

IV.11 Palladium-Catalyzed Carbozincation

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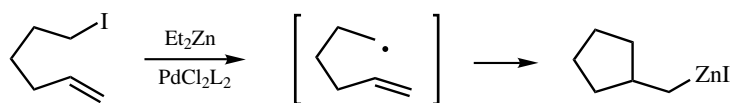
A. INTRODUCTION

The carbopalladation is a central reaction in organopalladium chemistry and is extensively presented in **Part IV**. In most reactions, a discrete organopalladium intermediate adds to a double or triple bond. In this section, the reaction of an alkyl iodide with diethylzinc in the presence of a palladium(0) catalyst is presented. Such reaction conditions generate an alkyl radical that readily adds intramolecularly to a double bond, leading to an organozinc derivative (**Scheme 1**). The combination of a radical cyclization with the formation of an organometallic product allows new synthetic applications that will be discussed. Closely related Ni-catalyzed cyclizations will also be briefly presented.

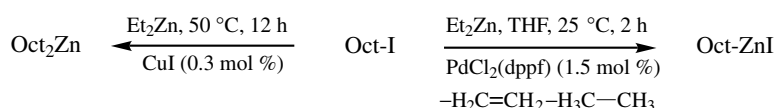
B. MECHANISTIC STUDIES

The iodine–zinc exchange^{[1],[2]} is a convenient method for preparing diorganozincs. It is catalyzed by copper(I) salts^[2] and proceeds at temperatures between 50 and 60 °C. Other metallic salts catalyze this exchange reaction and especially palladium(II) salts give excellent results, allowing the conversion of octyl iodide to octylzinc iodide (and not dioctylzinc as shown by gravimetric analysis)^[3] (**Scheme 2**). Functionalized primary alkyl iodides such as $\text{EtO}_2\text{C}(\text{CH}_2)_3\text{I}$ or $\text{NC}(\text{CH}_2)_3\text{I}$ react within 10–30 min at 25 °C (>90% yield) without the formation of any β -hydride elimination product. In order to clarify the mechanism of the reaction, other precursors were used. It was found that alkyl tosylates or mesylates do not react. The reaction is inhibited by small amounts of nitrobenzene and does not proceed with Me_2Zn . The exchange reaction is also very slow in ether. The treatment of either *exo*- or *endo*-7-iodobicyclo[2.1.0]heptane^[4] with Et_2Zn (ca. 2 equiv) in the presence of $\text{PdCl}_2(\text{dppf})$ in THF furnishes the *exo*-substituted bicyclic organozinc reagent, which was allylated in a stereoconvergent manner, suggesting a radical to be a reaction intermediate (**Scheme 3**).

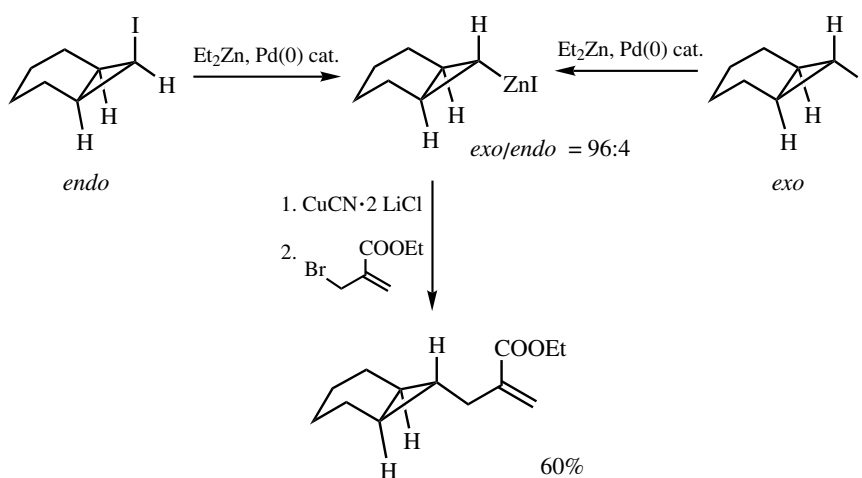
The insertion of $\text{Pd}(0)$ into an alkyl iodide may therefore proceed via a radical pathway.^{[5],[6]} The fast oxidative insertion may also indicate that a palladate species^[7] such as **1** may be responsible for an electron transfer reaction^[8] (**Scheme 4**). By using 5-hexenyl



