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Thiol-mediated radical cyclizations

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Contents

1. Introduction

Since the discovery of the triphenylmethyl radical by Gomberg more than a century ago,[1] radical chemistry has become a very important tool in preparative organic synthesis. Recently, in free radical chemistry, radical intermediates were considered too reactive to be used in synthetic chemistry.[2] These results underscore the importance of developing new methods for the synthesis of

Abbreviations: ACCN, azobis-cyclohexanecarbonitrile; AIBN, azobis(isobutyronitrile); AMBN, azobis(methylisobutyronitrile); Bn, benzyl; Cp, cyclopentadienyl; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; CTAN, ceric-tetra-*n*-butylammonium nitrate; DFT, density functional; DABCO, 1,4-diazobicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM, dichloromethane; DEPO, diethylphosphine oxide; DIBAL-H, diisobutylaluminum hydride; DLP, dilauroyl peroxide; DEAD, diethyl azodicarboxylate; DMF, dimethyl formamide; DMSO, dimethyl sulfoxide; DTBP, di-*tert*-butyl peroxide; DBPB, 2,2-di-*tert*-butylperoxybutane; EPHP, 1-ethylpiperidine hypophosphite; HAT, hydrogen atom transfer; LDA, lithium diisopropylamide; *m*-CPBA, *meta*-chloroperoxybenzoic acid; MO, molecular orbital; MOM, methoxymethyl; MW, microwave; PRC, polarity reversal catalysis; SET, single-electron transfer; TBHP, *tert*-butyl hydroperoxide; THF, tetrahydrofuran; TOCO, thiol–olefin co-oxygenation; TS, transition state; Ph, phenyl; Ts, tosyl; TFA, trifluoroacetic acid; TMS, trimethylsilyl; TTMSH, tris(trimethylsilyl)silane; TBST, tri-*tert*-butoxysilanethiol; UV, ultraviolet.

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various carbocycles, as well as heterocycles and natural products, which may be achieved by constructing five- and six-membered and larger rings,[3] either in separate or in multi-step processes. Radical reactions are generally conducted under very mild conditions. Thus, various sensitive functional groups are tolerated under free radical conditions. Primary, secondary, and tertiary radicals can be effectively carbonylated to transform them into carbonyl derivatives such as aldehydes,[4] ketones,[5] esters,[6] lactones,[7] thiolactones,[8] amides,[9] lactams,[10] and acyl selenides.[11] Some of these transformations are associated with atom or group transfer, inter- or intramolecular radical addition, cascade reactions, radical translocation, one-electron oxidation, or ionic chemistry. Spirocycles can be effectively synthesized by radical cyclization procedures employing an intramolecular radical attack onto a cyclic olefin,[12] intramolecular addition of tertiary cyclic radicals to an alkene[13] or alkyne,[14] or cyclization of a radical species containing a pre-occupied quaternary carbon center.[15] Recently, radical reactions are emerging as one of the leading methods in many industrial processes—especially for producing a whole class of useful 'plastics' or polymers. Radical reactions are also of vital importance in biology and medicine.

The search for various carbocycles, heterocycles, and natural products, and many new methodologies has been a central goal for radical chemists in recent years. The present review article will summarize recent achievements in tin-free radical cyclization reactions mediated by thiols.[16]

2. Reagents, solvents, and radical initiators used in radical cyclization

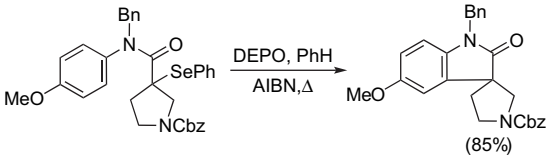
To date, most of the radical reactions were conducted using tin hydride reagents, such as tri-*n*-butyltin hydride ($^{n}Bu_3SnH$), trimethyltin hydride (Me_3SnH), and triphenyltin hydride (Ph_3SnH).[17] An alternative procedure involving the use of a small amount of tri-*n*-butyltin chloride ($^{n}Bu_3SnCl$) with sodium cyanoborohydride for the in situ generation of tri-*n*-butyltin hydride is also known.[3] There are, however, drawbacks associated with such tin-based radical reagents. One of the major problems in the tin-based procedures is the toxicity of the trialkyltin hydrides.[18] Furthermore, it is very difficult to completely remove the toxic tributyltin residues from the reaction mixtures. The purification of products is, therefore, very difficult, for which efficient purification protocols have been developed.[19] These drawbacks strongly limit the applications of radical chemistry in the areas of drugs and medicine.

Various efforts have been directed toward the application of tin-free radical chemistry.[16,19,20] Tributylgermanium hydride (Bu_3GeH),[21] tris(trimethylsilyl)silane [$(TMS)_3SiH$ or TTMSS],[21,22] and polymethylhydrosiloxanes[23] are superior alternatives to $^{n}Bu_3SnH$. Other reagents, such as samarium diiodide,[24] Cp_2TiCl_2,[25] and indium,[26] have good potential to replace the toxic Bu_3SnH for radical cyclizations. Triphenylgermanium hydride-mediated radical carbonylation/cyclization reactions[27] are also very useful. Triethylborane (Et_3B) is also a powerful reagent for radical cyclization.[28] These reagents are, however, extremely expensive.[21–28]

Although, in most cases, AIBN is used as a radical initiator, the substantial use of other diazine initiators, e.g., AMBN [azobis(methylisobutyronitrile)], in radical reactions has also been reported. Most of the radical reactions are carried out in organic solvents (benzene, toluene, xylene, THF, *tert*-butanol, etc.). The use of water as the solvent in radical cyclization reactions is an excellent achievement from both an economical and an environmental standpoint.[29] Phosphorous compounds have proved to be excellent alternatives to organotin hydrides in radical reactions.[30–32,37] Recently, Jang and Cho have reported[33] an efficient and mild methodology for the synthesis of heterocyclic compounds with phosphorous functionalities by the radical cyclization of dienes in water.

Nambu et al.[34] synthesized 1-methoxy-4-(4-methyl-2-oxolanyl)benzene from 2-iodo-1-(4-methoxyphenyl)-1-prop-2-enyloxyethane by using 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061) as the water-soluble initiator and 1-ethylpiperidine hypophosphite (EPHP) as the chain carrier. Recently, Barton et al. have reported a radical reaction using hypophosphorous acid.[35] Kita et al. reported a radical reduction in aqueous isopropyl alcohol using a combination of VA-061, hypophosphorous acid, and triethylamine.[36]

Murphy et al. synthesized indolones, in excellent yields, from the reaction of iodoarenes with diethylphosphine oxide (DEPO) in water at 80 °C via aryl radical formation, hydrogen atom abstraction, cyclization, and re-aromatization.[37] In order to synthesize the alkaloid, horsfiline, they also used a phosphorous-centered radical obtained from the reagents[38] EPHP and DEPO, and observed that DEPO was highly effective for the cyclizations at 80 °C that were difficult to achieve with Bu_3SnH (Scheme 1).

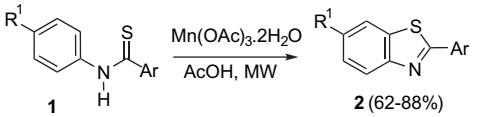


Scheme 1.

Diethyl phosphite,[39] $(EtO)_2P(O)H$, and diethyl thiophosphite,[40] $(EtO)_2P(S)H$, were also shown to be useful alternative and more versatile reagents for radical cyclization.

A novel indium-mediated atom transfer radical cyclization reaction has been explored[41] using a catalytic amount of indium and iodine, and reductive radical cyclization using an excess of indium and iodine without the use of a radical initiator such as AIBN or Et_3B/O_2. Many indium-mediated reactions have been initiated by single-electron transfer (SET) in tandem carbon–carbon bond-forming processes. Dihalogenoindium hydrides ($HInX_2$) are also effective alternative radical reagents to Bu_3SnH and can be generated from $InCl_3$ or $InBr_3$ and metal hydrides,[42–45] e.g., $NaBH_4$,[43] DIBAL-H,[44] and Et_3SiH.[45]

Manganese(III) triacetate[46] was found to be an excellent one-electron oxidant that has been widely employed to produce free radicals for cyclization reactions. Arylthioformanilides **1** were treated[47] with manganese triacetate dihydrate $Mn(OAc)_3\cdot 2H_2O$ in acetic acid under microwave irradiation, and the reaction was complete within 6 min to afford 2-arylbenzothiazoles **2** in 62–88% yield (Scheme 2).

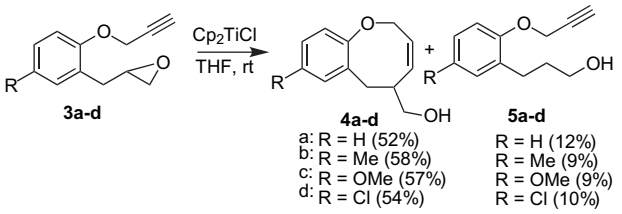


R^1 = H, OMe, Br, Cl
Ar = Ph, *p*-F-C_6H_4, *o*-Cl-C_6H_4, *p*-$C_8H_{17}O$-C_6H_4, *p*-$C_{10}H_{21}O$-C_6H_4

Scheme 2.

Cp_2TiCl_2 has also proved to be an excellent alternative to triorganotin hydrides in radical reactions.[48] Treatment of the epoxyethers **3a–d** with Cp_2TiCl in THF under argon afforded the eight-membered cyclic ethers **4a–d** in moderate yields, along with the reduced products **5a–d** in 9–12% yield (Scheme 3).[49]

Recently, Ce(IV) reagents, e.g., ceric ammonium nitrate (CAN)[50] and ceric-tetra-*n*-butylammonium nitrate (CTAN),[50,51] have been widely applied for the generation of radicals and radical cations that can further react with other substrates to form carbon–carbon bonds.[51,52] The use of CTAN has been exemplified in the oxidative additions of 1,3-dicarbonyl substrates to allyltrimethylsilane.[53] The oxidative couplings of β-carbonyl imines and allyltrimethylsilane with CTAN were investigated in MeCN and CH_2Cl_2 as the solvents.[54]



Scheme 3.

3. General aspects of thiol-mediated radical reactions

Recently, a cost-effective tin-free methodology has been developed for the construction of carbon–carbon bonds by a radical reaction based on sulfanyl radical addition–cyclization.[16] These radical reactions proceed via the formation of a carbon-centered radical species generated by the addition of a sulfanyl radical to an unsaturated bond and a subsequent intramolecular addition of the resulting carbon-centered radical to another multiple bond, followed by the abstraction of hydrogen from thiophenol to afford the product (Fig. 1).

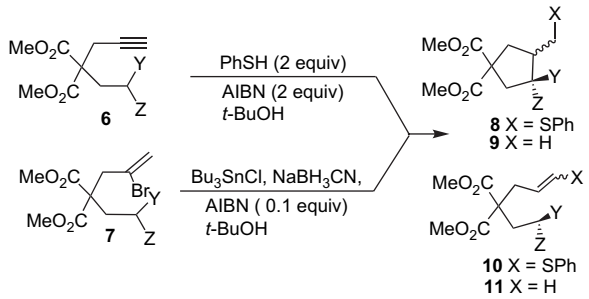
Otherwise, the sulfanyl radical, generated from thiophenol and AIBN, adds to the terminus of the triple bond to generate an alkenyl radical, which undergoes a 1,5-hydrogen atom transfer (HAT). After translocation, the new radical species can cyclize, intramolecularly, to give a cyclopentane derivative (Fig. 2).

This tin-free methodology afforded an extremely easy workup procedure, and a high yield of products, free from byproduct contamination. The cyclized products are highly functionalized compounds and are thus regarded as useful intermediates for target molecules. Their synthetic potentiality was demonstrated by the synthesis of anantine,[55] oxo-parabenzlactone,[56] α-kainic acid,[57] cispentacin,[58] an A-ring fragment of 1α,25-dihydroxyvitamin D_3,[59] balanol,[60] deoxynojirimycin,[61] martinelline,[62] (−)-erythrodiene,[63] lactones,[64] lactams and sultams,[28,65] and other various carbocycles and heterocycles.

4. Synthesis of carbocycles

The hydrogen atom abstraction is particularly interesting, since it allows the functionalization of remote unreactive positions.[66] The highly reactive alkenyl radicals are suitable precursors for efficient intramolecular 1,5-hydrogen abstraction at C–H bonds. After translocation, new radical species can cyclize via a 5-*exo*-*trig* mode to give a cyclopentane derivative.[67] Curran and Shen[68] have thoroughly investigated this process by the generation of a vinyl radical from the corresponding bromide. With stannyl radicals, however, this process is hampered by the formation of the uncyclized product.

Recently, Renaud et al.[69] reported the synthesis of cyclopentane derivatives **8a**–**e** from propargylmalonate precursors **6a**–**f** under a thiophenol-mediated radical addition–translocation process. Treatment of alkynes **6a**–**f** with 2 equiv of thiophenol and 2 equiv of AIBN as a radical initiator in *tert*-butanol afforded exclusively the cyclopentane derivatives **8a**–**e** in 57–90% yield. However, precursors **6g** and **6h** under the same reaction conditions afforded a diastereomeric mixture (**8g** and **10g**) and exclusively **10h**, respectively, whereas the corresponding ^{n}BuSnH-mediated radical cyclization of precursors **7a**,**b**,**d**–**g** afforded a diastereomeric mixtures of **9a**,**b**,**d**–**g** and **11a**,**b**,**d**–**g** (Scheme 4).



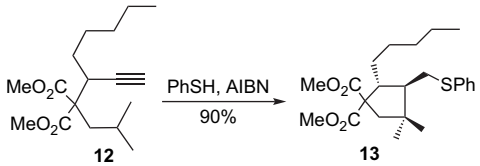
Scheme 4.

No reduced product was obtained, except in the cases of secondary alkyl radicals and primary alkyl radicals, generated from **6g** and **6f**, respectively. The corresponding tin hydride-mediated process gave significant amounts of the uncyclized products in all the cases (Table 1).

Table 1
Thiophenol versus tin hydride for the generation of radicals via 1,5-hydrogen transfer according to Scheme 4

Substrates **6** or **7** Y, Z	PhSH **8**/**10** (Yield, %)	Bu_3SnH **9**/**11** (Yield, %)
(a) OCH_2CH_2O	100:0 (90)	58:42 (81)
(b) OTBS, H	100:0 (89)	88:12 (87)
(c) PhS, H	100:0 (88)	—
(d) Ph, H	100:0 (85)	78:22 (76)
(e) CO_2Et, H	100:0 (57)	76:24 (83)
(f) Me, Me	100:0 (83)	87:13 (65)
(g) Et, H	57:17 (–)	48:52 (73)
(h) H, H	0:90 (54)	—

It was also observed that substrates bearing an alkyl substituent at the propargylic position undergo a hydrogen atom transfer in a highly regioselective manner. The generation of a tertiary alkyl radical from **12** afforded the cyclic compound **13** in 90% yield[69] (Scheme 5).



Scheme 5.

The phenylthiyl radical, PhS•, generated from thiophenol and AIBN, adds to the terminal alkynes **6** and **12** to generate the alkenyl radicals **14**, which undergo a 1,5-hydrogen atom transfer to give the radical intermediates **15** followed by a 5-*exo*-*trig* cyclization and reduction of the phenylthio-substituted alkyl radical **16** by thiophenol to afford the products **8** and **13** (Scheme 6).

Various oxime ethers and hydrazones underwent a sulfanyl radical addition–cyclization with diphenyl sulfide under photochemical conditions to produce the cyclic oxime ethers.[70] Recently, Naito et al.[71] investigated a similar radical cyclization of oxime ethers **17a**,**b** and hydrazone **17c** with thiophenol in the presence of

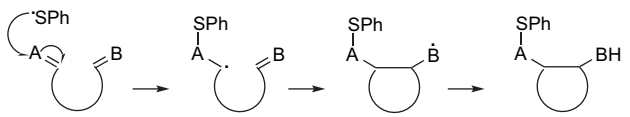


Figure 1.

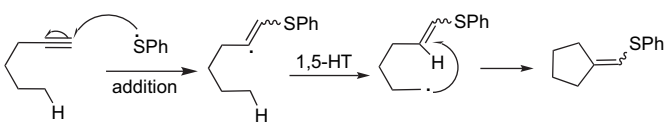
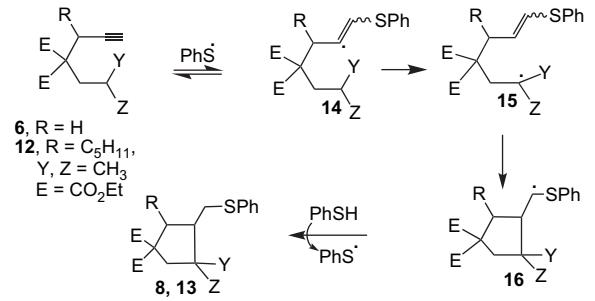
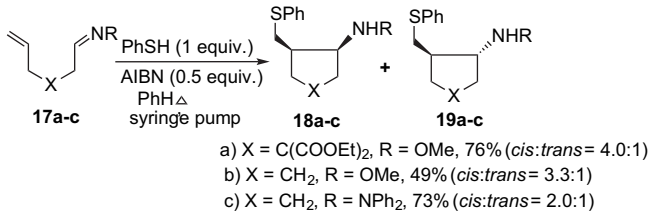


Figure 2.



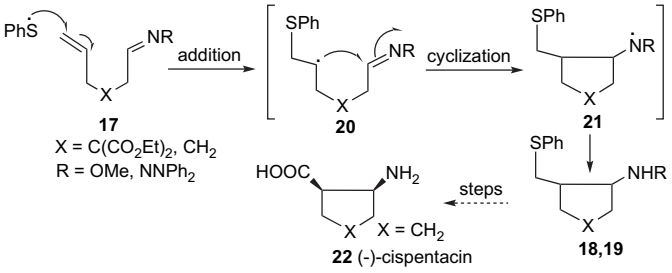
Scheme 6.

