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Intramolecular free radical conjugate additions

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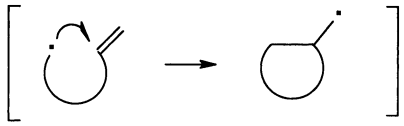
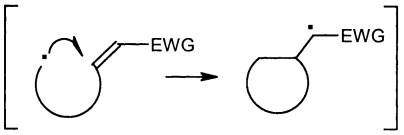
Contents

1. Introduction

Formation of carbon–carbon bonds by intramolecular additions (cyclizations) of carbon radicals onto alkenes are important reactions in organic synthesis (Scheme 1). The rate of cyclization largely depends on the substituents on the radicals and on the alkene bond. In general, electron donating groups on the radical and electron withdrawing groups on the alkene accelerate the cyclization. Frontier molecular orbital (FMO) theory offers a good explanation of the substituent effects. The singularly occupied molecular



Radical cyclization



Intramolecular Michael-type radical addition

Scheme 1.

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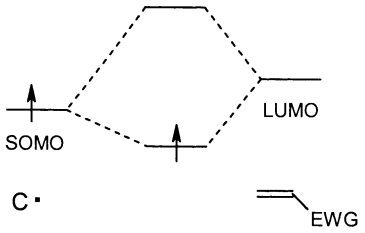


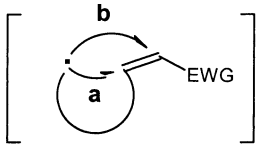
FMO intereaction of a nuclephilic radical with an electron-poor alkene

Scheme 2.

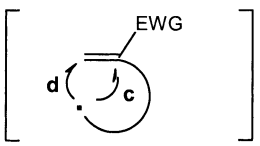
orbital (SOMO) of the radical interacts with either the lowest unoccupied molecular orbital (LUMO) or the highest occupied molecular orbital (HOMO) of the alkene bond (Scheme 2). Michael-type free radical conjugate additions involve the addition of nucleophilic radicals to alkenes (or alkynes) attached to an electron-withdrawing group (EWG) (Scheme 1). The addition rate of nucleophilic radicals is increased because the EWG at the alkene lowers the LUMO energy, reduces the SOMO–LUMO gap, and also stabilizes the cyclized radical.

Compared to their ionic counterparts, radical conjugate additions have a number of unique features:

(a) Radical additions typically proceed under mild conditions with significant functional group tolerance and high levels of regio- and stereoselectivity, which means intramolecular radical conjugate additions will have fewer limitations than ionic ones;
(b) Radical additions are relatively free from solvent, counterion and aggregation effects;
(c) Except for three- and four-membered rings, carbon radical cyclizations to alkenes are essentially irreversible, thus retro-Michael additions are not problematic for radical cyclizations;
(d) α,β-Unsaturated carbonyl derivatives are attacked by carbon centered radicals exclusively at the alkene carbon, with no competition at the carbonyl carbon;
(e) Relatively poor Michael acceptors in the ionic sense, such as Ph and TMS groups, can often be useful in radical reactions;
(f) Anti-Michael additions can be designed in radical series for special synthetic utilities.

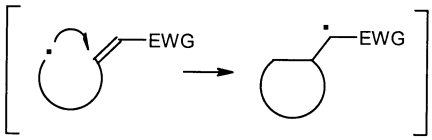


Pathway a: exo, Michael addition
Pathway b: endo, anti-Michael addition



Pathway c: exo, anti-Michael addition
Pathway d: endo, Michael addition

Scheme 3.



Scheme 4.

Free radical conjugate additions were first explored in intermolecular fashion in the studies of substituent effects of radical additions.[1b,g] In the early 80s, pioneers like Bachi, Danishefsky, Stork, Beckwith, Hanessian, among others, started to explore the synthetic utility of intramolecular free radical conjugate additions. This kind of reaction quickly gained attention, and many novel ring systems and natural products have been synthesized by this methodology. There are many reviews and monographs on synthetic use of free radicals,[1] such as Giese's chapter in Organic Reactions,[1n] and on conjugate additions.[2] However, there is no focused review on intramolecular free radical conjugate additions. The goals of this Report are to summarize the large body of literature from the early 1980s to the end of 2000, and to stimulate further studies in this continually evolving field. To help bring order to the diverse array of molecule structures, the reactions are classified into several categories based on the nature (linear or cyclic) of the radicals and radical acceptors along with the ring character (fused, bridged, or spiro) of the cyclization products. To keep the Report within a reasonable length, only representative examples are presented from the original papers.

2. Addition of acyclic radicals to acyclic radical acceptors

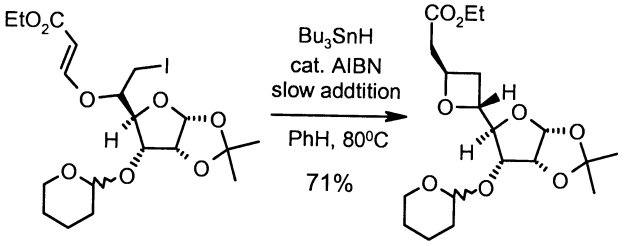
There are two competing pathways in every radical cyclization to an alkene: *endo* cyclization occurs when the radical attacks the terminal end of the multiple bond to form a larger ring, or *exo* cyclization occurs when it attacks the internal end to form a smaller ring. Radical cyclizations are usually regioselective and favor *exo* cyclizations. In the series of intramolecular free radical Michael additions, the position of EWG attached to the radical acceptor has significant influence on the regioselectivity (Scheme 3). The *exo* cyclization (pathway a) is enhanced if the EWG is at the terminus of the carbon–carbon double bond, whereas the *endo* cyclization (pathway d) for large ring closures is favorable if the EWG is at the inner position.

2.1. *exo* Cyclizations

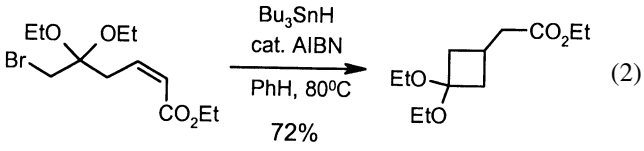
Activating suitable radical acceptors with an EWG will improve both the yield and the regioselectivity of the *exo* cyclization (Scheme 4).

2.1.1. Single rings. Radical cyclizations to form three- and four-membered rings do not compete well with the reverse

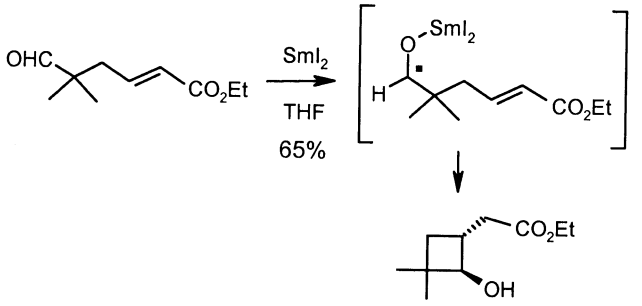
ring opening processes. The release of ring strain strongly favors the equilibrium toward the direction of acyclic radicals. Michael-type radical cyclizations that form three-membered rings have been observed in cascade reaction series (see Section 6). Many examples in the literature have demonstrated that the Michael acceptors can accelerate the 4-*exo* cyclizations and stabilized the ring closed radicals (Eq. (1)).[3] The combination of *gem*-disubstititution on the chain with Michael acceptors further promoted four-membered ring closures (Eq. (2)).[4] The samarium diiodide mediated ketyl–olefin coupling is an effective way for stereoselective synthesis of functionalized cyclobutanols (Eq. (3)).[5]



(1)

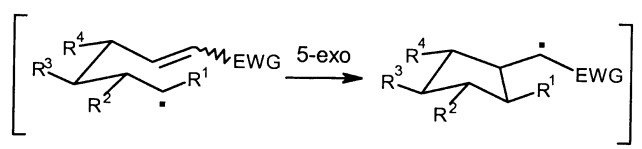


(2)



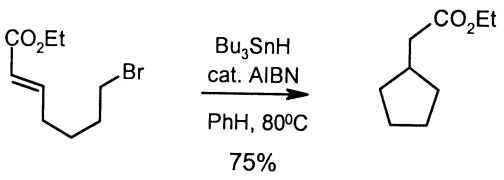
(3)

Formations of five-membered rings by 5-*exo* cyclizations of hexenyl radicals are the most useful radical cyclization reactions. However, products generated from this process are usually contaminated by a small amount of 6-*endo* cyclization byproducts. The employment of EWG substituted alkenes as radical acceptors efficiently addressed this problem. Indeed, Hanessian and coworkers have demonstrated that cyclizations of α,β-unsaturated esters reduced the *endo* ring closure byproducts to an undetectable level as analyzed by ^{1}H NMR spectroscopy (Eq. (4)).[6] Similar reactions promoted by samarium diiodide also led to the same results.[7] Introduction of additional EWGs onto the alkene

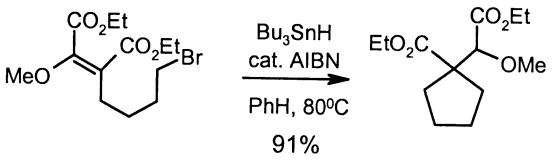


Scheme 5.

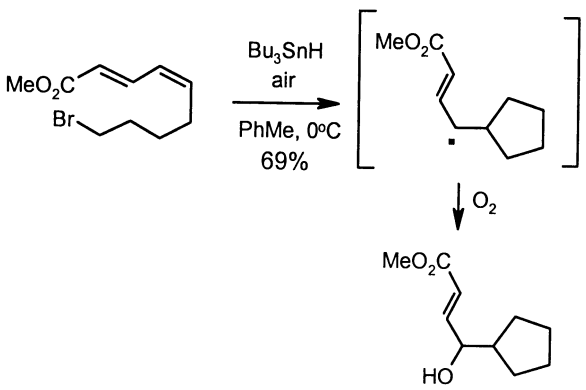
improved the yield (Eq. (5)).[8] Cyclized radicals can be trapped by aldehydes or molecular oxygen for further functionizations (Eq. (6)).[9]



(4)



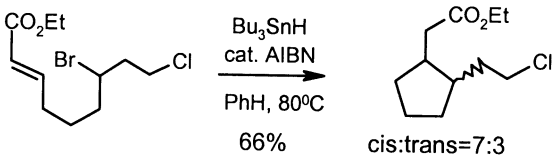
(5)



(6)

The largest body of stereoselective radical reactions relates to 5-*exo* cyclizations of the substituted hexenyl radicals. The Beckwith–Houk chair-like transition state model serves as the basis for predictions and rationalizations of stereoselectivity in 5-*exo* hexenyl radical cyclizations (Scheme 5).[10] This model also applies to conjugate cyclizations and predicts *cis* products from 1- or 3-substituted radicals, and *trans* products from 2- or 4-substituted radicals.

As predicted by the Beckwith–Houk model, the R^1 substituent at the 1-position of hexenyl radicals affords *cis*-1,2-disubstituted cyclopentanes as the major diastereomer. Results from reactions promoted by tin hydride, mercury(II) acetate, and samarium diiodide are consistent with the predictions (Eqs. (7) and (8)).[6,11]



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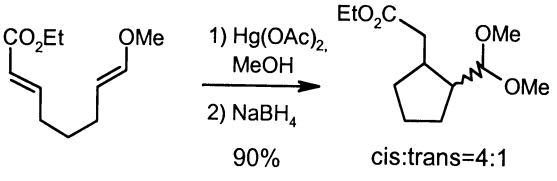
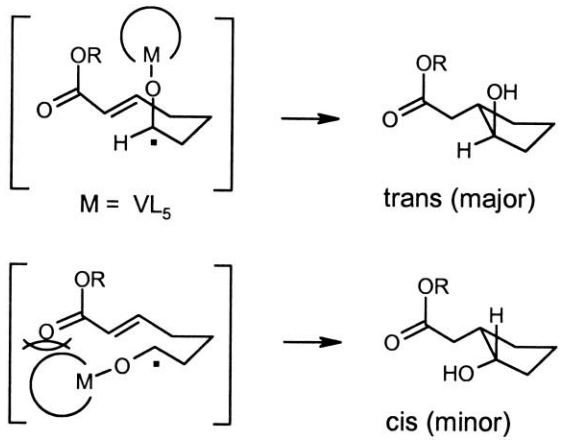


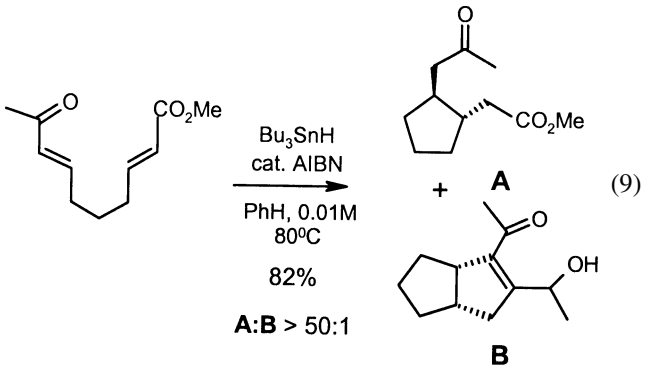
(8)

Higher percentages of *trans*-1,2-disubstituted cyclopentanes have been observed by the Enholm and Torii groups in the

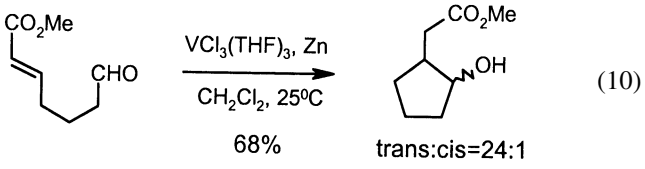


Scheme 6.

studies of the cyclizations of *O*-stannyl ketyls and *O*-vanadyl ketyls (Eqs. (9) and (10)).[12] In the latter case, it is suggested that the bulky organometallic group is axially-oriented at the chair-like transition state (Scheme 6).

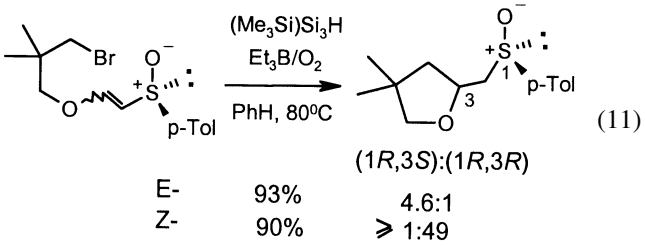


(9)



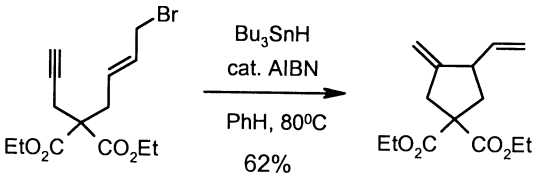
(10)

Using an enantiopure sulfoxide as a temporary auxiliary, Malacria and coworkers explored enantioselective synthesis of cyclopentanes (Eq. (11)).[13] A high enantiomeric excess was obtained by a system that has an anti-Michael addition–elimination sequence (see Section 8).

