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# Thiol-mediated radical cyclizations

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## 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

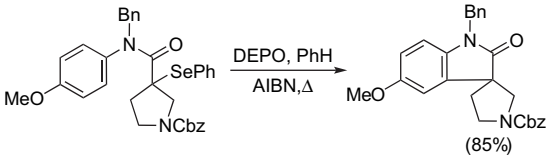
To date, most of the radical reactions were conducted using tin hydride reagents, such as tri-*n*-butyltin hydride ($^{n}Bu_3SnH$), trimethyltin hydride ($Me_3SnH$), and triphenyltin hydride ($Ph_3SnH$).[17] An alternative procedure involving the use of a small amount of tri-*n*-butyltin chloride ($^{n}Bu_3SnCl$) 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).

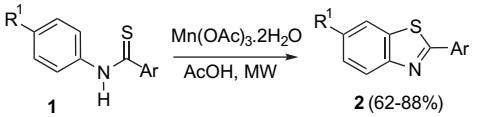



**Scheme 1.**

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]