

Palladium-Catalyzed Heck-Type Reactions of Alkyl Iodides

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S Supporting Information

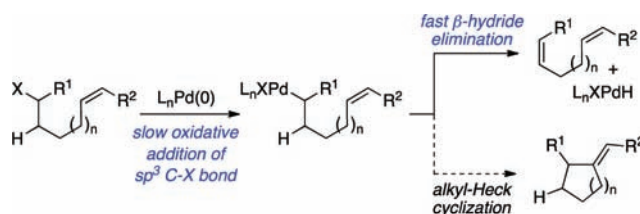
ABSTRACT: A palladium-catalyzed Heck-type reaction of unactivated alkyl iodides is described. This process displays broad substrate scope with respect to both alkene and alkyl iodide components and provides efficient access to a variety of cyclic products. The reaction is proposed to proceed via a hybrid organometallic-radical mechanism, facilitating the Heck-type process with alkyl halide coupling partners. Initial intermolecular studies are also reported, demonstrating the potentially wide applicability of this approach in synthesis.

The palladium-catalyzed Heck reaction is a fundamental synthetic transformation in chemical synthesis, enabling the direct cross-coupling of simple alkenes with aryl or vinyl halides (or sulfonates).¹ The utility of this process with aryl or vinyl coupling partners has been well demonstrated in synthesis. However, extending the Heck reaction to simple alkyl halide substrates has been a major challenge.² The difficulty is attributed to two main factors: the general reluctance of sp^3 -hybridized alkyl halides to undergo oxidative addition processes with low-valent transition metals,³ and the predisposition of putative alkylmetal species to undergo β -hydride elimination,⁴ resulting in overall dehydrohalogenation (Scheme 1).

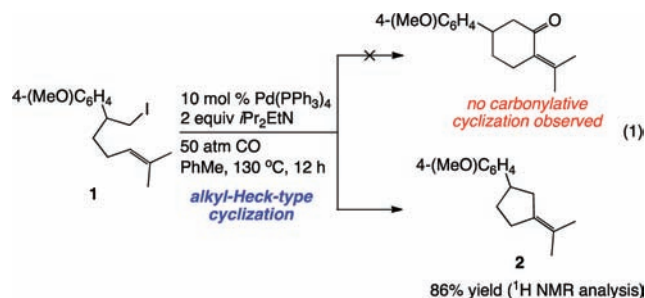
Despite these significant challenges, useful strategies have emerged to facilitate alkyl-Heck-type transformations in selected cases. The development of reactions catalyzed by transition metals other than palladium has shown promise, but these processes require the use of superstoichiometric amounts of highly reactive alkylmagnesium reagents, greatly limiting potential applications in organic synthesis.⁵ Seminal work by Fu demonstrated the possibility of a palladium-catalyzed intramolecular alkyl-Heck-type process.⁶ However, the scope of this process is strictly limited to cyclopentene synthesis utilizing only primary alkyl halides and terminal alkenes as substrates.⁷

Alkyl-Heck-type processes of broad substrate scope, capitalizing on the mild conditions afforded by palladium(0) catalysis while leveraging the synthetic accessibility of alkenes and alkyl halides, would constitute powerful transformations for organic synthesis. We recently reported our initial efforts toward the development of alkyl-Heck-type processes in the form of a palladium(0)-catalyzed carbonylative cyclization of simple unsaturated alkyl iodides, providing expedient access to numerous classes of cycloalkenones.⁸ Herein, we demonstrate that a similar catalytic system also facilitates the direct alkyl-Heck-type reaction of a wide variety of alkyl iodides and alkenes. The process employs mild reaction conditions using $Pd(PPh_3)_4$ as a catalyst and holds high potential in both intra- and intermolecular settings.

