DOI: 10.1002/ange.201311323

Palladium-Catalyzed Heck-Type Cross-Couplings of Unactivated Alkyl Iodides**

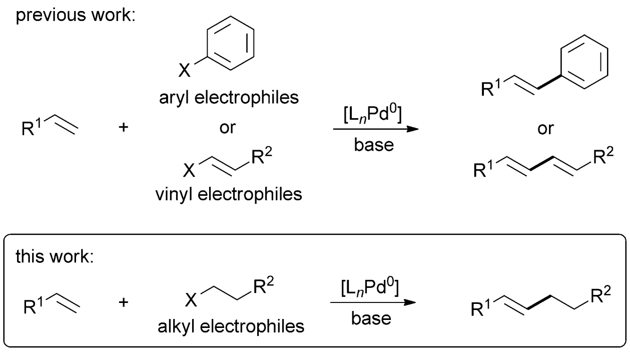
*Caitlin M. McMahon and Erik J. Alexanian**

Abstract: *A palladium-catalyzed, intermolecular Heck-type coupling of alkyl iodides and alkenes is described. This process is successful with a variety of primary and secondary unactivated alkyl iodides as reaction partners, including those with hydrogen atoms in the β position. The mild catalytic conditions enable intermolecular C–C bond formations with a diverse set of alkyl iodides and alkenes, including substrates containing base- or nucleophile-sensitive functionality.*

Palladium-catalyzed cross-couplings are invaluable to an array of disciplines that involve chemical synthesis, ranging from pharmaceuticals to materials science.[1] Among the most useful reactions of this type are Heck cross-couplings, which form an intermolecular C–C bond between a halide or sulfonate electrophile and an alkene under mild conditions.[2] However, this reaction has been largely limited to aryl or vinyl electrophiles, and palladium-catalyzed Heck-type reactions involving unactivated alkyl halides are considered a major challenge (Scheme 1).[3] This issue is commonly attributed to the decreased rates of oxidative addition using sp^3-hybridized electrophiles,[4] and the predisposition of putative alkylpalladium species to undergo dehydrohalogenation.[5] A number of catalytic systems involving first-row transition metals (e.g., Ni, Ti, Co) have been developed to facilitate intermolecular alkyl-Heck processes.[6] However, these methods commonly rely on stoichiometric amounts of alkylmetal reductants, limiting the general applicability of these reactions in synthesis. Furthermore, these processes have been solely limited to cross-coupling with styrenes.

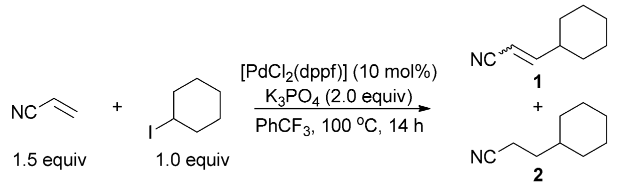
Recent studies have demonstrated the potential for palladium-and nickel-catalyzed alkyl-Heck-type carbocyclizations of alkyl halides.[3,7] We have also obtained promising preliminary results involving the intermolecular alkyl-Heck coupling of cyclohexyl iodide with a small sample of styrenes, albeit in moderate yield.[7a] Herein, we report the development of a general protocol for the palladium-catalyzed, alkyl-Heck-type cross-coupling. This process is applicable to a range of alkyl iodides and alkenes, and represents the first intermolecular alkyl-Heck coupling of any kind involving non-styrenyl substrates.

We commenced our studies by evaluating the intermolecular coupling of cyclohexyl iodide and acrylonitrile (Table 1). The use of an organic base (Cy$_2$NMe), as in our previously developed alkyl-Heck-type reactions,[7a] led to a large amount of undesired reductive product **2** (Table 1, entry 2). Fortunately, this problem could be mitigated by the



Scheme 1. Palladium-catalyzed Heck cross-couplings.

Table 1: Palladium-catalyzed cross-coupling of cyclohexyl iodide and acrylonitrile.



Entry	Deviation from conditions described above	Yield of **1** (**2**) [%][a]
1	none	72
2	Cy$_2$NMe instead of K$_3$PO$_4$	18 (24)
3	Cs$_2$CO$_3$ instead of K$_3$PO$_4$	57
4	80 °C instead of 100 °C	24
5	1.0 equiv of alkene, 2.0 equiv of iodide	54
6	[Pd(PPh$_3$)$_4$] (10 mol%) instead of [PdCl$_2$(dppf)]	55 (5)
7	Pd(OAc)$_2$ (10 mol%) and BINAP (20 mol%) instead of [PdCl$_2$(dppf)]	17
8	Pd(OAc)$_2$ (10 mol%) and dppe (20 mol%) instead of [PdCl$_2$(dppf)]	<2
9	Pd(OAc)$_2$ (10 mol%) and dppf (20 mol%) instead of [PdCl$_2$(dppf)]	73
10	no [PdCl$_2$(dppf)]	<2
11	reaction in the dark, 24 h	69

[a] Calculated by ^{1}H NMR spectroscopy of the crude reaction mixtures using an internal standard.