AIBN under thermal conditions and obtained a mixture of the cyclopentane derivatives *cis*-**18a–c** and *trans*-**19a–c** in 49–76% combined yield[71] (Scheme 7).



Scheme 7.

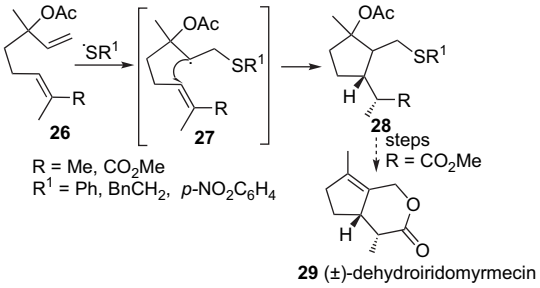
The cis-isomer **18b** was then easily converted into (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid **22**, (−)-cispentacin,[72] an antifungal antibiotic isolated by Konishi et al.[73] from the culture broth of a *Bacillus cereus* strain. In this approach, a sulfanyl radical may attack the terminus of the double bond of the substrates **17** to provide the alkyl radical species **20**, which are expected to form the substituted cyclopentylamines **18** and **19** via the aminyl radicals **21** as a result of a 5-*exo*-*trig* cyclization of **20** (Scheme 8).



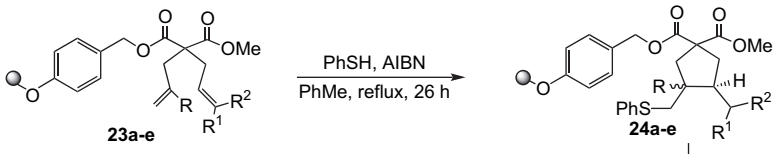
Scheme 8.

A few non-tin radical cyclization reactions have been conducted on solid-supported substrates.[74,75] Armstrong and Du showed that samarium(II) iodide can be effectively used in this context.[74] Ganesan and Zhu used the photolytic decomposition of Barton-type esters to trigger both intermolecular addition and cyclization reactions with solid-supported substrates.[76] Harrowven et al. described[77] the thiophenol-mediated co-cyclization reactions of solid-supported 1,6-dienes **23a–e**, leading to the formation of highly functionalized cyclopentane derivatives **24a–e**. Initial attempts to effect the co-cyclization of dienes **23** with *tert*-butylthiyl radicals did not give any cyclized product. The cyclized products were, however, obtained in reasonable yields by treatment of the dienes **23** with thiophenol in the presence of AIBN. Simply heating a fivefold excess of the thiol and 2.3 equiv of AIBN, in toluene at 80 °C for 5 h, effected the desired cyclization. Cleavage of the product **24** from the resin gave a mixture of *cis*- and *trans*-cyclopentane derivatives **25a–e** in 69–78% overall yield (Scheme 9). Similar radical cyclization reactions were carried out by using *p*-tolyl benzeneselenosulfonate in combination with AIBN.[77]

Monoterpenes with an iridane skeleton form an interesting group of natural products[78] having a wide range of physiological and biological properties, including antibiotic,[79] antitumor,[80] antioxidant,[81] antibacterial,[82] and antiviral[83] activities. The synthesis of a monoterpenoid **29**, (±)-dehydroiridomyrmecin, possessing a five-membered ring, via radical cyclization promoted by the regioselective addition of sulfanyl radical to suitable polyprenes was described by Barrero et al.[84] The key step of the strategy involves a 5-*exo*-*trig* cyclization promoted by the addition of sulfanyl radicals to the mono-substituted double bond of the linalyl acetate derivatives **26**. The reaction of **26** in the presence of thiol (2 equiv) and AIBN in refluxing benzene led to the cyclopentane derivatives **28** in excellent yields (Scheme 10). The use of the *p*-nitrophenylsulfanyl radical gives a lower yield (16%) of the cyclization product, due to the reversible addition of the phenylsulfanyl radicals to the mono-substituted double bonds.

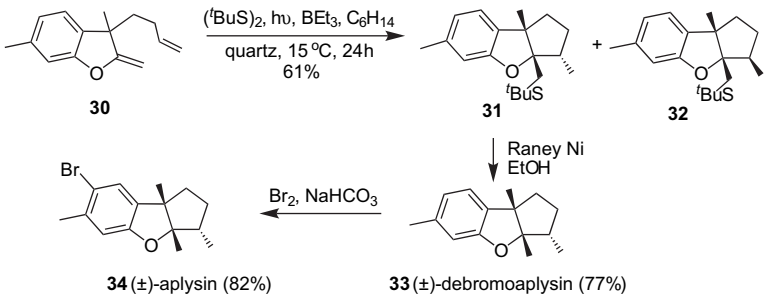


Scheme 10.



	R	R^1	R^2	Yield (%)	*cis*:*trans*
25a	H	H	H	78	5:1
25b	H	Me	Me	75	3:1
25c	H	H	Ph	76	7:2
25d	Me	H	Ph	69	1:1
25e	Me	Me	Me	69	1:1

Scheme 9.



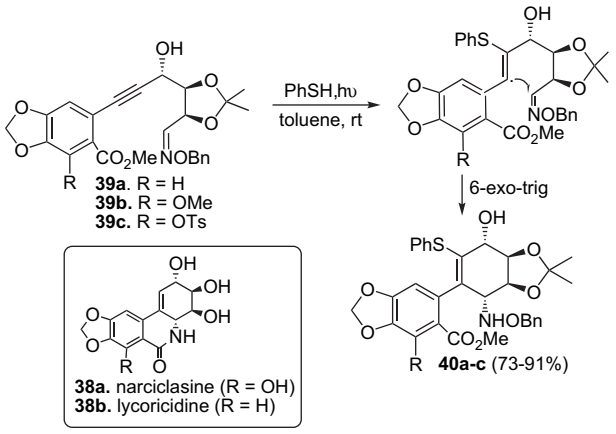
Scheme 11.

Markovnikov addition of a sulfanyl radical to the double bond of the precursor **26** led to a carbon-centered intermediate radical **27**, which undergoes an intramolecular addition to the other activated double bond to give **28**. The regioselective elimination of HOAc from **28**, followed by straightforward functional group transformation, leads to the biologically interesting (±)-dehydroiridomyrmecin (**29**) (Scheme 10).

Aplysin is a tricyclic sesquiterpene found in the extracts of the *Aplysia* sea hare. In nature, this class of compounds was found in North American opisthobranchs and the red sea alga *Laurencia*. Harrowven et al. described[85] the total synthesis of (±)-aplysin (**34**), based on a diastereoselective sulfur-mediated radical cyclization. Irradiation of a hexane solution of the diene **30**, containing di-*tert*-butyl disulfide and BEt_3 as a radical initiator, gave the tricyclic compounds **31** and **32** in 61% yield as a partially separable 8:1 mixture of diastereoisomers. Hydrogenolysis of the major isomer **31** with Raney nickel gave (±)-debromoaplysin **33**, which on bromination afforded (±)-aplysin (**34**) (Scheme 11).

Recently, Alonso and Fernandez[86] carried out thiophenol-mediated tandem radical addition and cyclization of ε-substituted δ-yne ketimines to obtain cyclized allylamine derivatives. The terminal alkyne group R and the attacking radical R′• greatly influenced the mode of the reaction. The terminal alkyne substituted with a CO_2Me group produced a mixture of the 5-*exo* and 6-*exo* products, whereas the terminal alkyne substituted with a phenyl group gave exclusively the 6-*exo* product. The formation of the products can be explained by the addition of PhS• to the δ-carbon of **35**, followed by a 6-*exo* cyclization of the resulting vinyl radical to give **36**, whereas addition of a sulfanyl radical to the ε-carbon, followed by a 5-*exo* cyclization of the intermediate vinyl radical gives the allylamine **37** (Scheme 12). Light-induced initiation, using a 300-W tungsten sun lamp, also proved to be effective, although slower, to afford 40% conversion of **35a** into **36a** and **37** after 19 h irradiation. In the case of compound **35b**, however, sun lamp irradiation was as effective as thermal initiation and it was observed that running the reaction at a lower concentration (0.02 M, 450-W medium-pressure Hg lamp) yielded the product **36b** in 75% yield. The terminal alkyne substituted with a diethoxymethyl group, $CH(OEt)_2$, did not, however, give any cyclized product under any of the above reaction conditions. A wide variety of cyclic allylamine derivatives could be obtained through similar tandem reactions by varying the C=N radical acceptor, the chain connecting the alkyne and C=N, and/or the reaction-initiating free radical R′•.

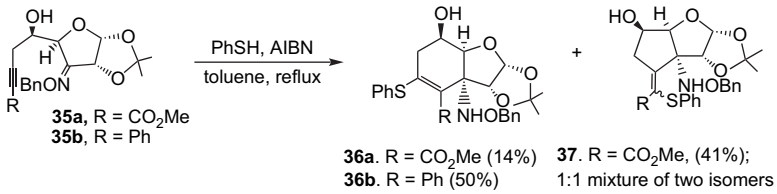
Keck et al. have exploited several approaches involving radical addition to C=N bonds to construct the various phenanthridone alkaloids.[87] In one approach, they described[88] a tandem thiol-mediated radical addition–cyclization for the synthesis of (+)-narciclasine (**38a**), and (+)- and (−)-lycoricidine (**38b**). The arylalkynes **39a–c** on treatment with thiophenol underwent an intermolecular thiyl radical addition followed by 6-*exo* alkenyl radical cyclization to afford **40a–c** as single isomers (Scheme 13). 5-*exo* Cyclization did not occur in this case due to steric hindrance of the oxime approach to the p-type vinyl radical due to the neighboring coplanar vinyl substituents. The corresponding Bu_3SnH-mediated process gave alkyne hydrostannylation without cyclization.



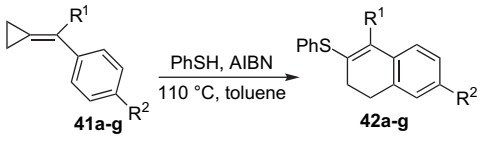
Scheme 13.

Thiophenol reacts with methylenecyclopropanes to give a mixture of double-bond adducts in a Markovnikov fashion and cyclopropyl ring-opened products, with poor selectivity.[89] Huang et al.[90] recently reported the synthesis of 3-phenylsulfanyl-1,2-dihydronaphthalenes **42a–g** by an AIBN-promoted radical reaction between the methylenecyclopropanes **41a–g** and thiophenol (Scheme 14). The reaction proceeded smoothly in refluxing toluene, under high dilution, to afford the cyclized products in moderate-to-good yields. In a similar reaction, the same workers synthesized 4-phenyl-3-phenylselanyl-1,2-dihydronaphthalene by the reaction of (diphenylmethylene)cyclopropane with benzeneselenol.[90]

The phenylthiyl radical, generated from thiophenol through initiation with AIBN, attacks the double bond of the



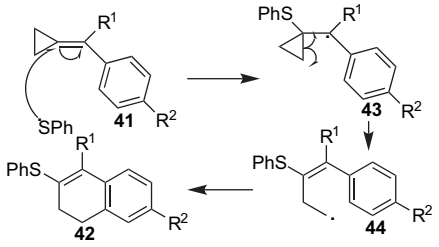
Scheme 12.



Substrate (**41**)	R^1	R^2	Yield of **42** (%)
41a	Ph	H	74
41b	*p*-F-C_6H_4	F	65
41c	*p*-Cl-C_6H_4	Cl	69
41d	*p*-Me-C_6H_4	Me	70
41e	*p*-OMe-C_6H_4	OMe	74
41f	H	Br	53
41g	Me	Br	51

Scheme 14.

methylenecyclopropane in a Markovnikov fashion to produce a cyclopropylbenzyl radical **43**. Opening of the cyclopropane ring in a homolytic fashion give its homoallylic counterpart **44** followed by intramolecular cyclization into a phenyl ring to afford the 3-phenylsulfanyl-1,2-dihydronaphthalenes **42** in a highly selective fashion (Scheme 15).

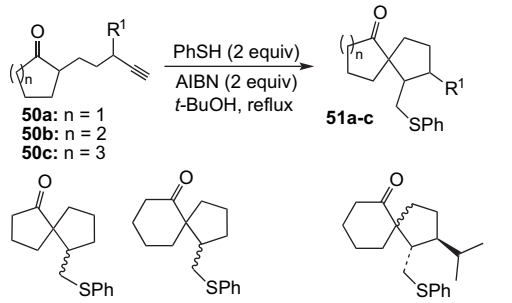


Scheme 15.

The synthesis of spirocyclic compounds continues to attract appreciable interest. Many radical approaches have been reported for the synthesis of this class of compounds.[91] One common strategy predominates, however, based on the formation of a radical from a suitable precursor, such as an alkyne, halide, or heteroatom, which then undergoes radical translocation, followed by cyclization to the spiro-product.[92]

Renaud et al.[63] reported the stereoselective synthesis of (−)-erythrodiene (**45**) starting from 4-isopropylcyclohexanone **46**. The key step of the synthesis is a highly diastereoselective radical cascade reaction involving the addition of a phenylthiyl radical to the terminal alkyne of ketone **46** to generate the alkenyl radical, followed by a 1,5-hydrogen translocation, giving the radical intermediate **47**, which undergoes an intramolecular 5-*exo*-cyclization to give the spirocycle **48**. This was readily converted into (−)-erythrodiene (**45**) in three steps via **49** (Scheme 16). The initiation of the reaction was achieved at room temperature using sun lamp irradiation. Elevated temperature resulted in either poor diastereoselectivity or even a reversal of stereoselectivity at the quaternary carbon. In a related reaction, thiophenol can be replaced by a dialkyl phosphate to permit the synthesis of spirocyclic compounds in good yields.[93]

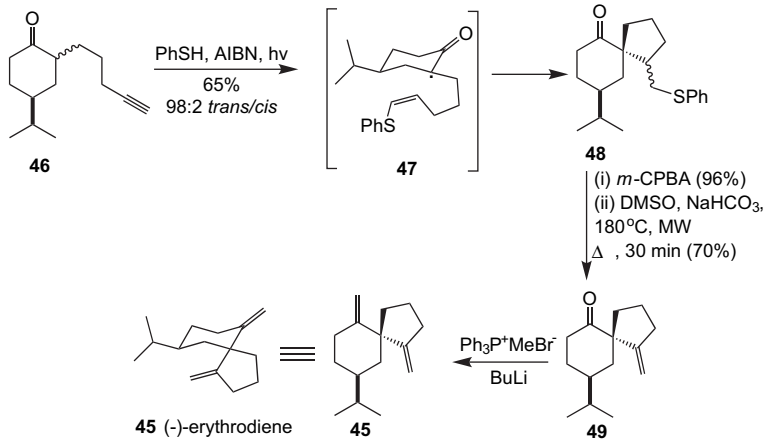
By the application of the same protocol, the same workers prepared various bicyclic ketones, spirocyclic ketones, fused bicyclic alkanes, and spirocyclic alkanes.[94] As an example, treatment of the cyclic ketones **50a–c** with thiophenol and AIBN affords the spirocyclic ketones **51a–c** in 73–92% yields and moderate stereoselectivity[94] (Scheme 17).



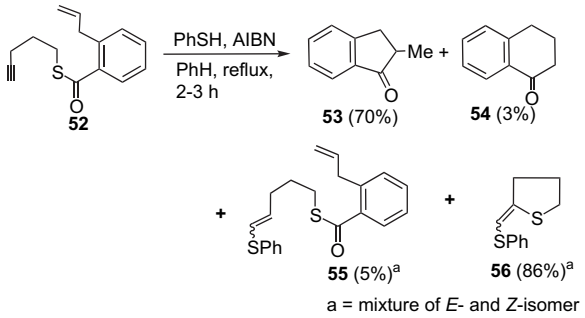
Scheme 17.

Recently, Benati et al. studied[95] the thiophenol-mediated radical cyclizations of 2-(2-allylphenyl)pentynylthiol esters, which led to the formation of cyclic ketones. The thiol ester **52** on treatment with PhSH and AIBN led to the isolation of the cyclized indanone (**53**) and tetralone (**54**) in a ca. 96:4 ratio (overall 73% yield) along with comparable amounts of *E*- and *Z*-dihydrothiophene (**56**). In this case, small amounts of the *E*- and *Z*-vinyl sulfide adducts **55** were obtained as by-products (Scheme 18).

Intramolecular addition of acyl radicals to the C–C double bonds of alkenals gave 2-substituted five- and six-membered cyclic ketones. This type of cyclization has been achieved with acyl radicals,[96] generated by a homolytic cleavage of C–S, C–Se, and other carbon–heteroatom bonds.[97] Simple thiols can also catalyze the generation of acyl radicals from aldehydes directly without the need to synthesize them from specific precursors such as acyl selenides.[98,99] The choice of the thiol catalyst is very important in this reaction. It must result in a non-stabilized thiyl radical and must

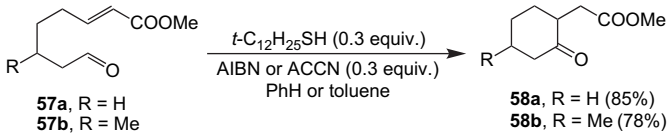


Scheme 16.