Scheme 1. Challenges in Developing Alkyl-Heck Processes



Our efforts commenced with the study of iodide **1**. We examined this substrate in order to test whether a noncarbonylative 5-*exo* alkyl-Heck-type process would outcompete a possible 6-*exo* carbonylative cyclization. Substrate **1** was subjected to identical conditions from our previous study comprised of 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of iPr_2EtN under 50 atm of CO pressure at 130 °C in PhMe. Cyclopentene **2** was formed in good yield from an alkyl-Heck-type process, and no formation of any carbonylative cyclization products was observed (eq 1).⁹



Following this promising initial result, we continued with further study of substrate **1** in order to determine whether CO played any role in this noncarbonylative cyclization process. Interestingly, while the cyclization did proceed in the absence of CO (76% yield), increasing CO pressure up to 10 atm greatly minimized the formation of alkene isomers of **2**.¹⁰ Reaction of substrate **1** under optimized reaction conditions employing 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of 1,2,2,6,6-pentamethylpiperidine (PMP) under 10 atm of CO pressure at 110 °C in PhH delivered cyclopentene **2** in 80% yield (Table 1, entry 1).¹¹

We next aimed to explore the substrate scope of the carbonylative cyclization using a wide variety of unsaturated alkyl halides (Table 1). In order to test the potential of the alkyl-Heck-type process to construct quaternary stereocenters, we examined the reaction of substrate **3** containing a trisubstituted alkene (entry 2). This substrate efficiently formed pyrrolidine **4**, demonstrating

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Table 1. Palladium-Catalyzed Carbocyclizations^a

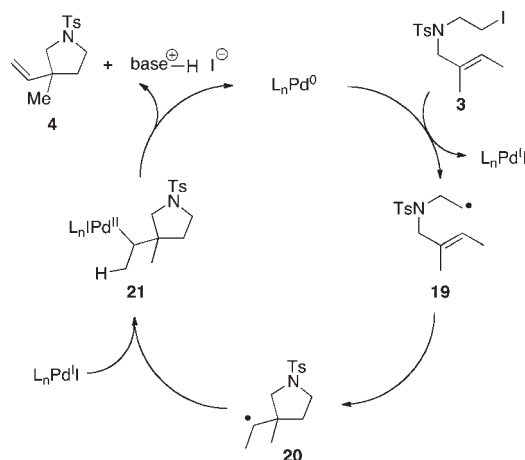
entry	substrate	product	% yield ^{b,c}
1			80
2			70 ^d
3			73 ^e 83:17 dr
4			74 9:1.2:1 8:9:10
5			70 2.3:1 12:13
6			62 ^f 58:42 dr
7			66 ^{d,f} >95:5 dr

^a Reactions run 0.5 M in PhH at 110 °C under 10 atm of CO in the presence of 10 mol % Pd(PPh₃)₄ and 2.0 equiv of PMP. ^b Yields of isolated product. ^c Product ratios were determined by ¹H NMR spectroscopy of crude reaction mixtures. ^d Yield calculated by ¹H NMR spectroscopy of crude reaction mixtures using internal standard. ^e Reaction temperature: 130 °C. ^f Reactions performed under Ar.

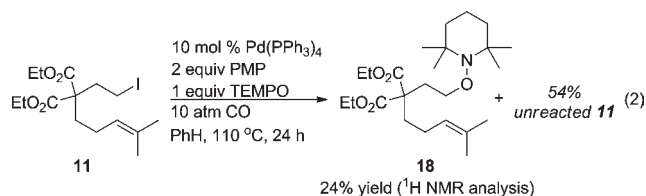
the ability of the carbocyclization to form quaternary centers (70% yield). Notably, the CO atmosphere was critical to the success of this reaction, as reaction under Ar led to the formation of a number of unidentified byproducts in addition to **4**. Cyclization of iodide **5** was also successful, providing substituted tetrahydrofuran **6** containing a quaternary stereocenter. This carbocyclization is capable of constructing bicyclic architectures, as demonstrated by the cyclization of cyclohexenyl substrate **7**. Importantly, this reaction is not limited to five-membered ring synthesis. For instance, alkyl iodide **11** delivered products **12** and **13** in 70% yield via 6-*exo* cyclization.

