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# Heck-type 5-*endo-trig* cyclizations promoted by vinylic fluorines: Ring-fluorinated indene and 3*H*-pyrrole syntheses from 1,1-difluoro-1-alkenes

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**Abstract**

Arylpalladium or aminopalladium species bearing a 2,2-difluorovinyl group undergo an unusual 5-*endo* alkene insertion followed by β-fluorine elimination. These processes provide a facile access to ring-fluorinated five-membered carbocyclic and heterocyclic compounds starting from an *o*-(3,3-difluoroallyl)phenyl trifluoromethanesulfonate and 3,3-difluoroallyl ketone *O*-pentafluorobenzoyloximes. In both systems, the two vinylic fluorine atoms are essential for Heck-type 5-*endo-trig* cyclizations.


*Keywords:* 5-*endo-trig* Cyclization; Heck-type reaction; Pyrrole; Indene; 5-*endo* Alkene insertion; β-Fluorine elimination; Palladium

## 1. Introduction

In contemporary organic synthesis, the Heck reaction is one of the most valuable bond-forming processes promoted by transition metals [1]. The Heck reaction proceeds via alkene insertion and β-hydrogen elimination, which are a palladium-catalyzed coupling of alkenes. The intramolecular version of the Heck reaction has been widely used to construct a variety of ring systems. Normally, *exo*-mode cyclization is the favored path, as *endo*-mode cyclization is less likely to form smaller rings (Scheme 1) [2].

In particular, 5-*endo-trig* cyclizations in the Heck reaction are limited [3,4], and all reports on such 5-*endo* Heck cyclizations have been confined to the palladium-catalyzed reaction of *N*-vinyl-2-haloarylamines [5] or *N*-vinyl-2-haloalkenylamines (Scheme 2, Path A) [6]. To the best of our knowledge, one exception is the efficient cyclopentenone formation via an alka-2,4-dienoylpalladium species [7]. However, the reactions of these vinylamine (enamine-type) substrates can be interpreted in terms of a mechanism other than a 5-*endo-trig* cyclization (Path B), which involves: (i) the oxidative addition of halides **1** to Pd(0); (ii) the formation of six-membered palladacycles **2** through nucleophilic substitution with the enamine on the palladium; (iii) a subsequent reductive elimination, which leads to the 5-*endo-trig* type products [6a,8].

In general, according to Baldwin's rules [9], the 5-*endo-trig* cyclization has long been considered a disfavored process for the construction of five-membered rings, because of the severe distortions required in the reaction geometry. In recent publications, we have reported on nucleophilic 5-*endo-trig* cyclizations of 1,1-difluoro-1-alkenes **3** with an *N*-, *O*-, or a *C*-nucleophile, providing five-membered ring-fluorinated hetero- and carbocycles, such as indoles, 2-pyrrolines, benzo[*b*]furans, 2,3-dihydrofurans, indenes, and cyclopentenes (Scheme 3) [10]. The remarkable reactivity of these alkenes towards nucleophilic 5-*endo-trig* cyclizations is probably due to: (i) the polarization of the carbon–carbon double bond caused by the two fluorine atoms [11], which exerts an electrostatic attraction for the intramolecular nucleophile, overcoming the difficulty of the initial ring formation; (ii) the leaving group ability of fluoride ions, which suppresses the reverse ring opening.

In the above 5-*endo-trig* cyclizations, typical metal species, such as lithium, sodium, and potassium compounds, were employed as intramolecular nucleophiles (Scheme 3). Thus, we turned our attention to organotransition metal chemistry to

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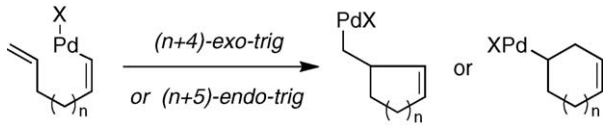
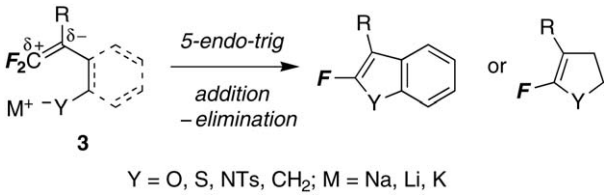
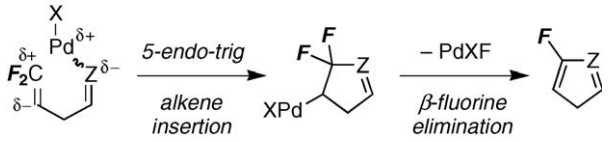



Scheme 1. *exo* or *endo* Alkene insertion in intramolecular Heck reactions.




