaction conditions afforded pure organosilicon-carbohydrate conjugates **54** with high regioselectivity and in moderate yields. This simplified route to structurally defined organosilicon carbohydrates allows a more diversified set of silicones with novel properties to be prepared for film, coating, gel, and surfactant applications.

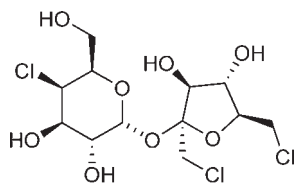


54

7.09.7.3 Flavors and Food Products

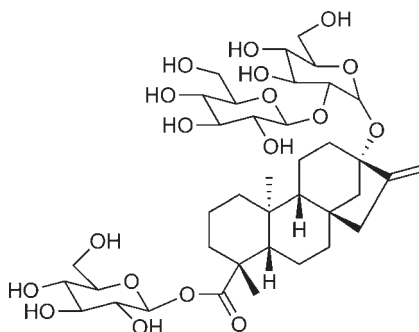
The search continues for noncaloric high-intensity sweeteners in the food industry because of the strong demand for low-calorie drinks and reduced-calorie foods. A common approach in the discovery of these new agents is to begin from existing natural sweeteners and improve upon their stability, toxicology, and flavor profile. Supporting these

efforts is research in the sweet taste receptor itself <2005MI1948>. The sweet taste receptor is made of two subunits, T1R2 and T1R3, which have distinct affinities for different saccharides. The nonsaccharide sweetener aspartame binds only to T1R2 and cyclamate only to T1R3; however, sucrose and the low-calorie sweetener sucralose **55** interact with both subunits. As expected from its high sweetness intensity, sucralose binds with either subunit with greater affinity than does sucrose.

**55**

Lactitol **40** has attracted substantial interest as a food sweetening additive in bakery, confectionary, and chewing gum products <2001FST297>. It is a sugar alcohol derived from lactose by hydrogenation of the glucose moiety that provides food with the bulk and texture normally given by sucrose, but with only half the calories. Lactitol **40** does not adversely affect blood glucose and insulin levels making it an excellent sweetener for diabetics. Additionally, it does not cause dental caries and thus is highly suited for use in sugar-free chewing and candy.

Stevioside **56**, a natural sweetener extracted from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni, tastes approximately 300 times sweeter than sucrose and is used as a low-calorie dietary replacement for diabetics, phenylketonurea patients, and obese persons intending to lose weight by avoiding sugar in their diet. A review of the toxicological effects and metabolism of stevioside **56** in relation to the possible formation of steviol, a controversial mutagenic metabolite, has concluded that *Stevia* and stevioside do not form steviol, an aglycone of **56**, when consumed by humans and therefore is a safe dietary supplement <2003P913>.

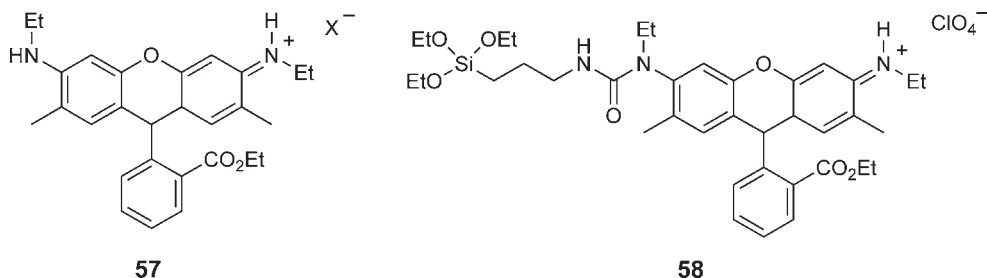
**56**

Polyphenolic compounds containing pyran moieties are ubiquitous plant secondary metabolites that are abundant in the human diet and include flavonoids, proanthocyanidins, ellagitannins, and gallotannins. Examples of dietary sources are fruits, nuts, and products derived from these foods such as beverages and snacks. Additionally, these botanical ingredients are often added to dietary supplements for their potential human health benefits. A recent overview examined the challenges, opportunities, and progress made of late in herbal research of bioactive dietary polyphenols, focusing on those most abundant in the diet <B-2006MI(925)25>.

7.09.7.4 Laser Dyes

The incorporation of dye molecules into solid matrixes provides the basis for the preparation of a variety of dye-doped solid-state devices including solid-state dye lasers <2001MI1>. The large oscillator strength and broad tunability of organic dyes combined with the advantages offered by a solid host relative to liquid solutions make these materials excellent candidates for laser applications <2003MI121>. Solid-state active media have been prepared by introducing the dye molecules into organic, inorganic, and hybrid solid matrixes, but among the possibilities, embedding dye molecules into silica glass via the sol-gel process has yielded the highest physical and chemical performances <2005MI13>.

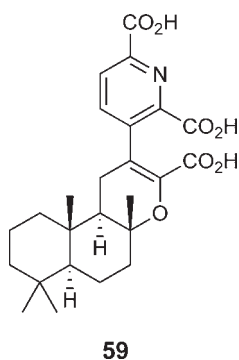
Rhodamine 6G **57** has been one of the most frequently used dye molecules in these applications because of its high quantum yield in fluorescence in the 500–600 nm range. Carbonaro *et al.* reacted the chloride and the perchlorate salts of Rhodamine 6G **57** with 3-isocyanatopropyltriethoxysilane in order to prepare an adduct that could be used to covalently graft the Rhodamine dye into the porous silica network <2006PCB12932>. A porous silica–Rhodamine 6G hybrid was successfully made using the perchlorate-containing organosilicon adduct **58**. Steady-state photoluminescence and photoluminescence photostability measurements on the hybrid material showed photochemical properties comparable to the dye molecule in solution and reduced photodegradation with respect to high power laser irradiation. The results indicate that hybrid organic–inorganic sol-gels are suitable for the development of a solid-state tunable dye laser.



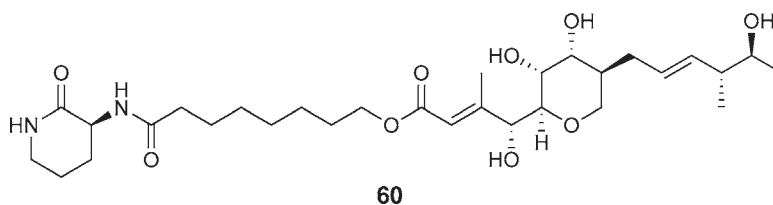
7.09.8 Miscellaneous Natural Products

7.09.8.1 Marine Natural Products

Sea lettuce and gut weed are intertidal marine algae that display a multicellular leafy state, which allows the algae to grow toward the sunlit surface. But these macroalgae can also lose their natural morphology when cultivated under aseptic conditions. The leafy yellow-green *Monostroma oxyspermum* only grew in loose aggregates of single cells when grown in a sterile Petri dish; however, these cells differentiated when infected by epiphytic marine bacteria that live on the flat surface of the algal leaves in their natural environment <2005SCI1598>. The bacterial extracellular metabolite thallusin **59** isolated and induced the normal morphogenesis of *M. oxyspermum*. In this unusual symbiotic relationship the algae need a constant low concentration of bacterial thallusin to maintain the leafy state that provides the bacteria with a home. The differentiation inducer **59** is potent at concentrations as low as 1 attogram per ml.

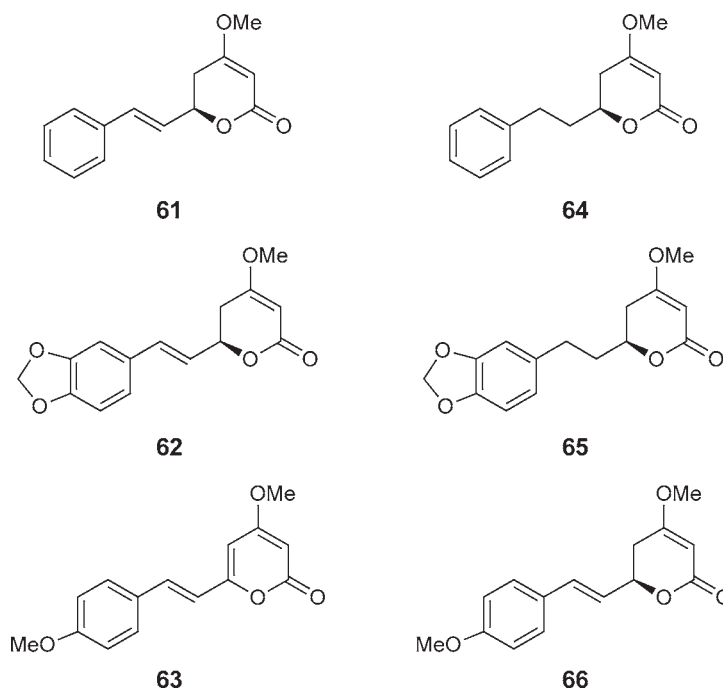


Thiomarinol A **60** is a rare marine natural product isolated from the bacterium *Alteromonas rava* and belongs to a family of pyran-containing pseudomonic acids. This class of compounds is under significant scrutiny in the search for improved, less toxic analogs of mupirocin, a commercially successful topical antimicrobial medication for skin infections <1995CRV1843>. Compound **60** was the first member of the thiomarinols to be stereoselectively synthesized and the route used should facilitate the development of structural analogs with higher potency and oral bioavailability than mupirocin <2005JA1628>.



7.09.8.2 Terrestrial Natural Products

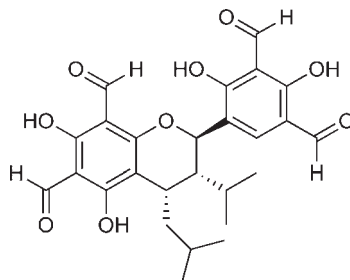
The Kava plant, *Piper methysticum*, has been used by Pacific Island societies for several thousand years to prepare an intoxicating ceremonial beverage renowned for its relaxing effects and purported health benefits [<1997MI84>](#). The psychoactive principles extracted from the Kava root are a family of 15 α -pyrone derivatives known as the kavalactones. The more prevalent of these include (+)-kavain **61**, (+)-methysticin **62**, yangonin **63**, and their more saturated derivatives **64**, **65**, and **66**, respectively.



Clinical studies indicate that the kavalactones have a substantial anxiety-reducing effect, but the experiments used mixtures extracted from cultivated Kava and not isolated individual kavalactones [<2001MI86>](#). Recent US Food and Drug Administration warnings on dietary supplements containing kava resulted from rare but severe cases of liver failure being linked with the use of kava. The warnings as well as the sale of these supplements being banned in some European countries accentuates the need for additional study on individual kavalactones, which are not readily available in enantiopure form. To address this issue Smith *et al.* have developed three asymmetric pathways to the kavalactones and have reported the first enantioselective synthesis of (+)-kavain **61** [<2004OL2317>](#). The most versatile synthetic route provides rapid access to the entire family of kavalactones and structural analogues using a Stille coupling between a common vinylstannane precursor and appropriate aryl iodides.

Although defense against wild vertebrate herbivores is thought to be the primary role of plant secondary metabolites, specific examples that demonstrate the phenomenon are few [<2001MI84>](#). The conclusions from a recently completed ten-year study of the dining habits of a wild population of koala strongly support the theory [<2005NAT488>](#). Koalas, which dine on eucalyptus leaves almost exclusively, prefer leaves that contain high concentrations of nitrogen for its nutritional value and low concentrations of the lipophilic phenolic metabolites known as formylated phloroglucinol compounds. One of the most common formylated phloroglucinols in eucalyptus

trees is sideroxylonal A **67** and this metabolic species induces nausea in the animals that consume too much foliage containing elevated levels of the substance. Consequently, secondary plant chemistry through deterrence directly affects the use of trees by the koalas, and potentially influences the koala populations by restricting the available food sources.



67

References

- 1984CHEC874 In 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, p. 874.
 1996CHEC-II469 In 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, p. 469.
 1986BBR397 T. Tamaoki, H. Nomoto, I. Takahashi, Y. Kato, M. Morimoto, and F. Tomita, *Biochem. Biophys. Res. Commun.*, 1986, **135**(2), 397.
 1986MI49 R. Mohan, M. V. Ram, and M. Yaseen, *J. Coatings Technol.*, 1986, **58**(743), 49.
 1991JOC1346 S. P. Gunasekera, M. Gunasekera, R. E. Longley, and G. K. Schulte, *J. Org. Chem.*, 1991, **56**(3), 1346.
 1992JOC3610 N. Acton and R. J. Roth, *J. Org. Chem.*, 1992, **57**(13), 3610.
 1992MI2155 M. Schadt, K. Schmitt, V. Kozinkov, and V. Chigrinov, *Jpn. J. Appl. Phys.*, 1992, **31**(7), 2155.
 1993MI465 M. P. Sauviat and J. F. Verbist, *Gen. Physiol. Biophys.*, 1993, **12**(5), 465.
 1994JNP1336 J.-F. Biard, C. Roussakis, J.-M. Kornprobst, D. Gouiffes-Barbin, J.-F. Verbist, P. Cotellet, M. P. Foster, C. M. Ireland, and C. Debitus, *J. Nat. Prod.*, 1994, **57**(10), 1336.
 1994USP5310946 R. K. Haynes and S. C. Vonwiller, *US Pat.* 5 310 946 (1994) (*Chem. Abstr.*, 1994).
 1995CRV1843 Y. J. Class and P. DeShong, *Chem. Rev.*, 1995, **95**(6), 1843.
 1995MM17 V. von Braunmühl, G. Jonas, and R. Stadler, *Macromolecules*, 1995, **28**(1), 17.
 1996CRV683 R. A. Dwek, *Chem. Rev.*, 1996, **96**(2), 683.
 1996HCA51 M. Ambrosio, A. Guerriero, C. Debitus, and F. Pietra, *Helv. Chim. Acta*, 1996, **79**(1), 51.
 1996JA11085 A. Zampella, M. V. D'Auria, L. Minale, C. Debitus, and C. Roussakis, *J. Am. Chem. Soc.*, 1996, **118**(45), 11085.
 1996MI1 J. Pusset, B. Maillere, and C. Debitus, *J. Nat. Toxins*, 1996, **5**(1), 1.
 1997MI84 V. Lebot and J. Levesque, *Recherche*, 1997, **295**, 84.
 1997MPH613 R. J. Kowalski, P. Giannakou, S. P. Gunasekera, R. E. Longley, B. W. Day, and E. Hamel, *Mol. Pharmacol.*, 1997, **52**(4), 613.
 B-1998MI96 S. M. Hudson and C. Smith; in 'Biopolymers from Renewable Resources', D. Kaplan, Ed.; Springer, Berlin, 1998, p. 96.
 1998MI595 N. Kubota and Y. Kikuchi, *Polysaccharides*, 1998, 595.
 1998MI979 O. Felt, P. Buri, and R. Gurny, *Drug Dev. Ind. Pharm.*, 1998, **24**(11), 979.
 1998T12269 F. Peri, P. Dumy, and M. Mutter, *Tetrahedron*, 1998, **54**(40), 12269.
 1998TL5957 T. Ziegler, R. Schlomer, and C. Koch, *Tetrahedron Lett.*, 1998, **39**(33), 5957.
 1999BP727 D. A. Gewirtz, *Biochem. Pharmacol.*, 1999, **57**(7), 727.
 1999HCA347 M. D'Ambrosio, M. Tato, G. Pocsfalvi, C. Debitus, and F. Pietra, *Helv. Chim. Acta*, 1999, **82**(3), 347.
 1999MI254 A. S. Monto, D. M. Fleming, D. Henry, R. De Groot, M. Makela, T. Klein, M. Elliott, O. N. Keene, and C. Y. Man, *J. Infect. Dis.*, 1999, **180**(2), 254.
 2000ACR269 A. Hagfeldt and M. Graetzel, *Acc. Chem. Res.*, 2000, **33**(5), 269.
 2000BMM259 A. E. J. De Nooy, D. Capitani, G. Masci, and V. Crescenzi, *Biomacromolecules*, 2000, **1**(2), 259.
 2000JA12894 K. R. Hornberger, C. L. Hamblett, and J. L. Leighton, *J. Am. Chem. Soc.*, 2000, **122**(51), 12894.
 2000JCH(875)89 S. Fanali, *J. Chromatogr. A*, 2000, **875**(1-2), 89.
 2000JOC445 L. M. West, P. T. Northcote, and C. N. Battershill, *J. Org. Chem.*, 2000, **65**(2), 445.
 B-2000MI7 In 'Oligosaccharides: Their Synthesis and Biological Role', H. M. Osborn and T. H. Khan, Eds.; 2000, p. 7.
 2000MI237 X. Allonas, J. P. Fouassier, M. Kaji, and M. Miyasaka, *J. Photopolym. Sci. Technol.*, 2000, **13**(2), 237.
 2000RFP1 M. N. V. Ravi Kumar, *React. Funct. Polym.*, 2000, **46**(1), 1.
 2001AGE603 I. Paterson, R. D. M. Davies, and R. Marquez, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**(3), 603.
 2001CEJ3798 K. C. Nicolaou, S. Y. Cho, R. Hughes, N. Winssinger, C. Smethurst, H. Labischinski, and R. Endermann, *Chem. Eur. J.*, 2001, **7**(17), 3798.
 2001FST297 P. H. J. Mesters, J. A. Van Velthuisen, and S. Broxk, *Food Sci. Technol.*, 2001, **112**, 297.
 2001MI1 R. Reisfeld, *Opt. Mater.*, 2001, **16**(1-2), 1.

- 2001MI86 K. K. Smith, H. R. W. Dharmaratne, M. W. Feltenstein, S. L. Broom, J. T. Roach, N. P. D. Nanayakkara, I. A. Khan, and K. J. Sufka, *Psychopharmacology*, 2001, **155**(1), 86.
- 2001MI84 G. Vourc'h, J. L. Martin, P. Duncan, J. Escarre, and T. P. Clausen, *Oecologia*, 2001, **126**, 84.
- 2001MI147 B. L. Seal, T. C. Otero, and A. Panitch, *Mater. Sci. Eng., R.*, 2001, **34**(4–5), 147.
- 2001MI315 G. Mocanu, D. Vizitiu, and A. Carpov, *J. Bioact. Compat. Polym.*, 2001, **16**(4), 315.
- 2001T2917 K. Mikami, M. Shimizu, H.-C. Zhang, and B. E. Maryanoff, *Tetrahedron*, 2001, **57**(15), 2917.
- 2002MI341 M. Singh, R. Sharma, and U. C. Banerjee, *Biotechnol. Adv.*, 2002, **20**(5–6), 341.
- 2002SM(127)95 P. O. Jackson, G. Bergmann, J. H. C. Hogg, M. O'Neill, P. Hindmarsh, S. M. Kelly, and G. F. Clark, *Synth. Met.*, 2002, **127**(1–3), 95.
- 2002TA2155 K. Ohe, K. Morioka, K. Yonehara, and S. Uemura, *Tetrahedron Asymmetry*, 2002, **13**(19), 2155.
- 2003AGE1648 X. Liao, Y. Wu, and J. K. De Brabander, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**(14), 1648.
- 2003MI49 G. Stiver, *Can. Med. Assoc. J.*, 2003, **168**(1), 49.
- 2003P916 S. Hecht, *Pharm. Biol.*, 2003, **41**(supplement 1), 68.
- 2003MI121 A. P. Rao and A. V. Rao, *Sci. Technol. Adv. Mater.*, 2003, **4**(2), 121.
- 2003MI157 S.-J. Park and R. Arshady, *Microspheres, Microcapsules Liposomes*, 2003, **6**, 157.
- 2003MI765 T. M. Cabrera-Vera, J. Vanhauwe, T. O. Thomas, M. Medkova, A. Preininger, M. R. Mazzoni, and H. E. Hamm, *Endocr. Rev.*, 2003, **24**(6), 765.
- 2003MI1467 X. Fu, C. Albermann, J. Jiang, J. Liao, C. Zhang, and J. S. Thorson, *Nat. Biotechnol.*, 2003, **21**(12), 1467.
- 2003NJC783 K. Hara, M. Kurashige, Y. Dan-oh, C. Kasada, A. Shinpo, S. Suga, K. Sayama, and H. Arakawa, *New. J. Chem.*, 2003, **27**(5), 783.
- 2003OL4477 I. Paterson, R. D. M. Davies, A. C. Heimann, R. Marquez, and A. Meyer, *Org. Lett.*, 2003, **5**(23), 4477.
- 2003P913 J. M. C. Geuns, *Phytochemistry*, 2003, **64**(5), 913.
- 2003P923 J.-M. Kong, L.-S. Chia, N.-K. Goh, T.-F. Chia, and R. Brouillard, *Phytochemistry*, 2003, **64**(5), 923.
- 2003SCI1488 D. Ferber, *Science*, 2003, **302**(5650), 1488.
- 2003SL1225 A. V. Demchenko, *Synlett*, 2003, 1225.
- 2004AAC728 A. Ruzin, G. Singh, A. Severin, Y. Yang, R. G. Dushin, A. G. Sutherland, A. Minnick, M. Greenstein, M. K. May, D. M. Shlaes, and P. A. Bradford, *Antimicrob. Agents Chemother.*, 2004, **48**(3), 728.
- 2004BMC1577 J. Yang, D. Hoffmeister, L. Liu, X. Fu, and J. S. Thorson, *Bioorg. Med. Chem.*, 2004, **12**(7), 1577.
- 2004BML2533 I. Brudzinska, Y. Mikata, M. Obata, C. Ohtsuki, and S. Yano, *Bioorg. Med. Chem. Lett.*, 2004, **14**(10), 2533.
- 2004BMM162 J. Jin, M. Song, and D. J. Hourston, *Biomacromolecules*, 2004, **5**(1), 162.
- 2004BP353 K. Ashikawa, S. Shishodia, I. Fokt, W. Priebe, and B. B. Aggarwal, *Biochem. Pharmacol.*, 2004, **67**(2), 353.
- 2004JA9546 A. V. Statsuk, D. Liu, and S. A. Kozmin, *J. Am. Chem. Soc.*, 2004, **126**(31), 9546.
- 2004JA15402 J. C. B. DeNap, J. R. Thomas, D. J. Musk, and P. J. Hergenrother, *J. Am. Chem. Soc.*, 2004, **126**(47), 15402.
- 2004JME3487 R. G. Dushin, T.-Z. Wang, P.-E. Sum, H. He, A. G. Sutherland, J. S. Ashcroft, E. I. Graziani, F. E. Koehn, P. A. Bradford, P. J. Petersen, K. L. Wheless, D. T. How, N. Torres, E. B. Lenoy, W. J. Weiss, S. A. Lang, S. J. Projan, D. M. Shlaes, and T. S. Mansour, *J. Med. Chem.*, 2004, **47**(14), 3487.
- 2004JNP1216 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2004, **67**(8), 1216.
- 2004LS2157 Y. Cai, Q. Luo, M. Sun, and H. Corke, *Life Sci.*, 2004, **74**(17), 2157.
- B-2004MI271 J. Szejtli; in 'Chemical and Functional Properties of Food Saccharides', P. Tomasik, Ed.; CRC Press, Boca Raton, 2004, p. 271.
- 2004MI5063 T. N. Gaitanos, R. M. Buey, J. F. Diaz, P. T. Northcote, P. Teesdale-Spittle, J. M. Andreu, and J. H. Miller, *Cancer Res.*, 2004, **64**(15), 5063.
- 2004NAT966 J. Clayden, A. Lund, L. Vallverdu, and M. Helliwell, *Nature*, 2004, **431**(7011), 966.
- 2004OL2317 T. E. Smith, M. Djang, A. J. Velander, C. W. Downey, K. A. Carroll, and S. Van Alphen, *Org. Lett.*, 2004, **6**(14), 2317.
- 2004OL3637 A. B. Smith, III, C. Sfougataakis, D. B. Gotchev, S. Shirakami, D. Bauer, W. Zhu, and V. A. Dougherty, *Org. Lett.*, 2004, **6**(20), 3637.
- 2004OPD92 S. J. Mickel, G. H. Sedelmeier, D. Niederer, R. Daeffler, A. Osmari, K. Schreiner, M. Seeger-Weibel, B. Berod, K. Schaer, R. Gamboni, S. Chen, W. Chen, C. T. Jagoe, F. R. Kinder, Jr., M. Loo, K. Prasad, O. Repic, W.-C. Shieh, R.-M. Wang, L. Waykole, D. D. Xu, and Xue., *Org. Process Res. Dev.*, 2004, **8**(1), 92.
- 2005CRV4237 K.-S. Yeung and I. Paterson, *Chem. Rev.*, 2005, **105**(12), 4237.
- 2005JA836 R. M. Mizanur, F. A. Jaipuri, and N. L. Pohl, *J. Am. Chem. Soc.*, 2005, **127**(3), 836.
- 2005JA1628 X. Gao and D. G. Hall, *J. Am. Chem. Soc.*, 2005, **127**(6), 1628.
- 2005JA4140 D. J. Maloney, J.-Z. Deng, S. R. Starck, Z. Gao, and S. M. Hecht, *J. Am. Chem. Soc.*, 2005, **127**(12), 4140.
- 2005JA12090 J.-H. Kim, H. Yang, J. Park, and G.-J. Boons, *J. Am. Chem. Soc.*, 2005, **127**(34), 12090.
- 2005JA16030 S. Yoon, A. E. Albers, A. P. Wong, and C. J. Chang, *J. Am. Chem. Soc.*, 2005, **127**(46), 16030.
- 2005MI13 S. Sakka, *Trans. Indian Ceram. Soc.*, 2005, **64**(1), 13.
- 2005MI383 A. V. Statsuk, R. Bai, J. L. Baryza, V. A. Verma, E. Hamel, P. A. Wender, and S. A. Kozmin, *Nat. Chem. Biol.*, 2005, **1**(7), 383.
- 2005MI453 R. Pettit, T. Woyke, S. Pon, Z. Cichacz, G. Pettit, and C. Herald, *Med. Mycol.*, 2005, **43**(5), 453.
- 2005JNP1696 J. M. Langenhan, B. R. Griffith, and J. S. Thorson, *J. Nat. Prod.*, 2005, **68**(11), 1696.
- 2005MI1948 Y. Nie, S. Vignes, J. R. Hobbs, G. L. Conn, and S. D. Munger, *Curr. Biol.*, 2005, **15**(21), 1948.
- 2005NAT488 B. D. Moore and W. J. Foley, *Nature*, 2005, **435**(7041), 488.
- 2005OL3857 B. Sahoo, K. F. Brandstadt, T. H. Lane, and R. A. Gross, *Org. Lett.*, 2005, **7**(18), 3857.
- 2005P1984 K. S. Feldman, *Phytochemistry*, 2005, **66**(17), 1984.
- 2005PCB15476 K. Hara, Z.-S. Wang, T. Sato, A. Furube, R. Katoh, H. Sugihara, Y. Dan-oh, C. Kasada, A. Shinpo, and S. Suga, *J. Phys. Chem. B*, 2005, **109**(32), 15476.
- 2005PNA12305 J. M. Langenhan, N. R. Peters, I. A. Guzei, F. M. Hoffmann, and J. S. Thorson, *Proc. Natl. Acad. Sci. USA*, 2005, **102**(35), 12305.
- 2005SCI1022 M. M. He, A. Stroustrup Smith, J. D. Oslob, W. M. Flanagan, A. C. Braisted, A. Whitty, M. T. Cancilla, J. Wang, A. A. Lugovskoy, J. C. Yoburn, A. D. Fung, G. Farrington, J. K. Eldredge, E. S. Day, L. A. Cruz, T. G. Cachero, S. K. Miller, J. E. Friedman, I. C. Choong, and B. C. Cunningham, *Science*, 2005, **310**(5750), 1022.
- 2005SCI1598 Y. Matsuo, H. Imagawa, M. Nishizawa, and Y. Shizuri, *Science*, 2005, **307**(5715), 1598.

- 2006AGE1580 J. E. Debreczeni, A. N. Bullock, G. E. Atilla, D. S. Williams, H. Bregman, S. Knapp, and E. Meggers, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**(10), 1580.
- 2006AGE7086 K. C. Nicolaou, A. Li, and D. J. Edmonds, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**(42), 7086.
- 2006CC4392 S. Ou, Z. Lin, C. Duan, H. Zhang, and Z. Bai, *J. Chem. Soc., Chem. Commun.*, 2006, 4392.
- 2006JA3882 S. A. Rizvi, V. Tereshko, A. A. Kossiakoff, and S. A. Kozmin, *J. Am. Chem. Soc.*, 2006, **128**(12), 3882.
- 2006JA6292 X. Chen, U. C. Tam, J. L. Czapinski, G. S. Lee, D. Rabuka, A. Zettl, and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2006, **128**(19), 6292.
- 2006LS2872 Y.-Z. Cai, M. Sun, X. Jie, Q. Luo, and H. Corke, *Life Sci.*, 2006, **78**(25), 2872.
- B-2006MI(925)25 N. P. Sceram; in 'ACS Symposium Series 925: Herbs', M. Wang, C.-T. Ho, L. S. Hwang, and S. Sang, Eds.; American Chemical Society, Washington, 2006, p. 25.
- 2006MI94 D. Festi, A. Vestito, G. Mazzella, E. Roda, and A. Colecchia, *Digestion*, 2006, **73**(supplement 1), 94.
- 2006MI298 G. S. Huang, L. Lopez-Barcons, B. S. Freeze, A. B. Smith, III, G. L. Goldberg, S. Band Horwitz, and H. M. McDaid, *Clin. Cancer Res.*, 2006, **12**(1), 298.
- 2006MI343 G. Cravotto, A. Binello, E. Baranelli, P. Carraro, and F. Trotta, *Curr. Nutr. Food Sci.*, 2006, **2**(4), 343.
- 2006MI375 M. H. Lim, D. Xu, and S. J. Lippard, *Nat. Chem. Biol.*, 2006, **2**(7), 375.
- 2006MI417 C.-Y. Zhang, L. E. Parton, C. P. Ye, S. Krauss, R. Shen, M. Wang, C.-T. Lin, J. A. Porco, Jr., and B. B. Lowell, *Cell Metab.*, 2006, **3**(6), 417.
- 2006JFA4041 F. Cimino, R. Ambra, R. Canali, A. Saija, and F. Virgili, *J. Agri. Food Chem.*, 2006, **54**(11), 4041.
- 2006NAT940 D.-K. Ro, E. M. Paradise, M. Ouellet, K. J. Fisher, K. L. Newman, J. M. Ndungu, K. A. Ho, R. A. Eachus, T. S. Ham, J. Kirby, M. C. Y. Chang, S. T. Withers, Y. Shiba, R. Sarpong, and J. D. Keasling, *Nature*, 2006, **440**(7086), 940.
- 2006NAT358 J. Wang, S. M. Soisson, K. Young, W. Shoop, S. Kodali, A. Galgoci, R. Painter, G. Parthasarathy, Y. S. Tang, R. Cummings, S. Ha, K. Dorso, M. Motyl, H. Jayasuriya, J. Ondeyka, K. Herath, C. Zhang, L. Hernandez, J. Allocco, A. Basilio, J. R. Tormo, O. Genilloud, F. Vicente, F. Pelaez, L. Colwell, S. H. Lee, B. Michael, T. Felcetto, C. Gill, L. L. Silver, J. D. Hermes, K. Bartizal, J. Barrett, D. Schmatz, J. W. Becker, D. Cully, and S. B. Singh, *Nature*, 2006, **441**(7091), 358.
- 2006OL3081 B. Li, H. Song, S. Hauser, and L.-X. Wang, *Org. Lett.*, 2006, **8**(14), 3081.
- 2006PCB12932 C. M. Carbonaro, A. Anedda, S. Grandi, and A. Magistris, *J. Phys. Chem. B*, 2006, **110**(26), 12932.
- 2006PNA16568 P. Maher, T. Akaishi, and K. Abe, *Proc. Natl. Acad. Sci. USA*, 2006, **103**(44), 16568.
- 2006SCI443 T. M. Bonacci, J. L. Mathews, C. Yuan, D. M. Lehmann, S. Malik, D. Wu, J. L. Font, J. M. Bidlack, and A. V. Smrcka, *Science*, 2006, **312**(5772), 443.
- 2007BBR177 A. R. Sannella, L. Messori, A. Casini, F. F. Vincieri, A. R. Bilia, G. Majori, and C. Severini, *Biochem. Biophys. Res. Commun.*, 2007, **353**(1), 177.
- 2007MI1 T. Loftsson and D. Duchene, *Int. J. Pharm.*, 2007, **329**(1–2), 1.
- 2007MI108 K. Kostarelos, L. Lacerda, G. Pastorin, W. Wu, S. Wieckowski, J. Luangsivilay, S. Godefroy, D. Pantarotto, J.-P. Briand, S. Muller, M. Prato, and A. Bianco, *Nat. Nanotechnol.*, 2007, **2**(2), 108.
- 2007OM1126 T. Nishioka, T. Shibata, and I. Kinoshita, *Organometallics*, 2007, **26**(5), 1126.

7.10

Thiopyrans and their Benzo Derivatives

J. D. Hepworth

University of Central Lancashire, Preston, UK

B. M. Heron

University of Leeds, Leeds, UK

© 2008 Elsevier Ltd. All rights reserved.

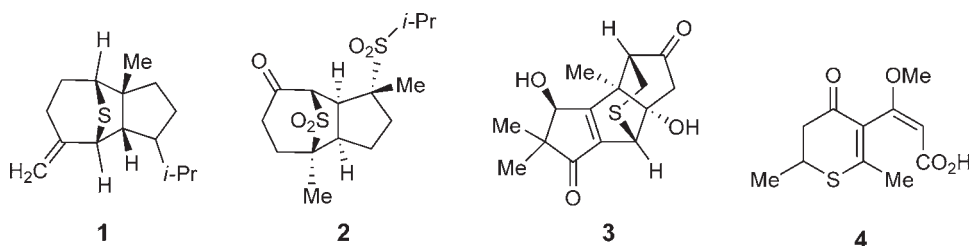
7.10.1	Introduction	728
7.10.1.1	Nomenclature	729
7.10.2	Structure	731
7.10.2.1	Theoretical Methods	731
7.10.2.2	Experimental Structural Methods	733
7.10.2.2.1	X-Ray crystallography and electron diffraction spectroscopy	733
7.10.2.2.2	Microwave spectroscopy	744
7.10.2.2.3	NMR spectroscopy	744
7.10.2.2.4	Mass spectrometry	778
7.10.2.2.5	UV spectroscopy	784
7.10.2.2.6	Infrared and Raman spectroscopy	789
7.10.2.2.7	Photoelectron spectroscopy	791
7.10.2.2.8	Electron spin resonance spectroscopy	792
7.10.2.3	Thermodynamic Aspects	794
7.10.2.3.1	Chromatography	794
7.10.2.3.2	Aromaticity	795
7.10.2.3.3	Conformations	798
7.10.2.3.4	Tautomerism	805
7.10.3	Reactivity	809
7.10.3.1	Electrophilic Attack at Ring Carbon	809
7.10.3.2	Electrophilic Attack at Sulfur	815
7.10.3.3	Nucleophilic Attack at Ring Carbon	816
7.10.3.4	Nucleophilic Attack at Hydrogen	820
7.10.3.5	Reactions with Radicals and Carbenes	824
7.10.3.6	Oxidation at Sulfur	828
7.10.3.7	Cycloaddition Reactions	830
7.10.3.8	Reactions of Substituents Attached to Ring Carbon Atoms	838
7.10.3.9	Reactions of Substituents Attached to Sulfur	856
7.10.4	Synthesis	858
7.10.4.1	Thiopyrans and Fused Thiopyrans	858
7.10.4.1.1	Thiopyranium salts	858
7.10.4.1.2	2 <i>H</i> -Thiopyrans	858
7.10.4.1.3	2 <i>H</i> -1-Benzothiopyrans	861
7.10.4.1.4	4 <i>H</i> -Thiopyrans	865
7.10.4.1.5	1 <i>H</i> -2-Benzothiopyrans	867
7.10.4.1.6	Thioxanthenes	868
7.10.4.2	Reduced Thiopyrans	869
7.10.4.2.1	Dihydrothiopyrans	869
7.10.4.2.2	Tetrahydrothiopyrans	881
7.10.4.2.3	Thiochromans	887
7.10.4.2.4	Isothiochromans	893

7.10.4.3 Thiopyranones and Fused Thiopyranones	897
7.10.4.3.1 Thiopyran-2-ones	897
7.10.4.3.2 Thiocoumarins	899
7.10.4.3.3 Isothiocoumarins	900
7.10.4.3.4 Thiopyran-4-ones	901
7.10.4.3.5 Thiochromones	903
7.10.4.3.6 Thioxanthenes	906
7.10.4.4 Reduced Thiopyranones	909
7.10.4.4.1 Dihydrothiopyranones	909
7.10.4.4.2 Tetrahydrothiopyranones	912
7.10.4.4.3 Dihydrothiocoumarins	913
7.10.4.4.4 Thiochromanones	913
7.10.4.4.5 Isothiochromanones	916
7.10.4.5 Thiopyrylium Salts and Their Benzo Derivatives	918
7.10.4.5.1 Formation of one bond	918
7.10.4.5.2 From other heterocycles	919
7.10.4.5.3 From a preformed heterocyclic ring	919
7.10.5 Applications	920
7.10.5.1 Pharmaceutical and Biological Applications	920
7.10.5.1.1 Thiopyrans, thiopyrylium salts and their benzologues	920
7.10.5.1.2 Thiopyranones and their benzologues	924
7.10.5.2 Materials Applications	925
7.10.5.2.1 Thiopyrans, thiopyrylium salts and their benzologues	925
7.10.5.2.2 Thiopyranones and their benzologues	932
7.10.6 Further Developments	938
References	939

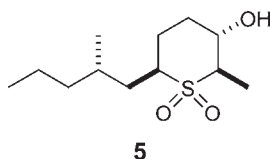
7.10.1 Introduction

The first edition of *Comprehensive Heterocyclic Chemistry* <1984CHEC(2)885> covered the literature up to 1982 and the second edition <1996CHEC-II(5)501> up to 1995. The present chapter commences coverage around 1994 and continues through to 2006. Although there has been an increased interest in thiopyran chemistry in the past 10 or so years, it still remains the poor relation of pyran chemistry. A rapid literature search revealed that the difference in the number of references to the two systems during this period was approximately an order of magnitude.

Interestingly, six 2-alkyl-2*H*-thiopyrans have been detected in the volatiles produced during the cooking of beef and lamb at 140°C. It is thought that H₂S generated by the degradation of cysteine reacts with lipid-derived aldehydes to form these thiopyrans and several 2-alkylthiophenes. The quantities formed vary with the source of the meat both in terms of breed and feedstock, but in all cases the aroma is quite weak <2000JFA2420>. Mint sulfide **1**, a sulfur-containing sesquiterpene which may be considered to possess the 2,6-bridged 3-methylene-3,4,5,6-tetrahydro-2*H*-thiopyran structural unit, has been identified in the buds, flowers, leaves, and stems of purple starthistle (*Centaurea calcitrapa* L.) a naturalized weed of rangelands in California <1990JFA1053>, in the essential oils from a variety of mosses (Musci), <2001P443> and also as a minor constituent in a variety of other plant species <2004MI360, 2005MI274, 2006FFJ650>. The structurally related sesquiterpene, orientanone **2**, has been isolated from the Chinese medicinal tuber *Alisma orientalis* Juzep.; an extensive battery of NMR investigations and X-ray crystallography were employed to determine the structure <2002T9045>. The sesquiterpene, Hersutenol-F **3** which possesses significant superoxide radical-scavenging abilities, along with other members of the Hersutenol family, was isolated from the fermentation broth of *Stereum hirsutum* <2006JAN110>. The structure of the metabolite citreothio-lactone, found in the culture filtrate of *P. citreo-viride* IFO 6200, has been revised to the dihydrothiopyran-4-one **4** on the basis of additional spectroscopic evidence and renamed citreothiopyrane B <1999TL6831>.



Detailed spectroscopic analysis of the 3-hydroxytetrahydrothiopyran 1,1-dioxide **5**, an oxidative degradation product of hedathiosulfonic acid A isolated from the deep-sea urchin *Echinocardium cordatum*, provided invaluable data for the determination of the stereostructure of the parent thiosulfonic acid <2002T6405>.



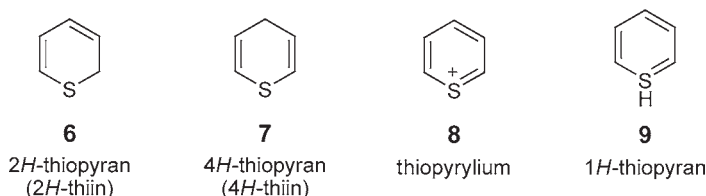
Major works published on thiopyrans and related compounds since the mid-1990s include a chapter on six-membered ring compounds with one chalcogen heteroatom in the second supplement to the second edition of Rodd's *Chemistry of Carbon Compounds* <1997SSRIVE547>. Six-membered heteroarenes with one chalcogen are discussed in *Science of Synthesis* with chapters devoted to thiopyrylium salts <2003HOU(14)649>, benzothiopyrylium salts <2003HOU(14)719>, thiopyranones, <2003HOU(14)771> and benzothiopyranones <2003HOU(14)787>, all of which contain some preparative examples.

The series *Advances in Heterocyclic Chemistry* contains reviews on pyrans, thiopyrans, and selenopyrans <1983AHC(34)146>, developments in the chemistry of thiopyran and the Se and Te analogues <1994AHC(59)179>, thiopyrones (thiopyranones) <1967AHC(8)219>, thiocoumarins <1980AHC(26)115>, thiochromanones and related compounds <1975AHC(18)60> and thiopyrylium, selenopyrylium, and telluropirylium salts <1994AHC(60)65>. Chapters on the tautomerism of heterocycles <2001AHC(81)254, 2006AHC(91)1> and on conformational analysis of saturated heterocyclic six-membered rings <2004AHC(86)42> make reference to thiopyrans.

All aspects of thiopyran chemistry feature in the review chapter on six-membered heterocycles containing one chalcogen heteroatom in the issues of *Progress in Heterocyclic Chemistry* <2006PHC(18)376>; these have been published since 1989. Reviews on 2*H*- and 4*H*-thiopyrans <1993SR161>, isothiochromans <1998OPP243>, the catalytic reduction of thiopyrylium salts <2001CHE797> and thiopyran and thiopyrylium salts <B-1998MI375> have been published. Reviews of the synthesis of 2,2-dimethyl-2*H*-1-benzopyrans <2000H(53)1193> and the synthesis and reactions of halogen-containing chromones <2003RCR489> contain references to the sulfur analogues.

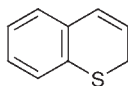
7.10.1.1 Nomenclature

Six-membered sulfur heterocyclic compounds are based on four molecules: 2*H*-thiopyran **6**, 4*H*-thiopyran **7**, thiopyrylium **8**, and 1*H*-thiopyran **9** which is formally named as 1 λ^4 -thiopyran and also referred to as thiabenzene. The systematic name thiin for six-membered rings containing a sulfur atom is infrequently used.

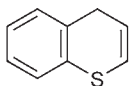


The benzologues of the thiopyrans are 2*H*-1-benzothiopyran **10**, which is also referred to as 2*H*-thiochromene, and 4*H*-1-benzothiopyran **11** (4*H*-thiochromene). Fusion on to the 3,4-bond of 2*H*-thiopyran leads to 1*H*-2-benzothiopyran **12** and 3*H*-2-benzothiopyran **13**. Higher benzologues are named as 9*H*-thioxanthene **14**, 1*H*-thioxanthene **15**,

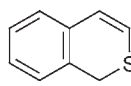
and 10*H*-thioxanthene (10 λ^4 -thioxanthene) **16**. The angular analogues are illustrated by 6*H*-dibenzo[*b,d*]thiopyran **17** and the naphthothiopyrans are exemplified by 2*H*-naphtho[1,2-*b*]thiopyran **18** and 3*H*-naphtho[2,1-*b*]thiopyran **19**.

**10**

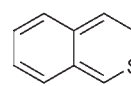
2*H*-1-benzothiopyran
(2*H*-thiochromene)
(2*H*-benzothiin)

**11**

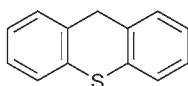
4*H*-1-benzothiopyran
(4*H*-thiochromene)

**12**

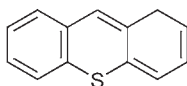
1*H*-2-benzothiopyran
(Isothiochromene)

**13**

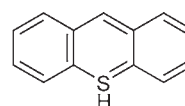
3*H*-2-benzothiopyran

**14**

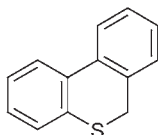
9*H*-thioxanthene

**15**

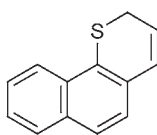
1*H*-thioxanthene

**16**

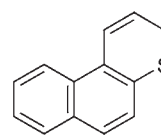
10*H*-thioxanthene
(10 λ^4 -thioxanthene)

**17**

6*H*-dibenzo[*b,d*]thiopyran

**18**

2*H*-naphtho[1,2-*b*]thiopyran
(7,8-benzothiochromene)

**19**

3*H*-naphtho[2,1-*b*]thiopyran
(5,6-benzothiochromene)

The partially reduced thiopyrans are 3,4-dihydro-2*H*-thiopyran **20** and 3,6-dihydro-2*H*-thiopyran **21** and the fully reduced compound is tetrahydrothiopyran or thiane **22**. The benzologues are 3,4-dihydro-2*H*-1-benzothiopyran or thiochroman **23** and 3,4-dihydro-1*H*-2-benzothiopyran or isothiochroman **24**. The fully saturated derivatives of **23** and **24** are known as thiadecalin and isothiadecalin, respectively.

**20**

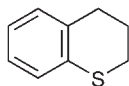
3,4-dihydro-2*H*-thiopyran

**21**

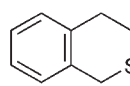
3,6-dihydro-2*H*-thiopyran

**22**

3,4,5,6-tetrahydro-2*H*-thiopyran
(thiane)

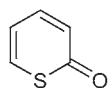
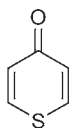
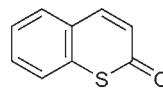
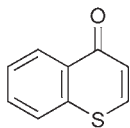
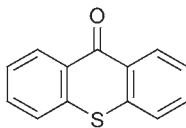
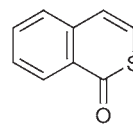
**23**

3,4-dihydro-2*H*-1-benzothiopyran
(thiochroman)

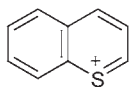
**24**

3,4-dihydro-1*H*-2-benzothiopyran
(isothiochroman)

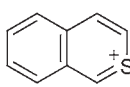
The ketones derived from thiopyrans are 2*H*-thiopyran-2-one **25** and 4*H*-thiopyran-4-one **26** and the benzologues are 2*H*-1-benzothiopyran-2-one or thiocoumarin **27**, 4*H*-1-benzothiopyran-4-one (thiochromone) **28**, and 9*H*-thioxanth-9-one or simply thioxanth-9-one **29**. The trivial names dihydrothiocoumarin and thiochroman-4-one are used for the partially reduced derivatives. 1*H*-2-Benzothiopyran-1-one **30** is usually known as isothiocoumarin. The 2- and 3- aryl derivatives of **10**, **28**, and **31** are generally referred to as the thioflavonoids.

**25***2H*-thiopyran-2-one**26***4H*-thiopyran-4-one**27***2H*-1-benzothiopyran-2-one
(Thiocoumarin)**28***4H*-1-benzothiopyran-4-one
(Thiochromone)**29***9H*-thioxanthen-9-one**30***1H*-2-benzothiopyran-1-one
(Isothiocoumarin)

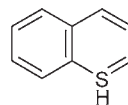
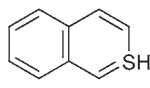
Benzologues of thiopyrylium are 1-benzothiopyrylium **31** and 2-benzothiopyrylium **32** and those of *1H*-thiopyran **9** are *1H*-1-benzothiopyran **33** and *2H*-2-benzothiopyran **34** or the $1\lambda^4$ -1- and $2\lambda^4$ -2- derivatives, respectively.

**31**

1-benzothiopyrylium

**32**

2-benzothiopyrylium

**33***1H*-1-benzothiopyran**34***2H*-2-benzothiopyran

7.10.2 Structure

The past two decades have seen a marked change in the reporting of the application of various techniques to the determination of structure. Most papers relating to the synthesis of organic molecules now confine comments on UV and IR data to a minimum. While NMR data are presented in more detail, much ^{13}C NMR spectral information is often presented simply as a catalogue of chemical shifts with little or no attempt at assignment. X-Ray structural determinations have become more commonplace and many papers now contain ORTEP representations of molecules. In addition, proposed structures are frequently supported by calculations and computer-assisted representations.

7.10.2.1 Theoretical Methods

With the advent of reliable, readily available, molecular modeling packages there has been an increase in the number of reports that compare and contrast theoretical geometries and conformations, orbital charge, polarizabilities, and NMR chemical shifts with experimental values. A selection of theoretical methods and the type of information thus obtained on six-membered sulfur heterocycles is presented in [Table 1](#).

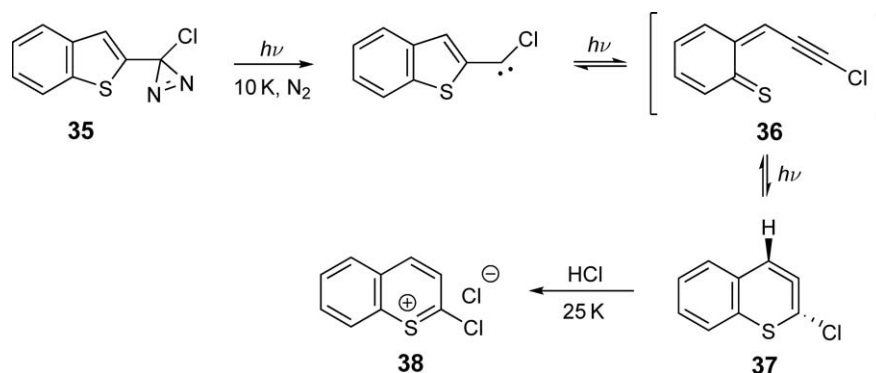
In addition, reference to calculated data will be found at various points throughout [Section 7.10.2](#) of this chapter.

Photolysis of the diazine **35** in an N_2 matrix at 10 K generates 2-benzothiénylchlorocarbene. Infrared spectroscopy, supported by B3LYP/6-31G** calculations, indicates the presence in the matrix of both *anti* and *syn* carbenes,

distinguished by bands at 1156 cm^{-1} and 1130 cm^{-1} . UV absorptions are noted at 355 and 415 nm. Further irradiation at 334 nm leads to a strong absorption at 907 cm^{-1} and bands in the UV at 310 and 424 nm associated with the strained allene, 2,3-didehydrothiochromene **37**. Initial irradiation of the diazirine at 366 nm leads directly to the allene. The allene and carbene are photochemically convertible, presumably via the thioquinonemethide **36**; a transient $\text{C}\equiv\text{C}$ absorption band at 2157 cm^{-1} supports this supposition. On warming to 25 K in an HCl-doped N_2 matrix containing the allene, the benzothiopyrylium salt **38** is formed. Calculations indicate that this didehydrothiopyran is more stable though less aromatic than the corresponding didehydropyran (**Scheme 1**) <2005OL4467>.

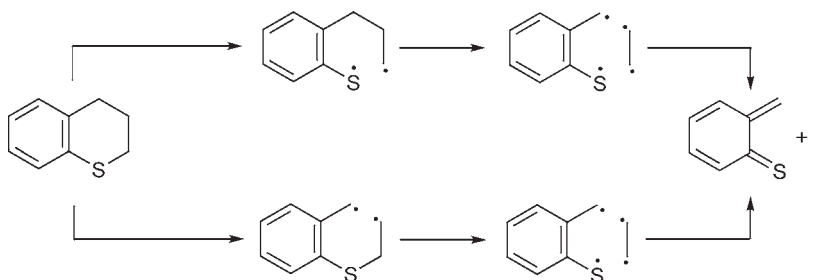
Table 1 Theoretical data obtained by molecular modeling

Compound type	Method	Information	Reference
4 <i>H</i> -Thiopyran	HF/STO-3G, HF/6-31G* B3LYP/6-31G*	Geometry	2004JST(678)171
Thiopyranoquinone	6-31G*, PM3, DFT	Orbital energies, hardness	2000H(53)585
Thioxanthene carbenes	3-21G	Geometry	1997JA8058
(Thiopyranylidene)thioxanthene	TRIPOS, MOPAC93 AM1	Conformation, rotational energy barriers	1997JOC4943
(Thiopyranylidene)thioxanthene	MOPAC93 AM1	Conformation	2002JA5037
Tetrahydrothiopyran	MNDO, PM3, TRIPOS	Geometry	1996J(P2)2623
Tetrahydrothiopyran	PP/IGLO-IIIB3LYP/ 6-31G(d,p)	Bond distances, $^1J_{\text{CH}}$ couplings	2002JA13088
Thiasteroid	MM3	Geometry	2005T3691
Thiabenzene	B3LYP/6-31G*	Aromaticity by nucleus-independent shift, geometry, energies	2001HCA1578
2-Amino-4 <i>H</i> -thiopyran-4-one	HF/6-31G*, HF/6-31G**, B3LYP/6-31G**	Rotation about C–N bond, geometry	2001JST(535)257
Thiopyranones	6-31G*	UV data orbital symmetry	1998EJO1989
Thiochromone	PM3	Orbital and charge properties	2005JFC(126)779
Thioflavanones	B3LYP/6-31G*, GIAO	Geometry, NMR	2001MRC251, 2003MRC193
Thiocoumarin	B3LYP/6-31G*	Charge density	2005PCA659
Thiocoumarin	DFT, B3LYP/6-31G**	Charge density	2005CEO608
Thiocoumarin	B3LYP/6-31G*	Geometry, frequencies	2002PCA10510
Thioxanthone	6-31G, 3-21G, ECP	Static polarizability	1996CPL(251)125
Thioxanthone	6-31G	Geometry, charge distribution	1997J(P2)1605
Thioxanthone	MP2 CASPT2	Geometry, absorption spectra	2006JPH(179)298
Thiopyrylium	6-311G(d, p), DFT	Geometry, NMR, energies	2003JFC(120)49
Thiopyrylium	B3LYP/6-31G*+GIAO	Aromaticity by nucleus-independent shift	2003JST(663)145



Scheme 1

Calculations by the AM1 method have shown that the thermolysis of thiochroman does not occur by a retro Diels–Alder reaction. Instead, two competing radical processes are indicated (**Scheme 2**) <1995JST(331)245>.



Scheme 2

7.10.2.2 Experimental Structural Methods

7.10.2.2.1 X-Ray crystallography and electron diffraction spectroscopy

In the past decade, X-ray structural determinations have become more commonplace and many papers on the synthesis of S heterocycles now contain ORTEP representations. In addition, proposed structures are now frequently supported by computer-assisted representations. Full crystallographic data are usually lodged with Cambridge Crystallographic Data Centre and assigned an individual code number (CCDC) and this information is freely available. Some examples are provided in **Table 2**. Furthermore, the previous edition of *Comprehensive Heterocyclic Chemistry* contained structural details of a range of thiopyran derivatives derived from X-ray crystallography <1996CHEC-II(5)501>. Nevertheless, some X-ray studies are discussed here in appreciable detail.

Table 2 Selected X-ray crystal structures (and where available CCDC deposition number)

<i>Compound</i>	<i>CCDC number</i>	<i>Reference</i>
Dibenzothiopyran	136441	2000BCJ155
Thioxanthylidenethanone		1996HCA855
Naphthothioxanthene	226047	2004JA3108
Thiasteroid	257342	2005T3691
Thiasteroid	265386, 265387	2005T9405
2,4,6-Triphenyl-4 <i>H</i> -thiopyrans	1267/305, 1267/306	2001NCS47
Thiopyran-4-thione complex	281752	2006CC206
Cyclobuta[<i>b</i>]thiopyranone	260927, 260928	2005HCA1922
Naphthothiopyranone	139671	2000T6763
Benzothiopyran-4-one 1-oxide		2000NCS217
		2000NCS219
Benzothiopyran	188981, 188982	2003T3621
1 <i>H</i> -2-Benzothiopyran-1-one		1997HCA1865
Cyclopropa[<i>c</i>]-1 <i>H</i> -2-benzothiopyran	182/103	1996CC1659
(Thiopyranylidene)-thioxanthene		2002JA5037
(Thiopyranylidene)-thioxanthene	271760	2005OBC4071

The gas-phase electron diffraction of tetrahydrothiopyran 1-oxide has established that it exists in a chair conformation with the oxygen atom occupying an axial position. Full structural details are given in **Figure 1**. Comparison with the data for tetrahydrothiopyran <1988ACA332> shows that while the S–C and C–C bond lengths are very similar, the CSC bond angle is smaller (cf. 97.6°) and the flap angles at S (56.8° vs. 49.6°) and at C-4 (−47.0° vs. −52.3°) are different <1991JST(243)123>.

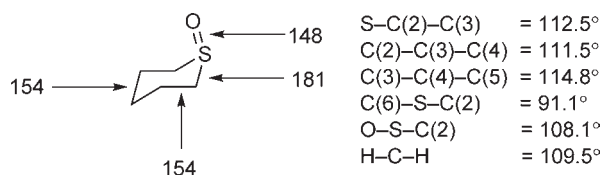
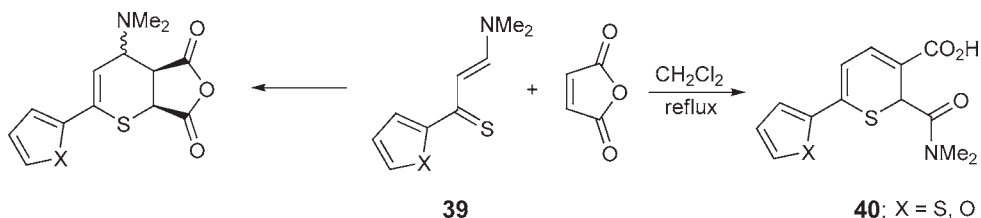


Figure 1 Bond lengths (pm) and bond angles (°) for tetrahydrothiopyran 1-oxide.

The hetero Diels–Alder (hDA) reaction between enaminothiones **39** and maleic anhydride yields the 2-substituted 2*H*-thiopyrans **40** (Scheme 3) rather than the expected *endo*-cycloadduct. X-Ray analysis of the products established the locations of the 2-dimethylamido and 3-carboxyl groups which also indicated that the cycloadduct rearranges via a five-membered transition state. The thiophene ring is twisted out of conjugation with the thiopyran unit more than the furan moiety and the hydrogen bonding network and packing in the crystal are different for the two compounds (Figure 2) <2002JST(609)169>.



Scheme 3

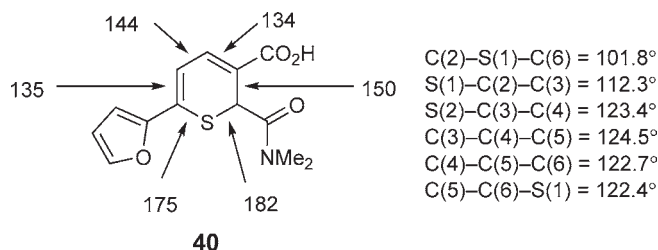
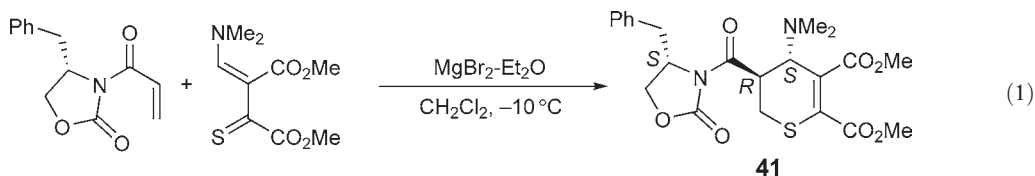
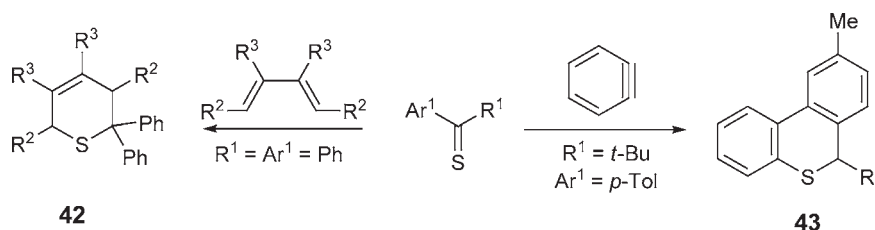


Figure 2 Bond lengths (pm) and bond angles (°) for 2*H*-thiopyran **40**.

Crystal structure determinations have been used to determine the stereochemistry of a variety of 3,4-dihydro-2*H*-thiopyrans that have been obtained from asymmetric hDA reactions involving homochiral thiabutadienes <1996TL123, 1999TL8383> or homochiral dienophiles <1996J(P1)1897>. In an example of the latter, the absolute stereochemistry of both stereogenic centers formed in the 3,4-hydro-2*H*-thiopyran cycloadduct **41** during the diastereoselective hDA reaction was established by X-ray crystallography (Equation 1) <2002AXEo1123>.

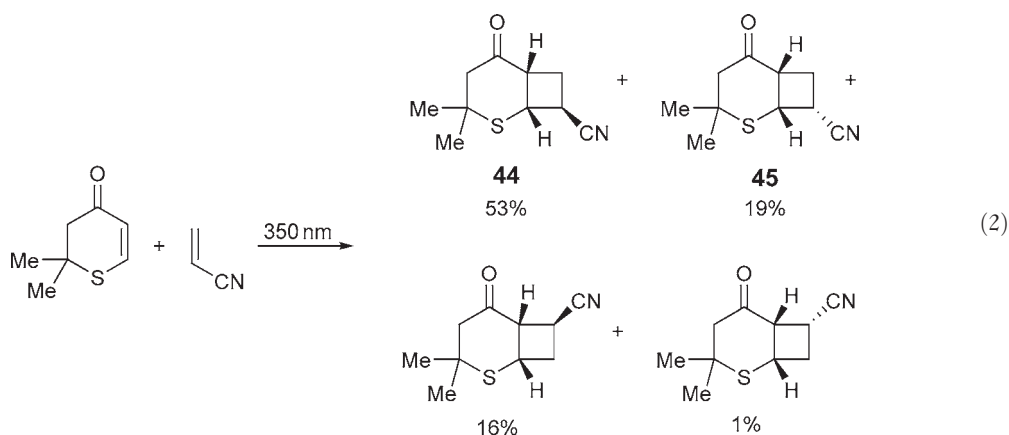


Similarly, the crystal structures of [4+2] cycloadducts from electronically stabilized thiones with either butadienes **42** <1998EJO2861> or benzyne **43** (Scheme 4) <2000BCJ155> have been determined to confirm the regiochemical assignments derived from ¹H NMR spectroscopy.

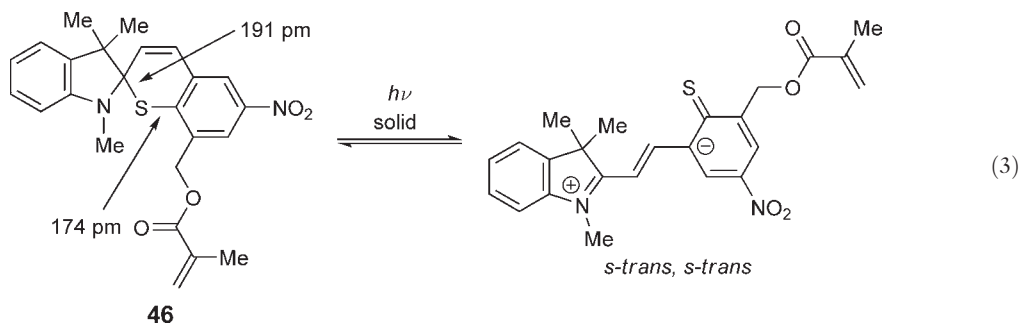


Scheme 4

The stereochemistries of the major [2+2] photo-cycloadducts **44** and **45** from 2,3-dihydro-2,2-dimethyl-4*H*-thiopyran-4-one and acrylonitrile have been established by crystallography. The magnitude of the geminal coupling constant of the methylene protons adjacent to the CO group of 13.5 Hz for **44** suggested a *trans*-fused bicyclic structure, but a single-crystal structure determination confirmed the *cis* fusion (Equation 2) <2005HCA1922>.



An X-ray structure of the photochromic spirobenzothiopyran **46** shows an elongated bond from sulfur to the spiro carbon atom while the bond from S to the aromatic ring is shortened. Irradiation at 365 nm cleaves the former bond and generates the zwitterionic blue-green merocyanine with an *s-trans*, *s-trans* conformation in the solid state (Equation 3). In solution, NMR studies indicate an *s-trans*, *s-cis* conformation <2002JOC533>.



Bond lengths and bond angles for the disubstituted 1*H*-2-benzothiopyran (Figure 3), derived by an electrophilic cyclization of a bisarylmethylthioacetylene have been measured <1998JOC4626>.

The structures of two 3,4-dihydro-4-hydroxynaphtho[2,3-*b*]thiopyranoquinones have been confirmed by X-ray analysis <2000H(53)585>.

An X-ray diffraction analysis of 4-(3,5-dimethylphenyl)tetrahydrothiopyran-4-ol **47** indicates that the aryl group occupies a pseudo-equatorial position in the chair conformer of the thiopyran ring. Some flattening at the sulfur end of the ring is indicated (Figure 4) <2005PS(180)53>.

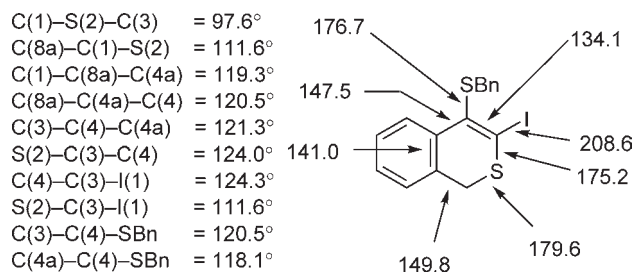


Figure 3 Bond lengths (pm) and bond angles for 4-benzylthio-3-iodo-1*H*-2-benzopyran.

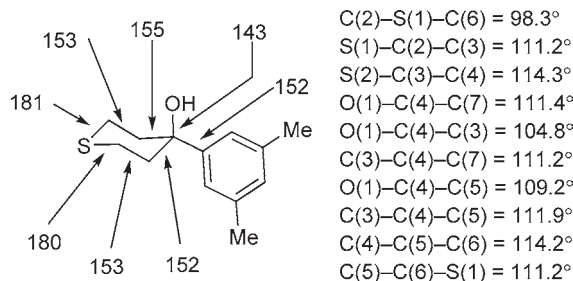
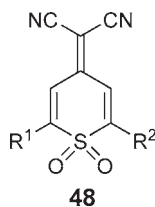
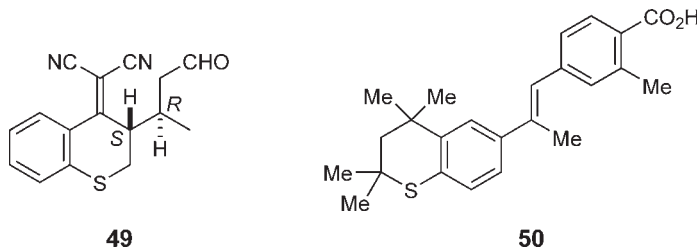


Figure 4 Bond lengths (pm) and bond angles for tetrahydrothiopyran-4-ol **47**.

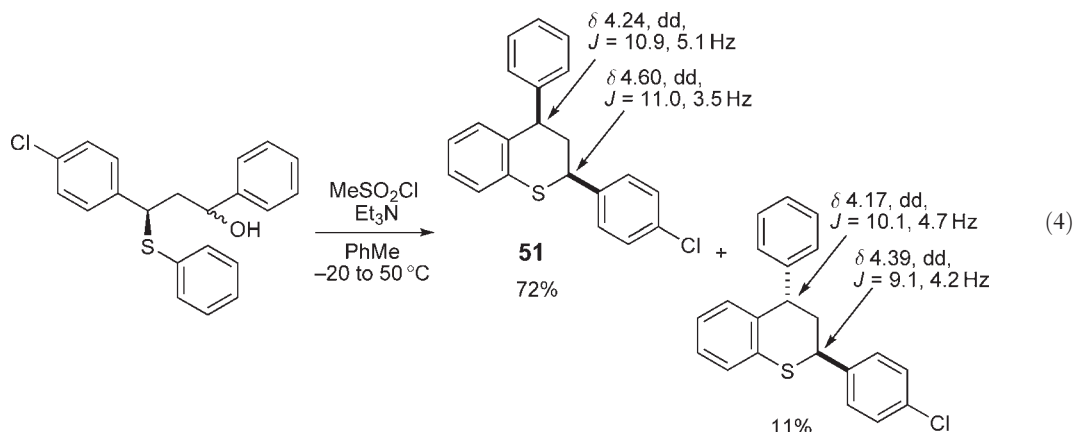
Structural analysis of several 2,6-disubstituted 4-(dicyanomethylidene)-4*H*-thiopyran 1,1-dioxides **48** has shown that the thiopyran ring is essentially planar in the unsubstituted, 2,6-diphenyl and 2-phenyl-2-thienyl derivatives. However, bulky *t*-butyl substituents distort the ring which becomes boat shaped. Interestingly, the 2-thienyl ring is coplanar with the thiopyran ring, whereas a 2-phenyl substituent is twisted with a dihedral angle of 36.6°. In all cases, the dicyanomethylidene unit is bent slightly from the plane of the ring <1995JOC1674>.



The absolute configuration of the *anti*-4-dicyanovinylthiochroman derivative **49** has been confirmed as *S* at C-3 and *R* at the adjacent side-chain C atom <2006CC1563> and the (*E*)-geometry of the alkene moiety of the heteroarotinoid **50** was established from a single-crystal analysis <2005PS(180)67>.



The unequivocal *cis* relationship between the diaryl groups of the 3,4-dihydro-2,4-diaryl-2*H*-1-benzothiopyran **51** was determined from a crystal study. The assignment could not be made from the analysis of the vicinal coupling constants from the ¹H NMR spectra of the *cis* and *trans* isomers because of their similarity (Equation 4) <2003T3621>.



Whereas 4-ethyl-3,5-dimethyl-2,4,6-triphenyl-4*H*-thiopyran forms orthorhombic crystals, the corresponding 4-*t*-butyl derivative is monoclinic. Both C-4 and S lie above the plane of the double bonds and the alkyl groups are oriented towards the S atom <2001NCS47>. These and other 4*H*-thiopyrans have 6 π electrons and can be considered homoaromatic; p- π overlap involving the heteroatom improves such character. *Ab initio* calculations with HF/STO-3G, HF/6-31G*, and B3LYP/6-31G* basis sets indicate a near planar or shallow boat conformation. Bulky 4-substituents increase the dihedral angles C-C-C=C and C=C-S-C <2004JST(678)171>.

The X-ray structure of 3,5-dibromo-2,4,4,6-tetraphenyl-4*H*-thiopyran **52** has been published and in the same study this technique was used to ascertain that bromination of 3',5'-dibromo-2',6'-diphenylspiro[fluorene-9,4'-thiopyran] **53** occurred at the 2-position (Figure 5) <2004CCCC1631>.

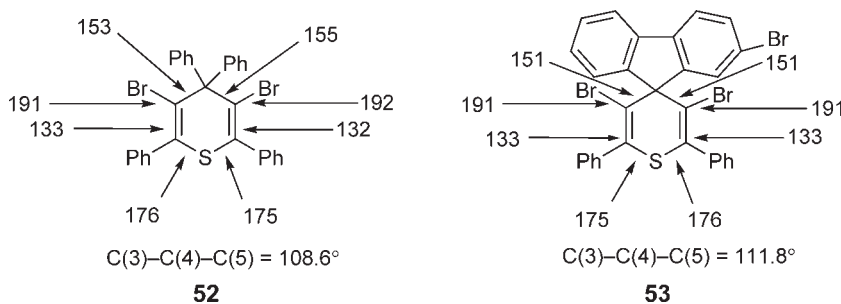


Figure 5 Selected bond lengths (pm) and bond angles (°) for 4*H*-thiopyrans **52** and **53**.

The oxidation of the S atom of 4-substituted 2,4,6-triphenyl-4*H*-thiopyrans with either NaIO₄/MeOH/AcMe or H₂O₂/AcOH affords mixtures of the respective *cis* and *trans* 4*H*-thiopyran 1-oxides as determined by crystal structures; when the 4-substituent is a methyl group <2005NCS165> the boat conformations are rather flattened, but the 4-benzyl compounds have planar thiopyran rings <2005NCS420>.

X-Ray diffraction analysis of differently 2-substituted 2-alkoxycarbonyl-3,6-dihydro-2*H*-thiopyran 1-oxides revealed that while the alkoxycarbonyl and sulfoxide units are *trans* disposed, they possess different conformations. Thus, for **54** X = H and CN, the oxygen and ester functions are equatorially disposed, whereas when **55** X is methyl or phenyl, the ester and sulfinyl oxygen occupy axial positions (Figure 6) <1995HAC631, 1999EJO2573>.

Several rigid disulfide molecules have been deposited as self-assembled monolayers on a gold electrode in order to study electron tunneling between CdSe quantum dots and the electrode. It appears that the dots are chemically bound to the bithiopyranylidene spacer, possibly by covalent Cd-S interaction. The distances between the sulfur atoms were determined either by X-ray diffraction or by *ab initio* calculations and are shown in Figure 7 <2000PCB7266>. The optimized geometries derived from 6-31G* and 6-311G* calculations for *anti*-4,4'-bis(tetrahydro-4*H*-thiopyranylidene) **56** are in good agreement with the data obtained from a single-crystal X-ray <2000JOC4584>.

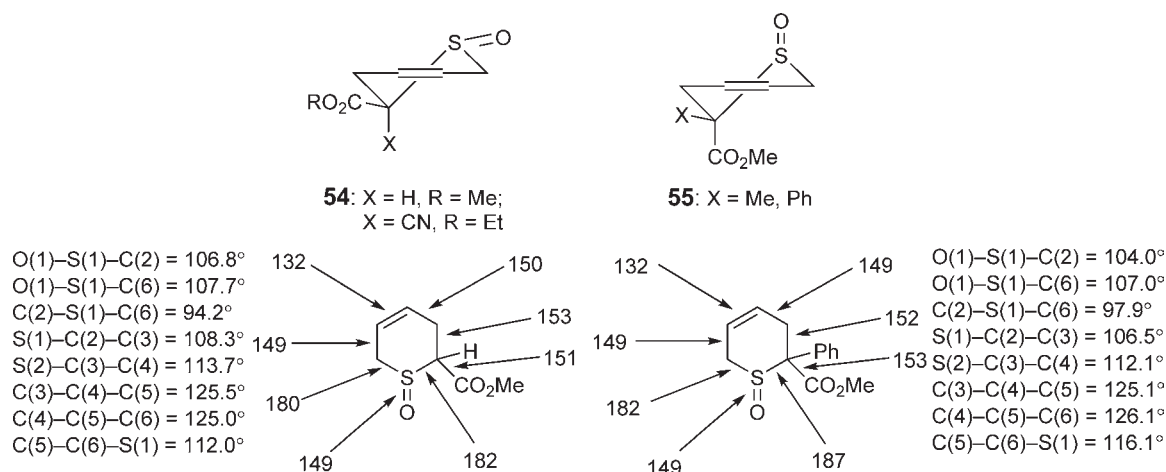


Figure 6 Bond lengths (pm) and bond angles (°) for two 3,6-dihydro-2*H*-thiopyran 1-oxides.

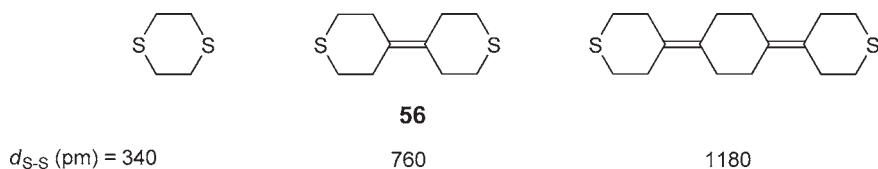


Figure 7 Intramolecular S–S distance (d_{S-S}) for bis-thiopyranylidene spacers.

4-(Tetrahydrothiopyran 1-oxide-4-ylidene)cyclohexanone oxime is axially dissymmetric and chiral HPLC confirms the presence of an enantiomer pair (**Figure 8**). The crystal of (oxime)₄.benzene consists of infinite chains which are interconnected by weak interactions to provide a two-dimensional network. Each chain is built up of molecules of one enantiomer linked head-to-tail through intermolecular hydrogen bonds between the oxime and sulfoxide functions; a similar hydrogen bonding array is found for the oxime itself. The benzene of crystallization sits in the channels which result from the stacking of the chains <2005OBC1402>.

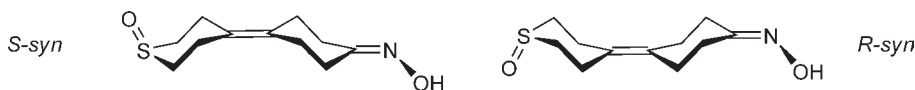
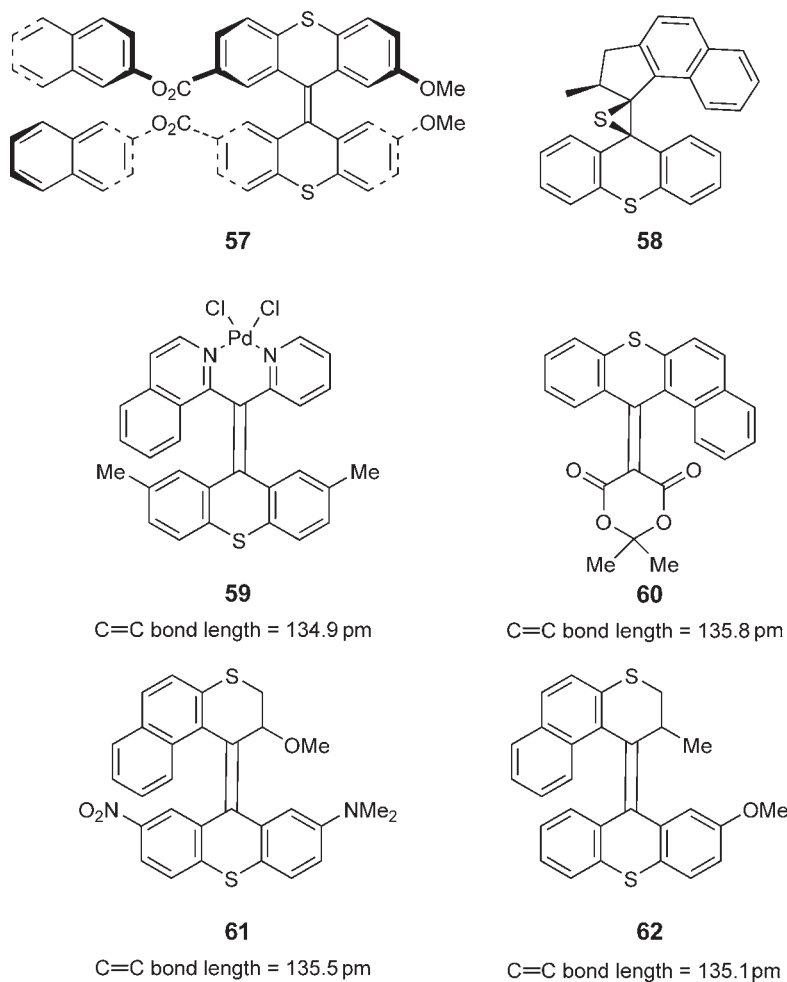


Figure 8 *S-syn* and *R-syn* enantiomer pair of 4-(tetrahydrothiopyran 1-oxide-4-ylidene)cyclohexanone oxime.

X-Ray analysis of the minor enantiomer of bi(thioxanthylidene) **57** attached to a chiral template has established the absolute configuration of both enantiomers and indicates a linear mode of coupling of the alkene to the template in the minor isomer. The folded arrangement of the alkene component (folding angle of 50.6°) results in a helical shape and a left-handed helix was found for this isomer. Removal of the template afforded the enantiomers of the bi(thioxanthylidene) derivative arising from axial double bond chirality with a 96% ee <2006EJO3596>. Similar structural details of a sterically crowded episulfide **58** <2005OBC28>, a chiral Pd-based alkene **59** <2002T2183>, thioxanthylidene-dioxandiones **60** <1995TL9381> and 9-(1'-naphtho[2,1-*b*]thiopyran-1'-ylidene)-9*H*-thioxanthenes **61** and **62** <1997JOC4943, 2000JA12005, 2002JA5037, 2003OBC33, 2005OBC4071> have been reported.



In the [4]radialene, 1,2-bis(diphenylmethylene)-3,4-bis[2-(thioxanthenylidene)-vinylidene]cyclobutane, the four-membered ring is virtually planar and trapezoidal and this causes repulsive interactions among the substituents. Thus the phenyl rings adopt a half-propeller conformation and the diphenylmethylene groups repel each other. As a consequence, the two thioxanthene units are brought closer together and twist. Both butatriene systems show bond alternation (136.4, 121.8, and 137.5 pm) indicative of bending and twisting of these cumulative bonds ([Figure 9](#) <2003OL3371, 2005BCJ2188>).

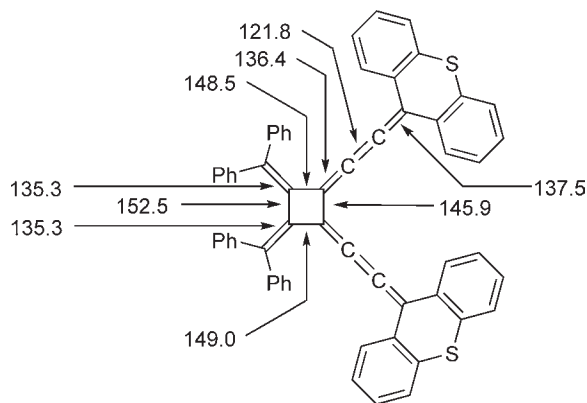
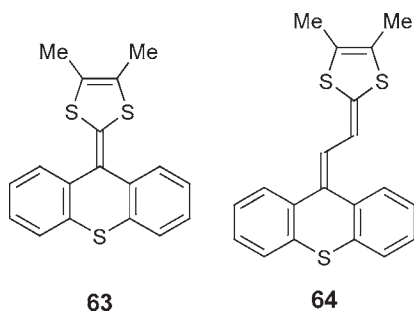
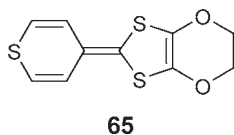


Figure 9 Selected bond lengths (pm) for 1,2-bis(diphenylmethylene)-3,4-bis[2-(thioxanthenylidene)-vinylidene]cyclobutane.

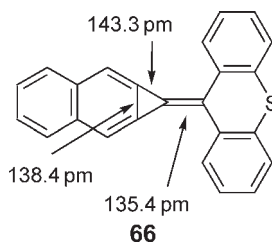
Crystals of 9-(1,3-dithiol-2-ylidene)thioxanthene derivatives (e.g., **63**), obtained by reaction of the carbanion from (1,3-dithiol-2-yl)phosphonates with thioxanthenes, adopt a butterfly conformation with the benzene rings of the thioxanthene unit forming a dihedral angle of 145° . Folding is greater in the 1,1-dioxide (138°). The dithiole ring is folded along the S–S axis and is twisted about the inter-ring C–C bond presumably as a result of repulsion involving the dithiole S and *peri* H atoms. Calculations at the B3P86/6-31G** level indicate that the butterfly conformation is more stable than a planar arrangement by $21.7 \text{ kcal mol}^{-1}$ and give bond lengths in good agreement with those derived from X-ray analysis. The folding of the thioxanthene unit is also predicted, with the dihedral angle in the 1-oxide notably calculated at 130° <2006CEJ3389>. In the vinylogue **64**, the interplanar angle in the thioxanthene unit is 143.0° and the butadiene moiety is twisted from planarity by 4.4° , 3.1° , and 8.0° about the three bonds. The B3LYP/6-31G(d) calculated bond lengths are in good agreement with the experimental values and indicate essential double (136 pm) and single (143.8 pm) bonds in the butadiene fragment. Upon oxidation to the radical cation these three bonds become virtually the same length (ca. 140 pm), whereas in the dication it is the central bond which has double-bond characteristics (135.3 pm) <2006CEJ5481>.



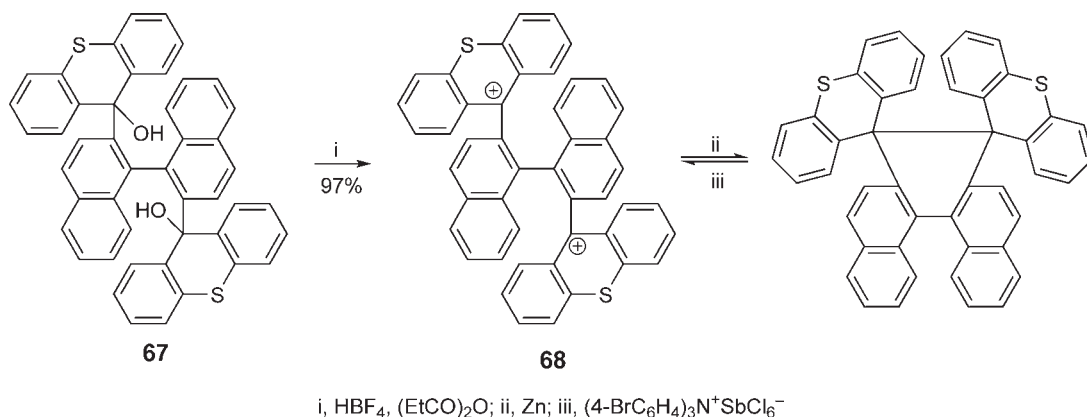
The averaged bond lengths of the thiopyranylidene-ethylenedioxythiolane (TP-EDOT) unit **65** in the 2:1 TP-EDOT PF_6^- complex and the $(\text{TP-EDOT})_3\text{Sb}_2\text{F}_{11}(\text{PhH})$ complex have been measured. The linking C=C double bond is ca. 5 pm longer in the Sb_2F_{11} complex <2006JMC550>.



X-Ray crystallographic analysis of 1-thioxanthenylidene-1*H*-cyclopropa[*b*]naphthalene **66** indicates that the molecule is almost planar. The molecules are stacked at an incline along the *b* axis, antiparallel adjacent stacks compensating the dipoles. Experimentally determined bond lengths and angles are in good agreement with those calculated using RHF/6-31G*, though calculations predict a bent structure <1998JOC1583>.

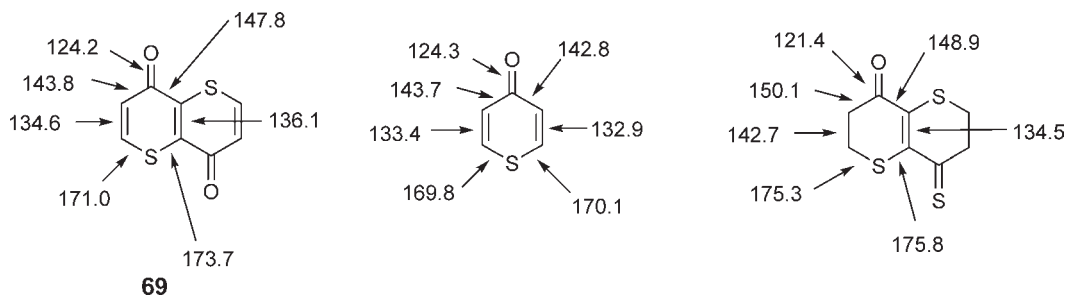


Treatment of the diol **67** obtained by the reaction of 2,2'-dilithiobinaphthyl with thioxanthone with HBF_4 generates the deeply colored dication **68**. X-Ray analysis shows that the distance between the two formally positive sites is 353 pm. Reduction with Zn creates a new C–C bond (165.1 pm) linking the 9-positions of the two thioxanthene units and producing a colorless dihydro[5]helicene. Oxidation subsequently regenerates the dication indicating that the two species are a reversible redox pair ($E_p^{\text{ox}} +0.93 \text{ V}$ and $E_p^{\text{red}} +0.37 \text{ V}$) with bond-making and bond-breaking being induced by electron transfer. Resolution of the cation through conversion to neutral diastereomeric ethers enabled absolute configurations of the axially chiral binaphthyls to be determined and allowed preparation of the chiral helicenes (Scheme 5) <2001AGE3251>.



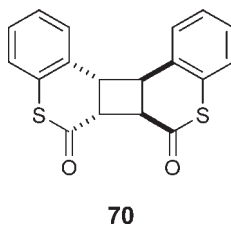
Scheme 5

X-Ray analysis of 4*H*,8*H*-thiopyrano[3,2-*b*]thiopyran-4,8-dione **69** shows that the bonds involving C-4a and C-8a are stretched relative to those attached to C-2 and C-3 <1998EJO1989>. Apart from that, the structural details are very similar to those of thiopyran-4-one itself (Figure 10) <1992OM2157>. In the tetraethyl tetracarboxylate derivative of the thiopyranothiopyrandione, the bonds to the central double bond are shortened by 1–2 pm but the others are longer by 1–3 pm <1994NCS376>. As expected, the structure of the tetrahydro derivative of the thiopyranothiopyrandione is puckered. The S–C bonds are longer than in the unsaturated molecule and both the C–O and C(4a)–C(8a) bonds are shortened in accord with the α,β-unsaturated carbonyl system. When the structures of the two molecules are considered together, evidence for charge delocalization from S to O is apparent with the implication of some quadrupolar character for the thiopyranothiopyrandione.

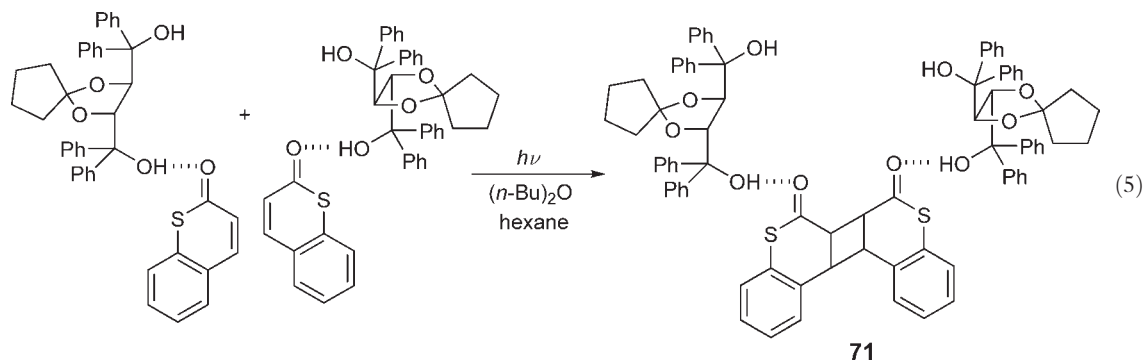
Figure 10 Bond lengths (pm) for thiopyranothiopyrandione, tetrahydrothiopyranothiopyrandione and 4*H*-thiopyran-4-one.

The crystal structure of thiocoumarin has been determined as monoclinic in the space group *Pc* at room temperature and the molecule is essentially planar <2002AXEo353>. Theoretical charge density calculations on crystals at the B3LYP/6-31G** level show good agreement with the crystallographic data <2005PCA659>.

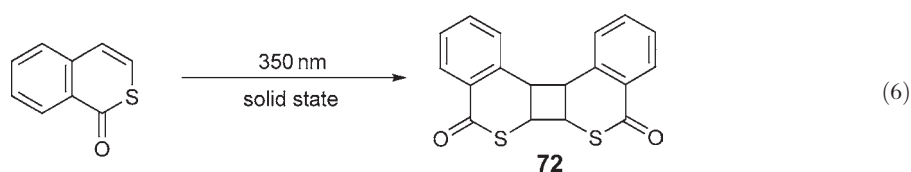
In the *anti* head-to-head dimer of thiocoumarin **70**, the cyclobutane ring is puckered and the thiopyran rings adopt conformations between half-chair and twist-boat. Bond lengths and angles have been reported <1994AXC1922, 1995HCA1079>.



Single-crystal-to-single-crystal intermolecular enantioselective [2+2] photodimerization of thiocoumarin proceeds efficiently in inclusion complexes with a chiral 1,4-diol to afford the 2:1 complex **71**, from which enantiomerically pure dimer was obtained by chromatography. Hydrogen bonding between the Ph_2COH group of the diol and the thiocoumarin $\text{C}=\text{O}$ unit results in formation of the *anti*-head-to-head dimer (Equation 5). X-ray crystallography was used to probe the distances between the thiocoumarin units before and after the photodimerization. The two alkenic bonds are close enough (ca. 360 pm) to allow reaction and the new C–C bonds in the dimer are 160 pm <2000T6853>. The progress of the reaction was followed by the continuous measurement of CD spectra <1998MCL179>.



Irradiation (350 nm) of 1*H*-2-benzothiopyran-1-one in the solid state affords the head-to-head *cis-cisoid-cis* cyclodimer **72**, the structure of which was confirmed by X-ray crystallography. The same dimer is obtained in lower yield on irradiation of the isothiocomarin in MeOH or MeCN, but no conversion is observed in benzene (Equation 6) <1997HCA1865>.



The X-ray structure of 6-chloro-3-[1-(6-chloro-2-methyl-4-oxothiochroman-3-yl)ethyl]-4*H*-thiochromone **73**, obtained as a by-product from the reaction of 6-chloro-2,2-dimethylthiochroman-4-one with ethyl formate, illustrates the differences in the geometries of the saturated and unsaturated thiopyranone ring systems (Figure 11) <2000J(P1)2930>. Interestingly, substituents in the thiochromanone ring possess a *trans*-diaxial orientation.

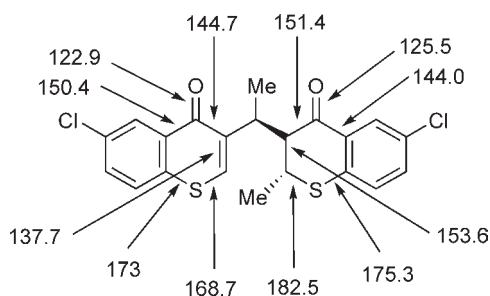


Figure 11 Selected bond lengths (pm) for **73**.

Analysis of the crystal structure of 1-chloro-4-propoxythioxanthone, widely used in UV curing <1994JCF83>, has confirmed the coplanarity of the three rings. The asymmetric unit is composed of two essentially identical units that are approximately parallel to each other with a head-to-head arrangement <2005AXEo149>.

An X-ray study of thioxanthone 10,10-dioxide (Figure 12) has established that the molecule is almost planar with a dihedral (fold) angle of 177°. The C–S–C bond angle of 105.2° is significant and the S–C bond lengths are comparable with those in thioxanthene and thioxanthone <1995JCX321>.

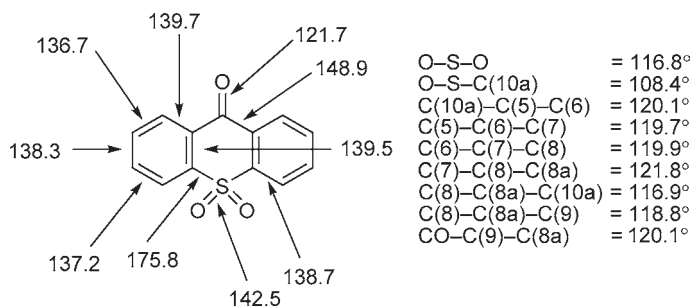


Figure 12 Bond lengths (pm) and bond angles (°) for 9H-thioxanthen-9-one 10,10-dioxide.

The near-edge region of the sulfur L-edge X-ray absorption spectrum (XANES) is very sensitive to the electronic environment and local symmetry of the sulfur atom, providing a fingerprint for a given species. Organic sulfur appears in the 162–168 eV region and thioxanthone absorbs uniquely at 165.0, 165.9 (highest intensity), and 167.1 eV with a photon resolution better than 0.2 eV <1992MI649>.

The thiopyrylium cation is essentially planar and the C–C bond lengths are approximately equal, averaging 142.8 pm and slightly longer than those in benzene (139.6 pm), suggesting an undisturbed aromatic bond distribution. The C–S bond lengths are shorter than in thiophene (171.4 pm) but similar to those in the 1,3-dithiolium ion (166.7 and 169.6 pm). Bond lengths and angles are given for the thiopyrylium triflate in Figure 13 <2001EJO2477>. Bond lengths calculated using the 6–311+G(d,p) basis set and the density functional method (DFT) and also by MP2 *ab initio* are in reasonable agreement, although the predicted bond lengths to the sulfur are slightly longer.

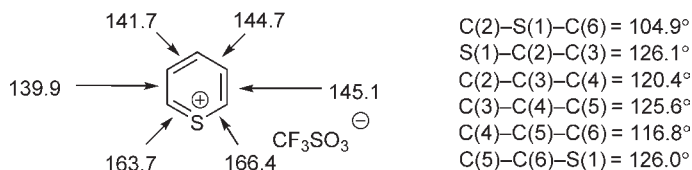


Figure 13 Bond lengths (pm) and bond angles (°) for thiopyrylium triflate.

Similar calculations for the unknown thiabenzene *S*-fluoride and thiabenzene *S*-trifluoride (Figure 14) indicate that these compounds are more stable as the 2- and 4-fluoro substituted isomers <2001HCA1578, 2003JFC(120)49>.

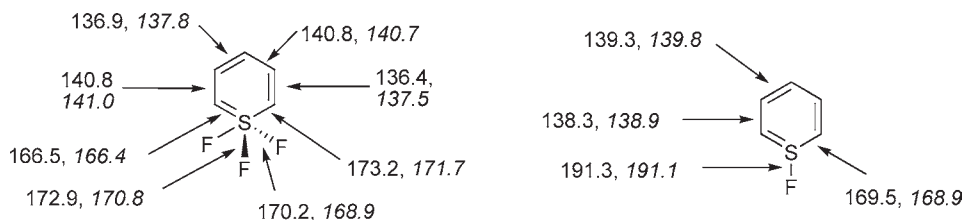
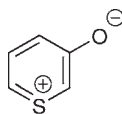


Figure 14 Theoretical (DFT or MP-2 *ab initio*) bond lengths (pm) for thiabenzene *S*-fluoride and *S*-trifluoride.

Calculations of the structure of the mesoionic thiopyrylium-3-olate **74** suggest that the C–S bond lengths are similar to those in the pyrylium cation at ca. 168 pm, perhaps supporting the fully charge-separated betaine structure. However, the charge at oxygen is closer to 0.5 than the 1.0 expected for such a structure. Furthermore, the nucleus-independent chemical shift value is appreciably lower than that for the thiopyrylium cation. These data point toward an ylidic structure with an acceptor moiety rather than an aromatic cation and an exocyclic oxyanion <2002IJQ(90)1055>.



74

7.10.2.2.2 Microwave spectroscopy

A complete analysis of the microwave spectrum of 3,6-dihydro-2*H*-thiopyran measured over the frequency range 12.4–40 GHz <1994JCF2849> supports the half-chair equilibrium conformation determined from its vibrational spectrum. The angle of twist is 32.5°, slightly larger than that of 3,6-dihydro-2*H*-pyran (31.5°) <1974JCP3987>, is of a similar order to those derived from IR spectroscopy (37.8°) and by molecular mechanics calculations (30.5°) <1989JCP2771>. The molecular dimensions are given in Figure 15.

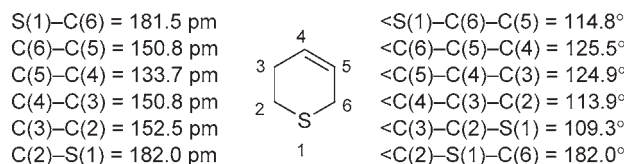


Figure 15 Molecular dimension of 3,6-dihydro-2*H*-thiopyran derived from microwave spectroscopy.

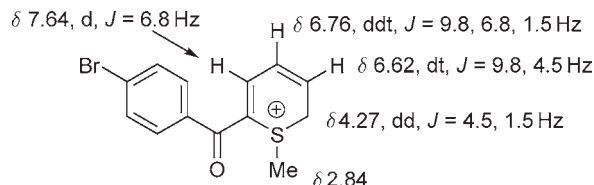
7.10.2.2.3 NMR spectroscopy

There is a wealth of NMR data available on sulfur-containing heterocyclic systems. There are however, still relatively few papers dedicated to discussion of their NMR spectra. The majority of the spectroscopic data discussed in this work has been selected from papers concerned with either the synthesis or reactivity of the six-membered sulfur heterocycles. Chemical shifts are reported in ppm for spectra recorded in CDCl₃ solution unless otherwise stated. Early NMR spectroscopic data have featured in the previous editions of *Comprehensive Heterocyclic Chemistry* and *NMR Spectra of Simple Heterocycles* by Batterham is still of fundamental importance for rapid access to ¹H NMR data on the parent sulfur heterocycles <B-1973MI451>.

7.10.2.2.3(i) ¹H NMR spectra

7.10.2.2.3(i)(a) Thiopyrans, their benzologues and their reduced derivatives

¹H NMR spectra have been recorded for several 6-substituted 1-alkyl-2*H*-thiopyranium fluoroborates **75** in mixed solvent systems (CD₃CN, CDCl₃); the *S*-methyl group resonates at ca. δ 2.8 and the 2-methylene protons are equivalent and show coupling to H-3 and H-4 <2001J(P1)2269>.



75

Unlike 2*H*-pyran, which is unstable at room temperature and prefers the 2,4-dienone valence isomer, 2*H*-thiopyran has been known for some time and its ¹H NMR spectrum and those of some simple alkyl derivatives and the 4*H*-isomer have been discussed <B-1973MI451>. The ¹H NMR spectra of several 2-alkyl-2*H*-thiopyrans have been reported, with larger coupling constants for the thiopyran ring protons noted for *J*_{3,4} ~ 10 Hz and *J*_{5,6} ~ 9 Hz for protons that are formally *cis*-disposed and *J*_{4,5} ~ 6 Hz for the *s-cis* arranged protons <2000JFA2420>. Chemical shifts for a range of substituted electron-rich 2*H*-thiopyrans is presented in Figure 16.

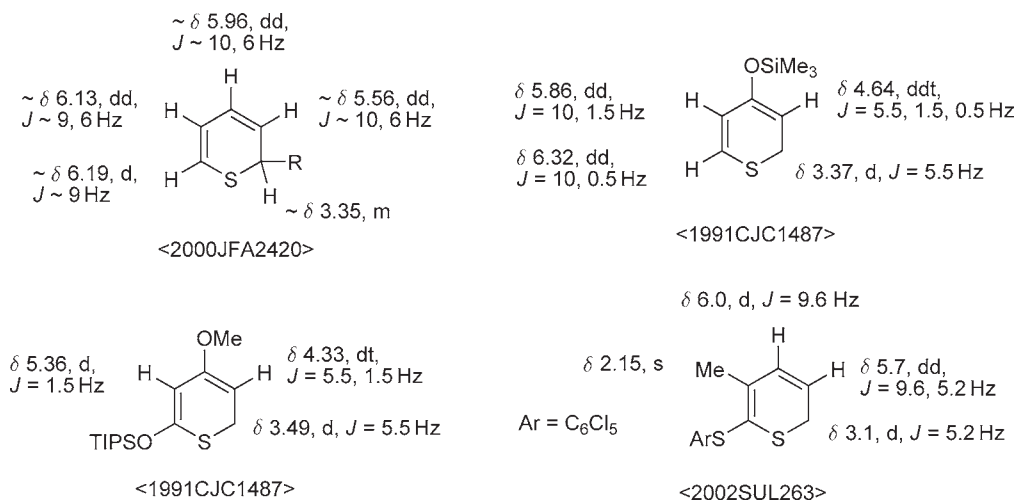


Figure 16 ^1H NMR chemical shifts and selected coupling constants for some $2H$ -thiopyrans.

Introduction of a 4-silyloxy group induces an upfield shift of both H-3 and H-5 though H-6 is shifted marginally downfield. Both H-3 and H-5 are shifted significantly upfield in the 4-methoxy-6-tri-*isopropylsilyloxy*- $2H$ -thiopyran. Analysis of chemical shifts and coupling constants enable differentiation between the isomeric 3- and 5-tri-*isopropylsilyloxy*- $2H$ -thiopyrans (Figure 17) <1991CJC1487>.

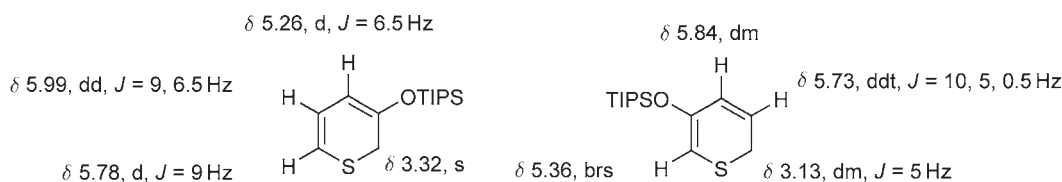
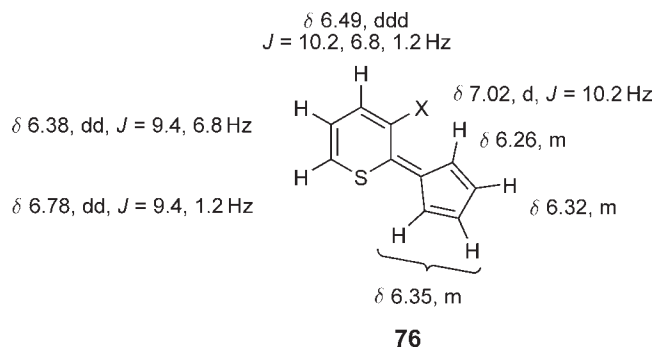


Figure 17 ^1H NMR data for isomeric tri-*isopropylsilyloxy*- $2H$ -thiopyrans.

Detailed assignment of the protons in the cyclopentadienyldiene- $2H$ -thiopyran (76, $X = \text{H}$) was accomplished by both two-dimensional correlation spectroscopy and nuclear Overhauser effect experiments. Selective deuteration at C-3 ($X = \text{D}$) simplified the couplings with H-4 appearing as a dd with $J = 6.8, 1.2$ Hz <1991TL3499>.



Chemical shifts for a range of substituted electron-deficient $2H$ -thiopyrans are presented in Figure 18. The incorporation of a phosphonate unit at C-6 results in a downfield shift for H-5 of ~ 0.9 ppm relative to that for the simple 2-alkyl- $2H$ -thiopyrans <2002JOC8123, 2004EJO160>. Interestingly, a 4-phosphonate group appears to induce slight upfield shifts in both H-3 and H-5 <1991CJC1487>. The introduction of a 2-phenyl substituent induces a significant downfield shift for the remaining H-2 as a consequence of its benzylic nature and a 3-nitro substituent exerts a ca. 2 ppm shift in H-4 which now resonates at ca. 8 ppm <1994JPR434>.

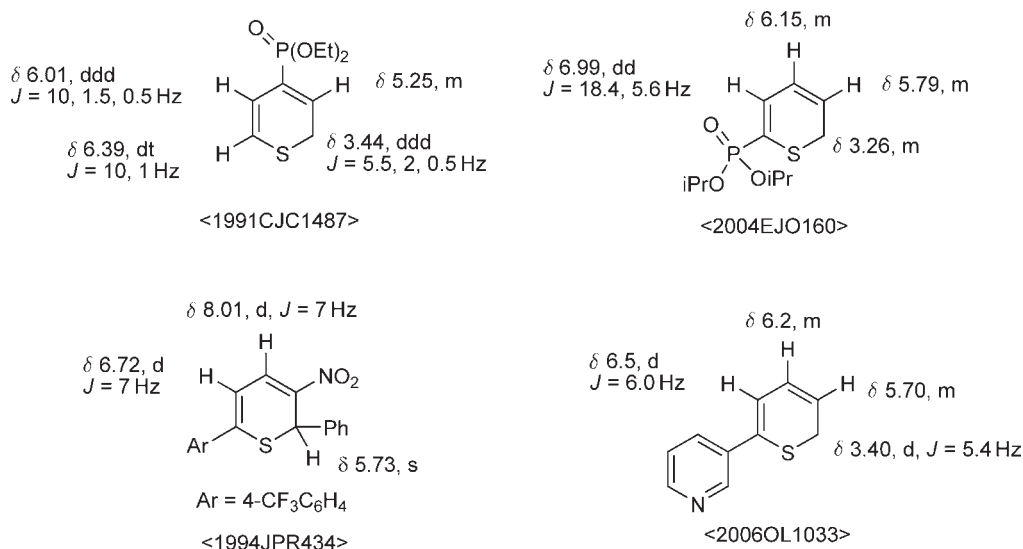
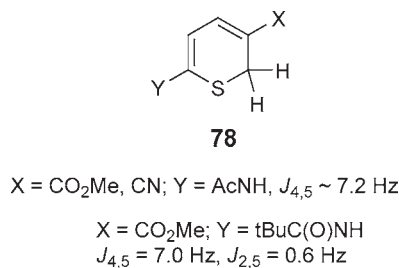
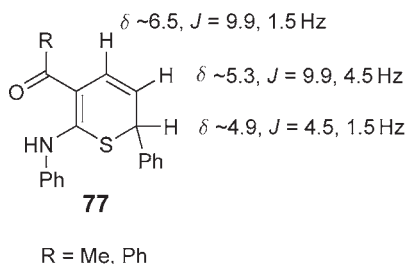


Figure 18 ^1H NMR chemical shifts and coupling constants for some electron-deficient $2H$ -thiopyrans.

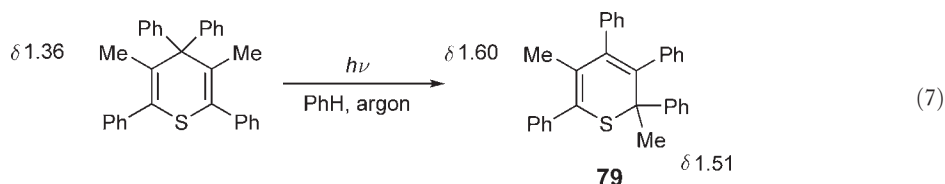
6-Substituted $2H$ -thiopyran-2-carboxylates show the expected four signals for the ring protons; H-5 (δ 5.9–6.3) is only coupled to H-4 (J = 6 Hz) and H-2 (δ 4.1–4.2) to H-3 (J = 6 Hz), while both H-3 and H-4 appear as double doublets with J = 6 and 10 Hz at ca. 5.6 and 6.1 ppm, respectively <1998T15499>.

Allylic (J ~ 1.5 Hz) coupling is observed in the ^1H NMR spectrum between H-2 and H-4 of the 2,5,6-trisubstituted $2H$ -thiopyrans **77**. Distinction between this structure and the corresponding $4H$ -thiopyran is provided by the two-dimensional NOESY spectrum which shows through-space interactions between the 5-Ac group and H-4, H-3, and H-4, H-2 and H-3, and H-2 and 2-Ph <2003T4183>. In 3-substituted 6-acylamino- $2H$ -thiopyrans **78**, $J_{4,5}$ is ca. 7.2 Hz. Interestingly for the 6-*tert*-butoxycarbonylamino analogues, long-range (^5J) coupling is observed between H-2 and H-5 of 0.6 Hz <2004S1633>.



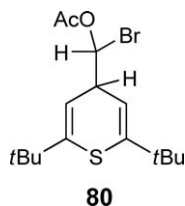
Allylic and longer-range couplings are not always observed. For example, in a range of 3-acyl-4-phenyl-5-trifluoromethyl- $2H$ -thiopyrans, H-4 and H-2 each appear as a singlet resonating at ca. 7.0 and 3.6 ppm, respectively <1995JFC(70)121>.

The photochemical conversion of $4H$ -thiopyrans into the $2H$ -isomers can be followed by ^1H NMR spectroscopy. Thus, the singlet at 1.36 ppm for the 3- and 5- methyl groups in the symmetrical 3,5-dimethyl-2,4,4,6-tetraphenyl- $4H$ -thiopyran disappears on irradiation to be replaced by individual singlets at 1.51 and 1.60 ppm for the 2- and 5-methyl groups in the resulting $2H$ -thiopyran **79** (Equation 7) <1996JPH(101)33>.

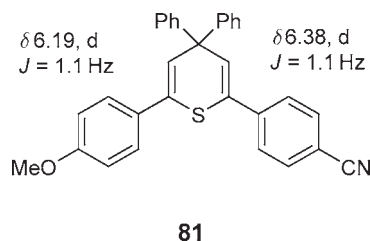


The ^1H NMR spectrum of 2,6-bis(*tert*-butyldimethylsilyl)-4*H*-thiopyran shows doublets ($J = 4.6$ Hz) for the 4- CH_2 group at 2.67 ppm and for 3- and 5- H at 5.99 ppm <2004TL87>.

In the 2,6-di-*tert*-butyl-4*H*-thiopyran **80**, H-3 and H-5 are nonequivalent as a consequence of the asymmetric C atom and appear as doublets at δ 5.60 and 5.68 with $J = 5.5$ Hz, in keeping with data for various 2,6-di-*tert*-butyl-4*H*-thiopyrans <1982TL3195>. The methine proton in the side-chain at C-4 at δ 6.58 is coupled to H-4 ($J = 7.0$ Hz) which resonates at δ 3.51 as a ddd ($J = 7.0, 5.5$ and 5.5 Hz) <1994J(P1)2631>. An asymmetric centre at C-4 also renders 2- and 6- protons nonequivalent <1989JOC2404>.



The alkenic protons in 2,4,4,6-tetraaryl-4*H*-thiopyrans appear as singlets (δ 6.22, Ar=Ph) when the 2- and 6- aryl groups are similarly substituted, but show ^4J coupling in unsymmetrically substituted examples **81** <1998CCCC662>. The corresponding protons in the 4,4-dicyano-2,6-diphenylthiopyran resonate as a singlet at δ 5.98 <2002PS(177)2791>.



The chemical shift of H-3 and H-5 are significantly influenced by the oxidation state of the sulfur atom (Figure 19). Oxidation of 4-methyl-2,4,6-triphenyl-4*H*-thiopyran to the *trans*-**82a** and *cis*-**82b** 1-oxides results in a downfield shift of ca. 0.75 ppm in the signal for H-3 and H-5 relative to those in the thioether <2006T2603>. Further oxidation to the 1,1-dioxide surprisingly induces a smaller downfield shift of 0.35 ppm relative to the thioether in spite of the stronger electron withdrawing nature of the sulfone unit <2005PS(180)2555>.

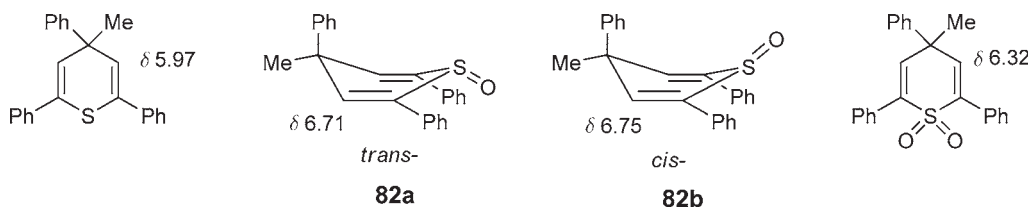
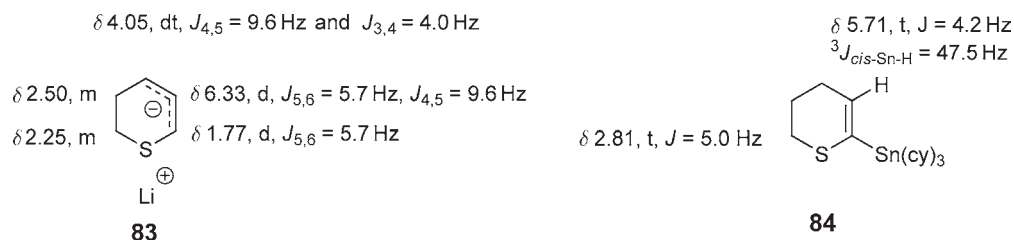
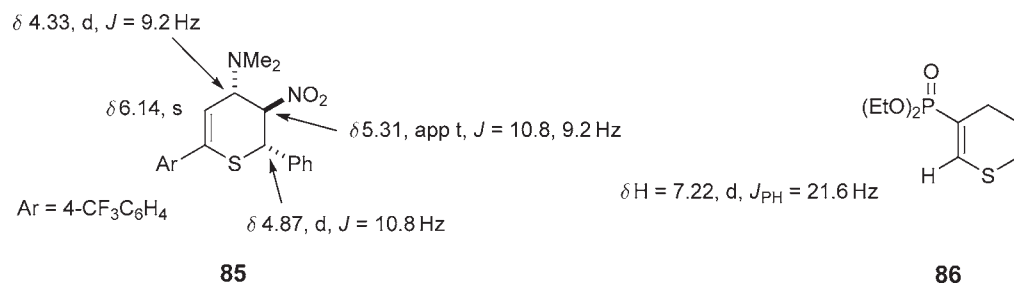


Figure 19 Comparable chemical shifts for some 4*H*-thiopyrans and their 1-oxides and 1,1-dioxides.

A detailed assignment of the ^1H NMR spectrum (THF- d_8) of 3,6-dihydro-2*H*-thiopyran and its lithio anion **83** have been reported <1995BCJ2739>. While the signals for the 3- and 4-methylene units overlap with those of the cyclohexyl groups of 6-(tricyclohexylstannyl)-3,4-dihydro-2*H*-thiopyran **84**, the signals for H-2 and H-5 are resolved and the latter shows 3 bond coupling (*cis*) to Sn of 47.5 Hz <1997T12273>.



The relative *trans* stereochemistry of the substituents in the tetrasubstituted 3,4-dihydro-2*H*-thiopyran **85**, an intermediate isolated from the [4+2] cycloaddition between an enaminothione and a nitroalkene, has been established by ^1H NMR spectroscopy <1994JPR434>. The methylene units of 5-(diethylphosphono)-3,4-dihydro-2*H*-thiopyran **86** appear as multiplets in the range 2.0–2.8 ppm and the vinyl proton (H-6) displays coupling to the P atom with $^3J = 21.6$ Hz <2005OBC924>.



Cycloaddition strategies have also featured widely in the synthesis of variously substituted 3,6-dihydro-2*H*-thiopyrans from thiocarbonyl-containing precursors and dienes. Selected ^1H NMR data for 3,6-dihydro-2*H*-thiopyrans feature in Figure 20.

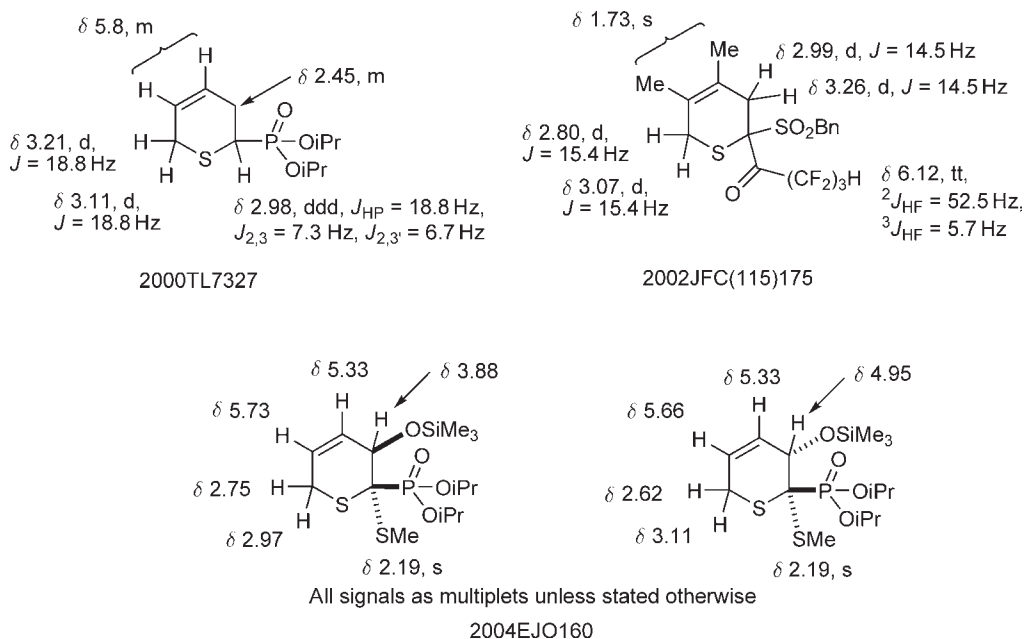


Figure 20 ^1H NMR spectroscopic data for a selection of 3,6-dihydro-2*H*-thiopyrans.

Geminal coupling in the range 14–19 Hz is observed for the 3- and 6- methylene units in asymmetrically substituted 3,6-dihydro-2*H*-thiopyrans <1999TL6473, 2000TL7327, 2002JFC(115)175, 2006OL1033>. The *cis* relationship between the 2- and 3- ester groups of the dihydropyran **87** was established from $J_{2,3} = 6.1$ Hz and confirmed by correlation peaks in the COSY spectrum <2000SL658>.

All four diastereoisomers of 3,6-dihydro-2,3,5,6-tetramethoxycarbonyl-2*H*-thiopyran have been identified from their coupling constants. Data for the two major isomers **88** and **89** ($\text{E} = \text{CO}_2\text{Me}$) are presented in Figure 21. Relatively rapid ring inversion leads to flattening of the conformation for **88** in CDCl_3 solution which is reflected in the decrease in magnitude of $^3J_{3\text{ax},2\text{ax}}$ from the predicted 13 to 10 Hz <1996J(P2)2623>. Detailed coupling constant and chemical shift data are also available for the four diastereoisomers of 3,6-dihydro-3,5,6-trimethoxycarbonyl-2*H*-thiopyran, though conformational assignments are not made <1997MI2185>.

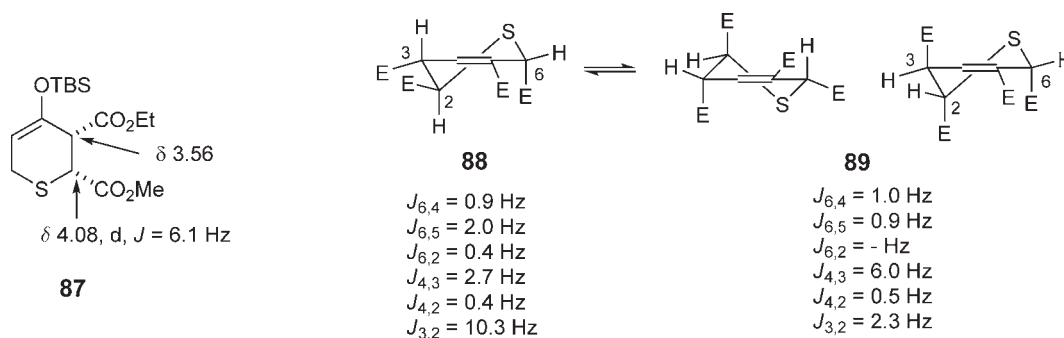
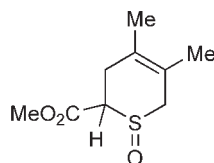


Figure 21 Coupling constants for 3,6-dihydro-2,3,5,6-tetramethoxycarbonyl-2*H*-thiopyrans.

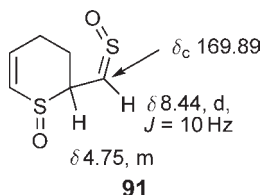
3,6-Dihydro-2*H*-thiopyran 1-oxides have been obtained from the cycloaddition of sulfines to various butadienes. The *cis* diastereoisomer of 2-methoxycarbonyl-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran 1-oxide **90** could not be isolated in a pure state, but its ¹H NMR spectrum could be obtained by subtracting the data for the *trans* isomer from the spectrum of the diastereomeric mixture. The signal for the OMe moiety was 0.03 ppm downfield of the corresponding signal for the *trans* isomer. When the spectrum was recorded in the presence of the chiral resolving agent, (+)-(*R*)-*tert*-butylphenylphosphinothioic acid, this small difference enabled the ee values of each epimer to be estimated <1999EJO2573>.



90

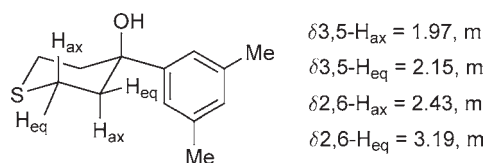
$\delta_{\text{H-6(trans)}}$ 3.86, dd, J = 7.6, 5.6 Hz
 $\delta_{\text{H-6(cis)}}$ 3.42, dd, J = 12.0, 4.7 Hz

The sulfine **91** obtained from the room-temperature dimerization of thioacrolein *S*-oxide was characterized by key NMR data <1997TL1385> and by comparison with chemical shift data for the 3,4-dihydro-2*H*-thiopyran-1-oxide <1985AJC119>.

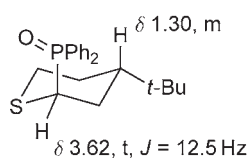


91

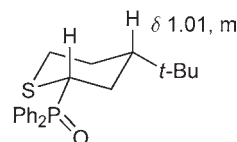
There have been relatively few recent reports containing detailed analysis of the ¹H NMR spectra of tetrahydrothiopyrans; early analysis of this system and the *S*-oxide may be found in Batterham <B-1973MI451>. The NMR spectra of several 4-aryltetrahydrothiopyran-4-ols such as **92**, have been reported. The aryl group was demonstrated to occupy a pseudo-equatorial site from ¹³C and gradient heteronuclear quantum correlation (gHMQC) experiments and the molecule was shown to exist as a single conformer. Analysis of the coupling constants for the -CH₂CH₂- fragment gave the ratio of J_{trans}/J_{cis} as 1.07 and an internal dihedral angle of ~46° that indicated that the ring was somewhat flattened which was in agreement with crystallographic data <2005PS(180)53>.

**92**

The methine proton at 2-C resonates at $\delta 3.63$ (t, $J = 3.9$ Hz) in 2-cyano- [<2006CL98>](#) and at $\delta 3.50$ (dt, $J = 9.9, 3.9$ Hz and $J_{\text{HP}} = 6.6$ Hz) in 2-diphenylphosphinoyl- [<1998T1375>](#) tetrahydrothiopyran. NMR data for the latter compound and the *cis*- and *trans*- 4-*t*-butyl analogues **93**, **94** were used to probe the conformation of the thiopyran ring and to evaluate the anomeric effect in the S–C–P unit.

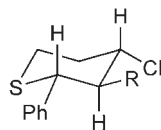
*trans*-**93**

$\delta 3.58, \text{ dq}, J = 12.5, 2.6 \text{ Hz}$
 $J_{\text{HP}} = 18.7 \text{ Hz}$

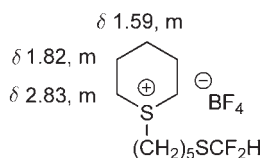
*cis*-**94**

All the substituents in the unsymmetrical 2,3,4-trisubstituted tetrahydrothiopyran **95** occupy a pseudo-equatorial site in the predominant isomer as indicated by the large vicinal coupling constants measured for the interactions between H-3, H-2 and H-4 [<2000TL1321>](#). Limited data for the tetrahydrothiopyranium fluoroborate **96** have been reported [<1995JFC\(73\)229>](#).

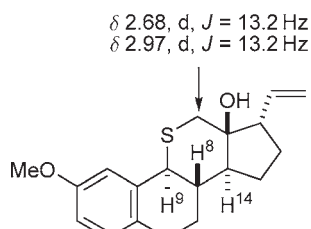
$\sim \delta 4.0, \text{ d}$
 $J = 10.8 \text{ Hz}$

**95**

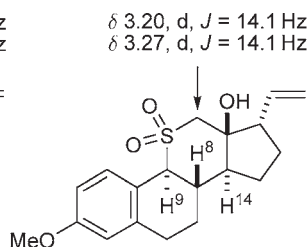
$\sim \delta 4.0, \text{ dt}$
 $J = 11.4, 3.5 \text{ Hz}$

**96**

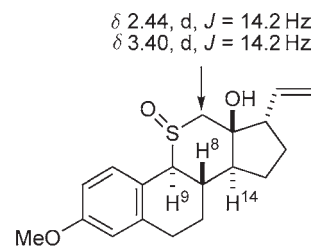
The relative stereochemistry of the ring fusion of the three 11-thiasteroids obtained from an intramolecular Diels–Alder reaction of a 1-alkylthiobenzocyclobutene was derived by COSY and NOESY experiments and simple NMR spectroscopy. The *trans*–*anti*–*trans* fusion in the major product **97** was established by the 10.2 Hz vicinal coupling between H-8 and H-9, by a cross-peak between H-9 and H-14, and through the use of X-ray crystallography [<2000SL418>](#). Downfield shifts are noted for the nonequivalent protons of the CH₂ unit in the 11-thiasteroid 11,11-dioxide **98** which now resonate at $\sim \delta 3.25$, whereas the analogous protons in the 11-oxide **99** appear at $\delta 2.44$ and $\delta 3.40$ [<2005T9405>](#).

**97**

$\delta_{\text{H-9}} 3.70, \text{ d}, J = 10.2 \text{ Hz}$

**98**

$\delta_{\text{H-9}} 4.03, \text{ d}, J = 10.4 \text{ Hz}$

**99**

$\delta_{\text{H-9}} 3.50, \text{ d}, J = 10.8 \text{ Hz}$

Selected ¹H NMR chemical shift data for several dimethyl substituted benzo- and naphthothiopyrans and some oxidized analogues are depicted in [Figure 22](#). The fusion of a benzene ring across the *b*-face of a 2*H*-thiopyran to afford the 2*H*-1-benzothiopyrans results in downfield shifts of both H-4 and H-3 by ca. 0.4 and 0.2 ppm, respectively, and also

simplification of the splitting patterns of the remaining signals. The *cis*-arrangement of the alkenyl ring protons is reflected in the ~ 10 Hz coupling constant. Oxidation of 2,2-dimethyl-2*H*-1-benzothiopyran to the 1-oxide **100** has only a marginal effect on the resonances of H-3 and H-4 and the corresponding signals for the 1-tosylimine **101** resonate at δ 5.79 and δ 6.51 with $J = 10.1$ Hz. The methyl groups in both 1-oxide **100** and **101** are nonequivalent as a consequence of their relative proximity to the S=O and S=NTs groups, respectively <1995T13277>. Conversion to 2,2-dimethyl-2*H*-1-benzothiopyran 1,1-dioxide results in a downfield shift of H-8 and H-3 though H-4 is relatively unaffected. The geminal methyl groups are now equivalent and resonate at δ 1.52 <1971IJB74, 1990J(P1)3187, 1992TH1>.

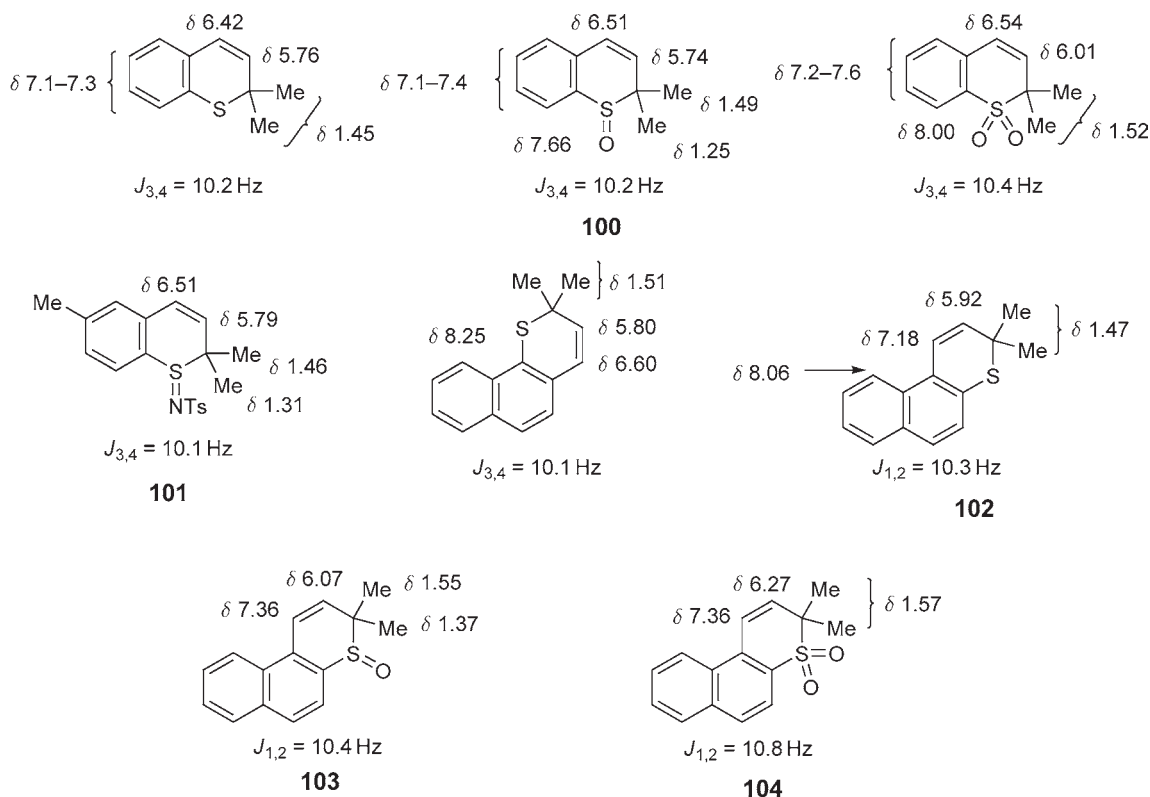


Figure 22 Selected ^1H NMR data for some 2,2-dimethyl-2*H*-1-benzothiopyrans.

The two angular isomeric naphthothiopyrans can be readily differentiated by NMR spectroscopy, with $\Delta\delta_{\text{H-3,H-4}} \sim 0.8$ and H-4 and H-10 resonating at δ 6.60 and δ 8.25, respectively for the 2*H*-naphtho[1,2-*b*]thiopyran while for the 3*H*-naphtho[2,1-*b*]thiopyran $\Delta\delta_{\text{H-1,H-2}} \sim 1.3$ and the corresponding protons resonating at δ 7.18 and δ 8.06, respectively. A similar trend is observed in the chemical shift of the thiopyran ring protons in the naphthologues when the S atom is oxidized, namely **102–104** <1992TH1>.

The isomeric 2*H*- and 4*H*- 1-benzothiopyrans cannot be readily differentiated by ^1H NMR spectroscopy (Figure 23) <1978TL3567>.

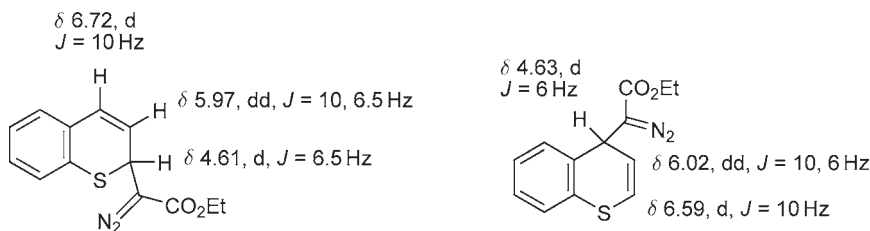


Figure 23 ^1H NMR data for the diazoester substituted benzothiopyran isomers.

The chemical shift of H-3 in 4-bromo-2,2-dimethyl-2*H*-1-benzothiopyran is δ 6.28 and at δ 6.14 in the corresponding 4-(2,4-dimethoxybenzoyl) derivative. In the latter compound, H-5 appears at δ 7.35 and is distinct from the other aromatic protons <1994T2507>. In 3-substituted 2*H*-1-benzothiopyrans, H-4 shifts progressively downfield as the electron-donating ability of the 3-substituent decreases (Figure 24); a maximum downfield shift for H-4 is recorded for the 2-phenyl-3-trifluoroacetyl derivative <1999CHE549> and H-4 in the 3-aldehyde is at δ 7.46 <2006TL8547>. In the 3-phenyl-2*H*-1-benzopyran 1,1-dioxide **105**, H-4 resonates at δ 6.97 <1982CJC243> and H-3 resonates at δ 5.19 (d, J = 6.5 Hz) in the TIPS enol ether **106** <2001T1005>.

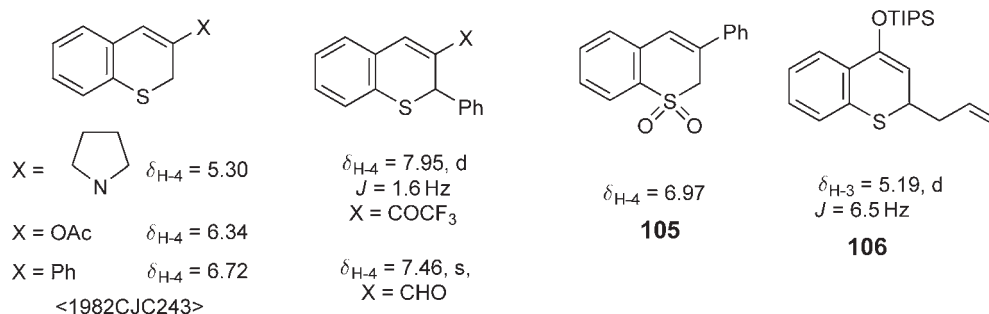
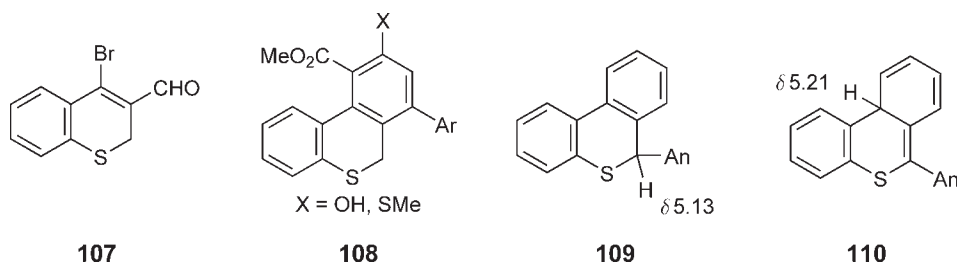


Figure 24 ^1H NMR data for substituted benzothiopyrans.

The 2-CH₂ group in 4-bromobenzothiopyran-3-carboxaldehyde **107** is observed at δ 3.66 <1999CEJ1038> and the corresponding protons in dibenzo[*b,d*]thiopyran **108** resonate in the range δ 3.5–3.8 <2001JOC5333, 2002CEJ2034, 2002J(P1)1426>. In dibenzo[*b,d*]thiopyran 5,5-dioxides, the 6-CH₂ unit appears at δ 4.83 (pyridine-*d*₅) <1971IJB74>. The methine proton in 6-anisyl-6*H*-dibenzo[*b,d*]thiopyran **109** appears at δ 5.13 and at δ 5.21 in the analogous 10*aH*-dibenzo[*b,d*]thiopyran **110** <2000BCJ155>.



The CH₂ moiety of thioxanthene resonates as a singlet at δ 3.85 shifted to δ 5.25 in the 9-phenyl derivative (Figure 25). In 9-D,9-H-thioxanthene, coupling with deuterium is observed and a characteristic broad triplet is seen at δ 3.82 with $J \sim 2$ Hz <1998JPH(113)53>. The methylene signals are shifted downfield upon benzannulation with δ CH₂ at 4.02 and 4.29 in the benzo[*c*]- and benzo[*a*]- thioxanthenes, respectively <1995JHC687>.

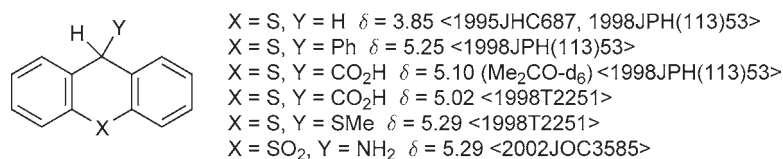
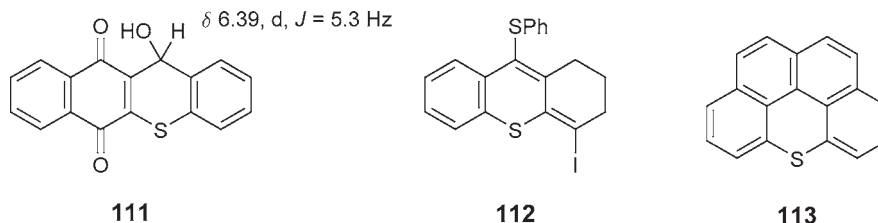


Figure 25 Selected ^1H NMR data for some 9*H*-thioxanthenes.

The methine proton in the 12-hydroxy-12*H*-benzo[*b*]thioxanthene dione **111** appears as a doublet ($J = 5.3$ Hz) at δ 6.39 and the ring protons *peri* to the carbonyl groups resonate at ca. δ 8.2. Data for a range of 12-aryl-12-hydroxy analogues <2004BCJ2095> and simple 9-aryl-9*H*-thioxanthen-9-ols are also reported <2002BCJ1325>. Limited data are available for the 2,3-dihydro-9-phenylthio-1*H*-thioxanthene **112** derived from the dimerization of an α,ω -diynyl sulfide <1998AGE3136>. Two independent approaches to the naphthothioxanthene **113** have been reported. The unassigned spectrum of this polycycle is relatively simple and exhibits signals at δ 7.64 (4H, s), 7.44 (2H, dd, $J = 8.0$, 1.2 Hz), 7.28 (2H, t, $J = 7.2$ Hz), 7.16 (2H, dd, $J = 7.2$, 1.2 Hz) <2004JA3108, 2005JOC10113>.



Detailed analysis of the ^1H NMR spectrum of both the *cis,cis*- and *trans,trans*- hexahydro-9-phenyl-9*H*-thioxanthenes has been reported (Figure 26) <1996SL396>. The geometry of the ring fusion was determined by comparison of the coupling constants between 4a-H and 9a-H, with the *trans* relationship having the larger coupling constant (11 Hz). The *trans* ring fusion of the hexahydrodibenzo[*bd*]thiopyran **114** was established by the 12 Hz coupling constant <2000TL2279>.

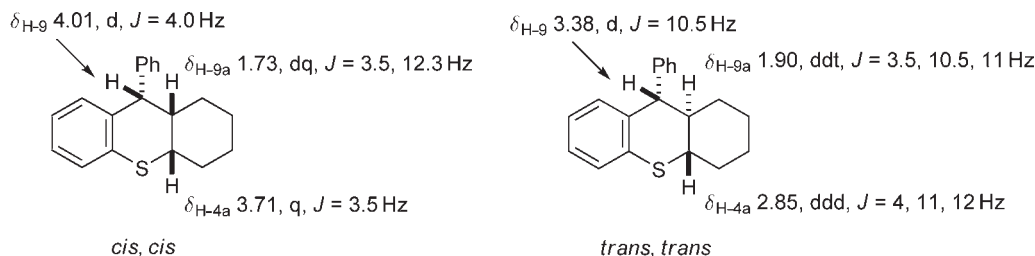
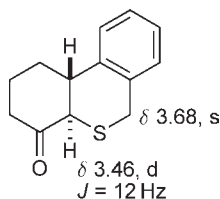
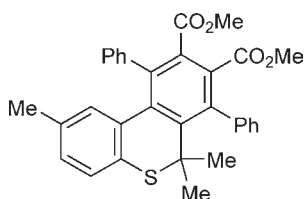


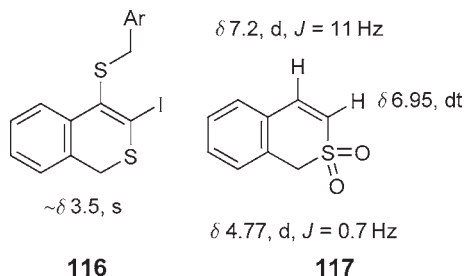
Figure 26 ^1H NMR data for *cis,cis*- and *trans,trans*- hexahydro-9-phenyl-9*H*-thioxanthenes.



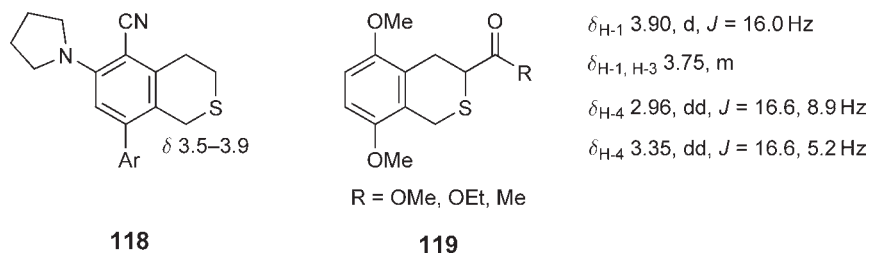
The signal for the geminal methyl unit of the polysubstituted 6*H*-dibenzo[*b,d*]thiopyran **115** exhibits temperature dependency due to hindered ring interconversion as a consequence of interaction of the methyl groups with the proximal phenyl unit. At 45 °C, a sharp singlet is evident at δ 1.22 which gradually broadens on cooling and then resolves into sharp singlets at δ 1.05 and at δ 1.39 at -40 °C with a coalescence temperature of ~ 12 °C <1994T7865>.



The methylene group in 1*H*-2-benzothiopyrans, for example, **116**, resonates at ca. δ 3.5 but this is shifted downfield to 3.9 ppm in the naphtho[1,2-*c*]thiopyran and upfield to δ 2.9 in the [2,1-*c*] isomer. This signal is lost when the thiopyrans are converted into the benzothiopyrylium salts by hydride abstraction when a singlet at δ 10.1–10.9 appears for H-1 <1998JOC4626>. The methylene function of 1*H*-2-benzothiopyran 2,2-dioxide **117** appears as a doublet, $J=0.7$ Hz, as a result of coupling to H-3. H-4 Displays the expected 11 Hz coupling consequent upon its *cis* relationship with H-3 <1971IJB74>.



In 3,4-dihydro-1*H*-2-benzothiopyrans **118**, the signals for the 3- and 4- methylene groups are unresolved at δ 2.8–3.0 but the 1-CH₂ resonates at 3.5–3.9 ppm <2001JOC5333, 2002J(P1)1426, 2005BML1341>. However, the introduction of an electron-withdrawing group at the 3-position, for example, **119**, allows at least partial resolution of the five heteroring protons <1994S363>.



¹H NMR signals have been assigned to the individual isomers of a mixture of the *cis*- and *trans*- 1-aryl-2-(trimethylsilylmethyl)-3,4-dihydro-1*H*-2-benzothiopyranium triflates on the basis of the chemical shift of the AB system associated with Me₃SiCH₂S⁺ protons (Figure 27) <1995J(P1)2845>.

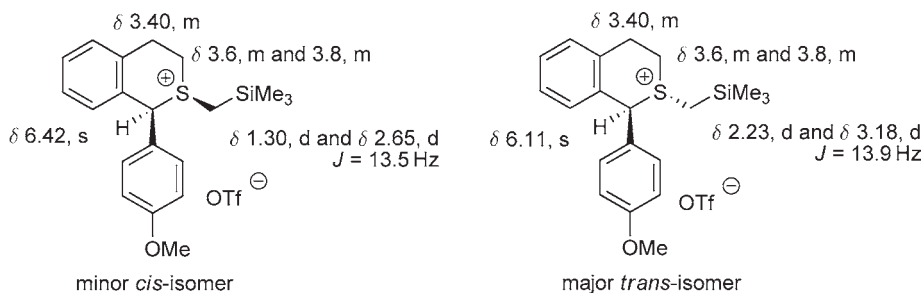


Figure 27 ¹H NMR assignments for *cis*- and *trans*- 1-aryl-2-(trimethylsilylmethyl)-3,4-dihydro-1*H*-2-benzothiopyranium triflates.

Only limited data are available for 3,4-dihydro-1*H*-2-benzothiopyran 1-oxide; H-1 appears as an AB system with a doublet at δ 3.78 and 4.02 and the remaining thiopyran ring protons as complex multiplets at δ 2.90 and 3.27 <1999CJC463>. ¹H NMR data for 3,4-dihydro-1*H*-2-benzothiopyran 2,2-dioxide and a linear naphthologue have been reported (Figure 28). Of the two methylene functions adjacent to the sulfone unit, H-1 resonates furthest downfield as a consequence of its benzylic character. The methine protons at the 5- and 10-positions of the naphthologue each appear as a singlet, confirming the linear ring fusion and resonate at ca. δ 7.6. The isomeric amino benzothiopyran dioxides **120** and **121** can be readily distinguished by their ¹H NMR spectra, with H-3 of the

2-*H*-1-benzothiopyran appearing as a multiplet at δ 1.69. Interestingly the benzylic protons (H-4) of **121** are shifted upfield as a consequence of the proximal butylamino group relative to that in the parent compound <2003T5691>. Detailed data are available for two 1,8-diamino-3,4-dihydro-2*H*-1-benzothiopyrans <2004MRC999>.

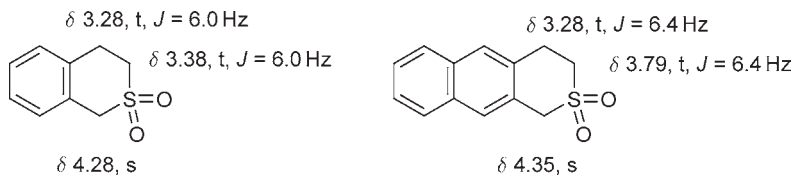
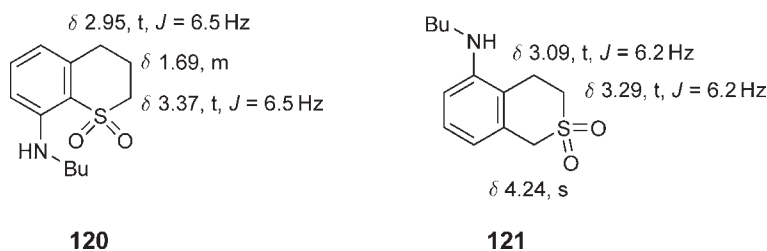


Figure 28 ^1H NMR data for 3,4-dihydro-1*H*-2-benzothiopyran 2,2-dioxide and a linear naphthopyrans.



^1H NMR chemical shift data for a selection of 3,4-dihydro-2*H*-1-benzothiopyrans together with that for the angular naphthologues are collated in **Figure 29**. Also relevant are data for the thiopyran ring protons of 1-thio- α -tocopherol **122** <1988JOC3739> and the liquid crystalline 2,6-disubstituted 3,4-dihydro-2*H*-1-benzothiopyran 1-oxide **123** <2003PS(178)993>.

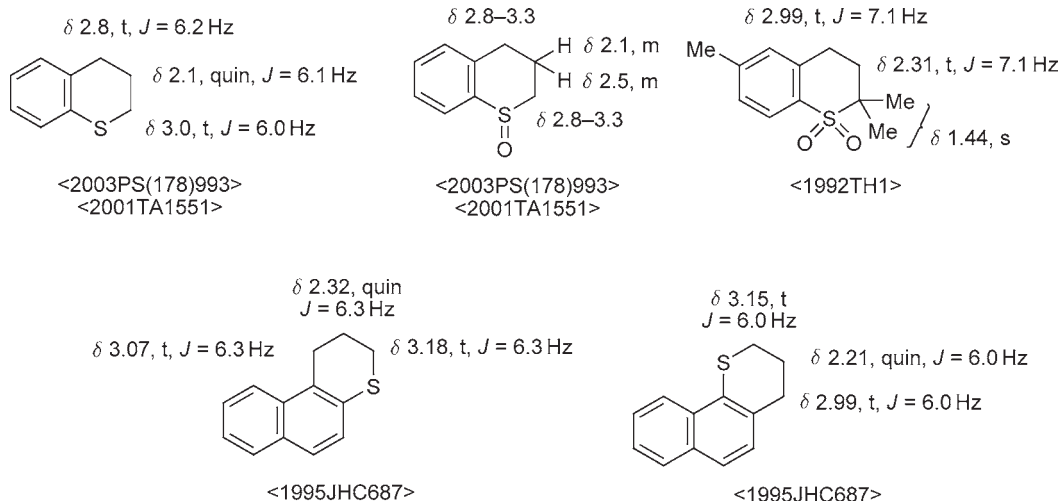
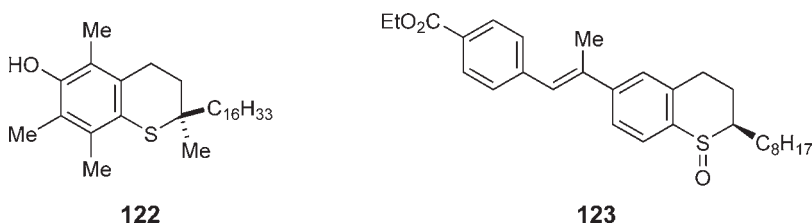


Figure 29 Selected ^1H NMR data for some 3,4-dihydro-2*H*-1-benzothiopyrans.



Extensive data are available for substituted 3,4-dihydro-2*H*-1-benzothiopyrans as these are frequently intermediates for the transformation of the readily available benzothiopyranones into the 2*H*-1-benzothiopyrans. Analysis of the coupling constants provides information on both the relative stereochemistries of ring substituents and on the conformation of the hetero-ring, though the latter is not always discussed.

The magnitude of the vicinal coupling constants between H-3 and H-4 of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzothiopyran-4-ols has enabled the orientation of the 4-hydroxyl group to be established in a range of substituted analogues. The H-3 protons in **124** are non-equivalent and display geminal coupling of ca. 13.2 Hz. Vicinal *trans* and *cis* coupling to H-4 of 9.8 and 5.4 Hz, respectively, are also observed. The magnitude of these vicinal couplings is suggestive of a pseudo-axial orientation of H-4 and hence a pseudo-equatorial arrangement for the 4-OH group (Figure 30). The presence of a 5-substituent, as in **125**, results in modification of the geminal and vicinal couplings which now arise from interaction with a pseudo-equatorial H-4 (Figure 31) <1992TH1>.

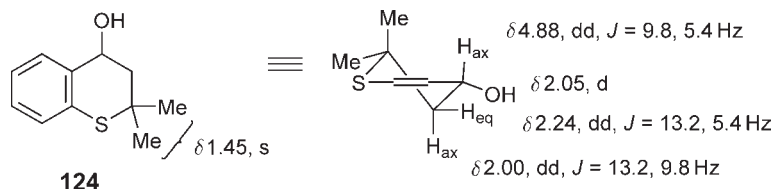


Figure 30 ^1H NMR chemical shifts and coupling constants for 2,2-dimethyl-3,4-dihydrobenzothiopyran-4-ol **124**.

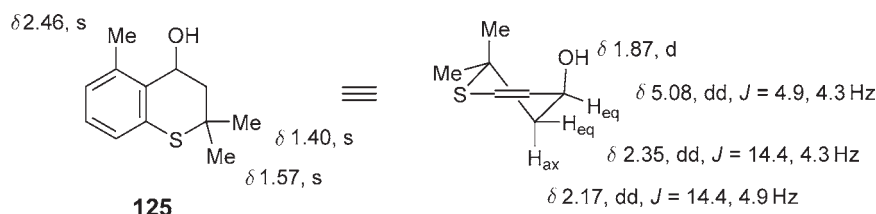


Figure 31 ^1H NMR chemical shifts and coupling constants for 2,2,5-trimethyl-3,4-dihydrobenzothiopyran-4-ol **125**.

^1H NMR data are also available for 4-amino-3-hydroxy-3,4-dihydro-2*H*-1-benzothiopyran and its oxidized analogues (Figure 32). The $^3J_{3,4}$ coupling constants measured for the three analogues are consistent with a *trans*-diequatorial disposition of the amino and hydroxy substituents <1990J(P1)3187>. A detailed examination of the coupling constants in the *cis*- and *trans*- 3-aryl-4-nitro-3,4-dihydro-2*H*-1-benzothiopyran 1,1-dioxides **126** has been reported, the most striking differences between the isomers being noted for $J_{3,4}$ (~ 11 Hz *trans*; ~ 4 Hz *cis*) and in the chemical shift of the pseudo-axial H-2 ($\sim \delta 3.7$ *trans*; $\sim \delta 4.7$ *cis*) <2004T4967>. ^1H NMR spectroscopy indicated that sodium borohydride reduction of 3,4-dihydro-2,2,6-trimethyl-2*H*-1-benzothiopyran-3,4-dione formed a mixture of the *trans*- and *cis*- diol based on the analysis of coupling constants derived from two AX patterns ($\delta 3.82$ and $\delta 4.49$; $J = 8.9$ Hz, *transoid* and $\delta 3.61$ and $\delta 4.62$; $J = 3.9$ Hz, *cisoid*) <1994T7865>.

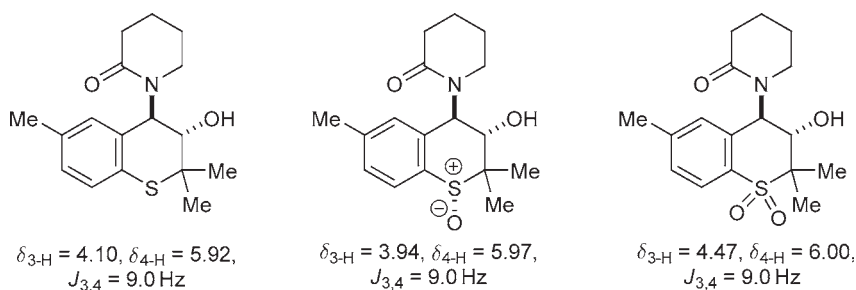
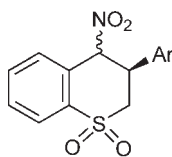
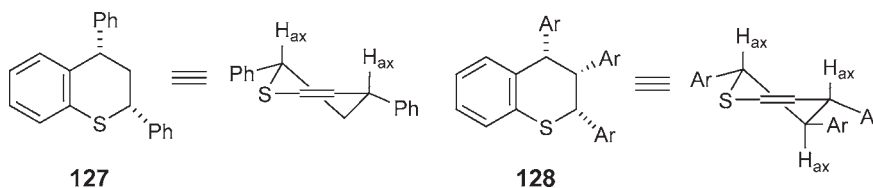


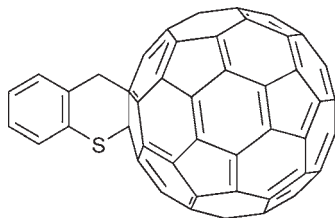
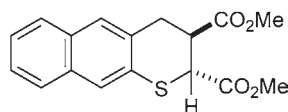
Figure 32 ^1H NMR data for 4-amino-3-hydroxy-3,4-dihydro-2*H*-1-benzothiopyrans.

**126**

The phenyl substituents in *cis*-2,4-diphenylbenzothiopyran **127** occupy pseudo-equatorial positions with vicinal axial–axial coupling constants of 10.4 Hz between H-4_{ax} and H-3_{ax} and H-2_{ax} and H-3_{ax}; the H-4_{ax} and H-2_{ax} coupling constants to H-3_{eq} are 6.1 and 4.4 Hz, respectively. The vicinal coupling constants in the *trans*-diphenyl isomer are smaller, $J_{3,4} = 7.6$ Hz and $J_{2,3} = 3.9$ Hz <2003T3621>. Extensive coupling constant data on a range of 2,4-diaryl substituted benzothiopyrans confirm the equatorial disposition of the *cis*-aryl groups <2001JOC5595>. Coupling constants in the range 10.2–11.1 Hz were measured for H-2 and H-4 in a series of 2,3,4-triaryl substituted thiochromans **128** <2001JOC5595> and confirm earlier observations made for 2,3,4-trisubstituted 3,4-dihydro-2*H*-thiopyrans <1990T1951> that all the hydrogen atoms are in a *trans*-triaxial conformation.

**127****128**

The cycloaddition between C₆₀ and the *o*-thioquinone methide derived by thermolysis of benzothiete affords the C₆₀-fused benzothiopyran **129**. The H-4 protons are nonequivalent and afford an AB system with doublets at δ 4.48 and δ 5.07 with $J_{\text{gem}} = 13$ Hz (CDCl₃/CS₂) at 20 °C which collapse to a singlet on warming to 120 °C. Data for the derived *S*-oxide are also reported <1995TL6899>. The ester groups in the linear naphthopyrans **130**, obtained by a similar *o*-thioquinone methide strategy, occupy pseudo-equatorial positions indicated by the large vicinal coupling constant of 8.1 Hz <1994TL2161>. Chemical shifts and coupling constants for a variety of 2,2,3,5,7-pentasubstituted 2*H*-1-benzothiopyran 1,1-dioxides have been tabulated <2003RJO397>.

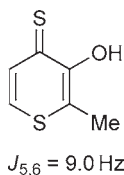
**129**

δ 4.42, d, $J = 8.1$ Hz

130

7.10.2.3(i)(b) Thiopyranones, their benzologues and their reduced derivatives

The effect of replacing the hetero O atom in maltol by S is a marked downfield shift of the two 'aromatic' doublets (δ 6.45 and 7.73 vs. δ 7.33 and 7.59) and this is accentuated in 3-hydroxy-2-methyl-4*H*-thiopyran-4-thione (dithio-maltol) **131** (δ 7.52 and 8.16) <2006CC206>.



$J_{5,6} = 9.0$ Hz

131

A wealth of data for a range of 2-alkyl-6-aryl-, 2,6-diaryl- and 2,6-diheteroaryl- 4*H*-thiopyran-4-ones and their 1,1-dioxides and a range of tetrahydrothiopyran-4-one precursors has been reported <1995JOC1665>. Data for representative examples with varying substitution patterns are presented in Figure 33. In the symmetrically substituted examples, 3- and 5-H are equivalent and resonate at ca. 6.7 ppm and 4-bond 'W-type' coupling of the order of 1–3 Hz is not uncommon. In the unsymmetrical analogues, $J_{3,5}$ coupling is always observed and H-3 and H-5 resonate at marginally different δ values, for example, 132. Interestingly in 2-alkyl-6-aryl-4*H*-thiopyran-4-ones 133 H-3 and H-5 resonate downfield relative to the analogous 1,1-dioxides 134. This trend is also noted for the signals for the 3-, 5-, and 6-protons in the 2-phenyl analogues 135 and 136, although notably ^4J and ^3J couplings are smaller in 136. A mixture of the *cis*- and *trans*- 2,6-bis(2-thienyl) isomers 137 and 138 was resolved and the *trans* assignment made on the basis of the ring coupling constants. Data are also available for the 3-bromo- and 3,5-dibromo- tetrahydrothiopyran-4-one 1,1-dioxides <1995JOC1665>.

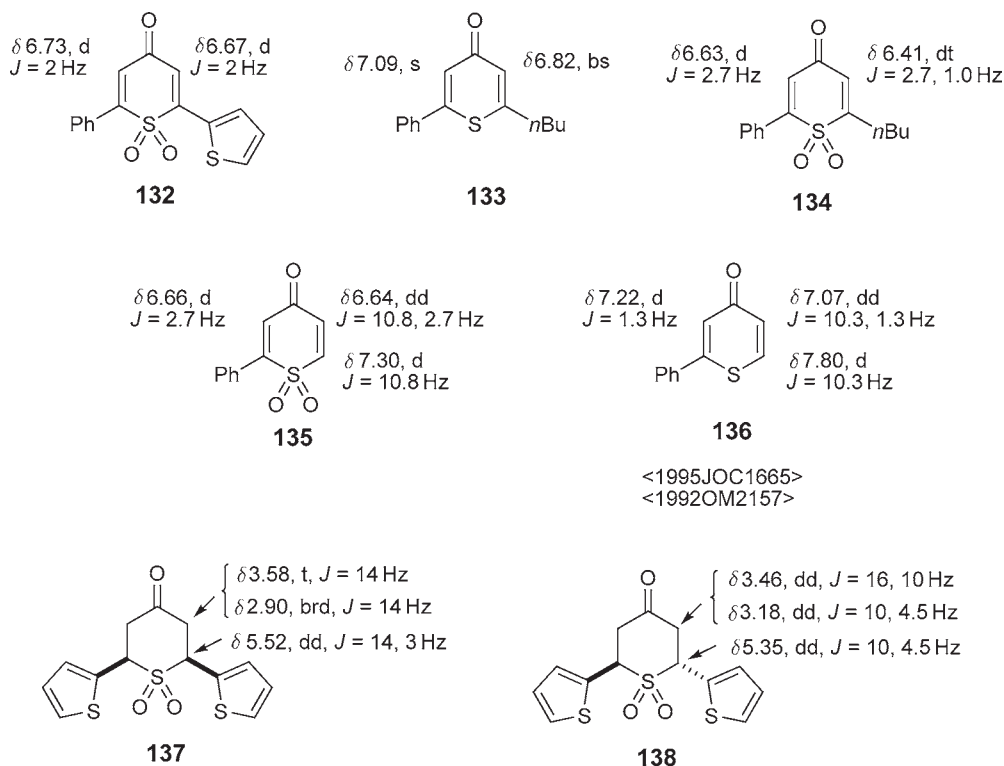
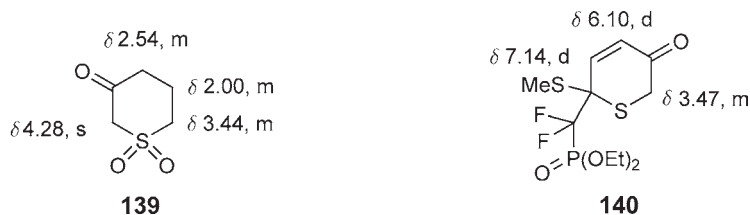
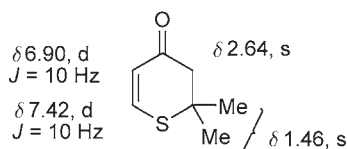
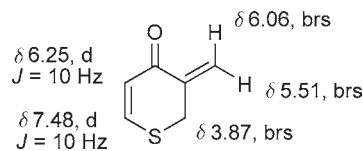


Figure 33 Selected ^1H NMR data for substituted thiopyran-4-ones.

Although coupling constants were not measured, the chemical shifts for the methylene units of tetrahydrothiopyran-3-one 1,1-dioxide 139 have been reported; H-2 resonates as a downfield singlet at δ 4.28 consistent with the adjacent electron-withdrawing CO and SO₂ groups <2004SC567>. The methylene function in the 3,6-dihydro-2*H*-thiopyran-3-one 140 appears as a multiplet at δ 3.47 and the alkene protons give rise to the expected doublets with $J_{3,4} = 10.9$ Hz <2002TL2033>.

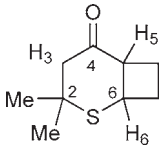
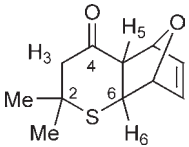


The 3-methylene unit in both the 2,2-dimethyldihydrothiopyran-4-one **141** and the tetrahydro analogue is poorly resolved such that the alkene signals appear as broadened singlets. The increased planarity of the thiopyran ring in **142** is manifest in a slight downfield shift of H-2 to δ 3.87 compared with δ 3.56 in the tetrahydro compound <1996SL261>.

**141****142**

Photocycloadditions of 2,2-dimethyldihydrothiopyran-4-one **141** with acrylonitrile and furan have been studied <1992HCA1925>. The mode of ring fusion in tetrahydrocyclobuta[*c*]thiopyran-4-ones can be inferred from their ^1H NMR spectra. Thus, the axial-axial disposition of the H atoms at the ring fusion sites in the *trans*-fused compounds gives a dihedral angle of 180° and so the vicinal coupling constant is larger than that of the *cis*-fused diastereoisomers. The opposite situation obtains for the geminal methylene H atoms at C-3. Confirmation of the ring fusion is provided by ^{13}C NMR data, where tetrahedral C-atoms in the *trans*-fused isomers resonate at lower field than those in the *cis* compounds (Table 3). A similar situation appears to exist for the [4+2] adducts with furan <2005HCA1922>.

Table 3 Selected ^1H NMR data for photocycloadducts of dihydro-2,2-dimethylthio-pyran-4-one **141**

				
	<i>Trans</i>	<i>Cis</i>	<i>Trans</i>	<i>Cis</i>
$J_{5,6}$ (Hz)	11.3–12.0	7.3–9.0	9.0	7.6–8.8
$J_{3,3}$ (Hz)	13.6–13.9	15.4–17.7	14.1–14.2	16.4–17.5
$\delta_{\text{C-2}}$ (ppm)	52–54	43–49	51	43–44
$\delta_{\text{C-3}}$ (ppm)	58–60	53–58	60	57
$\delta_{\text{C-4}}$ (ppm)	201–205	206–208	205–206	209–210
$\delta_{\text{C-5}}$ (ppm)	55–59	42–49	61–63	49–50
$\delta_{\text{C-6}}$ (ppm)	43–50	37–45	45–49	42–43

^1H NMR data for the adduct between $\text{C}_{60}\text{F}_{18}$ and 2*H*-thiopyran-2-thione, generated *in situ* from tetrathiofulvene (TTF), are shown in Figure 34; the magnitude of $J_{3,4} = 6.6\text{ Hz}$ is unusual as this is normally ca. 10 Hz <2003CEJ2008>.

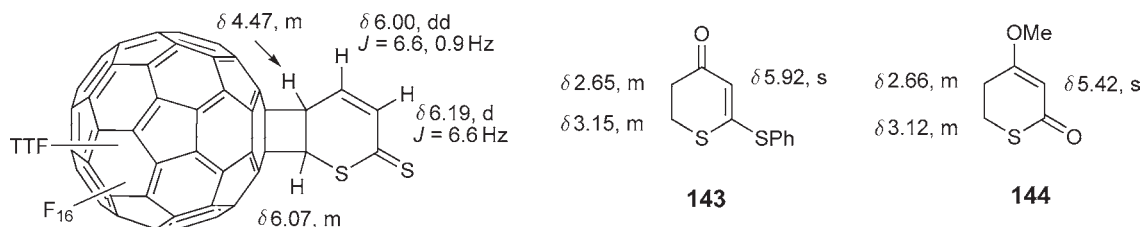
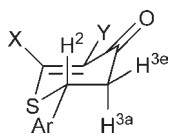


Figure 34 ^1H NMR data for the adduct between $\text{C}_{60}\text{F}_{18}$ and 2*H*-thiopyran-2-thione.

Analysis of the vicinal coupling constants in a selection of 2,5,6-trisubstituted dihydrothiopyran-4-ones <2000SL1804, 2005JOC10886, 2005RJO283> leads to the inference that the 2-substituent preferentially occupies a pseudo-equatorial site (Table 4).

Table 4 ^1H NMR data for 2,5,6-trisubstituted dihydrothiopyran-4-ones



	$\delta_{\text{H-2ax}}$	$J_{2,3 \text{ ax-ax}}$	$J_{2,3 \text{ ax-eq}}$	$\delta_{\text{H-3ax}}$	$J_{3,3}$	$\delta_{\text{H-3eq}}$
X = SEt, Y = PhCO, Ar = 4-MeC ₆ H ₄	4.80	14.0	3.0	3.27	16.5	
X = NHMe, Y = PhCO, Ar = 4-ClC ₆ H ₄	5.16	13.0	2.5	3.08	17.5	2.74
X = SCH=CH ₂ , Y = H, Ar = Ph	4.67	13.5	3.0	3.10	16.5	2.92

The methine protons resonate at δ 5.92 and δ 5.42 in the dihydrothiopyranones **143** and **144**, respectively, whereas the methylene protons in the SCH₂CH₂ unit have essentially identical chemical shifts <1991CJC1487>.

Replacement of the 4-dimethylamino group with a 4-anilino unit in 6-phenyl-5,6-dihydro-2*H*-thiopyran-2-thiones **145** has only a small influence on the chemical shift of the ring protons. The 6-phenyl group again occupies an equatorial position. The *syn*- (major) and *anti*- iminium iodides derived from 2*H*-thiopyran-2-thione **145** have significantly different ^1H NMR spectra with the chemical shift of H-5 changing from 8.14 ppm (*anti*) to 6.55 ppm (*syn*) as a consequence of shielding by the phenyl ring of the 4-iminium group (Figure 35) <2001T8305>.

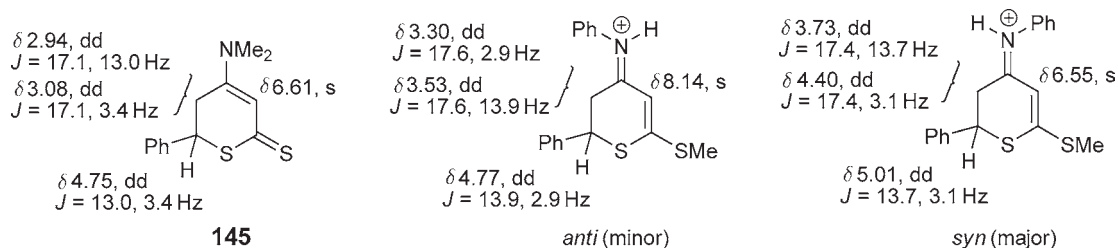
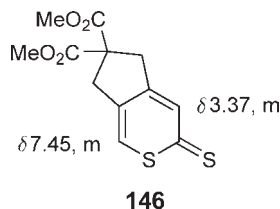


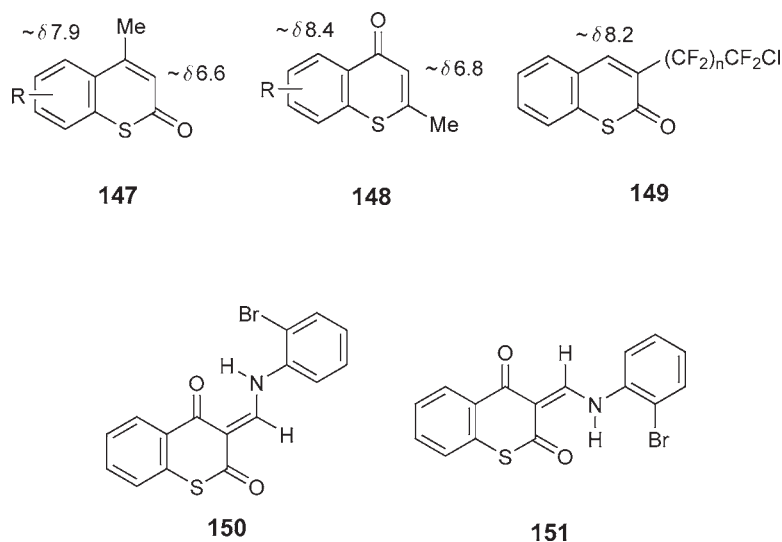
Figure 35 ^1H NMR data for *anti* and *syn* iminium iodides derived from 2*H*-thiopyran-2-thione **145**.

The Ru-catalyzed [2+2+2] cycloaddition of CS₂ with an α,ω -diyne gave the cyclopenta[*d*]-2*H*-thiopyran-2-thione **146**. The methylene groups appear as doublets at ca. δ 3.4 with $J \sim 1.6$ Hz from allylic coupling <2005JA605>. The signal for H-4 in 6-amino-5-ethoxycarbonyl-3-phenyl-2*H*-thiopyran-2-thione is superimposed on the aromatic ring signals <2003PS(178)2255>.



There have only been limited new data generated for substituted 2*H*-1-benzothiopyran-2-ones (thiocoumarins). Data for a range of 4-methylthiocoumarins **147** and some isomeric 2-methylthiochromones **148** have been reported. The key differences in their ^1H NMR spectra are the position of H-5, which appears as a multiplet in the range

7.7–8.0 ppm for **147** and further downfield ca. 8.3–8.6 in **148** as a consequence of its proximity to the carbonyl group, and the chemical shift of H-3 which appears at ca. δ 6.5–6.7 for **147** and further downfield in the thiochromones at ca. δ 6.8 <1980BCJ2046>. In a range of 3-(chloroperfluoroalkyl)thiocoumarins **149** H-4 resonates at ca. 8.2 ppm <1994J(P1)101>. Treatment of 4-hydroxythiocoumarin with either a primary amine or an amino acid and triethyl orthoformate affords 3-aminomethylenethiochroman-2,4-diones. Two doublets are apparent for the methine proton (δ 9.01 and 8.97) and also for the NH group (δ 14.3 and 12.9) all with mutual coupling of 13.2 Hz. It is likely that this adduct exists as a mixture of two geometrical isomers **150**, **151** and the significant difference in the chemical shift for the NH signals is due to intramolecular H-bonding to the 2- and 4- CO groups which have significantly different electronic characteristics <2004SC2053>.



Both thiocoumarin and 3-cyanothiocoumarin form [2+2] photo-cycloadducts with substituted ethenes; key ^1H NMR data for the major *cis*-fused cyclobutane isomers are presented in Figure 36 <2000HCA1168>.

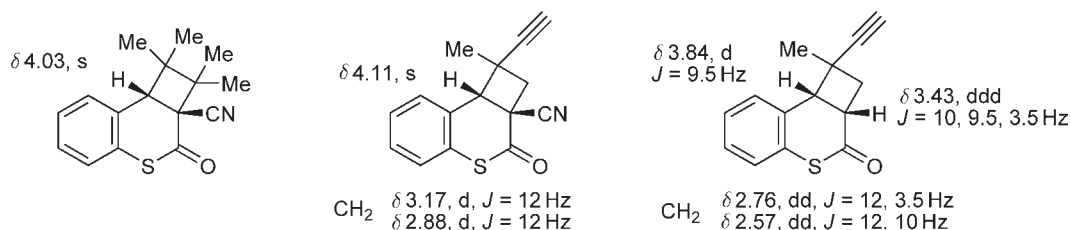
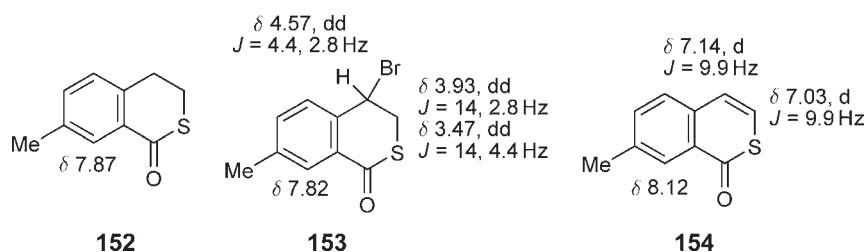
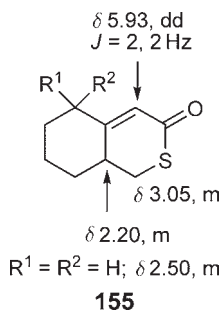


Figure 36 Selected ^1H NMR data for thiocoumarin-alkene photoadducts.

A range of 1*H*-2-benzothiopyran-1-ones (isothiocoumarins), their 3,4-dihydro precursors (dihydroisothiocoumarins) and a naphthologue have been characterized by ^1H NMR spectroscopy, and while full assignments were not made for each example, a knowledge of the chemical shifts is of value <2000T6763>. The methylene protons of the 3,4-dihydro compound **152** appear as an AA'XX' pattern with multiplets at 3.4 and 3.3 ppm; a similar spin pattern is observed for the *c*-fused naphthologue though both multiplets are shifted slightly downfield. The bromine atom in the 4-bromo-1*H*-2-benzothiopyran-1-one **153** occupies a pseudo-axial site as the largest vicinal coupling constant between H-4 and H-3 is smaller than the 10 Hz expected for the alternative pseudo-equatorial arrangement. It is noteworthy that H-1 in 1-bromo-1,2-dihydro-4*H*-naphtho[2,1-*c*]thiopyran-4-one resonates at δ 6.36, over 1.7 ppm further downfield than the corresponding proton (H-4) in **153**. Base promoted elimination of HBr from **153** affords the 1*H*-2-benzothiopyran-1-ones, **154**, in which the *cis* relationship between H-3 and H-4 is reflected in a ca. 10 Hz coupling constant.



^1H NMR data have been reported for three 1,5,6,7,8,8a-hexahydro-3*H*-2-benzothiopyran-3-ones **155** <1997CJC681>.



Data for the parent 4*H*-1-benzothiopyran-4-one (thiochromone) and its 1-oxide and 1,1-dioxide are presented in **Figure 37**. One interesting trend is the upfield shift of H-5 upon oxidation of the S atom.

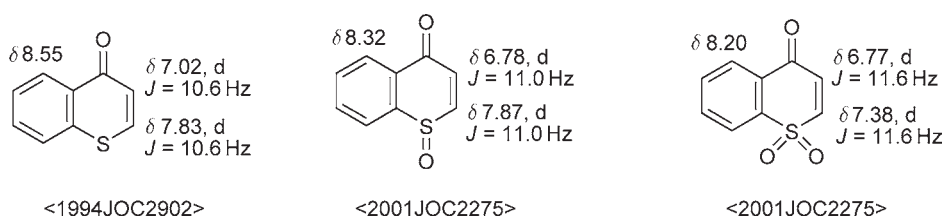


Figure 37 Chemical shifts and coupling constants for thiochromone and its 1-oxide and 1,1-dioxide.

Several 2-substituted thiochromones have been reported. Comparative ^1H NMR data for the selective replacement of the O heteroatom with S in 4*H*-1-benzopyran-4-one **156** to afford **157** and also replacement of the carbonyl to afford 4*H*-1-benzothiopyran-4-thione **158** are provided in **Table 5** <2006RCB523>. Replacement of the hetero oxygen atom in **156** results in downfield shifts of all of the signals with the exception of H-7 and $J_{5,6}$, $J_{5,8}$, and $J_{6,8}$ all increase. Coupling between H-3 and the F atoms is of the order of 0.8 Hz. Oxidation of **157** to the 1,1-dioxide results in an upfield shift of H-3 to 7.08 ppm and of H-5 to 8.19 ppm, while a downfield shift of H-8 to 8.08 ppm, is also noted.

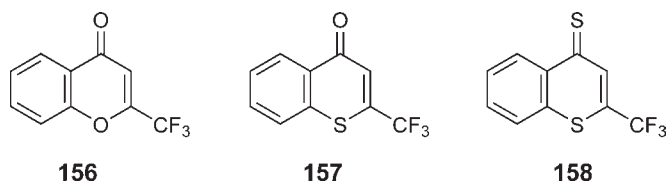


Table 5 Influence of replacing the O atoms in a chromone with S on ^1H NMR chemical shifts

δ						J (Hz)					
	H-3	H-5	H-6	H-7	H-8	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
156	6.74	8.21	7.49	7.77	7.56	8.0	1.7	0.4	7.2	1.0	8.6
157	7.33	8.52	7.62	7.71	7.68	8.1	1.4	0.7	6.5	1.9	8.2
158	8.16	8.88	7.60	7.71	7.67	8.3	1.4	0.5	6.6	1.8	8.2

Perhaps the greatest amount of attention has focussed upon the 3,4-dihydro-2*H*-1-benzopyran-4-one (thiochromanone) system with numerous synthetic studies providing much ^1H NMR data. Significant features of the ^1H NMR spectra of the parent compound **159**, some oxidized analogues **160**, **161**, benzologues, and simple substituted compounds are included in Figure 38. The multiplicity of the signals for the ring protons in the 2-alkyl- and 2-aryl- (thioflavanone) derivatives again confirms that the H-2 is pseudo-axially disposed. Complex splitting patterns for the $-\text{CH}_2\text{CH}_2-$ unit result for the 1-oxides as these protons are now diastereotopic, a feature that is readily illustrated in the 2,2-dimethyl substituted [2,1-*b*] naphthologue where $J_{3,3}$ is 17.6 Hz. In the absence of interfering aromatic substituents the two angular naphthothiopyranones can be readily distinguished by the chemical shift of the proton *peri* to the carbonyl group as these signals differ by over 1 ppm. in the two isomers. Whilst the *trans*-diastereoisomer of thioflavanone 1-oxide could not be resolved from the mixture, the signals for the pure *cis*-isomer were assigned and used to identify those of the *trans*-isomer in the mixture. In both isomers, the coupling constants for the thiopyran ring protons confirm that the 2-phenyl group prefers a pseudo-equatorial position <2001JOC2275>.

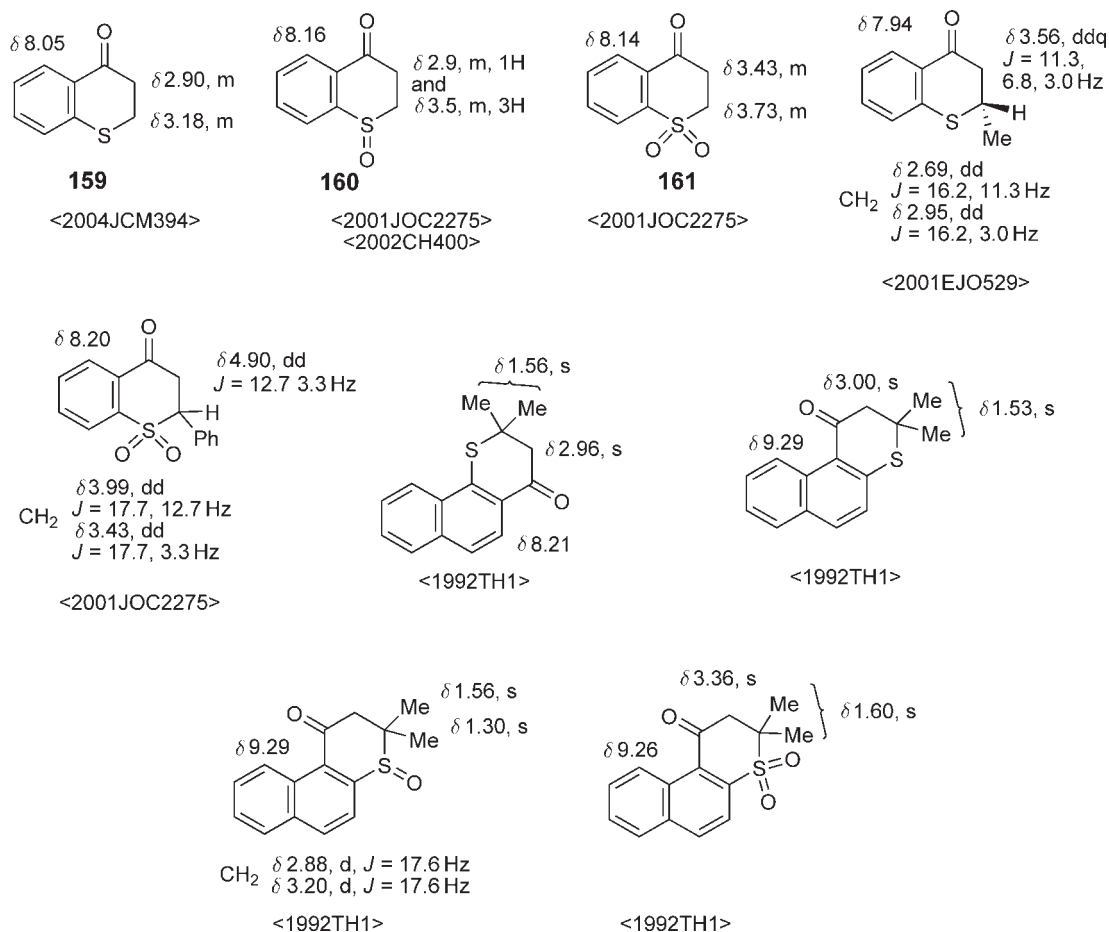
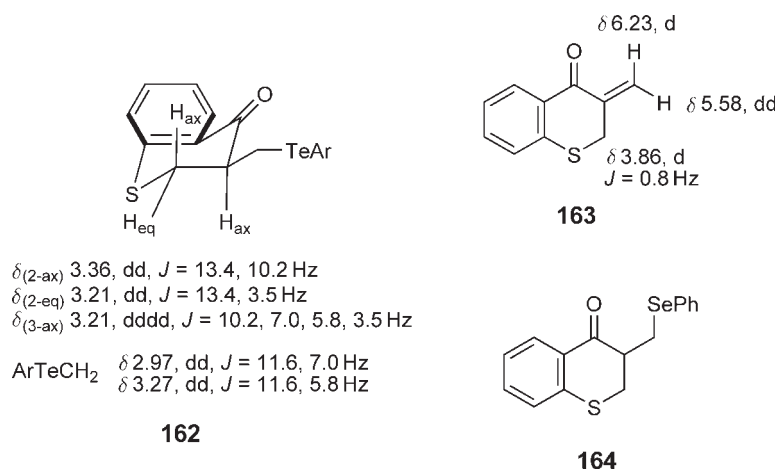


Figure 38 Selected ^1H NMR data for dihydrobenzothiopyranones.

The generation and intramolecular trapping of allylthioether tethered acyl tellurides affords 3-(aryltelluromethyl) substituted 3,4-dihydro-2*H*-1-benzothiopyran-4-ones **162**. Detailed analysis of the thiopyran ring protons indicate that H-3 is pseudo-axially disposed. The rapid passage of a solution of **162** through silica gel resulted in its decomposition and formation of 3,4-dihydro-3-methylene-2*H*-1-benzothiopyran-4-one **163** in which the ring methylene protons resonate at δ 3.86 as a doublet with allylic coupling to the upfield vinyl proton (δ 5.58, dd, $J = 0.8$ and 0.8 Hz). The remaining vinyl proton exhibits geminal coupling (0.8 Hz) and resonates at δ 6.23 as a consequence of its proximity to the anisotropic $\text{C}=\text{O}$ group <1994JA8937>. From the limited coupling constant data available for the 3-(phenylselenylmethyl)thiochromanone **164**, and by analogy with the data for **162**, H-3 is again assigned a pseudo-axial disposition <2003CC204>.