We also explored the potential of the palladium-catalyzed carbocyclization using secondary alkyl iodides. Our studies commenced with substrate **14**, which cyclized to afford product **15**.¹² Notably, CO does not have a significant effect on the efficiency of reactions using secondary iodides as substrates. The reaction of secondary iodide **16** was also successful, delivering **17** with high stereoselectivity.

Scheme 2. Plausible Catalytic Cycle for the Carbocyclization



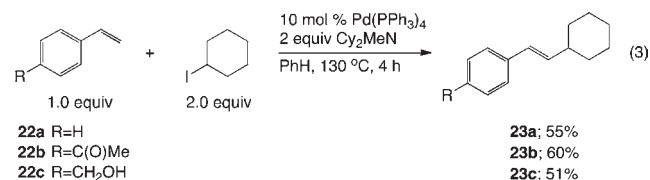
Alkyl halides are known to react with palladium(0) via both S_N2¹³ and single-electron transfer pathways.¹⁴ In order to probe for the potential intermediacy of carbon-centered radicals in the current reaction, we have attempted a cyclization in the presence of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl).¹⁵ The reaction of substrate **11** with 1 equiv of added TEMPO produced adduct **18** in 24% yield, with a significant amount of unreacted starting material, and no alkyl-Heck-type products were observed (¹H NMR analysis) (eq 2).¹⁶



Although the determination of a precise reaction pathway for this process requires further studies, our preliminary mechanistic hypothesis is outlined in Scheme 2 (with **3** as the substrate). We hypothesize that palladium(0) initiates this process via single-electron transfer to generate a carbon-centered free-radical **19** which then cyclizes onto the pendant alkene to deliver a second carbon-centered radical **20**.¹⁷ After interception of this radical species by a putative palladium(I) species, β -hydride elimination of an alkylpalladium(II) compound **21** provides product and regenerates the catalyst. Substrate dehydrohalogenation was not a significant side reaction in the carbocyclization, which is consistent with this proposal. At this time, the exact role of CO in increasing the efficiency of the present reaction with a number of substrates (Table 1, entries 1–5) is unclear. It is possible that the formation of less electron-rich Pd(PPh₃)_x(CO)_y species, which are formed under CO pressure,¹⁸ results in a more efficient hybrid organometallic-radical process. Studies to further elucidate the mechanistic pathway are underway.

Initial studies have also demonstrated the potential of the present catalytic system to facilitate an intermolecular variant of the palladium-catalyzed alkyl-Heck-type reaction. For example, the direct cross-coupling of styrene (**22a**) (1.0 equiv) and cyclohexyl iodide (2.0 equiv) delivers β -cyclohexyl styrene **23a** in 55% isolated yield (eq 3). The reactions of substituted styrenes **22b** and **22c** containing ketone and alcohol functional groups,

respectively, serve to demonstrate the functional group compatibility of this process. Future efforts will target the development of an efficient, general intermolecular variant of this fundamental transformation employing mild palladium(0)-catalyzed conditions.



In conclusion, we have developed a palladium-catalyzed Heck-type reaction of alkyl iodides of broad substrate scope. This process is applicable to the synthesis of many types of common cyclic frameworks and tolerates a variety of substituted alkenes and alkyl iodides. We have also demonstrated the potential of this process in an intermolecular direct palladium-catalyzed alkyl-Heck-type cross-coupling reaction. We propose that the wide scope of this transformation results from the hybrid organometallic-radical nature of the process, successfully overcoming the major challenges inherent in the development of palladium-catalyzed Heck reactions employing alkyl halide substrates.

ASSOCIATED CONTENT

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

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(9) The reaction yields determined by ¹H NMR were calculated from crude reactions using 1,3,5-trimethoxybenzene as an internal standard.

(10) For further details, including experiments run at other pressures of CO, see the Supporting Information.

(11) No product formed under these conditions in the absence of Pd(PPh₃)₄.

(12) Reaction of the alkyl bromide of substrate **14** was substantially slower, providing a 26% ¹H NMR yield of cyclization products after 24 h, with significant amounts of starting material remaining.

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