

Palladium-Catalyzed Carbonylative Heck-Type Reactions of Alkyl Iodides

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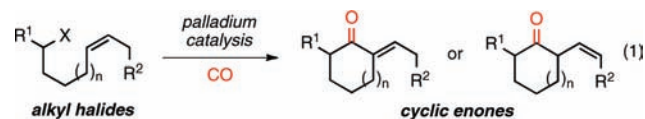
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Abstract: A palladium-catalyzed carbonylative Heck-type cyclization of alkyl halides is described. Treatment of a range of primary and secondary alkyl iodides with catalytic palladium(0) under CO pressure forms a variety of synthetically versatile enone products. The reactivity described represents a rare example of a palladium-catalyzed Heck-type cyclization involving unactivated alkyl halides with β -hydrogens. Alkene substitution is well tolerated, and mono- and bicyclic carbocycles may be easily accessed.

The use of palladium catalysts in organic synthesis has resulted in numerous methods for carbon–carbon bond construction of exceptional value.¹ The palladium-catalyzed Heck reaction is among the premier methods in this class and is broadly applicable using aryl or vinyl halide or sulfonate electrophiles.² Despite the impressive scope of the Heck reaction, unactivated alkyl halides are generally not viable electrophiles.³ Recently, the first example of a palladium-catalyzed intramolecular alkyl-Heck reaction was reported,⁴ although this process is limited to primary alkyl electrophiles and monosubstituted alkene substrates. Several other research groups have developed useful Heck-type processes using other transition metals that generally involve free radical intermediates.⁵

The development of general methods capable of extending palladium-catalyzed Heck-type processes to alkyl electrophiles could result in powerful synthetic transformations; however, there are a number of significant challenges impeding such developments. These include the general reluctance of sp^3 -hybridized alkyl electrophiles to undergo oxidative addition⁶ and the marked tendency of alkylpalladium species to undergo β -hydride elimination,⁷ resulting in dehydrohalogenation products. Despite this instability of alkylpalladium species containing β -hydrogens, migratory insertion of CO ligands is capable of outcompeting this process.⁸ We envisioned the carbonylative cyclization of alkyl halides as a potential approach to accessing alkyl-Heck-type transformations (eq 1). Carbonylative Heck-type reactions facilitate the preparation of diverse carbocyclic structures; however, these processes are currently limited to the use of aryl or vinyl electrophiles.⁹ In addition, carbonylative cyclizations of alkyl electrophiles would provide synthetically valuable enone products, which are important building blocks for organic synthesis.¹⁰ Herein, we report that readily available palladium catalysts are capable of catalyzing carbonylative Heck-type reactions of unactivated alkyl iodide electrophiles.



We began our studies using the commercially available palladium(0) source Pd(PPh₃)₄ as catalyst, which is commonly used

in carbonylative Heck reactions with aryl or vinyl electrophiles.⁹ Upon heating to 130 °C in toluene for 5 h under 50 atm CO in the presence of 10 mol % Pd(PPh₃)₄ and 2.0 equiv of *i*Pr₂EtN, cyclohexenyl substrate **1** provided cyclized enone **2** and minor isomer **3** in 79% combined yield (Table 1, entry 1). Reactions utilizing a variety of other palladium catalyst systems resulted in decreased yields (entries 2–4), and no product formed in the absence of Pd(PPh₃)₄ (entry 5). Performing the reaction at lower temperature (entry 6) or at lower CO pressure (entry 7) hampered reaction efficiency. We also found that inorganic bases such as Cs₂CO₃ (entry 8) proved inferior to amine bases. Substrate dehydrohalogenation was not a significant side reaction in these experiments. Polar solvent systems are much less effective (entry 9), which we attribute to increased formation of phosphonium salt byproducts.¹¹

Table 1. Influence of Reaction Conditions on the Carbonylative Cyclization

entry	variation from standard conditions above	% yield ^a
1	none	79
2	10 mol % Pd(OAc) ₂ and 20 mol % PPh ₃ , instead of Pd(PPh ₃) ₄	35
3	5 mol % Pd ₂ (dba) ₃ , instead of Pd(PPh ₃) ₄	2
4	10 mol % PdCl ₂ (PPh ₃) ₂ , instead of Pd(PPh ₃) ₄	60
5	no Pd(PPh ₃) ₄	<2
6	100 °C, instead of 130 °C	20
7	30 atm CO, instead of 50 atm CO	41
8	Cs ₂ CO ₃ , instead of <i>i</i> Pr ₂ NEt	12
9	1:1 THF:MeCN, instead of PhMe	28

^a Determined through GC analysis.

