Communication

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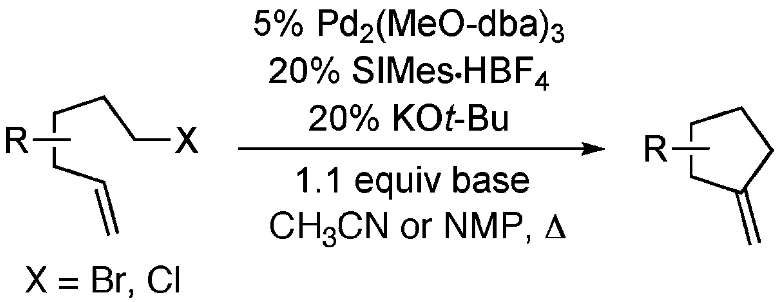

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Intramolecular Heck Reactions of Unactivated Alkyl Halides

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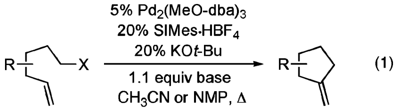
The palladium-catalyzed Heck reaction of olefins with *aryl* and *vinyl* halides and sulfonates has been developed into a method of broad scope that has found application throughout organic chemistry and related disciplines.[1] In contrast, there have been only isolated reports of corresponding couplings of *alkyl* electrophiles, in particular, unactivated substrates that bear β hydrogens.[2−4] It is worth noting that metals other than palladium can catalyze certain Heck-like reactions of alkyl halides with olefins; in these examples, the carbon−carbon bond-forming step generally involves a radical, rather than a metal-mediated, process.[5−7]

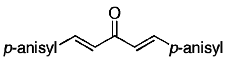
An expansion in the scope of palladium-catalyzed Heck couplings to include alkylations, in addition to arylations and vinylations, would significantly enhance the utility of this powerful transformation. Upon examination of the mechanism of the Heck reaction, it becomes clear that a key challenge in developing an "alkyl-Heck" coupling is to control the rate of β-hydride elimination relative to insertion (Figure 1). For the classic Heck reaction of an aryl or vinyl electrophile (R = aryl, vinyl), the situation is comparatively straightforward: facile β-hydride elimination is generally desirable. Since **A** is not prone to β-hydride elimination, if **B** proceeds faster to **C** than to **D**, efficient Heck arylation can be achieved.[8]

In the case of an alkyl-Heck reaction (Figure 1, R = alkyl), if β-hydride elimination is extremely facile, then **A** may not proceed to **B**. Thus, for a successful alkyl-Heck coupling, alkylpalladium species **A** and **B** should have opposite reactivity profiles: **A** should be prone to insert, rather than β-hydride eliminate, and **B** should prefer to β-hydride eliminate, instead of inserting.

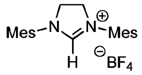
Because dictating this pattern of reactivity is likely to be a difficult challenge, we decided to pursue a more viable initial objective, namely, the development of an intramolecular alkyl-Heck reaction. Such a process relies upon **A** undergoing *intra*molecular insertion of a pendant olefin more rapidly than β-hydride elimination, and then **B** undergoing β-hydride elimination faster than *inter*molecular insertion. In this report, we establish that a palladium/*N*-heterocyclic carbene catalyst displays the desired reactivity profile, furnishing an effective method for achieving alkyl-Heck reactions (eq 1).



(1)



MeO-dba



SIMes·HBF4

On the basis of earlier studies of palladium-catalyzed *cross-couplings* of unactivated primary alkyl electrophiles,[9] we focused our catalyst-development efforts on the use of carbene and trialkylphosphine ligands (e.g., Table 1, entries 1−5). In comparison with the best ligand that we have discovered to date for the alkyl-Heck reaction (SIMes; entry 1), other carbenes (entries 2 and 3)[10] as well as phosphines (entries 4 and 5) are less effective. The choice of palladium complex is important: as observed with certain cross-couplings of *aryl* electrophiles, the MeO-dba adduct provides a superior result to dba (entry 6).[11,12] In the absence of SIMes or $Pd_2(MeO\text{-}dba)_3$, there is essentially no reaction (entries 7 and 8),[13] and the other Brønsted bases and solvents that we have examined furnish a less efficient process (e.g., entries 9 and 10).[14]

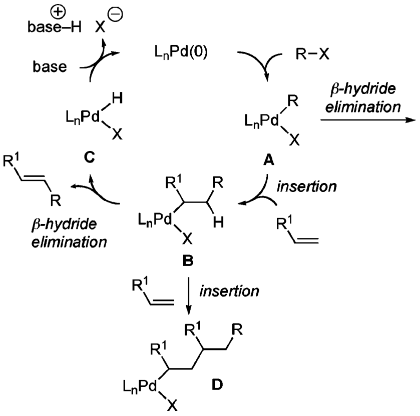
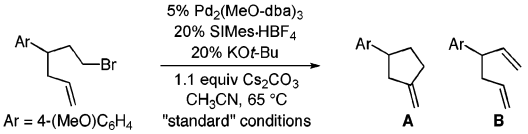


Figure 1. Outline of the catalytic cycle for the Heck reaction.