Scheme 18.

not be too sterically small, otherwise hemithioacetal formation with aldehyde or conjugate addition to the α,β-unsaturated ester becomes a competing reaction. Furthermore, if the thiol is too bulky, the reaction is suppressed. The optimum thiol was found to be the odorless *tert*-dodecanethiol. The reaction seems to proceed through a radical-chain process. Initially, a thiyl radical, generated from the thiol and AIBN, abstracts hydrogen from **57a**,**b** to produce the intermediate acyl radical, which undergoes cyclization onto the double bond of the molecule, intramolecularly, to afford **58a**,**b** in good-to-excellent yield (Scheme 19).[98]



Scheme 19.

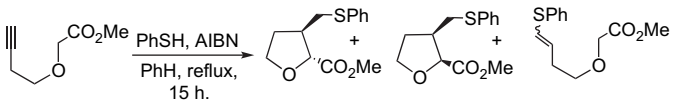
The reaction tolerated a wide range of substrates and has been applied to various combinations of alkenals and thiol to generate a series of five- and six-membered ketones. It was observed that aldehydes having electron-deficient olefins were cyclized more easily than those having unactivated olefins.

5. Synthesis of heterocycles

Free radical cyclization is a very useful and well-established procedure for the synthesis of oxygen- and nitrogen- as well as sulfur-containing heterocycles.[100,101] Five- and six-membered ring formation[3,102] via intramolecular free radical cyclizations is more common than that forming seven- and eight-membered rings.[103] Heteroatom-centered radicals are, however, less common in synthesis, because of tedious preparations and the instabilities of heteroatom radical precursors. Nitrogen-containing compounds are part of the basis of life and are one of the main classes of pharmacologically active agents. Thus, the search to find many new and advanced methodologies for the synthesis of various heterocycles and also natural products has been a central goal for radical chemists in recent years.

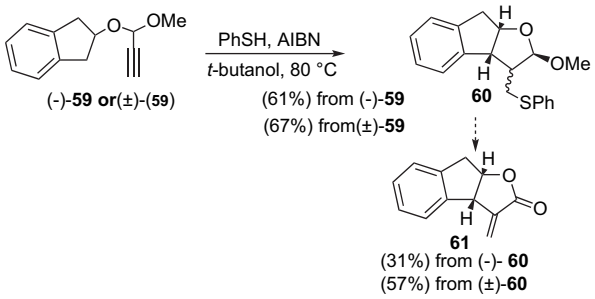
5.1. Synthesis of oxygen heterocycles

Montevecchi et al.[104] reported the radical addition of 2-phenylethanethiol to *tert*-butylacetylene, affording the corresponding β-sulfanylalkenyl radical, which can undergo a 1,5-hydrogen transfer in competition with the reduction process. Interestingly, Burke and Juang[105] has reported a radical translocation–cyclization process mediated by thiophenol. This particular example, however, involves the formation of a highly stable captodative radical and, even with this highly favorable system, the formation of the non-translocated product could not be avoided (Scheme 20).



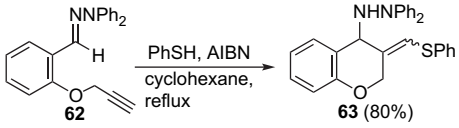
Scheme 20.

Recently, Renaud et al. described the synthesis[106] of α-methylenelactone (**61**) in which one of the key steps was a thiophenol-mediated stereoselective hydrogen atom abstraction–cyclization. The propynal acetal **59** was treated with thiophenol/AIBN to give the cyclic tetrasubstituted tetrahydrofuran **60** in 61% yield. Oxidation of the tetrahydrofuran **60** with an excess of CrO_3/H_2SO_4 followed by treatment of the crude product with DBU afforded the diastereomerically pure α-methylenelactone **61** in 31% yield (Scheme 21).



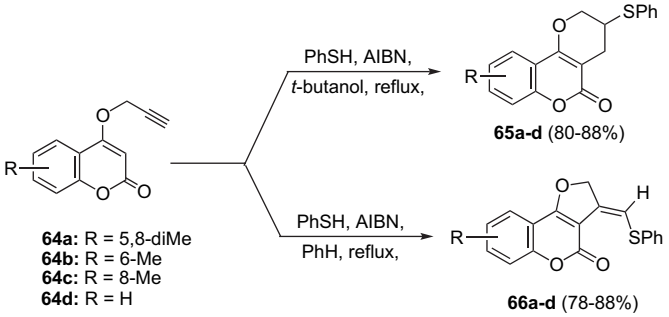
Scheme 21.

El Kaim et al. reported[107] a study of thiyl addition to alkenes and alkynes by using thiophenol and AIBN, as a means of effecting radical cyclization to a variety of C=N acceptors. In one example, on treatment of alkyne **62** with PhSH and AIBN, a 6-*exo* cyclization occurred smoothly to afford predominantly the *cis* alkenyl sulfides **63** in 80% combined yield. A similar treatment of the corresponding ethylenic compound with thiophenol and AIBN did not give any cyclized product[107] (Scheme 22).

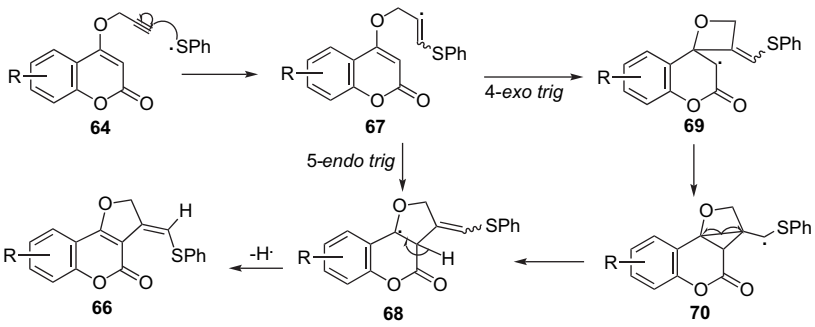


Scheme 22.

Recently, we have described the regioselective synthesis of dihydrofurocoumarins and dihydropyranocoumarins by thiol-mediated radical cyclization reactions.[108] The radical precursors, coumarin-4-yl-prop-2-ynyl ethers **64a**–**d**, were refluxed in dry *tert*-butanol under a nitrogen atmosphere with PhSH (2 equiv) and AIBN (1.5 equiv) for 1 h to afford the dihydropyranocoumarin derivatives **65a**–**d** in 80–88% yield (Scheme 23). When the same reactions were carried out in dry benzene instead of dry *tert*-



Scheme 23.



Scheme 24.

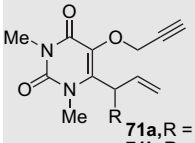
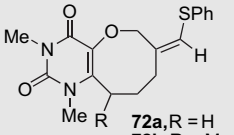
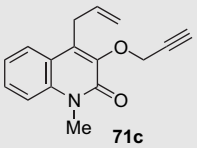
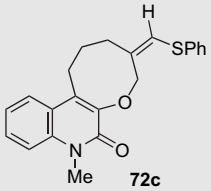
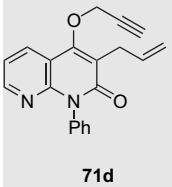
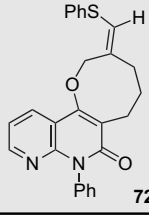
butanol, totally different products, *Z*-dihydrofurocoumarins **66a–d**, were obtained in 78–88% yield (Scheme 23).

From these two experiments, it was revealed that the polarity of the solvent affects the mode of the cyclization. In polar *tert*-butanol, thiophenol catalyzed the Claisen rearrangement of the ethers **64**, followed by the addition of a thiyl radical in the presence of AIBN, to afford **65**.

The formation of the products **66** from **64** may be explained by the generation of an alkenyl radical **67** by the radical addition of thiophenol to the terminal alkyne **64**. The alkenyl radical **64** may undergo either a 4-*exo*-*trig* or a 5-*endo*-*trig* cyclization at the double bond of the pyrone ring of the coumarin moiety. A 5-*endo*-*trig* cyclization of the radical **67** may produce the intermediate radical **68**, whilst a 4-*exo*-*trig* cyclization may give the spiroheterocyclic radical **69**, followed by a neophyl rearrangement[109] via **70**, to form the radical intermediate **68**. Oxidative elimination of hydrogen from **68** may afford **66** (Scheme 24).

We have also extended our efforts in the regioselective synthesis of eight-membered cyclic ethers via 8-*endo* radical cyclization mediated by thiophenol.[110] The radical precursors **71a–d** were refluxed in *tert*-butanol under a nitrogen atmosphere for 2 h with 2 equiv of thiophenol in the presence of the radical initiator AIBN to afford the cyclized products **72a–d** in 82–85% yield. The results are summarized in Table 2.

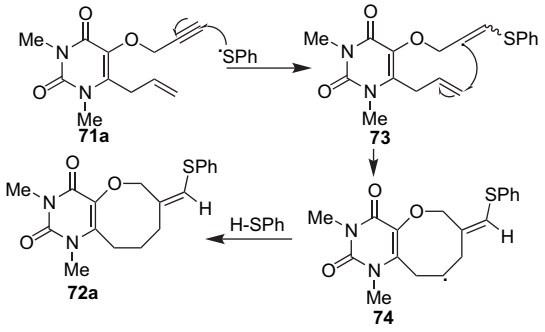
Table 2
Sulfanyl radical addition and cyclization of **71a–d**

Starting material (**71**)	Product (**72**)	Yield (%)
 **71a**,R = H **71b**,R = Me	 **72a**,R = H **72b**,R = Me	83 82
 **71c**	 **72c**	84
 **71d**	 **72d**	85

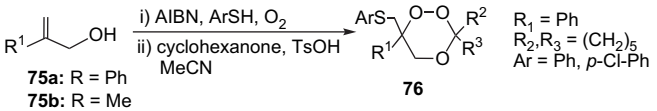
The phenylthiyl radical, generated from thiophenol and AIBN, was added to the terminal alkyne **71a** to form a vinyl radical **73**. Intramolecularly, this vinyl radical may undergo an 8-*endo*-*trig* cyclization with an adjacent alkene to form the intermediate radical **74**, which on abstraction of an H radical from thiophenol afforded the product **72a** (Scheme 25).

The 1,2,4-trioxane pharmacophore is an important functional group in medicinal chemistry. This unit is found in the artemisinin class of antimalarial agents such as artemether and artesunate.[111] More recently, artemisinin-derived 1,2,4-trioxane monomers and dimers have been found to be potent inhibitors of cancer cell proliferation.[112]

Recently, O'Neill et al.[113] have observed that thiol–olefin co-oxygenation (TOCO) of substituted allylic alcohols **75a**,**b** generates α-hydroxyperoxides that can be condensed in situ with various ketones in the presence of a catalytic amount of tosic acid to afford a series of functionalized 1,2,4-trioxanes **76** in good yields (Scheme 26).

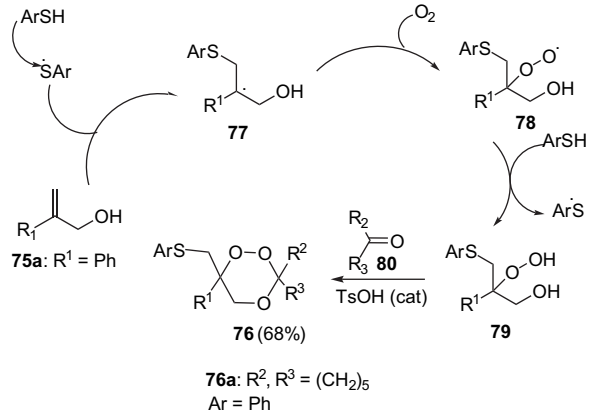


Scheme 25.



Scheme 26.

A phenylthiyl radical, generated from thiophenol through initiation with AIBN/hν, attacks the double bond of the allyl alcohol **75a** in a Markovnikov fashion to produce a tertiary carbon radical **77**. This radical traps oxygen to form a peroxy radical **78**. Radical hydrogen abstraction from thiophenol affords the α-hydroxyperoxide **79** and regenerates a phenylthiyl radical to propagate the reaction. The α-hydroxyperoxide **79** subsequently underwent a smooth condensation with cyclohexanone **80** in the presence of a catalytic amount of tosic acid to yield the 1,2,4-trioxane **76** (Scheme 27).



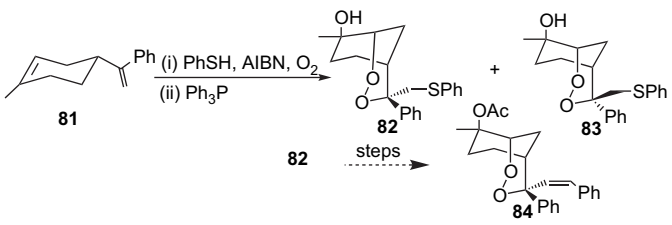
Scheme 27.

This methodology has been applied to various combinations of ketones **80**, e.g., cyclohexanone, and allylic alcohols **75a**,**b** to generate a series of spirotrioxanes **76a**–**e** as shown in Table 3. Finally, the methylthiophenyl group of the resulting trioxane was converted into the vinyl-substituted trioxane analogues in excellent yields. These analogues are of interest, since they have been shown to liberate chalcones, antimalarial parasite cysteine protease inhibitors in biomimetic Fe(II) degradation reactions.

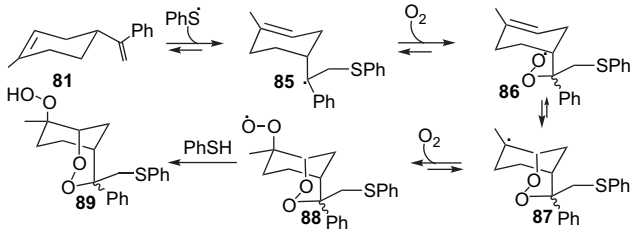
Table 3
Trioxanes synthesized via intermolecular trapping of the hydroperoxide products **79** of the TOCO reaction with ketones

Allylic alcohol (**75**)	Ketone (**80**)	Trioxane (**76**)	Yield (%)
75a: R^1=Ph	Cyclohexanone	**76a**: R^1=Ph, R^2 and R^3=$(CH_2)_5$, Ar=Ph	68
75a: R^1=Ph	Cyclopentanone	**76b**: R^1=Ph, R^2 and R^3=$(CH_2)_4$, Ar=Ph	54
75b: R^1=Me	Cyclohexanone	**76c**: R^1=Me, R^2 and R^3=$(CH_2)_5$, Ar=Ph	53
75b: R^1=Me	Cyclopentanone	**76d**: R^1=Me, R^2 and R^3=$(CH_2)_4$, Ar=*p*-Cl-Ph	46
75b: R^1=Me	Cyclobutanone	**76e**: R^1=Me, R^2 and R^3=$(CH_2)_3$, Ar=Ph	61

Similarly, TOCO reactions of 1,5-dienes, limonene, and similar monoterpenes were applied for the preparation of six-membered ring endoperoxides, including the 2,3-dioxabicyclo[3.3.1]nonane system.[114] The 2,3-dioxabicyclo[3.3.1]nonane system was first identified in yingzhaosu A, which exhibits potent antimalarial activity[115] and was synthesized by Bachi et al.[116] Recently, these workers developed a general synthetic route for the preparation of a promising class of antimalarial prodrug **84** by a four-component sequential free radical reaction based on a thiol–olefin co-oxygenation reaction of diene **81**.[117] Optimization of the reaction led to a protocol in which a solution of thiophenol was added during 30 min to a solution of the 1,5-diene **81** and AIBN in acetonitrile at 0 °C under a small pressure of pure oxygen and UV irradiation to afford the endoperoxide–hydroperoxide **89** (Schemes 28 and 29). The reactive hydroperoxy group was then reduced selectively with Ph_3P to give the stable hydroxyl endoperoxides **82** and **83** (ca. 4:3) in 70% yield as diastereomeric mixture (Scheme 28). Compound **82** is then converted into the endoperoxide prodrug **84**, which exhibits significant antimalarial activity.



Scheme 28.



Scheme 29.

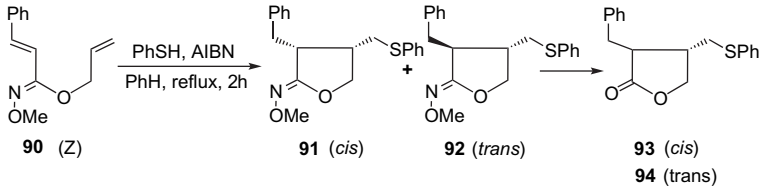
The mechanism of the sequential TOCO reaction is illustrated in Scheme 29. Initially, a phenylsulfanyl radical, generated from thiophenol and AIBN, added regioselectively to the terminus of the isopropenyl double bond of **81** to generate a tertiary carbon radical **85**, which was rapidly trapped by oxygen to give a peroxy-radical intermediate **86**. Intramolecular 6-*exo* addition of the peroxy radical **86** onto the *endo*-cyclic double bond afforded a tertiary carbon-centered radical, the 2,3-dioxabicyclo[3.3.1]nonanyl radical **87**. This radical was trapped by a second equivalent of oxygen to give the peroxy radical **88**, followed by abstraction of hydrogen from thiophenol, to afford the endoperoxide–hydroperoxide **89** and PhS$^{\bullet}$, which continued the chain reaction (Scheme 29).

Lactone rings are found in many biologically active compounds[118] and they are also known to be important intermediates for the synthesis of stereo-defined acyclic and other natural products. Syntheses of α,β-disubstituted γ-lactones by the radical cyclization methodology have led to low yields,[119] because the cyclization of the α-carbonyl radical takes place slowly. This may be due to the *s-trans* conformation of the ester precursors.