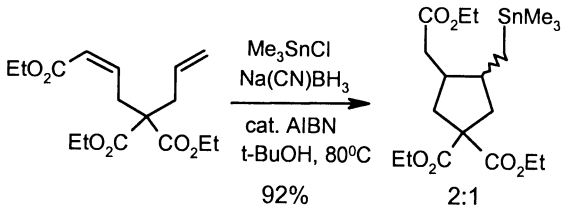


(11)

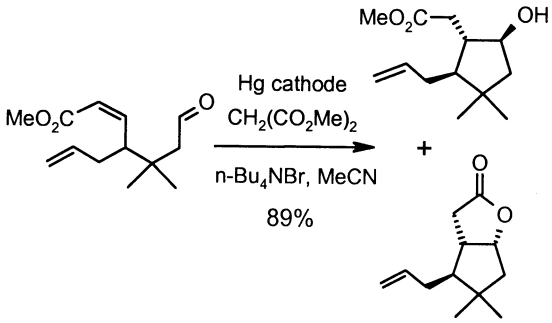
Cyclizations of hexenyl radicals generated from 1,6-terminal dienes, enynes, and olefinic ketones with *gem*-disubstituents at the 3-position have received much attention. In addition to tin hydride reduction of allylic radical precursors (Eq. (12)),[14a] the addition of radicals at the terminal position of the alkene bond is a common strategy to initiate the cyclization. R_3Sn, $(Me_3Si)_3Si$, and sulfonyl radicals have been used to promote the reaction (Eq. (13)).[14b–d] Little and coworkers developed an electroreductive method and applied it to stereoselective synthesis of the sesquiterpene 1-sterpurene and the bicyclic framework of quadrone (Eq. (14)).[15]



(12)

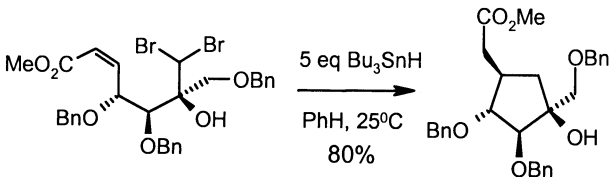


(13)



(14)

Conversions of carbohydrates to carbocyclic derivatives provide good examples of functional group tolerance and diastereoselectivity of free radical Michael additions. Wilcox and Gaudino discovered a practical synthetic approach to new analogs of fructofuranoid enzyme regulators (Eq. (15)).[16] Other groups further developed the cyclization of carbohydrates in the synthesis of densely functionalized cyclopentanes (Eq. (16)).[17]



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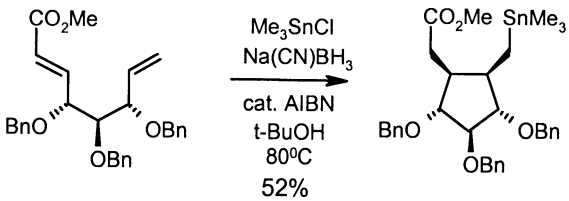
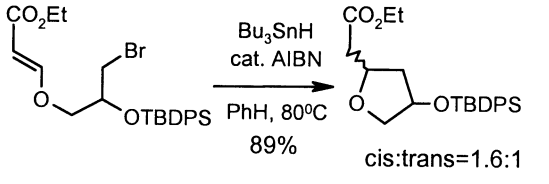


(16)

Oxacyclic ring systems are common in natural products and are targets of numerous synthetic studies. Radical-mediated

cyclizations have been extensively used for the constructions of oxygen-containing five-membered ring systems. Both β- and γ-alkoxyacrylates have been employed in the synthesis of C-substituted tetrahydrofurans (Eqs. (17) and (18)).[18,19] This strategy has been extended in gaining access to δ-lactones (Eq. (19))[20] and applied in the synthesis of (−)-kumausallene by Evans and coworkers.[20d]



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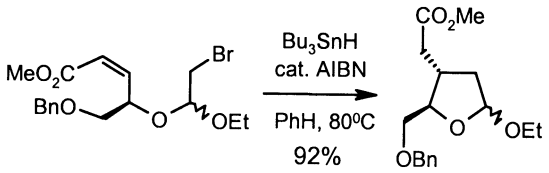

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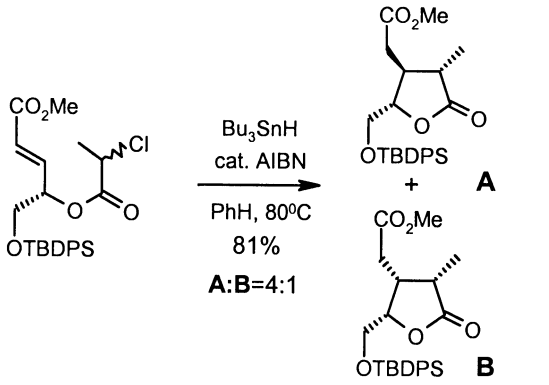
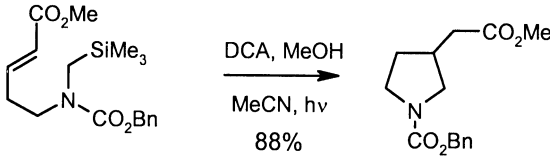
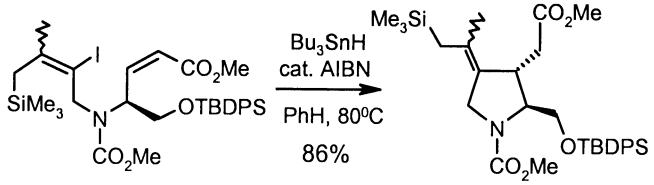


(19)

C-Substituted pyrolidines are another class of important heterocyclic compounds related to biologically active natural products and pharmaceuticals. In addition to intramolecular additions of *N*-centered radicals onto alkene,[21] the 5-*exo* cyclization of *N*-containing hexenyl radicals provides an alternative way to pyrolidines (Eq. (20)).[22] Using this protocol, Takano and coworkers developed an enantiospecific route to (−)-kainic acid and (+)-allokainic acid (Eq. (21)).[23]

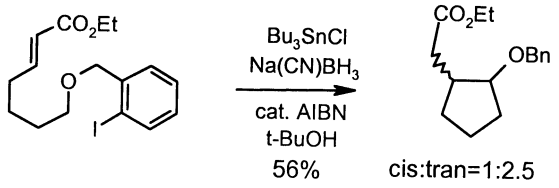


(20)

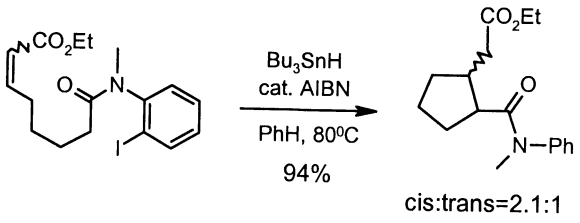


(21)

Carbonyl groups and heteroatoms such as oxygen or nitrogen stabilize adjacent carbon-centered radicals. Curran and Snieckus employed these functional groups in the design of reactions that rely on 1,5-hydrogen atom transfer to initiate the cyclizations (Eqs. (22) and (23)).[24]

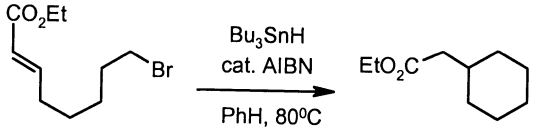


(22)



(23)

Although the *exo* mode is still favored, formation of six-membered rings by *exo* cyclizations of 6-heptenyl radicals is slower than that of 5-hexenyl radicals. The competition between the 6-*exo* cyclization, the 7-*endo* cyclization, 1,5-hydrogen atom transfer, and direct reduction is of much greater importance. Electron-withdrawing substituents at the terminus of the double bond have been employed to accelerate the 6-*exo* cyclizations and improve the yield and regioselectivity (Eqs. (24) and (25)).[6,25] This strategy also applies to ring closure of other sizes.



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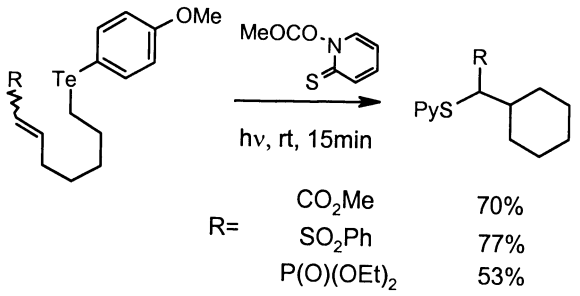
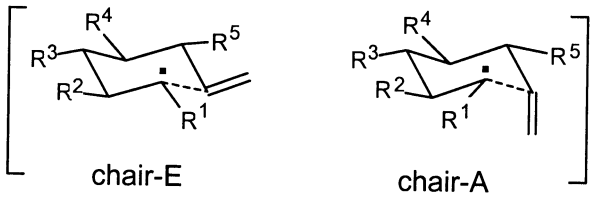


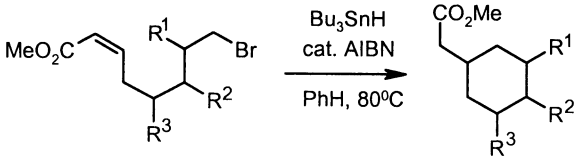
(25)

Stereoselectivities of 6-*exo* cyclizations of substituted heptenyl radicals are still predictable, but with some limitations, by using chair-E and chair-A transition states (Scheme 7).[1m] The preferred transition state adopts a chair-E conformation with the alkene in an equatorial-like orientation. This model predicts the formation of *cis* products from 2- and 4-substituted radicals, and *trans* from 1-, 3-, and 5-substituted radicals. Hanessian and coworkers systematically studied 6-*exo* ring closures of substituted heptenyl radicals (Eq. (26)).[6] More examples



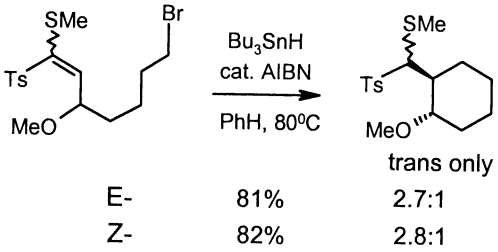
Scheme 7.

related to stereoselective 6-*exo* cyclizations can be found in the literature.[26]

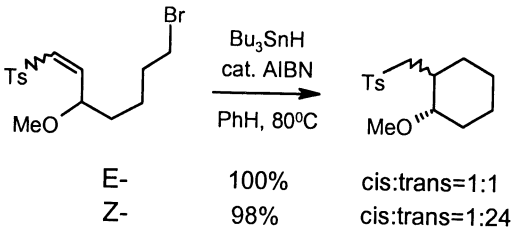


(26)

The geometrical (*E*/*Z*) isomerism of radical precursors has a different impact on the stereochemical outcome of products. Ogura, Fang and their coworkers, for example, investigated 5,7,7-substituted radicals and observed extremely high 1,2-asymmetric induction leading to *trans* ring-closures (Eq. (27)).[27b] This process seems unaffected by the *E*/*Z* geometry of the starting material. However, significantly different results have been obtained from the reactions of radical precursors with 5,7-substituents (Eq. (28)).[27b] In this case, the stereochemistry of the product is sensitive to the geometry of the starting material.

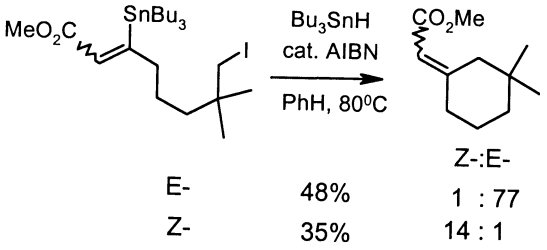


(27)



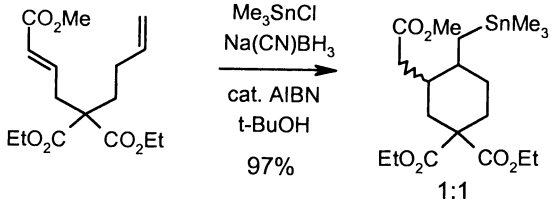
(28)

Weiler and Harris observed high retention of stereochemistry of the double bond in a cyclization reaction that has a sequence of addition of an alkyl radical to the β-stannyl acrylate followed by the elimination of the alkyltin radical (Eq. (29)).[28]

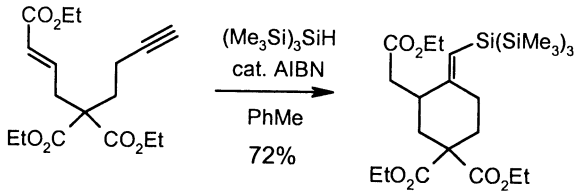


(29)

The Hanessian and Martin groups have demonstrated that cyclizations of 1,7-terminal dienes with *gem*-disubstituents led to the corresponding cyclohexanes (Eqs. (30) and (31))[29] like the 1,6-terminal dienes with *gem*-disubstituents discussed earlier in this section.

