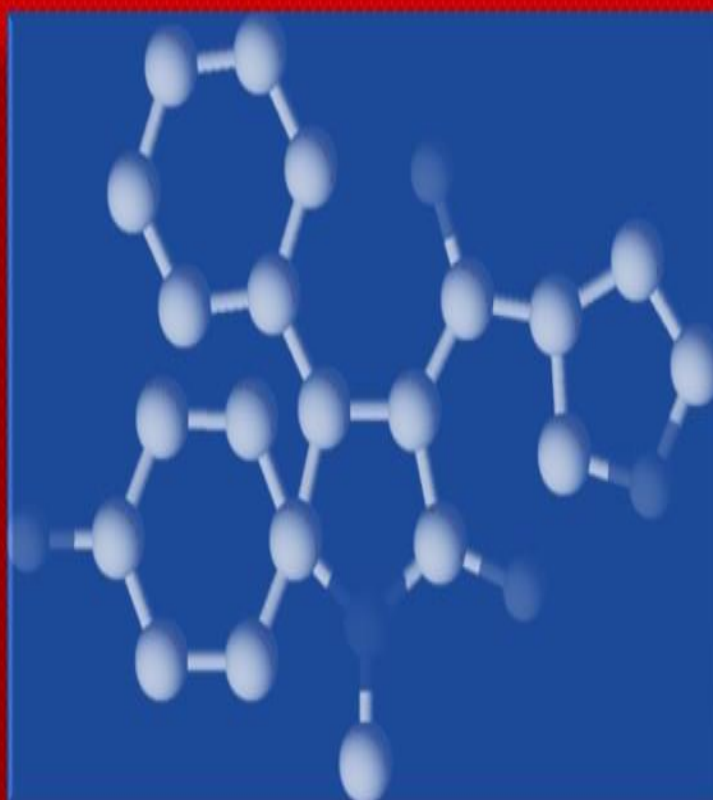


# Radical *Ips*o-Cyclization: Snapshot



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# Radical *Ips*o-Cyclization: Snapshot

Atef S. Iskander

Radical *ipso*-cyclization of arene is recognized as a robust strategy for the construction of quaternary carbon centers, such as spirocycles, or medium-sized benzannulated carbocycles. Such core skeletons are found in a variety of natural products and bioactive compounds. This snapshot briefly highlights selected examples of radical *ipso*-cyclization methodologies for the construction of spirocycles and miscellaneous of carbocycles.

KEYWORDS: Radical *ipso*-cyclization, Radical chemistry, Radical spirocycles, Spirocyclohexadienone.