Scheme 3. Nucleophilic 5-*endo-trig* cyclizations of 1,1-difluoro-1-alkenes.




Scheme 4. Heck-type 5-*endo-trig* cyclizations of 1,1-difluoro-1-alkenes.

broaden the scope of the 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes, as well as to open up a new 5-*endo-trig* pathway in Heck-type cyclizations. There is only one example describing a Heck-type reaction of a 1,1-difluoro-1-alkene [12]. Heitz reported that arylpalladium iodide complexes replaced the fluorine atom of 1,1-difluoroethene to afford α-fluorostyrenes via alkene insertion and subsequent β-fluorine elimination [13]. Based on these considerations, we expected that a Heck-type 5-*endo-trig* cyclization of difluoroalkenes could be promoted by the electrostatic attraction between the palladium species and the polarized difluoroalkene double bonds, even though this pathway is sterically hindered (Scheme 4). Herein, we report on the results of our studies on Heck-type 5-*endo-trig* cyclizations of 1,1-difluoro-1-alkenes, which provide an approach to ring-fluorinated five-membered carbocyclic and heterocyclic compounds.

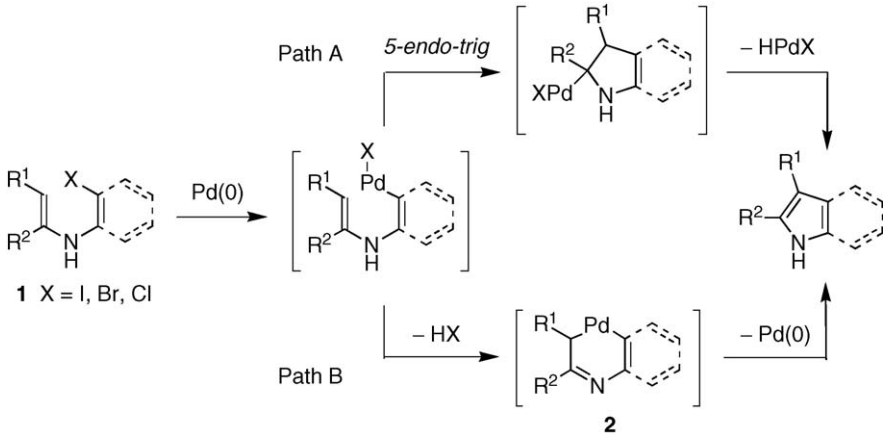
## 2. Results and discussion

### 2.1. Heck-type 5-endo-trig cyclizations with arylpalladium species

In the reported Heck-type reaction of 1,1-difluoroethene described above, arylpalladium species were employed as the intermolecular coupling partners. We first attempted an intramolecular version of this reaction using an aryl triflate substrate. Aryl triflate **4** bearing a 3,3-difluoroallyl group at the *ortho* position was designed and prepared as follows. Using the literature method, 2-methylpropanenitrile was treated with potassium hexamethyldisilazide to generate the corresponding carbanion, which reacted with 2-fluoroanisole (**5**) to replace the fluorine, leading to formation of nitrile **6** [14]. The cyano group of **6** was transformed by reduction with diisobutylaluminum hydride (DIBAL-H) followed by difluoromethylenation to give difluoroalkene **8** via aldehyde **7**. Demethylation of the methoxy group in **8** and successive trifluoromethanesulfonylation afforded the desired substrate **4** for the cyclization (Scheme 5).

When **4** was heated with a stoichiometric amount of $Pd(PPh_3)_4$ and $PPh_3$ in *N*,*N*-dimethylacetamide (DMA), the Heck-type 5-*endo-trig* cyclization proceeded to give indanone **12** (57% yield), instead of the expected 3-fluoroindene **11**. As the formation of **12** seemed to be caused by the hydrolysis of **11**, presumably due to the complexation with a Pd(II) generated during the reaction, the reaction mixture was treated with PhSH before quenching. Thus, the formation of fluoroindene **11** was confirmed, and we showed that the 5-*endo-trig* cyclization was achieved by arylpalladium(II) species **10**, generated via the oxidative addition of aryl triflate **4** to Pd(0) (Scheme 6). An attempt to promote this cyclization with a catalytic amount (10 mol%) of $Pd(PPh_3)_4$ and $PPh_3$ (1.0 equiv. vide infra) gave only a 15% yield of **12**.

To confirm the effect of fluorine, we examined the reaction of a fluorine-free substrate **13**, which gave only a trace amount of the cyclized product **14** (Scheme 7). These results clearly show that fluorine functions as an activator of the substrates in the Heck-type 5-*endo-trig* cyclization.




Scheme 2. Plausible mechanisms for the palladium-catalyzed cyclization of vinylamines.