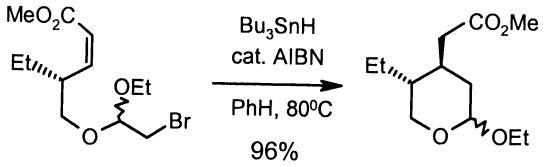


(30)

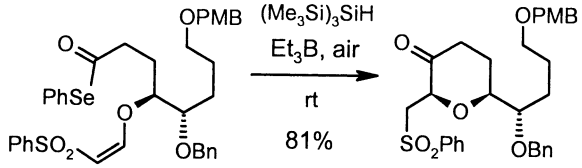


(31)

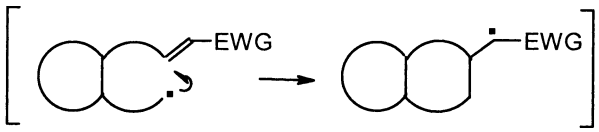
The tetrahydropyran moiety also appears in many biologically important molecules and has consequently attracted much attention from organic chemists. Taking advantage of forming *trans*-substituted tetrahydropyrans by radical cyclizations (Eq. (32)), Fukumoto and coworkers have achieved the asymmetric total synthesis of a series of indole alkaloids.[30] Rao and coworkers devised a highly enantioselective route toward the 3,5-*cis*-disubstituted valerolactone segment of rhizoxin, an antitumor macrolide antibiotic.[31] Takano and coworkers have demonstrated that a carbon radical derived from an α-bromoacetate can cyclize onto an activated alkene in the synthesis of (−)-methyl enolate, a secoridoid monoterpene isolated from olive.[32] Evans and coworkers have developed a general protocol for the synthesis of 2,5-disubstituted tetrahydrofuran-3-ones based on acyl radical cyclizations onto vinylogous carbonates or sulfonates.[33] Using this chemistry, they prepared the key intermediate in the synthesis of an antitumor agent mucocin (Eq. (33)).[33c] This method has been further developed to provide an iterative approach to polycyclic ethers.[33d]



(32)

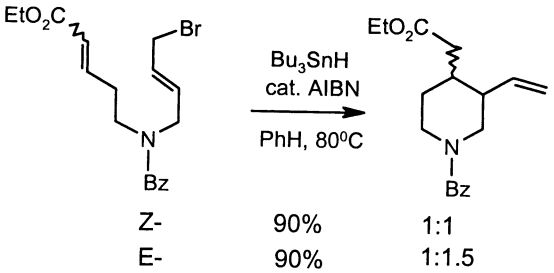


(33)

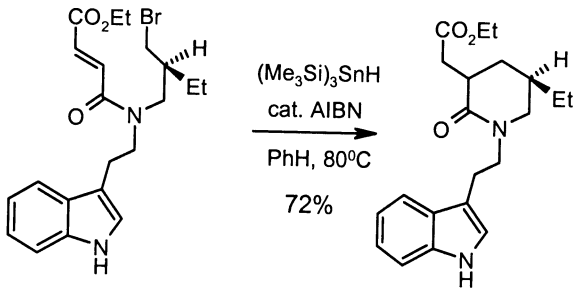


Scheme 8.

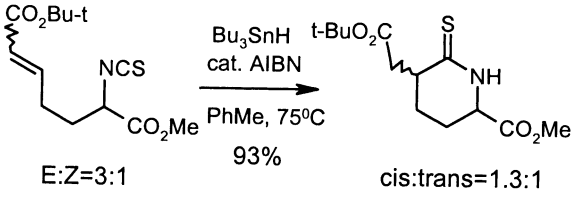
The radical cyclization route to piperidine systems has been exemplified by Yoo and Fukumoto's work in the synthesis of key intermediates of meroquinene and tacamonine (Eqs. (34) and (35)).[34] Mariano and coworkers employed single electron transfer photosensitizations to promote α-silyl amino radical cyclizations,[22a] whereas Bachi and Denenmark developed a method for δ-thiolactams based on tin hydride-mediated cyclizations of alk-4-enylisothiocyanates followed by hydrolysis (Eq. (36)).[35]



(34)

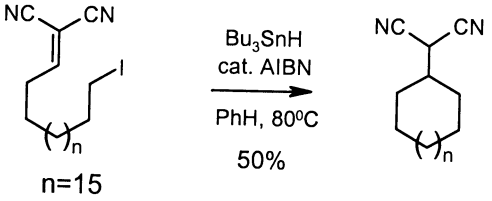


(35)

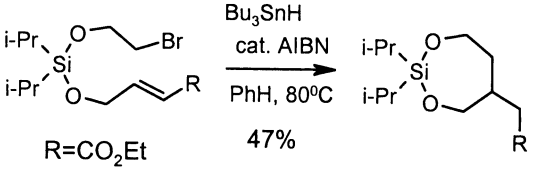


(36)

Formations of medium and large rings via *exo*-cyclizations can be achieved by placing an electron withdrawing group at the terminus of the alkene bond. The Porter and Hutchinson groups reported several cases of this kind transformation (Eqs. (37) and (38)).[36]



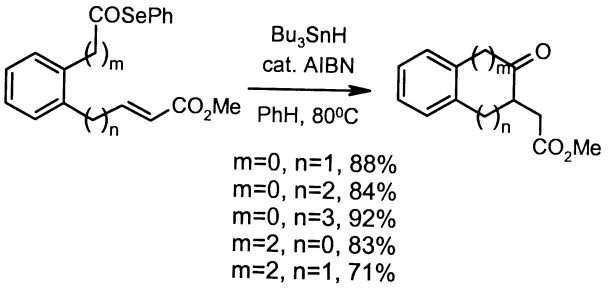
(37)



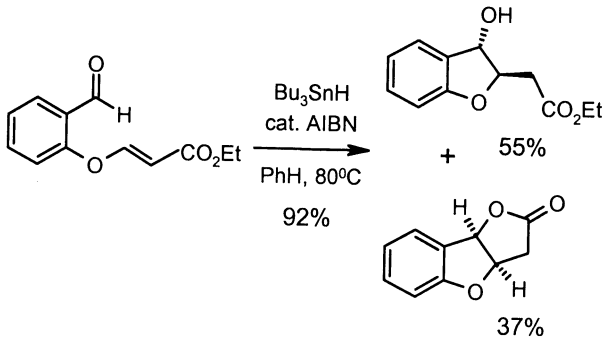
(38)

2.1.2. Bi-, tri- and polycyclic rings. The presence of an existing ring or rings in the radical precursor results in the formation of bi-, tri- and even polycyclic products (Scheme 8).

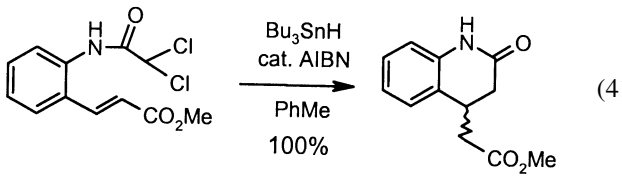
Several means of access to benzo-fused bicyclics have been developed. The scope of acyl radical cyclizations for making ketones has been extensively examined by Boger and coworkers (Eq. (39)).[37] Formations of benzo-fused heterocyclics such as benzofurans, benzopyrans, dihydroquinolones, and dihydroisoquinolones have also been developed (Eqs. (40) and (41)).[38]



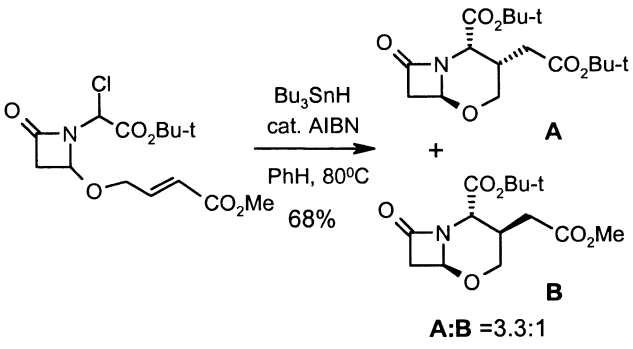
(39)



(40)

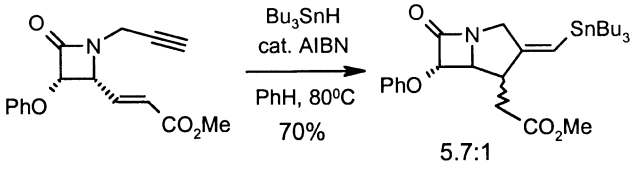


(41)

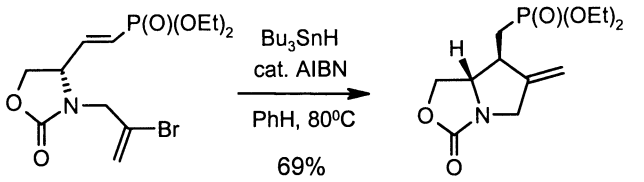


(42)

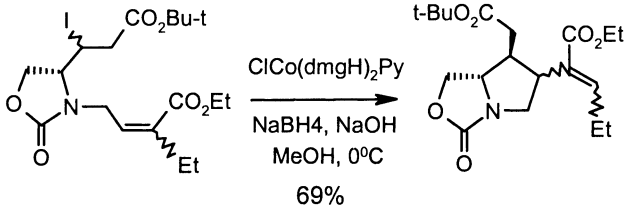
Bachi and others prepared a series of fused bicyclic β-lactams by radical annulations of non-fused β-lactams bearing appropriate appendages (Eqs. (42) and (43)).[39] A similar strategy has been applied to the synthesis of pyrroloxazolidinones from suitable 3,4-disubstituted oxazolidinones (Eqs. (44) and (45)).[40]



(43)

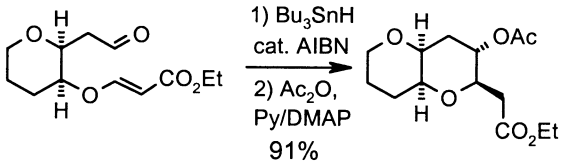


(44)

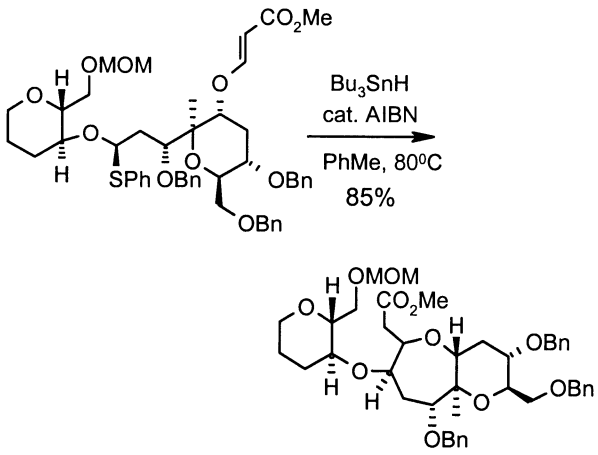


(45)

Lee and coworkers explored annulations of 2,3-disubstituted tetrahydropyrans in the synthesis of fused bistetrahydropyrans (Eq. (46)),[38a] whereas Sasaki and coworkers constructed a ring fragment of ciguatoxin (Eq. (47)).[41]

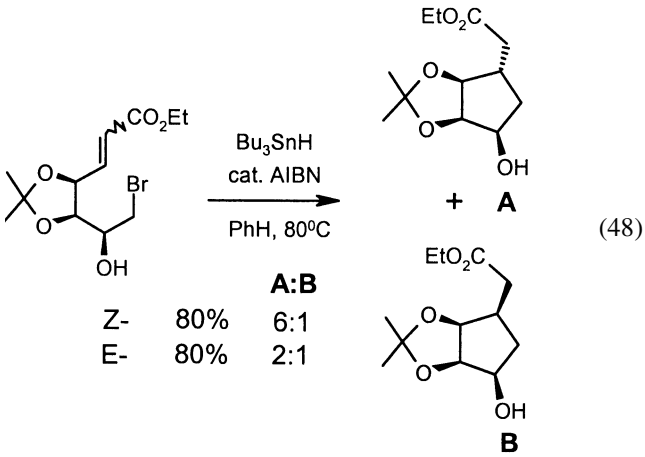


(46)

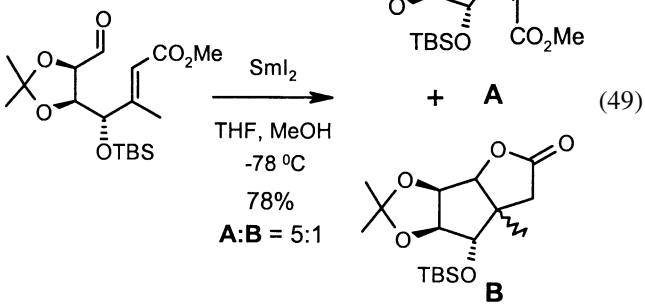


(47)

Taking advantage of easy accessibility to enantiomerically pure carbohydrates, Wilcox and Thomasco successfully converted carbohydrates to corresponding carbocycles that preserve the stereogenic nuclei present in the original aldose (Eq. (48)).[42] Other groups have extended the chemistry to 6-*exo* cyclizations[43] and used samarium diiodide-mediated cyclizations to synthesize the C ring of anguidine (Eq. (49)).[43b]

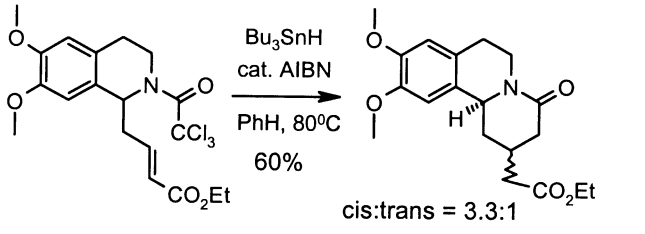


(48)

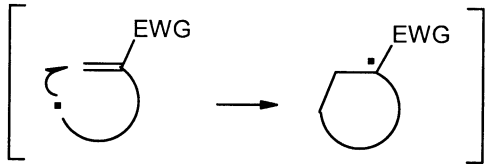


(49)

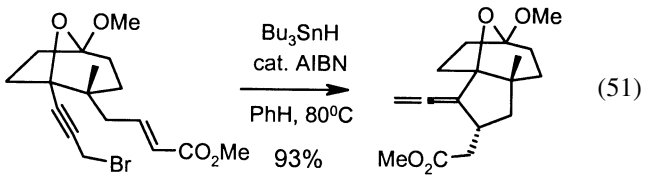
Some highly functionalized tricyclic systems such as benzo[*a*]quinolizines (Eq. (50)),[44a] vinylidene-substituted cyclopentanes (Eq. (51)),[44b] and the decalin moiety of insect antifeedant azadirachtin, have been prepared by cyclization of pre-existing bicyclic rings (Eq. (52)).[44c]



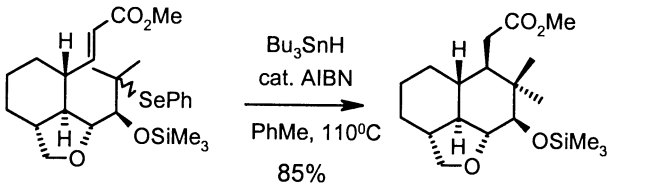
(50)



Scheme 9.