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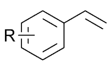
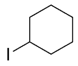
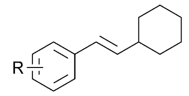
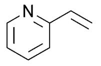
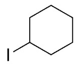
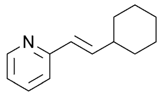
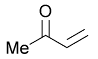
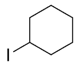
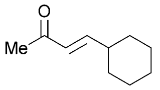
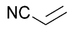
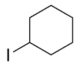
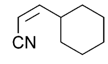
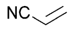
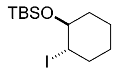
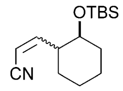
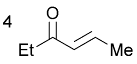
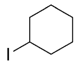
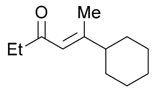
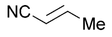
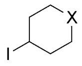
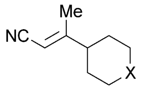
[**] This work was supported by UNC Chapel Hill, and a Burroughs-Wellcome Graduate Fellowship (C.M.M.).

Supporting information for this article (including experimental procedures and data) is available on the WWW under http://dx.doi.org/10.1002/anie.201311323.

use of inorganic bases instead of Cy_2NMe (Table 1, entries 1 and 3), with K_3PO_4 most effective. We determined that the use of solvents that lack abstractable hydrogen atoms limited the production of by-product **2**, and $PhCF_3$ was found to be a suitable choice. Lowering the reaction temperature to 80 °C resulted in a marked decrease in reaction efficiency (Table 1, entry 4). A slight excess of acrylonitrile was preferable in this cross-coupling (1.5 equiv), however, reactions using a slight excess of alkyl iodide proceeded in lower yield (Table 1, entry 5). Other palladium-based catalytic systems, including $[Pd(PPh_3)_4]$, which we used in our previous studies, were inferior to $[PdCl_2(dppf)]$ (Table 1, entry 6–8). The combination of $Pd(OAc)_2$ (10 mol %) and dppf (20 mol %) was a suitable substitute for $[PdCl_2(dppf)]$ (10 mol %; Table 1, entry 9). No product was formed in the absence of $[PdCl_2(dppf)]$ (Table 1, entry 10), and the reaction proceeded in the dark (entry 11). The success of this cross-coupling is particularly intriguing with regard to the potential for an undesired polymerization of acrylonitrile.[8]

Upon the identification of a viable reaction system, we first surveyed the cross-coupling of a variety of alkenes. As with acrylonitrile cross-coupling (Table 1), the use of $[PdCl_2(dppf)]$ was crucial to obtain a high yield. An electronically diverse set of styrenes, including those with base- and nucleophile-sensitive functionality, are viable coupling partners (Table 2, entries 1–9). In styrenyl cross-couplings, Cy_2NMe was used as base, because reductive by-products were not problematic. 2-Vinyl pyridine participates in the cross-coupling, albeit in modest yield (Table 2, entry 10). Electron-poor alkenes, such as methyl vinyl ketone (Table 2, entry 11) and acrylonitrile (entries 12 and 13), afforded the products in moderate to good yields. In the case of the highly polymerizable methyl vinyl ketone, substitution of $[PdCl_2(dppf)]$ for $[\{Pd(allyl)Cl\}_2]$ (5 mol %) and PPh_2tBu (40 mol %) was required. We studied the reaction of *trans*-2-(*tert*-butyldimethylsilyloxy)-1-iodocyclohexane in order to probe the diastereoselectivity of the reaction with simple cyclic substrates (Table 2, entry 13). The cross-coupling of this substrate with acrylonitrile delivered the product with a 50:50 ratio of *cis*- and *trans*-substituted cyclic diastereomers. Alkenes containing substituents in the β position also react efficiently (Table 2, entries 14–16) with either cyclohexyliodide or the heterocyclic 4-iodo-1-tosylpiperidine as coupling partners. In analogy to the standard Heck reaction using aryl electrophiles, the cross-couplings of β-substituted alkenes gave mixtures of geometric isomers as products, with the predominate isomer containing the incoming alkyl electrophile and the electron-withdrawing group in *trans* position to each other.[9] In the cross-couplings of β-disubstituted alkenes, we determined that $[Pd(PPh_3)_4]$ was superior to $[PdCl_2(dppf)]$ as catalyst.