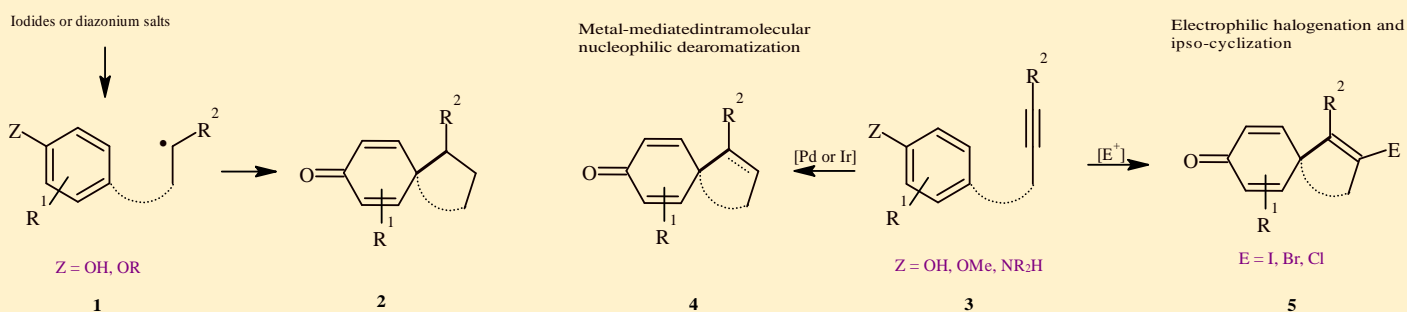
## 1. Introduction

Radical cyclization constitutes a valuable tool to construct high-value and complex compounds. Among this landscape of reactions, radical *ipso*-cyclization of arene is recognized as a powerful strategy with high economic viability for the construction of a quaternary carbon center forming spiro- or carbocycles, in which tethered radicals add to the *ipso*-carbon atom of the ring.<sup>1-3</sup> Indeed, the spirocyclohexadienone ring is a privileged structural moiety in a variety of natural products and pharmaceuticals,<sup>4-6</sup> along with serving as a versatile synthon in the synthesis of a wide variety of variable compounds.<sup>7,8</sup> The radical *ipso*-cyclization strategy serves as a good control and selectivity for the construction of poly-functionalized aryl compounds *via* intramolecular fashion by taking advantage of a removable tether. Moreover, the radical synthetic process is characterized by the ability to be applicable to more substrates with broader functional group tolerance compared to the electrophilic *ipso*-cyclization.<sup>9,10</sup> This snapshot briefly highlights selected examples of radical *ipso*-cyclization of arene, including some recent advances in this field. The presented examples provide a general view of constructing diverse scaffolds and synthesizing complex molecules that could potentially provide useful insights in exploring novel reactions.

## 2. Construction of spirocyclohexadienone rings

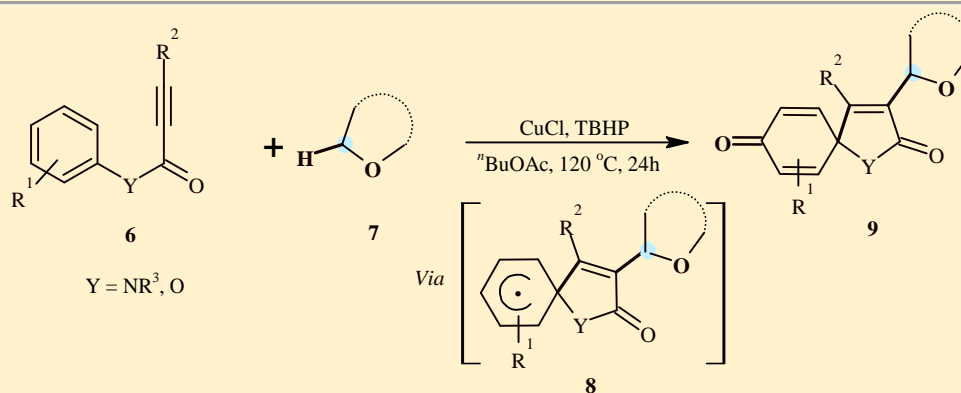
The synthesis of spirocyclohexadienones can be achieved through the dearomatization of phenols *via* the radical *ipso*-carbocyclization of an intermediate, that *in situ* is generated from the corresponding iodides or

diazonium salts;<sup>11,12</sup> transition-metal mediated intramolecular nucleophilic dearomatization of 5-(*p*-hydroxy-aryl)-1-alkenes or alkynes;<sup>13,14</sup> or electrophilic halogenation and *ipso*-carbocyclization of 4-aryl-1-alkynes (Scheme 1).<sup>15-17</sup> In another interesting strategy, the introduction of an unsaturated bond serving as a platform to trap radicals followed by *ipso*-carbocyclization and dearomatization would furnish the functionalized



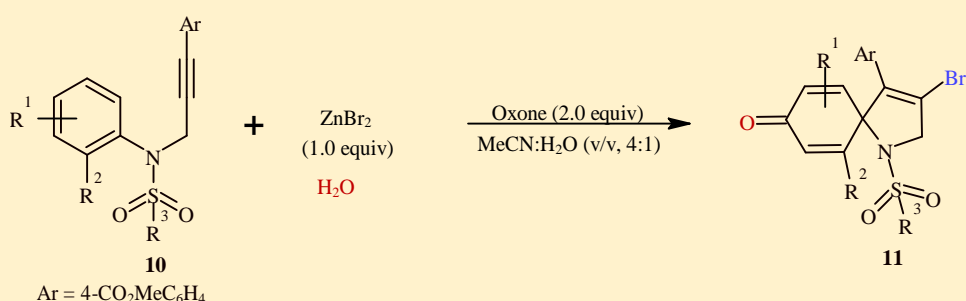
**Scheme 1:** Construction of Construction of spirocyclohexadienone rings.