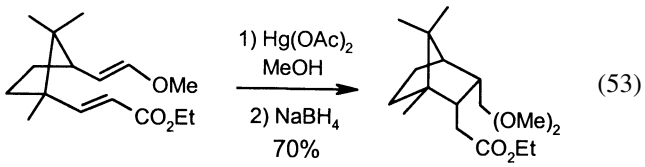


(51)

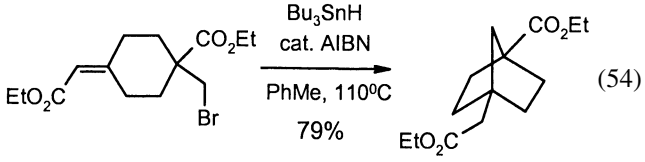


(52)

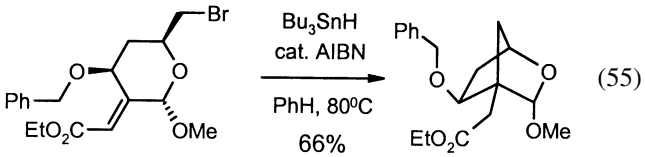
Intramolecular radical cyclizations have also been employed in the synthesis of bridged bicyclic ring systems (Eqs. (53)–(55)).[45]



(53)



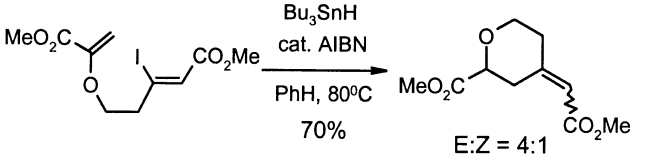
(54)



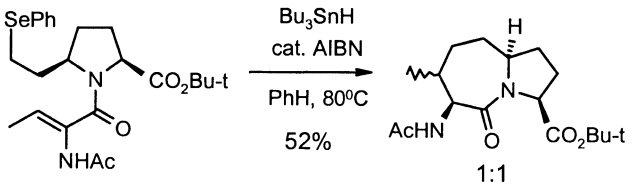
(55)

2.2. *endo* Cyclizations

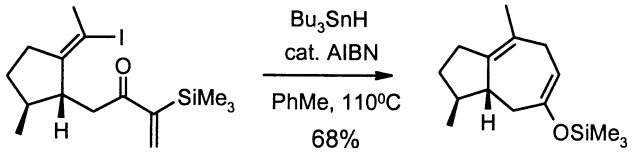
Compared to *exo* cyclizations, *endo* cyclizations are usually minor processes in the formation of standard and medium-sized rings. However, appropriately assembled radical acceptors have the capability to change the regioselectivity in favor of *endo* cyclization (Scheme 9). This concept is exemplified by several cases (Eqs. (56) and (57))[46] which include the synthesis of (+/−)-7-*epi*-β-bulnesene by Negishi and coworkers (Eq. (58)).[46d]



(56)

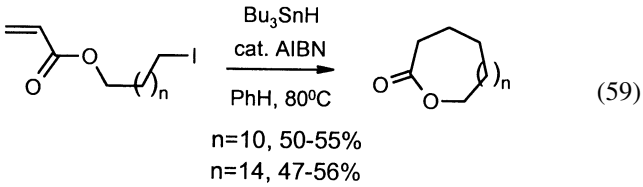


(57)

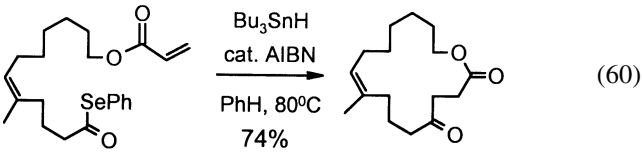


(58)

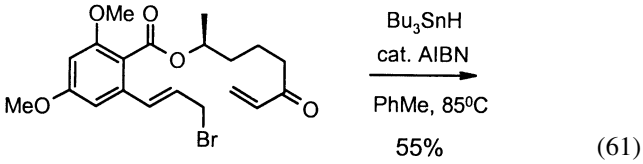
Since steric and electronic effects in the formation of large rings are very different from the formation of five- and six-membered rings, the Michael acceptor can be utilized to gain control of regiochemistry and activate the cyclization. Most radical macrocyclizations in the literature have been designed to be *endo* cyclizations. Porter and coworkers are the pioneers in the synthesis of macrocyclic ketones and lactones by radical cyclizations (Eq. (59)).[36b,47] They also applied this technique to stereoselective synthesis of (−)-(*R*)-muscone.[47b] Boger, Pattenden and others further extended this chemistry to include acyl and allyl radical cyclizations and synthesized a series of biologically interesting molecules (Eqs. (60)–(62)).[48]



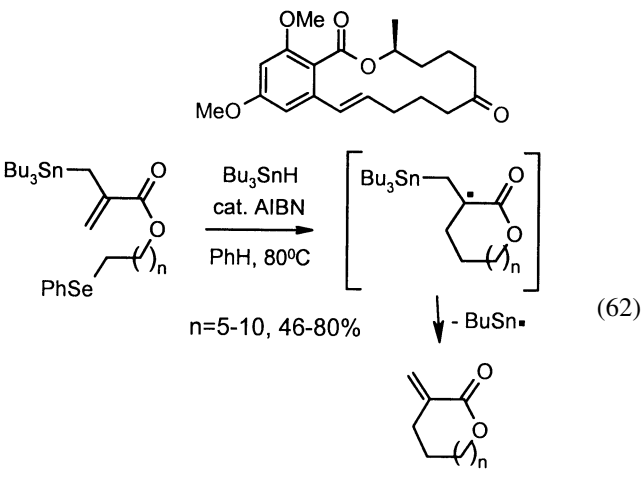
(59)



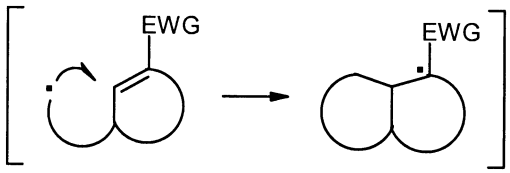
(60)



(61)



(62)



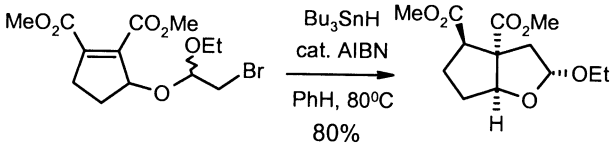
Scheme 10.

3. Addition of acyclic radicals to cyclic radical acceptors

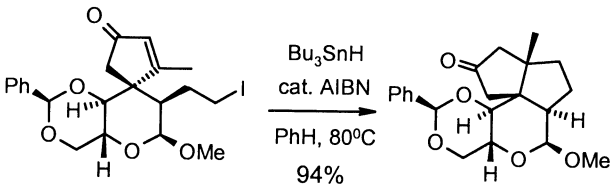
Additions of acyclic radicals to cyclic radical acceptors may lead to formation of fused-, bridged-, and spiro-bicyclic systems. The common radical acceptors are cyclic enones, esters, and their heterocyclic analogs.

3.1. Fused rings

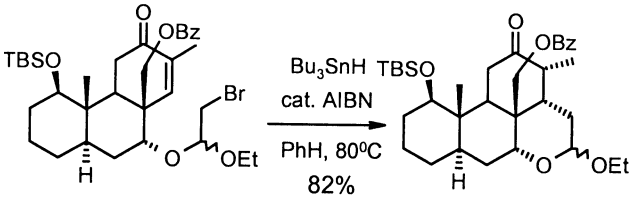
A general way to prepare fused rings is demonstrated in Scheme 10. Cyclic radical acceptors bearing a bromo- or iodoacetal side chain have been used by Stork,[49a] Pattenden and other groups in the synthesis of cyclic acetals (Eqs. (63) and (64))[49b–e] and even more complicated systems such as the ring skeleton of (+)-picrasin B (Eq. (65)).[49f]



(63)

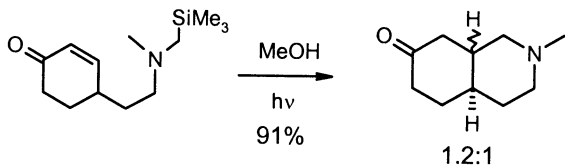


(64)

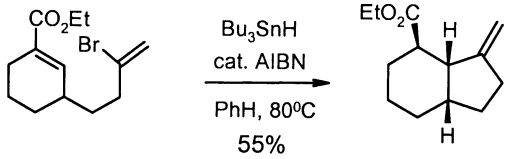


(65)

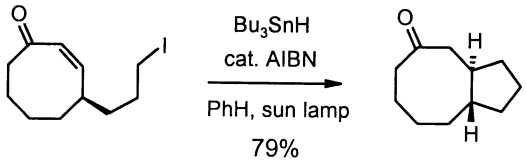
The use of cyclic enones as Michael acceptors for intramolecular free radical additions was first reported by Danishefsky and coworkers.[50] Many other groups have made their contributions to this area by modifying both the ring and the side chain (Eqs. (66) and (67)).[51] The synthetic scope has been extended to seven- and eight-membered cyclic ketones and benzo-fused bicyclic ketones (Eqs. (68) and (69)).[52]



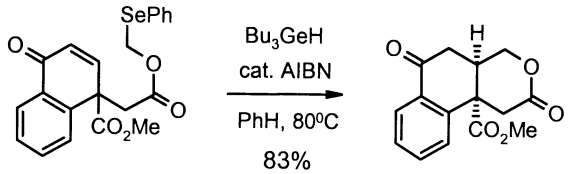
(66)



(67)

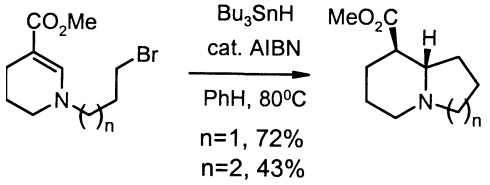


(68)

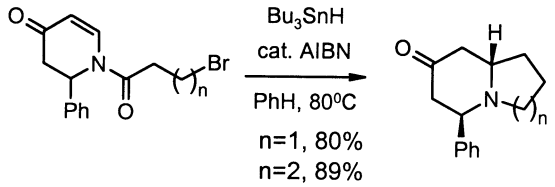


(69)

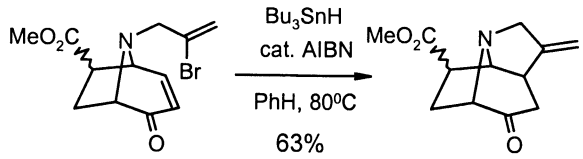
Cyclizations of 1,4,5,6-tetrahydropyridines or 2,3-dihydropyridinones bearing a side chain on the nitrogen have been used to obtain several key intermediates in natural product synthesis. Beckwith and coworkers developed a powerful method to access indolizidine and quinolizidine ring systems in the synthesis of (+/−)-epilupinine, (+/−)-myrtine, and lasubine-I (Eqs. (70) and (71)).[53] Kundig and Ratni accomplished the synthesis of (−)-lasubine-I via the cyclication of an enantiopure planar chiral arylaldehyde tricarbonylchromium complex.[54] Clive and Bergstra synthesized the substituted indolizine component of castoreum.[55] Hart and Ghosh used *N*-substituted bridged bicyclic dihydropyridinones as radical precursors to construct unique tricyclic systems (Eq. (72)).[56]



(70)



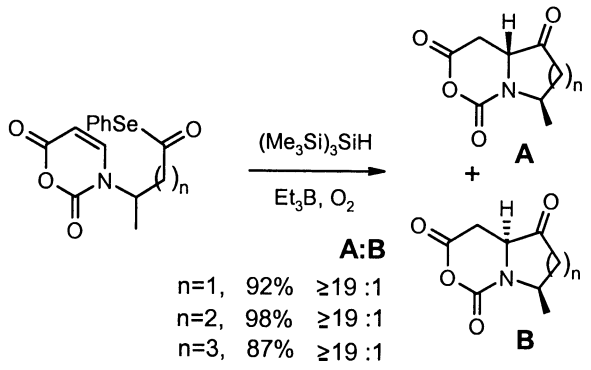
(71)



(72)

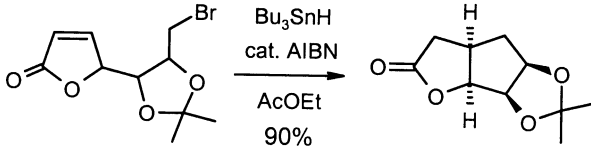
Other heterocycles such as uracils and oxauracils have been used by Falvey and Evans groups as radical acceptors.[57] The

acyl radical cyclizations of oxauracil derivatives provide a stereoselective route to 5,6-, 6,6- and 7,6-azabicycles in excellent yield (Eq. (73)).[57b]

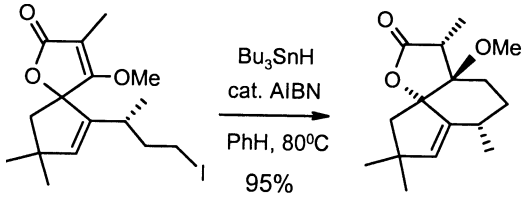


(73)

Cyclizations of appropriately substituted dihydrofurans or furanones have been employed in the synthesis of biologically interesting molecules such as carbasugars (Eq. (74)),[58] (−)-isoavenaciolide,[59] *ent*-Corey lactone alcohol derivatives,[60] and (+/−)-alliacolide (Eq. (75)).[61]

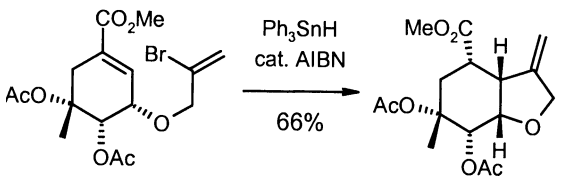


(74)

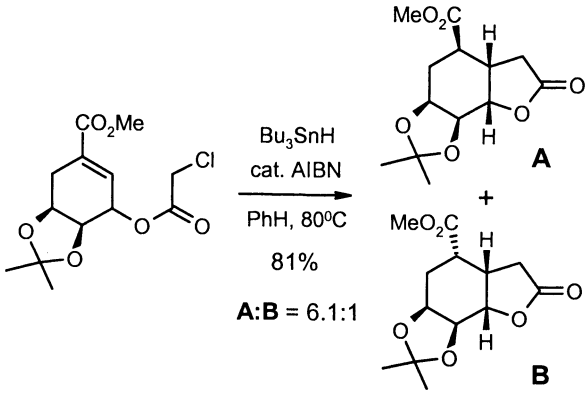


(75)

O-Alkylation, -acylation, and -silylation of the hydroxy group followed by radical cyclization onto a cyclic alkene are useful protocols in the construction of fused oxygen-containing ring systems (Eqs. (76) and (77)).[62] Using this strategy, Hanessian and coworkers synthesized substituted lactones and hexahydrobenzofuran subunit of avermectins and milbemycins.[62a]

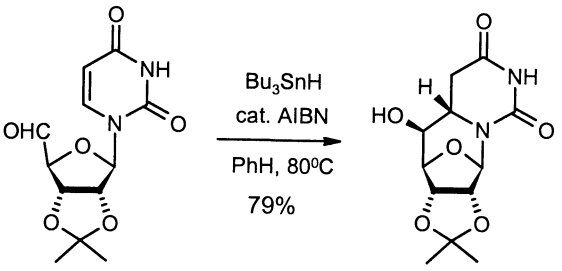


(76)

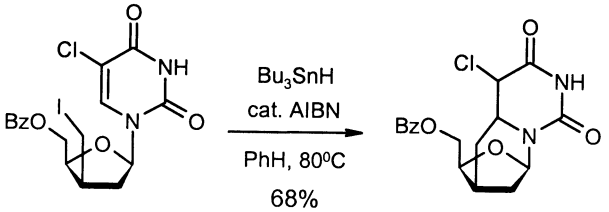


(77)