Other routes to 2-alkyl- and 2,2-dimethyl- 3-methylene 2*H*-1-benzothiopyran-4-ones have been reported. In the majority of these examples, coupling between the terminal alkene protons of ca. 0.7 Hz is observed and these protons resonate at ca. 5.4 and 6.1 ppm cf. **163**. The geminal methyl groups are equivalent and resonate at ca. 1.6 ppm, <1995JRM0805, 1999JOC9646> and H-2 resonates at ca. δ 3.5 in the 2-alkyl analogues <1999JOC9646>. The 3-CH₂ group and the alkenyl proton appear as singlets at δ 4.06 and δ 7.59, respectively, in (*E*)-2-ferrocenylmethylenethiochroman-4-one **165** <2000JST(524)297>. Several (*E*)-3-arylideneethiochroman-4-ones undergo photochemical rearrangement to afford 3-methylenethioflavanones, for example, **166**. The methine proton appears as a broadened singlet as a consequence of rapid equilibration between two conformers and the terminal methylene protons appear as triplets since $^2J_{\text{CH}=\text{CH}} \sim ^4J_{\text{H-2},=\text{CH}} \sim 1.5$ Hz. In the same work, (*E*)-3-arylideneethioflavanones have been photochemically isomerized to the (*Z*)-isomers; key ¹H and ¹³C NMR data for these geometrical isomers are presented in Table 6 <1996J(P2)547>. The 1.5 ppm difference in the chemical shift of the alkene proton between the two isomers is explained by the differing relationship of the methine proton to the anisotropic C=O group.

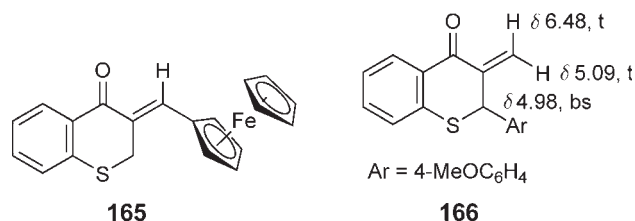
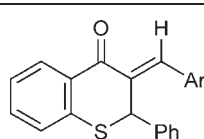
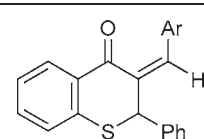


Table 6 ¹H NMR data for geometrical isomers of 3-arylideneethiochroman-4-ones

	 $\text{Ar} = 4\text{-ClC}_6\text{H}_4$ (<i>E</i>)-	 $\text{Ar} = 4\text{-ClC}_6\text{H}_4$ (<i>Z</i>)-
	δ C ₆ D ₆	δ C ₆ D ₆
H-2	5.53	4.93
=CH	8.04	6.48
C-2	46.0	53.2
C-4	185.4	186.9
=CH	137.0	136.1

Chemical shifts and coupling constants have been reported for (*E*)-3-benzylidenethiochroman-4-one 1-oxide and 1,1-dioxide (Figure 39). The 2-methylene unit appears as an AB system in the 1-oxide with $J = 12.5$ Hz but as a singlet in the 1,1-dioxide <1994T13113>.

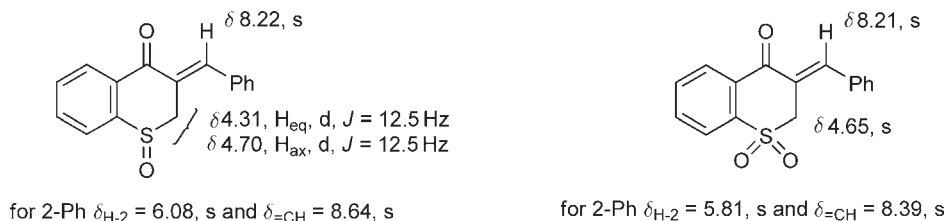


Figure 39 Chemical shift data for (*E*)-3-benzylidenethiochroman-4-one 1-oxide and 1,1-dioxide.

Extensive 1-D and 2-D NMR experiments coupled with in-depth analysis of the $^3J_{\text{CH}}$ coupling constants and *ab initio* MO calculations of the spiroepoxides derived from (*Z*)-3-arylideneethioflavanones revealed that both the *trans,cis* and *trans,trans* diastereoisomers prefer an envelope conformation in which the 2-phenyl group is pseudo-axially disposed <2001MRC251>. A similar detailed spectroscopic analysis of the derived 1-oxides and 1,1-dioxides revealed that the preferred ground-state conformation was a twisted envelope. Furthermore, a *trans* diaxial arrangement was evident for the 2-phenyl and 1-oxide groups (Figure 40) <2003MRC193>.

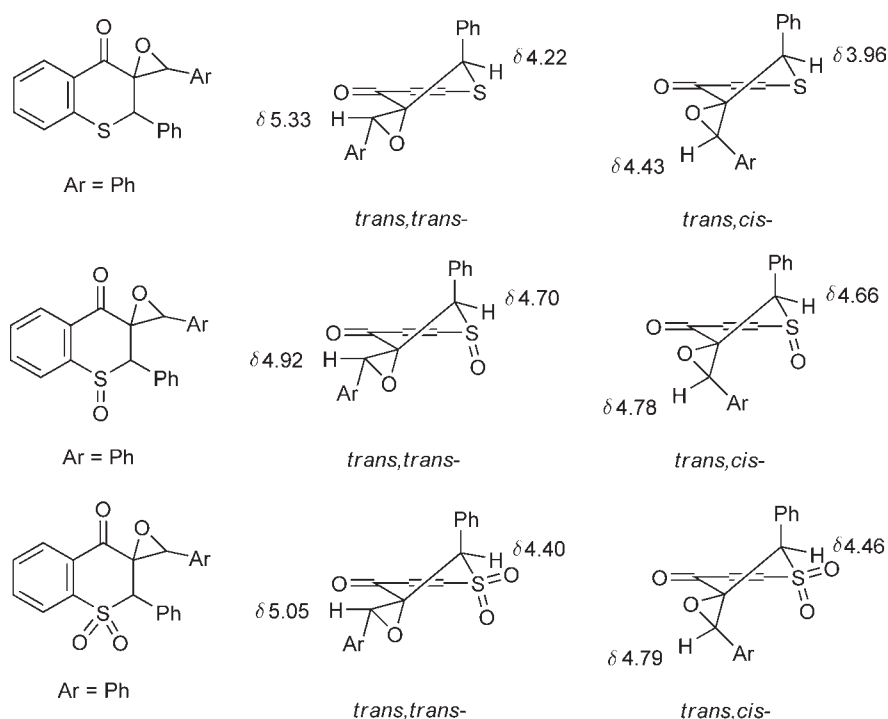
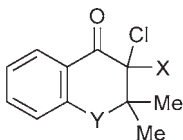


Figure 40 Chemical shifts for selected protons in spiroepoxides derived from (*Z*)-3-phenylthioflavanones.

Both 3-bromo- and 3-azido- substituents in thiochroman-4-one occupy a pseudo-equatorial site with H-3_{ax} appearing as a dd with $J = 8.5$ and 3.1 Hz at $\delta 4.98$ and at $\delta 4.54$ ($J = 12.5$ and 4.4 Hz), respectively <2002EJO285>. The geminal methyl groups in 3,3-dichloro-thiochroman-4-one 1,1-dioxide **167**, X = Cl, are equivalent and appear as a

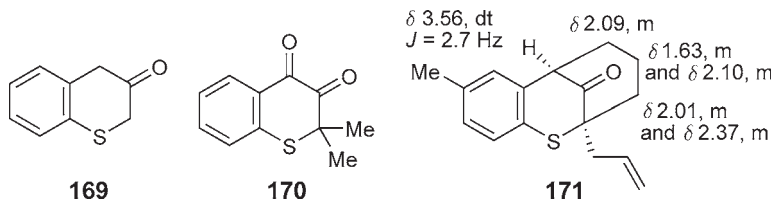
broad singlet at δ 1.82. The methyl groups in the 3-chloro-3-chlorosulfenyl precursor **167**, $X = \text{SCl}$, are nonequivalent and resonate at δ 1.72 and 1.92 <1994T5245>. The signals for the diethylamino unit in 3-chloro-3-(diethylamino-sulfenyl)-2,2,6-trimethylthiochroman-4-one **168** exhibit fluxional behavior over the range -20 to 55°C . At high temperature, broad signals are noted at δ 1.0 and 3.1 for the CH_3 and CH_2 units, respectively, but upon cooling multiplets for each proton of the NCH_2 groups are observed in the range δ 2.7–3.4. Interestingly, the signals for the C-2 methyl groups are unaffected in this temperature range <1994T827>.



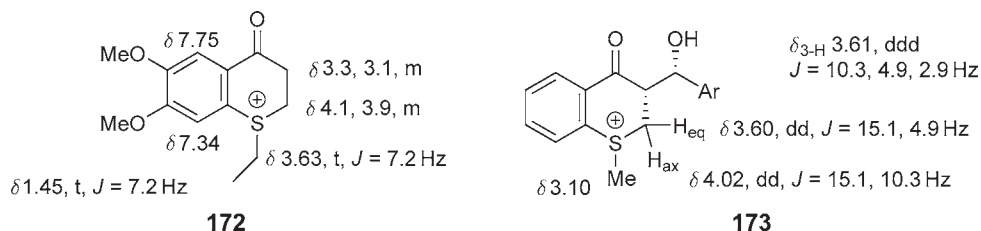
167: $X = \text{Cl}$ or SCl , $Y = \text{SO}_2$

168: $X = \text{SNEt}_2$, $Y = \text{S}$

The 2- and 4-methylene groups in thiochroman-3-one **169** appear as singlets at δ 3.33 and 3.75, respectively; the latter protons are relatively acidic and readily exchange with D_2O . 2,2-Dimethyl substitution (δMe_2 1.35, s) has a negligible influence on the chemical shift of H-4 <1982CJC243>, though the signal for the methyl groups is shifted downfield to ca. 1.6 ppm in the thiochroman-3,4-dione **170** <1994T7865>. The detailed ^1H NMR spectrum of the 2,4-propano-bridged thiochroman-3-one **171** has been reported <1999TA4427>.

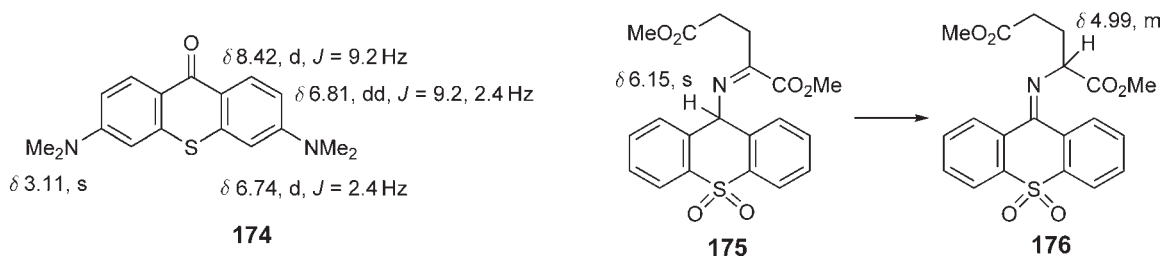


Limited data for the 1-ethyl thiochromanium fluoroborate **172** (CD_3CN) are available <1998T5599>. A more detailed analysis is provided for the aldol adduct **173** <2003EJO4852>. It is noteworthy that *S*-alkylation results in H-2 resonating further downfield than in the parent thiochroman-4-one and its 1-oxide.



Significant work on thioxanthenes has concentrated on novel synthetic approaches, often to known compounds. The ^1H NMR spectrum of 9*H*-thioxanthone displays signals at δ 7.48 (2H, td, $J = 6.7, 1.5$ Hz), 7.60 (4H, m) and 8.62 (2H, dd, $J = 7.4, 0.8$ Hz), the last of which is assigned to the protons (H-1, H-8) *peri* to the CO group. Introduction of a 1-methoxy group has a predictable influence on the ^1H NMR signals, although H-8 now resonates upfield at δ 7.56 perhaps as a consequence of modification of the conformation of the thioxanthone ring through steric interactions <2005OL4273>. ^1H NMR data have also been reported for 9*H*-thioxanthone 1-oxide [δ 7.74 (2H, t, $J = 7.6$ Hz), 7.86 (2H, t, $J = 7.6$ Hz), 8.19 (2H, dd, $J = 7.8, 1.2$ Hz), 8.39 (2H, dd, $J = 7.8, 1.2$ Hz)] and 9*H*-thioxanthone 1,1-dioxide [δ 7.78 (2H, td, $J = 8.0, 1.5$ Hz), 7.88 (2H, td, $J = 8.0, 1.5$ Hz), 8.19 (2H, dd, $J = 7.5, 1.5$ Hz), 8.35 (2H, dd, $J = 7.5, 1.5$ Hz)] <2006CEJ3389>. The protons at the 1- and 8-positions are equivalent and appear as a doublet at δ 8.42 in

3,6-bis(*N,N*-dimethylamino)-9*H*-thioxanthone **174** <2005OM3807>. ^1H NMR spectroscopy has been used to monitor the catalyzed conversion of **175** into the 9*H*-xanthen-9-imine **176** through the decrease in intensity of the singlet at δ 6.15 (H-9) and the simultaneous evolution of the multiplet at δ 4.99 <2002JOC3585>.



7.10.2.2.3(i)(c) Thiopyrylium salts

The majority of new work on thiopyrylium salts concerns symmetrically and unsymmetrically 2,4,6-triaryl substituted analogues since these have been extensively evaluated as photosensitizers for photodynamic therapy. Care must be exercised when comparing chemical shifts of thiopyrylium salts as CDCl_3 is not always the solvent of choice. Data for several 2,4,6-triaryl substituted compounds are presented in **Figure 41**. It is noteworthy that for symmetrical 2,4,6-trisubstituted compounds, the groups in the 2- and 6-positions have identical chemical shifts but the group in the 4-position is unique in giving rise to separate signals leading to a relatively complex spectrum overall. A significant upfield shift is noted in the signals for H-3 and H-5 for the 2,4,6-trimethylphenyl substituted analogue perhaps as a consequence of twisting of this aryl group. In unsymmetrically substituted thiopyrylium salts, H-3 and H-5 are nonequivalent and thus give rise to separate signals, though individual assignments have not been made <1999JME3953, 2000JME4488>.

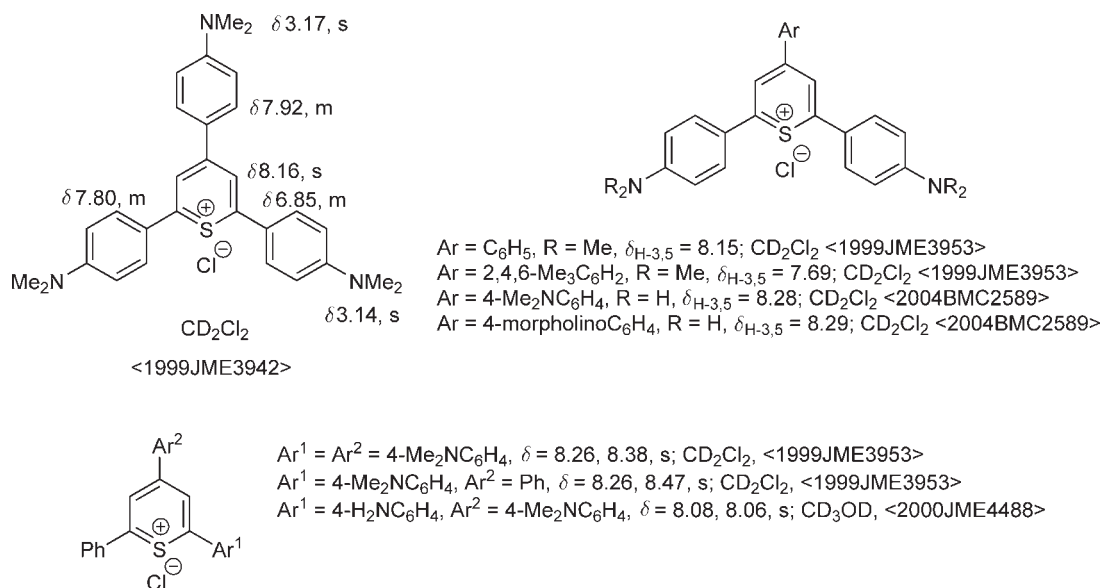
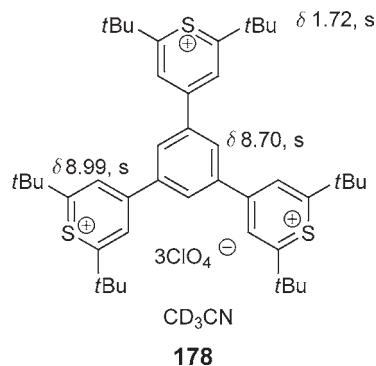
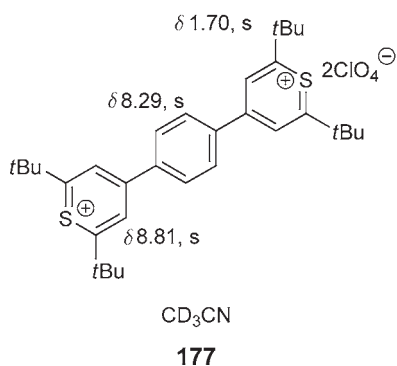
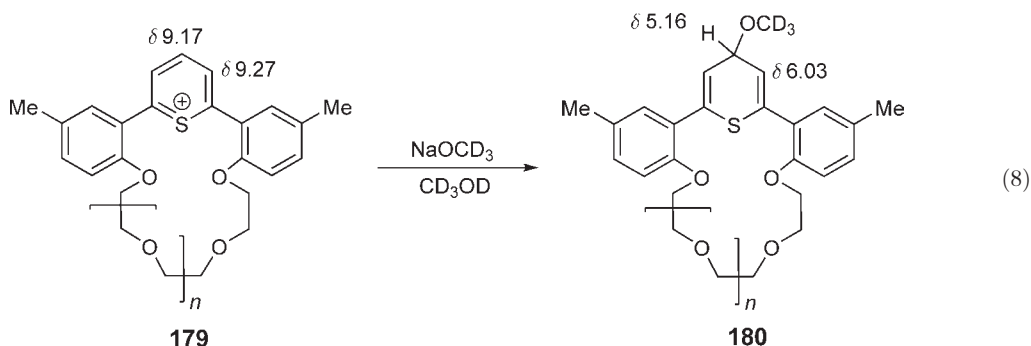


Figure 41 Selected ^1H NMR data for substituted thiopyrylium salts.

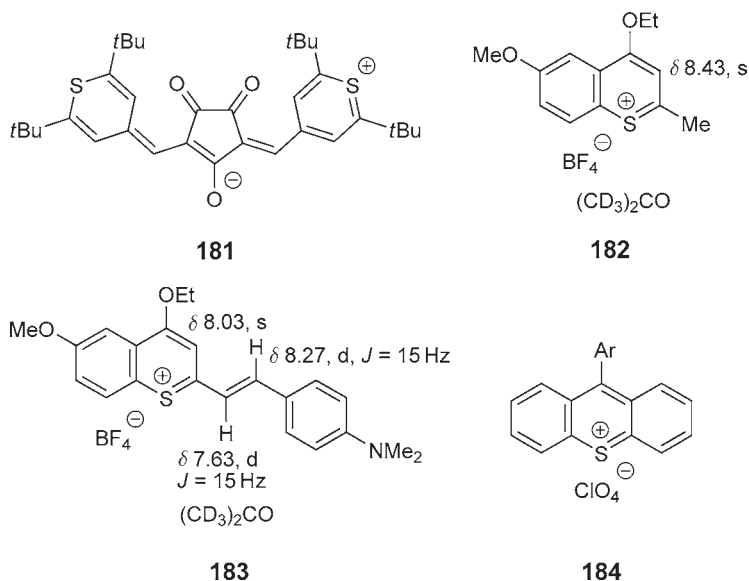
The reaction of bis- and of tris- thiopyrylium cations **177** and **178** with CD_3ONa in CD_3OD has been studied by ^1H NMR spectroscopy. At low temperature, kinetically controlled mixtures of 2*H*- and/or 4*H*- adducts were detected, but at room temperature the mixture equilibrated to afford the 2*H*-adducts exclusively <2005JOC6422>.



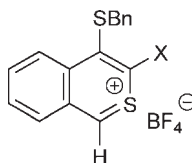
Changes in the ^1H NMR spectrum of thiopyrylium corands **179** following the addition of CD_3ONMe_4 in CD_3OD show that the heterocyclic moiety is converted exclusively into the 4*H*-thiopyran **180** through addition of methoxide ion (Equation 8). Binding to an alkali metal cation occurs preferentially with the latter species. Association constants for both the thiopyrylium cation and the 4*H*-thiopyran adduct binding to the metal ions are reported. Calculations indicate that the methoxy group might play a role in the binding process <1996T3509>.



The ^1H NMR spectrum of the zwitterionic, symmetrical croconium dye **181** is relatively simple and displays a sharp singlet at δ 1.44 (36H), and broadened singlets at δ 8.65, 7.41 and 6.76 all accounting for 2H as a consequence of the extended delocalization of the π -system <2000JOC2236>. The acidity of both 2- and 4- methyl groups in a range of 1-benzothiopyrylium salts for example, **182** has been exploited in the synthesis of numerous methine dyes for example, **183**; detailed ^1H NMR data are provided <1990JRM0546>. The ring protons of 9-arylthiopyrylium cations **184** resonate in the range 8.0–8.8 ppm <2002BCJ1325> and data for a 3,6-bis(dimethylamino)-9-phenylthiopyrylium chloride have been reported <2005BMC5927>.



For a series of 3-halogeno-2-benzothiopyrylium salts **185**, H-1 resonates in the range 10.09–10.66 ppm. In keeping with the observed trend of a downfield shift in hetero-ring protons upon benzo-fusion, the comparable proton in the naphtho[1,2-*c*] analogue resonates at δ 10.93 <1998JOC4626>.

**185**

7.10.2.2.3(ii) ^{13}C NMR spectra

Much ^{13}C NMR data have appeared in papers concerned with the synthesis and reactivity of the six-membered sulfur heterocyclic systems over the last decade. Unfortunately, much of these valuable data are frequently relegated to the experimental section of these reports and are invariably presented as a list of unassigned chemical shifts for each compound and as such are essentially only valuable for comparative purposes and structure verification.

7.10.2.2.3(ii)(a) Thiopyrans, their benzologues, and their reduced derivatives

New ^{13}C NMR data have appeared for 2*H*-thiopyran, several substituted analogues and some 4*H*-thiopyrans (Figure 42). A 2-CH₂ group in a 2*H*-thiopyran and a 4-CH₂ group in a 4*H*-thiopyran typically resonate in the range 20–30 ppm <2001EJO2477, 2004TL87>. Hydrolysis of the *N*-acetyl function in **186** leads to a downfield shift in 6-C of ca. 13 ppm <2004S1633>. ^{13}C NMR data (CD₃CN, CDCl₃) are available for several 6-substituted 2*H*-thiopyranium fluoroborates; from the unassigned data it is evident that the 2-CH₂ unit resonates at ca. δ 32 and the *S*-Me group at ca. δ 21 <2001J(P1)2269>.

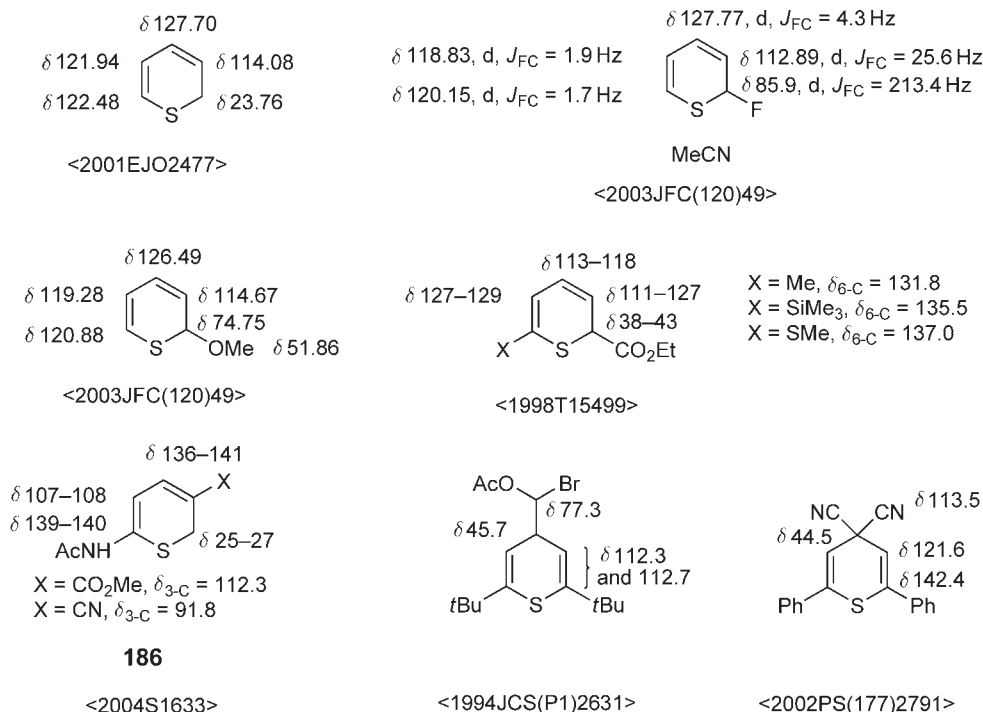
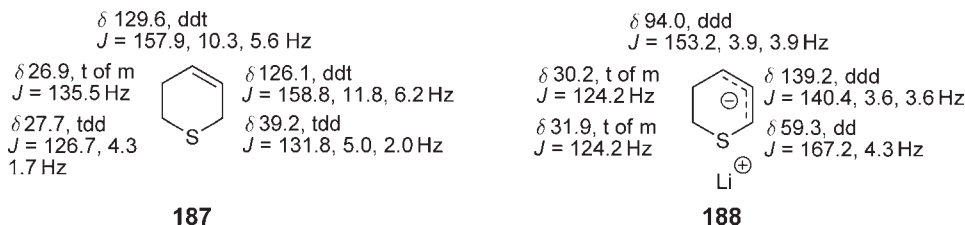
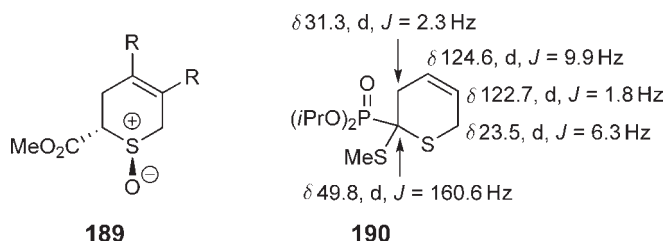


Figure 42 Selected ^{13}C NMR data for some 2*H*- and 4*H*-thiopyrans.

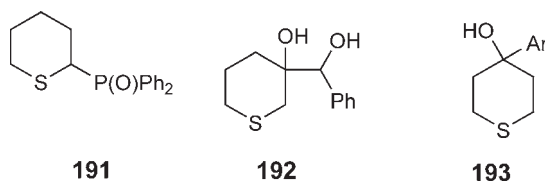
The ^{13}C NMR spectra (THF- d_6) of 3,6-dihydro-2*H*-thiopyran (300 K) **187** and its delocalized lithio anion (220 K) **188** have been analyzed <1995BCJ2739>. The following features are noteworthy from a comparison of their ^{13}C NMR spectra. The chemical shift of C-4 has decreased by ca. 36 ppm which is indicative of an increase in charge density and $^1J_{\text{CH}}$ for C-6 has increased by ca. 36 Hz which is suggestive of sp^2 hybrid character for C-6; both features support a delocalized allylic anion.



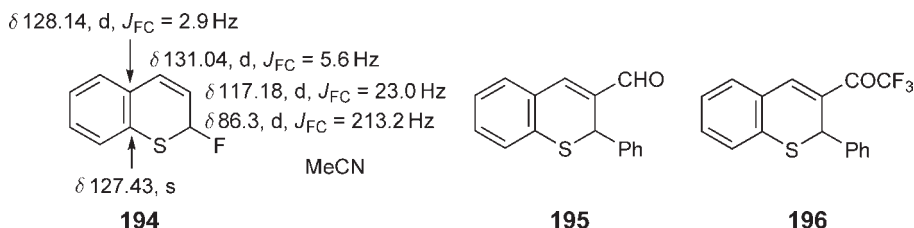
The ^{13}C NMR spectra of each individual diastereoisomer of 3,6-dihydro-2,3,5,6-tetramethoxycarbonyl-2*H*-thiopyran have been assigned <1996J(P2)2623> and chemical shift data are also available for the four diastereoisomers of 3,6-dihydro-3,5,6-trimethoxycarbonyl-2*H*-thiopyran, though individual conformers are not assigned. In the latter examples, selected $^1J_{\text{CH}}$ data are available with values of ca. 165 Hz and ca. 145 Hz for sp^2 hybridized and sp^3 hybridized C atoms, respectively <1997MI2185>. In the *trans* isomers of a series of 2-methoxycarbonyl-3,6-dihydro-2*H*-thiopyran 1-oxides **189**, C-2 resonates at $\sim\delta 61$ and C-6 at $\sim\delta 47$ <1999EJO2573>. Complete assignment of the ^{13}C NMR spectrum including measurement of J_{CP} values have been reported for several (3,6-dihydro-2*H*-thiopyran-2-yl)phosphonates, for example, **190** <2000TL7327>.



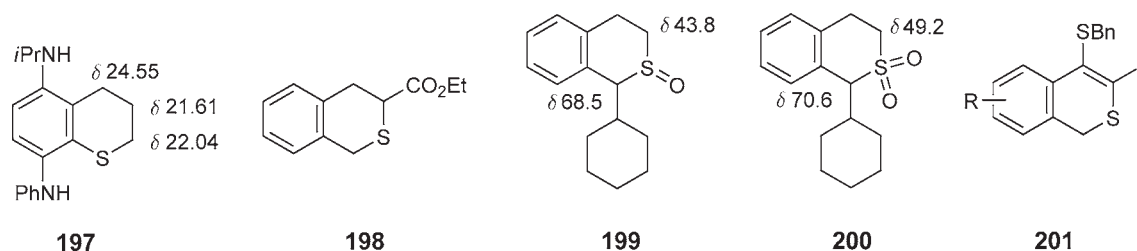
The ring carbons resonate between 21 and 30 ppm in 2-cyanotetrahydrothiopyran <2006CL98>, between 26 and 48 in 2-phenyltetrahydrothiopyran <1997T5563> and in 2-(diphenylphosphinoyl)tetrahydrothiopyran **191** signals are noted at δ 25.2 (d, $J = 8.8 \text{ Hz}$), 26.5 (s), 29.3 (d, $J = 5.5 \text{ Hz}$), 39.3 (d, $J = 70.5 \text{ Hz}$) for the hetero ring C atoms <1998T1375>. The four methylene groups of the tetrahydrothiopyran-3-ol **192** resonate in the range δ 23–38 and C-3 at δ 69.9 <1998JOC1910>. C-4 Resonates in the narrow range 71.1–71.8 ppm in the 4-aryltetrahydrothiopyran-4-ols **193** <2005PS(180)53>. As a consequence of the symmetry of the latter compounds, C-3 and C-5, and C-2 and C-6 are equivalent and appear at ~ 39.5 and 24.0 ppm , respectively.



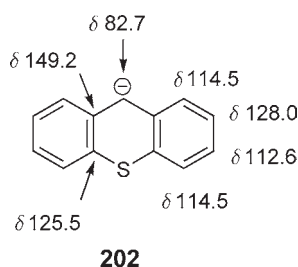
Chemical shifts and J_{CF} coupling constants have been assigned for the hetero ring carbons of 2-fluoro-2*H*-1-benzothiopyran **194** <2003JFC(120)49>. The C-2 resonates at 38.29 ppm in aldehyde **195** <2006TL8547> and at 38.96 ppm in the 3-trifluoroacetyl-2*H*-1-benzothiopyran **196** in which C-3 appears as singlet at δ 129.5 but C-4 as a quartet with $^4J_{\text{CF}} = 3.6 \text{ Hz}$. Data for a range of trifluoroacetyl compounds are also reported <1999CHE549>.



The ^{13}C NMR spectrum of 3,4-dihydro-2H-1-benzothiopyran (thiochroman) displays signals at δ 22.87, 27.56, 29.68, 123.91, 126.39, 126.58, 129.96, 132.86, 133.86, and (+)-1-thiochroman 1-oxide at δ 28.20, 29.59, 46.16, 127.18, 130.24, 130.53, 131.38, 135.59, 138.58 <2001TA1551>. ^{13}C NMR solvent induced shifts are only minimal, 1–2 ppm, (CDCl_3 versus $\text{DMSO}-d_6$) for the 5,6-diaminothiochroman **197** <2004MRC999>. The signals for the 1H-2-benzothiopyran hetero-ring carbons appear at δ 22.98, 25.57, and 41.3 in the ester **198** <1994S363> and the carbon atoms α to the sulfur function resonate at δ 68.5 (CH) and δ 43.8 (CH_2) and at δ 70.6 (CH) and δ 49.2 (CH_2) in the isothiochroman 1-oxide **199** and 1,1-dioxide **200**, respectively <2003T5691>. Unassigned ^{13}C NMR chemical shifts for a range of isothiochromenes **201** have been reported <1998JOC4626>.



The CH_2 unit in 9H-thioxanthene resonates at δ 39.2 (CDCl_3) and this signal is shifted to δ 82.7 (NH_3 liq.) upon deprotonation to the thioxanthene anion **202**. Extensive *ab initio* MO calculations at the Hartree–Fock SCF level using 6–31G(d) basis set indicates a significantly flattened molecule (dihedral angle = 150°) and calculated charge distributions correlate well with experimental ^{13}C chemical shifts. The combined data from these calculations and experimental measurements indicate that **202** may be characterized as an extensively delocalized 16π -electron system in which the S atom plays a role <1997J(P2)1605>.



7.10.2.2.3(ii)(b) Thiopyranones, their benzologues, and their reduced derivatives

There have been relatively few examples of fully assigned ^{13}C NMR spectra of thiopyranones over the last ten years; selected data for some substituted thiopyran 2- and 4-ones and related thiones have been assigned (Figure 43) <1976CJC280>.

The 4-keto function of 3-ethoxycarbonyltetrahydrothiopyran-4-one resonates at δ 205.2 with the ester CO at δ 170.8 <1999SL735> and the 4-CO group 2,2-dimethyltetrahydrothiopyran-4-one appears at δ 208.9 <2005HCA1922>. The exomethylene C atoms resonate at δ 121.2 and 139.0 in the thiopyran-4-ones **203** and **204**, respectively <1996SL261>.

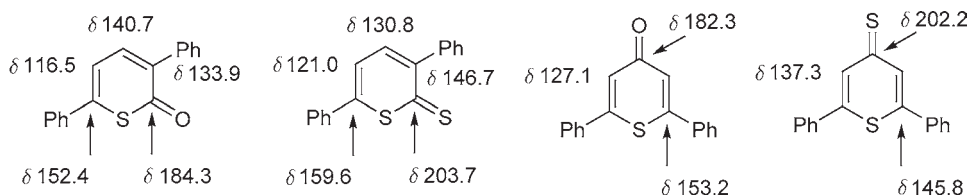
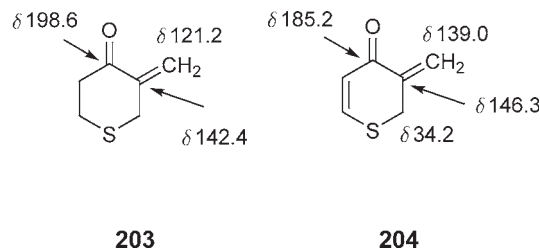
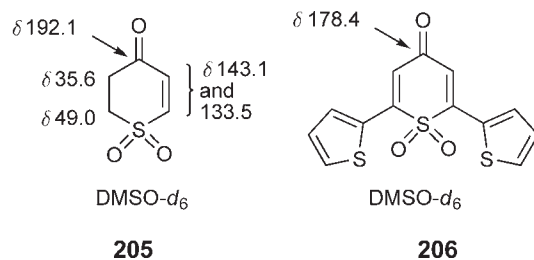


Figure 43 Selected ^{13}C NMR data for some thiopyran-4-ones and corresponding thiopyran-4-thiones.



The α,β -unsaturated CO group in **205** resonates at δ 192.1 and the doubly unsaturated CO in the 4*H*-thiopyran-4-one sulfones **206** at δ 178.4. The remaining signals in **206** appear at δ 145.9, 134.0, 132.8, 129.5, 129.0, and 124.5 <1995JOC1665>.



There have been extensive ^{13}C NMR data reported for benzo-fused thiopyranones (Figure 44) <1976CJC280, 1983SAA693, 1998PS(134)295>.

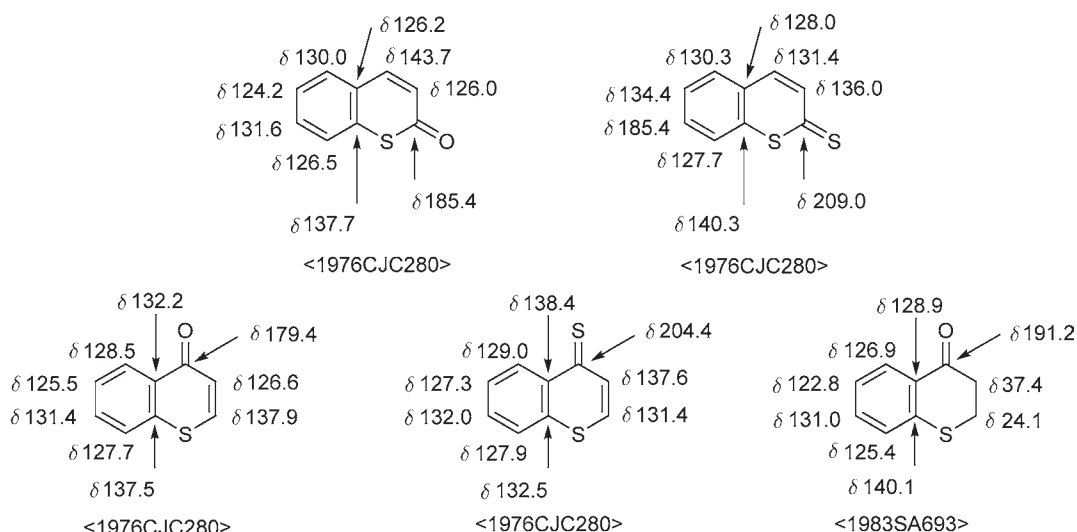
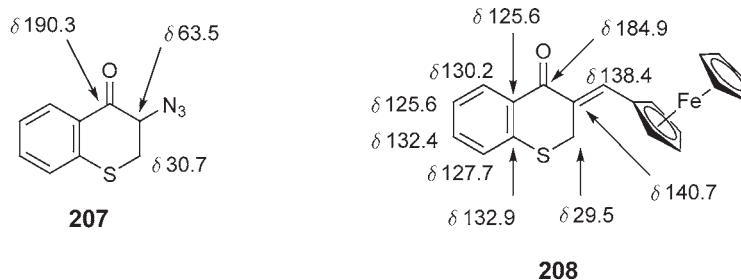


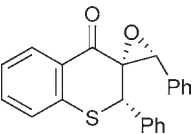
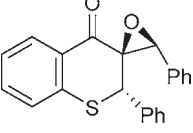
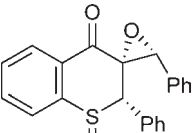
Figure 44 ^{13}C NMR chemical shifts for some benzothiopyranones.

Oxidation of the heteroatom in thiochroman-4-one with the complex formed *in situ* between $\text{Ti}(i\text{-PrO})_4$, (*R,R*)-1,2-diphenylethane-1,2-diol and aqueous *t*-BuOOH affords (+)-3,4-dihydro-2*H*-1-benzothiopyran-4-one 1-oxide which displays signals at 30.2, 46.6, 128.4, 128.8, 129.1, 132.0, 134.5, 145.5, 191.9 <2002CH400>. The introduction of a 2-methyl group in thiochroman-4-one results in a downfield shift in the signal for C-2 to δ 36.4 and also for C-3 to δ 47.8 <2001EJO529>. The 3-azido substituent in **207** causes a shift of C-3 to δ 63.5 <2002EJO285>. Unassigned ^{13}C NMR data have been reported for 3-(phenylselenomethyl)-<2003CC204> and 3-(aryltelluromethyl)- thiochroman-4-ones <1994JA8937>. 3-Methylenethiochroman-4-one affords signals at δ 33.73, 123.35, 125.78, 126.76, 127.93, 130.30, 133.18, 133.42, 140.46, 185.12 <1994JA8937> and data for several substituted analogues have been reported <1999JOC9646>. The ^{13}C NMR spectrum of (*E*)-3-ferrocenemethylene-2,3-dihydro-2*H*-1-benzothiopyran **208** has been fully assigned <2000JST(524)297>.



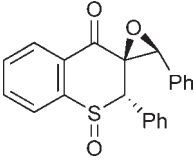
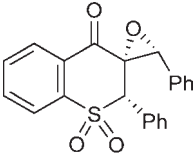
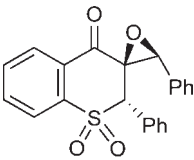
Complete NMR spectral assignments have been made for the *trans,cis* and *trans,trans* spiroepoxides derived by epoxidation of (*Z*)-3-arylideneethioflavanones, their 1-oxides and 1,1-dioxides (Table 7). As a consequence of the similarity of the chemical shifts of the signals in the ^{13}C NMR spectra of the isomer pairs, coupling constants data for $^3J_{\text{H-2,C-8a}}$ ($^3J_{\text{HC}}$ 7.0–7.6 Hz sulfide; $^3J_{\text{HC}}$ 6.2–6.5 Hz sulfoxide; $^3J_{\text{HC}}$ 2.0–3.4 Hz sulfone) and NOESY experiments were used extensively together with *ab initio* MO calculations to elucidate the conformation of the various isomers <2001MRC251, 2003MRC193>.

Table 7 Selected ^{13}C NMR data for spiroepoxides derived from (*Z*)-3-benzylidenethioflavanones

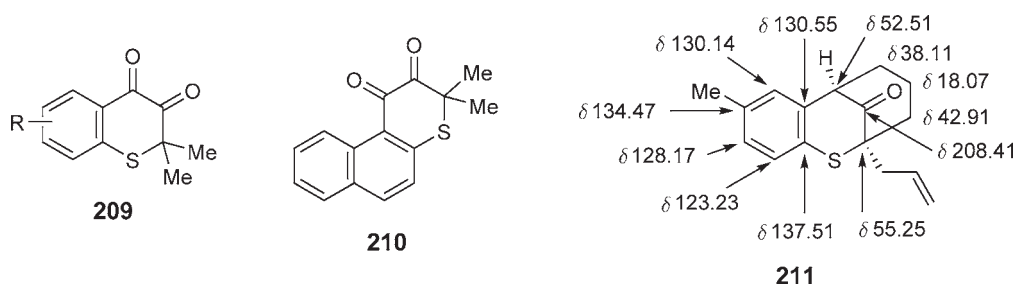
	Chemical shift (ppm)								
	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
 <i>trans,cis</i>	45.2	66.7	190.2	132.0	129.4	125.9	134.6	128.2	138.1
 <i>trans,trans</i>	46.5	64.2	189.4	131.1	129.8	125.9	134.6	128.6	139.9
^{13}C NMR spectra recorded in $\text{PhMe-}d_8$									
 <i>trans,cis</i>	61.2	60.8	189.5	131.7	129.6	133.1	135.1	131.2	140.1

(Continued)

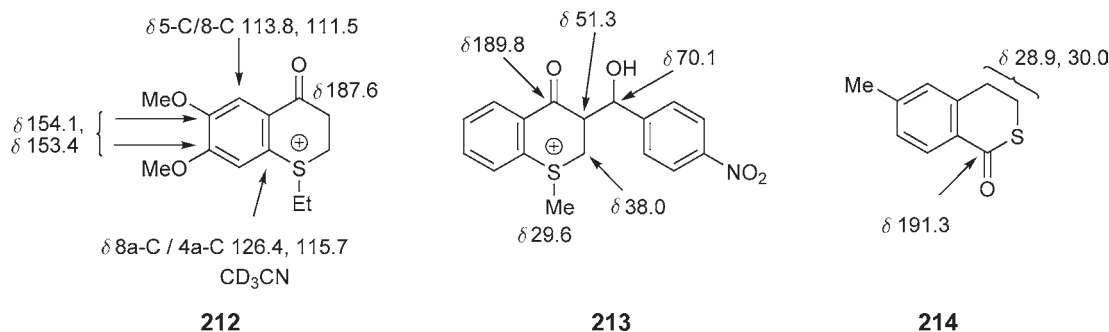
Table 7 (Continued)

	Chemical shift (ppm)								
	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
 <i>trans,trans</i>	65.3	59.1	190.1	130.7	129.9	133.4	134.6	130.7	141.9
 <i>trans,cis</i>	66.2	64.2	188.6	132.1	128.7	133.9	135.3	124.8	138.5
 <i>trans,trans</i>	68.5	63.7	188.0	132.3	129.0	134.0	135.2	125.4	138.8

The ^{13}C NMR spectra of 2,2-dimethylthiochroman-3,4-diones **209** and their naphthologues, for example, **210** are more informative than their ^1H NMR spectra and display low field signals at $\sim\delta$ 183 and 194, which are assigned to C-4 and C-3, respectively. The carbons of the geminal methyl groups are equivalent and absorb in the range δ 22–23, whilst C-2, adjacent to the sulfur heteroatom, resonates at ca. δ 54, shifted downfield compared with C-2 in 2,2-dimethylthiochroman-4-one (δ 44) <1994T7865>. The ^{13}C NMR spectrum of (–)-(2*S*,4*R*)-2-allyl-6-methyl-2,4-propanothiochroman-3-one **211** has been fully assigned as shown <1999TA4427>.



New chemical shift data have been reported for 9*H*-thioxanthone <2005OL4273>, 9*H*-thioxanthanthione <2001J(P2)2329>, 9*H*-thioxanthone 10-oxide and 9*H*-thioxanthone 10,10-dioxide <2006CEJ3389>. Limited ^{13}C NMR data are available for 4-oxo-2*H*-1-benzothiopyranium fluoroborates **212** and **213**. The unassigned methylene signals in the *S*-ethyl analogue resonate at δ 38.5, 32.5, and 29.7 <1998T5599> and C-2 resonates at δ 38.0 and the *S*-Me group at δ 29.6 in **213** <2003EJO4852>. The carbonyl carbon resonates at δ 186.7 in 7-methyl-1*H*-2-benzothiopyran-1-one and the remaining signals for the ring system fall in the range 121.7–139.3 ppm rendering precise assignments difficult. The 3- and 4-C atoms in the dihydro derivative **214** are also difficult to assign. It is noteworthy that the carbonyl group resonates ca. 4 ppm further downfield in the isothiochromanone <2000T6763>.



7.10.2.2.3(ii)(c) Thiopyrylium salts

Early work assigning and contrasting the ^{13}C NMR spectra of thiopyrylium salts with those of seleno- and telluropyrylium isosteres has featured in a review <1994AHC(60)65>. ^{13}C NMR data (Table 8) have been recorded for thiopyrylium salts with a range of different counter ions and in several solvents; from these data it is evident that C-2 is least influenced by these two variables.



Table 8 ^{13}C NMR chemical shifts for thiopyrylium salts

<i>Solvent</i>	<i>Anion</i>	$\delta_{\text{C-2}}$	$\delta_{\text{C-3}}$	$\delta_{\text{C-4}}$	<i>Reference</i>
CD_3CN	BF_4^-	158.78	138.25	150.80	2003JFC(120)49
$\text{DMSO}-d_6$	BF_4^-	158.65	136.80	149.24	2001EJO2477
$\text{DMSO}-d_6$	BPh_4^-	158.14	136.28	148.67	2001EJO2477
$\text{DMSO}-d_6$	I^-	158.67	136.59	148.95	2001EJO2477
$\text{DMSO}-d_6$	TFO^-	158.77	136.70	149.14	2001EJO2477
CD_3CN	TFO^-	158.92	138.21	150.74	2001EJO2477

The 2- and 6- *tert*-butyl groups are equivalent in 2,4,6-tri(*tert*-butyl)thiopyrylium perchlorate and resonate at δ 42.87 (C), δ 31.23 (CH_3) and the 4-*tert*-butyl resonates at δ 40.17, δ 30.32 (CH_3). The ring carbons appear at δ 185.71 (C-2), 131.00 (C-3) and 177.49 (C-4). Full ^{13}C (CD_3CN) assignments have also been made for 1-benzothiopyrylium, thioxanthylum and 9-phenylthioxanthylum fluoroborates (Figure 45) <2003JFC(120)49>. 9-Aryl-9*H*-thioxanthen-9-ols, the precursors to 9-arylthioxanthylum salts, display a signal at ca. 78 ppm assigned to C-9 which shifts to ca. 170 ppm upon dehydration to the thioxanthylum cation <2002BCJ1325>.

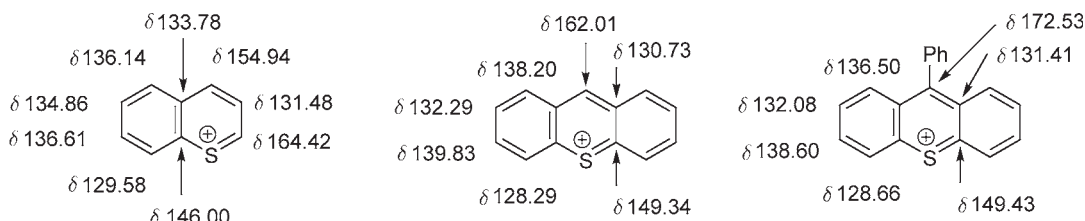


Figure 45 ^{13}C NMR chemical shifts for benzologues of thiopyrylium cations.

7.10.2.2.3(iii) Other nuclei

The equilibrium constant for the ring inversion of 2-(diphenylphosphinoyl)tetrahydrothiopyran has been measured from the integration of the ^{31}P signals in $\text{THF}-d_8$ at temperatures below the coalescence temperature ($\delta^{31}\text{P}$ at room temperature is 30.02). At 183 K the equilibrium constant (K) was calculated to be 0.20 with $\Delta G^\circ_{183\text{K}} = +0.59 \text{ kcal mol}^{-1}$. The difference in chemical shift between the signal for axial and equatorial diphenylphosphinoyl groups in **215** and **216** was 1.8 ppm <1998T1375>.

Cycloaddition of phosphonodithioformates to dienes has provided a fruitful route to 3,6-dihydro-2*H*-thiopyranylphosphonates. Chemical shifts for compounds derived by this methodology <2000TL7327, 2004EJO160> and by other transformations <2002JOC8123> are presented in Figure 46. From these data it would appear that the electronic nature of a geminal substituent has a marginal influence on the chemical shift of the ^{31}P signal.

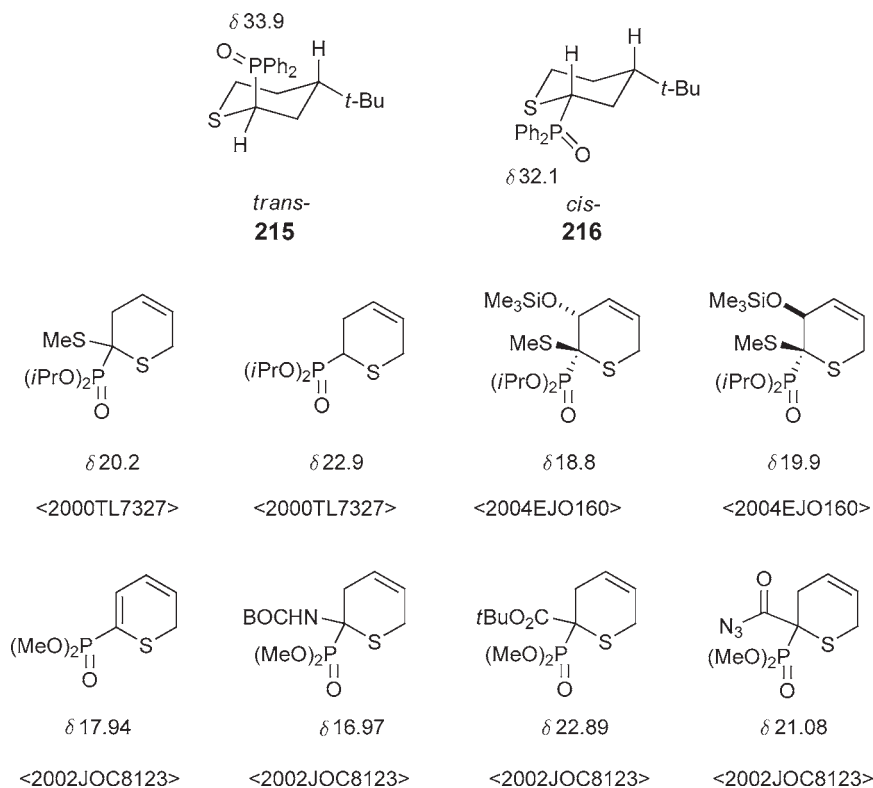
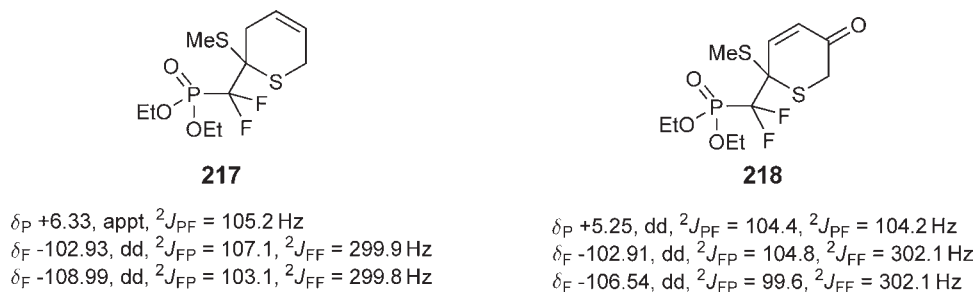
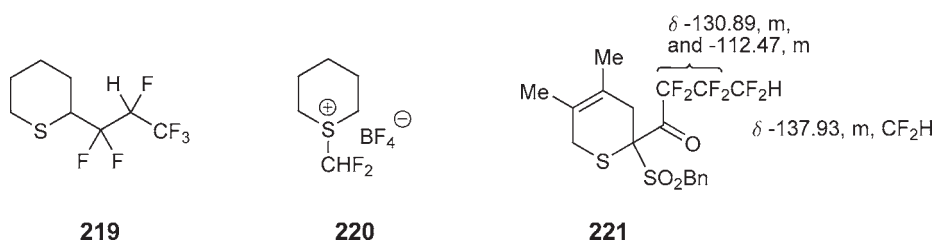


Figure 46 ^{31}P NMR shifts for some 3,6-dihydro-2*H*-thiopyranylphosphonates.

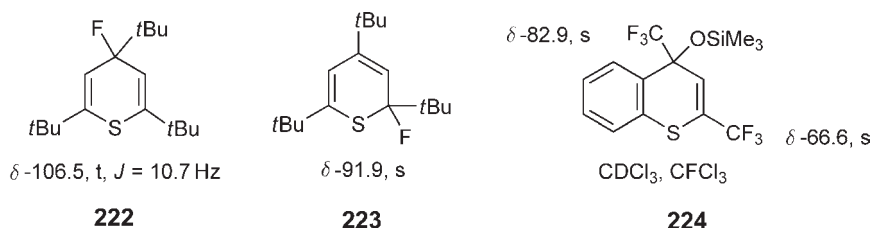
The use of phosphonodifluorodithioacetate as a 2π component in cycloadditions with a variety of dienes provides simultaneous direct access to fluorine and phosphorus containing 3,6-dihydro-2*H*-thiopyrans, for example, **217** and their 3-ones **218**. Complex signals result from the heteronuclear couplings <2002TL2033>.



The 2-perfluoroalkyltetrahydrothiopyran **219** was obtained as a mixture of diastereoisomers by radical perfluoroalkylation of tetrahydrothiopyran, a feature which is reflected in the multiple signals for the fluorine atoms in the ^{19}F NMR spectrum <1996IC6676>. The presence of the *S*-difluoromethyltetrahydrothiopyranium cation **220** in the formation of the *S*-difluoromethylthioalkyl thiopyranium fluoroborates is supported by the presence of a dd at δ -106.4 ($^2J_{\text{FH}}$ = 52.9 Hz, $^1J_{\text{FC}}$ = 270.8 Hz, (CCl_3F)] in the ^{19}F NMR spectrum <1995JFC(73)229>. The chemical shifts (C_6F_6) of the fluoromethylene units in several 2-perfluoroacyl-3,6-dihydro-2*H*-thiopyrans **221** have been assigned <2002JFC(115)175>.



The fluorine signal in 2-fluoro-2*H*-thiopyran appears at δ -104.60, dd J = 54.7 and 3.9 Hz; in 4-fluoro-4*H*-thiopyran at δ -108.29, d J = 53.5 Hz; in 2-fluoro-2*H*-1-benzothiopyran at δ -113.50 dd, J = 53.8 and 4.0 Hz; in 4-fluoro-4*H*-1-benzothiopyran at δ -117.30, d J = 55.2 Hz; in 9-fluoro-9*H*-thioxanthene at δ -137.1, d J = 51.3 Hz and in 9-phenyl-9-fluoro-9*H*-thioxanthene at δ -134.8, s (CFCl₃). Interestingly, the 4-fluorine atom in 2,4,6-tri-*t*-butyl-4*H*-thiopyran **222** couples to H-3 and H-5 with J = 10.7 Hz but appears as a singlet in the 2-fluoro isomer **223** <2003JFC(120)49>. 2,4-Bis(trifluoromethyl)-4-trimethylsilyloxy-4*H*-1-benzothiopyran **224**, obtained by the nucleophilic trifluoromethylation of 2-trifluoromethylthiochromone, gives rise to two signals in its ¹⁹F NMR spectrum; that further upfield is assigned to the 4-CF₃ group <2005JFC(126)779>.



The ¹⁹F NMR spectrum of the cycloadduct from the reaction between 2*H*-thiopyran-2-thione, derived from tetrathiofulvalene by loss of CS₂, and the fluorinated fullerene C₆₀F₁₈ shows only 16 fluorine atoms indicating that the [2+2]-cycloaddition involved the loss of two F atoms. The most upfield signal is associated with the F atoms adjacent to the donor sulfur addend <2003CEJ2008>.

The incorporation of various perfluoroalkyl side chains into sulfur heterocycles has been studied and some ¹⁹F NMR data for 3-perfluoroalkylthiocoumarins have been reported <1994J(P1)101>. ¹⁹F NMR data have been obtained in CF₃COOH for thiochromones bearing a fluorinated function at C-2. A CF₃ unit resonates at ca. 14.5 ppm and a CHF₂ group as a doublet at ca. -34 ppm with J = 55 Hz. The more complex side-chain (CF₂)₂CHF₂ exhibits multiplets at ca. -32, -50, and -57 ppm; the last signal is a double multiplet with J = 51.7 Hz <1994JFC(68)25>. The CF₃ group in 2-trifluoromethylchromone 1,1-dioxide resonates at δ -61.6 (CDCl₃, CFCl₃) and shows ⁴ J_{FH} coupling of 1.0 Hz <2005PS(180)1315>.

The selective replacement of O by S in the series chromone $\rightarrow$ thiochromone thione results in a downfield shift in the signal for the CF₃ group (Figure 47). Coupling between H-3 and the fluorine atoms is only evident for the thiochromone system <2006RCB523>.

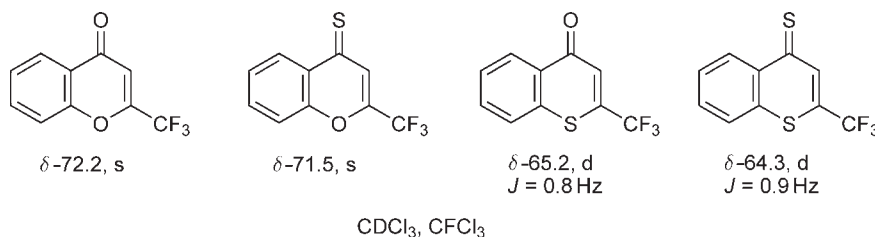


Figure 47 Influence of replacement of O by S in a series of 2-trifluoromethylchromones upon the ¹⁹F NMR chemical shift of the F atoms.

Anodic fluorination of (*E*)-3-arylidene-2,3-dihydrothiochroman-4-ones affords (*E*)-3-arylidene-2-fluoro-2,3-dihydrothiochroman-4-ones as the major products; the fluorine atom resonates in the range -98 to -100 ppm <2001JOC7030>.

A variety of six-membered sulfur heterocycles have been examined by ^{17}O and ^{33}S NMR spectroscopy and these studies have been summarized in the previous editions of *Comprehensive Heterocyclic Chemistry*. The ^{33}S NMR chemical shifts for both conformers of the *S*-methylthiopyranium ion (Figure 48) have been calculated using scaled DFT and EMPI approaches. The conformer with the equatorial methyl group is more stable than the axial conformer by approximately 0.7 kcal mol^{-1} <2004MRC1037>.



Figure 48 Calculated ^{33}S NMR chemical shifts for the *S*-methylthiopyranium ion.

^{17}O Chemical shift data (toluene- d_8) for the sulfoxides and sulfones obtained from the oxidation of 3-arylidene-thiochroman-4-ones using dimethyldioxirane are shown in Table 9 <2003MRC193>.

Table 9 ^{17}O NMR chemical shifts for spiroepoxides derived from 3-benzylidenethiochroman-4-ones

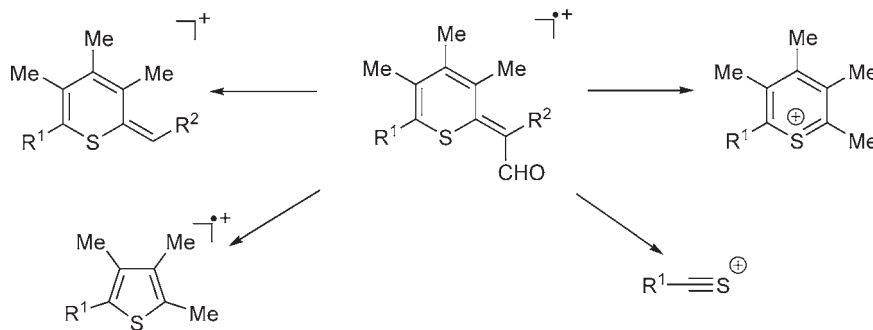
	<i>trans,cis</i>	<i>trans,trans</i>	<i>trans,cis</i>	<i>trans,trans</i>
$\delta\text{S=O}$	55.1	64.2	143.6, 180.9	138.8, 182.8
$\delta\text{ epoxide}$	43.5	64.2	56.7	77.9
$\delta\text{C=O}$	539.2	545.2	545.3	555.5

7.10.2.2.4 Mass spectrometry

Much published mass spectral information either simply gives the value of M^+ as a means of confirming molecular weight or lists the ions resulting from fragmentation without any suggestion of their derivation or attempt at identification. Clearly, such data are of limited value and are not presented here. It is noteworthy that the fragmentation pathways established for the mass spectrometry of six-membered oxygen heterocycles might also operate for the sulfur analogues <1996CHEC-II(5)325>.

2-Alkyl-2*H*-thiopyrans show a relatively weak molecular ion and fragment by loss of the alkyl chain giving a base peak at m/z 97 corresponding to the thiopyrylium cation <2000JFA2420>.

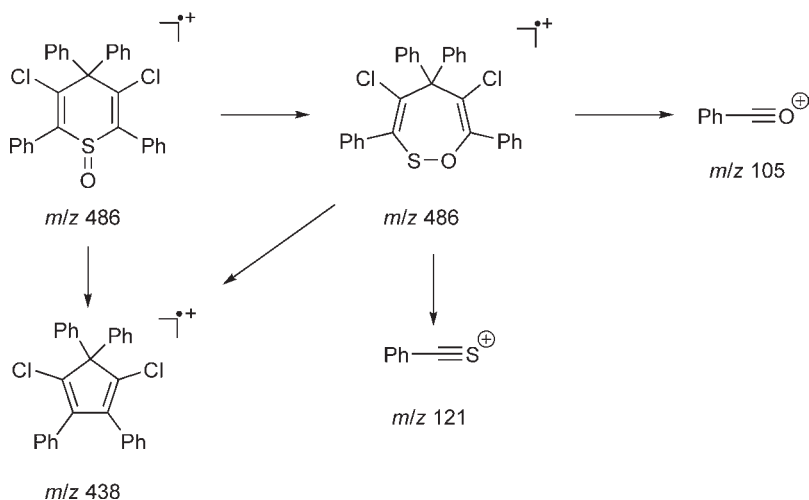
The fragmentation pathway for 2-formylmethylene-2*H*-thiopyrans is shown in Scheme 6. The loss of the formyl group leads to an intense $(\text{M}-29)^+$ ion with other fragments varying with the substituents present <1993SR161>.



Scheme 6

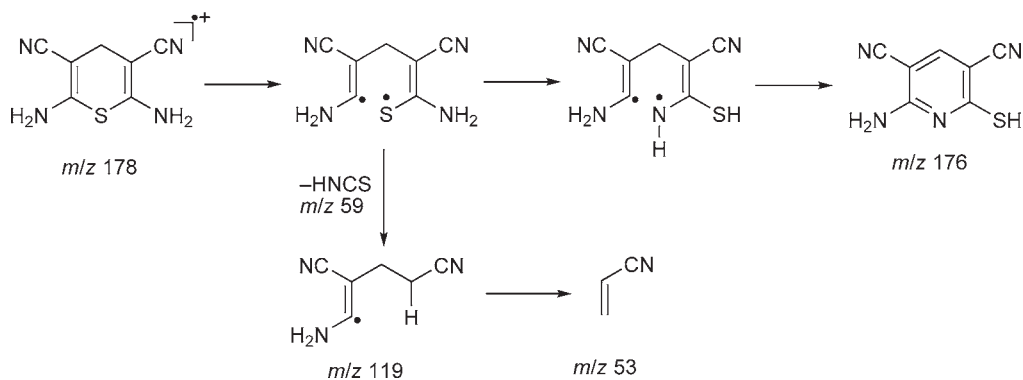
The fragmentation of the molecular ions derived from 2-phenyl-6-(4-trifluoromethylphenyl)-2*H*-thiopyrans that possess a further electron-withdrawing group at C-3, for example, CHO, NO₂, COCH₃, follows a common pathway, with initial loss of the electron-withdrawing substituent to afford the base peak and then loss of the 4-CF₃ substituent; the formation of a thiopyrylium species was not observed <1994JPR434>. The fragmentation patterns of a variety of highly substituted 2*H*- and 4*H*- thiopyrans have been reported; their spectra are dominated by the predictable fragmentation of the pendant functional groups <1995JFC(70)121, 1998RRC163, 1998T15499, 2003T4183, 2004S1633>.

The base peak at m/z 438 in the electron impact MS of 3,5-dichloro-2,4,4,6-tetraphenyl-4*H*-thiopyran 1-oxide is derived from loss of SO from the unobserved molecular ion (Scheme 7). The 2-thiabicyclo[3.2.1]octa-3,6-dienes, which are also formed during the chlorination of the tetraarylthiopyrans, fragment by sequential loss of Cl from the strong molecular ion, followed by loss of the individual aryl groups <1994CCC2269>.



Scheme 7

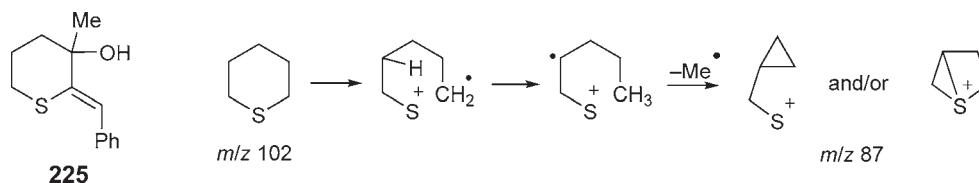
As part of a study of the pyrolysis and photolysis of some 4*H*-thiopyrans, mass spectrometry was used to evaluate fragmentation pathways. The fragmentation pattern of 2,6-diamino-3,5-dicyano-4*H*-thiopyran is representative of the range of compounds evaluated which included some 4-aryl analogues (Scheme 8) <1998RRC163>.



Scheme 8

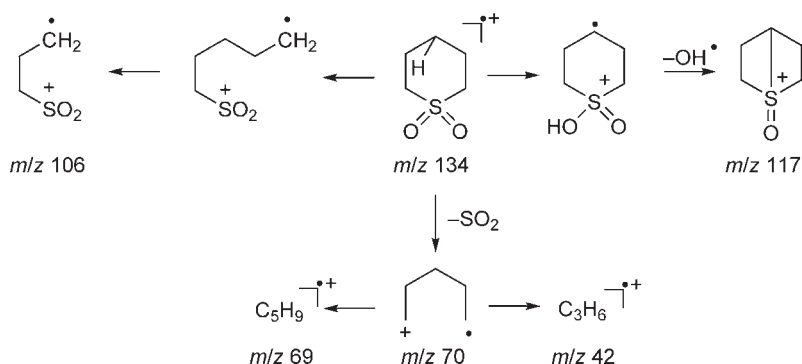
Fragments corresponding to the elimination of water (m/z 202) and ring cleavage (m/z 134) through loss of CH₃(CH₂)₂COCH₃ are prominent in the EI mass spectrum of the 2-benzylidenetetrahydrothiopyran-3-ol **225** in addition to the molecular ion m/z 220 <2000EJO2391>.

The fragmentation pathway for tetrahydrothiopyran is shown in **Scheme 9**. The base peak at m/z 87, marginally more significant than the molecular ion, has been shown by deuterium labeling to arise by loss of an α -methylene unit and a transferred β -hydrogen <B-1971MI236>.



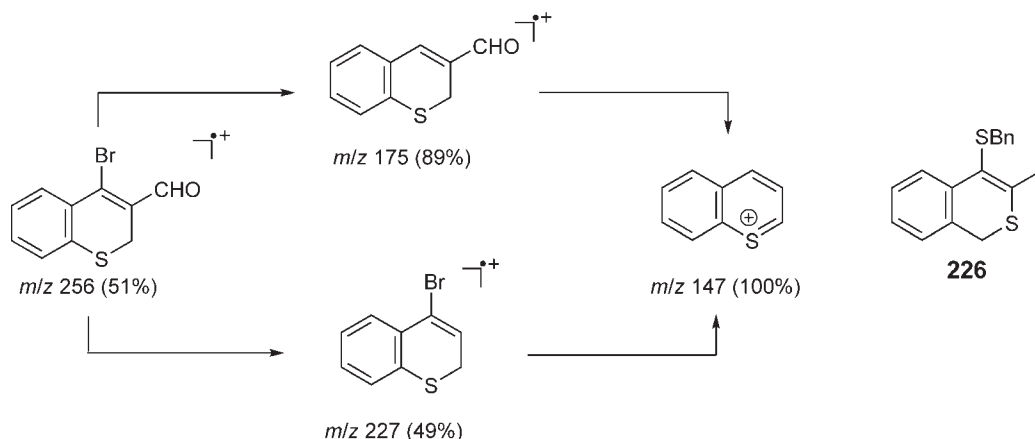
Scheme 9

In a similar manner, the fragmentation of the 1,1-dioxide has been elucidated (**Scheme 10**) <B-1971MI236>. Not surprisingly, the base peak of the three methyltetrahydrothiopyrans is $(M-15)^+$ and the thiadecalins also fragment by loss of alkyl moieties <B-1971MI236>. 2-Cyanotetrahydrothiopyran [molecular ion m/z 127 (100%)] similarly fragments by loss of a methyl group to give m/z 112 (31%) <2006CL98>. However, a different fragmentation pathway operates for 2-phenyltetrahydro-2H-thiopyran (molecular ion m/z 178 (62%), base peak m/z 87) <1997T5563>.



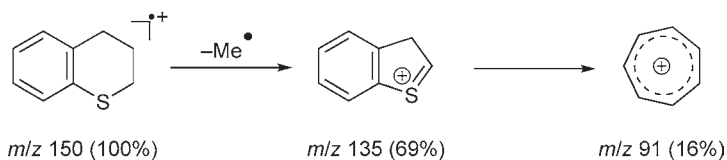
Scheme 10

The EI mass spectrum of 4-bromo-2H-1-benzothiopyran-3-carboxaldehyde indicated the loss of a Br radical and HCO from the molecular ion (m/z 256) to give fragments m/z 175 and m/z 227, respectively (**Scheme 11**). Subsequent eliminations from these mass fragments led to the base peak, m/z 147, which corresponds to the 1-benzothiopyrylium ion <1999CEJ1038>. It is notable that the 1H-2-benzothiopyran **226** with m/z 396 (base peak and molecular ion) fragments via an alternative process and fails to afford the corresponding 2-benzothiopyrylium ion but instead the tropylium ion ($C_7H_7^+$, m/z 91 (59%)) is prominent <1998JOC4626>.



Scheme 11

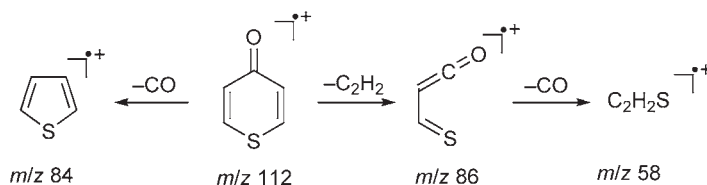
The molecular ion is the base peak in the MS of thiochroman but again the (M-15) ion is significant and the fragment with m/z 91 is likely to be the tropylium cation formed by expulsion of CS (Scheme 12). An alternative fragmentation pathway operates for thiochroman 1-oxide which exhibits the molecular ion, m/z 166 (30%) and a base peak at m/z 149 <2001TA1551>.



Scheme 12

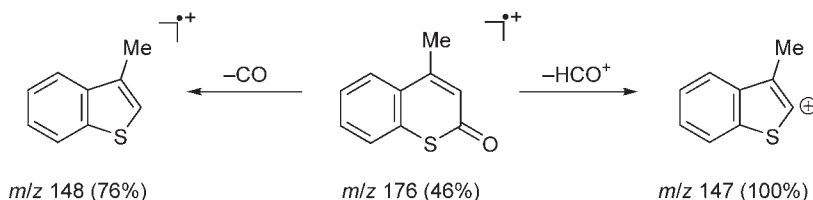
As part of a study to identify the degradation products of sulfur mustard, bis(2-chloroethyl) sulfide, the behavior of various sulfonium salts towards electrospray ionization mass spectrometry has been investigated. Among the compounds studied was *S*-(2-chloroethyl)pentamethylene sulfonium tetrafluoroborate. The ion was readily detected at the 0.01 M level with no ion fragmentation <1997JMP1247>.

Thiopyran-4-one fragments by way of a retro Diels–Alder (rDA) reaction followed by loss of CO. An alternative decomposition involves initial loss of CO which leads to the thiophene radical cation (Scheme 13) <B-1971MI236>.



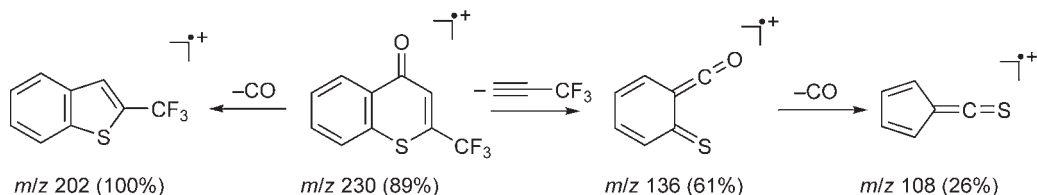
Scheme 13

4-Methylthiocoumarins fragment by either loss of CO (M-28) or protonated CO (M-29) with the latter process leading to the base peak (Scheme 14) <1980BCJ2046>.



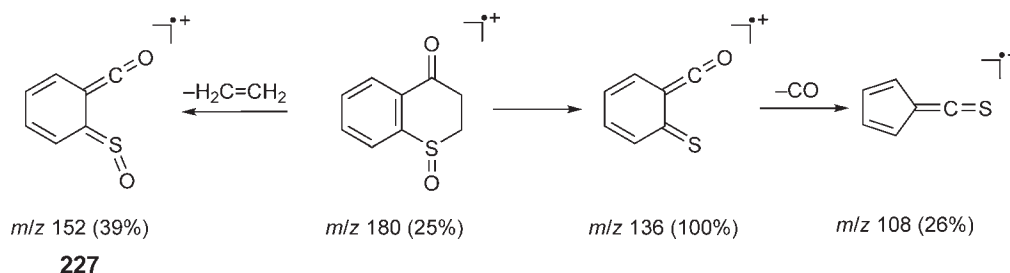
Scheme 14

2-Trifluoromethylthiochromone fragments under EI mass spectrometry (70 eV) by competitive processes involving either an rDA reaction or expulsion of CO (Scheme 15). The CF₃ radical cation fraction (m/z 69 (29%)) fragment was also detected, suggestive of a third pathway. Oxidation of 2-trifluoromethylthiochromone to the 1,1-dioxide has a significant influence on the fragmentation and loss of the CF₃ radical from the molecular ion (m/z 262) is observed <2006RCB523>.



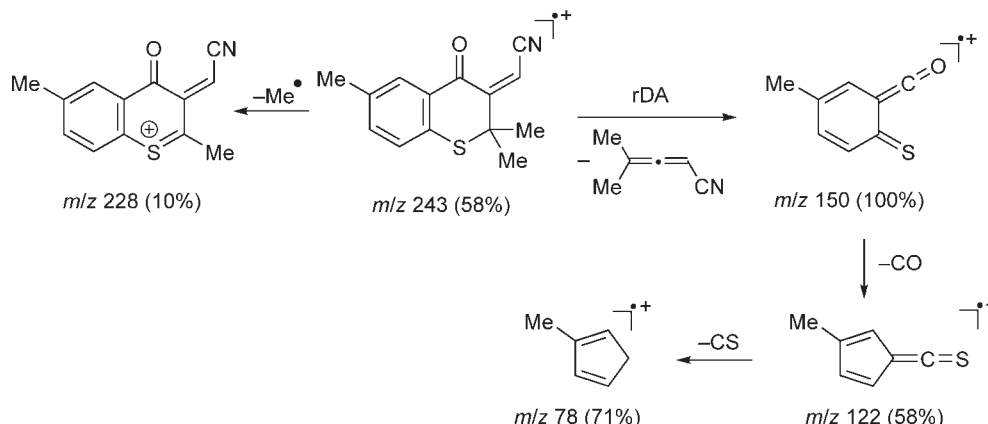
Scheme 15

Thiochroman-4-one 1-oxide also fragments by a rDA reaction though now with the loss of ethene to afford a putative ketene sulfine **227**. It is likely that a second fragmentation pathway of the molecular ion operates to afford the base peak, m/z 136 which subsequently eliminates CO to give m/z 108 (28%) rather than the direct loss of an oxygen atom from **227** (Scheme 16) <2002CH400>.



Scheme 16

The base peak in the electron impact mass spectrum of 3-cyanomethylene-2,2,6-trimethylthiochroman-4-one also arises from an rDA fragmentation of the molecular ion (Scheme 17) <2000J(P1)2930>.

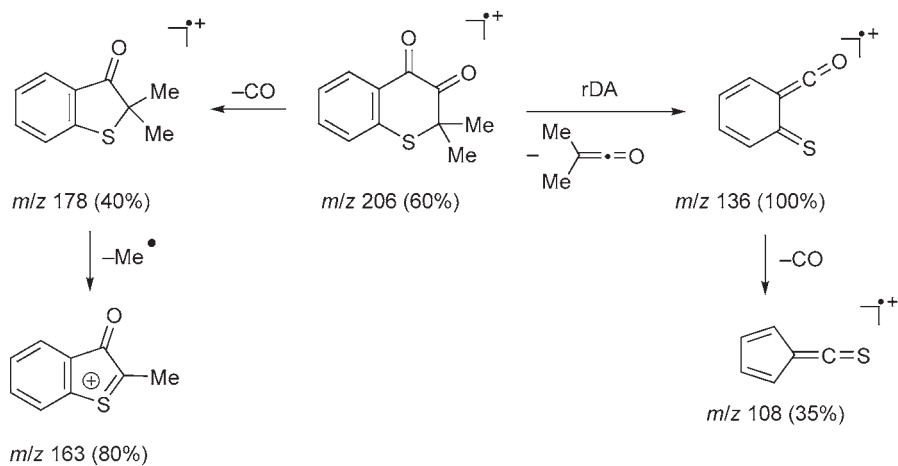


Scheme 17

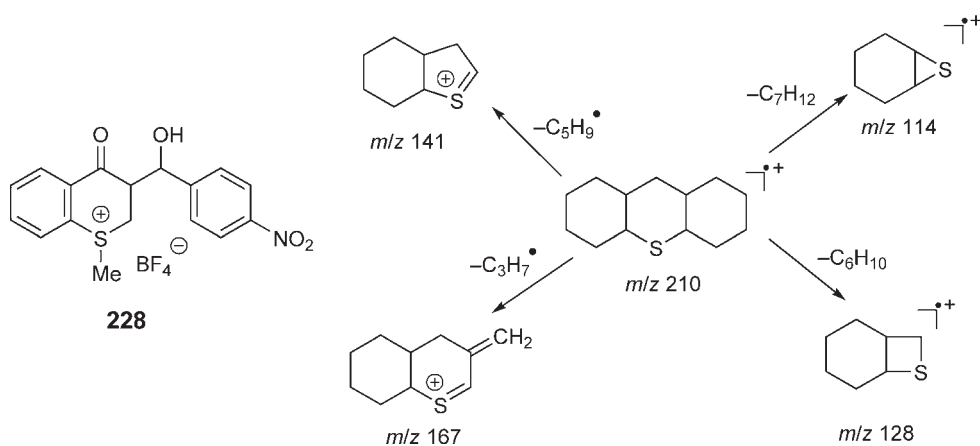
The mass spectrum and the proposed fragmentation pathways for 2,2-dimethylthiochroman-3,4-dione shown in Scheme 18 are typical of this class of compounds. The absence of an (M-15) fragment distinguishes these compounds from the analogous chromandiones <1994T7865>.

No molecular ion was detected in either the EI or FAB spectra of the thiochromanium fluoroborate **228** <2003EJO4852>. The positive ion liquid secondary ion mass spectrum of 9-phenylthioxanthylum ion has been recorded <1997PS(122)287> and 9*H*-thioxanthene displays a molecular ion (m/z 198) which undergoes the expected elimination of a hydrogen radical to give the thioxanthylum ion (m/z 197) as the base peak <B-1971MI236>.

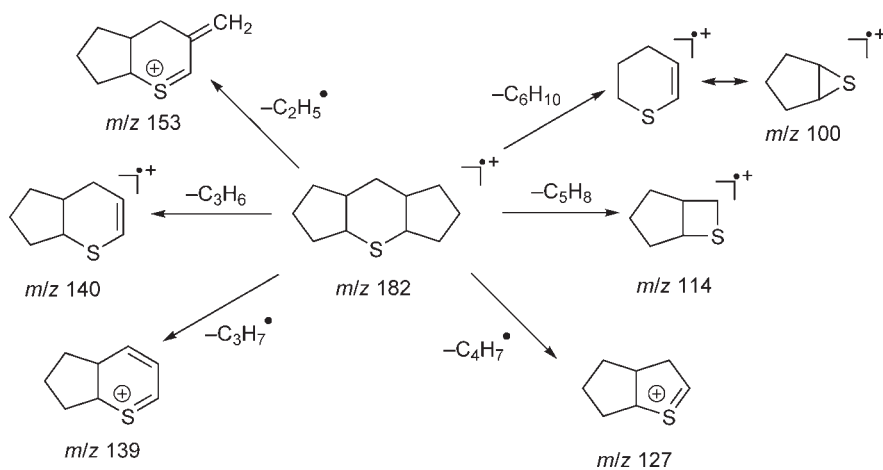
Using combined gas chromatography–mass spectrometry, the six stereoisomers of perhydrothioxanthene have been separated and identified through their different fragmentation behavior under electron impact supported by their ^{13}C NMR spectra. All show a strong molecular ion. Two processes dominate the fragmentation: β -cleavage gives $[\text{M}-\text{C}_3\text{H}_7]^+$ ions and α -cleavage which leads to $[\text{C}_6\text{H}_{10}\text{S}]^+$ and $[\text{C}_7\text{H}_{12}\text{S}]^+$ ions with m/z 114 and 128, respectively. The former ions (m/z 167) are predominant in the MS of *cis*-fused stereoisomers, but the base peak is at m/z 114 for the *trans*-fused isomers. The *cis-trans* isomers are less selective but the m/z 128 ion is quite significant for these. A plausible fragmentation pathway is shown in Scheme 19 <1992J(P2)965>. A similar study of perhydro-4-thia-*s*-indacene has identified six diastereomers and established the stereospecificity of their fragmentation. Fragmentation involves β -cleavage leading to $[\text{M}-\text{C}_2\text{H}_5]^+$ (m/z 153), $[\text{M}-\text{C}_3\text{H}_6]^+$ (m/z 140), and $[\text{M}-\text{C}_3\text{H}_7]^+$ (m/z 139) ions and α -cleavage producing $[\text{M}-\text{C}_5\text{H}_8\text{S}]^+$ (m/z 100) and $[\text{M}-\text{C}_6\text{H}_{10}\text{S}]^+$ (m/z 114), possibly as shown in Scheme 20 <2000J(P2)571>.



Scheme 18



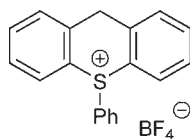
Scheme 19



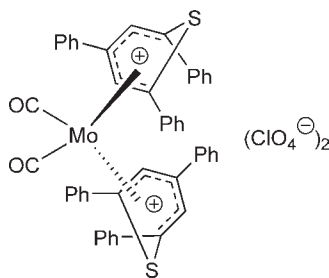
Scheme 20

The reaction of Grignard reagents with thioxanthenes containing electron-releasing groups affords *S*-pixyls which can be detected at the femtomolar level in the positive mode of laser desorption ionization and consequently they have potential as mass tags <2005SL2453>.

The positive ion liquid secondary ion mass spectrometry (LSIMS) of *S*-phenylthioxanthenium fluoroborate **229** shows the intact cation as the base peak and an (*M*+2) peak corresponds to a contribution from a sulfur isotope. Minimal fragmentation is observed but loss of benzene, presumably arising from the loss of the phenyl group after hydrogen transfer, generates an ion at *m/z* 197 and loss of sulfur leads to an ion at *m/z* 165. Peaks at *m/z* 637 and 999 are associated with cluster ions, the former from two cations and one anion (*CAC*⁺) and the other *C*₃*A*₂⁺ <1997PS(122)287>.

**229**

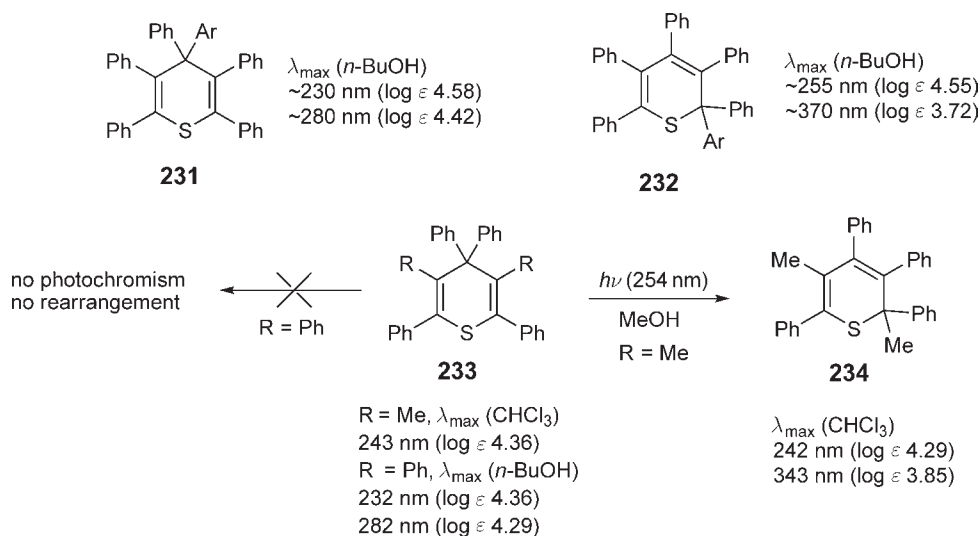
Early studies on the mass spectra of thiopyrylium salts have been reviewed <1994AHC(60)65>. The mass spectrum of the dicationic bis(2,4,6-triphenylthiopyrylium)dicarbonylmolybdenum perchlorate **230** shows a molecular ion with *m/z* 1001. The major fragments, which correspond to the loss of 2Ph, CO and 2ClO₄[−] from *M*⁺, show the favorable formation of an S-containing doubly charged ion as the base peak (*m/z* 310) <1999JOM(584)71>.

*m/z* 1001 (0.70%)**230**

7.10.2.2.5 UV spectroscopy

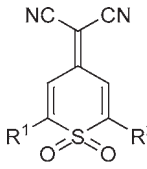
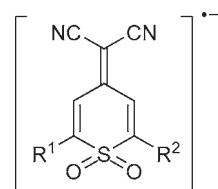
The influence of aryl substitution on the UV-visible spectra and photochromic properties of 4*H*- and 2*H*- thiopyrans has been investigated. In *n*-BuOH, 2,3,4,4,5,6-hexaryl-4*H*-thiopyrans **231** display absorption bands at ca. 230 and 280 nm. In the hexaaryl-2*H*-thiopyrans **232** these absorption bands are shifted bathochromically to 255 and 370 nm. The differences between the UV spectra of 3,5-dimethyl-2,4,4,6-tetraphenyl-4*H*-thiopyran **233**, R = Me, and 2,5-dimethyl-2,3,4,5-tetraphenyl-2*H*-thiopyran **234** are more striking, with the former exhibiting a single band at ca. 240 nm (CHCl₃) and the latter an additional long wavelength band at ca. 340 nm. It is noteworthy that the presence of phenyl groups at both the 3- and 5-positions inhibits both solid state photochromism and the photochemical rearrangement to the 2*H*-thiopyran in solution. However, the 3,5-dimethyl-4*H*-thiopyran is photo-active, exhibiting solid state photochromism with the reversible development of maroon crystals (reflectance λ_{max} 530–550 nm) and photo-rearranging to the 2,5-dimethyl-2,3,4,6-tetraphenyl-2*H*-thiopyran (Scheme 21) <1996JPH(101)33>.

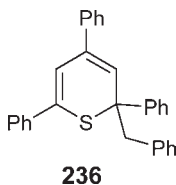
The one-electron reduction of a series of 4-dicyanomethylidene-4*H*-thiopyran 1,1-dioxides **235** generates an anion radical and these are sufficiently stable for their UV spectra to be measured. A second electron is accepted at higher potentials, producing the less stable sulfone dianions (Table 10) <1995JOC1674>.



Scheme 21

Table 10 Absorption spectra for sulfones **235** and their one-electron reduction products

 235					
<i>R</i> ¹	<i>R</i> ²	Sulfone 235 $\lambda_{\max}$ nm, (log ϵ) MeCN	Reduction product $\lambda_{\max}$ nm, (log ϵ) MeCN	<i>E</i> ^o (V) vs. SCE ^a	<i>t</i> _{1/2} (min) ^b MeCN
Ph	Ph	371 (4.45)	603 (sh, 4.15), 556 (4.25), 303 (4.29)	−0.203	825
H	H	309 (4.38)	615 (2.6), 460 (3.0), 295 (3.85), 235 (3.88)	−0.215	
<i>t</i> -Bu	<i>t</i> -Bu	319 (4.44)	550 (3.99), 506 (3.96), 366 (4.04), 320 (4.04)	−0.394	480
Ph	<i>t</i> -Bu	333 (4.43)	560 (sh 4.20), 528 (4.28), 307 (4.17)	−0.288	1750
2-Thienyl	2-Thienyl	420 (4.44)	612 (4.13), 595 (sh 4.11), 510 (3.99), 436 (4.09), 318 (4.19)	−0.171	1240

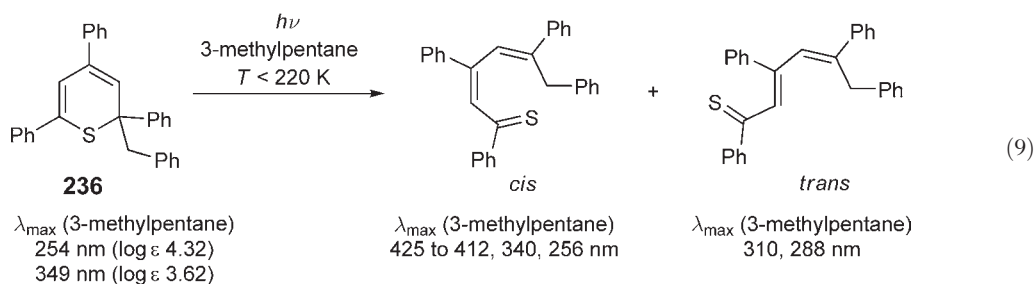
^aReduction potential.^bHalf life.

2-Benzyl-2,4,6-triphenyl-2*H*-thiopyran **236** shows two absorption peaks in the UV which are only marginally influenced by the polarity of the solvent, typical of π, π^* transitions, and which are in general agreement with those calculated using INDO/1-C1 for geometry optimized at the MNDO level (Table 11a).

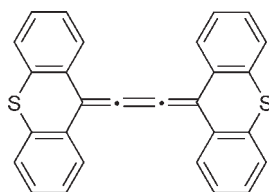
Laser flash photolysis at 347 nm generates a transient colored species ($\lambda_{\max}$ 325 and 405 nm) with a lifetime of 435 μ s in 3-methylpentane (3MP). Steady state UV irradiation at low temperature cleaves the S-C(2) bond and the merocyanine so produced absorbs at 425 nm, shifting to 412 nm on prolonged irradiation, with additional bands at 340 and 256 nm. Both thermal and photo-bleaching occurs but the original spectrum is not restored. It is suggested that the first photoproduct is the *cis* isomer which is converted in part to the *trans* isomer (Equation 9) <2006JPH(177)34>.

Table 11a Experimental and calculated spectral characteristics for **236** (f = oscillator strength)

<i>Experimental (at RT)</i>				<i>Calculated</i>		
<i>3MP</i>		<i>EtOH</i>		<i>Transition</i>	$\lambda_{\max}$ (nm)	f
$\lambda_{\max}$ (nm)	$\epsilon_{\max}$ ($\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$)	$\lambda_{\max}$ (nm)	$\epsilon_{\max}$ ($\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$)			
349	4200	346	4300	$S_0 \rightarrow S_1$	320	0.56
				$S_0 \rightarrow S_6$	273	0.45
254	21000	254	21300	$S_0 \rightarrow S_7$	253	0.37



A thiochroman-fused fullerene shows an absorption band at 441 nm in hexane which is characteristic of a 1:1 cycloadduct of C_{60} . It is shifted to 435 nm in the derived sulfoxide <1995TL6899>. The bands associated with 1,2-bis(thioxanthen-9-ylidene)ethene **237** are red shifted by 40–70 nm in its 1:1 complex with C_{60} in keeping with the interaction between the π -systems of the component parts. The IR spectrum is essentially a combination of the spectra of the two individual molecules. In the crystal, layers of C_{60} alternate with layers of the alkene <2005MI711>.

**237**

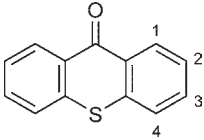
The UV absorption spectrum (MeCN) of 7-methyl-1*H*-2-benzothiopyran-1-one displays a single intense band at ~ 235 nm, whereas the oxygen analogue possesses slightly less intense bands at ~ 230 and 250 nm <2000T6763> and substituted 4-methyl-2*H*-1-benzopyran-2-ones display two sharp intense absorption bands at ca. 235 and 241 nm <1980BCJ2046>. 2-Perfluoroalkylthiochromones exhibit a sharp absorption band ($\log \epsilon$ 3.9–4.0) at ~ 340 –360 nm, shifted bathochromically relative to the analogous perfluoroalkylchromones (298–331 nm, $\log \epsilon$ 3.8–4.0) <1994JFC(68)25>.

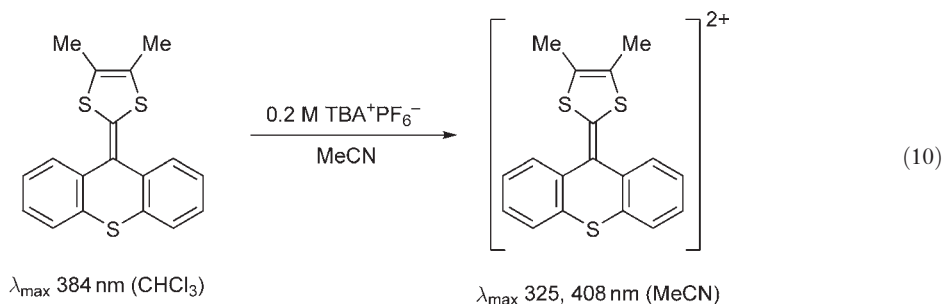
The absorption and emission spectra of thioxanthone have been recorded in a variety of protic and nonprotic solvents. Increased singlet lifetimes, fluorescence quantum yields, and red shifts in the emission spectra are noted in polar solvents (Table 11b) <2006MI597>. Similar observations follow the incorporation of electron-releasing groups at the 2-position <1997JCF1517>.

The changes in the triplet–triplet absorption spectra of thioxanthone in solvents of different polarity facilitate a study of its behavior as a guest molecule in β -cyclodextrins. In particular, the effects of structural changes to the host molecule on the complexation efficiency and dynamics have been found to be very similar to those of xanthone <2001PCB2122>.

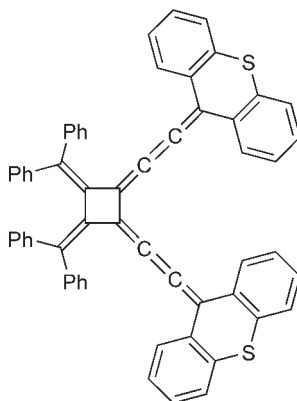
Changes are observed in the UV-visible absorption spectrum of 9-(4,5-dimethyl-1,3-dithiol-2-ylidene)thioxanthene during electrochemical oxidation. The absorption of the neutral molecule at 384 nm gradually decreases as oxidation to the dication occurs and new peaks appear at 325 and 408 nm (Equation 10). The oxidation potential for the single two-electron process as derived by cyclic voltametry is +0.23 V <2006CEJ3389>.

Table 11b Absorption spectra and singlet lifetimes for some thioxanthenes

			
		<i>Lifetimes (25°C)</i>	
<i>Substituent</i>	$\lambda_{\max}$ (MeCN), nm	<i>Singlet</i> (MeCN), ns	<i>Singlet</i> (MeOH), ns
H	407	0.13	2.59
2-O(CH ₂) ₂ CH ₃	438	1.74 (10%), 5.09 (90%)	1.02 (3%), 11.06 (97%)
4-O(CH ₂) ₂ CH ₃	438	1.01	7.80



The dark green thioxanthene-containing [4]radialene **238** exhibits several strong absorptions in the visible region, with the lowest-energy band appearing in the near IR, indicative of efficient conjugation of the π system and twisting of the cumulenenic bond ($\lambda_{\max}$ 754 nm, ($\log \epsilon$ 4.47), 498 (4.72), 434 (4.76)) [<2005BCJ2188>](#).

**238**

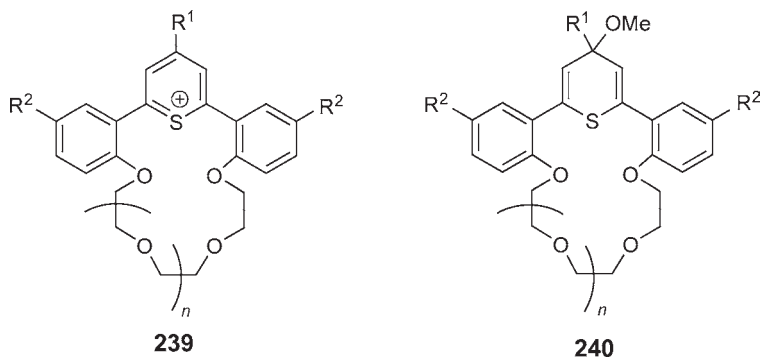
Discussion of the optical spectra of thiopyrylium salts has featured in a review [<1994AHC\(60\)65>](#). The UV spectrum (MeCN) of 2,4,6-triphenylthiopyrylium fluoroborate is characterized by the presence of relatively intense bands at 402 nm ($\log \epsilon$ 4.29), 370 nm ($\log \epsilon$ 4.36) and 272 nm ($\log \epsilon$ 4.46); the presence of electron-withdrawing substituents (CF₃, Cl) in *meta* or *para* positions results in small bathochromic shifts in the long-wavelength band [<1996J\(P2\)307>](#).

Thiopyrylium salts not only absorb in the visible region but also exhibit considerable fluorescence emission such that they have value as photosensitizers. The fluorescence properties of several thiopyrylium salts have been studied and are collated in [Table 12](#). Although the fluorescence ($\lambda_{\max}$) is red-shifted by 30–60 nm compared with the corresponding pyrylium salts, the quantum yields (ϕ_f) are appreciably lower, attributed to the higher efficiency of the forbidden singlet–triplet transition because intersystem crossing is efficient [<1995BCJ2791>](#).

Table 12 Excitation wavelength, fluorescence maxima and quantum yield of some thiopyrylium fluoroborates in MeCN at 25 °C

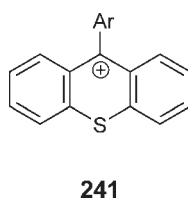
R^1	R^2	λ_{ex} (nm)	λ_{max} (nm)	Φ_f
Ph	Ph	420	502	0.05
4-ClC ₆ H ₄	Ph	380	520	0.04
4-BrC ₆ H ₄	Ph	380	528	0.03
4-MeOC ₆ H ₄	Ph	460	605	0.10
4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	420	600	0.10

Corands containing a thiopyrylium unit **239** show only a weak binding ability toward alkali metal ions although binding increases in basic solution when the neutral 4*H*-thiopyran **240** is formed. The size of the crown ether has little effect on the absorption spectra (Table 13) <1996T3509>.

**Table 13** UV-visible spectroscopic data for thiopyrylium derived corands **239** and their methanol adducts **240**

	R^1	R^2	n	λ_{max} /nm (log ϵ) in MeOH
239	H	Me	2	454 (4.06), 358 (3.81), 310 (3.84), 245 (4.31)
239	H	Me	3	460 (4.07), 358 (3.69), 307 (3.84), 244 (4.32)
240	H	Me	2	287 (3.91), 240 sh.
240	H	Me	3	289 (3.94), 240 sh.

The UV spectra of a range of 9-arylthioxanthylum salts **241** have been recorded and the influence of the substituents on the 9-phenyl ring on λ_{max} has been correlated with the HOMO and LUMO levels estimated from the redox potentials <2002BCJ1325>.



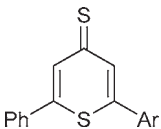
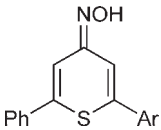
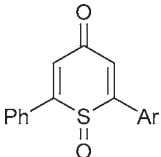
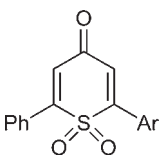
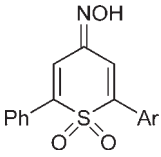
7.10.2.2.6 Infrared and Raman spectroscopy

There are few papers devoted to the detailed analysis of infrared spectra of six-membered sulfur containing ring systems. The majority of infrared spectroscopic data feature in the experimental section of papers concerned with either synthesis or reactivity of the ring system, and in these papers usually only IR bands associated with multiple bond ($C=C$, $C=S$, SO , and SO_2) stretching modes are assigned.

Carbonyl stretching bands appear in the typical range $ca. 1690\text{--}1730\text{ cm}^{-1}$ in the tetrahydrothiopyranones and are shifted to lower frequency as conjugation is increased such that the CO stretch in thioxanones can appear below 1600 cm^{-1} and, in thiochromones, fall between these extremes at $ca. 1640\text{ cm}^{-1}$. The $C=O$ stretching band appears at 1589 cm^{-1} (KBr) in 3,6-bis(dimethylamino)-9*H*-thioxanthone <2005OM3807>. The carbonyl stretching band appears in the range $1625\text{--}1650\text{ cm}^{-1}$ for substituted 4-methylthiocoumarins <1980BCJ2046> and is relatively uninfluenced by the presence of a 3-perfluoroalkyl group <1994J(P1)101>.

Infrared stretching frequencies for a range of 2-aryl-6-phenyl-4*H*-thiopyran-4-ones, -thiones, and oximes and some related 1-oxides and 1,1-dioxides have been reported (Table 14) <1993PS(81)101>.

Table 14 Selected IR stretching frequency bands (cm^{-1}) for some 4-substituted 4*H*-thiopyrans

	$C=S$	$C=N$	$C=O$	$S=O$	$O=S=O$
	1059–1138				
		1610–1624			
			1625–1645	1036–1060	
			1632–1665		1136–1145 1310–1322 1325–1340
		1622–1635			1132–1140 1300–1310 1328–1332

The $C=O$ stretching band is at lower wave number in the 2-perfluoroalkylthiochromones ($1610\text{--}1630\text{ cm}^{-1}$) than in the chromone analogues ($1650\text{--}1675\text{ cm}^{-1}$) <1994JFC(68)25>.

Insulating the $C=O$ group from the aromatic ring, for example, in thiochroman-3-ones, results in an increase in the wave number of the band which now appears at $1711\text{--}1723\text{ cm}^{-1}$ (neat) rather than the typical $1660\text{--}1670\text{ cm}^{-1}$ (KBr)

associated with the thiochroman-4-ones <1982CJC243>. A nice contrast between the stretching frequencies of conjugated and nonconjugated C=O groups in different environments is provided by the thiochroman-3,4-diones where 3-C=O appears at $1719\text{--}23\text{ cm}^{-1}$ and the 4-C=O at $1677\text{--}79\text{ cm}^{-1}$ <1994T7865>. The 4-C=O band appears in the range $1668\text{--}1673\text{ cm}^{-1}$ (neat) for a range of 2,2-disubstituted 3-methylenethiochroman-4-ones <1999JOC9646>.

The C=O stretching band appears at 1700 cm^{-1} (Nujol) for 1-ethyl-2,3-dihydro-6,7-dimethoxy-4-oxothiopyranium fluoroborate; there is at present insufficient information for this class of compounds to determine whether the shift is brought about by the influence of the S^+ atom or substituents in the aromatic ring <1998T5599>.

The C=S band is not particularly strong and is rarely assigned in thiocarbonyl analogues. There is little unusual about the S=O stretching band in thiopyran sulfoxides and values appear in the expected range $1030\text{--}1070\text{ cm}^{-1}$. Sulfones show characteristic stretching bands at ca. $1120\text{--}1160$ and $1300\text{--}1350\text{ cm}^{-1}$.

The far infrared spectrum of 3,4-dihydro-2*H*-thiopyran exhibits absorptions for ring-bending and single bond ring-twisting modes in the regions $100\text{--}125$ and $270\text{--}280\text{ cm}^{-1}$, respectively. The detailed study, in which a two-dimensional potential energy surface is derived, attributes the high barrier to planarity and the low bending energy to the low force constant for the C–S–C angle bending <1995JCP9506>. In comparison, the barrier to bending in 3,6-dihydro-2*H*-thiopyran is larger but that to planarity is smaller <1989JCP2771>.

The infrared stretching bands of a selection of thiopyrans and thiopyranones and some benzologues are documented in Figures 49 and 50. The 2,4,4,6-tetraaryl-4*H*-thiopyran ring is associated with bands in the $1583\text{--}1614\text{ cm}^{-1}$ region <1998CCC662>. Noteworthy is the shift to lower wave number for the SO stretching band in the *trans*-2,4,6-triphenylsubstituted 4*H*-thiopyran 1-oxides <2006T2603>.

An absorption at 527 cm^{-1} is observed in the 1:1 cycloadduct of thiochroman and C_{60} and in the derived sulfoxide and sulfone for which the S=O stretch is at 1051 and 1161 cm^{-1} , respectively <1995TL6899>.

Characteristic bands are observed for the carbonyl group at $1660\text{--}1670\text{ cm}^{-1}$, the alkenic double bond at $1588\text{--}1604\text{ cm}^{-1}$, and the sulfoxide function at $1042\text{--}1050\text{ cm}^{-1}$ in 3-arylidene-thiochroman-4-one sulfoxides. The corresponding sulfones show similar absorptions for the C=O and C=C bonds and the SO_2 bands are seen at $1148\text{--}1154$ and $1310\text{--}1318\text{ cm}^{-1}$ <1994T13113>.

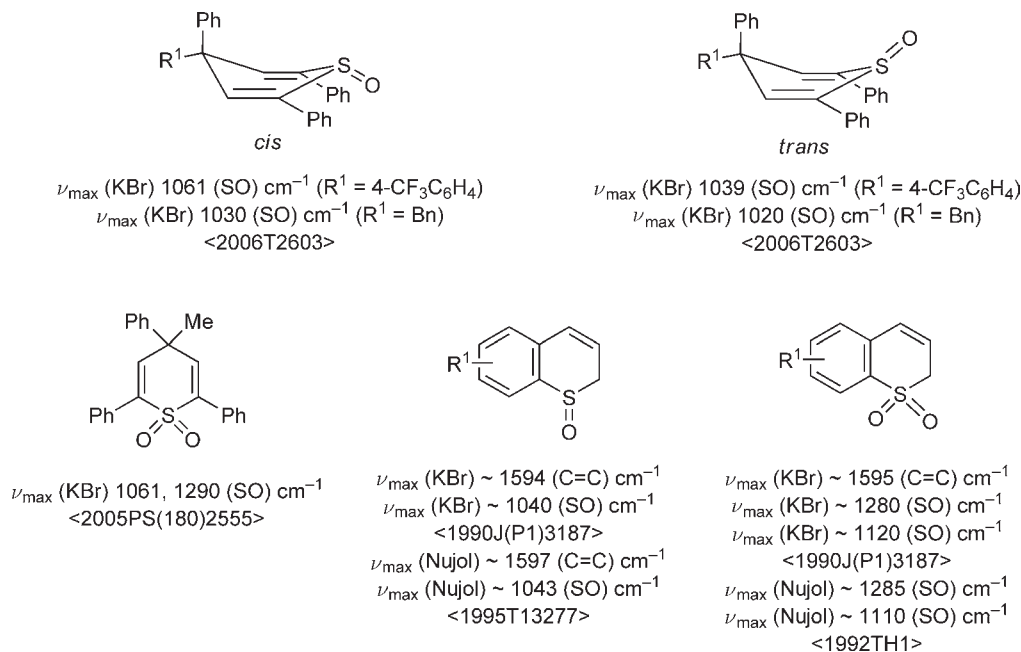


Figure 49 Infrared stretching bands for some thiopyrans and their benzologues.

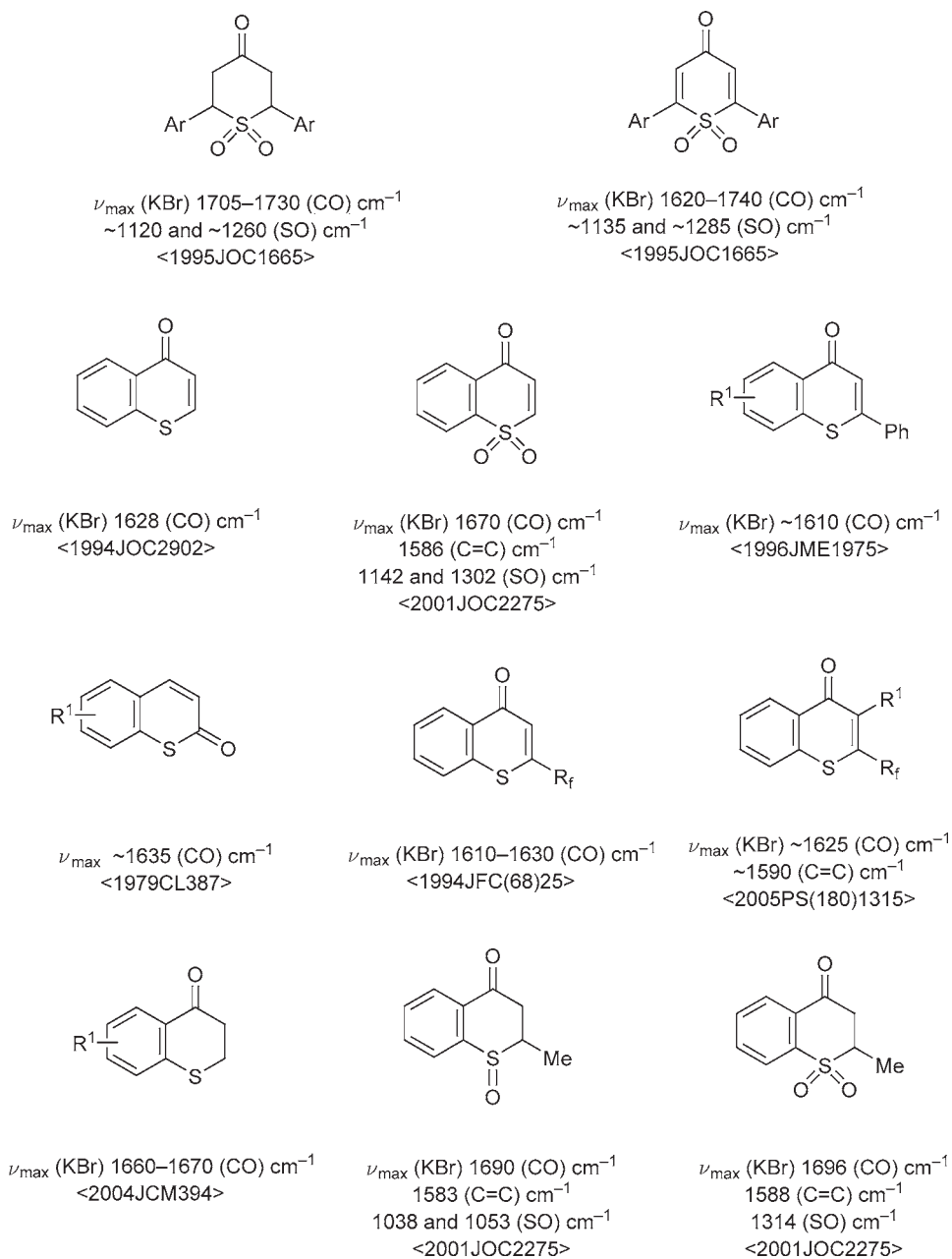


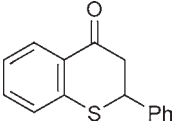
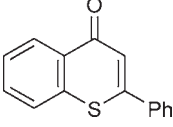
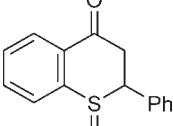
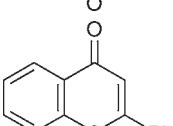
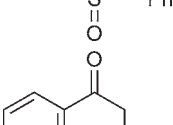
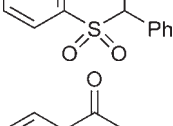
Figure 50 Infrared stretching bands for some thiopyranones and their benzologues.

Data for a thioflavanone <1995SC1495> and thioflavone <1996JME1975> and their 1-oxides and 1,1-dioxides are presented in **Table 15**; the C=O stretching band is more significantly influenced by conjugation rather than by the oxidation state of the heteroatom <2001JOC2275>.

7.10.2.2.7 Photoelectron spectroscopy

The lone-pair orbital ionization potential of tetrahydrothiopyran, measured by photoelectron spectroscopy, is 8.45 eV which is 1.05 eV less than that of tetrahydropyran <1972JA5599>.

Table 15 Selected infrared stretching bands (KBr), cm^{-1} for thioflavones and thioflavanones

	$\text{C}=\text{O}$	$\text{C}=\text{C}$	$\text{S}=\text{O}$	$\text{O}=\text{S}=\text{O}$
	1673			
	1610			
	1692		1030, 1052	
	1650	1584	1042	
	1694			1124, 1310
	1652	1588		1152, 1294

The He^1 photoelectron spectra of the four thiopyranylidene derivatives **242**, **243**, **244**, **245**, for which *anti* and *syn* conformers are present, have been measured (**Figure 51**). In **242** and **243**, the bands below 9 eV are assigned to ionizations from the π orbital and from the $3p$ sulfur lone pair ($\text{Lp}_\pi(\text{S})$) orbital; the spectra of **244** and **245** are more complex. For **242** and **245**, splitting of the $\text{Lp}_\pi(\text{S})$ bands indicate that σ – π interactions operate over distances of 8 and 12 nm between the terminal S atoms. The experimental data are supported by RHF/6-31G* calculations <2000JOC4584, 2006AGE2540>. Both tetrahydrothiopyran and these *S*-end-capped thiopyranylidenes form self-assembled monolayers on Au(III) substrates <2005L10497>.

The He^1 photoelectron spectra of thioxanthone have been measured and the four ionization energies of 8.04, 9.12, 9.34, and 10.87 eV compare favorably with the orbital energies calculated by the MINDO/3 method <1996JEO71>.

7.10.2.2.8 Electron spin resonance spectroscopy

The ESR spectra of the anion radicals **246** derived from a series of 4-dicyanomethylidene-4*H*-thiopyran sulfones show clearly resolved hyperfine structure centred around g values of ca. 2000. Large nitrogen splitting of 1.0–1.5 mT and H-3 and H-5 splitting of 0.3–0.93 mT are observed <1995JOC1674>.

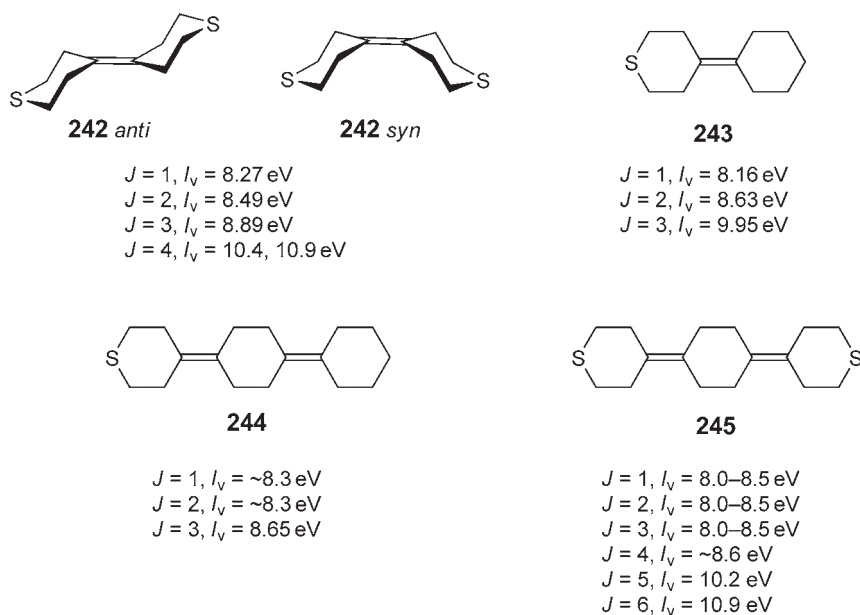
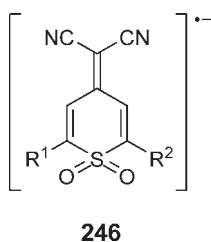
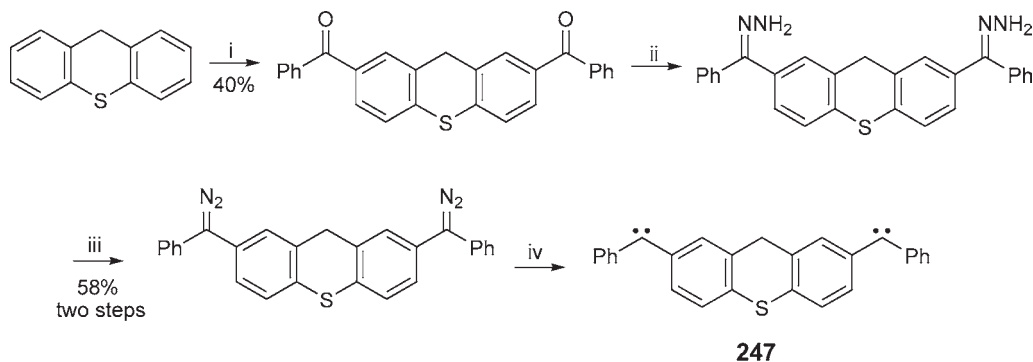


Figure 51 Vertical ionization energies (I_v) for bands (J) determined by photoelectron spectroscopy for thiopyranylidene derivatives **242–245**.



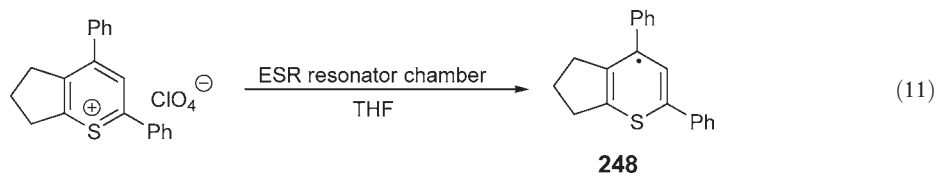
The ESR spectrum of the dicarbene **247** derived by photolysis of 2,7-bis(α -diazobenzyl)-thioxanthene has been measured. The three sets of signals correspond to an isolated triplet, a thermally populated triplet and a quintet species which is associated with interaction through the sulfur. The exchange interaction through the methylene bridge was estimated to be very small by comparison with data measured for carbenes derived from related diphenylsulfides (Scheme 22) <1997JA8058>.



i, PhCOCl, PhNO₂; ii, N₂H₄, N₂H₄•HCl, DMSO; iii, BaMnO₄, CH₂Cl₂; iv, 2-methyltetrahydrofuran, 9 K, $\lambda > 420 \text{ nm}$, 60–150 min

Scheme 22

The ESR spectrum of the 2,4-diphenylcyclopenta[*b*]thiopyranyl radical **248** is a 1:2:1 triplet attributed to interaction between the unpaired electron and the magnetic nuclei of the protons at the 7-position. Further splitting is associated with interaction with the phenyl rings (Equation 11) <2003MI1287>.



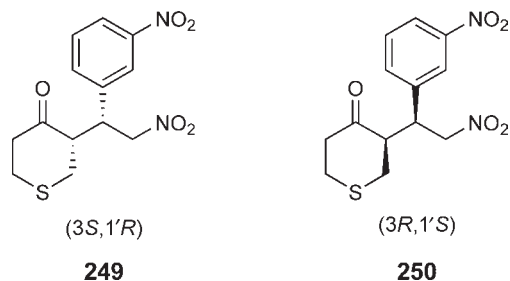
7.10.2.3 Thermodynamic Aspects

A report on the ideal gas thermodynamic properties of sulfur heterocyclic compounds lists data on tetrahydrothiopyran and 5,6-dihydrothiopyran <1995MI1351>.

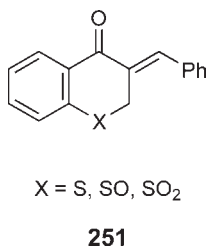
7.10.2.3.1 Chromatography

The solubilities of thioxanthone and three 1-hydroxythioxanthone derivatives in supercritical CO₂ have been determined over a wide range of temperature and pressure and found to correlate well with those derived from a semiempirical model. The solubilities decrease in order of their increasing melting points but increase with increasing pressure. The influence of temperature is variable <2003CED1088>.

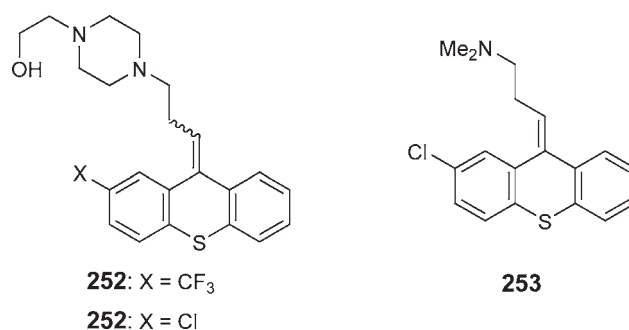
The resolution of 3,4-dihydro-2*H*-1-benzothiopyran-4-one 1-oxide has been achieved by capillary electrophoresis using heptakis-6-sulfato- β -cyclodextrin or, better, its 2,3-diacetyl derivative as the chiral selector; the *R*-sulfoxide migrated before the *S*-enantiomer <2001JSS766>. It has also been noted that (*R*)-thiochroman 1-oxide is eluted before the (*S*)-enantiomer from a Chiralcel cellulose tribenzoate column <2001TA1551> and a Daicel Chiralpak AD-H column using hexane/*i*-PrOH 90:10 has been used to resolve the (3*S*,1'*R*) **249** and (3*R*,1'*S*) **250** enantiomers of the substituted tetrahydrothiopyran-4-one <2005OBC84>.



The lipophilicities of (*E*)-3-benzylidenethiochroman-4-one **251** and its 1-oxide, 1,1-dioxide, and the 2-phenyl derivative have been determined by reverse phase HPLC and a good linear correlation with calculated values is observed. The stronger polarizability of the sulfinyl and sulfonyl compounds results in decreased retention time, but the thioflavanone has the greatest lipophilicity <2005JCH(819)283>.



The efficient separation of the geometrical isomers of clopenthixol **252**, X=Cl, flupenthixol **252**, X=CF₃, and chlorprothixene **253** has been accomplished using calixarene- and resorcinarene-bonded stationary phases in high-performance liquid chromatography <2002JCH(948)309> and in nonaqueous capillary electrophoresis <2003ELP1648>.



The stereoisomers of perhydrothioxanthene have been resolved on graphitized thermal carbon black and structures assigned on the basis of their mass spectral fragmentation patterns and their ¹³C NMR spectra. The structures are shown in [Table 16](#) together with the relative amounts present in the mixture obtained by the Pd-catalyzed hydrogenation of *sym*-octahydrothioxanthene [<1992J\(P2\)965>](#). In like manner, five of the six stereoisomers of perhydro-4-thia-*s*-indacene ([Table 17](#)) have been separated and characterized. Additionally, their thermodynamic adsorption characteristics [adsorption equilibrium constant (Henry constant) *K*₁] and their relative energies ($-\Delta U_1$) have been calculated based on optimized hypothetical molecular structures [<2000J\(P2\)571>](#).

Table 16 Stereoisomers of perhydrothioxanthene

Isomer	Structure	Percentage in mixture
<i>trans-syn-trans</i>		0.5
<i>trans-anti-cis</i>		4.7
<i>trans-anti-trans</i>		0.06
<i>trans-syn-cis</i>		7.2
<i>cis-syn-cis</i>		85.2
<i>cis-anti-cis</i>		2.3

7.10.2.3.2 Aromaticity

Aromaticity indices for 4*H*-thiopyran, thiopyran-4-one, and the related imine and methylene compounds are listed in [Table 18](#) [<1997JST\(412\)115>](#).

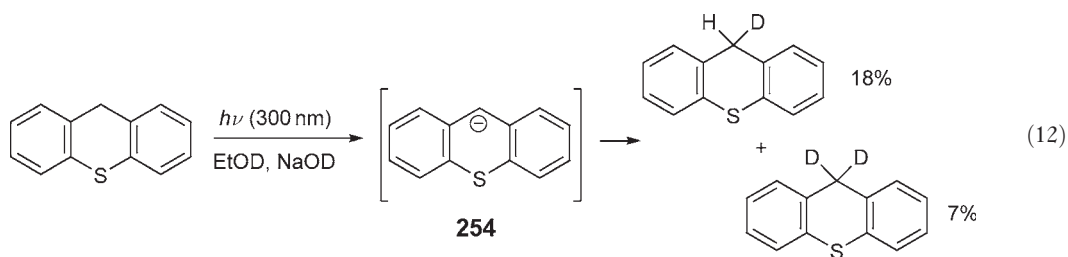
Generation of the ground-state antiaromatic 8π thioxanthenide anion **254** has been achieved both by excited state C-H bond deprotonation and by photolytic decarboxylation ([Equations 12 and 13](#)), although it is not as readily produced as the isoelectronic dibenzosuberonyl anion [<1998JPH\(113\)53>](#). The photochemically generated ylides **255** derived from *S*-methyl and *S*-phenyl thioxanthenium salts in MeCN are particularly stable and are formal carbanions with eight cyclically delocalized π electrons ([Equation 14](#)) [<1997CC709>](#).

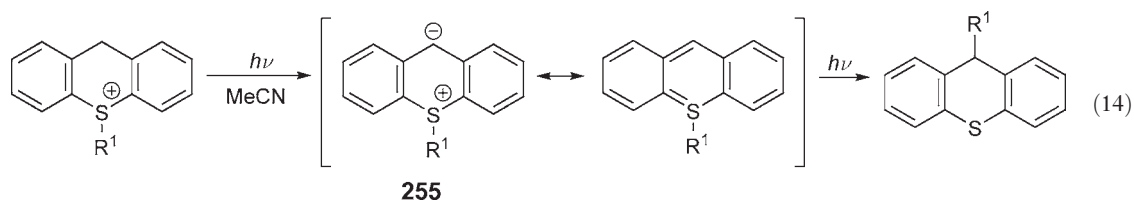
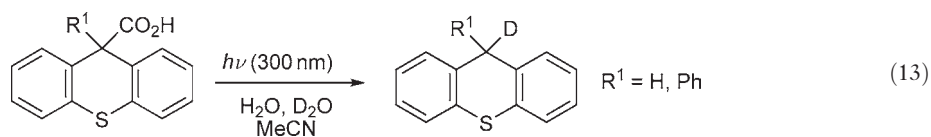
Table 17 Stereoisomers and thermodynamic properties of perhydro-4-thio-s-indacene

Isomer	Structure	$K_1^{220^\circ\text{C}}, \text{cm}^3 \text{m}^{-2}$		$-\Delta U_1, \text{kJ mol}^{-1}$		$\Delta E, \text{kJ mol}^{-1}$
		Calc.	Exp.	Calc.	Exp.	
<i>trans-syn-trans</i>		51	47	68	66	0
<i>trans-anti-trans</i>		40		67		18.8
<i>trans-anti-cis</i>		10.4	10.7	58	61	5.9
<i>trans-syn-cis</i>		9.9		58		5.0
		3.6		50		22.2
		4	13	51	62	10.0
<i>cis-syn-cis</i>		21	13	62	62	3.8
		12		58		7.1
		7.5	8.1	55	58	10.5
<i>cis-anti-cis</i>		7.8	8.1	56	58	7.9

Table 18 Aromaticity indices for some thiopyrans

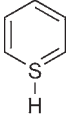
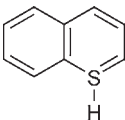
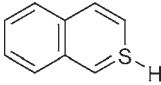
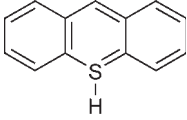
Bird (I^6)	1.1	24.8	19.4	20.7	100
Pozharsky (ΔN)	1.25	0.96	1.05	1.07	0





Thiabenzene **256** and its benzologues 1-thianaphthalene **257**, 2-thianaphthalene **258** and 9-thiaanthracene **259** are also potentially antiaromatic 8π electron systems provided they are planar. However, they adopt a boat conformation in which the S atom lies above the plane of the C atoms, thereby creating a 6π electron homoaromatic system with ylidic character. Calculations show that the energy barrier to inversion at S increases in the order **259** < **257** < **256** < **258** and the calculated dipole moments indicate the greatest ylide character is found in **259**. The relative stability is in the order **259** > **257** > **258** > **256** (Table 19) <2006HAC376>.

Table 19 B3LYP/6-31+G* calculated data for thiabenzene and related compounds

				
	256	257	258	259
ΔE kcal mol ^{-1a}	69.955	68.937	70.438	67.082
Charge on S ^b	0.393	0.385	0.392	0.420
Total dipole moment	0.824	1.198	1.658	1.848

^a ΔE = (energy of planar TS) – (energy of nonplanar boat minima).

^bMulliken charge distribution.

In a series of *S*-substituted thiabenzenes **260**, the molecules better approach planarity and become more aromatic as the electronegativity of the substituent increases. This is reflected in the nucleus-independent chemical shifts (NICS), significant negative values of which characterize aromaticity, and by the aromatic stabilization energies (ASE) and magnetic susceptibility exaltation data (Λ) given in Table 20. The Bird I^6 and HOMA indices are also presented together with the data for the thiopyrylium cation $C_5H_5S^+$ <2001HCA1578>. Somewhat related is the computational investigation of 1,1,1-trifluorothiabenzene, which suggested the molecule has more aromatic than ylidic character <1991JMT(234)247>.

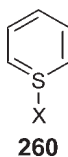


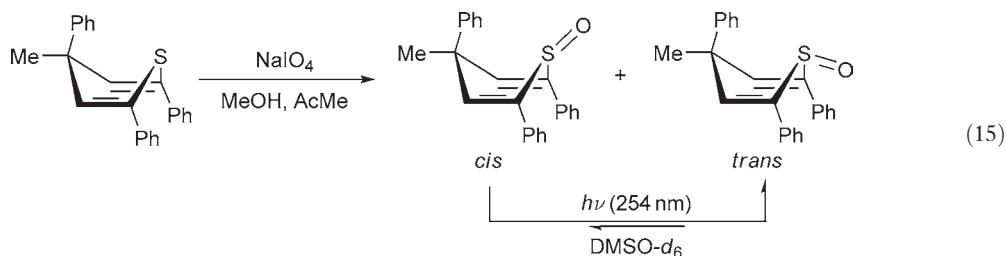
Table 20 Selected bond angles and aromaticity indices for S-substituted thiabenzenes

X	bond angle (°)		NICS	ASE	Λ	I^6	HOMA
	CSC	CCC					
F	167.5	177.9	−10.1	22.6	−12.4	78.0	0.983
Cl	170.2	178.2	−10.0			74.2	0.964
Br	170.8	178.4	−9.7			72.6	0.954
OH	164.8	177.3	−8.0			73.6	0.963
Me	153.9	168.9	−4.2			50.6	0.762
H	148.7	165.0	−5.2	19.8	−6.7	54.9	0.749
C ₅ H ₅ S ⁺			−10.7	26.3	−13.8	76.4	0.968

7.10.2.3.3 Conformations

The 4*H*-thiopyran molecule exhibits conformational flexibility. Calculations indicate that the energy change associated with the transition from a planar equilibrium conformation to a boat with the C=C–CH₂–C=C torsion angle of 30° is only 0.2 kcal mol^{−1} (6–31 *G*) and 0.7 kcal mol^{−1} (6–31 *G*^{**}). The presence of an unsaturated function (C=O, C=NH, C=CH₂) at the 4-position significantly increases the requirement to 1.6–2.9 kcal mol^{−1} as expected with the increase in conjugation. The data represent a balance between 1,2-allylic strain and conjugation which favor a planar structure and the bending strain and non-aromatic character of the π -system which support non-planar geometry <1997JST(412)115>.

The size of the substituents at C-4 in 2,6-diphenyl-4*H*-thiopyran 1-oxides influences the conformation of the ring. Small alkyl substituents allow a planar geometry which gradually changes to a boat conformation when two aryl groups are present. The sulfoxidation process leads to a mixture of two stereoisomers in which the *cis* sulfoxides predominate (3:2). The compounds undergo a photochemical stereomutation at S with the *trans* configuration and an equatorial sulfinyl group being preferred at equilibrium (Equation 15). Calculations support the greater stability of the *trans* arrangement and also give good agreement with X-ray data <2006T2603>.



Tetrahydrothiopyran adopts a chair structure similar to that of cyclohexane but it is slightly more puckered to accommodate the sulfur atom. The calculated and experimental (microwave MW, electron diffraction ED) bond lengths and bond angles are generally in good agreement (Table 21).

Similar data have been calculated for several 4-alkyltetrahydrothiopyrans. In all instances, the C–S bond lengths are in the range 181.5–181.8 pm and the C–S–C bond angles are between 97.1° and 99.4°. An equatorial disposition of the alkyl group is preferred and the conformational energies for the various derivatives are shown in Table 22. It is apparent that an axial substituent particularly can orient itself to minimize repulsive interactions and the overall picture is that 4-alkylthiacyclohexanes are subject to very similar influences as the alkylcyclohexanes <1998JPO831>. Related studies of the corresponding 2-alkyl <1999JPO176> and 3-alkyl <1999JST(492)225> derivatives and the 2-, 3-, and 4-methyltetrahydrothiopyrans have been reported <2000JMT(529)225> and the data are also reported in Table 22.

The free energy, enthalpy, and entropy of 2-, 3-, and 4-methyltetrahydrothiopyrans have been calculated using *ab initio* MO theory at various levels (Table 23). While the density functional theory (DFT) methods generally overestimated the conformational free energies the MP2/6-311*G(d,p)* calculated value for 2-methyltetrahydro-2*H*-thiopyran ($-\Delta G^\circ = 1.46$ kcal mol^{−1}) and the MP2/6-31*G(2d)* value for 3-methyltetrahydro-2*H*-thiopyran ($-\Delta G^\circ = 1.46$ kcal mol^{−1}) were in excellent agreement with experimentally determined values <2000JMT(529)225>. In a similar study, the energy differences between the chair, 1,4-twist and 2,5-twist conformers of tetrahydrothiopyran were computed. The chair conformer was 5.27 kcal mol^{−1} more stable than the 1,4-twist conformer which was in turn only slightly more stable (0.81 kcal mol^{−1}) than the 2,5-twist conformer <2003STC497>.

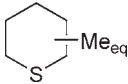
Table 21 Calculated and experimental bond lengths (pm) and bond angles (°) for tetrahydrothiopyran

Parameter	 Calculated values			Experimental values	
	MM3	MM4	6-31G*	MW	ED
Bond length (pm)					
C-H	111.4	111.3		109.5	111.4
CH-2 _{ax}			108.5		
CH-2 _{eq}			108.3		
C2-C3	153.6	153.1	152.8	153.3	152.8
C3-C4			153.2	153.3	152.8
C2-S1	181.3	181.4	181.7	183.2	181.1
Bond angle (°)					
H-C-H	106.4	106.4		108.5	105.9
H-C2-H			107.4		
H-C3-H			107.1		
C2-C3-C4	112.7	112.7	112.8	107.9	112.3
C3-C4-C5	112.6	112.9	113.2	109.2	113.8
C3-C2-S1	111.3	112.8	112.9	114.1	112.7
C2-S1-C6	97.5	97.4	98.5	99.2	97.6

Table 22 Calculated (6-31G*) conformational energies $-\Delta G^\circ$ (kcal mol⁻¹) for some 2-, 3-, and 4- equatorially substituted tetrahydrothiopyrans

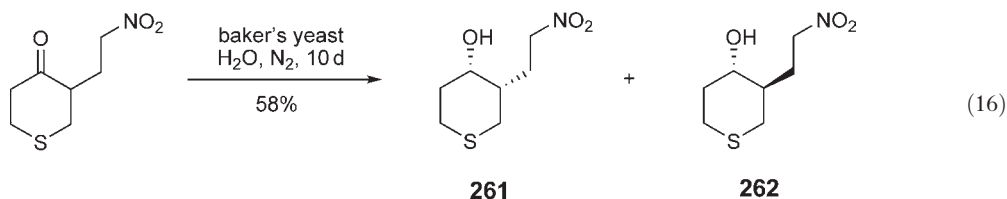
Location	Conformational energy $-\Delta G^\circ$ (kcal mol ⁻¹)					
	Me	Et	i-Pr	t-Bu	neo-C ₅ H ₁₁	SiMe ₃
C-2	1.91	1.57	1.71	4.11	1.62	2.96
C-3	1.95	1.81	1.83	5.47	1.67	2.97
C-4	2.24	2.17	2.41	6.14	2.02	3.67

Table 23 Calculated conformational enthalpy ($-\Delta H^\circ$), entropy (ΔS°) and free energy ($-\Delta G^\circ$) for methyltetrahydrothiopyrans

	 $-\Delta H^\circ$ (0 K) $-\Delta H^\circ$ (298 K) ΔS° (298 K) $-\Delta G^\circ$ (298 K)			
MP2/6-31G(2d)				
2-Me	1.66	1.61	-0.42	1.74
3-Me	1.40	1.37	-0.31	1.46
4-Me	1.93	1.89	-0.28	1.97
MP2/6-311G(d,p)				
2-Me	1.38	1.33	-0.42	1.46
3-Me	1.52	1.48	-0.31	1.57
4-Me	1.95	1.91	-0.28	1.99

Reduction of racemic 3-(2-nitroethyl)tetrahydrothiopyran-4-one by baker's yeast gives a mixture of the *cis* and *trans* tetrahydrothiopyran-4-ols in which the former predominates (85:15). NMR evidence suggests that the 4-hydroxy group is axial in the *cis* **261** and equatorial in the *trans* **262** isomer (Equation 16). Although it was not possible to obtain a pure sample of either compound, comparison of their CD spectra and those of the 3,5-dinitrobenzoates with

similar derivatives of known absolute configuration allowed the designation of the *cis* alcohol as 3*S*,4*S* and the *trans* isomer as 3*R*,4*S*. The unreduced ketone isolated from the reaction mixture had an ee of 77% and showed a positive CD band at ca. 285 nm and hence was assigned an *R* configuration <1997TA1811>.



Based on the chemical shifts of H-4 in the low-temperature ^1H NMR spectra of 4-benzyloxy and 4-silyloxy tetrahydrothiopyrans in CD_2Cl_2 , the equatorial preference appears to be related to the basicity of the oxygen atom of the substituent. In the case of both their *cis* and *trans* sulfoxides, a preferential axial disposition of the substituent is noted and is almost exclusive for the latter 1-oxide and for the corresponding 1,1-dioxide <1995H(41)419>. MM3 calculations confirm this preference <1996JPO159>.

A lanthanide-induced shift analysis of tetrahydrothiopyran 1-oxide based on calculated geometrical parameters indicated that the equilibrium mixture contained ca. 45% of the equatorial conformer in CDCl_3 solution. However, the conformational equilibrium is solvent dependent, with the equatorial conformer predicted to be favored by polar solvents. The calculated dipole moments for the equatorial and axial conformers are 4.39 and 4.17 D respectively, which compare favorably with the experimental value of 4.19 D <1994J(P2)2329>.

Calculated geometry for axial tetrahydrothiopyran 1-oxide is in good agreement with the bond lengths and angles determined experimentally by electron diffraction. The conformational preference for the axial conformer, $-\Delta G^\circ$, is calculated at between -0.39 and $-1.62 \text{ kcal mol}^{-1}$ <2001JST(535)287>, in agreement with the experimentally determined range of -0.2 to $-1.3 \text{ kcal mol}^{-1}$ dependent on the conditions used <1996JPO159>.

The equilibrium geometries and relative energies of the various chair, twist, and boat conformations of tetrahydrothiopyran 1-oxide have been calculated using MP2/6-311+ $G(d,p)$ level of theory. The greater stability of the axial chair conformation (calculated $-\Delta G^\circ$ of $0.75 \text{ kcal mol}^{-1}$) is attributed to attractive interactions between the axial sulfinyl oxygen and the partially positive axial hydrogen atoms at C-3 and C-5. Of the other conformers, the 1,4-twist is marginally more stable than the 2,5-twist for both the axial and equatorial 1-oxides <2005IJQ(101)40>.

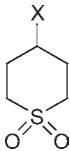
Geometrical parameters and conformational free energies have also been calculated for a range of 3-substituted <2001JST(535)287> and 4-alkyl <2001JST(549)203> equatorial tetrahydrothiopyran 1-oxides. It is suggested that repulsive steric interactions involving the axial 4-alkyl group and the axial hydrogen atoms are a major influence on the equatorial preference. Selected data are given in Table 24.

Table 24 Geometry optimized structures for equatorial 3- and 4- substituted thiopyran 1-oxides. $\Delta E = (\text{energy of axial conformer}) - (\text{energy of equatorial conformer})$

X	ΔE HF/6-31G(d,p)	X	ΔE B3LYP/6-31G(d)
CH_3	2.22	CH_3	1.83
CF_3	2.43	C_2H_5	1.83
CHO	0.92	<i>neo</i> - C_5H_{11}	2.82
COCH_3	0.98	<i>i</i> - C_3H_7	1.78
CN	0.88	<i>t</i> - C_4H_9	4.96
F	-0.86	SiMe_3	2.92
Cl	1.05		
Br	0.22		

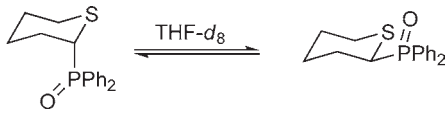
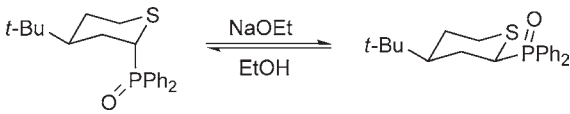
The structures and energies of various 4-substituted tetrahydrothiopyran 1,1-dioxides have been calculated. Axial $\text{S}=\text{O}$ bond lengths are shorter than equatorial $\text{S}=\text{O}$ bond lengths. Other data are presented in Table 25 <2002STC115>.

Table 25 Calculated [HF/6-31G(d)] conformational enthalpy ($-\Delta H^\circ$) and free energy ($-\Delta G^\circ$) for 4-substituted tetrahydrothiopyran 1,1-dioxides

				
4-Substituent (X)	$-\Delta H^\circ$ (180 K)	$-\Delta H^\circ$ (298 K)	$-\Delta G^\circ$ (180 K)	$-\Delta G^\circ$ (298 K)
CH ₃	2.07	2.04	2.12	2.16
CH ₂ OH	1.46	1.41	1.62	1.77
CHO	-0.05	-0.08	0.05	0.13
CH ₃ CO	-0.19	-0.22	-0.07	0.01
CN	-0.70	-0.74	-0.65	-0.60
F	-2.05	-2.09	-2.03	-1.99
Cl	-0.82	-0.86	-0.75	-0.68
Br	-1.79	-1.83	-1.67	-1.58

The equilibrium constants derived from the ^{31}P NMR spectra at temperatures below coalescence show that there is a considerable predominance of the axial conformer of 2-diphenylphosphinoyltetrahydrothiopyran (**Table 26**) which contrasts with the equatorial preference in the corresponding cyclohexane derivative. This result indicates a strong anomeric effect, estimated at $2.40 \text{ kcal mol}^{-1}$. The corresponding data for the ananomeric *cis* and *trans* 4-*t*-butyl derivative at chemical equilibration are presented in **Table 26**. The large difference in ΔG° at 173 and 323 K is compatible with a significant entropy effect, calculated $\Delta S^\circ = +4.8 \pm 0.7 \text{ cal K mol}^{-1}$, with $\Delta H^\circ = +1.29 \pm 0.12 \text{ kcal mol}^{-1}$. Thus, at low temperatures the axial conformer is dominant but the equatorial conformer is favored at higher temperatures <1998T1375>.

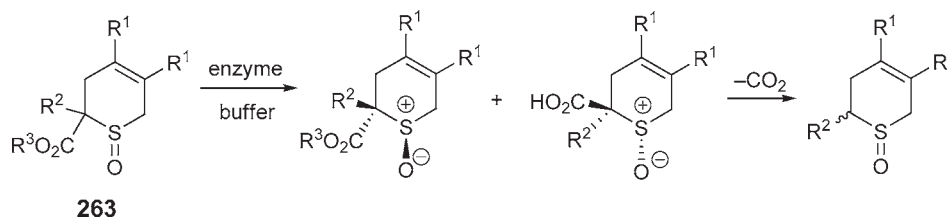
Table 26 Calculated thermodynamic data for some 2-diphenylphosphinoyltetrahydrothiopyrans

Temperature (K)	Equilibrium const (K)	$\Delta G^\circ \text{ kcal mol}^{-1}$
		
183	0.20	+0.59
173	0.27	+0.46
		
323	1.5	-0.26 ± 0.1

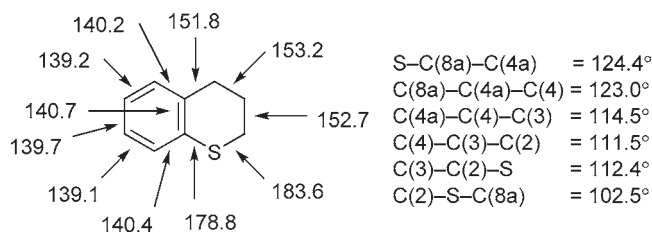
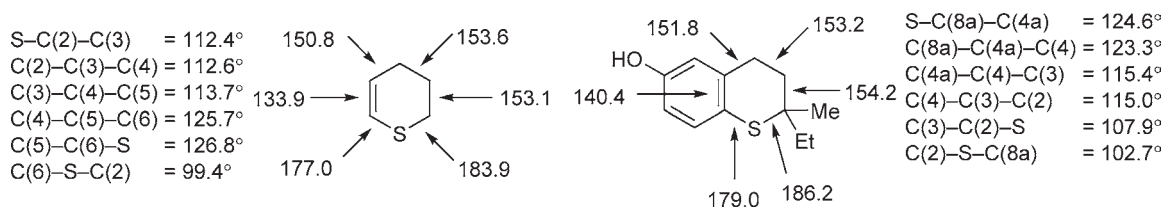
The controlled enzymic hydrolysis of racemic *trans*-2-alkoxycarbonyl-3,6-dihydro-2*H*-thiopyran 1-oxides **263** leads to a mixture of unchanged ester and the derived acid. Moderate to high enantiomeric purities resulted for both of the products depending on the structure of the substrate and on the enzyme used. Thus, pork liver esterase gave only one enantiomer of the 2-methyl methyl ester, while α -chymotrypsin gave the 2,4,5-trimethyl carboxylic acid in 90% ee. Some of the product acids are prone to decarboxylate under the conditions used giving a diastereomeric mixture of the sulfoxide (**Scheme 23**) <1999EJO2573>.

The optimized geometry of thiochroman has been computed at three levels of theory. Data for bond lengths and angles and dihedral angles using the higher level DFT (B3LYP/6-31G(*d*)) are given in **Figure 52**. Pertinent values relate to the C_{Ar}-S bond which is somewhat shorter than the C(2)-S bond and to the C_{Ar}-S-C(2) angle which closes up

from the tetrahedral value found in tetralin and which is compensated by opening of the S–C(2)–C(3) angle. Significantly different energies of activation for ring inversion for chroman and thiochroman are noted <2002JST(594)161>. Calculations have been extended to 3,4-dihydro-2*H*-thiopyran, 2-ethyl-2-methylthiochroman, and its 6-hydroxy derivative in order to assess the structural influence of the alkyl chains in vitamin E. Selected data are given in Figure 53; the most significant changes relative to cyclohexene and its derivatives are in the dihedral angles. The heteroatom slightly destabilizes the fused ring system <2002MI609>.



Scheme 23

Figure 52 Selected calculated bond lengths (pm) and bond angles ($^\circ$) for thiochroman.Figure 53 Selected calculated bond lengths (pm) and bond angles ($^\circ$) for 3,4-dihydro-2*H*-thiopyran and 2-ethyl-2-methylthiochroman-6-ol.

Application of the DFT (B3LYP/6–31*G*^{*}) method generated energies for the cationic species derived from acid treatment of 3-aryl-1-phenyl-3-phenylsulfanyl-propan-1-ols and their deprotonated products, thiochromanols. The *cis* and *trans* thiochromanols differ in energy by 1.8 kcal mol^{−1} and their precursor cations by 0.8 kcal mol^{−1} which is in reasonable agreement with the observed *cis/trans* selectivity of 7:1 during cyclization and lends support to the involvement of a [1,3]-PhS shift <2003T3621>.

An inseparable mixture of diastereomers of 3-aryl-4-nitrothiochroman 1,1-dioxides is produced by the five-step ring expansion of 3-nitrothiophenes, corresponding to *cis* and *trans* configurations at the C(3)–C(4) bond (Figure 54). Molecular mechanics calculations using the PCMODEL program indicate that a half-chair conformation is the most stable for both configurations. In the *trans* form, both the nitro and phenyl groups are pseudoequatorially disposed, but in the *cis* isomer the nitro group is pseudoaxial. The H(3)–C(3)–C(4)–H(4) dihedral angle approaches 180° in the former but is nearer to 60° in the latter. These spatial arrangements are manifest in the chemical shift of H-2_{ax} which is deshielded by the nitro group in the *cis* form by ca. 1 ppm. relative to that in the *trans* compound, and by the difference in the values of *J*_{3,4} <2004T4967>.

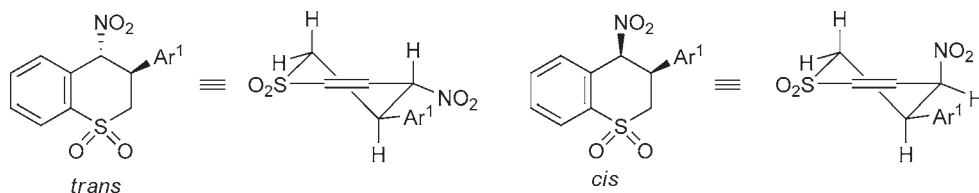


Figure 54 Diastereoisomers of 3-aryl-4-nitrothiochroman 1,1-dioxides.

Analysis of the vibrational circular dichroism (VCD) spectrum of thiochroman 1-oxide over the range 900–1240 cm^{-1} using DFT theory predicted three stable conformations differing in the orientation of the SO unit and in the puckering of the hetero ring and separated in energy by less than 1 kcal mol^{-1} . The predicted spectrum of (*S*)-thiochroman 1-oxide is in excellent agreement with the experimental spectrum of the (+) 1-oxide and hence the absolute configuration is (*R*)-(-)/ (*S*)-(+). The same methodology has been used to confirm that the absolute configuration of thiochroman-4-one 1-oxide is *R*(-)/*S*(+) as proposed earlier from a comparison of the UV circular dichroism of (-)-thiochroman-4-one 1-oxide with those of thiochroman 1-oxide and 2,3-dihydrobenzo[*b*]thiophene 1-oxide.

The experimental IR and VCD spectra of thiochroman 1-oxide in CCl_4 and CS_2 solutions are in good agreement with DFT calculations, which predict population of the three conformations (Figure 55). Similarly, the two predicted conformations for thiochroman-4-one 1-oxide are present in the experimental spectra.

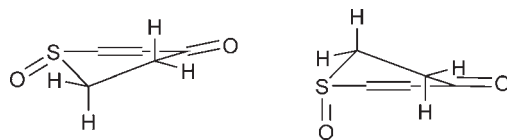


Figure 55 Conformations of thiochroman-4-one 1-oxide.

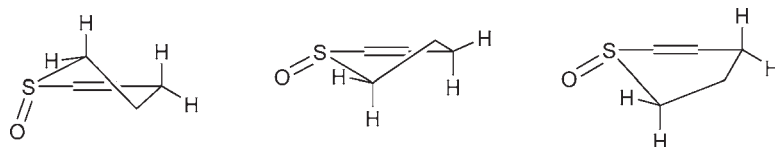


Figure 56 Conformations of thiochroman 1-oxide (H-3 omitted for clarity).

The enantiomers of thiochroman 1-oxide have been obtained by oxidation of thiochroman in the presence of (*R,R*)-1,2-diphenylethane-1,2-diol (DPED) or L-diethyl tartrate. In the case of the enantioselective oxidation of thiochroman-4-one, (*R,R*)-DPED and (*S,S*)-DPED were used as the chiral inducers. High yields of both (-)-(*R*)-thiochroman 1-oxide and (-)-(*R*)-thiochroman-4-one 1-oxide and with enantioselectivities of 98% and 96%, respectively result from the reaction of H_2O_2 with the heterocycles when significant amounts of chloroperoxidase are used as catalyst.

Detailed ^1H , ^{13}C , and ^{17}O NMR studies allied to *ab initio* calculations indicate that the preferred conformers of the epoxides of (*Z*)-3-arylidene-thioflavone 1,1-dioxides are twisted envelopes in which the 2-phenyl group occupies an axial position. In the corresponding 1-oxides, the $\text{S}=\text{O}$ group takes up an axial site and is *trans* to the axial 2-phenyl unit indicating that attack by dimethyldioxirane at S proceeds from the less hindered side.

Racemic thiochroman-4-ol has been resolved by conversion to the diastereomeric camphanyl esters by reaction with (-)-1*S*-camphanic chloride and fractional crystallization. A $\text{p}K_{\text{R}}$ value of -12.3 has been obtained for the ionization of this alcohol and rate constants for the racemization of chiral thiochroman-4-ol have been obtained in water and in a water-trifluoroethanol (1:1) mixture.

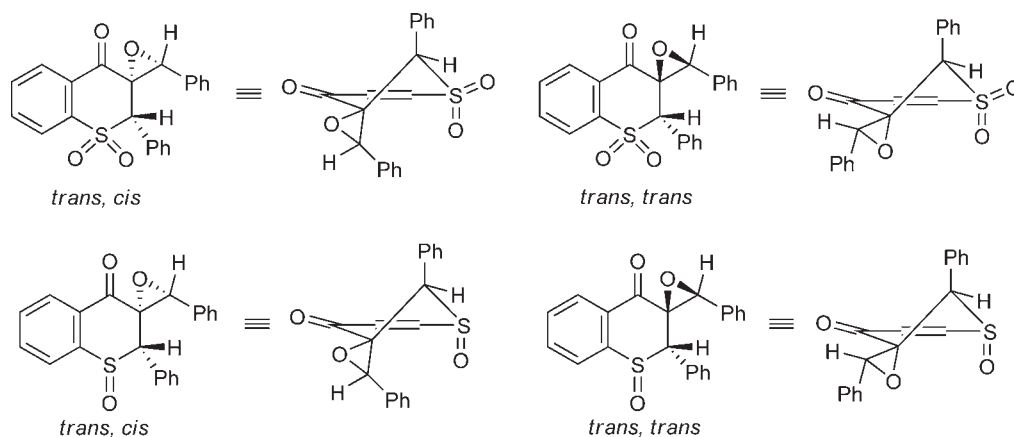


Figure 57 Preferred conformers of the epoxides of (Z)-3-benzylidenethioflavone 1-oxide and 1,1-dioxide.

Molecular geometries have been calculated at the DFT level of theory for naphtho[1,8-*c,d*]thiopyran **264** and acenaphtheno[5,6-*c,d*]thiopyran **265**, considered as nonclassical and quinoidal structures, respectively. The short C–S bond lengths of ca. 167 pm for the former, similar to that calculated for thioformaldehyde *S*-methide, supports this assignment. However, a nonclassical structure is also indicated for the acenaphthene derivative by the calculated geometry and charge distribution. Data are collated in [Figure 58](#) <1997JOC1766>.

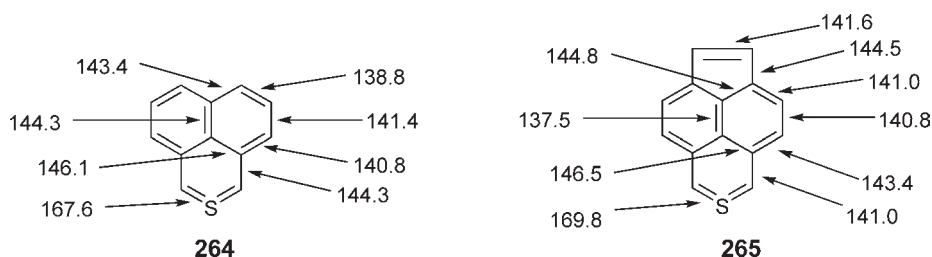
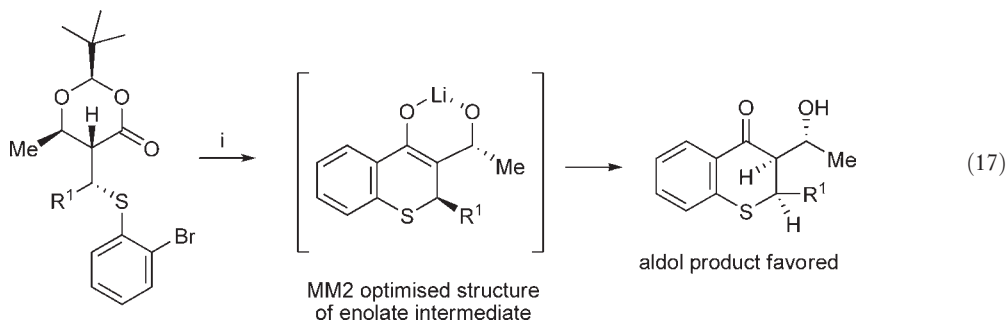
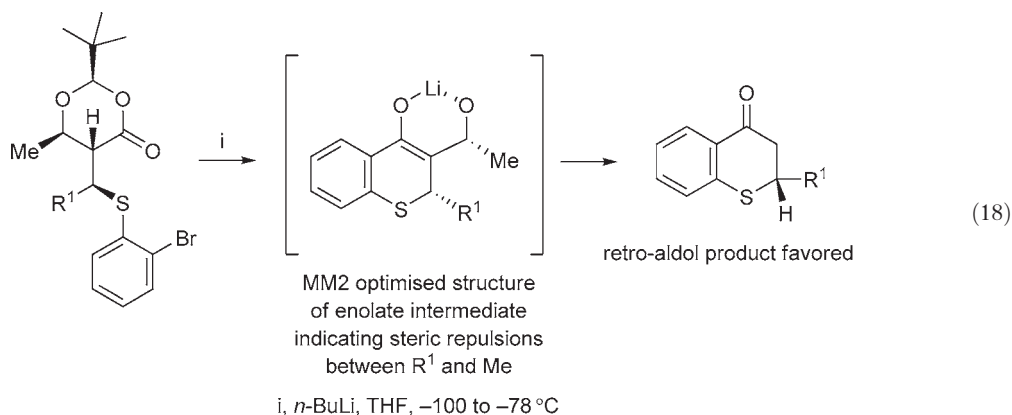


Figure 58 Calculated bond lengths (pm) for **264** and **265**.

The cyclizations of the adducts from 2-bromothiophenol and various (*E*)-5-ylidene-1,3-dioxan-4-ones lead exclusively to (+)-(1'*R*,2*R*,3*R*)-3-(1-hydroxyethyl)-2-methylthiochroman-4-ones through opening of the dioxanone ring and loss of Me₃C-CHO. However, the adducts from the (*Z*)-isomer also lose the hydroxyethyl unit, presumably as MeCHO by a retro-aldol reaction, and yield (–)-(2*S*)-2-methylthiochroman-4-ones. The structures of the supposed enolate intermediates arising from the initial loss of pivaldehyde have been MM2-optimized and show that steric repulsion between the R¹ and methyl group in the enolate from the latter isomer is sufficient to promote the retro-aldol reaction ([Equations 17 and 18](#)) <2001EJO529>.





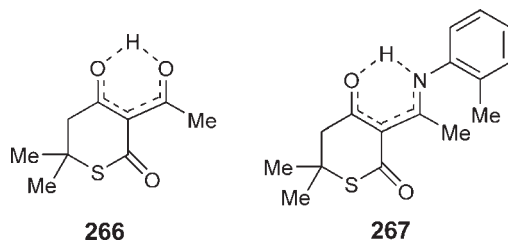
Calculations at the MP2/6-31G(*d*) level have indicated that planar and nonplanar conformers of thioxanthone differ in energy by less than 1 kcal mol⁻¹; the dihedral angle of the latter is 173.3°. Computed and experimental ionization potentials and absorption spectra suggest contributions from both conformers and a dynamic model involving a ‘butterfly-like motion’ is proposed <2006JPH(179)298>.

The magnetic circular dichroism spectrum of thioxanthone and the circular dichroism spectrum of its inclusion complex with cyclodextrin have been measured and interpreted with the aid of PPP and CNDO/S calculations. The first $\pi\pi^*$ state exhibits intramolecular charge transfer characteristics <1994JPC10432>.

7.10.2.3.4 Tautomerism

7.10.2.3.4(i) Prototropy

¹H NMR spectroscopy indicates that 3-acetyl-6,6-dimethyltetrahydrothiopyran-2,4-dione exists exclusively in a single enolic form **266** as does the derived enamine **267** <2003RJO235> and a similar situation obtains for 4-acetyltetrahydrothiopyran-3,5-diones for which the enolic proton resonates at ca. δ 18 <2003RJO1772>.



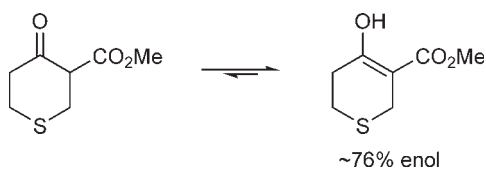
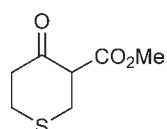
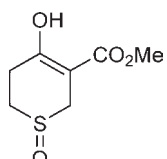
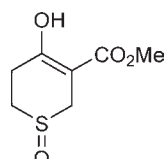
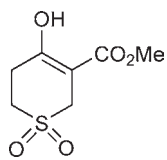
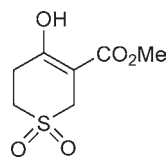
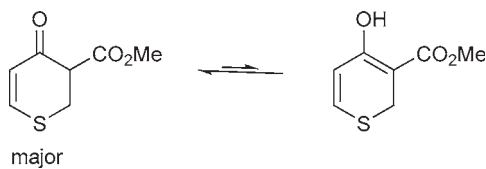
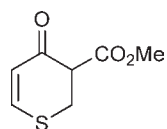
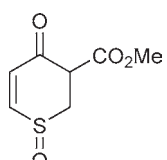
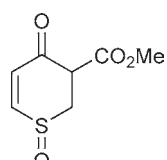
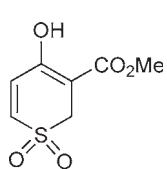
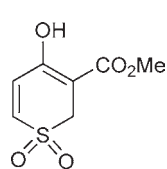
Although methyl 4-oxotetrahydrothiopyran-3-carboxylate and the corresponding 2,3-dihydro-4*H*-thiopyran-4-one exist as a mixture of keto and enol forms in solution, the 2,3-dihydro sulfoxide is present only as the ketone. However, the sulfone and the tetrahydro sulfoxide and sulfone are present exclusively in the enolic form. The picture is further complicated in the solid state, where the dihydro compound and its sulfoxide exist exclusively as the keto structure but the sulfone is found as the enol (Table 27) <1986J(P2)1887>. The related 2-esters of tetrahydrothiopyran-3-one **268** exist as a ca. 1:2 mixture of keto and enol <1981T2633>.

Both NMR and IR spectra indicate that methyl 3-hydroxy-4a,5,6,7,8,8a-hexahydro-4*H*-thiochromene-2-carboxylate **269** exists predominantly (74%) as such in solution rather than in the 3-keto form (Equation 19). In the solid state it exists as the enol with an intramolecular H bond <1994ACS417>.

The imines derived from 3-hydroxynaphtho[1,8-*c*]thiopyran-2-carbaldehyde and the corresponding 2-acetyl compound exist in solution in the keto-enamine **270**, R¹ = H, shown (Scheme 24). Irradiation at 436 nm results in reversible *Z*-*E* isomerization about the exocyclic double bond <1995ZOR1559>.

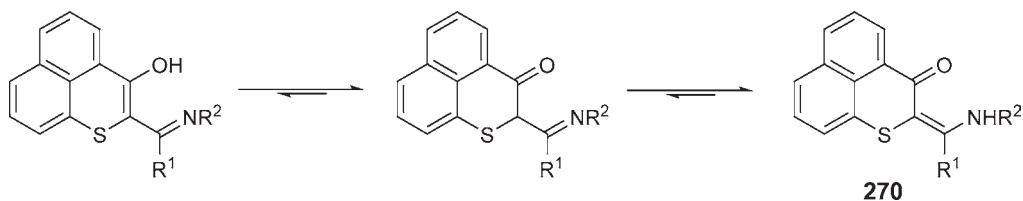
Yellow 4-hydroxy-2*H*-1-benzothiopyran-2-thiones result from the reaction of 2'-chloroacetophenones with CS₂ in the presence of NaH. Their IR spectrum shows no carbonyl stretching absorption band. However, treatment of a solution of the thione with concentrated acid results in the precipitation of the pale yellow 2-mercaptothiochromone **271** for which $\nu_{C=O}$ occurs at 1610–1620 cm⁻¹. Treatment with base and then dilute acid regenerates the thiocoumarin. Both tautomers appear to exist independently of each other (Equation 20) <1987AJC1179>.

Table 27 Tautomeric equilibria established by ^{13}C NMR spectroscopy for some thiopyranones in solution and solid state

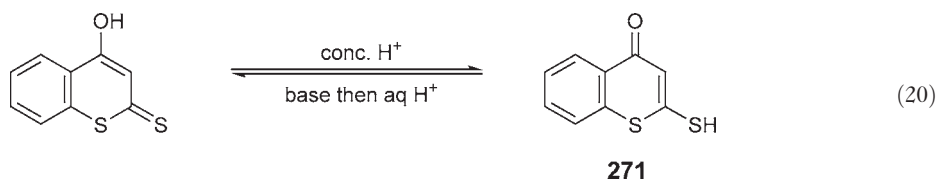
<i>Solution (CDCl_3)</i>		<i>Solid state</i>
 ~76% enol		
		
		
 major		
		
		

**268****269**

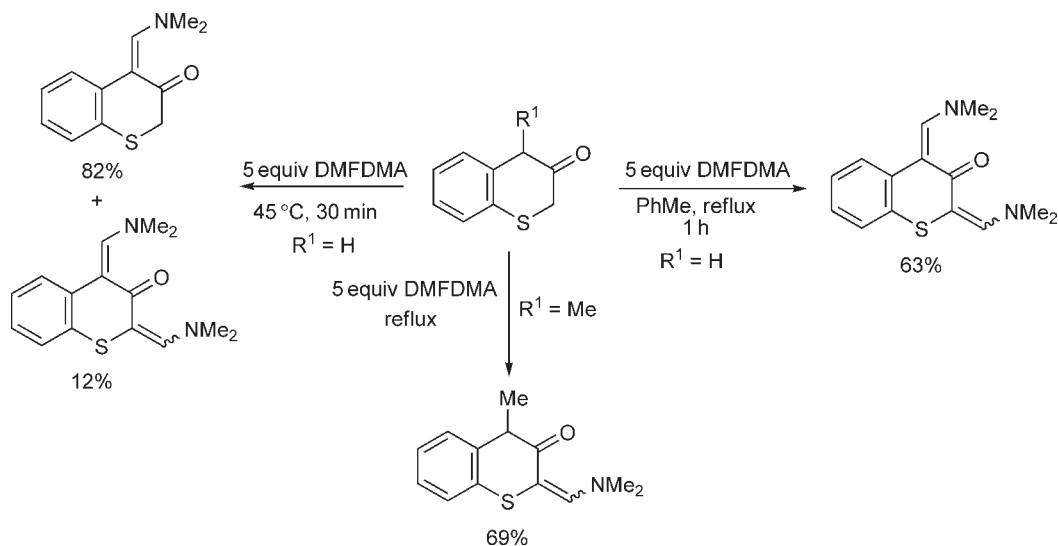
(19)



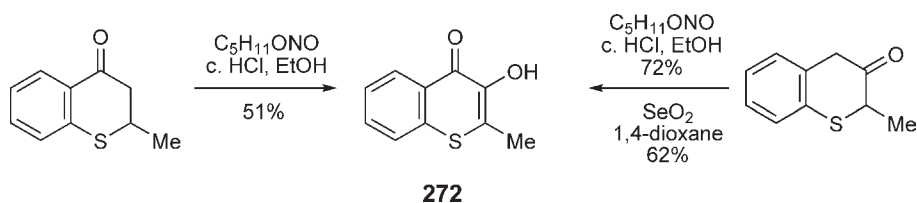
Scheme 24



While thiochroman-4-one exists exclusively in the keto form, the 3-one enolizes to form an extended conjugated system, a feature which may account for the facile 4-aminomethylation with DMF dimethylacetal. When the 4-position is blocked by a methyl group, attack occurs at C-2 though more forceful reaction conditions are required (**Scheme 25**) <1992TH1>. In like manner, hydrolysis of 3-(4-dimethylaminophenylimino)-2-methylthiochroman-4-one affords 3-hydroxy-2-methylthiochromone rather than the thiochromandione <1963CB1234>. This property was also apparent during the attempted synthesis of 2-methylthiochroman-3,4-dione by oxidation of the thiochroman-3-one with SeO_2 , when 3-hydroxy-2-methylthiochromone **272** was the only product isolated, as indicated by the signals at δ 7.51 (OH), δ 2.43 (2-Me) and at δ 8.50 (H-5). Treatment of both 2-methylthiochroman-4-one and the isomeric 3-one with isoamyl nitrite also gave only this thiochromone (**Scheme 26**) <1994T7865>.



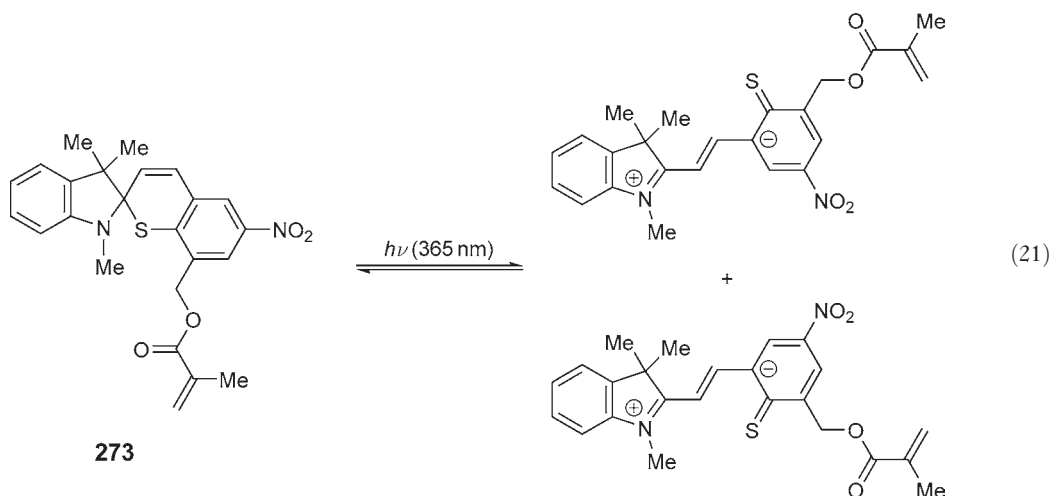
Scheme 25



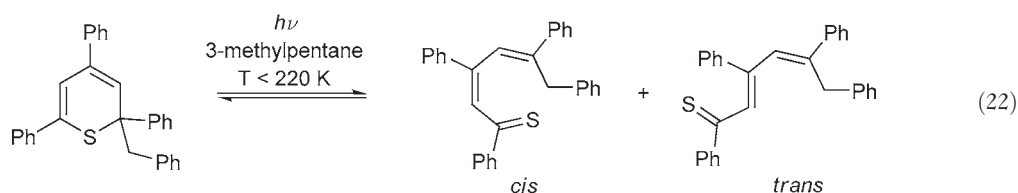
Scheme 26

7.10.2.3.4(ii) Ring-chain tautomerism

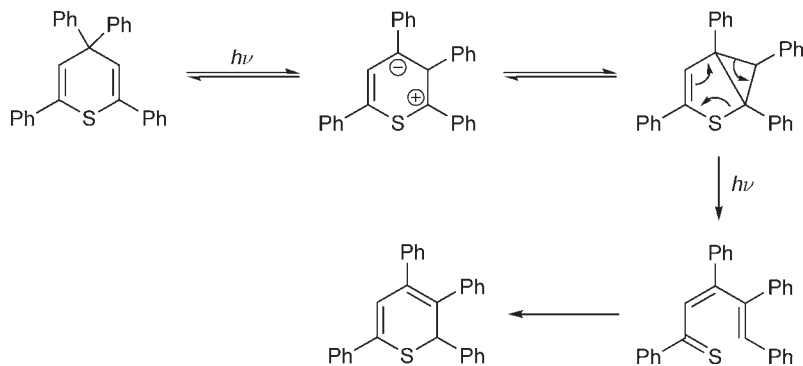
Unlike the still-unknown *2H*-pyran which exists exclusively in the ring-opened form, *2H*-thiopyran is a well-characterized molecule. Nevertheless, the S-C(2) bond can be cleaved and this is the basis of the photochromic properties observed with spirobenzothiopyrans. Irradiation at 365 nm of the spiro[*2H*-1-benzothiopyran-2,2'-indoline] **273** in both the solid state and in solution results in opening of the thiopyran ring and the formation of a colored metastable zwitterionic merocyanine (Equation 21). The open form exhibits solvatochromism, with $\lambda_{\max}$ 588 nm in methanol and 673 nm in acetone. In solution, the thiopyran unit reforms rapidly when irradiation ceases, but continuous irradiation leads to the growth of crystals of the open form <2002JOC533>.



Photochromism is also observed with 2-benzyl-2,4,6-triphenyl-*2H*-thiopyran in a rigid matrix at 77 K <1968JPC997>, using nanosecond flash photolysis at room temperature <1986MI187> and by steady-state irradiation at 220 K in solution. A transient ring-opened species is produced which is assigned *cis* geometry on the basis of calculations with INDO/1-C1. On irradiation at 435 nm, partial bleaching occurs and the *trans* isomer is produced (Equation 22) <2006JPH(177)34>.



Both 2,4,4,6-tetraphenyl and 4-methyl-2,4,6-triphenyl-*4H*-thiopyrans exhibit photochromic properties in the solid state and in solution on irradiation with UV light and eventually rearrange to a *2H*-thiopyran in which a 4-phenyl group has migrated to the 3-position. The mechanism proposed for the rearrangement is shown in Scheme 27 <1992J(P2)1301, 1994JPH(81)21>. The effects of 3,5-disubstitution are variable; the 3,5-diphenyl derivative does not rearrange but a phenyl group does shift in the 3,5-dimethyl analogue, though yields of the rearranged products are lower <1996JPH(101)33>.

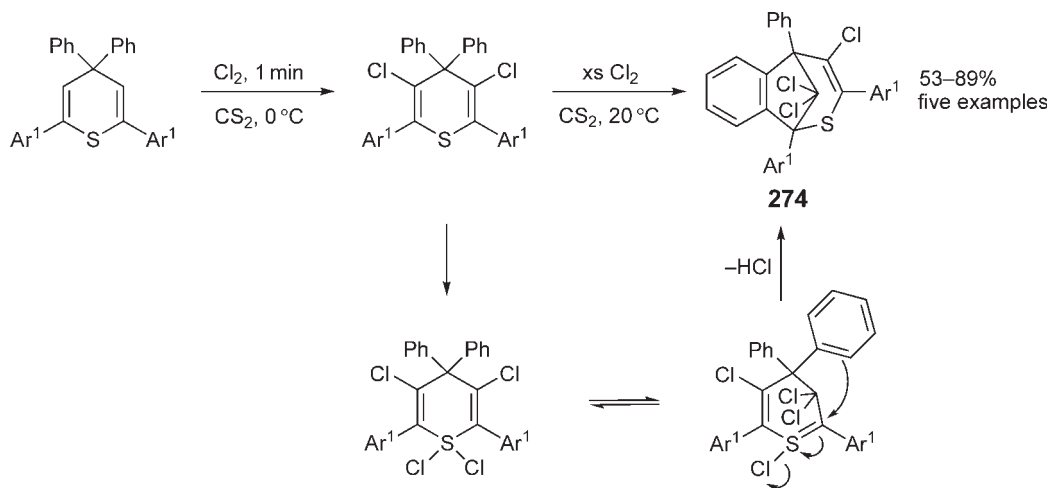


Scheme 27

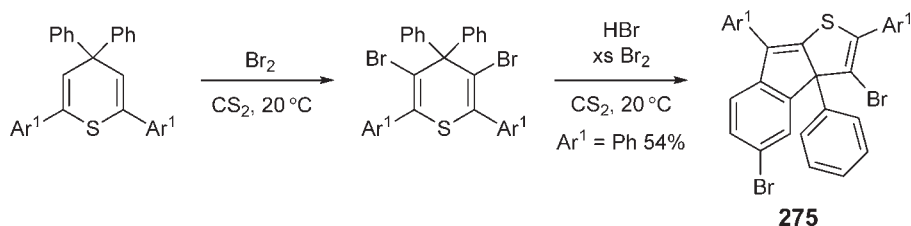
7.10.3 Reactivity

7.10.3.1 Electrophilic Attack at Ring Carbon

Initial facile halogenation at the 3- and 5-positions of 2,4,4,6-tetraaryl-4*H*-thiopyrans can be followed by further reactions in the presence of an excess of halogen. Thus, chlorine induces a rearrangement to a bridged benzothiepine **274** (Scheme 28) <1994CCC2269>. On the other hand, an excess of bromine results in rearrangement to a benzo[3,4]cyclopenta[1,2-*b*]thiophene **275** through protonation of the 3,5-dibromo compound possibly by HBr₃ and electrophilic attack at a 4-phenyl substituent (Scheme 29). Interestingly, 2',6'-diphenyl-spiro(fluorene-9,4'-thiopyran) does not rearrange presumably because of the rigidity of the fluorene moiety, which is therefore simply brominated <2004CCC1631>.

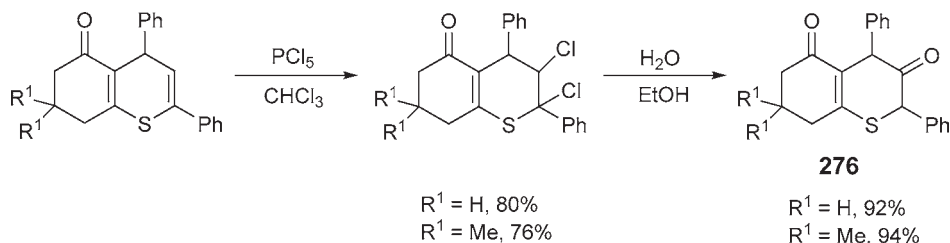


Scheme 28



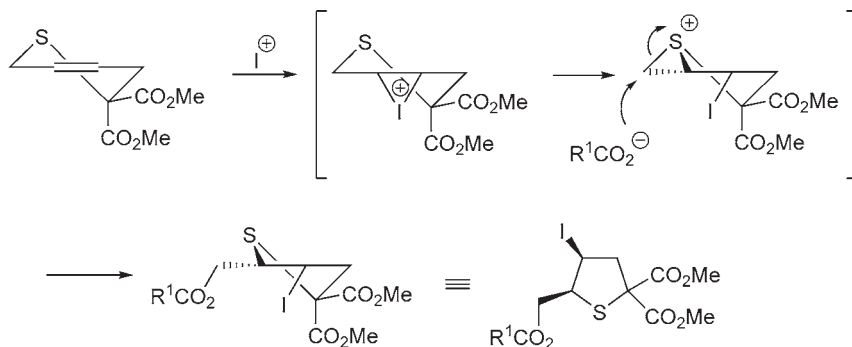
Scheme 29

Chlorination of cyclohexa[*b*]-4*H*-thiopyran-5-ones results in addition to the 2,3-double bond but the product is easily hydrolysed to the 3,5-diketone **276** (Scheme 30) <1999CHE746>.



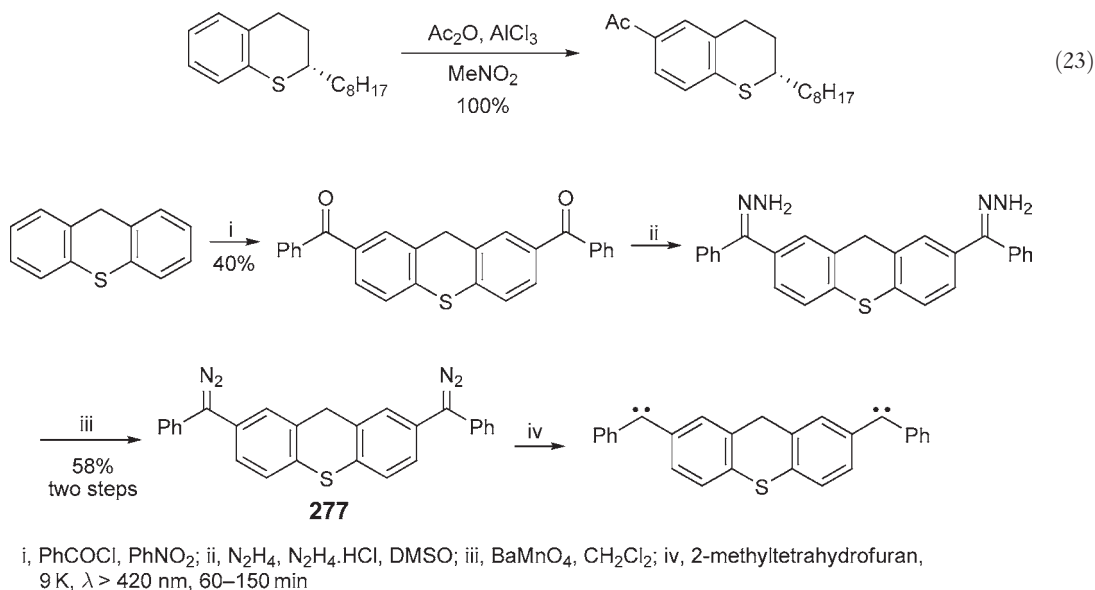
Scheme 30

Treatment of 3,6-dihydro-2*H*-thiopyrans with *N*-iodosuccinimide in the presence of a carboxylic acid results in ring contraction to a *cis*-4-iodo-5-carboxymethylthiolane. An iodonium ion is considered to be the initial product from which a bicyclic thiiranium species is generated which is attacked by carboxylate ion (**Scheme 31**) <2004EJO74>.



Scheme 31

Acylation of 2-*n*-octylthiochroman by Ac_2O is quantitative at the 6-position (**Equation 23**) <2003PS(178)993> and benzoylation of thioxanthene occurs at the 2- and 7-positions and both ketone functions have been converted into the hydrazones and thence the diazo compound **277**. The bis-carbene derived from **277** by cryogenic photolysis has been used to study magnetic coupling interactions through the sulfur atom (**Scheme 32**) <1997JA8058>.

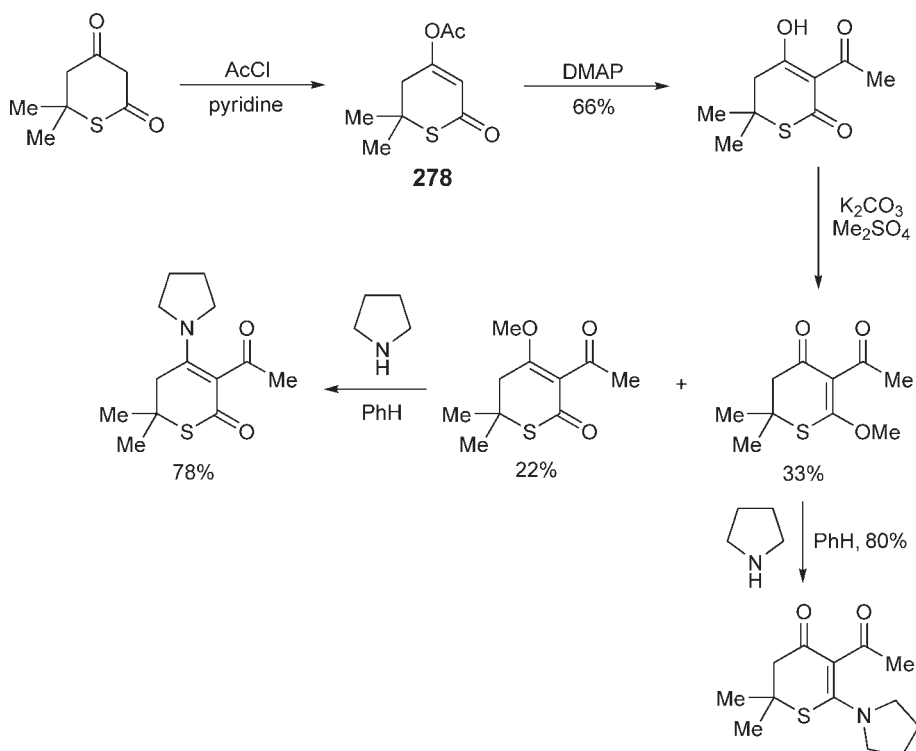


Scheme 32

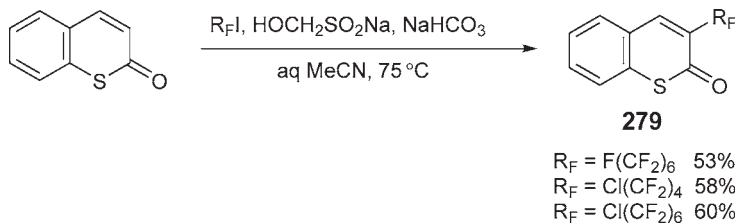
Acylation of 6,6-dimethyltetrahydrothiopyran-2,4-dione at C-3 is achieved by rearrangement of the initial 4-*O*-acylated product **278**. Subsequent methylation of the triketone occurs at both the 2- and 4- carbonyl groups and both resulting methoxy functions are readily displaced by amines (**Scheme 33**) <2003RJO235>.

Thiocoumarins react with perfluoroalkyl iodides in the presence of Rongalite, $\text{HOCH}_2\text{SO}_2\text{Na}$, to give 3-perfluoroalkyl derivatives **279** (**Equation 24**) <1994J(P1)101>.