spirocyclohexadienone ring system. For example, the synthesis of 3-etherified azaspiro[4.5]trienones **9** from *N*-arylpropiolamides **6** and ethers **7** was achieved by using copper catalyst and *tert*-butyl hydroperoxide oxidant (TBHP) (Scheme 2).<sup>17</sup> This tandem strategy makes the synthesis of higher-functionalized ethers from simple ethers versatile through C(sp<sup>3</sup>)-H functionalization, *ipso*-carbocyclization **8** and dearomatization cascade forming two carbon-carbon bonds and one carbon-oxygen double bond, which the oxygen atom of the newly formed carbonyl group comes from the hydroperoxide.

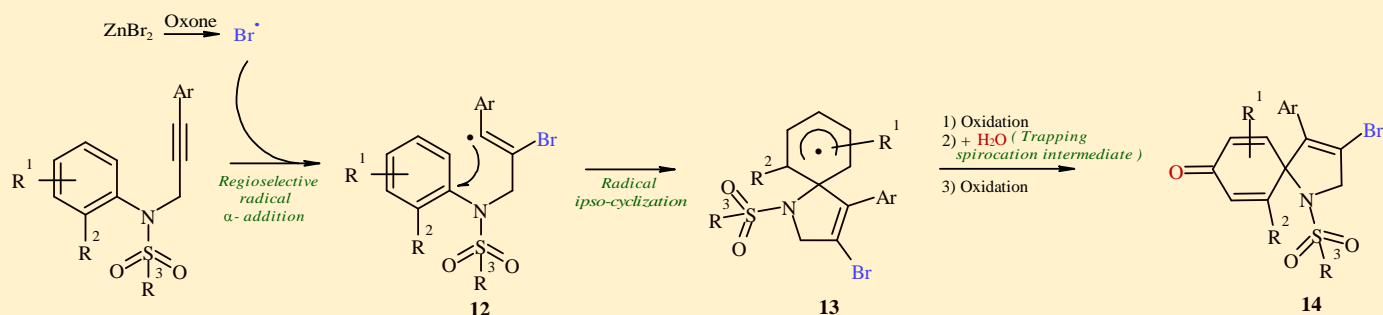


**Scheme 2.** Copper-catalyzed oxidative C–H functionalization/*ipso*-carbocyclization of *N*-arylpropiolamides **6** with ethers **7**.

Several approaches to alkyne based regioselective transformations *via* the radical *ipso*-cyclization of *N*-aryl propiolamides have been devised. One of elegant methods used *N*-tosyl-*N*-(prop-2-yn-1-yl)aniline **10** for the synthesis of 1-azaspiro[4.5]deca-3,6,9-trien-8-ones **11**, which the transformation proceeded smoothly in a mixed solvent system of MeCN/H<sub>2</sub>O when ZnBr<sub>2</sub> and Oxone were employed as the promoters (Scheme 3).<sup>18</sup> The reaction proceeded in a regioselective manner *via* a radical brominative *ipso*-cyclization of *N*-tosyl-*N*-(prop-2-yn-1-yl)aniline **13** by Oxone and ZnBr<sub>2</sub>.

