Cascade Radical Carbonylations Leading to 3-Substituted Cyclohexanones

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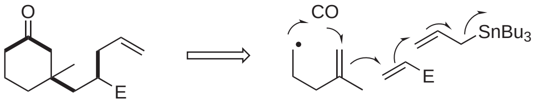
Abstract: Tin radical mediated [5+1]-annulation methods leading to 3-substituted cyclohexanones were investigated. Cyclohexanones having a quaternary center at the 3-position were synthesized in good yields by allyltin-mediated three- and four-component cascade reactions that involve (i) radical carbonylation, (ii) 6-*endo* cyclization, and (iii) alkene addition.

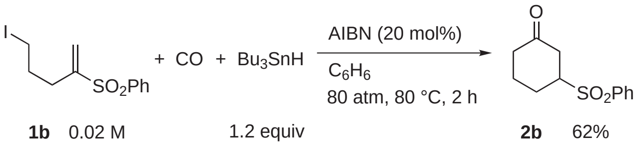
Key words: tributyltin radical, allyltributyltin, radical cyclization, casacde reaction, carbon monoxide

Free-radical-mediated annulation methods, which employ carbon monoxide as a C1 synthon, provide useful means for the synthesis of cycloalkanones.[1] General strategies involve (i) radical carbonylation[2] of an alkyl radical having an alkene moiety to give an acyl radical and (ii) the subsequent cyclization of the acyl radical onto carbon–carbon double bonds. Herein, we report a tin radical mediated [5+1]-annulation method which leads to cyclohexanone derivatives having a functionalized alkyl substituent at the 3-position. The key steps are a 6-*endo* acyl radical cyclization onto the carbon–carbon double bond,[3] followed by consecutive carbon–carbon bond-forming reactions (Scheme 1).



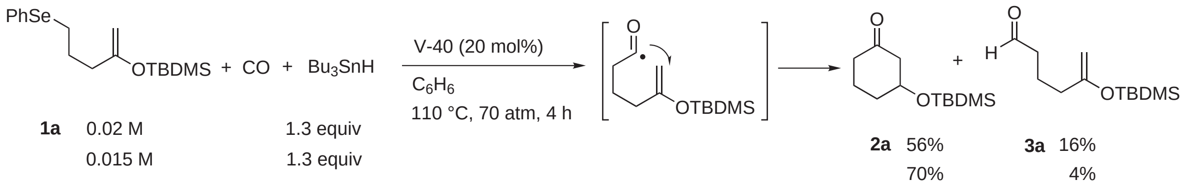
Scheme 1 Retrosynthetic analysis for 3-substituted cyclohexanones

We prepared 4-siloxy-4-pentenyl phenyl selenide **1a**, and exposed this substrate to typical tributyltin hydride mediated radical carbonylation conditions. At 80 °C, the conversion of **1a** was not complete, whereas the reaction at 110 °C resulted in the formation of the anticipated 3-siloxycyclohexanone **2a** (Equation 1). Premature quenching of the acyl radical by tributyltin hydride to give **3a** competed to some extent; however, at a lower concentration, the 6-*endo* cyclization course predominated to give **2a** in good yield. In the case of 5-iodo-2-sulfonyl-1-pentene (**1b**), the reaction at 80 °C proceeded smoothly to give the corresponding 3-sulfonylcyclohexanone **2b** in 62% yield (Equation 2).



Equation 2

We previously reported that allyltributyltin-mediated radical carbonylations provide a useful tool for the synthesis of a variety of unsaturated ketones,[4] in which the allyltin serves as a unimolecular chain transfer (UMCT) reagent.[5] The carbonylation of 5-iodo-1-pentene (**1c**) in the presence of allyltin/AIBN gave 3-allylcyclohexanone (**2c**) as the major product (Equation 3).[6] The formation of the 6-*endo* product is presumably due to isomerization of the initially formed 5-*exo*-type radical to the more stable 6-*endo* radical via consecutive 5-*exo*/3-*exo*/β-fission sequence, which would be permitted by the rather slow addition reaction of the 5-*exo* radical to allyltin.[5c] On the other hand, cyclohexanones having a quaternary carbon center at the 3-position were prepared smoothly from 5-bromo-2-methyl-1-pentene (**1d**). Thus, the reaction of **1d** with allyltributyltin and AIBN under CO pressure gave β-allylated 3-methylcyclohexanone **2d** in 85% yield (Equation 4).[7] Carbonylation of the 4-methyl-4-pentenyl radical and the subsequent 6-*endo* cyclization of the



Equation 1

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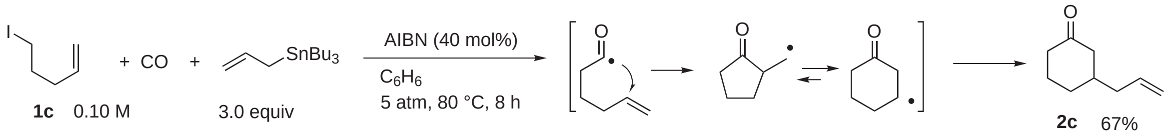
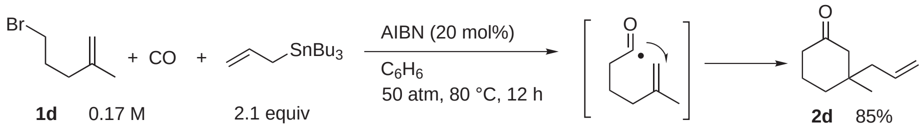
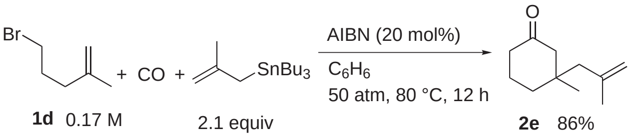


Equation 3



Equation 4

resultant acyl radical took place to give a tertiary radical, which was then allylated by allyltributyltin in an S_H2' fashion leading to **2d**. Similarly, the reaction of **1d**, CO, and methallyltin gave **2e** in 86% yield (Equation 5).