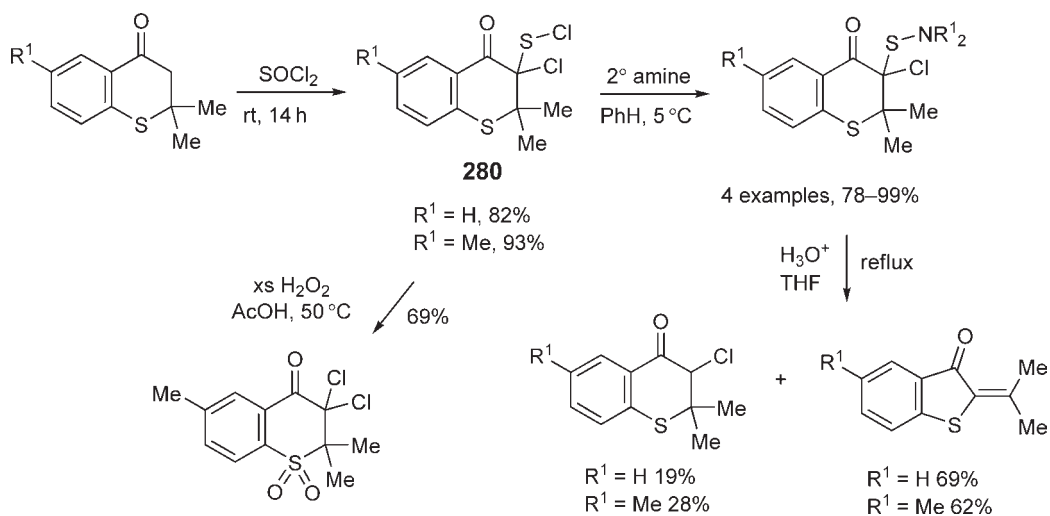
Thiochroman-4-ones react with an excess of thionyl chloride to give the bright yellow α -chlorosulphenyl chlorides **280** which react with secondary amines to give sulfenamides. Ring contraction occurs on acidic hydrolysis producing benzothiophenes (**Scheme 34**) <1994T827>. On the other hand, oxidation of the chlorosulphenyl chlorides with an excess of hydrogen peroxide leads to the 3,3-dichlorothiochroman-4-one 1,1-dioxides (**Scheme 34**) <1994T5245>.



Scheme 33

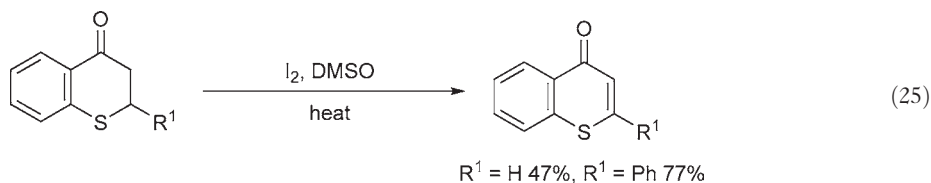


(24)

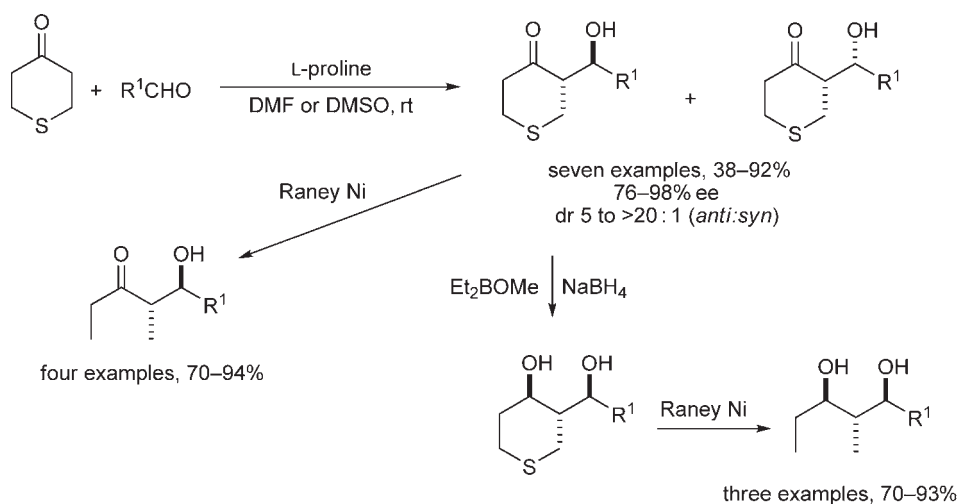


Scheme 34

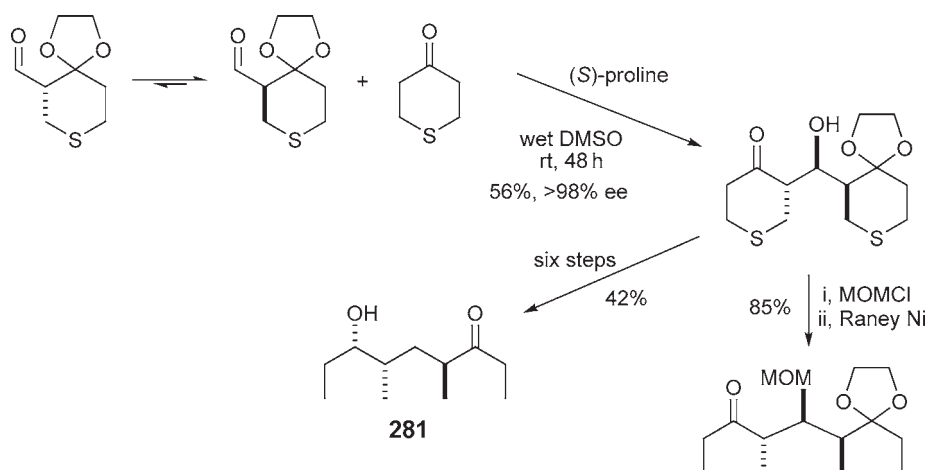
Thiochromanone and thioflavanone undergo dehydrogenation with I_2 in DMSO (Equation 25) <1997HCO223>.



The enantioselective aldol reaction of tetrahydrothiopyran-4-one with aldehydes is efficiently catalyzed by proline. In aqueous DMF, aromatic aldehydes give high yields of the *anti* adduct, characterized by the $^3J_{HH}$ of 7–10 Hz and confirmed by X-ray, with excellent enantioselectivity (Scheme 35). Aliphatic aldehydes give similar results but in DMSO <2004SL1891, 2004TL8347>. Application of this methodology to the reaction of the thiopyranone with racemic 1,4-dioxo-8-thiaspiro[4.5]decane-6-carbaldehyde and with the related meso-6,10-dicarbaldehyde gives a single adduct in each case (ee 98% and 92%, respectively) attributed to dynamic kinetic resolution (Scheme 36) <2005OL1181>. This strategy has been applied to the synthesis of serricornin **281**, the sex pheromone of the female cigarette beetle, in 31% overall yield (Scheme 36) <2006JOC8989>.

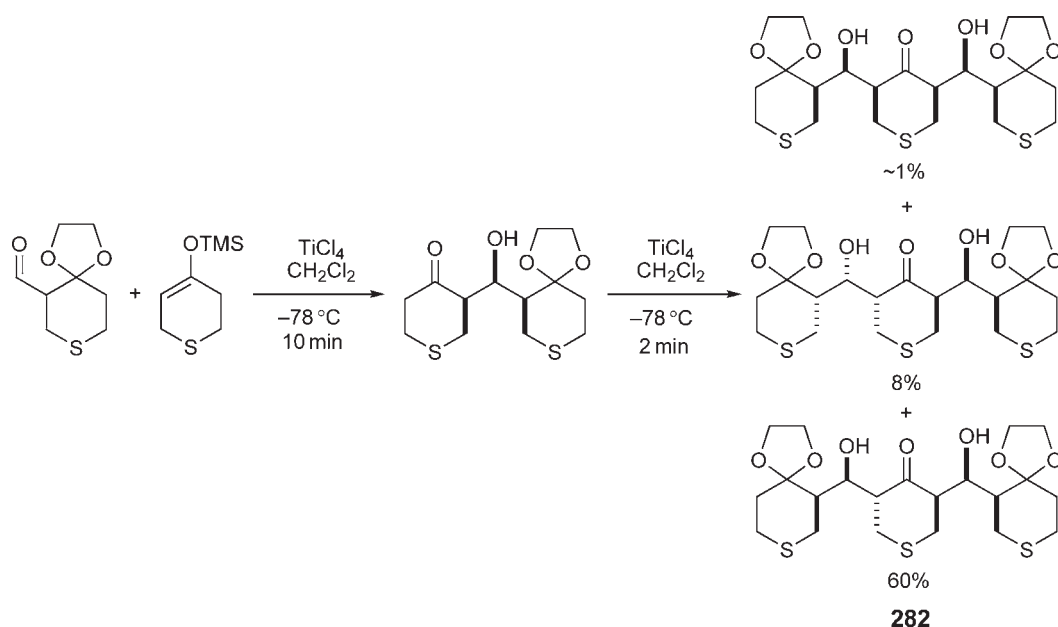


Scheme 35



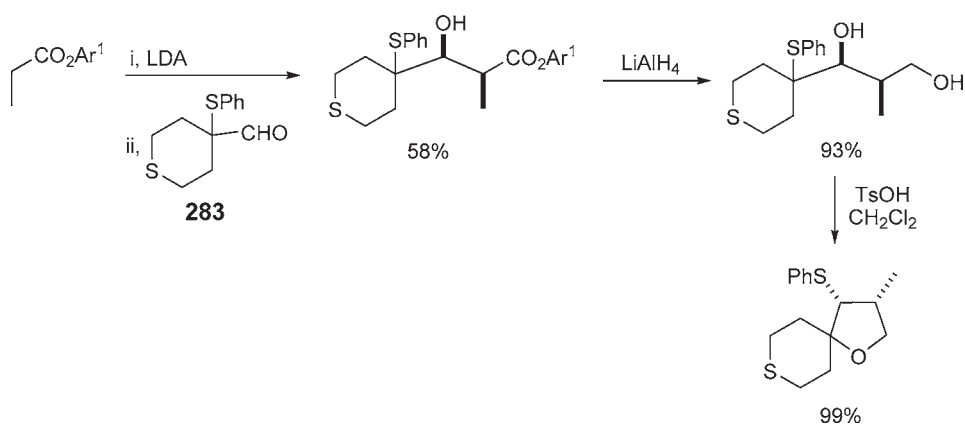
Scheme 36

A route to the individual enantiomers of 1,4-dioxo-8-thiaspiro[4.5]decane-6-carbaldehyde has been described and diastereoselective aldol reactions carried out with the thiopyranone <2004TA2425>. Tetrahydrothiopyran-4-one can also take part in a double aldol reaction, creating a linear array of three tetrahydrothiopyran units **282** (Scheme 37), while an aldol reaction on the adducts themselves allows a unidirectional linear homologation <2000OL1325>. The *syn-anti* isomerization of these aldol products proceeds through an enolization mechanism under imidazole catalysis <2004JOC4808>. Further control of these reactions can be achieved by varying the conditions and the promoters <2002JOC1618>. Desulfurization offers products with potential value in polypropionate synthesis.



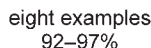
Scheme 37

Stereocontrol of aldol reactions of 4-phenylsulfanyltetrahydrothiopyran-4-carbaldehyde **283** forms an essential feature of syntheses of 1-oxa-8-thiaspiro[4.5]decanes (Scheme 38) <1996TL4581>.



Scheme 38

High yields of bis(arylmethylidene)tetrahydrothiopyran-4-ones are achieved through a double aldol reaction of tetrahydrothiopyran-4-one with benzaldehydes in the presence of *N*-(trimethylsilyl)diethylamine and LiClO_4 (Equation 26) <2005SL2317>.

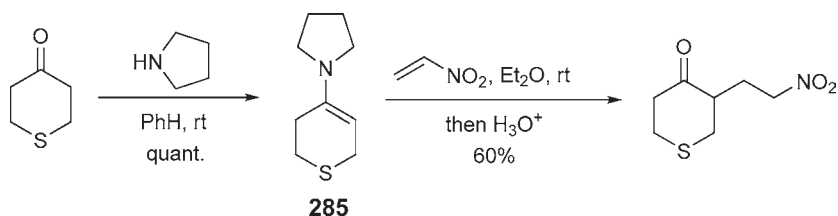
ylidene)cyclohexanone (**Scheme 39**) <2000JOC4584>.

Scheme 39

homoproline tetrazole catalyst (Equation 28) <2005SL611>.

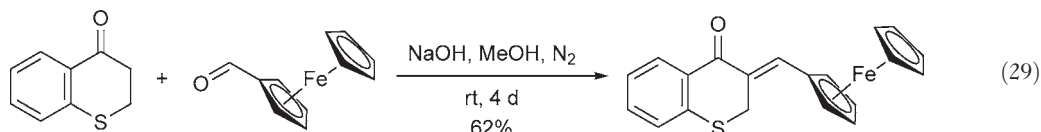


pyran **285** with nitroethene (**Scheme 40**) <1997TA1811>.

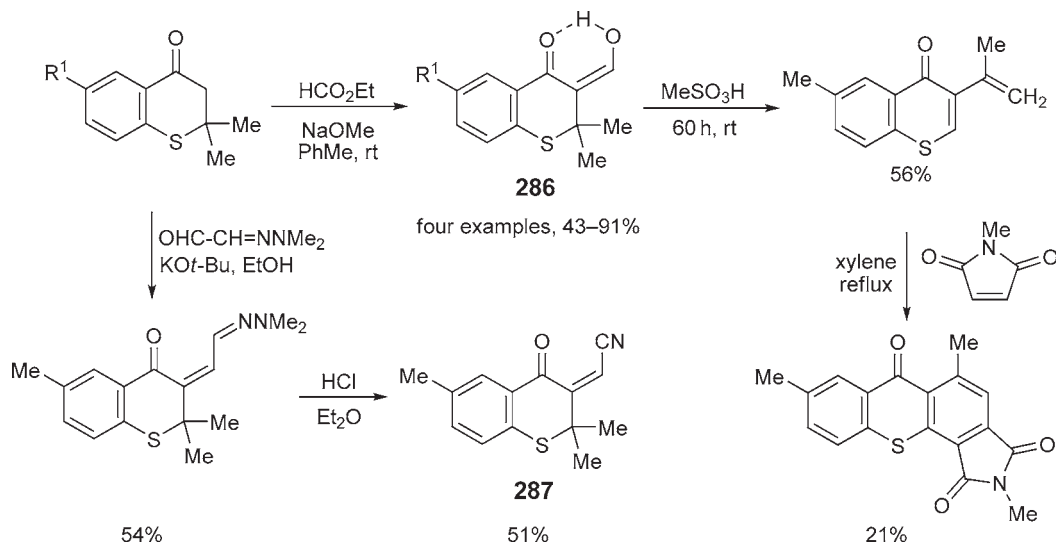


Scheme 40

Under basic conditions, thiochroman-4-one reacts with ferrocenecarbaldehyde to give the 3-(*E*)-2-ferrocenemethylenethiochroman-4-one (Equation 29) <2000JST(524)297>.



The base-catalyzed reaction of 2,2-dimethylthiochroman-4-one with ethyl formate affords 3-formylthiochroman-4-one which exists exclusively as the H-bonded 3-hydroxymethylene tautomer **286**. On stirring in MeSO₃H, this rearranges to 3-isopropylthiochromone which with *N*-methylmaleimide yields the cycloadduct, a heterofused thioxanthone (Scheme 41) <2000J(P1)2930>. 2,2-Dimethylthiochroman-4-ones and naphtho[2,1-*b*]thiopyran-1-one are attacked by glyoxal mono(*N,N*-dimethylhydrazone) to give the 3-(*N,N*-dimethylhydrazonoethylidene) <1997JCM102>, the controlled hydrolysis of which affords the (*Z*)-3-cyanomethylenethiochroman-4-one **287**; a precursor of fused benzothiopyranopyrazoles (Scheme 41) <2000J(P1)2930>.

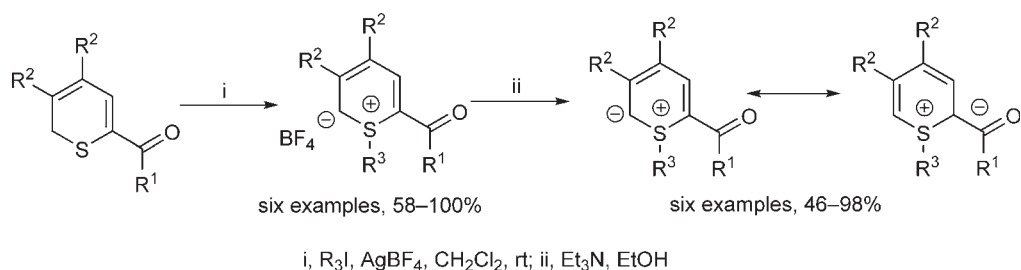


Scheme 41

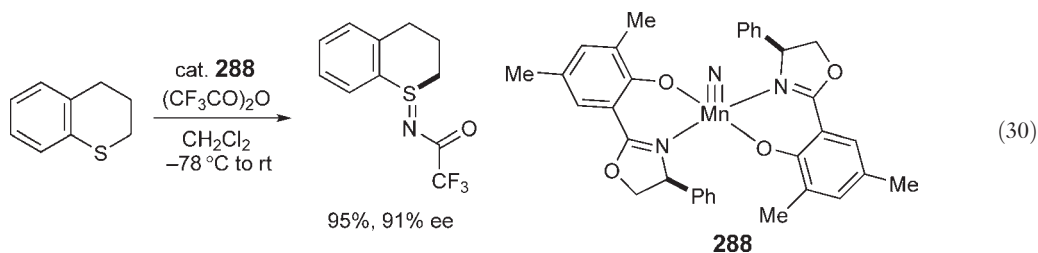
7.10.3.2 Electrophilic Attack at Sulfur

6-Aroyl-2*H*-thiopyrans are alkylated at S to give 1-alkylthiopyranium salts (Scheme 42) <2001J(P1)2269>. Deprotonation with triethylamine affords the stable, dark red thiabenzenes, a reaction which can be reversed by treatment with HBF₄.

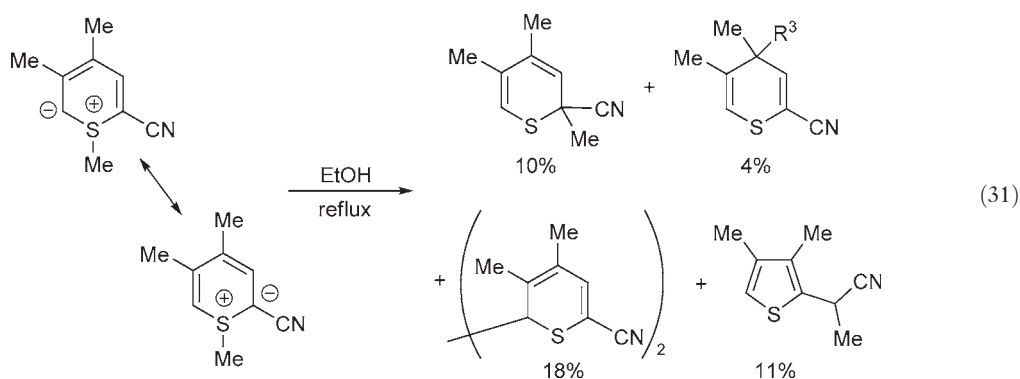
Electrophilic amination of thiochroman by chiral nitridomanganese(v) complexes **288** occurs in high yield but with only moderate enantioselectivity when promoted by (CF₃CO)₂O (Equation 30) <2002HCA3773>. A similar *N*-transfer occurs using *N,O*-bis(trifluoroacetyl)hydroxylamine in the presence of Cu(OTf)₂ <1999OL149>.



Scheme 42

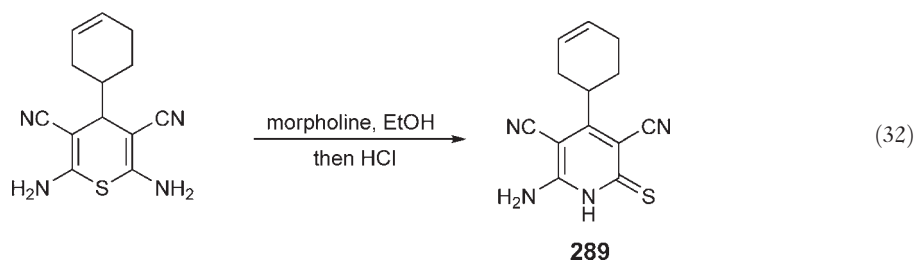


The products of thermolysis of ylidic thiabenzenes depend upon the solvent used but overall comprise 1-alkyl-migrated 2*H*- and 4*H*- thiopyrans and a 2*H*-thiopyran dimer together with ring-contracted thiophene-based derivatives arising from a rearranged 2*H*-thiopyran either via an episulfonium ylide or through an electrocyclic ring opening (Equation 31) <2001J(P1)2269>.

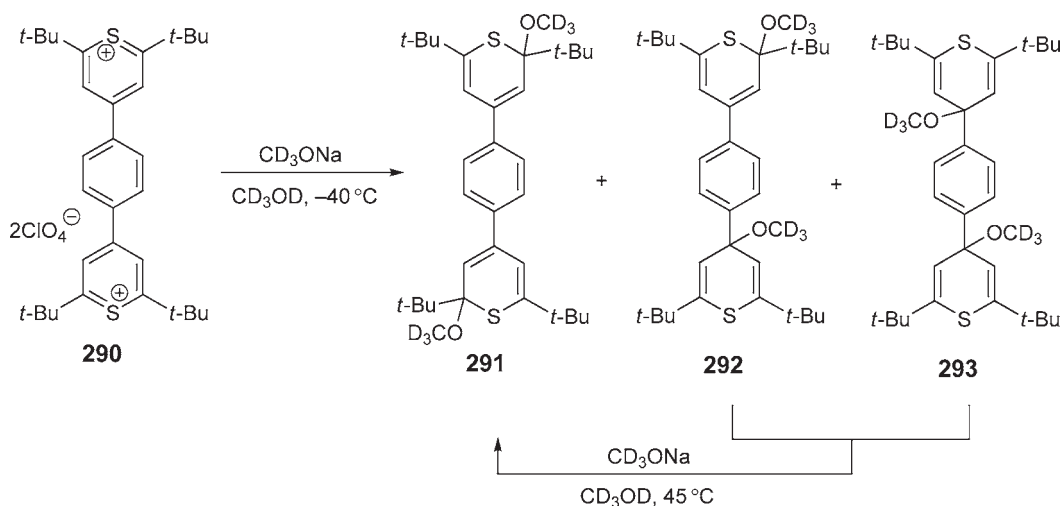


7.10.3.3 Nucleophilic Attack at Ring Carbon

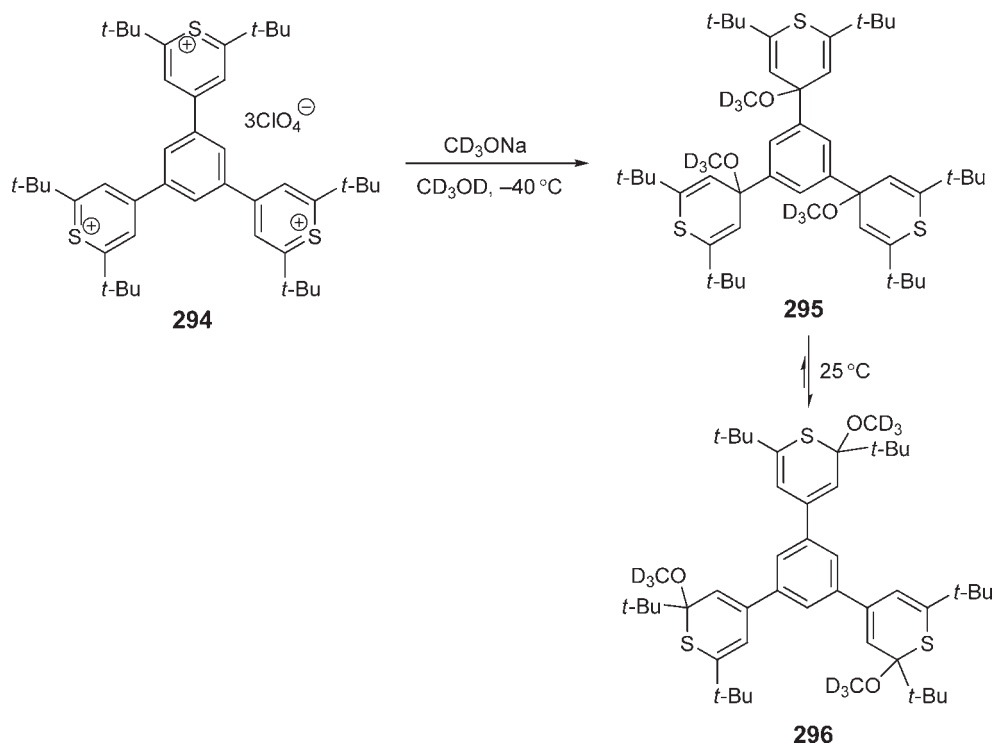
2,6-Diamino-4-(cyclohex-3-enyl)-4*H*-thiopyran-3,5-dicarbonitrile undergoes a 'ring opening–ring closing' sequence with base, here forming the pyridine-2-thione **289** (Equation 32) <2005RJC1537>.



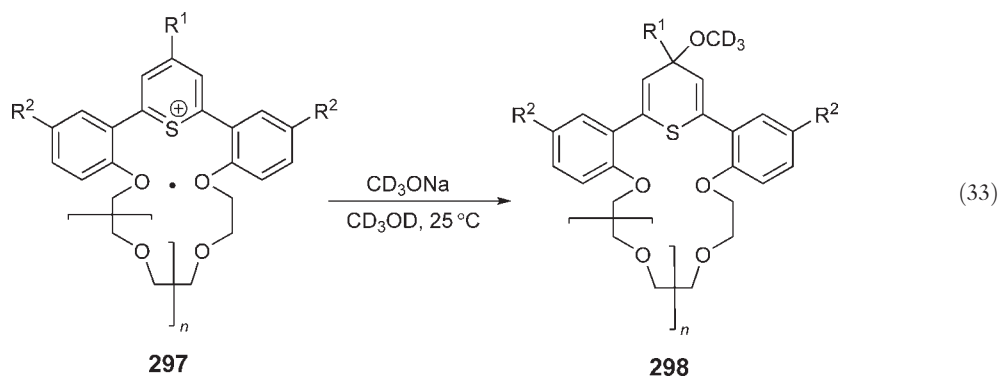
Early interest in the reaction of alkoxides with thiopyrylium salts and the subsequent equilibration between the resulting 4*H*- and 2*H*-thiopyrans <1986JA3409, 1986J(P)271, 1987J(P)1427> has continued. The reaction of the bis-thiopyrylium cation **290** with deuterated methoxide ion at -40°C gives mainly the bis-2*H*-thiopyran adduct **291** with ca. 10% of the mixed 2*H*- and 4*H*- adduct **292** and a trace of the bis-4*H*-thiopyran derivative **293**. After equilibration at 45°C , only the 2*H*-thiopyran product is present (Scheme 43). In contrast, the tris-thiopyrylium cation **294** yields only the tris-4*H*-thiopyran **295** at low temperatures, but only the more stable tris-2*H*-adduct **296** is found after equilibration at 25°C (Scheme 44) <2005JOC6422>. The reaction of the thiopyrylium containing corand **297** with deuterated methoxide ion at 25°C results in the 4*H*-thiopyran **298** (Equation 33) <1996T3509>.



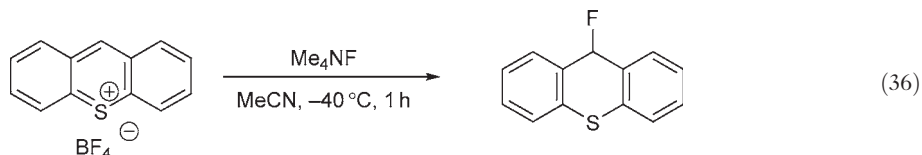
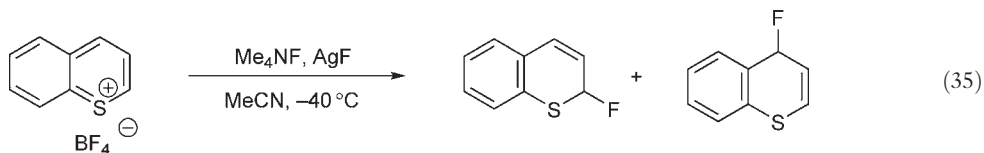
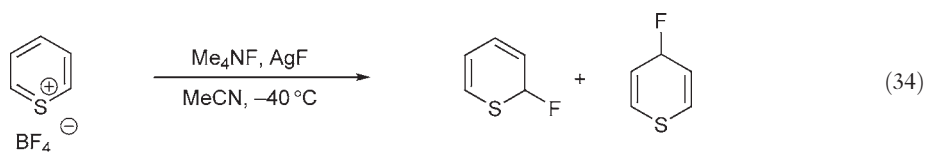
Scheme 43



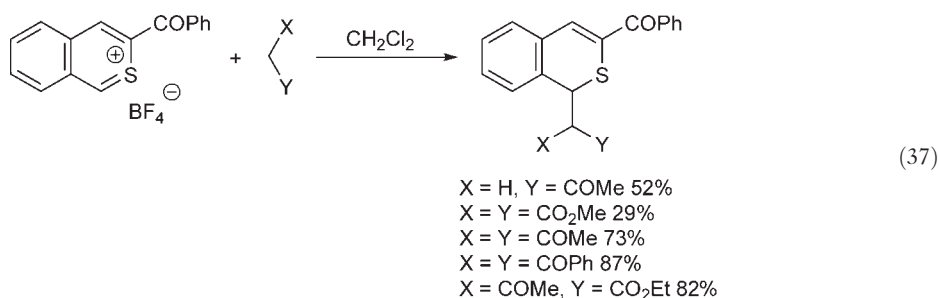
Scheme 44



The strongly basic F^- (as Me_4NF) adds to the 2-position of both thiopyrylium cation and its benzologue, though small amounts of the 4-adducts are also produced; thioxanthylum is attacked at the 9-position (Equations 34–36) <2003JFC(120)49>.

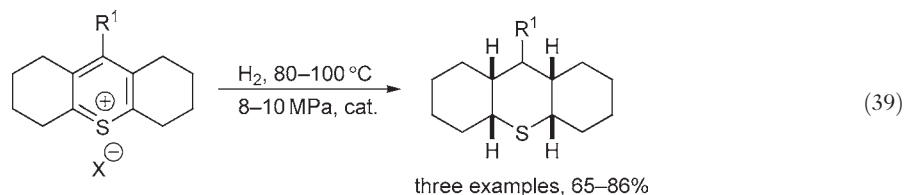
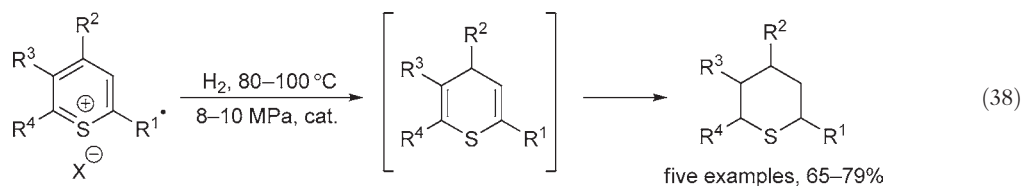


2-Benzothiopyrylium salts react with activated methylene compounds even in the absence of base to give the 1-substituted isothiochromene (Equation 37) <1994J(P1)3129>.

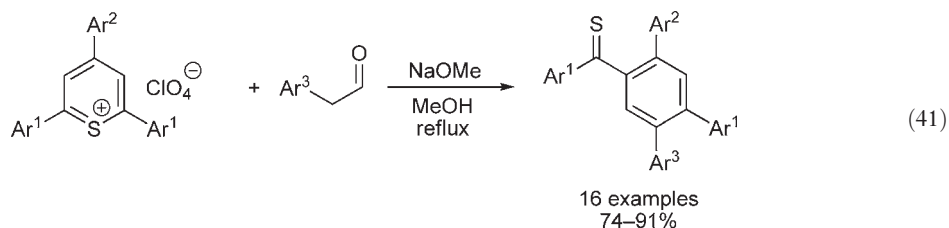
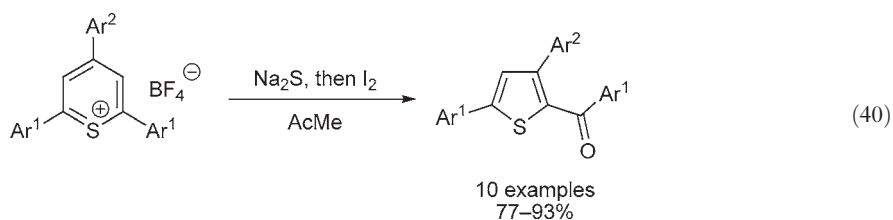


Chemical reduction of 2,4,6-triphenylthiopyrylium cation also yields 2*H*- and 4*H*- thiopyrans with slightly more of the former. However, when electron-withdrawing groups are present in the 2- and 6- phenyl rings, the balance swings significantly in favor of the 4*H*-thiopyran <2002JPO689>. The electrochemical reduction proceeds in two stages with a first wave reduction potential for the 2,4,6-tris(4-methylphenyl)thiopyrylium of -0.29 V corresponding to radical formation and -1.26 V for the subsequent formation of the antiaromatic anion <2002JPO689>. Related data for a series of aminophenyl derivatives and their Se and Te analogues are available <2002JME5123>. Catalytic reduction of the thiopyrylium cation proceeds through the intermediacy of 4*H*-thiopyran, which can be isolated under mild conditions. Various catalytic systems are successful; PtO_2 , Pd/C , $\text{PdS/Al}_2\text{O}_3$, Rh/C , and Pd complexes have all been

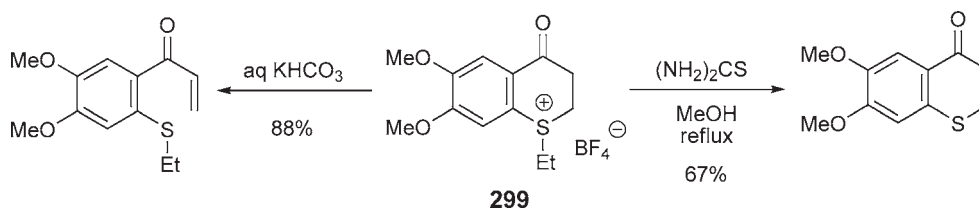
used. The anion plays some role in the reduction since yields decrease in the order CF_3COO^- , Cl^- , BF_4^- , I^- and the amount of catalyst required to effect complete reduction increases in the same sequence (Equation 38). The reduction is equally successful with 5,6,7,8-tetrahydro-1-benzothiopyrylium salts, the *cis*-octahydrothiochromenes being formed initially and leading to *cis*-thiadecalins, and with *sym*-dicyclohexa[*b,e*]thiopyrylium salts which yield *cis-syn-cis*-perhydrothioxanthenes (Equation 39) <2001CHE797>.



On treatment with Na_2S and I_2 , 2,4,6-triarylthiopyrylium salts are converted into 2-aryl-3,5-diarylthiophenes (Equation 40) <2003SC2849> and with arylacetaldehydes they yield 2,4,5-triarylthiobenzophenones (Equation 41) <1994S252>.



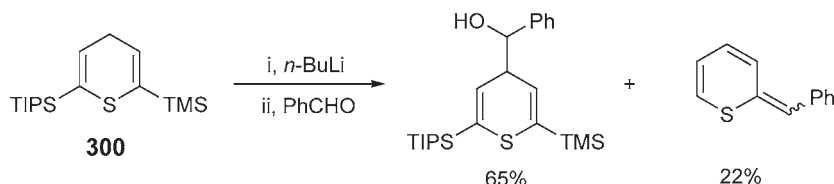
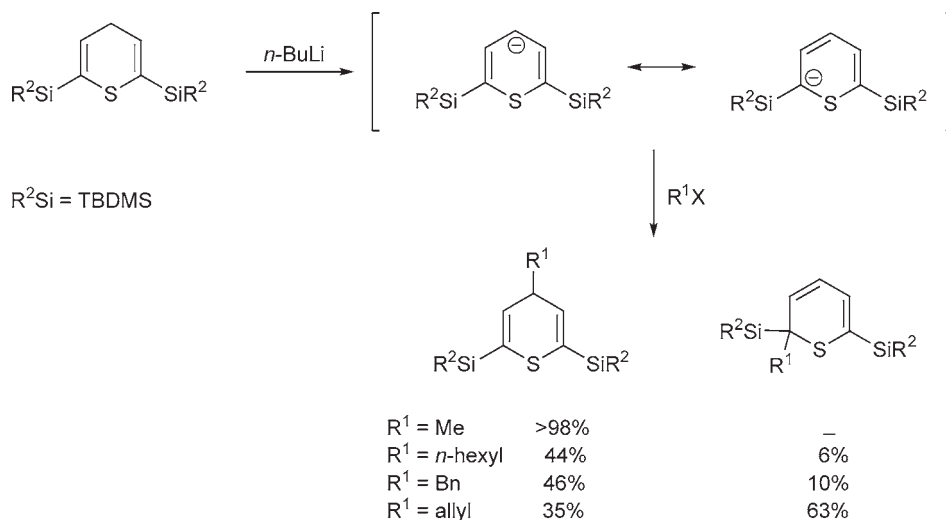
A base-promoted cleavage of the hetero ring of the 4-oxo-3,4-dihydro-2*H*-thiochromenium salt **299** results in the formation of an ethylsulfanyaryl vinyl ketone, while reaction with thiourea produces the thiochroman-4-one (Scheme 45) <1998T5599>.



Scheme 45

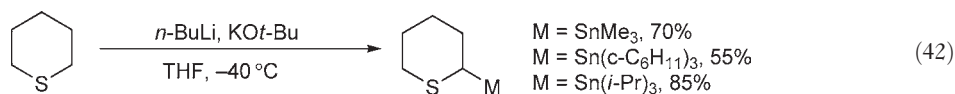
7.10.3.4 Nucleophilic Attack at Hydrogen

Treatment of 2,6-bis(trialkylsilyl)-4*H*-thiopyrans with strong bases generates a deep red color, indicating formation of the resonance stabilized carbanion; subsequent reaction with iodomethane results in exclusive alkylation at C-4. However, with other alkylhalides varying amounts of the 2-alkylated 2*H*-thiopyran are also formed and the overall yield decreases. Two products also result from reaction of the organolithium derived from **300** with benzaldehyde. The benzyl alcohol is the major product and the minor 2-benzylidenethiopyran results from a Petersen reaction (Scheme 46) <2005PS(180)1303>.



Scheme 46

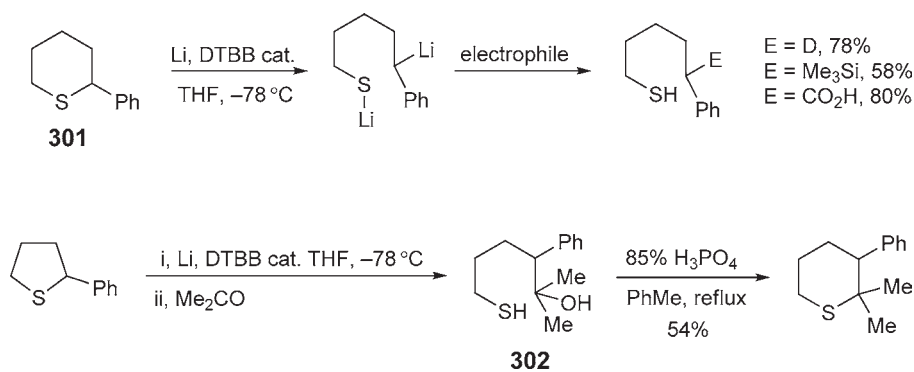
n-Butyllithium together with *KOt*-Bu metallates tetrahydrothiopyran at the 2-position allowing the introduction of trialkyltin moieties at this site (Equation 42) <1997TL8615>.



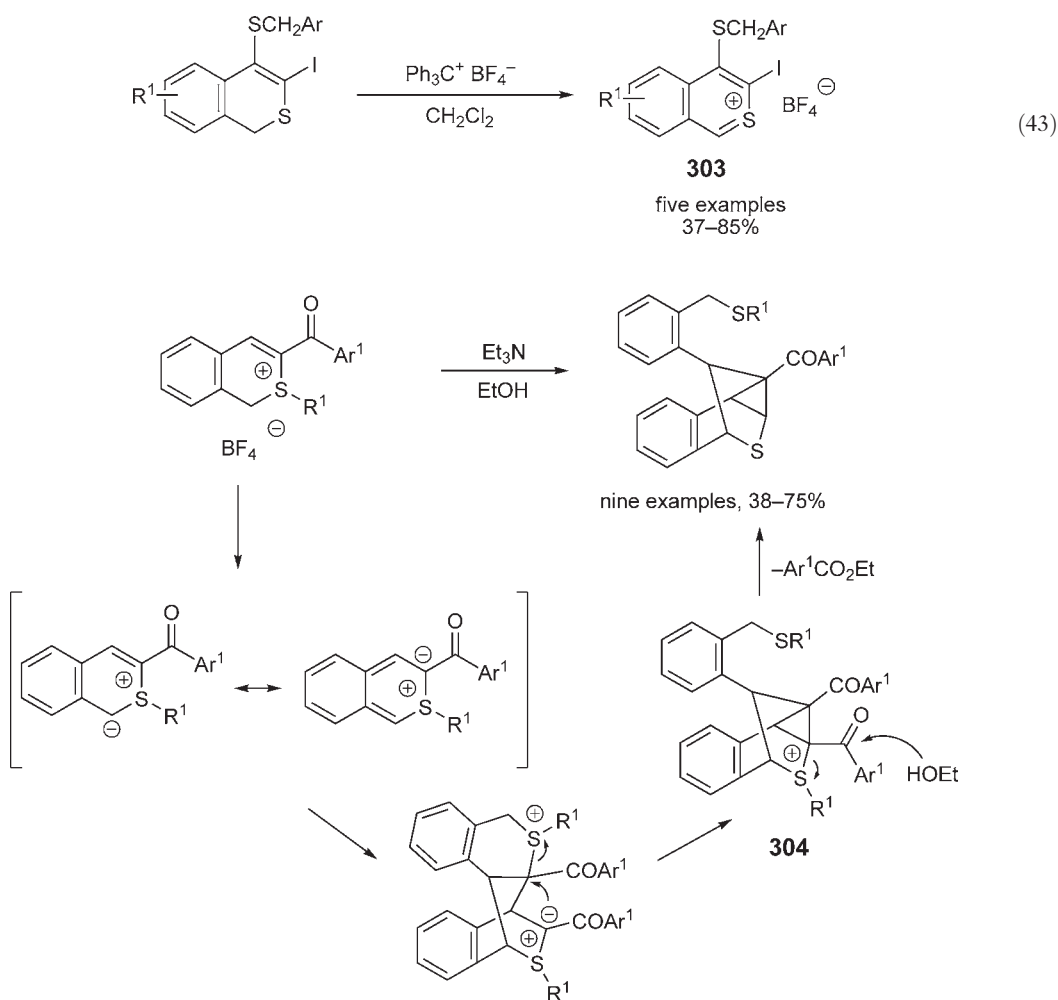
However, treatment of 2-phenyltetrahydrothiopyran **301** with Li and a catalytic amount of 4,4'-di-*t*-butylbiphenyl (DTBB) results in cleavage of the ring and the formation of a benzylic organolithium compound in which the sulfur is retained, thereby offering a regioselective route to functionalized mercaptans. When applied to 2-phenyltetrahydrothiophene, reaction of the Li derivative with acetone and cyclization of the resulting 6-mercaptohexan-2-ol **302** produces 2,2-dimethyl-3-phenyltetrahydrothiopyran (Scheme 47) <1997T5563>.

Hydride ion abstraction from 1*H*-2-benzothiopyrans by triphenylcarbenium fluoroborate produces the highly colored 2-benzothiopyrylium salts **303** (Equation 43) <1998JOC4626>.

Deprotonation of 2-alkyl-3-aryl-1*H*-2-benzothiopyranium salts by triethylamine generates an ylidic 2-thianaphthalene which is resonance stabilized by the 3-aryl group. Behaving as an *o*-quinodimethane, a cycloaddition with unchanged thiopyranium salt follows and a complex benzothiopyran is formed via the sulfonium compound **304** (Scheme 48) <1996CC1659>.

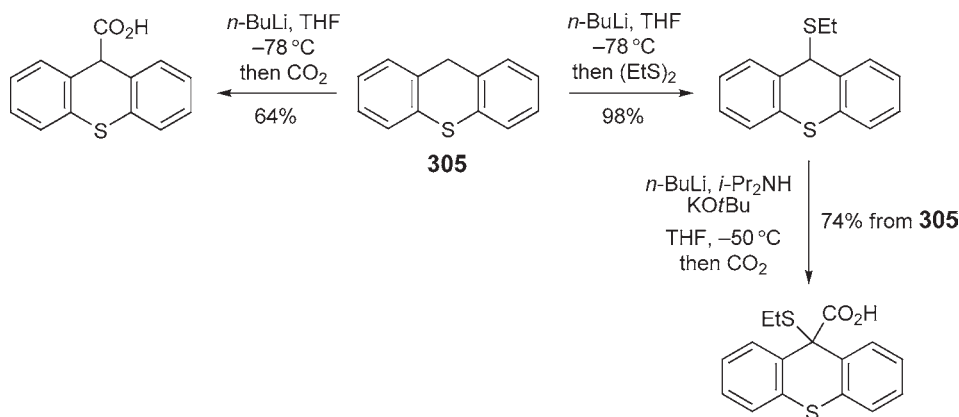


Scheme 47



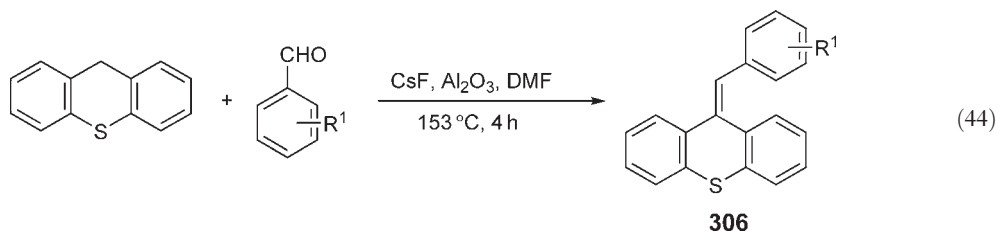
Scheme 48

Thioxanthene **305** is readily metallated by *n*-butyllithium at the 9-position giving access to the 9-carboxylic acid and the ethyl thioether. The latter gives the 9-carbanion on treatment with the superbasic mixture of *n*-BuLi, *i*-Pr₂NH, and KO^t-Bu, and hence gives access to 9-thioethylthioxanthene-9-carboxylic acid (**Scheme 49**) <1998T2251>.

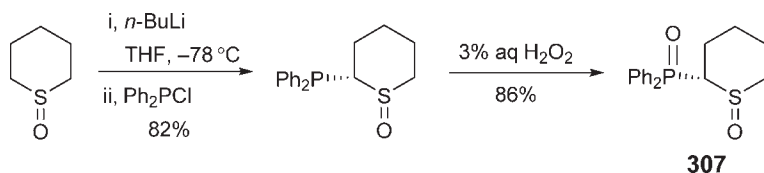


Scheme 49

Under strongly basic conditions, thioxanthene condenses with aromatic aldehydes to afford 9-benzylidene derivatives **306** (Equation 44) <1994S973>.

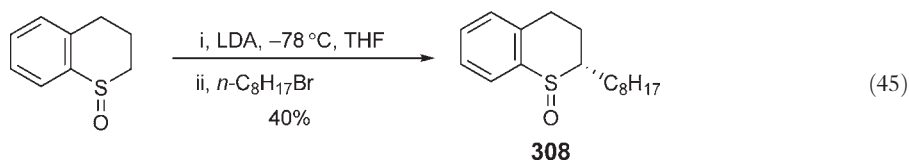


Tetrahydrothiopyran 1-oxide is readily metallated at C-2 with $n\text{-BuLi}$; quenching the reaction mixture with diphenylphosphinyl chloride and subsequent oxidation affords the *trans*-diphenylphosphine oxide **307** (Scheme 50) <1998T1375>.

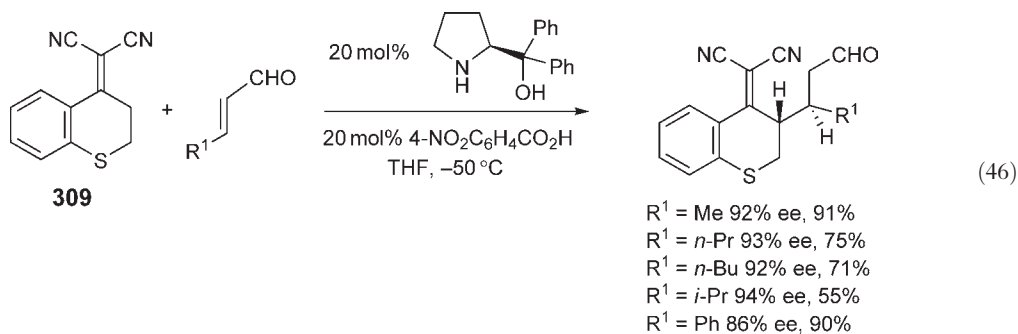


Scheme 50

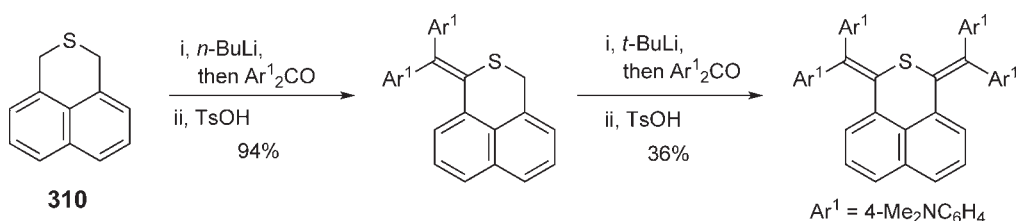
Thiochroman 1-oxide is deprotonated at C-2 with LDA at low temperature; quenching the anion with n -octyl bromide gave the 2-substituted product **308** (Equation 45) <2003PS(178)993>.



The asymmetric vinylogous Michael addition of 4-dicyanovinylthiochromans **309** to α,β -unsaturated aldehydes proceeds under catalysis by chiral α,α -diarylprolinol salts and exhibits excellent regio-, chemo-, diastereo-, and enantio- selectivities (Equation 46) <2006CC1563>.

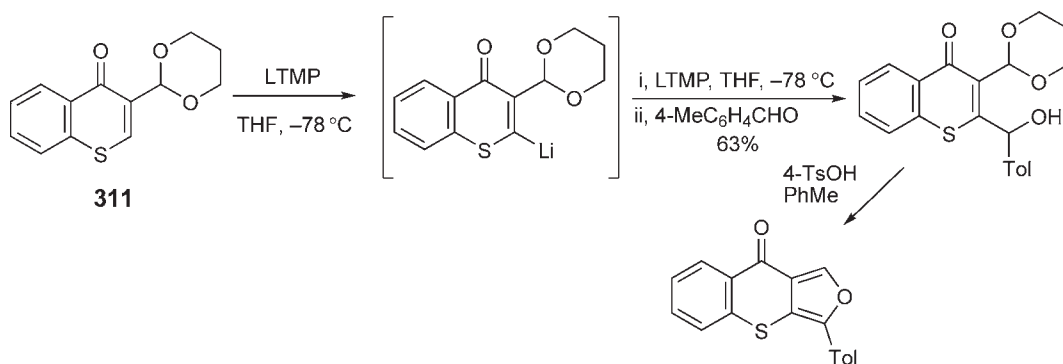


Sequential metallation occurs adjacent to the sulfur atom in *2H,9H*-naphtho[1,8-*cd*]thiin **310** allowing elaboration to 2- and 2,9- substituted derivatives (Scheme 51) <2006TL467>.



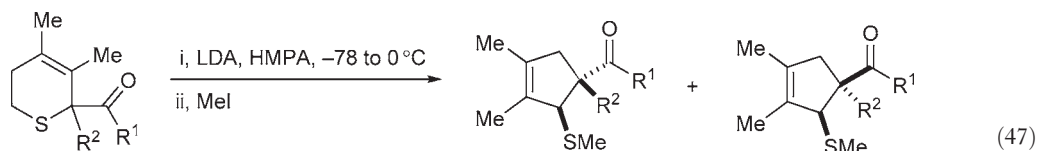
Scheme 51

The directed metallation of the acetal **311** occurs at C-2 with lithium tetramethylpiperide (LTMP) and interception of the anion with 4-tolualdehyde affords the benzylic alcohol. Facile unmasking of the acetal function gave the furo[3,4-*b*]benzothiopyran-9-one (Scheme 52) <2002TL4507>.

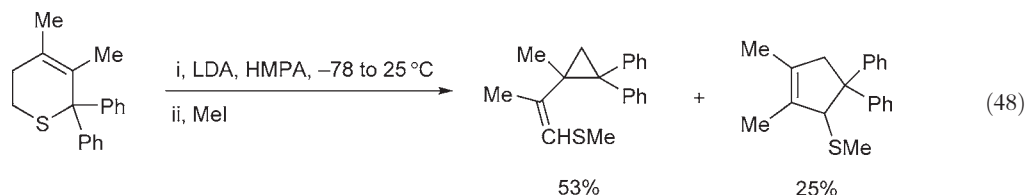


Scheme 52

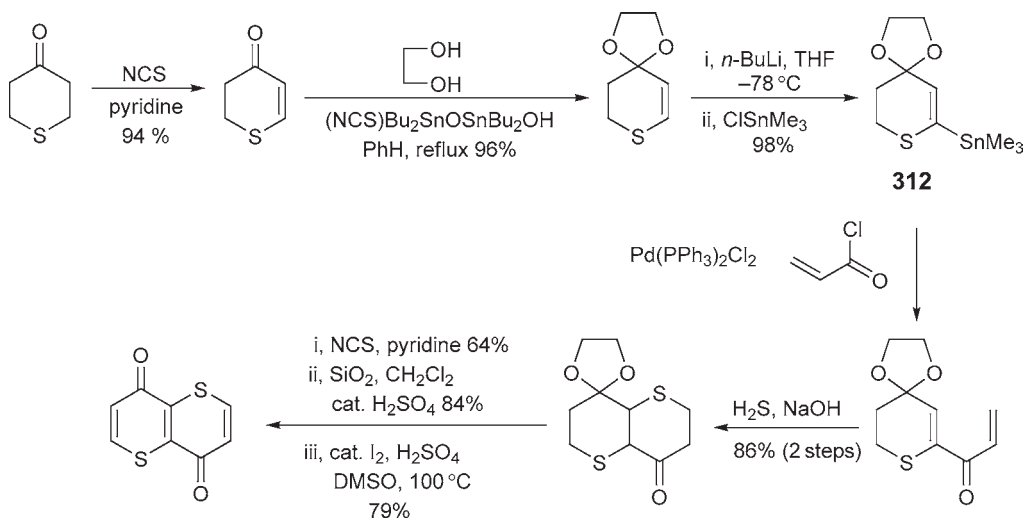
On treatment with LDA followed by quenching with iodomethane, 3,6-dihydro-2*H*-thiopyrans bearing an electron-withdrawing group at the 2-position ring contract to cyclopentenones (Equation 47). The diastereoselectivity of the process is dependent on the substituents both at C-2 and elsewhere in the thiopyran. Under controlled conditions, it is possible to isolate vinyl cyclopropanes, suggesting that these may be intermediates in the formation of the cyclopentenones (Equation 48) <1996JOC4725>.



Ratio 10 : 1 $R^1 = \text{Ph}$, $R^2 = \text{Me}$
 Ratio <1 : 20 $R^1 = \text{Ph}$, $R^2 = \text{Ph}$
 12 examples, 61–95%



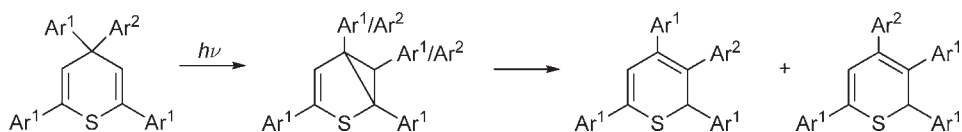
Protected 5,6-dihydro-4*H*-thiopyran-4-one is lithiated at the 2-position allowing the introduction of a 2-SnMe₃ function to give compound **312**. Sequential reactions with propenoyl chloride and H₂S yield the thiopyrano[3,2-*b*]-thiopyran system (**Scheme 53**) <1998EJO1989>.



Scheme 53

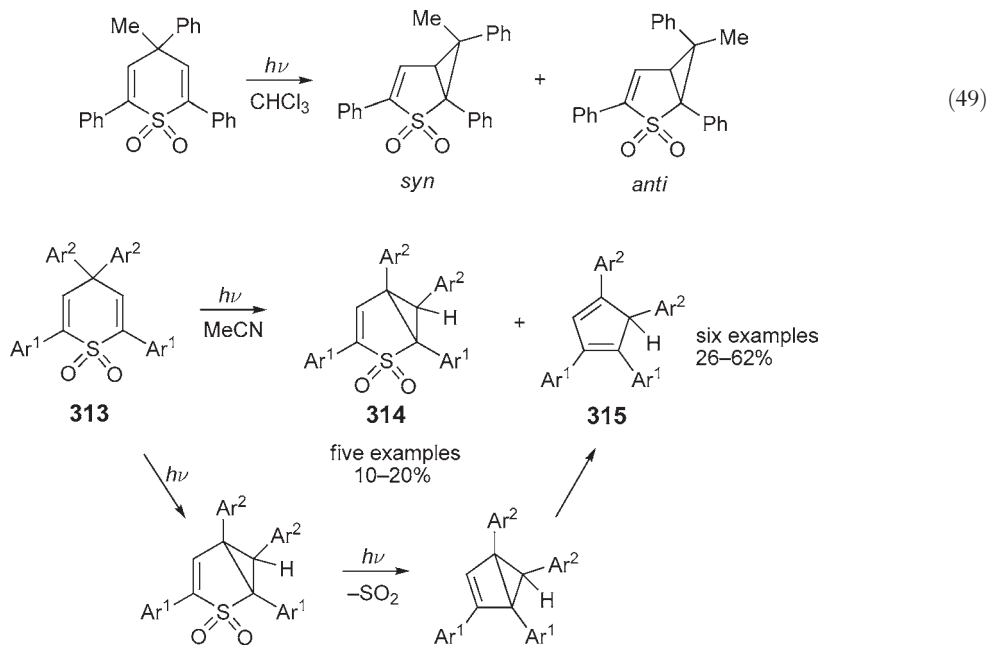
7.10.3.5 Reactions with Radicals and Carbenes

2,4,4,6-Tetrasubstituted 4*H*-thiopyrans are photoisomerized to 2,3,4,6-tetrasubstituted 2*H*-thiopyrans. Unsymmetrically 4,4-disubstituted derivatives can yield a mixture of isomeric 2*H*-thiopyrans. The progress of the reaction can be followed by ¹H NMR as the one singlet for H-3 and H-5 in the 4*H*-thiopyran is replaced by two singlets for H-2 and H-5 in the product <1994JPH(81)21>. The intermediate 2-thiabicyclo[3.1.0]hex-3-enes have been isolated and their conversion into 2*H*-thiopyrans studied (**Scheme 54**) <1997JPH(111)15, 2001JPH(139)45>. 4-Alkyl groups fail to migrate in this mechanism but instead a [1,3]-sigmatropic rearrangement leads to 2,2,4,6-tetrasubstituted 2*H*-thiopyrans characterized by allylic coupling between H-3 and the nonmigrated 4-alkyl group <2004M973>.

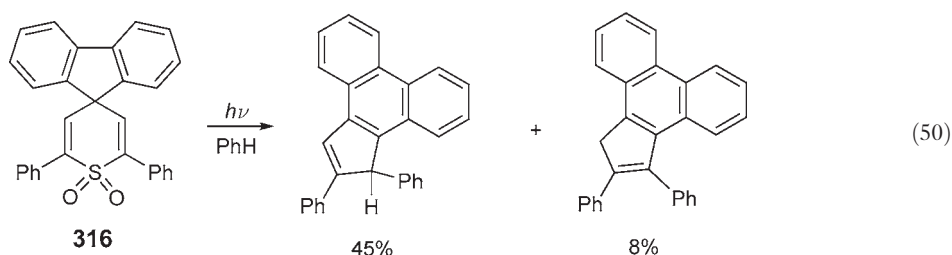


Scheme 54

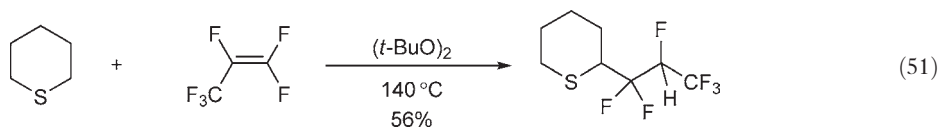
Irradiation of a CHCl_3 solution of 4-methyl-2,4,6-triphenyl-4*H*-thiopyran 1,1-dioxide results in rearrangement involving a *gem.* methylphenyl migration to give cyclopropa[*b*]thiophene 1,1-dioxide as a mixture of *syn* and *anti* isomers (Equation 49). The reaction can be monitored by the disappearance of the H-3/H-5 singlet at δ 6.32 and the growth of four doublets associated with H-4 and H-5 of the two stereoisomers at δ 3.0–3.7 and 6.9–7.0, respectively. A vinyl–vinyl thia-di- π -methane rearrangement is proposed <2001PS(176)203, 2001JPH(138)203, 2005PS(180)2555>. Interestingly, when the irradiation of tetraaryl-4*H*-thiopyran 1,1-dioxides **313** is performed in acetonitrile solution only small amounts of the alternative cyclopropa[*b*]thiophene 1,1-dioxides **314** are obtained and the relatively slow extrusion of SO_2 is observed resulting in the tetraarylcyclopentadienes **315** (Scheme 55). Formation of **314** was not observed in either benzene or methanol solution. Two isomeric cyclopentaphenanthrenes result from the irradiation of the spirofluorenyl analogue **316** (Equation 50) <1993CCC869>.



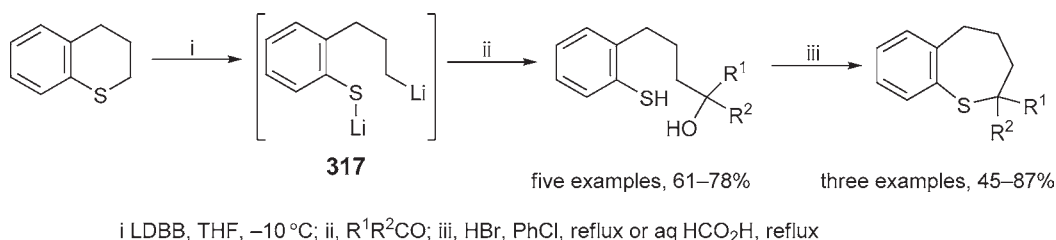
Scheme 55



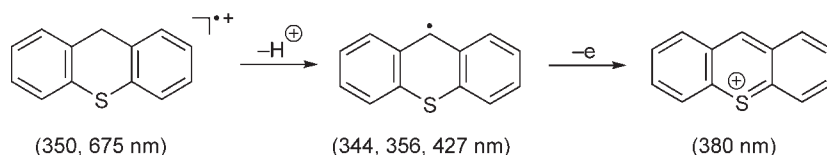
Hexafluoropropene reacts with tetrahydrothiopyran in the presence of di-*t*-butyl peroxide to give the 2-fluorinated heterocycle (Equation 51) <1996IC6676>.



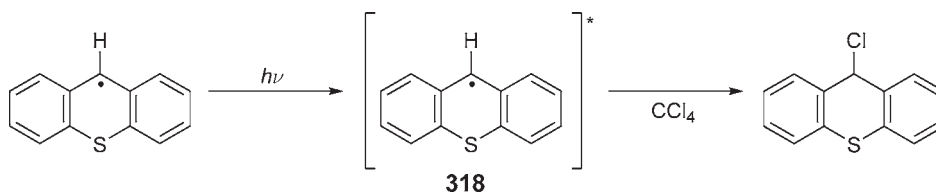
Cleavage of the S–C(2) bond occurs when thiochroman is treated with the radical anion 4,4'-di-*t*-butylbiphenylide (LDBB). The resulting ring-opened dianion **317** has good synthetic potential. For example, the alcohols arising from reaction with carbonyl compounds can be cyclized under acidic conditions to benzothiepines (Scheme 56) <1995TL4459>.

**Scheme 56**

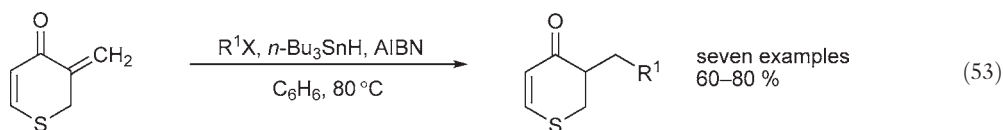
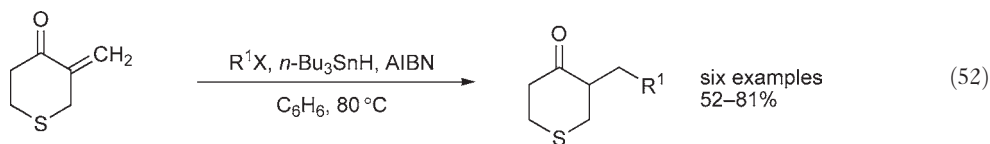
Transient radicals and radical cations generated by the γ - and photo-irradiative oxidation of thioxanthene in the presence of an electron scavenger have been characterized spectroscopically and kinetically (**Scheme 57**) <1996JPC13539>.

**Scheme 57**

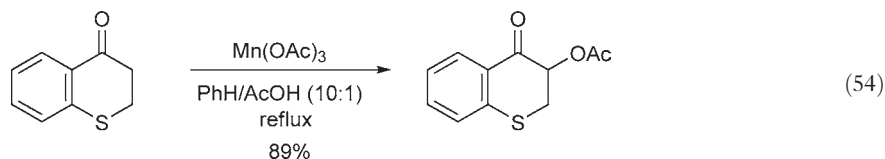
It appears that thioxanthene-Cl π -complexes are formed during the generation of the 9-thioxanthenyl radical in CCl_4 and that photobleaching is a result of transfer of chlorine from the solvent to the excited thioxanthene radical **318** (**Scheme 58**) <2001MI331>.

**Scheme 58**

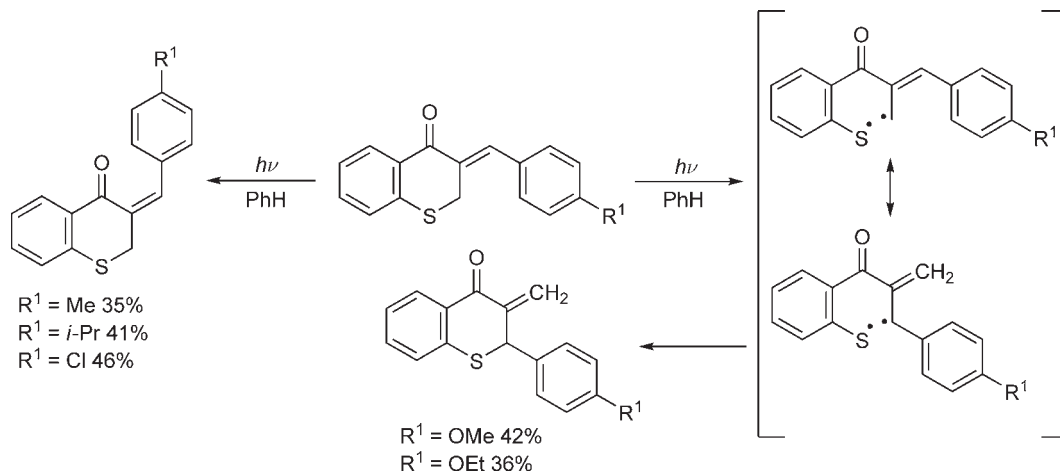
The 3-methylene derivatives of both 2,3-dihydro- and tetrahydro- 4*H*-thiopyran-4-ones undergo a radical-promoted addition of alkyl and aryl halides producing 3-substituted thiopyran-4-ones (**Equations 52 and 53**) <1996SL261>.



3-Acetoxylation of thiochroman-4-one can be accomplished in excellent yield using $\text{Mn}(\text{OAc})_3$ in a mixed benzene–acetic acid solvent (**Equation 54**) <2004T3427>.

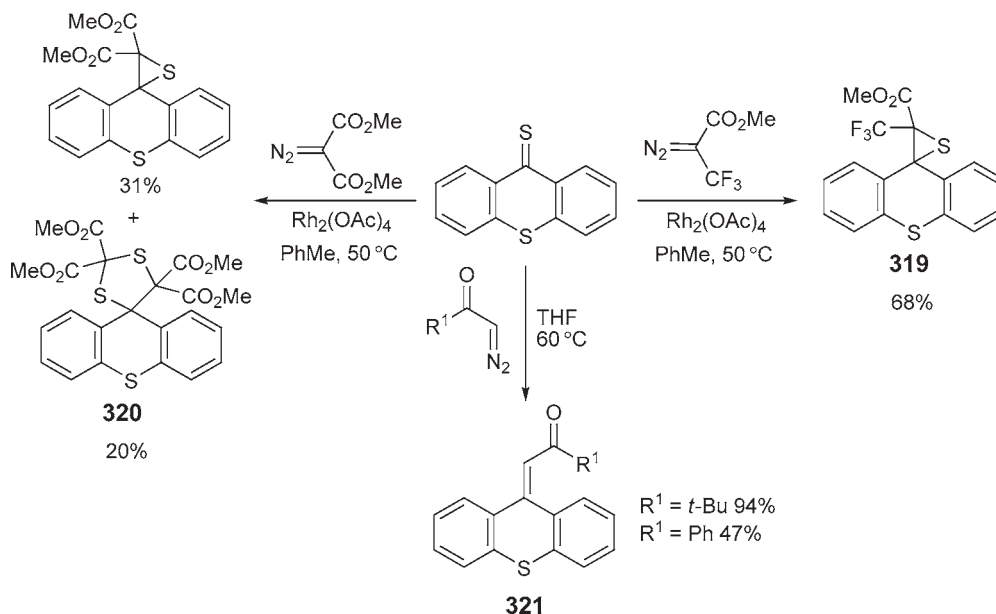


The products from the photoisomerization of (*E*)-3-arylidene-thiochroman-4-ones depend on the substituent in the arylidene moiety. Moderate yields of the (*Z*)-isomer result with the alkyl- and halogeno-substituted derivatives, but the alkoxyphenyl compounds rearrange to the 3-methylidene-thioflavanones. Homolytic cleavage of the S–C(2) bond and stabilization of the radical at the benzylic position by the alkoxy group allows recyclization at that site (Scheme 59). Similar irradiation of 3-arylidene-thioflavanones results in the same rearrangement accompanied by (*E*) → (*Z*) isomerization of both starting material and the rearranged product [1996J(P2)547].

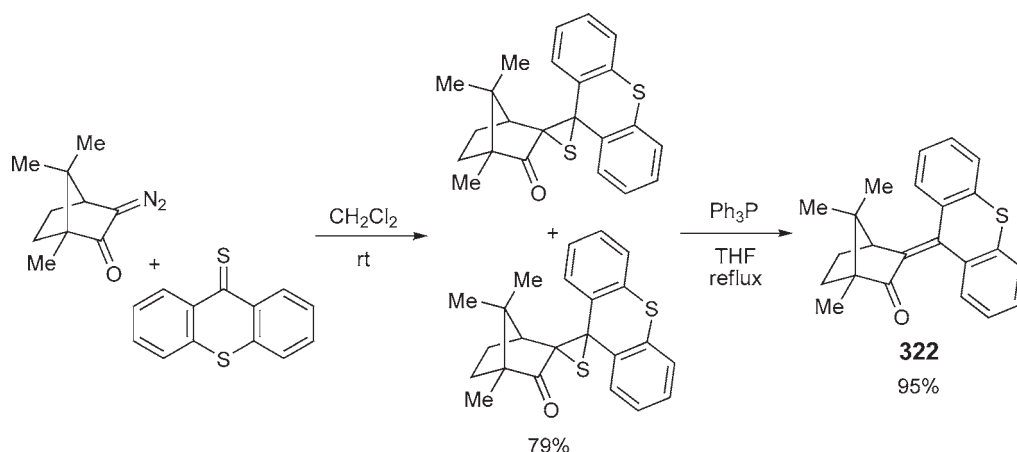


Scheme 59

The carbene generated from methyl 2-diazo-3,3,3-trifluoropropanoate in the presence of $\text{Rh}_2(\text{OAc})_4$ adds to the thiocarbonyl group of thioxanthen-9-one to give the thiirane **319** [1996HCA1537]. Using dimethyl diazomalonate as the carbene source, a spiro[1,3-dithiolane-4,9'-thioxanthene] **320** is also produced [1996HCA1785], while with α -diazoketones desulfurization follows the initial 1,3-dipolar electrocyclic cyclization and the unsaturated ketones **321** result (Scheme 60) [1996HCA855]. α -Diazocamphor also undergoes a [2+3] cycloaddition with this thione, yielding a mixture of isomeric thiiranes which has been desulfurized by Ph_3P to give a 3-(thioxanthen-9-ylidene)-norbornan-2-one **322** (Scheme 61) [2006H(68)33].



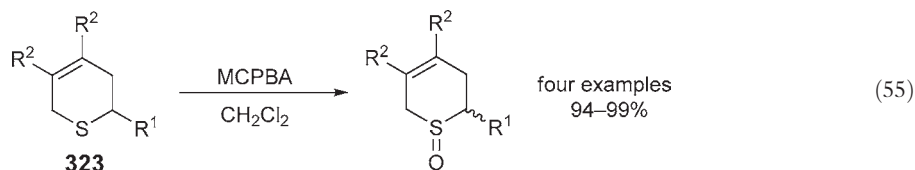
Scheme 60



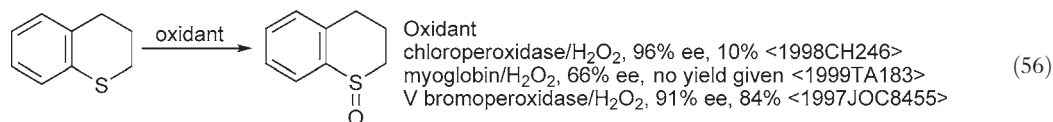
Scheme 61

7.10.3.6 Oxidation at Sulfur

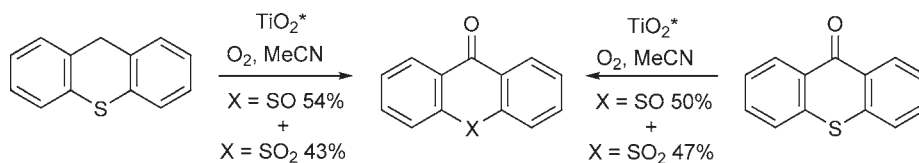
2-Substituted 3,6-dihydro-2*H*-thiopyrans **323** are oxidized to a mixture of the *cis* and *trans* 1-oxides by MCPBA, with the latter the major product (Equation 55) <2001J(P1)2269>.



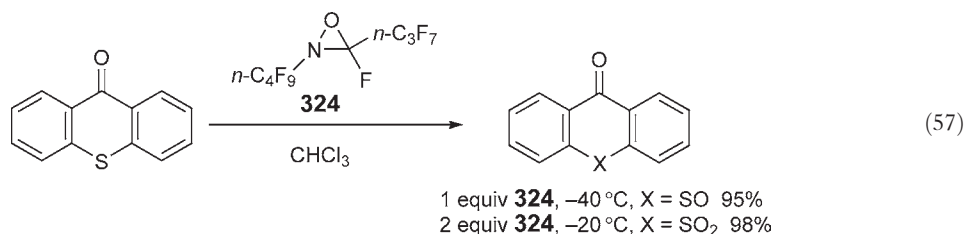
Both thiochroman and isothiochroman gave (*R*)-sulfoxides in moderate yield and enantioselectivity when biotransformed by *Mortierella isabellina* ATCC 42613 <1999CJC463>. Thiochromans are oxidized to the sulfoxides by H_2O_2 under catalysis by chloroperoxidase in good yield and with high enantioselectivity when the peroxide is added continuously to a mixture of the sulfide and enzyme in a citrate buffer at pH 5.0. Similar success attends the reaction with thiochromanone <1998CH246>. Enantiospecific oxidation of thiochroman to the (*S*)-1-oxide with up to 66% ee has been achieved using whale myoglobin mutant <1999TA183> and with up to 91% ee using vanadium bromoperoxidase as catalyst (Equation 56) <1997JOC8455, 1998T15293>.



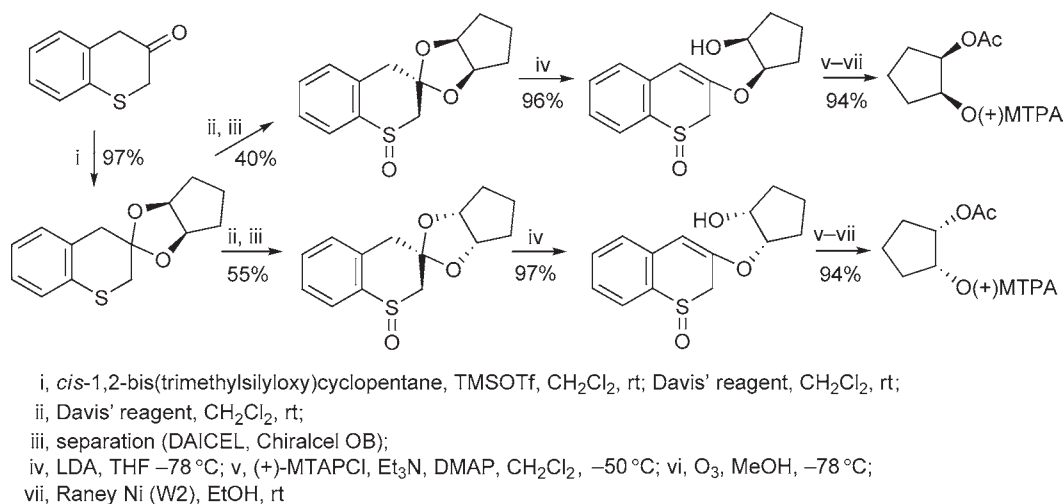
Both thioxanthene and thioxanthone give a ca. 1:1 mixture of sulfoxide and sulfone in high overall conversion in a TiO_2 -mediated photocatalytic oxidation (Scheme 62) <1998JPH(114)213>. Thioxanthone is oxidized to either its sulfoxide or sulfone in high yields and with excellent selectivity by stoichiometric quantities of perfluoro-*cis*-2,3-dialkyloxaziridines **324** at -40°C (Equation 57) <1994JOC2762>.



Scheme 62

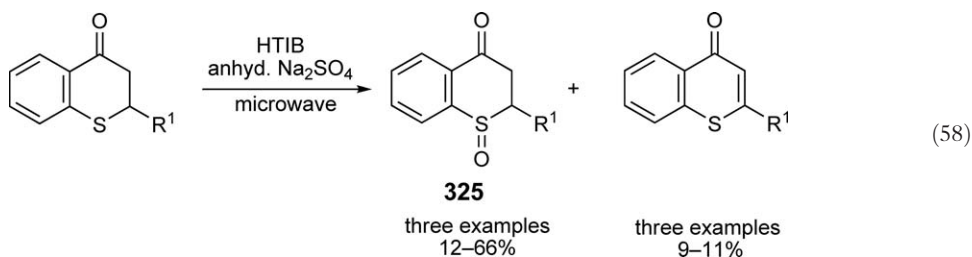


Acetalization of thiochroman-3-one gives a 1:1 diastereomeric mixture and subsequent oxidation with Davis' reagent, *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine, yielded the sulfoxides each with a 4:1 enantioselectivity. Chiral chromatographic separation of the diastereomers preceded isolation of the major enantiomers. β -Elimination and isomerization of the double bond then produced the individual thiochromene 1-oxide diastereomers. The generation of an α -sulfinyl carbanion effects the cleavage of one of the acetal C-O bonds with the protected diol released in a final ozonolysis step. The stereochemical results indicate that it is the C-O bond *syn* to the sulfoxide function that is cleaved (**Scheme 63**) <1996TA29>.

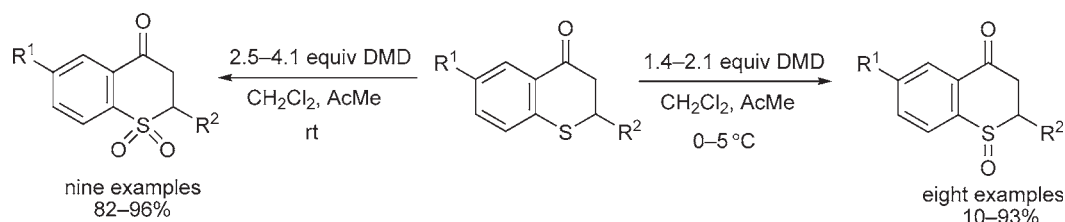


Scheme 63

Treatment of thiochroman-4-one and some 2-substituted derivatives with [hydroxy(tosyl)iodo]benzene (HTIB) admixed with anhydrous sodium sulphate and in the absence of solvent affords the sulfoxide **325** together with some thiochromone (**Equation 58**) <2004ARK183>.



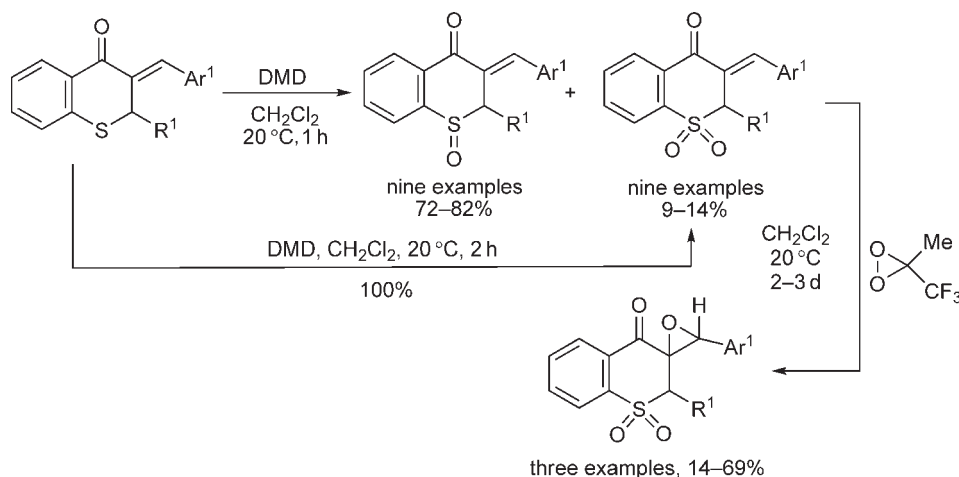
The sulfoxidation of 2-substituted thiochroman-4-ones by dimethyldioxirane (DMD) is high yielding but occurs with low diastereoselectivity, showing only a slight preference for the *cis* product. Nevertheless, chromatographic separation can be achieved, with the *cis*-sulfoxide being the more polar diastereomer, and assignment of the NMR signals to each isomer was possible. A downfield shift of ca. 0.7 ppm for H-3_{ax} and upfield shifts in the range 0.1–0.24 ppm for both H-2 and H-3_{eq} are noted for the *cis* compounds. With the aid of PM3 calculations, the S=O group was placed in a pseudoaxial position in the *cis* diastereoisomer and pseudoequatorial in the *trans*; in both isomers, the 2-methyl is pseudoequatorial. Using an excess of DMD results in complete conversion to the 1,1-dioxides (**Scheme 64**).



Scheme 64

Similarly, thiochromones are converted into their 1,1-dioxides; even using a deficiency of DMD very little 1-oxide is produced and it appears that the sulfoxide is very much more reactive towards DMD than the parent sulfide. This feature has been attributed to the different shapes, with the transannular stabilization of the transition state involving the lone pair of electrons on sulfur and the carbonyl function in the sulfoxide boat conformation not being possible for the planar sulfide. The amount of sulfoxide is increased in hydrogen bonding solvents <2001JOC2275>.

(*E*)-3-Arylidenthiochroman-4-ones possess thioether and α,β -unsaturated ketone functionalities both of which are susceptible to oxidation by DMD. In fact, chemoselective oxidation at sulfur is observed with a separable mixture of the sulfoxide and sulfone being produced in >5:1 ratio. A similar situation holds for the related thioflavanones. Epoxidation of the alkenic double bond in the thiochromanone 1,1-dioxides alone can be achieved using methyl(trifluoromethyl)-dioxirane (Scheme 65) <1994T13113>. However, reaction of NaOCl with 3-arylidenthioflavanones gives the epoxide and subsequent oxidation with DMD then gives a mixture of the sulfoxide and sulfone <2003MRC193>.



Scheme 65

A selection of methods which have been used to convert thiopyrans and related compounds to their 1-oxides or 1,1-dioxides is presented in Table 28 and reagents used to oxidize various thiopyranone derivatives at sulfur are collated in Table 29.

7.10.3.7 Cycloaddition Reactions

Reaction of the methylthiabenzene with DMAD affords three different 1:1 adducts in proportions influenced by the solvent used (Equation 59) <2000MI22>.

Electron-rich 2*H*-thiopyrans react readily with reactive dienophiles such as maleic anhydride, generally giving the *endo* adduct in good yield. However, less reactive dienophiles such as acrylates requires catalysis to prevent the need for elevated temperatures which may cause decomposition of the thiopyran. Lewis acids facilitate such reactions which can exhibit high stereoselectivity. Thus 4-*tri-isopropylsilyloxy*-2*H*-thiopyran shows a preference for the *exo*

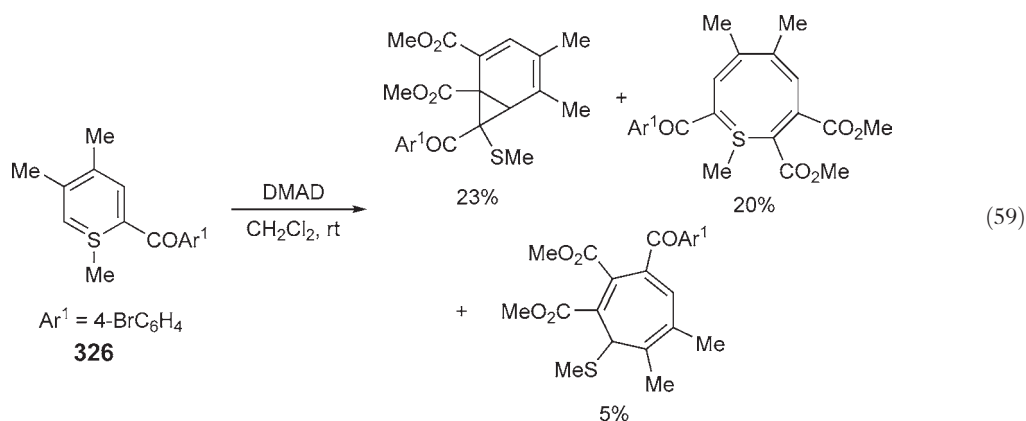
adduct (Equation 60), whereas the reaction with the corresponding 5-substituted thiopyran **327** is *endo* selective (Equation 61) <1992CJC2627>. The thiopyrans can serve as equivalents of unreactive *cis*-substituted dienes since desulfurization is facile <1990TL845, 1991CJC1487>.

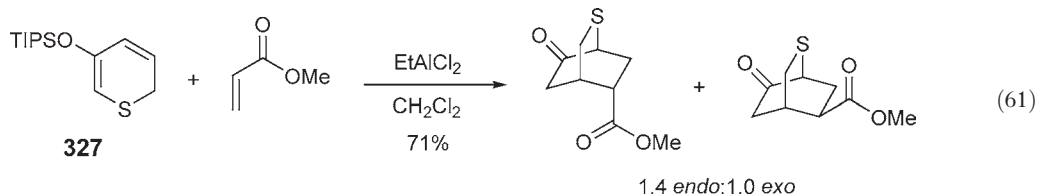
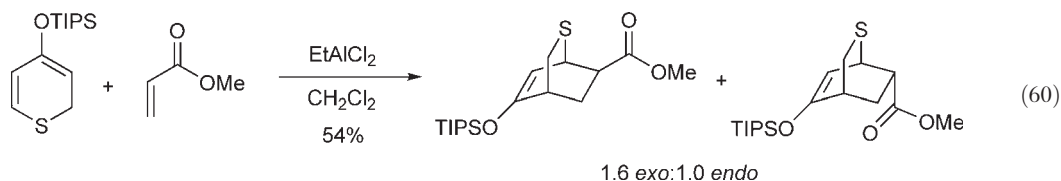
Table 28 Oxidation of thiopyrans and related compounds

Substrate	Reagent	Product	Yield (%)	Reference
Thiopyran	NaIO ₄	1-oxide	62	2006T2603
	H ₂ O ₂ /AcOH	1,1-dioxide	96	2005PS(180)2555
Dihydrothiopyran	MCPBA	1-oxide	95	2001J(P1)2269
Tetrahydrothiopyran	NaIO ₄	1-oxide	96	2005OBC1402
	H ₂ O ₂ , Na ₂ WO ₄ cat.	1,1-dioxide	59	2004SC567
	Fe(NO ₃) ₃ on SiO ₂	1-oxide	81	1996OPP705
	NaClO ₂ Mn(III) cat.	1-oxide	72	1996SC1875
Thiochromene	MCPBA	1-oxide	89	1995T13277
Thiochroman	DET, TBHP, Ti(OPr) ₄	1-oxide	82	2003PS(178)993
	H ₂ O ₂ /CH ₃ COCF ₃	1-oxide	75	2001TA1551
Thiasteroid	MCPBA	1-oxide	88	2000SL418
Thiasteroid	xs MCPBA	1,1-dioxide	85	2005T9405

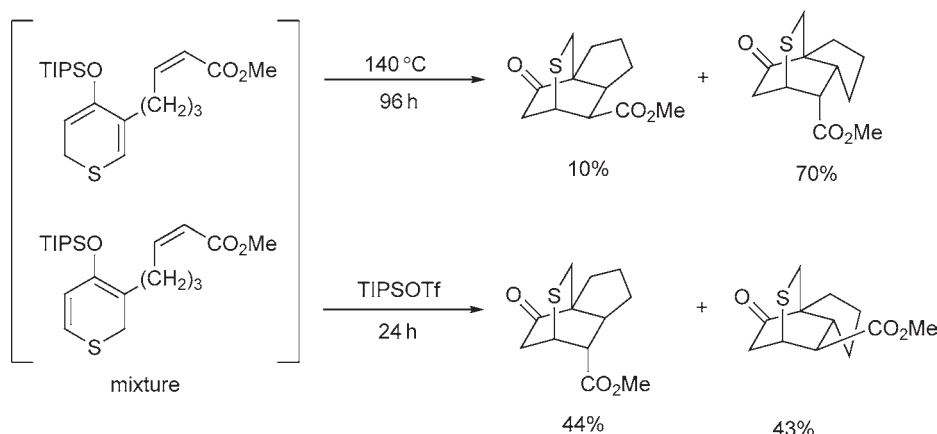
Table 29 Oxidation of thiopyranones and related compounds

Substrate	Reagent	Product	Yield (%)	Reference
Tetrahydrothiopyranone	MeCO ₃ H	1,1-dioxide	89	1995JOC1665
	NaClO ₂ Mn(III) cat.	1-oxide	66	1996SC1875
Reduced thiopyranone	MCPBA	1-oxide		2003RJO1772
Thiochromone	H ₂ O ₂ /AcOH	1,1-dioxide	89	2005PS(180)1315
Thioflavone	MCPBA	1-oxide	90	1996JME1975
Thioxanthone	NaIO ₄ , RuCl ₃ cat.	1,1-dioxide	92	1994TL4955
	14 equiv H ₂ O ₂ /ZrCl ₄	1-oxide	99	2006TL2009
	20 equiv H ₂ O ₂ /ZrCl ₄	1,1-dioxide	99	2006TL2009
	H ₂ O ₂ /(CF ₃) ₂ CHOH	1-oxide	14	2006CEJ3389
	H ₂ O ₂ /AcOH/reflux	1,1-dioxide	81	2006CEJ3389
	H ₂ O ₂ -urea/HCO ₂ H	1,1-dioxide	88	1999JPR184
	H ₂ O ₂ -urea/TFAA	1,1-dioxide	90	1999SC2235
Thiochromanone	H ₂ O ₂ /CH ₃ COCF ₃	1-oxide	50	2002CH400
	H ₂ O ₂ /Ti complex/SiO ₂	1-oxide	92	1998CC1807
	CAN/SiO ₂	1-oxide	85	1998SC2969
	MMPP/SiO ₂	1-oxide	100	1997S764
	NaIO ₄	1-oxide	60	1996TA1089
	MMPP on silica gel	1,1-dioxide	84	1998SC2983





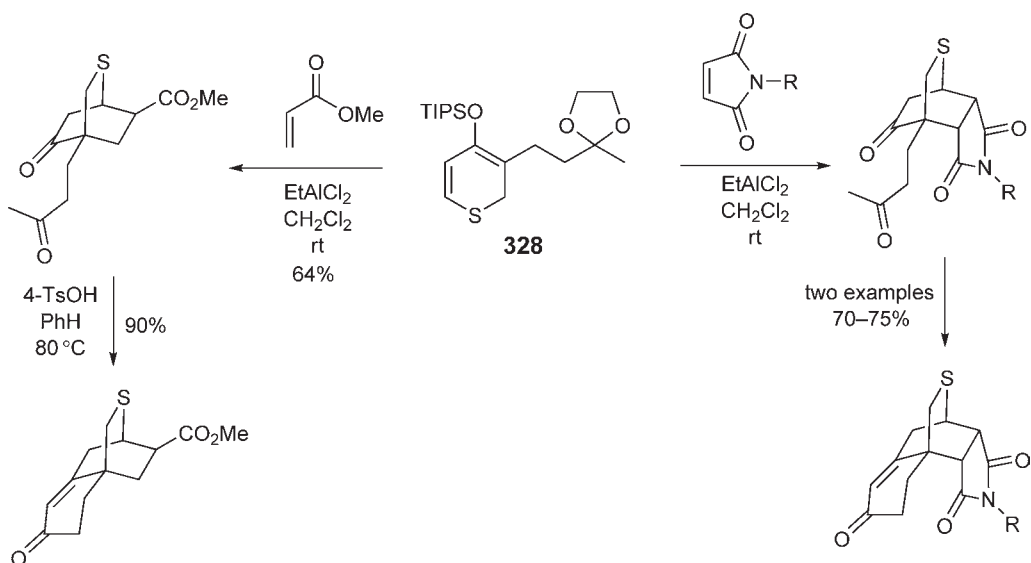
An intramolecular variant of the above reaction becomes possible following the attachment of a C₃-tethered carbomethoxy-activated dienophilic side chain at the 2-position of 4-(tri-*isopropylsilyl*)oxy-2*H*-thiopyran (**Scheme 66**) <1996CJC1418>.



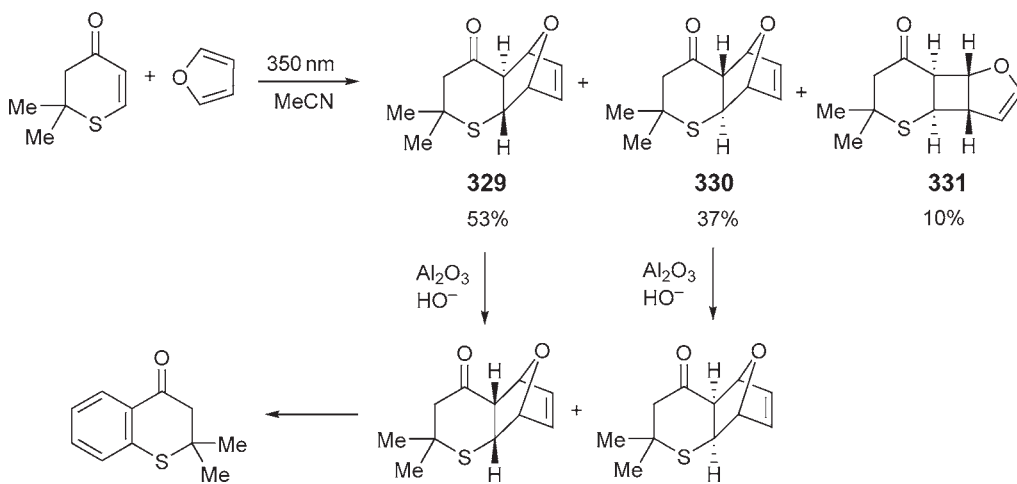
Scheme 66

A further example of the use of 2*H*-thiopyrans as surrogates for *cis*-substituted dienes involves the use of the protected 3,4-dihydro-3-(3-oxobutyl)-4*H*-thiopyran-4-one, 3-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-4-[tris(1-methylethyl)silyl]oxy-2*H*-thiopyran **328** as an equivalent of 1-ethenyl-2-methylcyclohexene in Diels–Alder reactions. The thiopyran reacted with various maleimides to yield the *endo* cycloadducts and with methyl propenoate to give the *exo* adduct under either thermal or Lewis-acid-catalyzed conditions. In the latter case concomitant release of the protected ketone functions occurs, acid-catalyzed cyclization of which generates a fused cyclohexenone ring (**Scheme 67**). Desulfurization, preferably before the aldol cyclization, leads to derivatives of 2,3,4,4a,5,6,7,8-octahydro-4a-methylnaphthalenes <1997CJC681>.

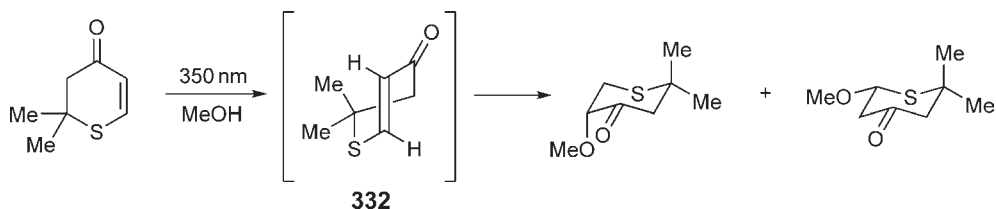
Under UV irradiation (350 nm) in MeCN, 2,3-dihydro-2,2-dimethyl-4*H*-thiopyran-4-one and furan give a mixture of the *trans*-fused [4+2] cycloadducts **329** and **330** (ca. 3:2 ratio), which is quantitatively isomerized to the *cis*-fused products on stirring with basic alumina. Both adducts undergo a facile thermal retro Diels–Alder reaction resulting in the formation of 2,2-dimethylthiochroman-4-one. A small amount of the [2+2] adduct **331** is also formed in the initial reaction (**Scheme 68**). The photocycloaddition of methanol leads to a 3:2 mixture of the 5- and 6- methoxytetrahydrothiopyranone. It is proposed that the initially produced triplet enone undergoes internal conversion to the (*E*)-thiopyranone **332** which reacts with the alcohol. When a solution of furan in methanol is used, the triplet enone is trapped by the furan prior to its deactivation (**Scheme 69**) <1992HCA1925>.



Scheme 67



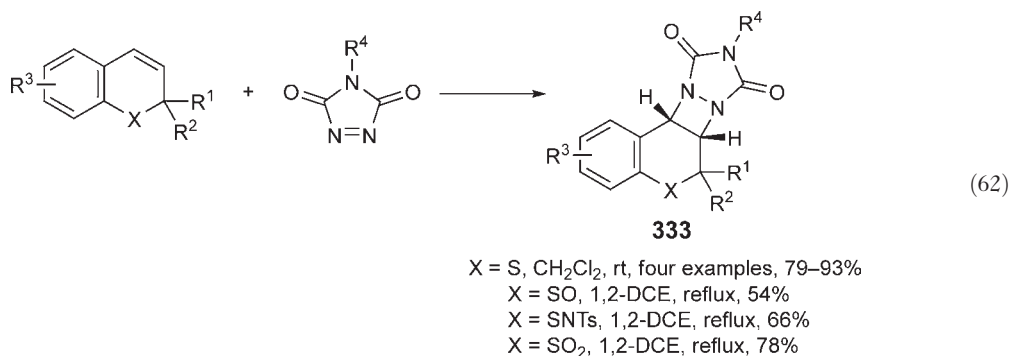
Scheme 68



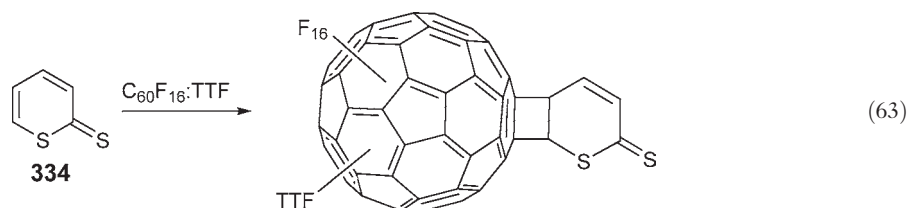
Scheme 69

Photocycloaddition of acrylonitrile in benzene gives a mixture of seven [2+2] cycloadducts, of which the three minor *trans*-fused components are rapidly isomerized. The major *cis*-fused cyclobuta[*b*]thiopyran products arise by head-to-tail addition which places the nitrile group at the 8-position. In the corresponding reaction with 2,3-dimethylbut-2-ene, the *trans*-fused adduct is the major product <2005HCA1922>.

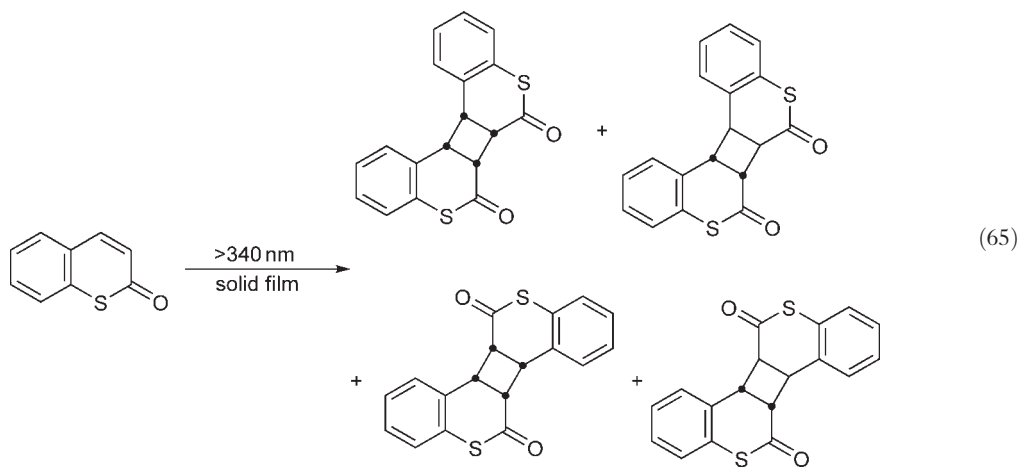
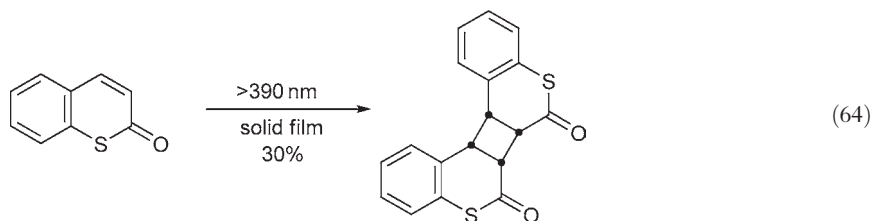
2*H*-1-Benzothiopyrans and their sulfoxides, sulfoximes, and sulfones form the [2+2] cycloadducts **333** with triazolidinediones (Equation 62) <1995T13277>.

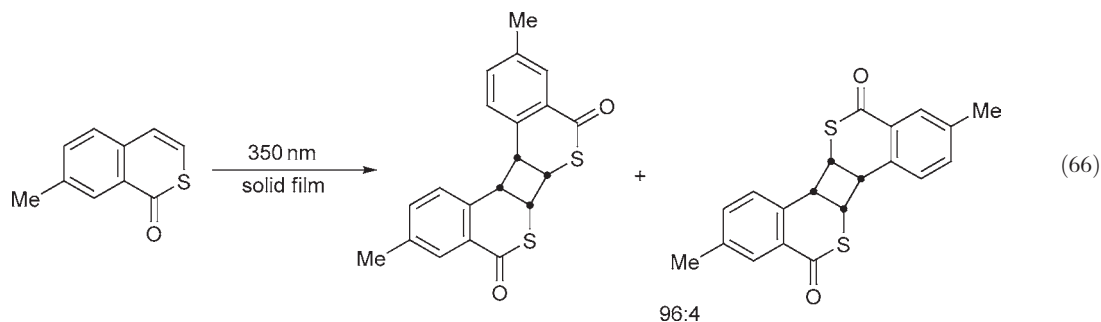


2*H*-Thiopyran-2-thione **334**, derived from tetrathiafulvalene by loss of CS₂, undergoes a [2+2] cycloaddition with the fullerene C₆₀F₁₈ involving the more electron rich 5,6-double bond (Equation 63) <2003CEJ2008>.

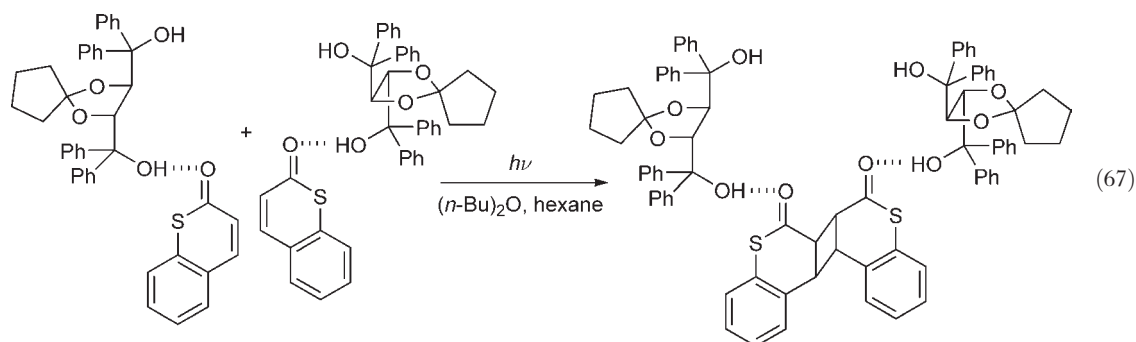


Both thiocoumarins and isothiocoumarins undergo a photocyclodimerization in the solid state. The former gives the head-to-head *cis-cisoid-cis* dimer exclusively on irradiation at $\lambda > 390$ nm (Equation 64), but with shorter wavelength ($\lambda > 340$ nm) a mixture of all four *cis*-fused dimers are formed (Equation 65) <1995HCA1079>. On the other hand, irradiation of isothiocoumarin at 350 nm leads only to the head-to-head and head-to-tail *cis-cisoid-cis* dimers (Equation 66) <2000T6763>. The observation that the 7-methyl derivative also shows the same selectivity but that the 5-trifluoromethyl analogue does not suggests that the latter substituent prevents a disposition of the alkene functions which is favorable to dimerization. Naphtho[2,1-*b*]isothiocoumarin is photostable, an X-ray analysis indicating that the distance between the two double bonds is too great for a cycloaddition reaction.

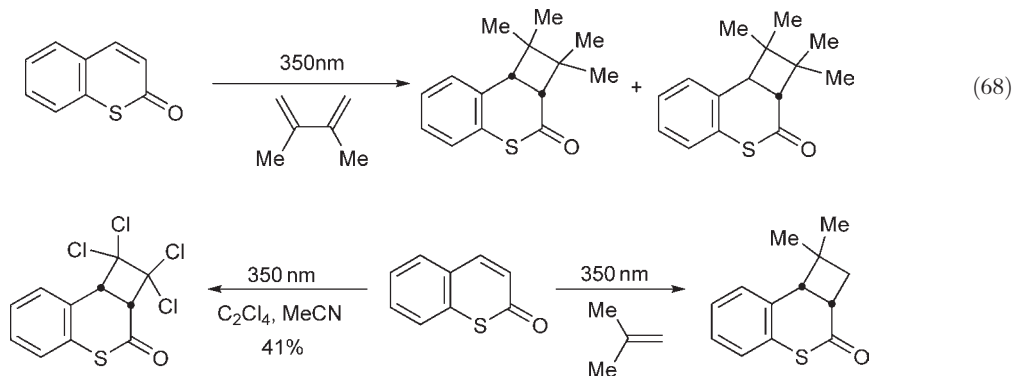




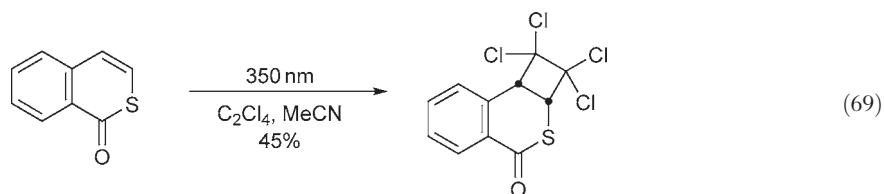
A 1:1 inclusion compound is formed when a mixture of thiocoumarin and (*R,R*)-(-)-*trans*-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane in butyl ether is maintained at room temperature for 12 h. Irradiation of a single crystal results in dimerization of the thiocoumarin unit and the formation of a new 1:2 complex of the reactants from which the thiocoumarin *anti* head-to-head dimer can be obtained by simple chromatography with 100% ee (Equation 67) <1999AGE3523, 2000T6853>. When the (*S,S*)-(+)-host compound was used, the (-)-dimer was obtained, again with 100% ee <1998MCL179>. The enantioselective photodimerization of thiocoumarin in the inclusion compound has been monitored by continuous measurement of the CD spectrum. As the absorptions of (-)-Cotton effect at 260 and 320 nm of the thiocoumarin disappeared over a 5 min period, new absorptions at 270 and 330 nm associated with the dimer appeared <1998MCL179>. Surprisingly, the crystalline inclusion complex also undergoes a thermal [2+2] cycloaddition to give the same dimer with >95% ee, but only under high vacuum. The thermal dimerization is considered to proceed by a radical mechanism, with the lifetime of the radicals increased by the removal of oxygen from the system <2005CC2732>.



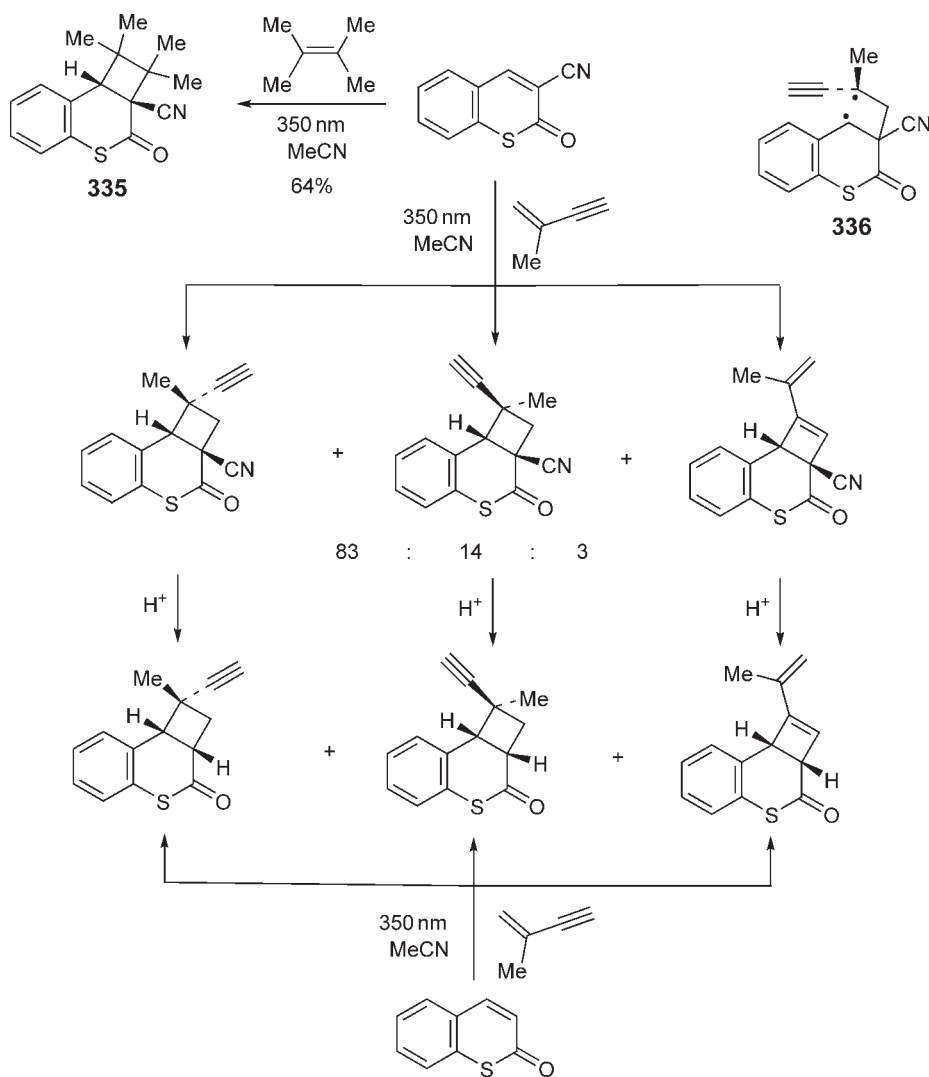
Thiocoumarin photodimerizes more efficiently than does coumarin in solution and yields the head-to-head product. The photocycloaddition with 2,3-dimethylbut-2-ene affords a 4:1 mixture of the *cis*- and *trans*-fused adducts, but terminal alkenes give only the *cis*-fused cyclobutane in which the unsubstituted C atom has added to C-3 of the thiocoumarin (Equation 68) <1991JPH(57)231>. Thiocoumarin reacts ca. 5 times faster under irradiation with tetrachloroethene than does isothiocoumarin (Scheme 70). Both thiocoumarins afford the appropriate *cis*-fused adduct (Equation 69) <1997HCA1865>.



Scheme 70

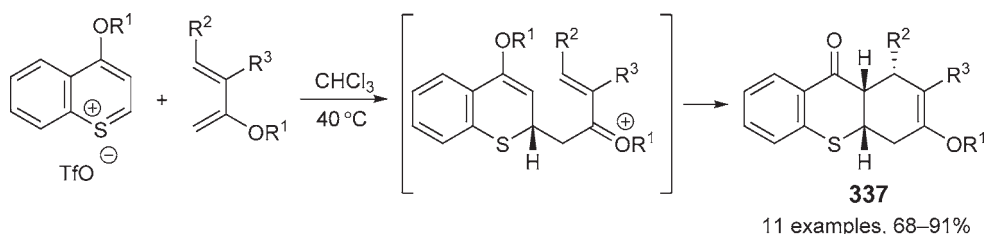


Irradiation of a mixture of thiocoumarin-3-carbonitrile and 2,3-dimethylbut-2-ene in MeCN solution leads exclusively to the *cis*-fused 3-oxocyclobuta[*c*]benzothiopyran-2a-carbonitrile **335**. However, cycloaddition to 2-methylbut-1-en-3-yne affords a mixture of three adducts, hydrolysis of which yields cyclobutabenzothiopyran-3-ones (Scheme 71). It is proposed that protonation and ring opening of the thiocoumarin generates a tertiary carboxylic acid and subsequent loss of CO₂ is followed by cyclization onto the nitrile function followed by hydrolysis. Thiocoumarin itself gives the same three thiopyranones in approximately the same ratio. That one diastereoisomer is formed in great preference suggests efficient stabilization of the diradical **336** <2000HCA1168>.



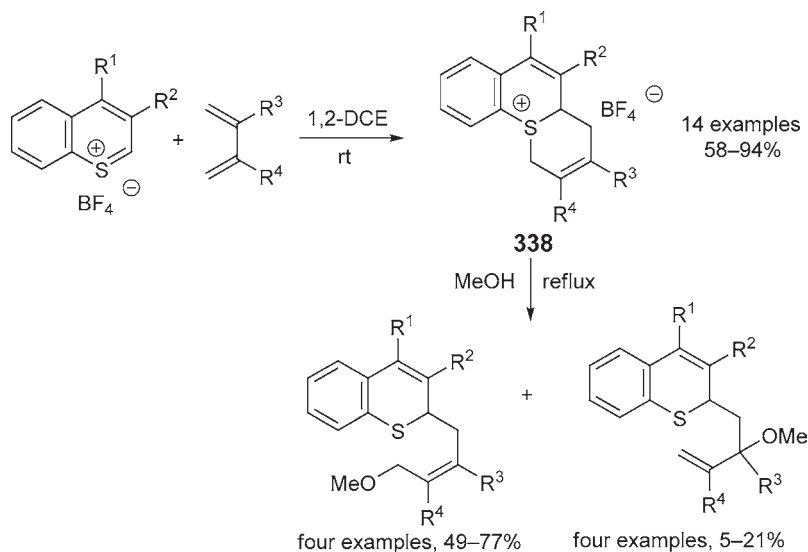
Scheme 71

Benzothiopyrylium triflates react with 2-silyloxybuta-1,3-dienes in a regio- and diastereo-selective cycloaddition which leads to annulated products **337** (Scheme 72) <1994PS(119)339, 1995AGE647>.

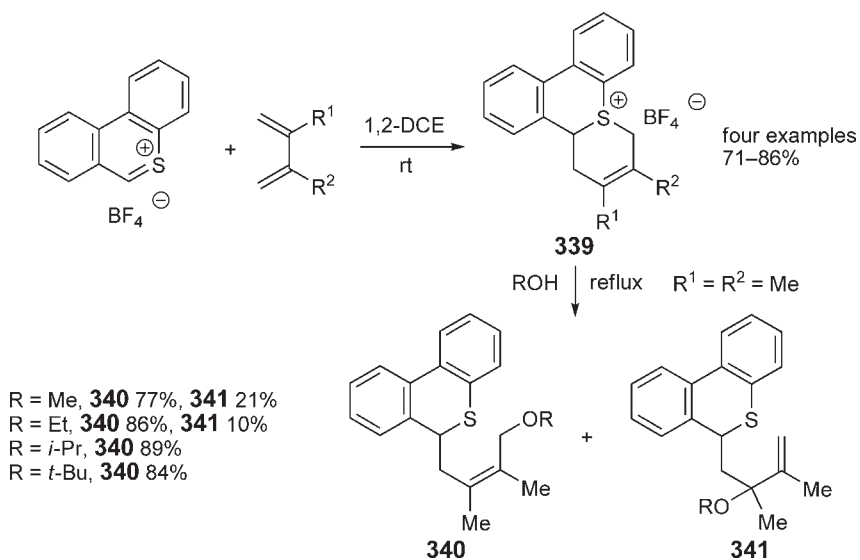


Scheme 72

Benzothiopyrylium and dibenzothiopyrylium salts also take part in polar cycloaddition reactions with 1,3-dienes to form fused bicyclic sulfonium salts **338** and **339**, respectively <1996J(P1)2227, 1997T4611>. Alcohols cleave an S–C bond to give mainly a but-2-enyl derivative **340** with some of the terminal alkenyl product **341** (Schemes 73 and 74).

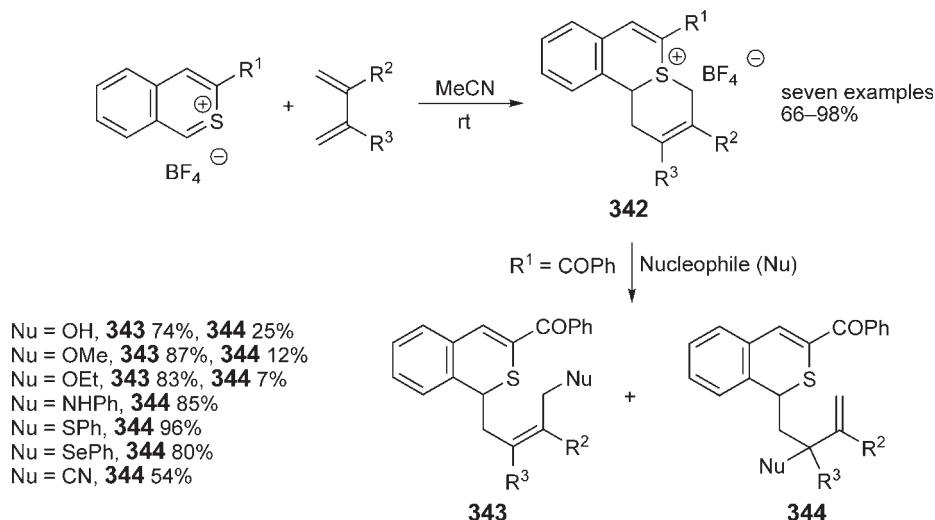


Scheme 73

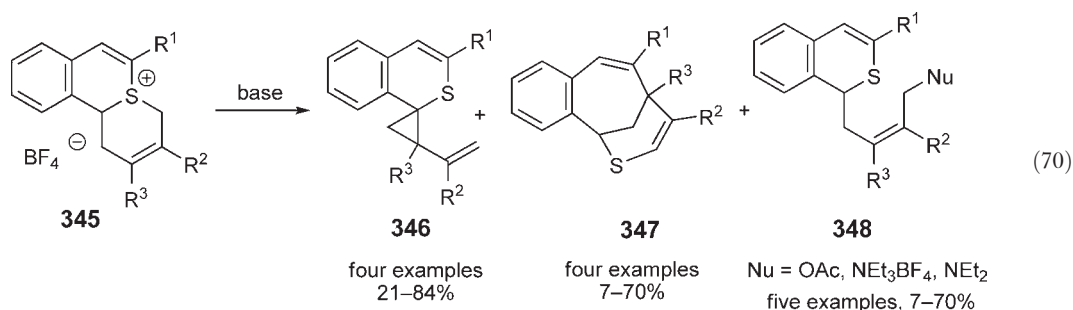


Scheme 74

2-Benzothiopyrylium salts undergo a polar cycloaddition with conjugated dienes to form bicyclic sulfonium salts **342**. Their reaction with oxygen-containing nucleophiles affords mixtures of 1-(substituted butenyl)-1*H*-2-benzothiopyrans **343** and **344**; other nucleophiles afford the latter adduct exclusively (Scheme 75) <1994J(P1)3129>. Treatment of **345** with a variety of base/solvent combinations results in the spirocyclopropanes **346** and either the 2,4-bridged 3,4-dihydro-2*H*-thiopyran **347** or the butenyl compound **348** (Equation 70) <1995J(P1)1583>.



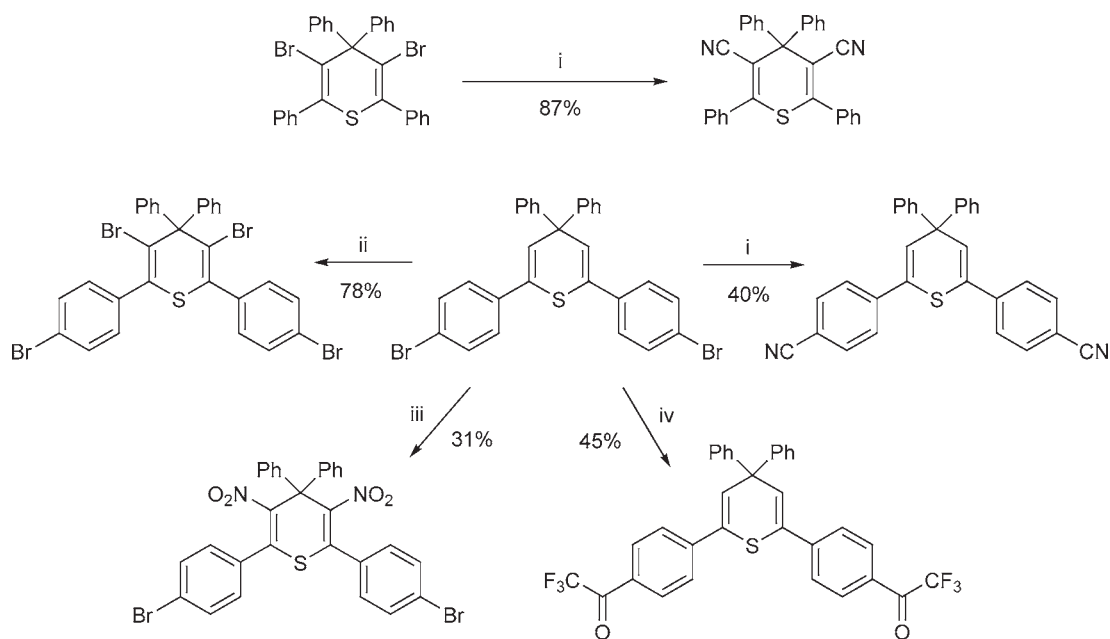
Scheme 75



7.10.3.8 Reactions of Substituents Attached to Ring Carbon Atoms

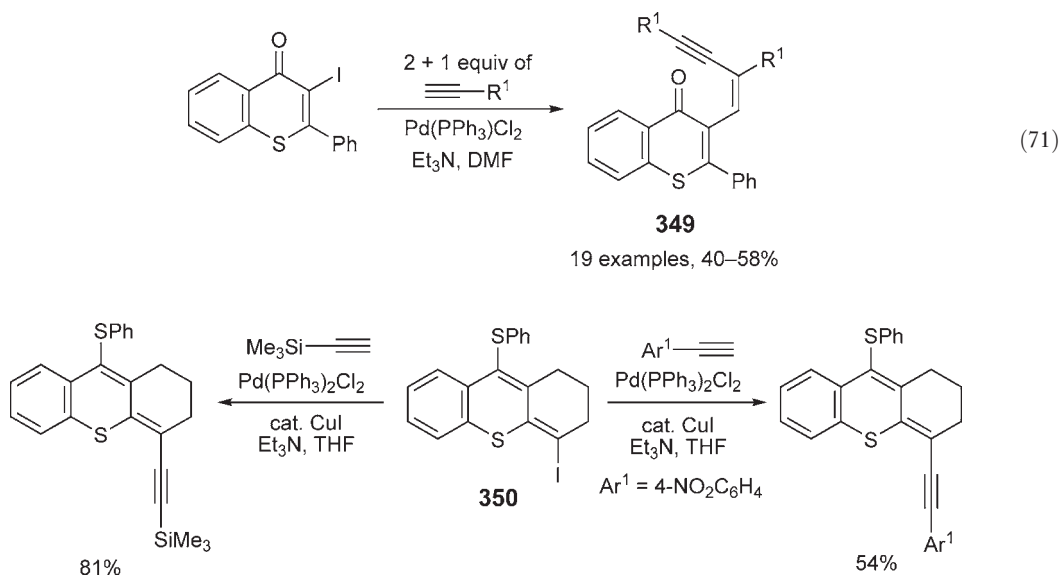
Both 3,5-dibromo-2,4,4,6-tetraphenyl-4*H*-thiopyran and 2,6-bis(4-bromophenyl)-4,4-diphenyl-4*H*-thiopyran are good substrates for the synthesis of highly substituted 4*H*-thiopyrans through reaction with various electrophilic and nucleophilic species (Scheme 76) <1998CCCC662>.

3-Iodothioflavones are converted into the 3-alkynyl and thence the 3-enynyl thioflavones **349** in one pot using Heck and Sonogashira methodology with an excess of a terminal alkyne (Equation 71) <2004TL2305, 2005JOC7179> and the iodo substituent introduced at the 4-position of the 2,3-dihydro-1*H*-thioxanthene **350** during its synthesis by the intramolecular cyclization of α,ω -diynes provides a handle for structural elaboration. In particular, the Pd-catalyzed reaction with alkynes leads to 4-alkynyl derivatives (Scheme 77) <1998AGE3136>.



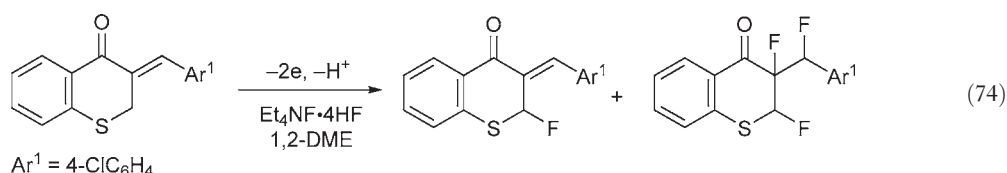
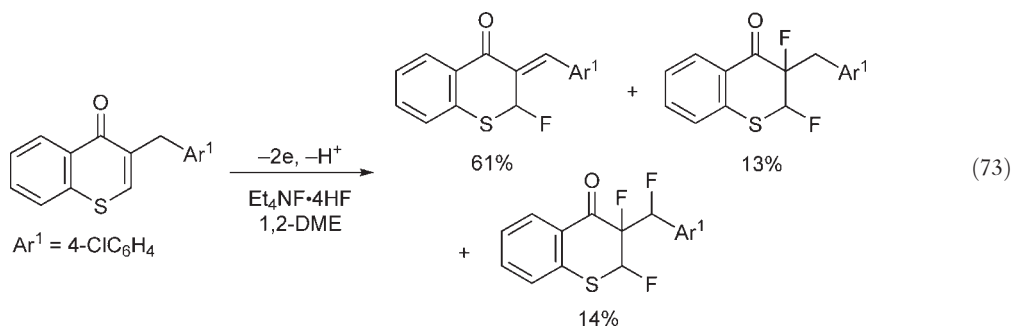
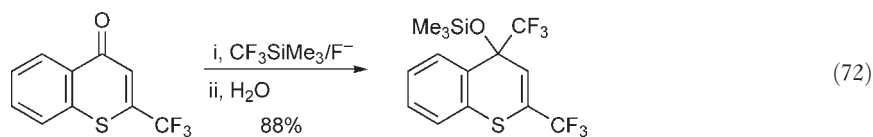
i, CuCN, DMF, N₂, reflux; ii, Br₂, CS₂, 0 °C; iii, f.HNO₃, CHCl₃, 0 °C; iv, *n*-BuLi, Ar, -78 °C then CF₃CO₂Et

Scheme 76

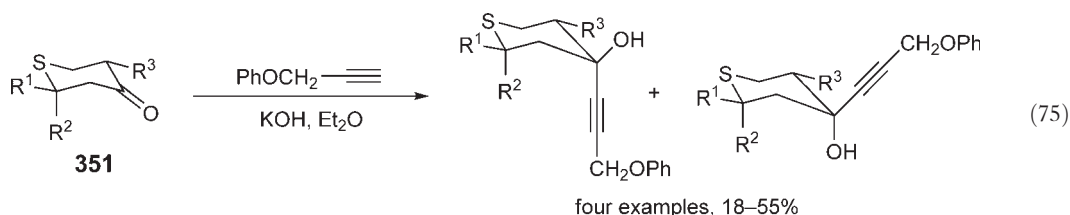


Scheme 77

2-Trifluoromethylthiochromone undergoes nucleophilic 1,2-trifluoromethylation with Ruppert's reagent, (trifluoromethyl)trimethylsilane, in contrast to chromones which react by 1,4-addition (Equation 72) <2005JFC(126)779>. The anodic fluorination of 3-(4-chlorobenzyl)thiochromone results in predominant attack at the 2-position to produce (*E*)-3-(4-chlorobenzylidene)-2-fluorothiochroman-4-one (Equation 73). The same monofluoro and trifluoro derivatives result from the fluorination of (*E*)-3-(4-chlorobenzylidene)thiochroman-4-one (Equation 74). Minor products arise from addition of fluorine to the 2,3-double bond of the thiochromone and with concomitant attack at the benzyl methylene group to give the trifluoro derivative <2001JOC7030>.



3-Phenoxypropyne adds to tetrahydrothiopyran-4-ones **351** to give epimeric mixtures of 4-hydroxy-4-alkynyl-tetrahydrothiopyrans (Equation 75) <2002RJC436>.



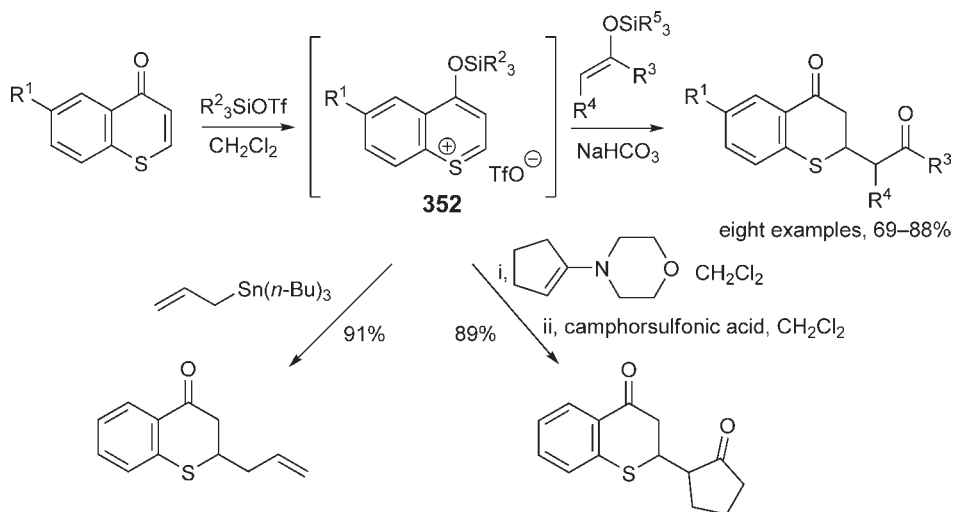
Conversion of thiochromones into 4-silyloxybenzothiopyrylium triflates **352** facilitates the 1,2-addition of nucleophiles across the S=C bond. Of course, the process corresponds to an overall 1,4-addition to the thiochromone. For example, reaction with silylenol ethers, readily derived from an enolizable ketone, affords the thiochroman-based 1,5-diketone or a silylenol ether derivative <1996SL182>. In like manner, allyltri-*n*-butyltin yields the 2-(2-propenyl)-4-silyloxy-2*H*-1-benzothiopyran <2001T1005> and 1-morpholinocyclopentene affords the 2-(2-oxocyclopentyl) derivative (Scheme 78) <1997J(P1)2807>.

The Pd-catalyzed cross-coupling reaction of (9-hydroxythioxanthene-9-yl)ethyne and 1,2-dibromo-3,4-bis(diphenylmethylene)cyclobutene under Sonogashira conditions affords the enediynediol **353**. Reductive dehydroxylation at low temperature gave the dark green extended [4]radialene in high yield (Scheme 79) <2003OL3371, 2005BCJ2188>.

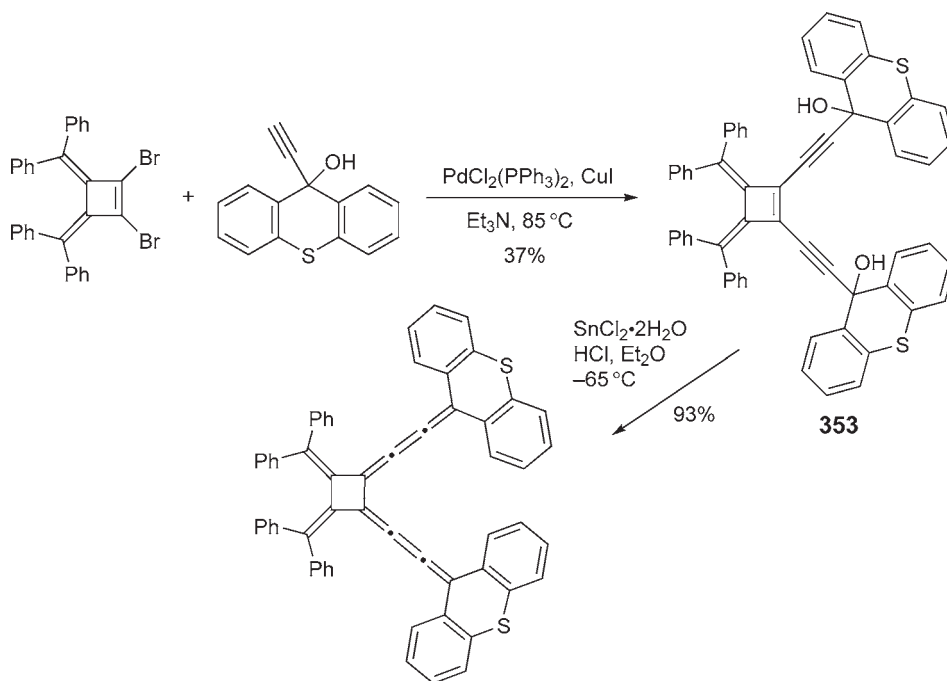
Introduction of an alkyl group at the 2-position of thioxanthone can be accomplished via the organozinc reagent derived from 2-chlorothioxanthone (Equation 76) <1999JA5819>.

N-Vinylacetamides and ethyl vinyl ether can behave as acetaldehyde anion equivalents and under acidic conditions convert 9-hydroxythioxanthene into thioxanthene-9-ylacetaldehyde **354** via dehydration to the cation (Equation 77) <2004JOC584>.

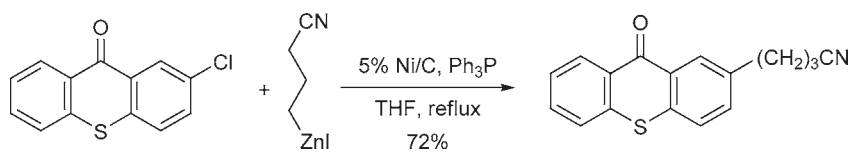
Thioxanthione and thiobenzophenone *S*-methylide, obtained by the elimination of N₂ from 2,5-dihydro-2,2-diphenyl-1,3,4-thiadiazole at –45°, give the spiro[thioxanthene-9,4'-[1,3]dithiolane] **355** through a 1,3-dipolar cycloaddition (Equation 78) <2000EJO1695>.



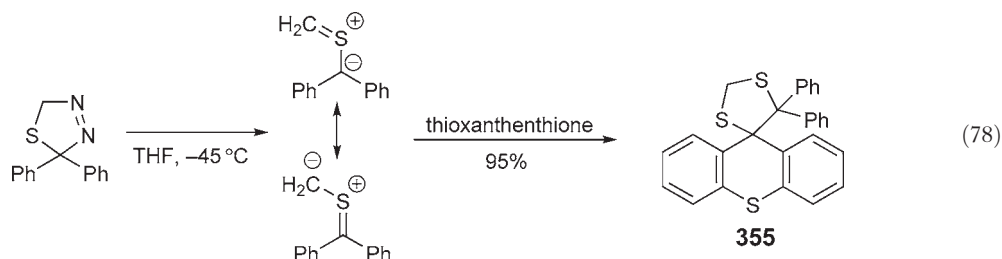
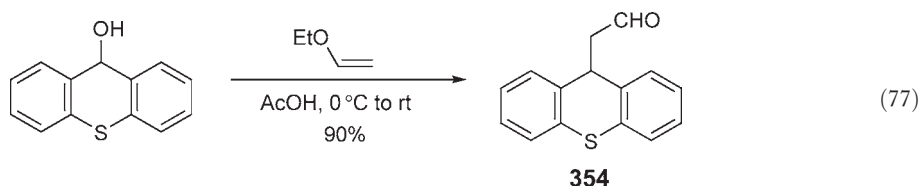
Scheme 78



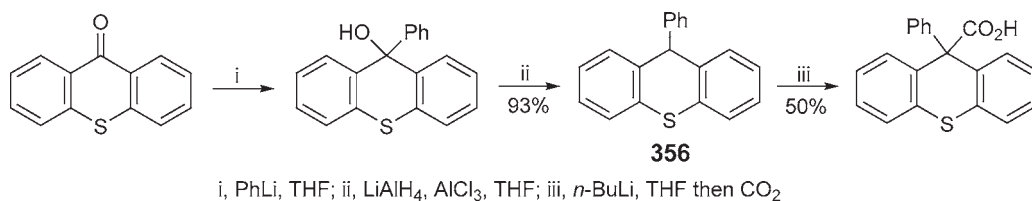
Scheme 79



(76)

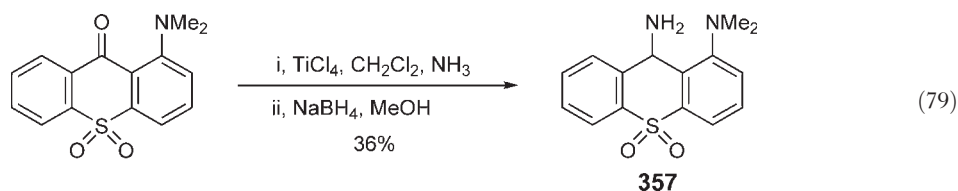


The reduction of thioxanthone with LiAlD_4 and AlCl_3 yields 9D-thioxanthene (93%) mp 147–148 °C and similar treatment of thioxanthene-9-ol affords the 9D,9H-thioxanthene. Reaction of thioxanthone with PhLi and the usual aqueous work-up yields 9-phenylthioxanthene-9-ol from which the 9-phenyl-9D-thioxanthene and the corresponding 9H-derivative **356** were obtained. Reaction of **356** with $n\text{-BuLi}$ and CO_2 gives 9-phenylthioxanthene-9-carboxylic acid (**Scheme 80**) <1998JPH(113)53>.



Scheme 80

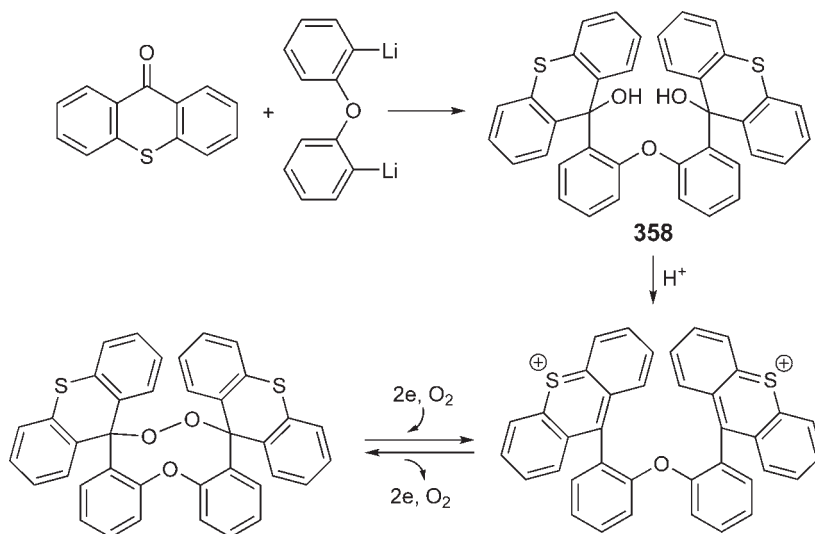
1-Dimethylaminothioxanthone 1,1-dioxide is reduced to the 9-amino compound **357** by conversion into the imine by ammonia in the presence of TiCl_4 and subsequent reaction with NaBH_4 (**Equation 79**) <2002JOC3585>.



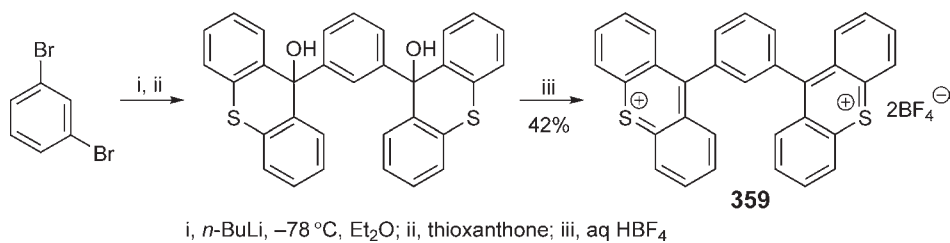
Reaction of thioxanthone with 2,2'-dilithiodiphenyl ether affords the diol **358** which on treatment with acid gives the highly colored salt. A two-electron reduction gives the 9-membered cyclic peroxide, a process which is reversible through electron transfer-induced oxidative deoxygenation. This redox system thus undergoes reversible trapping and extrusion of oxygen (**Scheme 81**) <2000AGE1804>.

Thioxanthone reacts sequentially with 1,3-dilithiobenzene derived from 1,3-dibromobenzene and the resulting diol also yields a salt **359** (λ 383 nm) on treatment with HBF_4 . Reduction with Zn under degassed conditions generates a diradical (λ 361 nm), the Curie plot for which indicates a singlet ground state with an energy gap of ca. 82 cal mol^{-1} between the singlet and thermally excited triplet states (**Scheme 82**) <1997JA5740>.

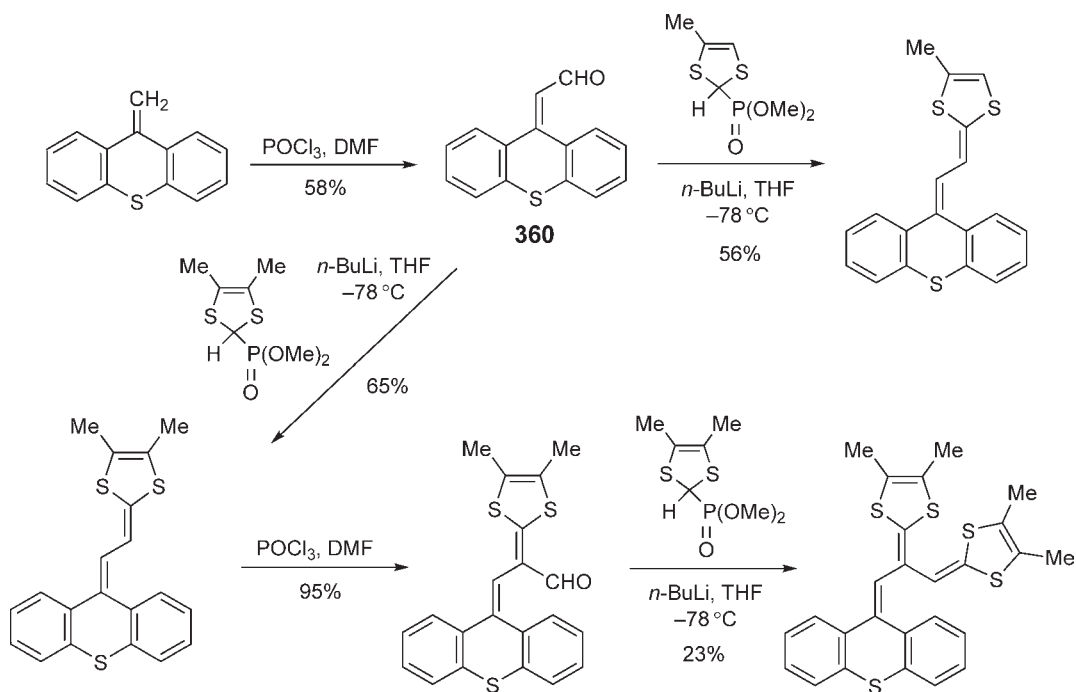
9-Methylenethioxanthene, which results from the reaction of thioxanthone with methyl magnesium bromide and subsequent dehydration <2005PS(180)1339, 2006CEJ5481>, affords thioxanthene-9-ylideneacetaldehyde **360** on Vilsmeier formylation. Conjugated vinylogous and cross-conjugated π -electron donor derivatives have been synthesized by reaction with (1,3-dithiol-2-yl)phosphonate reagents (**Scheme 83**) <2006CEJ5481>.



Scheme 81

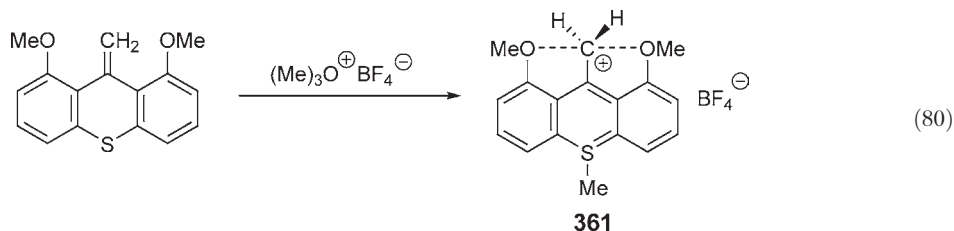


Scheme 82

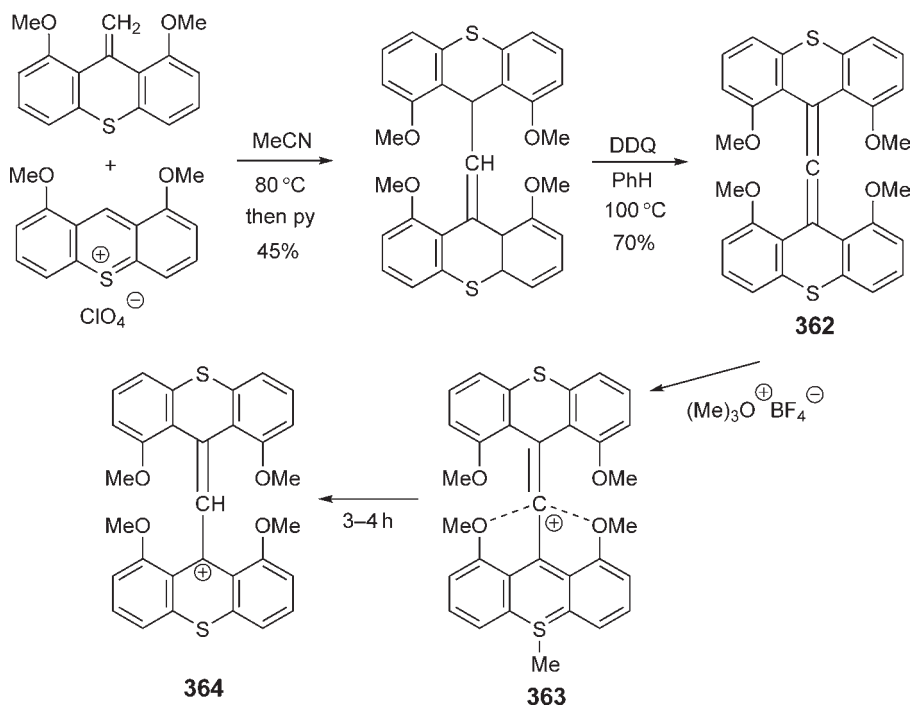


Scheme 83

Treatment of 9-alkyldithioxanthenes with trimethyloxonium fluoroborate affords the *S*-methylthioxanthenium salt **361**. In the case of the 1,8-dimethoxy derivative, X-ray analysis indicates that not only is the MeO–CH₂ bond length at 280 pm too long to allow hypervalent bonding and the generation of a pentacoordinate carbon species, but also the Me(S) and methylene groups are facing each other so that the central ring is not planar (Equation 80) <2005PS(180)1339>.



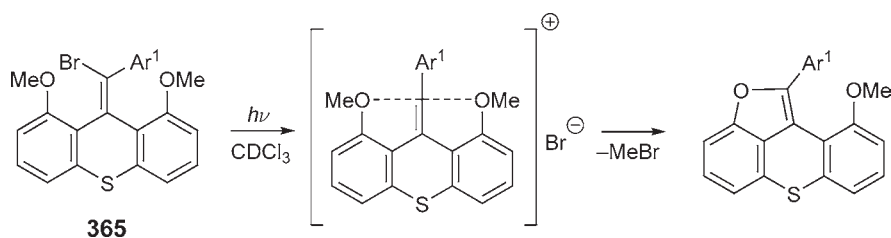
Reaction of 1,8-dimethoxy-9-methylenethioxanthene with 1,8-dimethoxythiopyrylium cation followed by sequential deprotonation and oxidation affords the allene **362** which shows only one methoxy signal in the ¹H NMR spectrum (Scheme 84) <2005PS(180)1339>. Methylation with Me₃O⁺BF₄[−] gives the resonance stabilized mono-methylated cation **363** which reverts to the mono cation **364** over a period of about 4 hours and which is accessible directly from the allene **362** by treatment with HBF₄ (Scheme 84) <2005PS(180)1339>.



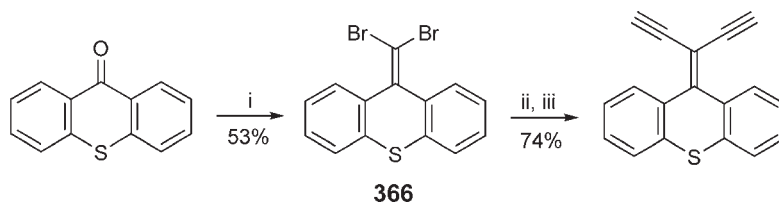
Scheme 84

During the laser flash photolytic conversion of the vinyl bromide **365** into the benzofuran, a transient broad peak (400–650 nm) was observed and was assigned to the cationic transition state model compound for the in-plane vinylic S_N2 reaction (Scheme 85). This interpretation is supported by calculations at the B3PW91/6-31G(*d*) level <2005OL2739>.

Application of the Corey–Fuchs olefination to thioxanthone affords the 1,1-dibromoalkene **366** from which the 1,1-bis(trimethylsilylethynyl)alkene can be obtained by a double Sonogashira coupling reaction. Desilylation yields the 1,1-diethynylalkene (Scheme 86) <2004JA3108>.



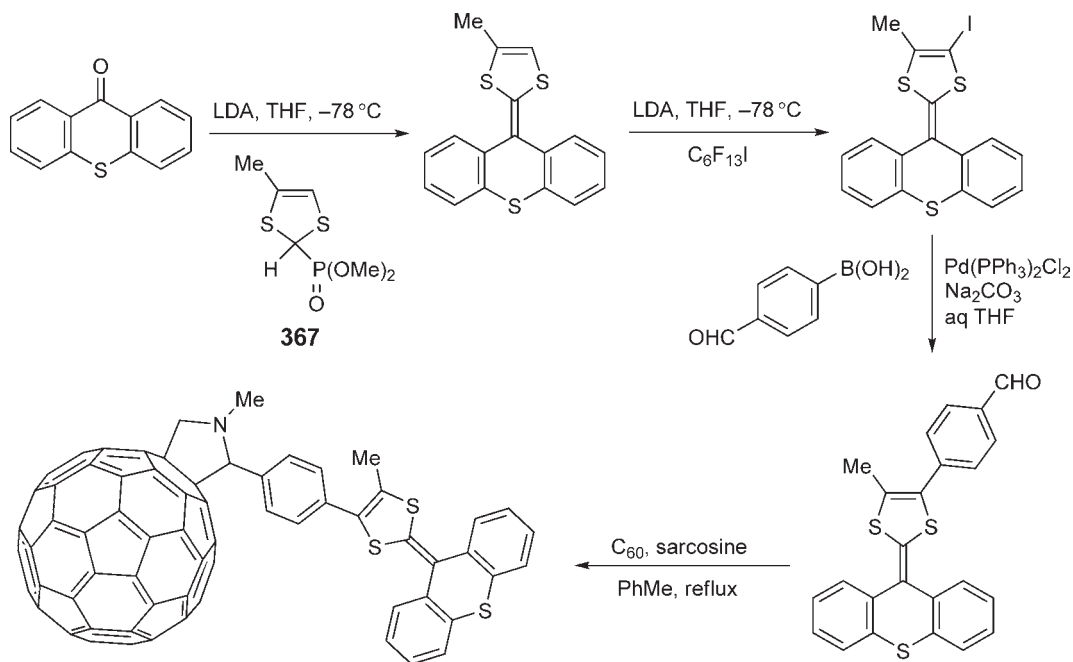
Scheme 85



i, CBr_4 , PhH, Ph_3P , $150\text{ }^\circ\text{C}$, 44 h; ii, $\text{PdCl}_2(\text{PPh}_3)_2$, CuI, Et_3N , TMS-acetylene, $95\text{ }^\circ\text{C}$, 21 h;
iii, TBAF, CH_2Cl_2 , rt

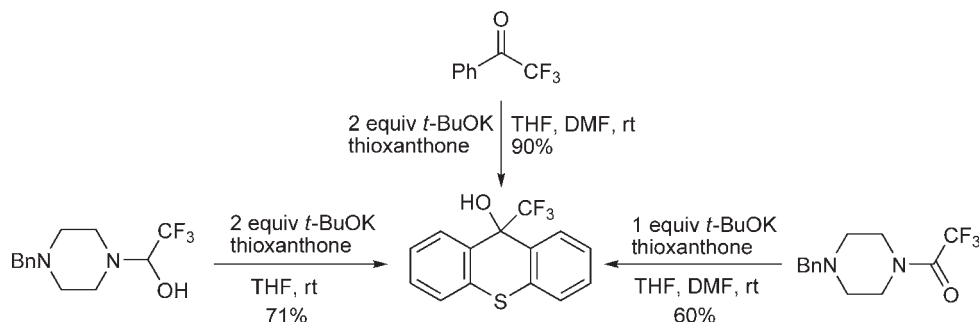
Scheme 86

The anion derived from the 1,3-dithiole **367** reacts with thioxanthone to give the 9-(1,3-dithiol-2-ylidene)thioxanthene derivative which is a π -electron donor system. The introduction of a benzaldehyde unit at the 4-position of the dithiole ring was achieved by iodination and a Pd-mediated cross-coupling with 4-formylbenzeneboronic acid. The aldehyde group allowed attachment to C_{60} via a 1,3-dipolar cycloaddition of an azomethine ylide (**Scheme 87**) [\[2005JMC1232\]](#).



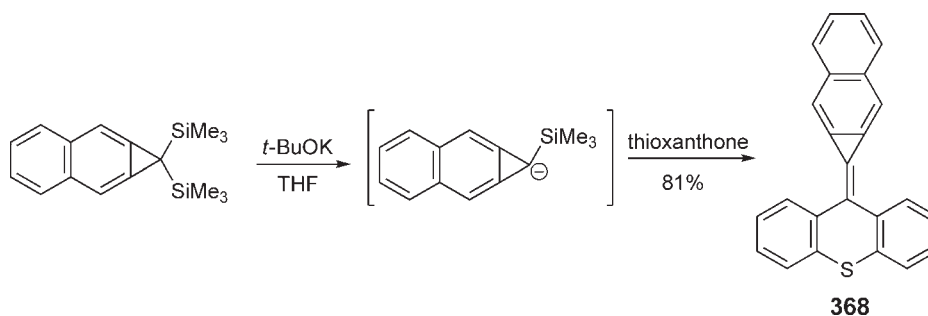
Scheme 87

In the presence of a strong base, trifluoromethylacetophenone trifluoromethylates thioxanthone; a haloform reaction is involved [<2003TL1055>](#). 1-(*N*-benzylpiperazino)-2,2,2-trifluoroethanol and *N*-trifluoroacetyl-*N*-benzylpiperazine behave in a similar manner (**Scheme 88**) [<2001EJO1467, 2003SL230>](#).



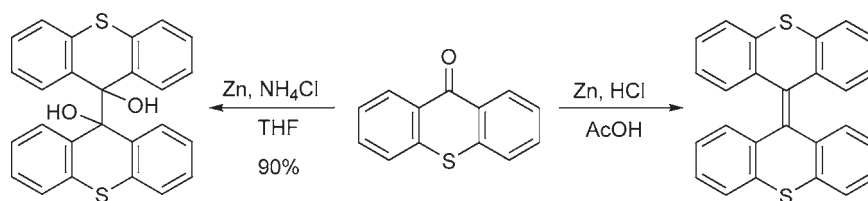
Scheme 88

The anion derived from 1,1-bis(trimethylsilyl)-1*H*-cyclopropa[*b*]naphthalene reacts with thioxanthone to yield the red 1-thioxanthenylidene-1*H*-cyclopropa[*b*]naphthalene **368** (**Scheme 89**) [<1998JOC1583>](#).

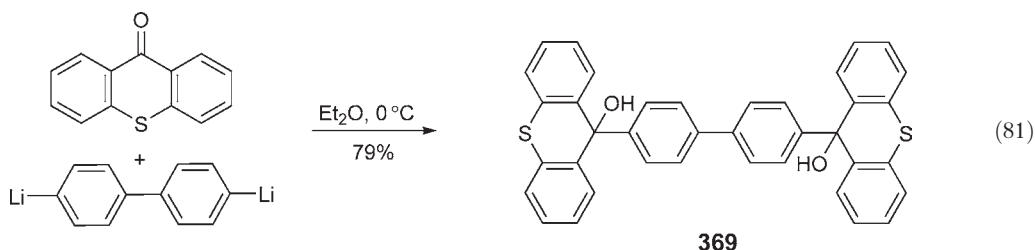


Scheme 89

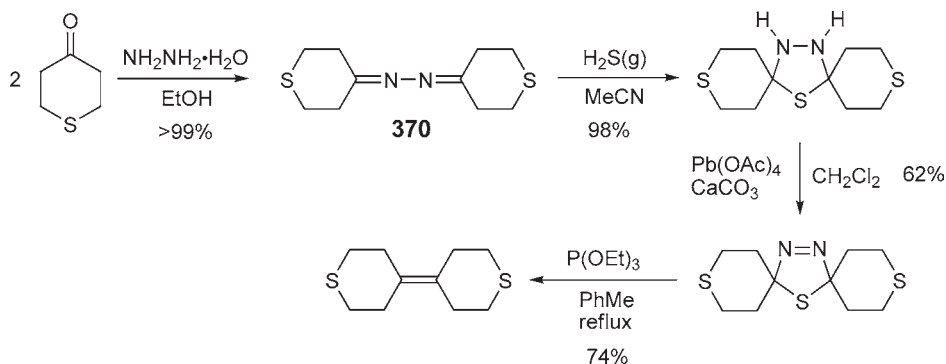
Reductive coupling of thioxanthone to the pinacol has been achieved in 90% yield using Zn in THF/saturated NH_4Cl [<2001M689>](#). However, in boiling acetic acid a mixture of 9,9'-bi(thioxanthen-9-ylidene) and 9,9'-bi(9*H*-thioxanthene) is formed (**Scheme 90**) [<2000TL6157>](#). A biphenyl spacer unit has been incorporated by effecting the coupling with biphenyl-4,4'-diyl dilithium and the behavior of the resulting diol **369** as a clathrate has been investigated ([Equation 81](#)) [<2002EJO856>](#).



Scheme 90

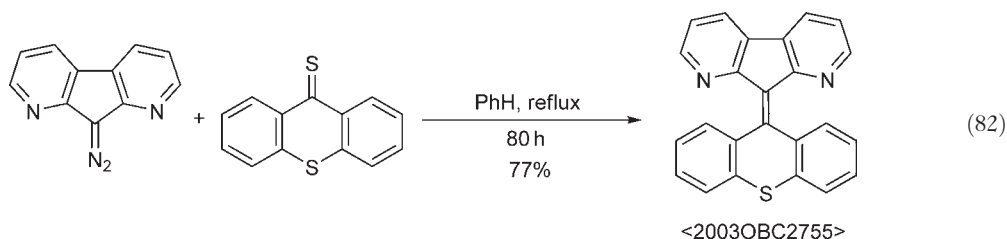


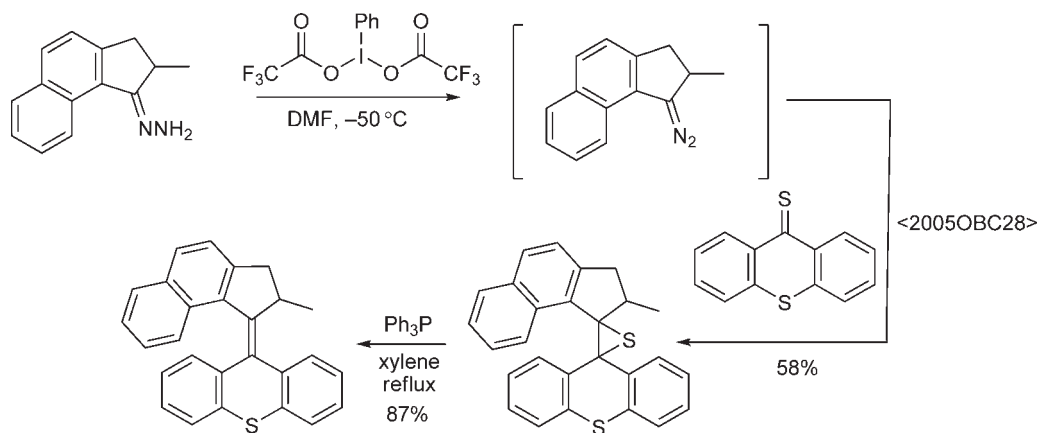
Tetrahydrothiopyran-4-one undergoes a Barton–Kellogg reaction with hydrazine hydrate to give the azine **370**. Sequential thiadiazolidine formation, oxidation to the thiadiazoline and extrusion of N₂ produces the 4,4'-bis(tetrahydro-4*H*-thiopyranylidene) (**Scheme 91**) <2000JOC4584>.



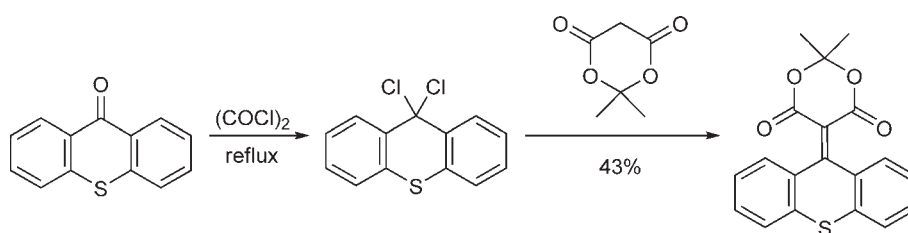
Scheme 91

Application of this methodology has led to the synthesis of a variety of bistricyclic aromatic enes, sterically crowded alkenes, from thioxanthene-9-thione (**Equation 82**), though an additional step, extrusion of sulfur from the episulfide formed by loss of N₂ from the thiadiazoline using PPh₃, is required (**Scheme 92**). The diazo component has been derived from naphthothiopyrans <1997JOC4943, 2002JA5037, 2004OBC1531, 2005OBC4071, 2006OL1713>, benzindanone <2005OBC28>, fluorenes <2001J(P2)2329>, and 1,8-diazafluorene <2003OBC2755>. An alternative approach utilizes the reaction between a *gem*-dichloride and an activated methylene compound, exemplified by the coupling of 9,9-dichlorothioxanthene with 2,2-dimethyl-1,3-dioxane-4,6-dione (**Scheme 93**) <1995TL9381, 2002T2183>. A third route, illustrated in **Scheme 94** for the synthesis of a bithioxanthylidene, involves coupling the two halves of the alkene to a chiral template followed by intramolecular coupling of the component parts. Removal of the template after separation of the diastereomers provides the sterically hindered enantiomeric alkene <2006EJO3596>. A variation on this latter theme has been used to synthesize several bithioxanthylidene mono-**371** and bis-**372** crown ethers, forming the crown moiety either before or after formation of the ethene linkage. Resolution by chiral HPLC preceded investigation of the optical and ion complexation properties <2006OBC4101>.

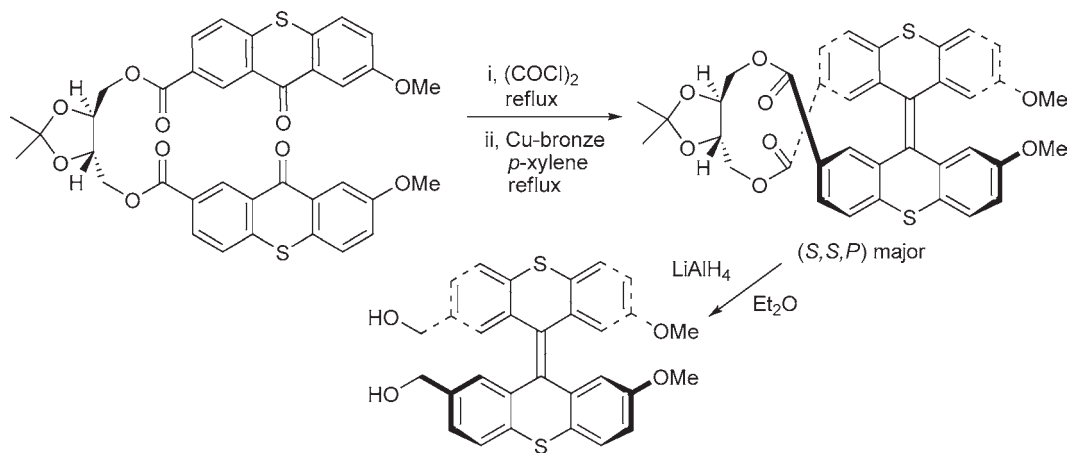




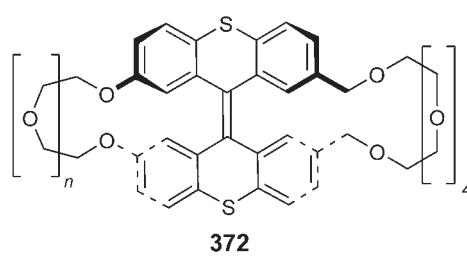
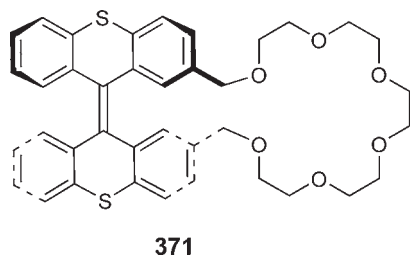
Scheme 92



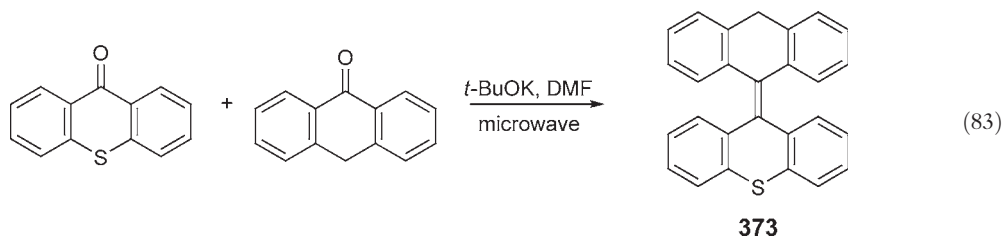
Scheme 93



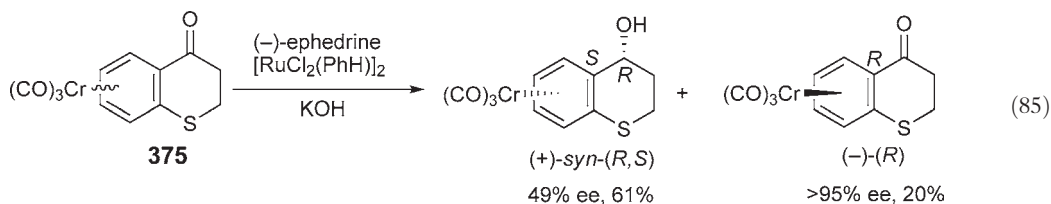
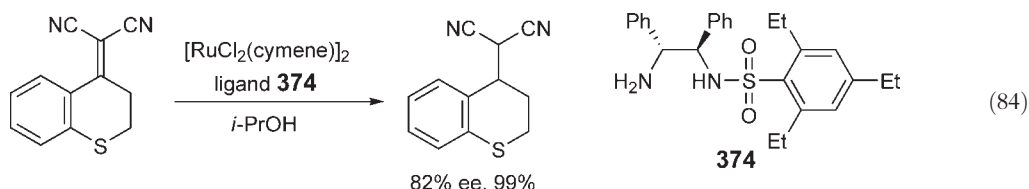
Scheme 94



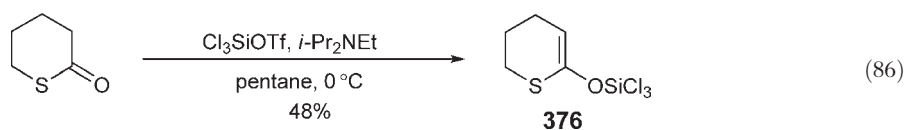
The thermochromic ethylene **373** has been efficiently prepared in 96% yield by the microwave promoted condensation of anthrone with thioxanthone (Equation 83) <2003JCM260>.



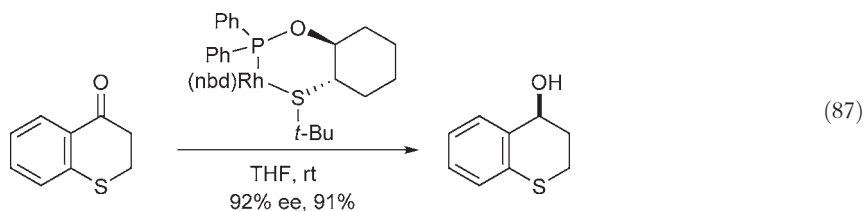
The quantitative transfer hydrogenation of 4-dicyanovinylthiochroman shows good enantioselectivity (82% ee) when catalyzed by a Ru(II)-arene complex in conjunction with the chiral diamine ligand **374** (Equation 84) <2005JOC3584>. The reduction of racemic (η^6 -thiochromanone)Cr(CO)₃ **375** yields *syn*-(*S,R*)-(η^6 -thiochroman-4-ol)Cr(CO)₃ and (*S*)-(η^6 -thiochroman-4-one)Cr(CO)₃ or the same products with inverted configuration depending on the chiral auxiliary employed with the Ru(II) catalyst (Equation 85). In like manner, thiochromanone itself yields either the (*R*)- or (*S*)-thiochroman-4-ol according to the choice of (–)-ephedrine or (+)-norephedrine Ru(II)(η^6 -benzene) complex as catalyst <2005JOM(690)3176>.



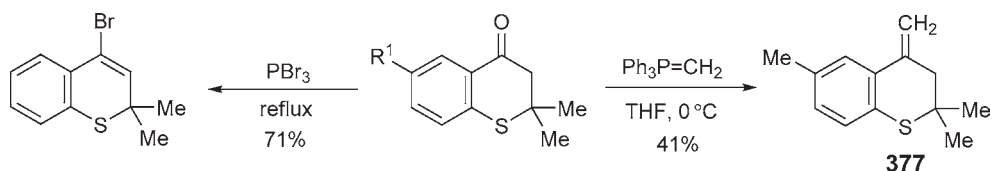
Tetrahydrothiopyran-2-one has been converted directly to its trichlorosilyl enolate **376** using trichlorosilyl triflate (Equation 86) <1998JOC9517>.



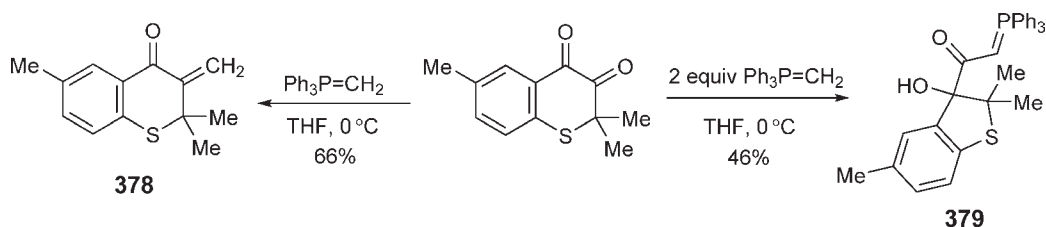
The asymmetric hydrosilylation of thiochroman-4-one catalyzed by a Rh norbornadiene (nbd) complex with a mixed P and S ligand occurs with both high enantioselectivity (92%) and yield (91%) (Equation 87) <2003JA3534>. Cr complexes with amino acids effect the reduction but with only low enantioselectivity <1999TL1373, 2004TA1735>.



The reaction of thiochroman-4-one with PBr₃ gives the 4-bromothiochromene <1994T2507> and treatment with methylenetriphenylphosphorane affords the 4-methylene derivative **377** (Scheme 95) <1994T2507>; thiochroman-3,4-diones yield the 3-methylene **378** derivative with one equivalent of the Wittig reagent. Treatment of the diketone with 2 equivalents of methylenetriphenylphosphorane result in an α -ketol rearrangement to the stabilized ylide **379** (Scheme 96) <1995JCM118, 1995JRM0805>.

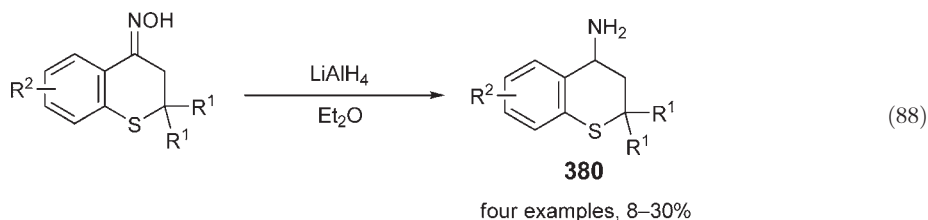


Scheme 95

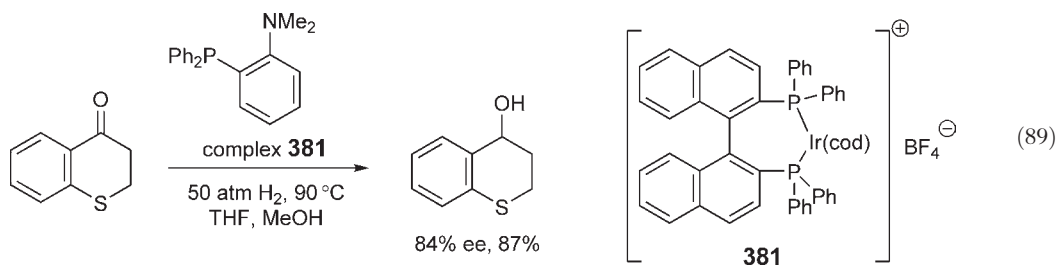


Scheme 96

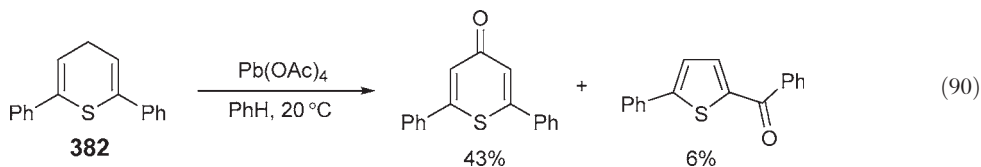
Catalytic reduction of thiochroman-4-ones and various benzologues at 240 °C over MoS₃ gives the thiochroman exclusively in high yields [\[1995JHC687\]](#) and 4-aminothiochromans **380** result from the reduction of thiochroman-4-one oximes by H₂/Raney Ni (Equation 88) [\[1998HCO547\]](#). Treatment of 8-halogeno-4-oximinothiochroman 1,1-dioxides with Pd/C and ammonium formate in aq. EtOH results in efficient dehydrohalogenation rather than reduction of the oxime function [\[2001USP6180797\]](#).

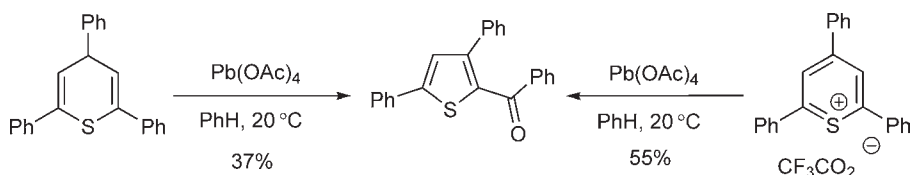


In the presence of the Ir-BINAP complex **381**, the asymmetric hydrogenation of thiochroman-4-ones proceeds in high yield and with good enantioselectivity such that optically pure material results after crystallization (Equation 89). Tetrahydrothiopyran-3-one is similarly reduced though with only moderate enantioselectivity [\[1993JA3318\]](#).



2,6-Diphenyl-4*H*-thiopyran **382** is oxidized to the thiopyran-4-one by Pb(OAc)₄; a minor amount of the 2-benzoylthiophene is also formed (Equation 90). The oxidation of the 2,4,6-triphenyl-4*H*-thiopyran and also the triphenylthiopyrylium trifluoroacetate results in the 2-benzoyl-3,5-diphenylthiophene in preparatively useful yields (Scheme 97) [\[1996CHE777\]](#).

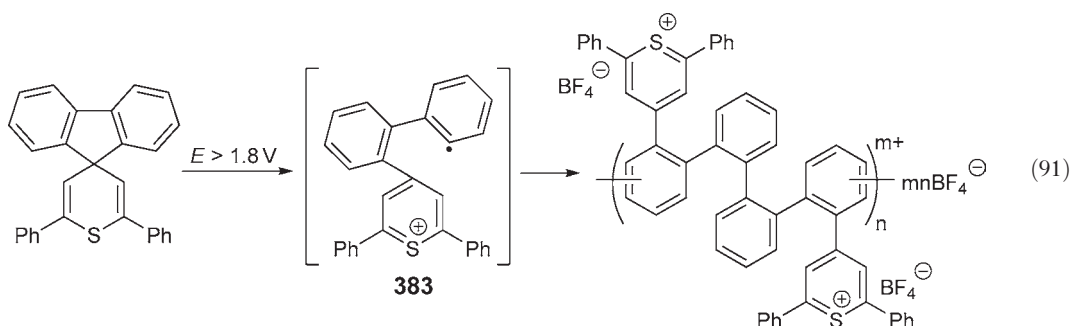




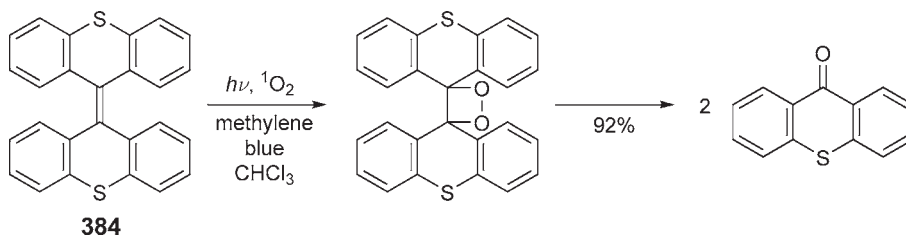
Scheme 97

The anodic oxidation of spiro[4,9'-fluorenyl]-2,6-diphenyl-4*H*-thiopyran at high potential leads to deposition on the anode of polymeric material which consists of a polyphenylene framework bearing thiopyran or thiopyrylium substituents depending on the oxidation state. This conducting material is electrochromic, appearing blue, red, or yellow according to its oxidation state. It is proposed that the reaction proceeds via a radical thiopyran cation.

Cleavage of the C(4)-fluorene bond produces a 4-(2-biphenyl)thiopyrylium radical **383** and initiates the polymerization process (Equation 91) <1996SM(83)153>.

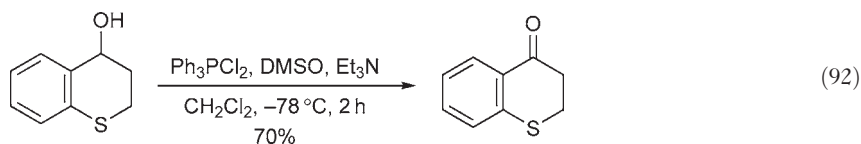


Thioxanthene is oxidized to thioxanthone by dinitrogen oxide in the presence of a Ru tetra(2,4,6-trimethylphenyl)porphyrin complex <2004BCJ1905>, by Ag(pyridine)₄S₂O₈ <1992BCJ2878> and by molecular oxygen in the presence of activated charcoal (Darco® KB) <2004TL5457>. Dithioxanthylene **384** is cleaved by singlet oxygen under UV irradiation to the ketone (Scheme 98) <1994T3595>.

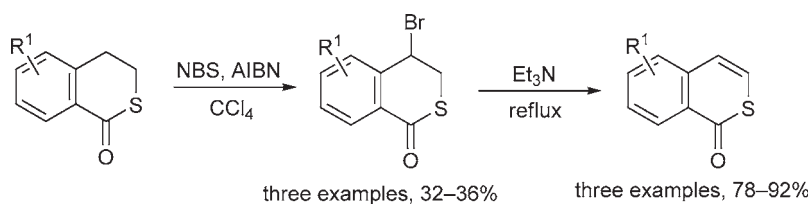


Scheme 98

Oxidation of thiochroman-4-ol to thiochroman-4-one can be achieved without competing Pummerer rearrangement using triphenylphosphine dihalides in DMSO (Equation 92) <2002TL8355>. This oxidation has also been achieved using polymer-bound periodinane (82% yield) <1999T6785> and 2-iodoxybenzoic acid is also effective (92%) <1995JOC7272>.

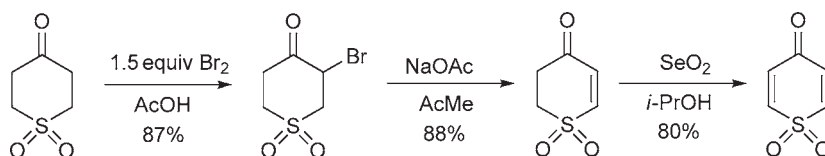
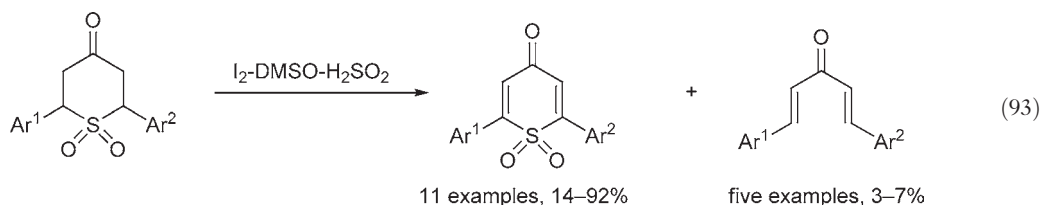


Dehydrogenation of tetrahydrothiopyran-4-ones to the 5,6-dihydro derivative has been achieved with *N*-chlorosuccinimide <1992HCA1925>. A similar approach converts dihydroisothiocoumarins to the isothiocoumarins, with initial bromination by NBS at the 4-position being followed by dehydrobromination using triethylamine (Scheme 99) <2000T6763>.



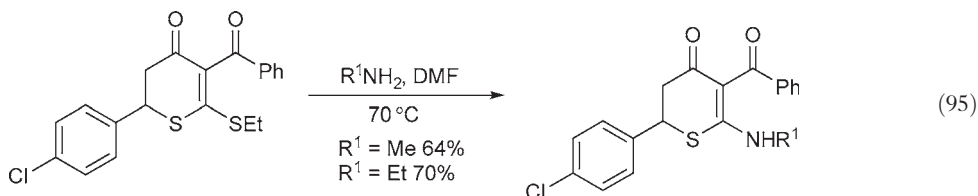
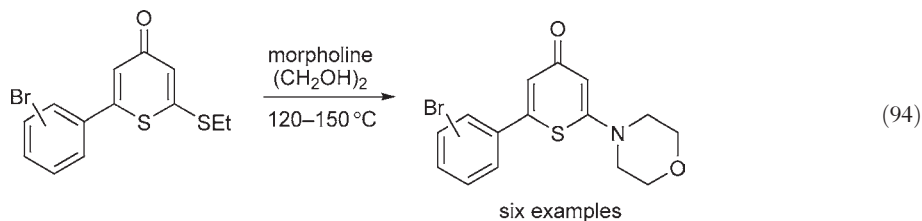
Scheme 99

Sulfones derived from tetrahydrothiopyran-4-ones are dehydrogenated to the corresponding thiopyran-4-one 1,1-dioxides by treatment with I_2 in $DMSO-H_2SO_4$; the reaction is particularly efficient when aryl groups, with the exception of furyl, are present at the 2- and 6-positions (Equation 93). For the formation of 4*H*-thiopyran 1,1-dioxide from the tetrahydro precursor a higher yielding three-step sequence (Scheme 100) is preferred <1995JOC1665>.

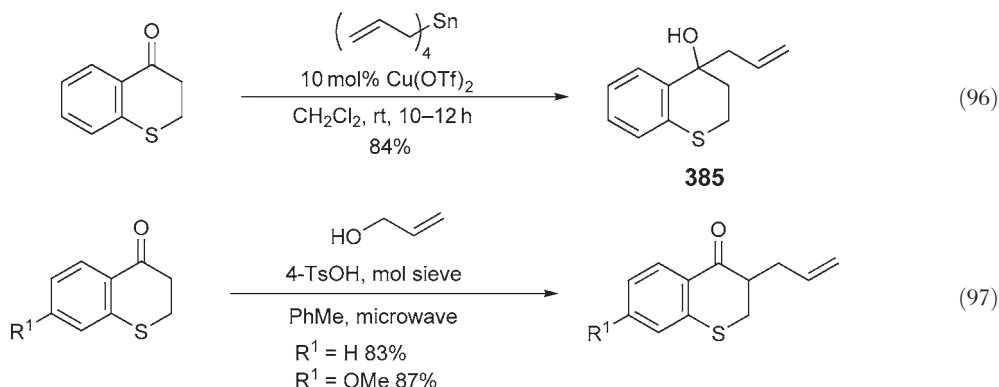


Scheme 100

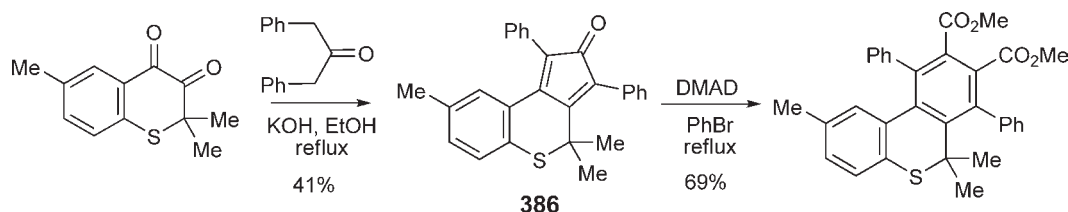
Amines displace the 2-thioethyl group in 6-arylthiopyran-4-ones (Equation 94) and a bromo substituent in these 6-aryl rings undergoes a facile Suzuki cross-coupling reaction with $ArB(OH)_2$ to generate a library of thiopyran-4-ones <2003BML3083>. Introduction of an amine functionality into some 5,6-dihydro-4*H*-thiopyran-4-ones has also been achieved in this manner (Equation 95) <2005JOC10886>.



Thiochroman-4-ones are allylated at the 4-position by tetra-allylstannane under $\text{Cu}(\text{OTf})_2$ catalysis to afford the thiochroman-4-ol **385** (Equation 96) <2001TL7525> and by allyl alcohol in dimethoxypropane under microwave irradiation at C-3 (Equation 97) <2004TL1133>.