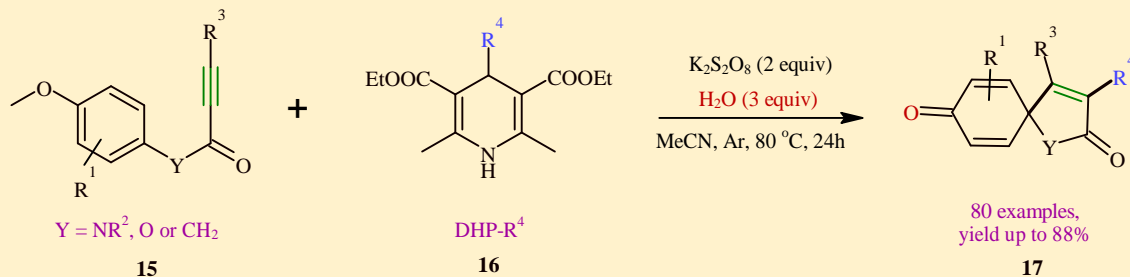


**Mechanistic proposal:**



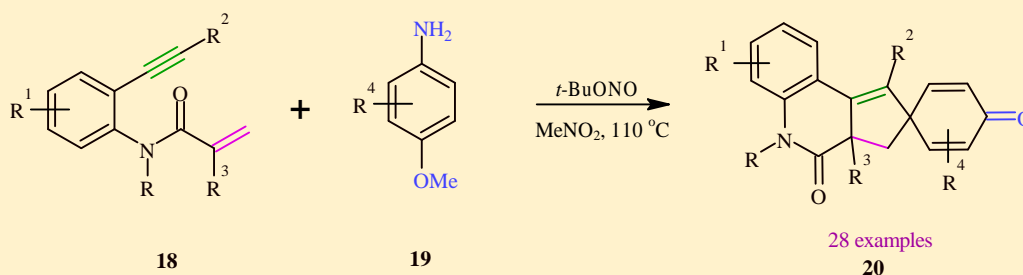
**Scheme 3.** Regioselective spirocyclization of *N*-tosyl-*N*-(3-arylprop-2-yn-1-yl)aniline.

In another radical *ipso*-carbocyclization reaction, a transition-metal-free procedure for the synthesis of 3-alkylated aza- and oxa-spiro[4.5]trienones has been achieved *via* radical alkylation/*ipso*-cyclization of activated alkynes with 4-alkyl-dihydropyridines (DHPs) (Scheme 4).<sup>19</sup> The alkylation underwent the generation of alkyl radicals, addition of alkyl radicals to the alkynes, and intramolecular *ipso*-cyclization. This procedure features good functional group tolerance.



**Scheme 4.** Synthesis of 3-alkylated aza- and oxa-spiro[4.5]trienones.

Another biologically interesting method for the synthesis of spirocyclohexadienone-containing cyclopenta[*c*]quinolin-4-ones **20** has been demonstrated *via* radical deaminative *ipso*-cyclization of 4-methoxyanilines **19** with 1,7-enynes **18** (Scheme 5).<sup>20</sup> The new C-center radical-triggered bicyclization cascade of *N*-tethered 1,7-enynes has been established through the *in situ* generated diazonium salts from 4-methoxyanilines and *t*-BuONO, which served as 4-methoxyphenyl precursors, allowing 6-*exo*-*dig* cyclization/5-*exo*-*trig*-*ipso*-cyclization to construct three new C–C bonds through dearomatization.