Table 1. An Alkyl-Heck Reaction of an Unactivated Electrophile: Influence of Reaction Parameters



entry	variation from the "standard" conditions	yield of **A**[a]	yield of **B**[a]
1	none	80	6
2	IMes·HBF_4, instead of SIMes·HBF_4	13	5
3	SIPr·HBF_4, instead of SIMes·HBF_4	27	20
4	$P(t\text{-Bu})_2Me$, instead of SIMes·HBF_4/KO*t*-Bu	43	52
5	PCy_3, instead of SIMes·HBF_4/KO*t*-Bu	53	23
6	$Pd_2(dba)_3$, instead of $Pd_2(MeO\text{-}dba)_3$	44	50
7	no SIMes·HBF_4	<2	2
8	no $Pd_2(MeO\text{-}dba)_3$	<2	<2
9	K_3PO_4, instead of Cs_2CO_3	37	8
10	NMP, instead of CH_3CN	46	15

[a] Determined through analysis by GC (average of two experiments).

With our optimized method, we can generate an array of five-membered rings via palladium-catalyzed intramolecular alkyl-Heck reactions of β-hydrogen-containing, unactivated alkyl bromides (Table 2). Cyclizations of a variety of substrates in which there is an aromatic group in the homoallylic position proceed smoothly with comparable efficiency (entries 1−4). A heteroaromatic substituent is also tolerated (entry 5). Of course, the method is applicable to compounds that bear groups other than aromatic rings (entries 6−8). A substrate that is more hindered with respect to oxidative addition undergoes alkyl-Heck cyclization in fairly good yield (entry 8), although the reaction is less facile. Finally, indane derivatives can be accessed through this procedure (entry 9).[15]

We were pleased to determine that Pd/SIMes catalyzes not only alkyl-Heck reactions of unactivated, β-hydrogen-containing alkyl

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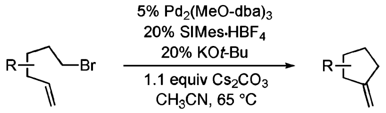
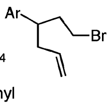
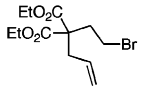
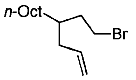
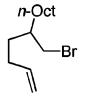
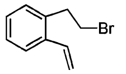
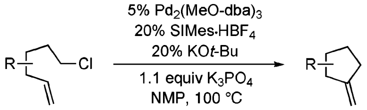
Table 2. Alkyl-Heck Reactions of Unactivated Alkyl Bromides

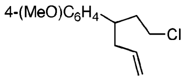
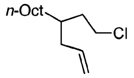
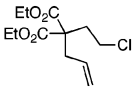
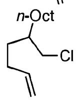


entry	substrate	yield[a]
1	Ar = Ph 	73
2	2-naphthyl	78
3	4-(MeO)C_6H_4	82
4	4-(F_3C)C_6H_4	79
5	2-benzofuranyl	83
6		85
7		75
8		73
9		71 (81)[b]

[a] Isolated yield (average of two experiments). [b] Base used: K_3PO_4. Purity of product: 95%. The value in parentheses is the yield according to GC analysis (the product is slightly volatile).

Table 3. Alkyl-Heck Reactions of Unactivated Alkyl Chlorides

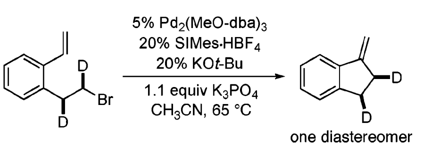


substrate	yield[a]	substrate	yield[a]
	72		71
	80		66

[a] Isolated yield (average of two experiments).

bromides, but also of the corresponding chlorides (Table 3). Perhaps not surprisingly, a higher reaction temperature is necessary.[16]

As indicated above, there have been previous reports of alkyl-Heck-like processes catalyzed by metals other than palladium. In these examples, it has generally been postulated that the carbon−carbon bond-forming step involves a radical, not an alkylmetal, intermediate,[5−7] which renders these processes mechanistically distinct from a true alkyl-Heck reaction. To determine if Pd/SIMes-catalyzed cyclizations also follow a radical pathway, we examined the reaction of the deuterium-labeled substrate illustrated in eq 2. In the presence of Pd/SIMes, a single diastereomer is produced, the stereochemistry of which is consistent with an S_N2 mechanism for oxidative addition.[17] Thus, our palladium-catalyzed alkyl-Heck reactions appear to proceed via a pathway distinct from related, radical-mediated transformations catalyzed by other metals.