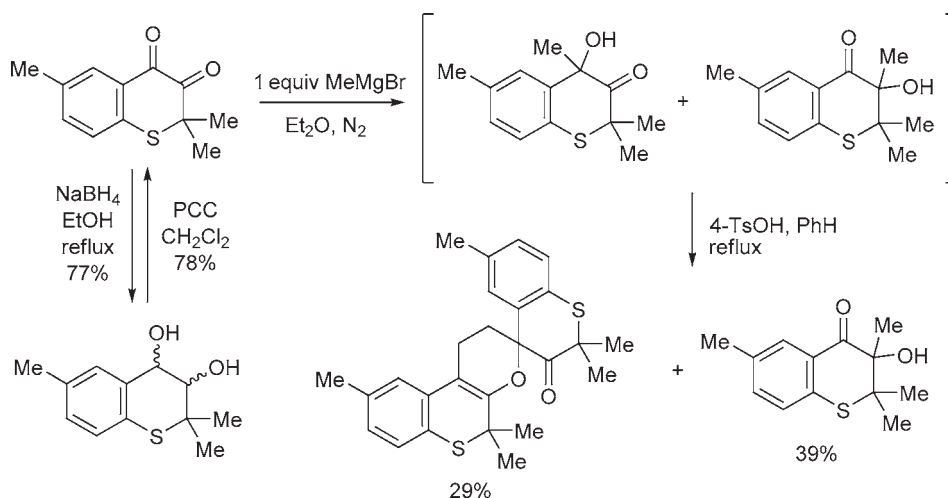


Thiochroman-3,4-diones react with various diamines to create the thiopyrano[*c*]pyrazine ring system, and reaction with *p*-anisaldehyde and NH_4OAc gives a thiopyrano[*c*]imidazole. The base-catalyzed condensation with dibenzyl ketone yields a red [$\lambda_{\text{max}} = 495 \text{ nm}$, $\epsilon = 8.4 \times 10^3 \text{ moldm}^{-3} \text{ cm}^{-1}$] cyclopenta[*c*][1]-benzothiopyran-2-one **386** which gives a dibenzo[*bd*]thiopyran on reaction with DMAD (Scheme 101) <1994T7865>.



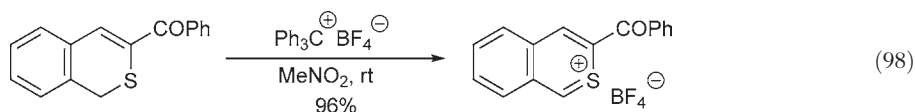
Scheme 101

Reaction of thiochroman-3,4-diones with NaBH_4 affords a mixture of the *cis*- and *trans*- 3,4-diols and two keto alcohols result from reaction with MeMgI . Attempts to separate the latter mixture by preferential dehydration of the thiochroman-4-ol gave unchanged 3-hydroxythiochroman-4-one, but no 4-methylenethiochroman-3-one was detected. Instead, a spiro-linked adduct arising from a hetero Diels–Alder cycloaddition between two molecules of the expected dehydration product was isolated (Scheme 102) <1994T7865>.

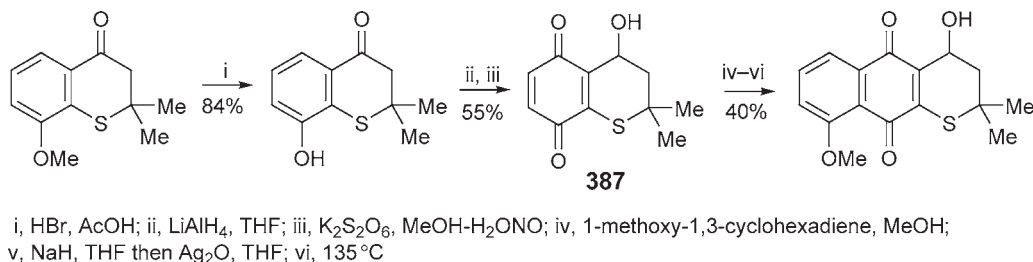


Scheme 102

3-Benzoylthiochromene is oxidized to the benzo[*c*]thiopyrylium salt by triphenylcarbenium fluoroborate in almost quantitative yield (Equation 98) <1994J(P1)3129>.

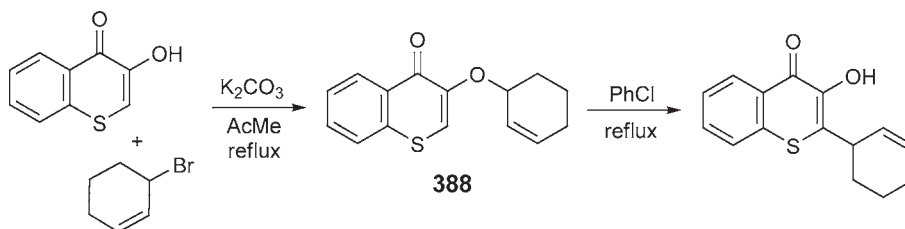


Oxidation of 2,2-dimethylthiochroman-4-ones to the 3,4-diones is readily achieved with isoamyl nitrite <1994T7865> and 8-hydroxy-2,2-dimethylthiochroman-4-one with Fremy's salt, potassium nitrodisulfonate, yields the benzothiopyranoquinone **387**. Following cycloaddition with a cyclohexa-1,3-diene, enolization, oxidation, and aromatization led to a naphtho[2,3-*b*]-thiopyranoquinone (Scheme 103) <1997TL153, 2000H(53)585>.



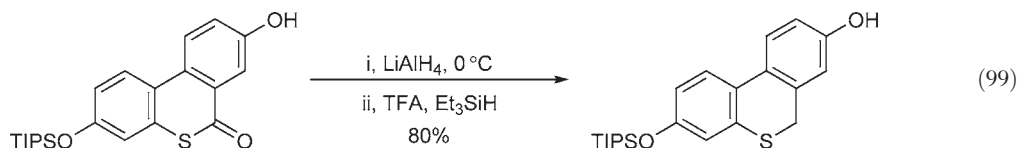
Scheme 103

3-Cyclohex-2-enyloxythiochromone **388**, derived from 3-hydroxythiochromone and 3-bromocyclohex-1-ene, undergoes a thermal Claisen rearrangement to afford 2-cyclohex-2-enyl-3-hydroxythiochromone which is a precursor of various heterocyclic systems (Scheme 104) <2003SC133>. Application of this methodology to thioethers derived from 4-hydroxydithiocoumarin and allyl halides <2004M581> and 1-aryloxy-4-chlorobut-2-yne <2003T5289> leads to a variety of annulated thiochromones.

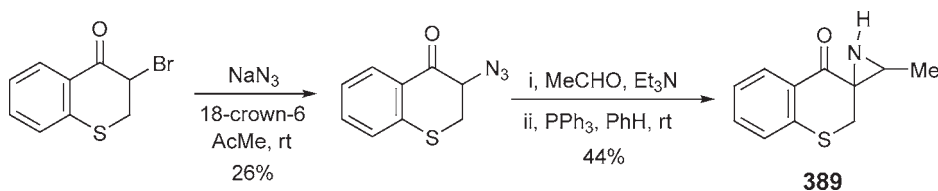


Scheme 104

Dibenzo[*b,d*]thiopyran-5-ones have been converted into the dibenzothiopyran by sequential reduction to the alcohol using LiAlH₄ and acid catalyzed dehydration (Equation 99). A dimeric ether was obtained when insufficient acid was used <2005OL411>.

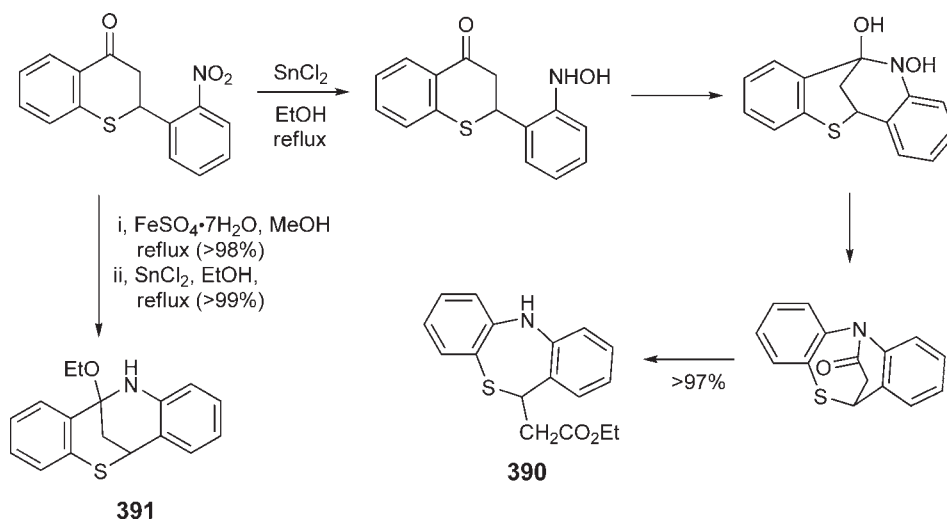


3-Azidothiochroman-4-ones have been synthesized from thiochromanone by initial bromination at C-3 and further reaction with NaN₃ in the presence of a crown ether. The corresponding thioflavanone can be similarly derived from the 3-nosylthioflavanone. The former reacts with acetaldehyde to give the 3-azido-3-(1-hydroxyethyl)thiochromanone from which 3'-methylspiro[thiochroman-3,2'-aziridin]-4-one **389** has been obtained by reaction with Ph₃P (Scheme 105) <2002EJO285>. 3-(α -Azidobenzyl)thiochromones have been obtained from thiochromanones by related methodology <2001T2895>.



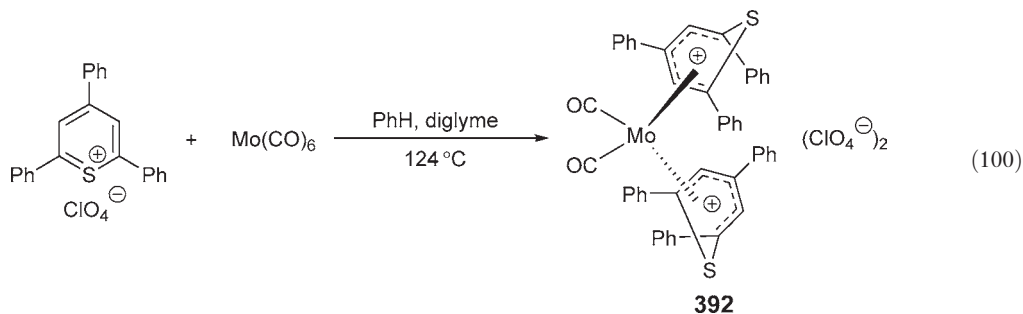
Scheme 105

Ethyl 3-(4-bromobut-2-enyl)-4-oxotetrahydrothiopyran-3-carboxylate undergoes a ring expansion in aqueous conditions to a 1-thiacyclooctane derivative [<1999SL735>](#). Ring expansion also accompanies the reduction of 2-(2-nitrophenyl)thiochroman-4-one by SnCl_2 . To account for the product, a dihydrodibenzo[*b,e*][1,4]thiazepine **390**, it is proposed that initial reduction of the nitro group to a hydroxylamine is followed by a semipinacol rearrangement. When the nitro function is first reduced to an amine, further reaction with SnCl_2 leads to a dihydromethanodibenzo[*b,f*][1,5]thiazocine **391** (Scheme 106) [<2002JOC8662>](#).

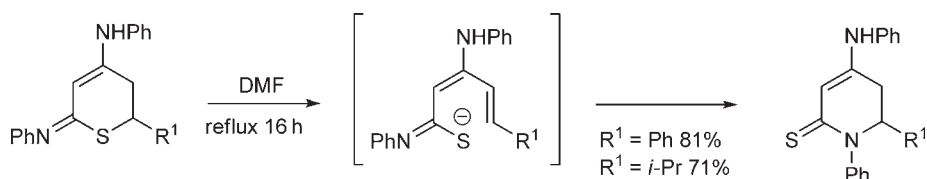


Scheme 106

Hexacarbonylmolybdenum forms a dicationic complex **392** with 2,4,6-triphenylthiopyrylium perchlorate. The sulfur atom appears to make no contribution to the metal-ring bonding and the heterocyclic rings are nonaromatic and nonplanar (Equation 100) [<1999JOM\(584\)171>](#).



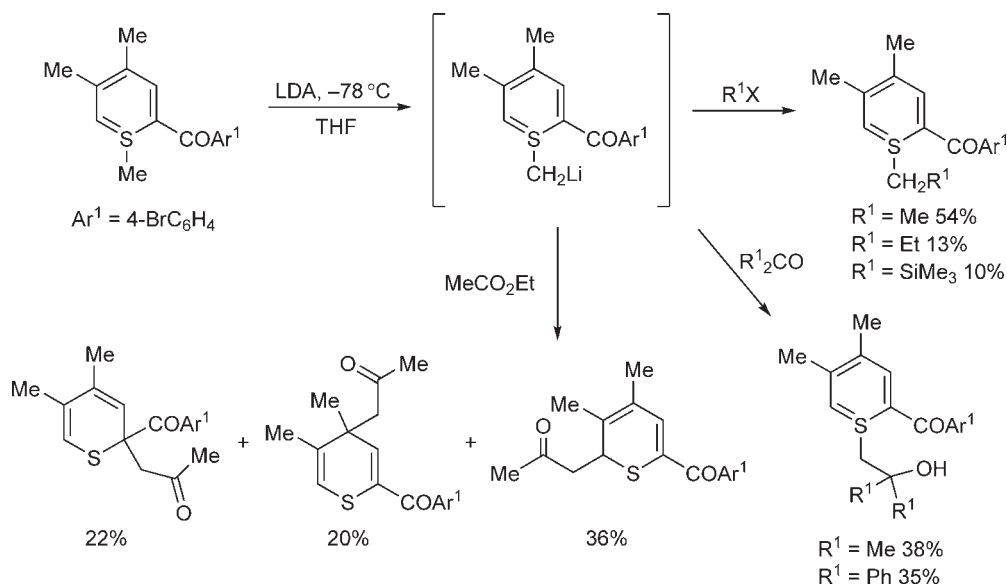
Various 2-substituted *N*-phenyl-6-phenylimino-3,6-dihydro-2*H*-thiopyran-4-amines, which are available from 6-substituted-5,6-dihydro-2*H*-thiopyran-2-thiones, thermally rearrange to 5,6-dihydropyridine-2(1*H*)-thiones. A resonance stabilized thioamide anion is proposed as the intermediate (Scheme 107) [<2001T8305>](#).



Scheme 107

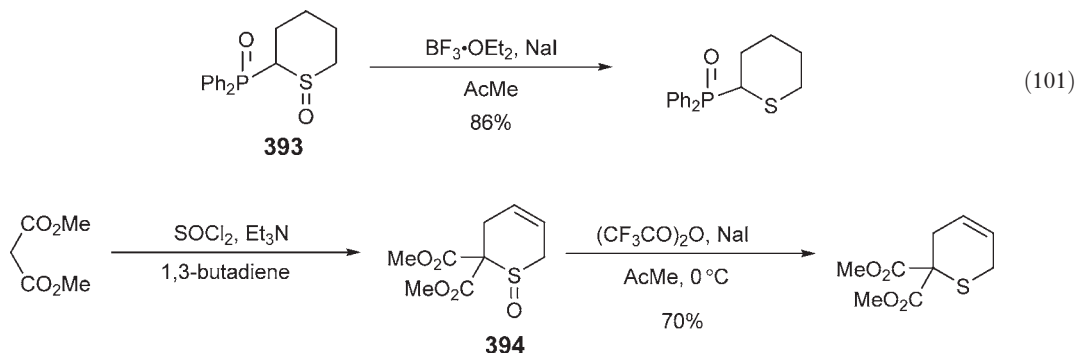
7.10.3.9 Reactions of Substituents Attached to Sulfur

S-Alkylthiabenzene derivatives are deprotonated by LDA and subsequent reaction of the anion with alkyl halides and ketones results in functionalization of the *S*-methyl group. However, reaction with esters leads to products arising from migration of the acylated methyl group (**Scheme 108**) <2000MI22>.

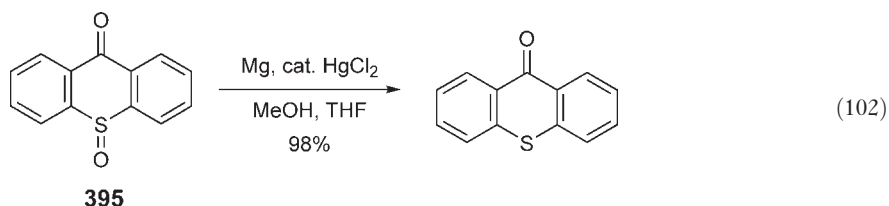


Scheme 108

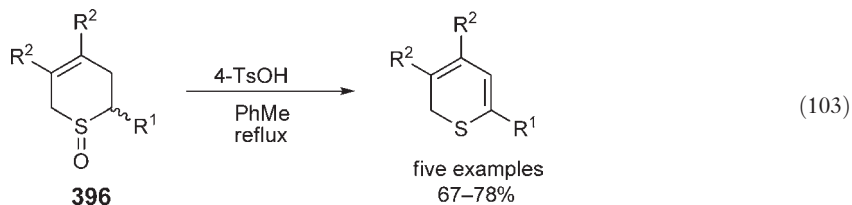
Tetrahydrothiopyran 1-oxide **393** is deoxygenated on treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and NaI (**Equation 101**) <1998T1375> and deoxygenation of 3,6-dihydro-2*H*-thiopyrans 1-oxides, for example, **394**, has been effected with NaI and $(\text{CF}_3\text{CO})_2\text{O}$ (**Scheme 109**) <1999PS(153)119, 2004EJO74>. Thiochroman 1-oxides are similarly deoxygenated with this reagent combination <2003PS(178)993>. Deoxygenation of thioxanthone sulfoxide **395** to thioxanthone has been accomplished in 98% yield using Mg/HgCl_2 in MeOH/THF (**Equation 102**) <1994TL2195>.



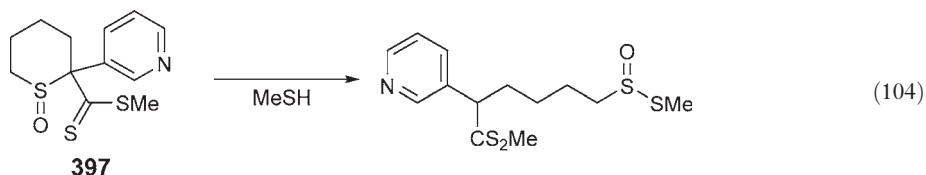
Scheme 109



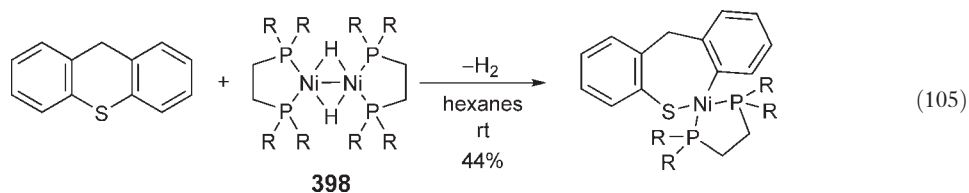
Substituted 3,6-dihydro-2*H*-thiopyran 1-oxides **396** are dehydrated on treatment with 4-TsOH to give 2*H*-thiopyrans (Equation 103) <2001J(P1)2269>.



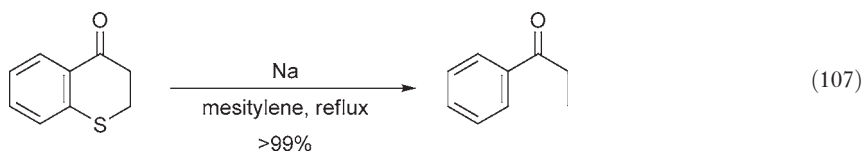
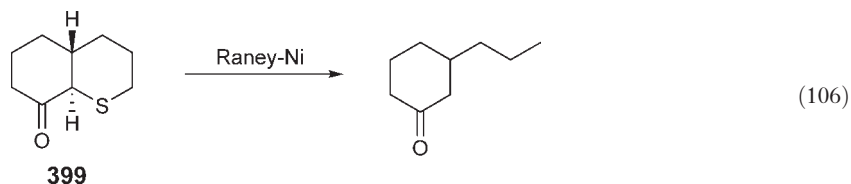
The 1-oxide function appears to play a major role in the cleavage of the tetrahydrothiopyran ring in the 2-(3-pyridinyl)tetrahydrothiopyran 1-oxide derivative **397**, promoting nucleophilic attack by the methanethiol anion at the tricoordinate S atom (Equation 104) <1996JOC8701>.



The nickel dihydride dimer **398** inserts into the C–S bond of thioxanthene, rapidly producing a thiametallacycle and paving the way toward a facile catalytic hydrodesulfurization process (Equation 105) <1999JA7606>.



Desulfurization of the *trans*-thiadecalin-8-one **399** with Raney nickel gives 3-propylcyclohexanone (Equation 106) <2000TL2279> and thiochroman-4-one is efficiently desulfurized to propiophenone on heating with metallic sodium in mesitylene after initial separation of the enolate (Equation 107) <1998TL2671>.

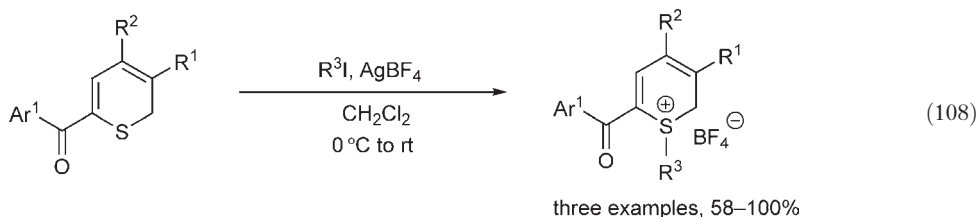


7.10.4 Synthesis

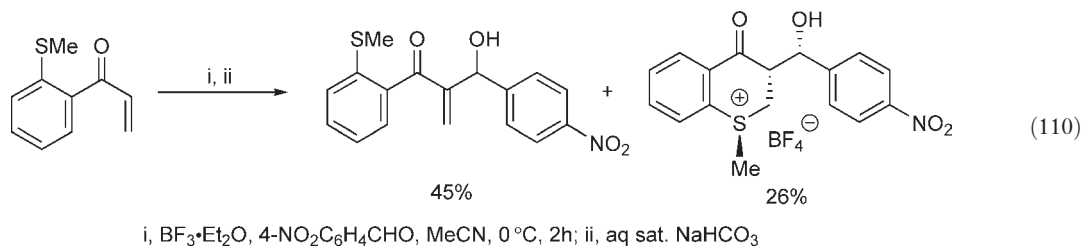
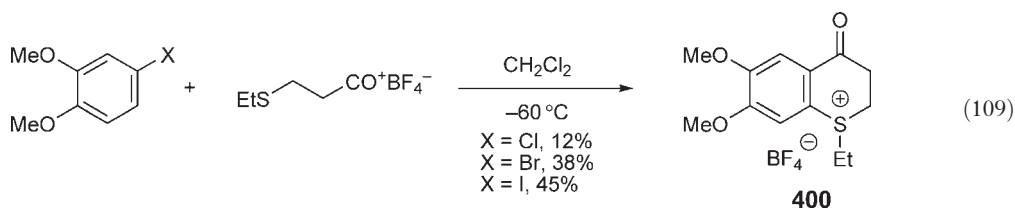
7.10.4.1 Thiopyrans and Fused Thiopyrans

7.10.4.1.1 Thiopyranium salts

S-Alkylation of 6-aryl-2*H*-thiopyrans with alkyl iodides in the presence of either silver fluoroborate or dialkoxycarbenium fluoroborates in CH₂Cl₂ proceeds smoothly to afford the 1-alkylthiopyranium fluoroborates (Equation 108). Methyl trifluoromethanesulfonate proved more efficient for the S-methylation of 6-cyano- and 6-methoxycarbonyl-2*H*-thiopyrans <1990TL115, 2001J(P1)2269>.



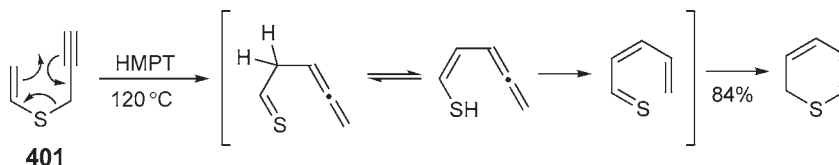
The initial 5-acylation of 4-halogeno-1,2-dimethoxybenzenes by 3-ethylsulfanylpropanoyl fluoride in the presence of BF₃ is followed by intramolecular nucleophilic displacement of the halide and the formation of the 1-ethyl-6,7-dimethoxy-4-oxo-3,4-dihydrobenzothiopyranium salt **400** (Equation 109) <1998T5599>. The same ring structure results when [2-(methylthio)phenyl]propanone is treated with BF₃ etherate. If the reaction is carried out in the presence of an aldehyde and provided the reaction is quenched with NaHCO₃, the Morita–Baylis–Hillman adduct can be isolated (Equation 110). Stereochemical assignments for these products have been derived from a study of the methylation of stereochemically pure 3-[1-hydroxy-1-(4-nitrophenyl)methyl]thiochroman-4-ones <2003EJO4852>.



7.10.4.1.2 2*H*-Thiopyrans

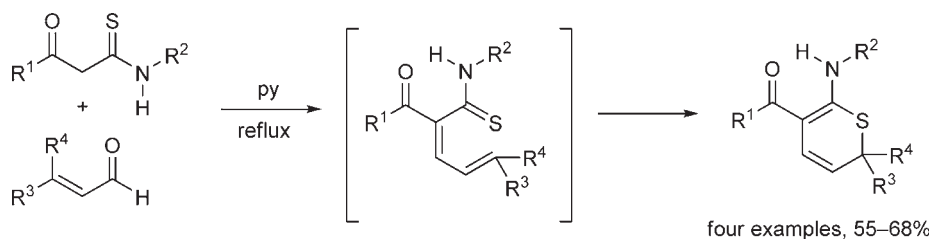
7.10.4.1.2(i) Formation of one bond

2*H*-Thiopyran has been obtained by the Claisen rearrangement and subsequent electrocyclic ring closure of 3-vinylsulfanylpropyne **401** on heating in HMPT at 120 °C (Scheme 110) <2001EJO2477>.



Scheme 110

The reaction between acetyl- and benzoyl- thioacetamides and α,β -unsaturated aldehydes in refluxing pyridine yields a dienic thioamide through a Claisen-like condensation. Spontaneous electrocyclization affords the 2*H*-thiopyran (**Scheme 111**). Substituted piperidine-2-thione derivatives result when the reaction is carried out in ethanol using triethylamine as the base [<2003T4183>](#).

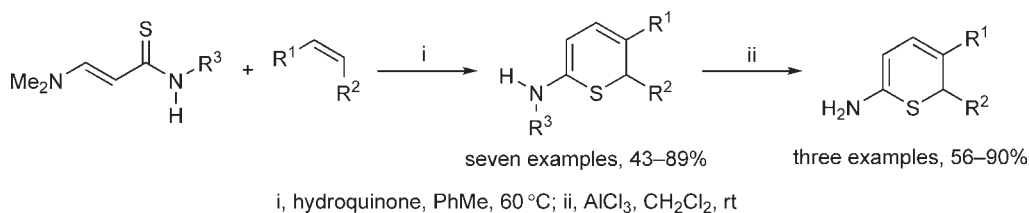


Scheme 111

7.10.4.1.2(ii) Formation of two bonds

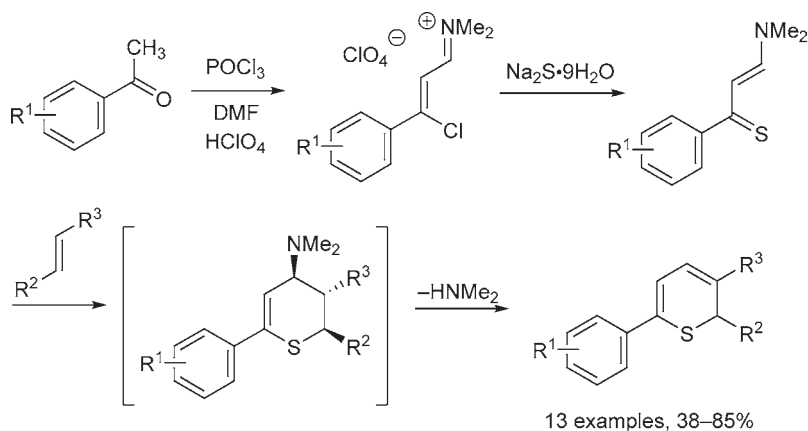
Enaminothiones are a versatile source of 2*H*-thiopyrans by [4+2] cycloaddition strategies [<1997AHC\(67\)267>](#).

2-Amino-2*H*-thiopyrans are produced when protected 2-amino-4-dimethylaminothiabutadienes react with acrylic dienophiles. The initial adduct eliminates dimethylamine and subsequent deprotection generates the amine (**Scheme 112**). Using methyl vinyl ketone, the protected amino function is butanoylated [<2004S1633, 2006T9226>](#).



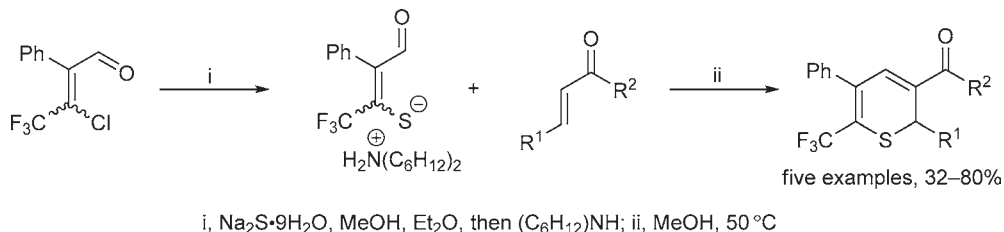
Scheme 112

Enaminothiones derived from acetophenones using Vilsmeier methodology yield substituted 2*H*-thiopyrans on reaction with various dienophiles. The dihydrothiopyran from the cycloadducts with propenal and but-3-enone spontaneously eliminate dimethylamine, but the cycloadduct can be isolated when 1-nitro-2-phenylethene is used as the dienophile and later converted to the thiopyran (**Scheme 113**) [<1994JPR434>](#).



Scheme 113

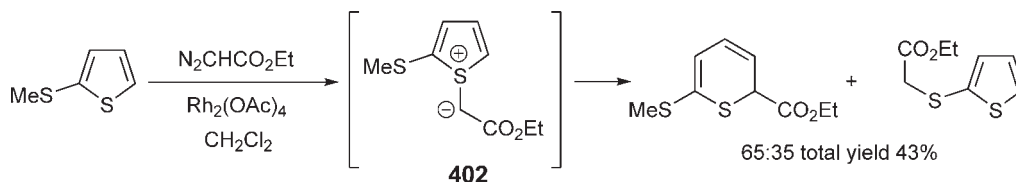
Cycloaddition of the thiolate derived from 3-chloro-2-phenyl-3-trifluoromethylpropenal by sequential reaction with Na_2S and dicyclohexylamine with propenals and butenones affords 6-trifluoromethyl-2*H*-thiopyrans in good yields (**Scheme 114**). In a similar manner, chlorovinylcarbonyl compounds give 2-methylene derivatives <1995JFC(70)121>.



Scheme 114

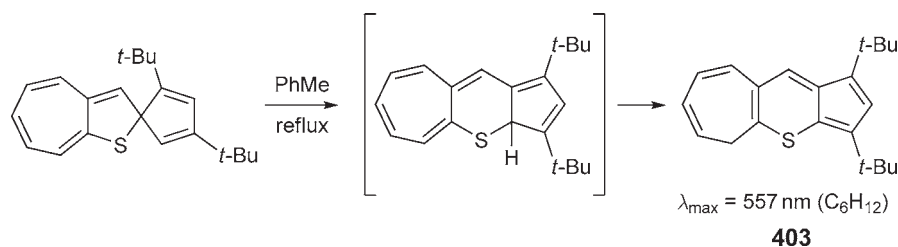
7.10.4.1.2(iii) From other heterocycles

Carbenoid insertion into the C-S bond of 2-substituted thiophenes competes with cyclopropanation at the $\text{C}=\text{C}$ bonds. Formation of the ylide **402** and hence a thiopyran by way of a Stevens rearrangement is the dominant pathway for 2-(methylthio)thiophene, but is less significant for the 2-methyl and 2-trimethylsilyl derivatives (**Scheme 115**) <1998T15499>.



Scheme 115

The deep blue cycloheptathialene **403** results from the thermal rearrangement of cyclohepta-1-thiaspiro[4,4]nonatriene (**Scheme 116**) <2000TL8255>.

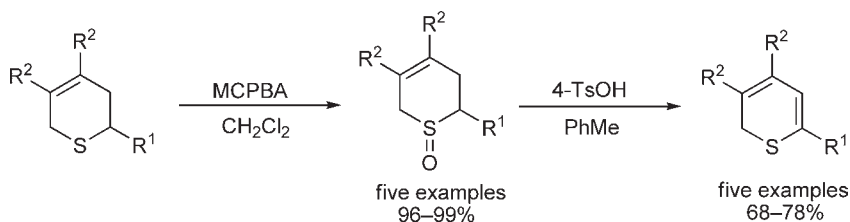


Scheme 116

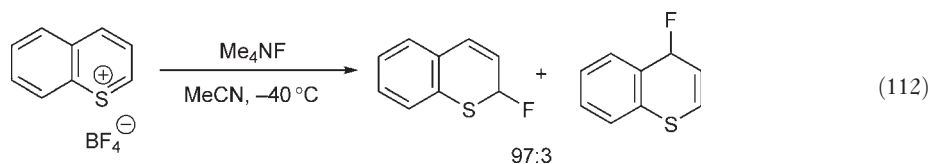
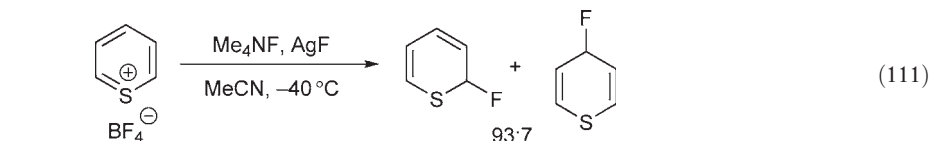
7.10.4.1.2(iv) From a preformed heterocyclic ring

Oxidation of 2-substituted 3,6-dihydro-2*H*-thiopyrans with MCPBA gives a mixture of the *cis* and *trans* sulfoxides which is dehydrated on heating with toluene-4-sulfonic acid to give good yields of the 2*H*-thiopyrans (**Scheme 117**) <2001J(P1)2269>.

The reaction of thiopyrylium salts with tetramethylammonium fluoride or AgF yields 2-fluoro-2*H*-thiopyran together with very minor amounts of 4-fluoro-4*H*-thiopyran (**Equation 111**). In like manner, the 2,4,6-tri-*t*-butyl derivative gives mainly the 2-fluoro compound and benzo[*b*]thiopyrylium salts mainly afford 2-fluoro-2*H*-1-benzothiopyran (**Equation 112**). Both thioxanthylum tetrafluoroborate and the 9-phenyl derivative give the 9-fluoro-thioxanthene. In no reaction was there any evidence of attack of F^- at sulfur <2003JFC(120)49>.



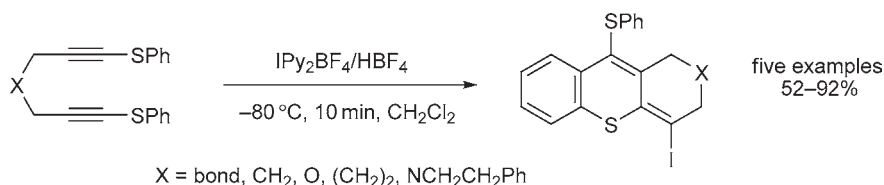
Scheme 117



7.10.4.1.3 2H-1-Benzothiopyrans

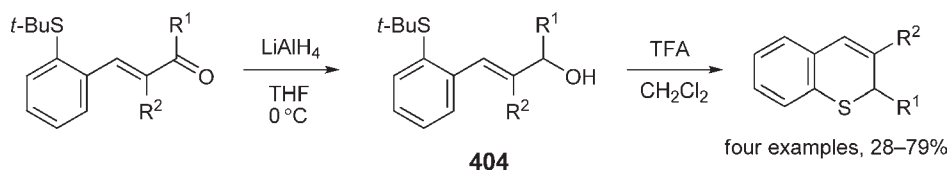
7.10.4.1.3(i) Formation of one bond

An *endo-exo* intramolecular cyclization of α,β -diynylsulfides is brought about by iodonium salts and leads to fused 2H-1-benzothiopyrans (**Scheme 118**). The reaction is successful with 1,5-, 1,6-, and 1,7 diynes and a heteroatom can be accommodated in the alkyl chain. Furthermore, a substituent can be present at the other terminal site and the iodine which is perforce introduced into the fused alicyclic ring allows elaboration by Pd-catalyzed coupling with a variety of acetylenes <1998AGE3136>.



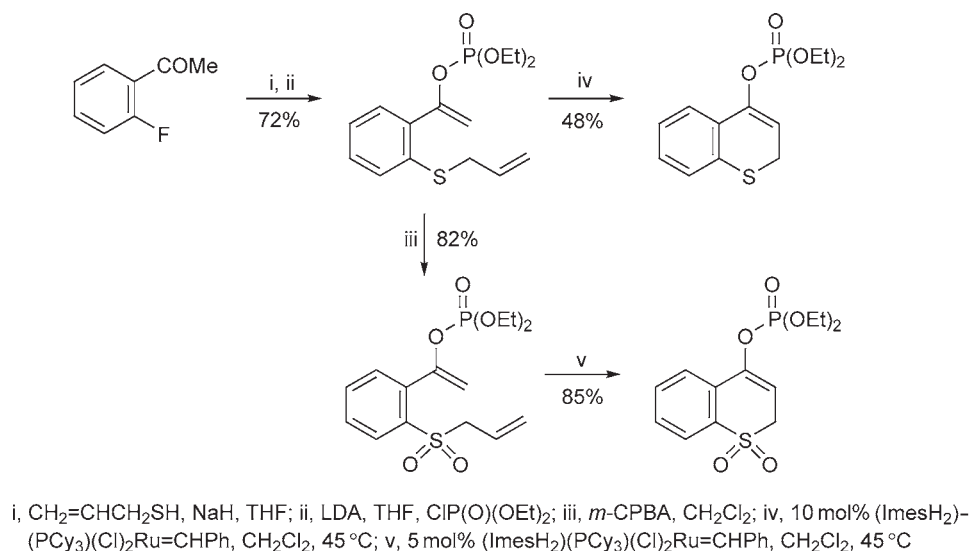
Scheme 118

The allylic alcohols **404** derived by reduction of the condensation product between methylketones and 2-*t*-butylthiobenzaldehyde readily cyclize to 2H-1-benzothiopyrans (**Scheme 119**) <1996TL5077>.



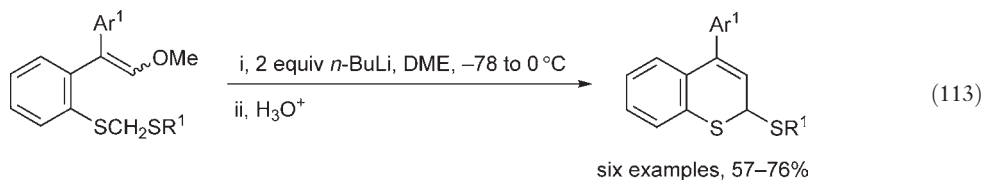
Scheme 119

Thiochromen-4-yl enol phosphates have been obtained from 2'-fluoroacetophenone through initial reaction with prop-2-enethiol followed by conversion to the enol phosphate. Ring closing metathesis (RCM) using a second generation Grubbs' catalyst delivered the *S*-heterocycle. Oxidation at sulfur prior to RCM provided access to the thiochromen-4-yl 1,1-dioxide enol phosphate (**Scheme 120**) <2003TL4275>.

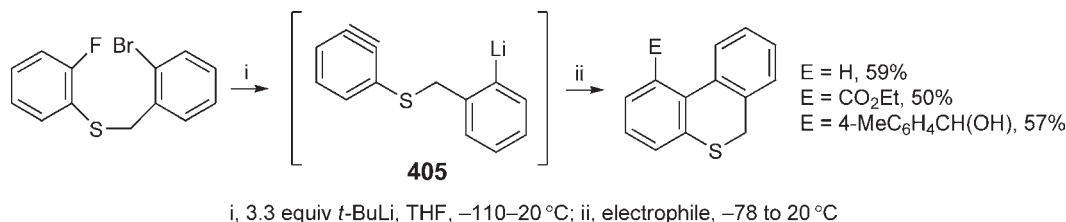


Scheme 120

Metallation of the SCH_2S group of 1-(1-aryl-2-methoxyethenyl)-2-(sulfenylmethylthio)-benzenes promotes an intramolecular attack at the vinylic group and leads to 4-aryl-2-sulfenylthiopyranes (Equation 113). It is necessary to use two moles of the metallating species for complete conversion to the thiopyran since C-2 in the product is sufficiently acidic to be deprotonated by the carbanion initially produced from the starting material <2006BCJ1977>.



2-Bromobenzyl 2-fluorophenyl thioether, derived from 2-fluorothiophenol and 2-bromobenzyl bromide, is a source of a benzyne through reaction with *t*-butyllithium. Simultaneously, the bromobenzyl moiety generates the tethered aryllithium **405** and an intramolecular anionic cyclisation is promoted. The sequence is completed by the addition of an electrophilic species leading to 1-substituted 6*H*-dibenzo[*b,d*]thiopyrans (Scheme 121) <2002CEJ2034>.

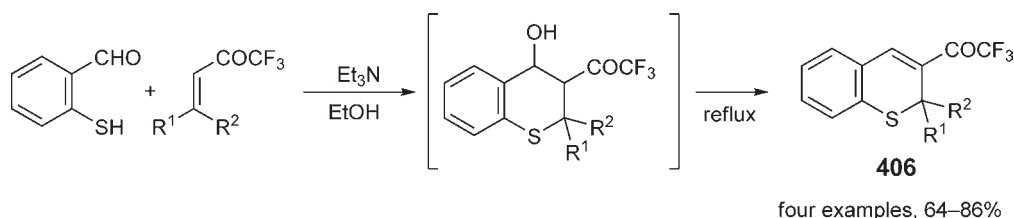


Scheme 121

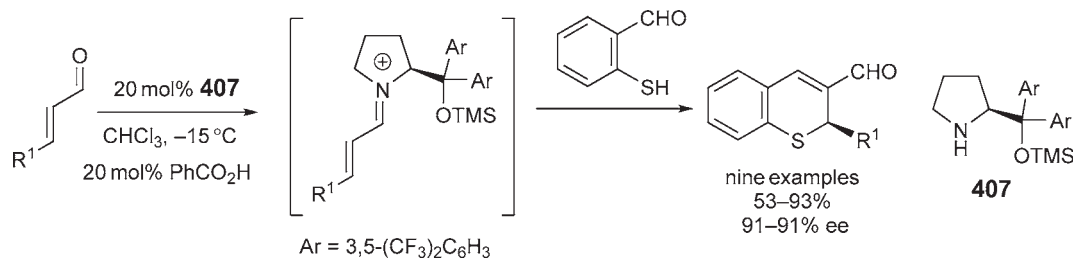
7.10.4.1.3(ii) Formation of two bonds

The reaction between thiosalicylaldehyde and trifluoromethylated enones under basic conditions affords 3-trifluoroacetylthiopyranes **406**. The initial product is the corresponding thiochroman-4-ol but this usually spontaneously dehydrates (Scheme 122) <1999CHE549>.

The asymmetric domino reaction between 2-mercaptobenzaldehyde and α,β -unsaturated aldehydes proceeds with excellent chemo- and enantio-selectivities to afford 2-substituted 3-formyl-2*H*-1-benzothiopyrans, products of a formal Baylis–Hillman reaction, when the *S*-proline derived catalyst **407** is employed (Scheme 123) <2006TL8547>.

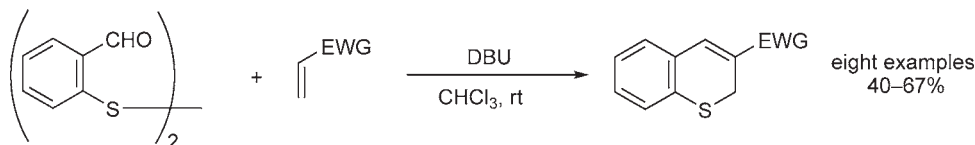


Scheme 122



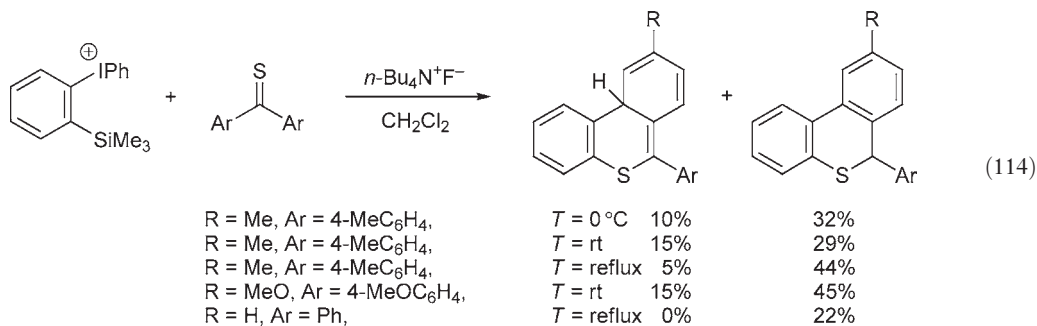
Scheme 123

2,2'-Dithiodibenzaldehyde behaves as a masked thiosalicylaldehyde and undergoes a Baylis–Hillman reaction with electron-deficient alkenes to give 3-substituted thiochromenes ([Scheme 124](#)) [<2001S2389>](#).



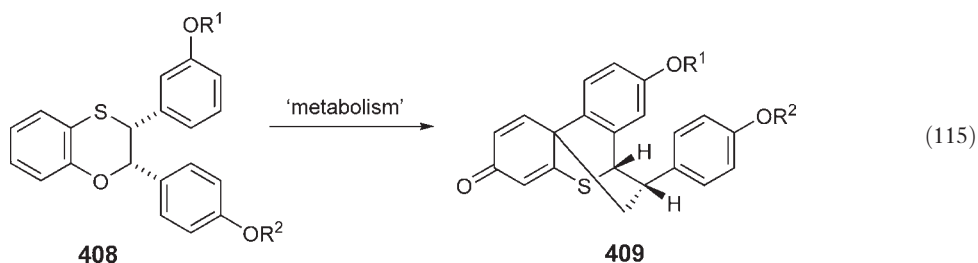
Scheme 124

Benzyne generated at room temperature from phenyl[2-(trimethylsilyl)phenyl]iodonium trifluoromethanesulfonate has been trapped in a [4+2] cycloaddition reaction with diarylthiones. The initial product, a 6-aryl-4*H*-dibenzo[*b,d*]thiopyran, is accompanied by 6-aryl-6*H*-dibenzo[*b,d*]thiopyran arising by 1,3-prototropic aromatization of the cycloadduct ([Equation 114](#)). The use of sterically congested thiones, such as thiopivalophenones, results in competition from a [2+2] cycloaddition and 2*H*-benzo[*b*]thietes are the sole products [<2000BCJ155>](#).



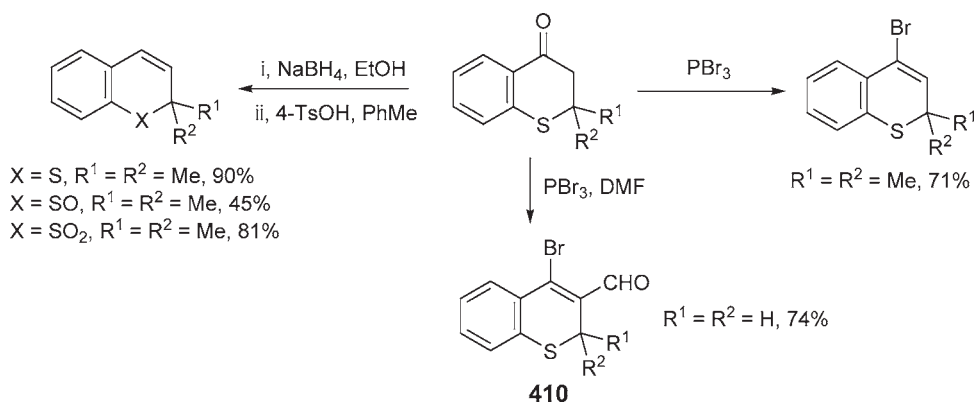
7.10.4.1.3(iii) From other heterocycles

The dihydrobenzoxathiin **408**, a potent selective estrogen receptor α modulator, is metabolized to the bridged dibenzo[*b,d*]thiopyran derivative **409**. It seems logical to assume that **409** is formed by initial cleavage of the O–C bond followed by an intramolecular acylation to generate the thiopyran ring. A 19-step total synthesis from resorcinol confirmed the structure of **409** (Equation 115) <2005OL411>.



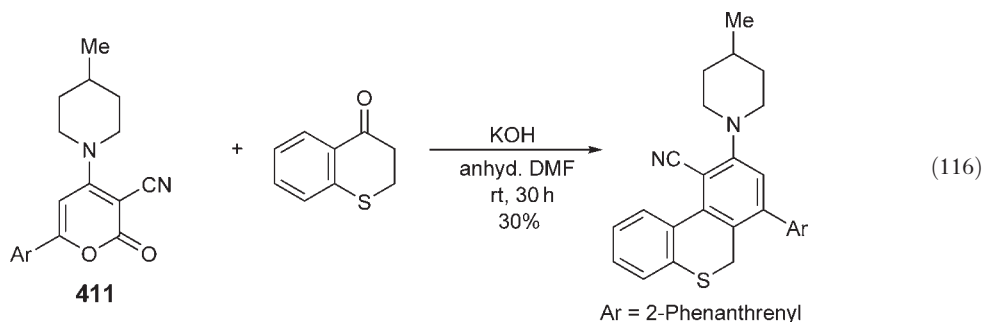
7.10.4.1.3(iv) From a preformed heterocyclic ring

Both thiochromenes and their 4-bromo derivatives are accessible from 2,2-disubstituted thiochroman-4-ones. The former result from reduction of the carbonyl group followed by acid-catalyzed dehydration, a method well developed for the *O*-heterocyclic analogues and also applicable to thiochroman-4-one 1,1-dioxides <1992TH1, 1995T13277>. The latter are formed in good yields by the reaction with PBr_3 though the reaction fails with thiochroman-4-one 1,1-dioxides (Scheme 125) <1994T2507>. Thiochroman-4-one undergoes a Vilsmeier reaction with PBr_3 in DMF to give 4-bromothiochromen-3-carbaldehyde **410** <1999CEJ1038>.



Scheme 125

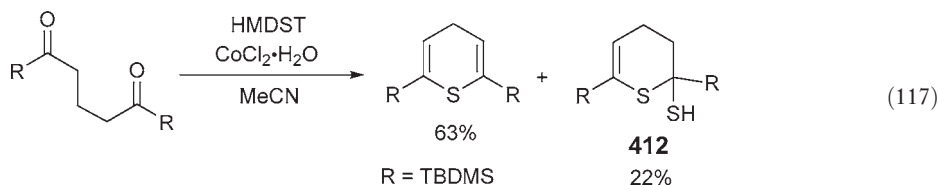
A substituted dibenzo[*b,d*]thiopyran results when the carbanion derived from thiochroman-4-one reacts with the highly substituted 2*H*-pyran-2-one **411**. Initial attack at C-6 prompts cyclization at the 4-position of the thiochromanone unit and subsequent decarboxylation and dehydration account for the formation of the product (Equation 116) <2004EJO886>.



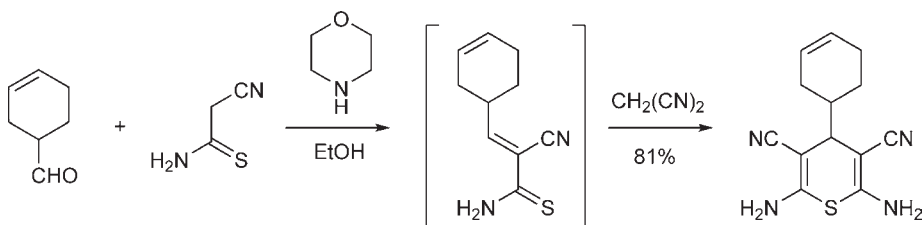
7.10.4.1.4 4*H*-Thiopyrans

7.10.4.1.4(i) Formation of one bond

There are several examples of the formation of a 4*H*-thiopyran ring by intramolecular cyclisation involving attack by a thiol function on an electron deficient site. Thus 1,5-bis(acylsilanes) are cyclized on thionation with hexamethyldisilathiane (HMDST) providing a route to 2,6-bis(trialkylsilyl)-4*H*-thiopyrans. Attack of the enethiol form of the initially formed thioacylsilanes on the other C=S unit leads to an aldol-like intermediate **412** which subsequently loses H₂S. Small amounts (6%) of the corresponding 4*H*-pyran are detected which arise from attack at an unchanged C=O group (Equation 117) <2004TL87, 2005PS(180)1303>.

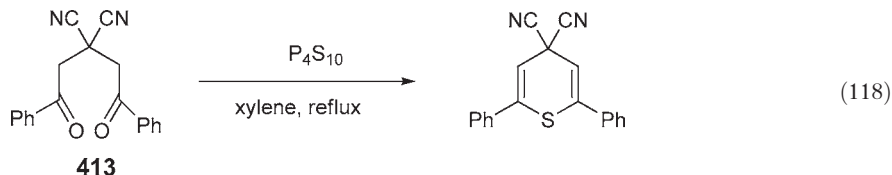


In the presence of morpholine and malononitrile, the initial reaction of cyclohex-3-enal with cyanothioacetamide is followed by a condensation with the dinitrile. Cyclization follows through attack of the thiol on a nitrile function and a penta-substituted 4*H*-thiopyran is formed (Scheme 126) <1998RJO557, 2005RJC1537>.

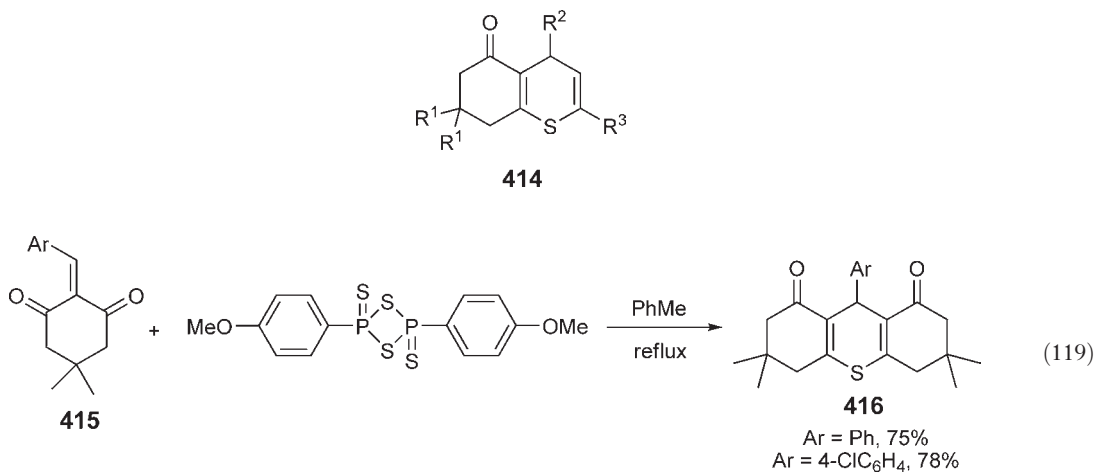


Scheme 126

Thionation of the 1,5-diketone **413** with P₄S₁₀ affords the 4,4-dicyanothiopyran (Equation 118) <2002PS(177)2791>.

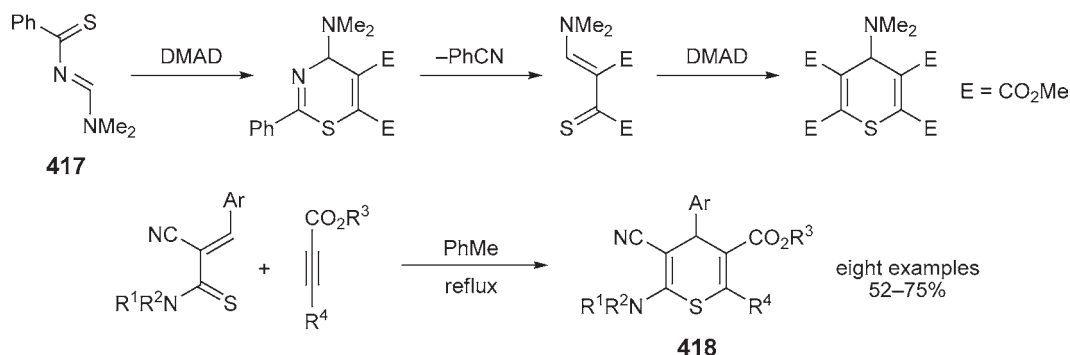


Cyclization of 2-(1,3-diphenyl-3-oxopropyl)cyclohexan-1,3-diketones with H₂S gives the cyclohexa-fused 4*H*-thiopyran **414** <2000CHE1032> and treatment of the arylidenecyclohexandione **415** with Lawesson's reagent in boiling toluene leads directly to bis-fused 4*H*-thiopyrans **416** (Equation 119) <2004PS(179)2387>.



7.10.4.1.4(ii) Formation of two bonds

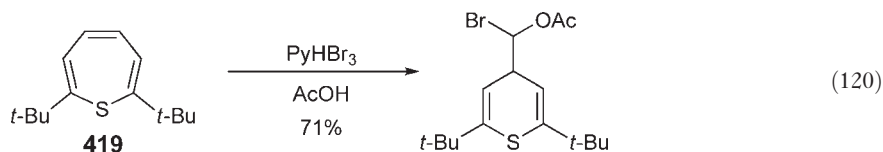
Highly substituted 4-dimethylamino-4*H*-thiopyrans result from a cycloaddition–cycloreversion–cycloaddition sequence commencing with the heterodiyne **417** and dimethyl acetylenedicarboxylate (DMAD) <1996J(P2)2623, 1997MI2185>. Activated alkynes cycloadd to 3-aryl-2-cyanothioacrylamides yielding 4-aryl-4*H*-thiopyrans **418** (Scheme 127) <1994J(P1)989>.



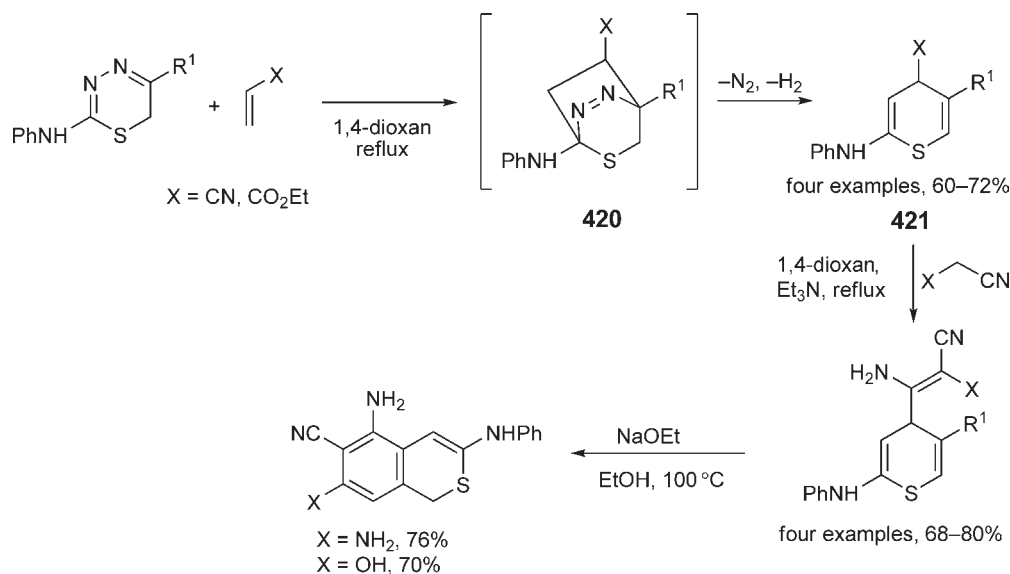
Scheme 127

7.10.4.1.4(iii) From other heterocycles

On bromination in acetic acid, 2,7-di-*t*-butylthiepine **419** undergoes a ring contraction to a 4*H*-thiopyran. Electrophilic attack at C-4 is considered to generate a homothiopyrylium ion and nucleophilic attack by the solvent completes the process (Equation 120) <1994J(P1)2631>.

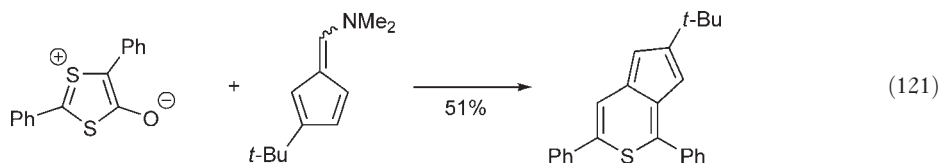


The cycloadduct **420** formed from the reaction between 1,3,4-thiadiazines and acrylate derivatives spontaneously loses N₂ to give 2,4,5-trisubstituted 4*H*-thiopyrans **421**. The products from the reaction of the 4-nitrile derivatives with malononitrile and ethyl cyanoacetate cyclize on treatment with base to give 1*H*-2-benzothiopyrans (Scheme 128) <2006AP608>.



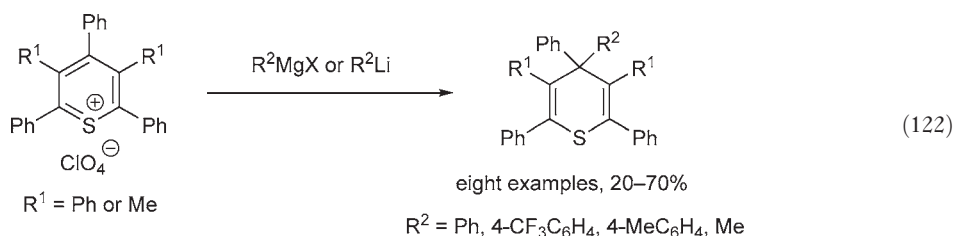
Scheme 128

A [4+6] cycloaddition is involved in the formation of cyclopenta[*c*]thiopyrans from the mesoionic diphenyldithioliumolate and a fulvene (Equation 121) <1996CC1011>.



7.10.4.1.4(iv) From a preformed heterocyclic ring

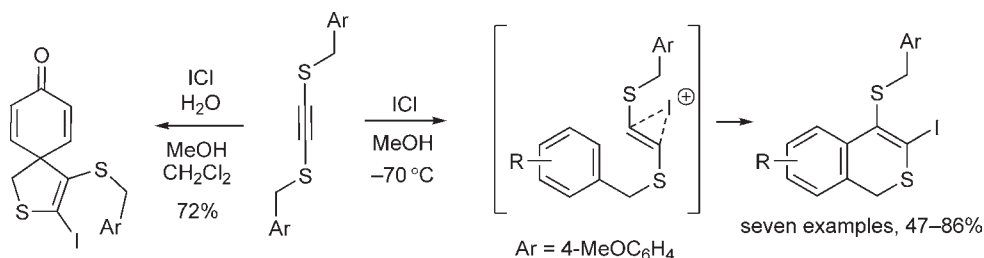
A range of 2,4,4,6-tetraaryl-4*H*-thiopyrans has been obtained by the reaction of 3,5-disubstituted 2,4,6-triphenylthiopyrylium salts with aryl Grignard and organolithium reagents (Equation 122) <1996JPH(101)33, 1997PS(120)403>.



7.10.4.1.5 1*H*-2-Benzothiopyrans

7.10.4.1.5(i) Formation of one bond

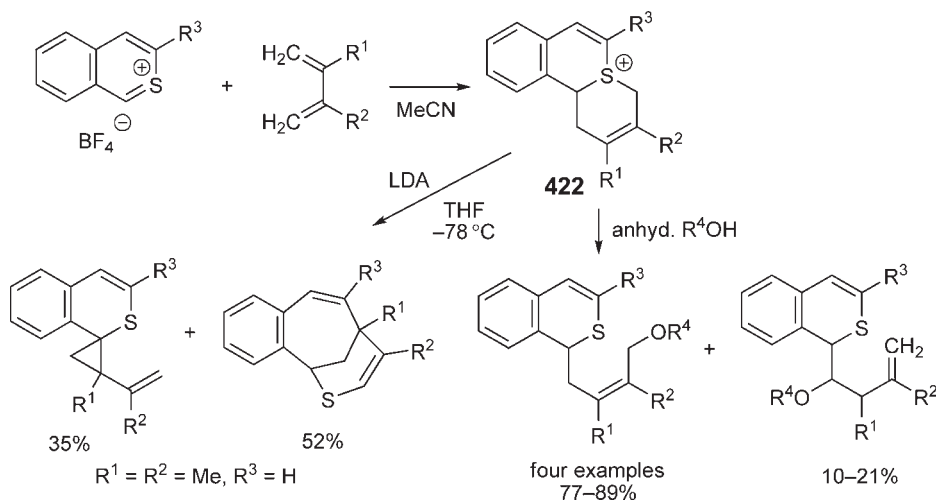
Treatment of symmetrically substituted bis(arylmethylthio)alkynes with either ICl or Br₂ and in the strict absence of water promotes cyclization to 1*H*-2-benzothiopyrans (Scheme 129). Initial formation of a cyclic halonium species induces the electrophilic ring closure. In the presence of nucleophiles, *ipso* attack is favored and a spirocyclohexadienone results. The alkynes are accessible from arylmethyl thiocyanates and sodium acetylide <1998JOC4626, 2003EJO47>.



Scheme 129

7.10.4.1.5(ii) From a preformed heterocyclic ring

Benzothiopyrylium and dibenzothiopyrylium salts take part in polar cycloaddition reactions with 1,3-dienes to form bridgehead sulfonium salts **422** <1994J(P1)3129, 1996J(P1)2227, 1997T4611>. Alcohols cleave an S-C bond to give mainly a but-2-enyl derivative with some of the terminal alkenyl product. Other bases promote further reaction of the ring-opened materials leading to substituted isothiochromenes and 1,5-methano-2-benzothionine derivatives (Scheme 130) <1995J(P1)1583>.

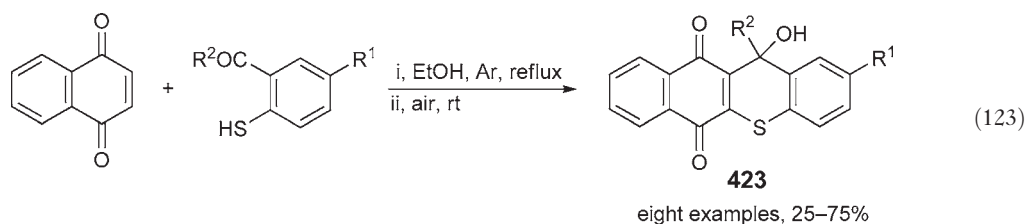


Scheme 130

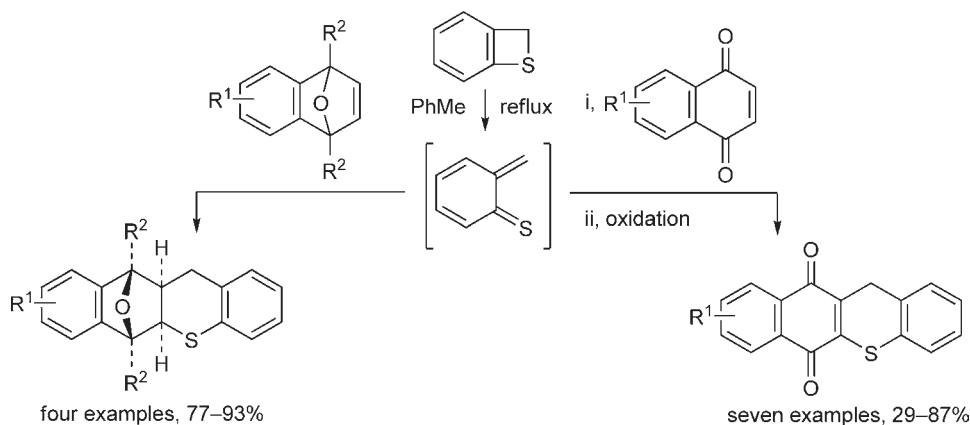
7.10.4.1.6 Thioxanthenes

7.10.4.1.6(i) Formation of two bonds

1,4-Naphthoquinone and 2-acylbenzenethiols react by sequential conjugate addition, aldol reaction, and atmospheric oxidation to produce 12*H*-benzo[*b*]thioxanthene quinones **423**. The exact conditions required depend on the nature of the thiol, but are quite mild (Equation 123) <2004BCJ2095>.



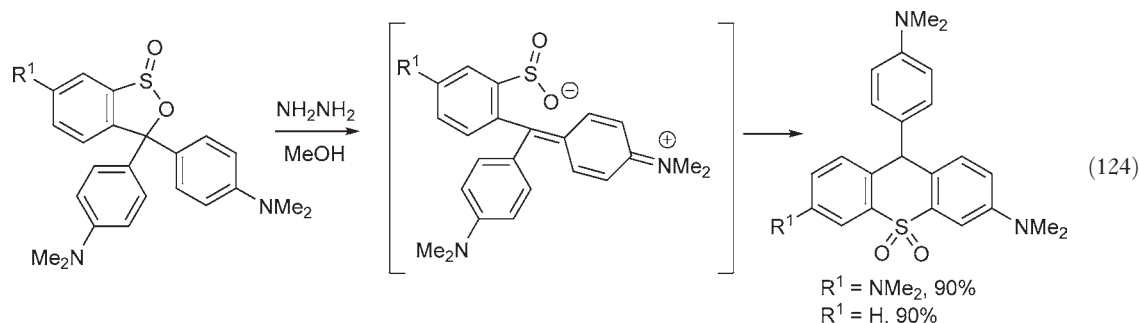
2*H*-Benzo[*b*]thiete is a source of *o*-thioquinone methides, heterodienes which react with 1,4-naphthoquinones or 1,4-epoxynaphthalenes to give the benzo[*b*]thioxanthene system. With the former reagents, the initial products undergo an autooxidation and 6,11-dihydro-12*H*-benzo[*b*]thioxanthene-6,11-diones result. The 6,11-epoxy adducts which are formed from the epoxynaphthalenes can be dehydrated to 12*H*-benzo[*b*]thioxanthenes or converted into the dihydrobenzothioxanthene-6-ol (Scheme 131) <1995JPR379>.



Scheme 131

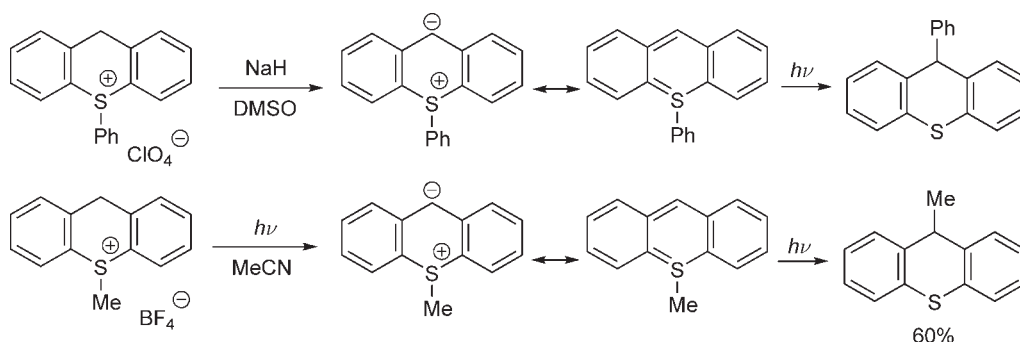
7.10.4.1.6(ii) From other heterocycles

3,3-Diaryl-3*H*-2,1-benzoxathiole 1-oxides react with hydrazine to give high yields of 9-aryl-9*H*-thioxanthene 10,10-dioxides. It is proposed that the role of the hydrazine is to initiate cleavage of the O–C bond which is followed by attack of S on the adjacent aromatic ring (Equation 124) <1998H(49)143>.



7.10.4.1.6(iii) From a preformed heterocyclic ring

10-Methyl and 10-phenyl thioxanthenium salts can be deprotonated at the benzylic group either by base or photolytically to generate the stable deep orange ylide or thiaanthracene. Secondary photolysis results in the conversion to the 9-substituted thioxanthene (Scheme 132) <1997CC709>.



Scheme 132

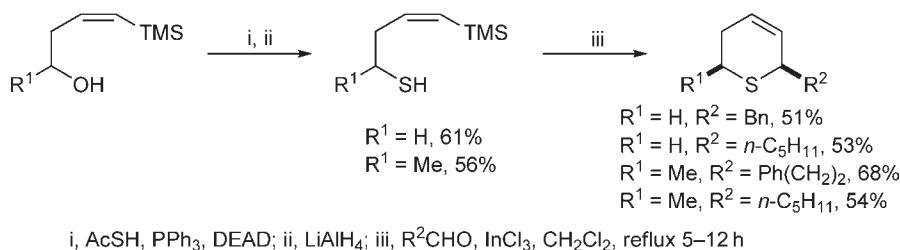
7.10.4.2 Reduced Thiopyrans

7.10.4.2.1 Dihydrothiopyrans

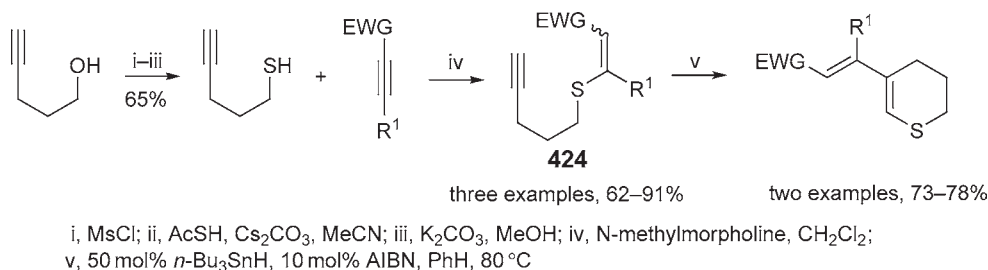
7.10.4.2.1(i) Formation of one bond

Reaction of 4-trimethylsilylbut-3-ene-1-thiol with aldehydes occurs readily using the mild Lewis acid InCl_3 to give substituted 3,6-dihydro-2*H*-thiopyrans. Upon introduction of a methyl group at the 1-position of the thiol, this silyl-Prins cyclisation reaction proceeds with *cis*-diastereoselectivity yielding the 2,6-disubstituted thiopyran (Scheme 133). The selectivity is attributed to the substituents adopting equatorial positions in the chair-like transition state of the developing ring. The thiols are obtained by a Mitsunobu reaction of the corresponding alcohols with thioacetic acid and subsequent reduction with LiAlH_4 <2003JOC7880>.

Michael addition of pent-4-yn-1-thiol to an activated alkyne produces ω -yne vinylsulfides **424** as a separable mixture of the *E* and *Z* isomers. On treatment with $n\text{-Bu}_3\text{SnH}$ and a radical initiator, these substrates undergo a double radical cyclization accompanied by β -fragmentation of the stannyl radical. The process is regio-, chemo-, and stereo-selective and produces the *E*-isomer of the 5-substituted 3,4-dihydro-2*H*-thiopyran (Scheme 134) <1997JOC8630>.

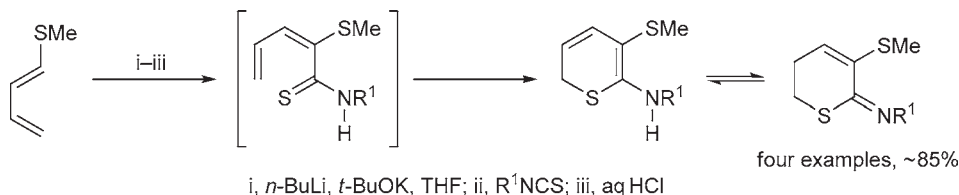


Scheme 133



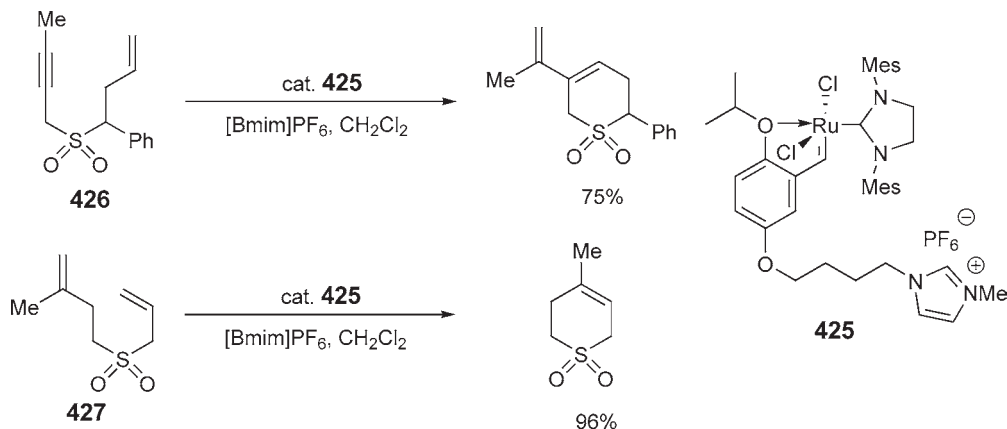
Scheme 134

Hydrolysis of the acyclic adducts formed when metallated 1-methylthiobuta-1,3-diene reacts with isothiocyanates using a stoichiometric amount of dilute acid results in electrocyclization to a 6-amino-2*H*-thiopyran which tautomerizes to the 2-imino-5,6-dihydro-2*H*-thiopyran ([Scheme 135](#) <1998TL2631>).



Scheme 135

Both the sulfone-tethered enyne **426** and diene **427** undergo RCM to give 5,6-dihydro-2*H*-thiopyran 1,1-dioxides when treated with a second generation Grubbs' ruthenium catalyst **425** tagged with an ionic liquid ([Scheme 136](#) <2005JOM(690)3577>).

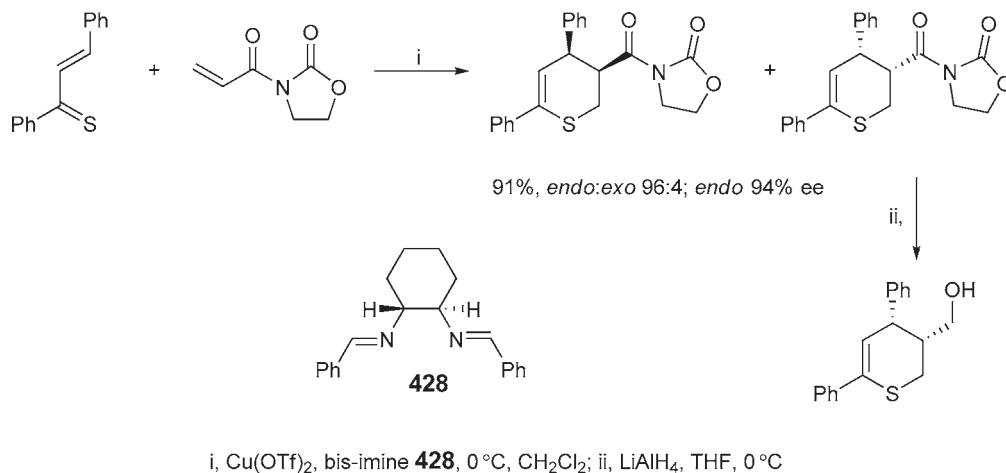


Scheme 136

7.10.4.2.1(ii) Formation of two bonds

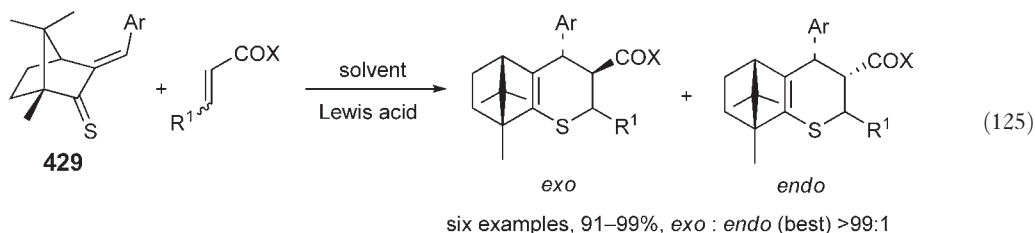
There are two approaches to the synthesis of dihydrothiopyrans by hDA methodology; the sulfur atom can be part of either the diene or the dienophile.

The first example of an enantioselective thiadiene cycloaddition involved the reaction of 2,4-diphenyl-1-thiabuta-1,3-diene with 1-propenyl-1,3-oxazolidin-2-one. Stoichiometric quantities of a copper triflate bis-imine complex catalyst **428** and 4 Å molecular sieves are necessary to achieve the highest enantioselectivity and the best *endo/exo* ratio. The absolute configuration of the major *endo* isomer was determined by reduction of the acyloxazolidine side chain to the known (3*R*,4*R*)-5-hydroxymethyl derivative (**Scheme 137**) <1997J(P1)2957>. The process is improved using a homochiral Cu triflate or Ni perchlorate bis(oxazoline) complex when catalytic amounts are adequate for a range of thiabutadienes <1999CC1001>.

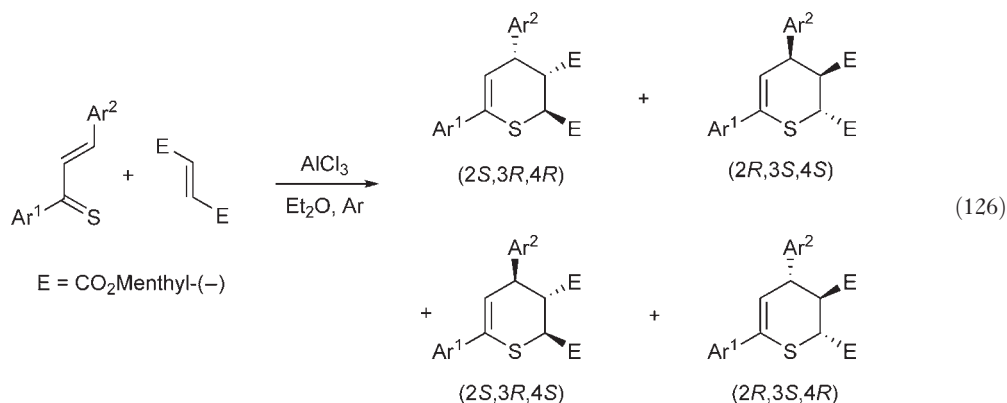


Scheme 137

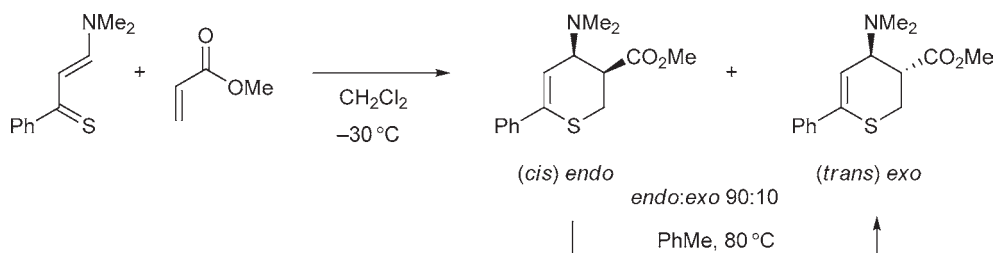
Incorporation of the thiabutadiene moiety into a camphor framework resulted in the reaction with various dienophiles proceeding with complete π -facial selectivity and, in some instances, *exo*-selectivity. The stereochemistry of one product was confirmed by X-ray analysis. The (arylmethylene)thiocamphor compounds **429** were prepared by thionation of the corresponding ketones with Lawesson's reagent and exist as stable monomers (**Equation 125**) <1999TL8383>.



The thermal asymmetric hDA (AHDA) reaction between 2,4-diaryl-1-thiabuta-1,3-dienes and di-(–)-menthyl fumarate proceeds in excellent yield to afford a mixture of four diastereomers with only moderate π -facial diastereoselectivity (**Equation 126**). The reaction is accelerated by Lewis acids without influencing the *endo* selectivity, although overall yields are lower. Chromatographic separation of the *cis* and *trans* adducts followed by recrystallization enabled the diastereomers to be obtained in a stereochemically pure state. Removal of the chiral auxiliary by reaction with LiAlH₄ from both *cis* adducts gave the enantiomers of various 2,3-bis(hydroxymethyl)-3,4-dihydro-2*H*-thiopyrans and desulfurization provides a route to optically pure diols <1996J(P1)1897>.

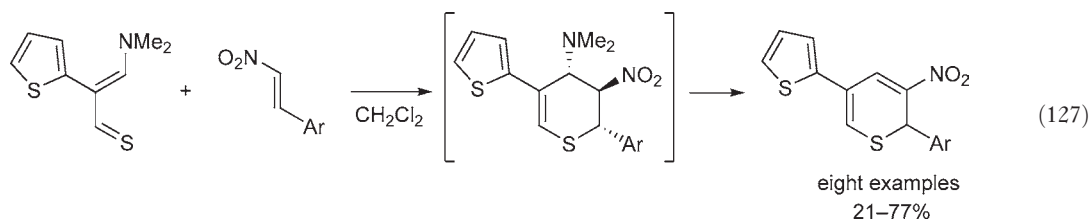


The reaction of 4-dimethylamino-2-phenylthiabuta-1,3,-diene with methyl acrylate affords the *endo* product at room temperature or below along with smaller amounts of the separable *trans*-4,5-disubstituted dihydrothiopyran. However, at 80 °C the *exo* adduct alone is formed together with a thiopyran arising from the loss of dimethylamine. When *N*-enoyloxazolidinone is used as the dienophile, the major product is the *exo* adduct except at low temperature and in the absence of a Lewis acid <1997TL1033>. The reversal of stereochemistry can be achieved by heating and by the addition of a Lewis acid (Scheme 138). Crossover experiments indicate that it proceeds by way of a retro Diels-Alder reaction of the kinetic *endo* adduct and generation of the more stable *exo* diastereomer through a second cycloaddition. A high level of diastereoselection results using a chiral dienophile in the presence of MgBr₂ with which it forms a chelate <2004T1827>.

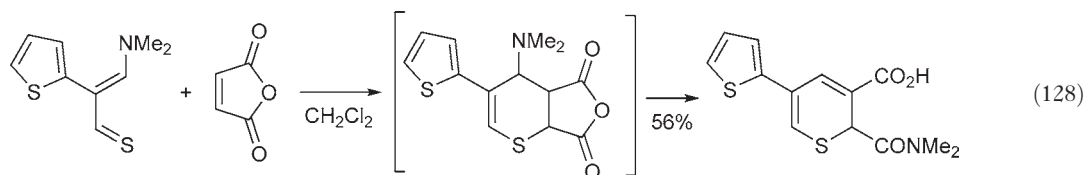


Scheme 138

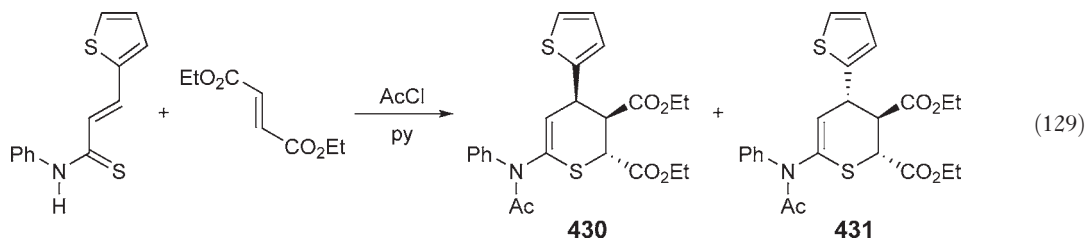
The reaction between the 1-thiabuta-1,3-diene, 3-dimethylamino-1-(2-thienyl)propene-1-thione, and various 1-aryl-2-nitroethenes affords 2-aryl-4-dimethylamino-3-nitro-5-(2-thienyl)-3,4-dihydro-2*H*-thiopyrans in which the stereochemistry depicted was derived from the ¹H NMR spectra (see Section 7.10.2.2.3.1). The products showed a tendency to eliminate dimethylamine, especially when the aryl group was electron-withdrawing, leading to the 2,3,5-trisubstituted 2*H*-thiopyran (Equation 127). The elimination is prompted by polar solvents and facilitated by treatment with either acetic acid or its anhydride. The cycloadditions with maleic and fumaric acids yielded a diastereomeric mixture of dihydrothiopyrans, but their esters and maleimide all afforded the 2*H*-thiopyran directly. Judged by the reaction with the monoanilide of maleic acid, the cycloaddition is highly regioselective since the sole product is the thiopyran-3-carboxylic acid <2001M947>. Similar reactions are shown by the analogous 1-(2-furyl)-propenethione <2002ZNB637>.



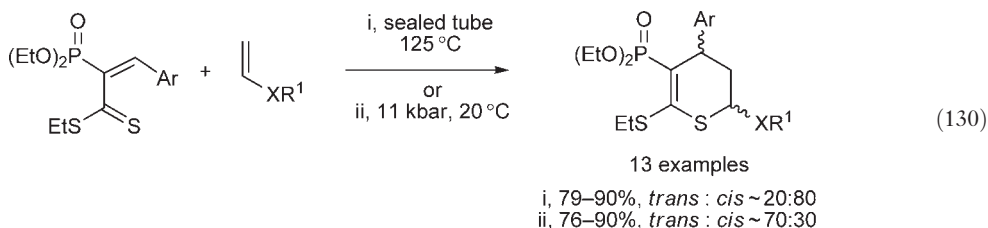
In an extension of the above hDA reaction, the cycloaddition of the thiabutadiene with maleic anhydride gives a 2-amido-2*H*-thiopyran by way of elimination and addition of Me₂NH to the anhydride unit (Equation 128) <2001M947>.



When the isomeric thiabutadiene, *N*-aryl-3-(2-thienyl)prop-2-enethioamide, reacts with diethyl fumarate in the presence of AcCl and pyridine, a 24:1 mixture of diastereomeric 3,4-dihydro-2*H*-thiopyrans **430** and **431** is formed (Equation 129) <2004M97>.



The hDA reaction between α -phosphono- α,β -unsaturated dithioesters and enol and thioenol ethers affords high yields of phosphono-substituted 3,4-dihydro-2*H*-thiopyrans as a mixture of diastereomers (Equation 130). The *cis/trans* ratio is influenced by the reaction conditions, with a high temperature favoring an *exo* transition state which leads to the *cis* product, whereas high pressure yields predominantly the *trans* isomer via the more compact *endo* transition state. Structural variation in both components also influences the diastereoselectivity. The reaction has been carried out without prior formation of the thiadiene, utilizing a domino Knoevenagel-hDA sequence <2000T3909>. The addition of pyridine to the high-pressure hDA cycloaddition causes a reversal of diastereoselectivity and accelerates the reaction. Thus, in its absence, the major product is the 2,4-*trans*-substituted 3,4-dihydrothiopyran but pyridine promotes an (*E*) $\rightarrow$ (*Z*) isomerization of the heterodiene, possibly via a transient Michael adduct, and the *cis*-adduct is formed via an *endo* [4+2] cycloaddition <2000CC1191>.

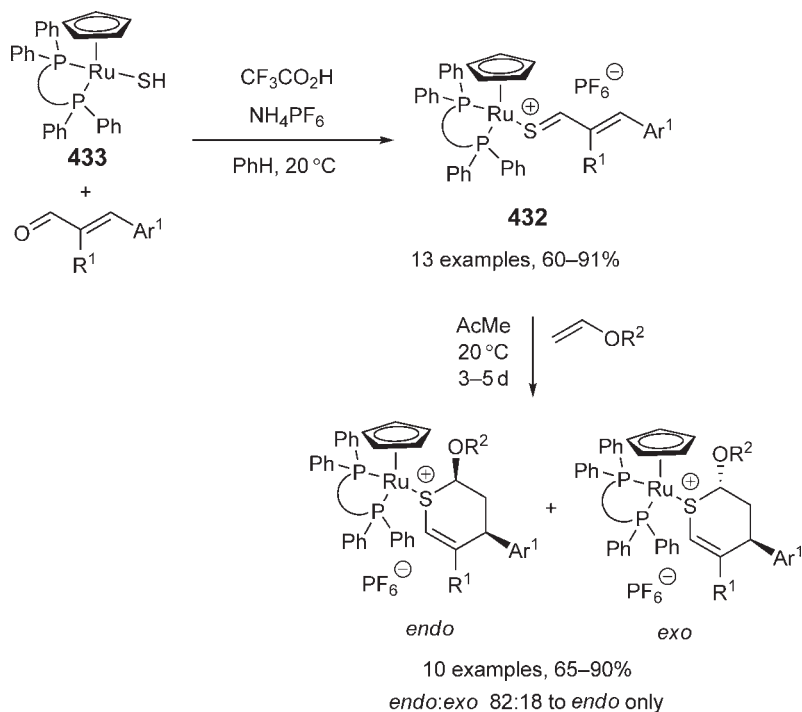


The complexes **432** derived from the reaction of cinnamaldehyde with Ru-SH complexes **433** undergo [4+2] cycloaddition reactions with a range of electron-rich, electron-deficient, and strained dienophiles. The products are Ru complexes of di- or tri-substituted 3,4-dihydro-2*H*-thiopyrans. Generally, the reaction shows high regioselectivity and good diastereoselectivity with a marked preference for the *endo* adducts (Scheme 139). Ethyl propynoate affords the 3,4-disubstituted-4*H*-thiopyran <2006CEJ4821>.

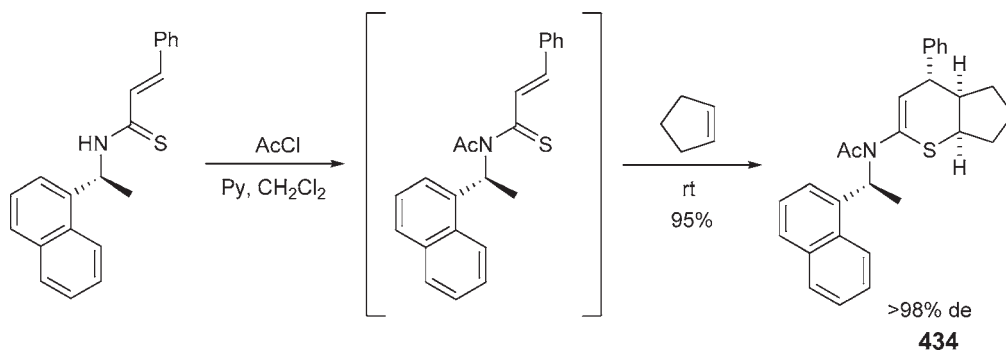
The introduction of a bulky, optically active amino function at C-2 of 4-phenyl-1-thiabutadiene and activation by the addition of AcCl prior to cycloaddition with *N*-phenylmaleimide, known to exhibit a high *endo* preference, results in the formation of two diastereomers. However, the *exo* product is the major component and indeed this diastereomer is the sole adduct when cyclopentene is used as the dienophile. Calculations point to a preference for *exo* addition from the same face of the molecule as the naphthyl moiety and this is supported by the observed *R* stereochemistry at the three chiral centers in the cyclopenta[*b*]dihydrothiopyran **434** (Scheme 140) <1996TL123>.

Both thiobenzophenones and thiofluorenones undergo [4+2] cycloadditions with acyclic and cyclic 1,3-dienes to give 3,6-dihydro-2*H*-thiopyrans (Scheme 141). The thiofluorenones are more reactive, even yielding adducts with electron-deficient cyclopentadienes at room temperature. In all cases, the progress of the reaction can be followed by the loss of color of the thione. Unsymmetrically substituted dienes show good to excellent regioselectivity.

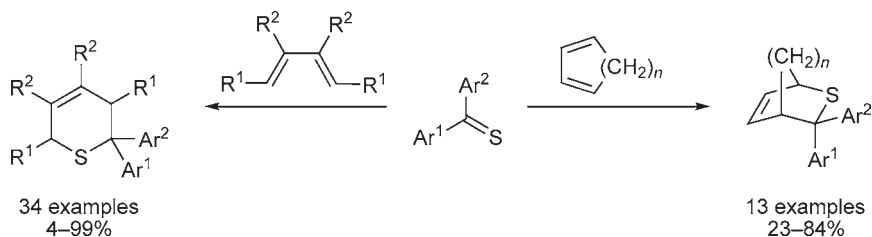
1-Substituted 1,3-dienes generally yield only the 2,2,3-trisubstituted dihydrothiopyran with no 2,2,6-isomer produced, while 2-substituted dienes exhibit a strong preference for the 2,2,5-derivative rather than the 2,2,4-product [<1998EJO2861>](#).



Scheme 139

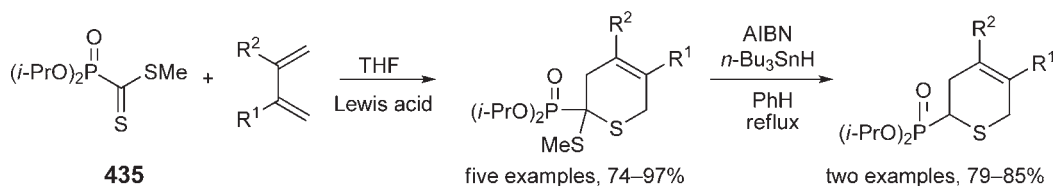


Scheme 140



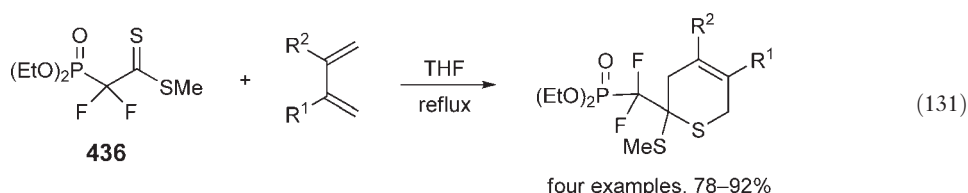
Scheme 141

Phosphonodithioformate **435** behaves as a masked thioformaldehyde and acts as a heterodienophile, offering a route to (3,6-dihydro-2-methylsulfanyl-2*H*-thiopyran-2-yl)phosphonates. Yields are excellent, Lewis acids significantly enhance the rate of reaction and radical-promoted desulfanylation is facile (**Scheme 142**) <2000TL7327, 2004EJO160>.

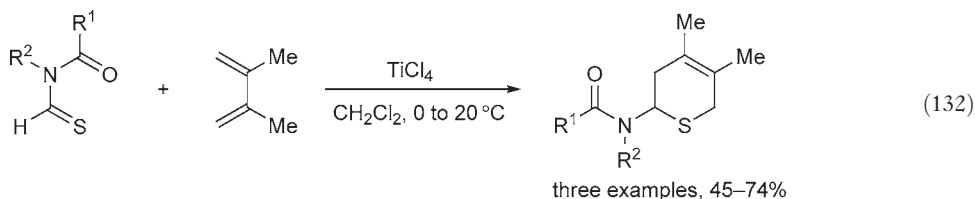


Scheme 142

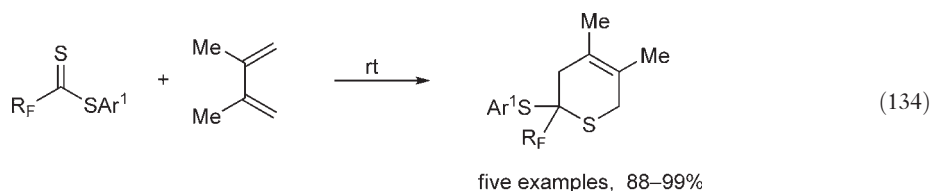
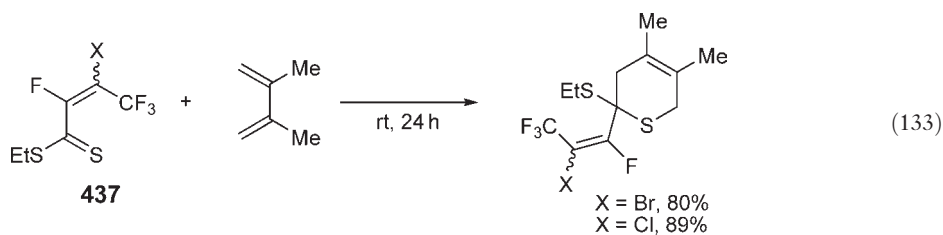
Phosphonodifluorodithioacetate **436** is also highly reactive toward dienes because of the presence of the two fluorine atoms and undergoes cycloadditions to afford dihydrothiopyrans in good yield (**Equation 131**). Dihydroxylation and desulfanylation of the adducts provides an efficient route to phosphonodifluorothioglycosides <2002TL2033>.



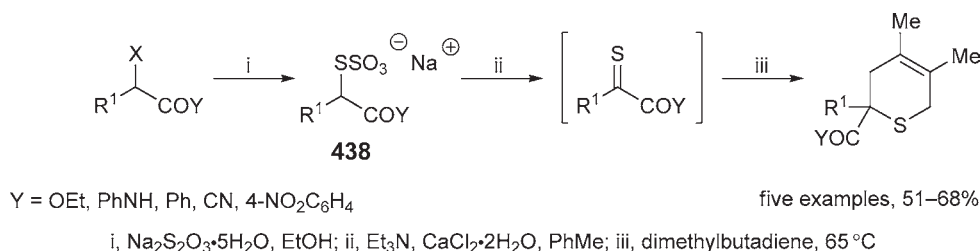
A Lewis acid facilitates the reaction of activated thioamides with dienes which leads to amino-substituted 3,6-dihydrothiopyrans (**Equation 132**) <1995CC1897>.



Reaction of the conjugated thioesters **437** with dienes occurs selectively at the thiocarbonyl group and provides fluorinated 3,6-dihydro-2*H*-thiopyrans (**Equation 133**) <2001TL2133>. Polyfluoroalkyl dithiocarboxylates are available from polyfluoroaldehyde dithioacetals <1992JFC(55)329, 1997BSF697> and more readily from 1,1-dichloro-polyfluoroalkylsulfenyl chlorides. These red aryl dithio esters react at room temperature with 2,3-dimethylbuta-1,3-diene to give pale yellow 2-polyfluoroalkyl derivatives of 3,6-dihydro-2*H*-thiopyrans (**Equation 134**) <2005JFC(126)361>.

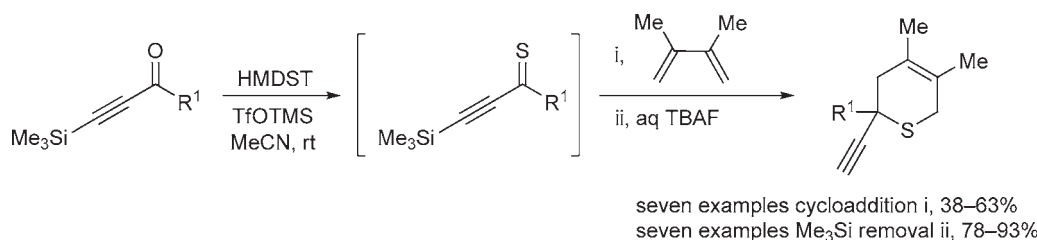


Activated alkyl halides react with sodium thiosulfate to form the Bunte salts **438** which, on treatment with base, generate thiocarbonyl compounds [<1984CC922>](#). Trapping with 1,3-dienes affords 3,6-dihydro-2*H*-thiopyrans in satisfactory yields and in a one-pot reaction, although with unsymmetrical dienes the regio and diastereo selectivities are not good (**Scheme 143**) [<1996JOC4725>](#).

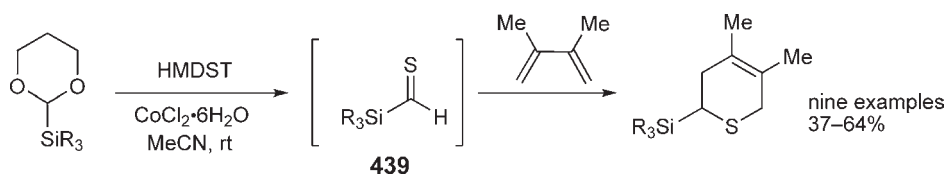


Scheme 143

Unstable trimethylsilyl protected α,β -alkynic thiocarbonyl compounds, generated by thionation of the corresponding ynones using hexamethyldisilathiane (HMDST), are readily trapped by dienes and yield 2-ethynyl derivatives of 3,6-dihydro-2*H*-thiopyrans after desilylation (**Scheme 144**). In like manner, a thioaldehyde can be accessed from the protected ynal or its acetal; trapping with cyclohexadiene exhibits some *exo* selectivity [<1999SL1739>](#). Thioformylsilanes **439** can be generated from silyl acetals by treatment with HMDST and trapped by dienes to yield silylated 3,6-dihydrothiopyrans with some control of the *exo:endo* ratio (**Scheme 145**) [<1997SL361>](#).



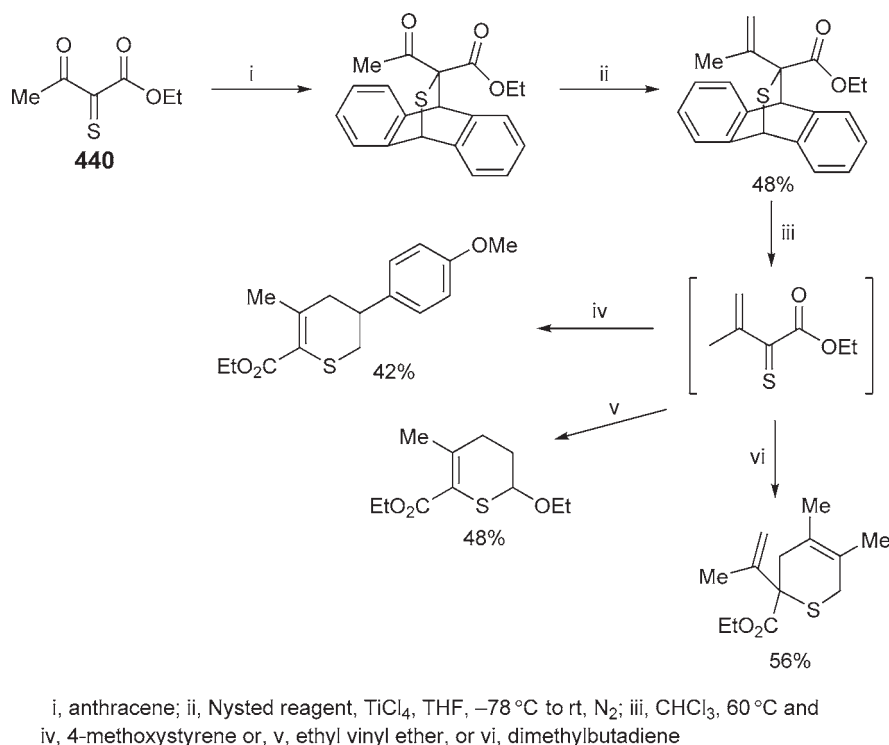
Scheme 144



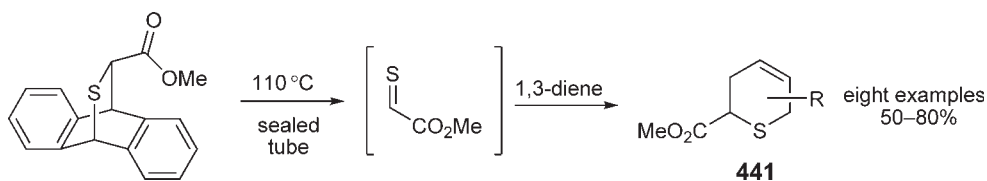
Scheme 145

As an alternative to the formation of thiocarbonyl compounds by thionation, they can be obtained by a retro Diels–Alder reaction of an anthracene adduct. Thus, the dieneophile α,α -dioxothione **440** can be trapped with anthracene, the ketone function reduced to a methylene unit, whereupon heating generates an α,β -unsaturated thioketone. Trapping both with ethyl vinyl ether and 4-methoxystyrene is regioselective and produces the 2,5,6- and 3,5,6-trisubstituted 3,4-dihydro-2*H*-thiopyrans, respectively, but methyl vinyl ketone gives a 1:1 mixture of the 2,5,6- and 3,5,6- derivatives. The α,β -unsaturated thioketone behaves as a dienophile towards 2,3-dimethylbuta-1,3-diene affording a 3,6-dihydro-2*H*-thiopyran (**Scheme 146**) [<2001S409>](#).

In a similar approach, methyl thioglyoxylate has been generated from its anthracene adduct and trapped with variously substituted 1,3-dienes to give 3,6-dihydro-2*H*-thiopyrans **441**. Although the products were usually obtained as a mixture of regio- and diastereo- isomers, these were often separable (**Scheme 147**) [<2000SL658>](#).

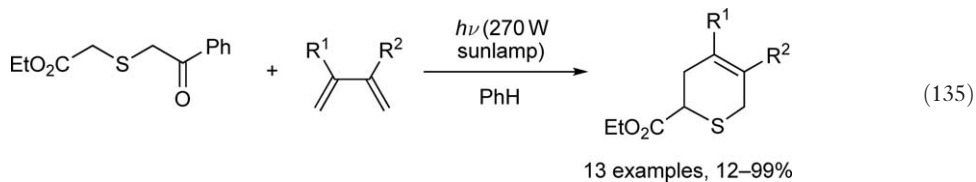


Scheme 146

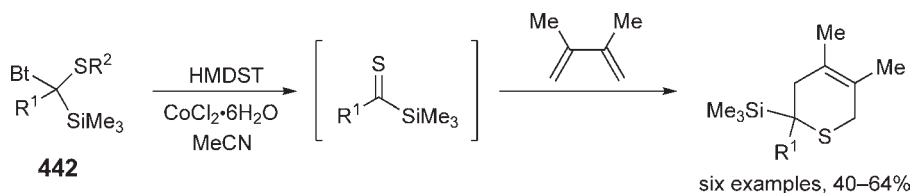


Scheme 147

Further examples of the photolytic generation of thioaldehydes from phenacyl sulfides include the synthesis of 3,6-dihydro-2*H*-thiopyrans bearing a variety of functions at C-2 of which some are potent acyl-CoA-cholesterol acyl-transferase inhibitors (Equation 135) <1996BMC1493>.

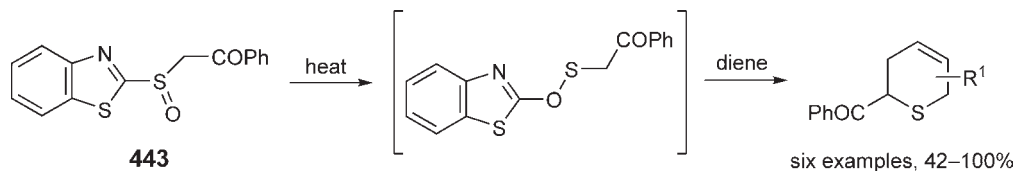


Thioacylsilanes, which are synthetic equivalents of thioaldehydes, are accessible using benzotriazole (BtH) methodology. Thus treatment of the trimethylsilylbenzotriazoles **442** with HMDST in the presence of dimethylbutadiene offers a simple route to 3,6-dihydro-2*H*-thiopyrans (Scheme 148) <2000JOC9206>. With 2-methylbuta-1,3-diene, silyl thioketones give a mixture of regioisomers in which the 5-methyl-3,6-dihydro-2*H*-thiopyran predominates. The behavior with other dienes is also reported <1999HCO217>.



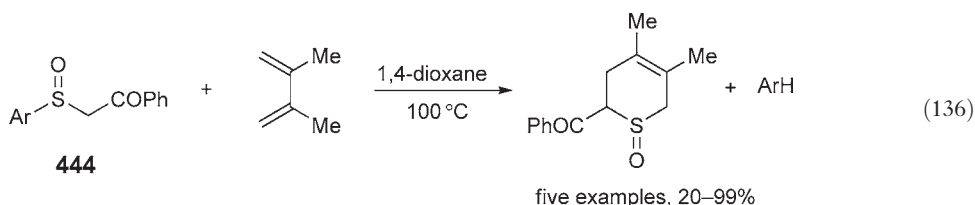
Scheme 148

2-Benzothiazolyl phenacyl sulfoxide **443** is a convenient precursor of thioaldehydes, thermally breaking down to 2-hydroxybenzothiazole and 2-oxo-2-phenylethanethial. Trapping with a range of 1,3-dienes produces 2-benzoyl-3,6-dihydro-2*H*-thiopyrans in good yields. Regioselectivity is only moderate with, for example, a 2:1 preference for the 5-methyl-2-phenacyldihydrothiopyran over the 4-methyl isomer in the reaction with 2-methylbutadiene; a greater preference was shown in the presence of NEt_3 . Only the more stable *exo* adduct is obtained with cyclopentadiene but the diastereoselectivity is lost when triethylamine is present in the reaction mixture. It is noteworthy that the *endo* adduct is the major product when the thioaldehyde is generated photochemically (Scheme 149) <1988JA5452>. With cyclohexadiene, a 10:1 preference for the *endo* adduct is observed <1999HAC363>. The thermal decomposition of 2-(*N*-oxypyridyl) phenacyl sulfoxide is an alternative source of PhCOCHS <1997JOC9018>.



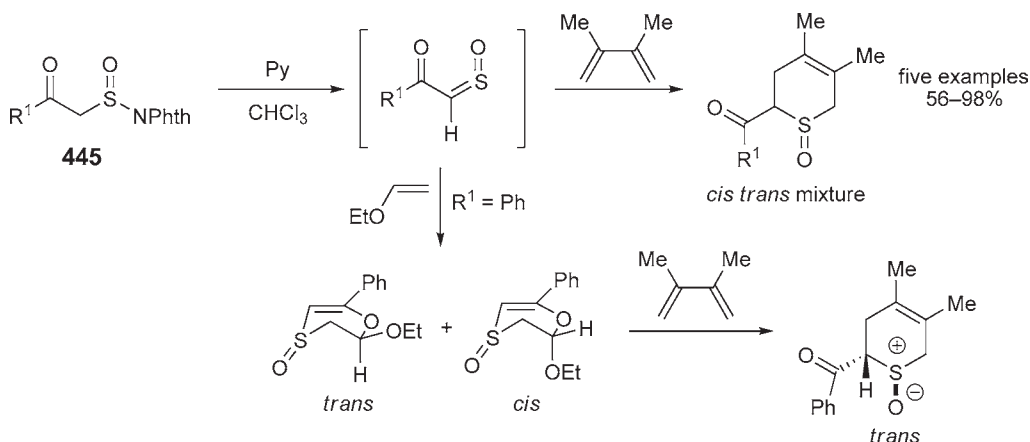
Scheme 149

The thermolysis of heteroaryl-substituted phenacyl sulfoxides **444** generates the sulfine $\text{PhCOCH}=\text{S}=\text{O}$ and cycloaddition to butadiene gives dihydrothiopyran 1-oxides. The normal formation of the *cis* adduct appears to be controlled by the elimination of the heterocyclic unit during sulfine formation. However, the presence of an external base both accelerates the reaction and leads to an increase in the *trans* product (Equation 136) <1999JOC6730>.

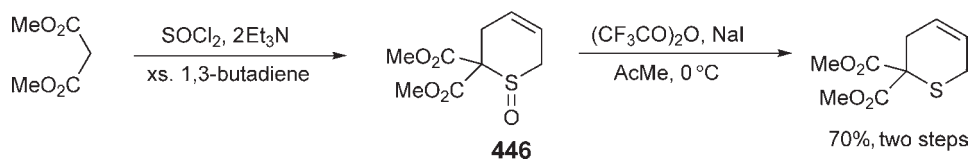


α -Oxothioaldehyde *S*-oxides are produced when the *N*-phthalimidesulfinamides **445** derived from ketones are treated with a mild base. Trapping with 2,3-dimethylbuta-1,3-diene affords the 2-acyldihydrothiopyran 1-oxides as a mixture of diastereomers. The reactive sulfines also behave as electron-poor dienes toward ethyl vinyl ether, giving 1,4-oxathiin 4-oxides again as a diastereomeric mixture. When heated in the presence of dimethylbutadiene, this mixture yields the *trans*-2-acyldihydrothiopyran 1-oxide via a retro Diels–Alder reaction of the *cis*-oxathiin 4-oxide which regenerates the sulfine, together with the corresponding unchanged and more stable *trans*-2-ethoxy-1,4-oxathiin 4-oxide (Scheme 150) <1997TL5041>.

Doubly activated methylene compounds react with thionyl chloride in the presence of triethylamine to generate sulfines which can be trapped by 1,3-dienes to give 3,6-dihydro-2*H*-thiopyran 1-oxides **446**. Facile deoxygenation makes this an attractive route to 2,2-disubstituted 3,6-dihydrothiopyrans (Scheme 151) <1999PS(153)119, 2004EJO74>.



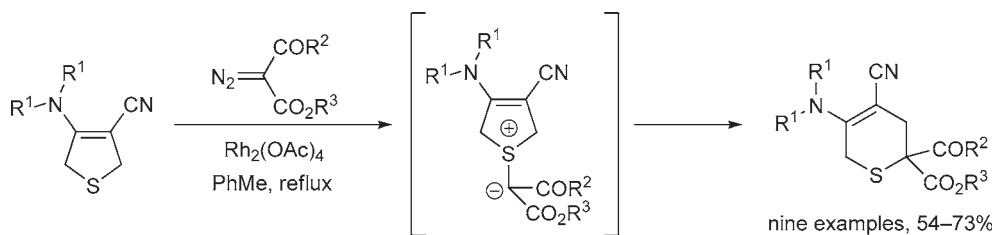
Scheme 150



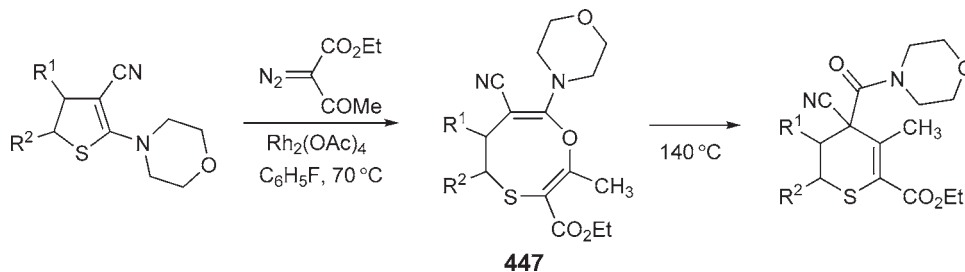
Scheme 151

7.10.4.2.1(iii) From other heterocycles

Only insertion into the S–C(2) bond of 4-amino-2,5-dihydrothiophene-3-carbonitriles is observed on reaction with α -diazocarbonyl compounds in the presence of rhodium(II) acetate. The ring expansion is regioselective and leads to the 4-cyano-3,6-dihydro-2*H*-thiopyrans; there is no evidence for the 5-cyano isomer (Scheme 152) <2000JPR494, 2001M721>. The reaction follows a different sequence when applied to 2-amino-4,5-dihydrothiophene-3-carbonitriles. The initial product is a 1,4-oxathiocine **447** which rearranges thermally to a 3,4-dihydro-2*H*-thiopyran (Scheme 153) <1996LA725>.

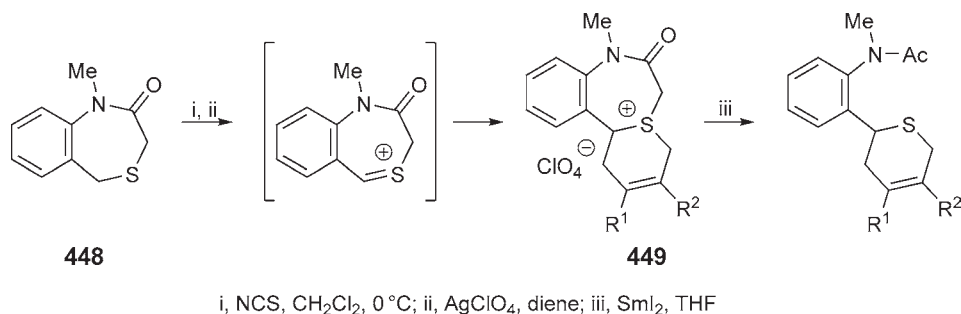


Scheme 152



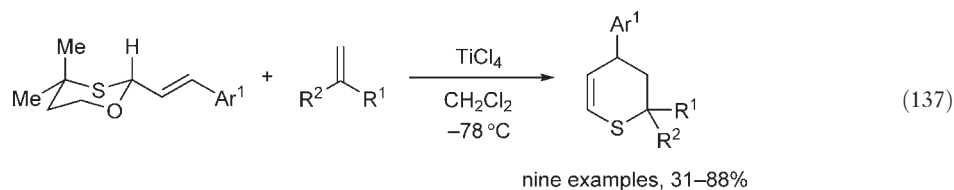
Scheme 153

The benzothiazepinone **448** is a source of 2-substituted 3,6-dihydro-2*H*-thiopyrans through its conversion to the bridgehead salt **449** by a [4+2⁺] cycloaddition with dienes and subsequent reduction (Scheme 154) <1997CPB265>.

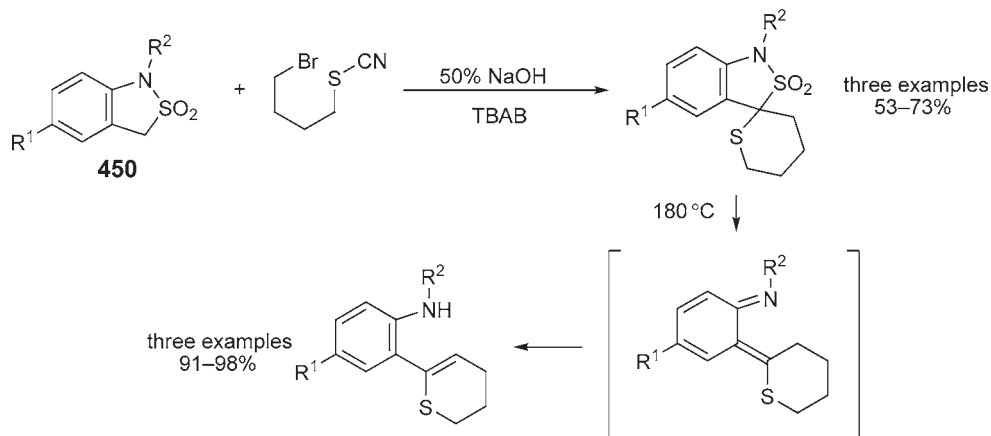


Scheme 154

4,4-Dimethyl-2-styryl-1,3-oxathianes yield 3,4-dihydro-2*H*-thiopyrans with good *cis* diastereoselectivity in a TiCl₄-promoted reaction with reactive alkenes (Equation 137). The hard Lewis acid is thought to coordinate to the hetero oxygen atom resulting in scission of the oxathiane ring; the oxathiane is thus a synthetic equivalent of thiocinnamaldehyde. A [4⁺+2] cycloaddition with the alkene ensues, accompanied by elimination of the *S*-substituent <2000TL371>.



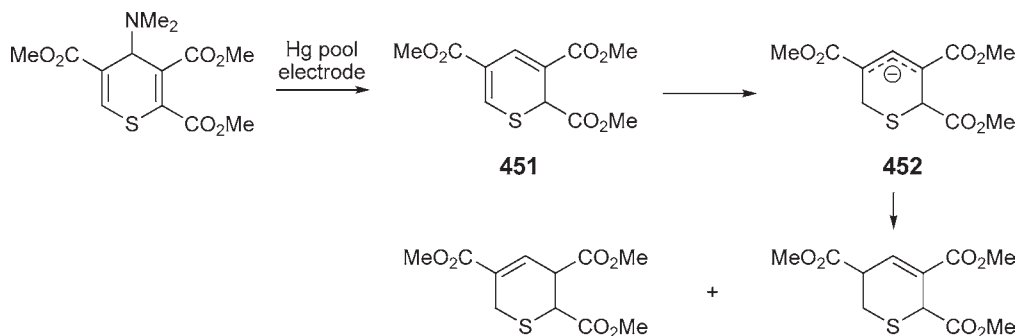
Benzosultams **450** undergo a tandem alkylation–sulfanylation on treatment with 4-bromobutyl thiocyanate under phase transfer conditions. Extrusion of SO₂ occurs on thermolysis of the resulting spiro-tetrahydrothiopyranobenzo-sultams, generating an azaxylene and thence 6-aryl-3,4-dihydro-2*H*-thiopyrans by a [1,5]-sigmatropic hydrogen shift (Scheme 155) <2005T8848>.



Scheme 155

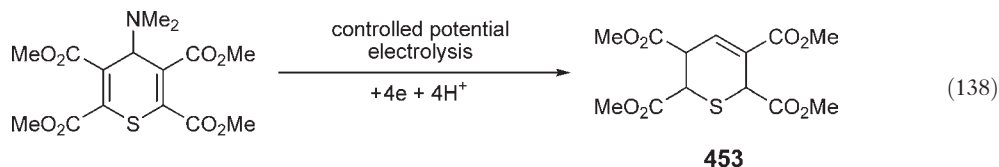
7.10.4.2.1(iv) From a preformed heterocyclic ring

The electrochemical reduction in protic media of thiopyrans substituted with electron-withdrawing groups yields dihydrothiopyrans. The initial product from the reduction of 4-dimethylamino-2,3,5-trimethoxycarbonyl-4*H*-thiopyran is the 3,4-dihydro-2*H*-thiopyran which arises from electron transfer to the doubly activated double bond. However, this compound is only stable in strongly acidic media and here loses Me₂NH to give the trisubstituted thiopyran **451**. Further reduction produces an equimolar mixture of the 3,6- and 5,6- dihydro-2*H*-thiopyrans as two pairs of diastereomers. The same mixture results from the electroreduction of both 4-dimethylamino-3,5,6-trimethoxycarbonyl-3,4-dihydro-2*H*-thiopyran and 3,5,6-trimethoxycarbonyl-2*H*-thiopyran in sulfuric acid, suggesting that a common intermediate **452** is involved (Scheme 156) <1997MI2185>.



Scheme 156

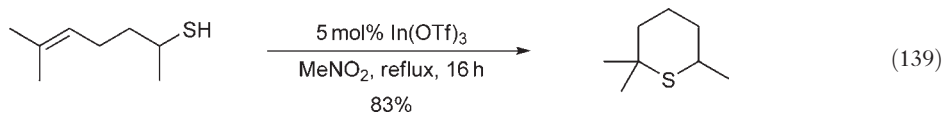
Similar electrochemical reduction of 4-dimethylamino-2,3,4,6-tetramethoxycarbonyl-4*H*-thiopyran affords the 3,6-dihydro-2*H*-thiopyran **453** as a mixture of four diastereoisomers in amounts dependent on the electrolytic conditions. Their conformations have been established using the vinylic proton as an NMR probe and in some cases by X-ray analysis (Equation 138) <1996J(P2)2623>.



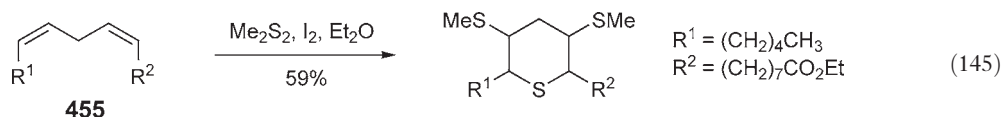
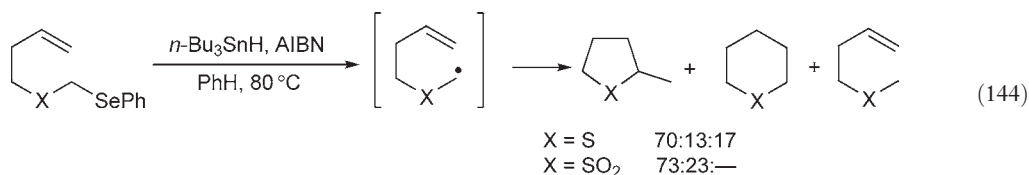
7.10.4.2.2 Tetrahydrothiopyrans

7.10.4.2.2(i) Formation of one bond

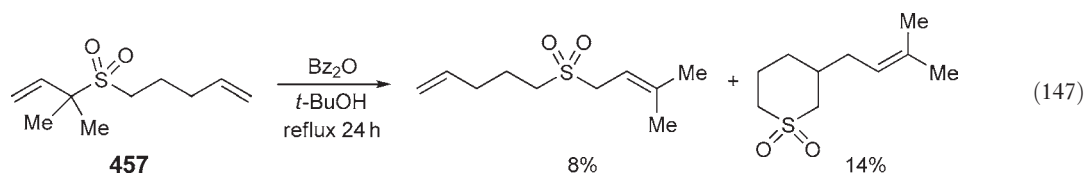
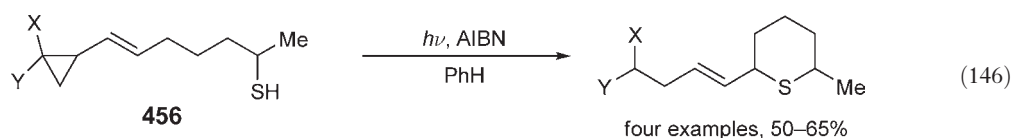
Indium(III) triflate is an efficient catalyst for the intramolecular cyclisation of γ,δ -unsaturated thiols although the nucleophilic attack can occur at either of the doubly bonded carbon atoms, leading to thiophene and thiopyran ring formation. It appears that the substitution pattern at the double bond controls the regioselectivity, with the product conforming to Markovnikov addition (Equation 139) <2006CC332>.



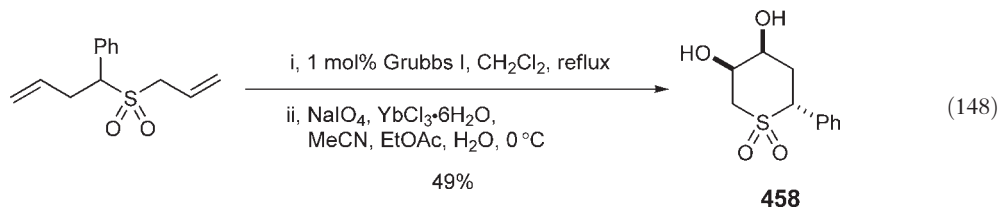
Homoallyl thiols react with aldehydes in a Prins-like reaction which is catalyzed by InCl₃ (Equation 140). 2,3-Disubstituted 4-chlorotetrahydrothiopyrans are formed with excellent diastereoselectivity; notably the *trans*-isomer of the thiol yields exclusively the *cis-trans-cis* product <2000TL1321>. Application of this method to 1-phenylbut-3-ene-1-thiol and benzaldehyde affords 4-chloro-2,6-diphenyltetrahydrothiopyran in almost quantitative yield and with an 8:1 preference for the all *cis*-isomer <2001JOC739>.



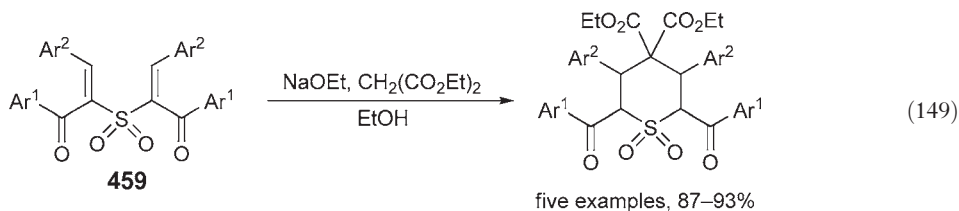
On treatment with a radical generator, the 4-mercaptopentyl derivatives of vinylcyclopropanes **456** cyclize to a mixture of stereoisomers of tetrahydrothiopyran (Equation 146) <1993SL827> and a tetrahydrothiopyran 1,1-dioxide results from a 1,3-rearrangement prior to the radical cyclization of allylic pentenyl sulfones **457** (Equation 147) <1993TL2537>.



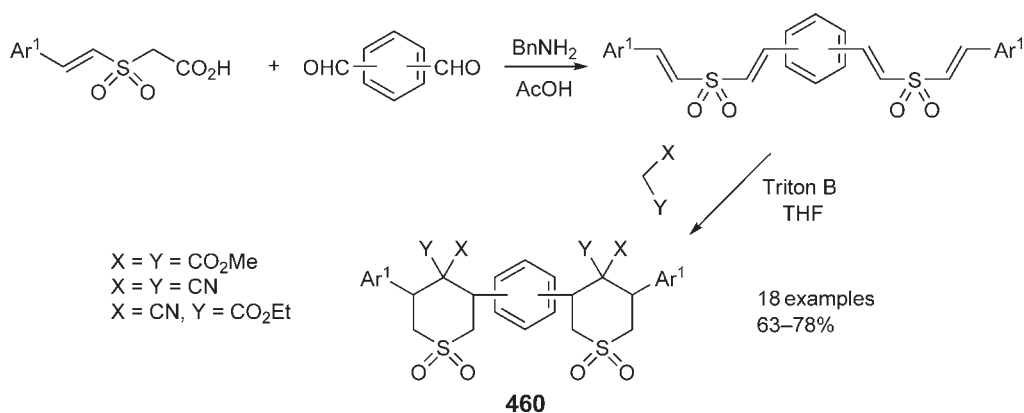
cis-4,5-Dihydroxy-2-phenyltetrahydrothiopyran 1,1-dioxide **458** is formed from 4-sulfonylocta-1,7-diene involving sequential RCM and dihydroxylation of the newly formed double bond. The same Ru catalyst serves both reactions (Equation 148) <2006AGE1900>.



Highly substituted tetrahydrothiopyran 1,1-dioxides result from the Michael addition of diethyl malonate to the bis-styryl sulfones **459**. On the basis of their NMR spectra, the aryl and aroyl substituents are equatorially disposed (Equation 149) <1999IJB376>.

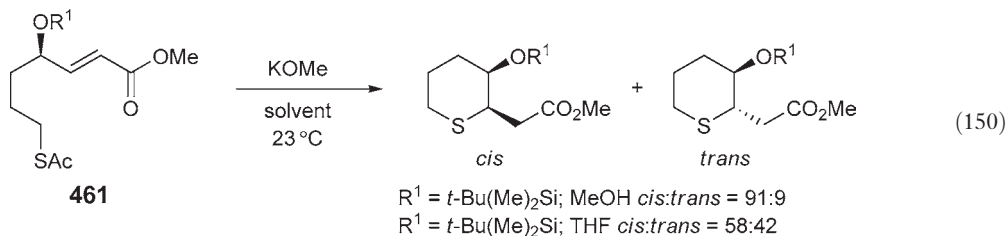


Both 1,3- and 1,4- bis[2-(2-arylethenesulfonyl)vinyl]benzenes, synthesized by a Knoevenagel reaction between the appropriate benzenedicarbaldehyde and 2-arylethenesulfonylacetic acid, behave as Michael acceptors and undergo double Michael addition reactions with activated methylene compounds. The products are phenylene-bis(tetrahydrothiopyran 1,1-dioxides) **460** (Scheme 158) <2005JHC255>.

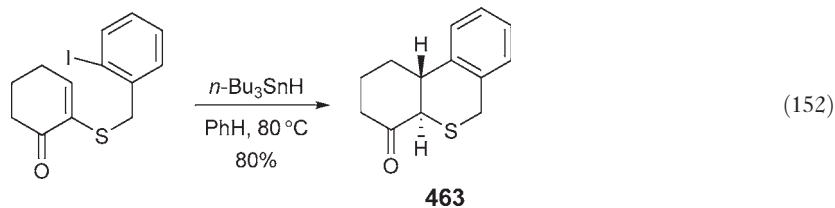
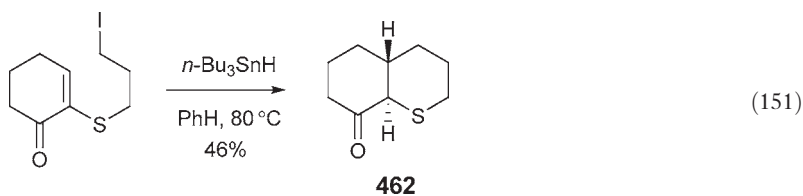


Scheme 158

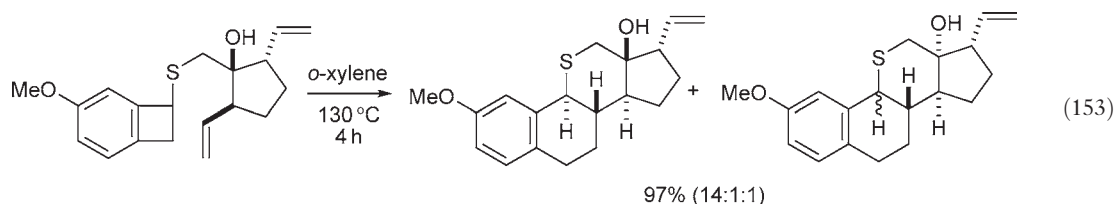
An intramolecular Michael addition spontaneously follows the basic hydrolysis of the thioacetate function in the enoate **461** leading to tetrahydrothiopyrans. In protic solvents a high *cis*-selectivity is observed, but in THF a ca. 1:1 mixture of the *cis* and *trans* isomers is produced (Equation 150) <1995TL2579>.



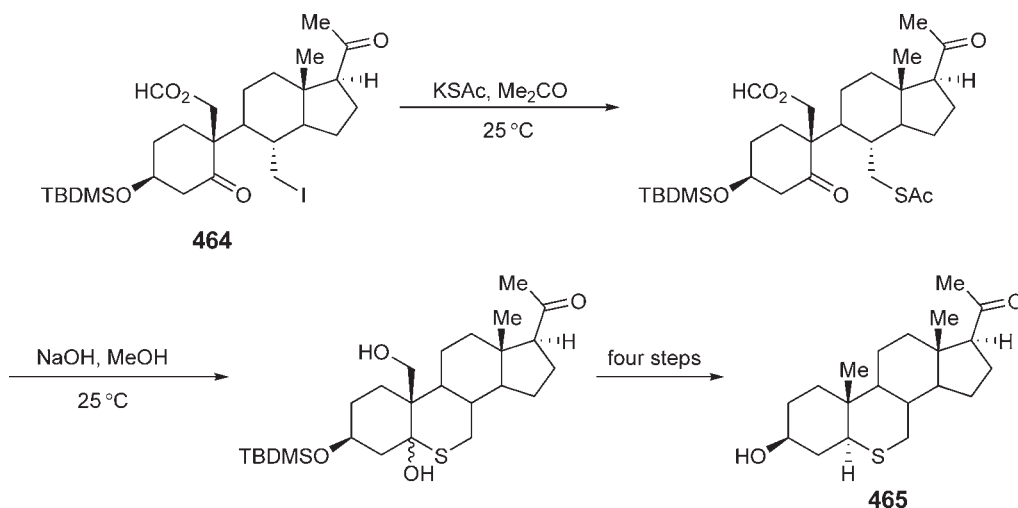
The *trans*-fused 1-thiadecalin **462** is the major product from the radical cyclisation of 2-(3-iodopropylthio)cyclohex-2-enone; a spiro-linked tetrahydrothiophene arising from 5-*endo* cyclization is also formed. The *trans*-fused benzo-[*c*]thiadecalin **463** is formed almost exclusively from the analogous 2-iodophenyl derivative (Equations 151 and 152) <2000TL2279>.



An intramolecular Diels–Alder reaction involving an *o*-quinonemethide features in the formation of the thiopyran ring of 11-thiasteroids from a 1-alkylthiobenzocyclobutene. The product is a separable 14:1:1 mixture of three diastereomers in which the major isomer has the *trans-anti-trans* fused skeleton of natural steroids (Equation 153) <2000SL418>. Oxidation of the 11-thiasteroid to afford the 11-oxide and 11,11-dioxide using MCPBA in CH_2Cl_2 is also reported <2000SL418, 2005T9405>.



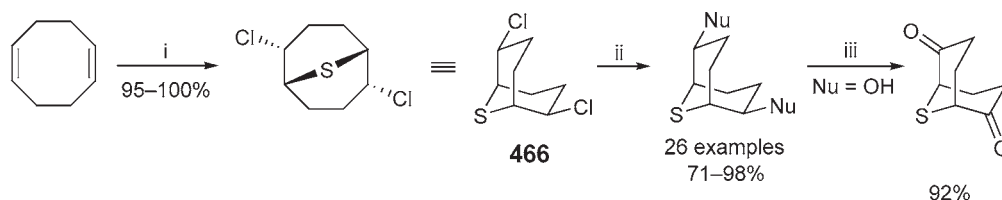
Nucleophilic displacement of iodide with thioacetate in the secosteroid **464** and subsequent simultaneous formate and thioacetate hydrolysis with concomitant cyclization provides the thiopyran ring; four further steps are required to afford the 6-thiaallopregnanolone **465** (Scheme 159) <2006T4762>.



Scheme 159

7.10.4.2.2(ii) Formation of two bonds

Successive treatment with either SCl_2 or S_2Cl_2 and SOCl_2 converts 1,5-cyclooctadiene into 2,6-dichloro-9-thiabicyclo-[3.3.1]nonane **466**. Both halogen atoms can be replaced by a wide variety of nucleophiles <2001JOC4386>. Following hydrolysis to the 2,6-diol, Swern oxidation affords the 2,6-dione (Scheme 160) <1998OSC692>.

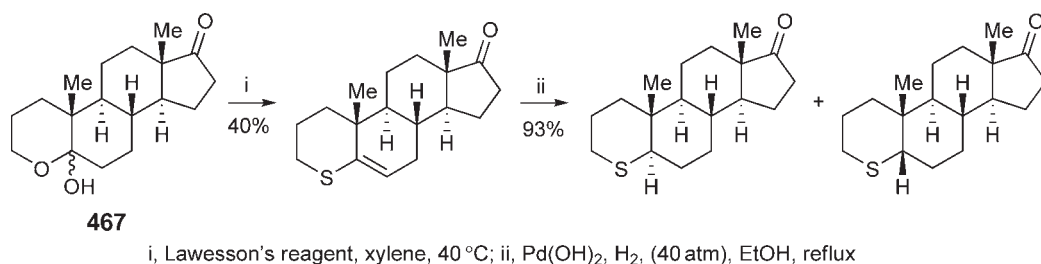


i, SCl_2 or S_2Cl_2 then SO_2Cl_2 , CHCl_3 ; ii, nucleophile (Nu), NaHCO_3 or K_2CO_3 or Ag_2O , MeCN or H_2O ;
iii, $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78 to rt

Scheme 160

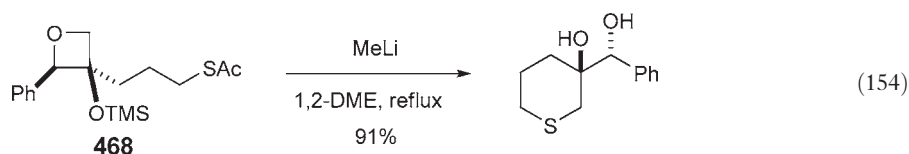
7.10.4.2.2(iii) From other heterocycles

Treatment of the 4-oxasteroid **467** with Lawesson's reagent effects the simultaneous $\text{O} \rightarrow \text{S}$ conversion and dehydration of the hemiacetal unit to give the 4-thia-5-androstene-17-one in 40% yield. Subsequent hydrogenation results in a (3:2) mixture of the 4-thia-5- α - and 5- β -androstane-17-ones (Scheme 161) <2005T3691>.

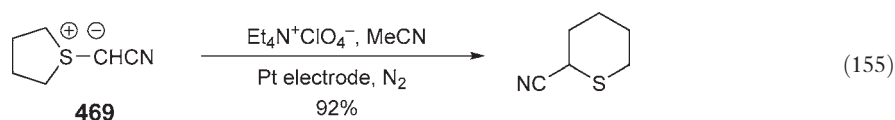


Scheme 161

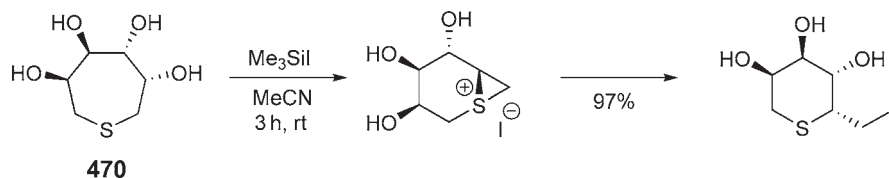
Intramolecular attack of a terminal thioalkoxide function, generated by the action of MeLi on the *S*-acetyl group, at the 4-position of the diastereomerically pure, TMS-protected 2-phenyloxetan-3-ol **468** results in cleavage of the 4-membered ring and formation of tetrahydrothiopyran-3-ol. The stereochemistry at C-2 and C-3 of the oxetane is retained in the product (Equation 154) <1996JOC7642, 1998JOC1910>.



Ring expansion of a tetrahydrothiophenonium ion **469** occurs on cathodic reduction. A Stevens rearrangement of the initially formed stabilized ylide is proposed which leads to a high yield of 2-cyanotetrahydrothiopyran (Equation 155) <2006CL98>.



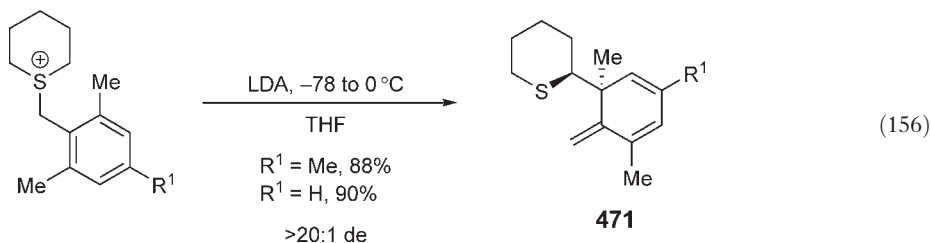
A regio- and stereo-specific ring contraction of tetrahydroxythiepanes **470** occurs on treatment with Me₃SiI involving an intramolecular S_N2 reaction which generates an episulfonium salt. The process offers an attractive route to trihydroxytetrahydrothiopyrans from D-mannitol (Scheme 162) <1997JOC8572>.



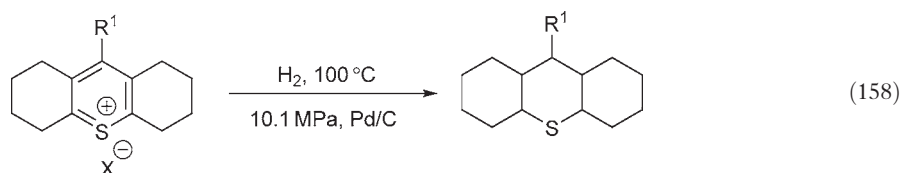
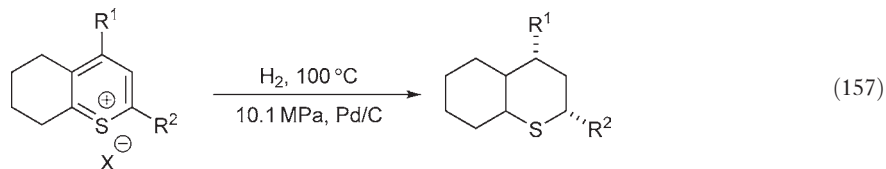
Scheme 162

7.10.4.2.2(iv) From a preformed heterocyclic ring

A cyclic sulfonium salt undergoes a thia-Sommelet rearrangement which results in dearomatization and production of the 2-substituted tetrahydrothiopyran **471** in a diastereoselective fashion (Equation 156) <1998JA841>.



Catalytic reduction of thiopyrylium salts at elevated temperature and pressure yields tetrahydrothiopyrans. In like manner, 5,6,7,8-tetrahydro-2,4-disubstitutedthiochromylium salts yield the *cis*-disubstituted tetrahydrocyclohexa-*[b]*thiopyran and octahydro-thioxanthylum salts afford the *cis*-fused tetrahydrodicyclohexa-*[b,e]*thiopyran (Equations 157 and 158) <2001CHE797>.

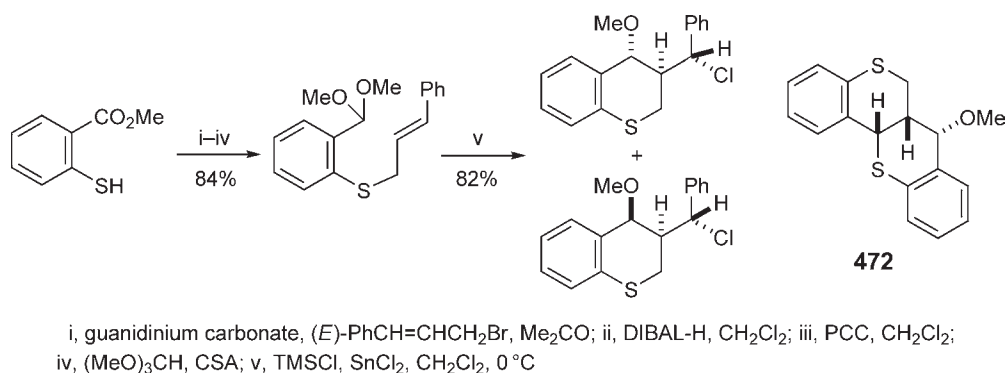


7.10.4.2.3 Thiochromans

7.10.4.2.3(i) Formation of one bond

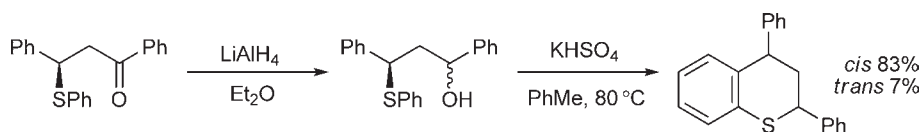
Construction of a side chain onto the S atom of thiophenols and similar molecules allows access to thiochromans through formation of the C(4)-ring bond.

The *S*-alkylation of methyl thiosalicylate with (*E*)-1-bromo-3-phenylprop-2-ene followed by conversion of the ester function into a protected aldehyde provides a substrate suitable for intramolecular nucleophilic attack and production of 3,4-disubstituted thiochromans. Two diastereomers are produced by stereospecific anti addition of the oxonium ion generated by the Lewis acid reagent and chloride ion to the pendant alkenic bond (Scheme 163). Unlike the equivalent reaction with a salicylate which exhibits complete selectivity with respect to the stereocentres on the newly formed heterocyclic ring, this cyclization is not stereoselective. Extension of this methodology to a substrate containing a second phenylpropenylthio unit resulted in both C-C and C-S bond formation to give the partially reduced 5,12-dithiabenz[*a*]anthracene **472** <2005TL3719>.

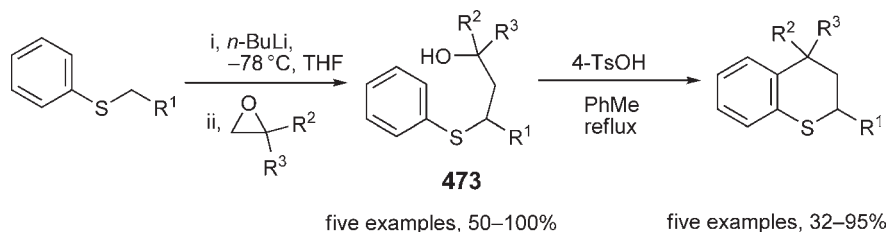


Scheme 163

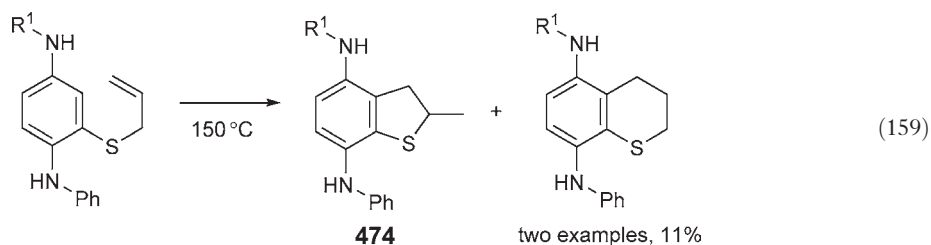
Optically pure (+)-(*R*)-3-phenylsulfanyl-1,3-diarylpropan-1-ones are readily available by the enantioselective Michael addition of thiophenols to chalcones. After reduction, acidic dehydration of the racemic alcohol affords a mixture of the racemic *cis*- and *trans*- 2,4-disubstituted thiochromans (Scheme 164). A detailed consideration of the stereochemical outcome of the reaction with unsymmetrically substituted diaryl derivatives suggests the involvement of a [1,3] PhS shift via a four-membered sulfonium intermediate and this is backed up by theoretical calculations <2003T3621>.

**Scheme 164**

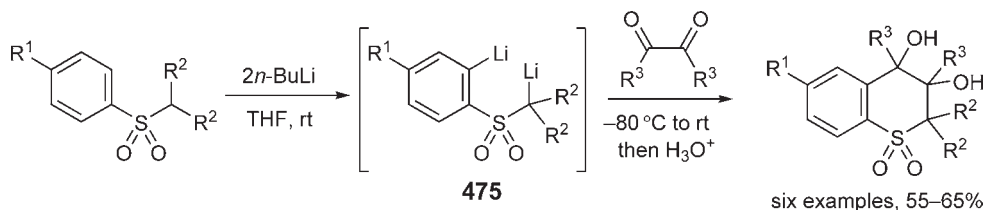
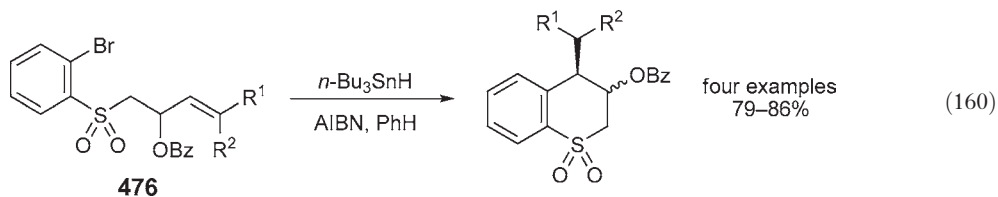
Cyclization of 4-thiophenylbutan-2-ols **473**, available by the reaction of sulfur-stabilized carbanions with epoxides, affords substituted thiochromans (**Scheme 165**) <2000JHC1527>.

**Scheme 165**

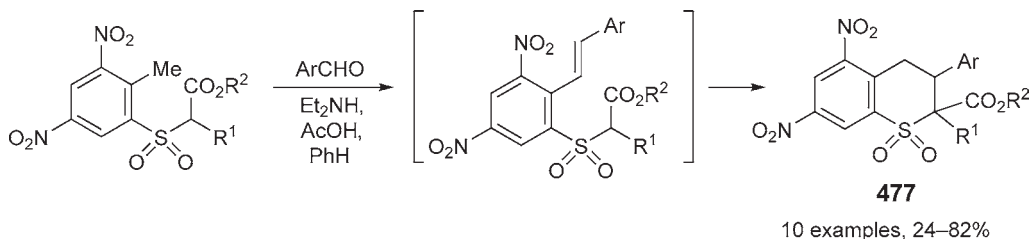
Thermolysis of allylsulfanyl derivatives of *N,N'*-disubstituted 1,4-phenylenediamines yields mainly the benzothio-**474** by way of a thio-Claisen rearrangement and Markovnikov addition of the SH function to the double bond. However, small amounts of the thiochroman-5,8-diamine are produced by anti-Markovnikov addition (**Equation 159**) <2004MRC999>.



1,2-Diketones react diastereoselectively with the dilithio compounds **475** obtained by the *ortho* and α -directed metallation of alkyl aryl thioethers and sulfones to give the *trans*-thiochroman-3,4-diols and their 1,1-dioxides (**Scheme 166**) <1998S1098>. *o*-Bromophenyl sulfones **476** yield the 3,4-disubstituted thiochroman dioxide by a radical cyclization; the *trans* isomer is the predominant or even exclusive product (**Equation 160**) <1995SL943>.

**Scheme 166**

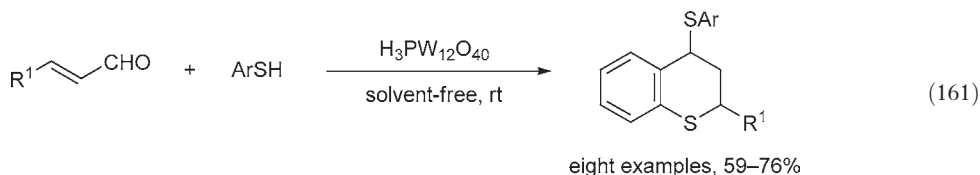
The selective nucleophilic displacement of one *ortho* nitro group from 2,4,6-trinitrotoluene by esters of mercaptoacetic acid followed by oxidation leads to 2-(alkoxycarbonyl)methylsulfonyl compounds. These sulfones react with aromatic aldehydes under Knoevenagel conditions to produce thiochroman 1,1-dioxides **477**, probably via a stilbene and a subsequent intramolecular Michael addition. Activating groups other than nitro are compatible with the route (Scheme 167) <2003RJO397>.



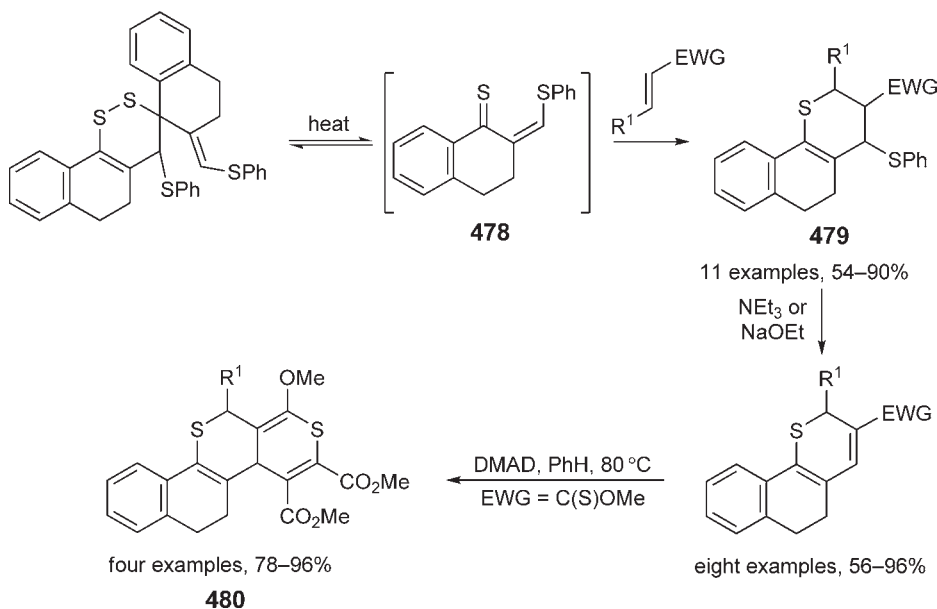
Scheme 167

7.10.4.2.3(ii) Formation of two bonds

The reaction between α,β -unsaturated aldehydes and thiophenols is catalyzed by tungstophosphoric acid and in the absence of solvent at room temperature thiochromans are formed rapidly and in good yield (Equation 161). The heteropolyacid is recoverable and reusable <2005TL7567>.

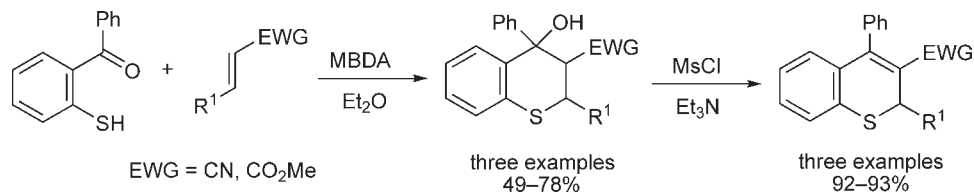


Reaction of the naphthalene-based α,β -unsaturated thioketone **478** with various acrylate dienophiles leads to the benzo-fused thiochromans **479** from which elimination of the phenylthio group, which may require the addition of base, affords the benzo-fused thiochromenes (Scheme 168) <1992BCJ2056>. These latter products are themselves suitable substrates for hDA reactions which produce dithiabenzoc[*c*]chrysenes **480** <1994BCJ2876>.



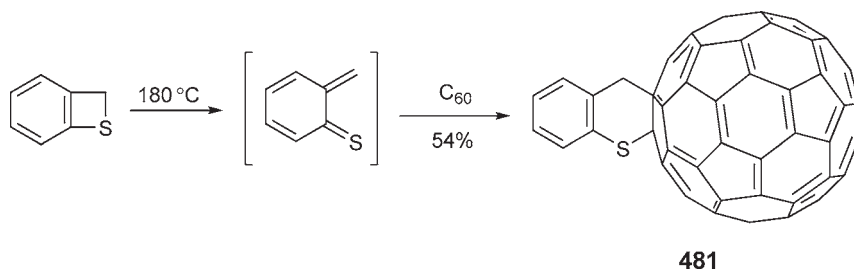
Scheme 168

2-Mercaptobenzophenone reacts with α,β -unsaturated esters and nitriles in the presence of magnesium bis(diisopropyl)amide (MBDA) to yield 4-hydroxythiochroman-3-carboxylic acid derivatives. Dehydration to the thiochromene is facile (Scheme 169) <1999J(P1)1547>.



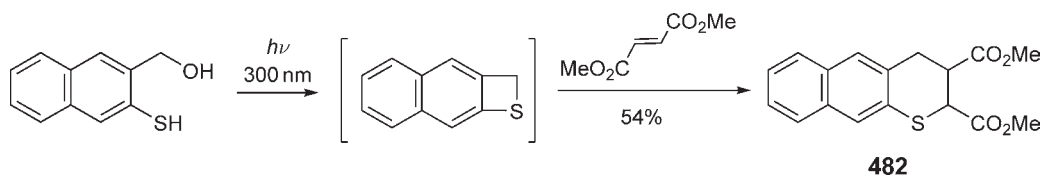
Scheme 169

Several approaches to thiochromans involve the generation of *o*-thioquinone methides. The thermal electrocyclic ring opening of benzothiete in the presence of fullerene leads to the 1:1 cycloadduct, a thiochroman-fused C₆₀ 481 (Scheme 170). Oxidation with MCPBA produces the sulfoxide which can be further oxidized to the sulfone <1995TL6899>. In a related manner, α,β -unsaturated thiocarbonyl compounds prepared *in situ* from thioacrylamide react with [60]fullerene to give the dihydrothiopyran-fused analogues <1995CC565>.



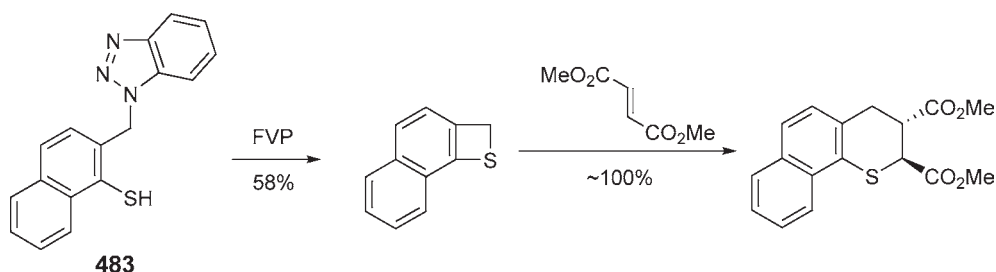
Scheme 170

Flash vacuum pyrolysis of hydroxymethylthionaphthols serves to synthesize the three isomeric naphthothietes. Their behavior toward thermolysis is similar in that it leads to a thioquinone methide, but the linear 2*H*-naphtho[2,3-*b*]thiete exhibits a significantly higher energy barrier to ring opening. However, all three readily form the reactive intermediate on photolysis at ca. 300 nm and these have been trapped by various dienophiles to produce dihydronaphthothiopyrans. This route is particularly attractive in view of the general difficulty in synthesizing the linear naphthothiopyran ring system 482 (Scheme 171) <1994TL2161, 1995LA2221>.



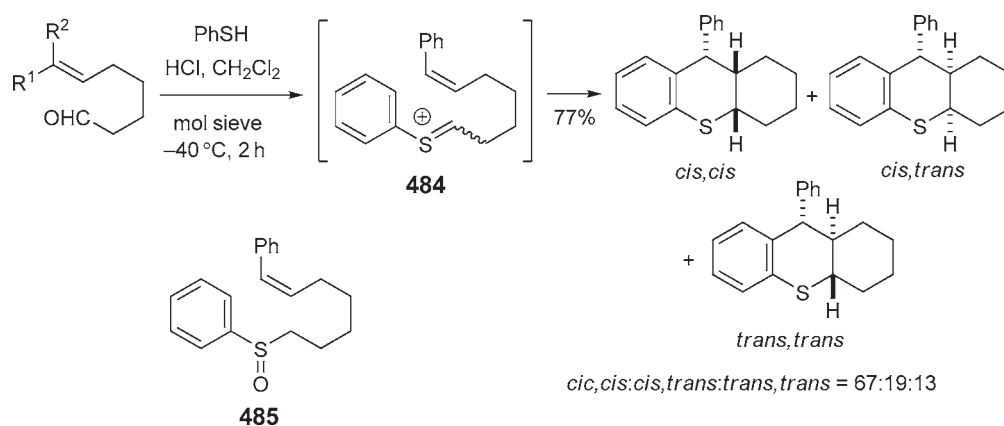
Scheme 171

Flash vacuum pyrolysis of 2-(1-benzotriazolylmethyl)-1-thionaphthol 483 produces the naphthothiete from which naphtho[1,2-*b*]thiopyrans are obtained by reaction with dienes (Scheme 172) <1998JHC1505>.



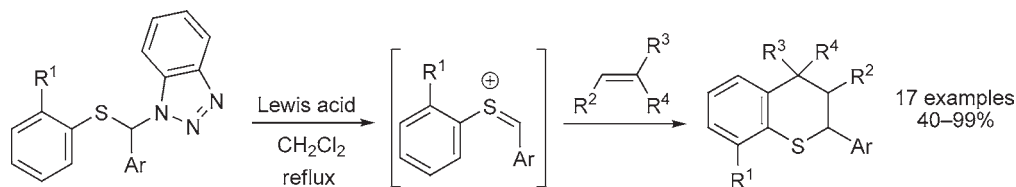
Scheme 172

An intramolecular polar cycloaddition involving a cationic 2-thiabuta-1,3-diene features in the synthesis of cyclohexa-*[b]*thiochromans (hexahydrothioxanthenes) from thiophenols. Thus, the reaction between thiophenol and 7-phenylhept-6-enal, promoted either by gaseous HCl or BF₃ etherate, generates a thionium cation **484** which undergoes a [4⁺+2] cycloaddition which leads to a mixture of three adducts (Scheme 173). In the case of the (*Z*)-enal, it is considered that the major *cis,cis*-annulated product arises through either an *endo-E-syn* or an *exo-Z-syn* transition state. It is postulated that the *cis,trans* and *trans,trans* minor products are derived from cationic intermediates in a nonconcerted process. The (*E*)-enal affords the *trans,trans* adduct as the major product via an *exo-E-anti* transition state. The same products result from a domino Pummerer–intramolecular cyclization sequence in which the diastereoselectivity depends, to some extent, on the reaction conditions. The ratio of the three products obtained from the sulfoxide **485** can be controlled by varying the amounts of 2,6-lutidine and trifluoroacetic acid. The *cis,cis*-annulated product results at 0 °C using 0.6 and 2.0 equiv of the two reagents, respectively, whereas the all *trans*-product is formed at –20 °C with 1.2 and 3.0 equiv <1996SL396>.



Scheme 173

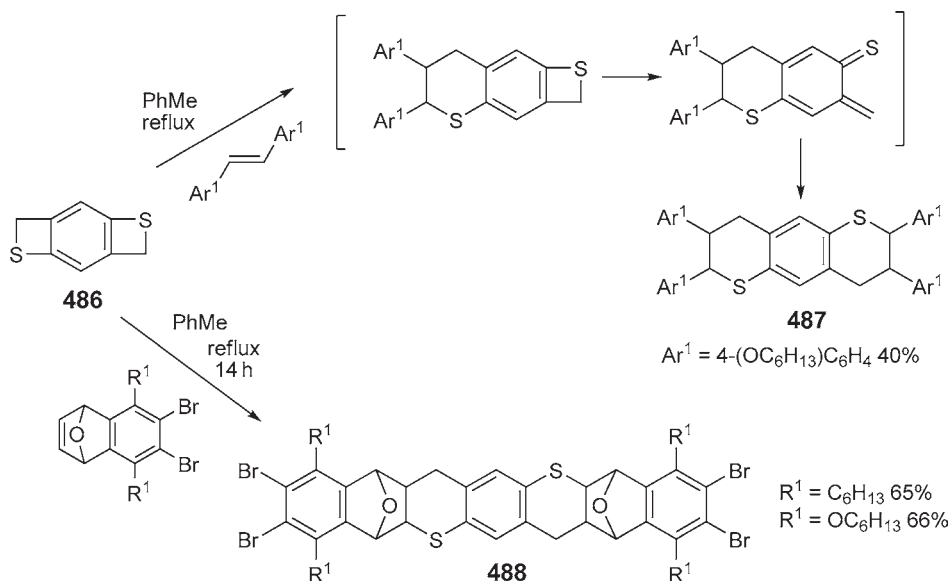
A wide range of variously substituted thiochromans has been obtained from the readily accessible α -(benzotriazolyl)methyl thioethers by their Lewis acid-catalyzed reaction with styrenes. Initial loss of the benzotriazole unit generates a thionium cation which undergoes an efficient cationic cycloaddition to the alkene. The reaction, which generally proceeds with high diastereoselectivity, is considered to occur in a stepwise manner rather than as a concerted [4⁺+2] process (Scheme 174) <2001JOC5595>.



Scheme 174

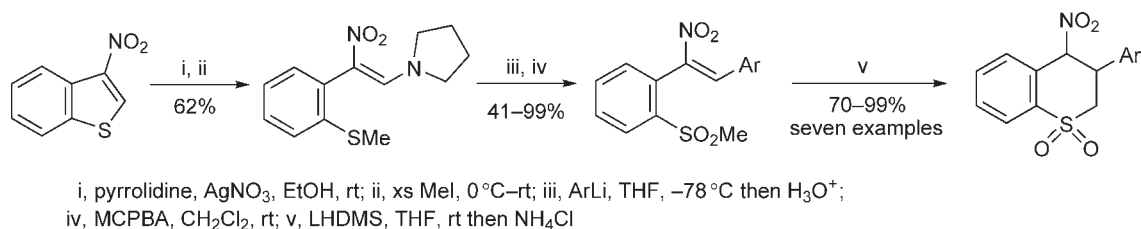
7.10.4.2.3(iii) From other heterocycles

Heating the benzobisthiete **486** in the presence of (*E*)-1,2-bis(4-hexyloxyphenyl)ethene affords the 2:1 adduct **487** <1994AGE465>. Similar treatment of **486** with an epoxynaphthalene produces the dithiaheptacene **488** (Scheme 175) <1997LA1173>. The stepwise opening of the four-membered rings to thioquinone methides operates.



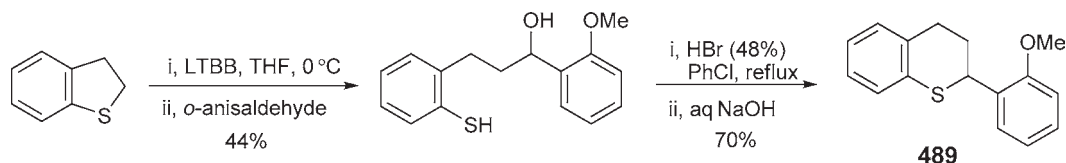
Scheme 175

Cleavage of the hetero ring of 3-nitrobenzo[*b*]thiophene is the first step in a synthesis of (*E*)-2-aryl-1-[2-(methylsulfonyl)phenyl]-1-nitroethenes (Scheme 176). The sulfonyl-stabilized anion derived from these alkenes by metallation adds in Michael fashion to the nitrovinyl unit to form 4-nitrothiochroman 1,1-dioxides as an inseparable mixture of two diastereomers. The overall process corresponds to expansion of a thiophene ring to a thiopyran unit <2004T4967>.



Scheme 176

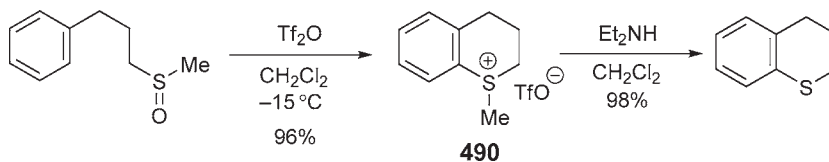
The product arising from cleavage of dihydrobenzothiophene by reaction with lithium 4,4'-di-*t*-butylbiphenylide (LTBB) and reaction with anisaldehyde undergoes an acid-catalyzed cyclization to 2-(*o*-anisyl)thiochroman **489** (Scheme 177) <1995TL4459>.



Scheme 177

7.10.4.2.3(iv) From a preformed heterocyclic ring

Trifluoroacetic anhydride effects the cyclization of 3-phenylpropyl methyl sulfoxide to the thiochromanium salt **490** in high yield. Demethylation to thiochroman is readily achieved by treatment with diethylamine (Scheme 178) <1996SUL75>.



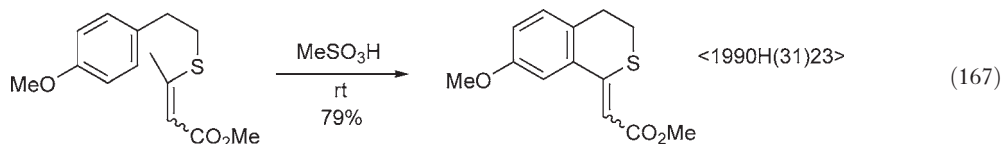
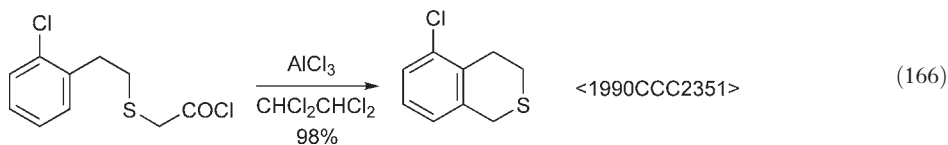
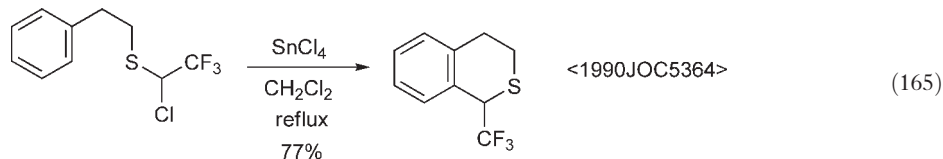
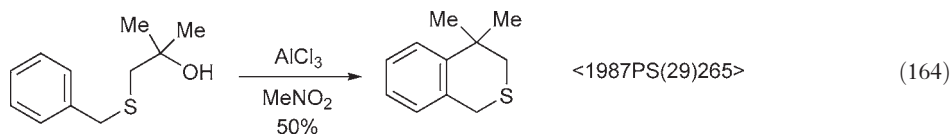
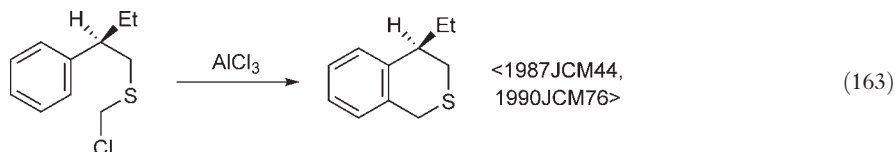
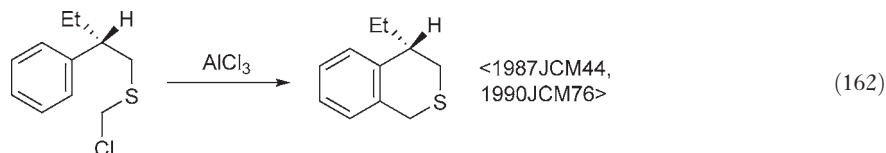
Scheme 178

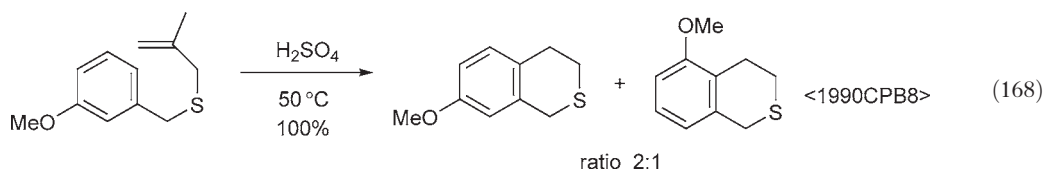
The reduction of benzo- and naphtho-thiopyran-4-ones to thiopyrans has been accomplished in high yield by hydrogenation under pressure over MoS_3 <1995JHC687>.

7.10.4.2.4 Isothiochromans

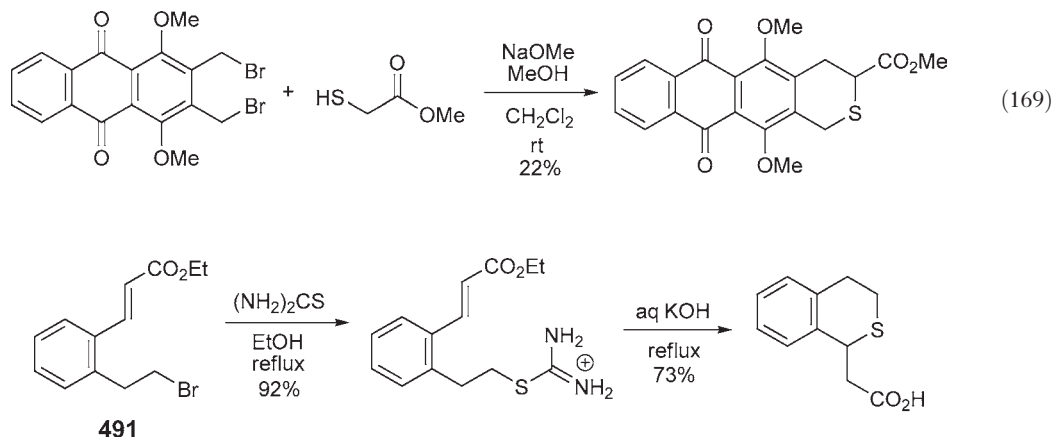
7.10.4.2.4(i) Formation of one bond

The major route to isothiochromans involves intramolecular cyclization under Friedel–Crafts conditions during which either the C(4)–ring or C(1)–ring bond is formed as illustrated in Equations (162)–(168). Of special note is the synthesis of both (*R*)- and (*S*)-4-ethylisothiochroman using this methodology (Equations 162 and 163).



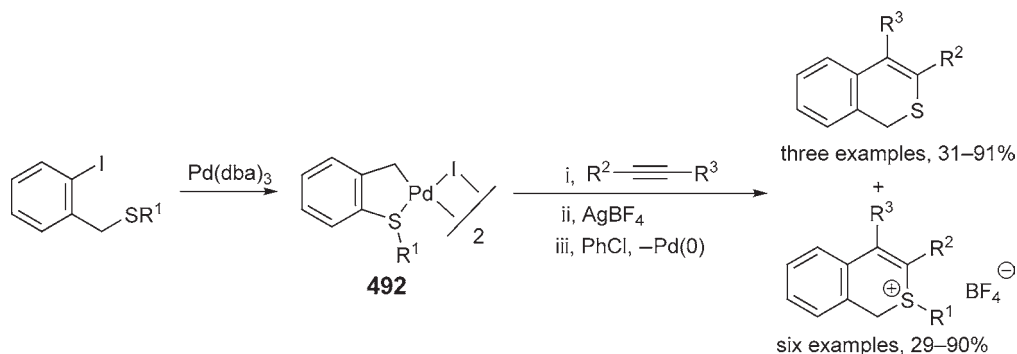


A facile route to isothiochromans involves the base-catalyzed reaction of a benzyl dibromide with an α -thiocarbonyl compound. The method has been extended to the synthesis of an anthraceno[2,3-*c*]thiopyran, a heterocyclic analogue of an anthracyclinone (Equation 169) <1994S363>. In like manner, alkylation of the 2-aryl-1-bromoethane **491** by thiourea and subsequent liberation of the thiol function creates an isothiochroman precursor. An intramolecular Michael addition to the α,β -unsaturated ester side chain yields the 1-substituted heterocycle (Scheme 179) <1992JOC1727>.



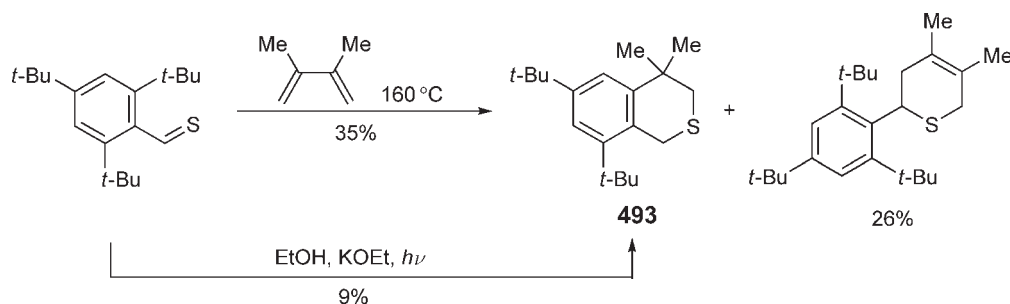
Scheme 179

Alkyne insertion into the Pd complexes **492** derived from 2-iodobenzyl sulfides provides a regiospecific route to mixtures of 1*H*-2-benzothiopyrans and 1*H*-2-benzothiopyranium fluoroborate salts. Thus, unsymmetrically substituted phenylalkynes afford the 3-phenyl derivatives (Scheme 180) <1995JOC1005>.



Scheme 180

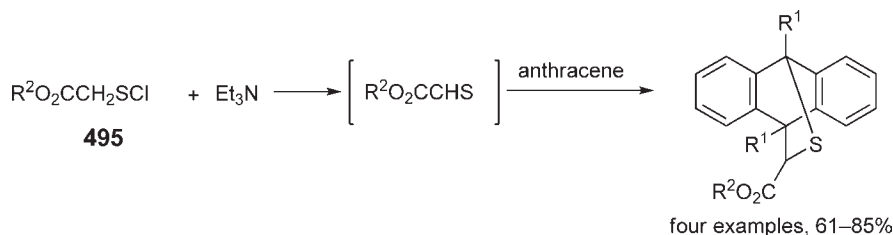
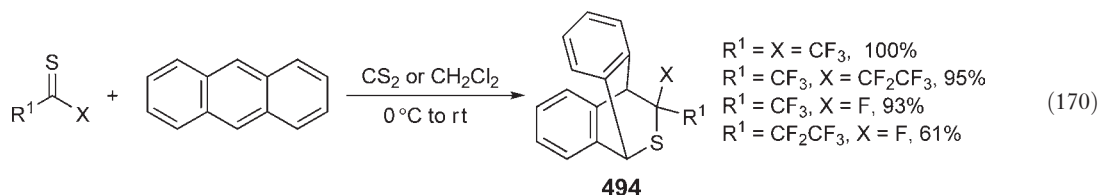
The cyclization of 2,4,6-tri-*t*-butylthiobenzaldehyde to the isothiochroman **493** has been accomplished both thermally <1996BCJ719> and by photolysis (Scheme 181) <1991J(P2)1045>; it appears that the reaction involves radical formation.



Scheme 181

7.10.4.2.4(ii) Formation of two bonds

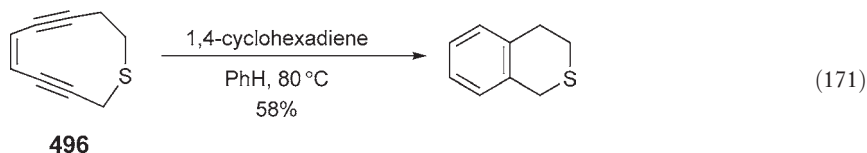
Fluorinated thioketones [<1965JOC1390>](#) and perhalogenoalkylthioacetyl fluorides [<1992CB1889>](#) are reactive dienophiles and rapidly add across the 9,10-bond of anthracene to form the isothiochroman nucleus **494** (Equation 170). Similar products result from the treatment of the sulfonyl chloride **495** with triethylamine when a thioaldehyde is generated (Scheme 182) [<1991J\(P1\)3225>](#).

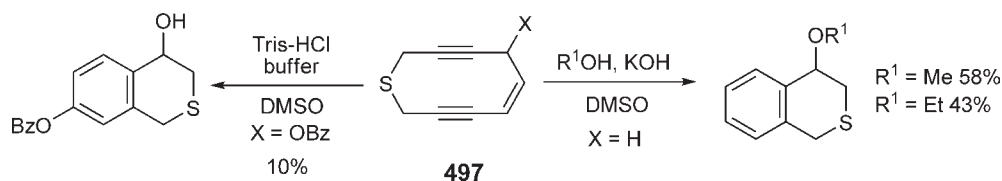


Scheme 182

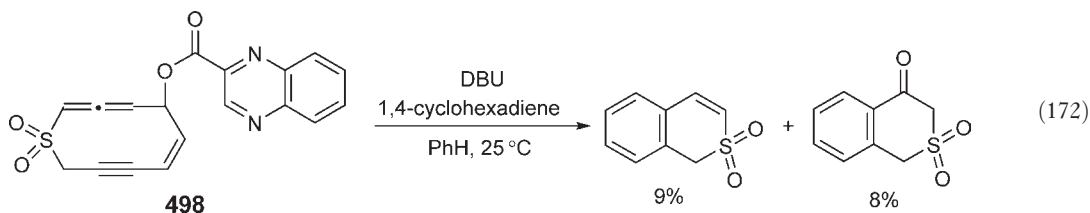
7.10.4.2.4(iii) From other heterocycles

The macrocyclic enediyne **496** undergoes a Bergmann–Masamune cyclization to isothiochroman (Equation 171) [<1991TL4363>](#) and treatment of the macrocyclic enediyne **497** ($X = H$) with alcohols under basic conditions affords 4-alkoxyisothiochromans (Scheme 183) [<1991TL391>](#). The benzoyleated enediyne **497** ($X = OBz$) cycloaromatized upon treatment with tris(hydroxymethyl)aminomethane hydrochloride (Tris-HCl) at pH 8.5 to afford the isothiochroman-4-ol (Scheme 183) [<1995JA4822>](#). In a related manner, the quinoxaline-substituted enyne-allene S,S -dioxide **498** underwent a base promoted cyclization in the presence of cyclohexa-1,4-diene to afford the isothiochromene and isothiochromanone (Equation 172) [<1993CC1406>](#).

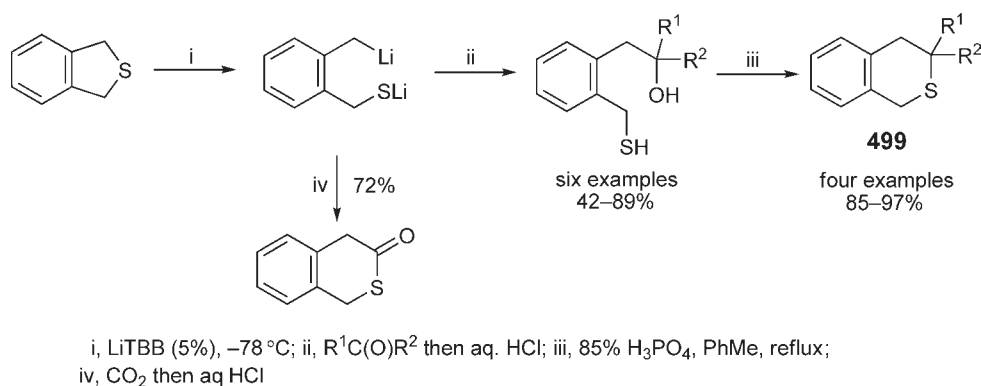




Scheme 183



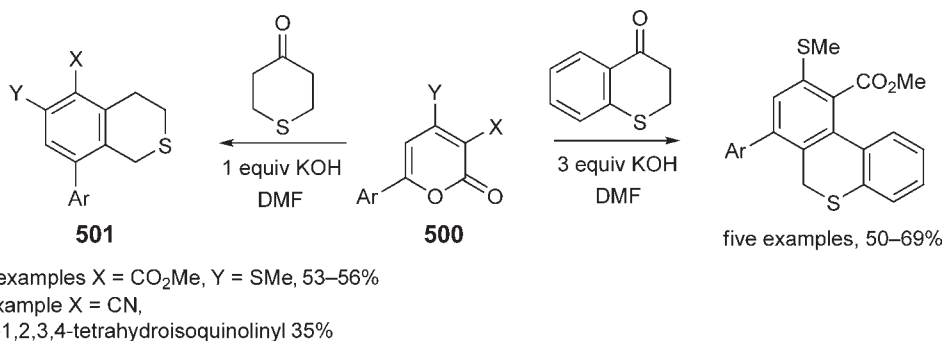
3-Substituted 3,4-dihydro-1*H*-2-benzothiopyrans **499** are formed from benzo[*c*]thiophenes by ring opening to the dianion and reaction with electrophiles (Scheme 184) <1996JOC1859>.