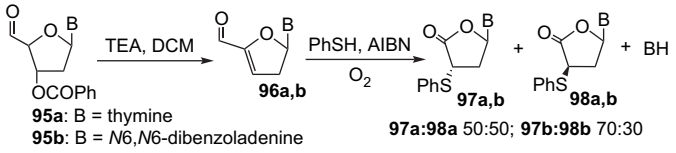
A combination of sulfanyl radical addition–cyclization of dienes connected with hydroximates followed by conversion of the resulting cyclic hydroximates into the lactones proved to be a unique method for the construction of α,β-disubstituted γ-lactones.[56] The radical cyclization of *Z*-hydroximates (**90**) in the presence of thiophenol and AIBN furnished a mixture of cyclized cis and trans products **91** and **92**, respectively, in 82% combined yield (Scheme 30). Hydrolysis of the cis- and trans-cyclized hydroximates with 10% hydrochloric acid in THF at room temperature gave the corresponding lactones **93** and **94**, respectively, in excellent yields. No such cyclized product was, however, obtained from the corresponding *E*-hydroximates. Applying this methodology, an oxo-parabenzlactone, isolated from the wood of *Protium tenuifolium*,[56] was also synthesized.

Recently, Montevecchi and Navacchia have described the synthesis[120] of 3′,4′-didehydroaldehydes **96a**,**b** by the treatment of C5′-aldehydes **95a**,**b** under mild basic neutral conditions. The C5′-aldehydes **96a**,**b** were then treated with thiophenol under radical conditions and it was observed that sulfanyl radical addition occurred at the C3′-position under oxygenated conditions, eventually leading to the unexpected lactone products **97a**,**b** and **98a**,**b** as a diastereomeric mixture, along with thymine and adenine as the major products (Scheme 31). The reactions were carried out with benzenethiol (1.2 equiv) in a sealed tube at 80 °C in the presence of oxygen and the radical initiator AIBN (0.2 equiv). Complete disappearance of **96a**,**b** was found to have occurred within 2 h.

The phenylsulfanyl radical, generated from thiophenol, attacks the C3′-position of **96** to produce a tertiary carbon radical **99**. This radical then traps oxygen to form a peroxy radical **100**, which abstracts a hydrogen radical from thiophenol to afford the hydroxyperoxide **101**. This hydroperoxide may give the 3-hydroxy-1,2-dioxetane **102** through nucleophilic addition to the α-carbonyl atom. Finally, the lactones **97** and **98** can easily be formed from **102**

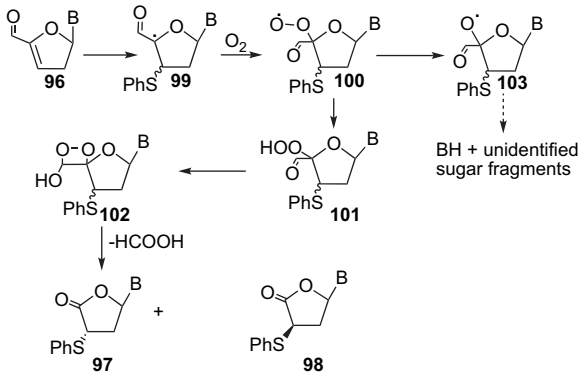


Scheme 30.



Scheme 31.

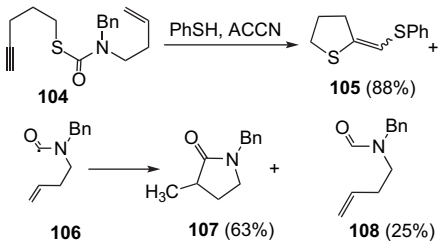
with the concomitant elimination of formic acid. Unidentified sugar fragments are formed from the peroxy radical **100** via **103** (Scheme 32).



Scheme 32.

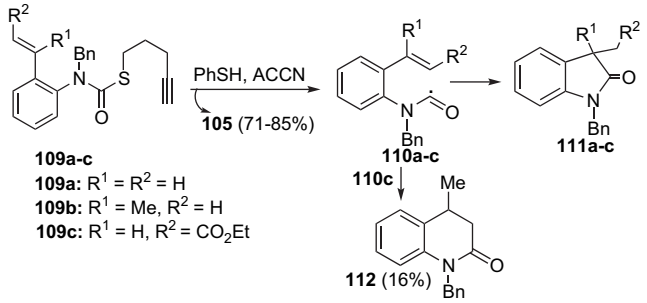
5.2. Synthesis of nitrogen heterocycles

The reaction of thiophenol with *S*-4-pentynyl carbamothioates provides a valuable protocol for the tin-free generation of carbamoyl radicals. This carbamoyl radical undergoes 5-*exo* cyclization leading to pyrrolidinones.[121] The reactions were performed by adding a toluene solution of PhSH (1.1 mmol) to a refluxing solution of the appropriate substrate (1 mmol) and an ACCN initiator (0.3 mmol) under a nitrogen atmosphere. The reaction of *N*-benzyl-*N*-3-butenylcarbamothiate **104** smoothly afforded the expected 2-methylidenetetrahydrothiophene **105** (88%) as a mixture of (*E*)- and (*Z*)-isomer, and the associated carbamoyl radical **106**, which provided a good yield of the desired pyrrolidinone **107**(63%) along with small amount of the reduction product **108** (25%) (Scheme 33).



Scheme 33.

A comparable efficiency was observed for the production of carbamoyl radicals **110a–c** from the corresponding *N*-benzyl-*N*-(2-alkenylphenyl)carbamothioates **109a–c**. The radicals **110a–c** did not give any reduced product, but underwent exclusive ring closure onto the internal alkene to furnish the indolinones **111a–c**. The congener **110c** also gave a minor amount of the six-membered ring quinolinone **112** (Scheme 34). The *N*-tosyl analogues of **109a**,**b**, however, furnished the corresponding quinoline derivatives exclusively, through the isocyanate intermediate, generated by β-elimination of a tosyl radical.[121]

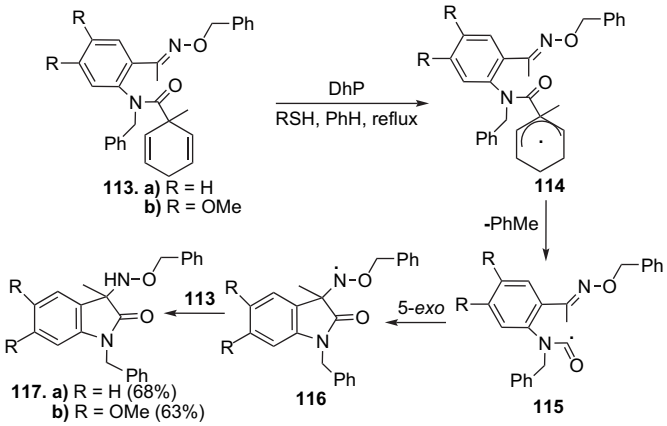


Scheme 34.

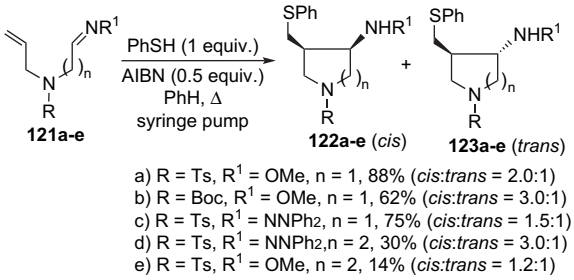
Similarly, when *N*-benzyl-*N*-[2{*N*-(benzyloxy)ethanimidoyl}phenyl]-1-methyl-2,5-cyclohexadiene-1-carboxamides **113a**,**b** were allowed to react[122] with dilauroyl peroxide (DLP) as the radical initiator and a catalytic amount of methyl thioglycolate (RSH) in refluxing benzene for 30 h, the indolinone derivatives **117a** and **117b** were formed in 68 and 63% yields, respectively. Mechanistically, the electrophilic sulfanyl radical RS$^{\bullet}$, obtained from methyl thioglycolate, preferentially abstracts hydrogen from the bisallylic site of **113a**,**b**, due to a favorable polar effect, to generate the cyclohexadienyl radical **114** and regenerate RSH. In refluxing benzene, the radical **114** may undergo rapid β-scission to produce the carbamoyl radical **115**. The indolinylaminyl radical **116** may be produced by the 5-*exo* ring closure of **115**. The indolinylaminyl radical **116** may readily abstract a hydrogen atom from the precursors **113a**,**b** and hence can propagate a chain reaction with the formation of the 3-substituted indoline derivatives **117a**,**b** as the end products. The cyclization steps were very rapid and took place regioselectively at the C-atoms of the C=N bonds, by 5-*exo* ring closure (Scheme 35).

1-(2-Aminophenyl)pent-1-yne reacts with benzenethiol at 150 °C under radical conditions to give the thiol/alkyne adduct along with benzothiophene and indole derivatives as minor products.[123] Similar reaction of 1-(2-aminophenyl)pent-1-yne with the phenylsulfanyl radical, however, generated from diphenyl disulfide, i.e, in the absence of hydrogen donors, gave only the indole derivatives in high yields.

Recently, Fukuyama et al. described[124] the synthesis of 3-substituted indole derivatives based on a thiol-mediated radical cyclization of 2-alkenylphenyl isocyanides. The radical precursors **119a–e** were prepared by the reaction of aliphatic or aromatic aldehydes with an anion of the Horner–Wadsworth–Emmons reagent **118**, generated by treatment with LDA at −78 °C. Among



Scheme 35.



Scheme 37.

the various thiols studied it was found that the use of an excess of ethanethiol was quite effective for the radical cyclization. Initial attempts to effect the cyclization of **119a**, using 1.5 equiv of ethanethiol and AIBN in acetonitrile at 100 °C, afforded the desired indole derivative **120a** in 29% yield. The use of 5 equiv of thiol, however, improved the yield to 67%. A range of 2-alkenylphenyl isocyanides **119b–e** were converted into the corresponding 3-substituted indoles **120b–e** by the optimized reaction conditions (Scheme 36).

Various pyrrolidine and piperidine derivatives based on the sulfanyl radical addition–cyclization of oxime ethers and hydrazones were synthesized by Naito et al.[71,125,126] The radical cyclizations of the diallylamines **121a–e** were carried out in refluxing benzene by the slow addition of thiophenol and AIBN to give the cyclized products **122a–e** and **123a–e** as a mixture of cis- and trans-isomers, respectively (Scheme 37). It was observed that the hydrazones undergo cyclization more efficiently than the oxime ethers, and that the yields of the five-membered products were higher than those of the six-membered products. Naito et al.[71] applied this protocol for the synthesis of a wide range of natural and unnatural cyclic β-amino acids by a combination of sulfanyl radical addition–cyclization of oxime ethers or hydrazones connected with alkenes and subsequent conversion of a phenylsulfanylmethyl group into a carboxyl unit.

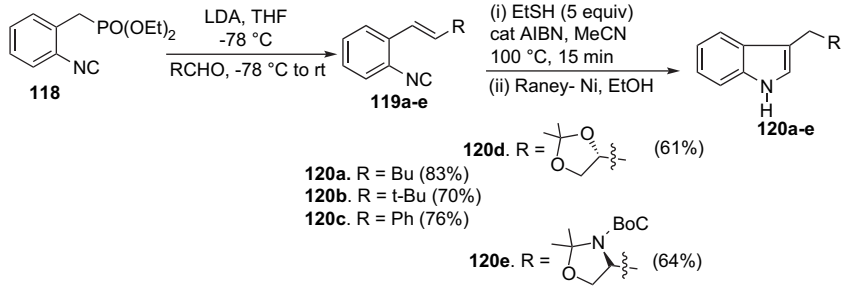
α-Kainic acid (**124**) is the prototype of the kainoids, a group of neuro-excitatory amino acids, which activate a particular subtype of glutamic acid receptors. These amino acids are important substrates in physiological and pharmacological studies of the central nervous system.[127] Several efforts have been made to synthesize α-kainic acid.[45] Naito et al.[128] reported a concise enantioselective synthesis of (−)-α-kainic acid by thiyl radical addition–cyclization–elimination reactions. The thiol-mediated radical reaction was carried out by the slow addition (by a syringe pump over 2 h) of a benzene solution of the thiophenol and AIBN to a refluxing solution of diallylamine **125** in benzene under a nitrogen atmosphere (Scheme 38). After completion of the addition, the reaction mixture was refluxed for an additional period of 6 h. The diene **125**, under the above reaction conditions, gave a mixture of 3,4-*cis*-**126** and 3,4-*trans*-**127** in an overall 94% yield. This cis-isomer **126** was then easily converted into (−)-α-kainic acid (−)-**124**.

Similarly, the diallylcarbamate **128** when refluxed in dry benzene under a nitrogen atmosphere with thiophenol under radical conditions afforded the cyclized product **129** in 85% yield[129] (Scheme 39).

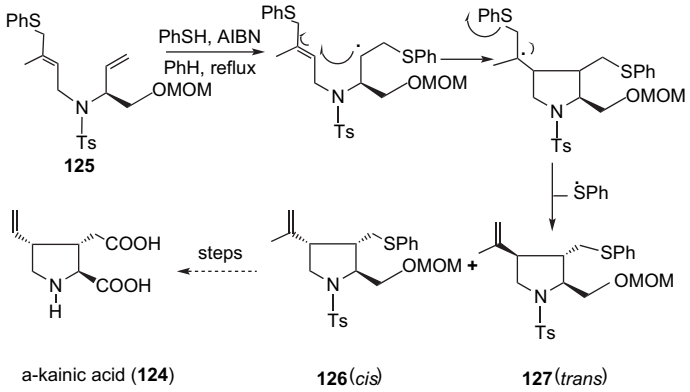
Very recently, Renaud et al. have described[130] the preparation of 1-azabicyclic alkanes, such as pyrrolizidine and indolizidine derivatives, in which the key step was a thiophenol-mediated radical cyclization of various monocyclic *N*-homopropargylic amines **130**. The precursors for the radical cyclization were readily prepared in two steps from pyrrolidine, piperidine, and tetrahydro-1*H*-azepine. The thiol-mediated cyclization was carried out in refluxing *tert*-butanol by the slow addition of thiophenol (2 equiv) over 24 h, in the presence of the radical initiator AIBN (2 equiv), to afford the azabicyclic derivatives **131** in moderate-to-excellent yields (Scheme 40).

The syntheses of functionalized pyrrolizidinones and indolizidinones by using a similar radical cyclization strategy were also reported by the same group.[130] The procedure is highly effective when the *N*-homopropargylic side chain is 1,1- or 1,2-disubstituted. The proposed mechanism of the reaction involves a cascade initiated by the addition of a thiyl radical onto the alkyne moiety, followed by an intramolecular 1,5-hydrogen transfer, a 5-*exo*-*trig* cyclization, and, finally, reduction of the cyclized radical by thiophenol.

Naito et al. synthesized five- to eight-membered lactams by a sulfanyl radical-mediated addition–cyclization of dienylamides.[131] The stereo- and regioselectivities of the sulfanyl radical addition–cyclization were established from the preferential formation of the trans-cyclized lactam and also from the substituent effects. Recently, Schiesser et al. described[132] the synthesis of four- to seven-membered α-thiomethylene lactams by free radical-mediated cyclizative carbonylations of azaenynes. In a typical reaction,

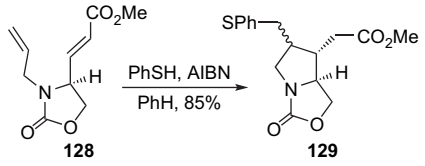


Scheme 36.

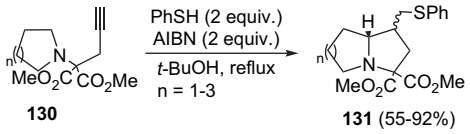


PhSH (equiv.)	AIBN (equiv.)	Yield (%)	Ratio *cis* (**126**)*: trans* (**127**)
1.0	0.5	94	1:1.3
0.2	0.2	95	1:1.5
1.8	0.6	27	1:1.4
1.0	0.5	64	1:1.6

Scheme 38.

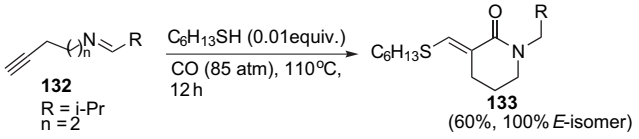


Scheme 39.



Scheme 40.

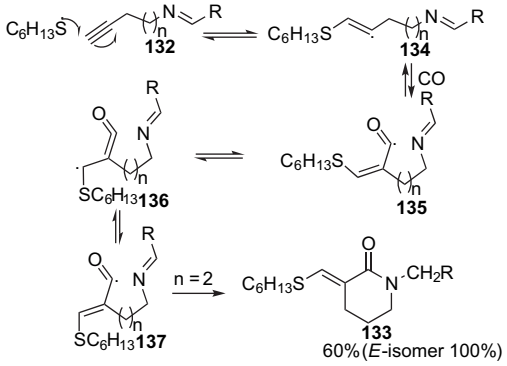
when a toluene solution of the azaenyne **132**, hexanethiol, and V-40 was treated with 85 atm of carbon monoxide at 110 °C for 12 h, the α-thiomethylene-2-azacyclohexanone **133** was obtained in 60% yield (Scheme 41).



Scheme 41.