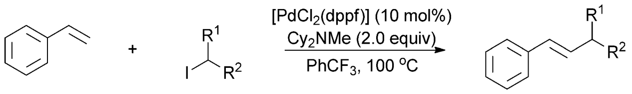
Table 2: Scope of palladium-catalyzed alkyl-Heck-type cross-couplings with respect to the alkene.[a]

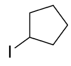
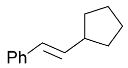
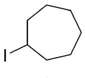
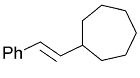
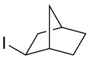
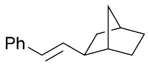
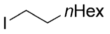
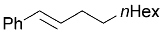
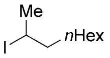
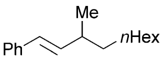
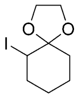
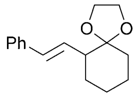
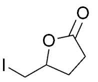
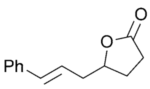
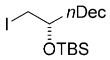
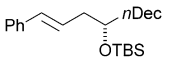
Entry	Alkene	Alkyl iodide	Product	Yield [%][b,c]
				
1	R = H			84
2	R = 4-OMe			66
3	R = 4-Me			64
4	R = 4-CF_3			82
5	R = 4-CH_2OH			64[d]
6	R = 4-F			76 (83:17 *E*:*Z*)
7	R = 4-C(O)Me			61[d] (80:20 *E*:*Z*)
8	R = 3-OMe			67
9	R = 2-Me			72 (50:50 *E*:*Z*)
10				35
11				35[e,f]
12				70[e] 29:71 *E*:*Z*
13			 50:50 d.r.	61[e] 33:66 *E*:*Z*
14				55[e,g,h] 66:33 *E*:*Z*
				
15		X = CH_2		80[e,g,i] (66:33 *E*:*Z*)
16		X = NTs		79[e,g,i] (66:33 *E*:*Z*)

[a] Reactions run using 1.0 equiv alkyl iodide and 1.5 equiv alkene 0.5 M in $PhCF_3$ at 100 °C in the presence of 10 mol % $[PdCl_2(dppf)]$ and 2.0 equiv Cy_2NMe for 14 h. [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 the crude reaction mixture using an internal standard. [e] 2.0 equiv K_3PO_4 used as base. [f] 5 mol % $[\{Pd(allyl)Cl\}_2]$ and 40 mol % PPh_2tBu used as catalyst, 5 h. [g] 10 mol % $[Pd(PPh_3)_4]$ used as catalyst. [h] 2.0 equiv alkyl iodide and 1.0 equiv enone. [i] 3.0 equiv crotononitrile. TBS = *tert*-butyldimethylsilyl, Ts = toluene-*p*-sulfonyl.

We next examined the scope of the reaction with a variety of alkyl iodides using styrene as the coupling partner (Table 3). Cyclopentyl and cycloheptyliodide reacted with similar efficiency to cyclohexyl iodide (Table 3, entries 1 and 2).[10] The cross-coupling of *exo*-2-norbornyl iodide provided the styrylation product with high diastereoselectivity (> 95:5 d.r.; Table 3, entry 3). The cross-coupling is also applicable to acyclic primary and secondary iodides, as demonstrated by the reactions of 1-iodooctane and 2-iodononane (Table 3, entries 4 and 5). Sterically congested 6-iodo-1,4-dioxaspiro-[4.5]decane was an excellent substrate, and coupled with styrene in 79 % yield (Table 3, entry 6). The reactions of alkyl iodide substrates containing nucleofuges in the α position are also useful intermolecular C−C bond-forming transformations, as demonstrated by the reactions of an iodo-γ-lactone and enantiopure TBS-protected (*S*)-1-iodododecan-2-ol (Table 3, entries 7 and 8). With regard to the array of useful methods for the asymmetric synthesis of such substrates,[11] we view this as a particularly attractive approach to the enantioselective preparation of highly functionalized small molecules.