Ude and coworkers developed a tributyltin hydride mediated cyclization of unsaturated aldehydes and halides in the synthesis of carbon-bridged cyclonucleosides (Eqs. (78) and (79)).[63] Additional examples related to this kind of transformations can be found in the literature.[64]

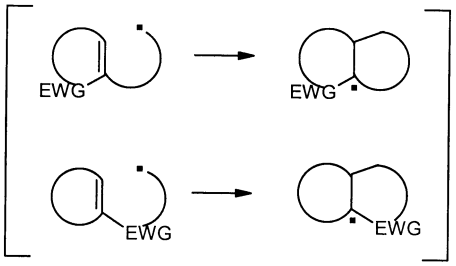


(78)



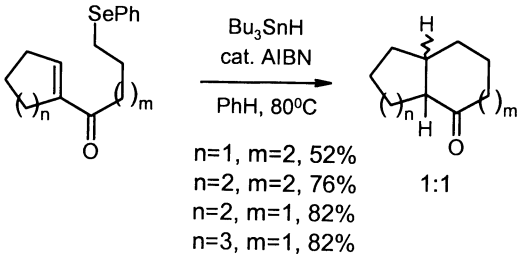
(79)

endo Cyclization reactions have been employed to make fused cyclic systems. In this series, the EWG can be located either on the side chain or on the ring (Scheme 11). Several examples with each kind of design have been reported in the literature. Yamakawa and coworkers examined cyclizations of primary carbon radicals that afforded the bicyclics as a nearly equal mixture of diastereomers (Eq. (80)).[65a] Better *trans*/*cis* selectivity has been reported by Mariano and

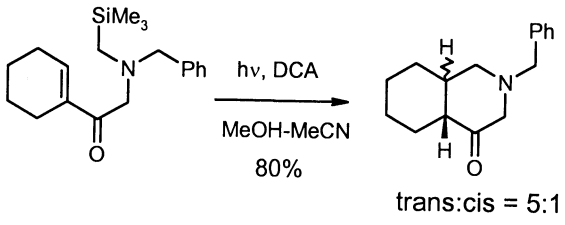


Scheme 11.

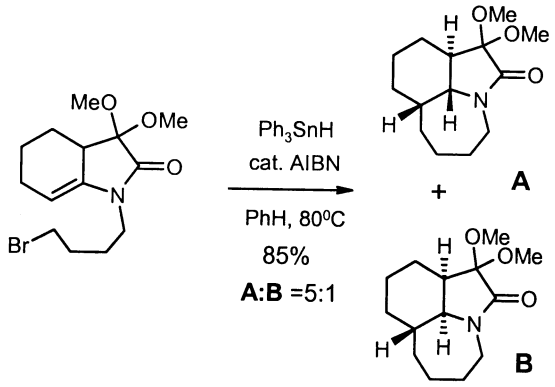
coworkers via cyclizations of allyl or α-amino carbon radicals (Eq. (81)).[22a] Rigby and coworkers constructed the azepinoindole core tricycle of the stemona alkaloids by 7-*endo* cyclizations (Eq. (82)).[66]



(80)



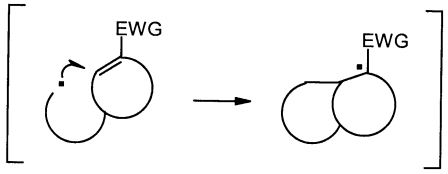
(81)



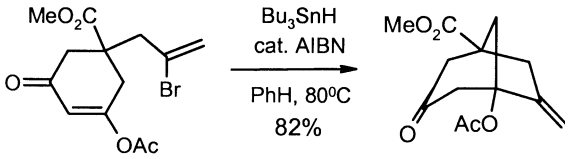
(82)

3.2. Bridged rings

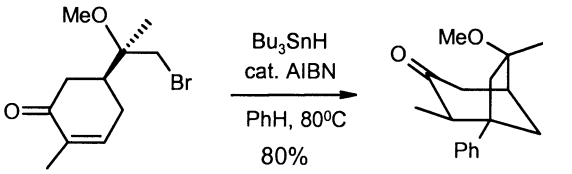
A general approach to bridged rings is outlined in Scheme 12. Placing an appropriate side chain at the 5-position of 2-cyclohexenones is a common practice in the synthesis of bicyclo[3.2.1]octan-3-ones.[67] Marinovic and coworkers explored vinyl radical cyclizations to form bicyclo[3.2.1]octanones (Eq. (83)).[51c] Both Srikrishna and Weinges groups made use of chiral carvone as radical precursors (Eq. (84)).[67a–c] Similar cyclization strategy has been used for the construction of tricyclo[6.2.1.0^{1,5}]-ring systems (Eq. (85)).[68] The tributyltin radical-induced cyclization of a 1,7-enyne derivative has been employed by Rao and Bhaskar in the total synthesis of (+/−)-seychellene (Eq. (86)).[69]



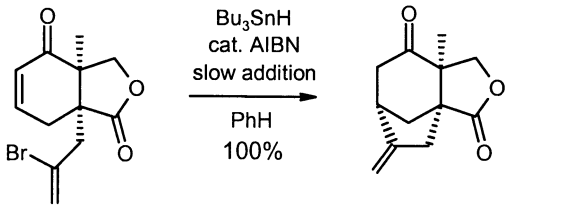
Scheme 12.



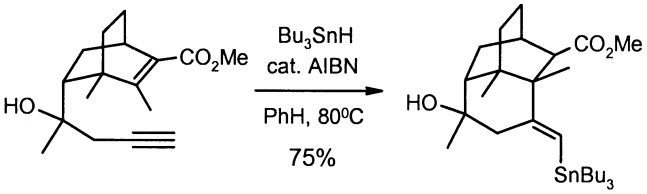
(83)



(84)

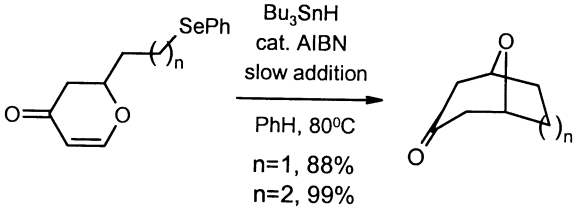


(85)

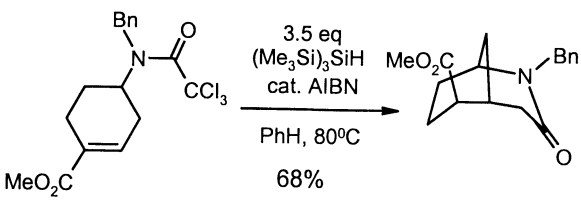


(86)

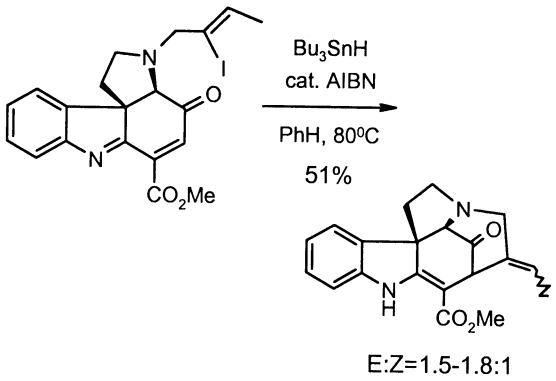
Construction of oxygen- or nitrogen-containing bridged rings have been carried out by Clive and coworkers in the synthesis of 8-oxabicyclo[3.2.1]-, and 9-oxabicyclo[3.3.1]-ring systems (Eq. (87)),[70] and by Bonjoch and coworkers for 6-azabicyclo[3.2.1]- and 2-azabicyclo[3.3.1] ring systems (Eq. (88)).[71] Kuehne and coworkers employed radical cyclization as a key-step in the total synthesis of mossambine (Eq. (89)).[72] Della and coworkers discovered an interesting approach to the synthesis of 1-azabicyclo[2.2.1]heptyl ring system (Eq. (90)).[73]



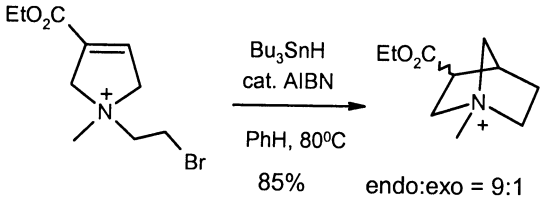
(87)



(88)



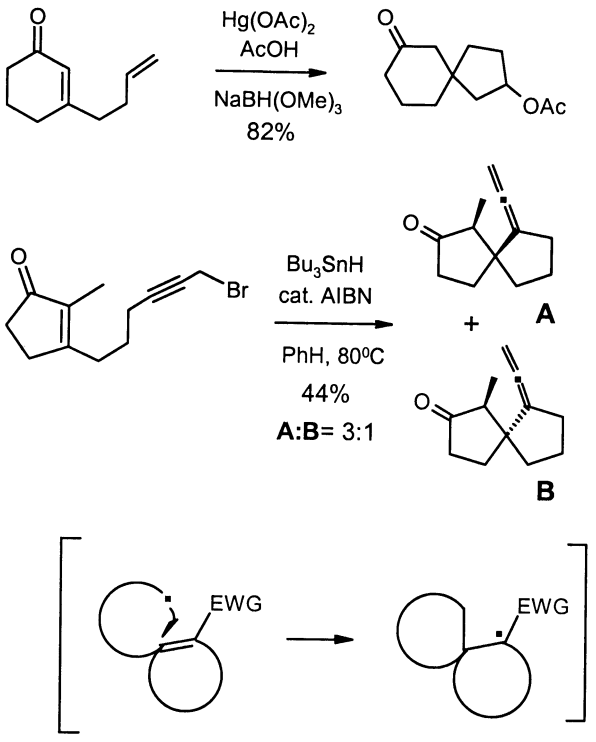
(89)



(90)

3.3. Spiro rings

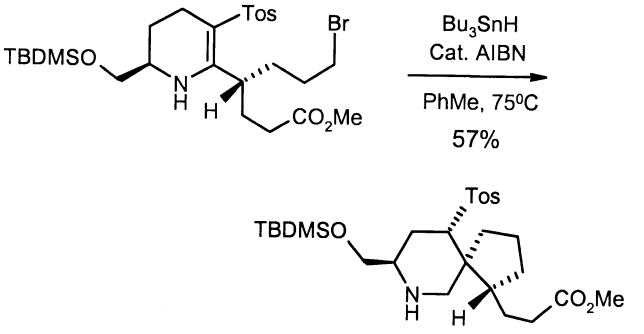
Scheme 13 shows a general method to make spiro rings. α,β-Unsaturated cyclic ketones bearing a side chain at 3-position are very useful systems for spirocyclizations. In addition to the mercury-mediated protocol (Eq. (91)),[50] organosilicon and vitamin-B_{12} induced spirocyclizations have also been reported in the literature.[67d,74] Cyclizations of allenyl radicals generated from propargyl bromides have been employed by Blechert and coworkers in the synthesis of vinylidene-substituted spirocyclopentanes (Eq. (92)).[44b] Clive and coworkers made use of α,β-unsaturated sulfones as radical acceptors for spirocyclization reactions (Eq. (93)).[70,75]



(91)

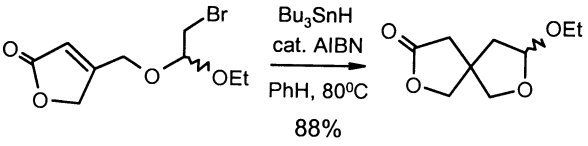
(92)

Scheme 13.

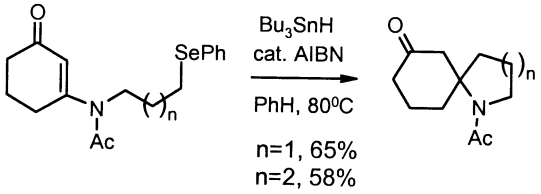


(93)

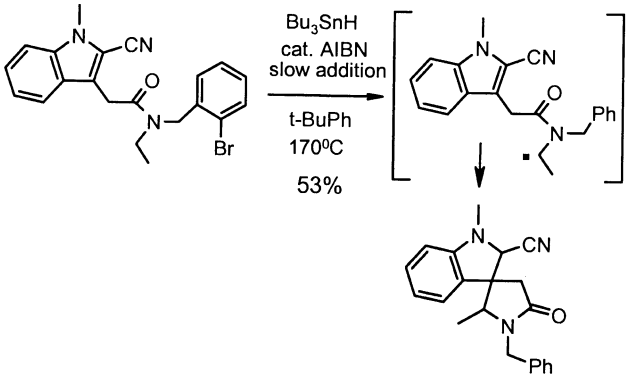
Simpkins,[76] Pattenden,[8] and Mariano[51a] groups have developed several general methods to incorporate oxygen or nitrogen atom into the side chain for the synthesis of heterocyclic spiro ring systems (Eqs. (94) and (95)). Using these protocols, Steel achieved the total synthesis of (+/−)-longianone,[77] whereas Jones and coworkers obtained highly functionalized spirooxindoles (Eq. (96)).[78]



(94)

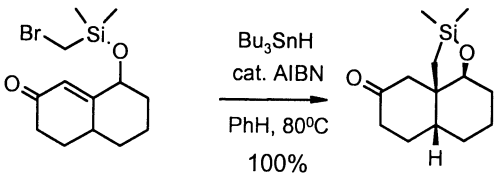


(95)

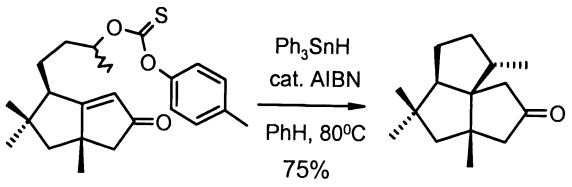


(96)

Spirocyclizations of fused α,β-unsaturated bicyclic ketones have been used by several research groups in gaining access to angular tricyclic ring systems (Eqs. (97) and (98)).[79]



(97)



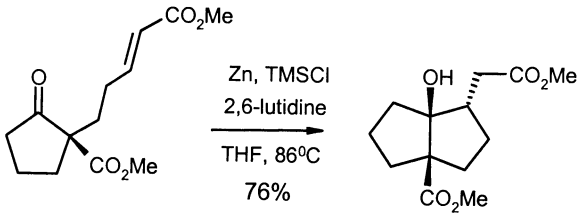
(98)

4. Addition of cyclic radicals to acyclic radical acceptors

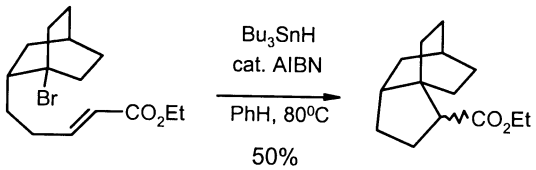
Addition of cyclic radicals to acyclic radical acceptors is an alternative way to construct fused-, bridged-, and spiro-ring systems.