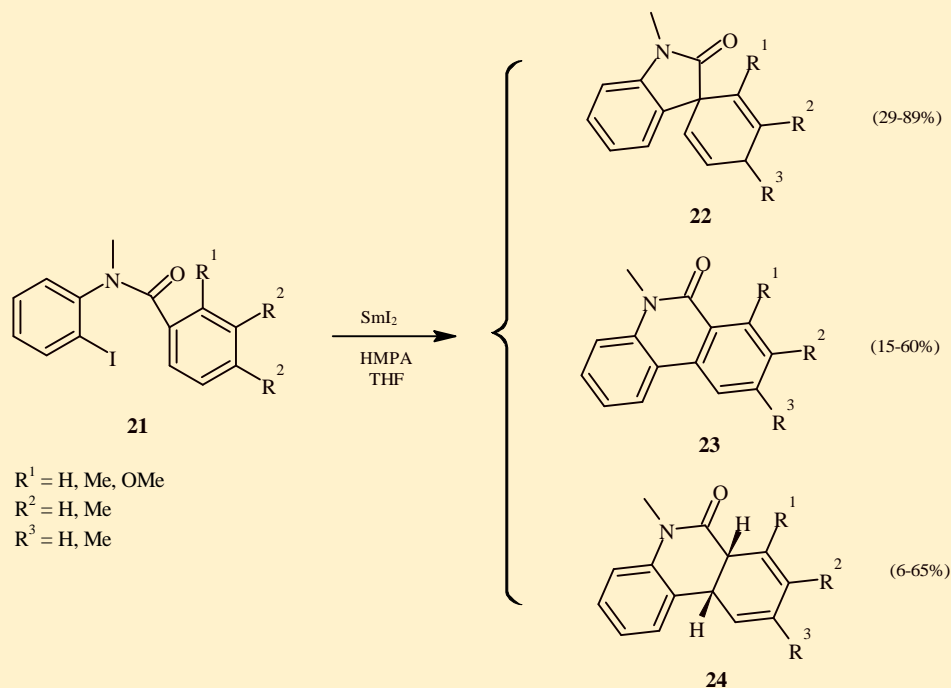


**Scheme 5.** The synthesis of spirocyclohexadienone-containing cyclopenta[*c*]quinolin-4-ones.

### 3. Intramolecular radical *ipso*-carbocyclization: *Miscellaneous*

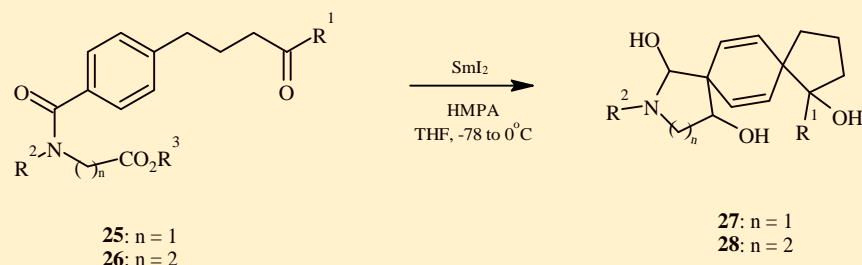
The samarium-mediated Pschorr cyclization shows the variety of products depending on the substitution pattern of the target aromatic core and the reaction conditions, either the spirocycles **22**, the reduced products **23**, or the dearomatized fused rings **24** (Scheme 6).<sup>21</sup> This reaction occurs through intramolecular radical

cyclization under reductive conditions. The presence of hexamethylphosphoramide (HMPA) as a cosolvent play a key role in the cyclization mode of the  $\text{SmI}_2$ -induced reaction, due to its strong chelating ability with the samarium atom. It worth to note that products **22** and **23** were obtained in the presence of *i*PrOH.



**Scheme 6.** Intramolecular aryl radical cyclization under reductive conditions.

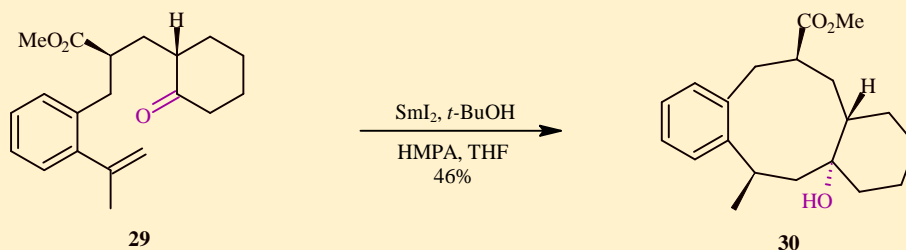
In another variant, a tandem spirocyclization reaction catalyzed by samarium (II) was demonstrated to construct dispiro[4.2.4.2]tetradecadiene and dispiro[4.2.5.2]pentadecadiene skeletons (Scheme 7).<sup>22</sup> The reaction was proceeded by intramolecular ketyl radical addition onto an aromatic ring bearing an electrophilic moiety followed by reductive capture of the spirohexadienyl radical intermediate by the catalyst.