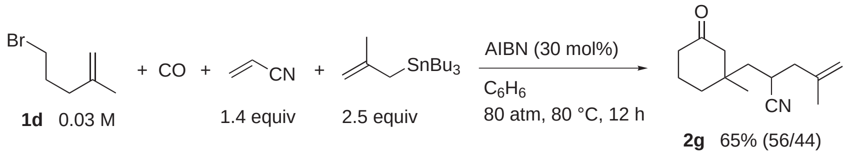


Equation 5

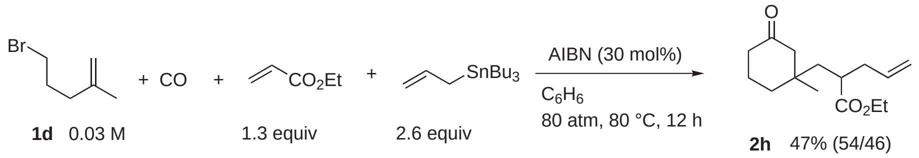
Then, we examined a four-component cascade reaction using a mixture of allyltin reagents and electron-deficient alkenes such as acrylonitrile and ethyl acrylate (Equations 6– 9). The reaction of **1d**, CO, acrylonitrile, and allyltributyltin in the presence of AIBN gave the 3,3-disubstituted cyclohexanone **2f** (Equation 6). Direct acyl radical addition to acrylonitrile also took place as a side reaction to give **3b**. This side reaction was effectively suppressed by using a lower concentration of **1d** (0.03 M). Methallyltin and ethyl acrylate also participated in the four-component cascade reaction to give the corresponding cyclohexanones (Equations 7– 9).

Scheme 2 summarizes the preferred reaction pathway leading to the four-component product **2h** starting from the 4-methyl-4-pentenyl radical and CO. Thus, in a mixed alkene system, a nucleophilic alkyl radical would favor an electron-deficient alkene, such as ethyl acrylate, over allyltributyltin, whereas the resulting radical, having an electron-withdrawing group, would favor electron-rich alkenes, such as allyltributyltin.

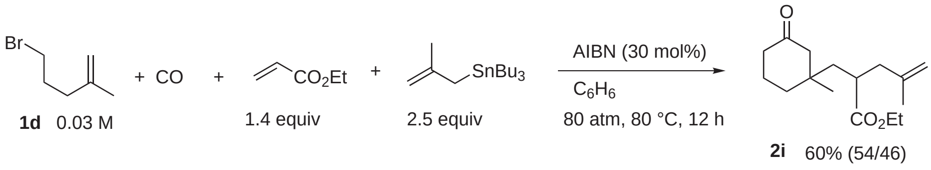
Equation 6



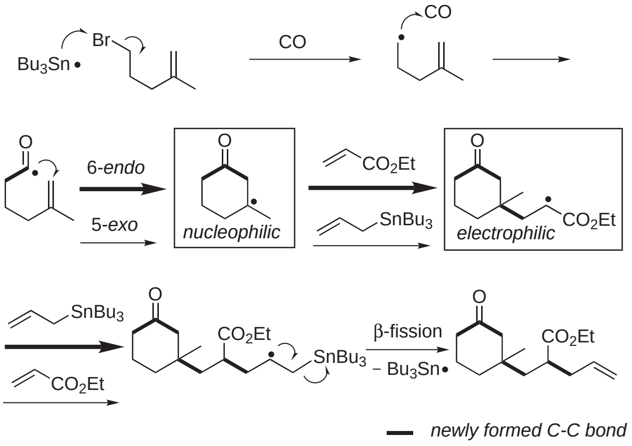
Equation 7



Equation 8



Equation 9



Scheme 2 Preferred radical reaction pathway for four-component cascade reaction.

In summary, the consecutive carbonylation and 6-*endo* cyclization sequence of 4-substituted 4-pentenyl radicals to give 1-substituted 3-oxo-cyclohexyl radicals was successfully coupled with the subsequent alkene addition reactions. By using this cascade radical carbonylation strategy, 3-substituted and 3,3-disubstituted cyclohexanones were prepared successfully.

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(3) For a 6-*endo* reaction using a Zn-induced system, see ref. 1h.

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(6) The reaction also gave the product via a 5-*exo*/allylation sequence in 5% yield. At higher CO pressures, the second carbonylation of the 5-*exo*-radical also took place. Details will be discussed in a full paper.

(7) **3-Allyl-3-methylcyclohexanone (2d)**
A magnetic stirring bar, AIBN (26.2 mg, 0.16 mmol), benzene (3.4 mL), 4-methyl-4-pentenyl bromide (**1d**; 92.3 mg, 0.56 mmol), and allyltributyltin (400.0 mg, 1.2 mmol) were placed in a 50-mL stainless-steel autoclave. The autoclave was closed, purged three times with CO, pressurized with 50 atm of CO, and then heated at 80 °C for 12 h. Excess CO was discharged at r.t. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane→hexane–EtOAc, 10:1) to give 3-allyl-3-methylcyclohexanone (**2d**; 73.3 mg, 85%).