The preferential *E*-stereochemistry of the *exo*-cyclic double bond may be due to steric factors and is also supported by ab initio and density functional theory (DFT) molecular orbital (MO) calculations. It was observed that the *E*-isomer of the five-membered lactam is stable by about 12 kJ mol^{-1} over the *Z*-isomer. Similarly, preferential *E*-isomers were obtained in higher yield when the carbonylation–cyclization reactions were carried out with TTMSH as a radical mediator. *Z*-Selectivity was, however, observed for the corresponding Bu_3SnH-mediated carbonylation reaction.[133]

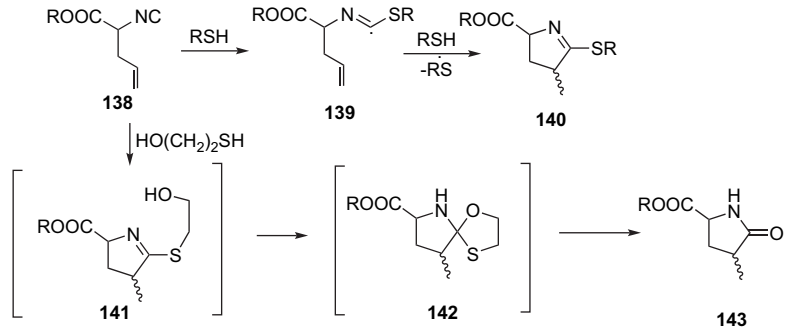
The formation of the lactam may be explained by the initial attack of a $(TMS)_3Si$ or a thiyl radical at the terminus of the acetylene unit of the azaenyne **132** to give a vinyl radical **134**. An acyl radical **135** may be formed by the addition of the vinyl radical to carbon monoxide. The generated acyl radical **135** is rapidly involved in a diastereomeric equilibrium with the α-ketenyl radical **136**. This α-ketenyl radical may undergo cyclization onto the N–C double bond to form the corresponding *E*-lactams **133** via radical **137** (Scheme 42).



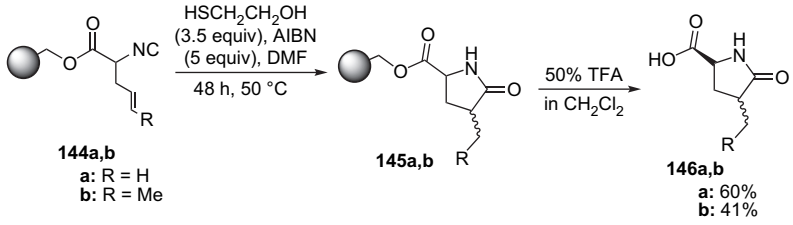
Scheme 42.

The microwave-assisted free radical cyclization of alkenyl and alkynyl isocyanides with thiols generated the five-membered nitrogen heterocycles.[134] In a typical reaction, a thiyl radical (RS$^{\bullet}$) was found to add to an alkenyl isocyanide **138**, generating a thioimidoyl radical **139**, which underwent a 5-*exo* cyclization and subsequent hydrogen atom abstraction to afford the *cis*- and *trans*-pyrrolines **140** (Scheme 43). By using 2-mercaptoethanol, *cis*- and *trans*-pyroglutamates **143** were obtained through the intermediate **141** followed by intramolecular cyclization to give a cyclic derivative **142**, which underwent hydrolysis under the reaction conditions (Scheme 43).

In a similar reaction, the polymer-supported isocyanides **144a**,**b** were reacted[135] with 2-mercaptoethanol and AIBN in DMF at 50 °C to obtain the cyclized products **145a**,**b**, which were cleaved from the solid support using TFA in DCM to produce the pyroglutamic acid derivatives **146a**,**b** (Scheme 44). Microwave flash heating was, however, found to give better yields than the traditional thermal heating technique and the reaction time was dramatically reduced.[136]

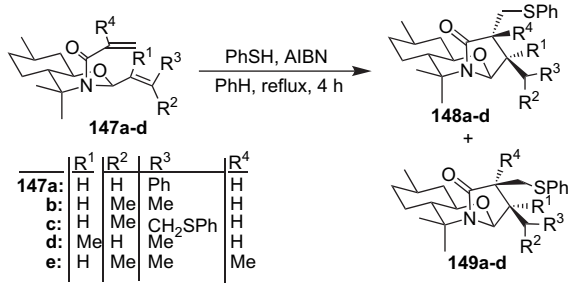


Scheme 43.



Scheme 44.

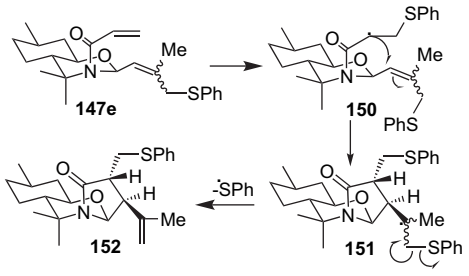
Thiophenol-mediated radical addition–cyclizations of 2-allyl-3-acyloyl-substituted perhydro-1,3-benzoxazines were reported to give the 3,4-disubstituted pyrrolidinone derivatives with high regioselectivity and good diastereoselectivity.[137] The key step of the reaction is a tandem addition-5-*exo*-cyclization promoted by a sulfanyl radical. The transformations of **147a–d** into the pyrrolidinones **148a–d** and **149a–d** were carried out by refluxing a 0.02 M solution of **147a–d** with thiophenol (1.1 equiv) and AIBN (0.2 equiv) in dry benzene under a nitrogen atmosphere (Scheme 45). Under these conditions, compounds **147b–d** gave a separable mixture of diastereoisomers. Only compound **147a** gave an inseparable mixture of four diastereoisomers.



Scheme 45.

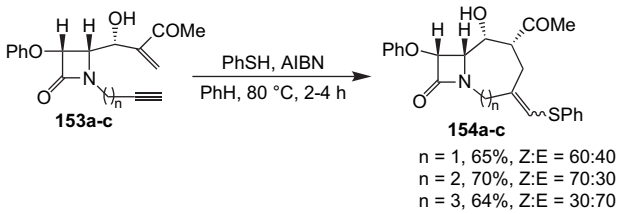
The allylphenyl sulfide derivative **147e** (0.06 M) with thiophenol (0.3 equiv) in refluxing toluene, however, afforded a single diastereoisomer **152** in 90% yield[137] through intermediates **150** and **151** (Scheme 46). The formation of the product can be interpreted by considering the fact that the cyclization reaction is followed by elimination of a phenylsulfanyl radical, which re-initiated the catalytic process.

Alcaide et al.[138] reported the synthesis of unusual 2-azetidinones fused to medium-sized rings **154** from the enyne **153** by thiophenol-mediated standard radical cyclization conditions. The radical precursors **153a–c** were prepared by the DABCO-promoted Baylis–Hillman reaction of various vinyl systems with the appropriate 4-oxoazetidine-2-carbaldehyde. Sulfanyl radical addition–



Scheme 46.

cyclization of ω-enyne-β-lactams **153a–c** in the presence of thiophenol and AIBN proceeded smoothly at 80 °C in refluxing benzene to give a separable mixture of *E*/*Z* isomers **154a–c** in 64–70% yield (Scheme 47).

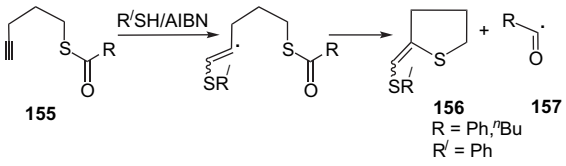


Scheme 47.

5.3. Synthesis of sulfur heterocycles

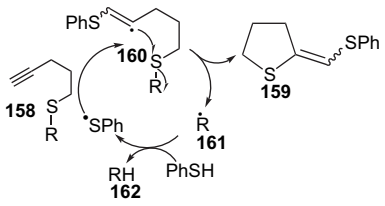
2-(Toluenesulfanyl)- and 2-(benzenesulfanyl)-phenylacetylene reacted with benzene- and toluene-thiol, respectively, in the presence of AIBN to give a vinyl radical intermediate, which underwent 5-(π-*endo*)*ortho* and 5-(π-*exo*)*exo* cyclization onto both the adjacent phenyl rings to furnish the benzothiophene derivative, along with other by-products, obtained from the side reactions of the vinyl radical intermediate.[139]

Crich and Yao first reported[140] a remarkable strategy based on the tributyltin hydride- or tris(trimethylsilyl)silane-mediated reactions of 2-(*o*-iodophenyl)ethanethiol esters. In these reactions, the thiol esters easily release acyl radicals upon intramolecular substitution at the sulfur atom by the aryl radicals. This aryl radical is initially generated by iodine atom abstraction by the tributylstannyl or tris(trimethylsilyl)silyl radicals. Benati et al.[141] have utilized this idea to prepare the thiophenes **156** by using pentynylthiol esters of the type **155** in combination with thiophenol. The thiol esters **155** were refluxed in dry benzene under a nitrogen atmosphere with thiol, R′SH and AIBN to afford the thiophenes **156** with the release of an acyl radical **157** (Scheme 48).



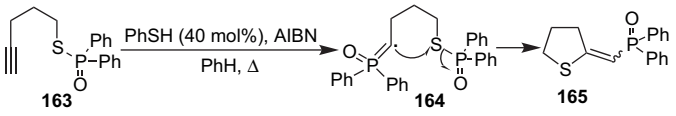
Scheme 48.

Very recently, Minozzi et al.[142] reported that homolytic substitution at the sulfur atom[143] of vinyl radicals, obtained by phenylsulfanyl radical addition to the terminus of the triple bond of 4-pentynyl sulfides, is a very effective tool for the generation of alkyl radicals and thiophene derivatives. The reaction mechanism involved the addition of a phenylsulfanyl radical to the triple bond of the 4-pentynyl sulfide **158** to give a vinyl radical **160**. This vinyl radical underwent a homolytic substitution at the sulfur atom to afford the alkyl radical **161**, together with the thiophene derivative **159** as a mixture of *E*- and *Z*-isomers (Scheme 49). Hydrogen atom transfer from benzenethiol to an alkyl radical gave the alkane **162** and regenerated the phenylsulfanyl radical.



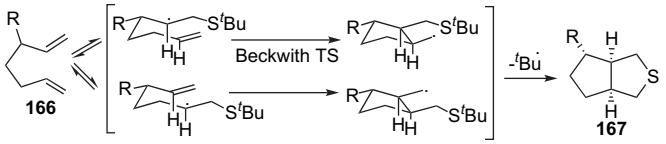
Scheme 49.

The thiyl radical can generate phosphorous-centered radicals by homolytic substitution of thiophosphine oxides, thiophosphonates, and thiodiaminophosphonates. The homolytic substitution was neatly triggered by the thiyl radical addition onto the triple bonds. In a typical reaction,[144] on treatment of the thiophosphine oxide **163** with thiophenol (40 mol %) in dry benzene, a clean thiophosphinoylation of the triple bond of **163** occurred, leading to the thiophene **165** (72%) as a 70:30 mixture of isomers (Scheme 50). The reaction might have proceeded through the intermediate **164**, which was formed by the attack of a phosphinoyl radical at the terminal of the triple bond of **163**. The phosphinoyl radical was formed by the reaction of **163** and a thiyl radical at the initiation process. When a similar reaction was carried out in the presence of olefins (5–10 equiv), however, P–C bond formation occurred with olefins only and no thiophene derivative was obtained.[144]



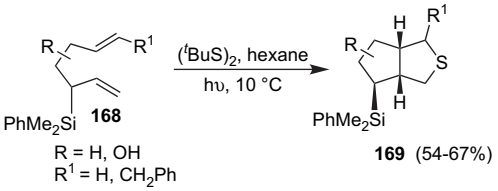
Scheme 50.

Harrowven et al.[145] developed a method for effecting the cyclization of 1,6-dienes with concomitant sulfur atom transfer. The key step was a cascade reaction involving the addition of a thiyl radical to an alkene **166**, followed by cyclization through a chair-like transition state to give an alkyl radical intermediate. This alkyl radical intermediate undergoes homolytic substitution at sulfur to give a cis-fused thiabicyclo[3.3.0]octane **167** (Scheme 51).



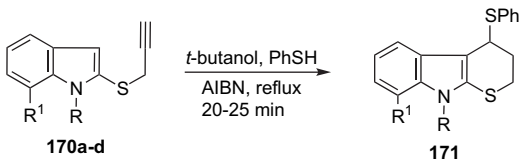
Scheme 51.

Recently, Landais et al.[146] have studied the regioselectivity of the sulfonyl radical-mediated 5-*exo*-*trig* cyclization of 3-silylhepta-1,6-diene systems (**168**). They observed that, at lower temperatures, the reaction of the sulfonyl radical occurs regioselectively at the allylsilane terminus, while a reversal of regioselectivity is observed at 80 °C. This general trend has been rationalized on the basis of polar effects and radical stabilization. The thiyl-mediated radical cyclizations of 3-silylhepta-1,6-dienes have, however, been achieved by $(^tBuS)_2$, with subsequent sulfur atom transfer to provide thiabicyclo[3.3.0]octane derivatives (**169**) in one step in moderate-to-good yields with excellent stereocontrol (Scheme 52).



Scheme 52.

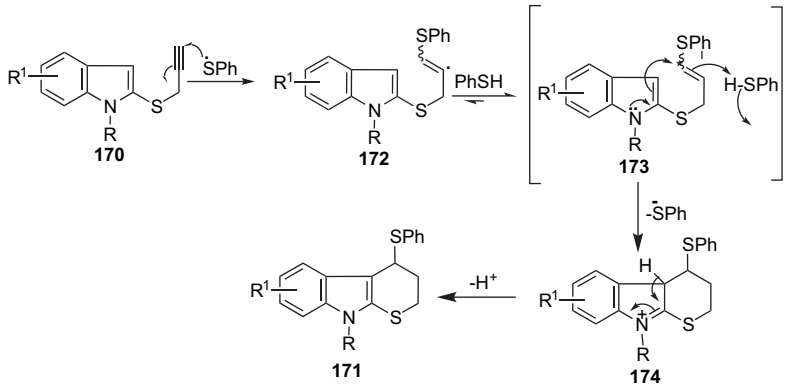
Recently, we have reported[147] the regioselective synthesis of indole-annulated sulfur heterocycles by tandem cyclization mediated by thiophenol. When the sulfides **170a–d** were treated with PhSH (2 equiv) in refluxing *tert*-butanol in the presence of a radical initiator AIBN (1.5 equiv) for 20 min, the tetrahydrothiopyrano[2,3-*b*]indole derivatives **171a–d** were obtained in 76–82% yield (Scheme 53).



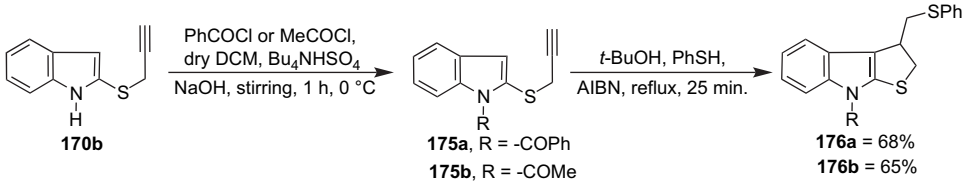
171a. R = Me, R^1 = H (82%)
b. R = R^1 = H (78%)
c. R = Et, R^1 = H (80%)
d. R = H, R^1 = Me(76%)

Scheme 53.

The formation of the products **171** from **170** may be explained by the abstraction of a hydrogen radical from thiophenol by the intermediate alkenyl radical **172** to afford the intermediate **173** followed by an intramolecular addition of the enamine (indole or indole with an electron-donating group) to the thioenol ether via an ionic pathway (via intermediate **174**) to afford the products **171**. This is possible due to the availability of a nitrogen lone pair (Scheme 54).



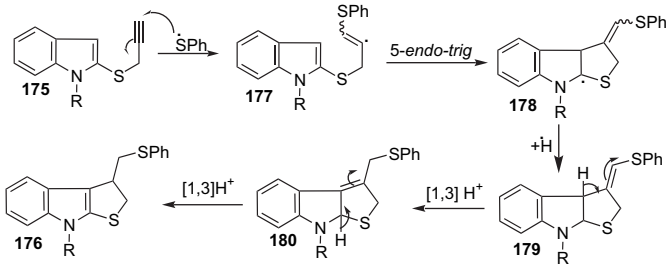
Scheme 54.



Scheme 55.

With a view to investigate the participation of the lone pair of the nitrogen atom of the indole moiety in the cyclization, we prepared the substrates **175a**,**b** by the reaction of the sulfide **170b** with benzoyl chloride and acetyl chloride, respectively. Compounds **175a**,**b** under similar radical-forming conditions afforded totally different types of products **176a**,**b** in 68 and 65% yield, respectively[147] (Scheme 55).

The formation of the five-membered products in **176a**,**b** from **175a**,**b** can be explained by 5-*endo*-*trig* cyclization of the initially generated vinyl radical onto the double bond of the pyrrole ring of the indole moiety. Abstraction of a hydride radical from thiophenol by the radical intermediate **178** may afford compound **179**. Due to the attachment of an electron-withdrawing group at the indole nitrogen, the pyrrole ring of the indole becomes much less aromatic and, hence, more alkene-like, thereby facilitating the 5-*endo*-*trig* radical cyclization of the radical **177** to form **179**, followed by two successive [1,3] proton exchanges, affording the products **176** (Scheme 56). Aromatization of the indole moiety via **180** may be the driving force for the formation of the products **176** from **179**.

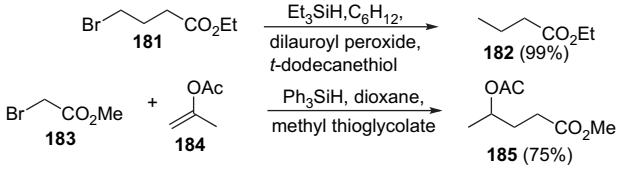


Scheme 56.