4.1. Fused rings

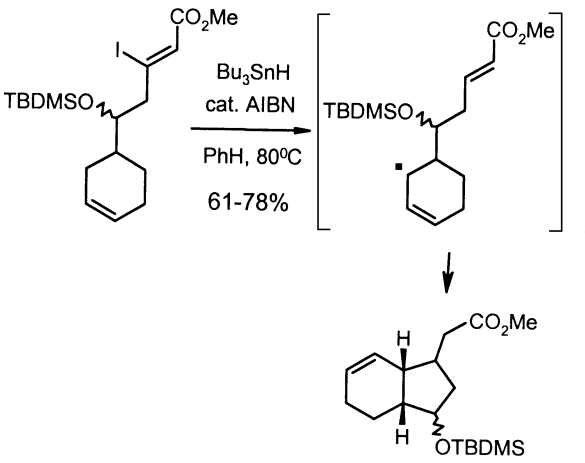
A general approach to fused rings is outlined in Scheme 14. Cyclizations of ketyls generated by reacting of cyclic ketones with Zn–TMSCl (Eq. (99))[80] or tributyltin hydride[11e] have been developed along with other processes such as tin hydride reductions (Eq. (100)),[81] electroreductions,[26a] and 1,5-hydrogen atom transfers (Eq. (101))[82] of halides for fused ring synthesis.



(99)

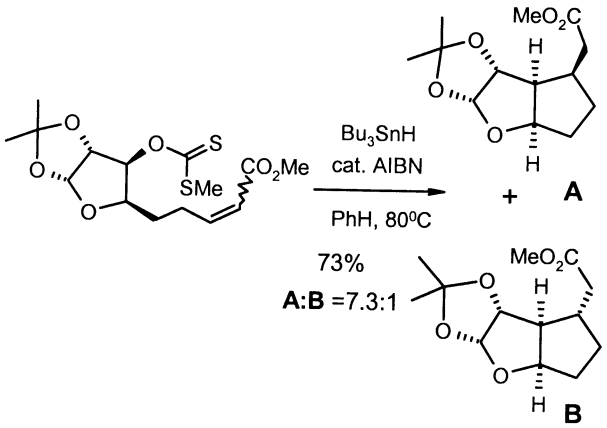


(100)

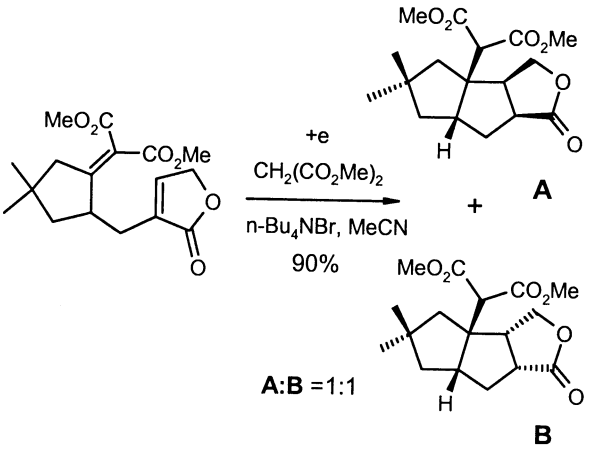


(101)

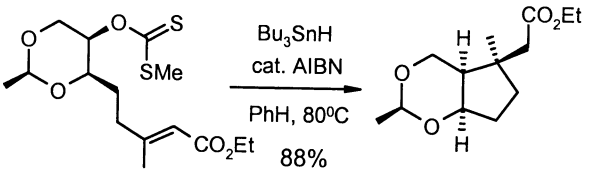
Various oxygen-containing cyclic radicals have been used for cyclizations. Examples include synthesis of (+)-cyclophellitol from the oxiranyl radical,[83] synthesis of functionalized cyclopentanoids from carbohydrates (Eq. (102)),[84] formation of tricyclic lactones (Eq. (103)),[85] and total synthesis of (+/−)-pleurotin[86] and dolabellanes (Eq. (104)).[87]



(102)

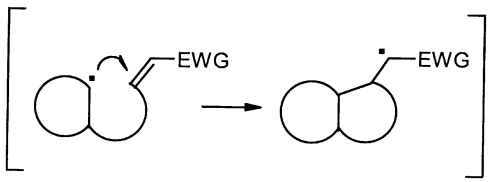


(103)

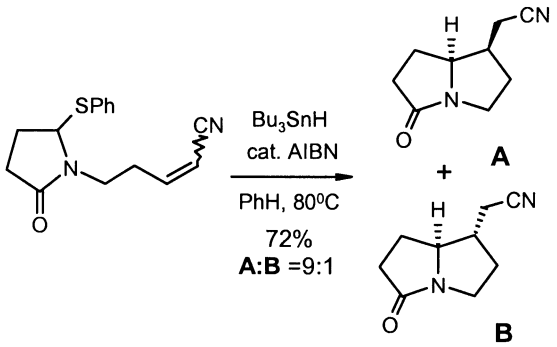


(104)

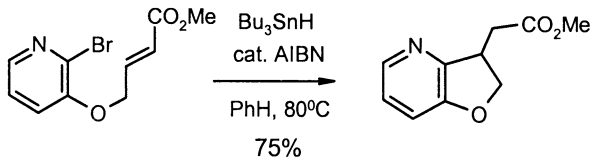
Nitrogen-containing cyclic radicals generated from γ-lactams (Eq. (105)),[88] pyrolidines,[89] pyridines (Eq. (106))[90] and indoles (Eq. (107))[91] have also been used in construction of highly functionalized polycyclic ring systems.



Scheme 14.



(105)



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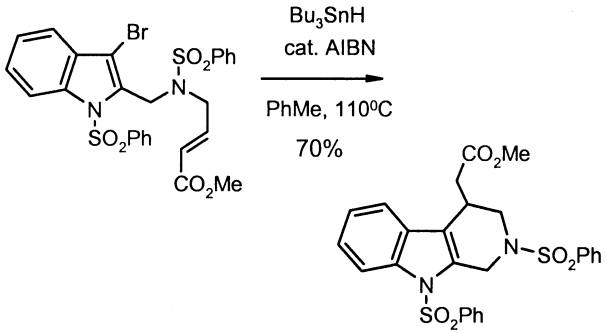
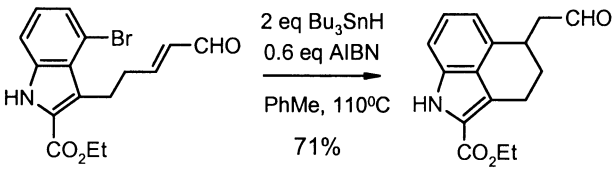
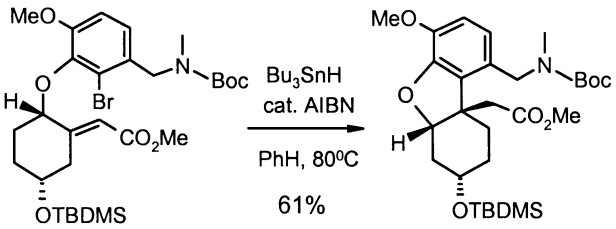


(107)

Cyclizations of aryl radicals provide an entry for the construction of benzo-fused cyclic ring systems.[92] This strategy has been used in the synthesis of functionalized tricyclic ring systems such as an intermediate for ergot alkaloids (Eq. (108))[93] and the ring skeleton of (+/−)-lycoramine (Eq. (109)).[94]

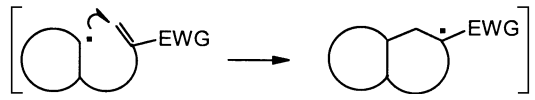


(108)



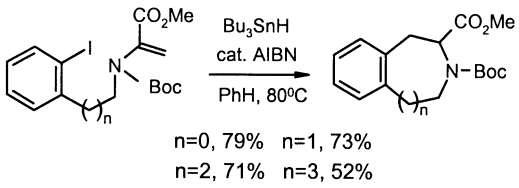
(109)

endo Cyclizations of cyclic radicals (Scheme 15) have been devised to construct fused-ring systems such as conformationally constrained amino acids (Eq. (110)),[95] the ring



Scheme 15.

skeleton of perhydronaphthalenes (Eq. (111)),[96] 4-substituted-β-carbolines (Eq. (112)),[91] and benzothienoindolizidinones (Eq. (113)).[97]



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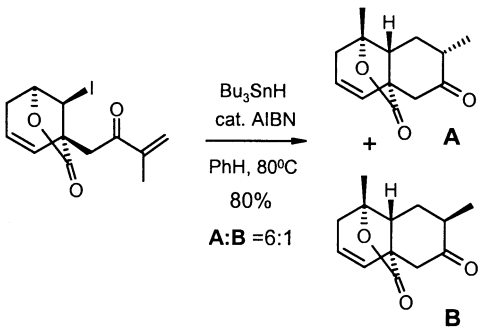
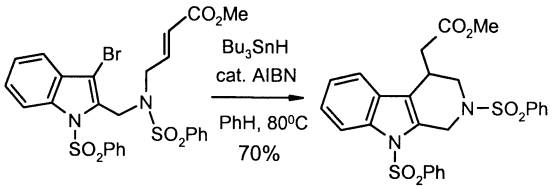
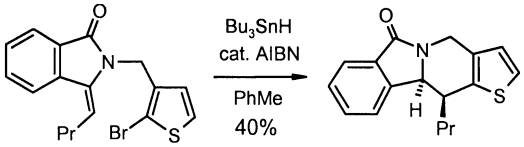


(111)



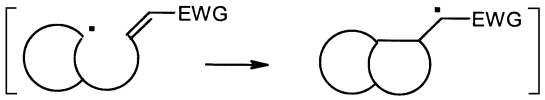
(112)



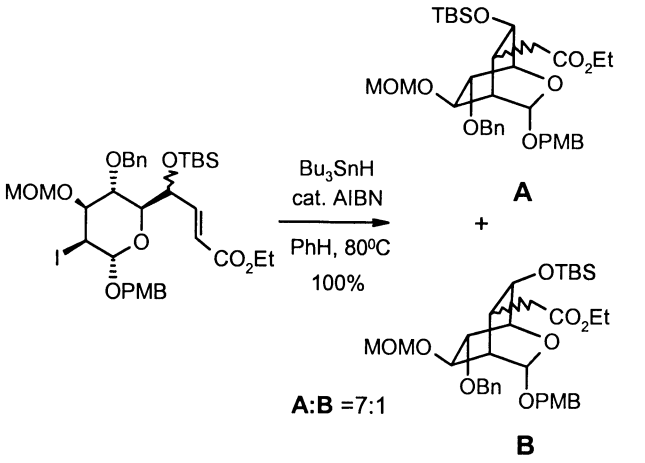
(113)

4.2. Bridged rings

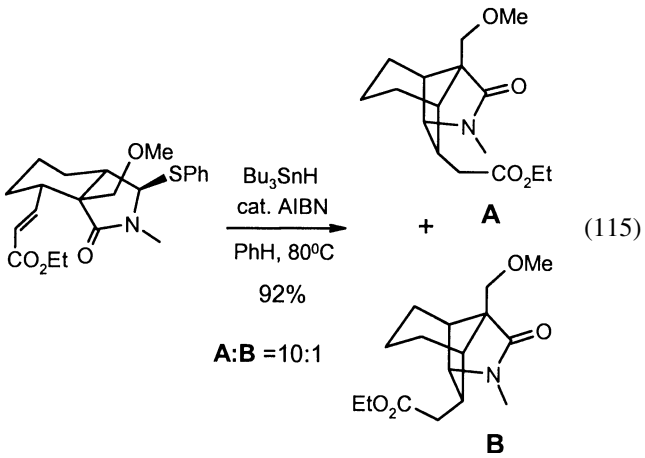
Many examples of forming bridged bicycles by annulation of cyclic radicals (Scheme 16) have been developed in carbohydrate chemistry. Fraser-Reid and coworkers developed a general method to access [2.2.1] and [2.2.2] oxabicycles subunit (Eq. (114))[98] and applied it to the synthesis of an azadirachtin.[99] Hart and coworkers extended this protocol to construct the substructure of gelsemine (Eq. (115)).[100]



Scheme 16.



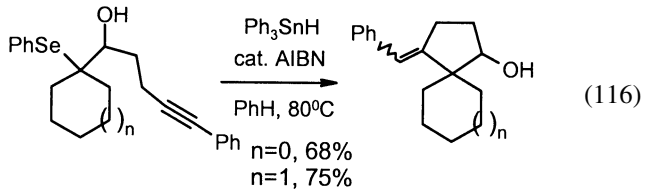
(114)



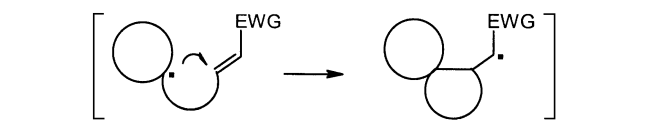
(115)

4.3. Spiro rings

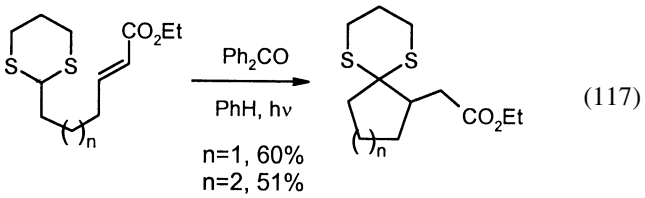
Cyclizations of tertiary cyclic carboradicals can lead to formation of quaternary spiro carbocenters (Scheme 17). In addition to tin hydride reduction of appropriate radical precursors (Eq. (116)),[101] the photo-reaction of dithioacetals (Eq. (117))[102] and 1,5-hydrogen atom transfers (Eq. (118))[82a,b,103] are good protocols to generate tertiary carboradicals.



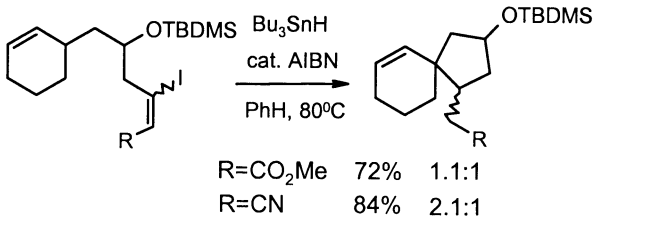
(116)



Scheme 17.