Scheme 184

7.10.4.2.4(iv) From a preformed heterocyclic ring

The reaction of carbanions derived from tetrahydrothiopyran-4-one and its benzologue with the pyran-2-one **500** (X = CO₂Me, Y = MeS) affords isothiochromans and 6*H*-dibenzo[*bc*]thiopyrans, respectively, through a carbanion-mediated annulation sequence outlined in Scheme 185. In the latter case, the actual product depends on the amount of base used; with an excess, Michael addition of hydroxide ion is preferred to a cyclocondensation and results in the displacement of MeS[–] and formation of a hydroxy-substituted dibenzo[*bc*]thiopyran <2001JOC5333, 2002J(P1)1426>.



Scheme 185

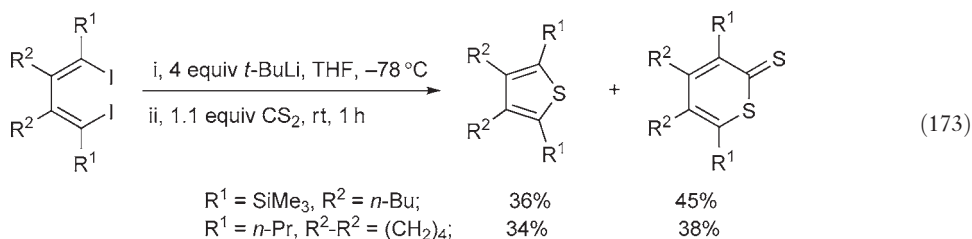
Treatment of 6-aryl derivatives of 4-substituted 2-oxo-2*H*-pyran-3-carbonitriles **500** ($X = \text{CN}$, $Y = N$ -1,2,3,4-tetrahydroisoquinoliny) with ketones under basic conditions results in cleavage of the pyran ring and formation of new heterocyclic systems. Thus, tetrahydrothiopyran-4-one affords the 3,4-dihydro-1*H*-2-benzothiopyran **501** (Scheme 185) <2005BML1341>.

7.10.4.3 Thiopyranones and Fused Thiopyranones

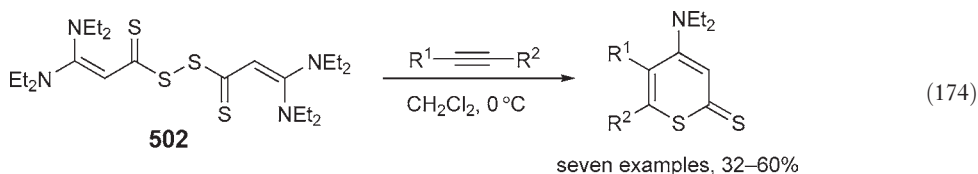
7.10.4.3.1 Thiopyran-2-ones

7.10.4.3.1(i) Formation of two bonds

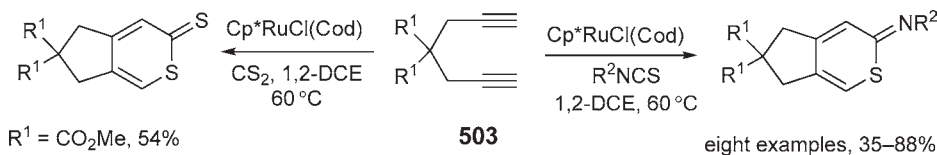
The cycloaddition of CS_2 to the 1,4-dithio species obtained from derivatives of 1,4-diiodobuta-1,3-diene affords thiopyran-2-thiones. However, formation of substituted thiophenes through cleavage of one of the $\text{C}=\text{S}$ bonds is a significant competing reaction (Equation 173) <2002TL3533>. It appears that bulkier substituents on the terminal C atoms favor thiopyranthione formation <2003ARK155>.



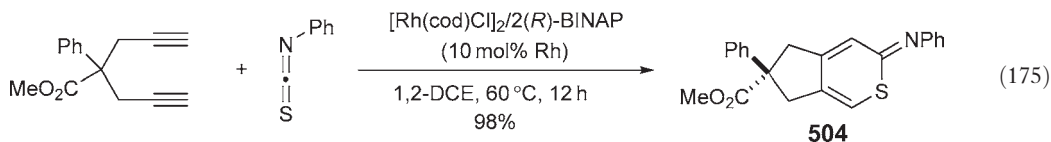
2*H*-Thiopyran-2-thiones can also be synthesized through the reaction of alkynic dienophiles with the disulfide **502** (Equation 174) <1996BCJ2091>.



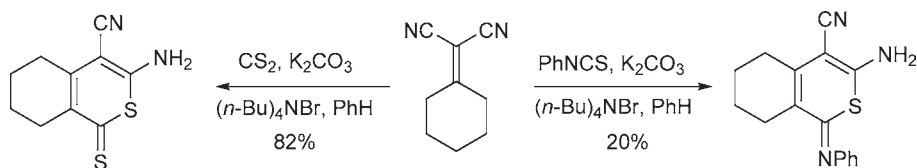
1,6-Diynes **503** react with CS_2 and with isothiocyanates in a Ru-catalyzed [2+2+2] cycloaddition to give cyclopenta[*c*]thiopyran-2-thiones and 2-imines, respectively. A requirement for success appears to be a quaternary center at C-4 of the diyne. With unsymmetrically substituted diynes, 2,6- rather than 2,3- disubstitution is much preferred with isothiocyanates (Scheme 186) <2005JA605>. A neutral $\text{Rh}(\text{I})$ -BINAP catalyst serves a similar purpose, giving high yields with a variety of diynes and isothiocyanates and with CS_2 . Using an unsymmetrically substituted diyne and phenyl isothiocyanate, the bicyclic thiopyranimine **504** was obtained in almost quantitative yield and with a 61% ee and from which an enantiopure sample was obtained by recrystallization (Equation 175) <2006OL907>. Under Ru-catalysis, the cyclotrimerisation of two alkynes with CS_2 yields thiopyran-2-thiones and thiopyran-2-imines with isothiocyanates <2002JA28>. A mechanism has been proposed for these reactions based on DFT calculations <2003JA11721, 2004NJC153>.



Scheme 186

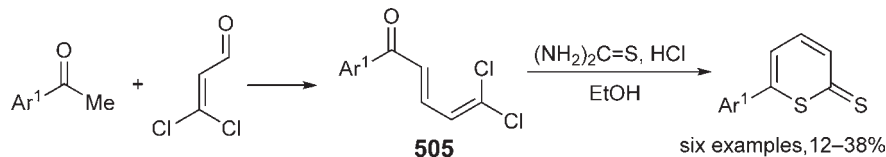


The reaction of cyclohexylidenemalononitrile with CS₂ under phase transfer conditions gives a 5,6,7,8-tetrahydroisothiochroman-1-thione. Under the same conditions, reaction with isothiocyanates produces the corresponding 1-imine, but tetrahydroisoquinoline thiones and/or ketones are also formed, often in the major quantities, and this detracts from the synthesis (Scheme 187) <2000JHC1233>.



Scheme 187

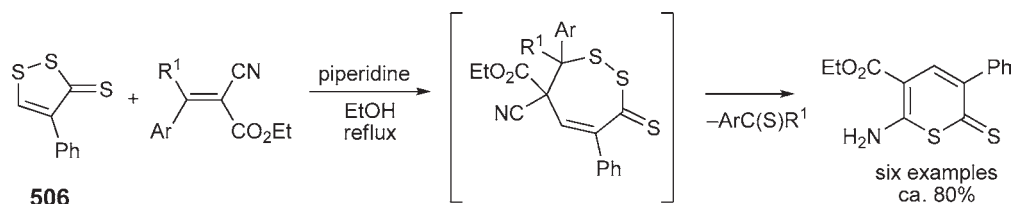
Acetophenones react with 3,3-dichloropropenal to give 1-aryl-5,5-dichloropenta-2,4-dienones **505** which on treatment with thiourea afford 6-aryl-2*H*-thiopyran-2-thiones (Scheme 188) <2000MC77>.



Scheme 188

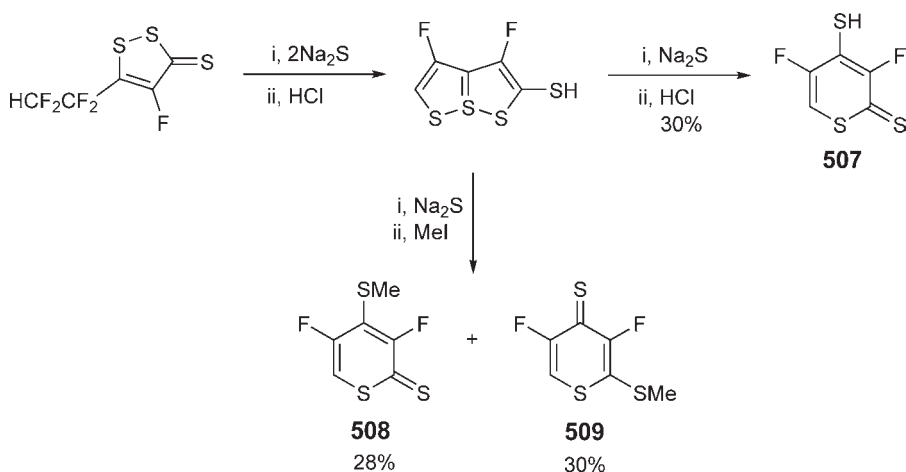
7.10.4.3.1(ii) From other heterocycles

The base catalyzed reaction of 4-phenyl-1,2-dithiole-3-thione **506** with α,β-unsaturated nitriles affords 6-aminothiopyran-2-thiones. A complex mechanism is postulated for the transformation with elimination of a thioketone from a dithiepin featuring in the key step (Scheme 189) <2003PS(178)2255>.



Scheme 189

Reaction of 4-fluoro-5-(1,1,2,2-tetrafluoroethyl)-3*H*-dithiole-3-thione with 2 equiv of Na₂S affords 3,4-difluoro-2-mercapto-1,6,6a⁴-trithiapentalene after an acidic work-up. Further reduction with Na₂S gives 3,5-difluoro-4-mercapto-2*H*-thiopyran-2-thione **507** in >30% overall yield. Methylation of the Na salt of the pentalene affords an ~1:1 mixture of methylsulfanyl derivatives of a 2*H*-thiopyran-2-thione **508** and 4*H*-thiopyran-4-thione **509** (Scheme 190). DFT calculations predict the stability sequence for the thiones is **507** > **508** > **509** <2006JFC(127)774>.

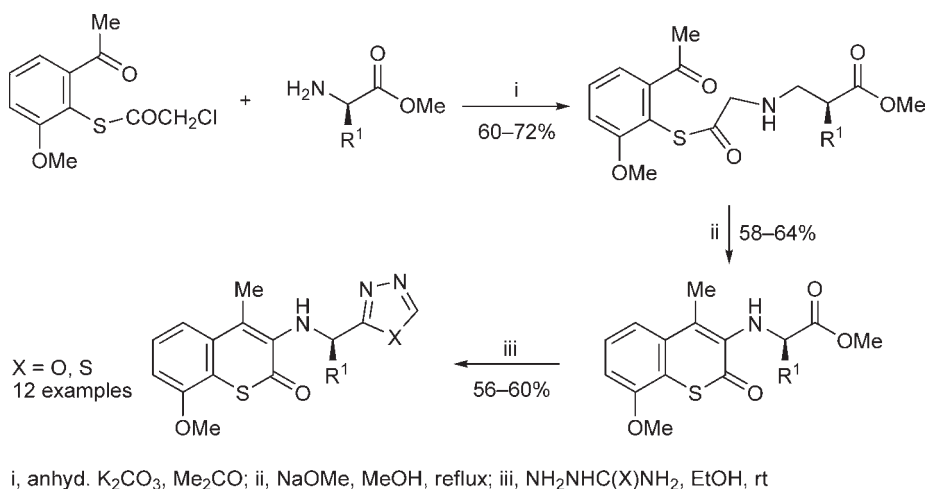


Scheme 190

7.10.4.3.2 Thiocoumarins

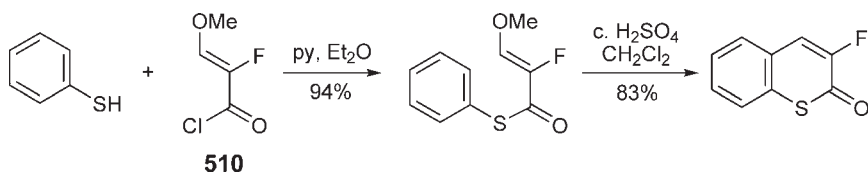
7.10.4.3.2(i) Formation of one bond

S-Acylated 2-acetylthiophenols are cyclized by treatment with base; the sequence has been used to prepare oxa- and thia-diazole derivatives of 3-aminothiocoumarins ([Scheme 191](#)) <2004PS(179)2059>.



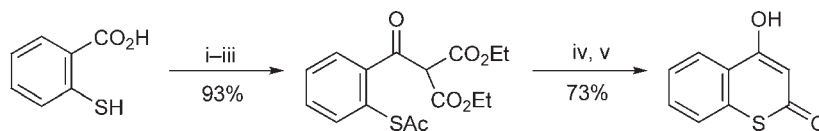
Scheme 191

Acylation of thiophenol with 2-fluoro-3-methoxypropenoyl chloride **510** and cyclization of the resulting propenethioate yields 3-fluorothiocoumarin ([Scheme 192](#)) <1996T4403>.



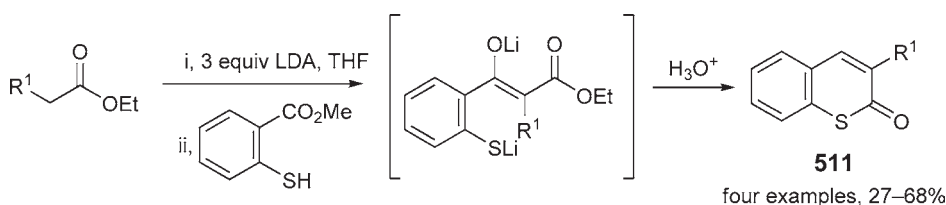
Scheme 192

An efficient large-scale synthesis of 4-hydroxythicoumarin from 2-mercaptobenzoic acid has been reported (**Scheme 193**) <2000SC1193>. 3-Substituted 4-hydroxythicoumarins **511** have been obtained by the reaction of the anion derived from ethyl alkanoates with methyl thiosalicylate followed by an acidic work-up (**Scheme 194**) <1997JHC1159> and the anion derived from 2'-chloroacetophenones reacts with CS₂ to give the 4-hydroxybenzothioiopyran-2-thione **512** on kinetic protonation. Subsequent treatment with strong acid induces tautomerisation to the 2-mercaptothiochromones (**Scheme 195**) <1987AJC1179>.

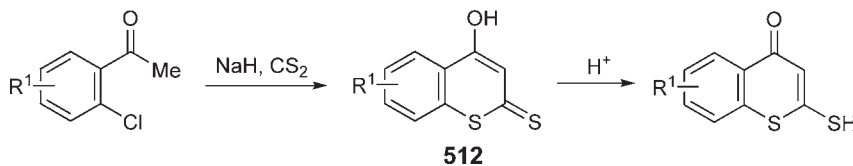


i, Ac₂O, py; ii, SOCl₂, urea, PhMe; iii, CH₂(CO₂Et)₂, Mg, EtOH; iv, aq HCl, EtOH; v, HCl

Scheme 193



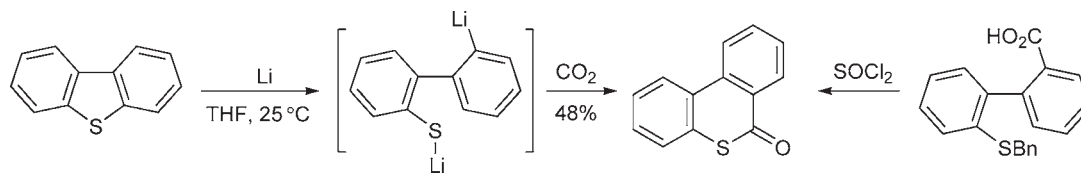
Scheme 194



Scheme 195

7.10.4.3.2(ii) From other heterocycles

The reductive cleavage of dibenzothiophene and carboxylation and acid-catalysed cyclization of the resulting biphenyl derivative affords dibenzo[*b,d*]thiopyran-6-one <1957JOC851>. The same product can be obtained by the intramolecular acylation of 2'-(benzylsulfanyl)biphenyl-2-carboxylic acid via the acid chloride (**Scheme 196**) <1996H(43)2567>.

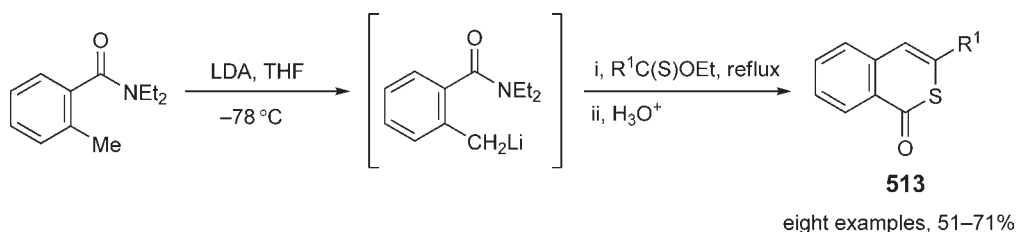


Scheme 196

7.10.4.3.3 Isothiocoumarins

7.10.4.3.3(i) Formation of two bonds

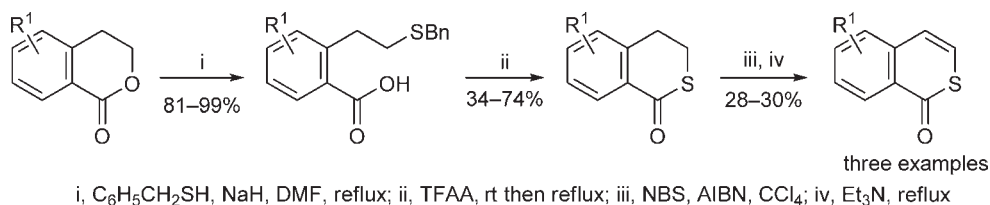
The organolithium derived from 2-methylbenzamide reacts with alkyl and aryl thioesters to give 3-substituted isothiocoumarins **513** (**Scheme 197**) <1990S1133>.



Scheme 197

7.10.4.3.3(ii) From other heterocycles

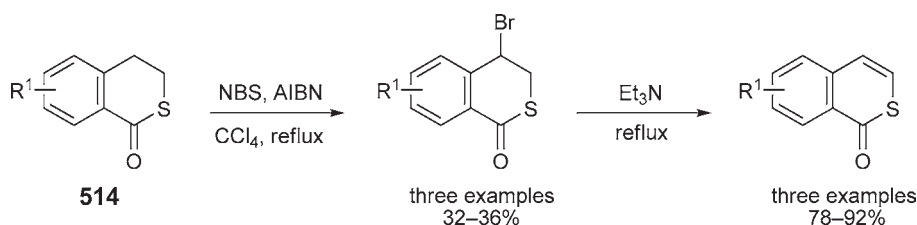
Treatment of 3,4-dihydroisocoumarins with 2-methylthiophenoxide results in cleavage of the pyran ring and formation of 2-thioethylbenzoic acid derivatives. Sequential cyclization, bromination and dehydrobromination afford the isothiocoumarins via the 3,4-dihydroisothiocoumarin (**Scheme 198**) <2000T6763>.



Scheme 198

7.10.4.3.3(iii) From a preformed heterocyclic ring

The radical bromination of 3,4-dihydroisothiocoumarins **514** and dehydrobromination of the resulting 4-bromo derivative provides a route to isothiocoumarins (**Scheme 199**) <2000T6763>.



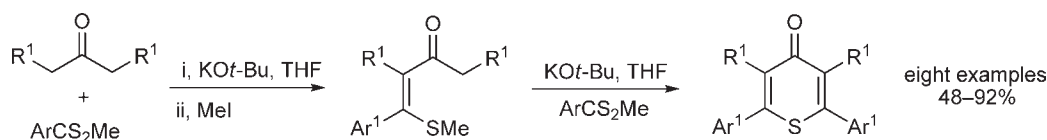
Scheme 199

7.10.4.3.4 Thiopyran-4-ones

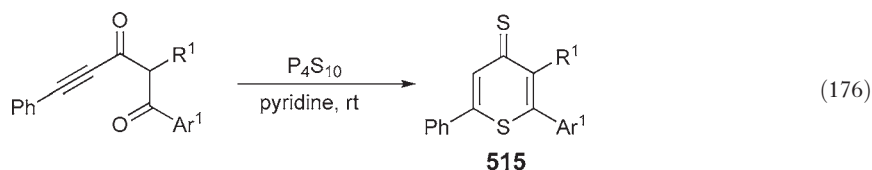
7.10.4.3.4(i) Formation of one bond

Two sequential thio-Claisen condensations convert dialkyl ketones into thiopyran-4-ones in a rapid, high-yielding process. Initial reaction with an aromatic dithioester produces an α,β -unsaturated ketone which, after alkylation at sulfur, undergoes reaction with a second dithioester and cyclization to the substituted thiopyranone follows (**Scheme 200**) <1993JOC3042>.

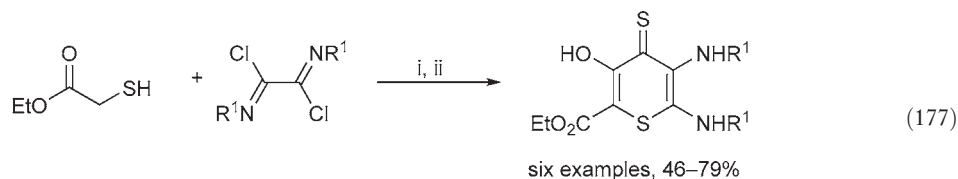
Treatment of 1-aryl-5-phenylpent-4-yn-1,3-diones with P_4S_{10} in pyridine results in cyclization to the 2-aryl-6-phenylthiopyran-4-thiones **515** (Equation 176) <1993PS(81)101>.



Scheme 200

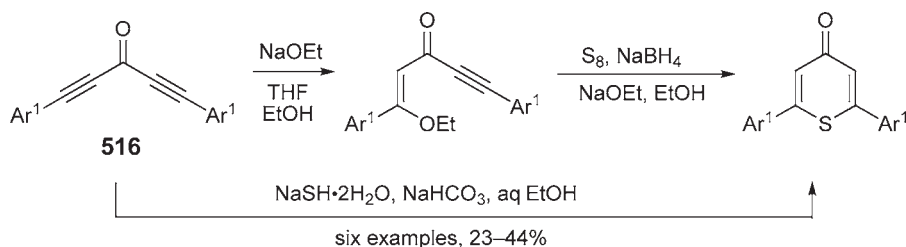


The reaction between lithiated ethyl thioglycolate and 1,2-diimidoyl-1,2-dichloroethanes is complex and the products depend on the reaction conditions. When a large excess of the monoanion of ethyl thioglycolate is used, good yields of 2,3-diamino-4-thioxo-4*H*-thiopyran-6-carboxylates are obtained (Equation 177) <2006JOC2332>.



i, 6.0 equiv LDA, TMEDA, THF, –40 to 0 °C; ii, addition of bis-imine, –78 to 20 °C

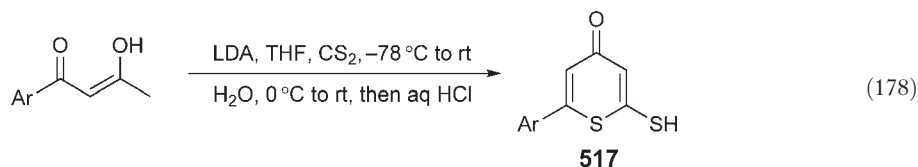
The reaction of penta-1,4-diyn-3-ones with H₂S is a potential source of thiopyran-4-ones, involving the initial formation of a thioenol followed by a 6-*endo-dig* cyclization. However, a 5-*exo-dig* process leading to thiophenones often competes successfully. The use of basic conditions, for example, NaSH/NaHCO₃ <1995JOC1665>, helps to alleviate this problem. A preferred approach involves the addition of ethanol to the penta-1,4-diyn-3-ones **516** in the presence of sodium ethoxide and treatment of the resulting enol ether with Na₂S to give the symmetrically or unsymmetrically 2,6-disubstituted thiopyran-4-ones (Scheme 201) <1999JHC707, 1999JME3942>.



Scheme 201

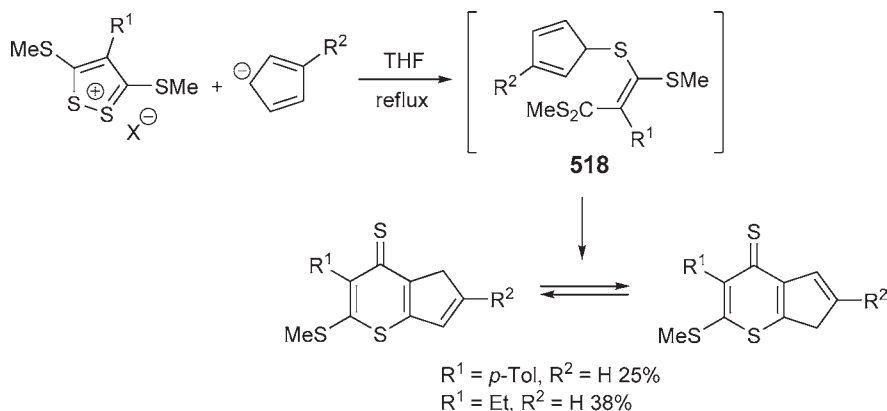
7.10.4.3.4(ii) Formation of two bonds

The dianion derived from 1-arylbutan-1,3-dione reacts with CS₂ to give 6-aryl-2-mercaptothiopyran-4-one **517** (Equation 178) <2003BML3083>.

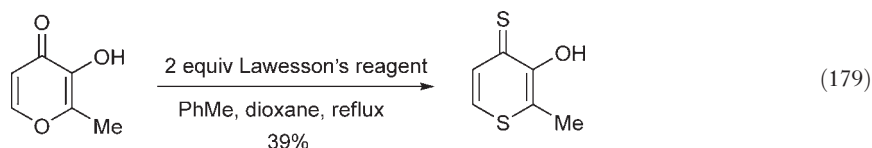


7.10.4.3.4(iii) From other heterocycles

Cleavage of the S–S bond in 4-aryl-3,5-bis(methylthio)-1,2-dithiolium salts occurs on treatment with a cyclopentadienide species which results in the formation of an α,β -unsaturated dithioester **518**. Deprotonation by excess reagent initiates an intramolecular cyclization which yields a 5*H*-cyclopenta[*b*]thiopyran-4-thione (**Scheme 202**) <1996LA109>.

**Scheme 202**

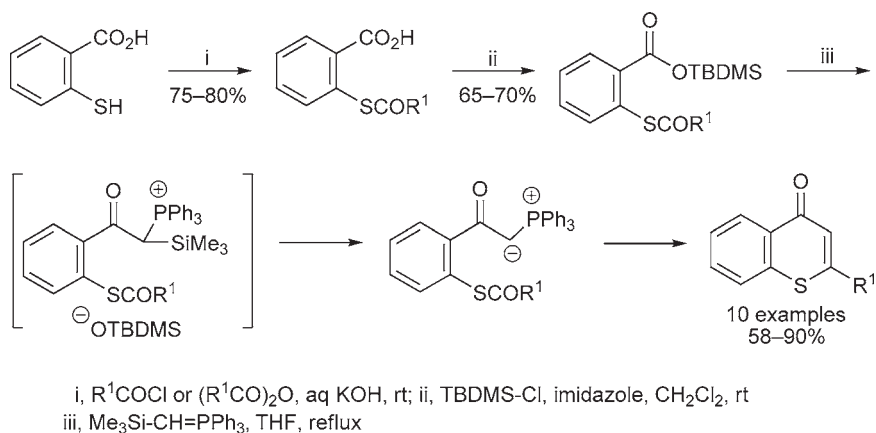
Both the hetero and carbonyl oxygen atoms of maltol, 3-hydroxy-2-methylpyran-4-one, are replaced by sulfur on treatment with Lawesson's reagent. While the 'ketone $\rightarrow$ thione' conversion can be achieved with various sulfur reagents, the heteroatom exchange is unusual and appears specific for Lawesson's reagent (**Equation 179**). This reaction does not occur with either related chromones or xanthenes <2006CC206>.



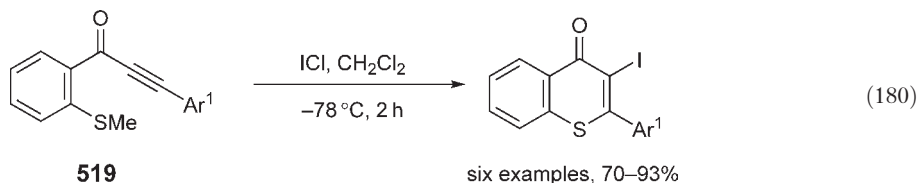
7.10.4.3.5 Thiochromones

7.10.4.3.5(i) Formation of one bond

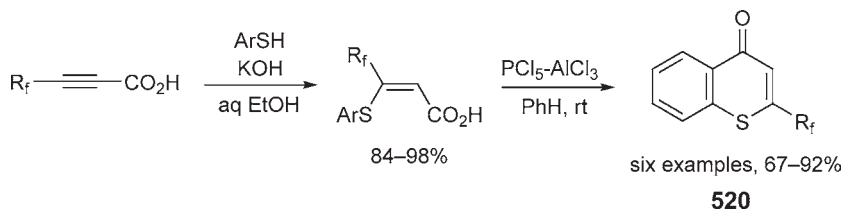
Acylation of the thiol moiety of thiosalicylic acid is the starting point for a synthesis of 2-substituted thiochromones in which the key step is an intramolecular Wittig reaction (**Scheme 203**) <2001T9755>.

**Scheme 203**

3-Substituted 1-(2-mercaptophenyl)propyn-1-ones **519** are efficiently cyclized by ICl under mild conditions to 2-substituted 3-iodothiochromones. The 3-iodo group allows further manipulation. There is no evidence for formation of a benzothiophenone by a 5-*exo* cyclization (Equation 180) <2006JOC1626>.

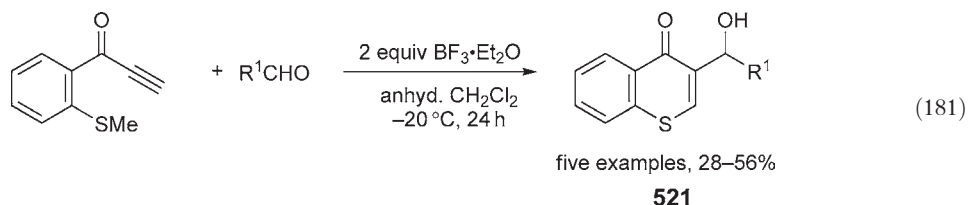


Michael addition of thiophenols to fluorinated alkynoic acids under basic conditions affords the (Z)-3-arylthio-2-alkenoic acids which undergo an intramolecular Friedel–Crafts acylation to give 2-fluoroalkylated thiochromones **520** (Scheme 204) <1994JFC(68)25>.



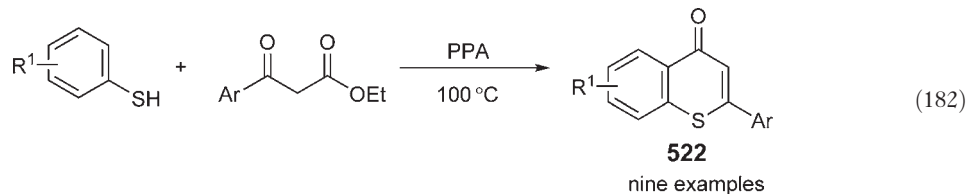
Scheme 204

Moderate yields of 3-hydroxyalkylthiochromones **521** result from a tandem Michael–aldol reaction of 1-(2-methylsulfanylphenyl)propynone with aldehydes in the presence of two moles of BF₃ etherate as a Lewis acid. The process involves a 6-*endo*-dig cyclization (Equation 181) <2002TL7039, 2005PS(180)989>.

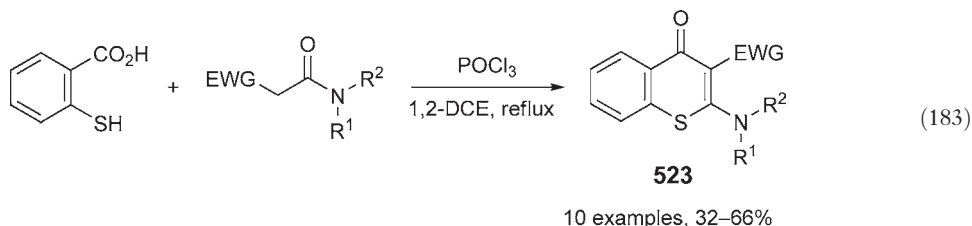


7.10.4.3.5(ii) Formation of two bonds

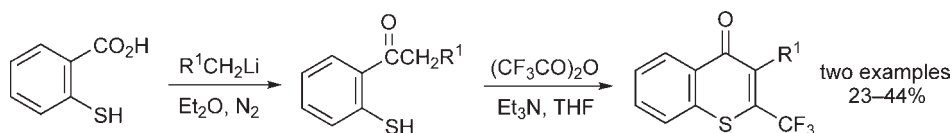
The condensation of thiophenols with ethyl aryloxyacetates is brought about by heating in PPA and yields 2-arylthiochromones **522** (Equation 182) <1996JME1975>. 2-Adamantan-1-ylthiochromone is obtained in like manner from ethyl 3-(1-adamantyl)-3-oxopropanoate <2004JME4268>.



A large-scale synthesis of 2-methylthiochromone has been devised from thiosalicylic acid <2000SC1193>, while the reaction of thiosalicylic acids with various 2-substituted *N,N*-dialkylacetamides is effected by POCl₃ which generates an electrophilic iminium salt. The products are 3-substituted 2-aminothiochromones **523** (Equation 183). Application of this protocol to cyclic amides such as piperidin-2-ones leads to tetrahydro[1]benzothiopyrano[2,3-*b*]pyridine-5-ones <2005AJC864>.



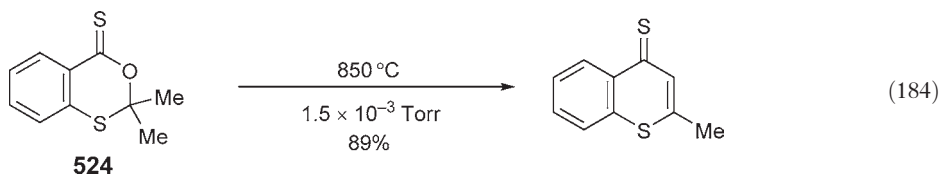
2-Trifluoromethyl derivatives of thiochromone are also available from thiosalicylic acid by conversion to alkyl 2-mercaptophenyl ketones followed by a Baker–Venkataraman reaction with trifluoroacetic anhydride in triethylamine (**Scheme 205**) <2005PS(180)1315>.



Scheme 205

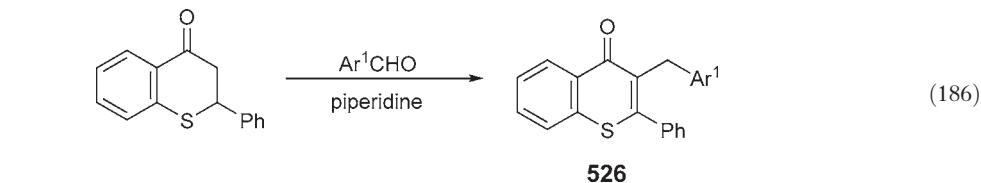
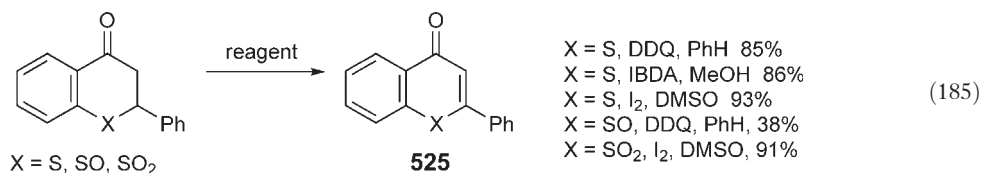
7.10.4.3.5(iii) From other heterocycles

Flash vacuum thermolysis of the 4*H*-3,1-benzoxathiin-4-thione **524** gave 2-methylthiochromone-4-thione in good yield (**Equation 184**) <2006HCA991>.

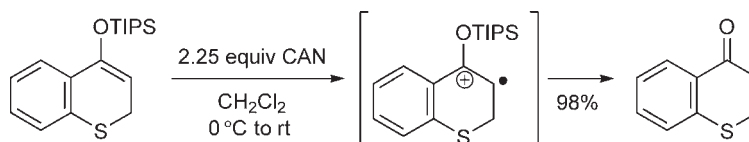


7.10.4.3.5(iv) From a preformed heterocyclic ring

The direct conversion of 2-phenylthiochroman-4-ones to thiochromones (thioflavones) **525** can be achieved with DDQ, iodobenzene diacetate (IBDA) or iodine (**Equation 185**) <1999SC1857>. Thioflavanones afford 3-substituted thioflavones **526** by isomerization of the initially formed aldol product from reaction with a substituted benzaldehyde (**Equation 186**) <1991BSF976>.



Thiochroman-4-ones are converted to thiochromones by conversion to their *triisopropylsilyl* enol ethers and dehydrogenation with ceric ammonium nitrate. It is proposed that the reaction proceeds via a radical cation which undergoes desilylation. β -Elimination from the cation generated by single-electron transfer completes the sequence (**Scheme 206**) <1995TL3985>.

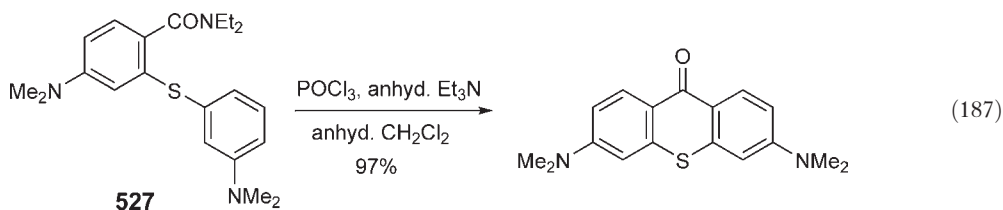


Scheme 206

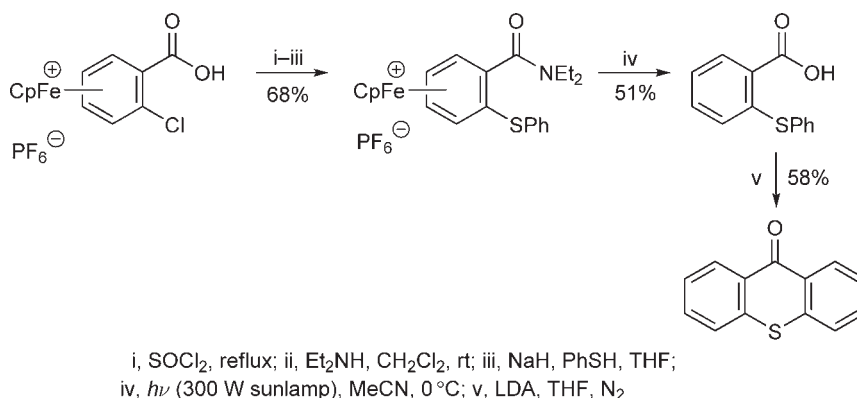
7.10.4.3.6 Thioxanthenes

7.10.4.3.6(i) Formation of one bond

The electrophilic cyclization of the benzamide **527** to 3,6-bis(dimethylamino)thioxanthone is accomplished in high yield using POCl₃ (Equation 187) <2005OM3807>.

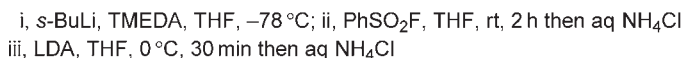


The use of transition-metal arene complexes to facilitate nucleophilic aromatic substitution features in a route to derivatives of thiosalicylic acid and hence to thioxanthone. The cyclopentadienyl iron complex of 2-chlorobenzoic acid is converted into the benzamide prior to displacement of the chloride by thiophenoxide. Photolytic decomplexation followed by directed remote metallation of the diaryl sulfide yielded the heterocycle (Scheme 207) <2000SL975>.



Scheme 207

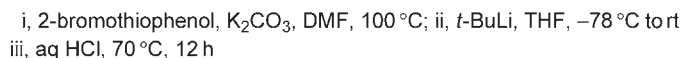
The same metallation methodology features in a synthesis of 1-dimethylaminothioxanthone 10,10-dioxide. A key step is the introduction of a 6-phenylsulfonyl group into 2-dimethylamino-*N,N*-diethylaminobenzamide by directed metallation (Scheme 208) <2002JOC3585>. Other substituted thioxanthone 1,1-dioxides have been accessed by the directed metallation of diarylsulfone 2-carboxamides (Equation 188) <1994JOC6508>, a neat variant on the standard route to xanthenes by the cyclization of benzoic acids.



Scheme 208



<2003JOC4091>.



Scheme 209

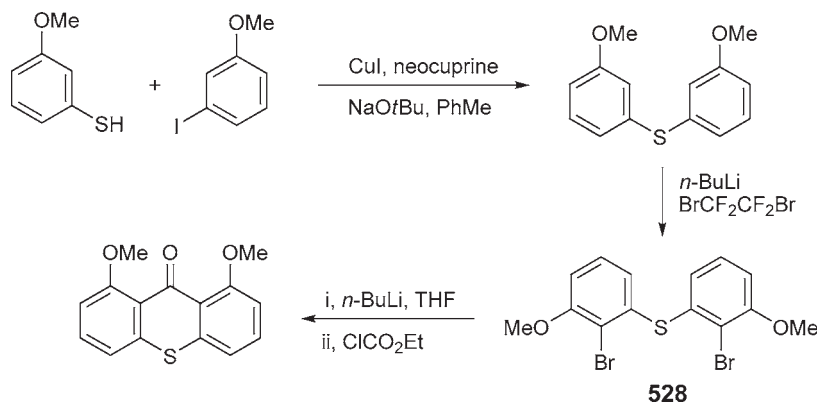
Hydroxythioxanthenes are readily obtained with good regioselectivity from the reaction of thiosalicylic acid with phenols effected by a mixture of methanesulfonic acid and alumina (Equation 189) <2004S2900>.



reaction with chlorosulfonic acid (Equation 190) <1995J CX321>.

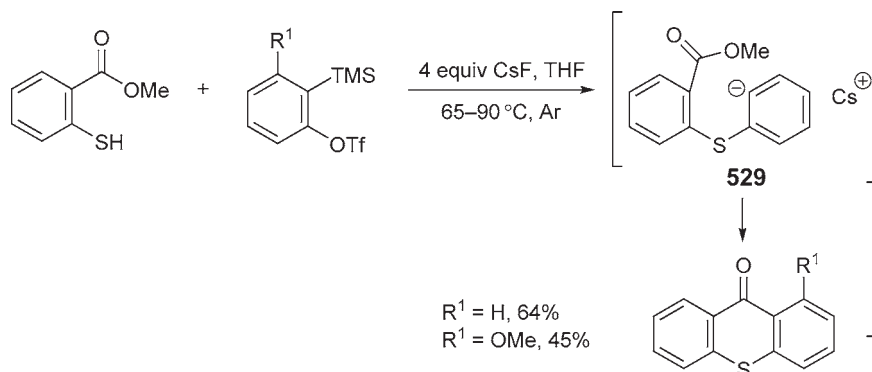


Dilithiation of the diarylsulfide **528** and reaction with methyl chloroformate affords the 1,8-disubstituted thioxanthone in ca. 40% overall yield from 3-methoxythiophenol (**Scheme 210**) <2005OL2739>.



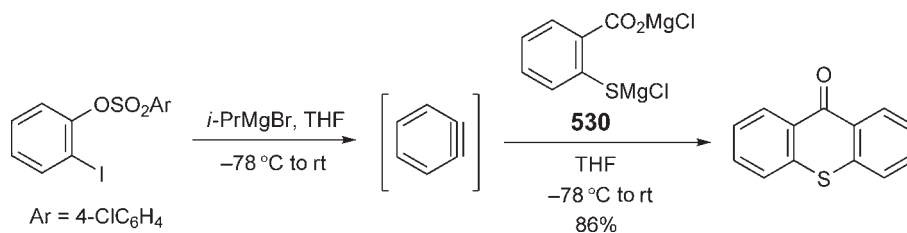
Scheme 210

Methyl thiosalicylate provides both electrophilic and nucleophilic sites for annulation of arynes generated from silylaryl triflates in the presence of CsF. An initial intermolecular nucleophilic coupling to afford a diaryl sulfide **529** is followed by an intramolecular electrophilic cyclization and thioxanthenes result. The use of THF as solvent suppresses the competitive proton abstraction which leads to methyl 2-thiophenoxybenzoate (**Scheme 211**) <2005OL4273>.



Scheme 211

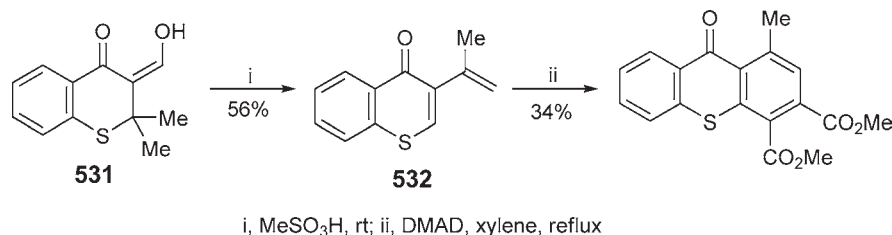
Benzyne generated from 2-iodophenyl 4-chlorobenzenesulfonate by treatment with *isopropyl* magnesium chloride at low temperature adds to the magnesium thiolate derived from thiosalicylic acid **530** to form thioxanthone. The carboxyl function behaves as an electrophile towards the intermediate aryl magnesium species and an intramolecular cyclization ensues (**Scheme 212**) <2005AGE4258>.



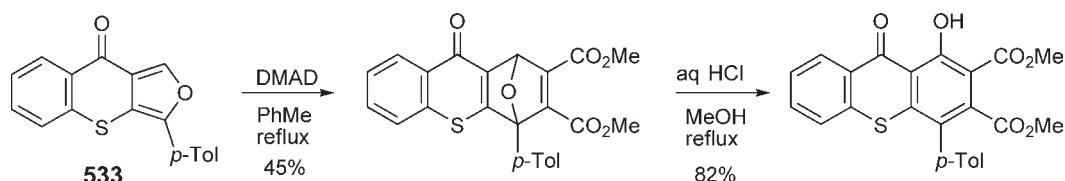
Scheme 212

7.10.4.3.6(iii) From a preformed heterocyclic ring

Rearrangement of the 3-hydroxymethylenethiochroman-4-one **531** by stirring in MeSO_3H yields 3-*isopropenyl*thiochromone **532**, which possesses a 1,3-diene unit. Reaction with various dienophiles yields the fully unsaturated thioxanthenes, offering a novel approach to the tricyclic system (Scheme 213) <2000J(P1)2930>. A variation of this novel methodology involves cycloaddition of DMAD to the furan ring of the furothiobenzothiopyran **533**. The initial cycloadduct undergoes facile hydrolysis to the red 1-hydroxythioxanthone (Scheme 214) <2002TL4507>.

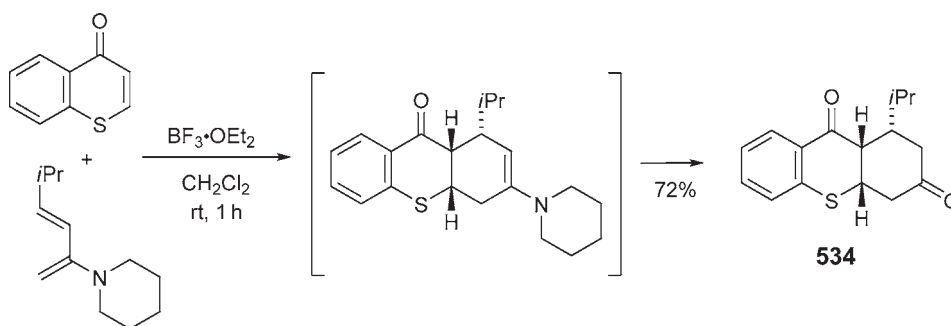


Scheme 213



Scheme 214

A good yield of the *cis*-fused hexahydrothioxanthen-3,9-one **534** results from the annulation of a 2-aminobuta-1,3-diene to thiochromone which is effected by $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 215) <1997J(P1)2807>.



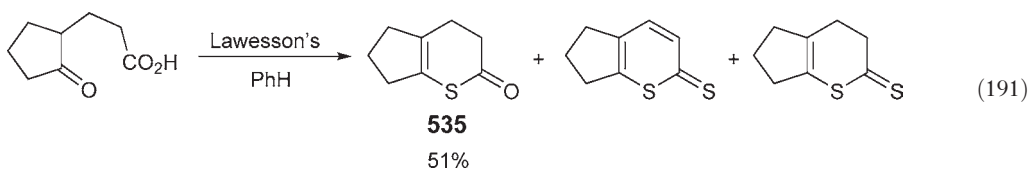
Scheme 215

7.10.4.4 Reduced Thiopyranones

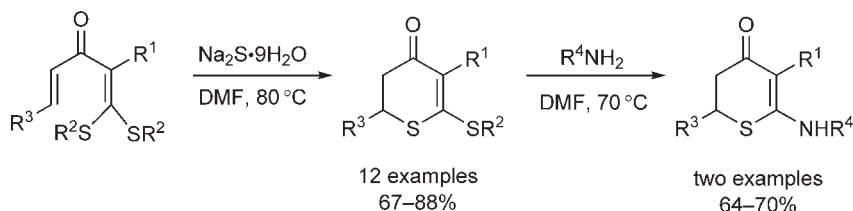
7.10.4.4.1 Dihydrothiopyranones

7.10.4.4.1(i) Formation of one bond

Treatment of 3-(2-oxocyclopentyl)propanoic acid with Lawesson's reagent gives 3,4-dihydrocyclopenta[*b*]thiopyran-2-one **535** together with smaller amounts of the thiones, cyclopenta[*b*]thiopyran-2-thione and a dihydrocyclopentathiopyran-2-thione (Equation 191) <1992DOK354>.

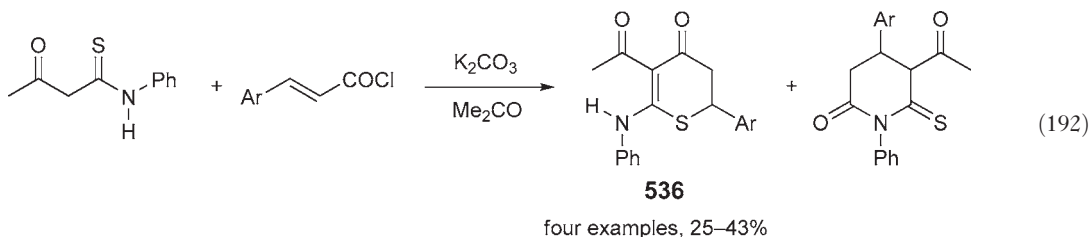


Highly substituted 2,3-dihydrothiopyran-4-ones are readily obtained through the reaction of α -alkenyl ketene-*S,S*-acetals with $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ in DMF. Further manipulation of the products is feasible (Scheme 216) <2005JOC10886>. The acetals, which behave as 1,5-biselectrophiles, are accessible through a base-catalyzed aldol reaction between aldehydes and α -acyl ketene-*S,S*-acetals <1991S15>.

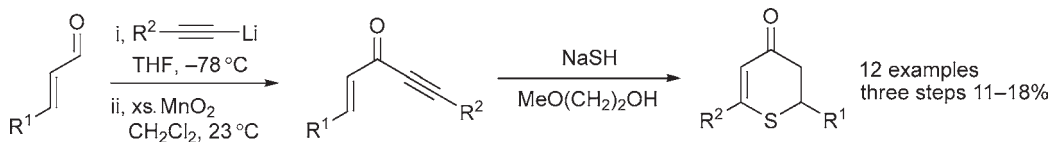


Scheme 216

Acylation of *N*-phenyl-3-oxobutanethioamide with 3-arylpropenoyl chlorides gives rise to a separable mixture of piperidin-2-ones and 2,3-dihydrothiopyran-4-ones **536** in approximately equal amounts. Acylation at C-2 is considered to compete with *N*-acylation and is followed by an intramolecular Michael addition (Equation 192) <2005RJO283>.



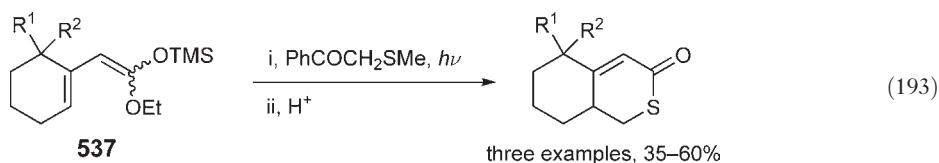
The synthesis of pent-4-en-1-yn-3-ones from alkynes involves their deprotonation and condensation with α,β -unsaturated aldehydes and subsequent oxidation of the allylic alcohol. A double thia-Michael addition occurs when the enynone is treated with sulfide which leads to 2,3-dihydrothiopyran-4-ones bearing different substituents at the 2- and 6-positions (Scheme 217) <2006TL5095>.



Scheme 217

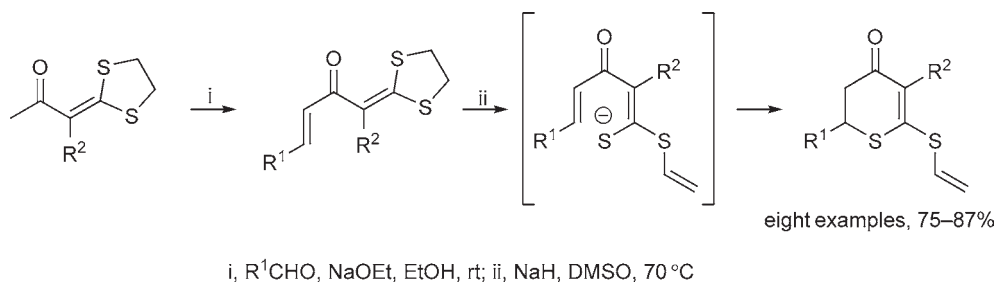
7.10.4.4.1(ii) Formation of two bonds

Irradiation of a mixture of the ketene acetal **537** and methyl phenacyl sulfide initiates a Diels–Alder cycloaddition via generation of thioformaldehyde which produces a 5,6-dihydrocyclohexa[*c*]thiopyran-2-one (Equation 193) <1997CJC681>.



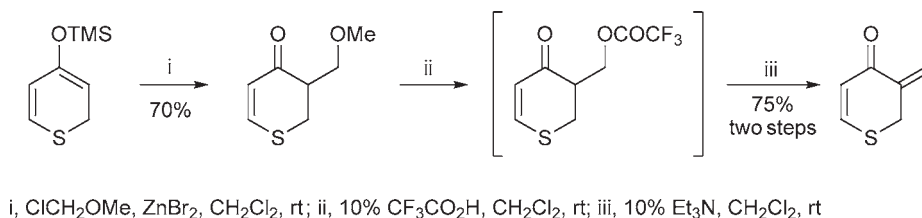
7.10.4.4.1(iii) From other heterocycles

Ring cleavage of α -alkenoyl cyclic ketene dithioacetals by dimethyl sodium generates a thiolate anion and induces an intramolecular Michael cyclization which produces 2,3-dihydrothiopyran-4-ones in good yields (**Scheme 218**) <2000SL1804, 2007S2115>.

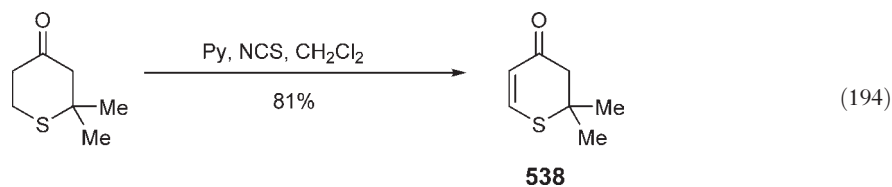
**Scheme 218**

7.10.4.4.1(iv) From a preformed heterocyclic ring

2,3-Dihydro-3-methylenethiopyran-4-one is available from the TMS enol ether of 2*H*-thiopyran-4-one by conversion to the 2,3-dihydro-3-methoxymethylthiopyran-4-one and successive treatment with trifluoroacetic acid and triethylamine (**Scheme 219**) <1996SL261>.

**Scheme 219**

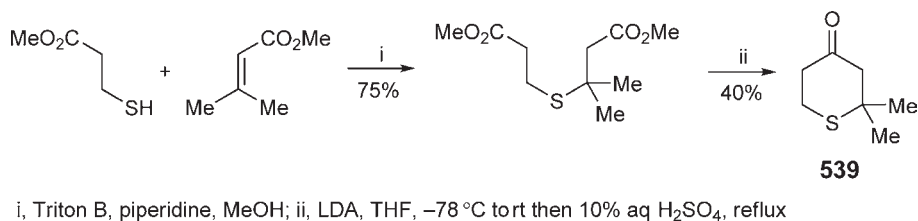
N-Chlorosuccinimide in pyridine effects the halogenation–dehydrogenation of tetrahydro-2,2-dimethylthiopyran-4-one to the 2,3-dihydro-4*H*-thiopyran-4-one **538** (Equation 194) <1992HCA1925>.



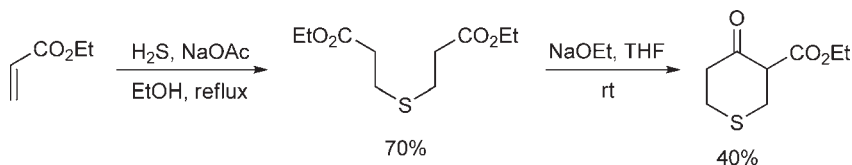
7.10.4.4.2 Tetrahydrothiopyranones

7.10.4.4.2(i) Formation of one bond

Michael addition of methyl 3-mercaptopropanoate to methyl 3-methylbut-2-enoate and Dieckmann cyclization of the resulting diester yields 2,2-dimethyltetrahydrothiopyran-4-one **539** (Scheme 220) <2005HCA1922>. Similarly, diethyl thiodipropionate, accessible from ethyl propenoate by treatment with NaSH in methanol, cyclizes to ethyl 4-oxotetrahydrothiopyran-3-carboxylate under basic conditions. The carbon skeleton has also been provided by 1,4-pentadienones <1995JOC1665> and H₂S in ethanol has been used as an alternative source of the heteroatom (Scheme 221) <1999SL735>.

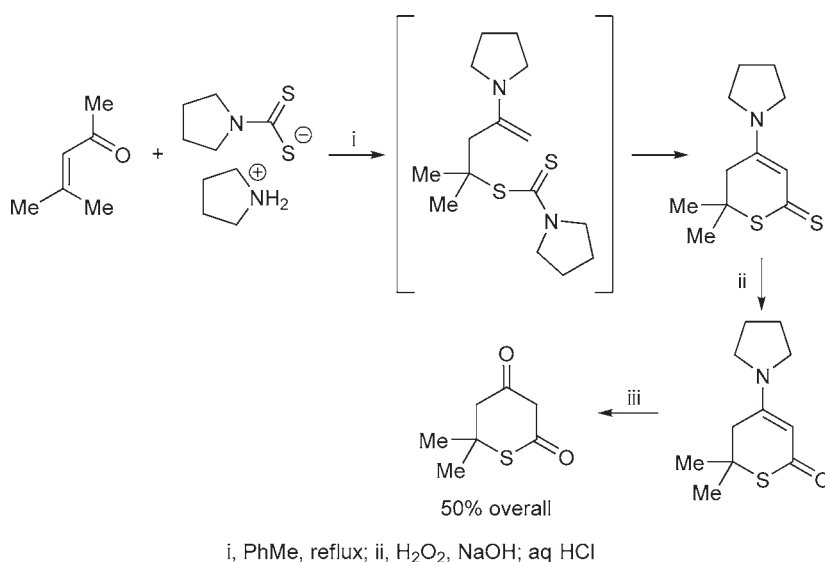


Scheme 220



Scheme 221

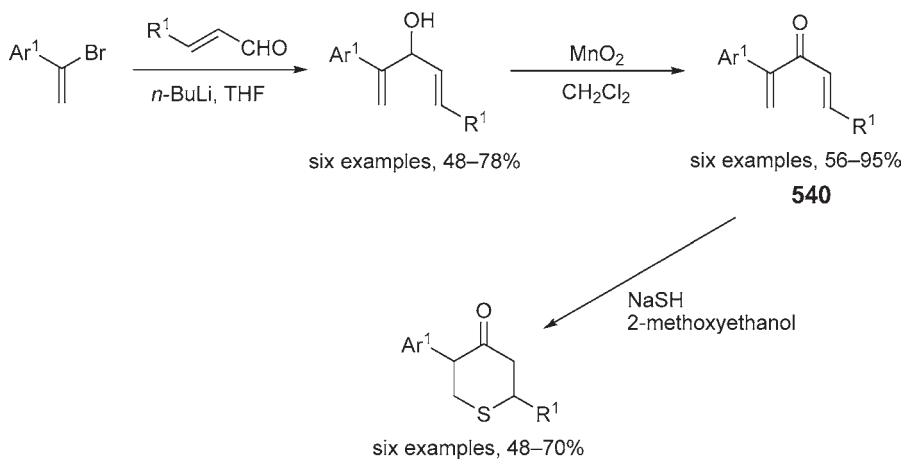
Sequential oxidation and hydrolysis of the enamine derived from the reaction between 4-methylpent-3-en-2-one and pyrrolidinium pyrrolidinedithiocarbamate affords 6,6-dimethylthiopyran-2,4-dione (Scheme 222) <2003RJO235>.



Scheme 222

7.10.4.4.2(ii) Formation of two bonds

The double conjugate addition of sulfide to the dienones **540** leads to 3-aryltetrahydrothiopyran-4-ones. The dienones are obtained from the reaction of electron-rich α -bromostyrenes with α,β -unsaturated aldehydes. When the latter is 3-phenylpropenal, a diastereomeric mixture resulted in which the *trans*-isomer was predominant (Scheme 223) <2006EJO4044>.

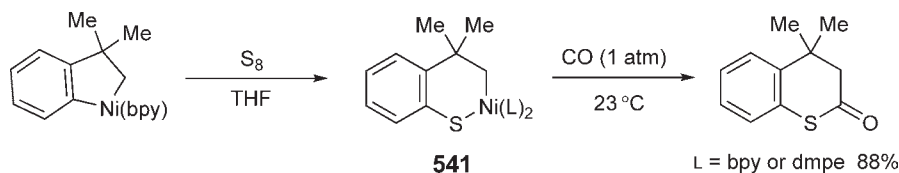


Scheme 223

7.10.4.4.3 Dihydrothiocoumarins

7.10.4.4.3(i) From other heterocycles

Incorporation of elemental sulfur into a Ni complex produces the thiametallacycle **541** which reacts with CO to give 4,4-dimethyl-3,4-dihydrothiocoumarin (Scheme 224) <1998JA7657>.

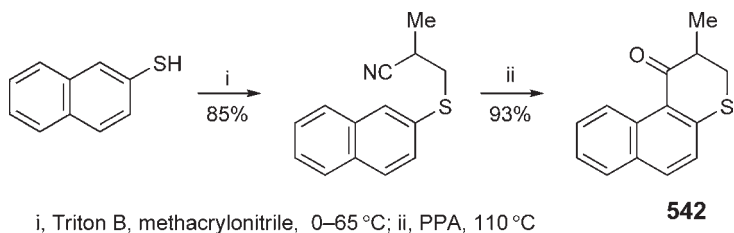


Scheme 224

7.10.4.4.4 Thiochromanones

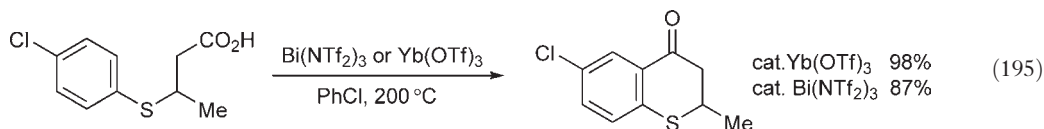
7.10.4.4.4(i) Formation of one bond

The base-catalyzed Michael addition of 2-thionaphthol to methacrylonitrile and cyclization of the product with PPA gives 2-methyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]thiopyran-1-one **542** (Scheme 225) <2002JA5037>.

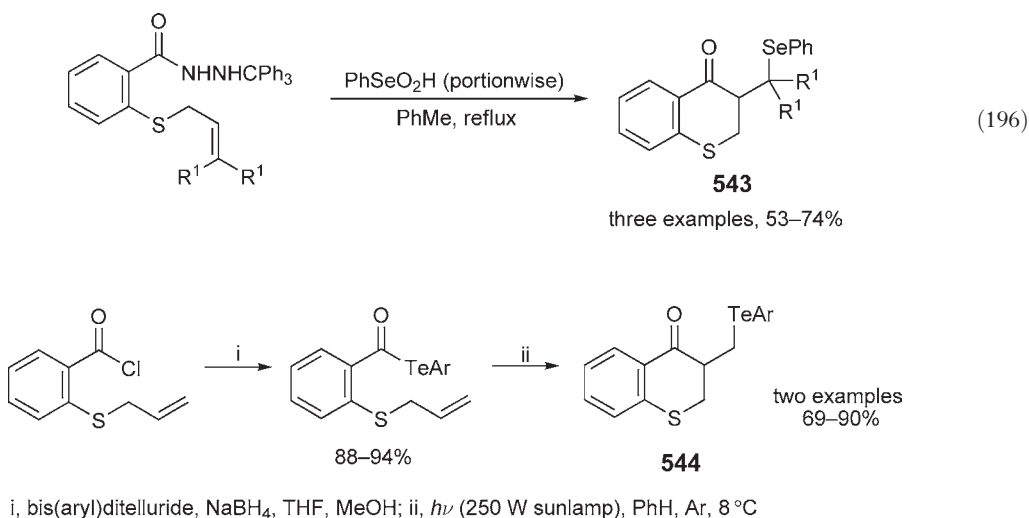


Scheme 225

The intramolecular Friedel–Crafts cyclization of 3-(4-chlorophenylthio)butanoic acid to 6-chloro-2-methylthiochroman-4-one is efficiently catalyzed by Bi and rare-earth triflates (Equation 195) <2003TL4007>. The cyclization of β -arylthiopropionic acids to thiochroman-4-ones by PPA is facilitated by microwave irradiation. Formation of these acids from the sodium salts of thiophenols and 3-chloropropionic acid is similarly accelerated <2004JCM394>.

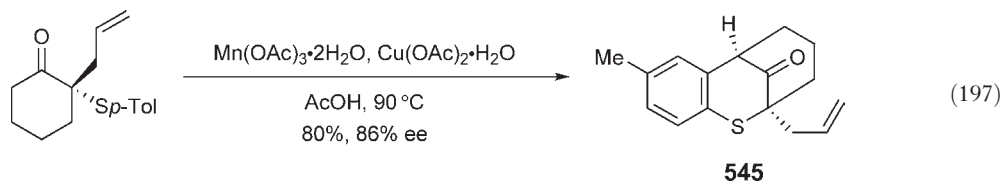


Acyl radicals generated by oxidation of triphenylmethylhydrazides, derived from *S*-allyl thiosalicyloyl chloride, with phenylseleninic acid and thermal decomposition of the resulting acylazo derivative have been trapped by the pendant alkene. The resulting thiochroman-4-ones **543** retain the phenylselenide moiety at the 3-position (Equation 196) <2003CC204>. The photolysis of aroyl tellurides, derived by the reduction of a bis(aryl) ditelluride and subsequent acylation with an aroyl chloride, also generates acyl radicals that cyclize to [3-(aryltelluro)methyl]thiochroman-4-ones **544** (Scheme 226) <1994JA8937>.



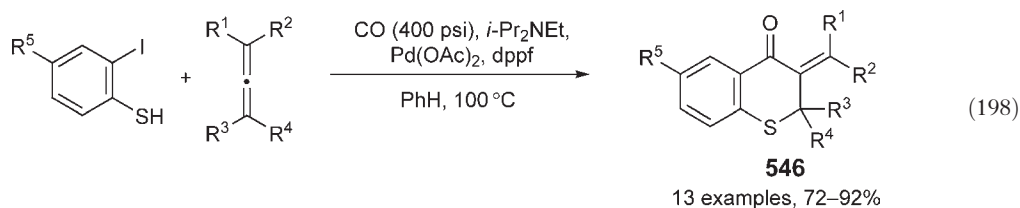
Scheme 226

2,4-Bridged derivatives of thiochroman-3-one **545** arise from the capture of the acyl radical generated by the Mn(III) oxidation of the thioether by the aryl ring rather than by the allyl group (Equation 197) <1999TA4427>.



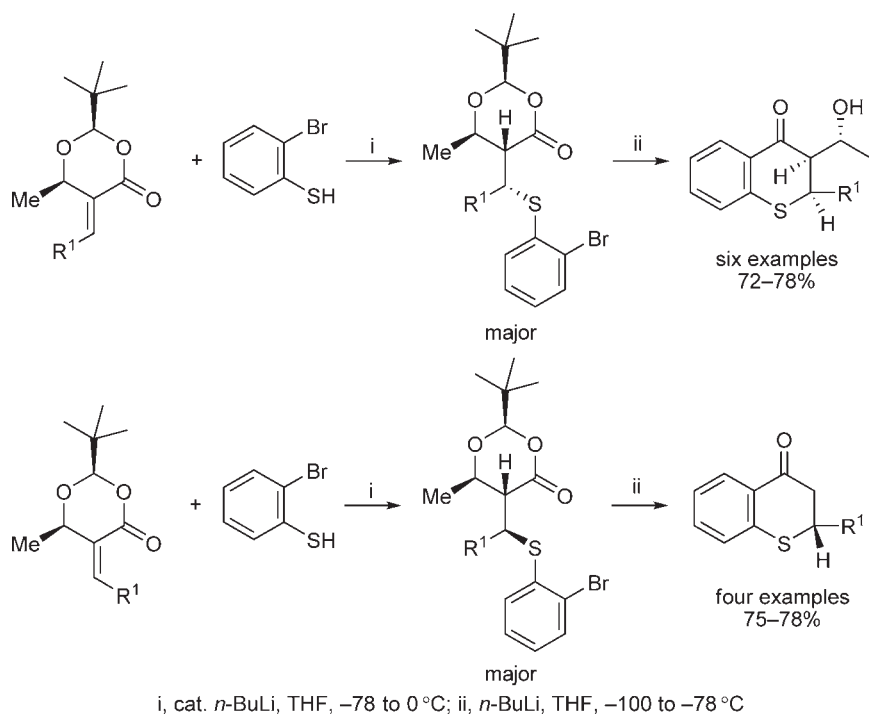
7.10.4.4(ii) Formation of two bonds

Allenes undergo a Pd-catalyzed regioselective carbonylative heteroannulation with 2-iodothiophenols and carbon monoxide and this offers an attractive route to 3-methylene-thiochromanones **546** (Equation 198) <1999JOC9646>.



7.10.4.4(iii) From other heterocycles

An asymmetric synthesis of thiochroman-4-ones involves the reaction of 2-bromothiophenols with chiral 5-alkylidene-1,3-dioxan-4-ones. Conjugate addition of the thiophenoxide ion gives a separable diastereomeric mixture of 5-[1'-(2-bromophenyl)sulfanylmethyl]dioxanones. Subsequent bromine–lithium exchange initiates attack at the carbonyl group resulting in formation of a thiochromanone and cleavage of the dioxane ring with loss of pivaldehyde. The actual product is dependent on the stereochemistry of the starting dioxanone, with the (*E*)-isomer giving a 3-(1-hydroxyethyl)thiochromanone. However, cyclization of the initial adduct from the (*Z*)-isomer is accompanied by a retro-aldol reaction and the 3-unsubstituted thiochromanone is obtained (**Scheme 227**) <2001EJO529>.

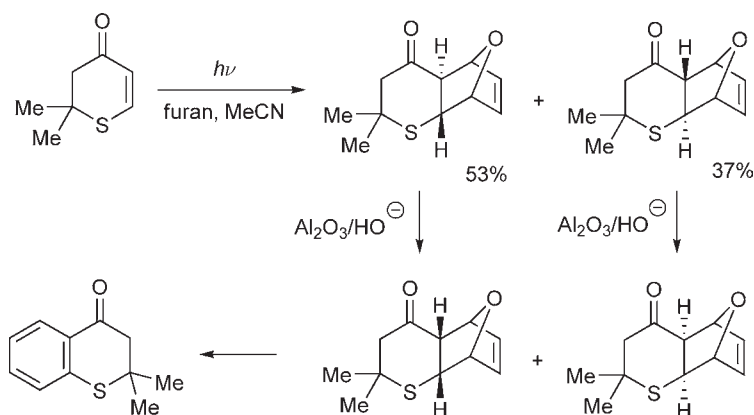


Scheme 227

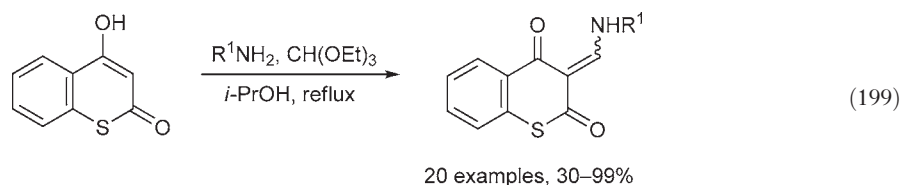
7.10.4.4(iv) From a preformed heterocyclic ring

The photocycloaddition of furan to 2,3-dihydro-2,2-dimethyl-4*H*-thiopyran-4-one gives a mixture in which the major products are two *trans*-fused [4+2] adducts. Prolonged stirring with basic alumina results in initial conversion to the *cis*-fused adducts and subsequently to 2,2-dimethylthiochroman-4-one (**Scheme 228**) <2005HCA1922>.

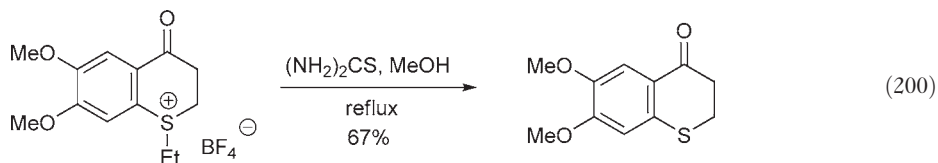
The reaction of 4-hydroxythiocoumarins with amines in the presence of triethyl orthoformate leads to 3-amino-methylenethiochroman-2,4-diones. A wide variety of primary amino compounds is compatible with the method, including ureas, carbamates, and α -aminoacids (**Equation 199**) <2004SC2053>.



Scheme 228



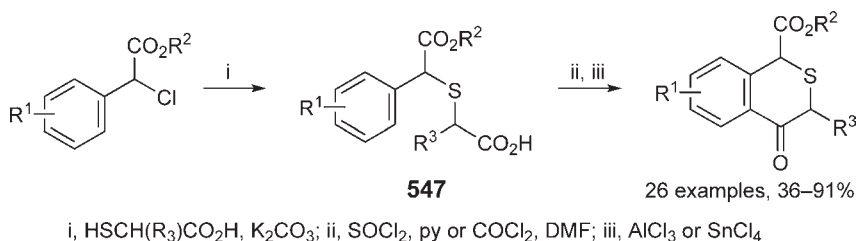
Treatment of a dihydrobenzothiopyranium salt with thiourea affords a thiochroman-4-one (Equation 200) <1998T5599>.



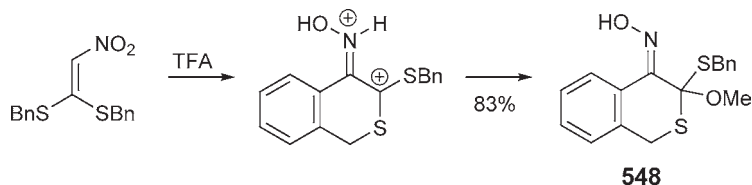
7.10.4.4.5 Isothiochromanones

7.10.4.4.5(i) Formation of one bond

Cyclization of the sulfides **547** under Friedel–Crafts conditions affords the 4-oxo-1*H*-2-benzothiopyran-1-carboxylates (Scheme 229) <1996JOM(507)215, 1999JME751> and treatment of 1,1-bis(benzylthio)-2-nitroethene with trifluoromethanesulfonic acid generates a dication which affords the isothiochroman-4-one oxime **548** upon quenching with MeOH (Scheme 230) <2001EJO1525>.

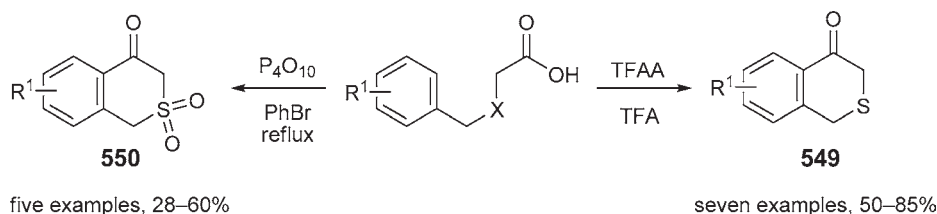


Scheme 229



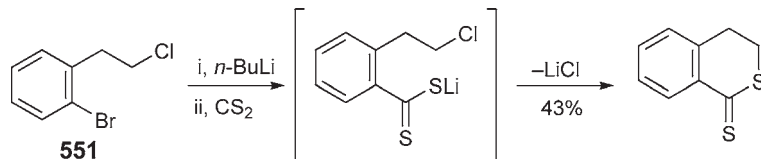
Scheme 230

Isothiochroman-4-ones **549** have been obtained by the cyclization of *S*-arylmethylacetic acids <1996BML2827>. The influence of substituents on the reaction time and temperature was noted; with electron-releasing substituents the reaction was complete in ca. 1 h at rt, but with F or Cl substituents the reaction required prolonged reflux. Benzyldisulfonylacetic acids are cyclized by P₄O₁₀ to the corresponding isothiochroman-4-one 2,2-dioxides **550** (Scheme 231) <2004SC2691>.



Scheme 231

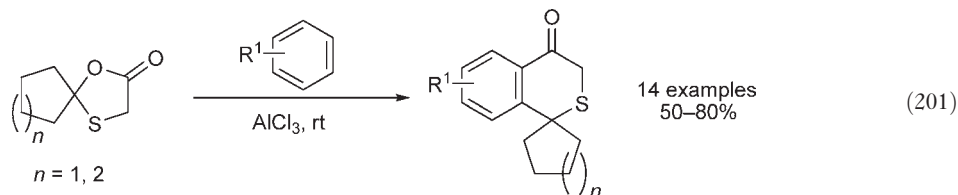
A direct synthesis of isothiochroman-1-thione involves the sequential treatment of 2-(2-bromophenyl)-1-chloroethane **551** with BuLi and CS₂, whereupon an intramolecular alkylation leads to the product (Scheme 232) <1992CB127>.



Scheme 232

7.10.4.4.5(ii) From other heterocycles

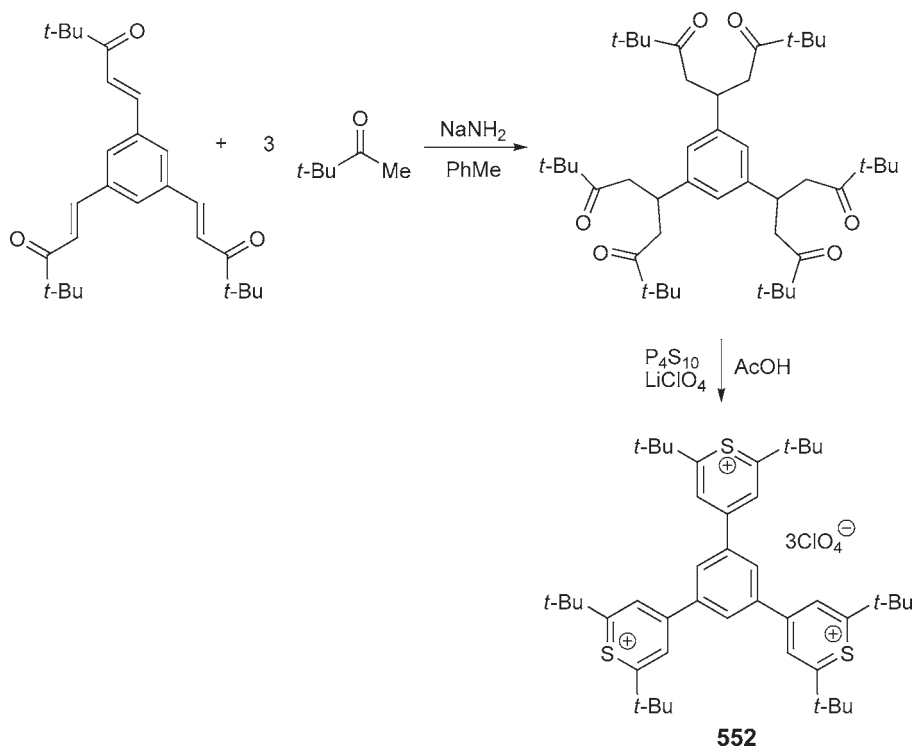
Both 1-oxa-4-thiaspiro[4.4]nonan-2-one and the corresponding [4.5]decan-2-one react with various aromatic compounds in the presence of AlCl₃ to give spiro[cycloalkane-1,1'-isothiochroman]-4'-ones. The synthesis proceeds through tandem inter- and intramolecular Friedel–Crafts reactions following initial cleavage of the O–C spiro linkage (Equation 201) <1992PS(66)311>.



7.10.4.5 Thiopyrylium Salts and Their Benzo Derivatives

7.10.4.5.1 Formation of one bond

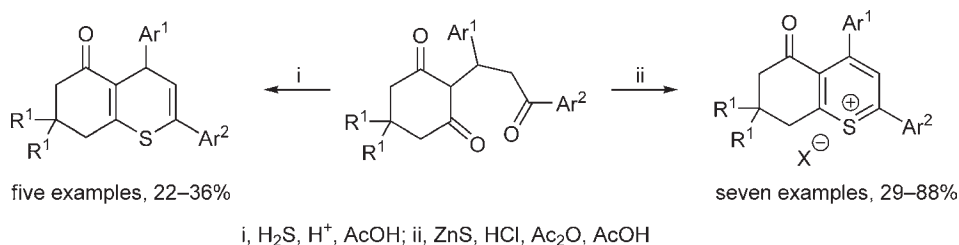
An improved route to both bis- and tris- thiopyrylium salts **552** involves the initial Michael addition of pinacolone to a bis-enone and tris-enone, respectively, promoted by NaNH_2 in toluene. The resulting pentandione derivatives are then cyclized by reaction with P_4S_{10} in the presence of LiClO_4 (Scheme 233) <2005JOC6422>.



Scheme 233

Adsorption of 2,4,6-triphenylpenten-1,5-dione onto thermally dehydrated zeolites presaturated with H_2S enables the thermal ring closure to a thiopyrylium salt to be achieved within the cavities. The result is encapsulated thiopyrylium salts in which the counter ion is derived from a hydroxyl group of the zeolite cage and which are suitable for use as photosensitizers <2004NJC631>.

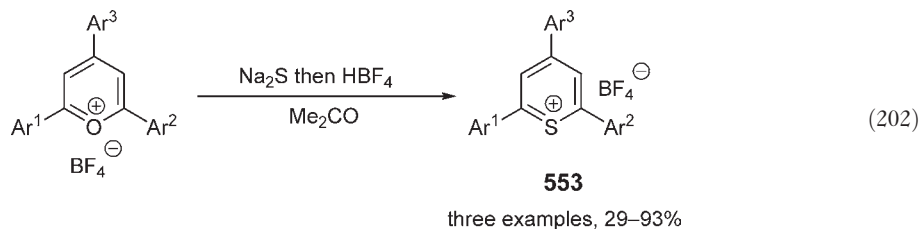
The cyclization of 2-(1,3-diaryl-3-oxopropyl)cyclohexan-1,3-diones to cyclohexeno[*b*]thiopyrylium salts by H_2S generated *in situ* from ZnS and acid is only successful with electron-rich aryl substituents. It is suggested that the reaction proceeds through the cyclohexeno[*b*]-4*H*-thiopyran which is produced in the absence of donor substituents and which yields the thiopyrylium salt on treatment with HClO_4 (Scheme 234) <2000CHE1032>.



Scheme 234

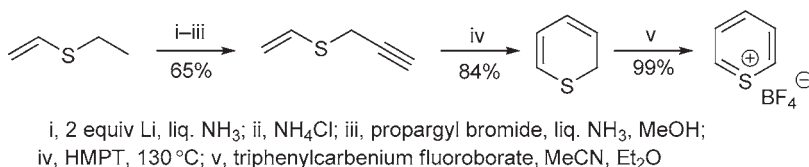
7.10.4.5.2 From other heterocycles

Provided electron-withdrawing groups are absent from the aryl substituents, pyrylium salts are converted into thiopyrylium salts **553** by reaction with Na₂S and HBF₄ (Equation 202) <1996J(P2)307, 2002JPO689, 2006EJO2644>.



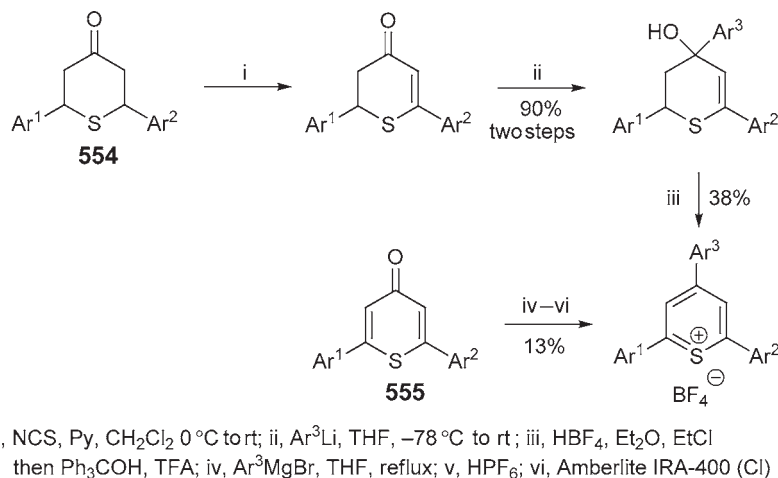
7.10.4.5.3 From a preformed heterocyclic ring

2*H*-Thiopyran, derived from ethyl vinyl sulfide, is converted into thiopyrylium fluoroborate by reaction with triphenylcarbenium fluoroborate in 54% overall yield (Scheme 235) <2001EJO2477>. 3-Benzoylisoethiochromene is oxidized to the 2-benzothiopyrylium salt in a similar manner <1994J(P1)3129>.



Scheme 235

2,4,6-Triarylthiopyrylium salts are accessible from 2,6-diaryltetrahydrothiopyran-4-ones **554** through sequential dehydrogenation with NCS in pyridine, reaction of the resulting 2,3-dihydrothiopyran-4-one with an aryllithium reagent and aromatization with HBF₄ and Ph₃COH <2002JPO689>. A similar approach to 2,4,6-tris(4-dialkylaminophenyl)thiopyrylium salts starts from a 2,6-bis(4-dialkylaminophenyl)pyran-4-one **555**, an acid catalyzed dehydration following reaction with 4-dialkylaminophenylmagnesium bromide (Scheme 236) <2002JME5123>. Improved yields result when HCl gas is bubbled into the reaction mixture after addition of the Grignard reagent <2004BMC2589>.



Scheme 236

7.10.5 Applications

Compared with either the nitrogen or oxygen six-membered heterocyclic systems, applications associated with the sulfur-containing rings remains a relatively uncultivated area. Perhaps the most significant reasons for this underrepresentation are (i) the poor diversity of commercially available sulfur-containing building blocks, (ii) the difficulties associated with their handling because of malodorous properties and their propensity to disulfide formation and oxidation, and (iii) the lack of naturally occurring six-membered sulfur-containing heterocyclic systems; oxygen- and nitrogen-containing natural products have for so long provided challenging synthetic targets for academic research groups and have also guided 'active molecule' design by pharmaceutical and agrochemical companies.

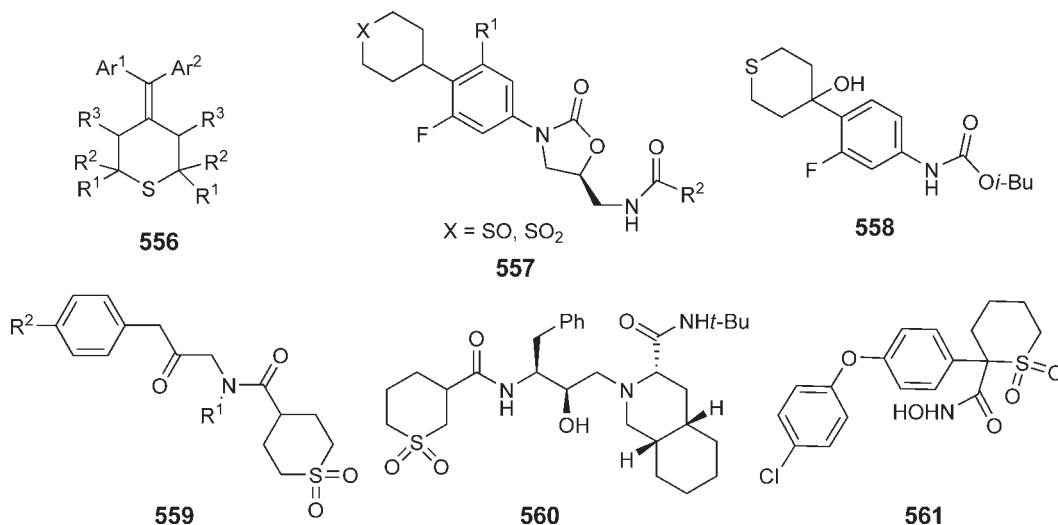
Where sulfur perhaps has the advantage over oxygen and nitrogen heteroatoms is in the materials and dyes arenas where its variable valency and dual behavior as a good electron donor and acceptor have much to offer.

7.10.5.1 Pharmaceutical and Biological Applications

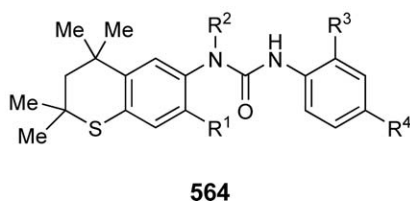
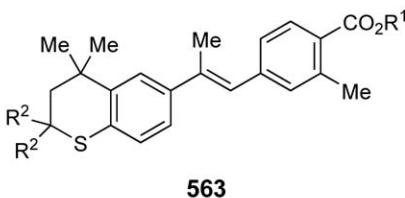
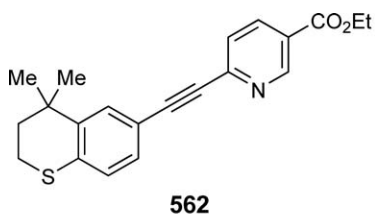
7.10.5.1.1 Thiopyrans, thiopyrylium salts and their benzologues

The thiopyran ring continues to be investigated alongside pyrans, where replacement of the oxygen atom by sulfur enables subtle manipulation of the physical parameters of biomolecules.

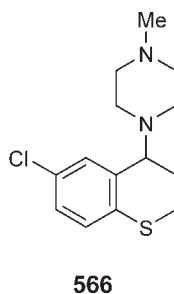
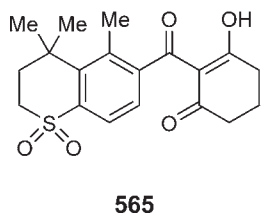
1,1-Diarylthiopyranlylidene derivatives **556** are useful estrogen receptor modulators <2005WO2005/012220>. 4-Aryl-substituted tetrahydrothiopyran 1-oxides and 1,1-dioxides feature as pendant groups in the antimicrobial oxazolidinones **557** <1999WO9929688>; the synthesis of the key intermediate, a 4-hydroxythiopyran **558**, has been optimized <2001OPD80>. 4-Acylthiopyran 1,1-dioxides **559** showed inhibitory activity in herpes simplex virus infected mice <2005USP2005032855> and 3-acylthiopyran 1,1-dioxides, for example, **560**, display HIV protease inhibition <1994WO9414793>. In an *in vitro* assay the 2-[4-(4-chlorophenoxy)phenyl]thiopyran 1,1-dioxide **561** suppressed metalloproteinase 13 activity <2000WO2000040576>. The preparation of (1*R*,2*S*)-3,4,5,6-tetrahydro-2-(3-pyridyl)-2*H*-thiopyran 1-oxide, a key intermediate for the synthesis of a range of hypertensive agents, involving a biomediated stereoselective reduction has been described <1995WO9511900>.



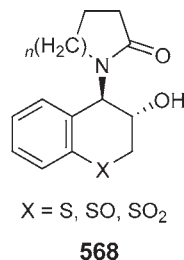
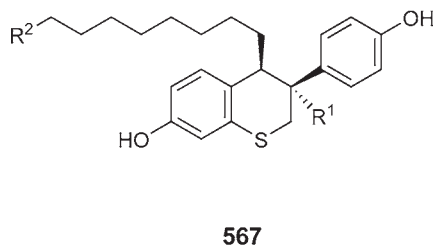
The 4,4-dialkyl-2*H*-1-benzothiopyran motif features in the diheteroarylethyne, Tazarotene **562**, a member of a new generation of receptor selective, synthetic retinoids that are topically effective in the treatment of acne, psoriasis, and photoageing <1997USP5602130>. Efficient synthetic strategies to 6-halo- <1995USP5420295> and 6-ethynyl- <2005USP2005004373> 3,4-dihydro-4,4-dimethyl-2*H*-1-benzothiopyran, key intermediates in the synthesis of Tazarotene, have been protected and complementary transition metal catalyzed coupling approaches have been optimized <2005OPD646>. Two series of heteroarotinoids **563** <1999JME4434, 2005PS(180)67> and **564** <2003CNR3826, 2003USP6586460> containing the 3,4-dihydro-4,4-dimethyl-2*H*-benzothiopyran unit have been synthesized and each has been shown to inhibit head and neck cancer cell lines through activation of retinoic acid receptors.



6-Acyl- and 6-heteroaryl- derivatives of 2*H*-1-benzothiopyran 1,1-dioxides, for example, **565** display significant herbicidal activity <1997JPP09025279, 2001WO2001029033, 2001WO2001044236> which is retained when the geminal dimethyl groups are absent <1999WO9933820>. Processes for the efficient preparation of thiochroman-4-ones using catalytic amounts of Lewis acids to cyclize 3-phenylthiopropionic acids <2004JPP2004189695> and for the synthesis of thiochroman-6-carboxylates, key intermediates for the preparation of 6-heteroarylthiochroman derived herbicides <1997WO9708163, 2001WO2001040176>, have been described. Formulations containing 4-(4-methylpiperazino)thiochroman **566** are effective for the control of nematode and insect pests <2004WO2004080170>.

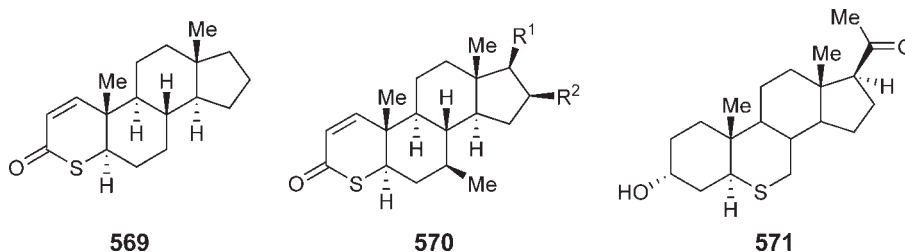


The *cis*-3,4-disubstituted 2*H*-1-benzothiopyran moiety has received significant attention since appreciable anti-estrogenic activity is observed for 4-alkyl-3-(4-hydroxyphenyl)-7-hydroxy analogues **567** which renders these compounds of interest for the treatment of breast cancer <1998WO9825916, 1999WO9965893, 2001WO2001042233, 2001WO2001042235, 2001WO2001042236>. Interestingly, *trans*-4-amino-2*H*-1-benzothiopyran-3-ols **568** are effective antihypertensives and bronchodilators that reduce systolic blood pressure in rats by ca. 20% 1 h after administration <1989EPP322251>.

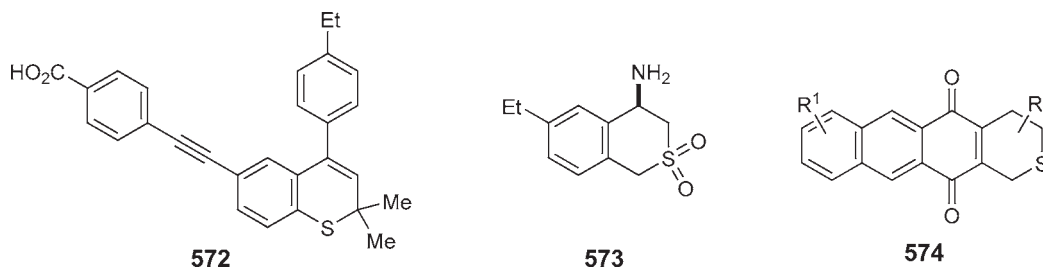


Both substituted 3-amino-2*H*-1-benzothiopyrans <1995EP648741> and 4-acyl-4-hydroxy-2*H*-1-benzothiopyrans <2001WO2001087879> inhibit thrombin activity and thus behave as anticoagulants and 4-(SCH₂CONR₂) derivatives of 3,4-dihydro-2*H*-1-benzothiopyran 1-oxide have been claimed as treatments for excessive sleepiness and fatigue <2005USP2005228040>.

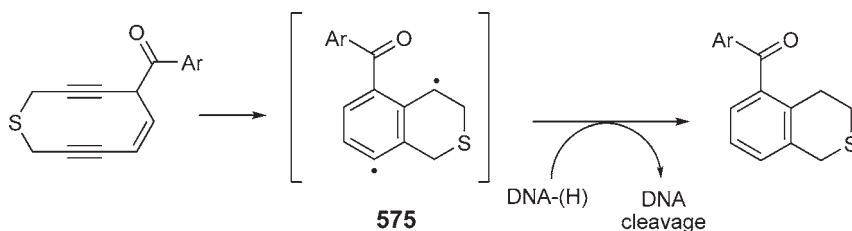
The selective replacement of C-atoms in steroid systems with sulfur has attracted moderate interest with 4-thiasteroids **569** and **570** proving useful for the treatment of hyperandrogenic conditions <1997WO9715305, 1997WO9715564>. γ -Aminobutyric acid activity comparable to that exhibited by natural neurosteroids is displayed by the 6-thia analogues **571** of allopregnanolone <2006T4762>.



Derivatives of 6-amino-2*H*-1-benzopyrans are retinoic acid receptor agonists <2001WO2001070668, 2003USP2003166932> and the 4-aryl-2,2-dimethyl-2*H*-1-benzothiopyran **572** inhibits spermatogenesis in mammals <2000WO2000019990>. The 4-amino-1*H*-2-benzothiopyran 1,1-dioxide **573** inhibits β -secretase which is responsible for the deposition of A- β protein in the cortex or plasma, increased deposition of which is associated with Alzheimer's disease <2005WO2005/087714, 2005WO2005/095326>. The sulfur-containing anthracycline analogue **574** displays anti-cancer properties and also may be used for the *ex vivo* treatment of cancerous bone marrow prior to retransplantation <1997USP5593970>.

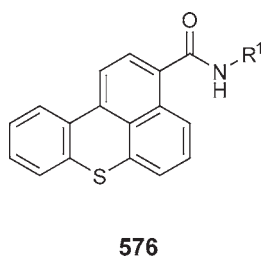


The isothiochroman diradical **575** bearing a DNA intercalating aryl moiety and formed during the cyclization of an ene-diyne has been demonstrated to preferentially cleave purine bases in DNA (Scheme 237) <1995JA4822>.

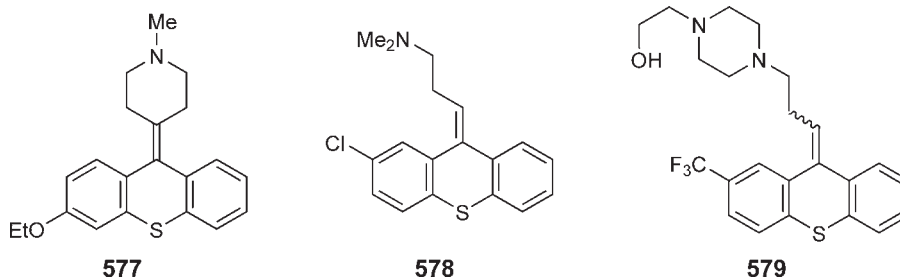


Scheme 237

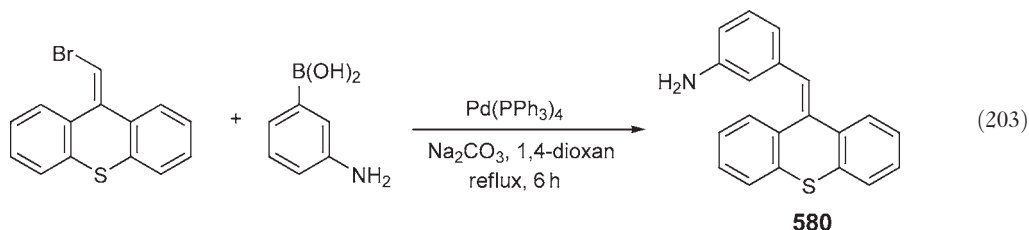
Benzothioxanthene carboxamides **576** efficiently photocleave DNA by a process involving the superoxide anion <2005T8711>.



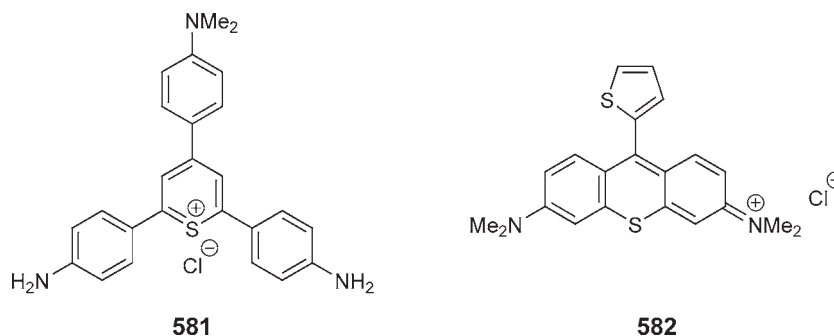
Derivatives of 9-acyl-9*H*-thioxanthenes modulate G-protein coupled metabotropic glutamate receptors <2002FA989> and also behave as chemokine receptor antagonists <1998WO9804554>. 9*H*-Thioxanthene-9-ylidenes, for example, **577**, are of value for the treatment of diseases which are responsive to 5-HT_{2B} or H₁ receptor antagonists <2002WO2002102797>. Related 9*H*-thioxanthene-9-ylidenes such as chlorprothixene **578** is useful for the treatment of smallpox virus in humans <2005WO2005/030125> and flupentixol **579** inhibits multidrug efflux pump activity in *Staphylococcus aureus* <1998JME1815>.



Arylidene thioxanthenes, for example, **580**, prepared by the Pd(0) coupling of 9-bromomethylenethioxanthene and 3-aminophenylboronic acid, are useful for treating congestive heart disease, hypertension, and inflammatory diseases (Equation 203) <2005WO2005/066153>.



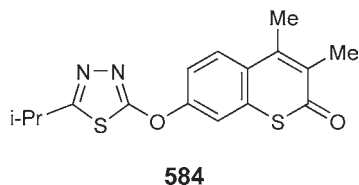
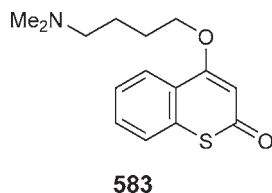
Several series of thiopyrylium dyes have been examined as potential candidates for the photodynamic therapy of cancer <1995EP659407, 1999JME3942, 1999JME3953, 2000JME4488> with the 2,6-bis-(4-aminophenyl)thiopyrylium salt **581** behaving as a mitochondrial specific anti-tumor agent under visible light irradiation <1994CNR1465>. This salt also shows significant whole-cell mitochondrial cytochrome *c* oxidase activity in the dark <2004BMC2589>. These aminophenyl-thiopyrylium dyes are of interest since they typically absorb above 600 nm, behave as photosensitizers with good quantum yields for the formation of singlet oxygen and possess reasonable lipophilicity. In addition to their use in cancer therapy, thiopyrylium <2005MI752> and thioxanthylum salts **582** <2005BMC5927> have also been explored for the photodynamic disinfection of blood.



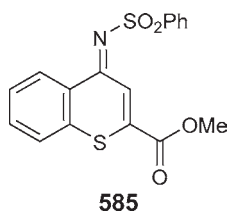
Thiopyrylium salts have been employed for the stabilization of triple-stranded nucleic acids thereby improving gene therapy <1998JPP10257889> and are also reported to mediate trans-membrane charge transport with high efficiency via a cyclic process in which reversible hydroxide ion cleavage of the thiopyrylium ring operates to produce neutral membrane permeable species <2001JA7352>.

7.10.5.1.2 Thiopyranones and their benzologues

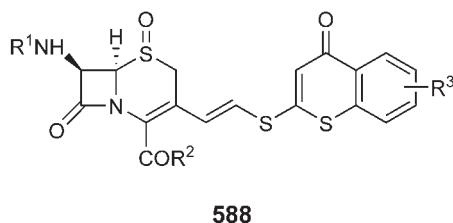
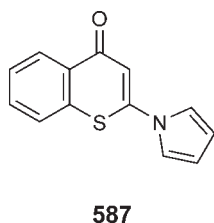
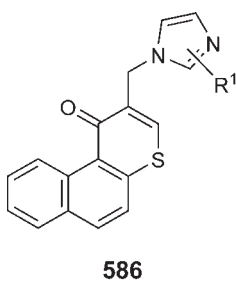
Tricyclic thiopyran-2-one derivatives are useful in the development of therapies for the treatment of viral infections and diseases including AIDS <1996USP5504104>. The thiocoumarin **583** has been identified as a weak inhibitor of inducible nitric oxide synthase <2005BMC2723> and the (1,3,4-thiadiazol-5-yl)thiocoumarin **584** is active against monoamine oxidase B in rat brains <1994EPP594036>.



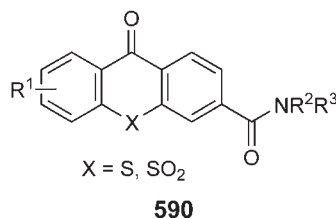
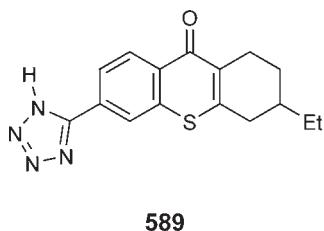
4-Tosyliminothiochromone-2-carboxylates **585** are inhibitors of interleukin-1 and are thus useful for the treatment of rheumatoid arthritis, multiple sclerosis, diabetes mellitus, atherosclerosis and septic shock <1995WO9514670>, and thiochromones possessing a sulfamoyloxy side chain at either C-6 or C-7 behave as steroid sulfatase inhibitors <1999WO9952890>.



Thiochromones that are substituted with an *N*-containing heterocyclic moiety at either the 2- or 3-position have received some attention since compounds **586** and **587** are useful for the treatment of stress-induced sexual dysfunction <1998JPP10120565>, display anti-emetic behavior through antagonism of the 5-hydroxytryptamine₃ receptor <1995EPH37> and possess some anti-cancer activity by inhibiting matrix metalloproteinase in human fibrosarcoma cells <1997EPP758649>. The thiochromone tethered cepheids **588** display *in vitro* antibacterial activity against *Staphylococcus aureus* <1998WO9829416>.



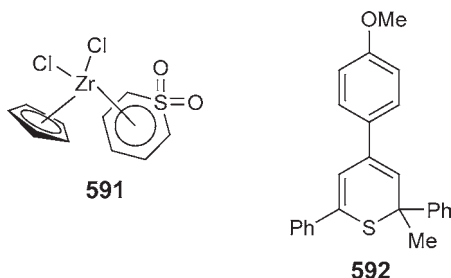
1,2,3,4-Tetrahydro-6-(5-tetrazolyl)-9H-thioxanthen-9-ones **589** are antagonists of metabotropic glutamate receptors and are useful for the treatment of pain <2002DEP10126434> and variously substituted 3-amidothioxanthenes and their 1,1-dioxides **590** are selective inhibitors of monoamine oxidase <1997JME2466>.



7.10.5.2 Materials Applications

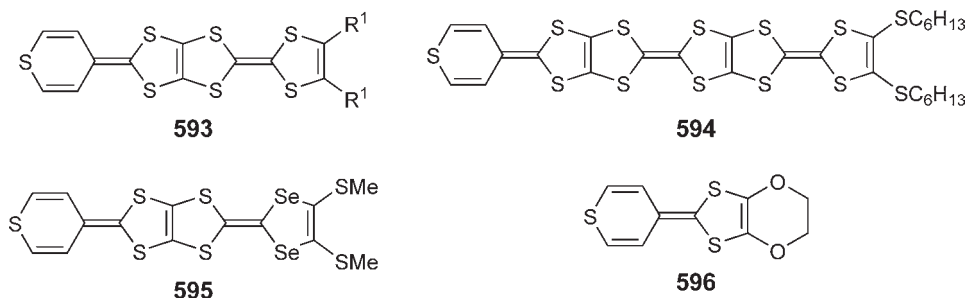
7.10.5.2.1 Thiopyrans, thiopyrylium salts and their benzologues

The anions derived from 2*H*-thiopyran 1,1-dioxides behave as ligands for various transition metal single site catalysts **591** that are employed for the polymerization of olefins <2002USP2002156211>. A nickel(II) ion selective PVC-membrane electrode based on the 2,6-diphenyl-2*H*-thiopyran **592** has been described. The electrode exhibits a Nernstian response over a wide concentration range of Ni^{2+} with a lower detection limit of $9 \times 10^{-6} \text{ M}$ and a response time of ca. 10 s <2000ELA1138>.

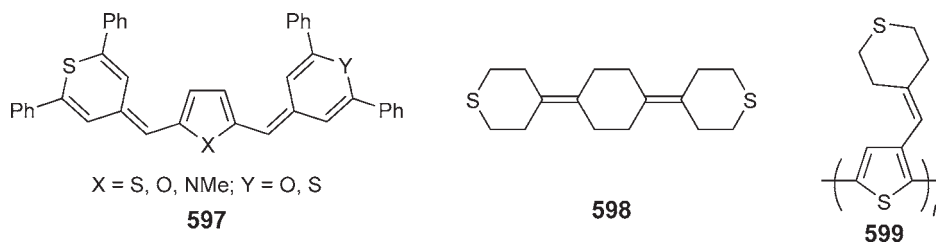


The planarity of the thiopyran-4-ylidene moiety has proved crucial in the development of substituted analogues for use in materials, for example, synthetic metals, organic light emitting diodes and conducting polymers, where good electron transport properties are required.

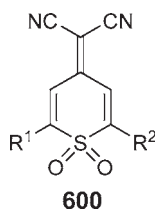
2-(1,3-Dithiol-2-ylidene)-5-(thiopyran-4-ylidene)-1,3,4,6-tetrathiapentalene derivatives **593** have been synthesized and both their TCNQ complexes and cation radical salts show relatively high (10^{-1} – 10^2 S cm^{-1}) electrical conductivity. Several of the salts show metallic temperature dependence of conductivity <1995SM(70)1147>. Cyclic voltammograms of **593** exhibit four pairs of single electron redox waves and the first oxidation potential is comparable to that of tetrathiafulvalene <1996JOC3650>. In a search for improved conductance properties the extended analogue **594**, which contains six redox-active sites, <1999SM(102)1737> and the 2-(1,3-diselenol-2-yl) analogue (TM-TPDS) **595** that displays metallic conductivity down to 4.2 K <1999SM(102)1621> have been evaluated. Single crystals of the latter compound [(TM-TPDS)₂AsF₆], grown by electrochemical oxidation of TM-TPDS in the presence of (*n*-Bu)₄NAsF₆ in 1,2-DCE containing EtOH, have a three-dimensional donor array and show metallic conductance down to 100 K <2000CL1274>. The donor molecule TP-EDOT **596** forms a 2:1 complex with PF₆[−] which is a Mott insulator and which displays antiferromagnetic behavior and the crystalline complex (TP-EDOT)₃Sb₂F₁₁(PhH) is semiconducting with a low lying electronic transition at $\sim 5000 \text{ cm}^{-1}$ which indicates a charge disproportionated ground state <2006JMC550>.



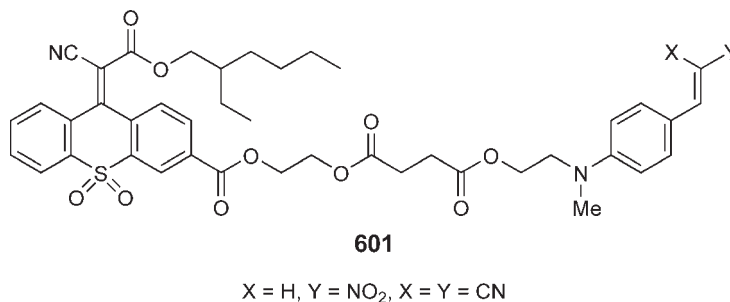
Good π -donor ability and large third-order nonlinear optical susceptibilities were measured for the bis-(thiopyran-4-ylidene) systems **597**. Additionally, high electrical conductivities of TCNQ salts derived from these compounds were observed which suggest that these compounds have potential as organic metals <1994CL255>. The temperature dependence of electron transport in the σ - π - σ conjugated system **598** has been studied over the range 10–300 K. For low bias voltages, temperature independent transport was observed below the crossover temperature of ca. 150 K; above this, the current increases exponentially with the inverse temperature <2006MI1031>. The polythiophene bearing a tetrahydrothiopyran-4-ylidene side-chain **599** exhibits a good affinity for the surface of CdTe quantum dots, resulting in strong fluorescence quenching and reduced fluorescence lifetimes <2006CEJ8075>.



Electron mobilities of thin films of 2,6-disubstituted 4-(dicyanomethylidene)-4*H*-thiopyran 1,1-dioxides **600**, conveniently obtained by the condensation of malononitrile with the appropriate 4*H*-thiopyran-4-one 1,1-dioxides <1995JOC1665>, were found to increase with increasing planarity of the 4-(dicyanomethylidene)-4*H*-thiopyran 1,1-dioxide unit and increased π -delocalization. Electrochemical reduction to the colored anion radicals and EPR spectra of anion radicals were reported <1995JOC1674> and electrochromic behavior of these compounds has been claimed for a variety of applications <2005USP2005219678>. The good electron transport properties of 2,6-diaryl derivatives of **600** have been studied in a wide variety of devices, such as light-emitting diodes <1995MI5619>, photorefractive <1999MI6506> and conducting <1996PSB575> polymers and single layer photoreceptors for copying and printing devices <2006SM(156)476>.



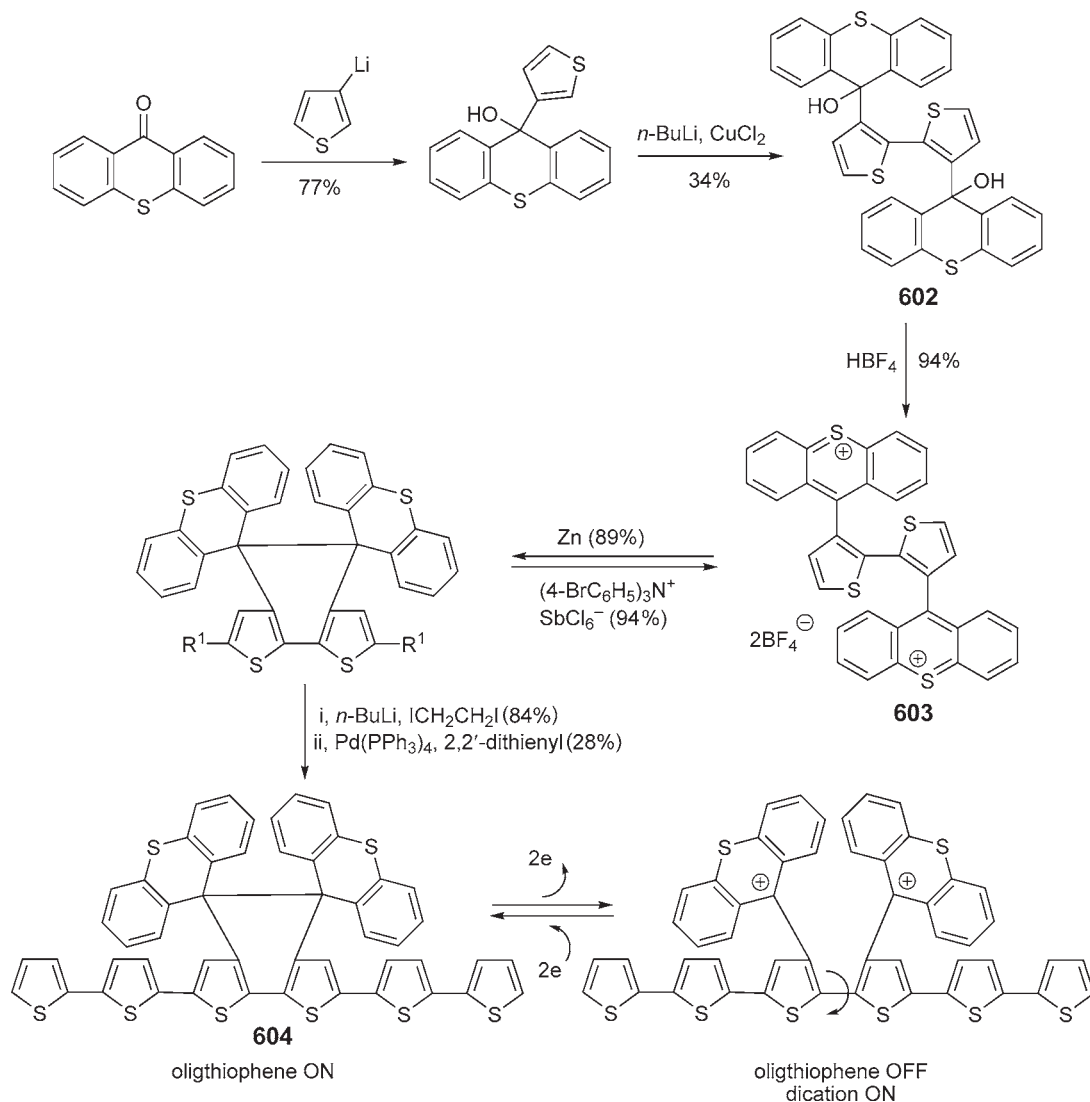
The electron transporting 9-(dicyanovinyl)thioxanthene moiety and electrooptically active vinylaniline units have been combined in the succinate esters **601**. The compounds exhibit good photorefractive properties with high optical quality <2003SM(139)11>.



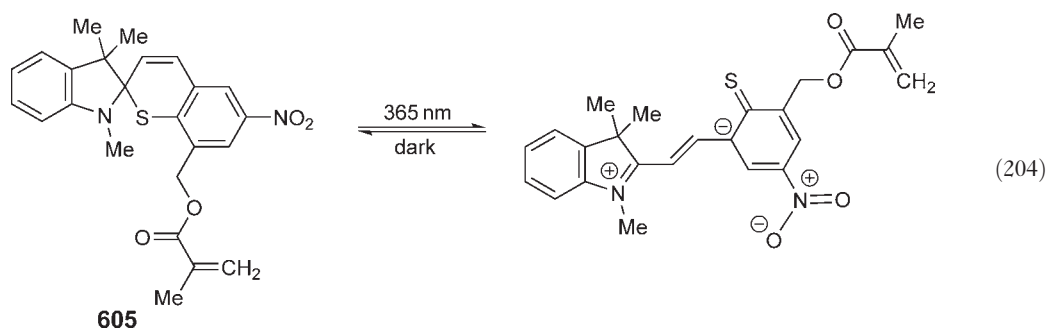
The reaction of thioxanthone with various 3-thienyllithium compounds is the initial step in the synthesis of the diols such as **602** from which the bis(thioxanthylum) dication **603** is obtained. This species functions as a reversible redox pair with its reduction product, the hexaarylethane, creating an electrochromic system in which electron transfer brings about bond making and bond breaking. These oligomers **604** may be considered to be a new class of molecular wires (Scheme 238) <2004OL2523>.

3,4-Dihydro-2*H*-1-benzothiopyran-4-ol has been used as a model sulfur-containing compound in a study of molecular metal sulfide cluster substrate binding to oil-refinery hydrosulfurization catalysts <2002IC1336> and also as a model compound in an evaluation of the removal of heterocyclic S-containing compounds from oil precursors by supercritical water <1995MI1485>.

The photochromism of the acrylate-substituted spiroindolinobenzothiopyran **605** is characterized by the unusual stability of the ring-opened colored species [λ_{max} 670 nm, (acetone)] (Equation 204) <2002JOC533>; other photochromic spiroindolinobenzothiopyrans have been incorporated in electrostatic toner compositions <1998USP5759729>.

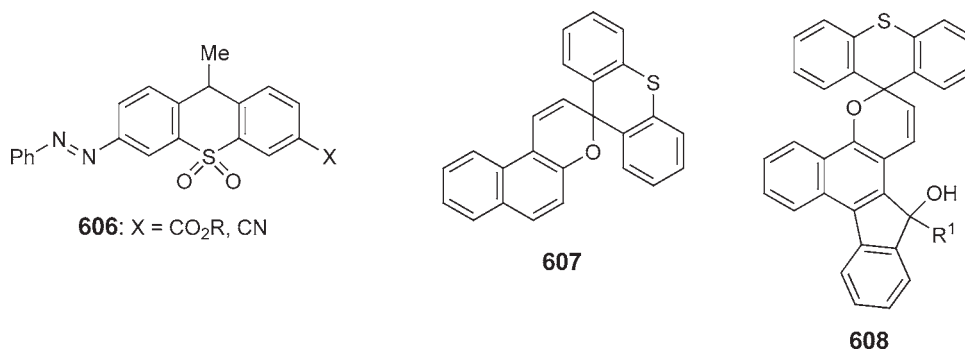


Scheme 238

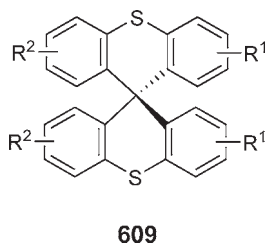


A new type of photochromism, based upon a photoresponsive acidity change, has been described for the phenylazo substituted 9*H*-thioxanthene 10,10-dioxides **606**. The photodissociation constants for H-9 are much larger in the *trans*-azo form compared with the *cis*-isomer. Color developing and bleaching are controlled by photoisomerization of the azo function with the conjugate bases absorbing at ca. 670 nm [<1996CL289>](#). A range of spiro(thioxanthene)

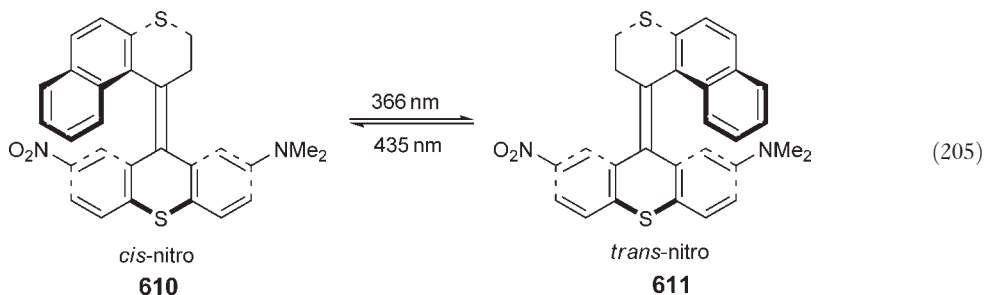
substituted photochromic naphthopyrans **607** <2002T9505> and indeno fused naphthopyrans **608** <2004T2593> have been characterized. The former offer bathochromic shifts in $\lambda_{\max}$, faster thermal bleaching kinetics and unusual fatigue resistance compared with simple diaryl substituted naphthopyrans <B-2006MI85>.



Chiral 9,9'-spirobithioxanthenes **609** have been prepared and their use as co-catalysts for asymmetric transformations described <2006USP2006047128>.



Much study has been devoted to the design of helical sterically overcrowded alkenes containing thioxanthene units which have potential as molecular switches and motors. Thus, photoswitching between the *cis* **610** and *trans* **611** forms of the naphthothiopyranylidene-thioxanthene is efficient and readily achieved by irradiation with light of two different wavelengths and is accompanied by a reversal of helicity (Equation 205). The excited state chirality can also be controlled photochemically, but in addition the choice of solvent can exert control. Circularly polarized luminescence spectroscopy showed that in benzene the two isomers retained their ground state chirality in the excited state, whereas in hexane identical excited state chirality was observed. Thus, a single enantiomer of *cis* **610** can be tuned to emit either right- or left-handed circularly polarized light <1995CC1095, 2003JA15659>. In the case of the fluorescent alkene **610**, irradiation results in a diastereoselective interconversion as above, but in addition the different fluorescence associated with the two isomers can be switched on and off by protonation and deprotonation of the dimethylamino function <1995CC1095>. A theoretical study of this proton switching phenomenon using PM3 and ZINDO/S-CI methods confirmed the presence of two stable conformers of similar energy with a barrier for rotation about the C=C bond of 40 kcal mol⁻¹ <2001SM(116)275>. Incorporation of one enantiomer of a crowded alkene with a given helical pitch into a liquid crystal in the nematic phase induces a switch to the cholesteric phase. Irradiation of a thin film with light of different wavelengths then results in photomodulation of the pitch of the cholesteric phase as the helicity of the crowded alkene changes <1995JA9929>.



When a methyl group is introduced at the 3-position of the thiopyran ring, the isomer in which it is axial is stable relative to that in which it is equatorially disposed. The upper half of the stable isomer rotates on irradiation but a thermally driven helix inversion returns the molecule to its more stable state. A second light and heat driven sequence generates the starting structure. The upper part of the molecule has thus undergone a four stage 360° rotation and the whole behaves as a unidirectional light driven molecular motor based on one stereogenic centre (**Figure 59**). Tuning of the energy required for the thermal stages can be achieved by variation in substituents <2000JA12005, 2002JA5037, 2003OBC33, 2004OBC1531>. A unidirectional motor based upon a naphthothiopyranylidene–thioxanthene system has been tethered to a gold surface through thiolate ligands from the 4- and 5-positions of the thioxanthene unit <2005NAT1337>.

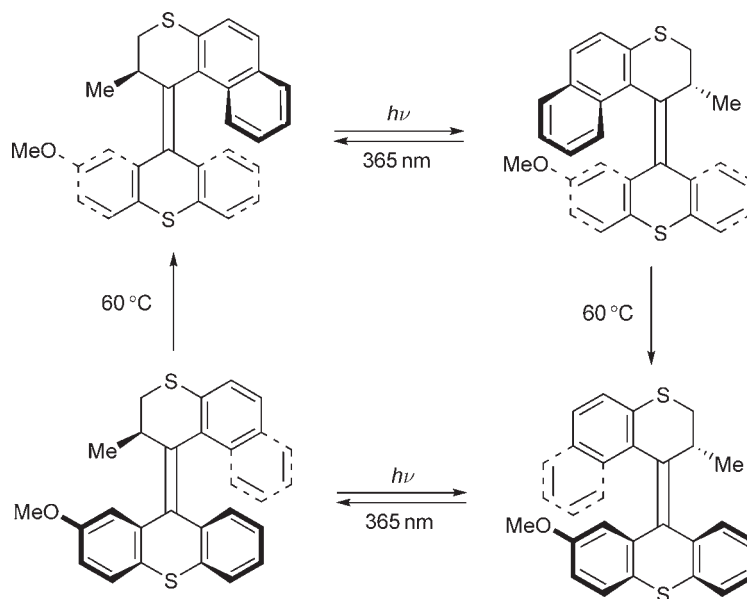


Figure 59 Photochemical and thermal precession in a sterically hindered alkene.

A further development introduced a 2,6-dimethylphenyl group at the 2-position of the thioxanthene unit as a rotor designed to control the isomerization about the alkenic bond. The compound has been likened to a molecular gearbox (**Figure 60**) <1997JOC4943, 2005OBC4071>.

Continuing with the theme of motors, coupling the bromoalkyne **612** with *p*-carborane produces a phenylene ethynylene axle with two carborane wheels. The crowded alkene **613** was then coupled through alkyne units to two axles producing a ‘motor car’ as a mixture of two pairs of enantiomers (**Scheme 239**). Photoisomerisation activates the unidirectional motor as above and the unstable state thermally reverts to the stable form. Fullerene units have also been introduced as the ‘wheels’ though these were less effective than the carborane unit <2006OL1713>.

A benzo[*k*]thioxanthene unit has been incorporated in the emission layer of an OLED display <2004USP2004140761> as part of a polycyclic pigment **614** employed for coloring polymers, inks and toners <2000USP6046335> and also as the key component **615** of a red fluorescence-conversion film and associated electroluminescent devices <1998JPP10316964>.

2,4,6-Triphenylthiopyrylium perchlorate has been shown to be more efficient than the analogous pyrylium salt for the photodynamic electron transfer [$2\pi+2\pi$] cyclodimerisation–cross-linking of poly(vinyl cinnamate) in solution <1998JPH(113)155>. Superior photosensitising activity was also noted for thiopyrylium salts over the oxygen analogues for the cycloreversion of the diaryloxetane **616** (Equation 206) <2001OL1965> and enhanced photocatalytic activity was noted for 2,4,6-triphenylthiopyrylium perchlorate over the oxygen analogue when either encapsulated within zeolites or deposited on amorphous silica and employed for the degradation of aqueous solutions of either aniline or phenol <2004NJC631>.

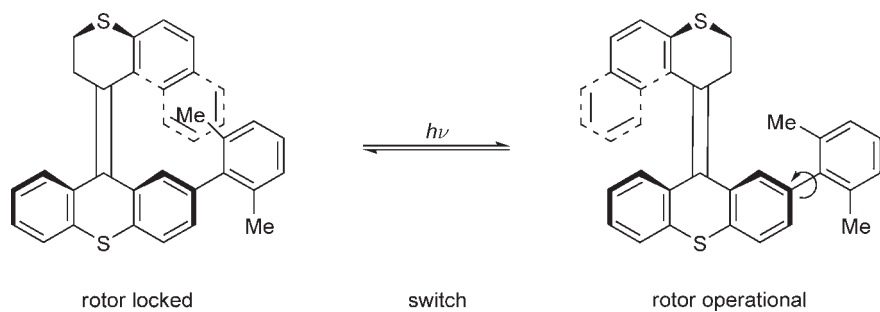
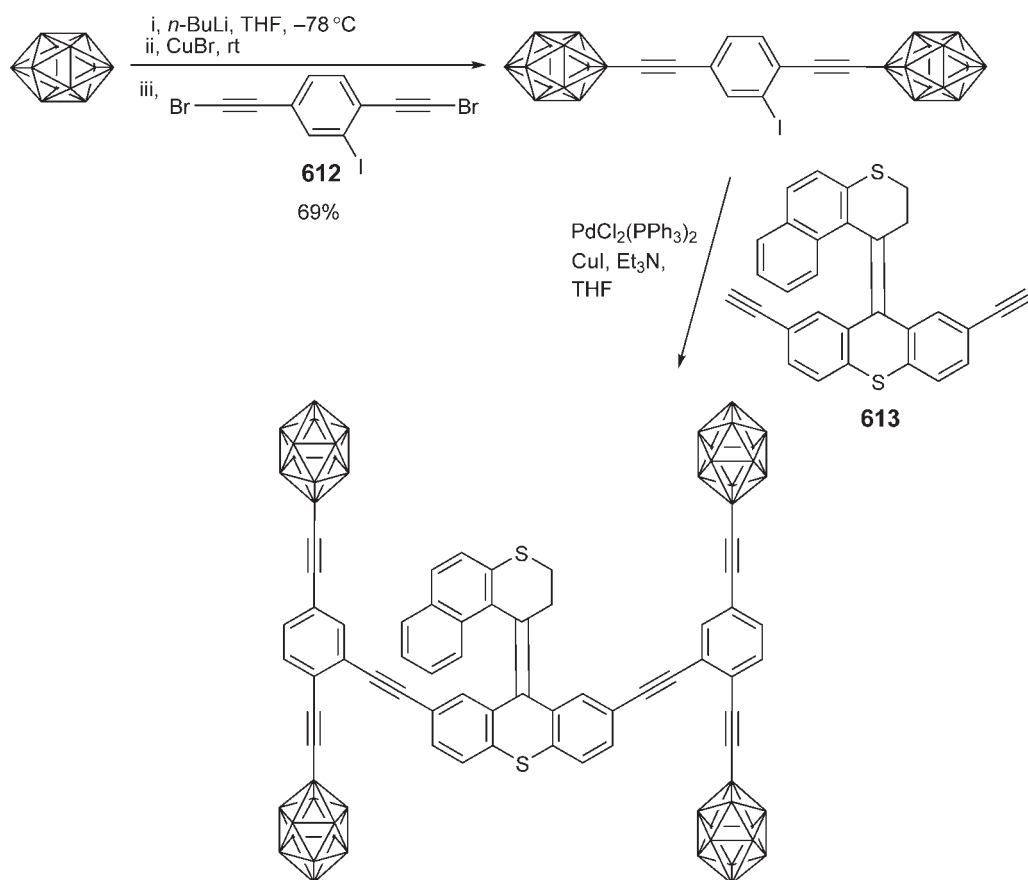
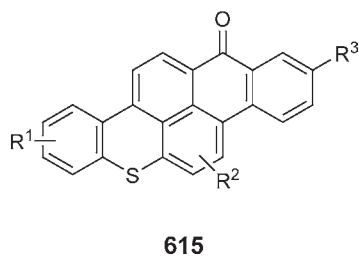
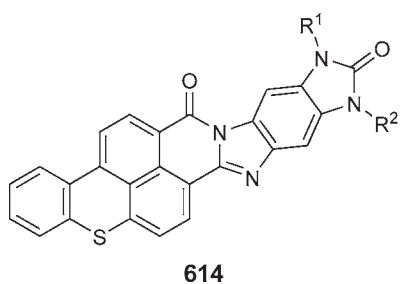
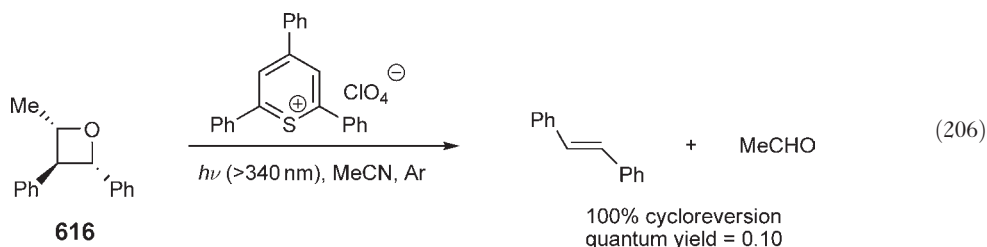


Figure 60 Photochemical switching of a molecular rotor.

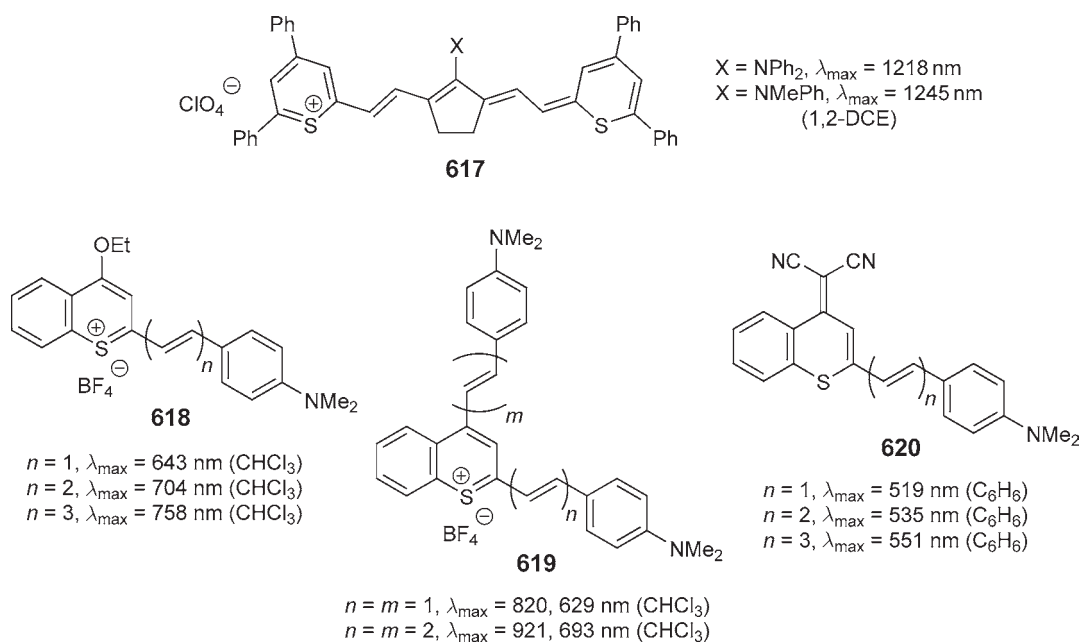


Scheme 239

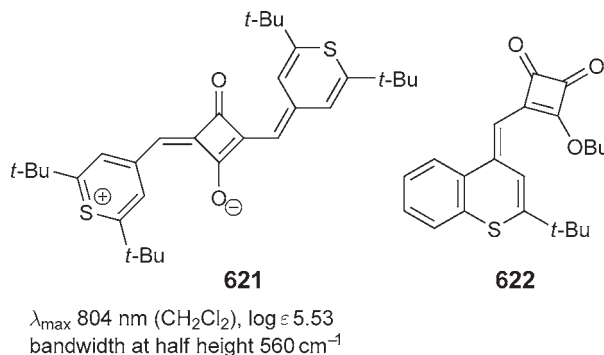




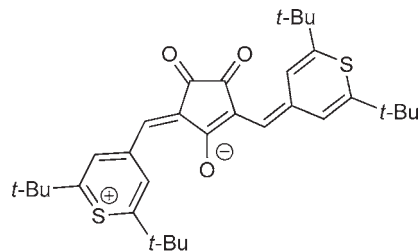
Interest has been maintained in the synthesis of near infrared absorbing polymethine thiopyrylium salt containing dyes, for example, **617** <1995DP(27)263, 1995DP(28)1, 2005MI12> and benzothiopyrylium salt analogues. For each additional vinyl unit (n) in the benzothiopyrylium salt dye **618** a bathochromic shift in $\lambda_{\max}$ of ca. 55 nm was noted. This vinylene shift is ca. 100 nm for the long-wavelength band in the 2,4-bis substituted analogues **619** but is significantly reduced in the 4-(dicyanovinyl)-4*H*-1-benzopyran system **620** <1990JRM0546, 1997CHE1400>. Thiopyrylium salts have been employed as fluorescent dopants <2005USP2005037232> and as charge transport materials <2004USP2004209114> in OLED devices.



Infrared absorbing squarylium dyes containing a terminal thiopyrylium salt unit **621** with $\lambda_{\max}$ in the range 700–1200 nm have been used in conjunction with iodonium salts for the photogeneration of acids <1995USP5401607> and for laser-induced thermal transfer printing <1993USP5256621>. Efficient routes to key intermediates, such as the hemi-squarylium ester **622**, for the preparation of asymmetrical squarylium dyes have been described <1999USP5919950>.

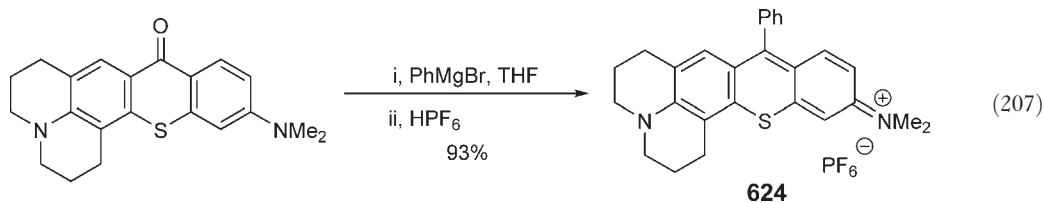


The reaction of croconic acid with 2,6-di-*t*-butyl-4-methylthiopyrylium salts yields the croconate dye **623** which absorbs in the infrared at 950 nm compared with 845 nm for the pyrylium analogue. This croconate dye is quite soluble in dichloromethane (180 mg ml^{-1}), a feature that renders it attractive for thin film applications <2000JOC2236>.

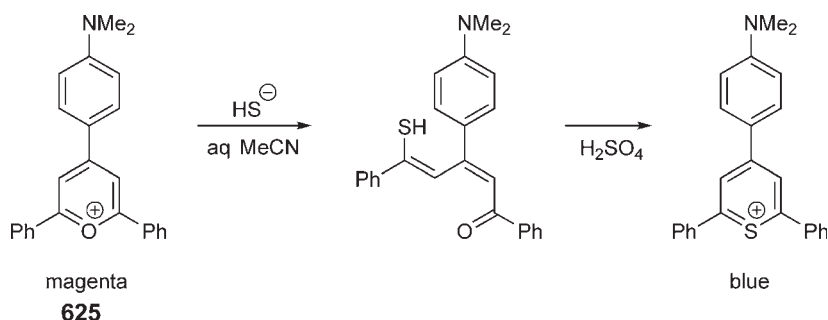
**623**

λ_{max} 950 nm (CH_2Cl_2), $\log \epsilon$ 5.26
bandwidth at half height 570 cm^{-1}

The pentacyclic thioxanthylum salt **624** absorbs at 582 nm ($\epsilon_{\text{max}} \sim 105\,000 \text{ M}^{-1} \text{ cm}^{-1}$) with a fluorescence emission maximum at 600 nm. The dye displays photodynamic activity *in vitro* against chemosensitive hamster ovary cell lines (Equation 207) <2006BMC8635>.

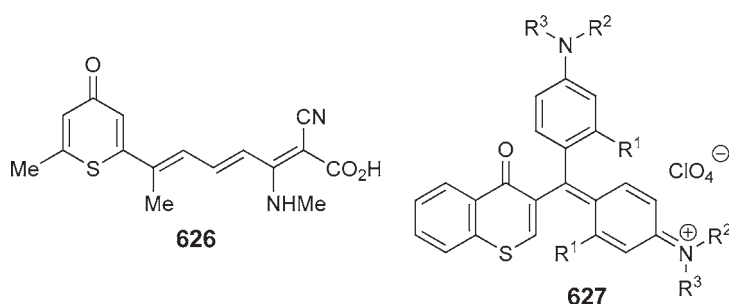
**624**

The presence of a 4-(4-dimethylaminophenyl) group enhances the visible absorption differences between the pyrylium and thiopyrylium salt analogues. Thus, on reaction of **625** with hydrosulfide ion a change in hue from magenta (540 nm) to blue (580 nm) is observed; this color change serves as the basis for a new chemodosimeter selective for hydrosulfide (Scheme 240) <2003JA9000>.

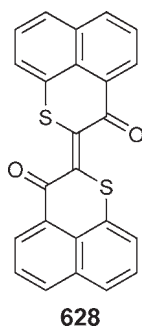
**Scheme 240**

7.10.5.2.2 Thiopyranones and their benzologues

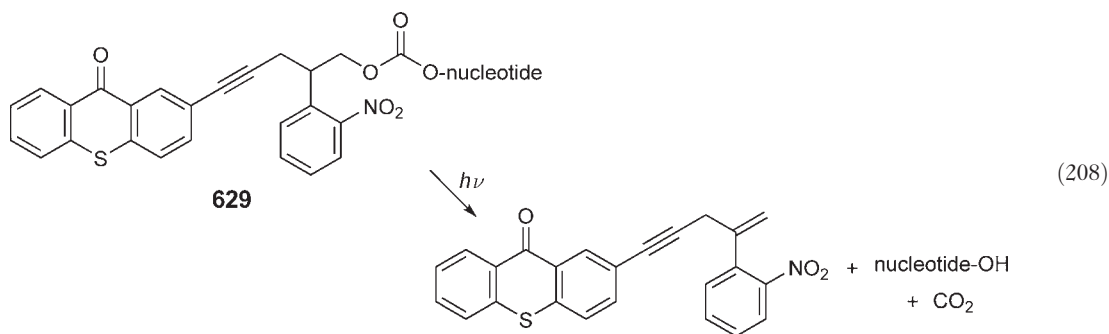
Dyes containing the thiopyran-4-one unit **626** have been employed in semiconductor devices for photoelectric converters and solar cells <2005JPP2005123013>. A 4-oxo-4*H*-1-benzothiopyran-3-yl unit has replaced the phenyl unit of Malachite green analogues to afford cationic dyes **627** which have been used in direct hair dyeing compositions <2004FRP2849373>. The replacement of the oxygen atom in dichroic coumarin dyes with sulfur results in improved low temperature solubility of the new thiocoumarin dyes in liquid crystalline formulations <1998BCJ1719>.



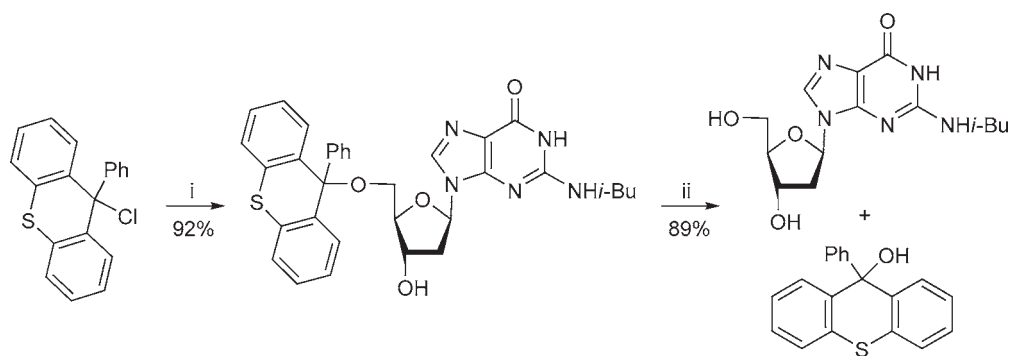
At 638 nm in cyclohexane, the wavelength of maximum absorbance of the bis(naphtho[1,8-*bc*]thiopyranone) **628** is 98 nm to the red of thioindigo (λ_{max} 540 nm). These values are in close agreement with those predicted by a TD-PBE0/6-311+*G*(2*d,p*)/PBE0/6-311*G*(*d,p*) approach that allowed for bulk solvent effects by means of a polarizable continuum model <2006JA2072>.



9*H*-Thioxanthen-9-one was shown to be the most useful triplet sensitizer, in terms of minimizing side reactions and efficient sensitization, for the intramolecular photo-deprotection of oligonucleotides protected with a 2-(2-nitrophenyl)propoxycarbonyl (NPPOC) group either in solution or on microarray chips <2004HCA28, 2005HCA891>. Covalently bonding a thioxanthone unit to the NPPOC moiety, for example, **629** further improves the efficiency of the deprotection. In examples with short linkages between the two units, a sensitization mechanism involving an excited sensitizer singlet state in addition to the usual triplet–triplet energy transfer process was involved (Equation 208) <2006AGE2975>.



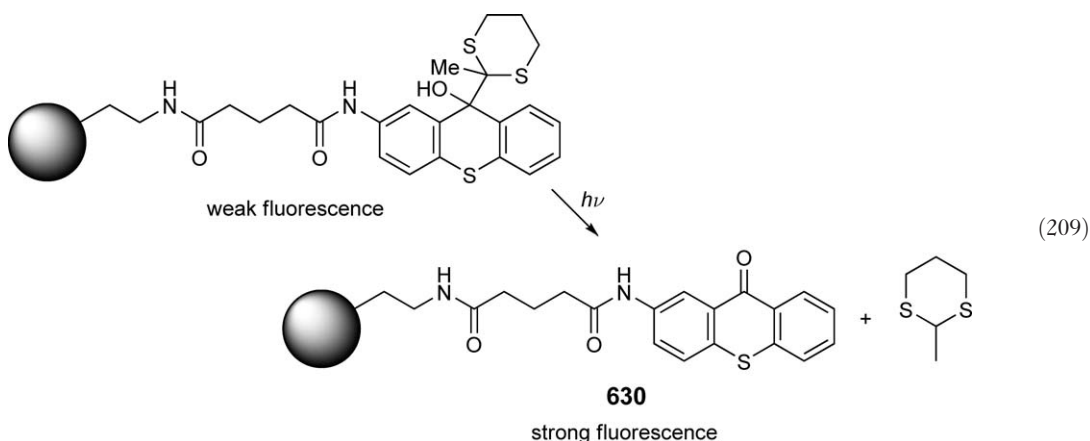
The *S*-pixyl (9-phenyl-9*H*-thioxanthen-9-yl) group has been successfully employed as a photocleavable protecting group for the 5'-hydroxy function of deoxyribonucleosides (Scheme 241) <1999TL7911>. The influence of substituents on the 9-phenyl ring and on the thioxanthone moiety on the photocleaving reaction have been studied; significantly lower yields were recorded for nitro-substituted analogues upon irradiation at 300 nm but 2,7-dibromo- or 3-methoxy- substituents on the thioxanthone allowed cleavage at a longer excitation wavelength (350 nm) <2002JOC7641>. Increased photosensitivities for photodeprotection were noted for halogenated thioxanthenes <2000WO2000031588>.



i, 5'-hydroxydeoxyribnucleoside, DMAP, pyridine; ii, $h\nu$, aq MeCN

Scheme 241

The concept of a photo-release and report system has been realized with the 9-(2-methyl-1,3-dithien-2-yl)-9*H*-thioxanthene-9-ol tethered to a PAMAM dendrimer. Irradiation of the dendrimer system with a U-360 broadband filter results in cleavage of the dithienyl unit to generate, after hydrogen radical transfer, 2-methyl-1,3-dithiane and the tethered thioxanthone **630**. The increased fluorescence of the latter confirms the successful photo cleavage. The system offers potential for the generation of high local concentrations of substituted dithianes in the vicinity of the dendrimer surface (Equation 209) <2005JA12458>.



The *S*-pixyl function, when substituted with electron-donating groups, has also proved useful since the stabilized cations derived from this function are readily detected by mass spectrometry at the femtomolar level by either laser desorption ionization or MALDI techniques <2005EPP1506959, 2005SL2453>. The readily available sulfoxide derivatives also function as efficient mass-tags in mass spectrometry applications <2005CC3466>.

Perhaps the most successful commercial application associated with the six-membered sulfur-containing heterocyclic ring system capitalizes upon the triplet sensitising properties of substituted thioxanthenes (Figure 61) and their use as type II photoinitiators for the UV curing of pigmented coatings and inks <B-1998MI375, B-2002MI1>. Several 2-substituted analogues have been investigated for UV curing purposes and mechanistic aspects are frequently included <1994JCF83, 1997JCF1517, 2002FA989, 2003MM2649, 2005MM4133>.

Thioxanthenes contrast with the widely used benzophenone photoinitiators in that they typically absorb strongly at longer wavelengths ca. 380–420 nm and offer reduced yellowing of the cured products. The influence of substituents on λ_{max} of thioxanthone has been investigated; electron donating groups at positions C-2 and C-7 of the thioxanthone nucleus and electron-withdrawing groups at positions C-3 and C-6 induce bathochromic shifts <B-1998MI375>.

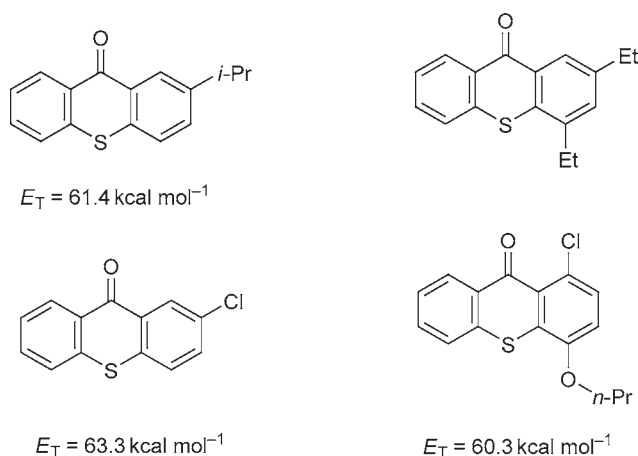
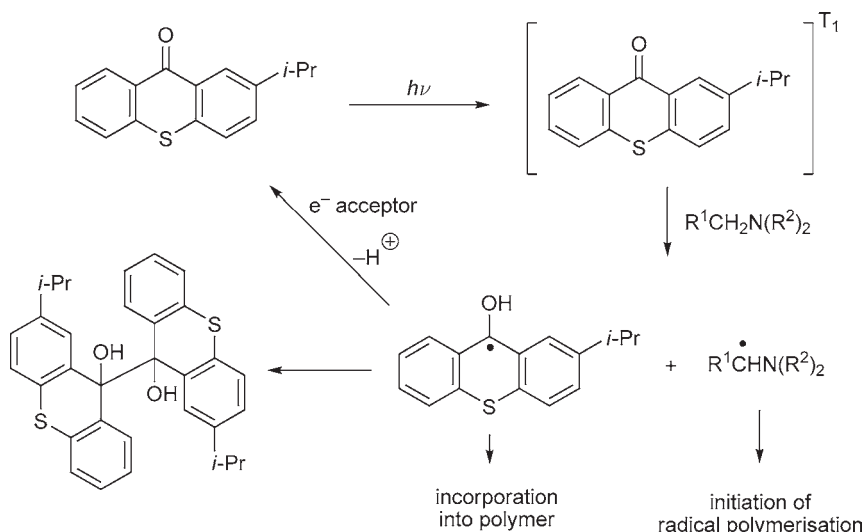


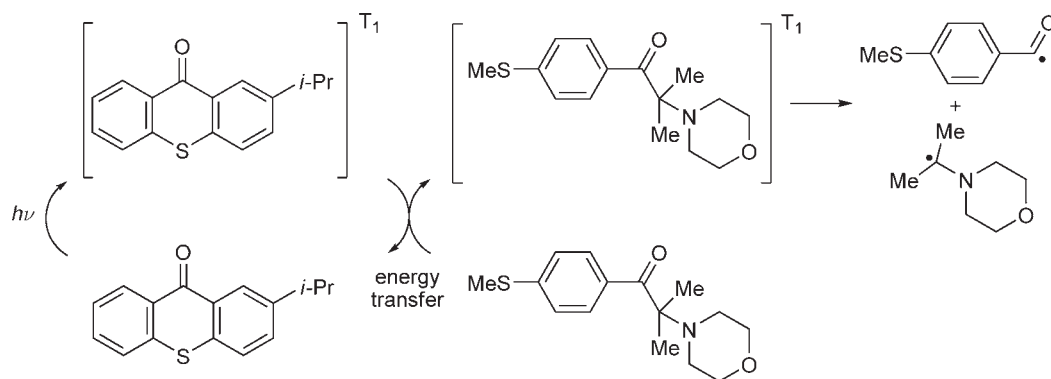
Figure 61 Substituted thioxanthenes used as photoinitiators and their triplet energies (E_T).

One of the most widely employed thioxanthenes is 2-*isopropyl*thioxanthone (ITX) though this is often a mixture of isomers with ca. 83% being the 2-isomer, with the balance being the 4-isomer with trace amounts of the 1- and 3-*isopropyl* derivatives. An investigation of the efficiency of each isomer revealed that the 2-, 3-, and 4-*isopropyl* compounds were comparable; the 1-*isopropyl* isomer was significantly less active, perhaps as a result of excited state proton transfer to the adjacent CO group <2002STC115>. Thioxanthenes are most frequently used with an amine synergist (co-initiator) with the primary photochemical process occurring from a triplet exiplex between excited thioxanthone and the amine. Electron transfer from the amine with subsequent proton transfer results in the formation of a ketyl radical and an α -aminoalkyl radical; the latter is the key monomer initiating species <B-2002MI1>. The fate of the thioxanthone moiety in UV curing formulations has been studied <1996PLM2477>. The process for the generation of initiating radicals for 2-*isopropyl*thioxanthone (ITX) and a tertiary amine is presented in **Scheme 242**.



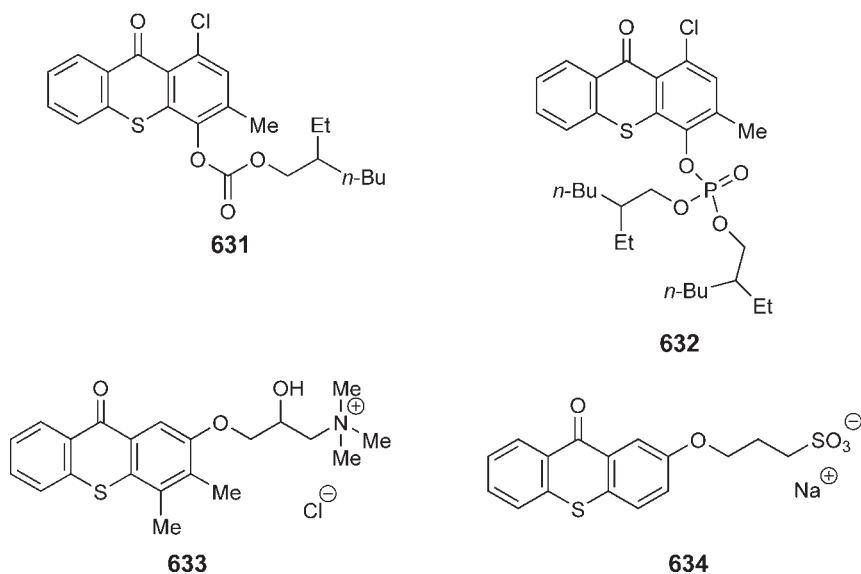
Scheme 242

Thioxanthone has also been used to improve the reactivity of α -aminoacetophenone photoinitiators in highly pigmented systems through an energy transfer process. The thioxanthenes, which have typical triplet energies of ca. 59–63 kcal mol⁻¹ (**Figure 61**), transfer energy to the acetophenone, for example 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one, which has a low triplet energy, and undergoes α -cleavage to generate the initiating radicals (**Scheme 243**). In these processes, the thioxanthenes are regenerated and thus serve as photosensitizers <B-1998MI375, 1995MI169>.



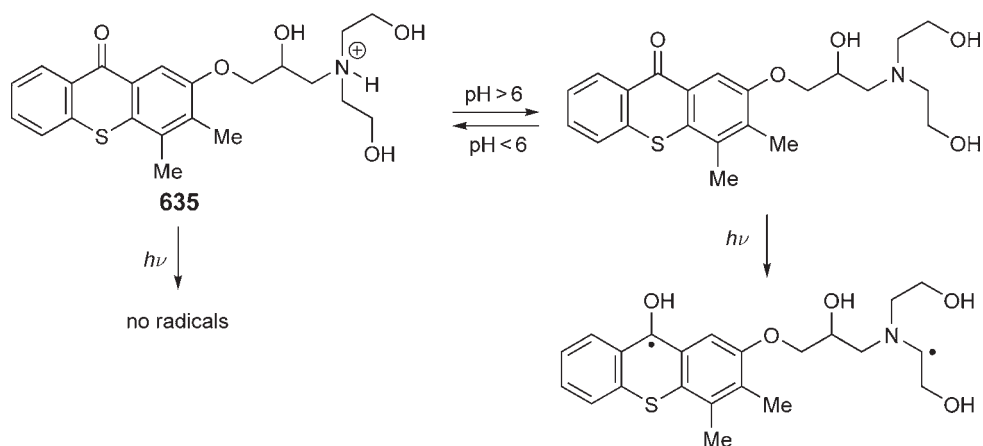
Scheme 243

Liquid thioxanthenes, for example, **631** and **632**, have been synthesized in order to improve formulation of photopolymerizable compositions <1998WO9842697> and thioxanthenes possessing either cationic **633** <1998WO9853369> or anionic **634** <2000MI212> hydrophilic substituents have been prepared and successfully employed for curing water-based ink formulations. The mode of action of the latter ionic compounds appears to involve both the lowest excited triplet and singlet states <B-1998MI1>.

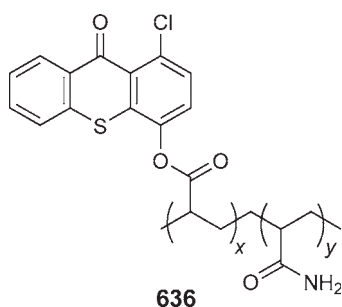


The photoinitiating efficiency is pH dependent, a feature which has been capitalized upon with the tethered thioxanthone-amine co-initiator system **635**, which at pH < 6 fails to generate free radicals as a result of protonation of the tertiary amino group, but at higher pH regains its normal initiator activity (Scheme 244) <1998PSA2563, B-2002MI1>.

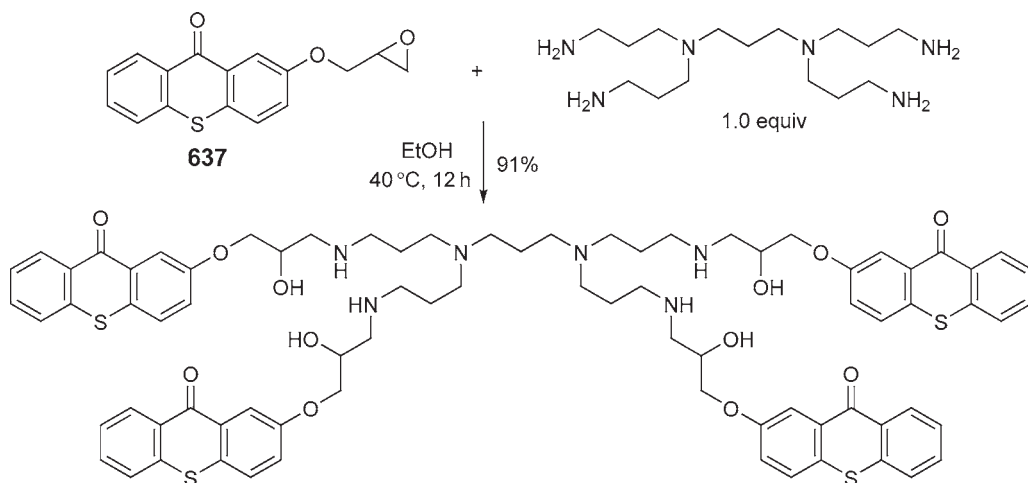
Recent concerns over the residual concentration of free thioxanthone photoinitiators and amine coinitiators in coatings and inks on food packaging have resulted in the evolution of macroinitiators <2002PLM4591, 2003JPH(159)103> or polymeric photoinitiators <1996MI379> wherein the thioxanthone unit and, in some instances, the amine coinitiator are covalently bound to a copolymer which is formulated with the ink or coating and then photocured in the normal way. Several copolymers, for example, **636**, based upon the polymerization of acrylate esters derived from 4-hydroxythioxanthenes with either acrylamide or 2-acryloxyethyltrimethylammonium iodide co-monomer have been explored as water-soluble photoinitiators <2005JPH(169)95>.



Scheme 244



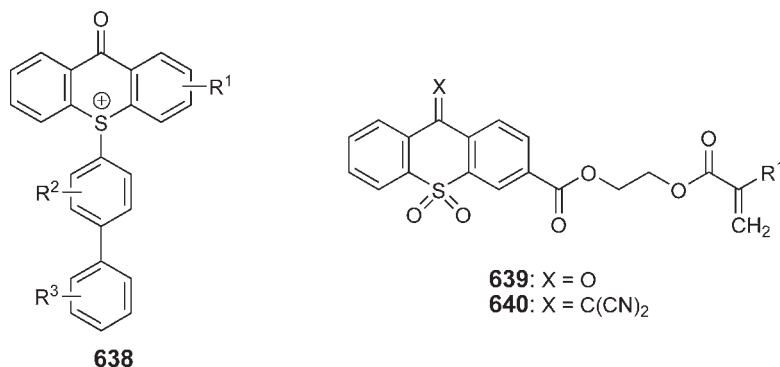
Dendritic photoinitiators have been assembled from 2-(2,3-epoxy)propyloxythioxanthone **637** and tetra-amines (**Scheme 245**) <2004MM7850> and this strategy has been employed to perform an electrostatic self-assembly of a polymer brush <2005CC4927>.



Scheme 245

Polymeric cationic curable formulations containing an *S*-biphenylthioxanthenium salt initiator **638** have been reported to reduce the residual odor and benzene levels associated with other *S*-phenyl cationic photoinitiator systems <2006WO2006/060281>. The mechanism of photo-acid generation from related *S*-aryl thiopyranium salts

has been explored <2004PPS1052>. Electron-transporting acrylate and methacrylate polymers containing the tethered thioxanthone 1,1-dioxide monomers **639** and **640** have been obtained by free radical polymerization <1999CM3279, 1999SM(105)55>. Electrochemical activity was established by cyclic voltammetry which indicated two well-defined pairs of reduction and oxidation peaks; notably derivatives of **640** were more easily reduced <1999SM(105)55>. The electron transporting potential of 9-oxo-9*H*-thioxanthen-3-carboxylates in highly sensitive electrophotographic photoreceptors has been documented <1996JPP08248656>.



7.10.6 Further Developments

A healthy interest in thiopyran chemistry has been maintained in the period January 2006 to October 2007, with over 1600 references and patents published on material pertinent to this chapter.

4*H*-Thiopyrans are produced in high yield by the microwave-induced one-pot reaction between α,β -unsaturated ketones, dienophilic alkynes, and Lawesson's reagent. The equivalent thermal reaction is unsuccessful <2006TL4925>. Calculations at the G3MP2B3 level show that the introduction of a 5-methyl substituent into α -sulfenyl-, α -sulfinyl-, and α -sulfonyl- hex-5-enyl radicals shifts the regioselectivity of cyclization to the 6-endo products, tetrahydrothiopyran derivatives <2006JOC9595>.

Stabilized carbenes derived from carbethoxy diazosulfones undergo selective C–H bond insertion to afford tetrahydrothiopyran 1,1-dioxides in moderate yield upon treatment with rhodium acetate <2007OL61>.

A large scale synthesis of a chiral tetrahydrothiopyran derivative (five steps, 56% overall yield) from (+)-10-camphor-sulfonic acid has been described; the sulfide is of value in the asymmetric synthesis of epoxides and aziridines <2006T11297>.

3,4-Dihydro-2*H*-thiopyran-6-yl trifluoromethanesulfonate undergoes a carbonylative Suzuki–Miyaura coupling with vinylboronic acids to give substituted 1-(3,4-dihydro-2*H*-thiopyran-6-yl)prop-2-en-1-ones together with minor amounts of the non-carbonylated coupled products <2007EJO2152>.

The application of ¹H NMR spectroscopy to probe both conformation and stereoelectronic effects in tetrahydro-2*H*-thiopyrans and the 1-oxides and 1,1-dioxides continues <2007CEJ4273, 2007MRC590>.

An optimized inexpensive synthesis of tetrahydrothiopyran-4-one which lends itself to scale-up involves a Dieckmann cyclization of dimethyl 3,3'-thiobispropanoate <2007S1584>. Efficient conversions to 3,6-dihydro-4-trimethylsilyloxy-2*H*-thiopyran <2007S1584>, the corresponding 4-vinylstannane <2007JOC1507> and the 4-oxo-tetrahydro-2*H*-thiopyran-3-yl *N*-methyl-*N*-phenylcarbamate <2007SL293> have been accomplished.

2,3-Dihydrothiopyran-4-ones have been efficiently obtained from terminal alkynes through conjugate addition to α,β -unsaturated aldehydes followed by oxidation to the enynone and cyclization <2007MC13>. The [2+2] photocycloaddition of ethylidenemalononitrile to the 2,2-dimethyldihydrothiopyranone is both regio- and stereo- specific <2007S1426>.

Enantioselective aldol reactions of tetrahydrothiopyran-4-one using proline-derived catalysts results in good yields of 3-substituted thiopyran-4-ones with both high diastereoisomeric ratios and enantiomeric excesses <2007SL1605, 2007TA265>. Similar success attends related aldol reactions in aqueous media <2007OBC2148, 2007OL2593> and when the proline-catalyzed reaction is carried out under solvent-free conditions, grinding the reactants together in a ball mill <2007CEJ4710>.

Further progress has been made in the stereochemical control of the reaction of tetrahydrothiopyran-4-one with 1,4-dioxo-8-thiaspiro[4.5]decane-6-carboxaldehyde (see Scheme 37). The resulting meso 1,9-diketones afford the

mono-TMS enol ethers in excellent yields and with >95% *ee* on treatment with a Li amide through a combination of enantiotopic group selective enolization and kinetic resolution <2006OL2631>. The formation of a single bisaldol adduct, the 1,9-doubly protected 1,5,9-triketone **282** from the reaction of the above racemic 6-carboxaldehyde with the individual diastereomers of the racemic aldol adduct is a consequence of high levels of double stereodifferentiation and mutual kinetic enantioselection <2007JOC1667>. The adducts are of value in polypropionate synthesis as exemplified by an enantioselective synthesis of membrenone B, a chemical secreted by sea slugs as part of their defence mechanism, in 9.5% yield over nine steps <2007JOC7805>.

When the Mannich reaction of tetrahydrothiopyran-4-one with aniline and aromatic aldehydes is catalyzed by a chiral phosphonic acid, the *anti* diastereoisomers are obtained in high yield and enantiomeric excesses <2007JA3790> and both cinchona alkaloid derivatives <2007OL599> and chiral proline derivatives are excellent catalysts for the enantioselective Michael addition to β -nitrostyrenes which yields the *syn* adducts <2007OL1117, 2007TA1443, 2007TL5803>. The related asymmetric vinylogous Michael addition of 4-dicyanovinylthiochroman to various β -nitrostyrene derivatives has been accomplished using a thiourea-tertiary amine catalyst <2007T5123>. The enolic nature of 4-hydroxythiocoumarin has been utilized in an asymmetric Michael addition to α,β -unsaturated ketones catalyzed by a quinine amine catalyst <2007OL413>.

An efficient enantioselective tandem Michael-aldol reaction between 2-mercaptobenzaldehyde and α,β -unsaturated amides has been employed for the synthesis of substituted thiochroman-4-ols and thence thiochromenes. The process is promoted by a hydrogen bonding bifunctional thiourea – tertiary amine catalyst which acts as a chiral scaffold presenting the nucleophilic sulfur atom to the β -carbon atom of the unsaturated amide <2006JA10354, 2007JA1036>. Various 2,4-disubstituted thiochromans have been obtained from α,β -unsaturated aldehydes and thiophenols using an acid- and base-supported reagent system, $\text{Na}_2\text{CO}_3/\text{SiO}_2\text{-PPA}/\text{SiO}_2$ <2007SL387> and 2,4-propano-linked thiochromans result from the rearrangement of dibenzothiophenes during a Birch reduction <2007TL5657>.

The intramolecular capture of a cyclobutyl thionium ion generated during the acid-catalyzed ring expansion of 1-phenylthiocyclopropyl carbinols leads to cyclobuta[*c*]thiochromans <2006SL2241> and non-terminal alkynyl aryl sulfoxides undergo a triphenylphosphinegold(I)-promoted rearrangement to the 4-substituted thiochroman <2007JA4160>.

2,4,6-Triphenylthiopyrylium salts have been employed as efficient electron transfer photosensitizers to promote the [4+2] cycloaddition between thiobenzophenone and substituted styrenes. A radical cation derived from the thiobenzophenone is involved in the formation of separable diastereoisomeric mixtures of 1,3,4-trisubstituted isothiochromans <2007OL3587>. Interest has been maintained in the photosensitizing properties of thiopyrylium salts for blood disinfection <2007BMCL4406>. Several new thioxanthylum salts have been reported <2007JOC2647, 2007JOC2690>.

Sterically hindered alkenes derived from naphtho[2,1-*b*]thiopyrans continue to attract attention as molecular motors; tethering the motor to a quartz surface enables controlled rotary motion in monolayer assemblies to be accomplished <2007AGE1278>. The reversible interconversion between a non-fluorescent and two fluorescent states of crowded bithioxanthylidenes can be achieved through irradiation and temperature and redox changes <2006JA12412>.

New thioxanthenes have been obtained from 3-iodothiochromone and propargyl alcohols by a transition metal-mediated benzannulation strategy <2007CC1035> and a regioselective synthesis of 3-chlorothioxanthone 10,10-dioxide has been described <2006SL3045>. The use of thiosalicylic acid and its derivatives in the synthesis of substituted and polycyclic thioxanthenes continues <2006TL8679, 2007HCA1373, 2007JOC583>.

References

- 1957JOC851 H. Gilman and J. J. Dietrich, *J. Org. Chem.*, 1957, **22**, 851.
 1963CB1234 B. Eistert and H. Selzer, *Chem. Ber.*, 1963, **96**, 1234.
 1965JOC1390 W. J. Middleton, *J. Org. Chem.*, 1965, **30**, 1390.
 1967AHC(8)219 R. Mayer, W. Broy, and R. Zahradnik; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 1967, vol. 8, p. 219.
 1968JPC997 R. S. Becker and J. Kolc, *J. Phys. Chem.*, 1968, **72**, 997.
 1971JCB74 S. Bradamante, S. Maiorana, A. Mangia, and G. Pagani, *J. Chem. Soc. (B)*, 1971, 74.
 B-1971MI236 Q. N. Porter and J. Balda; in 'Mass Spectrometry of Heterocyclic Compounds', Wiley-Interscience, New York, 1971, p. 236.
 1972JA559 D. A. Sweigart and D. W. Turner, *J. Am. Chem. Soc.*, 1972, **94**, 5599.
 B-1973MI451 T. J. Batterham; in 'NMR Spectra of Simple Heterocycles', Wiley, New York, 1973, p. 451.

- 1974JCP3987 J. A. Wells and T. B. Mallory, Jr., *J. Chem. Phys.*, 1974, **60**, 3987.
- 1975AHC(18)60 S. W. Schneller; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 1975, vol. 18, p. 60.
- 1976CJC280 I. W. J. Still, N. Plavac, D. M. McKinnon, and M. S. Chauhan, *Can. J. Chem.*, 1976, **54**, 280.
- 1978TL3567 K. Nishino, K. Nakasuji, and I. Murata, *Tetrahedron Lett.*, 1978, **19**, 3567.
- 1979CL387 H. Nakazumi, A. Asada, and T. Kitao, *Chem. Lett.*, 1979, 387.
- 1980AHC(26)115 O. Meth-Cohn and B. Tarnowski; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 1980, vol. 26, p. 115.
- 1980BCJ2046 H. Nakazumi, A. Asada, and T. Kitao, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2046.
- 1981T2633 F. Duus, *Tetrahedron*, 1981, **37**, 2633.
- 1982CJC243 P. D. Clark and D. M. McKinnon, *Can. J. Chem.*, 1982, **60**, 243.
- 1982TL3195 K. Yamamoto, S. Yamazaki, Y. Kohashi, I. Murata, Y. Kai, N. Kanehisa, K. Miki, and N. Kasai, *Tetrahedron Lett.*, 1982, **23**, 3195.
- 1983AHC(34)146 J. Kuthan; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 1983, vol. 34, p. 146.
- 1983SAA693 M. Baiwir, G. Llabrés, L. Christiaens, A. Luxen, and J.-L. Piette, *Spectrochimica Acta, Part A*, 1983, **39**, 693.
- 1984CC922 G. W. Kirby, A. W. Lochead, and G. N. Sheldrake, *J. Chem. Soc., Chem. Commun.*, 1984, 922.
- 1984CHEC(2)885 A. H. Ingall; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 2, p. 885.
- 1985AJC119 R. L. Crumbie, D. D. Ridley, and P. J. Steel, *Aust. J. Chem.*, 1985, **38**, 119.
- 1986JA3409 M. L. Di Vona, G. Doddi, G. Ercolani, and G. Illuminati, *J. Am. Chem. Soc.*, 1986, **108**, 3409.
- 1986J(P2)271 G. Doddi and G. Ercolani, *J. Chem. Soc., Perkin Trans. 2*, 1986, 271.
- 1986J(P2)1887 R. K. Harris, S. Lane, K. Metcalfe, K. L. Packer, A. Root, and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1887.
- 1986MI187 C. Lenoble and R. S. Becker, *J. Photochem.*, 1986, **33**, 187.
- 1987AJC1179 J. E. Anderson-McKay and A. J. Liepa, *Aust. J. Chem.*, 1987, **40**, 1179.
- 1987JCM44 M. Bavia and P. Biscarini, *J. Chem. Res.(S)*, 1987, 44.
- 1987J(P2)1427 G. Doddi, G. Ercolani, and P. Nunziante, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1427.
- 1987PS(29)265 A. M. El-Khawaga, M. F. El-Zohry, M. T. Ismail, A. A. Abdel-Wahab, and A. A. Khalaf, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1987, **29**, 265.
- 1988ACA332 G. Schultz, A. Kuczman, and I. Hargittai, *Acta Chem. Scand., Ser. A*, 1988, **42**, 332.
- 1988JA5452 E. Vedejs, J. S. Stults, and R. G. Wilde, *J. Am. Chem. Soc.*, 1988, **110**, 5452.
- 1988JOC3739 H. A. Zahalka, B. Robillard, L. Hughes, J. Luszyk, G. W. Burton, E. G. Janzen, Y. Kotake, and K. U. Ingold, *J. Org. Chem.*, 1988, **53**, 3739.
- 1989EPD322251 D. G. Smith and G. Stemp, *Eur. Pat.* 322251 (1989) (*Chem. Abstr.*, 1989, **112**, 55610).
- 1989JCP2771 M. M. J. Tecklenburg, J. P. Villareal, and J. Laane, *J. Chem. Phys.*, 1989, **91**, 2771.
- 1989JOC2404 J. H. Bushweller and P. A. Bartlett, *J. Org. Chem.*, 1989, **54**, 2404.
- 1990CCC2351 Z. Vejdeck and M. Protiva, *Collect. Czech. Chem. Commun.*, 1990, **55**, 2351.
- 1990CPB8 M. Hori, T. Kataoka, H. Shimizu, E. Imai, T. Koide, N. Iwata, and M. Kurono, *Chem. Pharm. Bull.*, 1990, **38**, 8.
- 1990H(31)23 M. Hori, H. Ozeki, T. Iwamura, H. Shimizu, T. Kataoka, and N. Iwata, *Heterocycles*, 1990, **31**, 23.
- 1990JCM76 P. Biscarini, A. Bongini, and D. Casarini, *J. Chem. Res. (S)*, 1990, 76.
- 1990JFA1053 R. G. Binder, C. E. Turner, and R. A. Flath, *J. Agric. Food Chem.*, 1990, **38**, 1053.
- 1990JOC5364 K. Uneyama, M. Momota, K. Hayashida, and K. Itoh, *J. Org. Chem.*, 1990, **55**, 5364.
- 1990J(P1)3187 D. G. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3187.
- 1990JRM0546 S. Watanabe, S. Kado, K. Maeda, and T. Kitao, *J. Chem. Res. (M)*, 1990, 0546.
- 1990S1133 A. Coutore, H. Cornet, and P. Grandelaudon, *Synthesis*, 1990, 1133.
- 1990T1951 P. D. Baruah, S. Mukherjee, and M. P. Mahajan, *Tetrahedron*, 1990, **46**, 1951.
- 1990TL115 H. Shimizu, N. Kudo, T. Kataoka, and M. Hori, *Tetrahedron Lett.*, 1990, **31**, 115.
- 1990TL845 D. E. Ward, W. M. Zoghaib, C. K. Rhee, and Y. Gai, *Tetrahedron Lett.*, 1990, **31**, 845.
- 1991BSF976 A. Lévai and Z. Szabó, *Bull. Soc. Chim. Fr.*, 1991, **128**, 976.
- 1991CJC1487 D. E. Ward, Y. Gai, and W. M. Zoghaib, *Can. J. Chem.*, 1991, **69**, 1487.
- 1991JMT(234)247 X. Xie and H. F. Schaefer, *THEOCHEM*, 1991, **234**, 247.
- 1991J(P1)3225 S. S. M. Choi and G. W. Kirby, *J. Chem. Soc., Perkin Trans. 1*, 1991, 3225.
- 1991J(P2)1045 M. A. Cremonini, L. Lunazzi, G. Placucci, N. Kumon, A. Ishii, T. Kawashima, and R. Okazaki, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1045.
- 1991JPH(57)231 C. Karbe and P. Margaretha, *J. Photochem. Photobiol. A*, 1991, **57**, 231.
- 1991JST(243)123 G. Forgács, I. Hargittai, I. Jalsovszky, and A. Kuczman, *J. Mol. Struct.*, 1991, **243**, 123.
- 1991S15 E. B. Choi, I. K. Youn, and C. S. Pak, *Synthesis*, 1991, 15.
- 1991TL391 K. Toshima, K. Ohta, T. Ohtake, and K. Tatsuta, *Tetrahedron Lett.*, 1991, **32**, 391.
- 1991TL3499 T. Kawase, S. Fujino, and M. Oda, *Tetrahedron Lett.*, 1991, **32**, 3499.
- 1991TL4363 Y. Sakai, E. Nishiwaki, K. Shishido, M. Shibuya, and M. Kido, *Tetrahedron Lett.*, 1991, **32**, 4363.
- 1992BCJ2056 S. Moriyama and S. Motoki, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 2056.
- 1992BCJ2878 H. Firoozabadi, P. Salehi, and I. Mohammadpour-Baltork, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 2878.
- 1992CB127 T. Gade, M. Streek, and J. Voss, *Chem. Ber.*, 1992, **125**, 127.
- 1992CB1889 J. Gradel and W. Sundermeyer, *Chem. Ber.*, 1992, **125**, 1889.
- 1992CJC2627 D. E. Ward and Y. Gai, *Can. J. Chem.*, 1992, **70**, 2627.
- 1992DOK354 E. V. Trushina, S. K. Klimenko, D. S. Yufit, and Yu. T. Struchkov, *Dokl. Akad. Nauk. SSSR*, 1992, **327**, 354.
- 1992HCA1925 R. Kowalewski and P. Margaretha, *Helv. Chim. Acta*, 1992, **75**, 1925.
- 1992JFC(55)329 Y. G. Shermolovich, E. I. Slusarenko, V. M. Timoshenko, A. B. Rozhenko, and L. N. Markovski, *J. Fluorine Chem.*, 1992, **55**, 329.
- 1992JOC1727 R. A. Bunce, C. J. Peebles, and P. B. Jones, *J. Org. Chem.*, 1992, **57**, 1727.

- 1992J(P2)965 V. G. Adeeva, M. S. Bobyleva, N. S. Kulikov, V. G. Kharchenko, and L. M. Yudovich, *J. Chem. Soc., Perkin Trans. 2*, 1992, 965.
- 1992J(P2)1301 P. Šebek, S. Nespurek, R. Hrabal, M. Adamec, and J. Kuthan, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1301.
- 1992MI649 J. R. Brown, M. Kasrai, G. M. Bnacraft, K. H. Tan, and J.-M. Chen, *Fuel*, 1992, **71**, 649.
- 1992OM2157 M. R. Detty and H. R. Luss, *Organometallics*, 1992, **11**, 2157.
- 1992PS(66)311 M. F. El-Zohry, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1992, **66**, 311.
- 1992TH1 B. M. Heron, Ph.D. Thesis, 1992, Council for National Academic Awards, UK.
- 1993CC1406 K. Toshima, K. Ohta, A. Ohtsuka, S. Matsumura, and M. Nakata, *J. Chem. Soc., Chem. Commun.*, 1993, 1406.
- 1993CCC869 P. Šebek, P. Sedmera, and J. Kuthan, *Collect. Czech. Chem. Commun.*, 1993, **58**, 869.
- 1993JA3318 X. Zhang, T. Taketomi, T. Yoshizumi, H. Kumobayashi, S. Akutagawa, K. Mashima, and H. Takaya, *J. Am. Chem. Soc.*, 1993, **115**, 3318.
- 1993JOC3042 N. W. Boaz and K. M. Fox, *J. Org. Chem.*, 1993, **58**, 3042.
- 1993PS(81)101 M. G. Marei, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1993, **81**, 101.
- 1993SR161 M. Weissenfels, M. Pulst, and D. Greif, *Sulfur Rep.*, 1993, **15**, 161.
- 1993SL827 K. S. Feldman and H. M. Berven, *Synlett*, 1993, 827.
- 1993TL2537 E. D. Philips and G. H. Whitham, *Tetrahedron Lett.*, 1993, **34**, 2537.
- 1993USP5256621 M. S. Burberry, L. W. Tutt, and M. R. Detty, *US Pat.* 5256621 (1993) (*Chem. Abstr.*, 1994, **120**, 167007).
- 1994ACS417 J. Koskimies, R. Ugglä, and M. R. Sundberg, *Acta Chem. Scand.*, 1994, **48**, 417.
- 1994AGE465 H. Meier and A. Mayer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 465.
- 1994AHC(59)179 J. Kuthan, P. Šebek, and S. Böhm; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 1994, vol. 59, p. 179.
- 1994AHC(60)65 G. Doddi and G. Ercolani; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 1994, vol. 60, p. 65.
- 1994AXC1922 J. Kopf, H. Maelger, C. Thiemann, and P. Margaretha, *Acta Crystallogr., Sect. C*, 1994, **50**, 1922.
- 1994BCJ2876 S. Moriyama, T. Mochizuki, Y. Ohshima, and T. Saito, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 2876.
- 1994CCC2269 P. Šebek, J. Kroulík, P. Sedmera, V. Havlíček, and J. Kuthan, *Collect. Czech. Chem. Commun.*, 1994, **59**, 2269.
- 1994CL255 K. Takimiya, T. Otsubo, F. Ogura, H. Ashitaka, K. Morita, and T. Suehiro, *Chem. Lett.*, 1994, 255.
- 1994CNR1465 X. Sun, J. R. Wong, K. Song, J. Hu, K. D. Garlid, and L. B. Chen, *Cancer Res.*, 1994, **54**, 1465.
- 1994EPP594036 B. Rendenbach-Mueller, U. Karl, and H. Weifenbach, *Eur. Pat.* 594036 (1994) (*Chem. Abstr.*, 1994, **121**, 108805).
- 1994JA8937 D. Crich, C. Chen, J.-T. Hwang, H. Yuan, A. Papadatos, and R. I. Walter, *J. Am. Chem. Soc.*, 1994, **116**, 8937.
- 1994JCF83 N. S. Allen, D. Mallon, A. W. Timms, W. A. Green, F. Catalina, T. Corrales, S. Navaratnam, and B. J. Parsons, *J. Chem. Soc., Faraday Trans.*, 1994, 83.
- 1994JCF2849 L. A. Leal, D. G. Lister, J. L. Alonso, M. M. J. Tecklenburg, J. R. Villarreal, and J. Jaane, *J. Chem. Soc., Faraday Trans.*, 1994, 2849.
- 1994JFC(68)25 K. Tamura, T. Ishihari, and H. Yamanaka, *J. Fluorine Chem.*, 1994, **68**, 25.
- 1994JOC2762 D. D. DesMarteau, V. A. Petrov, V. Montanari, M. Pregnotato, and G. Resnati, *J. Org. Chem.*, 1994, **59**, 2762.
- 1994JOC2902 T. Patonay and R. V. Hoffman, *J. Org. Chem.*, 1994, **59**, 2902.
- 1994JOC6508 F. Beaulieu and V. Snieckus, *J. Org. Chem.*, 1994, **59**, 6508.
- 1994J(P1)101 B.-N. Huang, J.-T. Liu, and W.-Y. Huang, *J. Chem. Soc., Perkin Trans. 1*, 1994, 101.
- 1994J(P1)989 J. Bloxham and C. P. Dell, *J. Chem. Soc., Perkin Trans. 1*, 1994, 989.
- 1994J(P1)2631 S. Yamazaki, A. Isokawa, K. Yamamoto, and I. Murata, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2631.
- 1994J(P1)3129 H. Shimizu, S. Miyazaki, T. Kataoka, M. Hori, and O. Muraoka, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3129.
- 1994J(P2)2329 R. J. Abraham, L. Pollock, and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2329.
- 1994JPC10432 S. Ishijima, M. Higashi, and H. Yamaguchi, *J. Phys. Chem.*, 1994, **98**, 10432.
- 1994JPH(81)21 H. Pirelahi, M. S. Hashtroudi, M. S. Abaie, and Y. R. Shariati, *J. Photochem. Photobiol. A*, 1994, **81**, 21.
- 1994JPR434 U. Dietrich, A. Feindt, M. Pulst, M. Wiessenfels, D. Greif, and W. Cao, *J. Prakt. Chem.*, 1994, **336**, 434.
- 1994NCS376 U. Baumeister and H. Hartung, *Z. Kristallogr., New Cryst. Struct.*, 1994, **209**, 376.
- 1994PS(119)339 U. Beifuss and H. Gehm, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1994, **119**, 339.
- 1994S252 T. Zimmermann, *Synthesis*, 1994, 252.
- 1994S363 Y.-C. Xu, E. Lebeau, G. Attardo, and T. Breining, *Synthesis*, 1994, 363.
- 1994S973 D. Hellwinkel, R. Göke, and R. Karle, *Synthesis*, 1994, 973.
- 1994T827 C. D. Gabbutt, J. D. Hepworth, B. M. Heron, and M. Kanjia, *Tetrahedron*, 1994, **50**, 827.
- 1994T2507 C. D. Gabbutt, D. J. Hartley, J. D. Hepworth, B. M. Heron, M. Kanjia, and M. M. Rahman, *Tetrahedron*, 1994, **50**, 2507.
- 1994T3595 W. M. Abdou, Y. O. Elkhoshnieh, and M. M. Sidky, *Tetrahedron*, 1994, **50**, 3595.
- 1994T5245 C. D. Gabbutt, J. D. Hepworth, and B. M. Heron, *Tetrahedron*, 1994, **50**, 5245.
- 1994T7865 C. D. Gabbutt, J. D. Hepworth, and B. M. Heron, *Tetrahedron*, 1994, **50**, 7865.
- 1994T13113 W. Adam, D. Golsch, L. Hadjarapoglou, A. Léva, C. Nemes, and T. Patonay, *Tetrahedron*, 1994, **50**, 13113.
- 1994TL2161 A. Mayer and H. Meier, *Tetrahedron Lett.*, 1994, **35**, 2161.
- 1994TL2195 G. H. Lee, E. B. Choi, E. Lee, and C. S. Pak, *Tetrahedron Lett.*, 1994, **35**, 2195.
- 1994TL4955 W. Su, *Tetrahedron Lett.*, 1994, **35**, 4955.
- 1994TL5575 N. M. Carballeira, F. Shalabi, and C. Cruz, *Tetrahedron Lett.*, 1994, **35**, 5575.
- 1994WO9414793 D. E. Bertenshaw, D. Getman, R. M. Heintz, J. J. Talley, K. L. Reed, R. A. Chrusciel, and M. Clare, *PCT WO 9414793* (1994) (*Chem. Abstr.*, 1994, **123**, 169509).
- 1995AGE647 U. Beifuss, H. Gehm, M. Noltemeyer, and H.-G. Schmidt, *Angew. Chem., Int. Ed.*, 1995, **34**, 647.
- 1995BCJ2739 L. Glendenning, L. D. Field, and R. K. Haynes, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2739.
- 1995BCJ2791 S. Parret, F. Morlet-Savary, J.-P. Fouassier, K. Inomata, T. Matsumoto, and F. Heisel, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2791.
- 1995CCS565 M. Ohno, S. Kojima, and S. Eguchi, *J. Chem. Soc., Chem. Commun.*, 1995, 565.
- 1995CC1095 N. P. M. Huck and B. L. Feringa, *J. Chem. Soc., Chem. Commun.*, 1995, 1095.
- 1995CC1897 R. Arnaud, P. Y. Chavant, K. Molvinger, and Y. Vallée, *J. Chem. Soc., Chem. Commun.*, 1995, 1897.