6. Uses of thiols as polarity reversal catalysts

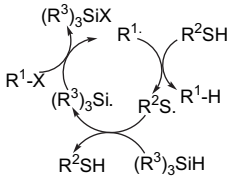
Polarity reversal catalysis (PRC) using thiols as catalysts has been investigated by Roberts et al.[96] This concept has been successfully applied in reductive radical-chain reactions, such as the reductions of alkyl halides, dialkyl sulfides, and xanthates,[148] using stoichiometric amounts of trialkylsilanes as the hydrogen atom donors in the presence of catalytic amounts of thiols. Thus, reduction of the xanthate derivatives of steroids with triethylsilane and dilauroyl peroxide as an initiator in refluxing cyclohexane produced the deoxygenated steroids in excellent yield.

Ethyl 4-bromobutyrate **181** was reduced to ethyl butyrate **182** by triethylsilane (4 equiv) and dilauroyl peroxide as an initiator in refluxing cyclohexane using *tert*-dodecanethiol as the polarity reversal catalyst. Reductive alkylations of electron-rich alkenes were also performed with the thiol–silane couple.[149] Reaction of bromoacetate **183** with olefin **184** using triphenylsilane and a catalytic amount of thioglycolate in dioxane under radical-forming conditions provided the reductive addition product **185** in 75% yield (Scheme 57).



Scheme 57.

Mechanistically, in this radical-chain reaction, the initially generated C-radical $R^{1\bullet}$ is readily reduced by the thiol catalyst to produce the corresponding reduced product R^1H, along with the formation of a thiyl radical $R^2S^{\bullet}$. This thiyl radical $R^2S^{\bullet}$ is then reduced by the trialkylsilane $(R^3)_3SiH$ to regenerate the thiol catalyst R^2SH and a silyl radical $(R^3)_3Si^{\bullet}$, which is able to propagate the radical-chain reaction (Scheme 58).



Scheme 58.

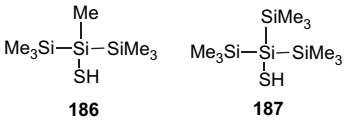


Figure 3.

Intramolecular[150] and intermolecular[151] hydrosilylations of alkenes can be carried out by a reaction involving the trialkylsilane–thiol couple. Hydroacylation of alkenes was also achieved by using thiols as catalysts and aldehydes as precursors of acyl radicals.[152]

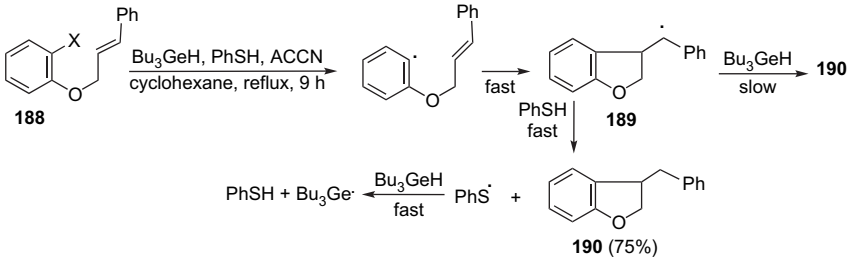
There are limited examples where thiols act as stoichiometric reducing agents in radical-chain reductions.[153] This is due to the fact that thiyl radicals are not able to propagate the reductive chain reaction. The silylated thiols **186** and **187** (Fig. 3) are, however, successfully used in reductive radical-chain reactions as tin hydride substitutes.[154] The thiol moiety acts as the reducing group in these reagents.

Mechanistically, an initially generated C-radical is reduced by the silylated thiol to afford the corresponding alkane and the thiyl radical. This thiyl radical undergoes a 1,2-silyl group migration to generate a silyl radical.[154a] This silyl radical can then continue the chain reaction by halogen abstraction.

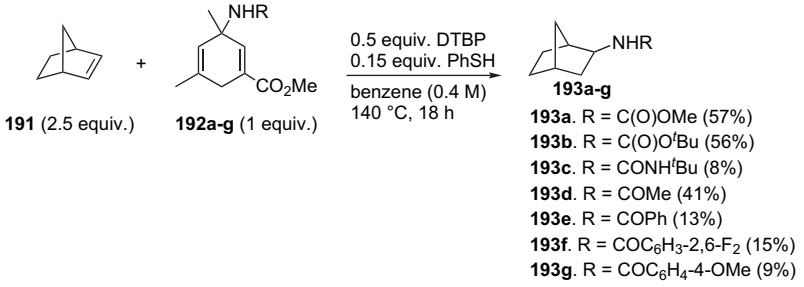
Germanes can also be used as tin hydride substitutes in reductive radical-chain reactions.[155] The kinetics of the H-transfer reaction from various germanes and silanes to C-centered radicals have been determined.[156] In general, germanes are more reactive than silanes, but less reactive than the corresponding tin hydrides. Bowman et al. reported[157] that the Bu_3SnH-mediated radical cyclization of the radical precursor **188** gave the cyclized product **190** in good yield, whereas the yields with Bu_3GeH were extremely poor. Various reaction conditions and initiators failed to improve the yield of the cyclized product. The poor reaction with Bu_3GeH was due to the slow rate of H-abstraction by the intermediate benzyl radical **189** from Bu_3GeH and the rate of H-abstraction from Bu_3GeH is too slow (20–30-fold slower than that with Bu_3SnH) to facilitate propagation and, hence, the chain reaction was inhibited. The yield of the cyclization product **190** was increased to 75% by using the polarity reversal catalysis (PRC) technique, in which the nucleophilic benzylic radical intermediate **189** reacts rapidly with the electrophilic source of hydrogen PhSH to generate PhS$^{\bullet}$, which reacted with Bu_3GeH to regenerate thiophenol and $Bu_3Ge^{\bullet}$ (Scheme 59).

Recently, Studer et al.[158] described the radical hydroamination of various unactivated and electron-rich double bonds by aminated cyclohexadienes using thiols as polarity reversal catalysts. It was observed that, among the various thiols studied, the best result was obtained with the commercially available thiophenol. Treatment of 2.5 equiv of norbornene **191** with aminated cyclohexadienes **192a**–**g** (1 equiv), di-*tert*-butyl peroxide (DTBP, 0.5 equiv), and PhSH (0.15 equiv) in benzene at 140 °C in a sealed tube for 18 h afforded the *exo*-hydroaminated products **193a**–**g** (Scheme 60). Due to the radical nature of the hydroamination reaction, many functional groups such as alcohols, silyl ethers, phosphonates, aryl bromides, imides, amides, and also acidic protons were tolerated under the reaction conditions. It was observed that hydroamination of 1-octene using thiophenol as the polarity reversal catalyst gave 51% of the hydroaminated product. In the absence of the thiophenol catalyst, however, only 10% of the hydroaminated products[158] were obtained.

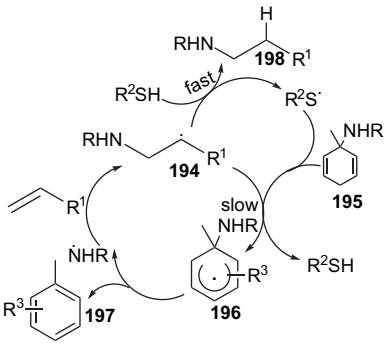
Mechanistically, addition of an N-centered radical to the alkene afforded the corresponding C-centered radical **194**, which may be reduced by the aminated cyclohexadiene **195** to provide the cyclohexadienyl radical **196** and the desired hydroaminated product. The reduction of the C-centered radical **194** by cyclohexadiene **195** is, however, very slow (Scheme 61) and the rate of the hydroamination is very low. An efficient chain was, however, obtained using a thiol as a polarity reversal catalyst. In this technique, the slow reduction of the C-centered radical with the cyclohexadiene **195** was replaced by an efficient H-transfer from the thiol. The C-centered radical reacts rapidly with the thiol to give the desired hydroaminated product **198** and a thiyl radical. This thiyl radical underwent H-abstraction from the 1,4-cyclohexadienyl amine **195** and regenerated the thiol catalyst and the cyclohexadienyl radical **196**. Chain propagation occurred via aromatization of the cyclohexadienyl radical **196** to the arene **197** (Scheme 61).



Scheme 59.

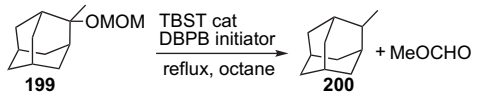


Scheme 60.



Scheme 61.

Roberts et al.[159] showed that on treatment of the methoxymethyl (MOM) ether of a tertiary alcohol with a thiol catalyst in the presence of a peroxide initiator, the MOM ether undergoes deoxygenation[160] to afford the corresponding alkane. Thus, the MOM ether of 2-methyl-2-adamantanol[159] **199**, when treated with tri-*tert*-butoxysilanethiol (TBST) and 2,2-di-*tert*-butylperoxybutane (DBPB) as initiator in refluxing octane for 2 h afforded 2-methyladamantane **200** (Scheme 62). In this reaction, the thiol acts as a polarity reversal catalyst.



Scheme 62.

A variety of homochiral carbohydrate-derived thiols, in which the SH group was attached to the anomeric carbon atom, act as protic polarity reversal catalysts.[161] As an example, the enantioselective radical-chain addition reactions of triphenylsilane to the $CH_2{=}CR^1R^2$ group in prochiral methylenelactones were catalyzed by carbohydrate thiols and afforded the chiral adducts of the general type $Ph_3SCH_2CHR^1R^2$.

Radical-chain epimerization of chiral tertiary CH centers adjacent to ethereal oxygen atoms was achieved in the presence of thiols.[162] The thiols act as polarity reversal catalysts. This strategy was demonstrated for the conversion of *trans*-cyclohexane-1,2-diol into the less stable cis-isomer and for the related contra-thermodynamic isomerization of some carbohydrates, as well as the conversion of *meso*-1,2-diphenylethane-1,2-diol into the DL-form.

Very recently, it was observed that UV irradiation in the presence of a thiol is a highly efficient route for the racemization of aliphatic amines under mild conditions. Racemizations of primary and secondary amines were faster than those of tertiary amines.[163]

7. Miscellaneous reactions

β-Amino acids are emerging as an interesting class of compounds for medicinal chemistry.[164] The most well known and medicinally important class of non-peptide β-amino acids are found in the β-lactams. The synthesis of β-lactam **201** and β-amino-γ-lactone **202** (Fig. 4) has been reported[165] by Naito et al. from the

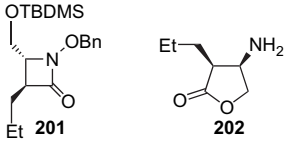
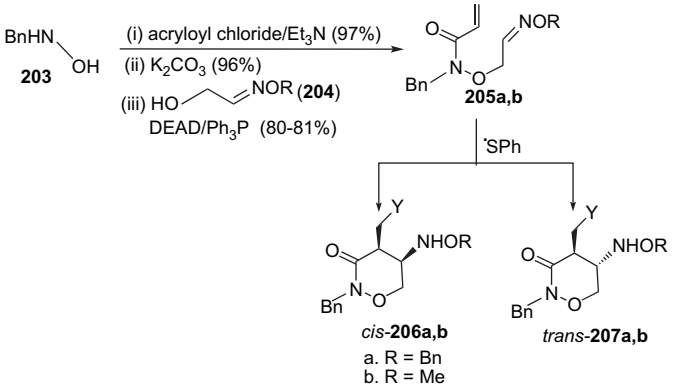


Figure 4.

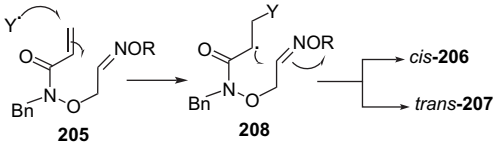
α,β-unsaturated hydroxamates using a thiophenol-mediated radical cyclization strategy.

The radical precursors **205** were prepared by acylation of *N*-benzylhydroxyamine **203** with acryloyl chloride, and partial hydrolysis of the resulting diacylated compound, followed by a Mitsunobu reaction with the hydroxyl oxime ether **204**. Sulfanyl radical addition–cyclization reaction of α,β-unsaturated hydroxamate **205a** having an *O*-benzyloxime ether in the presence of thiophenol (1 equiv) and AIBN (0.5 equiv) proceeded smoothly at 80 °C to give a ca. 3:1 separable mixture of the *cis*-amino-1,2-oxazinones **206a** and *trans*-**207a** in 80% yield.[165] Similarly, the hydroxamate **205b** with an *O*-methyloxime ether was found to give *cis*-**206b** and *trans*-**207b** in 76% combined yield (Scheme 63).



Scheme 63.

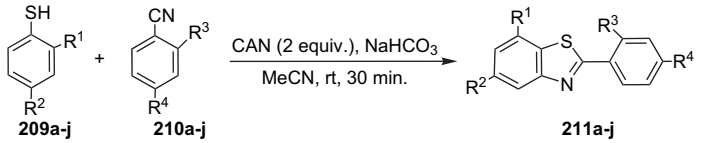
The alkyl radical addition–cyclization of **205a**,**b** has also been described using triethylborane as an ethyl radical source. Addition of sulfanyl and alkyl radicals to the alkene and subsequent cyclization onto the oxime ether in **205** took place regioselectively to produce substituted 1,2-oxazinones with an alkoxyamino group in the intermediate **208**, which underwent cyclization in a 6-*exo*-*trig* route to produce *cis*-1,2-oxazinones **206a**,**b** and the trans-isomers **207a**,**b** (Scheme 64). These amino-1,2-oxazinones **206** were then converted into the β-lactam **201** and β-amino-γ-lactone **202** by methanolysis followed by reduction.



Scheme 64.

The benzothiazole nucleus is very useful in medicinal chemistry and 2-(4-aminophenyl)benzothiazoles represent an important class of potent and selective antitumor agents.[166] Recently, Tale observed[167] that the reaction of thiophenols **209a**–**j** with aromatic nitriles **210a**–**j**, in the presence of ceric ammonium nitrate (CAN), proceeded smoothly to afford the corresponding 2-arylbenzothiazoles **211a**–**j** in excellent yields (Scheme 65).

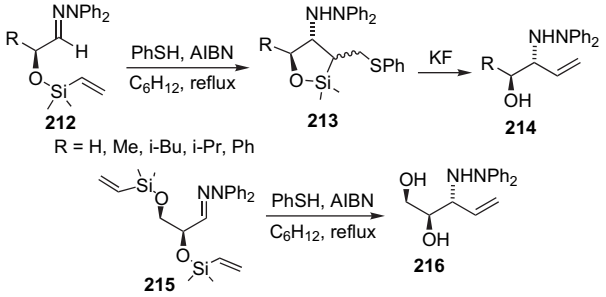
Recently, Friestad and Massari showed that a silicon tether transmitted stereochemical information to the new C–C bond through conformational constraints within the Beckwith–Houk model. They observed[168] that tributyltin hydride-mediated radical cyclization of bromomethyldimethylsilyl ethers furnished the oxasilacyclopentane products, but these cyclic silanes were not stable under normal silica gel chromatography. They could, however, be preserved in benzene at −5 °C without any significant decomposition.



209a-j 210a-j 211a-j

211 a) $R^1 = R^2 = R^3 = R^4 = H$ (95%)
b) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$ (95%)
c) $R^1 = R^3 = H$, $R^2 = R^4 = Me$ (90%)
d) $R^1 = H$, $R^2 = Me$, $R^3 = R^4 = OMe$ (89%)
e) $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = NO_2$ (85%)
f) $R^1 = F$, $R^2 = R^4 = H$, $R^3 = Cl$ (87%)
g) $R^1 = R^2 = R^4 = Cl$, $R^3 = H$ (87%)
h) $R^1 = R^3 = H$, $R^2 = CF_3$, $R^4 = Br$ (78%)
i) $R^1 = R^4 = H$, $R^2 = CF_3$, $R^3 = I$ (80%)
j) $R^1 = Br$, $R^2 = R^3 = H$, $R^4 = CN$ (96%)

Scheme 65.



212 213 214

R = H, Me, i-Bu, i-Pr, Ph

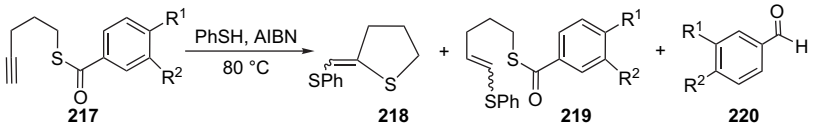
215 216

Scheme 66.

To apply the tandem addition–cyclization approach, silyl ether-linked vinylsilanes **212**, on treatment with thiophenol and AIBN in cyclohexane, underwent a 5-*exo* cyclization readily to give **213**. Oxidative removal of the silicon tether by treatment with KF furnished a chiral substituted vinylglycinol, *anti*-2-hydrazino-1,3-enol **214**. Thus, a neutral vinyl addition to a C=N bond was achieved via a tandem radical addition process mediated by thiophenol with diastereomeric ratios of 9:1 or higher. Similarly, bis-silyl ethers **215** afforded the highly functionalized vinyl adducts **216** in good yields[169] (Scheme 66).

The syntheses of aldehydes by using radical conditions are not well documented. Aromatic aldehydes could be synthesized by the reactions of acyl chlorides and selenides with stannane or silane reagents,[170,171] whereas for the aliphatic aldehydes there are serious problems, owing to the fact that the alkanoyl radical precursors undergo decarbonylation. In a recent approach, Benati et al.[172] have described a new tin-free procedure for the preparation of aromatic and aliphatic aldehydes from 4-pentynylthiol esters mediated by thiophenol. The radical reactions of pentynylthiol esters **217a–e** with PhSH were carried out by adding a benzene solution of the thiophenol (1.1 equiv) and AIBN (0.2 equiv) with a syringe pump over ca. 3 h to a refluxing solution of the appropriate substrate (2 mmol) in benzene under a nitrogen atmosphere. The reaction mixture was refluxed for an additional period of 1–2 h for the greater conversion of the starting material into the desired products. The benzocarbothiates **217a–e** under the above reaction conditions afforded benzaldehydes **220a–e** in good-to-excellent yield, along with equal amounts of (*E*)- and (*Z*)-dihydrothiophene **218**. Additionally, small amounts of the (*E*)- and (*Z*)-vinyl sulfide adducts **219a–e** were also isolated (Scheme 67).