(117)



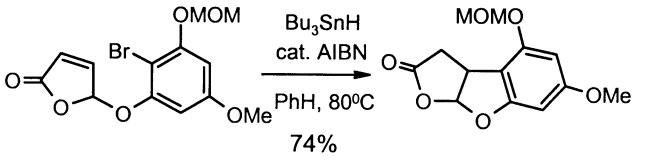
(118)

5. Addition of cyclic radicals to cyclic radical acceptors

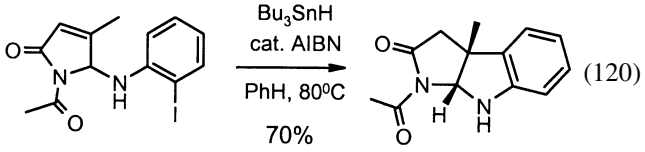
Additions of cyclic radicals to suitable cyclic radical acceptors can lead to formation of a new bond that serves as a linker to connect two pre-existing rings. This strategy has provided synthetic chemists a useful tool for the construction of fused–fused, fused–bridged, fused–spiro, and even spiro–bridged ring systems.

5.1. Fused–fused rings

A general method to make fused–fused rings is outlined in Scheme 18. α,β-Unsaturated lactones and lactams are good radical acceptors. Snieckus and Hoffmann groups prepared furobenzofurans by cyclization of butenlide ethers in the formal total synthesis of aflatoxins (Eq. (119)).[104] Hoffmann and coworkers also made use of pyrrolidinone derivatives as radical precursors in the synthesis of benzoannulated heterodiqinanes (Eq. (120)).[105]

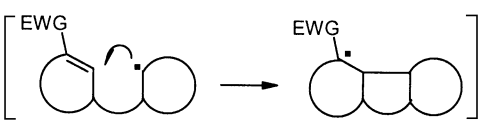


(119)



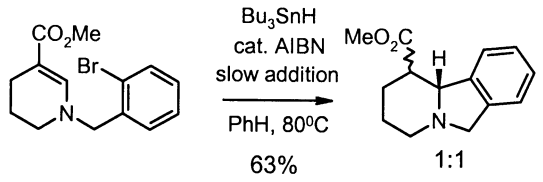
(120)

N-Substituted tetrahydropyridines and dihydropyridinones are versatile intermediates in the synthesis of heterocycles such as quinolizidines and indolizidines (Eqs. (121) and (122)).[53,106] Incorporating different nitrogen-containing

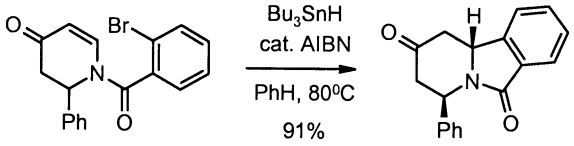


Scheme 18.

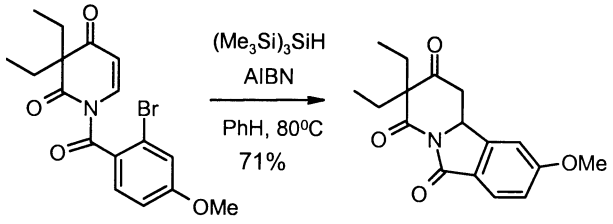
rings as radical acceptors further extends the synthetic scope of this reaction type (Eq. (123)).[107]



(121)

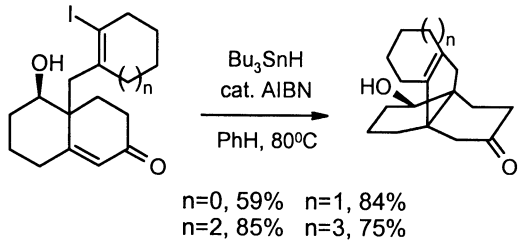


(122)



(123)

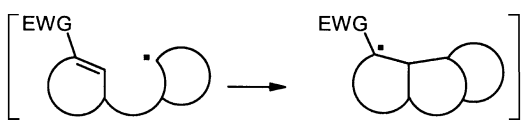
Rajamannar and Balasubramanian have demonstrated that addition of vinyl radicals onto the enone double bond can lead to formation of functionalized propellanes (Eq. (124)).[108]



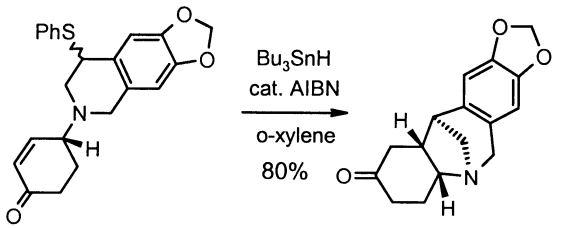
(124)

5.2. Fused–bridged rings

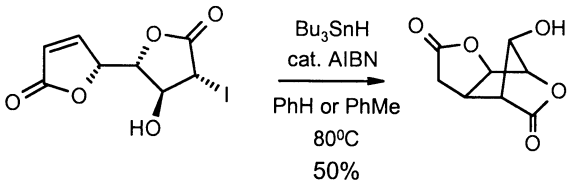
New synthetic approaches to fused–bridged ring systems (Scheme 19) have been developed in the synthesis of natural products. Examples include the synthesis of basic skeleton of montainine-type *amaryllidaceae* alkaloids (Eq. (125))[109] and the bridged framework related to beticolin and cebetin.[110] Unique fused–bridged lactones have also been prepared by intramolecular addition of cyclic radicals (Eqs. (126) and (127)).[98c,99]



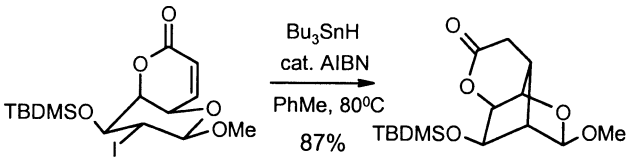
Scheme 19.



(125)



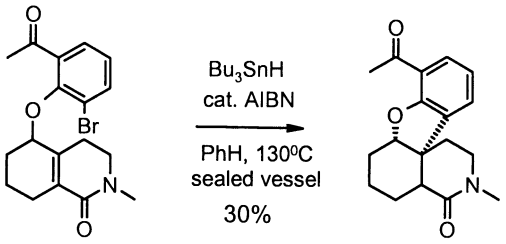
(126)



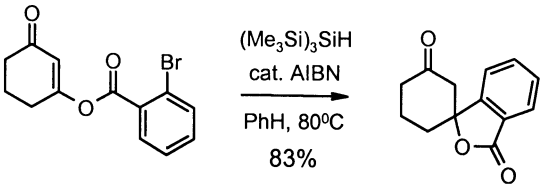
(127)

5.3. Fused–spiro rings

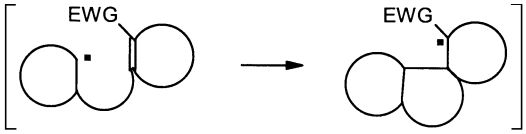
A general method to make fused–spiro rings is shown in Scheme 20. Chen and coworkers utilized aryl radical cyclizations to access the morphine ring fragment (Eq. (128)).[111] Using 2-bromobenzoic acids as the building block, Zhang and Pugh developed a general method to synthesize a number of spirobenzolactones (Eqs. (129)–(131)).[112]



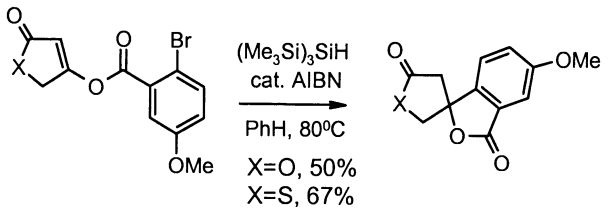
(128)



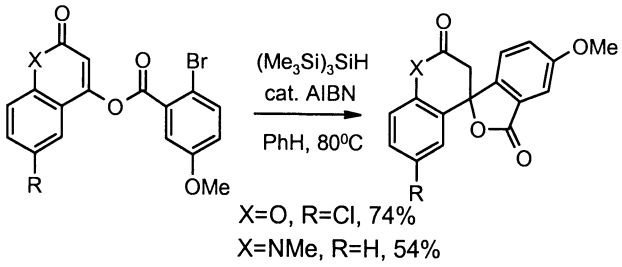
(129)



Scheme 20.



(130)



(131)

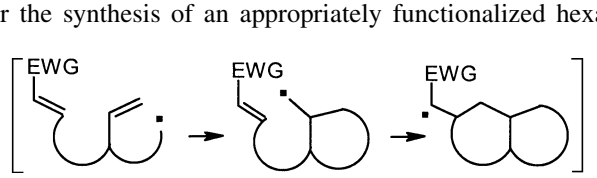
6. Cascade sequences

Tandem (cascade) reactions have high synthetic efficiency that sequentially generates more than one bond in a single reaction process. Numerous free radical tandem cyclizations have been developed for constructions of bi-, tri- and even polycyclic ring systems. A good portion of these are related to the Michael-type additions. Reactions discussed in this section will involve at least one step of conjugate addition during the tandem process. Reactions with a heteroatom addition–cyclization sequence have been discussed elsewhere in this Report and will not be included in this section.

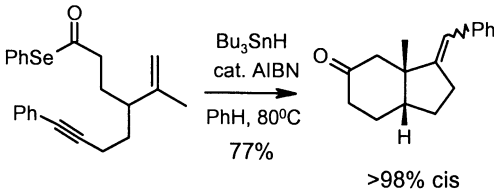
6.1. Cyclization–cyclization (transannulation) sequences

Scheme 21 represents only one particular case of cyclization–cyclization sequences. Examples with a variety of precursors and cyclization sequences will be discussed in this section.

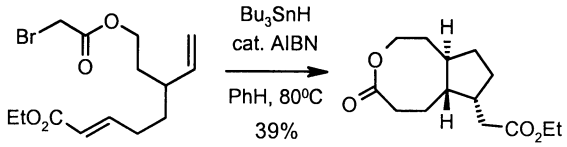
Boger and Mathvink have demonstrated that double cyclizations initiated by acyl radicals can lead to formation of fused [4.3.0] bicycles with excellent *cis* selectivity (Eq. (132)), while formations of [4.4.0] bicycles are less stereoselective.[48a] Lee and coworkers reported 8-*endo* cyclizations of α-ester carboradicals followed by 5-*exo* conjugate additions in stereoselective synthesis of bicyclic heptanolactones (Eq. (133)).[113] Carretero and Adrio studied the sequential cyclization of conjugated sulfones in the construction of highly substituted 2-oxa[3.3.0] and 9-oxa-[4.3.0] bicyclic compounds (Eq. (134)).[114] Parsons and coworkers utilized a tandem process to construct a model for the synthesis of an appropriately functionalized hexahydrobenzofuran moiety present in avermectins (Eq. (135)).[115] More examples can be found in the literature.[116]



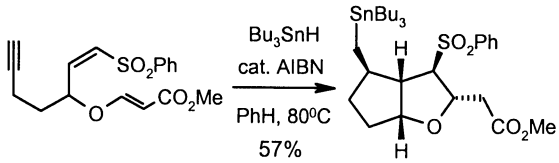
Scheme 21.



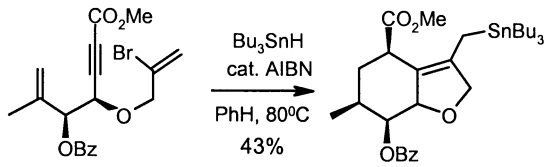
(132)



(133)

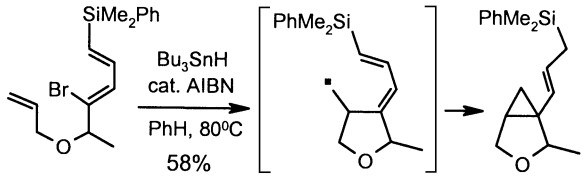


(134)

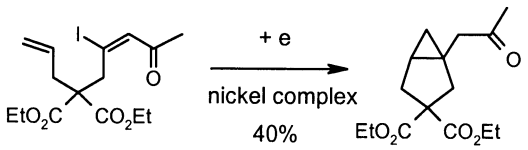


(135)

Luh and Weng investigated a tandem [2+1] cycloaddition based on sequential 5-*exo* and 3-*exo* cyclizations that led to formation of fused cyclopropanes (Eq. (136)).[117] Ozaki and coworker prepared a similar ring system by an electroreductive reaction (Eq. (137)).[118]

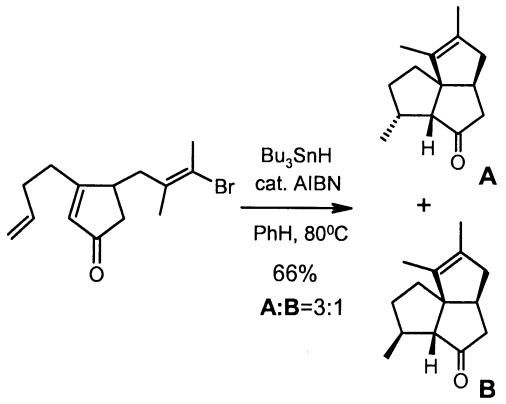


(136)

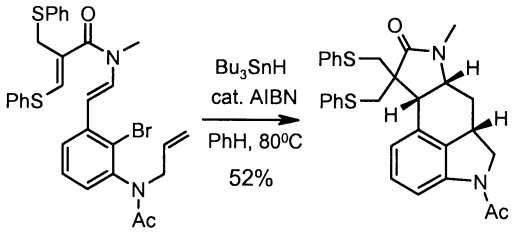


(137)

Several angular triquinanes have been synthesized by tandem cyclizations.[119] Curran and Kuo carried out a series of model studies in the total synthesis of (+/−)-silphiperfolene and (+/−)-9-episilphiperfolene (Eq. (138)).[119a,b] Schafer and coworkers utilized Kolbe electrolysis to initiate the cyclization of unsaturated carboxylic acids.[52c] Synthesis of more complicated fused-ring systems have been achieved by Parker and Fokas for a morphine fragment[120] and by Parsons and coworkers for lysergic acid derivatives (Eq. (139)).[121]

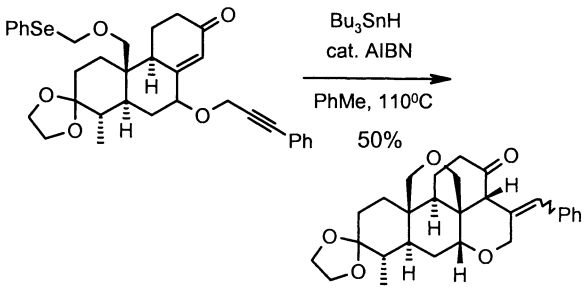


(138)