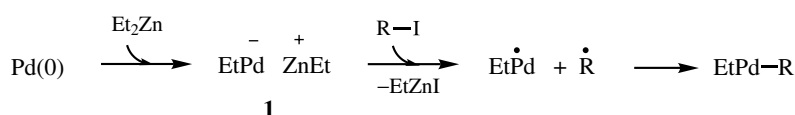
Scheme 1



Scheme 2



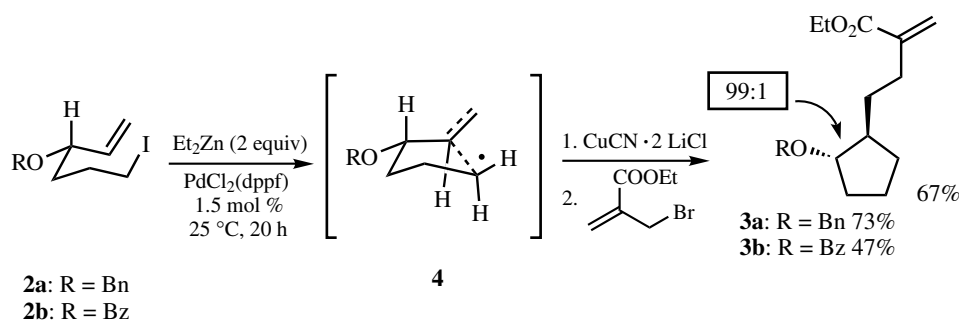
Scheme 3



Scheme 4

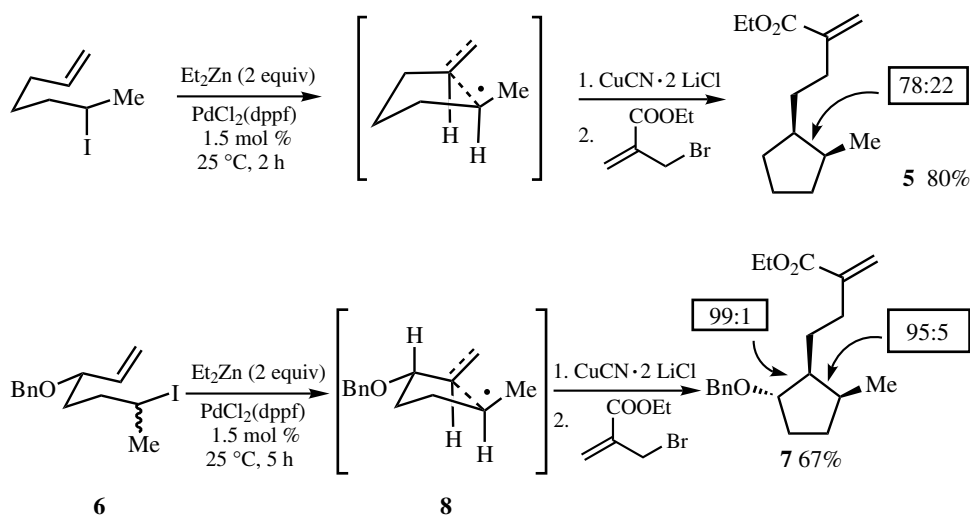
iodide as a substrate, a radical cyclization occurs, affording cyclopentylmethylzinc iodide (**Scheme 1**). This synthetic procedure allows one to perform radical ring closures^[9] but affords as a product an organometallic species (organozinc halide) that can be used to form further carbon–carbon bonds. The stereoselectivity observed in the ring closure follows Beckwith rules^[10] and is also stereoconvergent. Thus, the cyclization of the iodides **2a** and **2b** provides only the *trans*-product via a chair transition state such as **4** (**Scheme 5**).

A complete *trans*-stereoselectivity is observed between C(1) and C(2) of products **3a-b**. The cyclization leads as expected^[10] to lower stereoselectivity for the ring closure, affording the allylated product **5** as a *cis/trans* mixture of 78:22. This selectivity can dramatically be improved by using the 3-substituted secondary alkyl iodide **6**. Although



Scheme 5

6 is used as a 1:1 mixture of diastereoisomers, only one stereoisomer **7** is obtained. Its formation is easily rationalized by assuming a chair transition state such as **8** (Scheme 6).^{[4],[11]} The stereoconvergence of the reaction supports the radical mechanism of the ring closure.