This methodology has proved to be effective for the preparation of vinylic and secondary aldehydes, but it is not applicable to the tertiary compounds, because of the preferential formation of the decarbonylated alkane. The tertiary bridgehead aldehydes could, however, be prepared successfully.



217 218 219 220

217. a) $R^1 = R^2 = H$
b) $R^1 = Cl$, $R^2 = H$
c) $R^1 = NO_2$, $R^2 = H$
d) $R^1 = N_3$, $R^2 = H$
e) $R^1 = H$, $R^2 = N_3$

Products and yields (%)
218 (92%), **219a** (5 %), **220a** (93%)
218 (87%), **219b** (1 %), **220b** (88%)
218 (78%), **219c** (6 %), **220c** (65%)
218 (81%), **219d** (3 %), **220d** (70%)
218 (81%), **219e** (1 %), **220e** (80%)

Scheme 67.

8. Conclusions

The literature on the synthesis of heterocycles by radical cyclization is vast and, therefore, only recent representative examples of thiol-mediated radical reactions have been discussed in this brief review article. Thiyl radicals are easily generated from thiols or disulfides, and their radical cyclization has proved to be a very efficient and expedient route for the synthesis of various carbocycles and heterocycles including natural products. The methodology is cost effective over the tin substitutes as reagents and allows the functionalization of remote unreactive positions under mild conditions. Moreover, the cyclized products bear a phenylthio substituent that offers many opportunities for further transformation of the product into the target molecules. Mechanistic aspects of various radical cyclization reactions mediated by thiols have been studied in detail. From this brief review, it is evident that there is further adequate scope for generating exciting chemistry from thiol-mediated radical cyclizations.

Acknowledgements

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References and notes

1. Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 752.
2. (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986; (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 715; (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: London, 1992; (d) Leffler, J. E. *An Introduction to Free Radicals*; Wiley-Interscience: New York, NY, 1993; (e) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley and Sons: Chichester, New York, Brisbane, Toronto, Singapore, 1995; (f) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995; (g) Linker, T.; Schmittel, M. *Radikale and Radikalionen in der Organischen Chemie*; Wiley–VCH: Weinheim, 1998; (h) Malacria, M. *Chem. Rev.* **1996**, *96*, 289.
3. (a) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2004**, *60*, 6239; (b) Majumdar, K. C.; Basu, P. K.; Chattopadhyay, S. K. *Tetrahedron* **2007**, *63*, 793; (c) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803; (d) Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Heterocycles* **2004**, *63*, 1903; (e) Majumdar, K. C.; Basu, P. K. *Heterocycles* **2002**, *57*, 2413.
4. Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1295.
5. (a) Ryu, I.; Yamazaki, H.; Kusano, K.; Ogawa, A.; Sonoda, N. *J. Am. Chem. Soc.* **1991**, *113*, 8558; (b) Ryu, I.; Yamazaki, H.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 1187; (c) Brinza, I. M.; Fallis, A. G. *J. Org. Chem.* **1996**, *61*, 3580; (d) Nagahara, K.; Ryu, I.; Yamazaki, H.; Kambe, N.; Komatsu, M.; Sonoda, N.; Baba, A. *Tetrahedron* **1997**, *53*, 14615.
6. Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N.; Baba, A. *J. Am. Chem. Soc.* **1997**, *119*, 5465.
7. (a) Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 8692; (b) Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* **2000**, *2*, 389.
8. Ryu, I.; Okuda, T.; Nagahara, K.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1997**, *62*, 7550.
9. Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* **1998**, 1953.
10. Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838.
11. Ryu, I.; Muraoka, H.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1996**, *61*, 6396.
12. (a) Middleton, D. S.; Simpkins, J. S. *Tetrahedron Lett.* **1988**, *29*, 1315; (b) Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem.* **1993**, *58*, 3877; (c) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **1999**, *40*, 7595; (d) Koreeda, M.; Wang, Y.; Zhang, L. *Org. Lett.* **2002**, *4*, 3329.
13. (a) Rao, A. V. R.; Rao, B. V.; Reddy, D. R.; Singh, A. K. *J. Chem. Soc., Chem. Commun.* **1989**, 400; (b) Rao, A. V. R.; Singh, A. K.; Reddy, K. M.; Ravikumar, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3171; (c) Back, T. G.; Gladstone, P. L. *Synlett* **1993**, 699; (d) Kittaka, A.; Asakura, T.; Kuze, T.; Tanaka, H.; Yamada, N.; Nakamura, K. T.; Miyasaka, T. *J. Org. Chem.* **1999**, *64*, 7081.
14. (a) Clive, D. L. J.; Angoh, A. G.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339; (b) Srikrishna, A.; Nagaraju, S.; Sharma, G. V. R. *J. Chem. Soc., Chem. Commun.* **1993**, 285; (c) Sha, C.-K.; Ho, W.-Y. *Chem. Commun.* **1998**, 2709; (d) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S.; Hiremath, U. S.; Reddy, T. J.; Venugopalan, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2069.
15. (a) Harling, J. D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1380; (b) Cossy, J.; Poitevin, C.; Pardo, D. G. *Synlett* **1998**, 251; (c) Sulsky, R.; Gougoutas, J. Z.; DiMarco, J.; Biller, S. A. *J. Org. Chem.* **1999**, *64*, 5504; (d) Robertson, J.; Lam, H. W.; Abazi, S.; Roseblade, S.; Lush, R. K. *Tetrahedron* **2000**, *56*, 8959.
16. Previous review: Miyata, O.; Naito, T. *C.R. Acad. Sci.* **2001**, *4*, 401.
17. (a) Neumann, W. P. *Synthesis* **1987**, 665; (b) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Toronto, 1987; (c) Rajanbabu, T. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, NY, 1995; Vol. 7, p 5016; (d) Davies, A. G. *Organotin Chemistry*, 2nd ed; Wiley-VCH: Weinheim, 2004.
18. (a) Ingham, R. K.; Rosenberg, S. D.; Gilman, H. *Chem. Rev* **1960**, *60*, 459; (b) Boyer, I. J. *Toxicology* **1989**, *55*, 253; (c) See also: Davies, A. G. *J. Chem. Res.* **2006**, 141–148 (which contains information on the toxicity of, specially, organotin hydrides).
19. Studer, A.; Amrein. *Synthesis* **2002**, 835.
20. (a) Bertrand, M. P.; Ferreri, C. In *Radical in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 485; (b) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072; *Angew. Chem.* **1998**, *110*, 3272.
21. (a) Chatgilialoglu, C. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley–VCH: Weinheim, 2001; Vol. 1, Chapter 1.3, p 28; (b) Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599; (c) Berlin, S.; Engman, L. *Tetrahedron Lett.* **2000**, *41*, 3701; (d) Rigby, J. H.; Danca, D. M.; Horner, J. H. *Tetrahedron Lett.* **1998**, *39*, 8413; (e) Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1998**, *37*, 2864; (f) Batey, R. A.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 9183; (g) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 179; (h) Quirante, J.; Escolano, C.; Costeja, L.; Bonjoch, J. *Tetrahedron Lett.* **1997**, *38*, 6901; (i) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391; (j) Quirante, J.; Escolano, C.; Merino, A.; Banjoch, J. *J. Org. Chem.* **1998**, *63*, 968; (k) Dolbier, W. R.; Rong, X. X., Jr.; Smart, B. E.; Yang, Z.-Y. *J. Org. Chem.* **1996**, *61*, 4824; (l) Allin, S. M.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron* **2005**, *61*, 2689.
22. (a) Alajarin, M.; Vidal, A.; Ortin, M.-M.; Bautista, D. *Synlett* **2004**, 991; (b) Gandon, L. A.; Russell, A. G.; Snaith, J. S. *Org. Biomol. Chem.* **2004**, *2*, 2270; (c) Alajarin, M.; Vidal, A.; Ortin, M.-M.; Bautista, D. *Synlett* **2004**, 991; (d) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009; (e) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765; (f) Berlin, S.; Ericsson, C.; Engman, L. *J. Org. Chem.* **2003**, *68*, 8386; (g) Fischer, J.; Reynolds, A. J.; Sharp, L. A.; Sherburn, M. S. *Org. Lett.* **2004**, *6*, 1345; (h) Bressy, C.; Menant, C.; Piva, O. *Synlett* **2005**, 577.
23. Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.
24. (a) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171; (b) Jiang, Y.-Y.; Li, Q.; Lu, W.; Cai, J.-C. *Tetrahedron Lett.* **2003**, *44*, 2073; (c) Underwood, J. J.; Hollingworth, G. J.; Horton, P. N.; Hursthouse, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2004**, *45*, 2223; (d) Ohno, H.; Wakayama, R.; Maeda, S.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909; (e) Namy, J. L.; Girard, P.; Kagan, H. *Nouv. J. Chim.* **1977**, *1*, 5; (f) Dahlen, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, *43*, 7197; (g) Dahlen, A.; Hilmersson, G. *Chem.—Eur. J.* **2003**, *9*, 1123; (h) Dahlen, A.; Hilmersson, G.; Knettle, B. W.; Flowers, R. A., II. *J. Org. Chem.* **2003**, *68*, 4870; (i) Dahlen, A.; Petersson, A.; Hilmersson, G. *Org. Biomol. Chem.* **2003**, *1*, 2423; (j) Howells, D. M.; Barker, S. M.; Watson, F. C.; Light, M. E.; Hursthouse, M. B.; Kilburn, J. D. *Org. Lett.* **2004**, *6*, 1943; (k) Hwang, C. H.; Keum, G.; Sohn, K., II; Lee, D. H.; Lee, E. *Tetrahedron Lett.* **2005**, *46*, 6621; (l) Zhan, Z.-P.; Lang, K. *Org. Biomol. Chem.* **2005**, *3*, 727.
25. (a) Fuse, S.; Hanochi, M.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2004**, *45*, 1961; (b) Jana, S.; Guin, C.; Roy, S. C. *Tetrahedron Lett.* **2005**, *46*, 1155; (c) Banerjee, B.; Roy, S. C. *Synthesis* **2005**, 2913.
26. (a) Yanada, R.; Obika, S.; Nishimori, N.; Yamauchi, M.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 2331; (b) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417; (c) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835; (d) Yanada, R.; Nishimori, N.; Matsumura, A.; Fujii, N.; Takemoto, Y. *Tetrahedron Lett.* **2002**, *43*, 4585; (e) Ranu, B. C.; Samanta, S. *J. Org. Chem.* **2003**, *68*, 7130; (f) Ranu, B. C.; Samanta, S. *Tetrahedron* **2003**, *59*, 7901; (g) Ranu, B. C.; Banerjee, S.; Das, A. *Tetrahedron Lett.* **2004**, *145*, 8579; (h) Wang, C.-Y.; Su, H.; Yang, D.-Y. *Synlett* **2004**, 561; (i) Yanada, R.; Obika, S.; Kobayashi, Y.; Inokuma, T.; Oyama, M.; Yanada, K.; Takemoto, Y. *Adv. Synth. Catal.* **2005**, *347*, 1632; (j) Montevecchi, P. C.; Navacchia, M. L. *Tetrahedron* **2000**, *56*, 9339.
27. (a) Tsunoi, S.; Ryu, I.; Yamasaki, S.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1996**, *118*, 10670; (b) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16.
28. Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618.
29. (a) Garner, P. P.; Parker, D. T.; Gajewski, J. J.; Lubineau, A.; Ange, J.; Queneau, Y.; Beletskaya, I. P.; Cheprakov, A. V.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Kobayashi, S. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998; (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley and Sons: New York, NY, 1997; (c) Lubineau, A.; Auge, J. In *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Springer: Berlin, 1999.
30. (a) McCague, R.; Pritchard, R. G.; Stoodley, R. J.; Williamson, D. S. *Chem. Commun.* **1998**, 2691; (b) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791; (c) Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415; (d) Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071; (e) Jang, D. O.; Song, S. H. *Tetrahedron Lett.* **2000**, *41*, 247; (f) Martin, C. G.; Murphy, J. A.; Smith, C. R. *Tetrahedron Lett.* **2000**, *41*, 1833; (g) Takamatsu, S.; Katayama, S.; Hirose, N.; Naito, M.; Izawa, K. *Tetrahedron Lett.* **2001**, *42*, 7605; (h) Jang, D. O.; Cho, D. H.; Chung, C.-M. *Synlett* **2001**, 1923.
31. (a) Jang, D. O. *Tetrahedron Lett.* **1996**, *37*, 5367; (b) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anikumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157; (c) Jang, D. O.; Cho, D. Y. *Synlett* **2002**, 631.
32. (a) Graham, A. E.; Thomas, A. V.; Yang, R. *J. Org. Chem.* **2000**, *65*, 2583; (b) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 105; (c) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 225.
33. Cho, D. H.; Jang, D. O. *Synlett* **2005**, 59.
34. Nambu, H.; Anilkumar, G.; Matsugi, M.; Kita, Y. *Tetrahedron* **2003**, *59*, 77.
35. (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1992**, *33*, 5709; (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838; (c) See Ref. 31a; (d) Jang, D. O.; Cho, D. H.; Barton, D. H. R. *Synlett* **1998**, 39; (e) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104; (f) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 631; (g) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 1523; (h) Jang, D. O.; Cho, D. H. *Tetrahedron Lett.* **2002**, *43*, 5921; (i) Sugiura, M.; Hagio, H.; Kobayashi, S. *Chem. Lett.* **2003**, 898.
36. See Ref. 31b.
37. Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003**, *5*, 2971.
38. Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287.
39. Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. *Tetrahedron Lett.* **2003**, *44*, 479.
40. Healy, M. P.; Parsons, A. F.; Rawlinson, J. G. T. *Org. Lett.* **2005**, *7*, 1597.
41. See Ref. 26b.
42. (a) Miyai, T.; Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 1929; (b) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2001**, *42*, 4661; (c) Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2005**, *7*, 3093.
43. Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906.
44. Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993.
45. Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4981.
46. (a) Chen, H.-L.; Lin, C.-Y.; Cheng, Y.-C.; Tsai, A.-I.; Chuang, C.-P. *Synthesis* **2005**, 977; (b) Fujino, R.; Nishino, H. *Synthesis* **2005**, 731; (c) Asahi, K.; Nishino, H. *J. Heterocycl. Chem.* **2005**, *11*, 379; (d) Nishino, H. *J. Heterocycl. Chem.* **2005**, *42*, 1337.