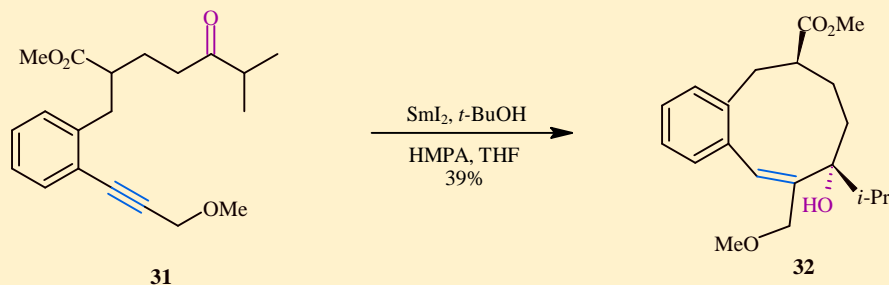
**Scheme 7.** The construction of dispiro[4.2.4.2]tetra- and penta-decadiene skeletons.

On the other hand, the use of a samarium(II) iodide-induced radical cyclization considered as a powerful tool for the construction of medium-sized benzannulated carbocycles. The formation of nine-membered carbocycles have been demonstrated by samarium(II) promoted *9-endo-trig* intramolecular cyclization of carbonyl-alkene substrate **29** to furnish tricyclic compound **30** in moderate yields with excellent stereoselectivity (Scheme 8 A).<sup>23</sup> Whereas alkynyl-substituted substrate **31** provided the nine-membered ring **32** via a *9-endo-dig* cyclization mode in moderate yield (Scheme 8 B).