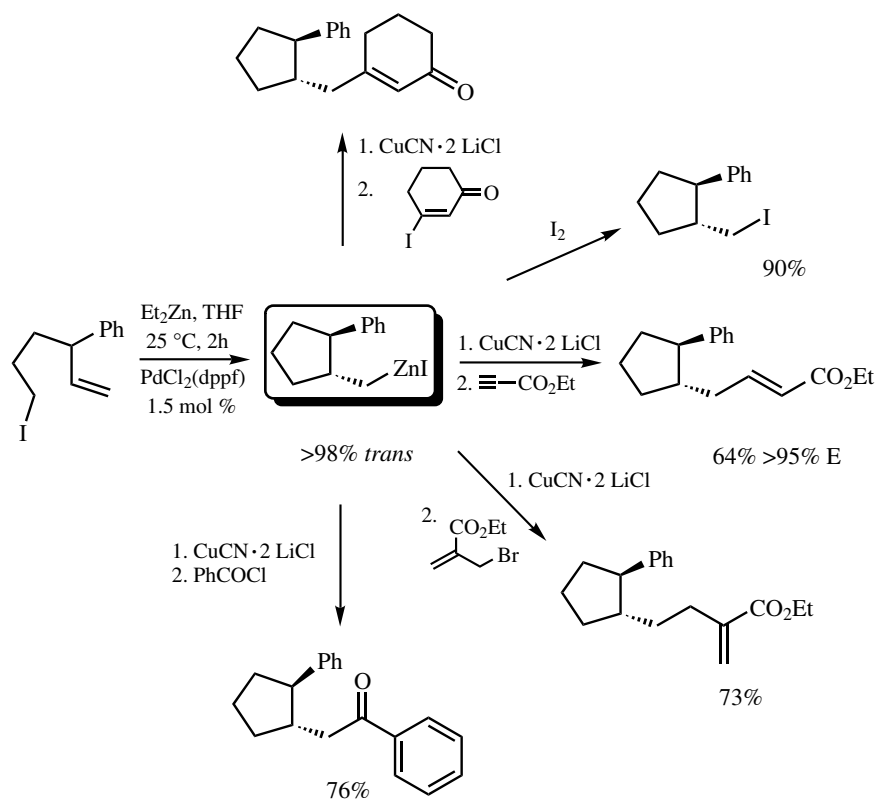
Scheme 6

C. SCOPE AND LIMITATION OF THE CYCLIZATION

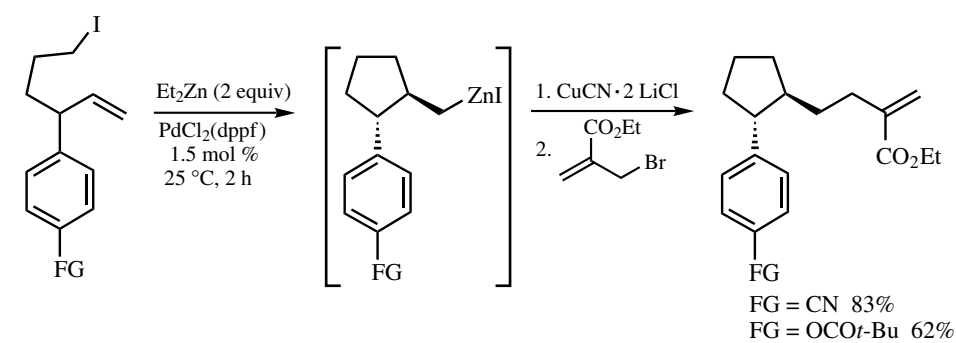
The cyclization of 4-substituted 5-hexenyl iodides proceeds well, leading to cyclopentylzinc iodides that can be trapped with various electrophiles such as 3-iodo-2-cyclohexenone, iodine, acid chlorides, allylic halides, and ethyl propiolate (carbocupration) (Scheme 7).^[4]

Various substitution patterns allow a successful cyclization. Also, a range of functional groups like esters or nitriles are tolerated in the ring closure (Scheme 8).