(2)

In summary, we have developed a method for achieving palladium-catalyzed intramolecular Heck reactions of unactivated, *β*-hydrogen-containing alkyl bromides and chlorides. The data from a stereochemical investigation are consistent with carbon−carbon bond formation via an alkylpalladium, rather than a radical, intermediate. Additional synthetic and mechanistic studies of this and related processes are underway.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) For a review of the Heck reaction, see: Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions;* de Meijere, A., Diederich, F., Eds.; Wiley−VCH: New York, 2004; Chapter 5.

(2) For examples of palladium-catalyzed Heck reactions of *activated* alkyl halides that *lack β* hydrogens, see: (a) benzylic electrophiles: Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320−2322. Wu, G.-z.; Lamaty, F.; Negishi, E.-i. *J. Org. Chem.* **1989**, *54*, 2507−2508. Pan, Y.; Zhang, Z.; Hu, H. *Synth. Commun.* **1992**, *22*, 2019−2029. Pan, Y.; Zhang, Z.; Hu, H. *Synthesis* **1995**, 245−247. Kumar, P. *Org. Prep. Proc. Int.* **1997**, *29*, 477−480. Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725−727. Higuchi, K.; Sawada, K.; Nambu, H.; Shogaki, T.; Kita, Y. *Org. Lett.* **2003**, *5*, 3703−3704. Narahashi, H.; Yamamoto, A.; Shimizu, I. *Chem. Lett.* **2004**, 348−349. (b) α-halocarbonyls: Mori, M.; Oda, I.; Ban, Y. *Tetrahedron Lett.* **1982**, *23*, 5315−5318. Glorius, F. *Tetrahedron Lett.* **2003**, *44*, 5751−5754.

(3) For leading references to related reactions of allylic electrophiles, see: Oppolzer, W. *Angew. Chem., Int. Ed.* **1989**, *28*, 38−52.

(4) For examples of palladium-catalyzed Heck reactions of an unactivated alkyl halide that is not prone to *β*-hydride elimination (1-bromoadamantane), see: Bräse, S.; Waegell, B.; de Meijere, A. *Synthesis* **1998**, 148−152.

(5) Cobalt-catalyzed coupling of alkyl halides with olefins (radical pathway): (a) Branchaud, B. P.; Detlefsen, W. D. *Tetrahedron Lett.* **1991**, *32*, 6273−6276. (b) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068−8077.

(6) Titanocene-catalyzed coupling of alkyl halides with styrenes (radical pathway): Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 663−672.

(7) Nickel-catalyzed coupling of alkyl bromides with styrene (no mechanistic experiments): Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *344*, 253−259.

(8) For the sake of simplicity, this discussion is based on irreversible elementary steps.

(9) For reviews of cross-coupling reactions of alkyl electrophiles, see: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. (b) Netherton, M. R.; Fu, G. C. *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: New York, 2005.

(10) For a recent review of palladium/carbene-catalyzed reactions, see: Diez-Gonzalez, S.; Nolan, S. P. *Topics in Organomet. Chem.* **2007**, *21*, 47−82.

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(12) For an overview of the role of dba in palladium-catalyzed coupling reactions, see: Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178*, 511−528.

(13) For a transition metal-free, *N*-heterocyclic carbene-catalyzed Heck-like reaction of alkyl halides and tosylates, see: Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472−1473.

(14) For entries 2, 3, 7, 8, 9, and 11 of Table 1, unreacted starting material accounts for the majority of the mass balance.

(15) Under our standard conditions, the following alkyl-Heck cyclizations were not successful (<30% yield): (1) reaction of a disubstituted olefin; (2) formation of a six-membered ring; and, (3) cyclization of an unactivated secondary alkyl bromide.

(16) Under the conditions described for alkyl-Heck cyclizations of alkyl bromides (Table 2), the reaction of an alkyl chloride (entry 1 of Table 3) proceeds in <5% yield.

(17) (a) For a discussion of the mechanism of oxidative addition of alkyl halides to metals such as palladium, see: Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434−442. (b) For a more recent example of a palladium-catalyzed reaction of a primary alkyl iodide that is believed to proceed through a radical pathway, see: Stadtmüller, H.; Vaupel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204−1220. (c) For another example of oxidative addition of an alkyl electrophile to a palladium/L complex (L = a bulky, electron-rich ligand (P(*t*-Bu_2)Me))) via an S_N2 pathway, see: Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910−3912.

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