We examined the scope of the reaction using a wide variety of unsaturated alkyl iodides and the optimized reaction conditions (Table 2). The reaction performs well using simple linear substrates, as predominantly (*E*)-disubstituted alkyl iodide **4** (85:15 *E*:*Z*) (entry 1) provided cyclopentenone **5** in 77% yield as a 10:1 mixture of *E*:*Z* isomers. Conjugated alkenes are also useful substrates, as (*Z*)-styrenyl substrate **6** (entry 2) provided (*E*)-disubstituted cyclopentenone **7** in 55% yield. We next explored the capability of the carbonylative alkyl-Heck-type reaction to construct a variety of ring systems. The carbonylative cyclization is capable of furnishing bicyclo[3.3.0]octenones (entry 3) and bicyclo[4.3.0]nonenones (entry 4), as demonstrated in the reactions of substrates **8** and **1**. We also found that both secondary alkyl electrophiles and trisubstituted alkenes participate in the process, as cyclohexyl substrate **11** cyclized to tetrasubstituted enone **12** (1.2:1 dr) in 91% yield (entry 5). The bicyclo[5.3.0]decenone framework was easily accessed from cycloheptyl substrate **13** (entry 6). Neopentyl iodide

15 was efficiently transformed to spirocyclic product **16** in 90% yield, demonstrating that α -disubstitution of the alkyl iodide is well tolerated. Notably, this process is also not limited to the synthesis of five-membered carbocycles, as cyclohexenyl alkyl iodide **17** underwent 6-*endo* cyclization to yield bicyclo[4.4.0]decenone derivative **18** in 69% yield (entry 8).

Table 2. Palladium-Catalyzed Carbonylative Cyclization^a

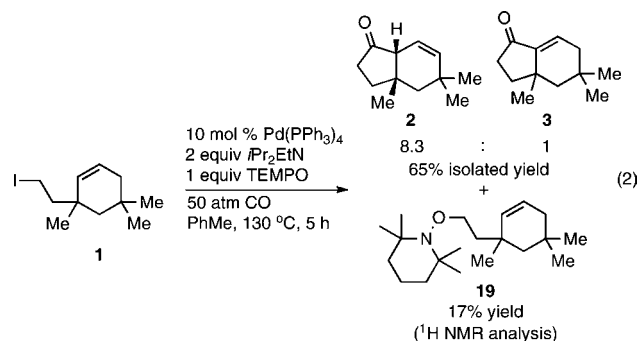
entry	Substrate	Product	% yield ^{b,c}
1			77 10:1 <i>E:Z</i>
2			55 >25:1 <i>E:Z</i>
3			63 1.3:1 9:10
4			74 7.1:1 2:3
5			91 1.2:1 dr
6			82 1.6:1 dr
7			90
8			69

^a All reactions run 0.5 M in PhMe at 130 °C under 50 atm CO in the presence of 10 mol % Pd(PPh₃)₄ and 2.0 equiv of *i*Pr₂EtN, 5–12 h.

^b All yields are isolated. ^c The diastereomeric ratios were determined by ¹H NMR spectroscopy of the isolated products.

The capability of palladium(0) to react with alkyl iodides via S_N2¹² as well as single-electron¹³ pathways opens the door to a number of mechanistic possibilities for this process. Subjecting primary alkyl halide substrate **1** to the standard carbonylative cyclization conditions in the presence of 1 equiv of persistent radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) produced the enone products **2** and **3** in 65% isolated yield, as well as TEMPO adduct **19** in 17% yield (eq 2).¹⁴ Although the efficiency of this reaction was comparable to that of the reaction performed in the absence of TEMPO (Table 2, entry 4), these results suggest the potential

involvement of carbon-centered radicals in the reaction.^{15,16} Further detailed studies to elucidate the precise reaction pathway are underway.



In conclusion, we have developed a palladium-catalyzed intramolecular carbonylative Heck-type reaction of unactivated alkyl iodides. This reaction proceeds efficiently with primary or secondary alkyl iodides to deliver a variety of synthetically valuable monocyclic and bicyclic enones. Further studies will extend this mode of alkyl halide activation in the discovery of other synthetic transformations and explore applications in complex molecule synthesis.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) The observed lack of stereocontrol in the cyclizations of substrates **11** and **13** is consistent with a radical mechanism for the reaction. For a possible catalytic cycle involving radical intermediates, see the Supporting Information.

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