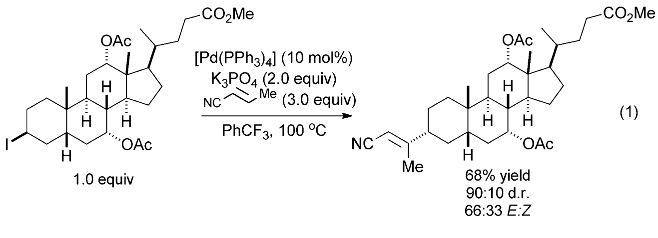
Table 3: Scope of palladium-catalyzed alkyl-Heck-type cross-couplings with respect to the alkyl halide.[a]



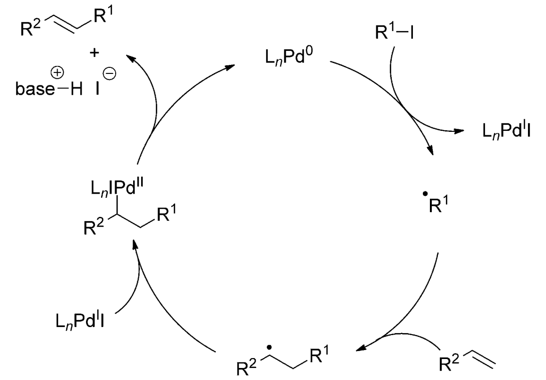
Entry	Alkyl iodide	Product	Yield [%][b,c]
1			70 86:14 *E*:*Z*
2			76
3		 >95:5 d.r.	80 88:12 *E*:*Z*
4			46[d]
5			74 88:12 *E*:*Z*
6			79
7			42[d,e]
8	 >99:1 e.r.	 >99:1 e.r.	51[d] 80:20 *E*:*Z*

[a] Reactions run using 1.0 equiv alkyl iodide and 1.5 equiv alkene 0.5 M in PhCF$_3$ at 100 °C in the presence of 10 mol% [PdCl$_2$(dppf)] and 2.0 equiv Cy$_2$NMe for 14 h. [b] Yields of isolated product. [c] Product ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [d] Reaction run at 130 °C. [e] Yield calculated by ^{1}H NMR spectroscopy of the crude reaction mixture using an internal standard.

Notable features of Heck cross-couplings are the mild catalytic conditions and simple substrates involved, which are ideal for late-stage intermolecular C–C bond formation in synthesis. For an initial demonstration of this concept with a substrate derived from a complex natural product, we prepared an iodide substrate in straightforward fashion from cholic acid.[12] The intermolecular alkyl-Heck coupling with crotononitrile delivered the alkenylation product in a highly stereoselective fashion with respect to the cyclohexyl ring [Eq. (1)].[13] In light of the many methods available for the preparation of alkyl iodides directly from alcohols,[14] this transformation holds promise as an enabling tool for C–C bond formation in complex synthesis.

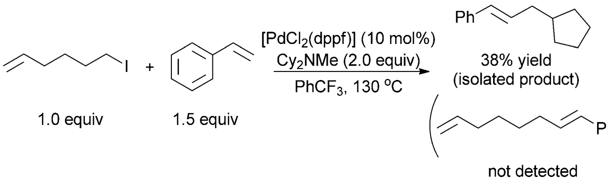


(1)



Scheme 2. Plausible catalytic cycle for the palladium-catalyzed alkyl-Heck-type cross-coupling.

We hypothesize that this cross-coupling proceeds through single-electron oxidative addition of the alkyl iodide substrate followed by alkene addition of the carbon-centered radical, as shown in Scheme 2.[15–17] The exclusive formation of the *exo*-substituted coupling product with *exo*-2-norbornyl iodide (Table 3, entry 3),[18] and the stereoablation observed in the reaction of a diastereomerically pure cyclic substrate (Table 2, entry 13) is consistent with a single-electron pathway. Additionally, the reaction of styrene with a radical-clock substrate (6-iodo-1-hexene) provided the cyclic coupling product in 38% yield [Eq. (2)], with no linear coupling product observed.



(2)

Following the addition step, the alkylpalladium(II) species is formed, and β-hydride elimination delivers the cross-coupling product. We hypothesize that the lack of significant amounts of polymer in reactions involving reactive monomers (e.g., methyl vinyl ketone, acrylonitrile) may be due to the unique reactivity of the Pd^I species, which may exhibit persistent radical-like character.[16] However, at this stage we cannot rule out pathways involving organometallic insertion.

In conclusion, we have developed a general strategy for the palladium-catalyzed intermolecular alkyl-Heck reaction. The approach includes the first examples of alkyl-Heck cross-couplings using non-styrenyl substrates. The observed reactivity is consistent with a hybrid organometallic–radical pathway, which may be crucial to avoiding undesired dehydrohalogenation of the simple alkyl halide substrates. A notable feature of the current process is the easy access to the involved substrates, which combined with the mild reaction conditions makes this approach attractive for complex synthesis.

Received: December 31, 2013
Revised: February 17, 2014

Keywords: alkenes · alkyl halides · cross-coupling · homogeneous catalysis · palladium

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