A) *9-endo-trig* cyclization

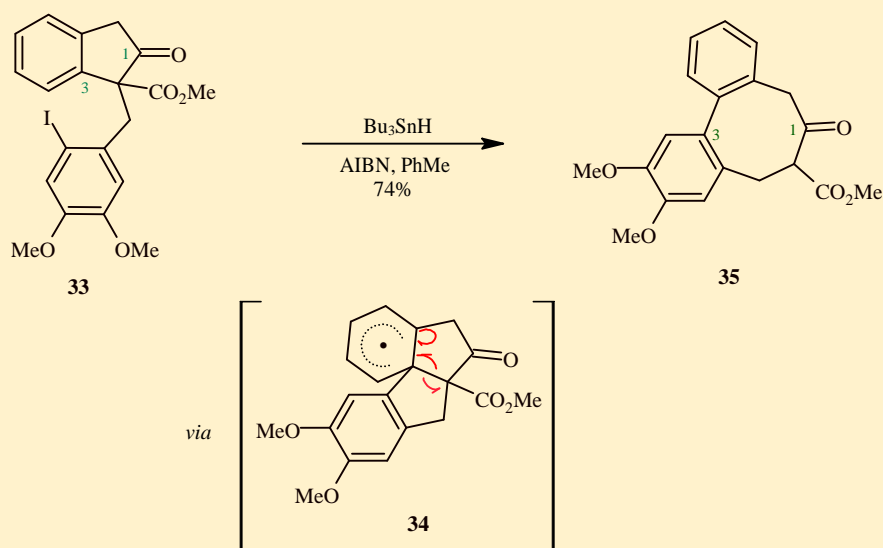


B) *9-endo-dig* cyclization



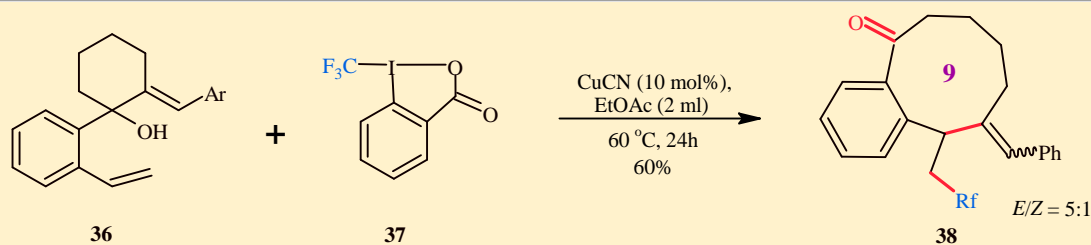
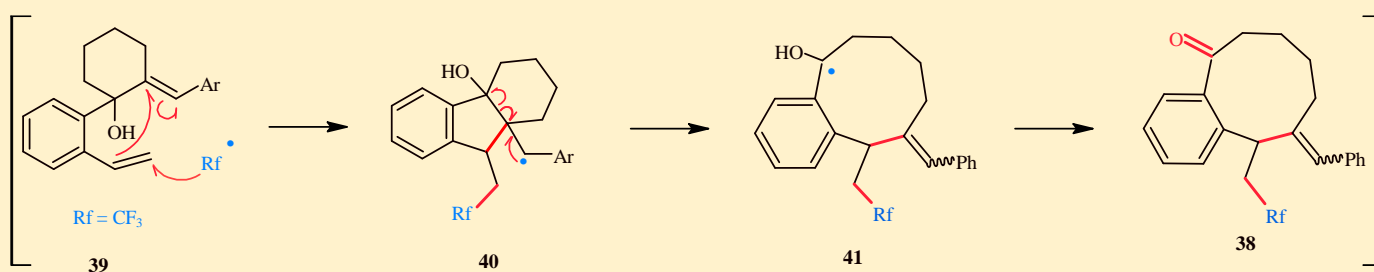
**Scheme 8.** Samarium(II) promoted intramolecular cyclization: A) carbonyl-alkene or B) carbonyl-alkyne coupling.

The radical *ipso*-cyclization strategy was also employed for the construction of medium and large ring size carbocycles *via* radical ring-expansion. The formation of eight- and nine-membered  $\beta$ -keto esters was realized by radical *ipso*-substitution, with 5-*exo-trig* cyclization **34** occurring at C3 position, followed by rearomatization and hydrogen abstraction from tributyltin hydride (Scheme 9).<sup>24</sup>



**Scheme 9.** Synthesis of eight- and nine-membered  $\beta$ -keto esters.

An elegant strategy based on a remot C-C bond reorganization *via* a radical 1,3-, 1,4-, and 1,5-vinyl migration has been performed to access skeletally and functionally a wide variety of fluoroalkyl-containing medium- and macrocyclic alkenes or bridged ring systems with excellent chemo-, regio-, and stereoselectivity.<sup>25</sup> The generation of  $\text{CF}_3$  radicals was realized by using hypervalent iodine(III) (Togin's reagent) and copper(I) cyanide. For example, the construction of benzannulated medium-sized cyclic alkenes *via* radical vinyl migration were obtained from the corresponding substrates bearing different opening ring sizes and distinctly electronic groups at different positions on the aryl ring directly connected with the migrating alkene. The external alkenol **36** produced the nine-membered product **38** with an external C=C double bond in 60% yield as a 5:1 mixture of *E/Z* isomers (Scheme 10).

Mechanistic proposal:

**Scheme 10.** Synthesis of external cyclic alkenes.

Mechanistically, the reaction commences with the addition of the generated fluoroalkyl radicals ( $\text{CF}_3$ ) to the less sterically hindered alkene of the substrate to provide a transient alkyl radical **39**, which subsequently undergoes exo cyclization and  $\beta$ -scission of intermediate **40**, leading to remote radical vinyl migration/ring expansion sequence to afford neutral ketyl radical **41**. Oxidation of the tertiary radical **41** to the ketone by the copper catalyst and loss of a proton yields the ring-expanded medium sized cyclic ketones **38**.

#### 4. Conclusions

Radical *ipso*-cyclization of arene has emerged as an efficient approach for the synthesis of spiro- and carbocycles. A wide variety of recent developments in these areas have been reported. However, there is no general rule which determines the direction of the reaction in these intramolecular radicals. In addition to the substituents and conformation that influence the selectivity of the reaction, the nature of the tether is an additional factor which must be taken into consideration. Generally, the preferred length of the linking chain is

that which allows the formation of stable five-membered intermediates. For the synthesis of medium-sized carbocycles, the approaches remain a major challenge due to their high ring strain.

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