- 1995DP(27)263 J. Zhang and Z. Zhu, *Dyes and Pigments.*, 1995, **27**, 263.
 1995DP(28)1 J. Zhang, W. Luo, and Z. Zhu, *Dyes and Pigments*, 1995, **28**, 1.
 1995EP648741 G. Lavielle, T. Dubuffet, O. Muller, M. Laubie, T. Verbeuren, S. Simonet, and J-J. Descombes, *Eur. Pat.* 648741 (1995) (*Chem. Abstr.*, 1995, **123**, 111683).
 1995EP659407 T. Okamoto, N. Yamamoto, and M. Kawaguchi, *Eur. Pat.* 659407 (1995) (*Chem. Abstr.* 1995, **123**, 221957).
 1995EPH37 C. Ito, Y. Isobe, H. Kijima, Y. Kiuchi, H. Ohtsuki, R. Kawamura, K. Tsuchida, and S. Higuchi, *Eur. J. Pharmacol.*, 1995, **285**, 37.
 1995HCA1079 C. P. Klaus, C. Thiemann, J. Kopf, and P. Margaretha, *Helv. Chim. Acta*, 1995, **78**, 1079.
 1995HAC631 M. W. Wiecezorek, J. Blaszczyk, B. Dziuba, P. Kielbasiński, M. Mikolajczyk, B. Zwanenburg, and J. B. M. Rewinkel, *Heteroatom Chem.*, 1995, **6**, 631.
 1995H(41)419 Y. Nagao, M. Goto, K. Kida, and M. Shiro, *Heterocycles*, 1995, **41**, 419.
 1995JA4822 K. Toshima, K. Ohta, A. Ohashi, T. Nakamura, M. Nakata, K. Tatsuta, and S. Matsumura, *J. Am. Chem. Soc.*, 1995, **117**, 4822.
 1995JA9929 B. L. Feringa, N. M. P. Huck, and H. A. van Doren, *J. Am. Chem. Soc.*, 1995, **117**, 9929.
 1995JCP9506 J. Choo, N. T. Meinander, J. R. Villarreal, and J. Laane, *J. Chem. Phys.*, 1995, **102**, 9506.
 1995JCM118 C. D. Gabbutt, J. D. Hepworth, and B. M. Heron, *J. Chem. Res. (S)*, 1995, 118.
 1995JR0805 C. D. Gabbutt, J. D. Hepworth, and B. M. Heron, *J. Chem. Res. (M)*, 1995, 0805.
 1995JFC(70)121 G. M. Alvernhe, D. Greif, A. J. Laurent, M. Pulst, and M. Weissenfels, *J. Fluorine Chem.*, 1995, **70**, 121.
 1995JFC(73)229 R. Möckel, W. Tyrra, and D. Naumann, *J. Fluorine Chem.*, 1995, **73**, 229.
 1995JHC687 T. Takedo, Y. Takagi, and K. Itabashi, *J. Heterocycl. Chem.*, 1995, **32**, 687.
 1995JOC1005 J. Spencer, M. Pfeffer, A. DeCian, and J. Fischer, *J. Org. Chem.*, 1995, **60**, 1005.
 1995JOC1665 N. G. Rule, M. R. Detty, J. E. Kaeding, and J. A. Sinicropi, *J. Org. Chem.*, 1995, **60**, 1665.
 1995JOC1674 M. R. Detty, R. S. Eachus, J. A. Sinicropi, J. R. Lenhard, M. McMillan, A. M. Lanzafame, H. R. Luss, R. Young, and J. E. Eilers, *J. Org. Chem.*, 1995, **60**, 1674.
 1995JOC6468 X.-F. Ren, E. Turos, C. H. Lake, and M. R. Churchill, *J. Org. Chem.*, 1995, **60**, 6468.
 1995JOC7272 M. Frigerio, M. Santagostino, S. Sputore, and G. Palmisano, *J. Org. Chem.*, 1995, **60**, 7272.
 1995J(P1)1583 H. Shimizu, S. Miyazaki, T. Kataoka, and M. Hori, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1583.
 1995J(P1)2845 T. Tanzawa, N. Shirai, Y. Sato, K. Hatano, and Y. Kurono, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2845.
 1995JPR379 D. Gröschl, A. Meyer, M. Schmidt, and H. Meier, *J. Prakt. Chem.*, 1995, **337**, 379.
 1995JST(331)245 S.-G. Hong, *J. Mol. Struct.*, 1995, **331**, 245.
 1995LA2221 A. Mayer, N. Rumpf, and H. Meier, *Liebigs Ann.*, 1995, 2221.
 1995MI169 J. P. Fouassier, D. Ruhlmann, B. Graff, and F. Wieder, *Prog. Org. Coatings*, 1995, **25**, 169.
 1995MI1351 O. V. Dorofeeva and L. V. Gurvich, *J. Phys. Chem. Ref. Data*, 1995, **24**, 1351.
 1995MI1485 O. M. Ogunsola and N. Berkowitz, *Fuel*, 1995, **74**, 1485.
 1995MI5619 A. Schmidt, M. L. Anderson, and N. R. Armstrong, *J. Appl. Phys.*, 1995, **78**, 5619.
 1995JCX321 J. W. Brock and S. G. Bott, *J. Chem. Crystallogr.*, 1995, **25**, 321.
 1995SL1495 P. T. Kaye and M. J. Mphahlele, *Synth. Commun.*, 1995, **25**, 1495.
 1995SL943 C. D. S. Brown, A. P. Dishington, O. Shishkin, and N. S. Simpkins, *Synlett*, 1995, 943.
 1995SM(70)1147 Y. Misaki, H. Fujiwara, and T. Yamabe, *Synth. Met.*, 1995, **70**, 1147.
 1995T13277 C. D. Gabbutt, J. D. Hepworth, and B. M. Heron, *Tetrahedron*, 1995, **51**, 13277.
 1995TL2579 B. W. Gung and M. B. Francis, *Tetrahedron Lett.*, 1995, **36**, 2579.
 1995TL3985 P. A. Evans, J. M. Longmire, and D. P. Modi, *Tetrahedron Lett.*, 1995, **36**, 3985.
 1995TL4459 T. Cohen, F. Chen, T. Kulinski, S. Florio, and V. Capriati, *Tetrahedron Lett.*, 1995, **36**, 4459.
 1995TL6899 M. Ohno, S. Kojima, Y. Shirakawa, and S. Eguchi, *Tetrahedron Lett.*, 1995, **36**, 6899.
 1995TL9381 N. P. M. Huck, A. Meetsma, R. Zijlstra, and B. L. Feringa, *Tetrahedron Lett.*, 1995, **36**, 9381.
 1995USP5401607 L. C. Takiff, S. J. Telfer, and K. C. Waterman, *US Pat.* 5401607 (1995) (*Chem. Abstr.*, 1995, **122**, 557393).
 1995USP5420295 M. E. Garst, L. J. Dolby, and A. N. Fedoruk, *US Pat.* 5420295 (1995) (*Chem. Abstr.*, 1995, **123**, 853).
 1995WO9511900 P. Pitchen, M. R. Powers, P. Leon, and D. Petre, *PCT WO 9511900* (1995) (*Chem. Abstr.*, 1995, **123**, 313769).
 1995WO9514670 G. Ku, B. L. Harrison, and D. M. Stemerick, *PCT WO 9514670* (1995) (*Chem. Abstr.*, 1995, **123**, 169528).
 1995ZOR1559 E. N. Shepelenko, A. D. Dubonosov, V. A. Bren, and V. I. Minkin, *Zh. Org. Khim.*, 1995, **31**, 1559.
 1996BCJ719 S. Watanabe, T. Yamamoto, T. Kawashima, N. Inamoto, and R. Okazaki, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 719.
 1996BCJ2091 K. Akimoto, K. Masaki, and J. Nakayama, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 2091.
 1996BMC1493 R. G. Wilde, J. T. Billheimer, S. J. Germain, E. A. Hausner, P. C. Meunier, D. A. Munzer, J. K. Stoltenborg, P. J. Gillies, D. L. Burcham, S.-M. Huang, J. D. Klaczekiewicz, S. S. Ko, and R. R. Wexler, *Bioorg. Med. Chem.*, 1996, **4**, 1493.
 1996BML2827 S. M. Bertenshaw, J. J. Talley, D. J. Rogier, M. J. Graneto, C. M. Koboldt, and Y. Zhang, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2827.
 1996CC1011 H. Kato, T. Kobayashi, M. Ciobanu, H. Iga, A. Akutsu, and A. Kakehi, *J. Chem. Soc., Chem. Commun.*, 1996, 1011.
 1996CC1659 H. Shimizu, T. Yonezawa, T. Watanabe, and K. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1996, 1659.
 1996CJC1418 D. E. Ward, T. E. Nixey, Y. Gai, M. Hrapchak, and M. S. Abaee, *Can. J. Chem.*, 1996, **74**, 1418.
 1996CHE777 B. I. Drevko, M. I. Smushkin, and V. G. Kharchenko, *Chem. Heterocycl. Compd.*, 1996, **32**, 777.
 1996CHEC-II(5)325 J. D. Hepworth, C. D. Gabbutt, and B. M. Heron, in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 325.
 1996CHEC-II(5)501 A. H. Ingall, in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 501.
 1996CL289 M. Sadao, I. Yasuyuki, and F. Koushi, *Chem. Lett.*, 1996, 289.
 1996CJC1418 D. E. Ward, T. E. Nixey, Y. Gai, M. J. Hrapchak, and M. S. Abaee, *Can. J. Chem.*, 1996, **74**, 1418.
 1996CPL(251)125 T. Sugino, N. Kambe, N. Sonoda, T. Sakaguchi, and K. Ohta, *Chem. Phys. Lett.*, 1996, **251**, 125.
 1996H(43)2567 A. Mohsine and L. Christiaens, *Heterocycles*, 1996, **43**, 2567.
 1996HCA855 M. Kägi, A. Linden, G. Mlostón, and H. Heimgartner, *Helv. Chim. Acta*, 1996, **79**, 855.

- 1996HCA1537
1996HCA1785
1996JC6676
1996JEO71
1996JME1975
1996JOC1859
1996JOC3650
1996JOC4725

1996JOC7642
1996JOC8701
1996JOM(507)215
1996JP11897
1996JP12227
1996JP2307
1996JP2547
1996JP2623
1996JPC13539
1996JPH(101)33
1996JPO159
1996JPP08248656
1996LA109
1996LA725
1996MI379
1996OPP705
1996PLM2477
1996PSB575
1996SC1875
1996SL182
1996SL261
1996SL396
1996SM(83)153
1996SL75
1996T3509
1996T4403
1996TA29

1996TA1089
1996TL123
1996TL4581
1996TL5077
1996USP5504104
1997AHC(67)267

1997BSF697
1997CC709
1997CJC681
1997CPB265

1997EPP758649
1997CHE1400
1997HCA1865
1997HCO223
1997JA5740
1997JA8058
1997JCF1517

1997JCM102
1997JHC1159
1997JME2466
1997JMP1247
1997JOC1766
1997JOC4943
1997JOC8455
1997JOC8572
1997JOC8630
1997JOC9018
1997JP12807
1997JP12957

G. Mlostón, T. Gendek, and H. Heimgartner, *Helv. Chim. Acta*, 1996, **79**, 1537.
G. Mlostón and H. Heimgartner, *Helv. Chim. Acta*, 1996, **79**, 1785.
J. Chen, R. L. Kirchmeier, and J. M. Shreeve, *Inorg. Chem.*, 1996, **35**, 6676.
S. Ishijima, M. Higashi, H. Yamaguchi, M. Kubota, and T. Kobayashi, *J. Electron Spectrosc.*, 1996, **82**, 71.
H.-K. Wang, K. F. Bastow, L. M. Cosentino, and K.-H. Lee, *J. Med. Chem.*, 1996, **39**, 1975.
J. Almena, F. Foubelo, and M. Yus, *J. Org. Chem.*, 1996, **61**, 1859.
Y. Misaki, H. Fujiwara, and T. Yamabe, *J. Org. Chem.*, 1996, **61**, 3650.
S. D. Larsen, P. V. Fisher, B. E. Libby, R. M. Jensen, S. A. Mizsak, W. Watt, W. R. Ronk, and S. T. Hill, *J. Org. Chem.*, 1996, **61**, 4725.
T. Bach and K. Kather, *J. Org. Chem.*, 1996, **61**, 7642.
H. J. Schostarez and T. M. Schwartz, *J. Org. Chem.*, 1996, **61**, 8701.
S. Lisac and V. Rapic, *J. Organomet. Chem.*, 1996, **507**, 215.
T. Saito, H. Fujii, S. Hayashibe, T. Matsushita, H. Kato, and K. Kobayashi, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1897.
H. Shimizu, S. Miyazaki, and T. Kataoka, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2227.
R. Beddoes, D. Heyes, R. S. Menon, and C. I. F. Watt, *J. Chem. Soc., Perkin Trans. 2*, 1996, 307.
G. Tóth, J. Halász, A. Lévai, C. Nemes, and T. Patonay, *J. Chem. Soc., Perkin Trans. 2*, 1996, 547.
D. Rondeau, E. Raoult, A. Tallec, L. Toupet, A. Imbert, and J. P. Pradère, *J. Chem. Soc., Perkin Trans. 2*, 1996, 2623.
A. Marcinek, J. Rogowski, J. Adamus, J. Gebicki, and M. S. Platz, *J. Phys. Chem.*, 1996, **100**, 13539.
H. Pirelahi, H. Rahmani, A. Mouradzadegan, A. Fathi, and A. Moudjoodi, *J. Photochem. Photobiol. A*, 1996, **101**, 33.
N. L. Allinger, Y. Fan, and T. Vernali, *J. Phys. Org. Chem.*, 1996, **9**, 159.
Y. Mizuta, H. Kawaguchi, and A. Kawahara, *Jpn. Pat.* 08248656 (1996) (*Chem. Abstr.*, 1996, **126**, 24848).
K. Hartke and X. Popp, *Liebigs Ann.*, 1996, 109.
K. Yamagata, K. Akizuki, and M. Yamazaki, *Liebigs Ann.*, 1996, 725.
C. Carlini, L. Angiolini, D. Caretti, and E. Corelli, *Polym. Adv. Technol.*, 1996, **7**, 379.
M. Hirano, K. Kamiya, S. Yakabe, J. H. Clark, and T. Morimoto, *Org. Prep. Proced. Int.*, 1996, **28**, 705.
D. G. Anderson, R. S. Davidson, and J. J. Elvery, *Polymer*, 1996, **37**, 2477.
P. M. Borsenberger and W. T. Gruenbaum, *J. Polym. Sci., Part B*, 1996, **34**, 575.
M. Hirano, S. Yakabe, J. H. Clark, H. Kudo, and T. Morimoto, *Synth. Commun.*, 1996, **26**, 1875.
U. Beifuss, M. Tietze, and H. Gehm, *Synlett*, 1996, 182.
D. E. Ward, Y. Gai, and Y. Lai, *Synlett*, 1996, 261.
U. Beifuss, H. Gehm, and M. Taraschewski, *Synlett*, 1996, 396.
J. Rault-Berthelot and C. Rozé, *Synth. Met.*, 1996, **83**, 153.
V. G. Nenajdenko, P. V. Verteletzkiy, and E. S. Balenkova, *Sulfur Lett.*, 1996, **20**, 75.
G. Doddi, M. C. Fazio, L. Luvidi, and P. Mencarelli, *Tetrahedron*, 1996, **52**, 3509.
G. Shi, Q. Wang, and M. Schlosser, *Tetrahedron*, 1996, **52**, 4403.
N. Maezaki, M. Soejima, A. Sakamoto, I. Sakamoto, Y. Matsumori, T. Tanaka, T. Ishida, Y. In, and C. Iwata, *Tetrahedron Asymmetry*, 1996, **7**, 29.
S. G. Allenmark and M. A. Andersson, *Tetrahedron Asymmetry*, 1996, **7**, 1089.
A. S. Bell, C. W. G. Fishwick, and J. E. Reed, *Tetrahedron Lett.*, 1996, **37**, 123.
J. Eames, M. A. de las Heras, R. V. H. Jones, and S. Warren, *Tetrahedron Lett.*, 1996, **37**, 4581.
S. Gauthier and F. Labrie, *Tetrahedron Lett.*, 1996, **37**, 5077.
E. L. Ellsworth and B. D. Tait, *US Pat.* 5504104 (1996) (*Chem. Abstr.*, 1996, **125**, 10616).
P. Lue and J. V. Greenhill, in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 1997, vol. 67, p. 267.
C. Portella, Y. G. Shermolovich, and O. Tschenn, *Bull. Soc. Chim. Fr.*, 1997, **134**, 697.
D. Brousmiche, D. Shukla, and P. Wan, *J. Chem. Soc., Chem. Commun.*, 1997, 709.
D. E. Ward and Y. Gai, *Can. J. Chem.*, 1997, **75**, 681.
T. Kataoka, Y. Nakamura, H. Matsunoto, T. Iwama, H. Shimizu, O. Muraoka, and G. Tanabe, *Chem. Pharm. Bull.*, 1997, **45**, 265.
K. Watanabe, T. Saito, and K. Niimura, *Eur. Pat.* 758649 (1997) (*Chem. Abstr.*, 1997, **126**, 199456).
N. A. Orlova, T. N. Gerasimova, and V. V. Shelkovnikov, *Chem. Heterocycl. Compd.*, 1997, **33**, 1400.
J. Bethke, J. Kopf, P. Margaretha, B. Pignon, L. Dupont, and L. E. Christiaens, *Helv. Chim. Acta*, 1997, **80**, 1865.
T. Patonay, J. A. S. Cavaleiro, A. Lévai, and A. M. S. Silva, *Heterocycl. Commun.*, 1997, **3**, 223.
K. Okada, T. Imakura, M. Oda, A. Kajiura, M. Kamachi, and M. Yamaguchi, *J. Am. Chem. Soc.*, 1997, **119**, 5740.
K. Matsuda, T. Yamagata, T. Seto, H. Iwamura, and K. Hori, *J. Am. Chem. Soc.*, 1997, **119**, 8058.
M. G. Neumann, M. H. Gehlen, M. V. Encinas, N. S. Allen, T. Corrales, C. Peinado, and F. Catalina, *J. Chem. Soc., Faraday Trans.*, 1997, **93**, 1517.
C. D. Gabbutt, J. D. Hepworth, and B. M. Heron, *J. Chem. Res. (S)*, 1997, 102.
S. E. Davies, A. C. Church, R. C. Tummons, and C. F. Beam, *J. Heterocycl. Chem.*, 1997, **34**, 1159.
M. Harfenist, D. M. Joseph, S. C. Spence, D. P. C. Mcgee, M. D. Reeves, and H. L. White, *J. Med. Chem.*, 1997, **40**, 2466.
D. K. Rohrbach and Y.-C. Yang, *J. Mass Spectrom.*, 1997, **32**, 1247.
J. Fabian and B. A. Hess, *J. Org. Chem.*, 1997, **62**, 1766.
A. M. Schoevaers, W. Kruizinga, R. W. J. Zijlstra, N. Veldman, A. L. Spek, and B. L. Feringa, *J. Org. Chem.*, 1997, **62**, 4943.
M. Andersson, A. Willetts, and S. Allenmark, *J. Org. Chem.*, 1997, **62**, 8455.
V. Ceré, F. Peri, and S. Pollicino, *J. Org. Chem.*, 1997, **62**, 8572.
M. Journet, A. Rouillard, D. Cai, and R. D. Larsen, *J. Org. Chem.*, 1997, **62**, 8630.
H. Morita, M. Takeda, T. Fujii, T. Yoshimura, and C. Shimasaki, *J. Org. Chem.*, 1997, **62**, 9018.
U. Beifuss and M. Taraschewski, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2807.
T. Saito, K. Takekawa, J. Nishimura, and M. Kawamura, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2957.

- 1997J(P2)1605 H. S. Kasmai and R. Liu, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1605.
- 1997JPH(111)15 H. Rahmani and H. Pirelahi, *J. Photochem. Photobiol. A*, 1997, **111**, 15.
- 1997JPP09025279 K. Nakamura, M. Shibata, and K. Koike, *Jpn. Pat.* 09025279 (1997) (*Chem. Abstr.*, 1997, **126**, 185985).
- 1997JST(412)115 O. V. Shishkin, *J. Mol. Struct.*, 1997, **412**, 115.
- 1997LA1173 H. Meier, B. Rose, and D. Schollmeyer, *Liebigs Ann.*, 1997, 1173.
- 1997MI2185 D. Rondeau, E. Raoult, and J. P. Pradere, *Electrochim. Acta*, 1997, **42**, 2185.
- 1997PS(120)403 H. Pirelahi, H. Rahmani, A. Mouradzadegan, A. Fathhi, and A. Moudjoodi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1997, **120–121**, 403.
- 1997PS(122)287 M. C. Melnyk and K. L. Busch, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1997, **122**, 287.
- 1997SL361 A. Degl'Innocenti, P. Scafato, A. Capperucci, L. Bartoletti, C. Spezzacatena, and R. Ruzziconi, *Synlett*, 1997, 361.
- 1997S764 M. H. Ali and W. C. Stevens, *Synthesis*, 1997, 764.
- 1997SSR(IVE)547 R. Livingstone; in 'Second Supplements to Rodd's Chemistry of Carbon Compounds', M. Sainsbury, Ed.; Elsevier, Amsterdam, 1997, vol. IVE, p. 547.
- 1997T4611 H. Shimizu, S. Miyazaki, and T. Kataoka, *Tetrahedron*, 1997, **53**, 4611.
- 1997T5563 J. Almena, F. Foubelo, and M. Yus, *Tetrahedron*, 1997, **53**, 5563.
- 1997T12273 R. S. Glass, Q. Guo, and Y. Liu, *Tetrahedron*, 1997, **53**, 12273.
- 1997TA1811 C. Forzato, P. Nitti, G. Pitacco, and E. Valentini, *Tetrahedron Asymmetry*, 1997, **8**, 1811.
- 1997TL153 R. A. Tapia, M. C. Garate, J. A. Valderrama, P. R. Jenkins, J. Fawcett, and D. R. Russell, *Tetrahedron Lett.*, 1997, **38**, 153.
- 1997TL1033 A. Marchand, J.-P. Pradère, and A. Guingant, *Tetrahedron Lett.*, 1997, **38**, 1033.
- 1997TL1385 N. Pelloux-Léon, R. Arnaud, J.-L. Ripoll, P. Beslin, and Y. Vallée, *Tetrahedron Lett.*, 1997, **38**, 1385.
- 1997TL5041 G. Capozzi, A. Corti, S. Menichetti, and C. Nativi, *Tetrahedron Lett.*, 1997, **38**, 5041.
- 1997TL8615 Y. Liu and R. S. Glass, *Tetrahedron Lett.*, 1997, **38**, 8615.
- 1997USP5593970 G. Attardo, J.-L. Kraus, M. Courchesne, S. Lamonthé, J.-F. Lavalée, E. Lebeau, D. Nguyen, R. Rej, Y. St. Denis, W. Wang, Y.-C. Xu, F. Barbeau, and B. Bellea, *US Pat.* 5593970 (1997) (*Chem. Abstr.*, 1997, **126**, 199791).
- 1997USP5602130 R. A. Chandraratna, *US Pat.* 5602130 (1997) (*Chem. Abstr.*, 1997, **126**, 225220).
- 1997WO9708163 I. Nasuno, S. Tomita, M. Shibata, and H. Yamamoto, *PCT WO 9708163* (1997) (*Chem. Abstr.*, 1997, **126**, 238301).
- 1997WO9715305 H. G. Bull, G. Harris, and R. W. Myers, *PCT WO 9715305* (1997) (*Chem. Abstr.*, 1997, **127**, 5231).
- 1997WO9715564 R. K. Bakshi, G. F. Patel, G. H. Rasmusson, and R. L. Tolman, *PCT WO 9715564* (1997) (*Chem. Abstr.*, 1997, **127**, 50846).
- 1998AGE3136 J. Barluenga, G. P. Romanelli, L. J. Alvarez-García, I. Llorente, J. M. González, E. García-Rodríguez, and S. García-Granda, *Angew. Chem., Int. Ed.*, 1998, **37**, 3136.
- 1998BCJ1719 H. Iwanaga, K. Naito, K. Sunohara, and M. Okajima, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1719.
- 1998CC1807 J. M. Fraile, J. I. Garcia, B. Lázaro, and J. A. Mayoral, *J. Chem. Soc., Chem. Commun.*, 1998, 1807.
- 1998CCC662 J. Kroulik, M. Chadim, M. Polasek, S. Nespurek, and J. Kuthan, *Collect. Czech. Chem. Commun.*, 1998, **63**, 662.
- 1998CH246 S. G. Allenmark and M. A. Andersson, *Chirality*, 1998, **10**, 246.
- 1998EJO1989 M. Hemmerling, S. Hünig, M. Kemmer, and K. Peters, *Eur. J. Org. Chem.*, 1998, 1989.
- 1998EJO2861 J. Breu, P. Höcht, U. Rohr, J. Schatz, and J. Sauer, *Eur. J. Org. Chem.*, 1998, 2861.
- 1998H(49)143 A. R. Katritzky, Z. Zhang, M. Qi, N. Jubran, and L. M. Leichter, *Heterocycles*, 1998, **49**, 143.
- 1998HCO547 P. Sebök, A. Lévai, and T. Timár, *Heterocycl. Commun.*, 1998, **4**, 547.
- 1998JA841 R. Berger, J. W. Ziller, and D. L. Van Vranken, *J. Am. Chem. Soc.*, 1998, **120**, 841.
- 1998JA7657 R. Han and G. L. Hillhouse, *J. Am. Chem. Soc.*, 1998, **120**, 7657.
- 1998JPP10120565 H. Yoshimura, Y. Isobe, and S. Higuchi, *Jpn. Pat.* (1998) (*Chem. Abstr.*, 1998, **129**, 45281).
- 1998JPP10257889 S. Yamamoto, H. Okamoto, T. Suzuki, and N. Sugimoto, *Jpn. Pat.* 10257889 (1998) (*Chem. Abstr.*, 1998, **129**, 311673).
- 1998JPP10316964 Y. Sato, A. Ichinosawa, and Y. Murata, *Jpn. Pat.* 10316964 (1998) (*Chem. Abstr.*, 1998, **130**, 87963).
- 1998JHC1505 N. Rumpf, D. Groschl, H. Meier, D. C. Oniciu, and A. R. Katritzky, *J. Heterocycl. Chem.*, 1998, **35**, 1505.
- 1998JME1815 I. Pajeva and M. Wiese, *J. Med. Chem.*, 1998, **41**, 1815.
- 1998JOC1583 B. Halton, M. J. Coony, R. Boese, and A. H. Maulitz, *J. Org. Chem.*, 1998, **63**, 1583.
- 1998JOC1910 T. Bach, K. Kather, and O. Kramer, *J. Org. Chem.*, 1998, **63**, 1910.
- 1998JOC4626 T. R. Klein, M. Bergemann, N. A. M. Yehia, and E. Fanghänel, *J. Org. Chem.*, 1998, **63**, 4626.
- 1998JOC9517 S. E. Denmark, R. A. Stavenger, S. B. D. Winter, K.-T. Wong, and P. A. Barsanti, *J. Org. Chem.*, 1998, **63**, 9517.
- 1998JPH(113)53 D. Shukla and P. Wan, *J. Photochem. Photobiol. A*, 1998, **113**, 53.
- 1998JPH(113)155 F. Galindo and M. A. Miranda, *J. Photochem. Photobiol. A*, 1998, **113**, 155.
- 1998JPH(114)213 A.-M. Abdel-Wahab and A. E.-A. M. Gaber, *J. Photochem. Photobiol. A*, 1998, **114**, 213.
- 1998JPO831 F. Freeman, A. Phornvoranunt, and W. J. Hehre, *J. Phys. Org. Chem.*, 1998, **11**, 831.
- 1998MCL179 K. Tanaka and F. Toda, *Mol. Cryst. Liq. Cryst.*, 1998, **313**, 179.
- B-1998MI1 J. V. Crivello and K. Dietliker; in 'Photoinitiators for Free Radical Cationic & Anionic Photopolymerisation Volume III', 2nd edn., G. Bradley, Ed.; J. Wiley and Sons, (Chichester), 1998.
- B-1998MI375 V. G. Kharchenko and S. N. Chalaya; in 'Poluchenie i Svoistva Organicheskikh Soedinenii Sery', L. I. Belen'kii, Ed.; Khimiya, Moscow, 1998, p. 375.
- 1998OPP243 Y.-C. Xu, *Org. Prep. Proced. Int.*, 1998, **30**, 243.
- 1998OSC692 R. Bishop; in 'Organic Syntheses, Collective Volume', J. P. Freeman, Ed.; Wiley, New York, 1998, vol. 9, p. 692.
- 1998PSA2563 J. Yang, Z. Zeng, and Y. Chen, *J. Polym. Sci. A, Polym. Chem. Part*, 1998, **36**, 2563.
- 1998PS(134)295 M. Schneider, M. J. Gil, A. Reliquet, J. C. Meslin, J. Levillain, M. Vazeux, D. Jury, J. L. Mieloszynski, and D. Paquer, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1998, **134–135**, 295.
- 1998RJO557 V. D. Dyachenko and V. P. Litvinov, *Russ. J. Org. Chem. (Engl. Transl.)*, 1998, **34**, 557.
- 1998RRC163 A. A. Atalla, A. M. Hussein, and M. Z. A. Badr, *Rev. Roum. Chim.*, 1998, **43**, 163.
- 1998S1098 M. G. Cabiddu, S. Cabiddu, E. Cadoni, P. Demurtas, C. Fattuoni, C. Floris, and S. Melis, *Synthesis*, 1998, 1098.
- 1998SC2969 M. H. Ali, D. R. Leach, and C. E. Schmitz, *Synth. Commun.*, 1998, **28**, 2969.
- 1998SC2983 M. H. Ali and G. J. Bohnert, *Synth. Commun.*, 1998, **28**, 2983.
- 1998T1375 M. Ordóñez and E. Juaristi, *Tetrahedron*, 1998, **54**, 1375.

- 1998T2251 F. Gualtieri, A. Mordini, S. Pecchi, and S. Scapecchi, *Tetrahedron*, 1998, **54**, 2251.
1998T5599 M. V. Lebedev, V. G. Nenajdenko, and E. S. Balenkova, *Tetrahedron*, 1998, **54**, 5599.
1998T15293 M. A. Andersson and S. G. Allenmark, *Tetrahedron*, 1998, **54**, 15293.
1998T15499 G. K. Tranmer and A. Capretta, *Tetrahedron*, 1998, **54**, 15499.
1998TL2631 N. A. Nedolya, L. Brandsma, H. D. Verkuijsse, A. H. T. M. van der Kerk, and B. A. Trofimov, *Tetrahedron Lett.*, 1998, **39**, 2631.
1998TL2671 Z. Yu and J. G. Verkade, *Tetrahedron Lett.*, 1998, **39**, 2671.
1998USP5759729 T. I. Martin, C. A. Jennings, E. G. Johnson, and J. F. Oliver, *US Pat.* 5759729 (1998) (*Chem. Abstr.*, 1998, **129**, 74000).
1998WO9804554 A. Naya, Y. Owada, T. Saeki, K. Ohwaki, and Y. Iwasawa, *PCT WO* 9804554 (1998) (*Chem. Abstr.*, 1998, **128**, 167352).
1998WO9825916 J. C. Jo, S. D. Park, H. S. Lim, J. S. Kim, S. J. Kim, K. Morikawa, Y. Kanbe, M. Nishimoto, and M.-H. Kim, *PCT WO* 9825916 (1998) (*Chem. Abstr.*, 1998, **129**, 81667).
1998WO9829416 H. Hanaki, H. Yamazaki, Y. Tsuchida, H. Sato, K. Keiichi, and S. Kawashima, *PCT WO* 9829416 (1998) (*Chem. Abstr.*, 1998, **129**, 122499).
1998WO9842697 L. E. Williams, R. Ran, C. U. Pittman, Jr., J. S. Bowers, Jr., and A. J. Muller, *PCT WO* 9842697 (1998) (*Chem. Abstr.*, 1998, **129**, 276511).
1998WO9853369 J. A. Bonham, *PCT WO* 9853369 (1998) (*Chem. Abstr.*, 1998, **130**, 45292).
1999AGE3523 K. Tanaka, F. Toda, E. Mochizuki, N. Yasui, Y. Kai, I. Miyahara, and K. Hirotsu, *Angew. Chem., Int. Ed.*, 1999, **38**, 3523.
1999CC1001 T. Saito, K. Takekawa, and T. Takahashi, *J. Chem. Soc., Chem. Commun.*, 1999, 1001.
1999CEJ1038 K. Rück-Braun and C. Möller, *Chem. Eur. J.*, 1999, **5**, 1038.
1999CHE549 V. G. Nenajdenko, A. V. Sanin, A. V. Churakov, J. A. K. Howard, and E. S. Balenkova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 549.
1999CHE746 L. I. Markova, N. G. Korobochkina, and V. G. Kharchenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 549.
1999CJC463 H. L. Holland, C. D. Turner, P. R. Andreana, and D. Nguyen, *Can. J. Chem.*, 1999, **77**, 463.
1999CM3279 K. Okamoto, T. Nomura, S.-H. Park, K. Ogino, and H. Sato, *Chem. Mater.*, 1999, **11**, 3279.
1999EJO2573 P. Kiełbasiński, B. Zwanenburg, T. J. G. Damen, M. W. Wiczorek, W. R. Majzner, and G. D. Bujacz, *Eur. J. Org. Chem.*, 1999, 2573.
1999HAC363 M. Takeda, T. Hashimoto, T. Fujii, S. Ono, T. Yoshimura, C. Shimasaki, and H. Morita, *Heteroatom Chem.*, 1999, **10**, 363.
1999HCO217 B. F. Bonini, G. Mazzanti, and P. Zani, *Heterocycl. Commun.*, 1999, **5**, 217.
1999IJB376 S. Selvaraj, S. Renuga, M. Gnanadeepam, S. Perumal, and S. Sivakolunthu, *Indian J. Chem., Sect. B*, 1999, **38**, 376.
1999JAS819 B. H. Lipschutz and P. A. Blomgren, *J. Am. Chem. Soc.*, 1999, **121**, 5819.
1999JA7606 D. A. Vicic and W. D. Jones, *J. Am. Chem. Soc.*, 1999, **121**, 7606.
1999JHC707 K. Leonard, M. Nelen, M. Raghu, and M. R. Detty, *J. Heterocycl. Chem.*, 1999, **36**, 707.
1999JME751 T. Oda, K. Notoya, M. Gotoh, S. Taketomi, Y. Fujisawa, H. Makino, and T. Sohda, *J. Med. Chem.*, 1999, **42**, 751.
1999JME3942 K. A. Leonard, M. I. Nelen, L. T. Anderson, S. L. Gibson, R. Hilf, and M. R. Detty, *J. Med. Chem.*, 1999, **42**, 3942.
1999JME3953 K. A. Leonard, M. I. Nelen, T. P. Simard, S. R. Davies, S. O. Gollnick, A. R. Oseroff, S. L. Gibson, R. Hilf, L. B. Chen, and M. R. Detty, *J. Med. Chem.*, 1999, **42**, 3953.
1999JME4434 D. Zacheis, A. Dhar, S. Lu, M. M. Madler, J. Klucik, C. W. Brown, S. Liu, F. Clement, S. Subramanian, G. M. Weerasekare, K. D. Berlin, M. A. Gold, J. R. Houck, Jr., K. R. Fountain, and D. M. Benbrook, *J. Med. Chem.*, 1999, **42**, 4434.
1999JOC6730 H. Morita, M. Takeda, T. Yoshimura, T. Fujii, S. Ono, and C. Shimasaki, *J. Org. Chem.*, 1999, **64**, 6730.
1999JOC9646 W.-J. Xiao and H. Alper, *J. Org. Chem.*, 1999, **64**, 9646.
1999JOM(584)171 M. Abedini, H. Pirelahi, and S. M. Moossavi, *J. Organomet. Chem.*, 1999, **584**, 171.
1999J(P1)1547 K. Kobayashi, R. Nakahashi, A. Shimizu, T. Kitamura, O. Morikawa, and H. Konishi, *J. Chem. Soc. Perkin Trans. 1*, 1999, 1547.
1999JPO176 F. Freeman, A. Phornvoranunt, and W. J. Hehre, *J. Phys. Org. Chem.*, 1999, **12**, 176.
1999JPR184 R. Balicki, *J. Prakt. Chem.*, 1999, **341**, 184.
1999ST(492)225 F. Freeman, A. Phornvoranunt, and W. J. Hehre, *J. Mol. Struct.*, 1999, **492**, 225.
1999MI6506 Goonesekera and S. Ducharme, *J. Appl. Phys.*, 1999, **85**, 6506.
1999OL149 C. S. Tomooka, D. D. LeCloux, H. Sasaki, and E. M. Carreira, *Org. Lett.*, 1999, **1**, 149.
1999PS(153)119 B. Zwanenburg, T. J. G. Damen, H. J. F. Philipse, R. C. De Laet, and A. C. B. Lucassen, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1999, **153-154**, 119.
1999SC1857 L. Somogyi, *Synth. Commun.*, 1999, **29**, 1857.
1999SC2235 R. Balicki, *Synth. Commun.*, 1999, **29**, 2235.
1999SL735 C.-J. Li and D.-L. Chen, *Synlett*, 1999, 735.
1999SL1739 A. Degl'Innocenti, A. Capperucci, P. Scafato, T. Mecca, G. Reginato, and A. Mordini, *Synlett*, 1999, 1739.
1999SM(102)1621 T. Kaibuki, Y. Misaki, K. Tanaka, K. Takimiya, A. Morikami, and T. Otsubo, *Synth. Met.*, 1999, **102**, 1621.
1999SM(102)1737 H. Fujiwara, T. Nishikawa, Y. Misaki, and T. Yamabe, *Synth. Met.*, 1999, **102**, 1737.
1999SM(105)55 H. Sato, H. Matsuda, K. Okamoto, K. Ogino, and Y. Pei, *Synth. Met.*, 1999, **105**, 55.
1999T6785 J. J. Parlow, B. L. Case, and M. S. South, *Tetrahedron*, 1999, **55**, 6785.
1999TA183 S. Ozaki, H.-J. Yang, T. Matsui, Y. Goto, and Y. Watanabe, *Tetrahedron Asymmetry*, 1999, **10**, 183.
1999TA4427 J. L. Garcia Ruano and A. Rumbero, *Tetrahedron Asymmetry*, 1999, **10**, 4427.
1999TL1373 T. Patonay, C. Haddu, J. Jekö, A. Lévai, K. Micskei, and C. Zucchi, *Tetrahedron Lett.*, 1999, **40**, 1373.
1999TL6473 B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, and G. Varchi, *Tetrahedron Lett.*, 1999, **40**, 6473.
1999TL6831 T. Nakada, S. Sudo, S. Kosemura, and S. Yamamura, *Tetrahedron Lett.*, 1999, **40**, 6831.
1999TL7911 M. P. Coleman and M. K. Boyd, *Tetrahedron Lett.*, 1999, **40**, 7911.
1999TL8383 T. Saito, J. Nishimura, D. Akiba, H. Kusuoku, and K. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 8383.
1999USP5919950 P. P. Garcia, J. W. Lee, J. L. Marshall, D. A. McGowan, A. J. Puttick, T. K. Spencer, S. G. Stroud, S. J. Telfer, and M. J. Zuraw, *US Pat.* 5919950 (1999) (*Chem. Abstr.*, 1999, **131**, 117479).
1999WO9929688 T.-J. Poel, J. P. Martin, Jr., and M. R. Barbachyn, *PCT WO* 9929688 (1999) (*Chem. Abstr.*, 1999, **131**, 31934).

- 1999WO9933820 K. Nakamura, M. Shibata, and K. Koike, *PCT WO 9933820* (1999) (*Chem. Abstr.*, 1999, **131**, 87819).
- 1999WO9952890 A. Billich, P. Nussbaumer, E. Schreiner, and I. Schuster, *PCT WO 9952890* (1999) (*Chem. Abstr.*, 1999, **131**, 399370).
- 1999WO9965893 J. C. Jo, H. S. Lim, J. M. Kim, J. S. Kim, K. Morikawa, Y. Kanbe, M. H. Kim, and M. Nishimoto, *PCT WO 9965893* (1999) (*Chem. Abstr.*, 1999, **132**, 49886).
- 2000AGE1804 T. Suzuki, J. Nishida, M. Ohkita, and T. Tsuji, *Angew. Chem., Int. Ed.*, 2000, **39**, 1804.
- 2000BCJ155 K. Okuma, K. Shiki, S. Sonoda, Y. Koga, K. Shioji, T. Kitamura, Y. Fujiwara, and Y. Yokomori, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 155.
- 2000CC1191 H. Al-Badri, N. Collignon, J. Maddaluno, and S. Masson, *J. Chem. Soc., Chem. Commun.*, 2000, 1191.
- 2000CL1274 Y. Misaki, T. Kaibuki, M. Taniguchi, K. Tanaka, T. Kawamoto, T. Mori, and T. Nakamura, *Chem. Lett.*, 2000, 1274.
- 2000CHE1032 L. I. Markova, N. G. Korobochkina, T. N. Serdyukova, and V. G. Kharchenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2000, **36**, 1032.
- 2000EJO1695 R. Huisgen, X. Li, G. Mloston, and C. Fulka, *Eur. J. Org. Chem.*, 2000, 1695.
- 2000EJO2391 A. F. Bonini, M. C. Franchini, M. Fochi, S. Mangini, G. Mazzanti, and A. Ricci, *Eur. J. Org. Chem.*, 2000, 2391.
- 2000ELA1138 M. R. Ganjali, M. R. Fathi, H. Rahmani, and H. Pirelahi, *Electroanalysis*, 2000, **12**, 1138.
- 2000H(53)585 R. A. Tapia, M. C. Garate, J. A. Valderrama, F. Zuloaga, P. R. Jenkins, J. Fawcett, and D. R. Russell, *Heterocycles*, 2000, **53**, 585.
- 2000H(53)1193 A. Lévai, T. Timár, P. Sebök, and T. Eszenyi, *Heterocycles*, 2000, **53**, 1193.
- 2000HCA1168 D. Schwebel and P. Margaretha, *Helv. Chim. Acta*, 2000, **83**, 1168.
- 2000JA12005 N. Koumura, E. M. Geertsema, A. Meetsma, and B. L. Feringa, *J. Am. Chem. Soc.*, 2000, **122**, 12005.
- 2000JFA2420 J. S. Elmore and D. S. Mottram, *J. Agric. Food Chem.*, 2000, **48**, 2420.
- 2000JHC1233 A. M. El-Sayed and H. Abdel-Ghany, *J. Heterocycl. Chem.*, 2000, **37**, 1233.
- 2000JHC1527 A. W. Jensen, J. Manczuk, D. Nelson, O. Caswell, and S. A. Fleming, *J. Heterocycl. Chem.*, 2000, **37**, 1527.
- 2000JME4488 K. A. Leonard, J. P. Hall, M. I. Nelen, S. R. Davies, S. O. Gollnick, S. Camacho, A. R. Oseroff, S. L. Gibson, R. Hilf, and M. R. Detty, *J. Med. Chem.*, 2000, **43**, 4488.
- 2000JMT(529)225 F. Freeman and W. J. Hehre, *J. Mol. Struct. Theochem*, 2000, **529**, 225.
- 2000JOC2236 T. P. Simard, J. H. Yu, J. M. Zebrowski-Young, N. F. Haley, and M. R. Detty, *J. Org. Chem.*, 2000, **65**, 2236.
- 2000JOC4584 A. W. Marsman, R. W. A. Havenith, S. Bethke, L. W. Jenneskens, R. Gleiter, J. H. van Lenthe, M. Lutz, and A. L. Spek, *J. Org. Chem.*, 2000, **65**, 4584.
- 2000JOC9206 A. Degl'Innocenti, A. Capperucci, D. C. Oniciu, and A. R. Katritzky, *J. Org. Chem.*, 2000, **65**, 9206.
- 2000JP1)2930 C. D. Gabbutt, J. D. Hepworth, B. M. Heron, S. J. Coles, and M. B. Hursthouse, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2930.
- 2000JP2)571 N. S. Kulikov and M. S. Bobyleva, *J. Chem. Soc., Perkin Trans. 2*, 2000, 571.
- 2000JPR494 K. Yamagata, F. Okabe, and M. Yamazaki, *J. Prakt. Chem.*, 2000, **342**, 494.
- 2000JST(524)297 P. Sohár, P. Perjési, K. W. Törnroos, S. Husebye, A. Vértes, Gy Vankó, and R. E. Bozak, *J. Mol. Struct.*, 2000, **524**, 297.
- 2000MC77 D. V. Kozhinov, S. A. Woznesensky, A. A. Dudinov, and M. M. Krayushkin, *Mendeleev Commun.*, 2000, **10**, 77.
- 2000MI22 H. Shimizu, N. Kudo, T. Kataoka, and M. Hori, *ITE Lett. Batteries, New Technol. Med.*, 2000, **1**, C22.
- 2000MI212 Y. Lin, Z. Qian, J. Wang, and G. Qi, *Huadong Ligong Daxue Xuebao*, 2000, **26**, 212 (*Chem. Abstr.*, 2000, **133**, 193518).
- 2000NCS217 K. Peters, E.-M. Peters, W. Adam, P. Kövér, A. Lévai, and T. Patonay, *Z. Kristallogr. New Cryst. Struct.*, 2000, **215**, 217.
- 2000NCS219 K. Peters, E.-M. Peters, W. Adam, P. Kövér, A. Lévai, and T. Patonay, *Z. Kristallogr. New Cryst. Struct.*, 2000, **215**, 219.
- 2000OL1325 D. E. Ward, C. Guo, P. K. Sasmal, C. C. Man, and M. Sales, *Org. Lett.*, 2000, **2**, 1325.
- 2000PCB7266 E. P. A. M. Bakkers, A. L. Roest, A. W. Marsman, L. W. Jenneskens, L. I. de Jong-van Steensel, J. J. Kelly, and D. Vanmackelbergh, *J. Phys. Chem. B*, 2000, **104**, 7266.
- 2000SC1193 J.-C. Jung, J.-C. Kim, and O.-S. Park, *Synth. Commun.*, 2000, **30**, 1193.
- 2000SL418 F. Cachoux, M. Ibrahim-Ouali, and M. Santelli, *Synlett*, 2000, 418.
- 2000SL658 J. Prabhakaran, H. Lhermitte, J. Das, T. K. Sasi-Kumar, and D. S. Grierson, *Synlett*, 2000, 658.
- 2000SL975 J. P. Storm, R. D. Ionescu, D. Martinsson, and C.-M. Andersson, *Synlett*, 2000, 975.
- 2000SL1804 R. Samuel, S. K. Nair, and C. V. Asokan, *Synlett*, 2000, 1804.
- 2000T3909 H. Al-Badri, N. Collignon, J. Maddaluno, and S. Masson, *Tetrahedron*, 2000, **56**, 3909.
- 2000T6763 M. A. Kinder, J. Klopff, and P. Margaretha, *Tetrahedron*, 2000, **56**, 6763.
- 2000T6853 K. Tanaka, E. Mochizuki, N. Yasui, Y. Kai, I. Miyahara, K. Hirotsu, and F. Toda, *Tetrahedron*, 2000, **56**, 6853.
- 2000TL371 K. Nishide, S. Ohsugi, and M. Node, *Tetrahedron Lett.*, 2000, **41**, 371.
- 2000TL1321 X.-F. Yang and C.-J. Li, *Tetrahedron Lett.*, 2000, **41**, 1321.
- 2000TL2279 A. A. Ponnaras and Ö.Zaim, *Tetrahedron Lett.*, 2000, **41**, 2279.
- 2000TL6157 A. Levy and I. Agranat, *Tetrahedron Lett.*, 2000, **41**, 6157.
- 2000TL7327 B. Heuzé, R. Gasparova, M. Heras, and S. Masson, *Tetrahedron Lett.*, 2000, **41**, 7327.
- 2000TL7987 E. W. Della and S. D. Graney, *Tetrahedron Lett.*, 2000, **41**, 7987.
- 2000TL8255 W. Schmack, T. Nakazawa, and K. Hafner, *Tetrahedron Lett.*, 2000, **41**, 8255.
- 2000USP6046335 P. Boeglin, B. L. Kaul, and B. Piatsra, *US Pat.* 6046335 (2000) (*Chem. Abstr.*, 2000, **132**, 252412).
- 2000WO2000019990 E. S. Klein, Y.-D. Yuan, and R. A. Chandraratna, *PCT WO 2000019990* (2000) (*Chem. Abstr.*, 2000, **132**, 274821).
- 2000WO2000031588 R. Y. Tsien and T. Furuta, *PCT WO 2000031588* (2000) (*Chem. Abstr.*, 2000, **133**, 17381).
- 2000WO2000040576 K. Taniguchi, M. Neya, T. Terasawa, H. Yamazaki, K. Sato, K. Hosoi, Y. Tomishima, N. Yoshida, Y. Imamura, H. Takasugi, and H. Setoi, *PCT WO 2000040576* (2000) (*Chem. Abstr.*, 2000, **133**, 104964).
- 2001AGE3251 J. Nishida, T. Suzuki, M. Ohkita, and T. Tsuji, *Angew. Chem., Int. Ed.*, 2001, **40**, 3251.
- 2001AHC(81)254 B. Stanovnik, M. Tišler, A. R. Katritzky, and O. V. Denisko; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 2001, vol. 81, p. 254.
- 2001CHE797 R. V. Sella, P. V. Reshetov, and A. P. Kriven'ko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2001, **37**, 797.
- 2001EJO529 A. Ali, V. U. Ahmad, and J. Liebscher, *Eur. J. Org. Chem.*, 2001, 529.
- 2001EJO1467 T. Billard, B. R. Langlois, and G. Blond, *Eur. J. Org. Chem.*, 2001, 1467.
- 2001EJO1525 J.-M. Coustard, *Eur. J. Org. Chem.*, 2001, 1525.
- 2001EJO2477 H. Poleschner and K. Seppelt, *Eur. J. Org. Chem.*, 2001, 2477.

- 2001HCA1578 Z.-X. Wang and P. von R. Schleyer, *Helv. Chim. Acta*, 2001, **84**, 1578.
2001JA7352 R. F. Khairutdinov and J. K. Hurst, *J. Am. Chem. Soc.*, 2001, **123**, 7352.
2001JOC739 X.-F. Yang, J. T. Mague, and C.-J. Li, *J. Org. Chem.*, 2001, **66**, 739.
2001JOC2275 T. Patonay, W. Adam, A. Lévai, P. Kövér, M. Németh, E.-M. Peters, and K. Peters, *J. Org. Chem.*, 2001, **66**, 2275.
2001JOC4386 A. Converso, K. Burow, A. Marzinik, K. B. Sharpless, and M. G. Finn, *J. Org. Chem.*, 2001, **66**, 4386.
2001JOC5333 V. J. Ram, P. Srivastava, and A. S. Saxena, *J. Org. Chem.*, 2001, **66**, 5333.
2001JOC5595 A. R. Katritzky and M. A. C. Button, *J. Org. Chem.*, 2001, **66**, 5595.
2001JOC7030 K. M. Dawood, H. Ishii, and T. Fuchigami, *J. Org. Chem.*, 2001, **66**, 7030.
2001JP12269 H. Shimizu, N. Kudo, T. Kataoka, and M. Hori, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2269.
2001JP22329 A. Levy, P. U. Biedermann, S. Cohen, and I. Agranat, *J. Chem. Soc., Perkin Trans. 2*, 2001, 2329.
2001JPH(138)203 A. Mouradzadegun and H. Pirelahi, *J. Photochem. Photobiol. A*, 2001, **138**, 203.
2001JPH(139)45 M. Tahhizadeh and H. Pirelahi, *J. Photochem. Photobiol. A*, 2001, **139**, 45.
2001JSS766 M. R. Hadley, M. Decrette, G. Guilleré, C. Rosini, M. I. Donnoli, S. Superchi, and A. J. Hutt, *J. Sep. Sci.*, 2001, **24**, 766.
2001JST(535)257 E. Kleinpeter, A. Koch, and F. Taddei, *J. Mol. Struct.*, 2001, **535**, 257.
2001JST(535)287 F. Freeman, F. Gomarooni, and W. J. Hehre, *J. Mol. Struct.*, 2001, **535**, 287.
2001JST(549)203 F. Freeman, T. Nguyen, and W. J. Hehre, *J. Mol. Struct.*, 2001, **549**, 203.
2001M689 R. Heikmatshoar, I. Yavari, Y. S. Beheshtiha, and M. M. Heravi, *Monatsh. Chem.*, 2001, **132**, 689.
2001M721 K. Yamagata, F. Okabe, and M. Yamazaki, *Monatsh. Chem.*, 2001, **132**, 721.
2001M947 K. Bogdanowicz-Szwed and A. Budzowski, *Monatsh. Chem.*, 2001, **132**, 947.
2001MI331 T. Sumiyoshi, S. Ueta, and S. Sawamura, *Radiat. Phys. Chem.*, 2001, **60**, 331.
2001MS251 G. Tóth, J. Kovács, A. Lévai, E. Kleinpeter, and A. Koch, *Magn. Reson. Chem.*, 2001, **39**, 251.
2001NCS47 H. Rahmani, A. Taeb, A. Tadjarodi, and H. Pirelahi, *Z. Kristallogr. New. Cryst. Struct.*, 2001, **216**, 47.
2001OL1965 M. A. Miranda, M. A. Izquierdo, and F. Galindo, *Org. Lett.*, 2001, **3**, 1965.
2001OPD80 P. M. Herrinton, C. E. Owen, and J. R. Gage, *Org. Process Res. Dev.*, 2001, **5**, 80.
2001PCB2122 L. T. Okano, T. C. Barros, D. T. H. Chou, A. J. Bennet, and C. Bohne, *J. Phys. Chem. B*, 2001, **105**, 2122.
2001P443 Y. Saritas, M. M. Sonwa, H. Iznaguen, W. A. König, H. Muhle, and R. Mues, *Phytochemistry*, 2001, **57**, 443.
2001PS(176)203 A. Mouradzadegun and H. Pirelahi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2001, **176**, 203.
2001S409 G. Capozzi, S. Giacomelli, S. Menichetti, and C. Nativi, *Synthesis*, 2001, 409.
2001S2389 P. T. Kaye and X. W. Nocanda, *Synthesis*, 2001, 2389.
2001SM(116)275 S. de O. Dantas, P. M. V. Barone, S. F. Braga, and D. S. Galvão, *Synth. Met.*, 2001, **116**, 275.
2001T1005 U. Beifuss, U. Schniske, and G. Feder, *Tetrahedron*, 2001, **57**, 1005.
2001T2895 T. Patonay, Z. Dinya, A. Lévai, and D. Molnár, *Tetrahedron*, 2001, **57**, 2895.
2001T8305 R. Weis, K. Schweiger, and W. Seebacher, *Tetrahedron*, 2001, **57**, 8305.
2001T9755 P. Kumar and M. S. Bodas, *Tetrahedron*, 2001, **57**, 9755.
2001TA1551 F. J. Devlin, P. J. Stephens, P. Scafato, S. Superchi, and C. Rosini, *Tetrahedron Asymmetry*, 2001, **12**, 1551.
2001TL2133 J.-P. Bouillon, Y. G. Shermolovich, and C. Portella, *Tetrahedron Lett.*, 2001, **42**, 2133.
2001TL7525 R. M. Kamble and V. K. Singh, *Tetrahedron Lett.*, 2001, **42**, 7525.
2001USP6180797 T. W. Drabb, Jr., *US Pat.* 6180797 (2001) (*Chem. Abstr.*, 2001, **134**, 131429).
2001WO2001029033 S. S. Szucs, *PCT WO* 2001029033 (2001) (*Chem. Abstr.*, 2001, **134**, 311110).
2001WO2001040176 M. Sakamoto, S. Tomoita, Y. Takashima, and H. Koga, *PCT WO* 2001040176 (2001) (*Chem. Abstr.*, 2001, **135**, 19546).
2001WO2001042233 S. Park, H. Kwon, H. Kim, P. Ho, K. Morikawa, Y. Kanbe, M. Nishimoto, and M. Kim, *PCT WO* 2001042233 (2001) (*Chem. Abstr.*, 2001, **135**, 46095).
2001WO2001042235 J. Jo, J. Kim, S. Ahn, J. Choi, K. Morikawa, Y. Kanbe, M. Nishimoto, and M. Kim, *PCT WO* 2001042235 (2001) (*Chem. Abstr.*, 2001, **135**, 46092).
2001WO2001042236 J. Jo, S. Park, H. Lim, S. Ahn, K. Morikawa, Y. Kanbe, M. Nishimoto, and M. Kim, *PCT WO* 2001042236 (2001) (*Chem. Abstr.*, 2001, **135**, 46097).
2001WO2001044236 G. J. Haley, R. W. Dexter, S. S. Szucs, and K. Rajamoorithi, *PCT WO* 2001044236 (2001) (*Chem. Abstr.*, 2001, **135**, 61243).
2001WO2001070668 R. L. Beard, T. Vu, D. F. Colon, V. Vuligonda, and R. A. Chandraratna, *PCT WO* 2001070668 (2001) (*Chem. Abstr.*, 2001, **135**, 257053).
2001WO2001087879 K. Andersson, T. Inghardt, O. Karisson, M. Linschoten, J. Nystroem, and G. Sundén, *PCT WO* 2001087879 (2001) (*Chem. Abstr.*, 2001, **135**, 371637).
2002AXEo353 P. Munshi and T. N. G. Row, *Acta Crystallogr., Sect. E*, 2002, **58**, o353.
2002AXEo1123 M. Evain, S. Collet, and A. Guingant, *Acta Crystallogr., Sect. E*, 2002, **58**, o1123.
2002BCJ1325 T. Erabi, M. Asahara, M. Miyamoto, K. Goto, and M. Wada, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1325.
2002CEJ2034 J. Barluenga, F. J. Fañanás, R. Sanz, and Y. Fernández, *Chem. Eur. J.*, 2002, **8**, 2034.
2002CH400 F. J. Devlin, P. J. Stephens, P. Scafato, S. Superchi, and C. Rosini, *Chirality*, 2002, **14**, 400.
2002DEP10126434 H. Meier, S. Allerheiligen, M. Gerisch, R. Schohe-Loop, A. Voerste, F. Mauler, J. De Vry, T. Meuller, and C. Methfessel, *Ger. Pat.* 10126434 (2002) (*Chem. Abstr.*, 2002, **138**, 24643).
2002EJO285 T. Patonay, E. Juhász-Tóth, and A. Bényei, *Eur. J. Org. Chem.*, 2002, 285.
2002EJO856 E. Weber, S. Nitsche, A. Wierig, and I. Csöreg, *Eur. J. Org. Chem.*, 2002, 856.
2002FA989 J. Wichmann, K. Bleicher, E. Vieira, T. Wolterling, F. Knoflach, and V. Mutel, *Farmaco*, 2002, **57**, 989.
2002HCA3773 C. S. Tomooka and E. M. Carreira, *Helv. Chim. Acta*, 2002, **85**, 3773.
2002IC1336 K. Herbst, M. Monari, and M. Brorson, *Inorg. Chem.*, 2002, **41**, 1336.
2002IJQ(90)1055 J. Fabian and B. A. Hess, Jr., *Int. J. Quantum Chem.*, 2002, **90**, 1055.
2002JA28 Y. Yamamoto, H. Takagishi, and K. Itoh, *J. Am. Chem. Soc.*, 2002, **124**, 28.
2002JA5037 N. Koumura, E. M. Geertsema, M. B. van Gelder, A. Meetsma, and B. L. Feringa, *J. Am. Chem. Soc.*, 2002, **124**, 5037.
2002JA13088 G. Cuevas and E. Juaristi, *J. Am. Chem. Soc.*, 2002, **124**, 13088.
2002JCH(948)309 T. Sokoliev, U. Menyess, U. Roth, and T. Jira, *J. Chromatogr. A*, 2002, **948**, 309.
2002JFC(115)175 S. V. Yemets, Yu. P. Bandera, V. M. Timoshenko, and Yu. G. Shermolovich, *J. Fluorine Chem.*, 2002, **115**, 175.

- 2002JME5123 N. K. Brennan, J. P. Hall, S. R. Davies, S. O. Gollnick, A. R. Oseroff, S. L. Gibson, R. Hilf, and M. R. Detty, *J. Med. Chem.*, 2002, **45**, 5123.
- 2002JOC533 M. Hirano, K. Osakada, H. Nohira, and A. Miyashita, *J. Org. Chem.*, 2002, **67**, 533.
- 2002JOC1618 D. E. Ward, M. Sales, C. C. Man, J. Shen, P. K. Sasmal, and C. Guo, *J. Org. Chem.*, 2002, **67**, 1618.
- 2002JOC3585 A. Hjelmencrantz and U. Berg, *J. Org. Chem.*, 2002, **67**, 3585.
- 2002JOC7641 M. P. Coleman and M. K. Boyd, *J. Org. Chem.*, 2002, **67**, 7641.
- 2002JOC8123 J. D. Moore, K. T. Sprott, and P. R. Hanson, *J. Org. Chem.*, 2002, **67**, 8123.
- 2002JOC8662 D. K. Bates and K. Li, *J. Org. Chem.*, 2002, **67**, 8662.
- 2002J(P1)1426 V. J. Ram, N. Agarwal, A. S. Saxena, Farhannullah, A. Sharon, and P. R. Maulik, *J. Chem. Soc. Perkin Trans. 1*, 2002, 1426.
- 2002JPO689 D. Heyes, R. S. Menon, C. I. F. Watt, J. Wiseman, and P. Kubinski, *J. Phys. Org. Chem.*, 2002, **15**, 689.
- 2002JST(594)161 D. H. Setiadi, G. A. Chass, L. L. Torday, A. Varro, and J. G. Papp, *J. Mol. Struct.*, 2002, **594**, 161.
- 2002JST(609)169 M. Chruszcz, K. Stadnicka, A. Budzowski, and K. Bogdanowicz-Szwed, *J. Mol. Struct.*, 2002, **609**, 169.
- B-2002MI1 K. Dietliker, A Compilation of Photoinitiators Commercially Available for UV Today; SITA Technology Ltd: Edinburgh, 2002.
- 2002MI609 D. H. Setiadi, G. A. Chass, L. L. Torday, A. Varro, J. G. Papp, and I. G. Csizmadia, *Eur. Phys. J. D*, 2002, **20**, 609.
- 2002PCA10510 F. J. Devlin, P. J. Stephens, P. Scafato, S. Superchi, and C. Rosini, *J. Phys. Chem. A*, 2002, **106**, 10510.
- 2002PLM4591 T. Corrales, F. Catalina, C. Peinado, N. S. Allen, A. M. Rufs, C. Bueno, and M. V. Encinas, *Polymer*, 2002, **43**, 4591.
- 2002PS(177)2791 V. Padmavathi, A. Balaiah, A. Padmaja, and D. B. Reddy, *Phosphorus, Sulfur Silicon*, 2002, **177**, 2791.
- 2002RJC436 A. P. Lugunov, M. S. Mukanova, B. M. Butin, and K. B. Erzhanov, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2002, **72**, 436.
- 2002STC115 F. Freeman, F. Gomarooni, and W. J. Hehre, *Struct. Chem.*, 2002, **13**, 115.
- 2002SUL263 I. El-Sayed and A. Senning, *Sulfur Lett.*, 2002, **25**, 263.
- 2002T2183 M. K. J. ter Wiel, A. Meetsma, and B. L. Feringa, *Tetrahedron*, 2002, **58**, 2183.
- 2002T6405 M. Kita, M. Watanabe, N. Takada, K. Suenaga, K. Yamada, and D. Uemura, *Tetrahedron*, 2002, **58**, 6405.
- 2002T9045 G.-P. Peng, F.-C. Lou, X.-F. Huang, and G. Tian, *Tetrahedron*, 2002, **58**, 9045.
- 2002T9505 P. J. Coelho, L. M. Carvalho, S. Abrantes, M. M. Oliveira, A. M. F. Oliveira-Campos, A. Samat, and R. Guglielmetti, *Tetrahedron*, 2002, **58**, 9505.
- 2002TL2033 E. Pfund, T. Lequeux, M. Vazeux, and S. Masson, *Tetrahedron Lett.*, 2002, **43**, 2033.
- 2002TL3533 J. Chen, Q. Song, and Z. Xi, *Tetrahedron Lett.*, 2002, **43**, 3533.
- 2002TL7039 T. Kataoka, H. Kinoshita, S. Kinoshita, and T. Iwamura, *Tetrahedron Lett.*, 2002, **43**, 7039.
- 2002TL4507 G. E. Daia, C. D. Gabbutt, J. D. Hepworth, B. M. Heron, D. E. Hibbs, and M. B. Hursthouse, *Tetrahedron Lett.*, 2002, **43**, 4507.
- 2002TL7039 T. Kataoka, H. Kinoshita, S. Kinoshita, and T. Iwamura, *Tetrahedron Lett.*, 2002, **43**, 7039.
- 2002TL8355 A. Bisai, M. Chandrasekhar, and V. K. Singh, *Tetrahedron Lett.*, 2002, **43**, 8355.
- 2002USP2002156211 G. G. Hlatky and S. Nagy, *US Pat.* 2002156211 (2002) (*Chem. Abstr.*, 2002, **137**, 311380).
- 2002WO2002102797 C. Ullmer, H. Luebbert, E. Bellott, M. Froimowitz, and D. Gordon, *PCT WO* 2002102797 (2002) (*Chem. Abstr.*, 2002, **138**, 55875).
- 2002ZNB637 K. Bogdanowicz-Szwed and A. Budzowski, *Z. Naturforsch., B*, 2002, **57**, 637.
- 2003ARK155 C. Wang, J. Chen, Q. Song, Z. Li, and Z. Xi, *ARKIVOC*, 2003, ii, 155.
- 2003BML3083 J. J. Hollick, B. T. Golding, I. R. Hardcastle, N. Martin, C. Richardson, L. J. M. Rigoreau, G. C. M. Smith, and R. J. Griffin, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3083.
- 2003CC204 S. Bath, N. M. Laso, H. Lopez-Ruiz, B. Quiclet-Sire, and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 2003, 204.
- 2003CED1088 M. Shamsipur, A. R. Karami, Y. Yamini, H. Sharghi, and A. R. Salimi, *J. Chem. Eng. Data*, 2003, **48**, 1088.
- 2003CEJ2008 A. D. Darwish, A. G. Avent, O. V. Boltalina, I. Gol'dt, I. Kuvtychko, T. D. Ros, J. M. Street, and R. Taylor, *Chem. Eur. J.*, 2003, **9**, 2008.
- 2003CNR3826 K.-H. Chun, D. M. Benbrook, K. D. Berlin, W. K. Hong, and R. Lotan, *Cancer Res.*, 2003, **63**, 3826.
- 2003EJO47 T. R. Appel, N. A. M. Yehia, U. Baumeister, H. Hartung, R. Kluge, D. Ströhl, and E. Fanghänel, *Eur. J. Org. Chem.*, 2003, 47.
- 2003EJO209 G. Jana, A. Viso, Y. Diaz, and S. Castellón, *Eur. J. Org. Chem.*, 2003, 209.
- 2003EJO4852 H. Kinoshita, S. Kinoshita, Y. Munchika, T. Iwamura, S. Watanabe, and T. Kataoka, *Eur. J. Org. Chem.*, 2003, **9**, 4852.
- 2003ELP1648 T. Sokoliess, M. Gronau, U. Menyes, U. Roth, and T. Jira, *Electrophoresis*, 2003, **24**, 1648.
- 2003HOU(14)649 W.-D. Rudolf; in 'Houben-Weyl Methoden der Organischen chemie Science of Synthesis', J. Thomas, Ed.; Thieme, Stuttgart, 2003, vol. 14, p. 649.
- 2003HOU(14)719 W.-D. Rudolf; in 'Houben-Weyl Methoden der Organischen chemie Science of Synthesis', J. Thomas, Ed.; Thieme, Stuttgart, 2003, vol. 14, p. 719.
- 2003HOU(14)771 S. Faulkner, R. C. Whithead, and R. J. Aarons; in 'Houben-Weyl Methoden der Organischen chemie Science of Synthesis', J. Thomas, Ed.; Thieme, Stuttgart, 2003, vol. 14, p. 771.
- 2003HOU(14)787 A. Nelson; in 'Houben-Weyl Methoden der Organischen chemie Science of Synthesis', J. Thomas, Ed.; Thieme, Stuttgart, 2003, vol. 14, p. 787.
- 2003JA3534 D. A. Evans, F. E. Michael, J. S. Tedrow, and K. R. Campos, *J. Am. Chem. Soc.*, 2003, **125**, 3534.
- 2003JA9000 D. Jiménez, R. Martínez-Máñez, F. Sancenón, J. V. Ros-Lis, A. Benito, and J. Soto, *J. Am. Chem. Soc.*, 2003, **125**, 9000.
- 2003JA11721 K. Kirchner, M. J. Calhorda, R. Schmid, and L. F. Veiros, *J. Am. Chem. Soc.*, 2003, **125**, 11721.
- 2003JA15659 R. A. van Delden, N. P. M. Huck, J. J. Piet, J. M. Warman, S. C. J. Meskers, H. P. J. M. Dekkers, and B. L. Feringa, *J. Am. Chem. Soc.*, 2003, **125**, 15659.
- 2003JCM260 D. Villemin, M. Hachémi, and M. Hammadi, *J. Chem. Res. (S)*, 2003, 260.
- 2003JFC(120)49 H. Poleschner and K. Seppelt, *J. Fluorine Chem.*, 2003, **120**, 49.
- 2003JOC4091 J. L. Kristensen, P. Vedsø, and M. Begtrup, *J. Org. Chem.*, 2003, **68**, 4091.
- 2003JOC7880 A. P. Dobbs, S. J. J. Guesné, S. Martinović, S. J. Coles, and M. B. Hursthouse, *J. Org. Chem.*, 2003, **68**, 7880.
- 2003JPH(159)103 T. Corrales, F. Catalina, C. Peinado, and N. S. Allen, *J. Photochem. Photobiol. A*, 2003, **159**, 103.
- 2003JST(663)145 A. Saieswari, U. D. Priyakumar, and G. N. Sastry, *J. Mol. Struct.*, 2003, **663**, 145.

- 2003MI1287 N. T. Berberova, S. K. Klimenko, E. V. Shinkar, O. N. Akimova, D. F. Sharafutdinov, and K. P. Pashchenko, *Russ. J. Electrochem. (Engl. Transl.)*, 2003, **39**, 1287.
- 2003MM2649 L. Cokbaglan, N. Arsu, Y. Yagci, S. Jockusch, and N. J. Turro, *Macromolecules*, 2003, **36**, 2649.
- 2003MRC193 J. Kovács, G. Tóth, A. Simon, A. Lévai, A. Koch, and E. Kleinpeter, *Magn. Reson. Chem.*, 2003, **41**, 193.
- 2003OBC33 R. A. van Delden, N. Koumura, A. Schoevaars, A. Meetsma, and B. L. Feringa, *Org. Biomol. Chem.*, 2003, **1**, 33.
- 2003OBC2755 A. Levy, S. Cohen, and I. Agranat, *Org. Biomol. Chem.*, 2003, **1**, 2755.
- 2003OL3371 Y. Kuwatani, G. Yamamoto, and M. Iyoda, *Org. Lett.*, 2003, **5**, 3371.
- 2003PS(178)993 G. M. Weerasekare, K. D. Berlin, H. Sunkara, and W. T. Ford, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 993.
- 2003PS(178)2255 M. A. Barsy, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 2255.
- 2003RCR489 V. Y. Sosnovskikh, *Russ. Chem. Rev. (Engl. Transl.)*, 2003, **72**, 489.
- 2003RJO235 T. A. Zheldakova, M. V. Budnikova, and D. B. Rubinov, *Russ. J. Org. Chem. (Engl. Transl.)*, 2003, **39**, 235.
- 2003RJO397 V. A. Tartakovskii, S. A. Shevelev, M. D. Dutov, O. V. Serushkina, and V. V. Kachala, *Russ. J. Org. Chem. (Engl. Transl.)*, 2003, **39**, 397.
- 2003RJO1772 T. A. Zheldakova, M. V. Budnikova, I. L. Rubinova, and D. B. Rubinov, *Russ. J. Org. Chem. (Engl. Transl.)*, 2003, **39**, 1772.
- 2003SC133 K. C. Majumdar and B. Roy, *Synth. Commun.*, 2003, **33**, 133.
- 2003SC2849 J.-X. Wang, X. Shi, X. Men, and L. Zhao, *Synth. Commun.*, 2003, **33**, 2849.
- 2003SM(139)11 J.-M. Jeong, K. Abe, H. Sato, J. Pretula, K. Kaluzynski, and K. Ogino, *Synth. Met.*, 2003, **139**, 11.
- 2003SL230 L. Jablonski, J. Joubert, T. Billard, and B. R. Langlois, *Synlett*, 2003, 230.
- 2003STC497 F. Freeman and E. Derek, *Struct. Chem.*, 2003, **14**, 497.
- 2003T3621 J. Skarzewski, M. Zielińska-Błajet, S. Roszak, and I. Turuwska-Tyrk, *Tetrahedron*, 2003, **59**, 3621.
- 2003TL4183 T. S. Jagodziński, J. G. Sośnicki, and A. Wesołowska, *Tetrahedron*, 2003, **59**, 4183.
- 2003T5289 K. C. Majumdar, A. Bandyopadhyay, and A. Biswas, *Tetrahedron*, 2003, **59**, 5289.
- 2003T5691 I. Suzuki, A. Shigenaga, A. Manabe, H. Nemoto, and M. Shibuya, *Tetrahedron*, 2003, **59**, 5691.
- 2003TL1055 L. Jablonski, T. Billard, and B. R. Langlois, *Tetrahedron Lett.*, 2003, **44**, 1055.
- 2003TL4007 D.-M. Cui, M. Kawamura, S. Shimada, T. Hayashi, and M. Tanaka, *Tetrahedron Lett.*, 2003, **44**, 4007.
- 2003TL4275 A. Whitehead, J. D. Moore, and P. R. Hanson, *Tetrahedron Lett.*, 2003, **44**, 4275.
- 2003USP2003166932 R. L. Beard, T. Vu, D. F. Colon, V. Vuligonda, and R. A. Chandraratna, *US Pat.* 2003166932 (2003) (*Chem. Abstr.*, 2003, **139**, 230485).
- 2003USP6586460 K. D. Berlin, D. M. Benbrook, and E. C. Nelson, *US Pat.* 6586460 (2003) (*Chem. Abstr.*, 2003, **139**, 69392).
- 2004AHC(86)42 E. Kleinpeter, in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 2004, vol. 86, p. 42.
- 2004ARK183 T. Patonay, A. Lévai, E. Rimán, and R. S. Varma, *ARKIVOC*, 2004, vii, 183.
- 2004BCJ1905 H. Tanaka, K. Hashimoto, K. Suzuki, Y. Kitaichi, M. Sato, T. Ikeno, and T. Yamada, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1905.
- 2004BCJ2095 K. Kobayashi, H. Umakoshi, A. Matsunaga, M. Tanmatsu, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 2095.
- 2004BMC2589 M. R. Detty, S. L. Gibson, and R. Hilf, *Bioorg. Med. Chem.*, 2004, **14**, 2589.
- 2004CCC1631 J. Kroulík, J. Čejka, P. Sedmera, A. Jegorov, B. Kratochvíl, and J. Kuthan, *Collect. Czech. Chem. Commun.*, 2004, **69**, 1631.
- 2004EJO74 A. C. B. Lucassen and B. Zwanenburg, *Eur. J. Org. Chem.*, 2004, 74.
- 2004EJO160 M. Heras, M. Gulea, S. Masson, and C. Philouze, *Eur. J. Org. Chem.*, 2004, 160.
- 2004EJO886 A. Sharon, P. R. Maulik, C. Vithana, Y. Ohashi, and V. J. Ram, *Eur. J. Org. Chem.*, 2004, 886.
- 2004FRP2849373 F. Guerin and A. Lagrange, *Fr. Pat.* 2849373 (2004) (*Chem. Abstr.*, 2004, **141**, 93968).
- 2004HCA28 D. Wöll, S. Walbert, K.-P. Stengele, T. J. Albert, T. Richmond, J. Norton, M. Singer, R. D. Green, W. Pfeiderer, and U. E. Steiner, *Helv. Chim. Acta*, 2004, **87**, 28.
- 2004JA3108 P. M. Donovan and L. T. Scott, *J. Am. Chem. Soc.*, 2004, **126**, 3108.
- 2004JA9982 M. Fujio, J. R. Keffe, R. A. More O'Ferrall, and A. C. O'Donoghue, *J. Am. Chem. Soc.*, 2004, **126**, 9982.
- 2004JCM394 J.-T. Li, H.-Y. Li, H.-Z. Li, and L.-W. Xiao, *J. Chem. Res.*, 2004, 394.
- 2004JME4268 A. Horvath, P. Nussbaumer, B. Wolff, and A. Billich, *J. Med. Chem.*, 2004, **47**, 4268.
- 2004JOC584 M. Prasad, Y. Lu, and O. Repič, *J. Org. Chem.*, 2004, **69**, 584.
- 2004JOC4808 D. E. Ward, M. Sales, and P. K. Sasmal, *J. Org. Chem.*, 2004, **69**, 4808.
- 2004JPP2004189695 S. Shimada and D.-H. Choi, *Jpn. Pat.* 2004189695 (2004) (*Chem. Abstr.*, 2004, **141**, 89011).
- 2004JST(678)171 E. Vessally, H. Kaviani, S. Arshadi, and H. Pirelahi, *J. Mol. Struct.*, 2004, **678**, 171.
- 2004M97 K. Bogdanowicz-Szwed and A. Budzowski, *Monatsh. Chem.*, 2004, **135**, 97.
- 2004M581 K. C. Majumdar and A. Bandyopadhyay, *Monatsh. Chem.*, 2004, **135**, 581.
- 2004M973 H. Pirelahi, A. Atarodiekashani, S. Seyyedmoossavi, and H. Daryanavardedargahani, *Monatsh. Chem.*, 2004, **135**, 973.
- 2004MI360 B. Kivcak, S. Akay, B. Demirci, and K. Baser, *Pharm. Biol. (Lisse, Netherlands)*, 2004, **42**, 360.
- 2004MM7850 X. Jiang and J. Lin, *Macromolecules*, 2004, **37**, 7850.
- 2004MRC999 A. R. Katritzky, N. G. Akhmedov, M. Wang, C. J. Rostek, and P. J. Steel, *Magn. Reson. Chem.*, 2004, **42**, 999.
- 2004MRC1037 L. C. Dickinson, D. B. Chesnut, and L. D. Quin, *Magn. Reson. Chem.*, 2004, **42**, 1037.
- 2004NJC153 G. Dazinger, R. Schmid, and K. Kirchner, *New J. Chem.*, 2004, **28**, 153.
- 2004NJC631 M. Alvaro, E. Carbonell, V. Fornés, and H. García, *New J. Chem.*, 2004, **28**, 631.
- 2004OBC1531 R. A. van Delden, M. K. J. ter Wiel, H. de Jong, A. Meetsma, and B. L. Feringa, *Org. Biomol. Chem.*, 2004, **2**, 1531.
- 2004OL2523 J. Nishida, T. Miyagawa, and Y. Yamashita, *Org. Lett.*, 2004, **6**, 2523.
- 2004PPS1052 C. N. Sanrame, M. S. B. Brandao, C. Coenjarts, J. C. Scaiano, G. Pohlers, Y. Suzuki, and J. F. Cameron, *Photochem. Photobiol. Sci.*, 2004, **3**, 1052.
- 2004PS(179)2059 B. Prasanna and G. V. P. Chandramouli, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 2059.
- 2004PS(179)2387 N. R. Mohamed, M. M. T. El-Saidi, T. A. Abdallah, and A. A. Nada, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 2387.
- 2004S1633 A. Robin, J.-C. Meslin, and D. Deniaud, *Synthesis*, 2004, 1633.
- 2004S2900 H. Sharghi and A. R. S. Beni, *Synthesis*, 2004, 2900.
- 2004SC567 R. J. Altenbach, L. Kalvoda, and W. A. Carroll, *Synth. Commun.*, 2004, **34**, 567.

- 2004SC2053 H.-J. Park and K.-I. Lee, *Synth. Commun.*, 2004, **34**, 2053.
- 2004SC2691 M. S. Reddy, E. P. Reddy, and M. V. R. Reddy, *Synth. Commun.*, 2004, **34**, 2691.
- 2004SL1891 A. I. Nyberg, A. Usano, and P. M. Pihko, *Synlett*, 2004, 1891.
- 2004T1827 A. Harrison-Marchand, S. Collet, A. Guingant, J.-P. Pradère, and L. Toupet, *Tetrahedron*, 2004, **60**, 1827.
- 2004T2593 P. J. Coelho, M. A. Salvador, M. M. Oliveira, and L. M. Carvalho, *Tetrahedron*, 2004, **60**, 2593.
- 2004T3427 A. S. Demir, O. Reis, and A. C. Igdir, *Tetrahedron*, 2004, **60**, 3427.
- 2004T4967 L. Bianchi, C. Dell'Erba, M. Maccagno, S. Morganti, M. Novi, G. Petrillo, E. Rizzato, F. Sancassan, E. Severi, D. Spinelli, and C. Tavan, *Tetrahedron*, 2004, **60**, 4967.
- 2004TA1735 K. Micskei, C. Hadju, L. A. Wessjohann, L. Mercs, A. Kiss-Szikszai, and T. Patonay, *Tetrahedron Asymmetry*, 2004, **15**, 1735.
- 2004TA2425 D. E. Ward, O. T. Akinnusi, I. Q. Alarcon, V. Jheengut, J. Shen, and J. W. Quail, *Tetrahedron Asymmetry*, 2004, **15**, 2425.
- 2004TL87 J.-P. Bouillon, A. Capperucci, C. Portella, and A. Degl'Innocenti, *Tetrahedron Lett.*, 2004, **45**, 87.
- 2004TL1133 J. M. Cid, J. L. Romera, and A. A. Trabanco, *Tetrahedron Lett.*, 2004, **45**, 1133.
- 2004TL2305 M. Pal, K. Parasuraman, V. Subramanian, R. Dakarapu, and K. R. Yeleswarapu, *Tetrahedron Lett.*, 2004, **45**, 2305.
- 2004TL5457 H. Kawabata and M. Hayashi, *Tetrahedron Lett.*, 2004, **45**, 5457.
- 2004TL8347 D. E. Ward and V. Jheengut, *Tetrahedron Lett.*, 2004, **45**, 8347.
- 2004USP2004140761 C.-S. Yang, *US Pat.* 2004140761 (2004) (*Chem. Abstr.*, 2004, **141**, 147844).
- 2004USP2004209114 X.-C. C. Li, K. Ueno, A. Saitoh, H. Tanabe, and T. Okamoto, *US Pat.* 2004209114 (2004) (*Chem. Abstr.*, 2004, **141**, 372555).
- 2004WO2004080170 G. Steiner, T. Schmidt, M. Kordes, W. Von Deyn, M. Hofmann, E. Baumann, M. Puhl, G. Heffernan, D. L. Culbertson, and M. F. Treacy, *PCT WO* 2004080170 (2004) (*Chem. Abstr.*, 2004, **141**, 277644).
- 2005AGE4258 W. Lin, I. Sapountzis, and P. Knochel, *Angew. Chem., Int. Ed.*, 2005, **44**, 4258.
- 2005AJC864 A. J. Liepa, O. Nguyen, and S. Saubern, *Aust. J. Chem.*, 2005, **58**, 864.
- 2005AXEo149 X.-G. Liu, W.-X. Hu, and G.-W. Roa, *Acta Crystallogr., Sect. E*, 2005, **61**, o149.
- 2005BCJ2188 Y. Kuwatani, G. Yamamoto, M. Oda, and M. Iyoda, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 2188.
- 2005BMC2723 S. A. Jackson, S. Sahni, L. Lee, Y. Luo, T. R. Nieduzak, G. Liang, Y. Chiang, N. Collar, D. Fink, W. He, A. Laoui, J. Merrill, R. Boffey, P. Crackett, B. Rees, M. Wong, J.-P. Guilloteau, M. Mathieu, and S. S. Rebello, *Bioorg. Med. Chem.*, 2005, **13**, 2723.
- 2005BMC5927 S. J. Wagner, A. Skripchenko, D. J. Donnelly, K. Ramaswamy, and M. R. Detty, *Bioorg. Med. Chem.*, 2005, **13**, 5927.
- 2005BML1341 A. Sharon, R. Pratap, B. Tripathi, A. K. Srivastava, P. R. Maulik, and V. J. Ram, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1341.
- 2005CC2732 Y. Wen, Y. Song, D. Zhao, K. Ding, J. Bian, X. Zhang, J. Wang, Y. Liu, L. Jiang, and D. Zhu, *J. Chem. Soc., Chem. Commun.*, 2005, 2732.
- 2005CC3466 P. L. Bernad, Jr., S. Khan, V. A. Korshun, E. M. Southern, and M. S. Shchepinov, *J. Chem. Soc., Chem. Commun.*, 2005, 3466.
- 2005CC4927 X. Jiang and J. Yin, *J. Chem. Soc., Chem. Commun.*, 2005, 4927.
- 2005CE0608 P. Munshi and T. N. G. Row, *CrystEngComm*, 2005, **7**, 608.
- 2005EPP1506959 M. S. Shchepinov, *Eur. Pat.* 1506959 (2005) (*Chem. Abstr.*, 2005, **142**, 240302).
- 2005HCA891 J. Smirnova, D. Wöll, W. Pfeleiderer, and U. E. Steiner, *Helv. Chim. Acta*, 2005, **88**, 891.
- 2005HCA1922 K. Schmidt, J. Kopf, and P. Margaretha, *Helv. Chim. Acta*, 2005, **88**, 1922.
- 2005IJQ(101)40 F. Freeman, N. Asgari, B. Entezam, F. Gomarooni, J. Mac, M. H. Nguyen, N. N. T. Nguyen, T. P. Nguyen, N. B. Pham, P. Sultana, T. S. Welch, and B. A. Shainyan, *Int. J. Quantum Chem.*, 2005, **101**, 40.
- 2005JA605 Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, and K. Itoh, *J. Am. Chem. Soc.*, 2005, **127**, 605.
- 2005JA12458 J. R. R. Majjigapu, A. N. Kurchan, R. Kottani, T. P. Gustafson, and A. G. Kutateladze, *J. Am. Chem. Soc.*, 2005, **127**, 12458.
- 2005JCH(819)283 B. Hallgas, Zs. Dobos, E. Ösz, F. Hollósy, R. E. Schwab, E. Z. Szabó, D. Erős, M. Idei, G. Kéri, and T. Lóránd, *J. Chromatogr. B*, 2005, **819**, 283.
- 2005JFC(126)361 V. M. Timoshenko, A. V. Tkachenko, and Y. G. Shermolovich, *J. Fluorine Chem.*, 2005, **126**, 361.
- 2005JFC(126)779 V. Y. Sosnovskikh, B. I. Usachev, D. V. Sevenard, and G.-V. Röschenthaler, *J. Fluorine Chem.*, 2005, **126**, 779.
- 2005JHC255 V. Padmavathi, D. R. C. V. Subbaiah, and B. J. M. Reddy, *J. Heterocycl. Chem.*, 2005, **42**, 255.
- 2005JMC1232 S. Amriou, A. Mehta, and M. R. Bryce, *J. Mater. Chem.*, 2005, **15**, 1232.
- 2005JOC3584 D. Xue, Y.-C. Chen, X. Cui, Q.-W. Wang, J. Zhu, and J.-G. Deng, *J. Org. Chem.*, 2005, **70**, 3584.
- 2005JOC6422 B. Branchi, G. Dodd, and G. Ercolani, *J. Org. Chem.*, 2005, **70**, 6422.
- 2005JOC7179 M. Pal, R. Dakarapu, K. Parasuraman, V. Subramanian, and K. R. Yeleswarapu, *J. Org. Chem.*, 2005, **70**, 7179.
- 2005JOC10113 H.-C. Shen, J.-M. Tang, H.-K. Chang, C.-W. Yang, and R.-S. Liu, *J. Org. Chem.*, 2005, **70**, 10113.
- 2005JOC10886 X. Bi, D. Dong, Y. Li, Q. Liu, and Q. Zhang, *J. Org. Chem.*, 2005, **70**, 10886.
- 2005JOM(690)3176 C. V. Ursini, G. H. M. Dias, and J. A. R. Rodrigues, *J. Organomet. Chem.*, 2005, **690**, 3176.
- 2005JOM(690)3577 Q. Yao and M. Sheets, *J. Organomet. Chem.*, 2005, **690**, 3577.
- 2005JPH(169)95 T. Corrales, F. Catalina, N. S. Allen, and C. Peinado, *J. Photochem. Photobiol. A*, 2005, **169**, 95.
- 2005JPP2005123013 K. Ofuku, S. Otsu, and N. Kagawa, *Jpn. Pat.* 2005123013 (2005) (*Chem. Abstr.*, 2005, **142**, 433130).
- 2005L10497 R. Dabiran, A. N. Zdravkova, P. Liljeroth, C. A. van Walree, and L. W. Jenneskens, *Langmuir*, 2005, **21**, 10497.
- 2005MI12 Y. Nagao, T. Osawa, K. Kozawa, and T. Urano, *Shikizai Kyokaishi*, 2005, **78**, 12 (*Chem. Abstr.*, 2005, **143**, 461688).
- 2005MI274 K. Morteza-Semnani, A. Goodarzi, and M. Azadbakht, *J. Essential Oil Res.*, 2005, **17**, 274.
- 2005MI711 D. K. Konarev, D. V. Lopatin, V. V. Rodaev, A. V. Umrikhin, S. S. Khasanov, G. Saito, K. Nakasuji, A. L. Litvinov, and R. N. Lyubovskaya, *J. Phys. Chem. Solids*, 2005, **66**, 711.
- 2005MI752 S. J. Wagner, A. Skripchenko, L. Cincotta, D. Thompson-Montgomery, and H. Awatefe, *Transfusion*, 2005, **45**, 752.
- 2005MM4133 M. Aydin, N. Arsu, Y. Yagci, S. Jockusch, and N. J. Turro, *Macromolecules*, 2005, **38**, 4133.
- 2005NAT1337 R. A. van Delden, M. J. K. ter Wiel, M. M. Pollard, J. Vicario, N. Koumura, and B. L. Feringa, *Nature*, 2005, **437**, 1337.
- 2005NCS165 F. Jafarpour and H. Pirelahi, *Z. Kristallogr., New Cryst. Struct.*, 2005, **220**, 165.
- 2005NCS420 F. Jafarpour and H. Pirelahi, *Z. Kristallogr., New Cryst. Struct.*, 2005, **220**, 420.
- 2005OBC28 M. K. J. ter Wiel, J. Vicario, S. G. Davey, A. Meetsma, and B. L. Feringa, *Org. Biomol. Chem.*, 2005, **3**, 28.
- 2005OBC84 A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, and S. V. Ley, *Org. Biomol. Chem.*, 2005, **3**, 84.
- 2005OBC924 T. Ageno, T. Okauchi, T. Minami, and M. Ishida, *Org. Biomol. Chem.*, 2005, **3**, 924.

- 2005OBC1402 A. W. Marsman, B. L. A. van Poecke, L. W. Jenneskens, A. L. Spek, E. T. G. Lutz, and J. H. van der Maas, *Org. Biomol. Chem.*, 2005, **3**, 1402.
- 2005OBC4071 M. K. J. ter Wiel, R. A. van Delden, A. Meetsma, and B. L. Feringa, *Org. Biomol. Chem.*, 2005, **3**, 4071.
- 2005OL411 S. Kim, J. Y. Wu, Z. Zhang, W. Tang, G. A. Doss, B. J. Dean, F. DiNinno, and M. L. Hammond, *Org. Lett.*, 2005, **7**, 411.
- 2005OL1181 D. E. Ward, V. Jheengut, and O. T. Akinnusi, *Org. Lett.*, 2005, **7**, 1181.
- 2005OL2739 T. Yamaguchi, Y. Yamamoto, Y. Fujiwara, and Y. Tanimoto, *Org. Lett.*, 2005, **7**, 2739.
- 2005OL4273 J. Zhao and R. C. Larock, *Org. Lett.*, 2005, **7**, 4273.
- 2005OL4467 A. F. Nikitina and R. S. Sheridan, *Org. Lett.*, 2005, **7**, 4467.
- 2005OPD646 S. Frigoli, C. Fuganti, L. Malpezzi, and S. Serra, *Org. Process Res. Dev.*, 2005, **9**, 646.
- 2005OM3807 D. J. Del Valle, D. J. Donnelly, J. J. Holt, and M. R. Detty, *Organometallics*, 2005, **24**, 3807.
- 2005PCA659 P. Munshi and T. N. G. Row, *J. Phys. Chem. A*, 2005, **109**, 659.
- 2005PS(180)53 K. Tran, K. D. Berlin, E. M. Holt, R. Hallford, M. A. Eastman, V. K. Yu, and K. D. Praliev, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 53.
- 2005PS(180)67 S. Subramanian, C. M. Smith, A. Tabatabai, C. D. Bryan, B. Beuttner, S. Hale, C. A. Wakefield, D. M. Benbrook, and K. D. Berlin, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 67.
- 2005PS(180)989 T. Kataoka and H. Kinoshita, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 989.
- 2005PS(180)1303 T. Nocentini, J.-P. Bouillon, A. Capprucci, C. Poertella, and A. Degl'Innocenti, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 1303.
- 2005PS(180)1315 B. I. Usachev, V. Y. Sosnovskikh, M. A. Shafeev, and G.-V. Rösenthaller, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 1315.
- 2005PS(180)1339 D. Kinoshita, Y. Kimura, M. Tada, and K. Akiba, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 1339.
- 2005PS(180)2555 H. Pirelahi, F. Jafarpour, G. Rezanejadbardajee, J. Amanishamsabaad, and A. Mouradzadegan, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 2555.
- 2005RJC1537 V. D. Dyachenko, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2005, **75**, 1537.
- 2005RJO283 V. N. Britsun, A. N. Borisevich, L. S. Samoilenko, and M. O. Lozinskii, *Russ. J. Org. Chem. (Engl. Transl.)*, 2005, **41**, 283.
- 2005SL611 C. E. T. Mitchell, A. J. A. Cobb, and S. V. Ley, *Synlett*, 2005, 611.
- 2005SL2317 M. S. Abaee, M. M. Mojtahedi, and M. M. Zahedi, *Synlett*, 2005, 2317.
- 2005SL2453 S. Khan, P. L. Bernad, V. A. Korshun, E. M. Southern, and M. S. Shchepinov, *Synlett*, 2005, 2453.
- 2005T3691 H. Iwamoto, T. Kawatani, and Y. Fukazawa, *Tetrahedron*, 2005, **61**, 3691.
- 2005T8711 Z. Li, Q. Yang, and X. Qian, *Tetrahedron*, 2005, **61**, 8711.
- 2005T8848 H. Modrzejewska and K. Wojciechowski, *Tetrahedron*, 2005, **61**, 8848.
- 2005T9405 K. Oumzil, M. Ibrahim-Ouali, and M. Santelli, *Tetrahedron*, 2005, **61**, 9405.
- 2005TL3719 J.-F. Bonfanti and D. Craig, *Tetrahedron Lett.*, 2005, **46**, 3719.
- 2005TL7567 M. Jafarzadeh, K. Amani, and F. Nikpour, *Tetrahedron Lett.*, 2005, **46**, 7567.
- 2005USP2005004373 B. V. S. Kumar, V. D. Patil, C. N. Raut, S. B. Bhirud, and B. Chandrasekhar, *US Pat.* 2005004373 (2005) (*Chem. Abstr.*, 2005, **142**, 113898).
- 2005USP2005032855 T. Kontani, J. Miyata, W. Hamaguchi, T. Kawano, A. Kamikawa, H. Suzuki, and K. Sudo, *US Pat.* 2005032855 (2005) (*Chem. Abstr.*, 2005, **142**, 219152).
- 2005USP2005037232 Y.-S. Tyan, G. Farruggia, J. D. Shore, J. C. Deaton, and S. A. Van Slyke, *US Pat.* 2005037232 (2005) (*Chem. Abstr.*, 2005, **142**, 248676).
- 2005USP2005219678 J. R. Lenhard and D. Shukla, *US Pat.* 2005219678 (2005) (*Chem. Abstr.*, 2005, **143**, 356711).
- 2005USP2005228040 E. R. Bacon, S. Chatterjee, M. Iqbal, B. Lesur, and P. Louvet, *US Pat.* 2005228040 (2005) (*Chem. Abstr.*, 2005, **143**, 386783).
- 2005WO2005/012220 J. E. Britton, J. Fang, D. Heyer, A. B. Miller, F. Navas, III, T. L. Smalley, Jr., W. J. Zuercher, and S. R. Kalamreddy, *PCT WO* 2005/012220 (2005) (*Chem. Abstr.*, 2005, **142**, 219151).
- 2005WO2005/030125 S. P. Radjenovich, *PCT WO* 2005/030125 (2005) (*Chem. Abstr.*, 2005, **142**, 349029).
- 2005WO2005/066153 M. J. Coghlan, P. K. Jadhav, J. J. Droste, J. E. Green, and D. P. Matthews, *PCT WO* 2005/066153 (2205), (*Chem. Abstr.*, 2005, **143**, 153290).
- 2005WO2005/087714 V. John, M. Maillard, L. Fang, J. Tucker, L. Brogley, J. Aquino, S. Bowers, G. Probst, and J. Tung, *PCT WO* 2005/087714 (2005) (*Chem. Abstr.*, 2005, **143**, 326226).
- 2005WO2005/095326 R. Hom, J. Tucker, V. John, and N. Shah, *PCT WO* 2005/095326 (2005) (*Chem. Abstr.*, 2005, **143**, 386930).
- 2006AGE1900 S. Beligny, S. Eibauer, S. Maechling, and S. Blechert, *Angew. Chem., Int. Ed.*, 2006, **45**, 1900.
- 2006AGE2540 Y.-V. Kervennic, J. M. Thijssen, D. Vanmaekelbergh, R. Dabirian, L. W. Jenneskens, C. A. van Walree, and H. S. J. van Zant, *Angew. Chem. Int. Ed.*, 2006, 2540.
- 2006AGE2975 D. Wöll, J. Smirnova, W. Pfeleiderer, and U. E. Steiner, *Angew. Chem., Int. Ed.*, 2006, **45**, 2975.
- 2006AHC(91)1 B. Stanovnik, M. Tišler, A. R. Katritzky, and O. V. Denisko; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 2006, vol. 91, p. 1.
- 2006AP608 W. W. Wardakhan, *Arch. Pharm.*, 2006, **339**, 608.
- 2006BMC8635 J. J. Holt, M. K. Gannon, II, G. Tomblin, T. A. McCarty, P. M. Page, F. V. Bright, and M. R. Detty, *Bioorg. Med. Chem.*, 2006, **14**, 8635.
- 2006BCJ1977 K. Kobayashi, M. Horiuchi, K. Miyamoto, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 1977.
- 2006CC206 D. Brayton, F. E. Jacobsen, S. M. Cohen, and P. J. Farmer, *J. Chem. Soc., Chem. Commun.*, 2006, 206.
- 2006CC332 M. Weiwer, L. Coulombel, and E. Dunach, *J. Chem. Soc., Chem. Commun.*, 2006, 332.
- 2006CC1563 J.-W. Xie, L. Yue, D. Xue, X.-L. Ma, Y.-C. Chen, Y. Wu, J. Zhu, and J.-G. Deng, *J. Chem. Soc., Chem. Commun.*, 2006, 1563.
- 2006CEJ3389 S. Amriou, C. Wang, A. S. Batsanov, M. R. Bryce, D. F. Perepichka, E. Ortí, R. Viruela, J. Vidal-Gancedo, and C. Rovira, *Chem. Eur. J.*, 2006, **12**, 3389.
- 2006CEJ4821 W. A. Schenk, T. Beucke, N. Burzlaff, M. Klüglein, and M. Stemmler, *Chem. Eur. J.*, 2006, **12**, 4821.
- 2006CEJ8075 R. van Beek, A. P. Zoombelt, L. W. Jenneskens, C. A. van Walree, C. de Mello Donegá, D. Veldman, and R. A. J. Janssen, *Chem. Eur. J.*, 2006, **12**, 8075.
- 2006CEJ5481 S. Amriou, I. F. Perepichka, A. S. Batsanov, M. R. Bryce, C. Rovira, and J. Vidal-Gancedo, *Chem. Eur. J.*, 2006, **12**, 5481.

- 2006CL98 Y. Okazaki, T. Asai, F. Ando, and J. Koketsu, *Chem. Lett.*, 2006, **35**, 98.
- 2006EJO2644 M. Álvaro, C. Aprile, E. Carbonell, B. Ferrer, and H. García, *Eur. J. Org. Chem.*, 2006, 2644.
- 2006EJO3596 E. M. Geertsma, R. Hoen, A. Meetsma, and B. L. Feringa, *Eur. J. Org. Chem.*, 2006, 3596.
- 2006EJO4044 A. Rosiak, W. Frey, and J. Christoffers, *Eur. J. Org. Chem.*, 2006, 4044.
- 2006FFJ650 K. H. C. Baser, G. Ozek, T. Ozek, A. Duran, and H. Duman, *Flavour Fragr. J.*, 2006, **21**, 650.
- 2006HAC376 M. Z. Kassae, H. Pirelahi, and E. Vessally, *Heteroatom Chem.*, 2006, **17**, 376.
- 2006H(68)33 G. Mostón, M. Celeda, A. Linden, and H. Heimgartner, *Heterocycles*, 2006, **68**, 33.
- 2006HCA991 T. Drewnowski, S. Leśniak, G. Młostoń, R. Siedlecka, and J. Skarzewski, *Helv. Chim. Acta*, 2006, **89**, 991.
- 2006JAC2072 D. Jacquemin, J. Preat, V. Wathélet, M. Fontaine, and E. A. Perpète, *J. Am. Chem. Soc.*, 2006, **128**, 2072.
- 2006JA10354 W. Wang, H. Li, J. Wang, and L. Zu, *J. Am. Chem. Soc.*, 2006, **128**, 10354.
- 2006JA12412 W. R. Browne, M. M. Pollard, B. de Lange, A. Meetsma, and B. L. Feringa, *J. Am. Chem. Soc.*, 2006, **128**, 12412.
- 2006JAN110 N.-H. Yoo, J.-P. Kim, B.-S. Yun, I.-J. Ryoo, I.-K. Lee, E.-S. Yoon, H. Koshino, and I.-D. Yoo, *J. Antibiotics*, 2006, **59**, 110.
- 2006JFCN(127)774 I. M. Fesun, A. B. Rozhenko, and V. M. Timoshenko, *J. Fluorine Chem.*, 2006, **127**, 774.
- 2006JMC550 H. Yamochi, J. Hagiwara, M. Soeda, and G. Saito, *J. Mater. Chem.*, 2006, **16**, 550.
- 2006JOC1626 C. Zhou, A. V. Dubrovsky, and R. C. Larock, *J. Org. Chem.*, 2006, **71**, 1626.
- 2006JOC2332 E. Bellur, H. Görls, and P. Langer, *J. Org. Chem.*, 2006, **71**, 2332.
- 2006JOC8989 D. E. Ward, V. Jheengut, and G. E. Beyce, *J. Org. Chem.*, 2006, **71**, 8989.
- 2006JOC9595 C.-W. Wu and J.-J. Ho, *J. Org. Chem.*, 2006, **71**, 9595.
- 2006JPH(177)34 G. Favaro, F. Ortica, F. Elisei, and R. S. Becker, *J. Photochem. Photobiol. A*, 2006, **177**, 34.
- 2006JPH(179)298 O. Rubio-Pons, L. Serrano-Andrés, D. Burget, and P. Jacques, *J. Photochem. Photobiol. A*, 2006, **179**, 298.
- 2006MI85 B. D. Hepworth and B. M. Heron; in 'Functional Dyes', S.-H. Kim, Ed.; Elsevier, Amsterdam, 2006, p. 85.
- 2006MI597 E. Krystowiak, A. Maciejewski, and J. Kubicki, *Chem. Phys. Chem.*, 2006, **7**, 597.
- 2006MI1031 M. Poot, E. Osorio, K. O'Neill, J. M. Thijssen, D. Vanmaekelbergh, C. A. van Walree, L. W. Jenneskens, and H. S. J. van der Zant, *Nano Lett.*, 2006, **6**, 1031.
- 2006OBC4101 E. M. Geertsma, A. M. Schoevaars, A. Meetsma, and B. L. Feringa, *Org. Biomol. Chem.*, 2006, **4**, 4101.
- 2006OL907 K. Tanaka, A. Wada, and K. Noguchi, *Org. Lett.*, 2006, **8**, 907.
- 2006OL1033 R. Bastin, H. Albadri, A.-C. Gaumont, and M. Gulea, *Org. Lett.*, 2006, **8**, 1033.
- 2006OL1713 J.-F. Morin, Y. Shirai, and J. M. Tour, *Org. Lett.*, 2006, **8**, 1713.
- 2006OL2631 D. E. Ward, H. M. Gillis, O. T. Akinnusi, M. A. Rasheed, K. Saravanan, and P. K. Sasmal, *Org. Lett.*, 2006, **8**, 2631.
- 2006PHC(18)376 J. D. Hepworth and B. M. Heron; in 'Progress in Heterocyclic Chemistry', G. Gribble and J. Joule, Eds.; Elsevier, Amsterdam, 2006, vol. 18, p. 376.
- 2006RCB523 B. I. Usachev, M. A. Shafeyev, and V. Ya. Sosnovskikh, *Russ. Chem. Bull.*, 2006, **55**, 523.
- 2006SL2241 G. Alberti, A. M. Bernard, A. Frongia, P. P. Piras, F. Secci, and M. Spiga, *Synlett*, 2006, 2241.
- 2006SL3045 P. M. J. Lory, A. Agarkov, and S. R. Gilbertson, *Synlett*, 2006, 3045.
- 2006SM(156)476 J. Kaladé, R. Maldzius, and E. Montrimas, *Synth. Met.*, 2006, **156**, 476.
- 2006T2603 F. Jafarpour and H. Pirelahi, *Tetrahedron*, 2006, **62**, 2603.
- 2006T4762 F. J. Durán, A. A. Ghini, H. Coirini, and G. Burton, *Tetrahedron*, 2006, **62**, 4762.
- 2006T9226 C. Landreau, P. Janvier, K. Julienne, J. C. Meslin, and D. Deniaud, *Tetrahedron*, 2006, **62**, 9226.
- 2006T11297 V. K. Aggarwal, G. Fang, C. G. Kokotos, J. Richardson, and M. G. Unthank, *Tetrahedron*, 2006, **62**, 11297.
- 2006TL467 T. Suzuki, S. Iwashita, T. Yoshino, H. Kawai, K. Fujiwara, M. Ohkita, T. Tsuji, K. Ono, and M. Takenaka, *Tetrahedron Lett.*, 2006, **47**, 467.
- 2006TL2009 K. Bahrami, *Tetrahedron Lett.*, 2006, **47**, 2009.
- 2006TL4925 M. G. Barthakur, A. Chetia, and R. C. Boruah, *Tetrahedron Lett.*, 2006, **47**, 4925.
- 2006TL5095 A. Rosiak and J. Christoffers, *Tetrahedron Lett.*, 2006, **47**, 5095.
- 2006TL8547 R. Rios, H. Sundén, I. Ibrahim, G.-L. Zhao, L. Eriksson, and A. Córdova, *Tetrahedron Lett.*, 2006, **47**, 8547.
- 2006TL8679 R. Rios, H. Sundén, I. Ibrahim, G.-L. Zhao, and A. Córdova, *Tetrahedron Lett.*, 2006, **47**, 8679.
- 2006USP2006047128 X. Zhang, *US Pat.* 2006047128 (2006) (*Chem. Abstr.*, 2006, **144**, 254240).
- 2006WO2006/060281 S. S. Standing, M. W. Walking, S. L. Herilhy, and J. R. Tucker, *PCT WO* 2006/060281 (2006) (*Chem. Abstr.*, 2006, **145**, 29634).
- 2007AGE1278 M. M. Pollard, M. Lubomska, P. Rudolf, and B. L. Feringa, *Angew. Chem. Int. Ed.*, 2007, **46**, 1278.
- 2007BMCL4406 R. E. McKnight, M. Ye, T. Y. Ohulchanskyy, S. Sahabi, B. R. Wetzel, S. J. Wagner, A. Skripchenko, and M. R. Detty, *Bioorg. Med. Chem. Lett.*, 2007, **15**, 4406.
- 2007CC1035 N. K. Swamy, L. K. Tatini, J. M. Babu, P. Annamalai, and M. Pal, *Chem. Commun.*, 2007, 1035.
- 2007CEJ4273 T. Wedel, M. Müller, J. Podlech, H. Goesmann, and C. Feldmann, *Chem. Eur. J.*, 2007, **13**, 4273.
- 2007CEJ4710 B. Rodríguez, A. S. Bruckmann, and C. Bolm, *Chem. Eur. J.*, 2007, **13**, 4710.
- 2007EJO2152 L. Bartali, A. Guarna, P. Larini, and E. G. Occhiato, *Eur. J. Org. Chem.*, 2007, 2152.
- 2007EJO3573 M. Hagel, J. Liu, O. Muth, H. J. E. Rivera, E. Schwake, L. Sripanom, G. Henkel, and G. Dyker, *Eur. J. Org. Chem.*, 2007, 3573.
- 2007HCA1373 H. Shargi, A. S. Beni, and R. Khalifeh, *Helv. Chim. Acta*, 2007, **90**, 1373.
- 2007JA1036 L. Zu, J. Wang, H. Li, H. Xei, W. Liang, and W. Wang, *J. Am. Chem. Soc.*, 2007, **129**, 1036.
- 2007JA3790 Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, and L.-Z. Gong, *J. Am. Chem. Soc.*, 2007, **129**, 3790.
- 2007JA4160 N. D. Shapiro and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 4160.
- 2007JOC583 J. Zhao and R. C. Larock, *J. Org. Chem.*, 2007, **72**, 583.
- 2007JOC1507 A. Darwish and J. M. Chong, *J. Org. Chem.*, 2007, **72**, 1507.
- 2007JOC1667 D. E. Ward, G. E. Beyce, M. Sales, I. Q. Alarcon, H. M. Gillis, and V. Jheengut, *J. Org. Chem.*, 2007, **72**, 1667.
- 2007JOC2647 M. K. Gannon II, and M. R. Detty, *J. Org. Chem.*, 2007, **72**, 2647.
- 2007JOC2690 J. J. Holt, B. D. Calitree, J. Vincek, M. K. Gannon II, and M. R. Detty, *J. Org. Chem.*, 2007, **72**, 2690.
- 2007JOC7805 V. Jheengut and D. E. Ward, *J. Org. Chem.*, 2007, **72**, 1667.
- 2007MC13 A. Rosiak, R. M. Müller, and J. Christoffers, *Monatsh. Chem.*, 2007, **138**, 13.

- 2007MM4138 D. K. Balta, N. Arsu, Y. Yagci, S. Jockusch, and N. J. Turro, *Macromolecules*, 2007, **40**, 4138.
- 2007MRC590 C. F. Tormena, J. D. Vilcachagua, V. Karcher, R. Rittner, and R. H. Contreras, *Mag. Reson. Chem.*, 2007, **45**, 590.
- 2007OBC2148 D. Gryko and W. J. Saletta, *Org. Biomol. Chem.*, 2007, **5**, 2148.
- 2007OL61 J. P. John and A. V. Novikov, *Org. Lett.*, 2007, **9**, 413.
- 2007OL413 J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, and Y.-C. Chen, *Org. Lett.*, 2007, **9**, 413.
- 2007OL599 S. H. McVoey and S. J. Connon, *Org. Lett.*, 2007, **9**, 599.
- 2007OL1117 V. Singh and V. K. Singh, *Org. Lett.*, 2007, **9**, 1117.
- 2007OL2593 V. Maya, M. Raj, and V. K. Singh, *Org. Lett.*, 2007, **9**, 2593.
- 2007OL3587 J. E. Arguello, R. Pérez-Ruiz, and M. A. Miranda, *Org. Lett.*, 2007, **9**, 3587.
- 2007S1426 P. Margaretha, K. Schmidt, J. Kopf, and V. Sinnwell, *Synthesis*, 2007, 1426.
- 2007S1584 D. E. Ward, M. A. Rasheed, H. M. Gillis, G. E. Beye, V. Jheengut, and G. T. Achonduh, *Synthesis*, 2007, 1584.
- 2007S2115 W. Pan, D. Dong, Y. Ouyang, R. Wu, Y. Yang, and Q. Liu, *Synthesis*, 2007, 2115.
- 2007SL293 A. Hall, E. P. Huguet, K. L. Jones, T. C. Jones, N. M. Killeen, S. C. Yau, and N. C. O. Tomkinson, *Synlett*, 2007, 293.
- 2007SL387 T. Aoyama, K. Okada, H. Nakajima, T. Matsumoto, T. Takido, and M. Kodomari, *Synlett*, 2007, 387.
- 2007SL1605 R. Dodda and C.-G. Zhao, *Synlett*, 2007, 1605.
- 2007T5123 L. Jiang, H.-T. Zheng, T.-Y. Liu, and Y.-C. Chen, *Tetrahedron*, 2007, **63**, 5123.
- 2007TA265 L. He, J. Jiang, Z. Tang, X. Cui, A.-Q. Mi, Y.-Z. Jiang, and L.-Z. Gong, *Tetrahedron Asymm.*, 2007, **18**, 265.
- 2007TA1443 B. Ni, Q. Zhang, and A. D. Headley, *Tetrahedron Asymm.*, 2007, **18**, 1443.
- 2007TTL5657 P. Kukula, A. Dutly, H. Rüegger, and R. Prins, *Tetrahedron Lett.*, 2007, **48**, 5657.
- 2007TTL5803 T. Mandal and C.-G. Zhao, *Tetrahedron Lett.*, 2007, **48**, 5803.

Biographical Sketch



John Hepworth was born in Huddersfield, England in 1937. Having graduated from London University in 1959, he was appointed as an ICI Research Scholar at Huddersfield College of Technology but in 1960 was given a lectureship there in the Department of Chemistry. He continued research on benzopyrans under the supervision of Professor Bob Livingstone on a part-time basis and was awarded a PhD degree (London University) in 1966. Lecturing appointments followed at North Lindsey College of Technology (1963–69) and Derby College of Technology (1969–72) before moving to the University of Central Lancashire (Preston), where he became Professor of Organic Chemistry and where he is now an Emeritus Professor. He has been a Visiting Professor at the University of Hull and a consultant to The Boots Co., Pilkingtons, and James Robinson Ltd.

His research interests include the chemistry of benzopyrans and benzothiopyrans and various aspects of color chemistry. These have resulted in the development of a range of photochromic naphthopyrans which are in commercial use in ophthalmic lenses, security materials, and novelty items.



Bernard Mark Heron was born in Workington, England in 1965. After graduation (GRSC) from Lancashire Polytechnic (Preston) in 1987 and a brief period in industry he obtained his PhD (CNAA) in Benzothiopyran Chemistry in 1992 under the supervision of Professor John Hepworth at the University of Central Lancashire. A postdoctoral fellowship in heterocyclic chemistry (1992–95) and an industrially funded lectureship at Central Lancashire (1995–98) were followed by appointment to a James Robinson Lectureship at the University of Hull (1998–2000). Dr. Heron was appointed as a senior lecturer (2000–present) in the Department of Colour and Polymer Chemistry at the University of Leeds. His research interests include the chemistry and applications of heterocyclic compounds, color chemistry, and organic photo- and thermochromic materials.

7.11

Six-membered Rings with One Selenium or Tellurium Atom

F. S. Guziec, Jr. and L. J. Guziec

Southwestern University, Georgetown, TX, USA

© 2008 Elsevier Ltd. All rights reserved.

7.11.1	Introduction	956
7.11.2	Theoretical Methods	957
7.11.3	Experimental Structural Methods	960
7.11.3.1	X-Ray Structures	960
7.11.3.2	NMR Spectroscopy	961
7.11.4	Thermodynamic Aspects	962
7.11.4.1	Conformations	962
7.11.4.2	Aromaticity	962
7.11.5	Reactivity of Fully Conjugated Rings	963
7.11.5.1	Reactions with Nucleophiles	963
7.11.5.2	Thermal Reactions	965
7.11.5.3	Oxidations and Reductions	965
7.11.5.4	Acid–Base Reactions	966
7.11.5.5	Hydrolysis Reactions	967
7.11.5.6	Coupling Reactions	967
7.11.6	Reactivity of Non-conjugated Rings	968
7.11.6.1	Reactivity of 2 <i>H</i> - and 4 <i>H</i> -Chalcogenins and Their Carbocyclic Condensed Derivatives	968
7.11.6.1.1	Reactions at the chalcogen atom	968
7.11.6.1.2	'Dimerization' reactions	970
7.11.6.1.3	Other reactions	971
7.11.6.2	Dihydrochalcogenopyrans and Their Carbocyclic Derivatives	972
7.11.6.2.1	Oxidation	972
7.11.6.2.2	Metalation reactions	974
7.11.6.2.3	Other reactions at the chalcogen atom	974
7.11.6.3	Tetrahydrochalcogenopyrans and Their Carbocyclic Derivatives	975
7.11.6.3.1	Reactions with nucleophiles	975
7.11.6.3.2	Oxidations	976
7.11.6.3.3	Reactions at the chalcogen atom	977
7.11.7	Ring Synthesis	978
7.11.7.1	Formation of One Bond	978
7.11.7.1.1	Se–C ₂	978
7.11.7.1.2	C ₂ –C ₃	981
7.11.7.1.3	C ₃ –C ₄	983
7.11.7.2	Formation of Two Bonds	983
7.11.7.2.1	Se plus C-5 unit	983
7.11.7.2.2	Se–C ₂ or Te–C ₂ plus C ₅ –C ₆	986
7.11.7.2.3	Se–C ₄ plus C ₅ –C ₆	990
7.11.8	Important Compounds and Applications	991
7.11.8.1	Compounds of Biological Interest	991

7.11.8.2	Compounds with Interesting Electronic and Optical Properties	991
7.11.8.3	Catalytic Activities	993
7.11.9	Further Developments	995
References		998

7.11.1 Introduction

The chemistry of six-membered heterocycles containing one selenium or tellurium atom was initially covered in CHEC-II(1996) (chapter 5.11). This updated chapter primarily deals with material dating from 1993 and is complete to 2005 with occasional references from 2006. The structures and nomenclature of the selenium- and tellurium-containing heterocycles discussed in this chapter are included in [Figure 1](#). One major review of tellurium-containing heterocycles has appeared [<B-1994MI1>](#). The chemistry of thiopyrans, selenopyrans, and telluropyrans has also been reviewed [<1994AHC180>](#).

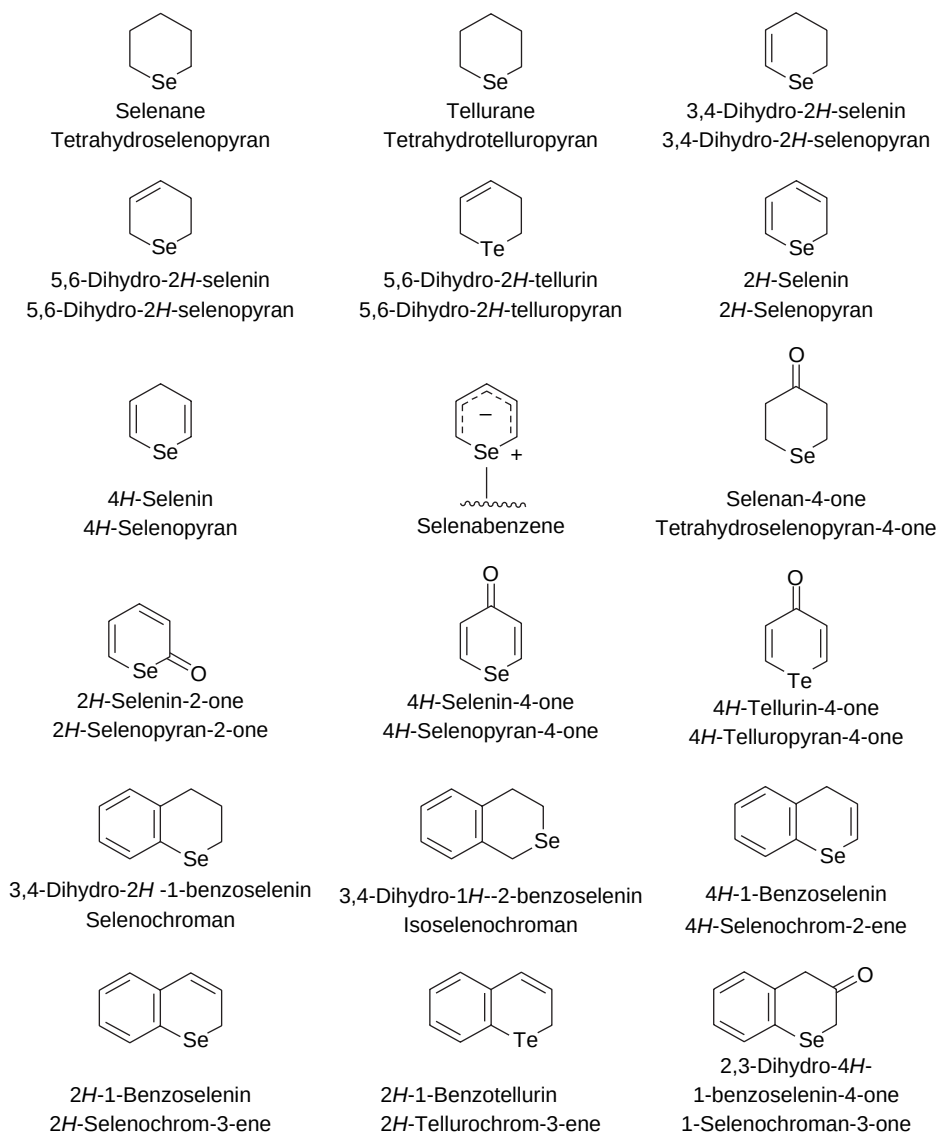


Figure 1 (Continued)

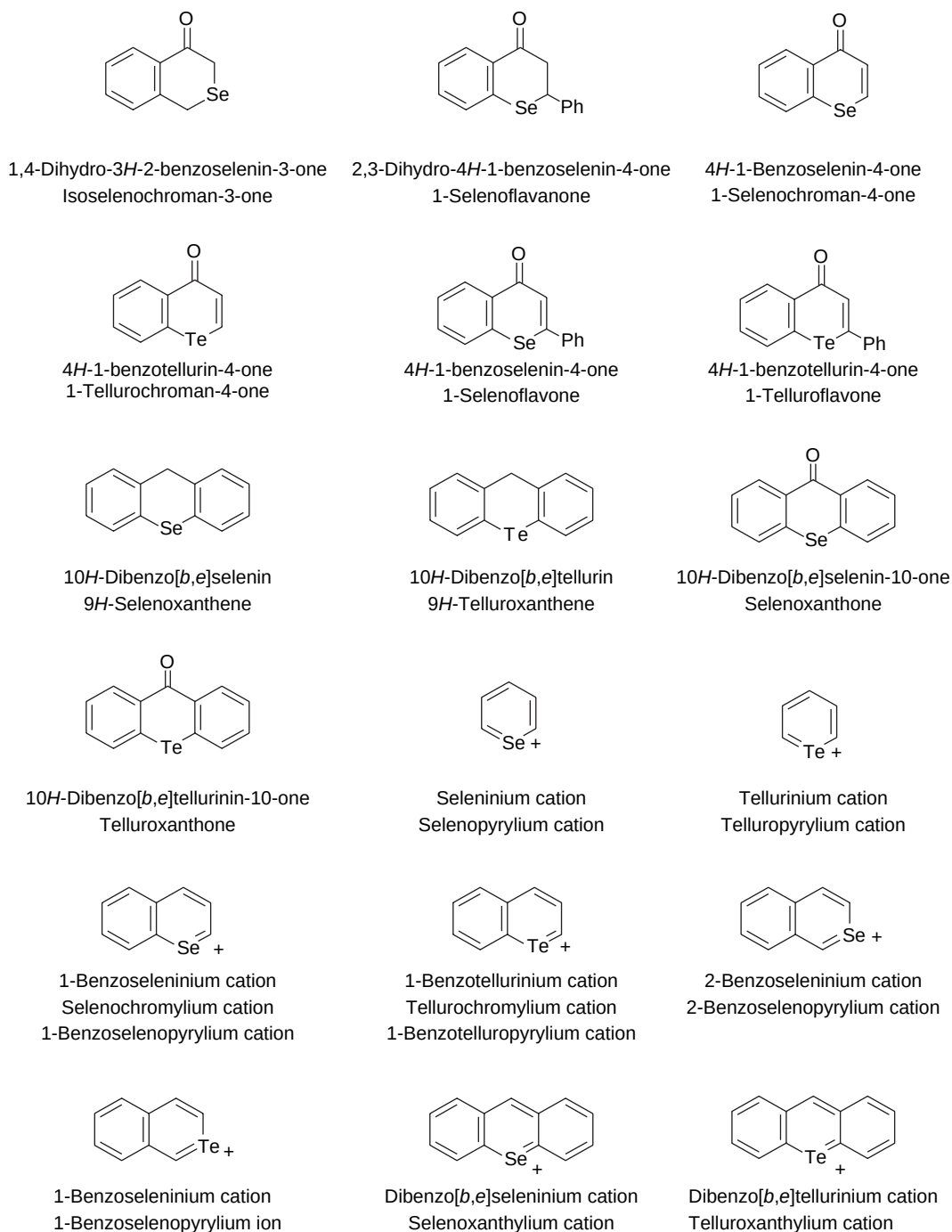
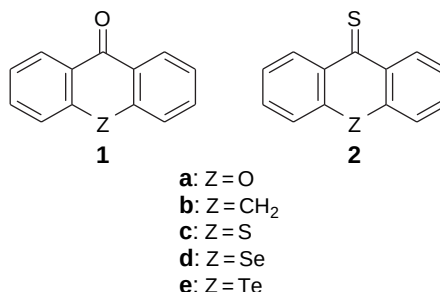


Figure 1 Structures and nomenclature of heterocyclic ring systems discussed in this chapter.

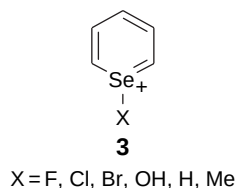
7.11.2 Theoretical Methods

A number of theoretical studies of six-membered heterocycles containing one selenium or tellurium atom were previously described in CHEC-II(1996) (section 5.11.2). All of these consisted of *ab initio* calculations. Several new reports have appeared since this time dealing with theoretical approaches to understanding the properties of these materials, their preparations, and their reactivity.

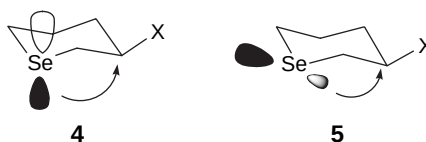
The static polarizabilities, α , of various xanthone analogues including seleno- and telluroxanthene-9-one **1d** and **1e** and seleno- and telluroxanthene-9-thione **2d** and **2e** have been estimated by *ab initio* molecular orbital calculations using the coupled perturbed Hartree–Fock (CPHF) method <1996CPL125>. The results indicate that the introduction of heavy elements in **1** and **2** increases all components of α with a greater effect observed in the case of the thione derivatives **2**.



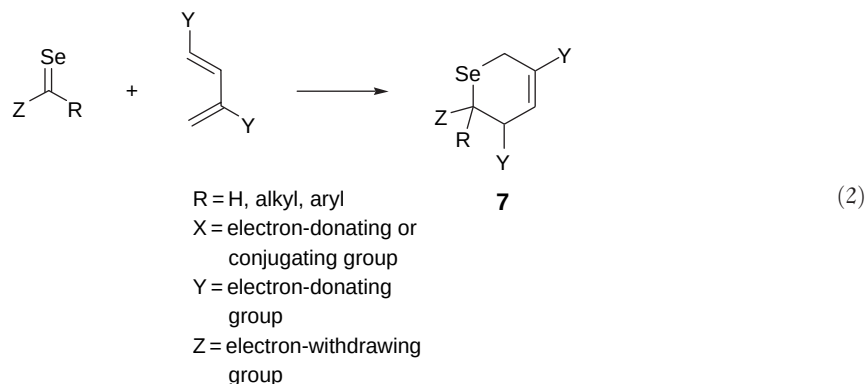
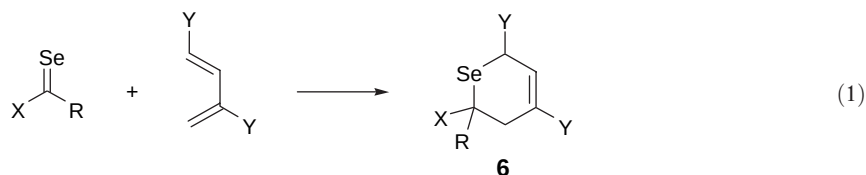
The aromaticity of a series of six-membered ring selenium compounds **3** has been evaluated by using magnetic criteria – nucleus-independent chemical shifts (NICSs), magnetic susceptibility anisotropies, and exaltations <2001HCA1578>. The energies and geometries of these compounds were also determined. These studies indicate that the nature of the selenium substituents significantly influences the extent of cyclic electron delocalization. As with the corresponding sulfur compounds, the selenium compounds with strongly electronegative substituents (F, Cl, Br, OH) exhibit more aromatic character than those with hydrogen or methyl groups.



Homoanomeric effects in six-membered ring heterocycles were studied computationally using both density functional theory (DFT) (B3LYP) and natural bond orbital (NBO) analysis <2003JA14014>. Selenanes, selenium analogues of cyclohexane, behave similarly to their oxygen and sulfur analogues in that the ‘Plough’ effect, as shown in **4**, is important while the ‘W-effect’ in **5** is negligible. The controlling factor in these interactions is hyperconjugation.



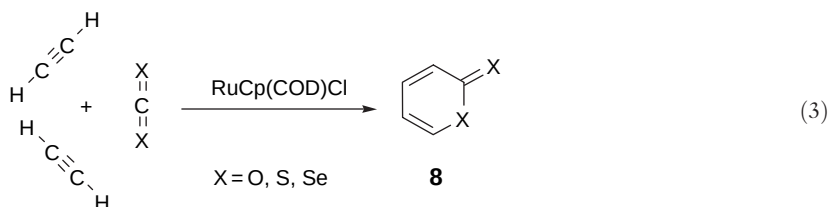
Theoretical studies of the mechanisms of formation of selenopyrans (selenins) and selenopyranones (seleninones) have been reported. Cycloadditions of selenals (selenoaldehydes) and selones (selenoketones) with substituted dienes provides a useful route for the preparation of dihydroselenins such as **6** and **7** (Equations 1 and 2) (see CHEC-II(1996), (section 5.11.7.2.1) and Section 7.11.7.2.1). These reactions have been examined using DFT (B3LYP) and compared with standard *ab initio* procedures <1999JOC8248>. This Diels–Alder reaction proceeds through a concerted, though asynchronous transition state. The reaction appears to be dominated by LUMO_{dienophile}–HOMO_{diene} interactions (LUMO = lowest unoccupied molecular orbital; HOMO = highest occupied molecular orbital), and the regiochemistry of the reaction has been explained by simple frontier molecular orbital (FMO) considerations <1988JA8671>.



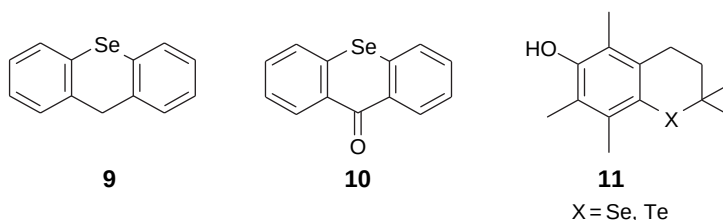
More recently, computational methods have been used to investigate this cycloaddition reaction [<1999JOC8248>](#). Use of B3LYP with a modified 6-31G basis set led to results that compared well standard *ab initio* methods. Transition state geometries, regiochemistry, and substituent effects can be understood in terms of FMO with theory. These methods also indicated that strong electron-withdrawing substituents significantly alter the cycloaddition mechanism leading to formation of an intermediate charge-transfer complex. The cycloaddition reactions of α,β -unsaturated selenals and selones have also been studied using B3LYP calculations and the theoretical results compared with experiment [<1999JOC1565>](#) (see [Section 7.11.7.2.2](#)).

Possible competition between a stepwise diradical mechanism and concerted mechanisms in chalcogeno-Diels–Alder reactions of formaldehyde analogues $\text{H}_2\text{C}=\text{X}$ ($\text{X} = \text{O, S, Se, Te}$) have been investigated in a DFT study [<2001JOC4026>](#). In all cases investigated, including those involving sterically hindered dienes, the diradical pathways were predicted to be less energetically favorable than concerted mechanisms.

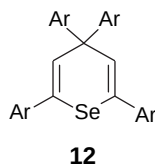
A theoretical study of the mechanism of ruthenium-catalyzed formation of pyran-2-one and the corresponding sulfur and selenium analogues **8** from acetylene and CX_2 ($\text{X} = \text{O, S, Se}$) has been reported ([Equation 3](#)) [<2004NJC153>](#). This cyclotrimerization reaction has been experimentally carried out using carbon disulfide as a substrate [<2002JA28>](#). The proposed mechanism involves formation of a bicyclic metal carbene intermediate. Formation of this intermediate seems to be particularly unfavorable energetically in the case of carbon diselenide.



Ab initio molecular mechanics calculations have been used to examine the electronic states of selenoxanthene **9** and selenoxanthone **10**. These results were used to explain differences in the formation of bromine adducts of these compounds (see [Section 7.11.6.1.2](#)) [<1998JOC8373>](#). Bond dissociation enthalpies and adiabatic ionization potentials of phenolic antioxidants containing selenium and tellurium have been carried out using DFT models in an attempt to design novel vitamin E analogues such as **11** [<2006OBC846>](#).



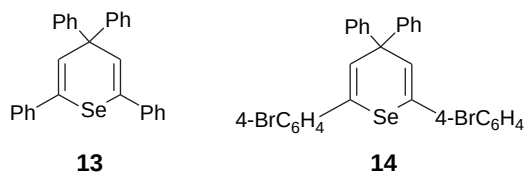
The influence of selenium on the geometry of a number of aryl-substituted selenopyrans **12** was determined using quantum semi-empirical PM3 and DFT calculations. These results were compared with experimentally determined X-ray structures <2002J(P2)1909> (see Section 7.11.3.1).



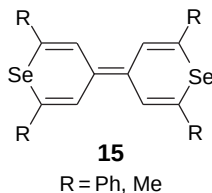
7.11.3 Experimental Structural Methods

7.11.3.1 X-Ray Structures

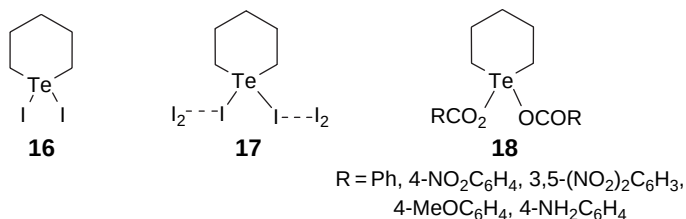
A number of novel X-ray structures of six-membered rings containing a single selenium or tellurium atom have appeared. The tetrasubstituted 4*H*-selenopyrans **13** and **14** are nearly planar, but slightly distorted toward a boat conformation, presumably due to the properties of the crystal matrix <2002J(P2)1909>.



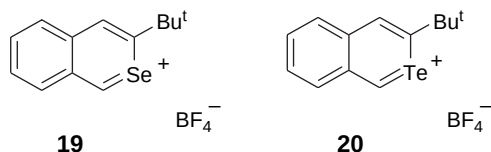
The crystal structures of polyiodide salts formed by oxidation of the biselenopyrans **15** with iodine have been reported. The stoichiometry of the salts was shown to be (**15**:I₂) = (1:2) <1995MCL143>.



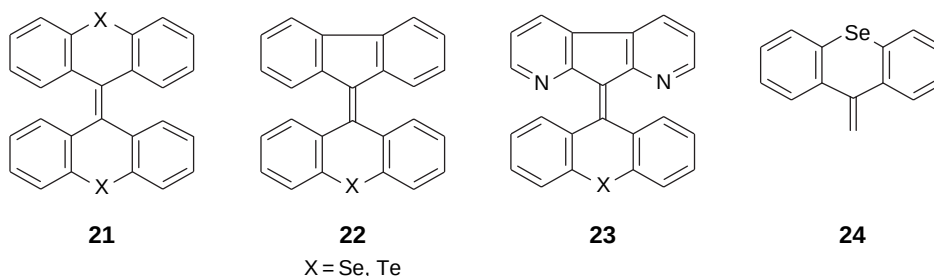
X-Ray structures of a number of tetravalent tellurium species **16** <2000JOM96>, **17** <2004JOM194>, and **18** <2002JOM34> have also been reported.



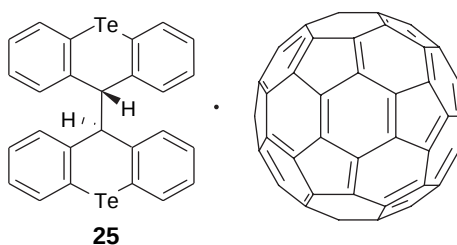
The crystal structures of 2-benzoselenopyrylium salt **19** and the corresponding tellurium compound **20** have been reported <2002J(P1)606>. The benzopyrylium rings in both compounds are planar. The C(1)–Se bond length is significantly shorter than normal carbon–selenium single bond lengths and is close to C=Se bond lengths observed in selenones (selenoketones). Similarly, the C(1)–Te bond is much shorter than a typical carbon–tellurium single bond and comparable in length to (sp²)C bonds to tellurium. These results confirm the aromatic character of these compounds.



Crystal structures have been determined for a series of highly crowded bistricyclic selenium- and tellurium-bridged compounds **21–23** as well as a nonhindered analogue **24** <2000J(P2)725>. The conformational behavior of the selenoxanthylidene and telluroxanthylidene moieties within these molecules has been described (see Section 7.11.4.1).



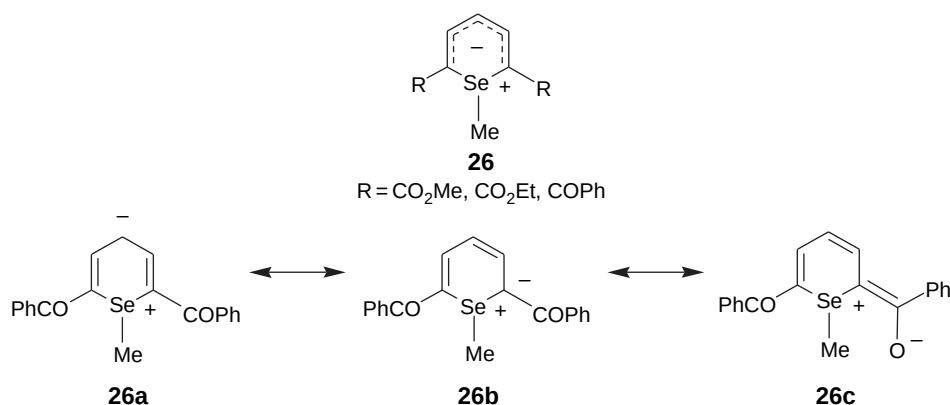
The X-ray crystal structure of the molecular complex of 9,9'-trans-bis-telluraxanthenyl **25** and fullerene has been reported <1997CPH407>. These types of fullerene complexes act as organic semiconductors (see Section 7.11.8.2).



7.11.3.2 NMR Spectroscopy

Detailed studies of the ¹H, ¹³C, ⁷⁷Se, and ¹²⁵Te nuclear magnetic resonance (NMR) have been carried out on the strained bis-tricyclic selenium- and tellurium-bridged compounds **21–24** <2000TL6157, 2000J(P2)725>.

¹H, ¹³C, and ⁷⁷Se NMR and infrared spectra of the first reported selenabenzenes **26** stabilized by electron-withdrawing groups have been reported <1999J(P1)1155>. The data indicate that these compounds are stabilized by significant contributions from structures such as **26c**.



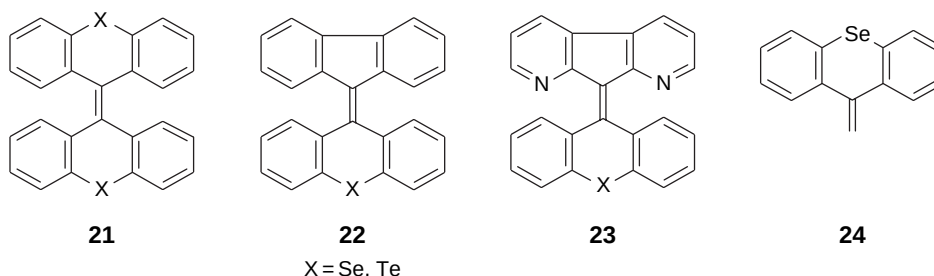
Detailed ¹H and ¹³C NMR data on a variety of dihydro-2*H*-selenopyrans have also been reported [<1995JA10922>](#).

7.11.4 Thermodynamic Aspects

7.11.4.1 Conformations

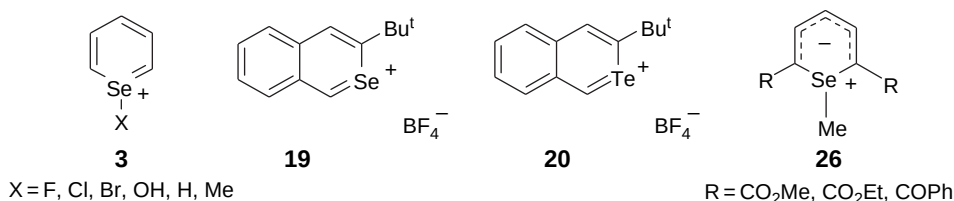
The effects of selenium and tellurium bridges on the conformations of bis-tricyclic aromatic alkenes **21–23** have been studied by X-ray crystallographic analysis (see [Section 7.11.3.1](#)) and spectroscopic techniques [<2000J\(P2\)725, 2000TL6157, 2001J\(P2\)2329, 2003OBC2755>](#). These molecules are highly overcrowded, requiring bond deformations to avoid close contacts between nonbonded atoms in the ‘fjord’ regions flanking the central double bond on these molecules. These deformations can consist of deviations from coplanarity, including twisting about the central double bond and out-of-plane bending leading to pyramidalization. Various distortions of bond lengths and bond angles are also possible.

Alkenes **21** and **22** showed a marked *anti*-folding ($\sim 53^\circ$ dihedral) between the pairs of benzene rings in the tricyclic portions of the molecules relative to the unhindered **24** which exhibited a dihedral angle of only 32.4° [<2000J\(P2\)725>](#). In the unsymmetrical 1,8-diazafluorenylidene derivatives **23**, the dihedral angles in the xanthyli-dene moieties were in the range of $60\text{--}63^\circ$ [<2003OBC2755>](#).



7.11.4.2 Aromaticity

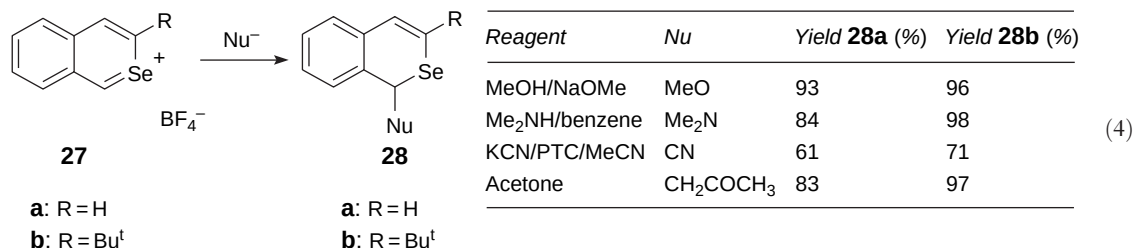
Calculations relating to the aromatic nature of selenabenzene derivatives such as **3** have been reported [<2001HCA1578>](#) (see [Section 7.11.2](#)). Crystal structure studies confirming the aromatic nature of 2-benzoselenopyrylium tetrafluoroborate **19** and 2-benzotelluropyrylium tetrafluoroborate **20** have been described [<2002J\(P1\)606>](#) (see [Section 7.11.3.1](#)). Spectroscopic studies on Se-methylselenabenzenes **26** also indicate the aromatic nature of these molecules [<1999J\(P1\)1155>](#) (see [Section 7.11.3.2](#)).



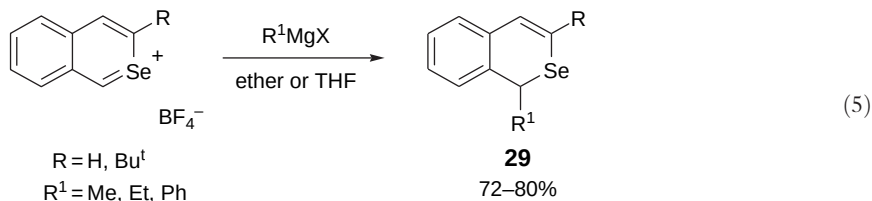
7.11.5 Reactivity of Fully Conjugated Rings

7.11.5.1 Reactions with Nucleophiles

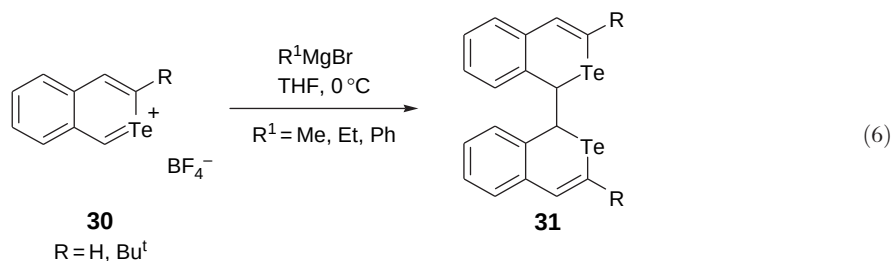
2-Benzoselenopyrylium salts **27** react with a variety of nucleophiles to afford the 1-substituted addition products **28** (Equation 4) <1999H(51)17>.

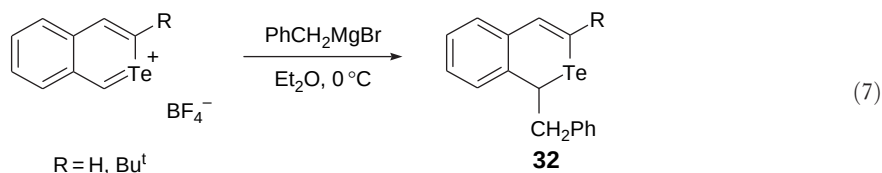


These salts also react with Grignard reagents to afford the corresponding carbon-substituted derivatives **29** which are very useful precursors for the preparation of more highly substituted 2-benzoselenopyrylium salts (Equation 5) <1999H(51)17>.

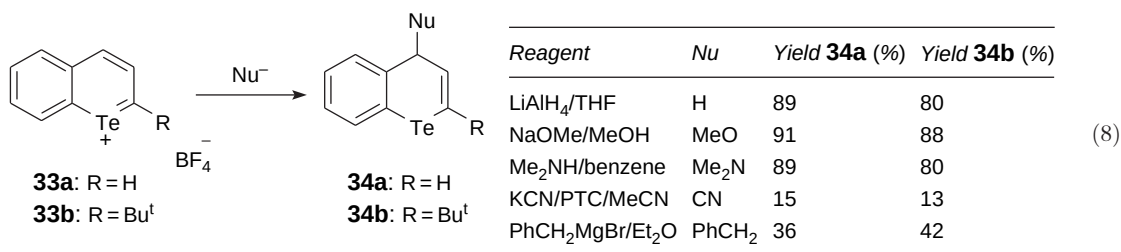


Benzotelluropyrilium salts react with a variety of nucleophiles via distinct mechanistic pathways. 2-Benzotelluropyrilium salts **30** react with common Grignard reagents to afford products of reductive dimerization **31** (Equation 6) <1998J(P1)2123>. Under similar conditions, the reactions of the 2-benzotelluropyrilium salts with benzyl magnesium bromide take a completely different course leading to addition of the benzyl group to the 1-position of the heterocycle **32** (Equation 7). The dimerization is also in sharp contrast to the reactions of 2-benzoselenopyrylium salts, which give products of addition with any Grignard reagent (Equation 5). Dimerization had been previously noted in the reductions of telluraxanthylum salts in which a radical mechanism was proposed for this reaction. The dimerization of **30** presumably follows a similar course.

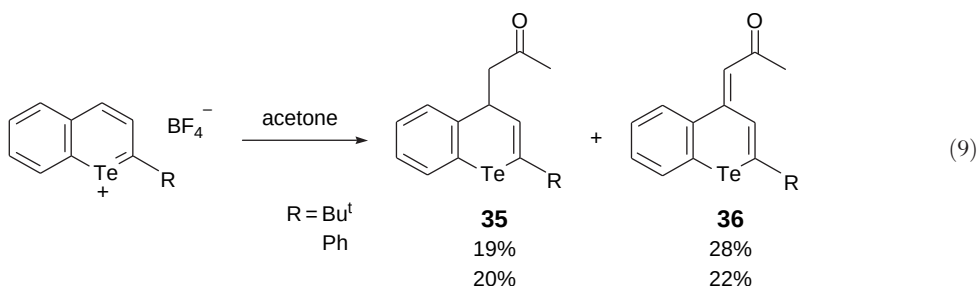




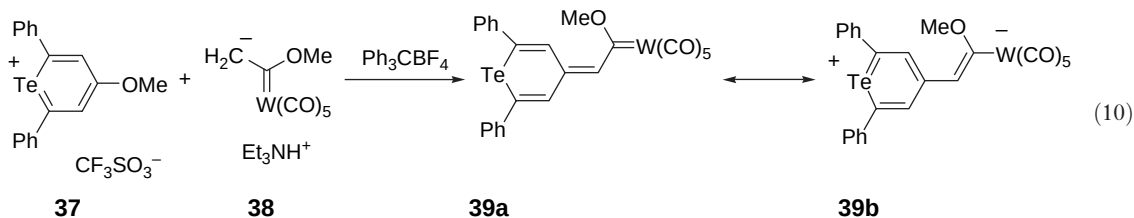
1-Benzotelluropyrylium salts **33** react with a variety of nucleophiles to afford 4-substituted-4*H*-tellurochromenes **34** (Equation 8) <1999J(P1)1665>.



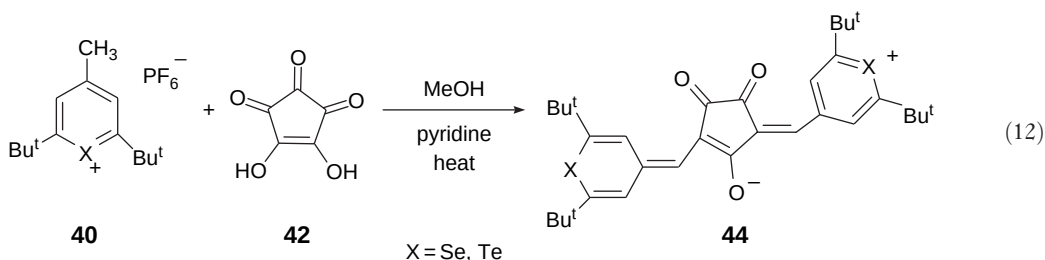
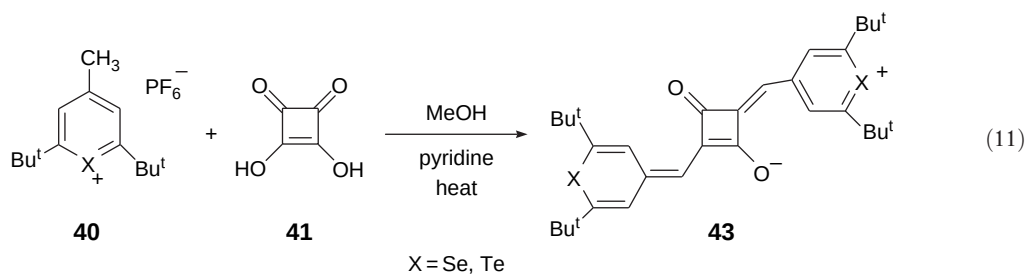
2-Substituted-1-benzotelluropyrylium salts react with dry acetone at room temperature to afford the corresponding acetone addition products **35** and **36** (Equation 9) <1999J(P1)1665>. The exocyclic unsaturated adduct **36** appears to form from acid-promoted dehydrogenation of the initially formed acetone adduct.



Treatment of γ -methoxytelluropyrylium salts **37** with nucleophilic Fischer carbene complexes **38** in the presence of trityl fluoroborate affords 'push-pull' carbene complexes **39a** and **39b** (Equation 10) <2005JOM4982>. These molecules are described in this way because of the ability of the donor and acceptor groups to interact via conjugation. The resulting molecules exhibit interesting nonlinear optical properties (see Section 7.11.8.2). Related 'push-pull' carbene complexes with extended conjugation can be prepared by nucleophilic reaction of the Fischer carbene complex with conjugated telluropyran aldehydes (see Section 7.11.6.1.3, Equation 34).



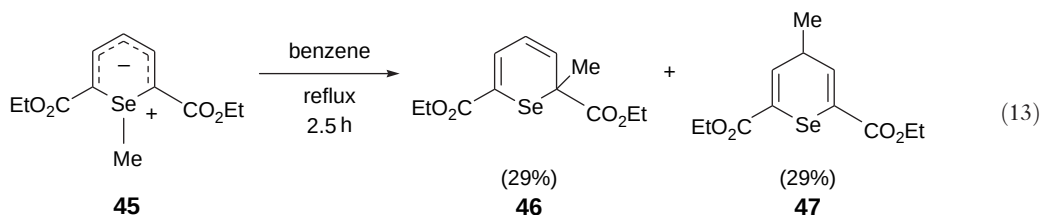
Sterically hindered seleno- and telluropyrylium salts **40** react with squaric acid **41** <1993H(35)1149> and also with 4,5-dihydroxy-4-cyclopentene-1,2,3-trione (croconic acid) **42** <2000JOC2236> in the presence of base to afford squarylium and croconate dyes **43** and **44**, respectively (Equations 11 and 12). Dyes of this type have important industrial applications (Section 7.11.8.2).



The key step in the hydrolysis of seleno- and telluropyrylium dyes involves nucleophilic addition of water to the substrate <1997JOC4692, 1998JOC5716>. This hydrolysis is discussed in Section 7.11.5.5.

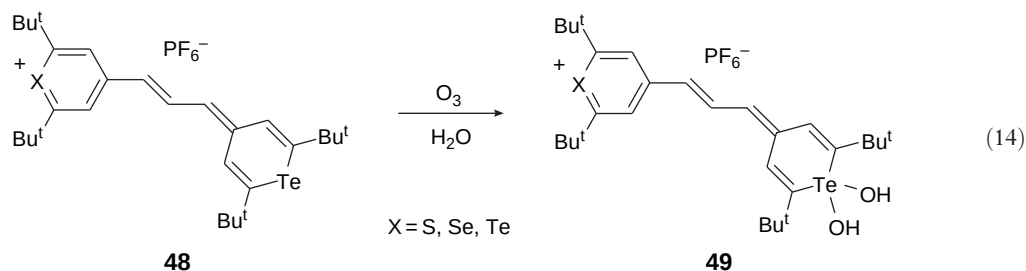
7.11.5.2 Thermal Reactions

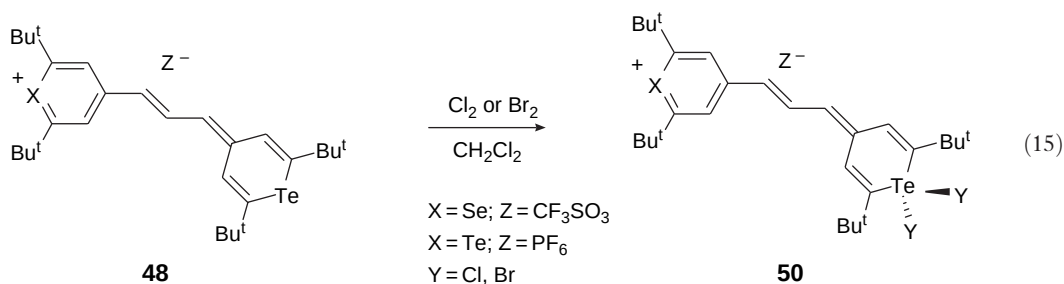
Se-Methyl-substituted selenabenzenes **45** with electron-withdrawing carboethoxy groups at the 2- and 6-positions rearrange in refluxing benzene to afford a mixture of 2- and 4-methyl-4*H*-selenines **46** and **47** (Equation 13) <1999J(P1)1155>.



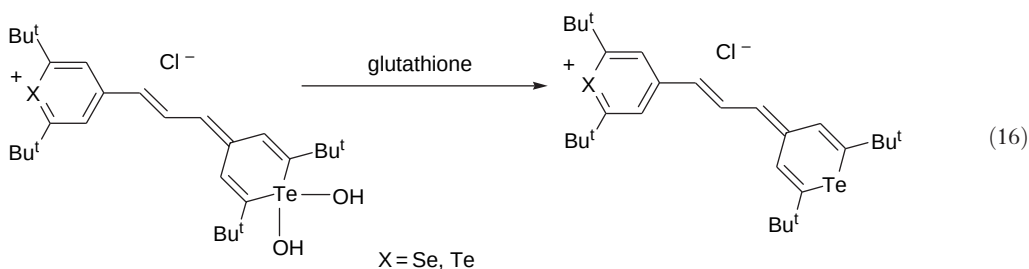
7.11.5.3 Oxidations and Reductions

Telluropyrylium dyes and their selenium analogues **48** are readily oxidized with ozone, chlorine, and bromine (Equations 14 and 15) <1994OM533>. Reaction at tellurium occurs faster than oxidation of the carbon framework affording hypervalent tellurium adducts **49** and **50**. Related chalcogen-containing dyes containing selenium react at a significantly lowered rate compared to the corresponding tellurium compounds.

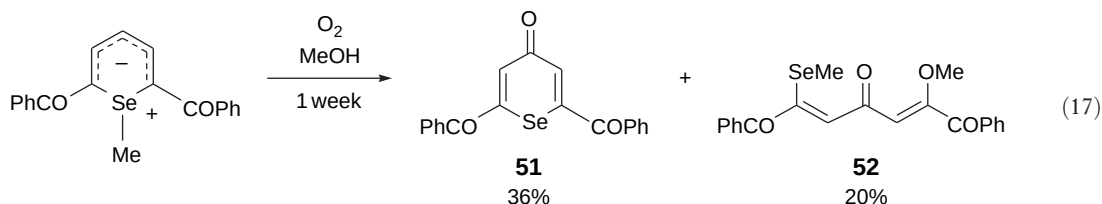




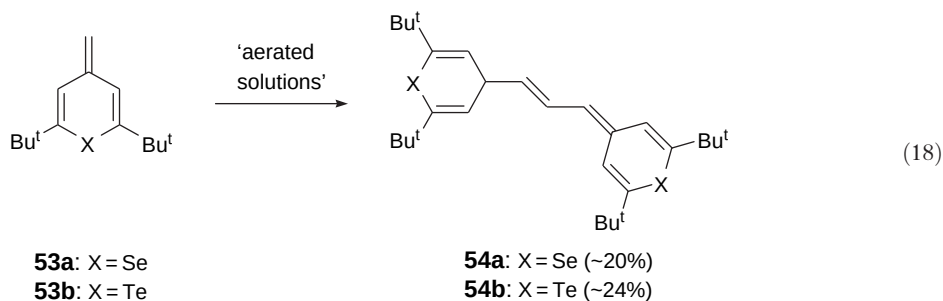
Telluroxides derived from telluropyrilium dyes can be reduced by glutathione to the parent dye (Equation 16). The reaction occurs via a two-step mechanism <1994JOC8245>. This reduction has important implications for photodynamic therapy and related oxidative chemotherapy (see Section 7.11.8).



Treatment of *S*-methyl-substituted selenabenzenes containing electron-withdrawing benzoyl groups at the 2- and 6-positions with oxygen in methanol leads to a slow oxidation affording a mixture of oxidative demethylation affording the selenopyranone **51** and the product of ring cleavage **52** (Equation 17) <1999J(P1)1155>.



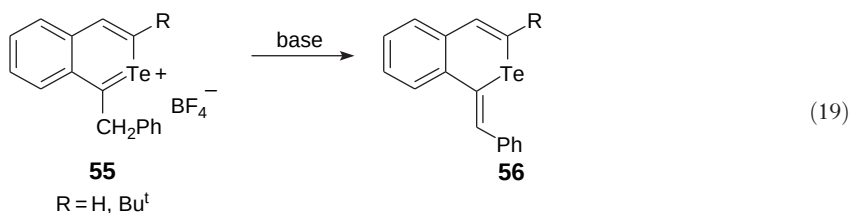
4-Methylideneseleno- and telluropyrans **53a** and **53b** are air oxidized to the corresponding bipyranilidenes **54a** and **54b** (Equation 18) <1995JOC6631>. This reaction is involved in the chalcogen scrambling observed in the preparation of unsymmetrical pyrylium trimethine dyes (see Section 7.11.5.6).



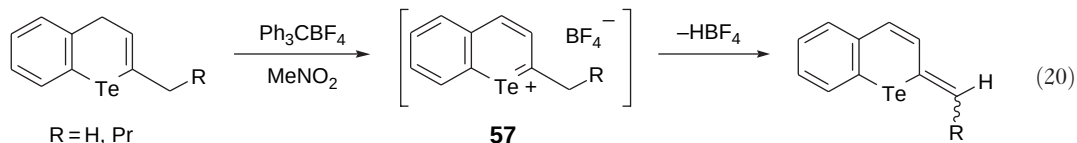
7.11.5.4 Acid-Base Reactions

Treatment of the 1-benzyl-2-benzotelluropyrilium salts **55** with base, or even upon alumina column chromatography, leads to deprotonation affording the corresponding exocyclic (*Z*)-olefin **56** quantitatively (Equation 19)

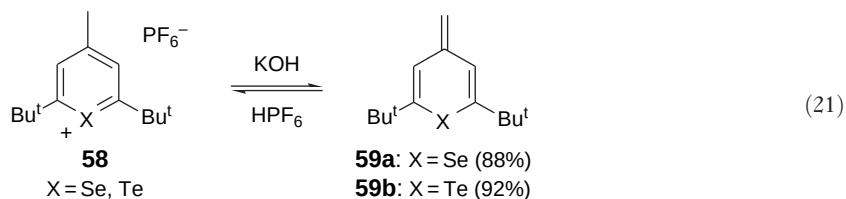
<1998J(P1)2123>. The resulting alkenes are unstable and cannot be isolated. This pronounced tendency toward deprotonation was observed even during NMR studies in polar solvents.



1-Benzopyrylium salts with benzylic hydrogens **57** cannot be isolated, apparently because of their tendency to deprotonate leading to the unstable heterocycles with exocyclic double bonds (Equation 20) <1999J(P1)1155>.

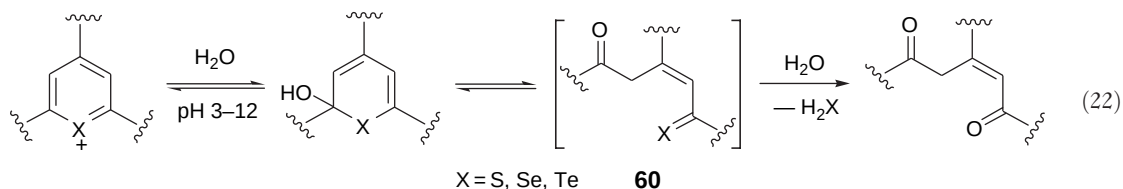


Base treatment of di-*tert*-butylseleno- and telluropirylium salts **58** leads to elimination reactions affording 4-methyleneseleno- and telluropyrans **59**, which can be isolated in high yields (Equation 21) <1995JOC6631> (cf. Equation 18). These compounds are stable to the conditions of alumina chromatography. The starting pyrylium salts can be regenerated in high yield by addition of HPF_6 .



7.11.5.5 Hydrolysis Reactions

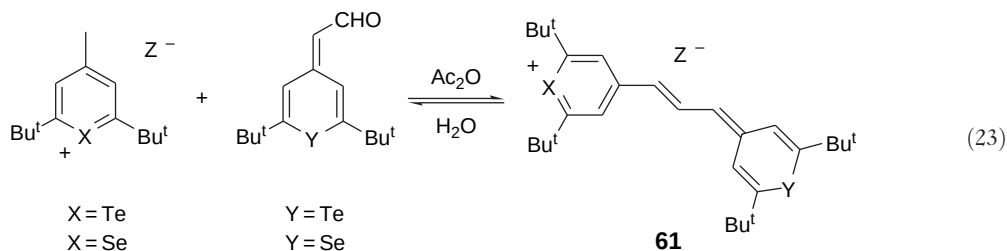
The hydrolysis of seleno- and telluropirylium dyes involves nucleophilic addition of water to the substrate. α,β -Unsaturated selones and -tellones **60** are intermediates in this reaction (Equation 22) <1997JOC4692, 1998JOC5716>. Diketones are the primary hydrolysis products isolated in high yields from these reactions. The tellurium derivative hydrolyzes most rapidly over the pH range 3–12, with the sulfur analogue least reactive under these conditions. Seleno- and telluropirylium dyes are important both for their biological activities and potential industrial applications (see Section 7.11.8).



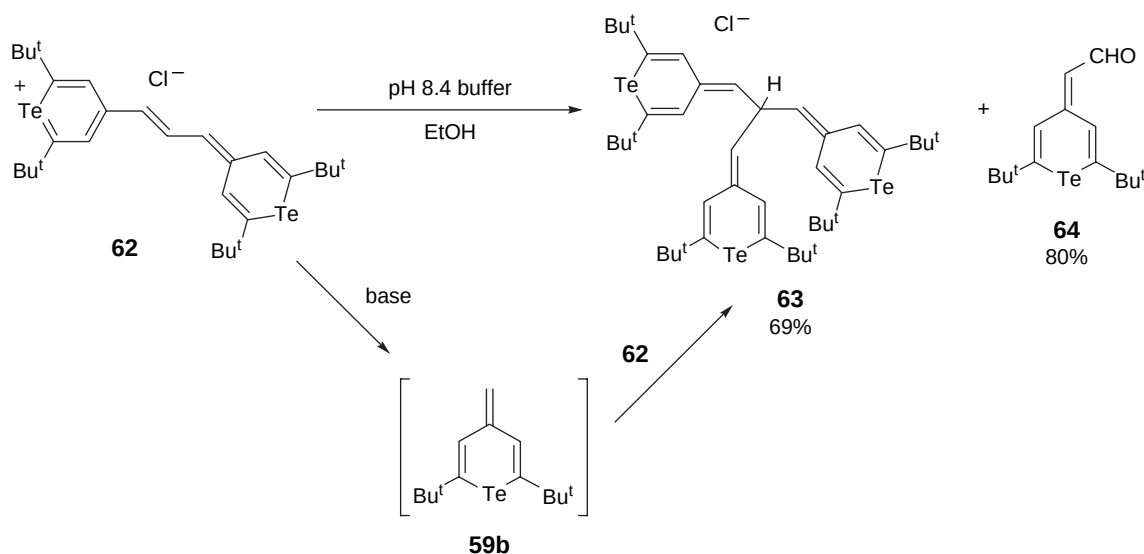
7.11.5.6 Coupling Reactions

Seleno- and telluropirylium trimethyne dyes **61** are prepared by treatment of seleno- or telluropirylium dyes with acetic anhydride (Equation 23) <1990JA3845, 1990JME1108> [also see CHEC-II, 5.11.8]. These reactions work well for the preparation of symmetrical dyes, however in attempts at the synthesis of unsymmetrical dyes, symmetrical

products are also formed [<1995JOC6631>](#). This is particularly pronounced in the case of the counter ions being chloride or bromide which lead to a statistical distribution of products.



One mechanism for this heteroatom scrambling involving a retroaldol reaction was discounted because of its relatively slow rate. An alternative mechanism for this transformation involves formation of tris(chalcogeno-pyran-yl-methylidene)methanes **63** as intermediates in the reaction. This highly symmetrical intermediate has been isolated from the telluropyrilium compound **62** by carefully controlled hydrolysis using a pH 8.4 phosphate buffer [<1995JOC6631>](#). Mechanistically, **63** forms by reaction of the tellurium dye with the previously mentioned telluropyranylmethylidene **59b** formed under alkaline conditions (Scheme 1) (see Equation 21). The expected elimination by-product, the telluropyranyl aldehyde **64**, could also be isolated from this reaction mixture in high yield.



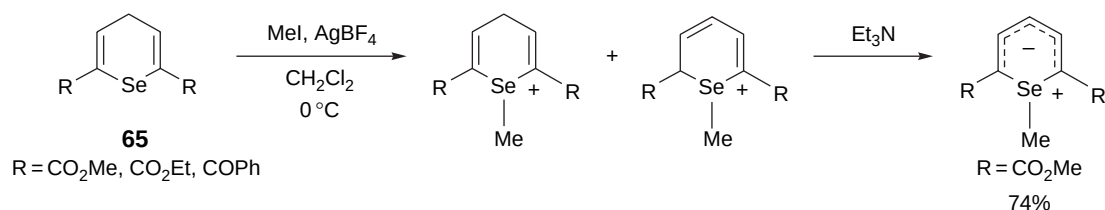
Scheme 1

7.11.6 Reactivity of Non-conjugated Rings

7.11.6.1 Reactivity of 2*H*- and 4*H*-Chalcogenins and Their Carbocyclic Condensed Derivatives

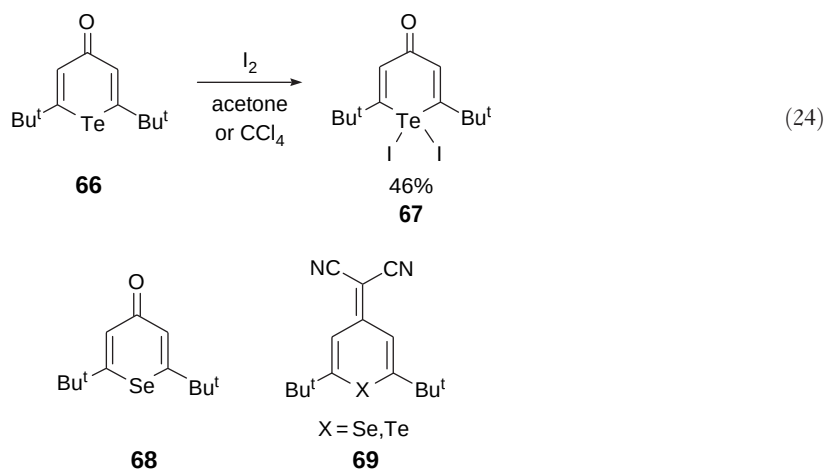
7.11.6.1.1 Reactions at the chalcogen atom

Treatment of 4*H*-selenines substituted with electron-withdrawing groups on the 2- and 6-positions **65** with methyl iodide and silver tetrafluoroborate affords a mixture of alkylated products. These products can be deprotonated with triethylamine affording the corresponding selenabenzenes (Scheme 2) [<1999J\(P1\)1155>](#).

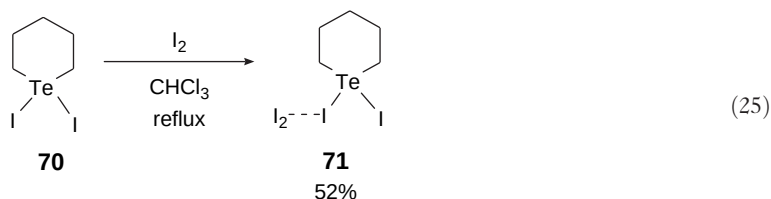


Scheme 2

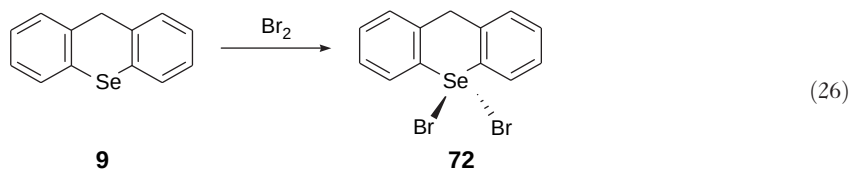
Numerous oxidative additions of halogens to cyclic selenium- and tellurium-containing heterocycles have been reported. Treatment of the telluropyrone **66** with iodine affords crystalline tetravalent tellurium species **67** (Equation 24) <1995OM1442>. The kinetics of this reaction <1995OM1442> and analogous oxidations of **68** and **69** with bromine <1994OM3338> have been studied using stopped-flow methods. These results indicate that the oxidative additions occur by stepwise mechanisms.

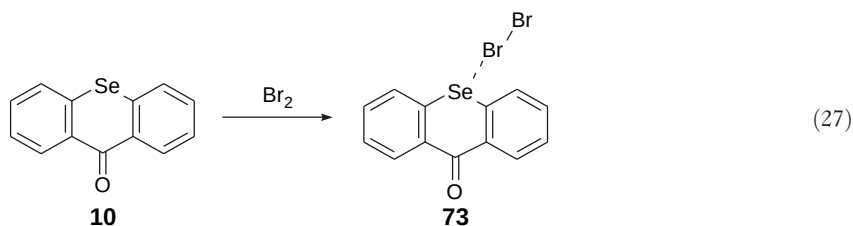


The hypervalent diiodotellurane **70** can be further oxidized by iodine to form unusual charge-transfer complexes such as **71** (Equation 25) <2004JOM194>. X-Ray structures of these compounds have been reported (see Section 7.11.3.1).



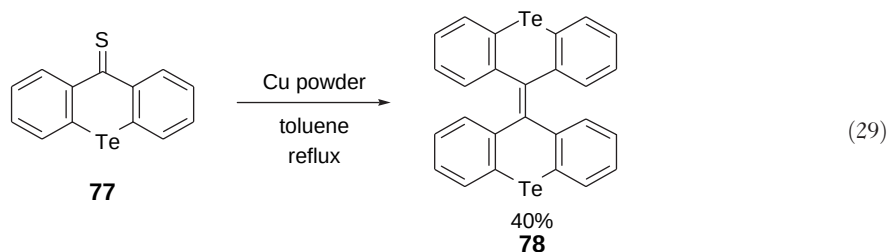
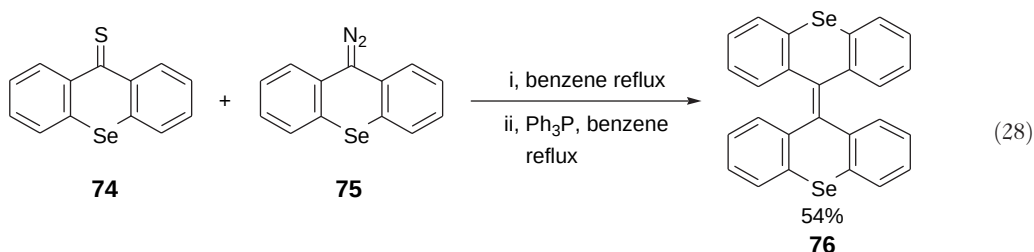
Reaction of selenoxanthene **9** with bromine affords the selenium addition product **72** (Equation 26); however, selenoxanthone **10** reacts with bromine to form a molecular complex **73** (Equation 27). The explanation of this difference in reactivity is based on the differences in ionization potentials of selenium in these molecules which were determined using penning ionization electron spectroscopy <1998JOC8373>. These results are consistent with *ab initio* calculations of the electronic states of the precursors (see Section 7.11.2).



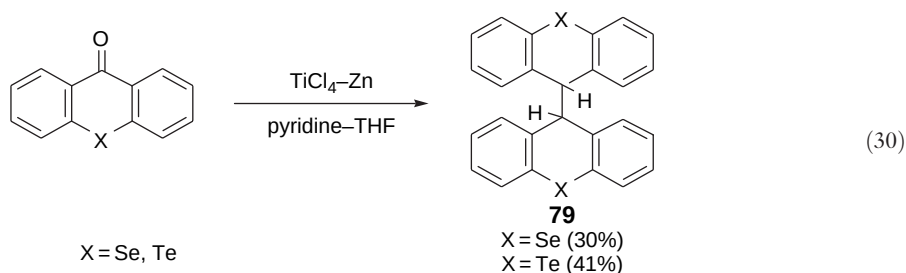


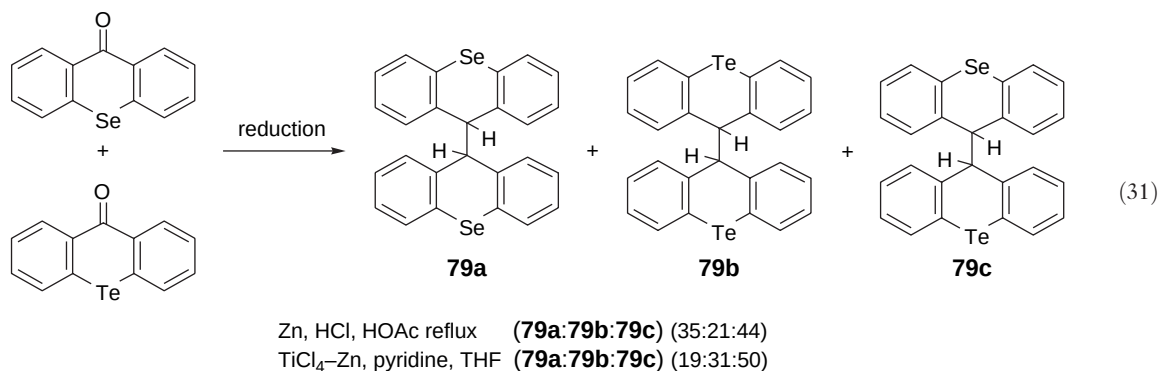
7.11.6.1.2 'Dimerization' reactions

Seleno- and telluroxanthones can be efficiently 'dimerized' to the corresponding 9,9'-bi(xanthen-9-ylidenes) [<2000TL6157, 2000J\(P2\)725>](#). 9*H*-Selenoxanthone **74** and 9-diazo-9*H*-selenoxanthene **75** react in a twofold extrusion reaction to afford 9,9'-bi(9*H*-selenoxanthen-9-ylidene) **76** (Equation 28). The tellurium analogue of **76** could not be prepared analogously using this extrusion procedure due to the relative instabilities of the telluroxanthone-derived thione and diazo compound. The telluroxanthenylidene **78** could however be prepared by copper-promoted 'dimerization' of the telluroxanthone **77** (Equation 29).

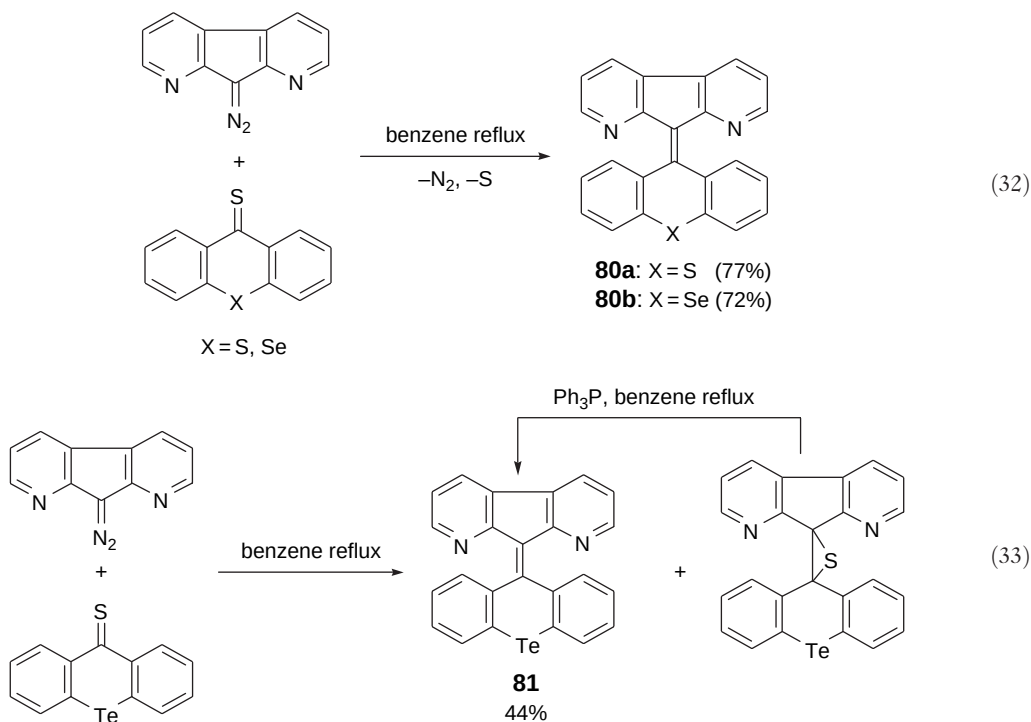


Attempts to prepare **76** and **78** using the McMurry coupling reaction on the seleno- and telluroxanthones failed, leading to formation of the corresponding dihydro compounds **79** (Equation 30) [<2000J\(P2\)725>](#). When the coupling reaction was attempted using Zn in HCl-refluxing acetic acid, the reductive dimerization again took place [<2000TL6157>](#). If equimolar amounts of selenoxanthone and telluroxanthone were used in the reaction, the dimerization did not exhibit the expected statistical distribution of products (Equation 31). Preference toward the formation of tellurium-bridged derivatives was explained by enhanced reactivity of a tellurium-derived radical anion intermediate. This was in marked contrast to the results observed using the McMurry conditions on the mixed substrates where formation of the symmetrical selenium derivative was favored over the ditellurium compound. This was explained by the favored initial formation of the selenium-substituted bixanthyldene compound under McMurry conditions. The central double bond of the bixanthyldene was then reduced to the C–C single bond under these reaction conditions.





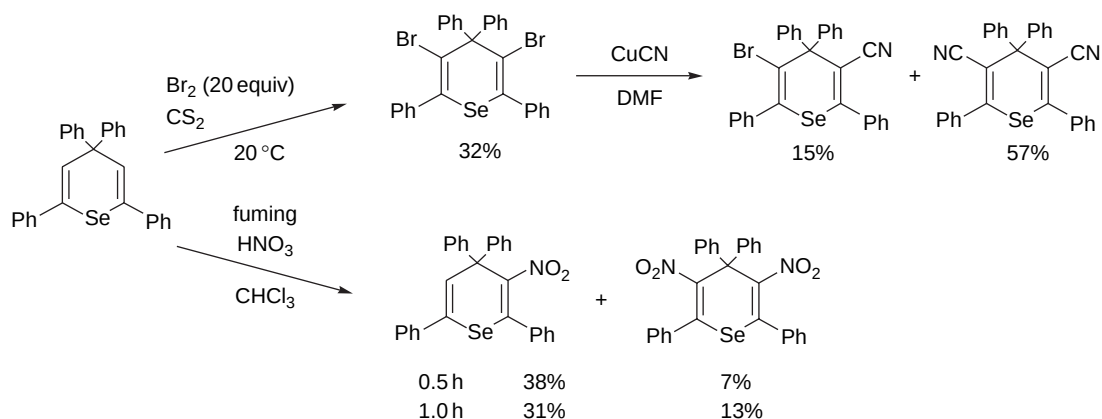
The above-mentioned twofold extrusion reaction proved to be particularly useful in the preparations of unsymmetrical 1,8-diazafluorenylidene derivatives such as **80** and **81** (Equation 32) <2003OBC2755>. In the case of sulfur and selenium, the alkenes were isolated directly in good yield. In the tellurium reaction, a mixture of the alkene and thiirane was obtained and could be desulfurized to the desired alkene **81** with triphenylphosphine in refluxing benzene (Equation 33).



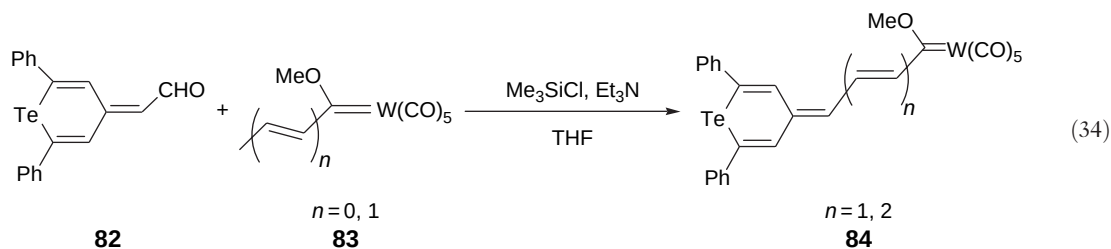
7.11.6.1.3 Other reactions

Ring hydrogens on highly substituted aryl selenopyrans can be selectively replaced by bromination or nitration. Halo substituents on the selenopyrans can be readily displaced using copper cyanide affording the mono- and dinitrile derivatives (Scheme 3) <2002J(P2)1909>.

Treatment of the conjugated telluropyran aldehyde **82** with the carbanion of the tungsten carbene **83** afforded the conjugated 'push-pull' Fischer-type carbene complexes with extended conjugation **84** (Equation 34) <2005JOM4982> (cf. Equation 10). These complexes exhibit interesting nonlinear optical properties (see Section 7.11.8.2).



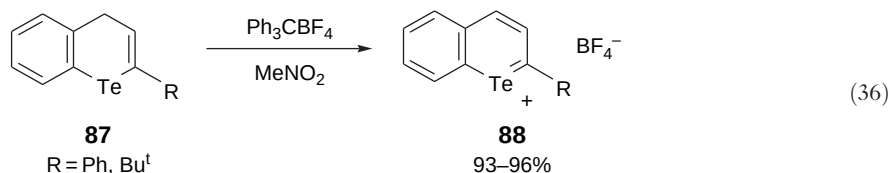
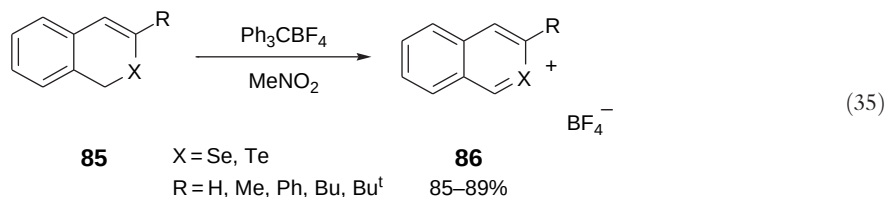
Scheme 3



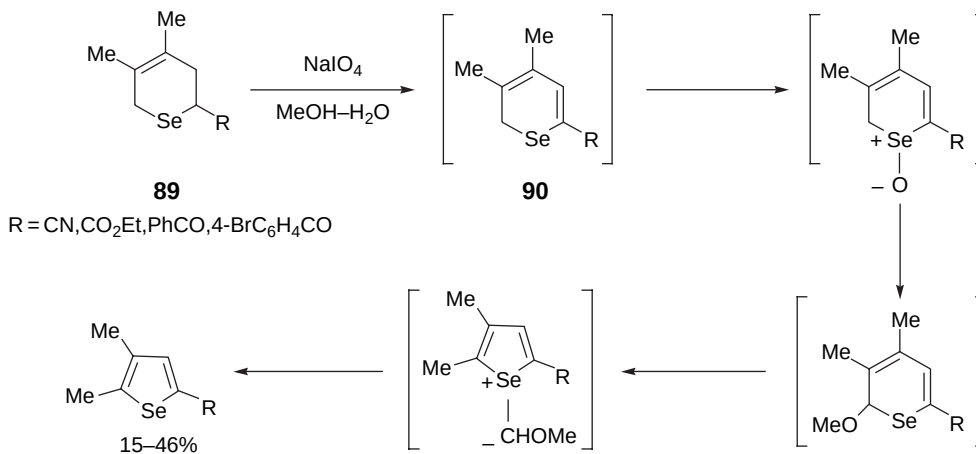
7.11.6.2 Dihydrochalcogenopyrans and Their Carbocyclic Derivatives

7.11.6.2.1 Oxidation

Isoseleno- and isotellurochromenes **85** can be readily converted to the corresponding 2-benzoseleno- and 2-benzotelluropyrylium tetrafluoroborates **86** by treatment with triphenylcarbenium tetrafluoroborate (Equation 35) <2002J(P1)606>. An analogous reaction has also been used for the conversion of tellurochromenes **87** to the corresponding 1-benzotelluropyrylium salts **88** (Equation 36) <1999J(P1)1665>. When the ring substituent was methyl or isopropyl, the desired benzotelluropyrylium salts formed but could not be isolated due to elimination of a proton from the substituent.