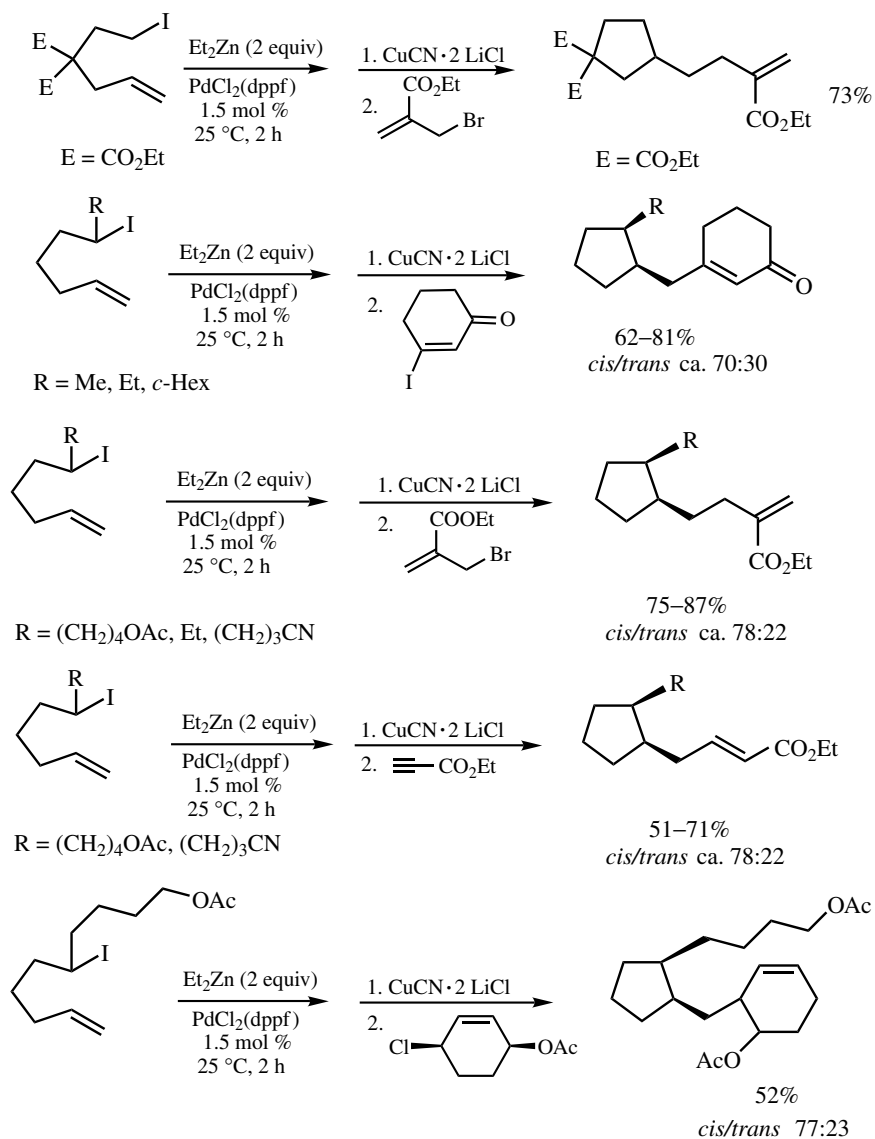
The presence of an oxygen functionality (O-centered leaving group) is also compatible with the reaction conditions and the 2-pivaloyloxyalkyl iodide **9** leads after allylation to the expected cyclopentane derivative **10** (Scheme 9).^[4]