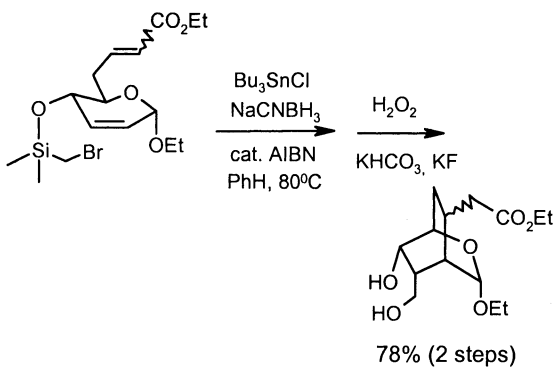


(139)

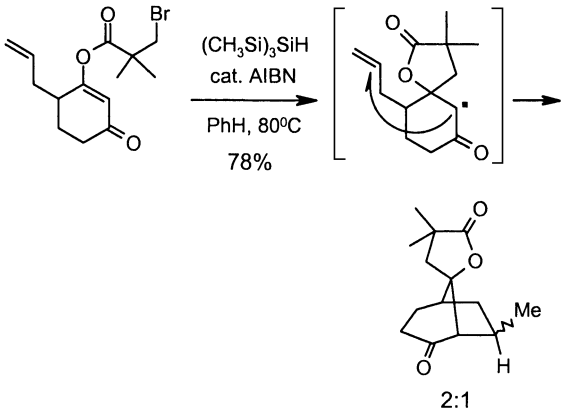
The use of tandem cyclizations to construct bridged- and spiro-ring systems has good synthetic potential. Employing this strategy, Kim and Fuchs constructed polycyclic rings (Eq. (140)),[122] Fraser-Reid and coworkers synthesized tricyclic carbohydrate derivatives containing [2.2.1] and [2.2.2] structures (Eq. (141)),[123] while Zhang and Pugh found a unique pathway to novel spiro–bridged tricyclic molecules (Eqs. (142) and (143)).[124]



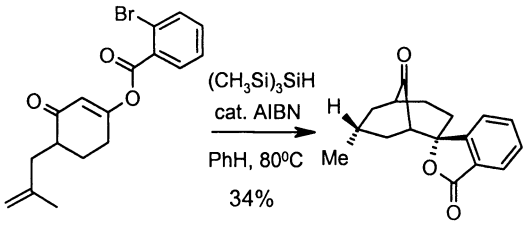
(140)



(141)

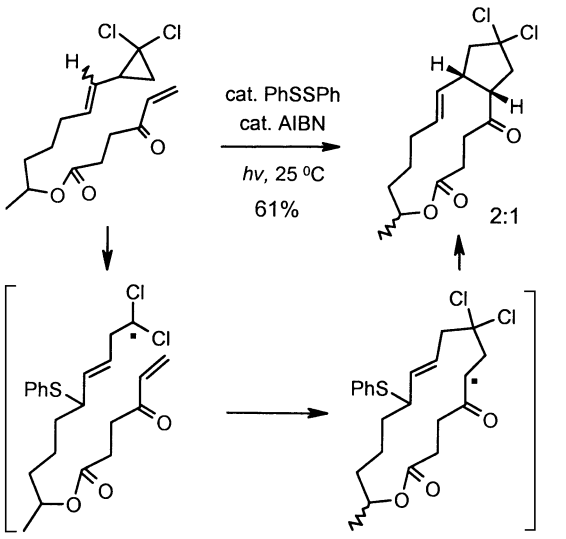


(142)

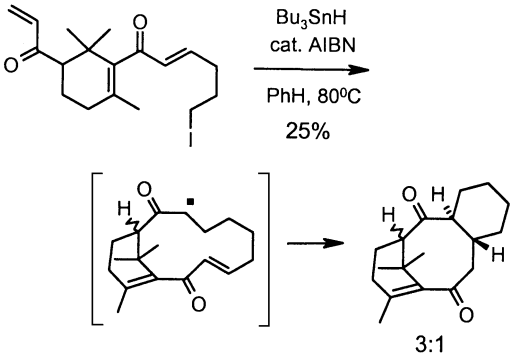


(143)

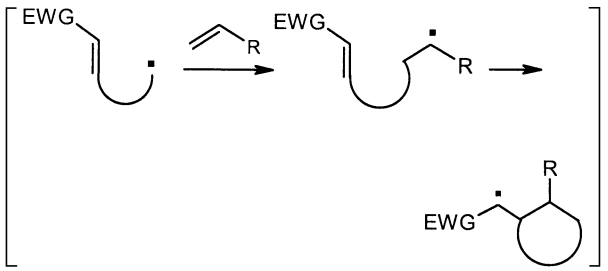
Tandem reactions with a cyclization–transannulation sequence have been used by Feldman and coworkers in the synthesis of the brefeldin ring system (Eq. (144))[125] and by Pattenden and coworkers for the taxane skeleton (Eq. (145)).[126] *endo* Cyclizations were involved in both cases.



(144)



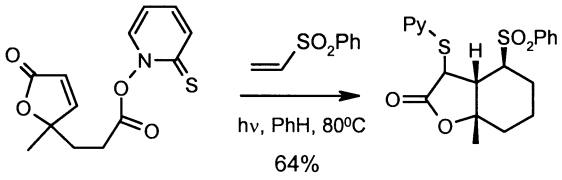
(145)



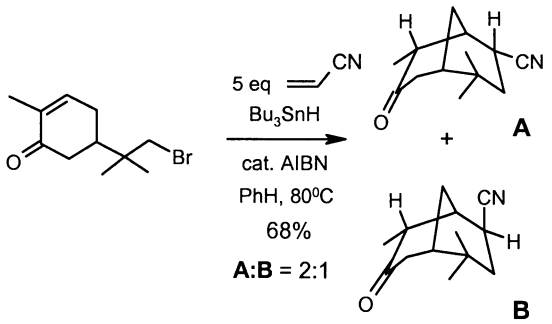
Scheme 22.

6.2. Addition–cyclization sequences

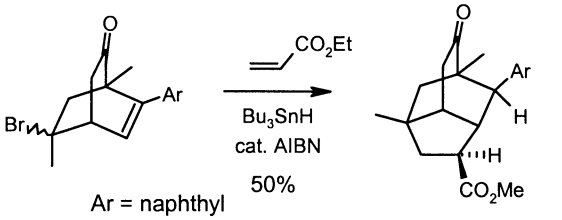
Tandem reactions with an addition–cyclization sequence can also combine inter- and intramolecular additions (Scheme 22). Several cases in the literature illustrated these transformations. Zard and coworkers designed a reaction initiated with decarboxylation of *N*-hydroxy-2-thiopyridone esters (Eq. (146)).[127] Srikrishna and coworkers employed carvone hydrohalides as starting material in the synthesis of functionalized chiral bicyclo[3.3.1]nonanes (Eq. (147)).[128] They further extended this methodology to construct tricyclo[4.3.1.$0^{3,7}$]decane carbon framework which is found in tricyclic sesquiterpenes (Eq. (148)).[129]



(146)



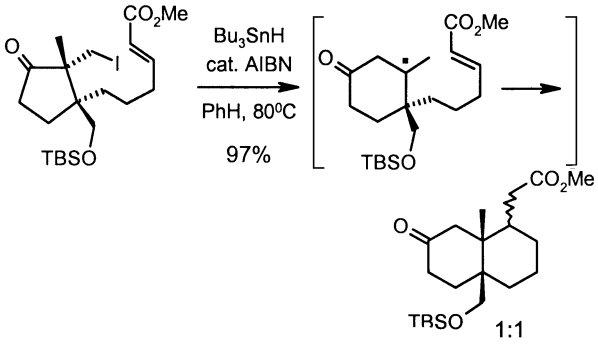
(147)



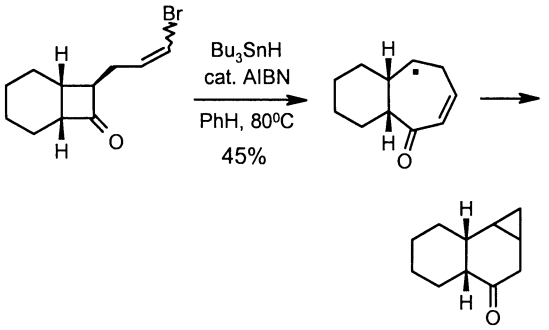
(148)

6.3. Ring expansion–cyclization (transannulation) sequences

Free radical ring expansion reactions have provided synthetic chemists an alternative route to access expanded ring systems.[130] The Boger and Nemoto groups coupled the ring expansion process with a Michael addition in the synthesis of fused-bicycles (Eq. (149)).[37b,131] In the study of cyclobutanone-based ring expansions, Dowd and Zhang observed an interesting Michael-type transannulation that led to formation of fused-cyclopropanes (Eq. (150)).[132]



(149)

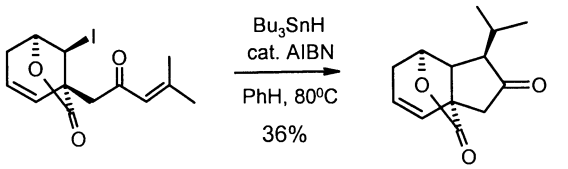


(150)

7. Anti-conjugate additions

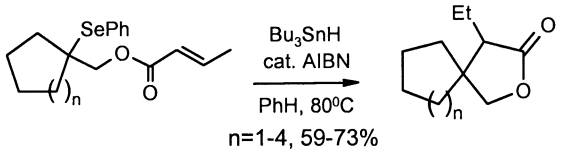
Since free radicals have the tendency to undergo 5-*exo* and 6-*exo* cyclizations, which in many cases can override the position directing effects contributed by Michael acceptors and results in five- or six-membered anti-Michael addition products via *exo*-cyclizations (Scheme 23). This preference is usually enhanced by introduction of substituents at the β-position of the Michael acceptor that sterically interfere with the conjugate addition.

A regio- and stereoselective anti-Michael addition has been observed by Hart and coworkers in the cyclization of lactone radical (Eq. (151)).[96] Clive and coworkers developed a lactone synthesis based on the cylization of tertiary cyclic radicals generated from phenylselenides (Eq. (152)).[101] Another lactone molecule related to anti-tumour antibitic (−)-methylenolactocin has been synthesized by Weavers and coworkers using anti-Michael addition of a chiral iodo acetylenic ester (Eq. (153)).[133]

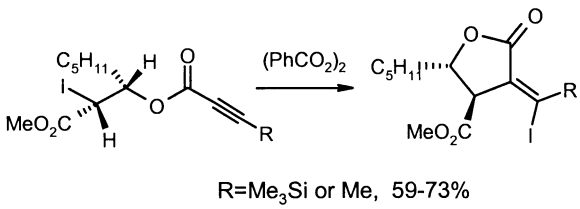


(151)

Scheme 23.

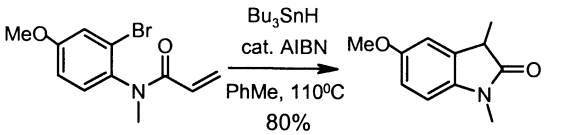


(152)

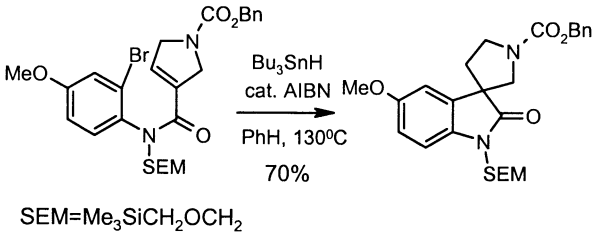


(153)

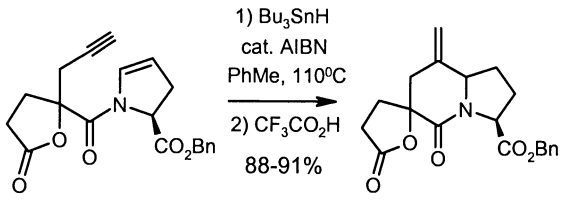
O-Haloacrylanilides are a good anti-Michael addition system that have been extensively used in the synthesis of ring skeletons related to some biologically interesting molecules, such as geneserine (Eq. (154)),[134] (+/−)-gelsemine,[135] and horsfiline (Eq. (155)).[136] *o*-Haloacrylanilides also have been used by Jones and Curran groups as model systems in studies of chiral induction[137] and chirality transfer.[138] Clive and coworkers made use of enyne radical cyclizations to synthesize angiotensin-converting enzyme inhibitors (+/−)-A58365A and (+/−)-A58365B (Eq. (156)).[139] 4-*exo* anti-Michael additions have also been used in the synthesis of β-lactams.[140]



(154)

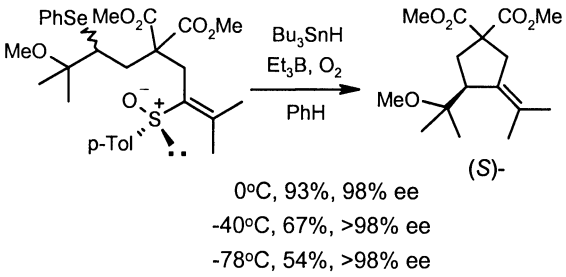


(155)



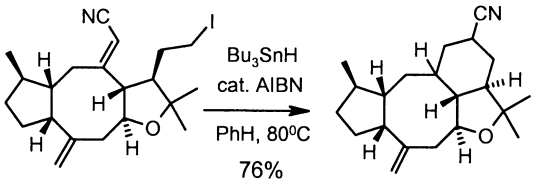
(156)

Malacria and coworkers designed an anti-Michael addition–elimination sequence in the synthesis of enantiomerically pure cyclopentanes by the use of enantiopure sulfoxide unit as a temporary auxiliary (Eq. (157)).[141] Interestingly, in the presence of the Lewis acid the stereochemical outcome of this reaction can be reversed.

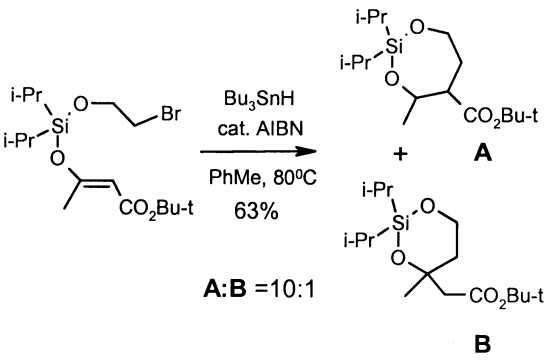


(157)

In addition to the 5-*exo* anti-Michael additions described above, anti-Michael additions with 6-*endo* or 7-*endo* cyclization pathways also have been reported in the literature (Eqs. (158) and (159)).[142,36b]



(158)



(159)

8. Conclusions

This review has demonstrated that intramolecular free radical conjugated additions are useful tools in the construction of cyclic molecules. There is no doubt this research area will keep enjoying further development in both synthetic methodology studies and natural product synthesis.

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Biographical sketch

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