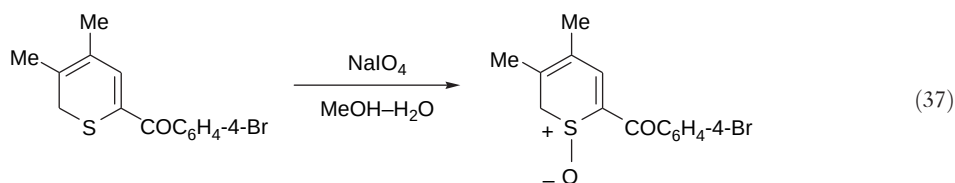


Oxidation of 3,6-dihydro-2*H*-selenopyrans **89** containing electron-withdrawing groups on the 2-position with sodium periodate affords the corresponding ring-contracted selenophenes (**Scheme 4**) <1993CC577>. The reaction seems to proceed through initial formation of the selenopyran **90** followed by oxidation to the selenoxide and subsequent Pummerer reaction. Yields in the ring contraction are very much dependent on the amount of sodium periodate used, with optimum yields of the selenophene obtained from reaction with 4 equiv of periodate.

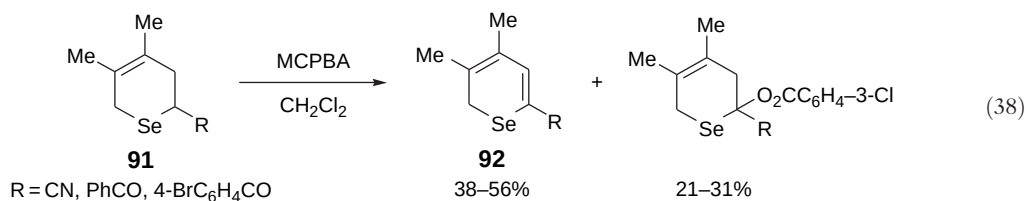


Scheme 4

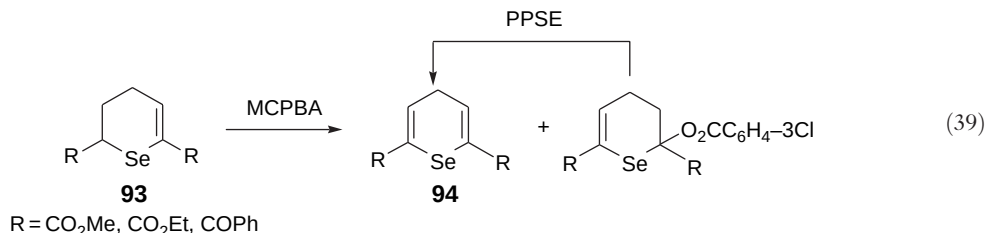
It should be noted that the oxidation of the thiopyran, the sulfur analogue of the proposed initially formed selenopyran intermediate **90** in **Scheme 4**, proceeds quite differently affording the sulfoxide in 31% yield without formation of the corresponding thiophene (**Equation 37**) <1993CC577>. Sulfoxides, and not thiophenes, were also obtained when *m*-chloroperoxybenzoic acid was used in the oxidation.



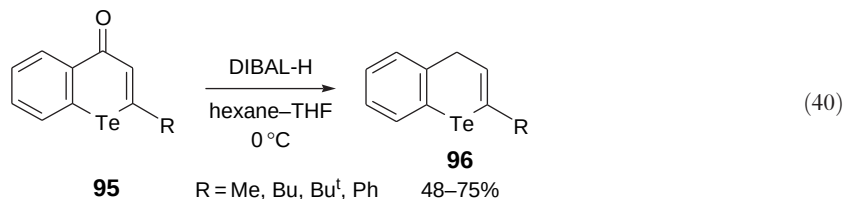
Oxidation of similarly substituted 3,6-dihydro-2*H*-selenines **91** with *m*-chloroperoxybenzoic acid affords the corresponding selenopyrans **92** as well as its 3-chlorobenzoic acid addition product (**Equation 38**) <1993CC577>. This reaction and that mentioned in **Scheme 4** presumably proceed through initial oxidation at selenium followed by a Pummerer-type α -oxidation. Typical yields of the selenopyrans were relatively modest. The effect of base on this reaction was investigated; however, it was not clear whether added base was really helpful in improving yields in the reaction.



Treatment of the isomeric dihydroselenines **93** containing electron-withdrawing groups in both the 2- and 6-positions with *m*-chloroperbenzoic acid also leads to formation of Pummerer-type oxidation products, the 4*H*-selenines **94** and the corresponding *m*-chlorobenzoate ester by-products (Equation 39) <1999J(P1)1155>. The esters could be converted to the corresponding 4*H*-selenines by treatment with polyphosphoric acid trimethylsilyl ester (PPSE), a useful reagent for eliminations under neutral conditions. These 4*H*-selenines were key intermediates in the synthesis of selenabenzene.

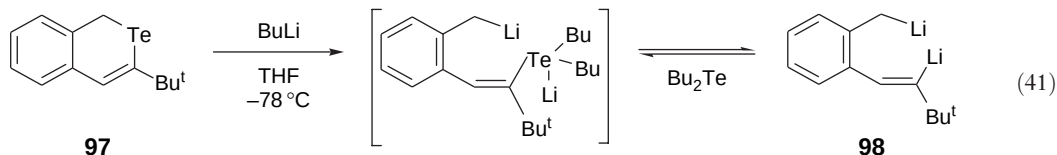


Tellurochromen-4-ones **95** can be selectively reduced to the corresponding 4*H*-tellurochromenes **96** using diisobutylaluminum hydride (DIBAL-H) (Equation 40) <1999J(P1)1665>.



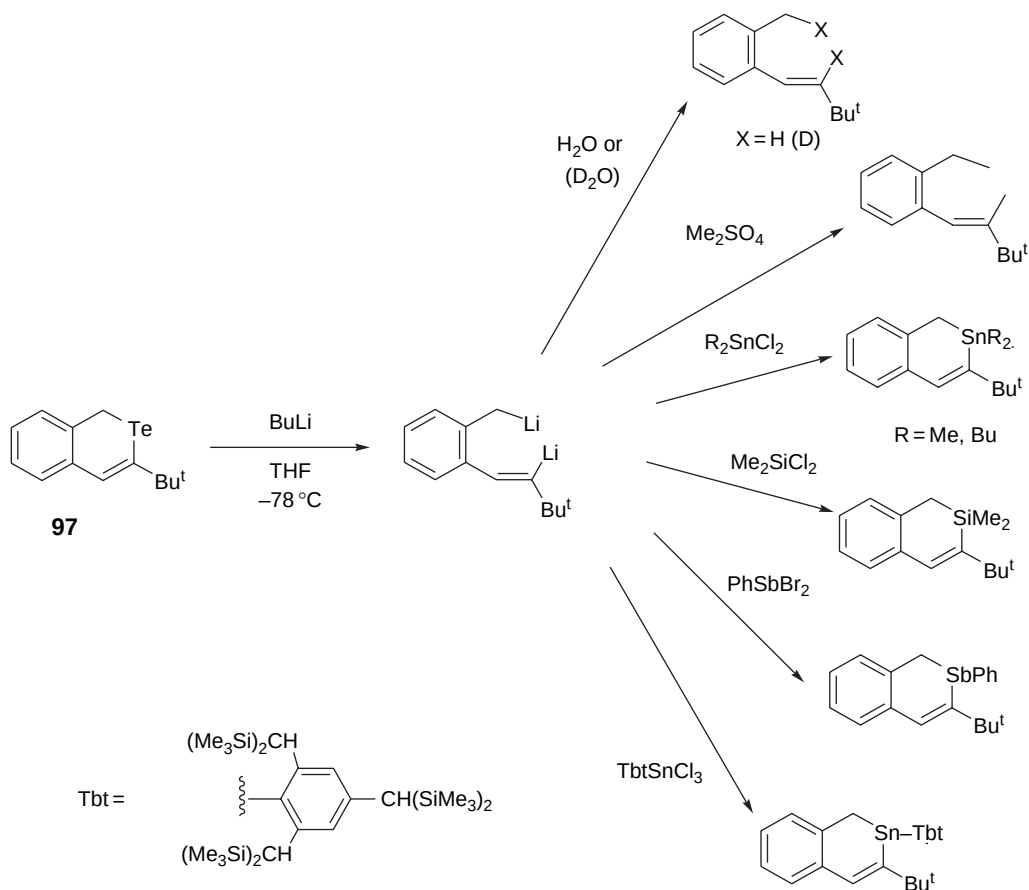
7.11.6.2.2 Metalation reactions

3-*tert*-Butylisotellurochromene **97** is a key starting material for the preparation of 1,2-dihydro-2-metalnaphthalenes <1999S1866> and 2-stannanaphthalene <2006JA1050>. Metalation of **97** readily occurs using *n*-butyllithium at low temperature affording (*E*)-2-(2'-lithiovinyl) benzyl lithium **98**, presumably via an addition–elimination sequence (Equation 41). Quenching of the dilithium compound leads to the styrene derivatives. A variety of other useful synthetic transformations can be carried out using **97** as a synthetic precursor (Scheme 5). For the reaction to be useful, the *tert*-butyl substituent was necessary. Other alkyl or phenyl substituents led to complex mixtures of products. Related reactions using 3-*tert*-butylisosenochromene did not give similar results despite the fact that selenium–lithium exchange in several other systems has previously been well documented <1982TL3411, 1984TL3629, 1985TL1093>.

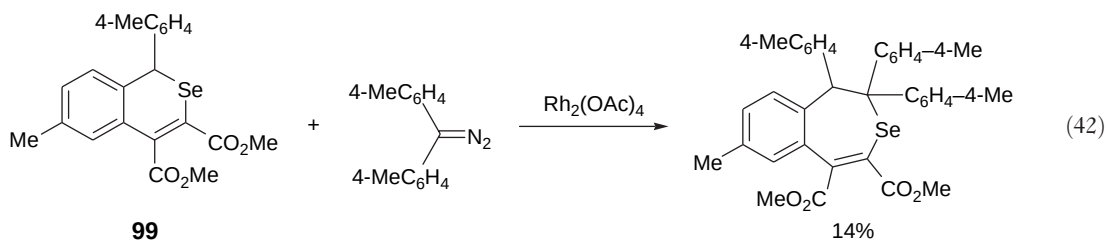


7.11.6.2.3 Other reactions at the chalcogen atom

In a single example, an isoselenochromene **99** has been shown to react with a carbene to afford the ring-expanded product in low yield. The reaction appears to proceed via initial addition of the carbene to selenium (Equation 42) <2000JOC2090>.



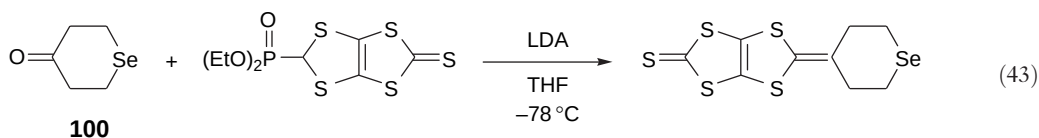
Scheme 5



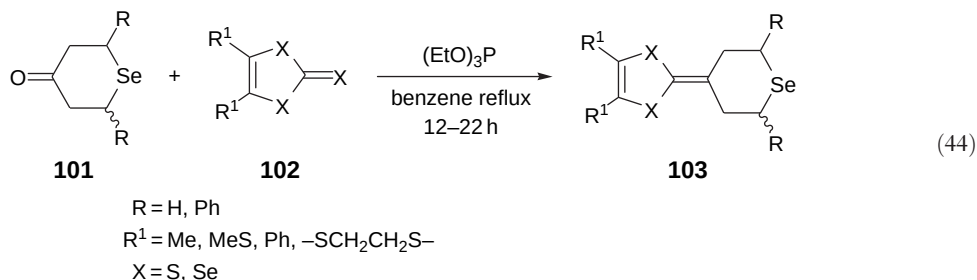
7.11.6.3 Tetrahydrochalcogenopyrans and Their Carbocyclic Derivatives

7.11.6.3.1 Reactions with nucleophiles

Tetrahydroselenopyran-4-one **100** readily reacts with Wittig–Horner-type reagents (Equation 43) <2002MCL107>. Reactions of this type provide convenient routes to precursors of selenium-containing organic conducting materials (see Section 7.11.8.2).

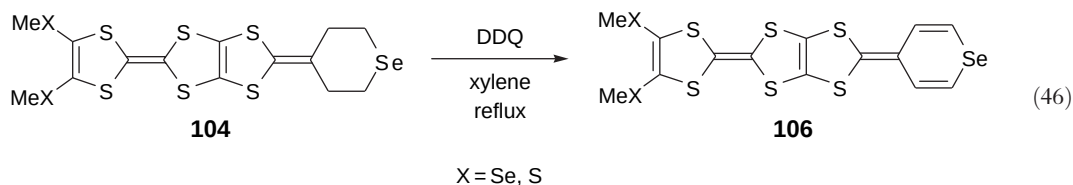
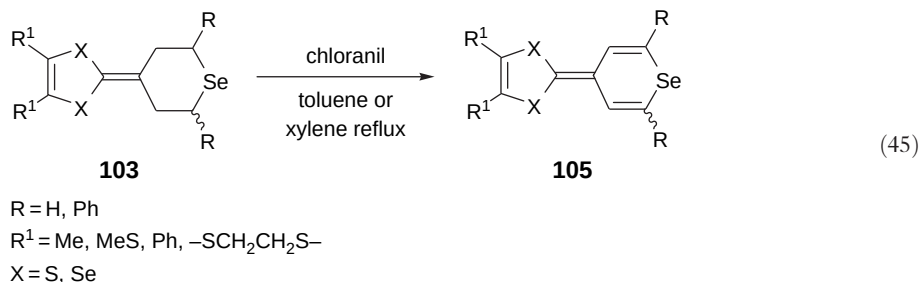


A related reaction involves directly treating a mixture of the tetrahydroselenopyran-4-one **101** with a dithiathione or dithiaselone **102** with triethylphosphite in refluxing benzene (Equation 44) <1993J(P2)1815>. A variety of selenotetrahydropyranylidene-1,3-dithioles and diselenoles **103** has been prepared using this method.

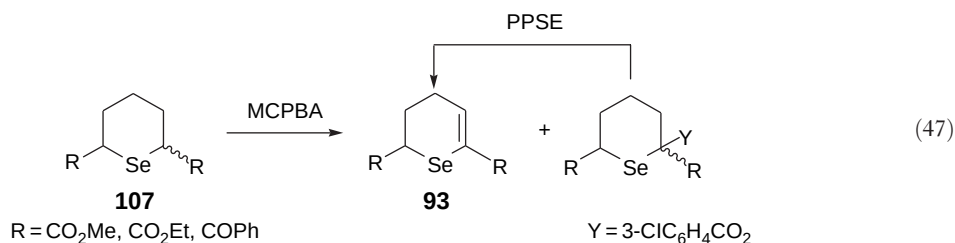


7.11.6.3.2 Oxidations

Selenotetrahydropyran derivatives such as **103** and **104** can be oxidized to the corresponding selenopyrans **105** and **106** using chloranil (Equation 45) <1993J(P2)1815> or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) <2002MCL107> (Equation 46). Compounds of this type show interesting electronic properties (see Section 7.11.8.2).

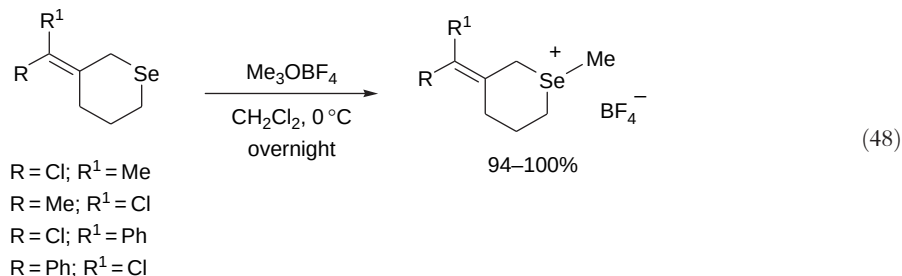


Treatment of selenanes **107** containing electron-withdrawing groups in the 2- and 6-positions with *m*-chloroperbenzoic acid leads to formation of Pummerer-type oxidation products (Equation 47) <1999J(P1)1155> (cf. Equations 38 and 39). The chlorobenzoate by-products could be converted to the desired dihydroselenines **93** by treatment with PPSE. The dihydroselenines were important intermediates in the synthesis of the corresponding selenabenzenes (see Scheme 2, Equation 39).

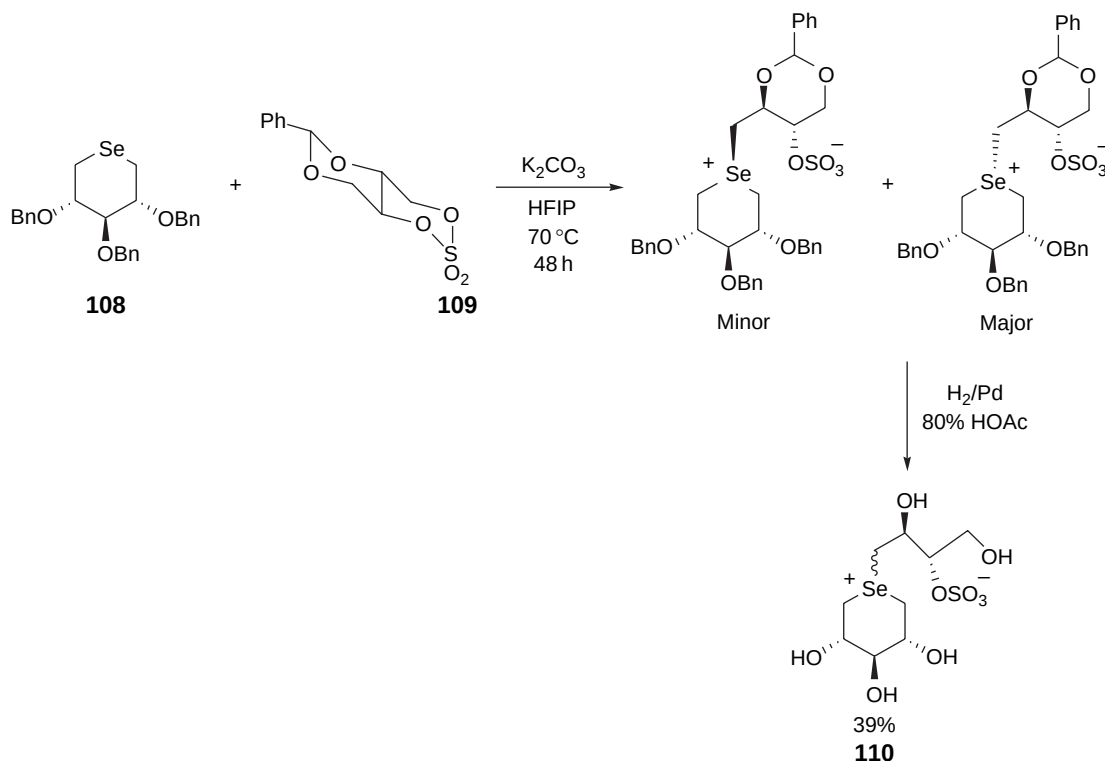


7.11.6.3.3 Reactions at the chalcogen atom

Selenanes with exocyclic methylene substituents can be efficiently methylated at the selenium atom using trimethyloxonium tetrafluoroborate (Equation 48) <1994JOC1011>.



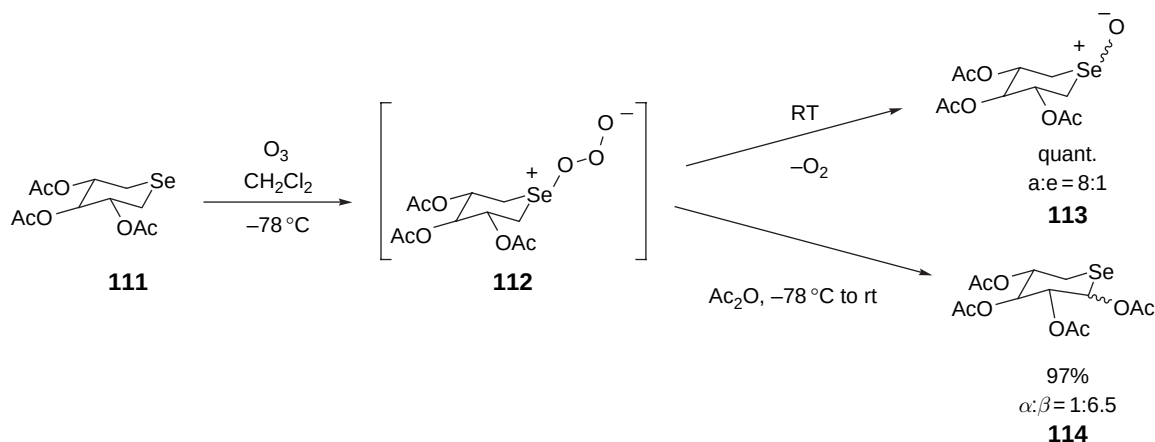
Se-Alkylation is a key step in the preparation of a series of biologically interesting tetrahydroselenopyran derivatives <2004JA12458>. Coupling of the protected derivative **108** with the D-cyclic sulfate **109** in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) afforded a diastereomeric mixture of isomers at the selenium center which could be reduced to the desired unprotected selenonium salt **110** (Scheme 6). It is worth noting that different stereochemical preference was observed in this alkylation compared to that in the case of the sulfur analogue. This was explained by lowered steric interactions in the selenium case due to the increased length of the C–Se bond. As expected, catalytic poisoning was observed in the hydrogenation reaction, significantly lowering the deprotection yield in this step.



Scheme 6

Ozonation of carbohydrate-based heterocycles containing selenium **111** (or sulfur) afford the corresponding selenoxides **113** (or sulfoxides) <2006JA227>. Low-temperature treatment of the initially formed ozonation products leads to Pummerer-like reactions affording interesting selenosugars **114** (Scheme 7). Thiosugars are formed from the

corresponding sulfur compounds. These reactions may at first appear to proceed by intermediate selenoxides or sulfoxides. However, this is not consistent with a number of observations. While the selenoxides readily undergo the Pummerer reaction with acetic anhydride at room temperature, the sulfoxides require much more vigorous conditions – acetic anhydride in refluxing toluene for 2 days – for the corresponding reaction to take place. This and other evidence indicates that these reactions may proceed by the initial generation of a selenide ozonide **112**. The sulfide ozonide also is likely to be an intermediate in the corresponding sulfur reactions.



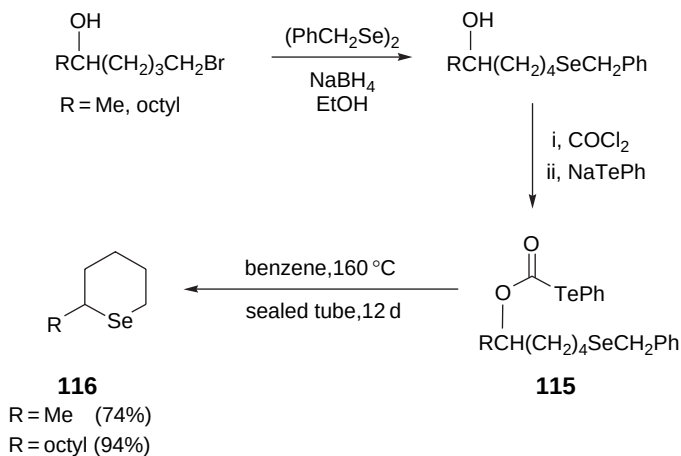
Scheme 7

7.11.7 Ring Synthesis

7.11.7.1 Formation of One Bond

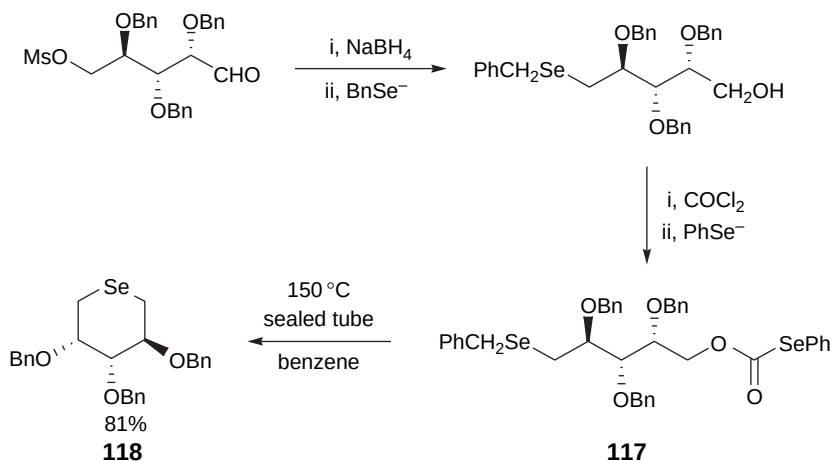
7.11.7.1.1 Se–C₂

Thermolysis of readily prepared telluroformates **115** leads to scission of the bond between tellurium and the carbonyl group. Extrusion of carbon dioxide leads to a radical cyclization affording 2-substituted selenanes **116** (Scheme 8) <1996JOC5754, 1998JOC3032>.

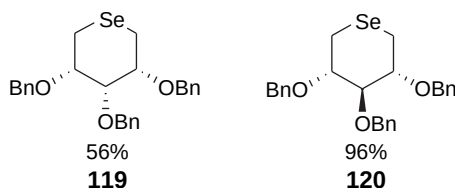


Scheme 8

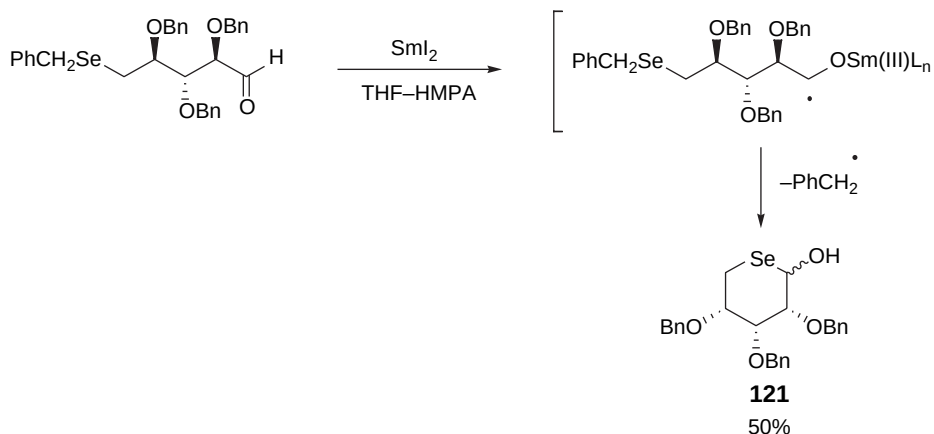
Similar cyclizations take place with both the corresponding phenylselenoderivatives **117**. This reaction has proved useful in the preparation of 5-deoxy-5-selenopentapyranose sugars such as **118** from pentoses (**Scheme 9**) <2000T3995>. Other deoxyselenosugars such as **119** and **120** could also be prepared using appropriately substituted starting phenylselenoformates.



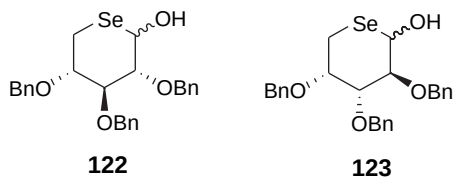
Scheme 9



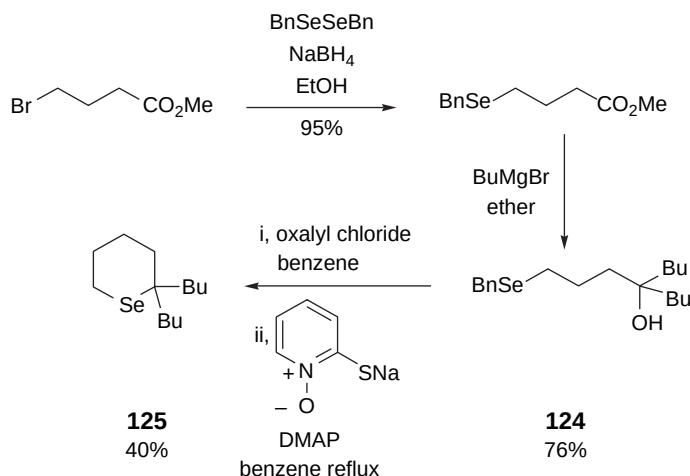
The benzylselenoaldehyde could be reduced using samarium(II) iodide to the corresponding carbon radical. This underwent an intramolecular radical substitution affording the two anomers of deoxyseleno-D-ribopyranose **121** in quite a reasonable yield (**Scheme 10**) <2000T3995>. Other selenopyranoses such as **122** and **123** could also be prepared using this method.



Scheme 10

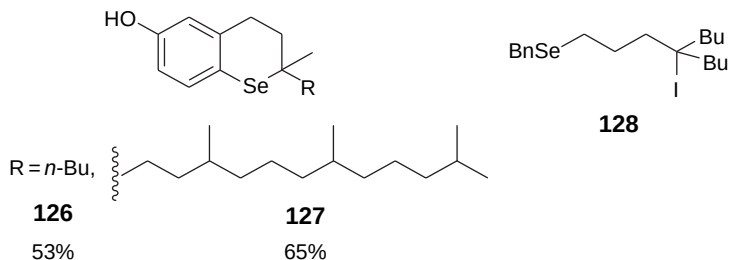


A related radical transformation can be used to prepare 2,2-disubstituted selenanes. Treatment of the alcohol **124** with oxalyl chloride followed by addition of 2-mercaptopyridine *N*-oxide and heating afforded the selenane **125** in moderate yield (**Scheme 11**) <2001JOC6286>. The required alcohol precursor for this reaction can be readily prepared from the bromo ester and *in situ*-generated sodium benzyl selenide, followed by Grignard addition.



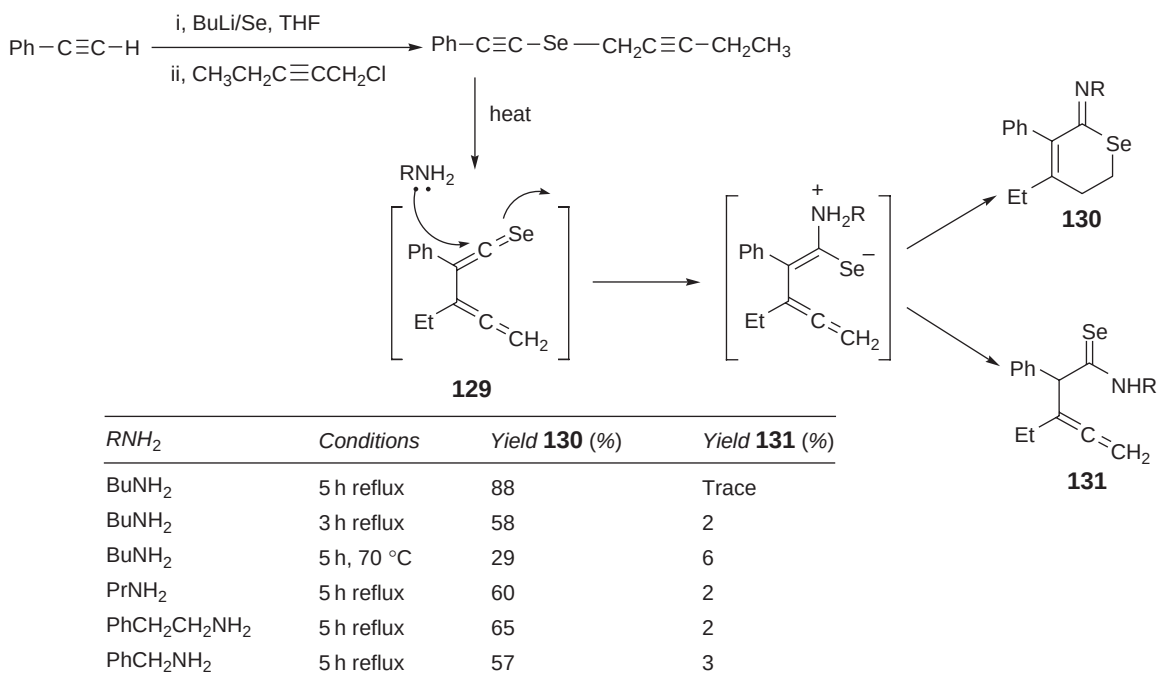
Scheme 11

This cyclization method could also be used for the preparation of vitamin E analogues such as **126** and **127**. It is interesting to note that the iodide **128** under free radical conditions leads to only low yields of cyclized product with elimination being the main reaction.

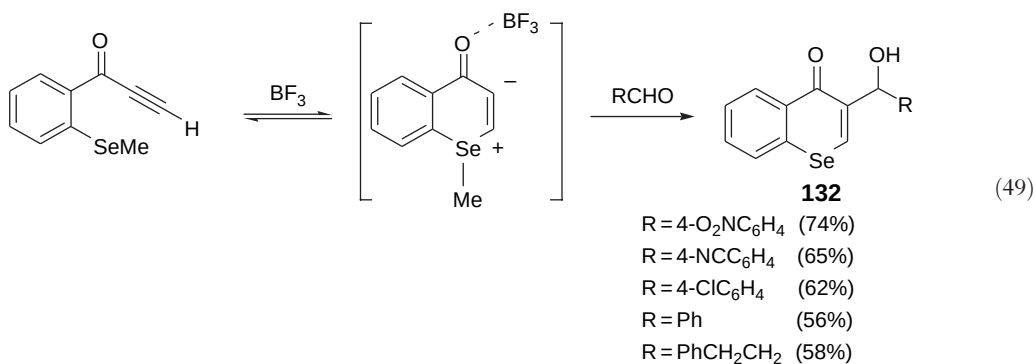


Allenic selenoketenes **129**, generated by [3,3] sigmatropic rearrangements, react with primary amines to afford 2-imino-2*H*-5,6-dihydroselenines **130** (**Scheme 12**) <2001JOC4099>. This reaction appears to be the first example of a selenoketene-allene cycloaddition. Uncyclized allenic selenoamides **131** are by-products in the reactions and are the only products when the reaction is carried out with secondary amines.

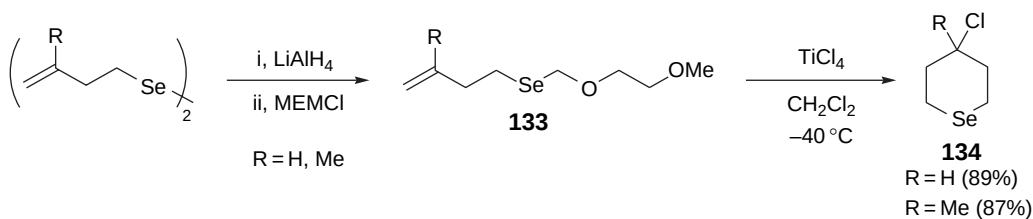
A tandem Michael-aldol reaction of ynone selenides with aldehydes provides a convenient route to 3-substituted selenochromen-4-ones **132** (Equation 49) <2002TL7039>. The reaction proceeds via an intermediate zwitterion formed via a 6-*endo-dig*-cyclization.



Scheme 12

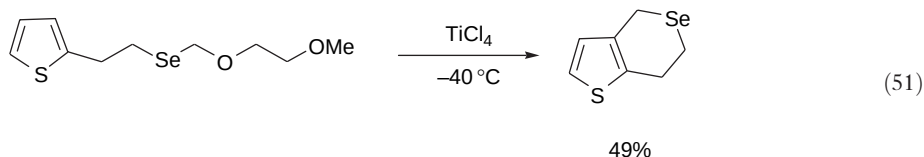
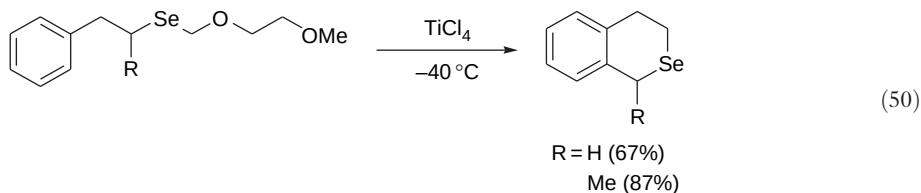
7.11.7.1.2 C₂-C₃

Cyclization of olefinic Se,O-heteroacetals **133** in the presence of titanium tetrachloride affords 4-chloroselenanenes **134** in good yields (Scheme 13) <1994JOC1011>. The reaction proceeds through the formation of an α -selenocarbocation which reacts with the olefinic bond followed by chloride addition. The required precursors for the reaction can be readily prepared by reduction of the corresponding diselenides followed by alkylation.

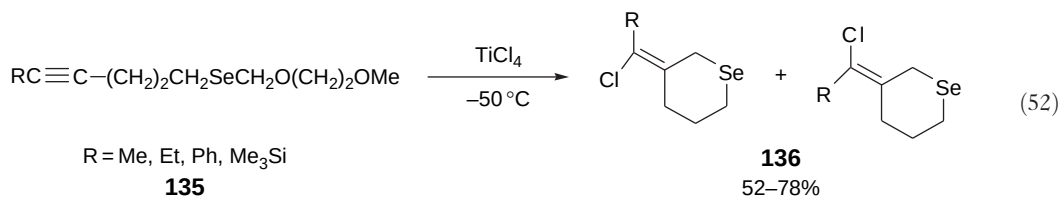


Scheme 13

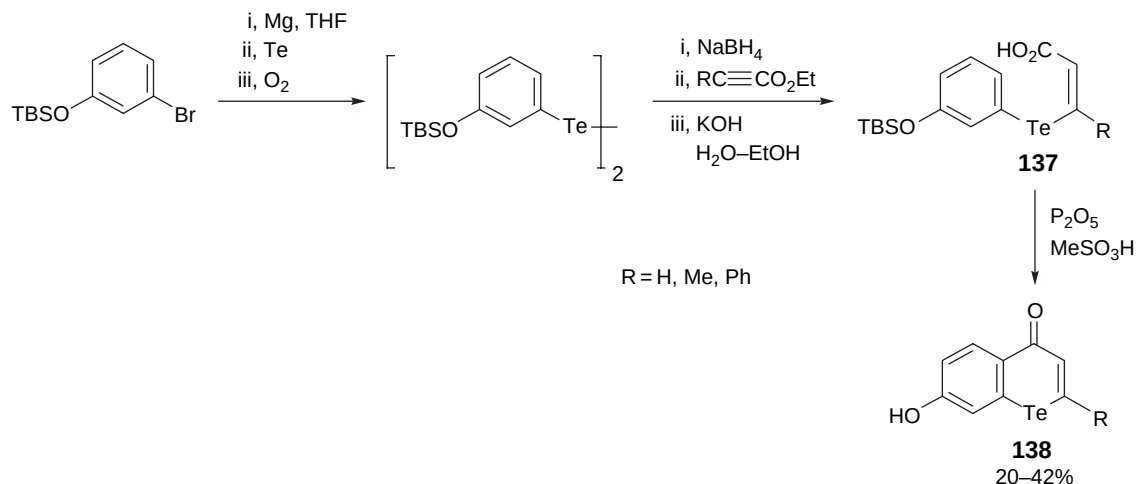
Ring-fused derivatives can also be prepared using this method (Equations 50 and 51) <1994JOC1011>.



Treatment of acetylenic heteroacetals **135** with TiCl_4 at low temperature leads to formation of mixtures of exocyclic chloromethyleneselenanes **136** (Equation 52) <1994JOC1011>. The (*E*)-isomer predominates in the cases examined. No cyclization occurs in the case of the terminal acetylene ($\text{R} = \text{H}$).



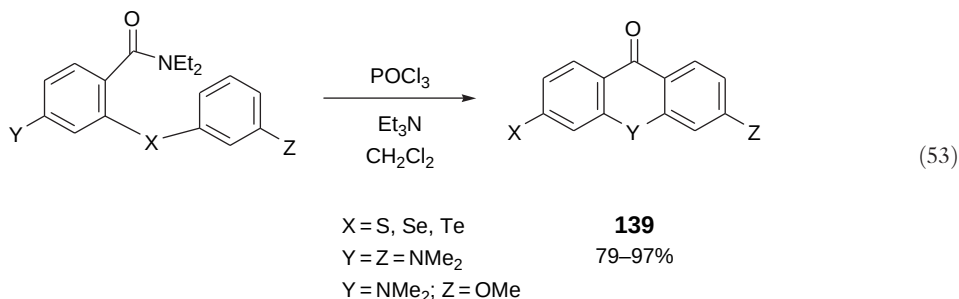
A direct synthetic route to 4*H*-7-hydroxybenzo[*b*]tellurin-4-ones **138** involves acid-promoted dehydration of the corresponding (*Z*)-unsaturated carboxylic acid derivatives **137** (Scheme 14) <1998OM3588>. These precursors can be readily prepared by a metallation-telluration sequence. Previous attempts to prepare molecules of this type, particularly the telluroflavones ($\text{R} = \text{Ph}$), were unsuccessful due to the unexpected reactivity of the C–Te bond relative to the C–Se and C–S bonds.



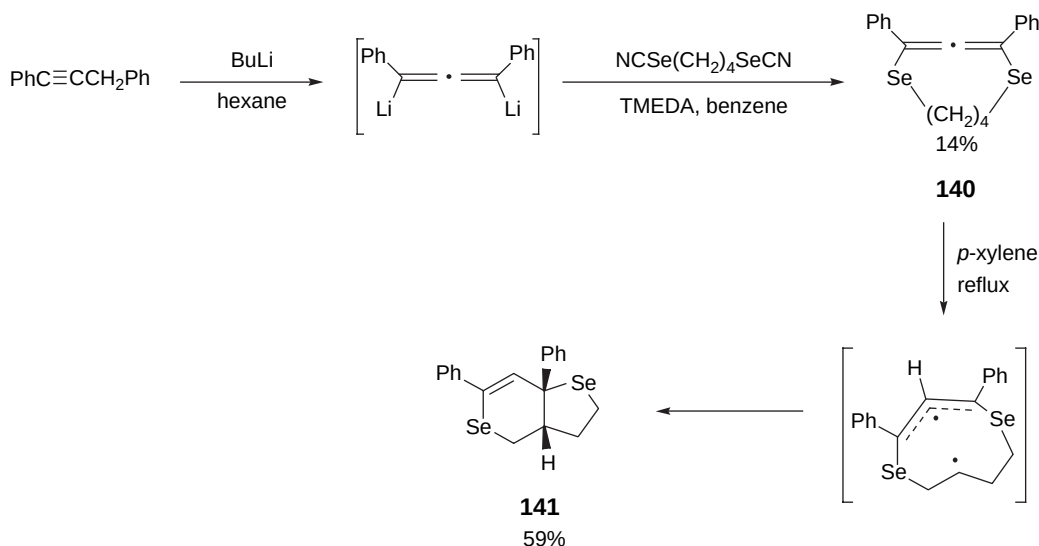
Scheme 14

7.11.7.1.3 C₃–C₄

Treatment of substituted aryl thio-, seleno-, and tellurobenzamides, containing very electron-rich substituents, with phosphoryl chloride leads to efficient cyclization to the corresponding chalcogenoxanthen-9-ones **139** (Equation 53) <2005OM3807>. Attempts to carry out this cyclization using methanesulfonic acid or aluminium chloride were unsuccessful. The dimethoxysubstituted precursor (Y=Z=OMe) and the monophenyl compounds (Y=NMe₂, Z=H) failed to cyclize under all conditions which were investigated.



Heating the diselenoallene **140** leads to an intramolecular cycloaddition affording the fused selenin **141** (Scheme 15) <2001JOC1787>. The reaction appears to take place by an initial intramolecular hydrogen abstraction by the sp-hybridized carbon of the allene affording a diradical intermediate. Radical coupling then leads to the selenin. The cyclic allene precursor could be prepared by dilithiation of the benzylacetylene followed by treatment of the bis-selenocyanate.

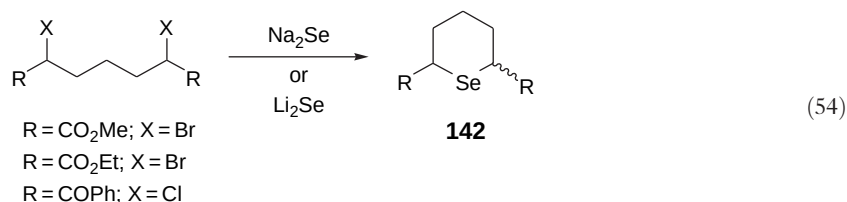


Scheme 15

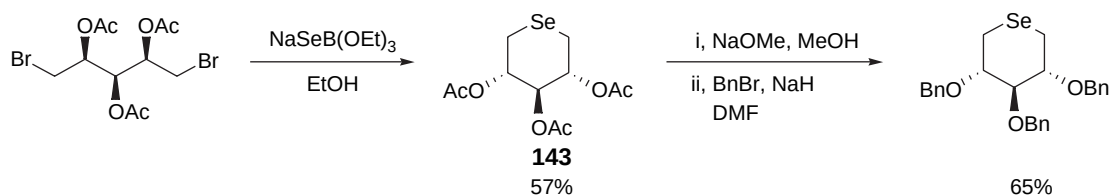
7.11.7.2 Formation of Two Bonds

7.11.7.2.1 Se plus C-5 unit

Selenanes containing electron-withdrawing groups on the 2- and 6-positions **142** were prepared by treatment of the corresponding dihalo compounds with sodium and lithium selenides (Equation 54) <1999J(P1)1155>. Preparation of selenanes such as **142** proved to be a key step in the preparation of dihydroselenines, 4*H*-selenines, and selenabenzenes (see Equations 47 and 39; Scheme 2).

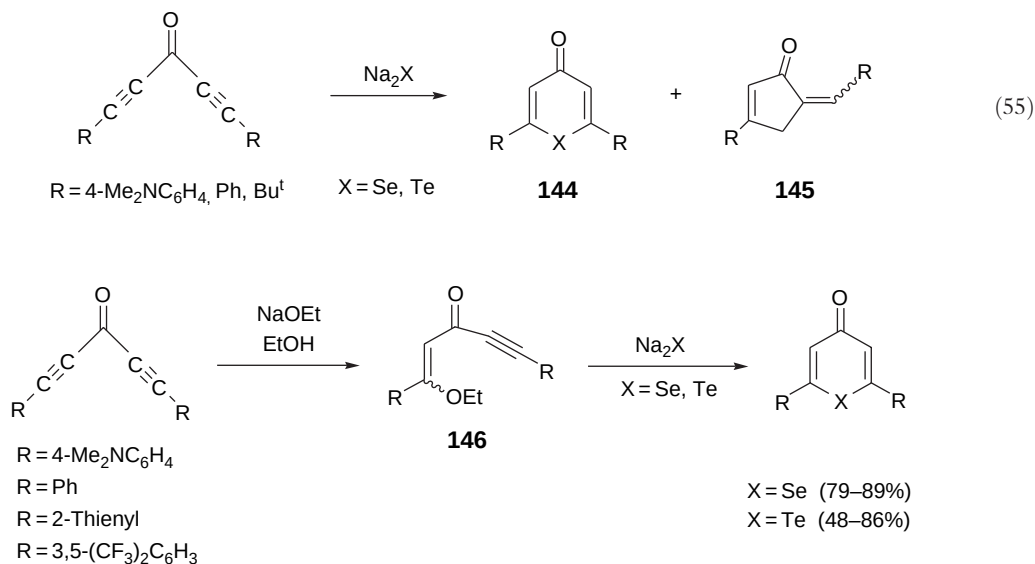


Treatment of the acetylated 1,5-dibromoxylitol with $\text{NaSeB}(\text{OEt})_3$ (formed *in situ* by the reaction of selenium with sodium borohydride in ethanol) afforded the selenane **143** (Scheme 16) <2004JA12458>. Methanolysis and benzylation afforded a key synthetic intermediate in the synthesis of potential glycosidase inhibitors (see Section 7.11.6.3.3, Schemes 6 and 7).



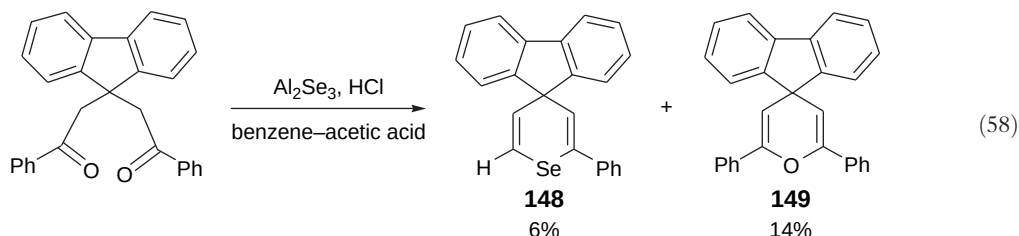
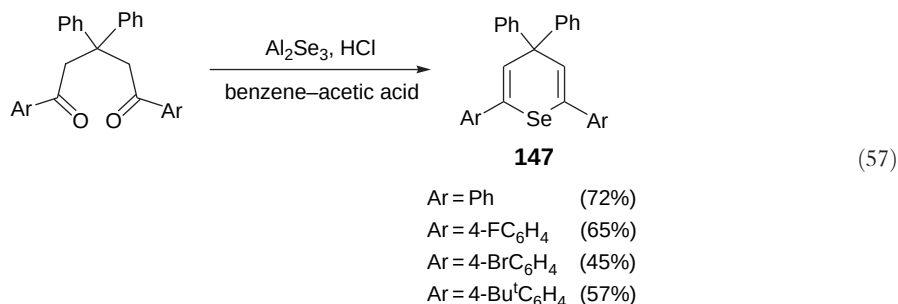
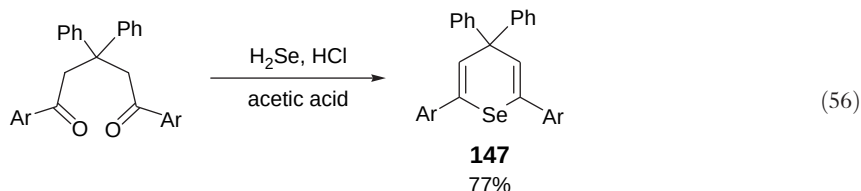
Scheme 16

Seleno- and telluropyranonones have been prepared by the reaction of 1,4-pentadiyn-3-ones with disodium selenide or telluride (see CHEC-II(1996), section 5.11.2.2). The desired seleno- and telluropyranonones **144** are, however, often minor products in the reaction with formation of dihydroselenophenes and -tellurophenes **145** as major by-products (Equation 55). Acetylenic enol ethers **146** appear to be important intermediates in the formation of the desired seleno- and telluropyranonones (Scheme 17) <1999JHC707>. Initial treatment of the 1,4-pentadiyn-3-ones with sodium ethoxide in ethanol affords the isomeric mixture of enol ethers in high yield and these can then be made to react with the disodium selenide or telluride affording the seleno- and telluropyranonones in very good yield without formation of the dihydroselenophene or -tellurophene by-products.

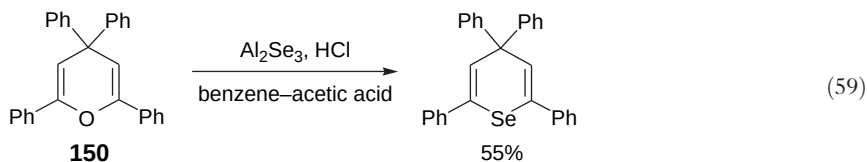


Scheme 17

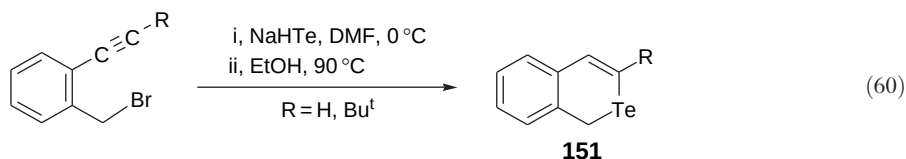
2,4,4,6-Tetrasubstituted 4*H*-selenopyrans **147** have generally been prepared by reaction of 2,5-diones with $\text{H}_2\text{Se}-\text{HCl}$ (Equation 56) <2002J(P2)1909> (also see CHEC-II(1996), Section 5.11.7.2.1, equation 32). To avoid the necessity of generating toxic H_2Se gas, an alternative approach was developed by generating H_2Se *in situ* from aluminium selenide–HCl. The yield of the desired 4*H*-selenopyran was comparable to that obtained using externally generated H_2Se . The reaction could be conveniently carried out on a number of related substrates (Equation 57). The rate of this reaction is very much influenced by the substitution pattern on the aromatic system. The *tert*-butyl derivative is formed in about 2 h while the 4-fluorophenyl derivative requires over 8 h for complete reaction. The spiro indane system required 54 h, affording the desired 4*H*-selenopyran **148** in only 6% yield (Equation 58). Unreacted starting material (80%) as well as the corresponding pyran **149** were the main materials isolated from the reaction even after 54 h.



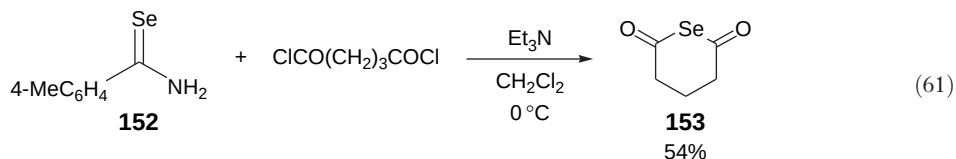
Treatment of the pyran **150** with aluminium selenide–hydrogen chloride under the same conditions afforded the selenopyran in 55% yield (Equation 59) <2002J(P2)1909>.



Isotellurochromenes **151** can be prepared by a ring-closure reaction of 2-ethynylbenzyl bromides with sodium hydrogen telluride (Equation 60) <1998J(P1)2123>. This reaction provided key synthetic intermediates for the preparation of 2-benzotelluropyrilium salts (see Equation (35), Section 7.11.6.2.1).

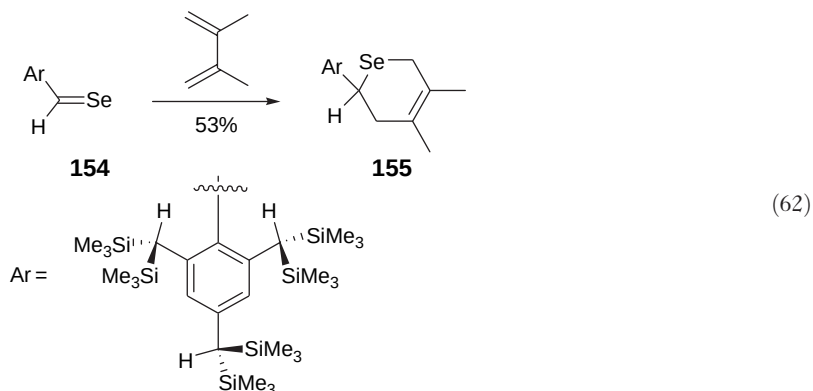


The selenium analogue of glutaric anhydride **153** has been prepared by reaction of glutaryl chloride with seleno-4-toluidine **152** in the presence of triethylamine (Equation 61) <1999CL485>. A significantly lower yield of **153** was obtained without added base.

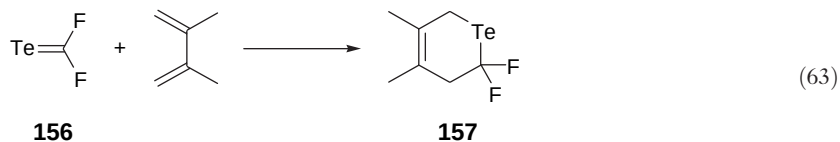


7.11.7.2.2 Se-C₂ or Te-C₂ plus C₅-C₆

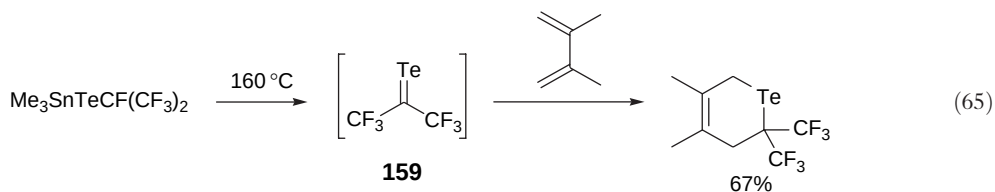
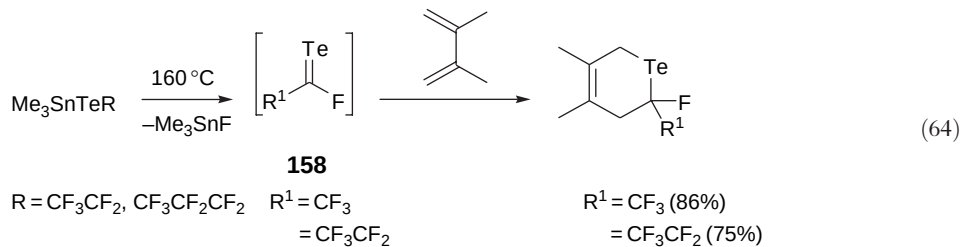
The [2+4] cycloaddition of selenocarbonyl (selenoxo) or tellurocarbonyl (telluroxo) compounds to diene systems remains one of the most widely used reactions for the preparation of various six-membered rings containing selenium or tellurium (see CHEC-II(1996), Section 5.11.7.2.1). The extremely sterically hindered selenal **154** has been isolated in monomeric form in solution and reacts with 2,3-dimethylbutadiene to afford the corresponding dihydro-selenin cycloadduct **155** (Equation 62) <1996AGE660, 1997T12167, 1998PS633>.



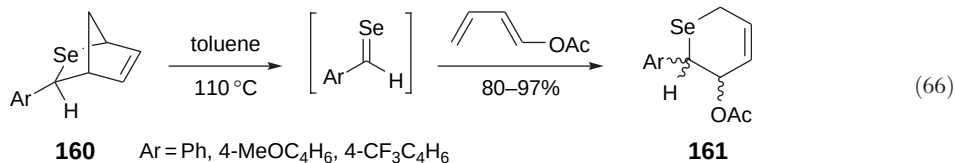
As expected, similar cycloaddition reactions have been used to prepare analogous tellurium-containing heterocycles. *In situ*-generated tellurocarbonyl difluoride **156** can be trapped as the difluorodihydro-2*H*-tellurin **157** using 2,3-dimethylbutadiene (Equation 63) <1993JCD2547>.



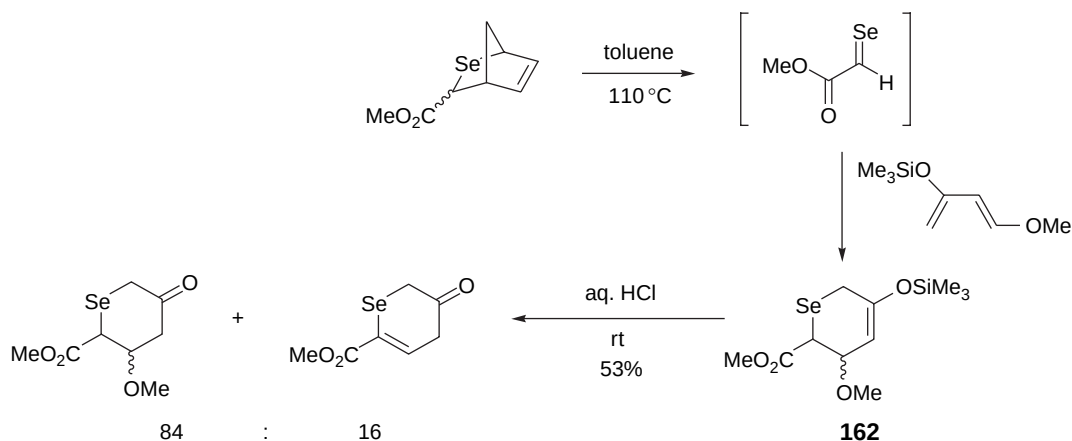
The perfluorinated tellurocarbonyl fluorides **158** have been trapped similarly (Equation 64) <1996JCD4463, 1997PS413> as has been perfluorotelluroacetone **159** (Equation 65) <2000JCD11>.



The utility of the cycloaddition route to dihydro-2*H*-selenins such as **161** can be significantly expanded by the *in situ* generation of the selenocarbonyl component. This can be done by the thermal retrocyclization of previously prepared cycloadducts such as **160** and trapping by another diene (Equation 66) <1993TL4925>.

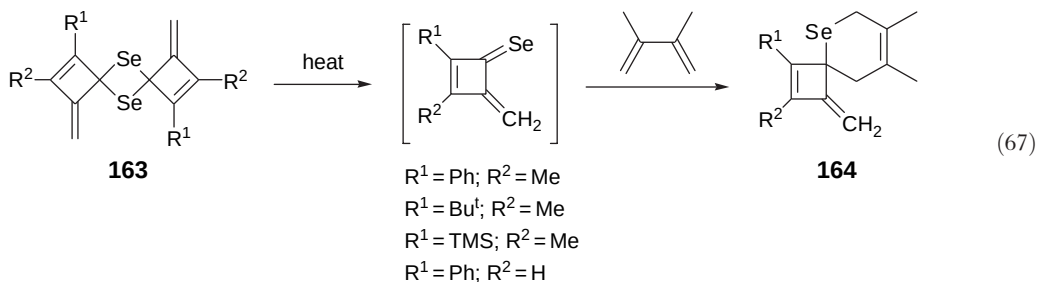


Similar retrocyclization–trapping reactions have been used to prepare highly functionalized dihydroselenins such as **162** (Scheme 18) <1998PS599>.



Scheme 18

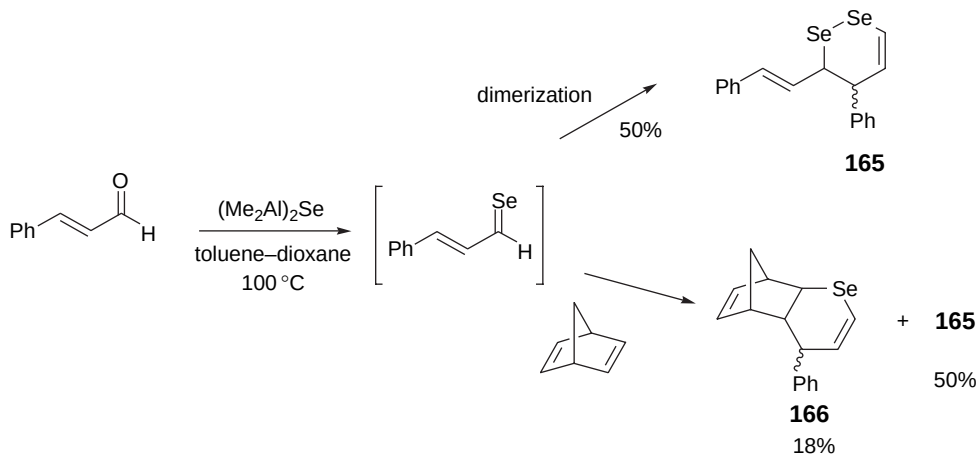
Other selenocarbonyl cycloaddition products react similarly. Thermal cleavage of the dimeric **163** leads to unstable α,β -unsaturated selones which can be trapped by a diene affording the selenin **164** (Equation 67) <1994CL2283>.



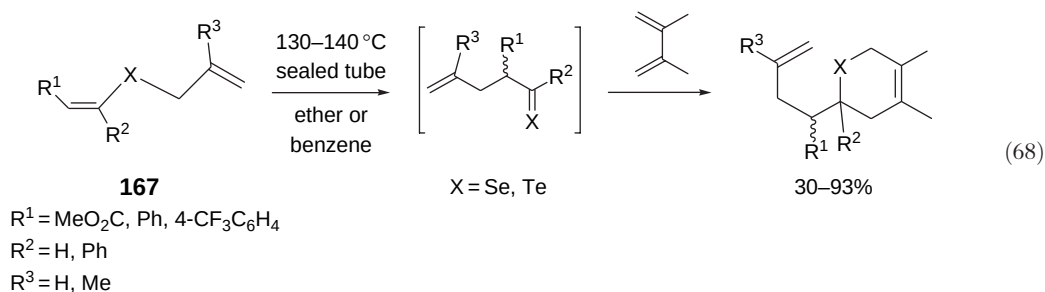
Reactions of *in situ*-generated α,β -unsaturated selenals with norbornadiene afford 3,4-dihydro-2*H*-selenins such as **166**, although dimerization to **165** is a significant side reaction (Scheme 19) <1992TL3515, 1999JOC1565>.

Selenals, selones, and tellurals generated *in situ* via [3,3] sigmatropic rearrangements of allyl alkenyl selenides and tellurides **167** can be trapped by 2,3-dimethyl-1,3-butadiene affording the expected cycloadducts (Equation 68) <1995CL135>. Higher yields were noted in less-hindered cases where the selenium and tellurium aldehyde

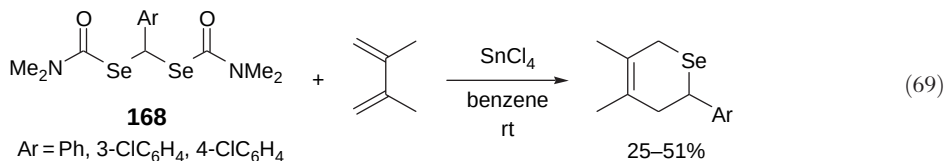
analogues were generated and trapped. The required allyl alkenyl telluride and selenide precursors for these cycloadditions could also be readily prepared starting from bis(*N,N*-dimethylcarbamoyl)ditelluride or -selenide <1972CL401, 1992CL1389>.



Scheme 19

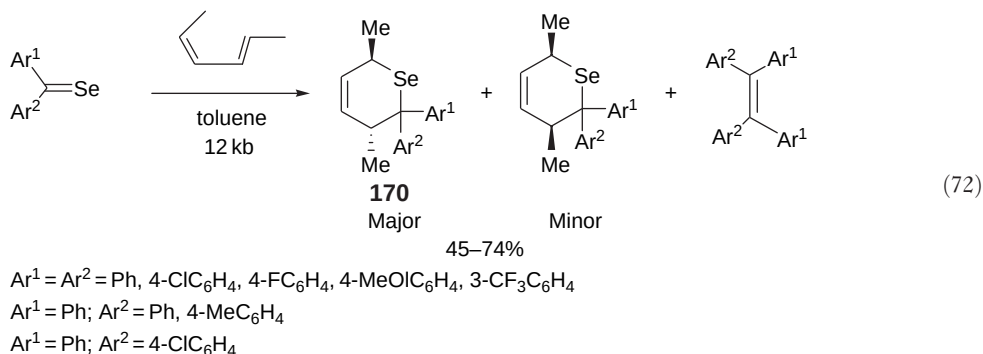
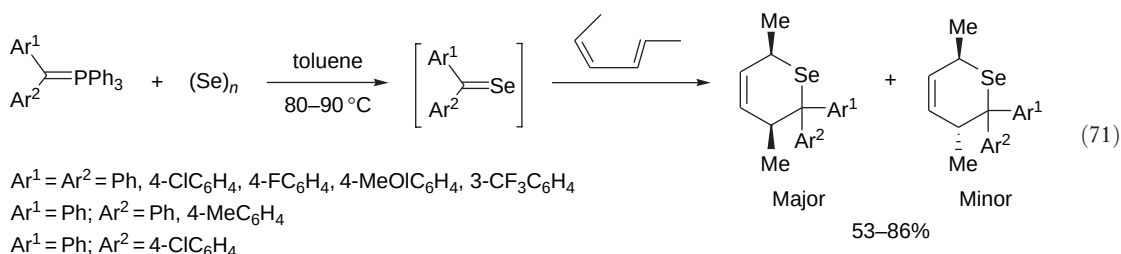
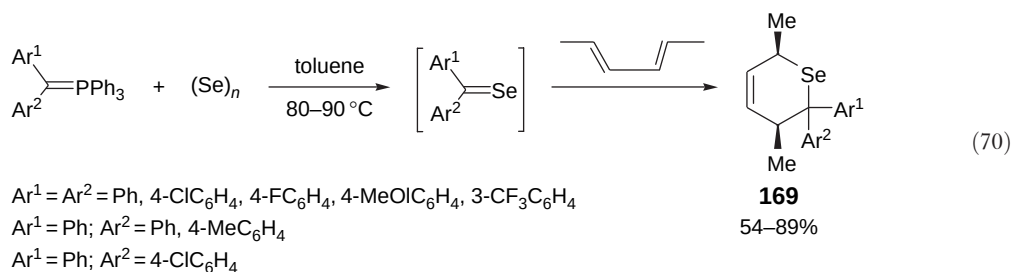


Treatment of aryl-substituted bis(*N,N*-dimethylcarbamoylseleno)methanes **168** with stannic chloride provides a convenient room temperature method for the generation of selenals which can be trapped by dienes (Equation 69) <2005TL3775>.

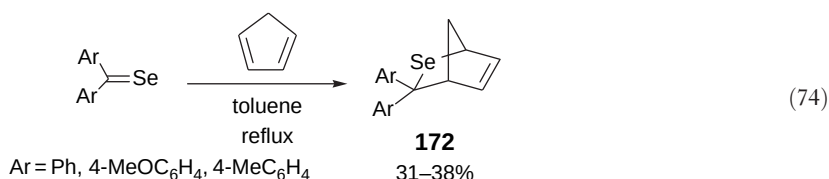
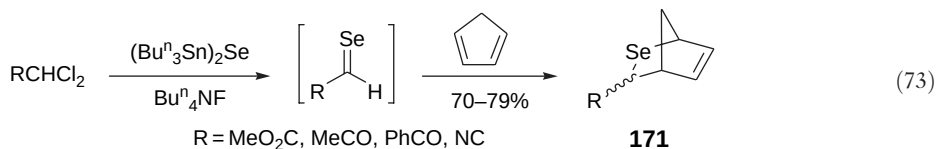


The stereochemistry of the cycloaddition of diarylselones with conjugated dienes to afford tetrasubstituted 2*H*-selenapyrans has been investigated <1995JA10922>. Reaction with *trans,trans*-2,4-hexadiene proceeds stereospecifically at $80\text{--}90^\circ\text{C}$, affording the *cis*-2*H*-selenapyran **169** (Equation 70). The reaction of selones with *cis,trans*-2,4-hexadiene under similar conditions proceeds stereoselectively, giving primarily the same *cis*-2*H*-selenapyran (Equation 71). These results suggested that diarylselones react with very reactive conjugated dienes such as *trans,trans*-2,4-hexadiene via a concerted [4+2] cycloaddition. Less reactive dienes such as *cis,trans*-2,4-hexadiene appear to react in a stepwise manner leading to formation of a diradical intermediate which undergoes cleavage regenerating the selone and affording *trans,trans*-2,4-hexadiene. These mechanisms are supported by solvent

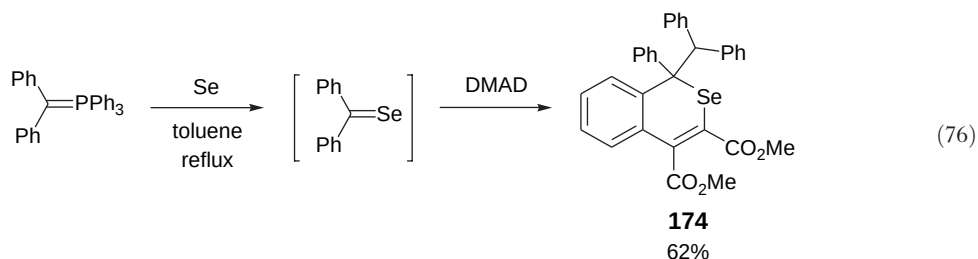
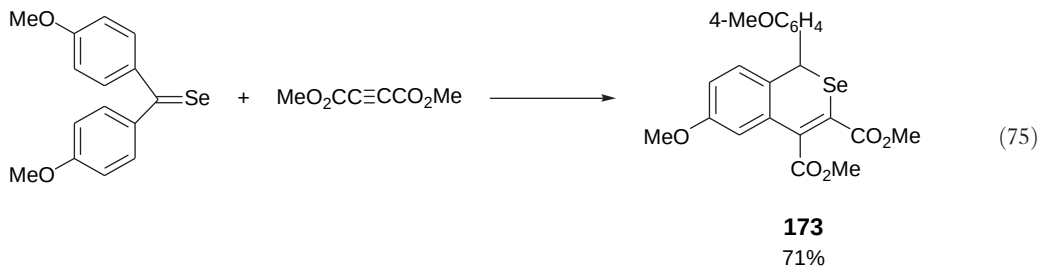
effects and studies of the effects of aryl substituents on the reactions. If the reaction with *cis,trans*-2,4-hexadiene is carried out under a pressure of 12 kb at ambient temperature however, *trans*-2*H*-selenapyran **170** is the major cycloaddition product (Equation 72). These high-pressure conditions are known to favor concerted cycloaddition processes. The tetraarylethylene by-product is formed by decomposition of the selone. The corresponding thiones react similarly.



Isolated or *in situ*-generated selenals and selones can also be trapped by cyclic dienes affording bicyclic 3,4-dihydro-2*H*-selenins **171** and **172** (Equations 73 and 74) <1994J(P1)2151, 1996BCJ2235>.



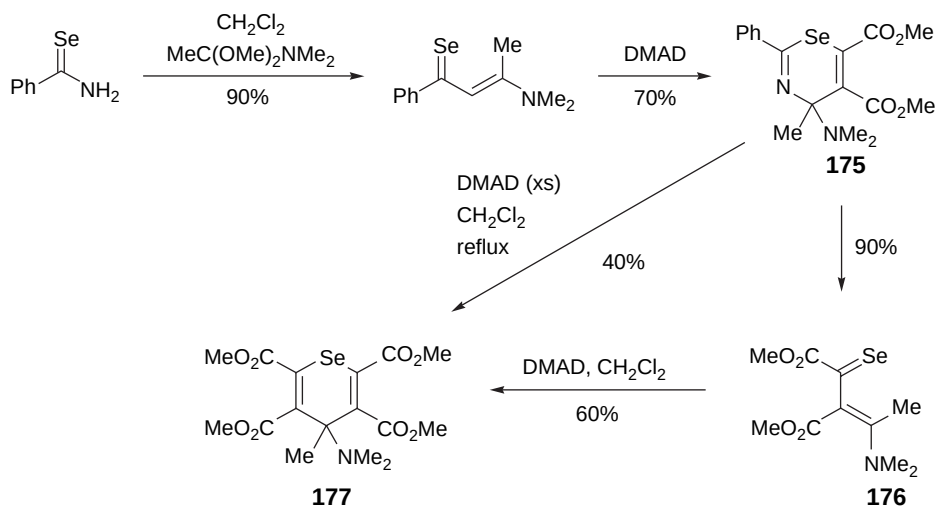
Isolated 4,4'-dimethoxyselenobenzophenone reacts with dimethyl acetylenedicarboxylate (DMAD) to afford an addition product **173** in good yield (Equation 75) <2000JOC2090>. A variety of other *in situ*-generated selones, with the exception of selenobenzophenone, react similarly. *In situ*-generated selenobenzophenone gave exclusively a diadduct **174**, presumably through a diphenylcarbene intermediate (Equation 76).



Alternative methods for the preparation of selenals and selones which could be applied to the synthesis of related selenium and tellurium heterocyclic systems have been recently reviewed <2005COFGT-II(3)397>.

7.11.7.2.3 Se-C₄ plus C₅-C₆

A route to the multiply substituted 4*H*-selenopyran **177** involves the cycloaddition of DMAD to the *N*-selenoacylamidine **176**. This compound can be readily prepared via 4*H*-1,3-selenazine **175** starting from the corresponding selenoamide (Scheme 20) <1995TL237, 1998T2545>. Direct treatment of the 4*H*-1,3-selenazine with excess DMAD in refluxing dichloromethane also affords the 4*H*-selenopyran.

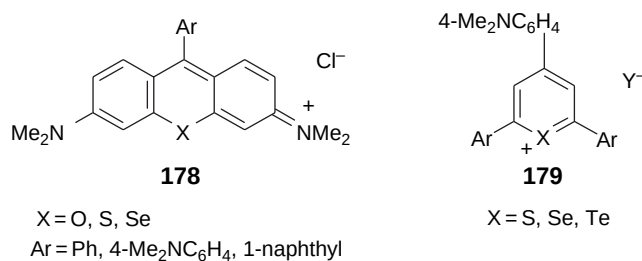


Scheme 20

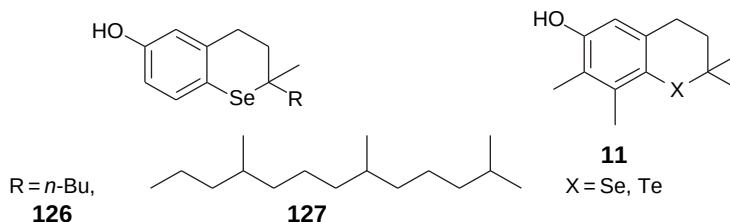
7.11.8 Important Compounds and Applications

7.11.8.1 Compounds of Biological Interest

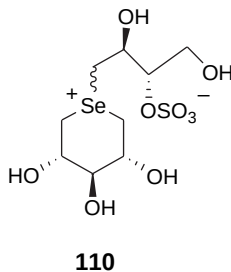
A variety of six-membered ring organoselenium compounds have shown promise in biological studies. The photodynamic properties of selenium analogues **178** of the thiopyrylium antitumor agent AA1 have been described <1999JME3953, 2000JME4488, 2002JME5123, 2004BMC2537>. AA1 (**178**: X = O) is known to target mitochondria in photodynamic therapy (PDT). PDT involves using a light-activated sensitizer to generate a cytotoxic reagent or a cytotoxic reaction in tumor cells. In general, photochemically mediated singlet oxygen or superoxide brings about this cytotoxicity. PDT using selenoxanthylum photosensitizers has also been investigated as a method for purging blood-borne viral and bacterial pathogens <2005BMC5927>. When Ar = Ph and X = Se, the resulting compound is expected to be an efficient photosensitizer for the generation of singlet oxygen in biological and chemical applications <2004PCB8668>. Triarylseleno- and telluropyrylium dyes **179** have also been investigated in photodynamic cancer therapy <1999JME3942>.



The preparations of selenium analogues of various tocopherols (vitamin E constituents) **126** and **127** have been described <2001JOC6286> (see Section 7.11.7.1.1). Calculations have also been used to design selenium- and tellurium-containing α -tocopherol analogues such as **11** (see Section 7.11.2).



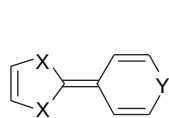
The selenium analogue of salacinol **110** has been prepared. Salacinol is a sulfonium-salt glucosidase inhibitor. This analogue shows at best only weak biological activities relative to the parent sulfonium salt <2004JA12458>.



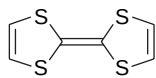
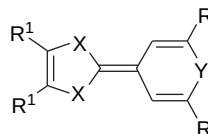
7.11.8.2 Compounds with Interesting Electronic and Optical Properties

As mentioned in CHEC-II(1996) (Section 5.11.9), there remains significant interest in the technical potential of compounds containing six-membered rings with one selenium or tellurium atom. The electronic properties of selenium-containing organic semiconductors such as **180** and **182** are particularly interesting <1993J(P2)1815>. As

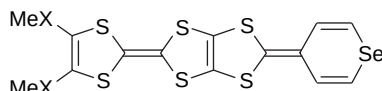
expected, thio- and selenopyranylidene derivatives such as **180** show two reversible one-electron waves in cyclic voltammetry. Each of the selenium-containing derivatives has lower oxidation potentials than tetrathiafulvalene (TTF) **181**. Replacement of sulfur by selenium enhances the first half-wave oxidation potential, although the effect is more pronounced by selenium replacement in the five-membered ring rather than the six-membered ring. The effects of ring substitution on oxidation potential in compounds such as **182** have also been investigated. Related structures such as tetrathiapentalene derivatives **106** have also been investigated <2002MCL107>. Cyclic voltammetry of these compounds shows three reversible one-electron oxidation waves and one additional irreversible one-electron wave.

**180**

X = Y = S
 X = Y = Se
 X = S; Y = Se
 X = Se; Y = S

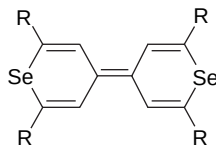
**181****182**

X = Y = S
 X = Y = Se
 X = S; Y = Se
 X = Se; Y = S
 R = H, Ph
 R¹ = H, Me, MeS, SCH₂CH₂S, Ph

**106**

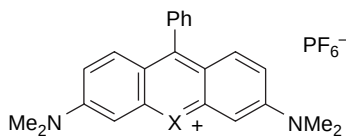
Y = S, Se

Charge-transfer complexes of biselenopyranylidenes **15** also show interesting optical and electronic properties <1995MCL143>. The crystal structure of the tetraphenyl derivative has also been described (see Section 7.11.3.1).

**15**

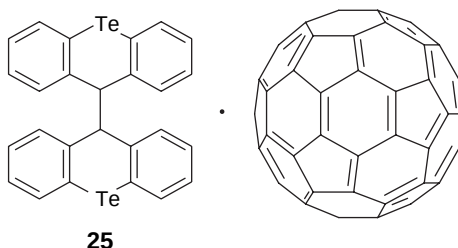
R = Ph, Me

The photophysics of a series of heteroatom-substituted tetramethyrosamine dyes has been investigated <2004PCB8668>. Compounds of this type may prove to be useful fluorescence probes in chemistry and cell biology (see Section 7.11.8.1).

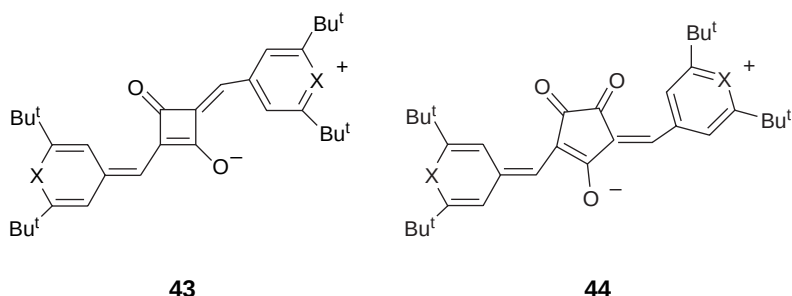
**183**

X = O, S, Se

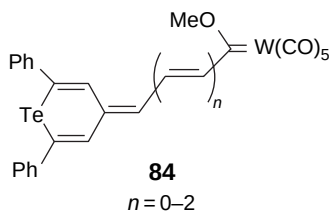
A crystalline complex of 9,9'-*trans*-bis-telluraxanthenyl and fullerene has been reported <1997CPH407>. This type of fullerene complex acts as an organic semiconductor. The photoluminescence of this complex has been studied. The optical reflectivity spectrum of the complex also differs from that of uncomplexed C₆₀ <1997ESO1200>.



Infrared absorbing dyes such as **43** and **44** have proved to be useful in a variety of industrial applications including thermal imaging, photography, lithography, electrophotography, optical recording, and as infrared optical filters (see Equations 9 and 10) <1993H(35)1149, 2000JOC2236>.



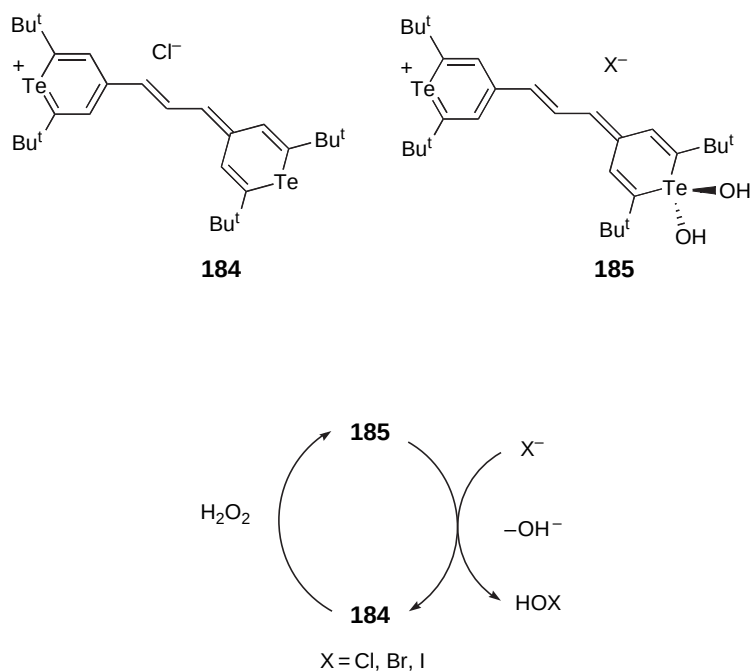
A number of ‘push–pull’ Fischer-type carbene complexes **84** have been prepared and exhibit interesting nonlinear optical properties <2005JOM4982> (see Equations 10 and 34). The influence of changing the chalcogen atom and the effect of varying the chain length on these optical properties have also been investigated.



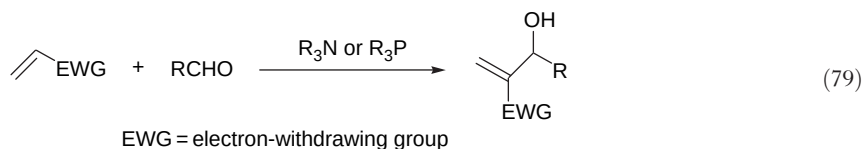
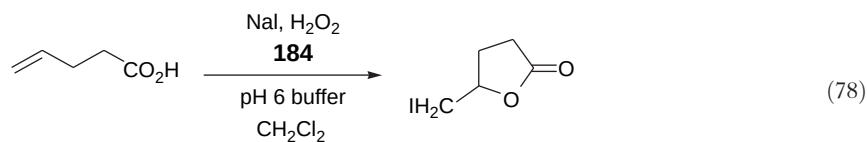
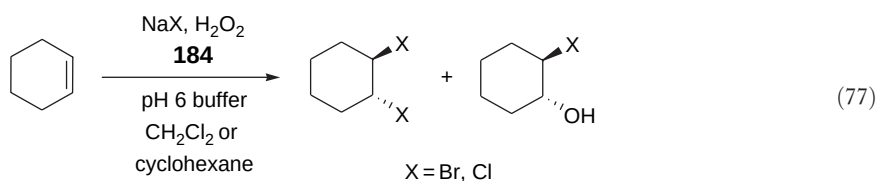
7.11.8.3 Catalytic Activities

Hydrogen peroxide is a powerful oxidant which is under-utilized in industrial organic synthesis. Because of the environmentally friendly nature of hydrogen peroxide, it would be useful to increase its use in various synthetic transformations. Organotellurium compounds such as **184** in the presence of hydrogen peroxide catalyze the conversion of chloride and bromide anions to the corresponding positive halogen species (Scheme 21) <1996JA313> (cf. Equations 12 and 13). This oxidation can be applied in tandem to carry out very useful synthetic transformations such as those shown in Equations (77) and (78).

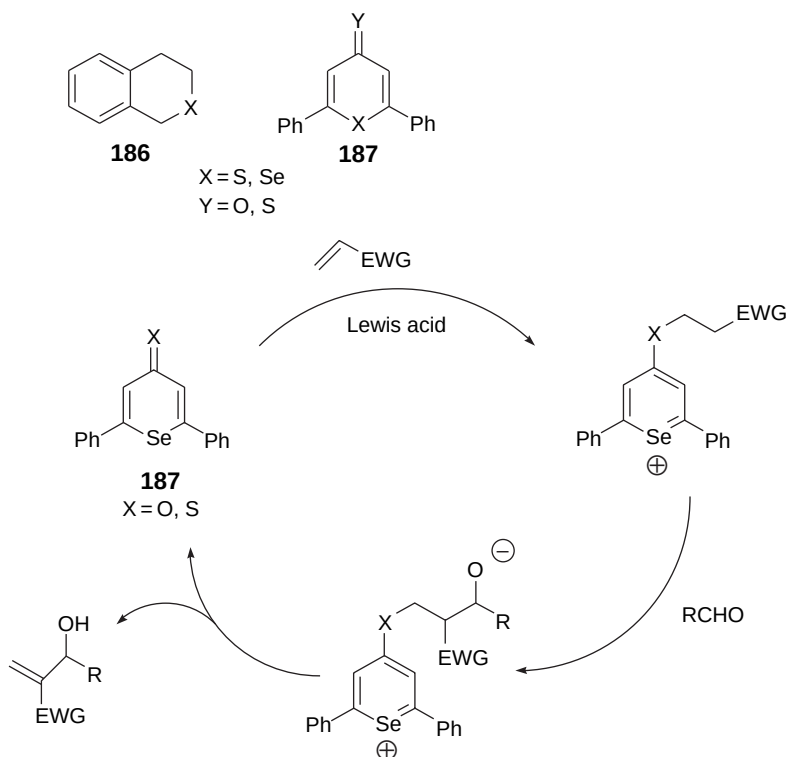
Selenium-containing six-membered ring heterocycles have proved to be useful catalysts in a variety of transformations. The Baylis–Hillman reaction involves the reaction of alkenes containing electron-withdrawing groups such as α,β -unsaturated carbonyl compounds with aldehydes leading to carbon–carbon bond formation (Equation 79). The reaction is promoted by tertiary amines such as 1,4-diazabicyclo[2.2.2]octane (DABCO), or tertiary phosphines and Lewis acids. Unfortunately, the Baylis–Hillman reaction is severely limited because it proceeds only very slowly <1998CC197>. Much research has been carried out in attempts to increase the rate of this reaction.



Scheme 21



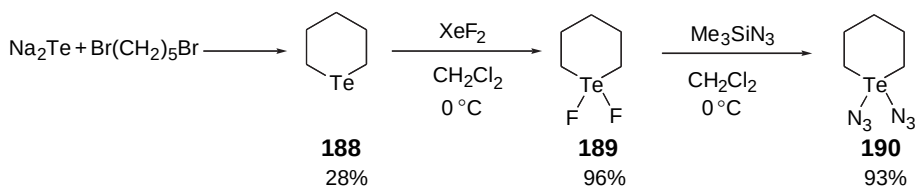
Sulfur- and selenium-containing heterocycles such as **186** and **187** in the presence of Lewis acids have recently been shown to be useful catalysts in this transformation, generally leading to complete reaction within an hour. This reaction is now termed the chalcogeno-Baylis-Hillman reaction <1998CC197, 1998T11813, 1999TL3741, 2000T4725>. The mechanism of this reaction involves initial conjugate addition of the heterocycle to the unsaturated species followed by carbon-carbon bond formation (Scheme 22). The chalcogeno-Baylis-Hillman reaction has subsequently been extended to thioacrylates and also to acetylenic substrates <2000AGE2358, 2000JOM455>.



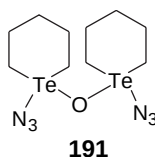
Scheme 22

7.11.9 Further Developments

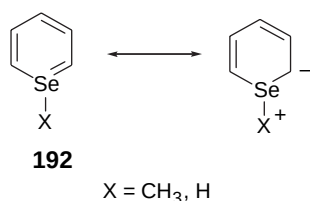
Tellurane **188** was prepared by reaction of sodium telluride with 1,5-dibromopentane, and was converted to the tellurane difluoride **189** with XeF_2 <2006ZN(B)528>. The difluoride could be converted to the corresponding diazide **190** by treatment with trimethylsilyl azide. The products were characterized spectroscopically, including using ^{125}Te NMR. After extended storage of **190** at -20°C , a crystalline oxygen bridged tellurium(IV) azide **191** could be isolated and its structure determined crystallographically.



Scheme 23

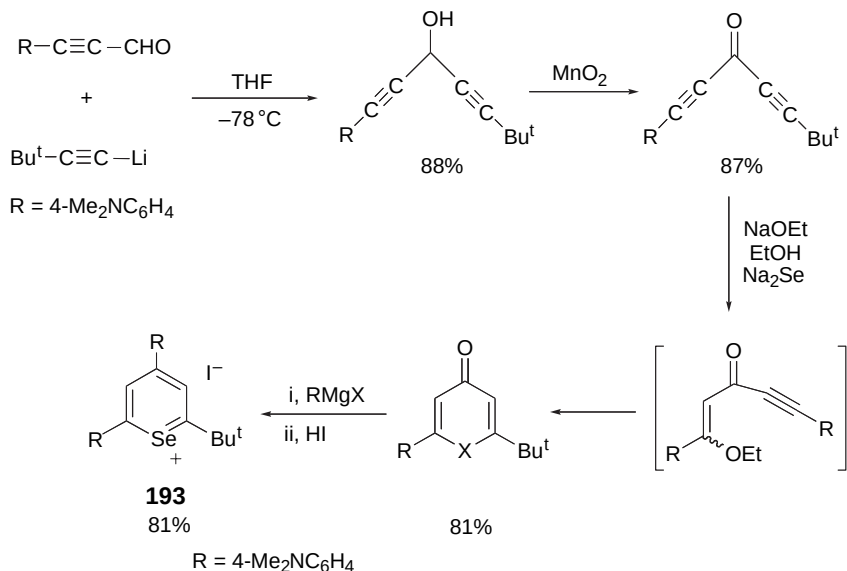


A theoretical study on *Se*-methylselenabenzene **192** and its oxygen and sulfur analogues has been carried out using *ab initio* calculations with the DFT method <2006M1791> (cf. Section 7.11.2, structure **3**). The X–H compounds were also evaluated. These structures have 6π electrons and are homoaromatic with ylide character. Structural parameters were also determined for these structures. The substituent on the chalcogen atom is calculated to be more stable in a pyramidal rather than a planar conformation.

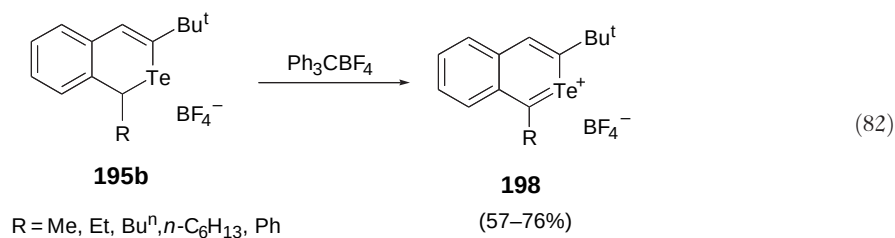
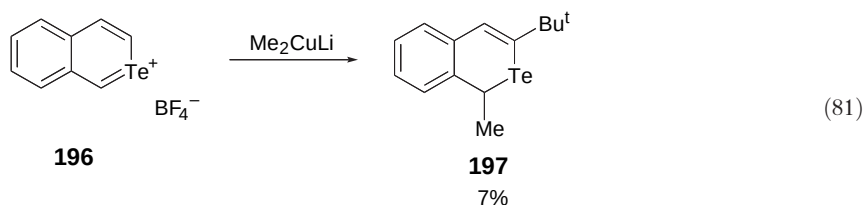
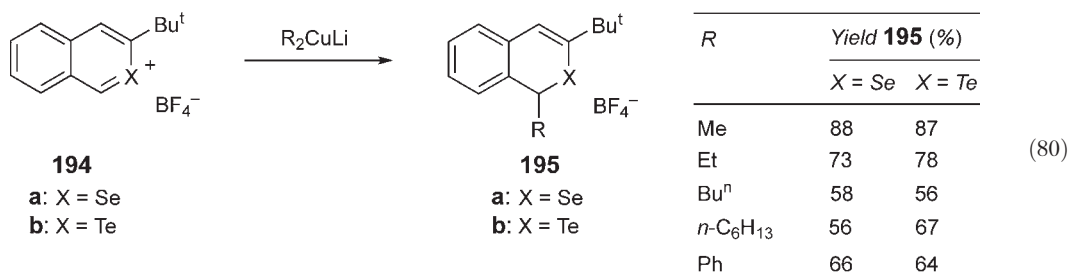


Another series of thio- and selenopyrylium photosensitizers were prepared and evaluated for their ability to purge blood-borne pathogens <2007BMC4406>. The preparative route is illustrated for selenopyrylium iodide **193** (Scheme 23) (see Section 7.11.8.1).

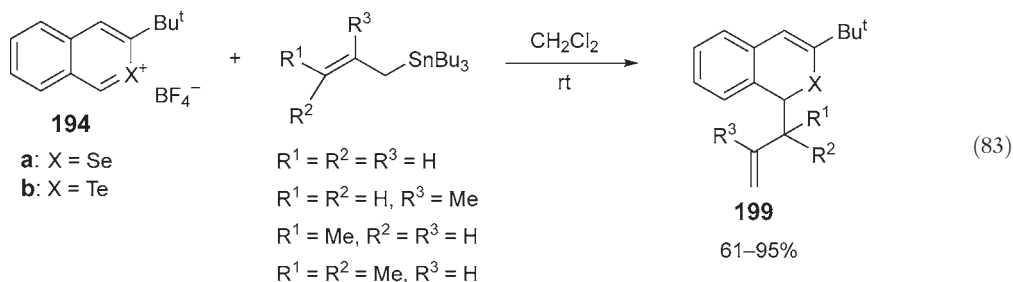
3-*tert*-Butyl-2-benzoselenopyrylium tetrafluoroborate **194a** and the corresponding telluropirylium salt **194b** react with lithium dialkylcopper and lithium diphenylcopper reagents to afford the corresponding isoselenochromenes **195a** and isotellurochromenes **195b** in good yields (Equation 80) <2004H309> (see Section 7.11.5.1). The *tert*-butyl substituent is very important for the success of the reaction. The unsubstituted telluropirylium salt **196** reacts with dimethylcopper lithium to afford isotellurochromene in only poor yield (Equation 81). The isotellurochromenes **195b** could be oxidized to the 2,4-disubstituted telluropirylium salts **196** in good yields using triphenylmethyl tetrafluoroborate (Equation 82).

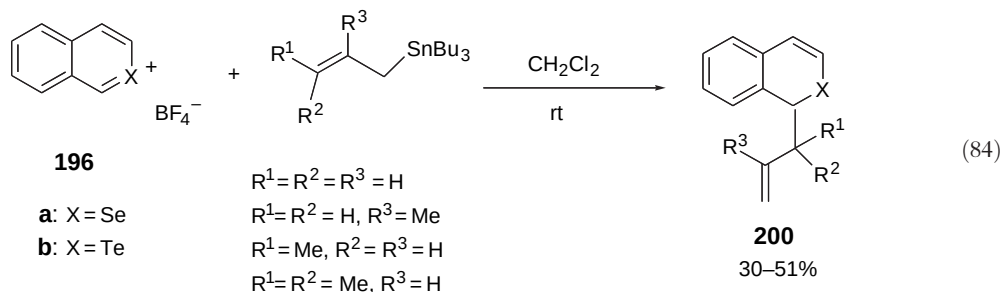


Scheme 24



Reaction of 3-*tert*-butyl-substituted 2-benzoselenopyrylium and -benzotelluropirylium salts **194** with allylstannanes afforded the corresponding substituted 1-allyl-1*H*-isoselenochromenes and 1-allyl-1*H*-isotellurochromenes **199** in moderate to excellent yields (Equation 83) <2006H505>. It should be noted that the products are those derived from nucleophilic attack of the terminal carbon of the vinyl group on the heterocycle followed by loss of the tin substituent. In the case of the unsubstituted 2-benzoselenopyrylium and 2-benzotelluropirylium salts **196**, yields of the 1-allyl-1*H*-isoselenochromenes and 1-allyl-1*H*-isotellurochromenes **200** were considerably lower than those observed in the *tert*-butyl derivatives (Equation 84).





An improved method for the preparation of selenoaldehydes from the reaction of bis(N,N-dimethylcarbamoyl-seleno)methanes with stannic chloride led to formation of a 2H-selenin by *in situ* trapping with 2,3-dimethyl-1,3-butadiene (cf. Equation 69) <2006HAC125>.

References

- 1972CL401 K. Konda, N. Sonoda, K. Yoshida, M. Koishi, and S. Tsutsumi, *Chem. Lett.*, 1972, 401.
 1982TL3411 J. N. Denis and A. Krief, *Tetrahedron Lett.*, 1982, **23**, 3411.
 1984TL3629 M. Clarembeau and A. Krief, *Tetrahedron Lett.*, 1984, **25**, 3629.
 1985TL1093 M. Clarembeau and A. Krief, *Tetrahedron Lett.*, 1985, **26**, 1093.
 1988JA8671 P. T. Meinke and G. A. Krafft, *J. Am. Chem. Soc.*, 1988, **110**, 8671.
 1990JA3845 M. R. Detty and P. B. Merkel, *J. Am. Chem. Soc.*, 1990, **112**, 3845.
 1990JME1108 M. R. Detty, P. B. Merkel, R. Hilf, S. L. Gibson, and S. K. Powers, *J. Med. Chem.*, 1990, **33**, 1108.
 1992CL1389 K. Shimada, S. Oikawa, and Y. Takikawa, *Chem. Lett.*, 1992, 1389.
 1992TL3515 G. Li, M. Segi, and T. Nakajima, *Tetrahedron Lett.*, 1992, **33**, 3515.
 1993CC577 T. Kataoka, Y. Ohe, A. Umeda, T. Iwamura, M. Yoshimatsu, and H. Shimizu, *J. Chem. Soc., Chem. Commun.*, 1993, 577.
 1993H(35)1149 M. R. Detty and B. Henne, *Heterocycles*, 1993, **35**, 1149.
 1993JCD2547 R. Boese, A. Haas, and C. Limberg, *J. Chem. Soc., Dalton Trans.*, 1993, 2547.
 1993J(P2)1815 T. Otsubo, Y. Shiomi, M. Imamura, R. Kittaka, A. Ohnishi, H. Tagawa, Y. Aso, and F. Ogura, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1815.
 1993TL4925 V. Duchenet and Y. Vallee, *Tetrahedron Lett.*, 1993, **34**, 4925.
 1994AHC180 J. Kuthan, P. Sevek, and S. Bohm, *Adv. Heterocycl. Chem.*, 1994, **59**, 180.
 1994CL2283 K. Shimada, S. Akimoto, Y. Takikawa, and C. Kabuto, *Chem. Lett.*, 1994, 2283.
 1994JOC1011 M. Yoshimatsu, T. Sato, H. Shimizu, M. Hori, and T. Kataoka, *J. Org. Chem.*, 1994, **59**, 1101.
 1994JOC8245 M. R. Detty, A. E. Friedman, and A. R. Oseroff, *J. Org. Chem.*, 1994, **59**, 8245.
 1994J(P1)2151 K. Okuma, K. Kojima, I. Kaneko, Y. Tsujimoto, H. Ohta, and Y. Yokomori, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2151.
 B-1994MI1 M. R. Detty and M. B. O'Regan, 'Tellurium-Containing Heterocycles, Chemistry of Heterocyclic Compounds', Wiley: New York, 1994.
 1994OM533 M. R. Detty and A. E. Friedman, *Organometallics*, 1994, **13**, 533.
 1994OM3338 M. R. Detty, A. E. Friedman, and M. McMillan, *Organometallics*, 1994, **13**, 3338.
 1995CL135 K. Shimada, S. Oikawa, H. Nakamura, and Y. Takikawa, *Chem. Lett.*, 1995, 135.
 1995JA10922 S. Wilker and G. Erker, *J. Am. Chem. Soc.*, 1995, **117**, 10922.
 1995JOC6631 M. R. Detty, D. N. Young, and A. J. Williams, *J. Org. Chem.*, 1995, **60**, 6631.
 1995MCL143 A. Leclaire, H. Leligny, C. R. DuMottier, G. LeCoustumer, Y. Mollier, and C. Sourisseau, *Mol. Cryst. Liq. Cryst.*, 1995, **268**, 143.
 1995OM1442 M. R. Detty, A. E. Friedman, and M. McMillan, *Organometallics*, 1995, **14**, 1442.
 1995TL237 D. Dubreuil, J. P. Pradere, N. Giraudeau, M. Goli, and F. Tonnard, *Tetrahedron Lett.*, 1995, **36**, 237.
 1996AGE660 N. Takeda, N. Tokitoh, and R. Okazaki, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 660.
 1996BCJ2235 K. Shimada, M. Yamaguchi, R. Sasaki, K. Ohnishi, and Y. Takikawa, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 2235.
 1996CPL125 T. Sugino, N. Kambe, N. Sonoda, T. Sakaguchi, and K. Ohta, *Chem. Phys. Lett.*, 1996, **251**, 125.
 1996JA313 M. Detty, F. Zhou, and A. E. Friedman, *J. Am. Chem. Soc.*, 1996, **118**, 313.
 1996JCD4463 J. Beck, A. Haas, W. Herrendorf, and H. Heuduk, *J. Chem. Soc., Dalton Trans.*, 1996, 4463.
 1996JOC5754 M. A. Lucas and C. H. Schiesser, *J. Org. Chem.*, 1996, **61**, 5754.
 1997CPH407 V. V. Kveder, E. A. Steinman, B. Zh. Narymbetov, S. S. Khasanov, L. P. Rozenberg, R. P. Shibaeva, A. V. Bazhenov, A. V. Gorbunov, M. Yu. Maksimuk, D. V. Konarev, *et al. Chem. Phys.*, 1997, **216**, 407.
 1997ESO1200 E. A. Steinman, V. V. Kveder, A. V. Bashenov, R. N. Lyubovskaya, Yu. A. Ossipyan, and H. G. Grimmeiss, *Electrochem. Soc. Proc.*, 1997, **97**, 1200.
 1997JOC4692 D. N. Young and M. R. Detty, *J. Org. Chem.*, 1997, **62**, 4692.
 1997PS413 M. Baum, H. Bock, A. Haas, Z. Havlas, C. Monse, and B. Solouki, *Phosphorus Sulfur Silicon Relat. Elem.*, 1997, **124**, 413.
 1997T12167 N. Takeda, N. Tokitoh, and R. Okazaki, *Tetrahedron*, 1997, **53**, 12167.
 1998CC197 T. Kataoka, T. Iwama, and S.-i. Tsujiyama, *J. Chem. Soc., Chem. Commun.*, 1998, 197.
 1998JOC3032 M. A. Lucas and C. H. Schiesser, *J. Org. Chem.*, 1998, **63**, 3032.
 1998JOC5716 D. N. Young, P. Serguevski, and M. R. Detty, *J. Org. Chem.*, 1998, **63**, 5716.

- 1998JOC8373 W. Nakanishi, S. Hayashi, Y. Kusuyama, T. Negoro, S. Masuda, and H. Mutoh, *J. Org. Chem.*, 1998, **63**, 8373.
- 1998J(P1)2123 H. Sashida and K. Ohyanagi, *J. Chem. Soc., Perkin Trans. I*, 1998, 2123.
- 1998OM3588 D. Shtern, G. Manchala, and M. Detty, *Organometallics*, 1998, **17**, 3588.
- 1998PS599 M. Segi, H. Yamamoto, T. Hori, and T. Nakajima, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1998, **136–138**, 599.
- 1998PS633 N. Takeda, N. Tokitoh, and R. Okazaki, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1998, **136–138**, 633.
- 1998T2545 F. Purseigle, D. Dubreuil, A. Marchand, J. P. Pradere, M. Goli, and L. Toupet, *Tetrahedron*, 1998, **54**, 2545.
- 1998T11813 T. Kataoka, T. Iwama, S.-i. Tsujiyama, T. Iwamura, and S.-i. Watanabe, *Tetrahedron*, 1998, **54**, 11813.
- 1999CL485 M. Koketsu, S. Hiramatsu, and H. Ishihara, *Chem. Lett.*, 1999, 485.
- 1999H(51)17 H. Sashida and K. Ohyanagi, *Heterocycles*, 1999, **51**, 17.
- 1999JHC707 K. A. Leonard, M. I. Nelen, M. Raghu, and M. R. Detty, *J. Heterocycl. Chem.*, 1999, **36**, 707.
- 1999JOC1565 G. Li, S. Niu, M. Segi, R. A. Zingaro, Y. Yamamoto, K. Watanabe, T. Nakajima, and M. Hall, *J. Org. Chem.*, 1999, **64**, 1565.
- 1999JOC8248 S. M. Bachrach and S. Jiang, *J. Org. Chem.*, 1999, **64**, 8248.
- 1999JME3942 K. A. Leonard, M. I. Nelen, L. T. Anderson, S. L. Gibson, R. Hilf, and M. R. Detty, *J. Med. Chem.*, 1999, **42**, 3942.
- 1999JME3953 K. A. Leonard, M. I. Nelen, T. P. Simard, S. R. Davies, S. O. Gollnick, A. R. Oseroff, S. L. Gibson, R. Hilf, L. B. Chen, and M. R. Detty, *J. Med. Chem.*, 1999, **42**, 3953.
- 1999J(P1)1155 T. Kataoka, E. Honda, T. Iwamura, T. Iwama, and S.-i. Watanabe, *J. Chem. Soc., Perkin Trans. I*, 1999, 1155.
- 1999J(P1)1665 H. Sashida and H. Minamida, *J. Chem. Soc., Perkin Trans. I*, 1999, 1665.
- 1999S1866 H. Sashida, *Synthesis*, 1999, **11**, 1866.
- 1999TL3741 T. Iwama, H. Kinoshita, and T. Kataoka, *Tetrahedron Lett.*, 1999, **40**, 3741.
- 2000AGE2358 T. Kataoka, H. Kinoshita, S. Kinoshita, T. Iwamura, and S.-i. Watanabe, *Angew. Chem., Int. Ed.*, 2000, **39**, 2358.
- 2000JCD11 M. Baum, J. Beck, A. Haas, W. Herrendorf, and C. Monse, *J. Chem. Soc., Dalton Trans.*, 2000, 11.
- 2000JOC2090 K. Okuma, Y. Koga, K. Kojima, K. Shioji, H. Matsuyama, and Y. Yokomori, *J. Org. Chem.*, 2000, **65**, 2090.
- 2000JOC2236 T. Simard, J. H. Yu, J. M. Zebrowski-Young, N. F. Haley, and M. R. Detty, *J. Org. Chem.*, 2000, **65**, 2236.
- 2000JOM96 P. C. Srivastava, S. Bajpai, R. Lath, and R. J. Butcher, *J. Organomet. Chem.*, 2000, **608**, 96.
- 2000JOM455 T. Kataoka, T. Iwama, H. Kinoshita, Y. Tsurukami, S. Tsujiyama, M. Fujita, E. Honda, T. Iwamura, and S.-i. Watanabe, *J. Organomet. Chem.*, 2000, **611**, 455.
- 2000JME4488 K. A. Leonard, J. P. Hall, M. I. Nelen, S. R. Davies, S. O. Gollnick, S. Camacho, A. R. Oseroff, S. L. Gibson, R. Hilf, and M. R. Detty, *J. Med. Chem.*, 2000, **43**, 4488.
- 2000J(P2)725 A. Levy, P. U. Biedermann, S. Cohen, and I. Agranat, *J. Chem. Soc., Perkin Trans. 2*, 2000, 725.
- 2000T3995 M. A. Lucas, O. T. K. Nguyen, C. H. Schiesser, and S.-L. Zheng, *Tetrahedron*, 2000, **56**, 3995.
- 2000T4725 T. Kataoka, H. Kinoshita, T. Iwama, S.-i. Tsujiyama, T. Iwamura, S.-i. Watanabe, O. Muraoko, and G. Tanabe, *Tetrahedron*, 2000, **56**, 4725.
- 2000TL6157 A. Levy and I. Agranat, *Tetrahedron Lett.*, 2000, **41**, 6157.
- 2001HCA1578 Z.-X. Wang and P. v. R. Schleyer, *Helv. Chim. Acta*, 2001, **84**, 1578.
- 2001JOC1787 T. Shimizu, D. Miyasaka, and N. Kamigata, *J. Org. Chem.*, 2001, **66**, 1787.
- 2001JOC4026 G. Orlova and J. D. Goddard, *J. Org. Chem.*, 2001, **66**, 4026.
- 2001JOC4099 M. Kotetsu, M. Kanoh, E. Itoh, and H. Ishihara, *J. Org. Chem.*, 2001, **66**, 4099.
- 2001JOC6286 N. Al-Maharik, L. Engman, J. Malmstrom, and C. H. Schiesser, *J. Org. Chem.*, 2001, **66**, 6286.
- 2001J(P2)2329 A. Levy, P. U. Biedermann, S. Cohen, and I. Agranat, *J. Chem. Soc., Perkin Trans. 2*, 2001, 2329.
- 2002JA28 Y. Yamamoto, H. Takagishi, and K. Itoh, *J. Am. Chem. Soc.*, 2002, **124**, 28.
- 2002JME5123 N. K. Brennan, J. P. Hall, S. R. Davies, S. O. Gollnick, A. R. Oseroff, S. L. Gibson, R. Hilf, and M. R. Detty, *J. Med. Chem.*, 2002, **45**, 5123.
- 2002JOM34 P. C. Srivastava, S. Bajpai, R. Lath, C. Ram, M. Srivastava, S. Bajpai, R. J. Butcher, M. Zimmer, and M. Veith, *J. Organomet. Chem.*, 2002, **658**, 34.
- 2002J(P1)606 H. Sashida, K. Ohyanagi, M. Minoura, and K. Akiba, *J. Chem. Soc., Perkin Trans. I*, 2002, 606.
- 2002J(P2)1909 J. Kroulik, J. Cejka, S. Bohm, P. Sebek, S. Nespurek, I. Koshets, P. Sedmera, P. Halada, V. Havlicek, B. Kratochvil, *et al.*, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1909.
- 2002MCL107 K. Takahashi, T. Nakayashi, Y. Misaki, and K. Tanaka, *Mol. Cryst. Liq. Cryst.*, 2002, **376**, 107.
- 2002TL7039 T. Kataoka, H. Kinoshita, S. Kinoshita, and T. Iwamura, *Tetrahedron Lett.*, 2002, **43**, 7039.
- 2003JA14014 I. V. Alabugin, M. Manoharan, and T. A. Zeidan, *J. Am. Chem. Soc.*, 2003, **125**, 14014.
- 2003OBC2755 A. Levy, S. Cohen, and I. Agranat, *Org. Biomol. Chem.*, 2003, **1**, 2755.
- 2004BMC2537 M. R. Detty, P. N. Prasad, D. J. Donnelly, T. Y. Ohulchanskyy, S. L. Gibson, and R. Hilf, *Bioorg. Med. Chem.*, 2004, **12**, 2537.
- 2004H309 H. Sashida, H. Satoh, and K. Ohyanagi, *Heterocycles*, 2004, **63**, 309.
- 2004JA12458 M. G. Szczepina, B. D. Johnson, Y. Yue, B. Svensson, and B. M. Pinto, *J. Am. Chem. Soc.*, 2004, **126**, 12458.
- 2004JOM194 P. C. Srivastava, S. Bajpai, S. Bajpai, C. Ram, R. Kumar, J. P. Jasinski, and R. J. Butcher, *J. Organomet. Chem.*, 2004, **689**, 194.
- 2004NJC153 G. Dazinger, R. Schmidt, and K. Kirchner, *New J. Chem.*, 2004, **28**, 153.
- 2004PCB8668 T. Y. Ohulchanskyy, D. J. Donnelly, M. R. Detty, and P. N. Prasad, *J. Phys. Chem. B*, 2004, **108**, 8668.
- 2005BMC5927 S. J. Wagner, A. Skripchenko, D. J. Donnelly, K. Ramaswamy, and M. R. Detty, *Bioorg. Med. Chem.*, 2005, **13**, 5927.
- 2005COFGT-II(3)397 L. J. Guziec and F. S. Guziec, Jr., in 'Comprehensive Organic Functional Group Transformations II', A. R. Katritzky and R. J. K. Taylor, Eds.; Elsevier, Amsterdam, 2005, vol. 3, p. 397.
- 2005JOM4982 N. Faux, B. Caro, F. Robin-Le Guen, P. Le Poul, K. Nakatani, and E. Ishow, *J. Organomet. Chem.*, 2005, **690**, 4982.
- 2005OM3807 D. J. Del Valle, D. J. Donnelly, J. J. Holt, and M. R. Detty, *Organometallics*, 2005, **24**, 3807.
- 2005TL3775 K. Shimada, Y. Gong, H. Nakamura, R. Matsumoto, S. Aoyagi, and Y. Takikawa, *Tetrahedron Lett.*, 2005, **46**, 3775.
- 2006H505 K. Ohyanagi and H. Sashida, *Heterocycles*, 2006, **68**, 505.
- 2006HAC125 Y. Gong, K. Shimada, H. Nakamura, M. Fujiyama, A. Kodama, M. Otsuki, R. Matsumoto, S. Aoyagi, and Y. Takikawa, *Heteroatom Chem.*, 2006, **17**, 125.
- 2006JA227 N. Veerapen, S. A. Taylor, C. J. Walsby, and B. M. Pinto, *J. Am. Chem. Soc.*, 2006, **128**, 227.

- 2006JA1050 Y. Mizuhata, T. Sasamori, N. Takeda, and N. Tokitoh, *J. Am. Chem. Soc.*, 2006, **128**, 1050.
2006M1791 M. Z. Kassae, E. Vessally, S. Arshadi, A. R. Bekhradnia, and M. Esfandiari, *Asian J. Chem.*, 2006, **18**, 1791.
2006OBC846 D. Shanks, H. Frisell, H. Ottosson, and L. Engman, *Org. Biomol. Chem.*, 2006, **4**, 846.
2006ZN(B)528 T. M. Klapoetke, B. Krumm, P. Meyer, and M. Scherr, *Z. Naturforsch., Teil B*, 2006, **61**, 528.
2007BMC4406 R. E. McKnight, M. Ye, T. Y. Ohulchanskyy, S. Sahabi, B. R. Wetzels, S. J. Wagner, A. Skripchenko, and M. R. Detty, *Bioorg. Med. Chem.*, 2007, **15**, 4406.

Biographical Sketch



Frank Guziec was born in Chicago and studied at Loyola University of Chicago, where he received a B.S. (Honors) degree in 1968. He received his Ph.D. degree in 1972 at MIT under the direction of Professor John C. Sheehan. He carried out postdoctoral work at Imperial College, London with Professor D. H. R. Barton, at MIT with H. G. Khorana, and at Wesleyan University with Max Tishler. He has served on the chemistry faculties of Tufts University, New Mexico State University, and is currently Dishman Professor of Science at Southwestern University. He carried out sabbatical research in the Pharmaceutical Sciences Department at De Montfort University, Leicester, UK, with Laurence Patterson under a Fulbright Fellowship and with Henk Hiemstra at the University of Amsterdam. His scientific interests include the chemistry of organoselenium compounds, extrusion reactions, functionalizing deamination reactions, and sterically hindered molecules. Collaborating with his wife Lynn Guziec, he is also involved in the design and synthesis of anticancer compounds.



Lynn James Guziec was born in Long Beach, California; she studied at Russell Sage College, Troy, NY, where she received her B.A., special honors, in chemistry, in 1979. She received her Ph.D. in 1988 from New Mexico State University under the direction of Frank Guziec, Jr. She remained as a college professor at New Mexico State University until 1995. She has worked in her present position at Southwestern University as assistant professor since 1996. In 1998, she received an M.Sc. in biological sciences from the University of Warwick, UK. Her research interests include heterocycles, organosulfur and organoselenium compounds, as well as the synthesis of medicinal and anticancer compounds.

7.12

Six-membered Rings with One Phosphorus Atom

G. L. Edwards

The University of New South Wales, Sydney, NSW, Australia

M. Balasubramanian

Pfizer Inc., Groton, CT, USA

R. Murugan

Vertellus Specialties Inc., Indianapolis, IN, USA

© 2008 Elsevier Ltd. All rights reserved.

7.12.1	Introduction	1004
7.12.2	Theoretical Methods	1005
7.12.3	Experimental Structural Methods	1012
7.12.3.1	NMR Spectroscopy	1012
7.12.3.2	X-Ray Crystallography	1013
7.12.3.2.1	Metal-free heterocycles	1013
7.12.3.2.2	Metal complexes	1015
7.12.3.3	Miscellaneous Spectroscopic Methods	1015
7.12.4	Thermodynamic Aspects	1015
7.12.5	Reactivity of Fully Conjugated Rings	1016
7.12.5.1	Reactions at the Heteroatom	1016
7.12.5.2	Reactions at Carbon	1016
7.12.5.3	Ring Reactions	1017
7.12.6	Reactions of Nonconjugated Rings	1017
7.12.6.1	Reactions at the Phosphorus Atom	1017
7.12.6.1.1	P-Alkylation	1017
7.12.6.1.2	P-Arylation	1018
7.12.6.1.3	P-Thioalkylation	1018
7.12.6.1.4	P-Dealkylation	1018
7.12.6.1.5	P-Selenation	1018
7.12.6.1.6	P-Amination	1019
7.12.6.1.7	P-Deoxygenation (P=O to P)	1019
7.12.6.1.8	Thione (P=O to P=S)	1020
7.12.6.1.9	P-Oxidation (phosphine oxide)	1020
7.12.6.1.10	Formation of P-BH ₃ complex	1021
7.12.6.2	Reactions at the Ring Carbons	1021
7.12.6.2.1	Reduction of ketone to alcohol	1021
7.12.6.2.2	Wolf-Kishner reduction	1022
7.12.6.2.3	Wittig reaction	1022
7.12.6.2.4	Carboxylation (to COOH)	1022
7.12.6.2.5	Ketone protection	1022
7.12.6.3	Ring Reactions (Multiple Atoms)	1023
7.12.6.3.1	Aromatization via oxidation	1023
7.12.6.3.2	Ring rearrangements	1023
7.12.6.3.3	Diels-Alder reaction	1024
7.12.6.3.4	Retro-Diels-Alder reaction	1024
7.12.6.3.5	Ring enlargement reactions	1025
7.12.7	Reactivity of Substituents Attached to Ring Carbon Atoms	1025
7.12.7.1	O-Acylation/N-Acylation/O-Alkylation	1025

7.12.7.2 Hydrogenation	1026
7.12.8 Reactivity of Substituents Attached to Ring Heteroatoms	1026
7.12.8.1 Ester Hydrolysis to Acids	1026
7.12.8.2 O-Methylation	1026
7.12.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms in Each Component	1027
7.12.9.1 P–C(5) Cyclization	1027
7.12.9.1.1 Formation of P–C bond	1027
7.12.9.1.2 Formation of C(2)–C(3) bond	1028
7.12.9.1.3 Formation of C(3)–C(4) bond	1028
7.12.9.2 [2+4] Cycloadditions Involving P–C Multiple Bonds	1028
7.12.9.2.1 PC + C-4 Cycloaddition	1028
7.12.9.2.2 P–C(3) + C-2 Cycloaddition	1028
7.12.9.2.3 P + C-5 Cyclizations	1029
7.12.9.2.4 P–C(2) + C-3 Reactions	1030
7.12.10 Ring Synthesis by Transformation of Another Ring	1030
7.12.10.1 Synthesis via Ring Expansion of Dihydropospholes Using Carbenes	1031
7.12.10.2 Ring Expansion of Furanoside to Pyranose	1031
7.12.10.3 Diphosphaindenoindene to Alkenyl Phosphinane	1032
7.12.10.4 Oxadiphosphole to Phosphinane	1032
7.12.10.5 Zircona Cyclohexadienes to Phosphinane	1032
7.12.11 Critical Comparison of Various Routes	1032
7.12.12 Important Compounds and Applications	1033
7.12.12.1 Hydrogenations	1033
7.12.12.2 Metathesis	1033
7.12.12.3 Allylic Substitution	1034
References	1034

7.12.1 Introduction

In the period of interest well over 500 papers have been published on various aspects of the chemistry of molecules containing, in one form or another, a six-membered ring containing one phosphorus atom.

Several key reviews have appeared, including an overview of the role of transition metals in phosphinine chemistry, incorporating metal-mediated ring syntheses, transformations of phosphinines achieved using transition metals, as well as aspects of coordination chemistry <1999CCR771>, a review of the aromaticity of phosphorus-containing heterocycles, including phosphinine and λ^5 -phosphorin <2001CRV1229>, a review on the structure, stereochemistry, synthesis, and reactivity of reduced phosphinines <B-2001MI463>, and a review of the synthesis and chemistry of various phosphorus heterocycles, with an emphasis on 1,2,3,6-tetrahydroposphinine 1-oxides <2005JHC451>. As part of studies on heteroarenes, reviews have been written on six membered heteroarenes, λ^5 -phosphinines <2004SOS(15)1157>, λ^3 -phosphinines <2004SOS(15)1097>, and their benzfused and other annulated phosphinines <2004SOS(15)1181>.

A brief comment on nomenclature of phosphorus heterocycles is appropriate. Hewitt provided a thorough summary of the various permutations in CHEC-II(1996) <1996CHEC-II(5)639>. Several variations have been used in recent years (see Figure 1); however, many authors appear to have adopted nomenclature based on the advanced Hantzsch–Widman system, as recommended by the IUPAC, ‘phosphinine’. Confusingly, the (relatively few) papers concerning compounds of higher valency at phosphorus tend to adopt the ‘phosphorin’ nomenclature, although derivatives of λ^5 -phosphinine have been reported. For consistency, names based on ‘phosphinine’ will be used throughout this chapter, in keeping with the general trend in more recent literature.

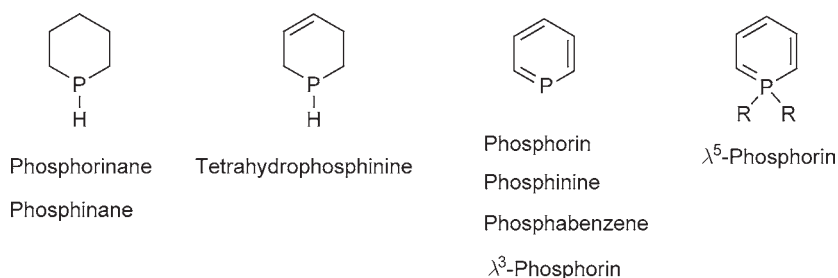
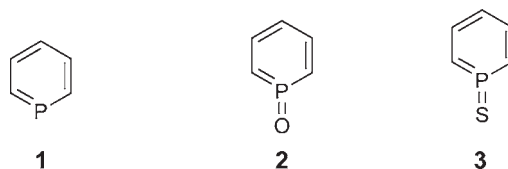


Figure 1

7.12.2 Theoretical Methods

Greater access to relatively powerful computing capability has seen theoretical studies move even further into ‘mainstream’ chemistry over the past 10 years. In particular, the availability of a multitude of computer programs that support density functional theory (DFT) has seen a variety of applications of relatively complex molecules and reactive intermediates that would not have been possible at the time of the last review. Individual applications of DFT will not be covered here; however, specific examples will be included in subsequent sections where pertinent.

Phosphinine and its derivatives have reasonable stability despite some air sensitivity and they are generally formulated as analogues of pyridine. As a result, a major area of interest has been the aromaticity of phosphinine and its derivatives, as reviewed by Nyulászi <2001CRV1229>. Schleyer and co-workers <1996JA6317> have introduced the concept of nucleus-independent chemical shift (NICS) values as a theoretical tool to evaluate aromaticity, and the use of NICS values has become widespread in recent times. The NICS is an absolute value, and is the negative of the absolute magnetic shielding of a system, and it is computed (for example) at the center of a ring, a negative NICS value indicates aromaticity, and a positive value represents antiaromaticity. Values around zero signify nonaromatic systems. Reports of the NICS value for phosphinine **1** vary from -6.4 to 11.4 ppm, but the values are consistently negative and large <1998NJC651, 1999JOC5524, 2001HCA1578, 2002JOM(643)39, 2003JMT(663)145, 2004JMT(674)125, 2005PCA9118>. A comparison of NICS values is also complicated by the differing sizes and geometries of the rings, however all reports confirm that phosphinine is indeed aromatic beyond doubt. The magnitude of the aromaticity can be better gauged in comparative studies, although even here results are conflicting: in one study <1999JOC5524> on phosphinine **1** and a series of aza analogues, it was shown that the NICS for phosphinine **1** was only slightly less negative than pyridine; this result contrasts with later works that report slightly lower NICS values for pyridine than for phosphinine <2002JOM(643)39, 2004JMT(674)125>. Calculations on phosphinine and its oxide **2** and sulfide **3** have also been reported <2005PCA9118>. (Note that the structures are represented here with $P=X$ double bonds for convenience only.) It is apparent that while the phosphorus heterocycles are less aromatic than benzene, they are undoubtedly aromatic, and their aromaticity compares well with pyridine according to the NICS criteria. The sulfide is predicted to be less aromatic than either the oxide, or the parent phosphinine. Calculated endothermic heats of hydrogenation likewise support the aromaticity of these molecules.

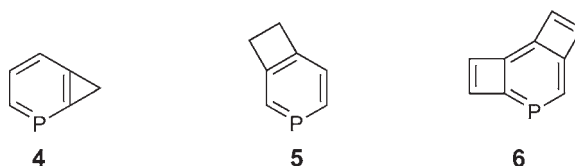


Determination of electron configurations can provide insight into reactivity. Calculations <1996JA6317> of the percentage of s character of lone pairs at the heteroatom revealed that there was a dramatic increase in s character upon going from pyridine ($\%s = 29.1$) to phosphinine ($\%s = 83.8$), correlated with a lower basicity of the heteroatom lone pair. A comparison of the Mulliken charge values for pyridine and phosphinine demonstrate a change from a significant negative charge on nitrogen (-0.28), to an almost neutral phosphorus (-0.012) <2004JMT(674)125>. The trend compares favorably with the CHELPG (charges from electrostatic potentials using a grid-based method) atomic charges, where a noticeably higher atomic charge is predicted for pyridine (-0.665) compared with phosphinine (-0.208) <2005PCA9118>. An electron localization function (ELF) study was used to determine the reactivity of phosphinine and other heterocycles <2000JCC509>; calculations confirmed that phosphinine is substantially

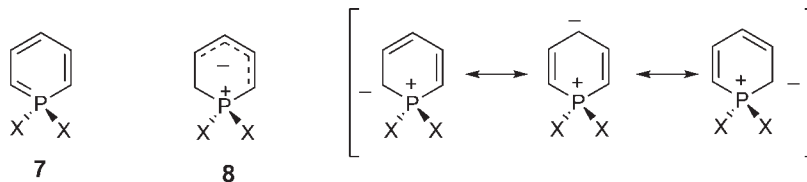
aromatic in character, and is electron deficient compared with benzene. It was also predicted that nucleophilic attack might occur on C-3/C-5 of the phosphinine ring <2000PCP3127>. Another ELF study demonstrated that resonance forms of phosphinine with formal positive and negative charges on phosphorus are valid, supporting experimental observations where electrophilic and nucleophilic reactions can occur on phosphorus <2004PCP303>.

Calculated bond lengths and bond angles for phosphinine **1** have been reported by many authors <1999JOC5524, 1996JPC6456, 1999EJO3291, 2001CPL(336)343, 2002JOM(643)39, 2002NJC347, 2003JMT(663)145, 2005PCA2957, 2005PCA9118> and there is generally good agreement between the reports. The greatest variation appears in determination of the P–C(2) bond length, where values from 1.724 Å <2005PCA2957> to 1.751 Å <2005PCA9118> have appeared. Carbon–carbon bond lengths are similar, with the C(2)–C(3) bond (≈ 1.383 – 1.395 Å) being slightly shorter than the C(3)–C(4) bond (≈ 1.388 – 1.400 Å). There is also good agreement on bond angles, with the C(2)–P–C(6) angle (99.9 – 100.2°) being significantly smaller than the other ring angles (P–C(2)–C(3) 125.4 – 125.6° ; C(2)–C(3)–C(4) 123.2° ; C(3)–C(4)–C(5) 122.6 – 122.8°). The calculated dipole moment of phosphinine **1** (1.61 D) is significantly less than that for the oxide **2** (4.08 D) or sulfide **3** (3.91 D) <2005PCA9118>.

Annulated phosphinines were studied and their aromaticity evaluated in terms of bond alternation, NICS values, and resonance energy parameters <2002JOM(643)39>. A range of mono- and bis-annulated structures (e.g., structures **4**–**6**) was studied, and the bond lengths compared with unsubstituted phosphinine **1**. The most significant deviations were observed for the cyclobutena-annulated systems, which was evidence of the tendency of these systems to minimize the significance of resonance structures with cyclobutadiene subunits. Comparison of the NICS values indicated that phosphinines annulated with saturated (cyclopropa- and cyclobuta-) rings had negative NICS values of similar magnitude to phosphinine **1**, suggesting that these heterocycles were of comparable aromaticity. The cyclobutena-annulated phosphinines had NICS values around zero (-0.1 to 1.8), indicative of nonaromatic systems. Finally, calculation of resonance energies provided a complex picture; however, this parameter again indicated that the cyclobutena-structures were nonaromatic. The conclusion was that the cyclopropa-systems were aromatic, the cyclobuta-systems were also aromatic but less convincingly than the cyclopropa-analogues, and the cyclobutena-systems were definitely not aromatic.



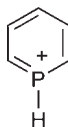
Wang and Schleyer <2001HCA1578> surveyed a series of λ^5 -phosphinines to determine whether the electronic nature of these heterocycles is best described as aromatic **7**, or ylide **8**. Calculations for a series of seven λ^5 -phosphinines showed that all ring atoms were coplanar, and the 1,1-substituents were perpendicular. In a series of λ^5 -phosphinines [(CH)₅PX₂], it was found that the electronegativity of the substituents X influenced the degree of aromaticity dramatically. Heterocycles **9**–**12** with more electronegative substituents (X = F, Cl, Br, OH) were considerably aromatic, but somewhat less so than phosphinine **1**; their structures are more correctly a hybrid of ylide and Hückel aromatic contributors. Wang and Schleyer <2001HCA1578> found that other λ^5 -phosphinines **13**–**15** with electropositive substituents (X = H, Me, SiH₃) were only weakly aromatic, or nonaromatic. In the latter cases, cyclic electron delocalization was reduced and the structures were better represented as ylides. The authors found no evidence for any d-orbital interactions with the aromatic sextet. It is noteworthy that this is in contrast to the earlier findings of Nyulászi and Veszprémi <1996JPC6456> who determined that λ^5 -phosphinine **13** (X = H) was aromatic.



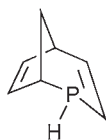
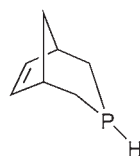
λ^5 -phosphinine

9 : X = F	13 : X = H
10 : X = Cl	14 : X = Me
11 : X = Br	15 : X = SiH ₃
12 : X = OH	

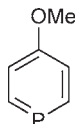
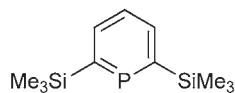
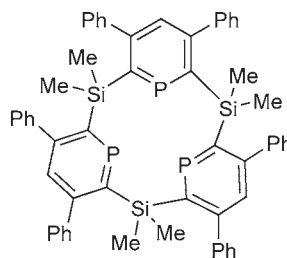
As a caveat to the use of NICS values as the sole determinant of aromaticity, Sastry and co-workers <2003JMT(663)145> have examined the use of this parameter for a range of heteroaromatic systems, including phosphinine **1** and its monoprotonated form **16**. Their conclusion is that NICS values should not be used as the sole criterion for aromaticity for heteroaromatic molecules containing group III and IV row main group elements.

**16**

A theoretical study was carried out to evaluate some bicyclic heterocyclic systems related to the bicyclo[3.2.1]-octane skeleton for evidence of neutral homoaromaticity <2005JOC1998>. Included in the study were phosphines **17** and **18**. Consideration of a series of factors including NICS values, diamagnetic susceptibility exaltations, and stabilization energies led to the conclusion that, while bicyclic compound **17** was nonhomoaromatic, the analogue **18** displayed evidence of homoaromaticity.

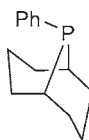
**17****18**

Theory has also provided a means by which features of the structures of functionalized phosphorus heterocycles could be predicted. The structure of 4-methoxyphosphinine **19** was determined and bond lengths in the heterocycle are unremarkable <2003JMT(635)141>. Calculation of the torsional potentials for rotation about the C(4)–O bond demonstrated that the preferred conformation has the methoxy group eclipsed with the ring, and the conformation where the methoxy group is orthogonal to the ring is predicted to be a saddle point with a torsional barrier of 3.4 kcal mol^{−1}. The conformation where the methoxy group lies coplanar with the phosphinine ring is similar to that observed for anisole, where it is argued that overlap of the lone pair on oxygen with the π -orbitals of the aromatic ring provides a stabilizing influence. Phosphinines with *ortho*-trimethylsilyl groups have attracted significant interest as ligands for transition metals, and several complex structures such as **20** and **21** have been studied. Calculations have demonstrated that *ortho*-SiMe₃ substitution in structures such as **20** enhances both the π -accepting and σ -donating properties of the phosphinine <2003HAC160>, and the C–Si–C bridges in **21** are remarkably flexible, allowing the synthesis of rather crowded and otherwise strained structures. Additionally, in silacalix[3]phosphinine **21**, the P–P distances are short, forming the base (2.55 Å) and sides (2.50 Å) of an isosceles triangle, indicating the presence of a P–P bonding interaction. The existence of this P–P bonding interaction was provided as an explanation for the quasi-planar conformation of the macrocycle. A semi-empirical study of silacalix[3]phosphinine **21** and an analogous silacalix[4]phosphinine produced structural parameters in good agreement with experimental data <2004MCL191>.

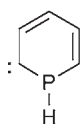
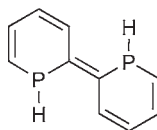
**19****20****21**

The widespread use of functionalized phosphines as versatile ligands for transition metal catalysis has revealed that subtle changes in ligand structure can lead to dramatic variation in reaction outcomes. Quantum mechanical

calculations on a range of phosphines, including the bicyclo[3.3.1]nonane derivative **22**, were used to determine structural and electronic features of the molecules <1996IC5805>. The optimized geometry of **22** revealed that the P–C(phenyl) distance is comparable to PPhMe₂, but the P–C(sp³) distances are somewhat longer and the C(sp³)–P–C(sp³) bond angle is smaller, suggesting some strain about phosphorus. Interestingly, calculations revealed some double bond character between the phosphorus and attached phenyl rings, with a more substantial conjugative effect being noted for the bicycle **22**. This effect was attributed to steric effects whereby the octane ring forces the phenyl ring to lie in a particular orientation relative to the lone pair on phosphorus, maximizing overlap.

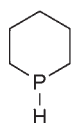
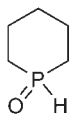
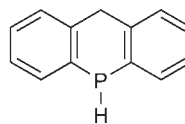
**22**

Interest in stable singlet carbenes has led to the investigation of phosphinin-2-ylidene **23**, an isomer of phosphinine **1**. At several levels of theory, the cyclic singlet phosphinocarbene **23** was determined to exist in an energy minimum as a planar structure. While significant equalization of C–C bond lengths was detected and the heterocycle was considered to be potentially aromatic, it was likely to be significantly less aromatic than phosphinine **1** <1995JOC1647>. The dimer **24** is predicted to be more stable than the monomeric carbene by 105.95 kcal mol^{−1} at the HF/6-31G*+ZPE level <1995JOC1647> and by −94.8 kcal mol^{−1} at the B3LYP/6-311+G(2D) level <2000PCP3127>. Calculations have shown that significant stabilization against dimerisation can be achieved with judicious structural variation; however, a discussion of these more elaborate structures is beyond the scope of this chapter <2002JOM(643)278>.

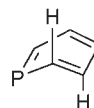
**23****24**

Phosphinine is the phosphorus analogue of pyridine and, as such, there has been interest in the basicity/proton affinity of phosphinines. Examples of calculated bond lengths and angles for protonated phosphinine **16** are given <1995JST(338)51>, and these results are in general agreement with those reported elsewhere <2002JOC271, 2005PCA9118>. As was the case for neutral phosphinine **1**, the greatest variation is in the P–C(2) bond length. In the protonated phosphinine values vary from 1.572 to 1.717 Å <1995JST(338)51> with most calculated P–C(2) bond lengths being concentrated between 1.696 and 1.706 Å, indicating a contraction of the P–C distance on protonation. The C–C bond lengths are predicted to be essentially unchanged. It is noteworthy that all methods show a marked increase in the C–P–C bond angle compared to phosphinine **1**, from 100° to around 110°. Accompanying this change is a slight decrease in P–C(2)–C(3) bond angle by about 5°, and a smaller increase in C(3)–C(4)–C(5) angle by around 2.5°. The relative heats of formation of pyridinium and its analogues were determined using PM3 semi-empirical methods and the P-protonated phosphinine **16**, like pyridinium, was clearly of lower energy than any C-protonated tautomer; this agrees with gas-phase experimental studies <1995JST(338)51>. Electronic and structural reasons were postulated to explain the reluctance of phosphinine to be protonated. The lower electronegativity of phosphorus compared to nitrogen reduces the ability to obtain electron density inductively, lowering the stabilization of a positive charge. Calculations clearly showed that the protonated phosphinine ring is planar, and the energetic costs for planarization of the ring and rehybridization of the heteroatom with the accompanying expansion of the C–P–C angle are not offset or compensated by the *p*_π–*p*_π overlap between the protonated heteroatom fragment and the π-system in the rest of the ring, which is relatively poor in the protonated phosphinine. Pham-Tran and co-workers <2005PCA2957> used mass spectrometric and quantum chemical methods to determine the proton affinity (195.8 ± 1.0 kcal mol^{−1}) and gas-phase basicity

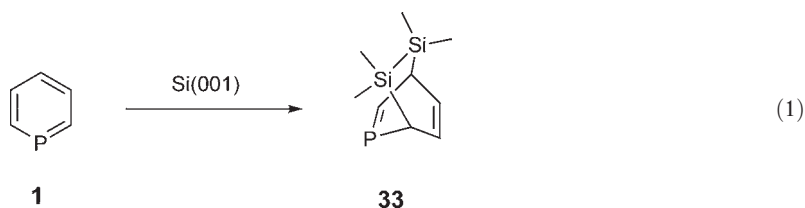
($188.1 \pm 1.0 \text{ kcal mol}^{-1}$) of phosphinine, as well as a $\text{p}K_{\text{a}}$ in aqueous solution (-16.0 ± 1.0). The latter value is significantly higher than the previously accepted value for $\text{p}K_{\text{a}}(\text{C}_5\text{H}_6\text{P}^+)$ of -10 . Other organophosphorus compounds are considerably less acidic, and a theoretical protocol has been shown to evaluate their $\text{p}K_{\text{a}}$ values in dimethyl sulfoxide (DMSO) <2006T4453>. The method was initially shown to predict successfully the $\text{p}K_{\text{a}}$ values of a range of amines and thiols to within 1.1 $\text{p}K_{\text{a}}$ units, and it was then applied to prediction of the P–H acidity of a range of organophosphorus compounds including heterocycles **25**, **26**, and **27**. The saturated trivalent phosphine **25** ($\text{p}K_{\text{a}}=35.2$) is considerably less acidic than the oxide **26** ($\text{p}K_{\text{a}}=26.9$), and the dihydroacridophosphine **27** ($\text{p}K_{\text{a}}=21.7$) has a comparable acidity in DMSO to diphenylphosphine (22.9).

**25****26****27**

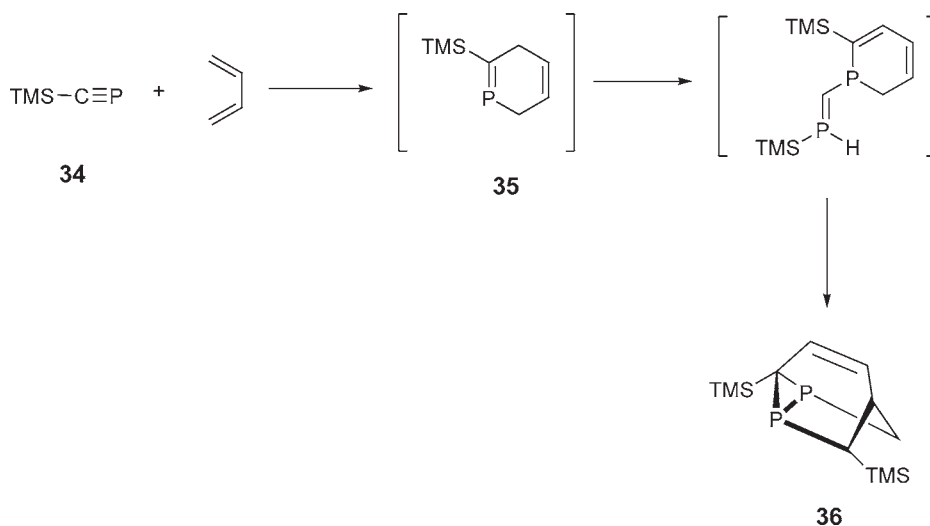
Theoretical methods have also been used to study proposed chemical reactions. Quantum chemical methods were used to evaluate the pericyclic ring opening reactions of Dewar phosphinines, analogous to Dewar benzene <2003OM5454>. The situation is complicated somewhat by the possibility of isomeric *cis*-Dewar structures; the more symmetrical bicyclic compound **28** is lower in energy than its isomer **29** by 5.2–8.4 kcal mol^{-1} . This is in good agreement with the results of Sastry and co-workers <2001CPL(336)343, 2002NJC347>. While two isomeric *trans*-Dewar structures could potentially exist, calculations could only predict the existence of isomer **30**, lying 126.7–133.6 kcal mol^{-1} above phosphinine **1** <2003OM5454>. Conrotatory ring opening of symmetrical *cis*-Dewar isomer **28** gave phosphinine **1** with an energy barrier of 43.8–48.7 kcal mol^{-1} , whereas calculations characterized the Möbius phosphinine **31** as a product of conrotatory ring opening of **29**; the energy barrier here was 26.2–30.7 kcal mol^{-1} . The dihedral angle H–C=C–H of the *trans* double bond in **31** is calculated to be 170.8° with a bond order of 1.669, yet the *trans* π -bond is substantially pyramidalized. Partial bond localization was noted, most obviously the P–C bond adjacent to the *trans* double bond, which had a calculated bond order of 1.01, being typical of a single bond. The Möbius phosphinine **31** undergoes π -bond rotation to give the aromatic phosphinine **1**, with an energy barrier of 11.2–19.1 kcal mol^{-1} . It was concluded that Möbius phosphinine **31** is a nonaromatic structure lying 80.2–85.0 kcal mol^{-1} above phosphinine **1**. The analogous ring opening of the *trans*-Dewar structure **30** is predicted to give phosphabenzvalene **32**. It is noteworthy that members of a series of phosphabenzvalenes were evaluated to lie between 50.6 and 67.6 kcal mol^{-1} above phosphinine **1** <2003OM5454>; these are somewhat higher than the value (43.29 kcal mol^{-1}) obtained elsewhere <2003PS(178)869>.

**28****29****30****31****32**

A semi-empirical PM3 study has shown that alkyl substituents on the phosphinine generally decrease the energy for a cycloaddition at the 1- and 4-position of the ring to give a 1-phosphabarrelene, and sterically demanding groups at C-4 hinder the reaction <2004CEC34>, although smaller electron-donating methyl and ethyl groups on C-4 decrease the reaction energy <2003MI87>. A theoretical study of the adsorption of phosphinine **1** by a [4+2] cycloaddition onto a Si(001)- 2×1 surface (Equation 1) has been reported <2001MI1>. The process was analyzed in terms of two components: bond localization, which would be expected to have an energy cost that equates to the resonance energy of the heterocycle, and the cycloaddition of the heterotriene to the Si=Si unit, which would be predicted to be exothermic. Adsorption of phosphinine **1** was shown to be exothermic, yielding a σ -bonded species **33**. The binding energy was calculated to be $-29.0 \text{ kcal mol}^{-1}$ (cf. $-21.8 \text{ kcal mol}^{-1}$ for benzene).

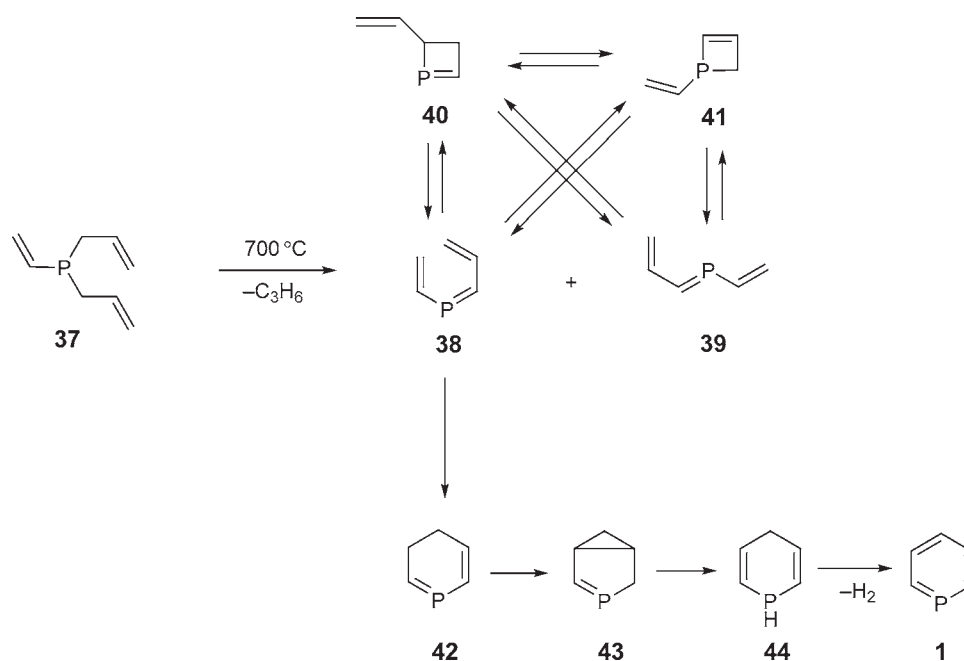


The reaction of trimethylsilylphosphaacetylene **34** with dienes (**Scheme 1**) proceeds via a cycloaddition to the 3,6-dihydrophosphinine **35**, ultimately giving complex structures such as the tricyclic compound **36** <1999EJO363>. Theoretical study of the reaction pathway confirmed that the cycloaddition to give **35** is a normal electron demand HOMO_{diene}–LUMO_{dienophile} controlled process (HOMO – highest occupied molecular orbital; LUMO – lowest unoccupied molecular orbital). Calculations revealed that the lower energy of the π^* -LUMO of the TMS-phosphaalkyne **34** was the main reason for the increased reactivity compared with the analogous *t*-butyl phosphaalkyne. Modeling the reaction using H–CP instead of TMS–CP, it was shown that the energy of activation of the primary intermolecular Diels–Alder reaction was 11.28 kcal mol^{–1}. Activation energies for subsequent steps (a phospho-ene reaction and an intramolecular Diels–Alder reaction) were somewhat lower, which explains why the tricyclic compound is formed and the intermediate dihydrophosphinine is not isolated.



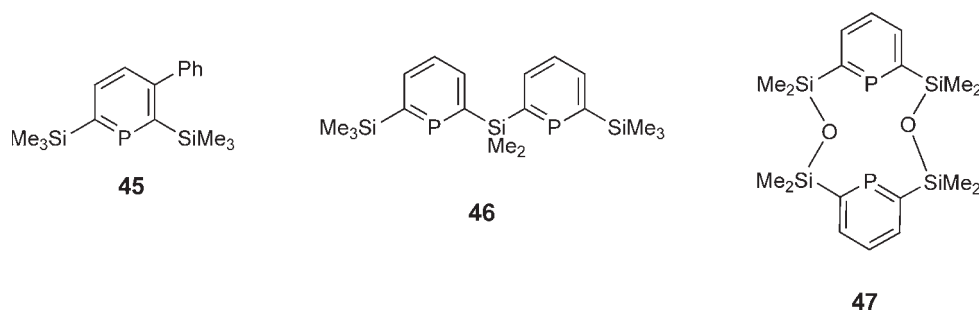
Scheme 1

Gas-phase (flash vacuum thermolysis) decomposition of diallylvinylphosphine **37** at 700 °C giving phosphinine **1** was reported by Le Floch and Mathey <1993CC1295>, and DFT methods were used to elucidate the mechanism <2005JOC4637>. The first step is an endothermic retro-ene reaction ($\Delta E = 22\text{--}23$ kcal mol^{–1}), yielding isomeric phosphatrienes; calculated activation energies (E_A) for each isomer were 45.8 kcal mol^{–1} for formation of **38**, and 42.7 kcal mol^{–1} for formation of **39** (**Scheme 2**). The phosphatrienes could equilibrate through a reversible 4π conrotatory electrocyclic ring closure giving the dihydrophosphetes **40** and **41**. Ultimately the (*Z*)-phosphatriene **38** then undergoes an exothermic 6π -disrotatory electrocyclization ($\Delta E = -21.8$ kcal mol^{–1}; $E_A = +30.0$ kcal mol^{–1}) to give the 3,4-dihydrophosphinine **42**. Direct elimination of H₂ from the dihydrophosphinine **42** was energetically not accessible, and a series of symmetry-allowed hydrogen shifts was invoked; however, these were not productive. Direct [1,1]-elimination of H₂ from λ^5 -phosphinine **13** is symmetry forbidden; however, cyclization of the 3,4-dihydrophosphinine **42** to give a 3-phosphabicyclo[3.1.0]hex-2-ene **43** and subsequent ring opening gives the 1,4-dihydrophosphinine **44**. Finally, a [1,4]-elimination can proceed to give phosphinine **1**.



Scheme 2

Treatment of phosphinines with reducing agents such as sodium naphthalenide-generated radical anions, and various physical and theoretical methods have been applied to their analysis. Various structural and electronic aspects of substituted phosphinines **45**, **46** <2004CEJ4080> and **47** <2001JA6654> and their reduction products have been determined. A slight increase in P–C bond lengths ($<0.1\text{ \AA}$) and almost negligible lengthening of the C(2)–C(3) bonds ($\leq 0.02\text{ \AA}$) were observed on one-electron reduction of phosphinine **45**. The reduced phosphinine ring is almost planar, making an angle of 102° with the phenyl ring, which does not appear to alter spin densities around the phosphinine ring compared with previously published structures. Calculation of $[\text{46}^{\cdot-} \text{Na}^+]$ revealed that, at a distance of $2.4\text{ \AA}$ between the sodium atom and a phosphinine ring, charge separation occurs and significant positive charge is located on the sodium atom, with slight positive charge on the silicon atoms, whereas the negative charge is largely centered on the ring closest to the sodium atom. Addition of a second electron generated a dianion, and calculated structural features could be compared with crystal structures of an analogous neutral compound **48** and the dianion derived from **46**. It is noteworthy that advancing from the neutral structure (whose parameters were derived by crystallography) to progressively more reduced species led to a more constrained structure with a diminished angle between the two phosphinine rings and a much shorter phosphorus–phosphorus distance. Excellent agreement between experiment and theory was seen for the dianion 46^{2-} <2004CEJ4080>. Stepwise reduction of macrocycle **47** likewise showed a decrease in phosphorus–phosphorus distance <2001JA6654>, and the rings showed marked deviation from planarity to boat-like conformations in the dianion. The result of the stepwise reduction is that the monoanion forms a weak one electron P–P bond, which shortens and becomes a more classical P–P bond on addition of a second electron.



Theory has also been used to predict certain nuclear magnetic resonance (NMR) parameters. Schleyer and co-workers <1999EJO3291> computed ^1H NMR chemical shifts for phosphinine **1**, and the strongly deshielded chemical shifts which were attributed to diatropic ring currents were indicative of aromaticity. The ^{31}P – ^{13}C and ^{13}C – ^{13}C spin–spin coupling constants in phosphinine **1** and phosphinium **16** were determined using *ab initio* equation-of-motion coupled cluster calculations <2006MRC784>. While experimental values for most coupling constants were not available for comparison, the $J(\text{P}–\text{C})$ coupling constants for phosphinine **1** have been previously reported and the correlation with theory was very good. It is noteworthy that the magnitude of the three bond $J(\text{P}–\text{C})$ is greater than the two bond coupling, and that protonation of phosphorus changes not only the magnitude, but also the sign, of $^1J(\text{P}–\text{C}2)$. Theoretical evaluations of phosphorus NMR chemical shieldings for a range of compounds, including phosphinine **1**, have also been published <1996HAC307>. It was shown that inclusion of correlation in the calculations gave a much better agreement with experiment. More recently, Chesnut has published DFT shieldings which provide a constant scaling that reduces the paramagnetic component, improving the reliability of this approach <2003CPL(380)251>. For instance, calculation for phosphinine **1** gave a shielding of +51.5 ppm (unscaled) which improved to +137.6 ppm (scaled), providing a much better correlation with the experimental value of +117 ppm.

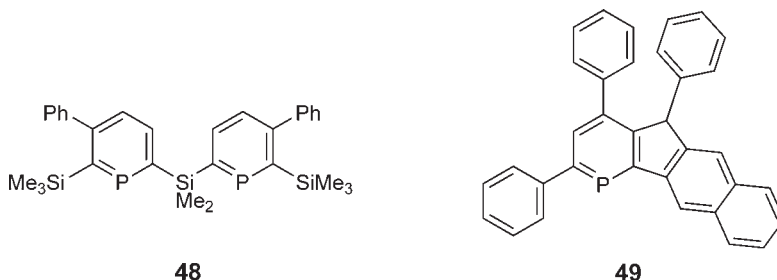
7.12.3 Experimental Structural Methods

7.12.3.1 NMR Spectroscopy

The application of NMR spectroscopy to structure elucidation has expanded as access to higher-resolution instruments has become more commonplace. The greater peak dispersion offered by higher resolution instruments has also enabled a higher degree of spectroscopic interpretation, allowing users to determine the structures of increasingly complex molecules. Of primary relevance to this chapter are studies of ^1H , ^{13}C , and ^{31}P , as well as additional nuclei where appropriate. Relatively few reports have appeared dedicated primarily to NMR spectroscopy, as references relate mainly to practical structure determination and stereochemical assignments. Several theoretical studies have been discussed in Section 7.12.2.

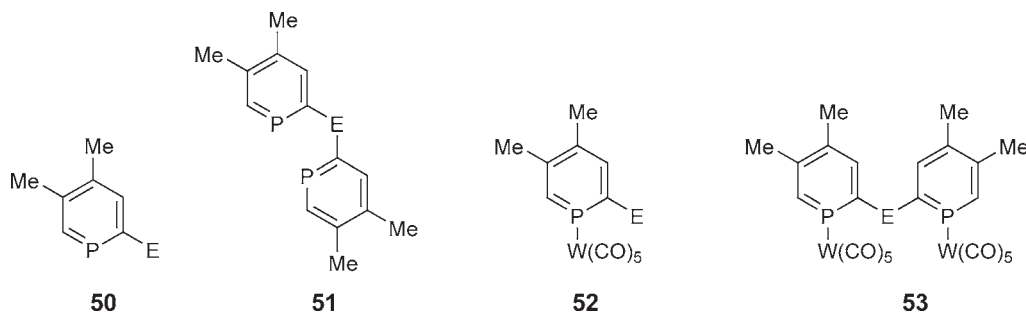
NMR spectra of simple heterocycles have been reported, and some key data are given. Unsubstituted phosphinane gives a ^{31}P NMR absorption at –66 ppm, and various 2-methyl and 2,6-dimethyl phosphinanes have been reported with δ_{P} in the range –25.6 to –62.1 ppm, with $^1J(\text{P}–\text{H})$ routinely between 180 and 195 Hz <2001JA10221>.

A series of 2,4,6-trisubstituted phosphinines was prepared, and their ^1H , ^{13}C , and ^{31}P NMR data reported <2001CEJ3106>. Phosphorus-31 chemical shifts for the phosphinines were generally found in the range 180–200 ppm; however, a significant shift to higher ppm values (255–270 ppm) occurs with 2,6-substitution by SiMe_3 or PPh_2 groups <1996JA11978>. Phosphinines with a single 2-silyl substituent and a 2-alkyl group tend to give ^{31}P resonances intermediate between the two ranges (240–250 ppm) <2000EJI2565>. One noteworthy phosphinine derivative is the benzo[*a*]fluorene derivative **49**, where $\delta_{\text{P}} = 162$ ppm. In the ^{13}C spectra, $^1J(\text{P}–\text{C}2)$ usually falls in the range 45–60 Hz when the 2- or 6-substituents are alkyl or aryl <2001CEJ3106>, with significantly higher coupling constants (80–90 Hz) being observed for 2- or 6-silyl substitution <2000EJI2565>. Longer range couplings within the phosphinine ring for polyaryl derivatives were harder to pinpoint, as P–C couplings were observed in substituents and unequivocal assignments were not always possible <2001CEJ3106>. Complexation of several of the phosphinines to Rh(I) giving *trans*-[(phosphinine) $_2$ RhCl(CO)] saw δ_{P} move upfield to 166–174 ppm, with $^1J(\text{P}–\text{Rh}) = 174$ –175 Hz. Two-bond P–CO coupling of 21–22 Hz was also noted.



Reaction of organozinc C-2 derivatives of phosphinines with electrophilic sources of P, As, Sn, Cu, and Hg provided a series of 2-elementa-phosphinines **50** and **51**, where P–E coupling constants could be measured

<1996OM802>. In some cases the tungsten pentacarbonyl complexes **52** and **53** were prepared as more stable products, to aid characterization. Key NMR data are presented.



Coupling of two electron-rich indolyl units to a trivalent phosphorus results in shielding of approximately 30 ppm relative to an acyclic mono-indolyl analogue <2005OM37>. The shielding is not a result of any ring strain as an acyclic bis(indolyl) phosphine has a similar chemical shift (−65.1 ppm) to the dihydrophosphinine (−91.9 ppm).

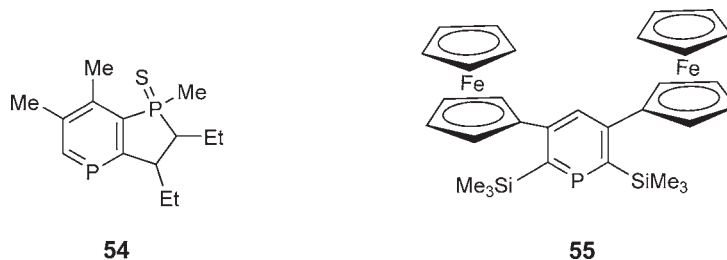
A range of polyhydroxylated phosphorus containing heterocycles, known generically as ‘phosphasugars’ due to their obvious structural similarity to standard monosaccharides, has been prepared and their structures elucidated by NMR spectroscopy, and confirmed by X-ray crystallography. Phosphasugars were generally shown to exist preferentially in chair conformations, and ¹H NMR assignments were invaluable in some aspects of the conformational analyses due to the relatively large axial–axial couplings. <2003CAR283, 2005CAR31, 2002HCA2608>.

7.12.3.2 X-Ray Crystallography

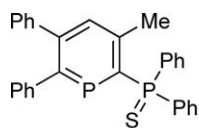
7.12.3.2.1 Metal-free heterocycles

There have been numerous reports over the review period on the synthesis and structural determination of six-membered rings containing phosphorus with varying degrees of structural complexity, and many of the heterocycles have been prepared as a prelude to their use as ligands. Most studies have focused on substituted phosphinines, and one important class contains compounds with a single phosphinine ring, whether as a potential unidentate ligand, or a multidentate ligand with other donor sites. A second class of potential ligands includes biphosphinines and related bi- and multidentate ligands that incorporate two or more phosphinine rings.

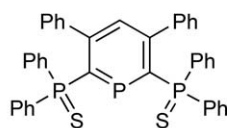
Examples of substituted unidentate phosphinines include the bicyclic compound **54**, and the ferrocenylphosphinine **55**. The phosphinine **54** shows no deviations from regular phosphinine structural parameters, indicating that the fusion of the phosphole unit does not perturb the structural geometry significantly <1999CC537>. An interesting contrast is the diferrocenylphosphinine **55** where the ferrocenyl units lie above and below the mean plane of the ring, and the steric congestion introduced by the ferrocenyl units and two trimethylsilyl groups imparts a significant twist on the phosphinine ring, with a torsion angle (P–C(5)–C(4)–C(3) of 11.65°). The nonplanar conformation results in distortion of internal angles: C(2)–C(3)–C(4) and C(5)–P–C(1) increase to 126.4° and 106.1°, respectively <1997OM4089>. While this angle of 106.1° is claimed to be unusually large for a C–P–C angle in a phosphinine, similar bond angles are seen in phosphinines in macrocycles (see below).



Potentially bidentate ligands for which structures have been determined include the mixed *P,S*-bidentate ligand **56** <2005EJ1125> and the related *S,P,S*-tridentate pincer ligand **57** <2003EJ13878>. Bond lengths and angles are similar for both structures, and they fall within the usual ranges for phosphinines; the C–P bonds in the phosphinine ring of **57** are very slightly different (1.742 Å vs. 1.824(2) Å).

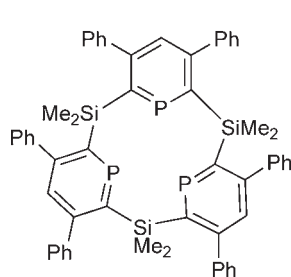


56

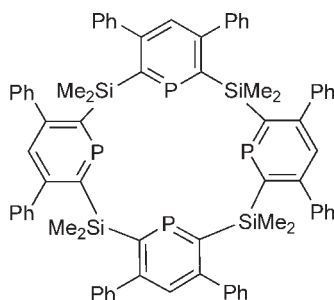


57

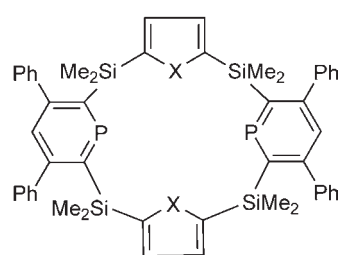
Several structures of multidentate ligands incorporating more than one phosphinine ring have also been reported. Among the more elaborate examples in this class are the phosphinine-containing macrocycles reported by Mathey and Le Floch. Noteworthy examples include the silacalix[*n*]phosphinines **58** and **59**, and the mixed thiophen and furan-containing analogues **60** and **61** <1999CEJ2109>. The calix[3] structure **58** adopts a partial cone structure where two phosphorus lone pairs point toward the top of the cavity and are located above the plane described by the three silicon atoms, and the third points below this plane. In comparison, the calix[4] analogue **59** crystallized in an opened out partial cone conformation where two opposite phosphinine rings are essentially coplanar with the four silicon atoms, and the remaining two phosphinines are roughly perpendicular. The two hybrid structures **60** and **61** likewise exist as opened-out partial cones with the phosphinine rings lying in parallel planes, nearly perpendicular to the thiophen or furan rings. It is noteworthy that for all structures **58** to **62** the C–P–C bond angles are all reported to be relatively large for phosphinines, and fall within the narrow range of 105.0–106.9°.



58



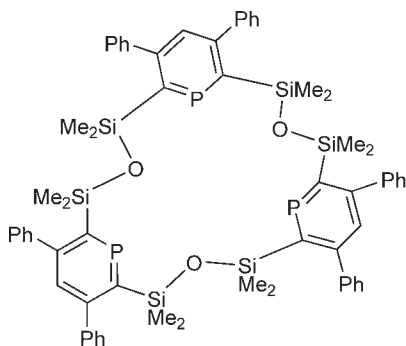
59



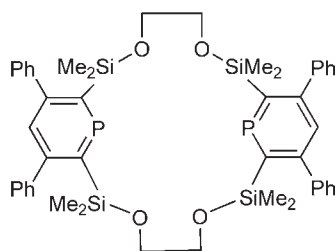
60: X = O

61: X = S

Other phosphinine-containing macrocycles for which structures have been determined, with more flexible linkers between the phosphinine rings, include the 18-membered macrocyclic assemblies **62** and **63**. In macrocycle **63**, the phosphinine rings lie in parallel planes, with the phosphorus atoms pointing in opposite directions, although NMR spectroscopy reveals that the molecule is totally fluxional in solution <2001JOC1054>. Likewise, macrocycle **62** is completely fluxional in solution <2002EJI2034>. Otherwise, all structural parameters from the phosphinine rings lie within normal bounds.



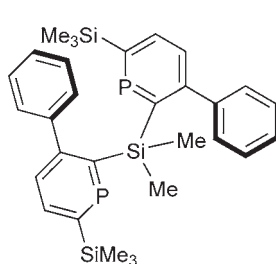
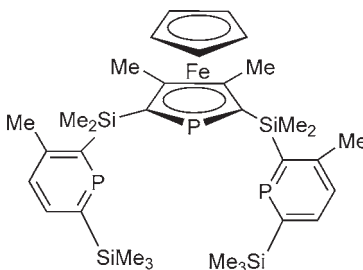
62



63

Other multidentate ligands have been prepared and their structures determined. The bisphosphinine **64** crystallized with the two phosphinine planes almost orthogonal (91.59°), and the two phosphorus atoms oriented away from each other (P–P distance 5.8 Å). However, even at low temperature (–95 °C) there was no evidence in either the ³¹P

or ^1H NMR spectrum of line broadening, indicating that the barrier to interconversion between the conformations is very low <2004CEJ4080>. The hybrid bisphosphinine/phosphaferrocene structure **65**, prepared as a novel tridentate ligand, showed standard structural parameters for the phosphinine and phosphaferrocene units <1999OM4205>.

**64****65**

An important reaction of phosphinines is their reduction, and structures of reduced phosphinines have been reported. The radical anion of 4,4',5,5'-tetramethyl-2,2'-biphosphinine (tmbp) was prepared by reduction of the neutral biphosphinine with lithium-naphthalene in the presence of one equivalent of Kryptofix (2.2.1) <2000JA12227>. The structure, which crystallized as a monomeric ion pair as a result of the added cryptand ligand, consisted of distinct cryptated lithium ions, and the radical anion in a perfectly planar *trans* conformation. Features of the structure, when compared with the neutral, *trans*-biphosphinine indicated that the negative charge was delocalized on both rings. Key points include the lengthening of the P=C bonds (1.731–1.784 Å) and shortening of the bond between the rings (1.484–1.440 Å). Significant changes in the C–C bonds around the rings were also noted, indicating disruption of the aromatic system: C(2)–C(3) and C(4)–C(5) appeared slightly lengthened, while C(5)–C(6) contracted and C(3)–C(4) was essentially unchanged. Interestingly, bond angles were not changed significantly.

Reduction of tmbp with 2 equiv of sodium-naphthalene in 1,2-dimethoxyethane (DME) generated the dianion as a polymeric product of general formula $[(\text{tmbp})\text{Na}_2(\text{DME})_{1.5}]_n$, whereas reduction with 2 equiv of lithium-naphthalene in THF in the presence of the cryptand Kryptofix (2.2.1) gave a monomeric complex with formula $[(\text{tmbp})][\text{Li}(2.2.1)]_2$ <2001AGE4476>. In the polymeric product, the biphosphinine ligand adopts a cisoid configuration and each phosphorus atom is coordinated to three sodium atoms. Relatively long P–Na distances (2.925–3.096 Å) suggest that the interaction is largely electrostatic in nature. The loss of aromaticity results in the ligand developing an overall curvature. Similar effects are seen in the monomeric complex, except the ligand adopts an overall transoid configuration. In both dianions, the bond length between the two rings is reduced further (1.40 Å), and the C–P bond lengths in the reduced phosphinine rings are lengthened and now resemble single bonds (1.773–1.827 Å). The C–C bonds in the reduced rings also now vary between single bonds (≈ 1.44 Å) and double bonds (≈ 1.36 Å).

7.12.3.2.2 Metal complexes

Rhodium(III) and palladium(II) complexes of some P-heterocycles including six membered have been synthesized and their X-ray structures studied <2005JOM(690)704>.

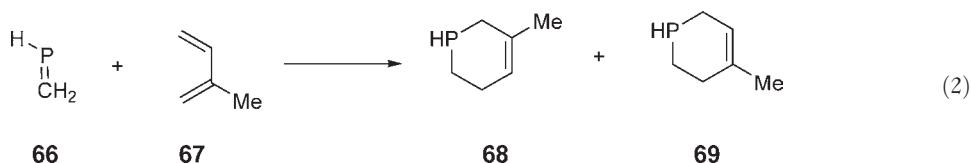
7.12.3.3 Miscellaneous Spectroscopic Methods

One photoelectron spectroscopic study, focusing largely on the aromaticity of five-membered rings but including six-membered rings, has been published <1995JST(347)57>. It was established that conjugated systems containing a $-\text{P}=\text{C}$ unit had nearly identical ionisation energies compared to $\text{C}=\text{C}$ analogues.

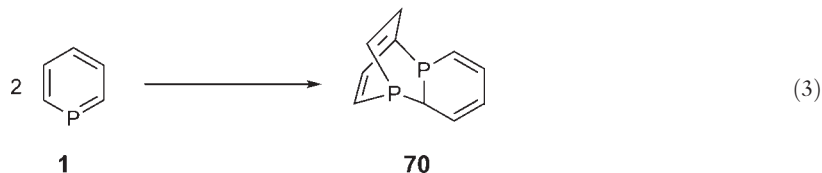
7.12.4 Thermodynamic Aspects

An extremely efficient approach to the synthesis of six-membered rings is the Diels–Alder reaction, and phosphinine derivatives can be prepared using this methodology. Schleyer and co-workers <2002JOC9162> have reported comprehensive high-level calculations on the reaction of phosphaethene **66** ($\text{HP}=\text{CH}_2$) with 1,3-butadiene and with isoprene. Cycloaddition occurs in an asynchronous manner via early transition states that are aromatic in character, to give the six-membered rings. Calculated activation energies are much lower than for the corresponding ethene-butadiene reaction, as

a result of the weaker C=P bond in the dienophile component. It is noteworthy that the overall exothermicities of the cycloadditions are in the same range (-29 to -33 kcal mol $^{-1}$) for the hetero-Diels–Alder reaction as for the all-carbon case. Study of the reaction of phosphathene **66** with isoprene **67** (Equation 2) provided some insight into stereo- and regioselectivity. Lower activation energies (by *c.* 2 kcal mol $^{-1}$) for approach of phosphathene with an *endo* P–H group show that this is the kinetically favoured path, due to the location of the phosphorus lone pair away from the diene. The slightly higher exothermicity for the *exo* approach reveal that these products are thermodynamically more stable than their *endo* isomers. In both cases there was very little difference between the reaction paths to regioisomers **68** and **69** revealing that regioselectivities would be modest, at best. Higher regioselectivities had been reported for other reactions, and it was suggested that a radical cation mechanism may account for the greater selectivity in these cases.



Phosphinine **1** is a relatively stable heterocycle with respect to cycloaddition, as it does not dimerize readily, unlike silabenzene which dimerizes at low temperatures. Forcing conditions are generally required to cause phosphinine to undergo a Diels–Alder reaction unless the dienophiles are highly reactive. Calculations of the enthalpy of dimerization to give tricyclic compound **70** (Equation 3) showed it to be a highly endothermic process, with $\Delta H = +32.6$ kcal mol $^{-1}$. An analysis of the dimerization of phosphinine versus silabenzene is presented <2000OM2208>.



The enthalpies of solvation of four geometric isomers of 2,5-dimethyl-1-phenyl-1-thioxophosphorinan-4-one in chloroform, nitrobenzene, and methanol were calculated using the enthalpies of vaporization of the isomers determined by the modified Solomonov-Konovalov method from the enthalpies of solution of the compounds in CCl₄ and *p*-xylene and molar refractions <2000RCB1522>.

A detailed *ab initio* and modified neglect of diatomic overlap (MNDO) study of structural parameters and pyramidal phosphorus atom inversion and also enthalpy differences between the participants in the conformational equilibrium (axial and equatorial) of 1-R-phosphorinanes (R = H, CH₃, C₂H₅) has been investigated and is in good agreement with the observed NMR and X-ray values <1999IJB660>.

7.12.5 Reactivity of Fully Conjugated Rings

Phosphinine and its derivatives are clearly aromatic; however, they are considerably more reactive than benzene. The most significant influence on the reactivity of these molecules is the presence of the lone pair on phosphorus, and two significant reactions are its complexation with a variety of metals, and nucleophilic attack to form (ultimately) λ^5 -phosphorins. The π -system can undergo [4+2] cycloadditions, under milder conditions than benzene. Electrophilic substitution reactions on carbon are considered to be impossible <2001CRV1229>.

7.12.5.1 Reactions at the Heteroatom

Phosphinines like pyridines behave as ligands and their coordination complexes with various metals such as titanium, vanadium, chromium, iron, manganese group, and cobalt group has been reviewed <2005AHC(89)125>.

7.12.5.2 Reactions at Carbon

Reactions like acylation of λ^5 -phosphorins, nucleophilic substitution of 3-halo- λ^3 -phosphorins, coupling reactions, and formation of organometallic reagents of 2-halo- λ^3 -phosphorins have already been reported <1996CHEC-II(5)639>.

7.12.5.3 Ring Reactions

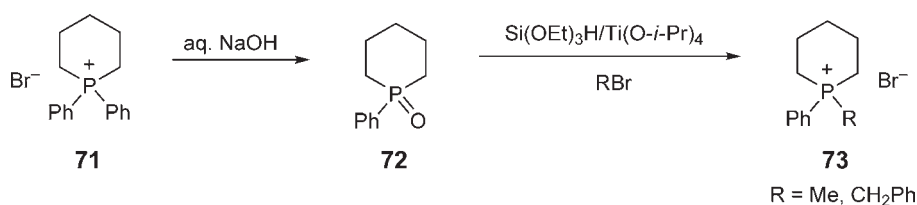
2,4,6-Triphenylphosphinine underwent unprecedented cofacial oxidative coupling in the presence of a Cu(I) catalyst to form a novel C-2-symmetric cage compound, having extremely long C–C bonds. The structure has been established by X-ray crystallography and the authors claim that this type of reactivity of phosphinines could lead to new cage compounds containing phosphorus <2004CC366>.

7.12.6 Reactions of Nonconjugated Rings

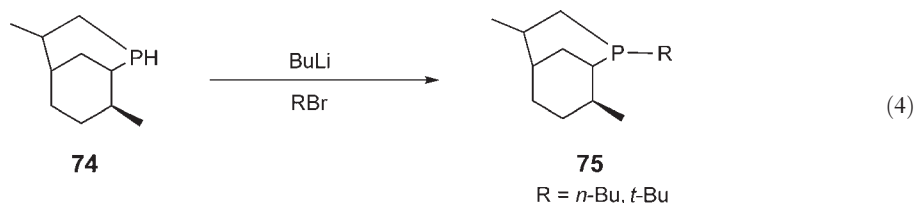
7.12.6.1 Reactions at the Phosphorus Atom

7.12.6.1.1 P-Alkylation

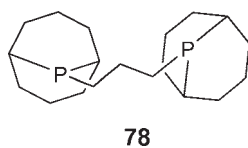
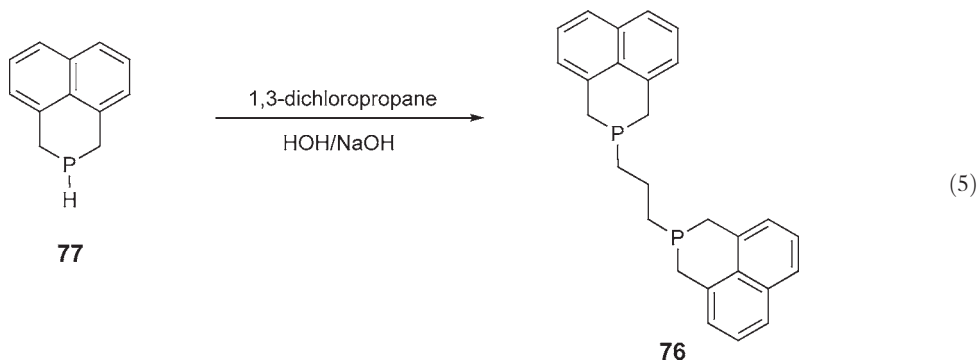
Hydrolysis of 1,1-diphenylphosphorinanium bromide **71** with aq NaOH gave phosphine oxide **72** in 99% yield. Phosphine oxide was further reductively alkylated to **73** using $\text{Si}(\text{OEt})_3\text{H}/\text{Ti}(\text{O}-i\text{-Pr})_4$ with various alkyl bromides <1998SL497> (Scheme 3). Bicyclic phosphines **74** were alkylated to **75** using BuLi/RBr (Equation 4) <2003JCD2036, 2003JCD4669>.



Scheme 3

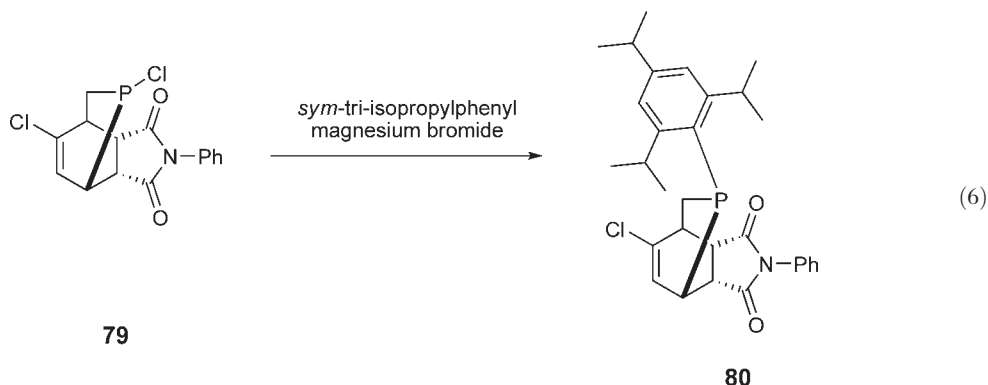


Bis(benzoisophospholine) derivatives **76** were prepared from benzoisophospholine **77** by alkylation with 1,3-dichloropropane using KOH/NaOH <2000EJO3497, 1998TL4291> (Equation 5). A bicyclic secondary phosphine was treated with $(\text{CH}_2)_3\text{I}_2$ and NEt_3 to give diphosphine derivative **78** <1997CC1527>.



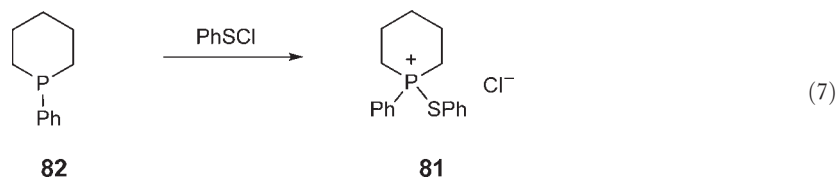
7.12.6.1.2 P-Arylation

Tricyclic phosphinous chloride **79** reacted with tri-isopropylphenyl magnesium bromide and gave P-arylated phosphine **80** <2002HAC626> (Equation 6).



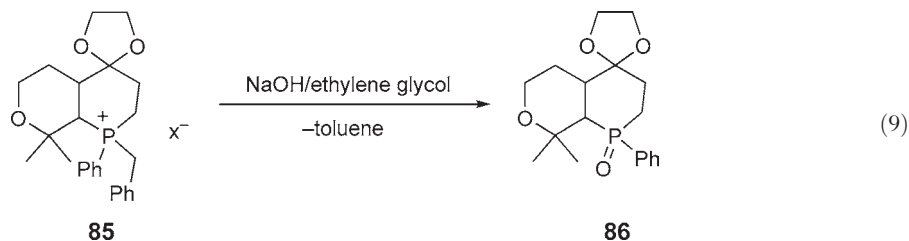
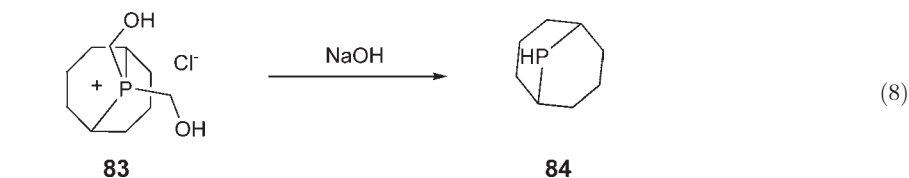
7.12.6.1.3 P-Thioalkylation

Thiophenoxy phosphonium chloride **81** used in kinetic studies was synthesized from phenylphosphinane **82** and phenyl sulfonyl chloride <1996PS(115)43> (Equation 7).



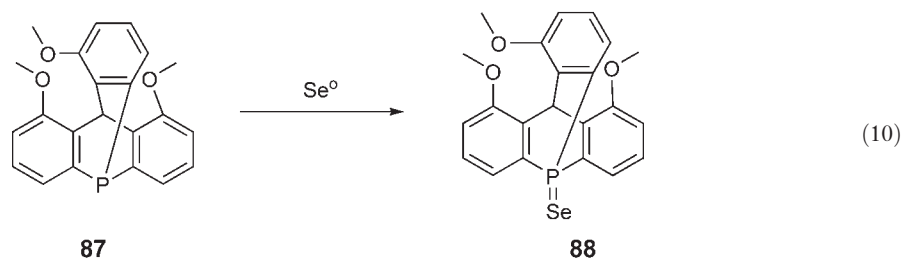
7.12.6.1.4 P-Dealkylation

Dealkylation of phosphonium salts **83** is promoted by NaOH, and isomeric phosphabicyclononanes **84** are readily separated by a sequence of hydrophosphination/dehydrophosphination steps <1997CC1527> (Equation 8). Decomposition of phosphonium salt **85** with NaOH/ethylene glycol resulted in the elimination of toluene and bicyclic compound **86** <1996RJC567> (Equation 9).



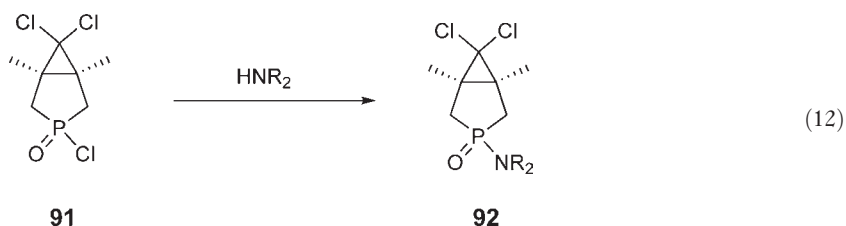
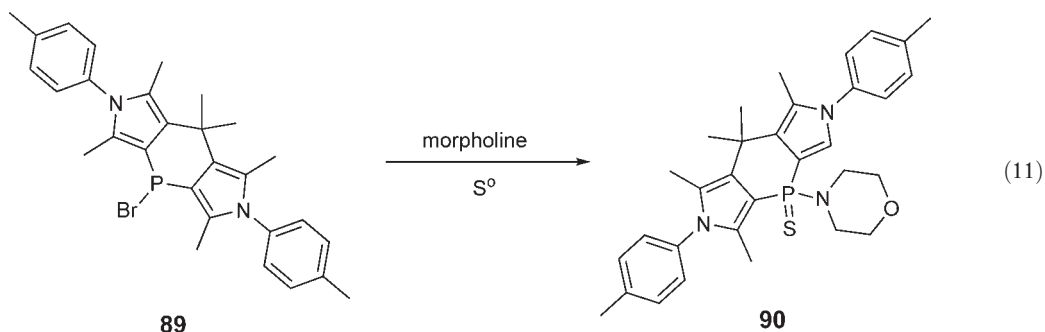
7.12.6.1.5 P-Selenation

Phosphatriptycene **87** reacts with elemental selenium to give the corresponding 9-phosphatriptycene selenide **88** <2004HAC437> (Equation 10).



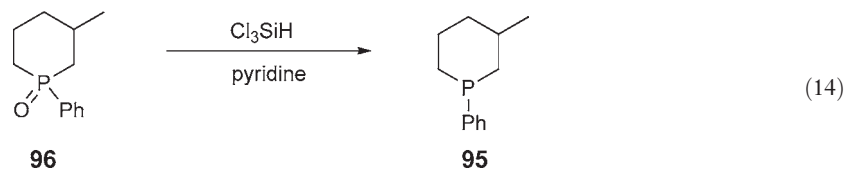
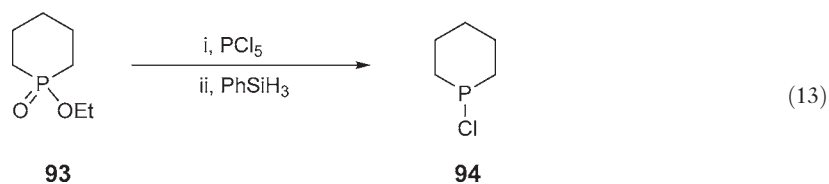
7.12.6.1.6 P-Amination

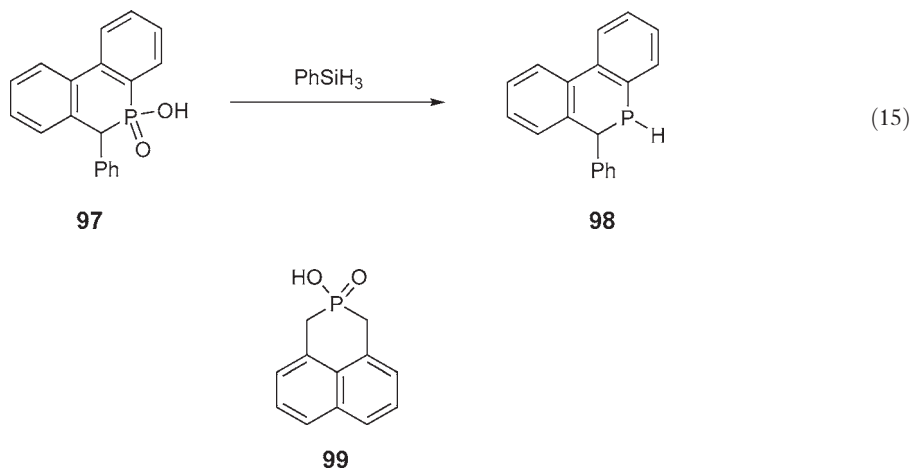
Bromophosphine **89** is thermally unstable and it reacts with $\text{O}(\text{CH}_2\text{CH}_2)_2\text{NH}/\text{S}$ to give dihydropyrrolophosphorins **90** <1999CHE1383> (Equation 11). Similarly, chlorophosphorites **91** may be aminated to **92** with various alkylamines <1996PS(109)457> (Equation 12).