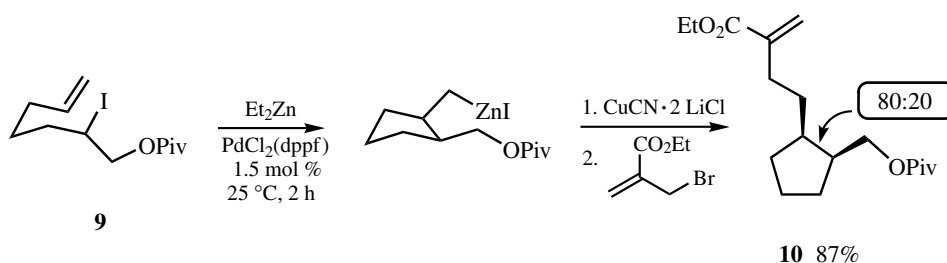
Scheme 7



Scheme 8



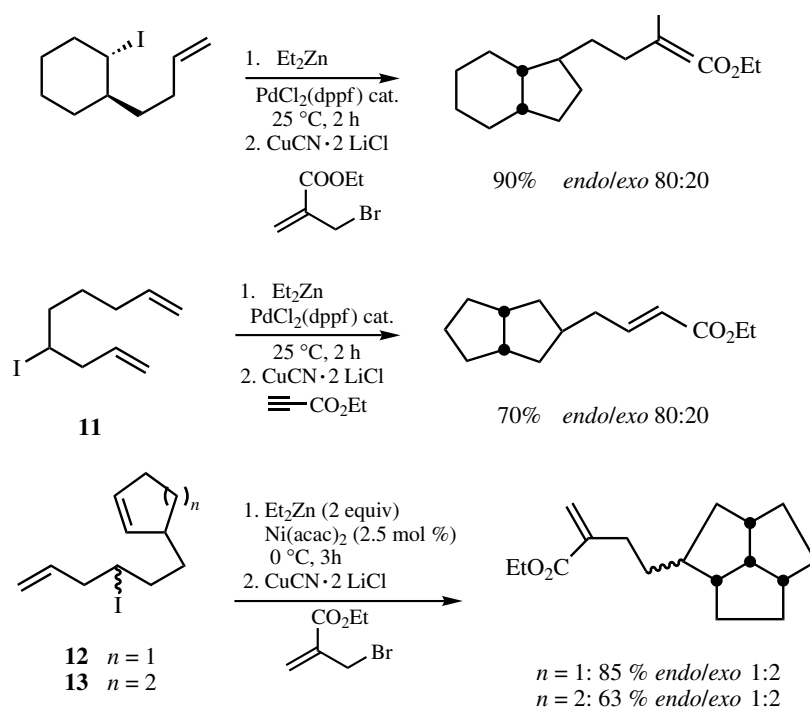
Scheme 8 (Continued)



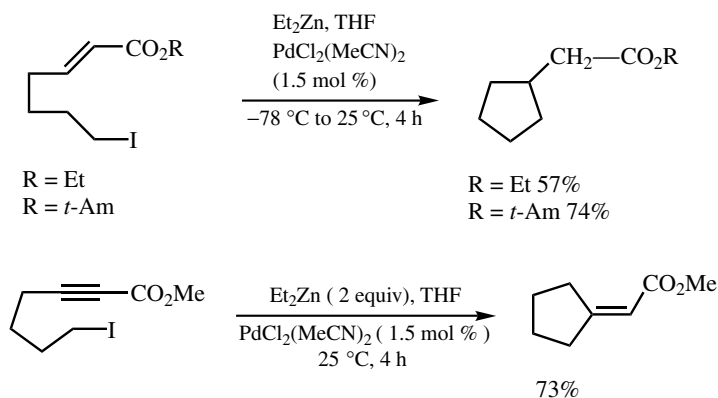
Scheme 9

Various domino cyclizations using substrates like **11–13** have been used successfully (**Scheme 10**).^{[4],[11]}

The intramolecular addition to unsaturated esters was also possible. Best results are obtained with a *t*-amyl ester, which leads to a product that is less prone to undergo Claisen condensation. The same reaction is observed with the corresponding acetylenic ester (**Scheme 11**).^[4]