47. Mu, X.-J.; Zou, J.-P.; Zeng, R.-S.; Wu, J.-C. *Tetrahedron Lett.* **2005**, *46*, 4345.
48. (a) Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2006**, *47*, 1599; (b) Xu, L.; Huang, X. *Tetrahedron Lett.* **2008**, *49*, 500.
49. (a) Mandal, S. K.; Roy, S. C. *Tetrahedron* **2007**, *63*, 11341; (b) Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2007**, *48*, 4131.
50. Chuang, C.-P.; Wu, Y.-L. *Tetrahedron* **2004**, *60*, 1841; Durand, A.-C.; Dumez, E.; Rodriguez, J.; Dulcere, J.-P. *Chem. Commun.* **1999**, 2437.
51. (a) Muathen, H. A. *Indian J. Chem.* **1991**, *30B*, 522; (b) Chen, C.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 3252.
52. (a) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21; (b) Nair, V.; Mathew, J.; Prahakaran, J. *J. Chem. Soc. Rev.* **1997**, 127; (c) Molander, A. G. *Chem. Rev.* **1992**, *92*, 29.
53. Zhang, Y.; Raines, A. J.; Flowers, R. A., II. *Org. Lett.* **2003**, *5*, 2363.
54. Zhang, Y.; Raines, A. J.; Flowers, R. A., II. *J. Org. Chem.* **2004**, *69*, 6267.
55. Naito, T.; Honda, Y.; Bhavakul, V.; Yamaguchi, S.; Fujiwara, A.; Miyata, O.; Ninomiya, I. *Chem. Pharm. Bull.* **1997**, *45*, 1932.
56. Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 6922.
57. (a) Bachi, M. D.; Melman, A. *Pure Appl. Chem.* **1998**, *70*, 259; (b) Bachi, M. D.; Bar-Ner, N.; Melman, A. *J. org. Chem.* **1996**, *61*, 7116; (c) Bachi, M. D.; Melman, A. *Synlett* **1996**, 60; (d) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Synlett* **1997**, 275.
58. Miyata, O.; Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 271.
59. Miyata, O.; Nakajima, E.; Naito, T. *Chem. Pharm. Bull.* **2001**, *49*, 213.
60. Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397.
61. Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 5833.
62. Takeda, Y.; Nakabayashi, T.; Shirai, A.; Fukumoto, D.; Kiguchi, T.; Naito, T. *Tetrahedron Lett.* **2004**, *45*, 3481.
63. Lachia, M.; Denes, F.; Beaufils, F.; Renaud, P. *Org. Lett.* **2005**, *19*, 4103.
64. Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Naito, T. *Tetrahedron Lett.* **1996**, *37*, 229.
65. See Ref. 26c.
66. Feray, L.; Kuznetzov, N.; Renaud, P.; Renaud, P.; Sibi, M. P. *Radical in Organic Synthesis*; Wiley-VCH: Weinheim, 2001; Vol. 2, 246.
67. (a) Curran, D. P.; Dooseop, K.; Hong Tao, L.; Wang, S. *J. Am. Chem. Soc.* **1998**, *110*, 9500; (b) Curran, D. P.; Kim, D.; Ziegler, C. *Tetrahedron* **1991**, *47*, 6189.
68. Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.
69. Beaufils, F.; Denes, F.; Renaud, P. *Org. Lett.* **2004**, *15*, 2563.
70. Miyata, O.; Yamanaka, R.; Ueda, M.; Naito, T. *Arkivoc* **2003**, *viii*, 220.
71. Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459.
72. (a) Theil, F.; Ballschuh, S. *Tetrahedron: Asymmetry* **1996**, *7*, 3565; (b) Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411; (c) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *Synlett* **1993**, 461.
73. Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1989**, *42*, 1749.
74. (a) Du, X. H.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678; (b) Armstrong, R. W. *Tetrahedron Lett.* **1998**, *39*, 2281.
75. (a) Plourde, R., Jr.; Johnson, L. L., Jr.; Longo, R. K. *Synlett* **2001**, 439; (b) Taddei, M.; Attardi, M. E. *Tetrahedron Lett.* **2001**, *42*, 3519; (c) Yim, A. M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1999**, *40*, 4535; (d) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443; (e) Miyabe, H.; Fujii, K.; Tanaka, H.; Naito, T. *Chem. Commun.* **2001**, 831.
76. Ganesan, A.; Zhu, X. *J. Comb. Chem.* **1999**, *1*, 157.
77. Harrowven, D. C.; May, P. J.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 503.
78. Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron* **1997**, *53*, 14507; (b) Chavez, D. E.; Jacobsen, E. N. *Org. Lett.* **2003**, *5*, 2563; (c) Chauhan, K.; Zhang, Q.; Aldrich, J. *Tetrahedron Lett.* **2004**, *45*, 3339; (d) Pungitore, C.; Ayub, M.; Garcia, M.; Borkowski, E.; Sosa, M.; Ciuffo, G.; Giordano, O.; Tonn, C. *J. Nat. Prod.* **2004**, *67*, 357.
79. Wang, Y.; Wei, Q.; Yang, L.; Liu, Z.-L. *J. Chem. Res., Synop.* **2003**, 676.
80. Tanaka, N.; Nishikawa, K. *J. Agric. Food Chem.* **2003**, *51*, 5906.
81. Graikou, K.; Aligiannis, N.; Chinou, I. B.; Harvala, C. *Z. Naturforsch., C: Biosci.* **2002**, *57*, 95.
82. Bermeji, P.; Abad, M. J.; Diaz, A. M.; Fernandez, L.; De Santos, J.; Sanchez, S.; Villaescusa, L.; Carrasco, L.; Irurzun, A. *Planta Med.* **2002**, *68*, 106.
83. Sakai, T.; Nakajiama, K.; Sakan, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3683.
84. Barrero, A. F.; Arseniyadis, S.; Herrador, M. M.; de Moral, J. F. Q.; Arteaga, J. F. *Synlett* **2005**, 591.
85. Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **2001**, *57*, 791.
86. Fernandez, M.; Alonso, R. *Org. Lett.* **2005**, *1*, 11.
87. (a) Keck, G. E.; Wager, T. T.; McHardy, S. E. *J. Org. Chem.* **1998**, *63*, 9164; (b) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289; (c) Keck, G. E.; Wager, T. T. *J. Org. Chem.* **1996**, *61*, 8366.
88. Keck, G. E.; Wager, T. T.; Rodriguez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176.
89. (a) Kozhushkov, S. I.; Brandl, M.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1535; (b) Xu, B.; Chen, Y.; Shi, M. *Tetrahedron Lett.* **2002**, *43*, 2781.
90. Yu, L.; Huang, X.; Xie, M. *Synlett* **2006**, 423.
91. (a) Majumdar, K. C.; Sarkar, S.; Bhattacharrya, T. *Tetrahedron* **2003**, *59*, 4309; (b) Majumdar, K. C.; Mukhopadhyay, P. P. *Synthesis* **2004**, 1864; (c) Majumdar, K. C.; Kundu, N. *Synth. Commun.* **2006**, *36*, 1879; (d) Majumdar, K. C.; Chattopadhyay, S. K. *Tetrahedron Lett.* **2004**, *45*, 6871; (e) Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Synth. Commun.* **2005**, *35*, 1291; (f) Majumdar, K. C.; Debnath, P.; Pal, A. K.; Chattopadhyay, S. K.; Biswas, A. *Can. J. Chem.* **2007**, *85*, 445; (g) Majumdar, K. C.; Alam, S. *Org. Lett.* **2006**, *18*, 4059.
92. (a) Xu, X. X.; Che, X.; Gao, S.; Wu, J. C.; Bai, X. *Synlett* **2005**, 1865; (b) Martin, A.; Perez-Martin, I.; Suarez, E. *Org. Lett.* **2005**, *7*, 2027; (c) Meilert, K.; Brimble, A. *Org. Lett.* **2005**, *7*, 3497.
93. Beaufils, F.; Denes, F.; Renaud, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 5273.
94. Beaufils, F.; Denes, F.; Becattini, B.; Renaud, P. *Adv. Synth. Catal.* **2005**, *347*, 1587.
95. Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett.* **2003**, *5*, 1313.
96. (a) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25; (b) Dang, H. S.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2452.
97. (a) Ozaki, S.; Adachi, M.; Sekiya, S.; Kamikawa, R. *J. Org. Chem.* **2003**, *68*, 4586; (b) Evans, P. A.; Roseman, J. D. *J. Org. Chem.* **1996**, *61*, 2252; (c) Bath, S.; Laso, N. M.; Lopez-Ruiz, H.; Quinclet-Stire, B.; Zard, S. Z. *Chem. Commun.* **2003**, 204.
98. Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2005**, *70*, 681.
99. Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K.; Tomioka, K. *Chem. Pharm. Bull.* **2005**, *53*, 586.
100. (a) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2005**, *61*, 10603; (b) Aldabbagh, F.; Bowman, W. R. *Cont. Org. Synth.* **1997**, *4*, 261; (c) Bowman, W. R.; Cloonan, M. O.; Krintel, S. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2885; (d) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P.; Sarkar, S.; Ghosh, S. K.; Biswas, P. *Tetrahedron* **2003**, *59*, 2151; (e) Majumdar, K. C.; Mukhopadhyay, P. P.; Biswas, A. *Tetrahedron Lett.* **2005**, *46*, 6655.
101. (a) Majumdar, K. C.; Mukhopadhyay, P. P. *Synthesis* **2003**, 97; (f) Majumdar, K. C.; Muhuri, S. *Synthesis* **2006**, 2725; (g) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695; (h) Majumdar, K. C.; Biswas, A.; Mukhopadhyay, P. P. *Synthesis* **2003**, 2385.
102. (a) Bialy, S. A. A.; Ohtani, S.; Sato, T.; Ikeda, M. *Heterocycles* **2001**, *54*, 1021; (b) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977; (c) Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537.
103. (a) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731; (b) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639; (c) Bremner, J. B.; Sengpracha, W. *Tetrahedron* **2005**, *61*, 941.
104. Capella, L.; Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1996**, *61*, 6783.
105. Burke, S. D.; Jung, K. W. *Tetrahedron Lett.* **1993**, *34*, 131.
106. Renaud, P.; Beaufils, F.; Feray, L.; Schenk, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4230.
107. El Kaim, L.; Gacon, A.; Perroux, A. *Tetrahedron Lett.* **1998**, *39*, 371.
108. Majumdar, K. C.; Debnath, P.; Maji, P. K. *Tetrahedron Lett.* **2007**, *48*, 5265.
109. (a) Aureliano Antunes, C. S.; Bietti, G.; ErcolaniLanzalunga, O.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 3884; (b) Parker, K. A.; Spero, D. M.; Inman, K. C. *Tetrahedron Lett.* **1986**, *27*, 2833; (c) Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072.
110. (a) Majumdar, K. C.; Maji, P. K.; Roy, K.; Debnath, P. *Tetrahedron Lett.* **2007**, *48*, 9124; (b) Majumdar, K. C.; Roy, K.; Debnath, P.; Maji, P. K.; Kundu, N. *Tetrahedron Lett.* **2008**, *49*, 5597.
111. (a) Posner, G. H.; Meshnick, S. R. *Trends Parasitol.* **2001**, *17*, 266; (b) Hindley, S.; Ward, S. A.; Storr, R. C.; Searle, N. L.; Bray, P. G.; Park, B. K.; Davies, J.; O'Neill, P. M. *J. Med. Chem.* **2002**, *45*, 1052.
112. Posner, G. H.; Paik, I.-H.; Sur, S.; McRiner, A. J.; Borstnik, K.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **2003**, *46*, 1060.
113. O'Neill, P. M.; Mukhtar, A.; Ward, S. A.; Bickley, J. F.; Davies, J.; Bachi, M. D.; Stocks, P. A. *Org. Lett.* **2004**, *6*, 3035.
114. (a) Bachi, M. D.; Korshin, E. E. *Synlett* **1998**, 122; (b) Korshin, E.; Hoos, R.; Szpilman, A. M.; Konstantinovski, L.; Posner, G. H.; Bachi, M. D. *Tetrahedron* **2002**, *58*, 2449.
115. Liang, X. In *Advances in Chinese Medicinal Materials*; Chang, H. M., Yeung, H. W., Tso, W. W., Koo, A., Eds.; World Scientific: Singapore, 1985; p 427.
116. Bachi, M. D.; Korshin, E. E.; Hoos, R.; Szpilman, A. M. *J. Heterocycl. Chem.* **2000**, *37*, 639.
117. (a) O'Neill, M. P.; Stocks, P. A.; Pugh, M. D.; Araujo, N. C.; Korshin, E. E.; Bickley, J. F.; Ward, S. A.; Bray, P. G.; Pasini, E.; Davies, J.; Verissimo, E.; Bachi, D. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4193; (b) Bachi, D. M.; Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Ploypradith, P.; Xie, S.; Shapiro, T. A.; Posner, G. *J. Med. Chem.* **2003**, *46*, 2516.
118. (a) Ward, R. S. *Nat. Prod. Rep.* **1993**, 1; (b) Driori, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem.* **1998**, *63*, 2385.
119. (a) Wang, C.; Russell, G. A. *J. Org. Chem.* **1999**, *64*, 2066; (b) Curran, D. P.; Timine, J. *J. Org. Chem.* **1991**, *56*, 2746; (c) Barth, F.; Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121; (d) Russell, G. A.; Li, C.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 9831; (e) Surzur, J.-M.; Bertrand, M. P. *Pure Appl. Chem.* **1988**, *60*, 1659.
120. Navacchia, M. L.; Montevecchi, P. C. *Org. Biomol. Chem.* **2006**, *4*, 3754.
121. Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2006**, *71*, 3192.
122. Bella, A. F.; Slawin, A. M. Z.; Walton, J. C. *J. Org. Chem.* **2004**, *69*, 5926.
123. Montevecchi, P. C.; Navacchia, M. L. *Tetrahedron Lett.* **1998**, *39*, 9077.
124. Tokuyama, H.; Watanable, M.; Hayashi, Y.; Kurokawa, T.; Peng, G.; Fukuyama, T. *Synlett* **2001**, 1403.
125. (a) Miyabe, H.; Tanaka, H.; Naito, T. *Chem. Pharm. Bull.* **2004**, *52*, 74; (b) Miyata, O.; Kajisa, S.; Ueda, M.; Yamauchi, M.; Naito, T. *Chem. Pharm. Bull.* **2005**, *53*, 995.
126. (a) Miyabe, H.; Tanaka, H.; Nato, T. *Tetrahedron Lett.* **1999**, *40*, 8387; (b) Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 271.
127. Shinozaki, H. In *Exitatory Amino Acid Receptors Design of Agonists and Antagonists*; Larsen, P. K., Hansen, J. J., Eds.; Horwood, E: New York, NY, 1992; pp 161–191.

128. See Ref. 56.
129. Miyata, O.; Ozawa, Y.; Ninomiya, I.; Aoe, K.; Hiramatsu, H.; Naito, T. *Heterocycles* **1997**, *46*, 321.
130. Denes, F.; Beaufils, F.; Renaud, P. *Org. Lett.* **2007**, *21*, 4375.
131. Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19.
132. Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Schiesser, C. H.; Kuriyama, H.; Miyazato, H.; Minakata, S.; Komatsu, M.; Ryu, I. *Org. Biomol. Chem.* **2003**, *1*, 4262.
133. Ryu, I.; Miyazato, H.; Kuriyama, H.; Matsu, K.; Tojino, M.; Fukuyama, T.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2003**, *125*, 5632.
134. Lamberto, M.; Corbett, D. F.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1347.
135. Lamberto, M.; Corbett, D. F.; Kilburn, J. D. *Tetrahedron Lett.* **2004**, *45*, 8541.
136. Akamatsu, H.; Fukase, K.; Kusumoto, S. *Synlett* **2004**, 1049.
137. Pedrosa, R.; Andres, C.; Duque-Soladana, J. P.; Maestro, A.; Nieto, J. *Tetrahedron: Asymmetry* **2003**, *14*, 2985.
138. Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612.
139. Melandri, D.; Montevecchi, P. C.; Navacchia, M. L. *Tetrahedron* **1999**, *55*, 1227.
140. Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566.
141. (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2103; (b) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1305; (c) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Org. Chem.* **1994**, *59*, 2818; (d) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Org. Chem.* **1995**, *60*, 7941.
142. Bencivenni, G.; Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *Org. Lett.* **2008**, *9*, 1061.
143. (a) Schiesser, C. H.; Wild, L. M. *Tetrahedron* **1996**, *52*, 13265; (b) Beckwith, A. L. J.; Boate, D. R. *J. Org. Chem.* **1988**, *53*, 4339; (c) Beckwith, A. L. J.; Boate, D. R. *J. Chem. Soc., Chem. Commun.* **1986**, 189; (d) Beckwith, A. L. J.; Duggan, S. A. M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1509.
144. Carta, P.; Puljic, N.; Robert, C.; Dhimane, A. L.; Fensterbank, L.; Lacote, E.; Malacria, M. *Org. Lett.* **2007**, *6*, 1061.
145. Harrowven, D. C.; Hannam, J. C.; Lucas, M. C.; Newman, N. A.; Howes, P. D. *Tetrahedron Lett.* **2000**, *41*, 9345.
146. James, P.; Schenk, K.; Landais, Y. *J. Org. Chem.* **2006**, *71*, 3630.
147. Majumdar, K. C.; Debnath, P.; Alam, S.; Maji, P. K. *Tetrahedron Lett.* **2007**, *48*, 7031.
148. Cole, S. J.; Kirwan, J. N.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 103.
149. Dang, H.-S.; Elsegood, M. R. J.; Kim, K.-M.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2061.
150. (a) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1995**, *36*, 2875; (b) Haque, M. B.; Roberts, B. P. *Tetrahedron Lett.* **1996**, *37*, 9123.
151. Cai, Y.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 467.
152. (a) Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 67; (b) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1999**, *40*, 8929.
153. (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901; (b) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1461.
154. (a) Ballestri, M.; Chatgilialoglu, C.; Seconi, G. *J. Organomet. Chem.* **1991**, *408*, C1; (b) Daroszewski, J.; Lusztyk, J.; Degueil, M.; Navarro, C.; Maillerd, B. *J. Chem. Soc., Chem. Commun.* **1991**, 586.
155. (a) Chatgilialoglu, C.; Ballestri, M. *Organometallics* **1995**, *14*, 5017; (b) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 747; (c) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188; (d) Bennasar, M.-L.; Juan, C.; Bosch, J. *Chem. Commun.* **2000**, 2459; (e) Romeo, R.; Wozniak, L. A.; Chatgilialogu, C. *Tetrahedron Lett.* **2000**, *41*, 9899.
156. (a) Lusztyk, J.; Maillard, B.; Lindsay, D. A.; Ingold, K. U. *J. Am. Chem. Soc.* **1983**, *105*, 3578; (b) Chitagilialoglu, C.; Newcomb, M. *Adv. Organomet. Chem.* **1999**, *44*, 67.
157. Bowman, W. R.; Krintel, S. L.; Schilling, M. B. *Org. Biomol. Chem.* **2004**, *2*, 585.
158. Guin, J.; Muck-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498.
159. Dang, H.-S.; Franchi, P.; Roberts, B. P. *Chem. Commun.* **2000**, 499.
160. (a) Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1161; (b) Dang, H.-S.; Roberts, B. P.; Sekhon, J.; Smits, T. M. *Org. Biomol. Chem.* **2003**, *1*, 1330.
161. Cai, Y.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 376.
162. Dang, H.-S.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2452.
163. Routaboul, L.; Vanthuyne, N.; Gastaldi, S.; Gil, G.; Bertrand, M. *J. Org. Chem.* **2008**, *73*, 364.
164. (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991; (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3; (c) Sewald, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5794.
165. Miyata, O.; Namba, M.; Ueda, M.; Naito, T. *Org. Biomol. Chem.* **2004**, *2*, 1274.
166. Bradshaw, T. D.; Wrigley, S.; Shi, D. F.; Schulz, R. J.; Paull, K. D.; Stevens, M. F. G. *Br. J. Cancer* **1998**, *77*, 745.
167. Tale, R. H. *Org. Lett.* **2002**, *4*, 1641.
168. Friestad, G. K.; Massari, S. E. *J. Org. Chem.* **2004**, *69*, 863.
169. Friestad, G. K.; Massari, S. E. *Org. Lett.* **2000**, *2*, 4237.
170. Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.
171. (a) Chatgilialoglu, C.; Lucarini, M. *Tetrahedron Lett.* **1995**, *36*, 1299; (b) Graf, W.; Heuberger, C.; Pfenninger, J. *Helv. Chim. Acta* **1980**, *63*, 2328.
172. Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *Synlett* **2004**, 987.

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