7.12.6.1.7 P-Deoxygenation (P=O to P)

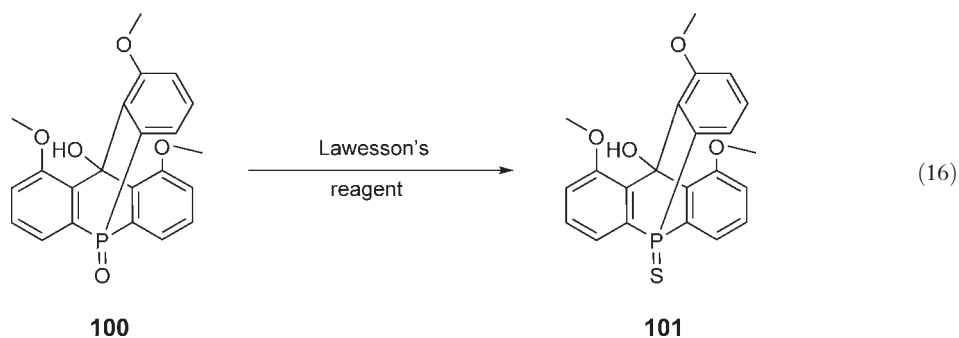
Phosphine ester **93** was converted to the corresponding phosphinic chloride with PCl_5 , which then gave the phosphinous chloride **94** by deoxygenation with PhSiH_3 <2004SC4159> (Equation 13). 1-Phenylphosphine **95** was obtained by a conventional deoxygenation of the oxide **96** using Cl_3SiH /pyridine <2000J(P1)4451> (Equation 14). Phosphinic acid **97** was reduced to secondary phosphane **98** with PhSiH_3 <2000EJO3497> (Equation 15). Tricyclic phosphate **99** was reduced to phosphine **77** using trichlorosilane <2003ZNB782>.



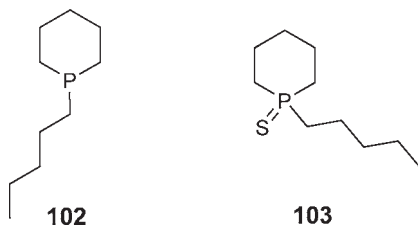


7.12.6.1.8 Thione (P=O to P=S)

Sulfur transfer from Lawesson's reagent is reported [<2004HAC437>](#). Sulfurization of 9-phosphatriptycene oxide **100** proceeded with excess of Lawesson's reagent to 9-phosphatriptycene sulfide **101** in quantitative yield [<2004HAC437>](#) (Equation 16).

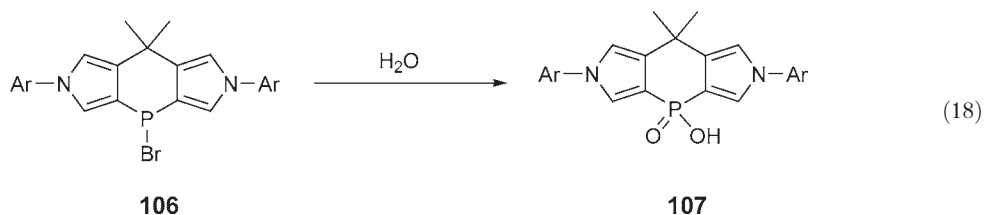
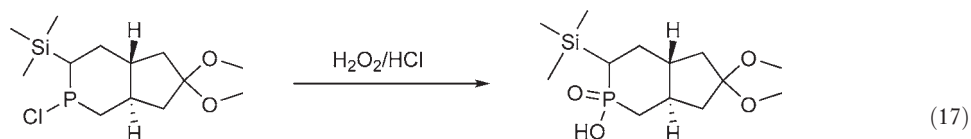


The new phosphorus-donating reagent benzothiadiphosphole was used in a one-pot preparation of 1-alkylcyclic phosphines **102** and their sulfides **103** from simultaneous addition of mono-, and bis-Grignard reagents [<2000SL1685>](#).



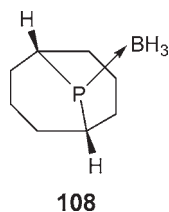
7.12.6.1.9 P-Oxidation (phosphine oxide)

1-Chlorophosphinane **104** was oxidized to the corresponding phosphinic acid **105** with $\text{H}_2\text{O}_2/\text{HCl}$ [<2004TL7633>](#) (Equation 17). Hydrolysis of 1,1-diphenylphosphorinanium bromide **71** with NaOH gave phosphine oxide **72** [<1998SL497>](#). Bromodipyrrolophosphorin **106** was treated with water to give tricyclic phosphate **107** [<1999CHE1383>](#) (Equation 18).



7.12.6.1.10 Formation of P-BH₃ complex

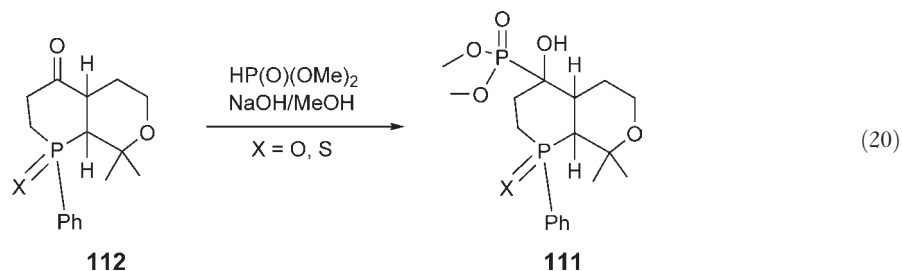
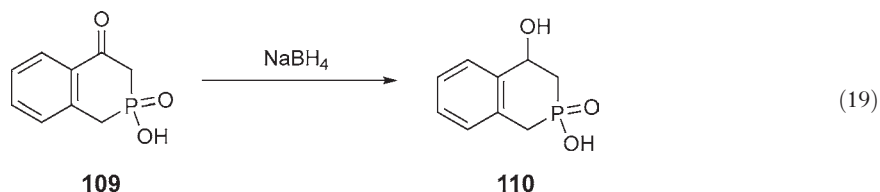
A highly efficient general synthesis of phosphine–borane complexes **108**, proceeding in high yield by a safe green process from BH₃ generated in situ from NaBH₄, has been reported [\[2004TL407\]](#).

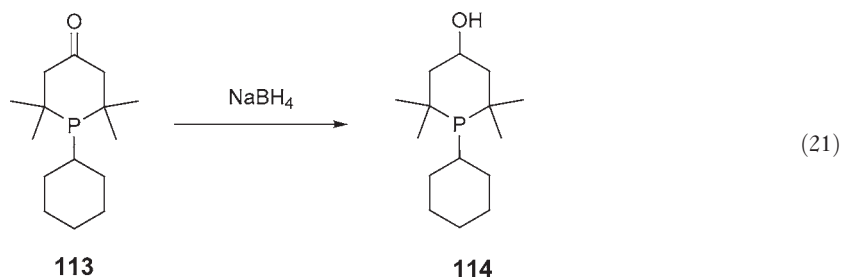


7.12.6.2 Reactions at the Ring Carbons

7.12.6.2.1 Reduction of ketone to alcohol

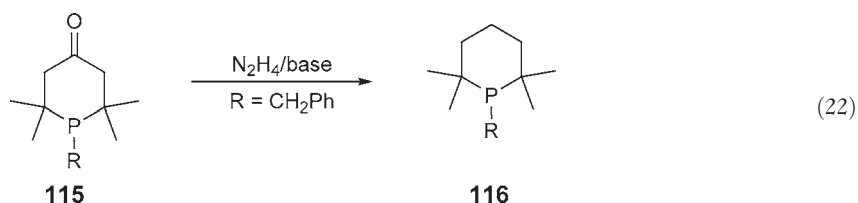
Sodium borohydride reduction of cyclic ketone **109** produced alcohol **110** [\[1997BMC1327\]](#) (Equation 19). Biheterocyclic 2-hydroxyphosphonates **111** were synthesized by reactions of phospho-bicyclodecanones **112** with dimethylphosphonates in the presence of NaOH/MeOH [\[1996RJC567\]](#) (Equation 20). 1-Cyclohexylphosphin-4-one **113** was reduced to the corresponding alcohol **114** by sodium borohydride [\[2004TL407\]](#) (Equation 21).





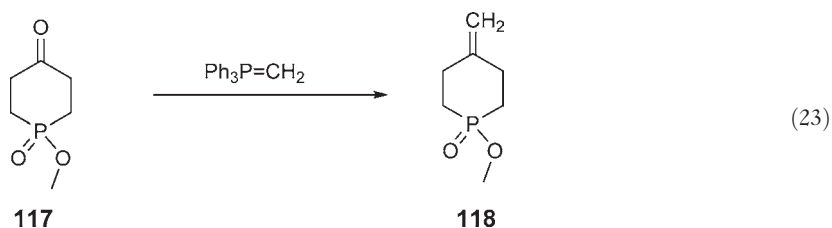
7.12.6.2.2 Wolf–Kishner reduction

Reduction of the carbonyl groups of **115** and **116** was achieved by treatment with N_2H_4 under basic conditions <2006OL103> (Equation 22).



7.12.6.2.3 Wittig reaction

The Wittig reaction of methylenetriphenylenephosphorane with ketones **117** gave 4-methyleneoxo-phosphorinane **118** in 66% yield <1996JA10168> (Equation 23). Reaction of the phenyl phosphonium bromide **73** with 3,4,5-trimethoxybenzaldehyde gave alkenes with greater trans selectivity <1998SL497>.

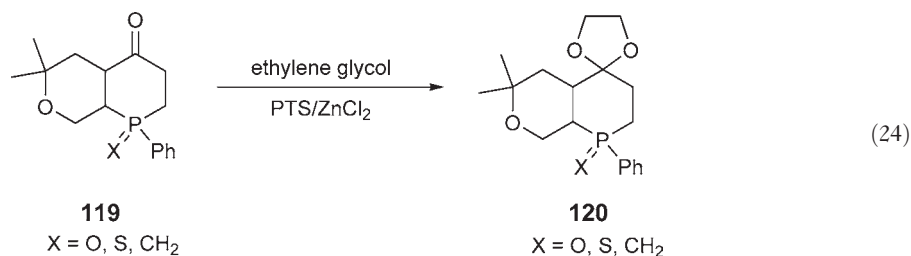


7.12.6.2.4 Carboxylation (to COOH)

Carboxylation of 1-phenylphosphorinane was achieved via deprotonation (BuLi)–carboxylation (CO_2) to give 1-phenylphosphorinane-2-carboxylic acid <2001TL7303>.

7.12.6.2.5 Ketone protection

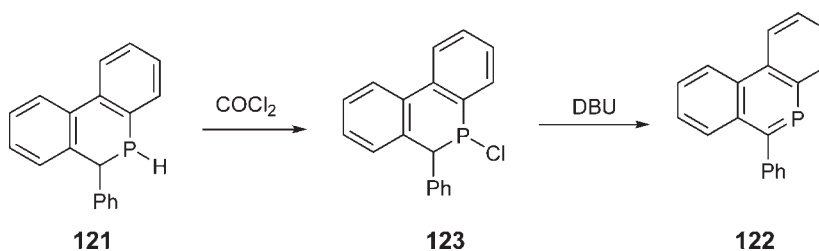
Condensation of derivatives of phosphabicyclodecanones **119** with ethylene glycol in the presence of PTS/ZnCl_2 gave cyclic ketals **120** of the phosphabicyclodecane series <1996RJC564> (Equation 24). Oximes and semicarbazones were prepared from bicyclic ketones <1996RJC567>.



7.12.6.3 Ring Reactions (Multiple Atoms)

7.12.6.3.1 Aromatization via oxidation

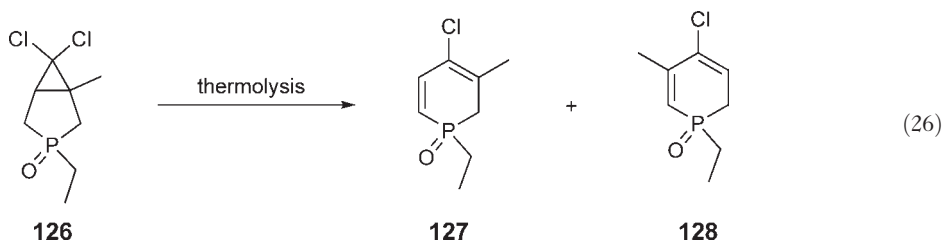
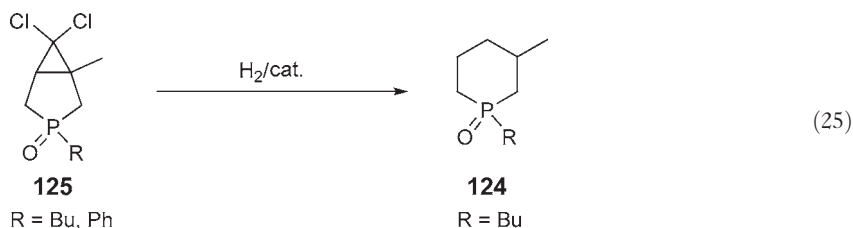
Dihydrophosphaphenanthrene **121** was aromatized to **122** in two steps: chlorination with phosgene produced chlorophosphaphenanthrene **123** and was followed by elimination of HCl by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [<2003ZNB782>](#) (**Scheme 4**).

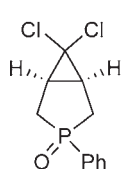
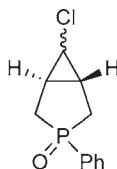
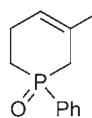


Scheme 4

7.12.6.3.2 Ring rearrangements

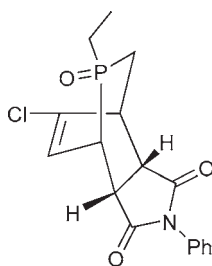
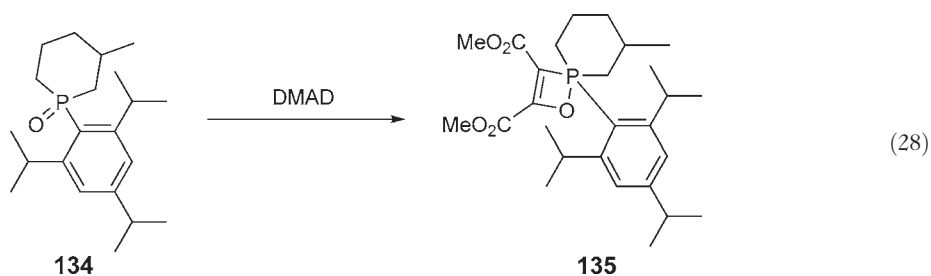
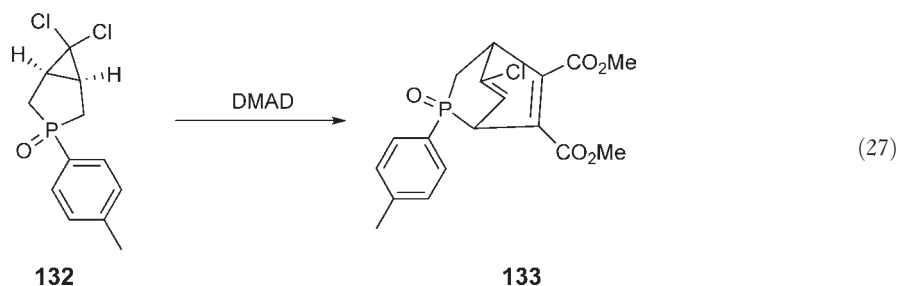
Hexahydrophosphinine oxides **124** are obtained in good yield by the catalytic hydrogenation of phosphabicyclohexane oxides **125** [<1996JCM528>](#) (**Equation 25**). Thermolysis of dichlorocyclopropane **126** furnished dihydrophosphine oxides **127** and **128** [<1996PS\(109\)457>](#) (**Equation 26**). Catalytic hydrogenation of phosphabicyclohexanes **129** and **130** led to the diastereoisomers of tetra- and hexa-hydrophosphinine oxides **131** and **96** [<1999PS\(144\)593, <1997JCM290>](#).



**129****130****131**

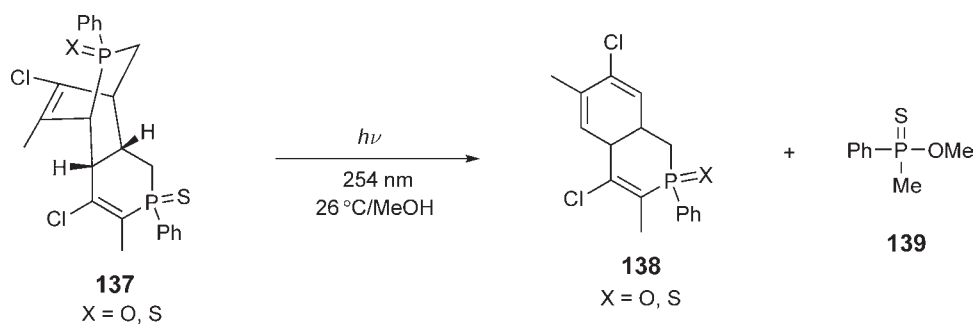
7.12.6.3.3 Diels–Alder reaction

p-Tolyldihydrophosphine oxide **132** with dimethyl acetylene dicarboxylate (DMAD) afforded the phosphabicyclocotadiene oxide **133** as expected via [4+2] cycloaddition <2001J(P1)1062> (Equation 27). On the other hand, with triisopropylphenylphosphine oxide **134**, the cycloaddition of P=O with acetylene via [2+2] cycloaddition gave spirocyclic oxaphosphate **135** <2003HAC443, 2001J(P1)1062> (Equation 28). Phosphine oxides **127** were reacted with *N*-phenylmaleimide in boiling toluene to give phosphabicyclocotene oxide **136** as a mixture of regioisomers <2005HAC196, 2002HAC626, 2002HCO31>.

**136**

7.12.6.3.4 Retro-Diels–Alder reaction

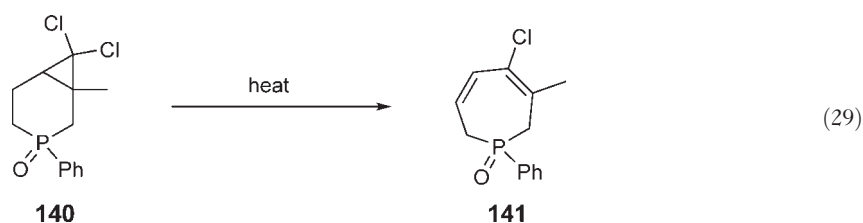
Diphosphatricyclic compound **137** was photolyzed at 254 nm at 26 °C in MeOH to furnish retro-Diels–Alder products dihydrophosphinoline **138** and thiophosphinate **139** <2004HAC97> (Scheme 5).



Scheme 5

7.12.6.3.5 Ring enlargement reactions

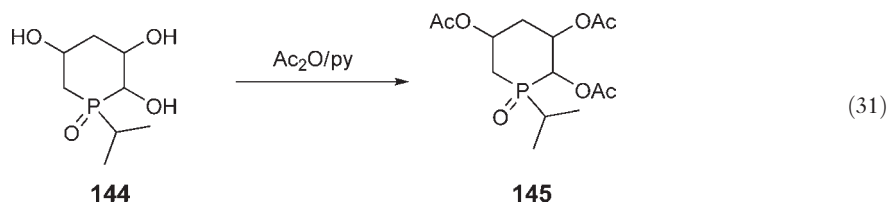
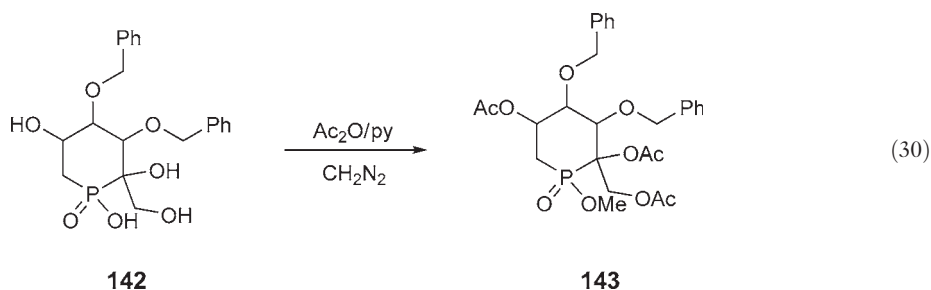
Tetrahydrophosphinine oxide **131** was reacted with dichlorocarbene generated from CHCl_3 by addition of sodium hydroxide under phase-transfer conditions to give adduct **140** which underwent thermal expansion to give 2,7-dihydrophosphepin oxide **141** <1998JCM210> (Equation 29).

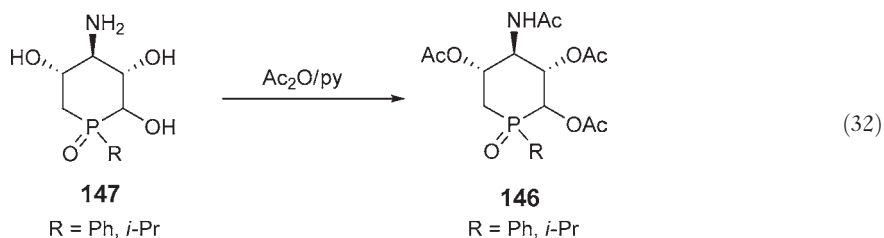


7.12.7 Reactivity of Substituents Attached to Ring Carbon Atoms

7.12.7.1 O-Acylation/N-Acylation/O-Alkylation

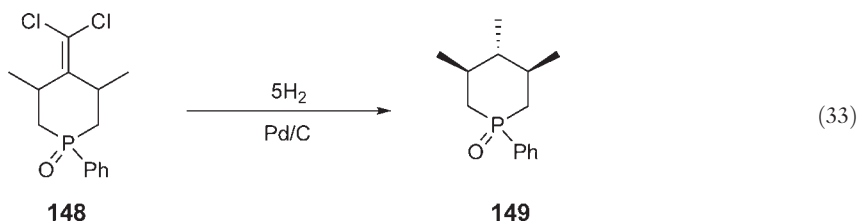
D-Fructosepyranose derivatives **142** were further derivatized with $\text{Ac}_2\text{O/py}$ and CH_2N_2 to produce methoxyphosphinyl-1,2,5-acetates **143** <2005CAR31, 1999H(50)323> (Equation 30). Acetylation of trihydroxyphosphinane **144** with $\text{Ac}_2\text{O/py}$ gave triacetylpyranose derivatives **145** <2003HCO559, 1998JCM790> (Equation 31). A mixture of isomers of O- and N-acetylated D-xylopyranose derivatives **146** was obtained from treatment of **147** with $\text{Ac}_2\text{O/py}$ <1996CR307, 2003CAR283> (Equation 32).





7.12.7.2 Hydrogenation

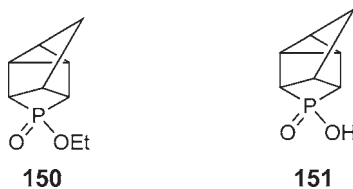
The complete hydrogenation of vinylphosphine oxide **148** and **149** was achieved in one step by hydrogenation with palladium on carbon catalyst using 5 equiv of hydrogen <2000SC4221> (Equation 33).



7.12.8 Reactivity of Substituents Attached to Ring Heteroatoms

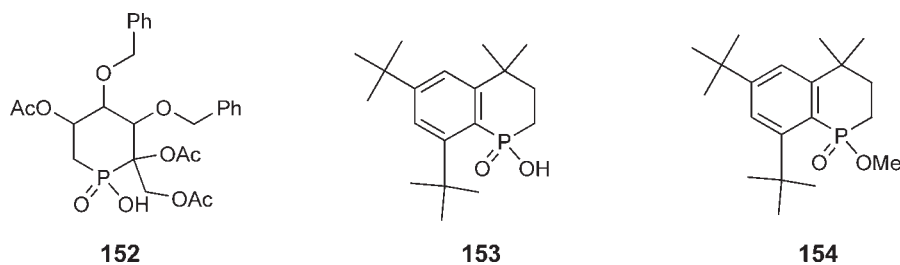
7.12.8.1 Ester Hydrolysis to Acids

Phosphinate **150** was hydrolyzed on standing in moist ethyl acetate to the parent phosphinic acid **151** <1996JHC979>.



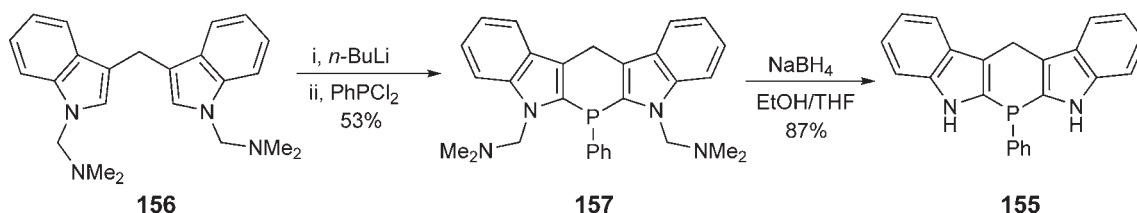
7.12.8.2 O-Methylation

O-Methylation of triacetyl derivative **152** with CH_2N_2 gave 1-methoxyphosphinyl-1,2,5-triacetates **143** <2005CAR31, 1999H(50)323>. Phosphinic acid **153** was further converted to the corresponding methylphosphinate **154** by the addition of $\text{CH}_2\text{N}_2/\text{Et}_2\text{O}$ <1997CC1637>.



7.12.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms in Each Component

One synthesis of a dihydrophosphinine **155** was achieved by reaction of a dilithiated bis(3-indolyl)methane **156** with dichlorophenylphosphine <2005OM37> (Scheme 6). The dimethylaminomethyl groups on nitrogen of **157**, which serve both to protect the nitrogen atoms and direct metallation to the indolyl 2-positions, could be removed using NaBH_4 .

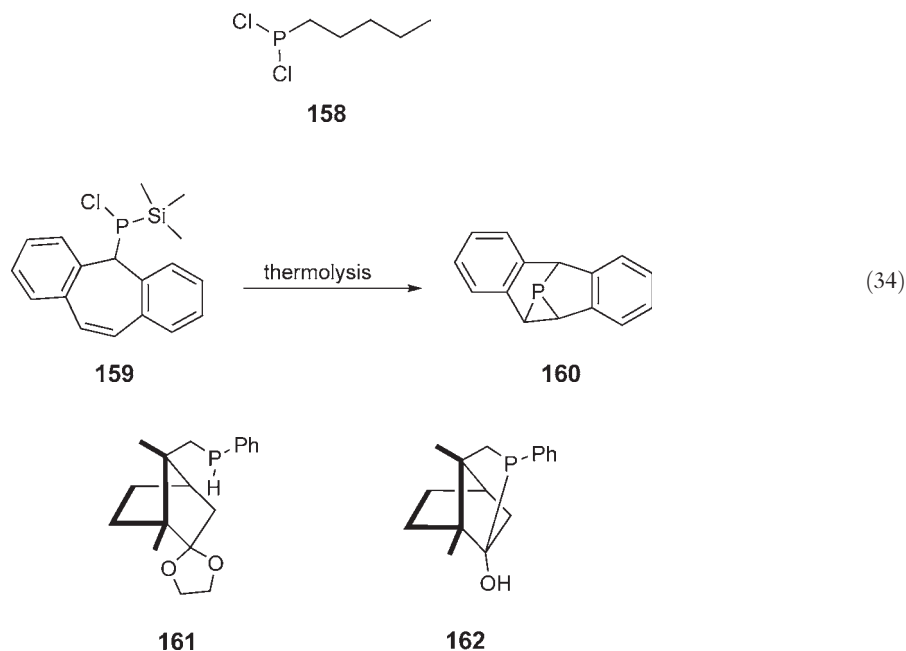


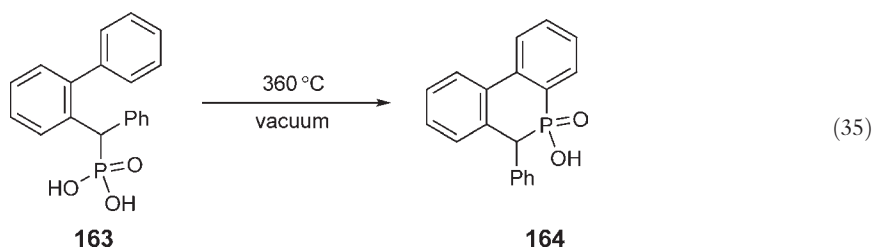
Scheme 6

7.12.9.1 P-C(5) Cyclization

7.12.9.1.1 Formation of P-C bond

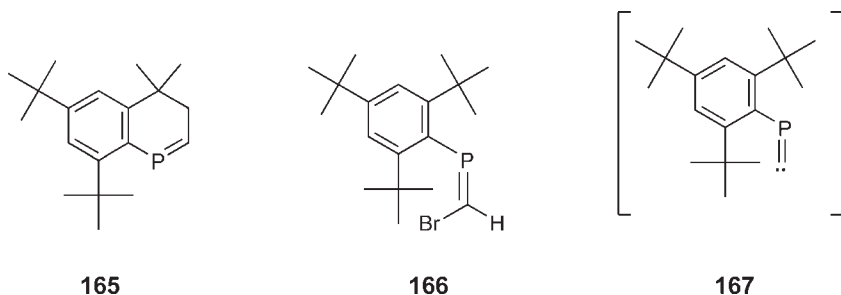
Flash vacuum pyrolysis of pentyldichlorophosphine **158** over magnesium at 600°C gave a small amount of phosphinine **25** <1997TL8417>. Intramolecular hydrophosphination/cyclization of phosphinoalkenes using $\text{Cp}_2\text{SmCH}(\text{TMS})_2$ have been reported <2001JA10221>. Catalytic intramolecular hydrophosphination/cyclization of phosphinoalkenes using organo lanthanides of type $\text{Cp}_2\text{LaCH}(\text{TMS})_2$ yielded six-membered phosphorinane <2000JA1824>. Controlled thermolysis of chlorotrimethylsilyl phosphanyl dibenzo cycloheptene **159** gave dibenzo-1-phospha semibullvalene **160** in quantitative yield <2003AGE3955> (Equation 34). Phosphine ketal **161** was hydrolyzed under acidic conditions to liberate a ketone which was subsequently subjected to nucleophilic addition to afford 2-hydroxyphospholane **162** <2003CC2240>. Cyclization of 2-phenylbenzhydrylphosphonic acid **163** was effected by heating at 360°C under vacuum to afford phenyldibenzophosphine **164** <2003ZNB782> (Equation 35).





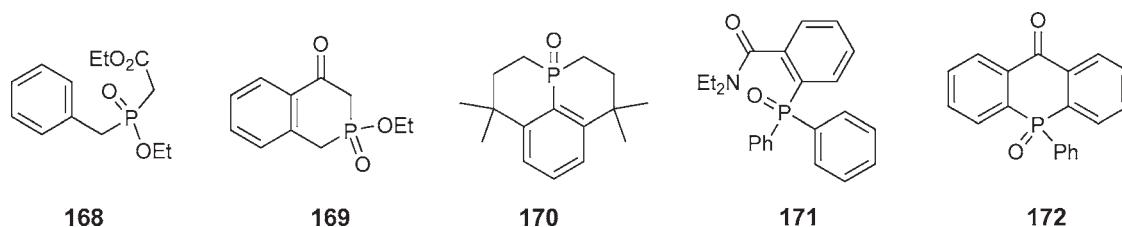
7.12.9.1.2 Formation of C(2)–C(3) bond

1-Phosphanaphthalene **165** is derived from 2-bromo-1-phosphaethene **166** via intramolecular insertion of an intermediate phosphindene carbene **167** into one of the C–H bonds of the two *O*-*tert*-butyl groups <1997CC1637>.



7.12.9.1.3 Formation of C(3)–C(4) bond

Polyphosphoric acid cyclization of phosphinate **168** provided isophosphinone derivative **169** <1997BMC1327>. The fused tricyclic dialkyl (phenyl)phosphine 1,1,6,6-tetramethylphosphajulolidine **170** has been synthesized on a large scale from dimethyl(phenyl) phosphine oxide. The steps involved are deprotonation/addition of butyraldehyde followed by polyphosphoric acid (PPA) cyclization and afforded a bicyclic compound. Repeating these steps yielded the tricyclic compound <2000J(P1)3122>. Cyclization of phosphate **171** with lithium diisopropylamide (LDA) provided dibenzophosphininone **172** <1996AG1609, 2004PS(179)959>.



7.12.9.2 [2+4] Cycloadditions Involving P–C Multiple Bonds

7.12.9.2.1 PC + C-4 Cycloaddition

Substituted phosphorus heterocycles of varying degrees of unsaturation were easily obtained via Diels–Alder reaction and such adducts may be further aromatized or functionalized to provide phosphorus containing cage compounds <1996PS(109)425, 1999S644, 1999EJO363>.

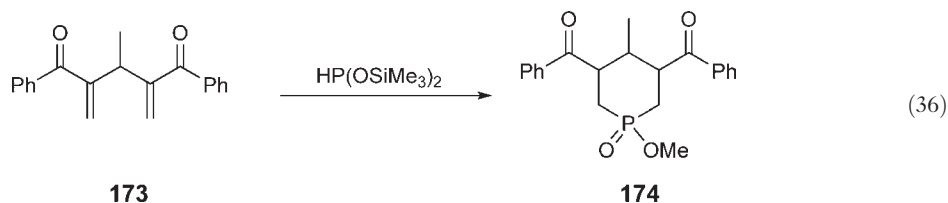
7.12.9.2.2 P–C(3) + C-2 Cycloaddition

The cycloaddition of phospholes with alkynes to synthesize phosphorins comes under this classification. For phosphorins to form, the transient 2H-phosphole has to react with alkynes followed by elimination of a carbene. This type of synthetic approach is less common and is discussed in the earlier chapter <1996CHEC-II(5)639>.

7.12.9.2.3 P + C-5 Cyclizations

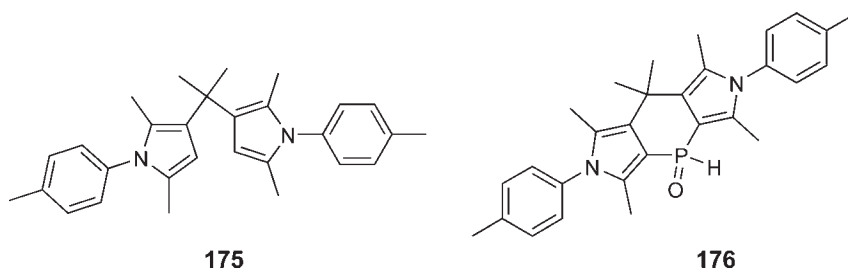
7.12.9.2.3(i) Addition of P(III) to alkene unsaturated to C=O

2,4-Dimethylene-1,5-diketone **173** reacted with $\text{HP}(\text{OSiMe}_3)_2$ to form stereoisomeric 3,5-dibenzoylphosphorinane **174** <1996RJC223> (Equation 36). Phorone, a precursor for phosphorinane, is prepared via direct double Michael addition of monoalkylphosphine to unsaturated ketone. Phorone was further reduced to phosphorinane via Wolf-Kishner reduction. Phosphorinane is a class of ligand for organopalladium cross-coupling chemistry (Suzuki and Sonogashira) <2006OL103>.

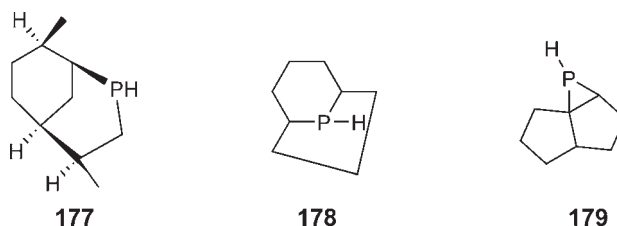


7.12.9.2.3(ii) Addition of P(III) to dienes

Norbornadiene reacted with diethylphosphonochloridite $[\text{ClP}(\text{OEt})_2]$ to afford phosphinate ester **150** and it was characterized by single crystal diffraction analysis <1996JHC979>; the Lewis acid, POCl_3 accelerated the reaction. Reaction of bispyrrolylpropane **175** with PBr_3 led to the formation of bromophosphine derivative, which proved to be thermally unstable and was further converted to phosphate **176** with water <1999CHE1383>.

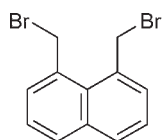


The radical addition of PH_3 to limonene resulted in the formation of 2-phoshabicyclononane **177** which has been characterized by X-ray crystallographic analysis <2001TL2609>. Phobane is a mixture of the sym- and asym-bicyclic secondary phosphines **178** and **179**, formed by the reaction of PH_3 with 1,5-dicyclooctadiene. The mixture of phobanes may be separated efficiently by selective protonation of the syn isomer with HCl <2005ASC1345>.

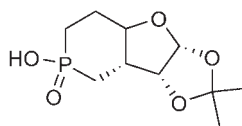


7.12.9.2.3(iii) Addition of P(III) to 1,5-dihalocompounds

Six-membered phosphorus-containing heterocycles were prepared by (1) reactions of 1,5-dihalo compounds with phosphites <1996TL5425, 2000TL8211, 1996PS(109)601, 1996AG2686, 2004AGE3058, 2001S1938>, (2) reactions of 1,5-bis-Grignard reagents with dichlorophosphine <2001TL7303>, and (3) reactions of 1,5-dihalo compounds with phosphines <1997JPR482, 1998SL497>. Phosphenalene **99** was obtained from 1,8-bis(bromomethyl)naphthalene **180** in quantitative yield <1996TL5425>. Cyclic phosphinic acid **181** was obtained by a double Arbuzov-type reaction with bistrimethylsilyl phosphonite (BTSP) with the dibromide <2000TL8211>.

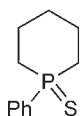


180

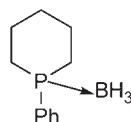


181

Treatment of phosphorus-donating agent, benzothiadiphosphole with bis-Grignard, PhMgBr and S_8 afforded 1-phenylcyclic phosphine sulfide **182** <2001S1938, 2004AGE3058, 2000SL1685>. The reaction of the bis-Grignard reagent of 1,5-dibromopentane with dichlorophenylphosphine followed by protection using $\text{BH}_3\text{-THF}$ (THF – tetrahydrofuran) gave 1-phenylphosphorinane-borane **183** <2001TL7303>. 1-Phenyl and 1,1-bisphenyl phosphorinane derivatives mentioned were prepared from 1,5-dihalopentanes using H_2PPh_2 and $\text{Ph}_2\text{P-PPh}_2$, respectively <1997JPR482, 1998SL497>. Intramolecular cyclization of 5-bromopentyl diphenyl phosphine borane under high pressure gave cyclic phosphonium salt <1997TL3405>.



182



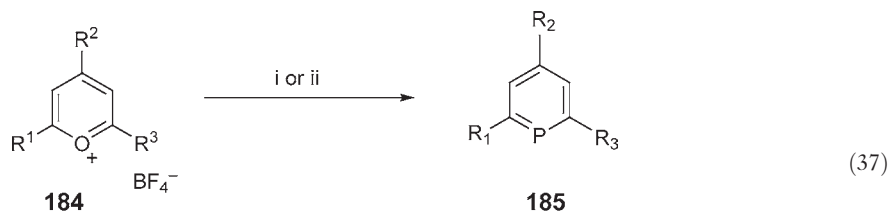
183

7.12.9.2.4 P-C(2) + C-3 Reactions

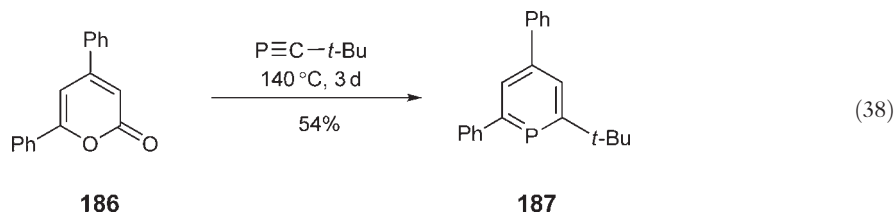
This type of reaction is very common in the nitrogen equivalent pyridine system (the ready formation of enamines and the ready availability of 1,3-electrophiles, such as acrolein and their equivalents). With the phosphorus system, the not so common enamine equivalent makes it a not so common synthetic approach. However, with proper substituents 1,3-dinucleophilic P-C(2) fragments have been reacted with 1,3-electrophiles, and have been used in the synthesis of λ^5 -phosphinolines <1996CHEC-II(5)639>.

7.12.10 Ring Synthesis by Transformation of Another Ring

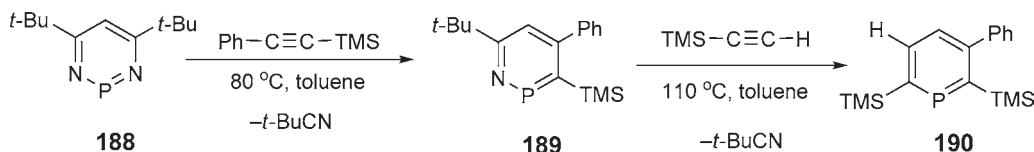
A convenient synthesis of phosphinines **185** involves the reaction of pyrylium salts **184** with either an excess of tris(trimethylsilyl)phosphine in acetonitrile, or alternatively with PH_3 under pressure at 110°C <2001CEJ3106>. Better yields are often obtained using the direct reaction with PH_3 (Equation 37). 2-*t*-Butyl phosphinines **187** can be prepared by reaction under pressure of *t*-butylphosphaacetylene with the α -pyrone **186** (Equation 38).



i, P(TMS)_3 , 2–2.5 equiv, CH_3CN , reflux, 5 h, 15–51%
 ii, PH_3 , 30 bar, *n*-BuOH, 110°C , 4 h, 28–84%



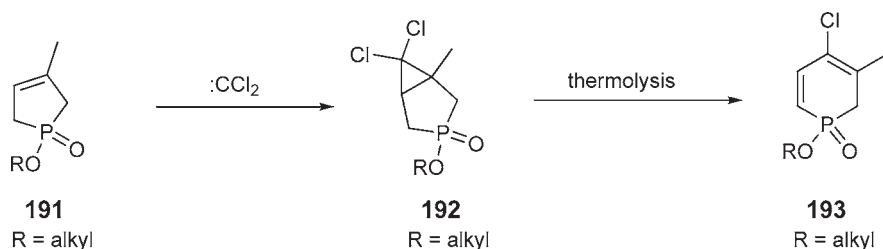
Another valuable method involves a sequential cycloaddition–cycloreversion sequence commencing with the highly reactive 1,3,2-diazaphosphinine **188** (Scheme 7). Initial reaction with a substituted alkyne results in a [4+2]/retro-[4+2] sequence extruding 1 mol of nitrile, providing the 1,2-azaphosphinine **189**. The intermediate product **189** can be converted, via a second [4+2]/retro-[4+2] sequence at higher temperature, into a substituted phosphinine **190** in very good (typically 80–85%) yields^{<1996JA11978>}. Excellent regioselectivity is seen with unsymmetrical alkynes. The differential reactivities of the diazaphosphinine and azaphosphinine allow for variation in the alkynes used in each of the steps, expanding the usefulness of this process.



Scheme 7

7.12.10.1 Synthesis via Ring Expansion of Dihydrophospholes Using Carbenes

Dihydrophospholes have been found to react readily with dichloro carbenes with ring expansion to form six-membered rings with phosphorus at various substitutions and oxidation levels both at carbenes and phospholes. The general procedure is as follows: dichlorocarbene is added to the double bond of phosphole **191** to afford phosphabicyclohexene **192** which on thermolysis leads to dihydrophosphine derivative **193** ^{<1996JCM528>} (Scheme 8). Thermolysis of phosphole thione **194** afforded phosphothione **195** ^{<1996PS(109)457>} (Equation 39).



Scheme 8

(39)

The base and thermally induced cyclopropane ring opening of the bicyclic compound led to distinct dihydrophosphine isomers ^{<1999J(P1)1801, 2001HAC528, 2003HAC443, 2004HCO283, 2001J(P1)1062>}. Catalytic hydrogenation of phosphabenzene derivatives led to di-, tetra-, and hexa-hydrophosphinine oxides ^{<1999PS(144)593, 1996JCM528>}.

7.12.10.2 Ring Expansion of Furanoside to Pyranose

This section represents new advances in this area of phosphasugars. Sugar analogues having phosphorus in the ring (phosphor sugar) such as D-glucopyranose, and D-mannopyranose were prepared from sugars containing heteroatoms ^{<1999H(50)323>}. A large number of phosphasugars have been reported recently and their conformational analysis

has been studied <2002HCA2608>, for example, D-glucose, D-mannose, D-galactose, and L-fructose derivatives <2002HCA2608>. Ring enlargement of furanosides was effected by HCl to open up the ring and then close it to afford pyranose derivatives <2003CAR283>.

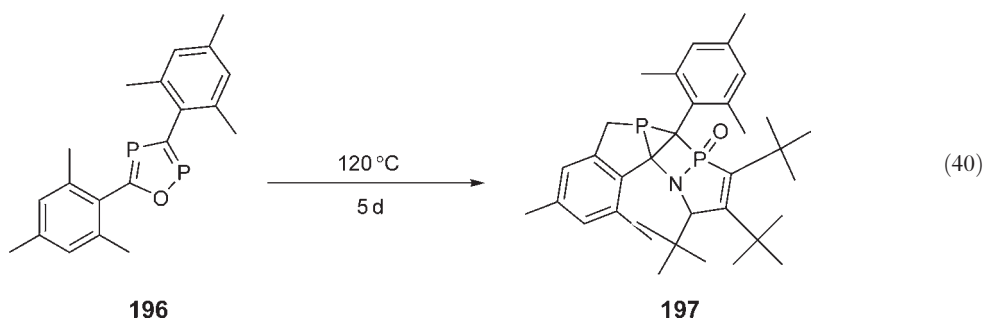
Analogues of D-mannosamine were prepared from D-glucopyranose via acid hydrolysis followed by oxidation with H_2O_2 <1998JCM790>. X-Ray crystallographic analysis, absolute configuration at the phosphorus, and conformational analysis were carried out for pyranose derivatives <2001HCO113, 2003HCO559>. Dibenzoxypyranose and amino derivatives have been prepared similarly <2005CAR31, 1999H(50)323, 1996CR307>.

7.12.10.3 Diphosphaindenoindene to Alkenyl Phosphinane

1-Alkyl- or 1-arylphosphinanes were prepared using phosphorus-donating reagent, namely benzothiadiphosphole in reaction with mono- and bis-Grignard reagents <2002TL9299, 2001EJO3421>.

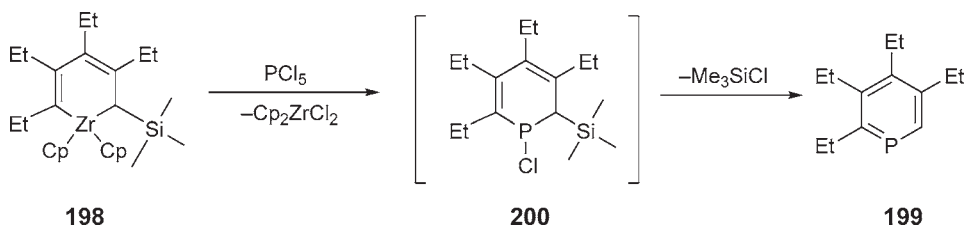
7.12.10.4 Oxadiphosphole to Phosphinane

Reaction of 1,2,4-oxadiphosphole **196** with tri-*tert*-butylazete showed no reaction at room temperature but under drastic conditions (120°C , 5 days) resulted in the formation of the polycyclic compound **197** <1999EJO587> (Equation 40).



7.12.10.5 Zircona Cyclohexadienes to Phosphinane

Zirconacyclohexadienes **198** reacted with PCl_5 to give the desired phosphinine **199** via metathesis with loss of Cp_2ZrCl_2 from the intermediate **200** followed by the elimination of Me_3SiCl <2004TL7633> (Scheme 9).



Scheme 9

7.12.11 Critical Comparison of Various Routes

From the various approaches to the synthesis of six-membered rings with one phosphorus atom, it is easy to see that all the possible approaches have been explored. The method of choice for a particular synthetic target would greatly depend upon the nature of the substituents on the phosphorus as well as on the ring carbons.

The ring transformation approach, either ring expansion of phospholes using carbenes or ring contraction of larger phosphorus containing ring compounds, are more specific than general and also it requires the availability of the precursor phosphorus containing ring compounds.

The synthetic methods using acyclic carbon fragments and phosphorus containing acyclic carbon fragments are specific as well as general. From the volume of the work done in this area it is clear that the strategies were developed for the syntheses of these six-membered phosphorus containing compounds following the benzene ring system (where Diels–Alder approach is more common) rather than the pyridine ring system (where two two-carbon fragment with one-carbon fragment along with ammonia or its equivalent approach is more common). Another reason for choosing the Diels–Alder approach is the readily availability of $P=C$ containing compounds.

An important point to remember when choosing the synthetic method for a phosphorus containing six-membered ring compound is the oxidation state of the phosphorus atom which could be 3, 4, or 5. The different oxidation states could be either included in the starting phosphorus compound or could be interconverted once the six membered ring system containing the phosphorus is built.

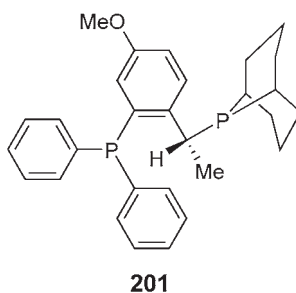
An approach similar to the synthesis of the Hantzsch pyridine synthesis could be explored for its feasibility in the synthesis of these six-membered rings with one phosphorus atom in the ring. By proper choice of the phosphorus compound (with the right oxidation state) a simple approach may be feasible to synthesize various substituted (in all positions) phosphonines.

7.12.12 Important Compounds and Applications

The major application of phosphorus heterocycles covered in this chapter is their use as ligands, especially for generation of catalysts for organic synthesis.

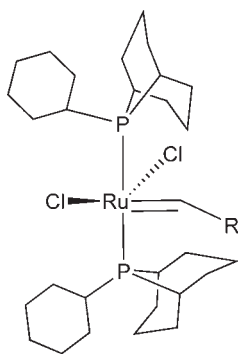
7.12.12.1 Hydrogenations

Reetz and Mehler have used a 2,4,6-triarylphosphinine as a coligand in asymmetric rhodium-catalyzed hydrogenations of an acetamidoacrylate; while the enantiomeric excesses are modest (52.6–84.2%), the phosphinine sometimes allows for reversal of enantioselectivity <2003TL4593>. Salzer and co-workers have studied a range of phosphine ligands for synthesis of elaborate diphosphine ligands <2004AC191>. One incorporated a bicyclic phosphine **201**. Its use in rhodium-catalysed hydrogenations of a range of substrates gave uniformly modest enantioselectivity.



7.12.12.2 Metathesis

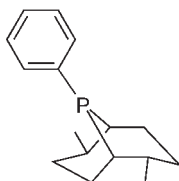
In an attempt to prepare a more stable olefin metathesis catalyst, Forman and co-workers have developed and tested a new ruthenium complex containing a rigid bicyclic phosphine ligand. The complex **202** displayed excellent stability, could be recovered by chromatography, and showed good catalytic activity in both self-metathesis and ring-closing metathesis reactions <2004OM4824>. Interestingly, while the efficiency of a Grubbs catalyst was enhanced in self-metathesis reactions by addition of phenol to the reaction mixture, conversion was not enhanced by addition of phenol <2005OM4528>.



202

7.12.12.3 Allylic Substitution

Palladium-catalyzed nucleophilic substitutions of activated allylic alcohols have been investigated using a bicyclic phosphine as the chiral element. Reactions have been reported with racemic acyclic allylic acetates <1999TL7791> and cycloalkenyl carbonates <2001TL1297> using the phosphine **203**, with good to excellent enantiomeric excesses.



203

References

- 1993CC1295 P. Le Floch and F. Mathey, *J. Chem. Soc., Chem. Commun.*, 1993, 1295.
 1995JOC1647 L. Nyulászi, D. Szieberth, and T. Veszprémi, *J. Org. Chem.*, 1995, **60**, 1647.
 1995JST(338)51 D. J. Berger, P. P. Gaspar, and J. F. Liebman, *J. Mol. Struct.*, 1995, **338**, 51.
 1995JST(347)57 L. Nyulászi and T. Veszprémi, *J. Mol. Struct.*, 1995, **347**, 57.
 1996AG1609 M. Gray, B. J. Chapell, N. J. Taylor, and V. Snieckus, *Angew. Chem.*, 1996, **108**, 1609.
 1996AG2686 S. E. Denmark, K. A. Swiss, and S. R. Wilson, *Angew. Chem.*, 1996, **108**, 2686.
 1996CHEC-II(5)639 D. G. Hewitt; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 639.
 1996CR307 K. Seo, M. Yamashita, T. Oshikawa, and J. Kobayashi, *Carbohydr. Res.*, 1996, **281**, 307.
 1996HAC307 D. B. Chesnut and E. F. C. Byrd, *Heteroatom Chem.*, 1996, **7**, 307.
 1996IC5805 S. T. Howard, J. P. Foreman, and P. G. Edwards, *Inorg. Chem.*, 1996, **35**, 5805.
 1996JA6317 P. von Rague Schleyer, C. Maerker, A. Dransfeld, H. Jiao, and N. J. R. van Eikema Hommes, *J. Am. Chem. Soc.*, 1996, **118**, 6317.
 1996JA10168 A. E. Wroblewski and J. G. Verkade, *J. Am. Chem. Soc.*, 1996, **118**, 10168.
 1996JA11978 N. Avarvari, P. Le Floch, and F. Mathey, *J. Am. Chem. Soc.*, 1996, **118**, 11978.
 1996JCM528 G. Keglevich, A. Tungler, T. Novak, and L. Toke, *J. Chem. Res. (S)*, 1996, 528.
 1996JHC979 V. Roussis, N. C. Baenziger, and D. F. Wiemer, *J. Heterocycl. Chem.*, 1996, **33**, 979.
 1996JPC6456 L. Nyulászi and T. Veszprémi, *J. Phys. Chem.*, 1996, **100**, 6456.
 1996OM802 H. T. Teunissen and F. Bickelhaupt, *Organometallics*, 1996, **15**, 802.
 1996PS(109)425 M. Regitz, T. Weitling, R. Fassler, B. Breit, B. Geissler, M. Julino, A. Hoffmann, and U. Bergstrasser, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1996, **109–110**, 425.
 1996PS(109)457 G. Keglevich, L. Toke, K. Ujszaszy, and A. Szollosy, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1996, **109–110**, 457.
 1996PS(109)601 B. Trofimov, N. Gusarova, and L. Brandsma, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1996, **109–110**, 601.
 1996PS(115)43 G. Aksnes, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1996, **115**, 43.
 1996RJC223 V. I. Vysotskii and A. G. Vilitkevich, *Russ. J. Gen. Chem.*, 1996, **66**, 223.
 1996RJC564 B. M. Butin, A. P. Logunov, G. T. Maishinova, and I. G. Ugarina, *Russ. J. Gen. Chem.*, 1996, **66**, 564.

- 1996RJC567
1996TL5425
1997BMC1327
1997CC1527
1997CC1637
1997JCM290
1997JPR482
1997OM4089
1997TL3405
1997TL8417
1998NJC651
1998JCM210
1998JCM790
1998SL497
1998TL4291
1999CC537
1999CC8771
1999CEJ2109
1999CHE1383
1999EJO363
1999EJO587
1999EJO3291
1999H(50)323
1999JIB660
1999JCOS524
1999JP(1)1801
1999OM4205
1999PS(144)593

1999S644
1999TL7791
2000EJI2565
2000EJO3497
2000JA1824
2000JA12227

2000JCC509
2000JP(1)3122
2000JP(1)4451
2000OM2208
2000PCP3127
2000RCB1522
2000SC4221
2000SL1685
2000TL8211
2001AGE4476
2001CEJ3106
2001CPL(336)343
2001CRV1229
2001EJO3421
2001HAC528
2001HCA1578
2001HCO113
2001JA6654

2001JA10221
2001JOC1054
2001JP(1)1062
2001MI1
B-2001MI463

2001S1938
2001TL1297
2001TL2609
2001TL7303
2002EJI2034
2002HAC626
2002HCA2608
2002HCO31
- B. M. Butin, A. P. Logunov, G. T. Maishinova, and I. G. Ugarina, *Russ. J. Gen. Chem.*, 1996, **66**, 567.
E. A. Boyd, M. E. K. Boyd, and F. Kerrigan, *Tetrahedron Lett.*, 1996, **37**, 5425.
Y. Q. Mu and R. A. Gibbs, *Bioorg. Med. Chem.*, 1997, **5**, 1327.
J. H. Downing, V. Gee, and P. G. Pringle, *Chem. Commun.*, 1997, 1527.
S. Ito, K. Toyota, and M. Yoshifuji, *Chem. Commun.*, 1997, 1637.
G. Keglevich, T. Novak, A. Tungler, L. Hegedus, L. Toke, A. Szollosy, and K. Ludanyi, *J. Chem. Res. (S)*, 1997, 290.
H. Schmidt, *J. Prakt. Chem.*, 1997, **339**, 482.
N. Avarvari, P. Le Floch, L. Ricard, and F. Mathey, *Organometallics*, 1997, **16**, 4089.
J. Uziel, N. Riegel, B. Aka, P. Figuiere, and S. Juge, *Tetrahedron Lett.*, 1997, **38**, 3405.
R. A. Aitken, W. Masamba, and N. J. Wilson, *Tetrahedron Lett.*, 1997, **38**, 8417.
L. Nyulász, U. Bergsträsser, M. Regitz, and P. v. R. Schleyer, *New J. Chem.*, 1998, **22**, 651.
G. Keglevich, H. T. T. Thanh, K. Ludanyi, T. Novak, K. Ujszaszy, and L. Toke, *J. Chem. Res. (S)*, 1998, 210.
T. Hanaya, Y. Fujii, and H. Yamamoto, *J. Chem. Res. (S)*, 1998, 790.
N. J. Lawrence and H. Beynek, *Synlett*, 1998, 497.
E. Soulier, J. C. Clement, J. J. Yaouanc, and H. des Abbayes, *Tetrahedron Lett.*, 1998, **39**, 4291.
P. Rosa, L. Ricard, F. Mathey, and P. Le Floch, *Chem. Commun.*, 1999, 537.
P. Le Floch and F. Mathey, *Coord. Chem. Rev.*, 1999, **179–180**, 771.
N. Avarvari, N. Maigrot, L. Ricard, F. Mathey, and P. Le Floch, *Chem. Eur. J.*, 1999, **5**, 2109.
S. P. Ivonin, *Chem. Heterocycl. Compd.*, 1999, **35**, 1383.
W. Fiedler, O. Löber, U. Bergsträsser, and M. Regitz, *Eur. J. Org. Chem.*, 1999, 363.
A. Mack, U. Bergstrasser, G. J. Reiss, and M. Regitz, *Eur. J. Org. Chem.*, 1999, 587.
M. Hofmann, P. V. R. Schleyer, and M. Regitz, *Eur. J. Org. Chem.*, 1999, 3291.
T. Hanaya, Y. Fujii, S. Ikejiri, and H. Yamamoto, *Heterocycles*, 1999, **50**, 323.
J. Azizian, K. Jadidi, M. Mehrdad, and Y. Sarrafi, *Indian J. Chem., Sect. B*, 1999, **38**, 660.
G. Frison, A. Sevin, N. Avarvari, F. Mathey, and P. Le Floch, *J. Org. Chem.*, 1999, **64**, 5524.
G. Keglevich, G. M. Keseru, H. Forintos, A. Szollosy, K. Ludanyi, and L. Toke, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1801.
X. Sava, N. Mézailles, N. Maigrot, F. Nief, L. Ricard, F. Mathey, and P. Le Floch, *Organometallics*, 1999, **18**, 4205.
G. Keglevich, L. Toke, K. Steinhauser, T. Novak, and K. Ludanyi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1999, **144–146**, 593.
O. Lober, U. Bergstrasser, and M. Regitz, *Synthesis*, 1999, 644.
Y. Hamada, N. Seto, Y. Takayanagi, T. Nakao, and O. Hara, *Tetrahedron Lett.*, 1999, **40**, 7791.
U. Rhöric, N. Mézailles, N. Maigrot, L. Ricard, F. Mathey, and P. Le Floch, *Eur. J. Inorg. Chem.*, 2000, 2565.
E. Soulier, J. J. Yaouanc, P. Laurent, H. des Abbayes, and J. C. Clement, *Eur. J. Org. Chem.*, 2000, 3497.
M. R. Douglass and T. J. Marks, *J. Am. Chem. Soc.*, 2000, **122**, 1824.
S. Choua, H. Sidorenkova, T. Berclaz, M. Geoffroy, P. Rosa, N. Mézailles, L. Ricard, F. Mathey, and P. Le Floch, *J. Am. Chem. Soc.*, 2000, **122**, 12227.
F. Fuster, A. Sevin, and B. Silvi, *J. Comput. Chem.*, 2000, **21**, 509.
P. G. Edwards, S. J. Paisey, and R. P. Tooze, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3122.
G. Keglevich, M. Fekete, T. Chuluunbaatar, A. Dobo, V. Harmat, and L. Toke, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4451.
E. C. Brown and W. T. Borden, *Organometallics*, 2000, **19**, 2208.
L. Nyulász, T. Veszprémi, and A. Forró, *Phys. Chem. Chem. Phys.*, 2000, **2**, 3127.
V. V. Ovchinnikov, L. I. Lapteva, E. Y. Sitnikova, and A. I. Kononov, *Russ. Chem. Bull.*, 2000, **49**, 1522.
G. Keglevich, M. Fekete, T. Chuluunbaatar, A. Dobo, Z. Boeskei, and L. Toke, *Synth. Commun.*, 2000, **30**, 4221.
G. Baccolini, C. Boga, and U. Negri, *Synlett*, 2000, 1685.
A. C. Regan, N. Sciammetta, and P. I. Tattersall, *Tetrahedron Lett.*, 2000, **41**, 8211.
P. Rosa, N. Mézailles, L. Ricard, F. Mathey, and P. Le Floch, *Angew. Chem., Int. Ed.*, 2001, **40**, 4476.
B. Breit, R. Winde, T. Mackewitz, R. Paciello, and K. Harms, *Chem. Eur. J.*, 2001, **7**, 3106.
U. D. Priyakumar, T. C. Dinadayalane, and G. N. Sastry, *Chem. Phys. Lett.*, 2001, **336**, 343.
L. Nyulász, *Chem. Rev.*, 2001, **101**, 1229.
G. Baccolini, C. Boga, and R. A. Buscaroli, *Eur. J. Org. Chem.*, 2001, 3421.
G. Keglevich, H. Forintos, M. Sipos, A. Dobo, K. Ludanyi, K. Vekey, A. Tungler, and L. Toke, *Heteroatom Chem.*, 2001, **12**, 528.
Z.-X. Wang and P. von Ragué Schleyer, *Helv. Chim. Acta*, 2001, **84**, 1578.
T. Oshikawa, K. Seo, M. Yamashita, M. Takahashi, and Y. Hamauzu, *Heterocycl. Commun.*, 2001, **7**, 113.
L. Cataldo, S. Choua, T. Berclaz, M. Geoffroy, N. Mézailles, L. Ricard, F. Mathey, and P. Le Floch, *J. Am. Chem. Soc.*, 2001, **123**, 6654.
M. R. Douglass, C. L. Stern, and T. J. Marks, *J. Am. Chem. Soc.*, 2001, **123**, 10221.
N. Mézailles, N. Maigrot, S. Hamon, L. Ricard, F. Mathey, and P. Le Floch, *J. Org. Chem.*, 2001, **66**, 1054.
G. Keglevich, A. G. Vasko, A. Dobo, K. Ludanyi, and L. Toke, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1062.
X. Lu, M. C. Lin, X. Xu, N. Wang, and Q. Zhang, *PhysChemComm*, 2001, **13**, 1.
M. J. Gallagher, Six membered rings: Phosphinanes, dihydro- and tetrahydrophosphinanes, in 'Phosphorus–Carbon Heterocyclic Chemistry', F. Mathey, Ed.; Pergamon Press, Oxford, 2001, p. 463.
G. Baccolini, C. Boga, and R. A. Buscaroli, *Synthesis*, 2001, 1938.
Y. Hamada, K. Sakaguchi, K. Hatano, and O. Hara, *Tetrahedron Lett.*, 2001, **42**, 1297.
A. Robertson, C. Bradaric, C. S. Frampton, J. McNulty, and A. Capretta, *Tetrahedron Lett.*, 2001, **42**, 2609.
S. Kobayashi, N. Shiraishi, W. W. L. Lam, and K. Manabe, *Tetrahedron Lett.*, 2001, **42**, 7303.
A. Moores, N. Mézailles, N. Maigrot, L. Ricard, F. Mathey, and P. Le Floch, *Eur. J. Inorg. Chem.*, 2002, 2034.
G. Keglevich, H. Szelke, A. Tamas, V. Harmat, K. Ludanyi, A. G. Vasko, and L. Toke, *Heteroatom Chem.*, 2002, **13**, 626.
T. Hanaya and H. Yamamoto, *Helv. Chim. Acta*, 2002, **85**, 2608.
G. Keglevich, J. Kovacs, K. Ludanyi, and L. Toke, *Heterocycl. Commun.*, 2002, **8**, 31.

- 2002JOC271 U. D. Priyakumar and G. N. Sastry, *J. Org. Chem.*, 2002, **67**, 271.
2002JOC9162 C. S. Wannere, R. K. Bansal, and P. v. R. Schleyer, *J. Org. Chem.*, 2002, **67**, 9162.
2002JOM(643)39 S. M. Bachrach, *J. Organomet. Chem.*, 2002, **643–644**, 39.
2002JOM(643)278 A. Fekete and L. Nyulászi, *J. Organomet. Chem.*, 2002, **643–644**, 278.
2002NJC347 U. D. Priyakumar, T. C. Dinadayalane, and G. N. Sastry, *New J. Chem.*, 2002, **26**, 347.
2002TL9299 G. Baccolini, C. Boga, G. Guizzardi, and S. Ponzano, *Tetrahedron Lett.*, 2002, **43**, 9299.
2003AGE3955 J. Geier, G. Frison, and H. Grutzmacher, *Angew. Chem., Int. Ed.*, 2003, **42**, 3955.
2003CAR283 T. Oshikawa, K. Seo, M. Yamashita, T. Hanaya, Y. Hamauzu, and H. Yamamoto, *Carbohydr. Res.*, 2003, **338**, 283.
2003CC2240 I. V. Komarov, A. Spinnenberg, J. Holz, and A. Börner, *Chem. Commun.*, 2003, 2240.
2003CPL(380)251 D. B. Chesnut, *Chem. Phys. Lett.*, 2003, **380**, 251.
2003EJI3878 M. Doux, N. Mézailles, L. Ricard, and P. Le Floch, *Eur. J. Inorg. Chem.*, 2003, 3878.
2003HAC160 V. R. Ferro, S. Omar, R. H. González-Jonte, J. M. García, and de la Vega,, *Heteroatom Chem.*, 2003, **14**, 160.
2003HAC443 G. Keglevich, A. Szelke, A. Balint, T. Imre, K. Ludanyi, Z. Nagy, M. Hanusz, K. Simon, V. Harmat, and L. Toke, *Heteroatom Chem.*, 2003, **14**, 443.
2003HCO559 T. Oshikawa, K. Seo, M. Yamashita, T. Hanaya, Y. Hamauzu, and H. Yamamoto, *Heterocycl. Commun.*, 2003, **9**, 559.
2003JCD2036 C. Crause, L. Bennie, L. Damoense, C. L. Dwyer, C. Grove, N. Grimmer, W. J. van Rensburg, M. M. Kirk, K. M. Mokheseng, S. Otto, and P. J. Steynberg, *Dalton Trans.*, 2003, **663**, 145.
2003JCD4669 A. Polas, J. D. E. T. Wilton-Ely, A. M. Z. Slawin, D. F. Foster, P. J. Steynberg, M. J. Green, and D. J. Cole-Hamilton, *J. Chem. Soc., Dalton Trans.*, 2003, 4669.
2003JMT(635)141 J. Klocker, A. Karpfen, and P. Wolschann, *J. Mol. Struct. Theochem*, 2003, **635**, 141.
2003JMT(663)145 A. Saiewari, U. D. Priyakumar, and G. N. Sastry, *J. Mol. Struct. Theochem*, 2003, **663**, 145.
2003MI87 L. Pacureanu, M. Mracec, and Z. Simon, *Ann. West Univ. Timisoria, Ser., Chem.*, 2003, **12**, 87.
2003OM5454 J. Jeevanandam, E. J. P. Malar, and R. Gopalan, *Organometallics*, 2003, **22**, 5454.
2003PS(178)869 I. Yavari, S. Dehghan, and M. Nikpoor-Nezhati, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 869.
2003TL4593 M. Reetz and G. Mehler, *Tetrahedron Lett.*, 2003, **44**, 4593.
2003ZNB782 P. de Koe and F. Bickelhaupt, *Z. Naturforsch., B*, 2003, **58**, 782.
2004AC191 W. Braun, A. Salzer, F. Spindler, and E. Alberico, *Appl. Catal. A*, 2004, **274**, 191.
2004AGE3058 G. Baccolini, C. Boga, and M. Galeotti, *Angew. Chem., Int. Ed.*, 2004, **43**, 3058.
2004CC366 T. Kojima, Y. Ishioka, and Y. Matsuda, *Chem. Commun.*, 2004, 366.
2004CEC34 L. Pacureanu, M. Mracec, and Z. Simon, *Cent. Eur. J. Chem.*, 2004, **2**, 34.
2004CEJ4080 S. Choua, C. Dutan, L. Cataldo, T. Berclaz, M. Geoffroy, N. Mézailles, A. Moores, L. Ricard, and P. Le Floch, *Chem. Eur. J.*, 2004, **10**, 4080.
2004HAC97 G. Keglevich, J. Kovacs, T. Kortvelyesi, G. parlagh, T. Imre, K. Ludanyi, L. Hegedus, M. Hanusz, K. Simon, A. Marton, G. Marosi, and L. Toke, *Heteroatom Chem.*, 2004, **15**, 97.
2004HAC437 T. Agou, J. Kobayashi, and T. Kawashima, *Heteroatom Chem.*, 2004, **15**, 437.
2004HCO283 J. Kovacs, G. Keglevich, A. Kerenyi, T. Imre, K. Ludanyi, and L. Toke, *Heterocycl. Commun.*, 2004, **10**, 283.
2004JMT(674)125 R. Salcedo, *J. Mol. Struct. Theochem*, 2004, **674**, 125.
2004MCL191 L. Pacureanu, M. Mracec, and Z. Simon, *Mol. Cryst. Liq. Cryst.*, 2004, **416**, 191.
2004OM4824 G. S. Forman, A. E. McConnell, M. J. Hanton, A. M. Z. Slawin, R. P. Tooze, W. J. van Rensburg, W. H. Meyer, C. Dwyer, M. M. Kirk, and D. W. Serfontein, *Organometallics*, 2004, **23**, 4824.
2004PCP303 C. Lepetit, V. Peyrou, and R. Chauvin, *Phys. Chem. Chem. Phys.*, 2004, **6**, 303.
2004PS(179)959 J. Kobayashi, T. Agou, and T. Kawashima, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 959.
2004SC4159 G. Keglevich, M. Sipos, D. Lengyel, H. Forintos, T. Kortvelyesi, T. Imre, and L. Toke, *Synth. Commun.*, 2004, **34**, 4159.
2004SOS(15)1097 F. Mathey and P. LeFloch; in 'Science of Synthesis', D. Black, Ed.; Thieme, Stuttgart, 2004, vol. 15, p. 1097.
2004SOS(15)1157 R. Streubel; in 'Science of Synthesis', D. Black, Ed.; Thieme, Stuttgart, 2004, vol. 15, p. 1157.
2004SOS(15)1181 U. Bergstrer; in 'Science of Synthesis', D. Black, Ed.; Thieme, Stuttgart, 2004, vol. 15, p. 1181.
2004TL407 J. McNulty and Y. Zhou, *Tetrahedron Lett.*, 2004, **45**, 407.
2004TL7633 R. A. Hunter, R. J. Whitby, M. E. Light, and M. B. Hursthouse, *Tetrahedron Lett.*, 2004, **45**, 7633.
2005AHC(89)125 A. P. Sadimenko; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Elsevier, Amsterdam, 2005, vol. 89, p. 125.
2005ASC1345 M. R. Eberhard, E. Carrington-Smith, E. E. Drent, P. S. Marsh, A. G. Orpen, H. Phetmung, and P. G. Pringle, *Adv. Synth. Catal.*, 2005, **347**, 1345.
2005CAR31 T. Hanaya, K. Imai, Y. V. Prikhod'ko, and H. Yamamoto, *Carbohydr. Res.*, 2005, **340**, 31.
2005EJI125 M. Dochnahl, M. Doux, E. Faillard, L. Ricard, and P. Le Floch, *Eur. J. Inorg. Chem.*, 2005, 125.
2005HAC196 H. Szelke, A. Balint, E. Kiraly, K. Ludanyi, J. Kovacs, and G. Keglevich, *Heteroatom Chem.*, 2005, **16**, 196.
2005JHC451 G. Keglevich, *J. Heterocycl. Chem.*, 2005, **42**, 451.
2005JOC1998 P. K. Freeman, *J. Org. Chem.*, 2005, **70**, 1998.
2005JOC4637 O. Piechaczyk, Y. Jean, and P. Le Floch, *J. Org. Chem.*, 2005, **70**, 4637.
2005JOM(690)704 I. L. Odinet, N. M. Vinogradova, K. A. Lyssenko, D. G. Golovanov, P. V. Petrovskii, T. A. Mastryukova, H. Szelke, N. B. Szabo, and G. Keglevich, *J. Organomet. Chem.*, 2005, **690**, 704.
2005PCA2957 N.-N. Pham-Tran, G. Bouchoux, D. Delacre, and M. T. Nguyen, *J. Phys. Chem. A*, 2005, **109**, 2957.
2005PCA9118 D. S. Shobe, *J. Phys. Chem. A*, 2005, **109**, 9118.
2005OM37 J. O. Yu, E. Lam, J. L. Sereda, N. C. Rampersad, A. J. Lough, C. S. Browning, and D. H. Farrar, *Organometallics*, 2005, **24**, 37.
2005OM4528 G. S. Forman, A. E. McConnell, R. P. Tooze, W. J. van Rensburg, W. H. Meyer, M. M. Kirk, C. L. Dwyer, and D. W. Serfontein, *Organometallics*, 2005, **24**, 4528.
2006MRC784 J. E. Del Bene and J. Elguero, *Magn. Reson. Chem.*, 2006, **44**, 784.
2006OL103 T. Brenstrum, J. Clattenburg, J. Britten, S. Zavorine, J. Dyck, A. J. Robertson, J. McNulty, and A. Capretta, *Org. Lett.*, 2006, **8**, 103.
2006T4453 J.-N. Li, L. Liu, Y. Fu, and Q.-X. Guo, *Tetrahedron*, 2006, **62**, 4453.

Biographical Sketch



Marudai Balasubramanian “BALU” obtained his Ph.D. degree in Organic Chemistry from the Indian Institute of Technology, Chennai, India in 1987. He carried out postdoctoral work with Dr. Alan R. Katritzky at the Department of Chemistry, University of Florida, Gainesville, Florida (1988–1992). He subsequently moved to Reilly Industries Inc., Indianapolis, Indiana, where he was a research chemist until 2002. His research interests include synthesis of heterocyclic compounds, particularly pyridine derivatives, and synthesis of intermediates for pharmaceuticals, agrochemicals, performance products and heterocyclic polymers. In 2002, he joined Research Informatics, Pfizer at Ann Arbor, Michigan, as information professional. Currently he works at Pfizer, Groton and manages content and vendor relationship for the chemical related commercial databases. He is author/co-author of more than fifty scientific papers and has written several reviews, chapters for monographs and comprehensive heterocyclic chemistry series. He currently serves as an international editorial board member of *Heterocyclic Communications* an international journal of heterocyclic chemistry.

7.13

Six-membered Rings with One Arsenic, Antimony, or Bismuth Atom

A. J. Ashe, III

University of Michigan, Ann Arbor, MI, USA

© 2008 Elsevier Ltd. All rights reserved.

7.13.1	Introduction	1039
7.13.2	Theoretical Methods	1040
7.13.3	Experimental Structural Methods	1041
7.13.3.1	Structures Determined by X-Ray Diffraction	1041
7.13.4	Reactions of Arsenins	1043
7.13.4.1	Cycloaddition Reactions	1043
7.13.4.2	Reactions with Transition Metals	1044
7.13.5	Syntheses of Arsenins	1044
7.13.5.1	Arsinolines	1044
7.13.5.2	Substituted Arsenins	1045
7.13.6	Further Developments	1046
	References	1046

7.13.1 Introduction

Six-membered ring heterocycles with one arsenic, antimony, or bismuth were treated in both CHEC(1984) and CHEC-II(1996) <1984CHEC-I(1)539, 1996CHEC-II(5)669>. As in these prior editions, major coverage is on the fully conjugated rings, the group 15 element heterobenzenes, arsenin **1**, stibinin **2**, and bismin **3**. Since 1996, there has been a marked fall-off in interest in these heterobenzenes. Arsenins have been the subject of only three recent experimental papers. However, there have been a larger number of computational papers on **1–3**. In order to put the newer work in context, it is necessary to selectively review older work.



Arsenin
1

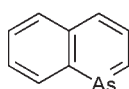


Stibinin
2

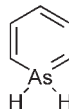


Bismin
3

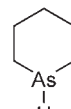
Nomenclature used in this chapter follows current usage in *Chemical Abstracts*, although the replacement nomenclature system is also used. The parent fully unsaturated heterocycles arsenin, stibinin, bismin, are often called arsabenzene, stibabenzene, and bismabenzene, respectively. Fused ring heterocycles are usually named by analogy with the better-known nitrogen compounds. Thus, arsinoline **4** is named after quinoline. Arsinoline is also called 1-arsanaphthalene. 1,1-Dihydroarsenin **5** has been commonly referred to as 1,1-dihydro- λ^5 -arsabenzene. When **5** is compared to **3**, compound **3** is usually referred to as λ^3 -arsabenzene. Analogous 1,1-dihydrostibinins and 1,1-dihydrobismins have yet to be reported. The saturated ring arsenane **6** is also called arsacyclohexane.



Arsinoline
4



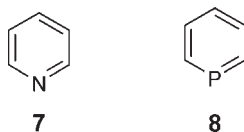
1,1-Dihydroarsenin
5



Arsenane
6

7.13.2 Theoretical Methods

Most of the computational work on **1–3** has focused on the aromaticity of these compounds which are often compared with pyridine **7** and phosphorin **8**. Aromaticity itself is an important but rather ill-defined concept. A good concise description of the application of aromaticity to heterocycles is given in the *Handbook of Heterocyclic Chemistry* <B-2000MI43>. The most frequently used criteria for aromaticity are: (1) structure, the tendency of conjugation to favor planar rings with equalized bond lengths; (2) magnetic properties, the tendency to display an exaltation of diamagnetic susceptibility and the consequent ring current; and (3) resonance energy, a stability due to aromaticity.

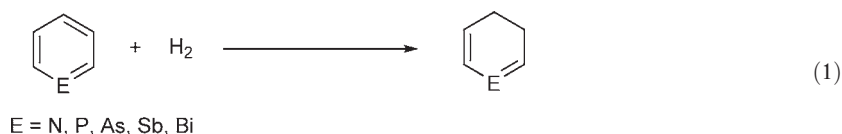


Unfortunately, experimental data relative to all of these criteria are not readily available. Moreover, computational work has become particularly attractive because of the availability of high-quality commercial packages such as the Gaussian suite of programs <1998MI1, 1995MI1>. In 1996, Schleyer *et al.* developed the nucleus-independent chemical shift (NICS) metric as a measure of the ring current in aromatic and antiaromatic systems <1996JA6317>. The NICS(1) values are defined as negative of the isotropic magnetic shielding at a point 1 Å above the ring plane <2001OL2465>. NICS values, which have no experimental basis, have become widely used for evaluating the magnetic criteria for aromaticity.

The more important computational papers which have appeared from 1995 to 2005 are summarized below.

Salcedo has evaluated the complete family of heterobenzenes **7**, **8**, **1**, **2**, and **3** at the BPW91/6-311-G** level <2004JST125>. The experimental geometries of **7**, **8**, **1**, and **2** were nicely reproduced. The NICS values varied over only a small range (−7.85 to −8.43), indicating an appreciable aromaticity for all the compounds. On the other hand, a homodesmotic reaction showed a regular drop-off in stabilization from phosphorin to bismin.

Shobe has performed calculations on the same series as well as their datively bonded oxides and sulfides at the B3LYP level <2005PCA9118>. The oxides or sulfides of **1–3** are unknown. Again the geometries of all of the heterobenzenes matched experimental data except for **3**, for which there is no experimental structure. The NICS(1) values range from −8.28 to −10.08, compared with a value for benzene of −9.85. Thus, they are all indicated to be aromatic. The heats of hydrogenation of all of the heterobenzenes to the 3,4-dihydro compounds have been evaluated (Equation 1). The values range from +35 to +38 kJ mol^{−1} in comparison to a value of +45 kJ mol^{−1} for benzene. All five of the heterobenzenes are aromatic and to approximately the same degree by geometric, energetic, and NICS criteria.



Ghiiasi has evaluated **1** and a number of polyarsenic heterocycles at the B3LYP level <2005JOM4761>. The experimental structure and ¹H NMR chemical shift values of **1** are well reproduced. Karpfen and co-workers have evaluated the structure and the rotation barrier about the OMe group of 4-methoxyarsenin using large-scale *ab initio* calculations at the Møller–Plesset second order (MP2) level and with density functional theory (DFT) calculations <2003JST141>. Comparison with anisole shows a lower barrier but a similar in-plane structure.

Wang and Schleyer have investigated various 1,1-disubstituted-phosphorins **9** and arsenins **10** at the B3LYP/6-31G* DFT level <2001HCA1578>. Based on the NICS(1) values, they find that the compounds are nonaromatic ylides (resonance structures **9'** and **10'** dominant) for electropositive substituents. However, for electronegative substituents, the compounds are aromatic.



Sastry and co-workers have published a series of papers in which arsenin and many other heterocycles have been investigated using *ab initio* (HF and MP2) and hybrid DFT (B3LYP). Arsenin was found to be more stable than nine of its valence isomers <2002NJC347>. As-Protonated arsenin has a low barrier for out-of-plane distortion <2002JOC271, 2003IAS49>. The NICS(1) values of arsenin (−11.4) and As-protonated arsenin (−11.8) are in the aromatic range <2003JST145>.

Mracec and co-workers have used PM3 semi-empirical molecular orbital (MO) and Hückel molecular orbital (HMO) methods to evaluate the 1,4-cycloaddition reactions of the heterobenzenes with dienophiles <2000RRC1021>. It is felt that these reactions <1972JA7596> are under thermodynamic rather than kinetic control. Mracec and co-workers have found that PM3 calculations give good geometries for **1**, **2**, and **3** <1997RRC319>.

Liebman and co-workers have explored the proton affinity of **7**, **8**, **1**, and **2** using PM3 semi-empirical MO studies <1995JST51>. The experimentally determined proton affinities of **7**, **8**, and **1** drop off relative to those of Me₃N, Me₃P, and Me₃As <1985OM457>. The primary reason for this reduction was found to be the increasing energetic cost of planarization of the EH fragment of C₅H₅EH⁺ combined with decreasing compensation for this cost by the π -orbital overlap of the planar EH fragment with the (CH)₅ moiety. Sb-Protonated stibinin is nonplanar.

7.13.3 Experimental Structural Methods

7.13.3.1 Structures Determined by X-Ray Diffraction

Arsenin **11** has been structurally characterized by X-ray crystallography <1997OM4089>. 2,3,6-Triphenylarsenin **12** had been the only prior arsenin so characterized <1973JCD511>, although the structure of the parent arsenin **1** had been determined in the gas phase using electron diffraction <1975JST65> and microwave spectroscopy <1975JSP428>. Selected structural parameters of **11**, **12**, and **1** are collected in Table 1.

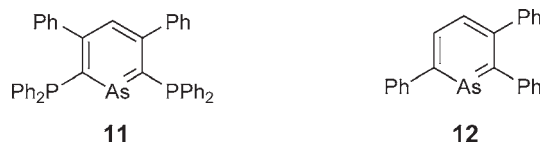
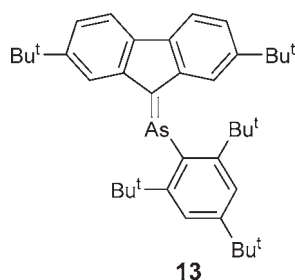


Table 1 Intraring bond distances (Å) of arsenin and arsenin metal complexes

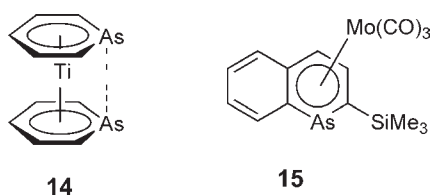
Compound	As–C(2)	C(2)–C(3)	C(3)–C(4)	C(4)–C(5)	C(5)–C(6)	C(6)–As	Reference
1	1.85	1.39	1.40	1.40	1.39	1.85	1975JST65
11	1.87	1.40	1.40	1.40	1.41	1.87	1997OM4089
12	1.88	1.43	1.35	1.40	1.44	1.86	1973JCD511
14 ^a	1.90	1.43	1.45	1.40	1.45	1.89	1999OM1495
15	1.88	1.43	1.40	1.45	1.43	1.93	2001OM2109

^aAverage value for two different molecules in the unit cell.

These structural data are consistent with the aromatic character of the arsenin ring. In particular, the lack of appreciable C–C bond alternation and the multiple bond character of all the ring bonds indicate aromaticity. The C–C bond distances of **11** and **1** differ by no more than 0.01 Å and their mean value of 1.396 Å is identical to that of benzene. The As–C bond distances of **11** (1.87 Å) and **1** (1.85 Å) are shorter than the As–C single bond of trimethylarsine (1.96 Å) <1959SA473> but longer than the congested As–C double bond of **13** (1.79 Å) <1997IC3741>. Clearly the As–C bond length of arsenins indicates a partial multiple bond consistent with a delocalized aromatic structure.



X-Ray structures have also been determined for bis(arsenin)titanium **14** and the Mo(CO)₃ complex of 1-trimethylsilylarsinoline **15**. Selected structural parameters for **14** and **15** are also included in Table 1. In contrast to planar **1**, the arsenin rings of **14** are slightly folded so that the arsenic atoms on opposite rings approach each other in the eclipsed conformations populated in the solid state. The inter-ring As...As distances (3.2–3.4 Å) are below the sum of the van der Waals radii (3.95 Å), suggesting a weak secondary bonding. The intraring As–C and C–C bond distances of **14** are all somewhat longer than the corresponding distances in **1**. This change is consistent with a partial removal of the π -electron density by the metal on complexation.



Compound **15** is the only fused ring arsenin which has been structurally characterized. The molecular structure of **15** shown in Figure 1 is that of a piano-stool arene-metal tricarbonyl. This structure shows that the As–C and C–C bonds to the fused benzo ring are 0.05 Å longer than the corresponding bonds that do not involve the second ring. Similar differentiation of the C–C bonds is found in naphthalene–Cr(CO)₃ <1967HCA1052>, and seems generally to reflect a localization of bonding relative to monocyclic aromatics.

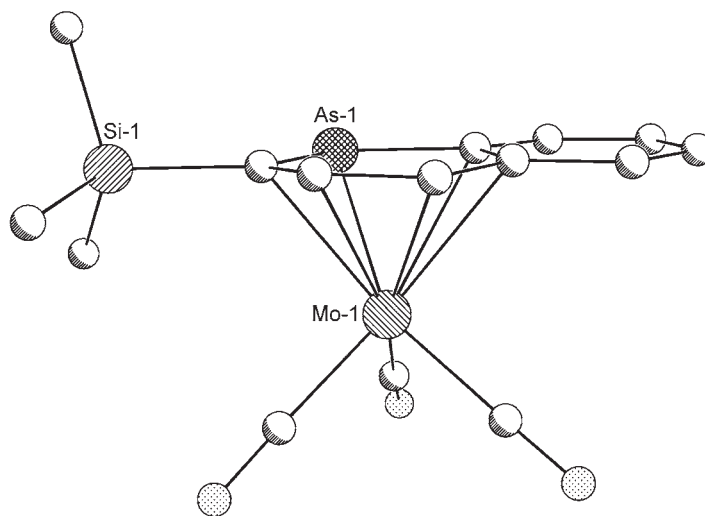
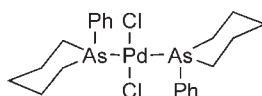


Figure 1 The molecular structure of **15**.

The structure of *trans*-bis(1-phenylarsenane)PdCl₂ **16** has been determined <1999AOM47>. The arsenane rings of **16** adopt a chair conformation which is very similar to that shown by related noncomplexed arsenanes <1996CHEC-II(5)671>.

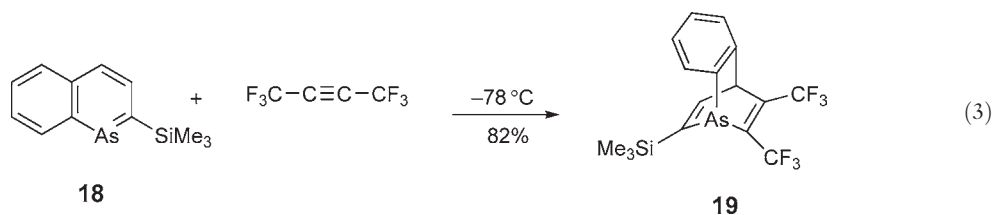
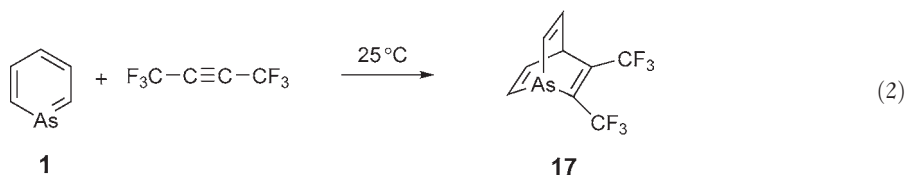


16

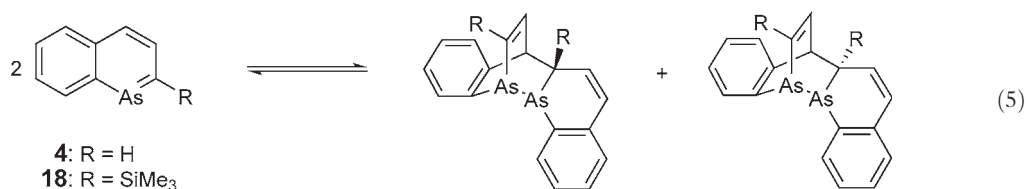
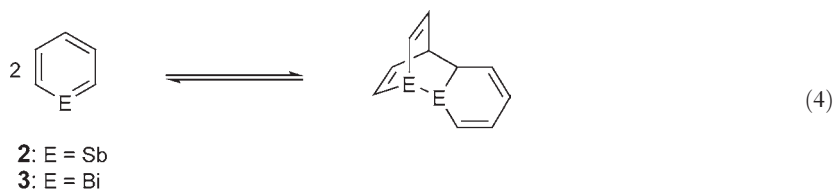
7.13.4 Reactions of Arsenins

7.13.4.1 Cycloaddition Reactions

Arsenins, stibinins, and bismins react with dienophiles in the Diels-Alder reaction [<1996CHEC-II\(5\)675>](#). The reactions usually occur 1,4 with respect to the heterobenzene, which behaves as a diene. Arsenin reacts with hexafluorobutyne at 25 °C to give arsabarrelene **17** (Equation 2) [<1972JA7596>](#). On the other hand, 2-trimethylsilylarsinoline **18** reacts with the same dienophile at –78 °C to give adduct **19** (Equation 3) [<2000TH1>](#). As in the carbocyclic series, a higher reactivity of the fused ring aromatic is consistent with a smaller loss of resonance stabilization for the starting material.

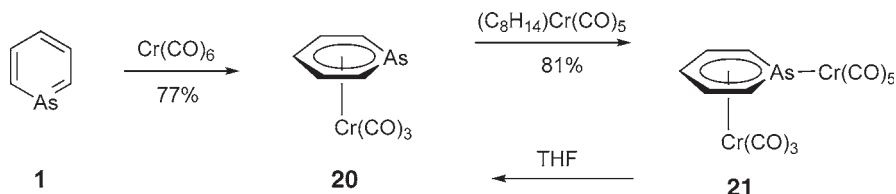


Stibinin **2** and bismin **3** are more reactive dienes than arsenin in the Diels-Alder reaction. In fact they are so reactive that they are in equilibrium with their dimers at low temperature (Equation 4) [<1982JA5693>](#). No dimerization could be detected for arsenin. However, both arsinoline **4** and 2-trimethylsilylarsinoline **18** form dimers (Equation 5) [<2001OM2109>](#). Because of the lower symmetry of **4** and **18**, there are *exo*- and *endo*-isomers for the dimers.



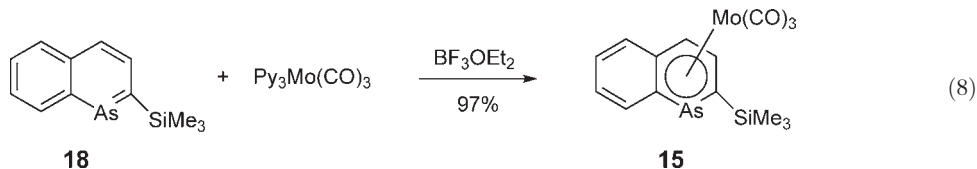
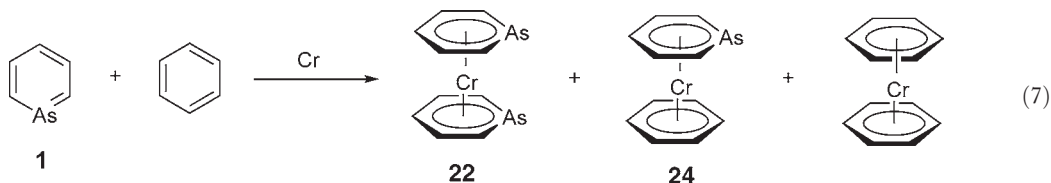
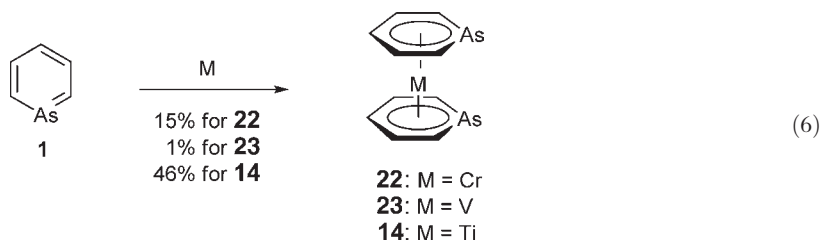
7.13.4.2 Reactions with Transition Metals

The coordination chemistry of arseninins and stibinins has been reviewed [<2005AHC126>](#). Arsenin is a rather good six-electron π -ligand and a rather weak two-electron σ -ligand toward transition metals [<1996CHEC-II\(5\)676>](#). When arsenin is heated to 100 °C with $\text{Cr}(\text{CO})_6$, it forms the $\text{Cr}(\text{CO})_3$ complex **20** in good yield [<1999OM1495>](#). Treating **20** with $(\eta^2\text{-cyclooctene})\text{Cr}(\text{CO})_5$ in hexane gives the labile mixed π,σ -complex **21**. However, when **21** is exposed to tetrahydrofuran (THF), it re-forms **20** ([Scheme 1](#)).



Scheme 1

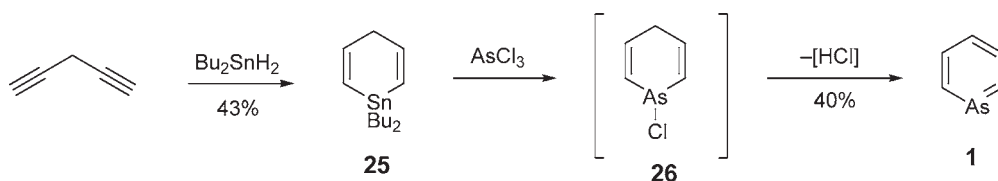
Arsenin will form bis-sandwich complexes **22**, **23**, and **14** when it is condensed with vapors of the metals Cr, V, and Ti, respectively ([Equation 6](#)). When Cr is condensed with arsenin and a 25-fold excess of benzene, it forms **22**, the mixed arsenin/benzene sandwich **24**, and bis(benzene)chromium in the ratio of 6:3:1 ([Equation 7](#)) [<1999OM1495>](#). Clearly arsenin complex formation is favored over the benzene complexes even when the benzene is in large excess. Another example of the preference for π -complexation of an arsenin ring versus a benzocyclic ring is shown in [Equation \(8\)](#). The reaction of **18** with $(\text{Py})_3\text{Mo}(\text{CO})_3$ gives exclusively **15**. No product with metal complexation to the benzocyclic ring was detected [<2001OM2109>](#).



7.13.5 Syntheses of Arsenins

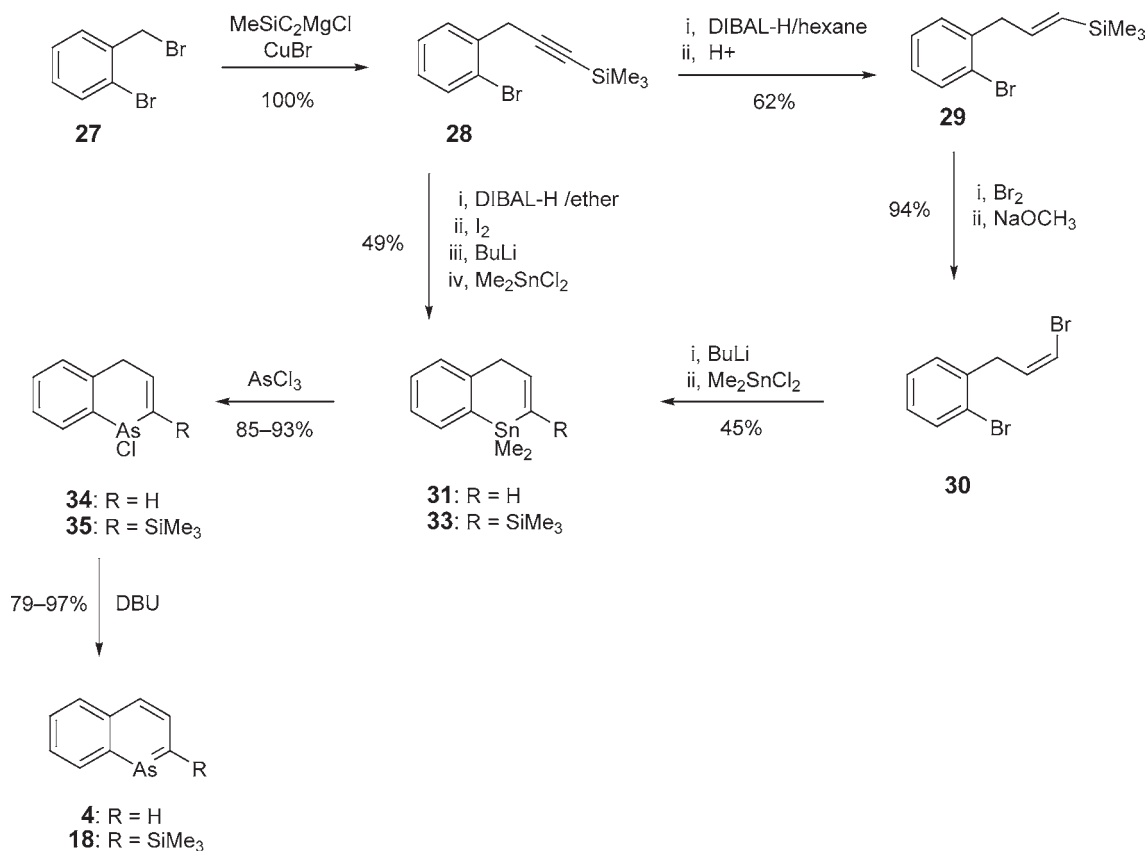
7.13.5.1 Arsinolines

The most important synthesis of arsenins remains the originally reported synthesis of the parent compound illustrated in [Scheme 2](#) [<1971JA3293, 1979JOC1409>](#). The key feature of the synthesis is the tin/arsenic exchange of stannacyclohexadiene **25** to produce the 1-chloro-1-arsa-1,4-cyclohexadiene **26**, which loses HCl on gentle heating to form **1**. The synthesis has been modified to prepare various 2- and 4-substituted arsenins [<1996CHEC-II\(5\)681>](#).



Scheme 2

A new related synthesis of arsinolines **4** and **18** from the corresponding 1,4-dihydro-1.1-dimethyl-1-benzostannins **34** and **35** has been reported [<2001OM2109>](#). The benzostannins have been prepared by a long but high-yield route outlined in [Scheme 3 <1999OM466>](#). The CuBr-catalyzed coupling of trimethylsilylacetylenemagnesium chloride with commercially available **27** afforded **28**. The DIBAL-H reduction of **28** in hexane followed by hydrolysis gave **29**, which on treatment with bromine followed by NaOMe afforded the substitution/inversion product **30**. Lithiation of **30** followed by reaction with Me_2SnCl_2 gave benzostannin **31**. The above route could be modified by quenching the DIBAL-H reduction of **28** with iodine to give an iodovinyl silane **32**, which on lithiation followed by reaction with Me_2SnCl_2 afforded **33**.

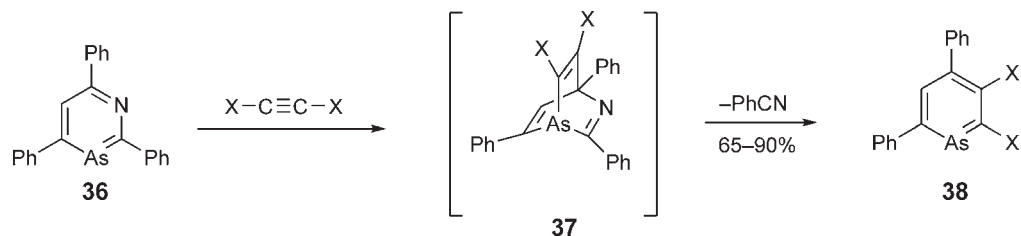


Scheme 3

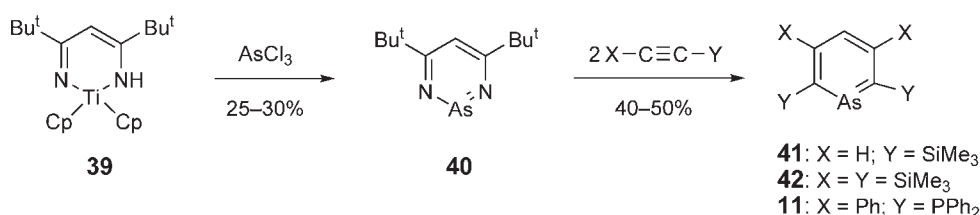
7.13.5.2 Substituted Arsenins

It had previously been shown that 2,4,6-triphenyl-1,3-azaarsenin **36** could be converted to highly substituted arsenins **38** via a reaction with dienophiles followed by Alder–Rickert cleavage of the intermediate adduct as illustrated in

Scheme 4 <1996CHEC-II(5)683>. It has now been found that 1,3,2-diazaarsenin **40** undergoes a similar reaction with 2 mol of alkynes to give substituted arsenin **41**, **42**, and **11** (**Scheme 5**) <1997OM4089>. This method seems particularly useful since **40** can be easily prepared from the readily available titanium heterocycle **39** <1988JA7239>.



Scheme 4



Scheme 5

7.13.6 Further Developments

Recently Fernandez and Frenking have performed calculations at the BP86/TZ2P level on the complete family of group 15 element heterobenzenes **1**, **2**, **3**, **7**, and **8** <2007FD403>. The calculations have allowed them to perform an energy decomposition analysis (EDA) which has been used to estimate the strength of π -bonding in the series. The aromatic stabilization was found to be substantial for all members of the series but declined in the order of $7 > 8 > 1 > 2 > 3$.

Su has published a high order computational study of the photoisomerization of arsenin to possible Dewar-type valence isomers <2007JPC971>. The reaction has yet to be observed experimentally.

References

- 1959SA473 D. R. Lide, Jr., *Spectrochim. Acta*, 1959, **15**, 473.
 1967HCA1052 V. Kunz and W. Nowacki, *Helv. Chim. Acta*, 1967, **50**, 1052.
 1971JA3293 A. J. Ashe, III, *J. Am. Chem. Soc.*, 1971, **93**, 3293.
 1972JA7596 A. J. Ashe, III, and M. D. Gordon, *J. Am. Chem. Soc.*, 1972, **94**, 7596.
 1973JCD511 F. Sanz and J. J. Daly, *J. Chem. Soc., Dalton Trans.*, 1973, 511.
 1975JSP428 R. P. Lattimer, R. L. Kuczkowski, A. J. Ashe, III, and A. L. Meinzer, *J. Mol. Spectrosc.*, 1975, **57**, 428.
 1975JST65 T. C. Wong, A. J. Ashe, III, and L. S. Bartell, *J. Mol. Struct.*, 1975, **25**, 65.
 1979JOC1409 A. J. Ashe, III, and W.-T. Chan, *J. Org. Chem.*, 1979, **44**, 1409.
 1982JA5693 A. J. Ashe, III, T. R. Diephouse, and M. Y. El-Sheikh, *J. Am. Chem. Soc.*, 1982, **104**, 5693.
 1984CHEC-I(1)539 R. E. Atkinson; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1996, vol. 1, p. 539.
 1985OM457 R. V. Hodges, J. L. Beauchamp, A. J. Ashe, III, and W.-T. Chan, *Organometallics*, 1985, **4**, 457.
 1988JA7239 K. M. Doxsee and J. B. Farahi, *J. Am. Chem. Soc.*, 1988, **110**, 7239.
 1995JST51 D. J. Berger, P. P. Gaspar, and J. F. Liebman, *J. Mol. Struct.*, 1995, **338**, 51.
 1995MI1 M. J. Frisch, *et al.*, 'Gaussian 94', Gaussian, Inc., Pittsburgh, PA, 1995.
 1996CHEC-II(5)669 J. A. Ashe, III; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 669.
 1996CHEC-II(5)671 J. A. Ashe, III; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 671.

- 1996CHEC-II(5)675 J. A. Ashe, III; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 675.
- 1996CHEC-II(5)676 J. A. Ashe, III; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 676.
- 1996CHEC-II(5)681 J. A. Ashe, III; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 681.
- 1996CHEC-II(5)683 J. A. Ashe, III; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 5, p. 683.
- 1996JA6317 P. v. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao, and, and N. J. R. v. E. Hommes, *J. Am. Chem. Soc.*, 1996, **118**, 6317.
- 1997IC3741 A. Denken, C. J. Carmalt, J. A. C. Clyburne, and A. H. Cowley, *Inorg. Chem.*, 1997, **36**, 3741.
- 1997OM4089 N. Avarvari, P. Le Floch, L. Ricard, and F. Mathey, *Organometallics*, 1997, **16**, 4089.
- 1997RRC319 M. Mracec, M. Mracec, and L. Kurunczi, *Rev. Roum. Chim.*, 1997, **42**, 319.
- 1998MI1 M. J. Frisch, *et al.*, 'Gaussian 98', Gaussian Inc., Pittsburgh, PA, 1998.
- 1999AOM47 S. S. Garje, V. K. Jain, and B. Varghese, *Appl. Organomet. Chem.*, 1999, **13**, 47.
- 1999OM466 A. J. Ashe, III, X. Fang, and J. W. Kampf, *Organometallics*, 1999, **18**, 466.
- 1999OM1495 C. Elschenbroich, J. Kroker, M. Nowotny, A. Behrendt, B. Metz, and K. Harms, *Organometallics*, 1999, **18**, 1495.
- B-2000MI43 A. R. Katritzky and A. F. Pozharskii; 'Handbook of Heterocyclic Chemistry', 2nd edn., A. R. Katritzky and A. F. Pozharskii, Eds.; Pergamon, Oxford, 2000, pp. 43.
- 2000TH1 X. Fang, Ph.D. dissertation, University of Michigan, 2000 (*Chem. Abstr.*, 2000, **136**, 247620.).
- 2000RRC1021 M. Mracec, M. Mracec, and Z. Simon, *Rev. Roum. Chim.*, 2000, **45**, 1021.
- 2001HCA1578 Z.-X. Wang and P. v. R. Schleyer, *Helv. Chim. Acta*, 2001, **84**, 1578.
- 2001OL2465 P. v. R. Schleyer, M. Manoharan, Z.-X. Wang, B. Kiran, H. Jiao, R. Puchta, and N. J. R. v. E. Hommes, *Org. Lett.*, 2001, **3**, 2465.
- 2001OM2109 A. J. Ashe, III, X. Fang, and J. W. Kampf, *Organometallics*, 2001, **20**, 2109.
- 2002JOC271 U. D. Priyakumar and G. N. Sastry, *J. Org. Chem.*, 2002, **67**, 271.
- 2002NJC347 U. D. Priyakumar, T. C. Dinadayalane, and G. N. Sastry, *New J. Chem.*, 2002, **26**, 347.
- 2003IAS49 U. D. Priyakumar and G. N. Sastry, *Proc. Indian Acad. Sci.*, 2003, **115**, 49.
- 2003JST145 A. Saieswari, U. D. Priyakumar, and G. N. Sastry, *J. Mol. Struct.*, 2003, **663**, 145.
- 2003JST141 J. Klocker, A. Karpfen, and P. Wolschann, *J. Mol. Struct.*, 2003, **635**, 141.
- 2004JST125 R. Salcedo, *J. Mol. Struct.*, 2004, **674**, 125.
- 2005AHC126 A. D. Sadimenko, *Adv. Heterocycl. Chem.*, 2005, **89**, 126.
- 2005JOM4761 R. Ghiasi, *J. Organomet. Chem.*, 2005, **690**, 4761.
- 2005PCA9118 D. S. Shobe, *J. Phys. Chem A*, 2005, **109**, 9118.
- 2007FD403 I. Fernandez and G. Frenking, *Faraday Discuss.*, 2007, **135**, 403.
- 2007JPC971 M.-D. Su, *J. Phys. Chem. A*, 2007, **111**, 971.

Biographical Sketch



Arthur J. Ashe, III, is a professor of chemistry and professor of macromolecular science and engineering at the University of Michigan, Ann Arbor. In 1962, he received a B.A. in chemistry from Yale University, where he did a senior project with William Doering. He then spent a year on a Henry Ford Fellowship at Cambridge University where he worked in the laboratory of F. G. Mann. After returning to Yale as an NSF Graduate Fellow, he received his Ph.D. in organic chemistry under the supervision of Kenneth B. Wiberg.

In 1966, Ashe joined the faculty of the Chemistry Department of the University of Michigan, where he remains. He was chairman of the department during a crucial period of planning for a new chemistry building. He has been a Fellow of the AP Sloan Foundation. Ashe has supervised the research work of more than 30 doctoral and postdoctoral fellows as well as many undergraduates. He has published 150 scientific publications, most of which are in the area of heterocycles of boron and group 15 elements.

7.14

Six-membered Rings with One Other Element

P. Norris

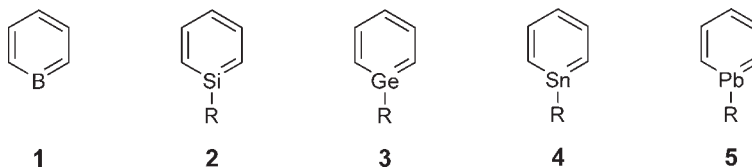
Youngstown State University, Youngstown, OH, USA

© 2008 Elsevier Ltd. All rights reserved.

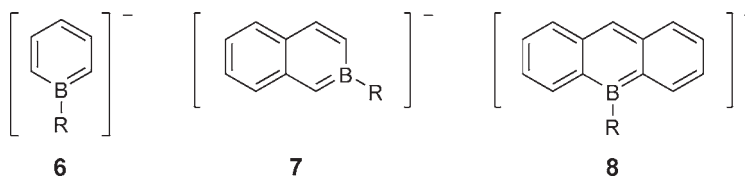
7.14.1	Introduction	1049
7.14.2	Theoretical Methods	1049
7.14.3	Experimental Structural Methods	1051
7.14.4	Thermodynamic Aspects	1055
7.14.5	Reactivity of Fully Conjugated Rings	1056
7.14.6	Reactivity of Nonconjugated Rings	1058
7.14.7	Ring Synthesis	1060
7.14.8	Further Developments	1062
References		1063

7.14.1 Introduction

The fully conjugated heteroaromatic analogs of benzene to be treated in this chapter are borabenzene **1**, silabenzene **2**, germabenzene **3**, stannabenzene **4**, plumbabenzene **5**, and their higher analogs such as heteronaphthalenes and heteroanthracenes. There has been significant growth in theoretical studies on these systems, mainly into their aromatic character and application in the doping of fullerene-type materials; however, the synthetic work from the period covered is centered mainly on B- and Si-derivatives, with Ge- and Sn-based compounds featuring to a lesser extent and Pb-containing compounds not at all. Nonaromatic, reduced forms of these systems will be discussed mainly as precursors to the heteroaromatic compounds.



The use of such heterobenzenes as ligands in organometallic complexes has been studied extensively as they are considered to be isoelectronic with the cyclopentadienyl anion. The trivalent boron-containing analogs differ from the other compounds considered here in that the tetravalent species are anionic, namely the boratabenzenes, 2-boratanaphthalenes, and 9-borataanthracenes, etc., as exemplified by **6**, **7**, and **8**. The employment of ligands containing B, Si, and Ge as pyridine analogs in organometallic complexes has been reviewed [<2005AHC125>](#), and the chemistry of the bora- and boratabenzenes in the period 1986–2000 has been discussed in detail [<2001AOC101>](#).

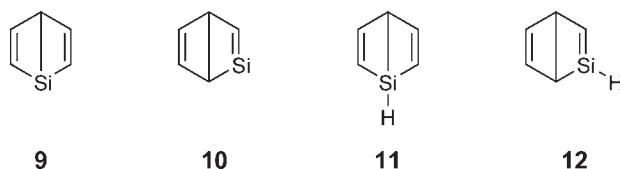


7.14.2 Theoretical Methods

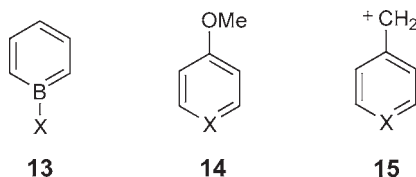
The extent to which these heterobenzenes are actually aromatic has been the topic of extensive computational work; spin-coupled valence bond theory suggesting that borabenzene has an aromatic sextet [<1997IJQ441>](#), and hybrid

density functional theory (DFT) studies (B3LYP/6-31G^{*}) propose that the most stable forms of the rings in model examples of boratabenzene, silabenzene, and germabenzene are actually planar <2002JOC271>. Similar DFT work by Ghiasi and Monnajemi on Si-containing analogs of indene and naphthalene, along with consideration of magnetic criteria (magnetic isotropic and anisotropic susceptibilities), provides evidence for aromaticity within the sila-substituted ring(s) <2006JKC281, 2005JST(718)225>. Higher levels of theory (e.g., CCSD(T)/cc-pVTZ) have been used to study the electronic structure and properties of a series of silabenzenes and compared with results from DFT methods (B3LYP/cc-pVTZ) <2000OM1477>, and Sastry and co-workers have applied DFT methods to polyaromatic systems containing silicon in order to gauge the effect of the heteroatom position on aromaticity. It was found that having Si in the outer rings stabilizes the systems versus examples with the Si-atom central and at the junction of two rings <2003JOC1168>.

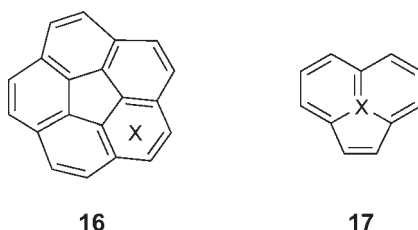
Detailed studies on potential valence isomers of silabenzene using *ab initio* and DFT methods <2002OM1493, 2003PS869> lead to the conclusion that the six-membered ring isomer is only 20 kcal mol⁻¹ more stable than one of the possible benzvalene isomers; benzene itself is seen to be about 70 kcal mol⁻¹ more stable than any of its possible valence isomers. Several groups have investigated the relative stabilities and properties of silabenzene Dewar-type isomers; the symmetrical isomer **9** is found to be more stable by almost 30 kcal mol⁻¹ than the unsymmetrical isomer **10** by *ab initio* methods <2003PS869>. Calculations on theoretical electrocyclic ring-opening reactions of Dewar silabenzenes such as **11** and **12** led to the conclusion that the *trans*-isomer of **12** is capable of existing and would be around 130 kcal mol⁻¹ higher in energy than silabenzene itself <2003OM5454>. B3LYP/6-31G^{*} studies on the dimerization of silabenzene versus the P-analog (phosphabenzene) show the former process to be exothermic by 21.5 kcal mol⁻¹, while the latter is endothermic by 32.6 kcal mol⁻¹ <2000OM2208>; this correlates well with the known instability of silabenzenes, which dimerize even at low temperatures, compared to phosphabenzenes. Further DFT work has probed the stabilization/destabilization effects of bulky groups <2002JST(618)173>, as well as electron-donating substituents <2003OM5556>, on silabenzene and its valence isomers.



Structures and dipole moments of borabenzene adducts (and also the corresponding pentafluoroborabenzenes) with N₂ (**13**: X=N₂) and Xe (**13**: X=Xe) have been calculated using DFT methods <2006RJC580>; it was concluded that a Kr-analog of these compounds (**13**: X=Kr) would not be formed. MP2 and DFT calculations on 4-methoxy sila- and germabenzenes **14** (X=Si, Ge) reveal the minimum energy conformation in each about the C(4)–O bond to be the same as for anisole, that is, having the methoxy group coplanar with the aromatic ring <2003JST(635)141>. Assessing the relative energies of different contributors to the overall structure of carbocations such as **15** (X=C, Si, or Ge) by *ab initio* methods leads to the conclusion that for **15** (X=C) the tropylium ion is the global minimum, the benzylic cation (i.e., **15**) is slightly higher in energy, and nonclassical isomers are much higher in energy. Substitution with Ge (**15**: X=Ge) reverses this preference and nonclassical structures are actually the minima; for **15** (X=Si), the situation is intermediate between the other two <1997JA11933>.



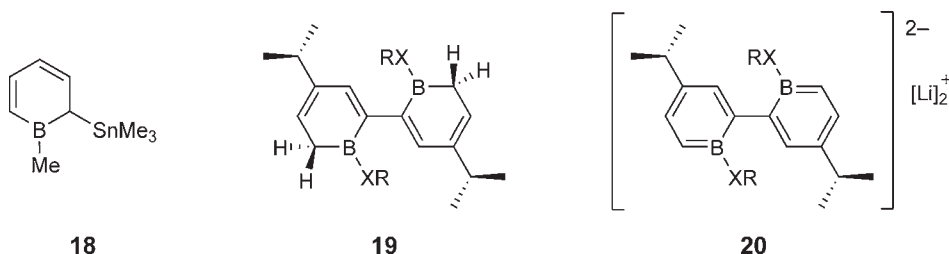
With the continuing general interest in the chemistry and properties of fullerene-type materials, there has been a large number of theoretical studies on such compounds that have at least one carbon atom of the parent system replaced by B, Si, Ge, or Sn. The corannulene-based ‘bucky-bowls’ (**16**: X=B or Si) have been studied by *ab initio* and DFT methods with the heteroatom serving to alter the curvature and rigidity of the bowls relative to the parent (**16**: X=C); the substituents also significantly raise the barrier to bowl-to-bowl inter-conversion compared with the parent corannulene <2006JST(771)141, 2001J(P2)30, 2000CC843>. The application of *ab initio* and DFT methods to C₅₉X (X=Si, Ge, Sn) and C₅₉X⁻ (X=B) based on the fragment (**17**: X=B, Si, Ge, Sn) show little distortion for X=B compared to C₆₀ itself but significant alteration in shape for the other analogs <2005IJQ429>.



7.14.3 Experimental Structural Methods

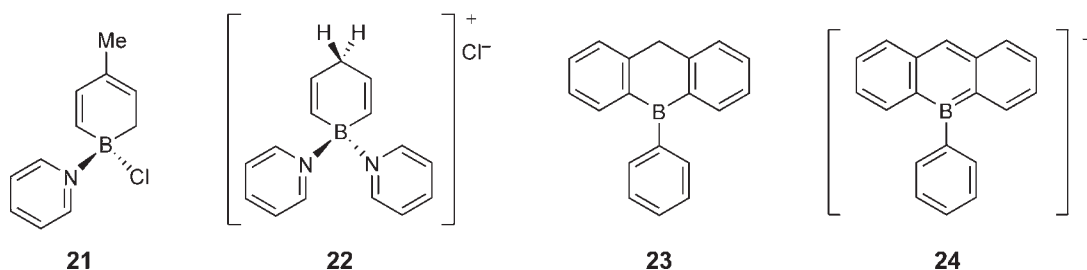
Nuclear magnetic resonance (NMR) spectroscopy has been applied to the structural characterization of many heterobenzene analogs although the most important and widely used tool is X-ray diffraction, which will be the main topic of discussion here. This section will begin with examples of structural methods applied to mainly noncoordinated heteroaromatics to detail ring geometries and progress through each element (B, Si, Ge, Sn) sequentially. The extensive recent application of the featured heterobenzene analogs as ligands in transition metal chemistry is beyond the scope of this chapter; however, X-ray structural studies on such compounds provide useful information about the ligand geometries. Selected examples of organometallic complexes are therefore collected in [Figure 1](#).

Reaction of lithium(1-methylboratabenzene) with Me_3SnCl (see [Section 7.14.5](#)) gives 1-methyl-2-(trimethylstannyl)-1,2-dihydroborinine **18** as a low melting solid (m.p. = -10°C) which crystallizes from pentane. The X-ray structure of **18** shows that the single C(2)–Sn bond is somewhat longer than the Sn–CH₃ bonds and that the heteroaromatic ring is essentially planar [<1997OM926>](#). Similarly, the 1,2-dihydro rings in **19** (XR = NPh or OBn) are planar despite the presence of the sp^3 C-atom in each. These compounds serve as precursors to the boratabenzene biphenyl analogs **20** (XR = NPh or OBn) (see [Section 7.14.6](#)), both of which crystallize as dimers about the lithium ions and have planar heteroaromatic rings [<2006CJC81>](#). The ^{11}B NMR spectra of **19** versus **20** show an upfield shift for the latter, for example from ~ 48 ppm in **19** (XR = OBn) to ~ 31 ppm in **20** (XR = OBn), which is consistent with delocalized negative charge in the boratabenzene rings.



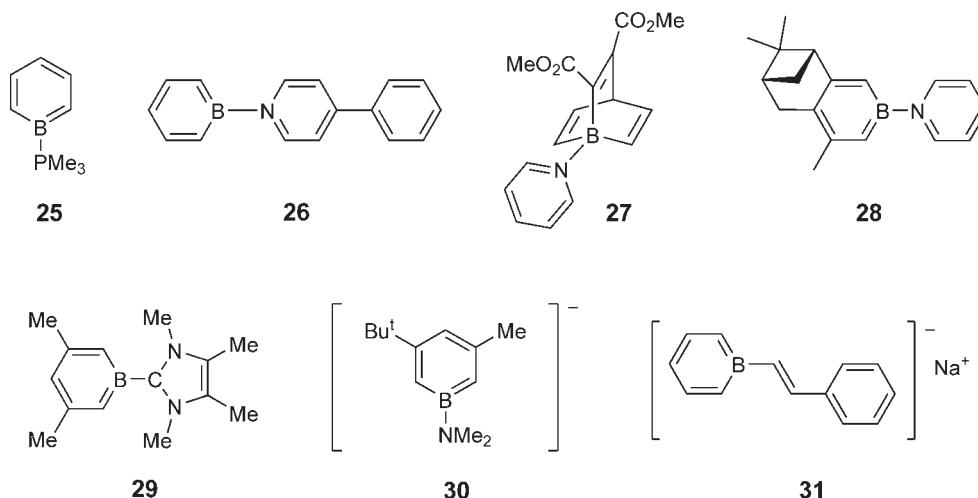
In studies to produce cyclic boronium and borenium cations, **21** crystallizes in the $P2_12_12_1$ space group as orthorhombic crystals in which the 1,2-dihydroborinine is again essentially flat; the B-atom is $0.12\text{ \AA}$ above the plane of the rest of the ring [<2005CC2480>](#). Crystals of the related cationic 2,5-cyclohexadiene analog **22**, which are monoclinic and belong to the $P2_1/n$ space group, also feature a planar boracyclohexadiene ring and bond lengths within the ring support a localized π system [<2005CC2480>](#).

The X-ray crystal structure of 9-phenyl-9,10-dihydro-9-borataanthracene **23** shows a planar system in the dihydroanthracenyl portion of the molecule with the 9-phenyl ring skewed at $\sim 62^\circ$, which precludes overlap between the phenyl substituent and the boron atom [<1998JA6037>](#). Deprotonation of precursor **23** with lithium 2,2,6,6-tetramethylpiperidine serves to produce the lithium salt of 9-phenyl-9-borataanthracene **24**, the tetramethylethylenediamine (TMEDA) chelate of which crystallizes as yellow needles. When compared to **23**, the X-ray structure of **24** shows shorter bonds within the central boratabenzene ring, thereby supporting the ring's aromatic character, but bond lengths in the outer rings suggest that they have more localized character [<1998JA6037>](#).



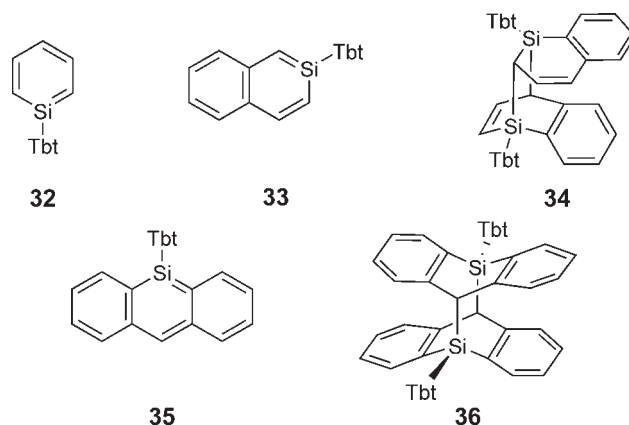
Borabenzene analogs coordinated at B have been of significant interest since the earlier reports of a neutral borabenzene–pyridine adduct [<1985CB1644>](#) and several related compounds such as phosphine adduct [25](#) [<1996OM1315>](#) (see [Section 7.14.6](#)). The X-ray crystal structure of [25](#) reveals the borabenzene to be essentially flat although somewhat distorted compared to benzene. The 4-phenylpyridine adduct [26](#) forms monoclinic crystals, belonging to the $P2_1/c$ space group, the structure of which shows the borabenzene ring to be planar and to be almost coplanar with the phenyl ring [<1997OM1501>](#); the dihedral angle between the borabenzene and pyridinyl rings is 49° , which correlates well with the 43° angle seen in the related borabenzene–pyridine analog [<1985CB1644>](#). The Diels–Alder reaction between the borabenzene–pyridine adduct and dimethyl acetylenedicarboxylate represents an entry into 1-borabarrelene structures such as [27](#) [<2006OL2875>](#) (see [Section 7.14.5](#)). The X-ray crystal structure of [27](#) shows the B-atom adopting an approximately pyramidal geometry and the B–N bond distance to be $1.584 \text{ \AA}$, which is shorter than in any of the other examples in borane–pyridine adducts recorded to date. The chiral borabenzene–pyridine adduct [28](#), derived from (–)- α -pinene, forms orthorhombic crystals that belong to the $P2_12_12_1$ space group and shows a planar borabenzene ring [<1999OM3406>](#); the interplanar angle between the two aromatic rings is considerably smaller at 35° than those seen in related examples [<1985CB1644, 1997OM1501>](#).

Closely related to a borabenzene–isocyanide adduct first reported by Fu and co-workers [<1996OM1315>](#), the carbene–borabenzene complex [29](#) affords monoclinic crystals in the $P2_1/c$ space group, the X-ray structure of which shows that the two rings are planar and at an angle of $\sim 35^\circ$ to each other [<2000OM3751>](#). An inter-ring C–B bond length of $1.59 \text{ \AA}$ indicates a different bonding situation to that observed when the ligand is, for example, PMe_3 [<1996OM1315>](#) or pyridine [<1985CB1644>](#), and that the boraheterocyclic portion of [29](#) more closely resembles the anionic boratabenzene structure. The boratabenzene adduct [30](#) crystallizes as the Li-(TMEDA) salt in triclinic form, the X-ray structure revealing a planar heterocyclic ring with a B–N bond length of $1.45 \text{ \AA}$ [<1996OM2707>](#). Bazan and co-workers have reported a series of compounds related to stilbene and studied their structures and photophysical properties. The sodium salt of boratastilbene [31](#) crystallizes from ether–benzene at low temperature and shows structural parameters for the boratabenzene ring that are in close agreement with previous values [<2000JA3969>](#). The same workers have also described the related, highly conjugated 4-boratastyrylstilbene and 1,4-bis(boratastyryl)benzene, the X-ray crystal structure of the latter having similar structural parameters to [31](#) about the boratabenzene portions of the molecule [<2000JA8577>](#).



Isolation of silabenzenes had proven an elusive goal; however, the employment of the bulky 2-(2,4,6-tris[bis(trimethylsilyl)methyl]phenyl) (Tbt) group by Tokitoh *et al.* has allowed for the analysis of [32](#) by X-ray diffraction

performed at -180°C <2001PS31, 2000JA5648>; the silabenzene portion of the molecule proved to be planar and evidence for aromaticity was provided from ^1H NMR and ultraviolet (UV) data. Tokitoh has also used the Tbt group to produce the related kinetically stabilized 2-silanaphthalene **33** <2000BCJ2157>, which proved to be unreactive even upon heating at 120°C in C_6D_6 . In stark contrast, the 1-silanaphthalene analog, while stable but moisture sensitive in the solid state, is quite unstable in solution and dimerizes in C_6D_6 to give **34** <2005BCJ977, 2002OM4024>, crystals of which are triclinic. Crystals of the 1-Tbt-substituted 1-silanaphthalene were unsuitable for diffraction; however, spectral data were sufficient to conclude that the 1-silanaphthalene system is aromatic, showing for example a signal at 91.7 ppm in the ^{29}Si NMR spectrum, which indicates an sp^2 -hybridized silicon <2002OM4024>. Tokitoh and co-workers have also reported the kinetically stabilized Tbt-blocked 9-silaanthracene **35**, which forms triclinic crystals belonging to the $P_{\bar{1}}$ space group <2002OM256>. The X-ray crystal structure of **35** shows the silaanthracene system to be completely planar and evidence from ^1H , ^{13}C , and ^{29}NMR , for example the signal at 87.2 ppm indicating sp^2 -hybridized Si, all point to aromaticity. Heating a C_6D_6 solution of **35** in a sealed tube at 110°C , or as a solid to 180°C , caused dimerization resulting in the [4+4] adduct **36**, the colorless crystals of which are monoclinic and occupy space group $P2_1/c$ <2003JA10804>. The X-ray crystal structure of **36** confirmed the head-to-tail mode of dimerization and this compound is thermally stable, undergoing no cycloreversion upon heating up to 200°C in solution.



Tokitoh and co-workers have been successful in isolating and characterizing the kinetically stabilized germabenzene **37**, which is moisture sensitive but thermally stable (m.p. $118\text{--}122^{\circ}\text{C}$) <2002JA6914>. In the ^1H NMR spectrum of **37**, the signals for the heterocyclic ring appear in the region 6.72–8.06 ppm and the corresponding ^{13}C signals in the region 114–141 ppm, providing evidence for aromaticity. The compound forms orthorhombic crystals belonging to the $Pna2_1$ space group and the X-ray crystal structure shows an essentially planar heterocyclic ring thus providing evidence for its aromatic character <2002JA6914>. Reaction of germabenzene **37** with elemental sulfur (see Section 7.14.5) resulted in two 1,2-addition products **38** and **39**, both of which proved amenable to characterization by X-ray diffraction <2003JOM(672)66>.

The first stable heteroaromatic germanium compound actually isolated was the 2-germanaphthalene **40** <2003OM481>, the X-ray crystal structure of which shows the heterocyclic system to be planar with the phenyl ring of the Tbt substituent almost perpendicular to the germanaphthalene. ^1H and ^{13}C NMR chemical shifts, as well as ultraviolet–visible (UV–vis) and Raman data, lead to the conclusion that the 2-germanaphthalene structure has aromatic character. The synthesis and structures of the 9-germaanthracene **41** and the 9-germaphenanthrene **42** have been reported more recently <2006OM3533>. ^1H and ^{13}C NMR data all point to these systems being aromatic and the X-ray crystal structures of both **41** and **42** show that the heteroaromatic systems are planar. The angles between the germaanthracene and germaphenanthrene rings and the phenyl ring of the Tbt groups are 87° and 86° , respectively, thereby indicating the lack of conjugation in each case.

Use of the Tbt group has also resulted in the successful isolation of the elusive 2-stannanaphthalene system, that is, **43**, which is quite stable in the solid state and in solution <2006JA1050>. X-Ray diffraction studies on **43** reveal an essentially planar aromatic ring system with a completely trigonal planar arrangement about the Sn-atom.

Many transition metal complexes utilizing the heteroaromatic systems of interest as ligands have been reported over the period of interest, mainly featuring derivatives of the borabenzene system. Notable examples of such compounds that have yielded to analysis by X-ray diffraction are collected in Figure 1 beginning with borabenzene derivatives and progressing through silabenzene and germabenzene examples. Within the borabenzene examples highlighted here, the organization is based on the element directly attached at the B-atom of the heterocyclic ring beginning with C, then N, O, etc.

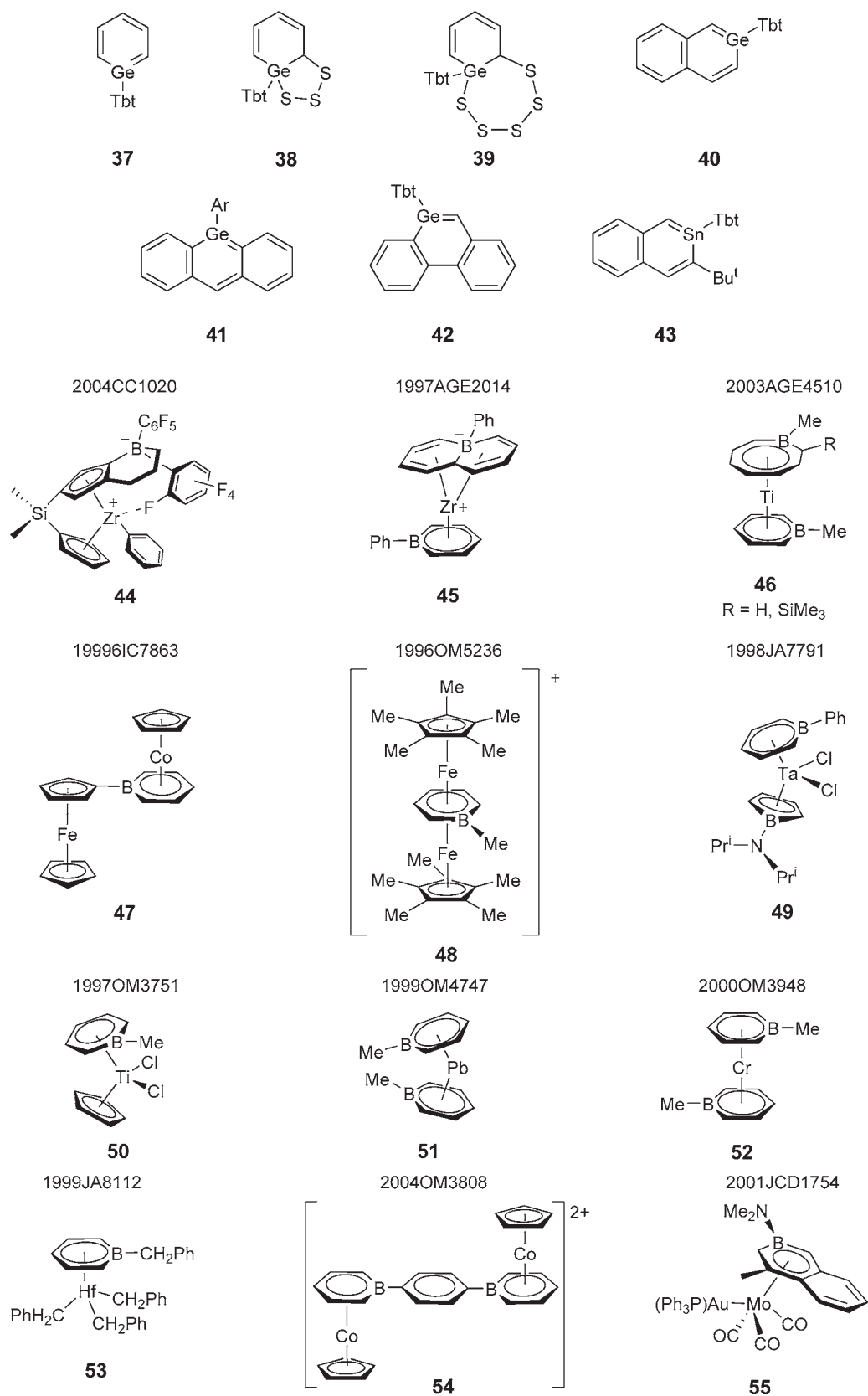


Figure 1 (Continued)

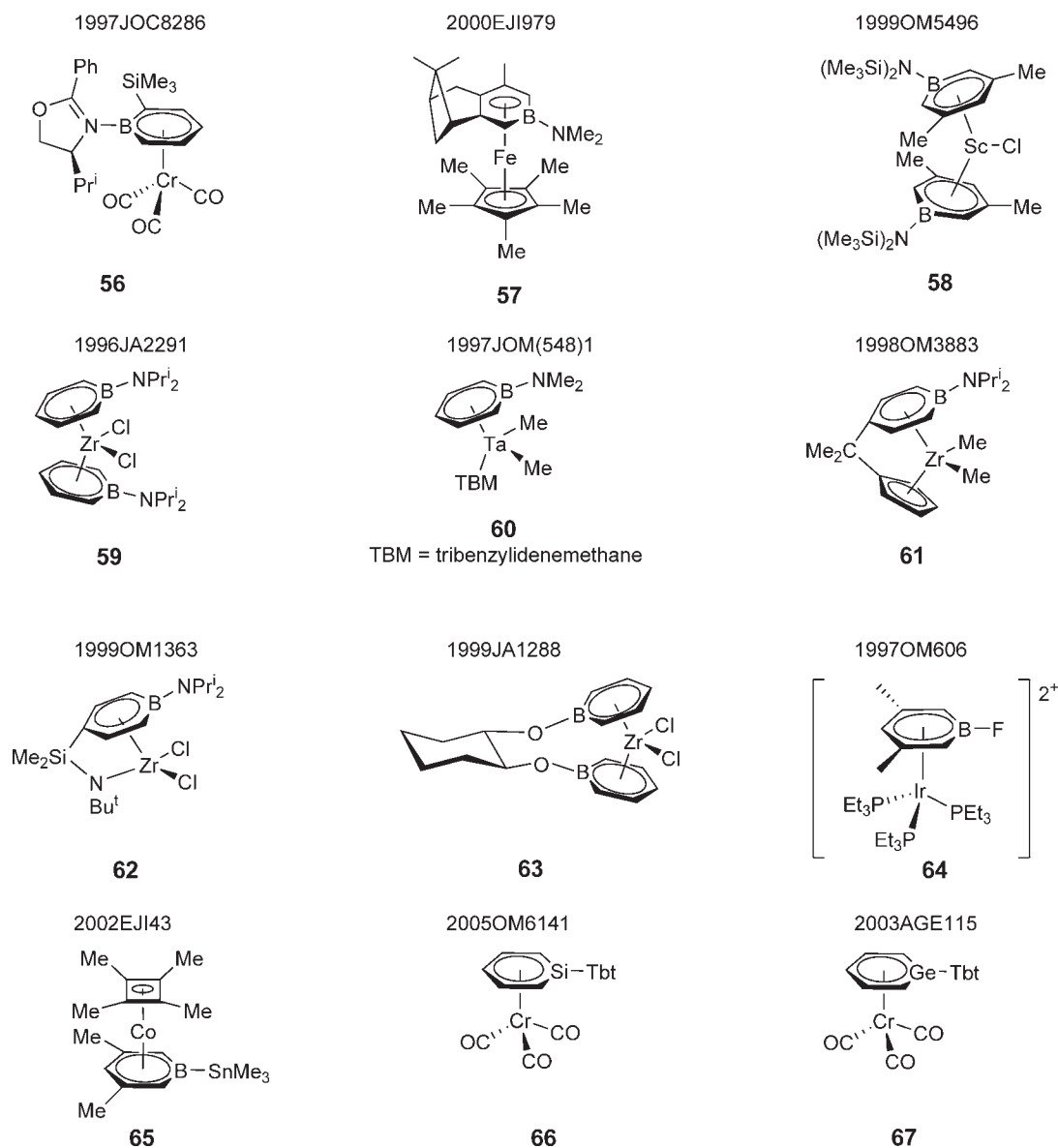


Figure 1 Transition metal complexes containing six-membered ring ligands with B, Si, Ge.

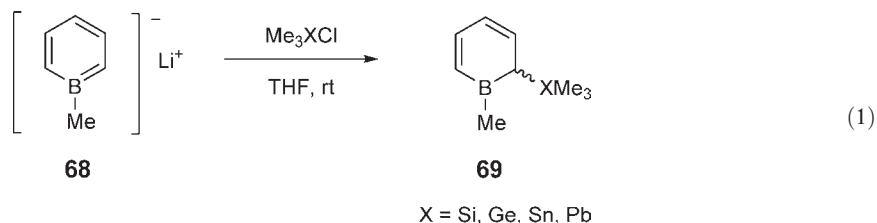
7.14.4 Thermodynamic Aspects

The aromatic stabilization of the heteroaromatic systems detailed here has been probed extensively by theoretical methods (see Section 7.14.2) and experimental structural methods, particularly X-ray diffraction (see Section 7.14.3).

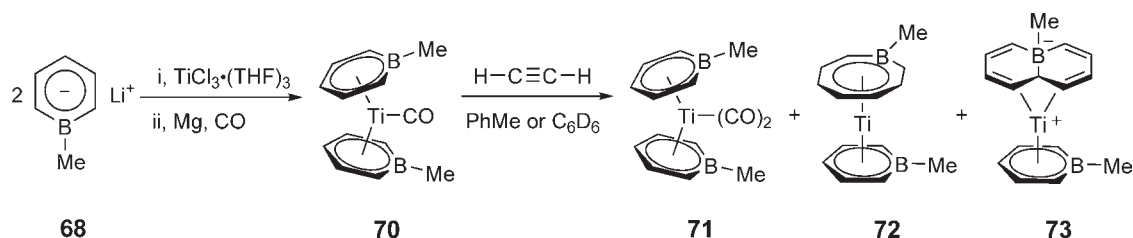
Boratabenzenes are considered useful replacements for cyclopentadienyl ligands in transition metal complexes since the replacement of the exocyclic substituent at B changes the electronic character of the boratabenzene ring <1997OM163>. To quantify such interactions between exocyclic N-containing substituents and B, Ashe III *et al.* have systematically studied a variety of boratabenzenes by NMR and X-ray crystallography <1996OM387, 1997OM163>. Accordingly, barriers to B–N bond rotation were measured by variable-temperature NMR, and pK_a values deduced for the dialkylaminoboracyclohexadiene precursors that undergo deprotonation to yield the aromatic boratabenzenes.

7.14.5 Reactivity of Fully Conjugated Rings

Herberich *et al.* have shown that boratabenzenes, for example, lithium salt **68** (Equation 1), behave as nucleophiles in the presence of Me_3XCl and undergo addition at C-2 to yield 1-methyl-1,2-dihydroborinines such as **69** <1997OM926>. X-Ray diffraction studies on the products have been discussed earlier (see Section 7.14.3).

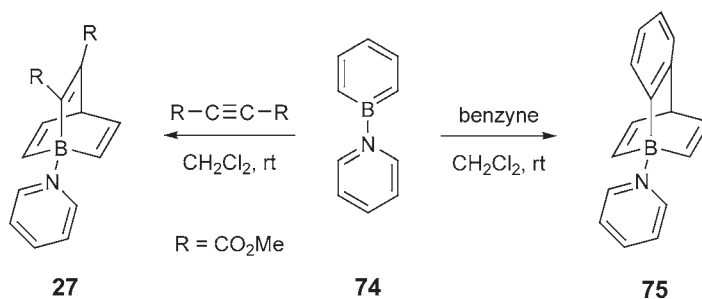


Using the same boratabenzene **68**, Bazan and co-workers have formed titanium complex **70** and then studied its further reactions with acetylenes. Treatment of **70** with acetylene itself resulted in **71** as well as two ring-expanded products, **72** and **73** (Scheme 1) <2003AGE4510>. Formation of **72** was favored at low concentrations of acetylene in toluene solution whereas **73** becomes prevalent at high concentrations; a mechanism involving initial coordination of acetylene to titanium was proposed. Similar reaction of **70** with (trimethylsilyl)acetylene gave a 79% yield of the product analogous to **72**, the structure of which was determined by X-ray diffraction (see Section 7.14.3).



Scheme 1

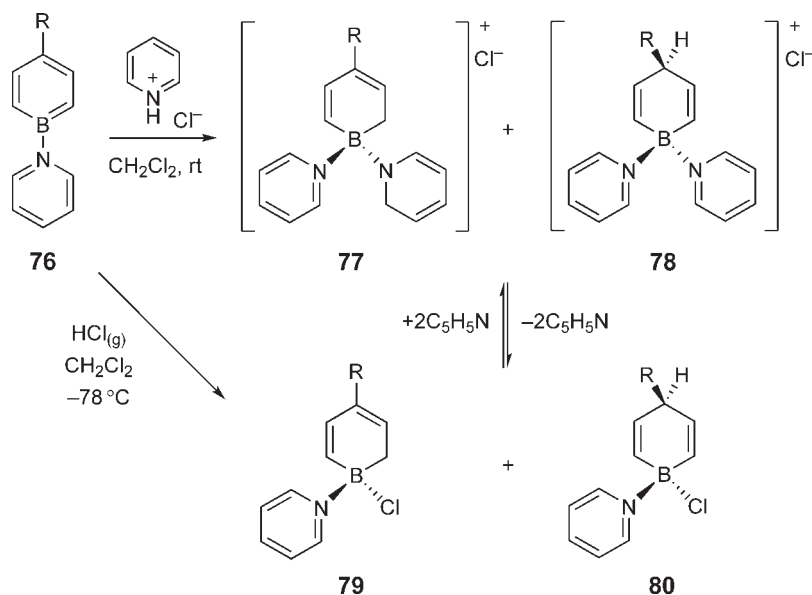
Neutral borabenzene complexes with pyridine undergo interesting addition processes. For example, the reaction of **74** with dimethyl acetylenedicarboxylate leads to the [4+2] adduct **27**, a new borabarrelene derivative, via a Diels–Alder reaction in 90% isolated yield (Scheme 2) <2006OL2875>. Similarly, trapping of the borabenzene ring of **74** with *in situ*-generated benzyne affords the novel benzoborabarrelene **75** in 23% yield. The X-ray crystal structure of **27** has been discussed in Section 7.14.3 and features a pyramidalized boron atom at the ring junction <2006OL2875>.



Scheme 2

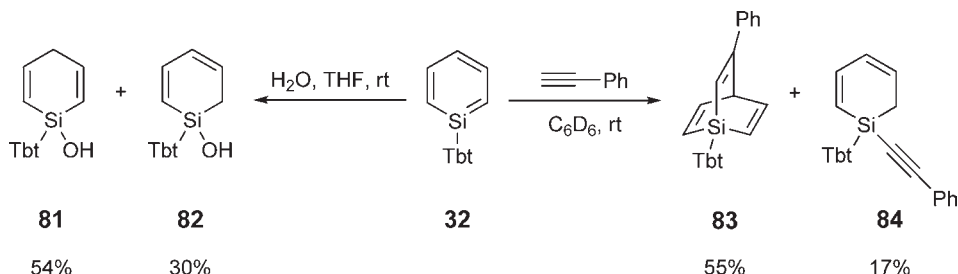
Piers and co-workers have shown that pyridine-stabilized borabenzenes **76** ($\text{R} = \text{H}, \text{Me}, \text{Pr}^i$) react with cationic Brønsted acids such as pyridinium hydrochloride to produce the boronium ions **77** and **78** in ~1:1 ratio. Protonation occurs at C-2 and C-4, respectively, followed by addition of pyridine at electrophilic boron <2005CC2480>.

Treatment of **76** with HCl gas affords chlorides **79** and **80** and it was shown by ^1H NMR that **77** and **78** actually interconvert with the chlorides upon dissolution in dichloromethane (Scheme 3). The ^{11}B NMR spectra of the precursors **76** feature signals in the 31–33 ppm range, which is typical for the pyridine-coordinated borabenzenes. The corresponding signals for borenium cations **77–80** show a significant shift upfield to the 1–5 ppm region. X-Ray crystal structures for **78** ($\text{R} = \text{H}$) and **79** ($\text{R} = \text{Me}$), which clearly indicate the pyramidal nature of the B-atom in each case, have been discussed earlier (see Section 7.14.3). Similar chemistry has also been described with 2,2'-diboratabiphenyls featuring P-coordinated boron, which undergo reaction with alcohols and amines at the carbon α to boron to produce 1,2-bis(alkoxy)boranes <2006CJC81>.



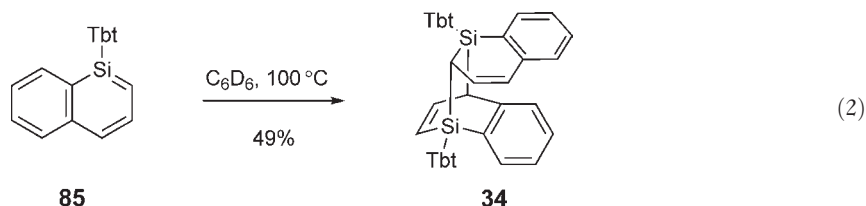
Scheme 3

Kinetically stabilized silabenzene **32**, the crystal structure of which has been discussed in Section 7.14.3, undergoes 1,2- and 1,4-addition reactions similar to those of the boron analogs, for example, with water to afford 1-hydroxy-silacyclohexadienes **81** and **82** (Scheme 4) <2005OM6141>. Reaction of **32** with phenylacetylene results in two addition products, the silabarrelene derivative **83** formed by a [4+2] cycloaddition, and the 1,2-addition product **84**.

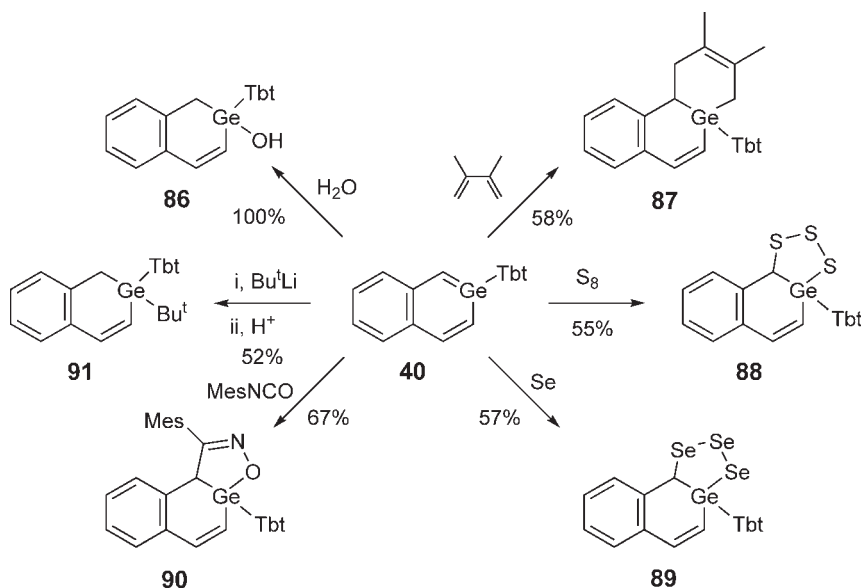


Scheme 4

Although protected 1-silanaphthalene **85** is stable in the solid state under argon atmosphere, it undergoes slow dimerization at room temperature to give **34**, the crystal structure of which has been discussed (see Section 7.14.3). It was found that heating a solution of **85** to 100°C resulted in faster conversion (12 h) and **34** could be isolated in 49% yield <2002OM4024> (Equation 2). The ready conversion of **85** into **34** is in stark contrast to the 2-silanaphthalene isomer **33** (see Section 7.14.3) which does not undergo [4+2] cycloaddition even upon heating at 100°C in C_6D_6 .



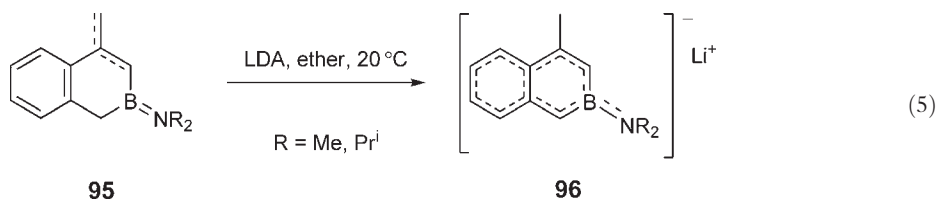
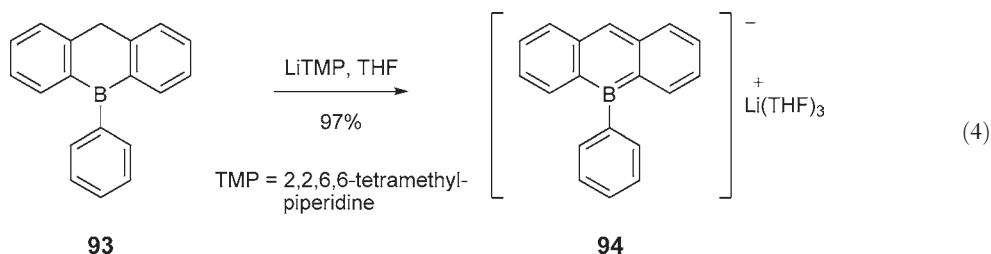
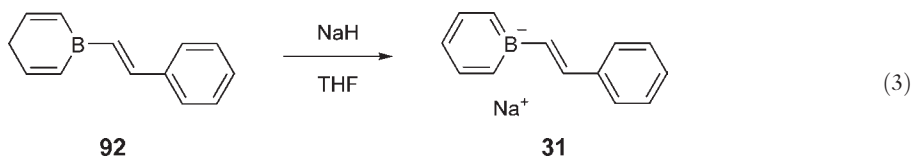
The successful isolation of the kinetically stabilized 2-germanaphthalene **40** by Tokitoh and co-workers has allowed for extensive studies into its reactivity. Addition of water occurs in a 1,2-fashion to yield **86** while exposure to 2,3-dimethyl-1,3-butadiene sees **40** react as a dienophile in a [4+2] cycloaddition to give **87** (Scheme 5) <2003OM481>. Reaction of **40** with elemental S or Se produces addition products **88** and **89**, again involving the 1,2-carbons of the 2-germanaphthalene system. Exposure of **40** to an isocyanate results in [3+2] cycloaddition and the formation of the unique heterocycle **90**, while addition of Bu^tLi occurs at Ge and, after quenching with acid, gives the 1,2-dihydrogermanaphthalene **91**.



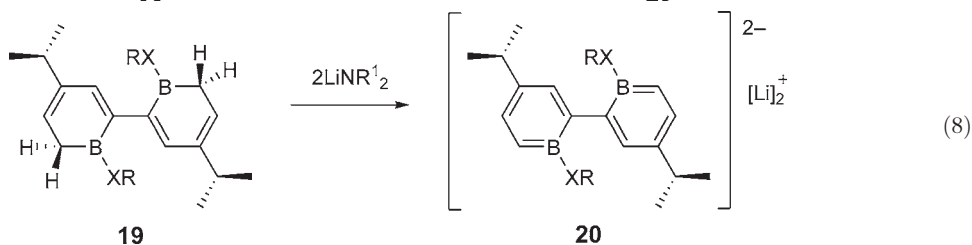
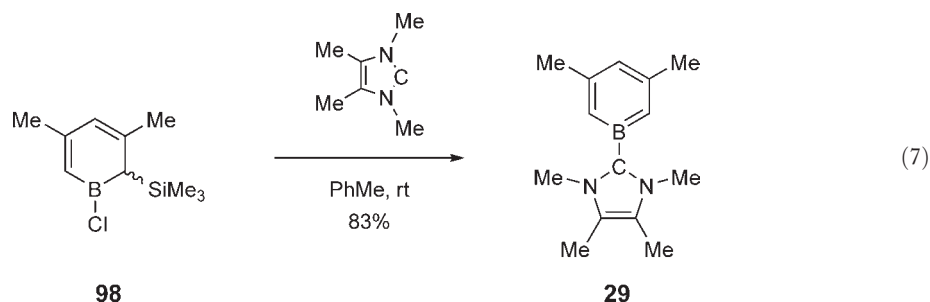
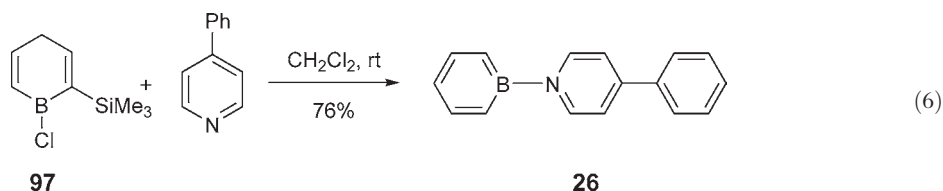
Scheme 5

7.14.6 Reactivity of Nonconjugated Rings

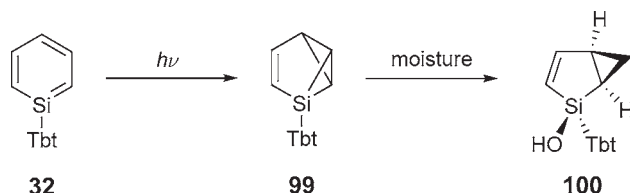
1-Substituted boracyclohexadienes undergo ready deprotonation to produce the corresponding aromatic borata-type systems. Reaction of **92** with base generates the boratastilbene **31** (Equation 3) <2000JA8577>, which is of interest for its photophysical properties; the X-ray crystal structure of **31** is discussed in Section 7.14.3. Dihydroanthracene analog **93** reacts with lithium tetramethylpiperidine in a similar way to give the 9-phenylborata compound **94** as an orange solid in 97% yield (Equation 4) <1998JA6037>. The ¹H NMR spectra of **93** and **94** proved useful in assigning their structures with the C-10 methylene signal of the precursor appearing at 4.14 ppm and the C-10 proton of the aromatic product at 7.36 ppm. The crystal structure of a TMEDA chelate related to **94** is detailed in Section 7.14.3. Use of lithium diisopropylamide (LDA) to deprotonate the mixture of regioisomeric amine-chelated precursors **95** provided 2-boratanaphthalenes **96** (R = Me, Prⁱ) as bright yellow powders in 77% and 90% yield, respectively (Equation 5) <1999ICC503>.



Fu and co-workers have shown that the 1-chloro-boracyclohexa-2,4-diene **97** reacts with 4-phenylpyridine at room temperature to provide the *p*-terphenyl analog **26** in 76% yield as an early example of a borabenzene–pyridine-type complex (Equation 6). The X-ray structure of **26**, discussed in Section 7.14.3, shows the three rings not to be coplanar <1997OM1501>. Exposure of the 1-chloro-boracyclohexa-2,4-diene **98** to a stabilized carbene results in formation of the complex **29** in 83% yield as an air- and moisture-sensitive colorless powder (Equation 7), crystals of which were grown from toluene; the X-ray structure of **29** has been discussed in Section 7.14.3. The use of bulky lithium bases to deprotonate the bis(amido) or bis(alkoxy)boranes **19** allows for the formation of the dianionic 2,2'-diboratabiphenyl derivatives **20** (X = NHPH, OBn), the solid-state structures of which have been discussed (Equation 8) <2006CJC81>.

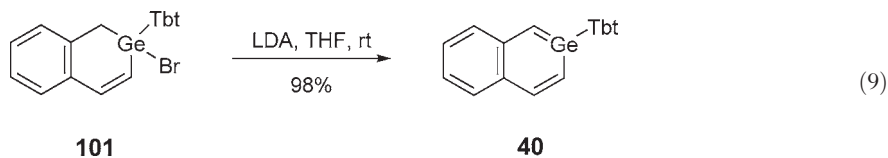


After the structural characterization by Tokitoh and co-workers of stabilized 1-silabenzene **32** by X-ray diffraction, its photochemical behavior has been of interest in the search for novel isomers related to Dewar benzene and benzvalene <2000JA5648>. Thus, photolysis of **32** in C₆D₆ for 15 h gave a 1:4 mixture of **32** and a new compound that was identified as the silabenzvalene **99** from the ²⁹Si spectrum (Scheme 6). The upfield signal for the Si-atom in **99** at –71.6 ppm, compared to 93.6 ppm for the aromatic precursor **32**, is characteristic of a three-membered ring containing Si <2000JA5648>. Attempted chromatographic separation of **32** and **99** in the open atmosphere resulted in the isolation of silanol **100**, thus providing further evidence for the identity of silabenzvalene **99**.



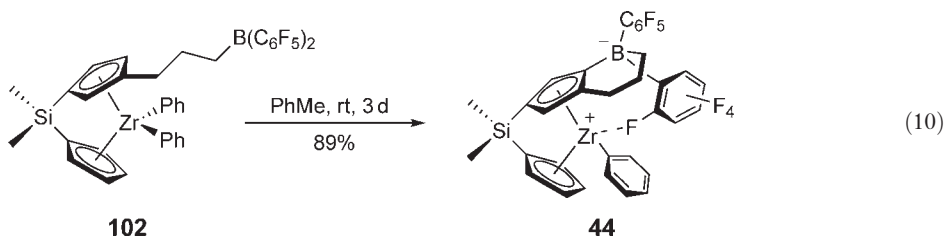
Scheme 6

Analogous to the dehydrohalogenation methodology employed to prepare kinetically stabilized 2-silanaphthalenes <1997JA6951> and 2-stannanaphthalenes <2006JA1050>, treatment of the 2-bromo-1-hydro-2-germanaphthalene **101** with LDA in THF provides access to the aromatic 2-germanaphthalene **40** in very high yield (Equation 9) <2003OM481>. The X-ray structure of **40** has been covered in Section 7.14.3 and some of its representative chemistry in Section 7.14.5.



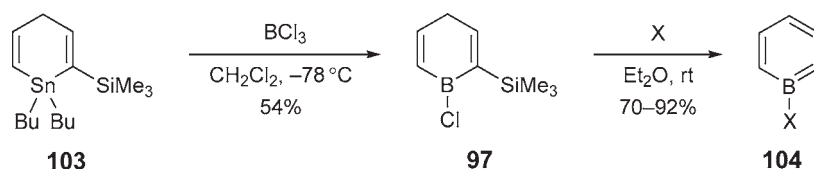
7.14.7 Ring Synthesis

Diphenyl zirconocene complex **102** is unstable at room temperature and undergoes electrophilic substitution at the alkylated cyclopentadienyl ligand to produce the boratacycle **44** in high yield (Equation 10). The reaction involves loss of 1 equiv of benzene from the central zirconium, and the X-ray crystal structure of **44** (detailed in Section 7.14.3) clearly shows interaction between the zirconium and one of the perfluorophenyl ligands attached at boron <2004CC1020>.



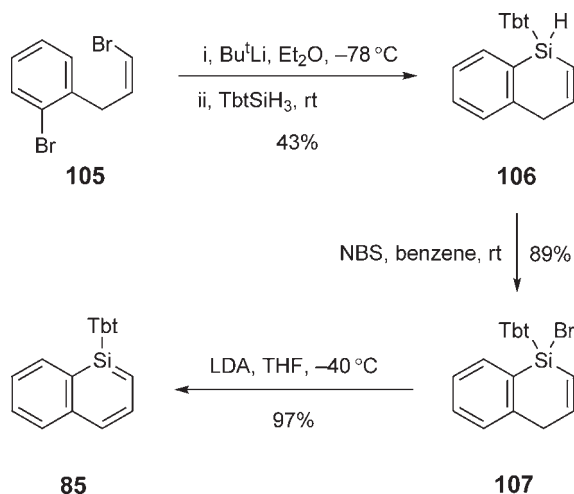
Fu and co-workers have employed stannacyclohexadienes (e.g., **103**) as the precursors to 1-chloro-1-boracyclohexadienes (Scheme 7) <1996OM1315>. For example, reaction of **103** with BCl₃ at low temperature affords **97** as a distillable oil in 54% isolated yield; treatment of **97** with Lewis bases such as amines and phosphines then provides efficient access to the ligand-complexed borabenzenes **104**.

Tokitoh and co-workers have shown that lithiation of dibromide **105** followed by trapping with TbtSiH₃ gives the 1,4-dihydro-1-silanaphthalene **106**, which is then brominated at silicon in high yield to provide the 1-bromosilyl product **107** (Scheme 8). Dehydrohalogenation of **107** with LDA at low temperature results in a very high yield of the aromatic 1-silanaphthalene **85**, the dimerization of which has been discussed in Section 7.14.5 <2005BCJ977, 2002OM4024>.



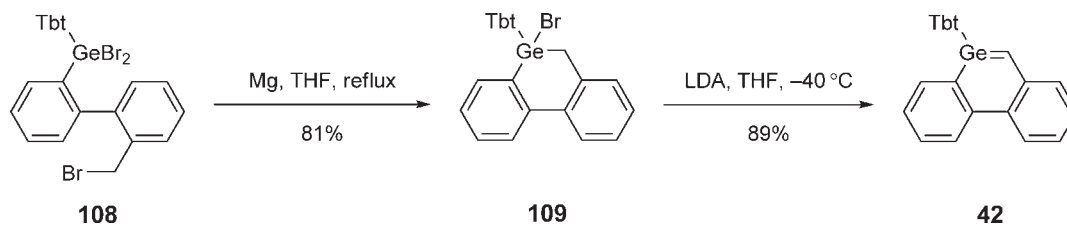
X = pyridine, 2,6-lutidine, NEt_3 , PMe_3 , CN-Bu^t

Scheme 7



Scheme 8

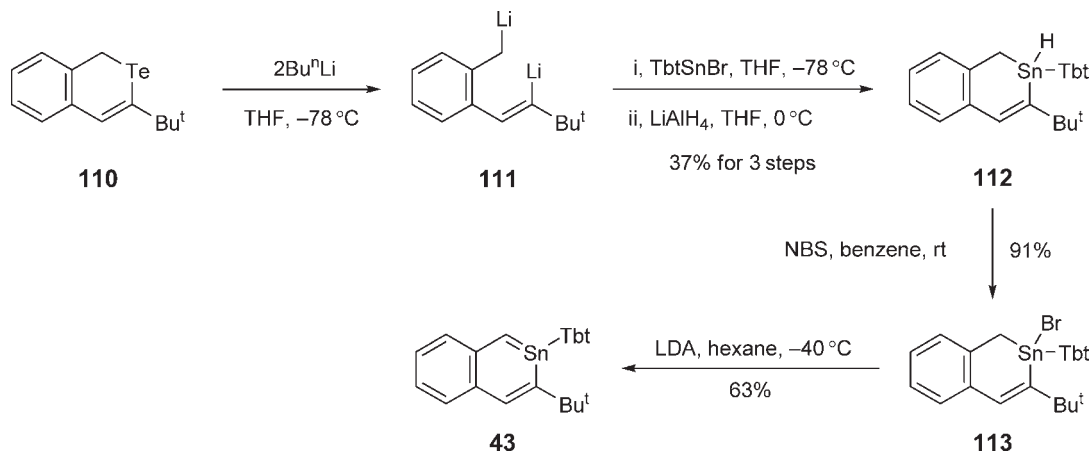
Similar treatment of benzylic bromide **108** with magnesium resulted in ring closure to the brominated 9,10-dihydro-9-germanaphenanthrene **109** in good yield (Scheme 9) <2006OM3533>. Elimination with LDA then occurs cleanly to produce the kinetically stabilized 9-germanaphenanthrene **42**, which yielded to X-ray analysis (see Section 7.14.3) and was stable upon heating in C_6D_6 solution up to 100°C .



Scheme 9

In pursuit of stannaphthalene derivatives, Tokitoh and co-workers found that lithiation of the isotellurochromene **110** at low temperature gave the bis(lithiated) derivative **111** that was trapped effectively by TbtSnBr (Scheme 10) <2006JA1050>. Reduction of the intermediate gave the 1,2-dihydrostannaphthalene **112** in a 37% overall yield for the three steps from **110**. Reaction of **112** with *N*-bromosuccinimide provided bromide **113** in

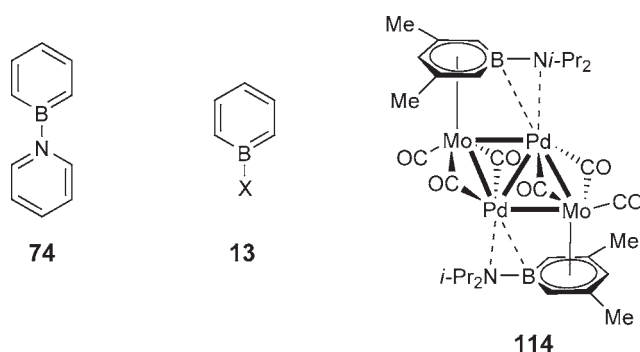
excellent yield and elimination with LDA at low temperature yielded the kinetically stabilized 2-stannanaphthalene **43** (see Section 7.14.3 for discussion of the X-ray structure).



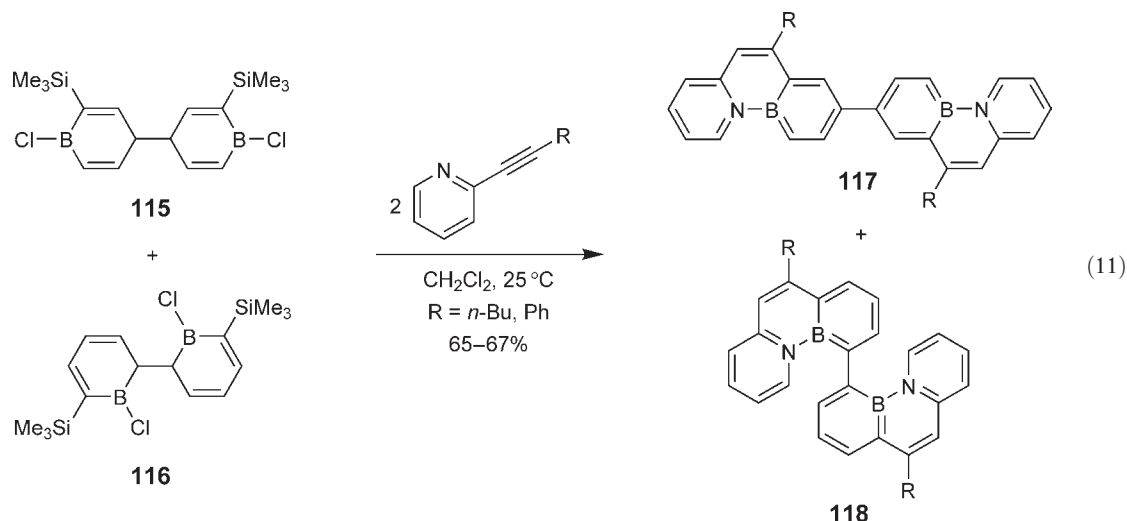
Scheme 10

7.14.8 Further Developments

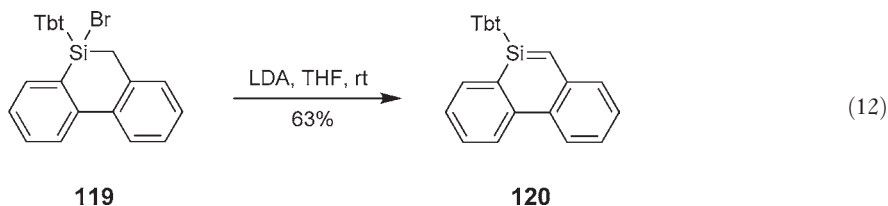
Quantum-chemical studies on the borabenzene-pyridine adduct **74** (see Section 7.14.5) in various solvents, using B3LYP/6-311G methods, have been carried out and results compared with those obtained for N_2 and Xe adducts **13** (see Section 7.14.2). The B–N bond in pyridine adduct **74** is significantly stronger than the corresponding bond in **13** ($\text{X} = \text{N}_2$) <2006RJC1925>. A series of heterometallic complexes and clusters containing amino-boratabenzene ligands has been reported with several examples providing X-ray diffraction data <2006IC5852>. The Mo–Pd tetranuclear cluster **114** shows clear interaction between Mo and the boratabenzene aromatic system, as well as between Pd and the B–N moiety.



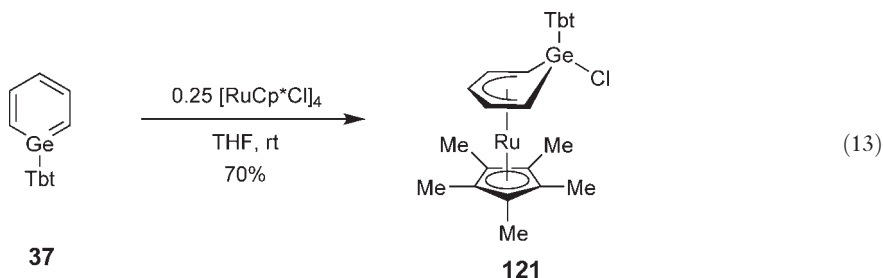
Reaction of a 40:60 mixture of 4,4'-bi(boracyclohexa-2,5-diene) **115** and the isomeric 2,2'-bi(boracyclohexa-2,5-diene) **116** with 2-alkynylpyridines results in the isolation of biphenanthrenyl analogs **117** and **118** through a coordination–cycloisomerization sequence <2007JOC5234>. The products exhibited interesting fluorescence properties with emission colors from green to red; similar compounds made by the same workers were shown to emit blue light <2007OL1395>.



Tokitoh and colleagues have shown that dehydrohalogenation on 9-bromo-9,10-dihydro-9-silaphenanthrene, **119**, to be an efficient route to the first example of a kinetically stabilized 9-silaphenanthrene, i.e., **120** (Equation 12). Spectroscopic and X-ray diffraction studies on **120** prove the compound to be highly aromatic <2007OM4048>.



Kinetically stabilized germabenzene **37**, the synthesis and X-ray structure of which were reported earlier (see Section 7.14.3) <2002JA6914>, reacts with transition metals to produce stable η^6 -germabenzene complexes such as **67** (see Figure 1, Section 7.14.3), as well as addition products such as **121** (Equation 13). A mechanism involving initial coordination to give an η^6 -germabenzene complex followed by attack of chloride nucleophile at germanium has been suggested <2007CEJ1856>.



References

- 1985CB1644 R. Boese, N. Finke, J. Henkelmann, G. Maier, P. Paetzold, H. P. Reisenauer, and G. Schmid, *Chem. Ber.*, 1985, **118**, 1644.
 1996IC7863 U. Hagenau, J. Heck, E. Hendrickx, A. Persoons, T. Schuld, and H. Wong, *Inorg. Chem.*, 1996, **35**, 7863.
 1996JA2291 G. C. Bazan, G. Rodríguez, A. J. Ashe, III, S. Al-Ahmad, and C. Müller, *J. Am. Chem. Soc.*, 1996, **118**, 2291.
 1996OM387 A. J. Ashe, III, J. W. Kampf, C. Müller, and M. Schneider, *Organometallics*, 1996, **15**, 387.
 1996OM1315 D. A. Hoic, J. R. Wolf, W. M. Davis, and G. C. Fu, *Organometallics*, 1996, **15**, 1315.
 1996OM2707 G. E. Herberich, U. Englert, M. U. Schmidt, and R. Standt, *Organometallics*, 1996, **15**, 2707.

- 1996OM5236 G. E. Herberich, U. Englert, B. Ganter, and C. Lamertz, *Organometallics*, 1996, **15**, 5236.
- 1997AGE2014 A. J. Ashe, III, S. Al-Ahmad, J. W. Kampf, and V. G. Young, Jr., *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2014.
- 1997IJQ441 P. B. Karadakov, M. Ellis, J. Gerratt, D. L. Cooper, and M. Raimondi, *Int. J. Quantum Chem.*, 1997, **63**, 441.
- 1997JA6951 N. Tokitoh, K. Wakita, R. Okazaki, S. Nagase, P. von Ragué Schleyer, and H. Jiao, *J. Am. Chem. Soc.*, 1997, **119**, 6951.
- 1997JA11933 A. Nicolaidis and L. Radom, *J. Am. Chem. Soc.*, 1997, **119**, 11933.
- 1997JOC8286 J. Tweddell, D. A. Hoic, and G. C. Fu, *J. Org. Chem.*, 1997, **62**, 8286.
- 1997JOM(548)1 C. K. Sperry, G. Rodriguez, and G. C. Bazan, *J. Organomet. Chem.*, 1997, **548**, 1.
- 1997OM163 A. J. Ashe, III, J. W. Kampf, and J. R. Waas, *Organometallics*, 1997, **16**, 163.
- 1997JA606 J. R. Blecke, R. Behm, Y.-F. Xie, M. Y. Chiang, K. D. Robinson, and A. M. Beatty, *Organometallics*, 1997, **16**, 606.
- 1997OM926 G. E. Herberich, J. Rosenplänter, B. Schmidt, and U. Englert, *Organometallics*, 1997, **16**, 926.
- 1997OM1501 S. Qiao, D. A. Hoic, and G. C. Fu, *Organometallics*, 1997, **16**, 1501.
- 1997OM3751 G. E. Herberich, U. Englert, and A. Schmitz, *Organometallics*, 1997, **16**, 3751.
- 1998JA6037 R. A. Lee, R. J. Lachicotte, and G. C. Bazan, *J. Am. Chem. Soc.*, 1998, **120**, 6037.
- 1998JA7791 C. K. Sperry, W. D. Cotter, R. A. Lee, R. J. Lachicotte, and G. C. Bazan, *J. Am. Chem. Soc.*, 1998, **120**, 7791.
- 1998OM3883 A. J. Ashe, III, S. Al-Ahmad, X. Fang, and J. W. Kampf, *Organometallics*, 1998, **17**, 3883.
- 1999ICC503 G. E. Herberich, E. Cura, and J. Ni, *Inorg. Chem. Commun.*, 1999, **2**, 503.
- 1999JA1288 J. S. Putzer, J. S. Rogers, and G. C. Bazan, *J. Am. Chem. Soc.*, 1999, **121**, 1288.
- 1999JA8112 M. A. Putzer, J. S. Rogers, and G. C. Bazan, *J. Am. Chem. Soc.*, 1999, **121**, 8112.
- 1999OM1363 A. J. Ashe, III, X. Fang, and J. W. Kampf, *Organometallics*, 1999, **18**, 1363.
- 1999OM3406 G. E. Herberich, U. Englert, B. Ganter, M. Pons, and R. Wang, *Organometallics*, 1999, **18**, 3406.
- 1999OM4747 G. E. Herberich, X. Zheng, J. Rosenplänter, and U. Englert, *Organometallics*, 1999, **18**, 4747.
- 1999OM5496 G. E. Herberich, U. Englert, A. Fischer, J. Ni, and A. Schmitz, *Organometallics*, 1999, **18**, 5496.
- 2000BCJ2157 K. Wakita, N. Tokitoh, and R. Okazaki, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 2157.
- 2000CC843 G. N. Sastry, H. S. P. Rao, P. Bednarek, and U. D. Priyakumar, *J. Chem. Soc., Chem. Commun.*, 2000, 843.
- 2000EIJ979 G. E. Herberich, U. Englert, B. Ganter, and M. Pons, *Eur. J. Inorg. Chem.*, 2000, 979.
- 2000JA3969 B. Y. Lee, S. Wang, M. Putzer, G. P. Bartholomew, X. Bu, and G. C. Bazan, *J. Am. Chem. Soc.*, 2000, **122**, 3969.
- 2000JA5648 K. Wakita, N. Tokitoh, R. Okazaki, N. Takagi, and S. Nagase, *J. Am. Chem. Soc.*, 2000, **122**, 5648.
- 2000JA8577 B. Y. Lee and G. C. Bazan, *J. Am. Chem. Soc.*, 2000, **122**, 8577.
- 2000OM1477 K. B. Aldridge, O. Uzan, and J. M. L. Martin, *Organometallics*, 2000, **19**, 1477.
- 2000OM2208 E. C. Brown and W. T. Borden, *Organometallics*, 2000, **19**, 2208.
- 2000OM3751 X. Zheng and G. E. Herberich, *Organometallics*, 2000, **19**, 3751.
- 2000OM3948 J. S. Rogers, X. Bu, and G. C. Bazan, *Organometallics*, 2000, **19**, 3948.
- 2001AOC101 G. C. Fu, *Adv. Organomet. Chem.*, 2001, **47**, 101.
- 2001JCD1754 P. Braunstein, E. Cura, and G. E. Herberich, *J. Chem. Soc., Dalton Trans.*, 2001, 1754.
- 2001JP230 G. N. Sastry and U. D. Priyakumar, *J. Chem. Soc., Perkin Trans. 2*, 2001, 30.
- 2001PS31 N. Tokitoh, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2001, **168**, 31.
- 2002EIJ43 G. E. Herberich, T. S. Basu Baul, and U. Englert, *Eur. J. Inorg. Chem.*, 2002, 43.
- 2002JA6914 N. Nakata, N. Takeda, and N. Tokitoh, *J. Am. Chem. Soc.*, 2002, **124**, 6914.
- 2002JOC271 U. D. Priyakumar and G. N. Sastry, *J. Org. Chem.*, 2002, **67**, 271.
- 2002JST(618)173 D. M. Dhevi, U. D. Priyakumar, and G. N. Sastry, *J. Mol. Struct.*, 2002, **618**, 173.
- 2002OM256 N. Takeda, A. Shinohara, and N. Tokitoh, *Organometallics*, 2002, **21**, 256.
- 2002OM1493 U. D. Priyakumar and G. N. Sastry, *Organometallics*, 2002, **21**, 1493.
- 2002OM4024 N. Takeda, A. Shinohara, and N. Tokitoh, *Organometallics*, 2002, **21**, 4024.
- 2003AGE115 N. Nakata, N. Takeda, and N. Tokitoh, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 115.
- 2003AGE4510 X. Fang, D. Woodmansee, X. Bu, and G. C. Bazan, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 4510.
- 2003JA10804 A. Shinohara, N. Takeda, and N. Tokitoh, *J. Am. Chem. Soc.*, 2003, **125**, 10804.
- 2003JOC1168 D. M. Dhevi, U. D. Priyakumar, and G. N. Sastry, *J. Org. Chem.*, 2003, **68**, 1168.
- 2003JOM(672)66 N. Nakata, N. Takeda, and N. Tokitoh, *J. Organomet. Chem.*, 2003, **672**, 66.
- 2003JST(635)141 J. Klocker, A. Karpfen, and P. Wolschann, *J. Mol. Struct.*, 2003, **635**, 141.
- 2003OM481 N. Nakata, N. Takeda, and N. Tokitoh, *Organometallics*, 2003, **22**, 481.
- 2003OM5454 J. Jeevanandam, E. J. P. Malar, and R. Gopalan, *Organometallics*, 2003, **22**, 5454.
- 2003OM5556 A. M. El-Nahas, M. Johansson, and H. Ottosson, *Organometallics*, 2003, **22**, 5556.
- 2003PS869 I. Yavari, S. Dehghan, and M. Nikpoor-Nezhati, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 869.
- 2004CC1020 M. Hill, G. Kehr, G. Erker, O. Kataeva, and R. Fröhlich, *J. Chem. Soc., Chem. Commun.*, 2004, 1020.
- 2004OM3808 T. Hascall, V. Beck, S. Barlow, A. R. Cowley, and D. O'Hare, *Organometallics*, 2004, **23**, 3808.
- 2005AHC125 A. P. Sadimenko, *Adv. Heterocycl. Chem.*, 2005, **89**, 125.
- 2005BCJ977 A. Shinohara, N. Takeda, T. Sasamori, and N. Tokitoh, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 977.
- 2005CC2480 I. Ghesner, W. E. Piers, M. Parvez, and R. McDonald, *J. Chem. Soc., Chem. Commun.*, 2005, 2480.
- 2005IJQ429 T. M. Simeon, I. Yanov, and J. Leszczynski, *Int. J. Quantum Chem.*, 2005, **105**, 429.
- 2005JST(718)225 R. Ghiasi, *J. Mol. Struct.*, 2005, **718**, 225.
- 2005OM6141 A. Shinohara, N. Takeda, T. Sasamori, T. Matsumoto, and N. Tokitoh, *Organometallics*, 2005, **24**, 6141.
- 2006CJC81 I. Ghesner, W. E. Piers, M. Parvez, and R. McDonald, *Can. J. Chem.*, 2006, **84**, 81.
- 2006IC5852 P. Croizat, N. Auvray, P. Braunstein, and R. Welter, *Inorg. Chem.*, 2006, **45**, 5852.
- 2006JA1050 Y. Mizuhata, T. Sasamori, N. Takeda, and N. Tokitoh, *J. Am. Chem. Soc.*, 2006, **128**, 1050.
- 2006JKC281 R. Ghiasi and M. Monnajemi, *J. Korean Chem. Soc.*, 2006, **50**, 281.
- 2006JST(771)141 G. N. Sastry, *J. Mol. Struct.*, 2006, **771**, 141.
- 2006OL2875 T. K. Wood, W. E. Piers, B. A. Keay, and M. Parvez, *Org. Lett.*, 2006, **8**, 2875.
- 2006OM3533 T. Sasamori, K. Inamura, W. Hoshino, N. Nakata, Y. Mizuhata, Y. Watanabe, Y. Furukawa, and N. Tokitoh, *Organometallics*, 2006, **25**, 3533.

- 2006RJC580 S. G. Semenov and Y. F. Sigolaev, *Russ. J. Gen. Chem.*, 2006, **76**, 580.
2006RJC1925 S. G. Semenov and Y. F. Sigolaev, *Russ. J. Gen. Chem.*, 2006, **76**, 1925.
2007CEJ1856 N. Tokitoh, N. Nakata, A. Shinohara, N. Takeda, and T. Sasamori, *Chem. Eur. J.*, 2007, **13**, 1856.
2007JOC5234 C. A. Jaska, W. E. Piers, R. McDonald, and M. Parvez, *J. Org. Chem.*, 2007, **72**, 5234.
2007OL1395 M. J. D. Bosdet, C. A. Jaska, W. E. Piers, T. S. Sorensen, and M. Parvez, *Org. Lett.*, 2007, **9**, 1395.
2007OM4048 N. Tokitoh, A. Shinohara, T. Matsumoto, T. Sasamori, N. Takeda, and Y. Furukawa, *Organometallics*, 2007, **26**, 4048.

Biographical Sketch



Peter Norris is a professor of organic chemistry in the Department of Chemistry at Youngstown State University in northeastern Ohio, USA. He was born in Whiston, a suburb of Liverpool in England in 1965, and grew up near Wigan in Lancashire. After receiving his B.Sc.(Honours) degree from Salford University in 1986, Norris headed to the United States for doctoral training at The Ohio State University under the direction of Harold Shechter. After graduating with his Ph.D. in 1992, he moved to Washington, DC, to pursue postdoctoral work with Derek Horton at American University and in 1996 joined the faculty at Youngstown State as an assistant professor; he received tenure, and promotion to associate professor, in 2000, and promotion to full professor in 2004. Norris has interests in the chemistry of monosaccharides and other heterocycles such as triazoles; he has received funding from the National Institutes of Health, the National Science Foundation, the Petroleum Research Fund of the American Chemical Society, and Research Corporation. Norris has mentored 32 master's degree students and numerous undergraduates at Youngstown State and produced 40 publications thus far.