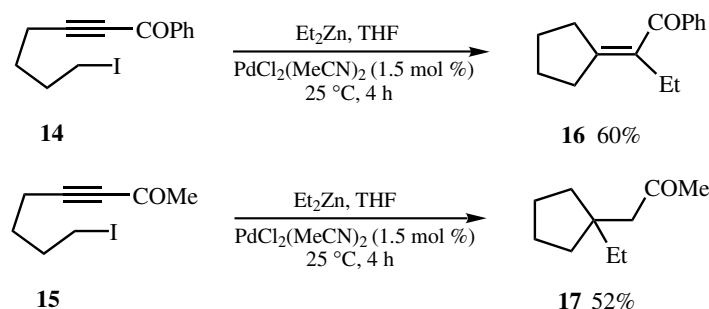


Scheme 10



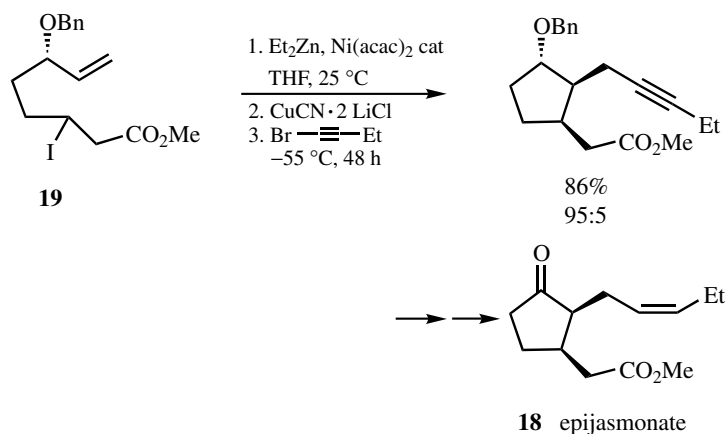
Scheme 11

The reactivity observed with acetylenic ketones is more complex and the two iodoalkynyl ketones **14** and **15** behave in a different way (Scheme 12). Thus, the phenyl ketone **14** undergoes carbopalladation of the triple bond followed by a reductive elimination, furnishing the *exo*-alkylidenecyclopentane derivative **16**. On the other hand, the methyl ketone **15** undergoes, after carbopalladation, a subsequent Michael addition, leading to the ketone **17** in 52% yield.



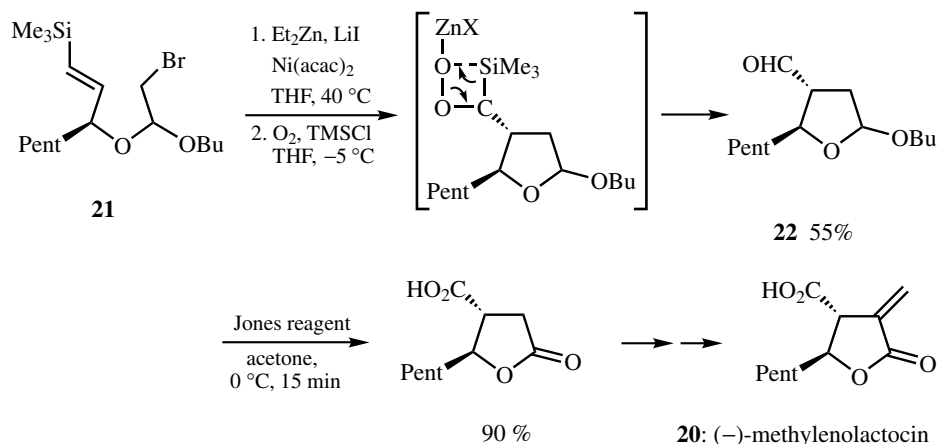
Scheme 12

The scope of the reaction can be extended to unsaturated alkyl bromides as substrates by using $\text{Ni}(\text{acac})_2$ as a catalyst^{[12],[13]} instead of Pd(II) complexes. The use of $\text{Ni}(\text{acac})_2$ as a catalyst even with several polyfunctional alkyl iodides gives better results. Thus, in the key step for the synthesis of methyl epijasmonate **18**, the alkyl iodide **19** undergoes a smooth cyclization using $\text{Ni}(\text{acac})_2$ and Et_2Zn (Scheme 13).^[12]



Scheme 13

Polyfunctional alkyl bromides have been cyclized with $\text{Ni}(\text{acac})_2/\text{Et}_2\text{Zn}$ for the construction of various heterocycles^[13] as well as for the antitumor antibiotic (–)-methylenolactocin **20**. In this case, the alkyl bromide **21** is cyclized and selectively oxidized to the aldehyde **22**, which is converted in a standard way to the natural product **20** (Scheme 14).



Scheme 14

D. SUMMARY

1. The treatment of an alkyl iodide with Et_2Zn in the presence of catalytic amounts of palladium(II) salts leads to the corresponding organozinc iodide.
2. The reaction proceeds via a radical intermediate and can be used to perform radical cyclizations affording five-membered rings. However, the products of these reactions are organozinc reagents, which can be reacted with a wide range of electrophiles.
3. The cyclizations are stereoselective following the Beckwith rules and allow the elaboration of highly substituted cyclopentane derivatives.
4. Domino cyclizations can be performed.
5. Unsaturated alkyl bromides can be used as substrates if the $\text{Pd}(\text{II})$ catalyst is replaced by $\text{Ni}(\text{acac})_2$.

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