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Studies in Acyl C−H Activation via Aryl and Alkyl to Acyl "Through Space" Migration of Palladium

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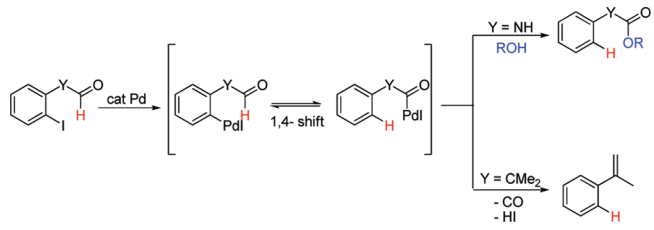
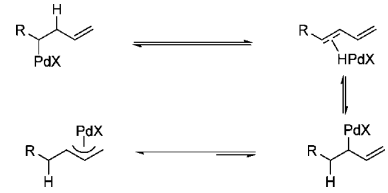
ABSTRACT



Examples of the 1,4-migration of a palladium moiety in aryl- and alkylpalladium intermediates to the acyl position of an aldehyde or formamide have been observed. The resulting acylpalladium intermediate can undergo ester or carbamate formation by reaction with an alcohol; decarbonylation, followed by β hydride elimination to an alkene; reaction with an organomercurial to form an ester; or alkene insertion. Deuterium-labeling studies have been used to confirm the palladium migration mechanism.

The migration of palladium along an alkyl chain has been employed for the synthesis of long-chain compounds and heterocycles.[1] This chemistry involves migration of palladium down a saturated carbon chain by a palladium hydride elimination/addition sequence until a stable palladium intermediate is formed (Scheme 1).

Scheme 1



Recently, we[2] and others[3] have reported the "through space" migration of palladium in *o*-iodobiaryls, where palladium migrates from one ring to the other by the apparent

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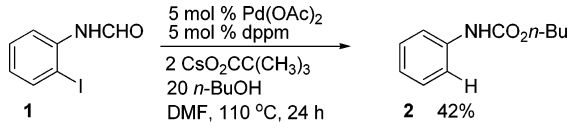
formation of a five-membered-ring palladacycle. These migration reactions provide an alternate way to introduce a palladium moiety into organic molecules and have been found to be quite general. Recently, aryl to aryl,[2,3] vinylic to aryl,[4] alkyl to aryl,[5] aryl to alkyl,[6] vinylic to aryl to allylic,[7] benzylic to aryl,[8] aryl to benzylic,[9] and aryl to imidoyl[10] migrations have been reported to be a useful tool for the synthesis of a variety of carbocyclic and heterocyclic ring systems.

Herein, we report that an acyl C−H bond can also be activated under palladium migration reaction conditions to form carbamates when starting from formamide **1** (Scheme 2). Although there are currently more efficient routes for the

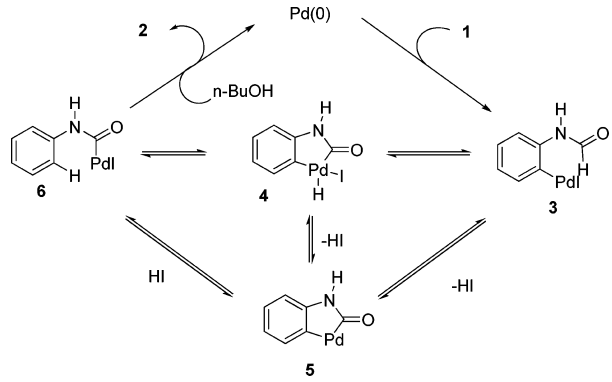
Scheme 2



synthesis of carbamates, this migration chemistry provides a unique new route to acylpalladium intermediates of considerable value in organic synthesis.

A possible mechanism for this palladium migration reaction is outlined in Scheme 3. After oxidative addition of the

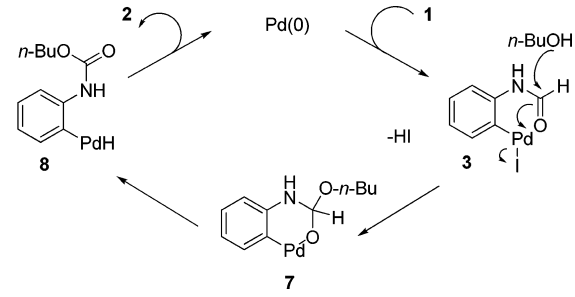
Scheme 3



aryl halide **1** to Pd(0), the resulting intermediate **3** can insert palladium into the neighboring acyl C−H bond to form palladium(IV) intermediate **4** or cyclize to palladium(II) intermediate **5**. Intermediate **5** can also be formed by the loss of HI from intermediate **4**. Acylpalladium species **6**, which can be formed from either **4** or **5**, can be trapped by butanol to furnish the corresponding carbamate **2**.

The formation of carbamate **2** can also be explained by a mechanism similar to one first proposed by Wei and coworkers[11] in their esterification−hydroarylation reaction of 2-(1-alkynyl)benzaldehydes (Scheme 4). The intermediate

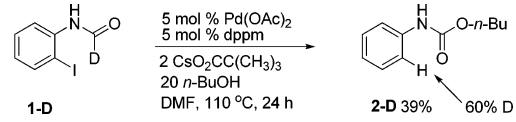
Scheme 4



3 can produce six-membered ring palladacycle **7** by reaction of the alcohol at the acyl carbon and nucleophilic displacement of the halide on palladium. Intermediate **7** can undergo β-hydride elimination to form arylpalladium intermediate **8**, which can then undergo reductive elimination to generate carbamate **2**.

To further study the mechanism of this reaction, deuterium-labeled compound **1-D** was subjected to our standard palladium migration conditions, affording 60% incorporation of deuterium into the *ortho* position of carbamate **2-D** (Scheme 5). While this experiment establishes the migration

Scheme 5



of deuterium from an acyl position to an aryl position, the results are consistent with either of the two proposed mechanisms. H−D exchange, presumably with the solvent, accounts for the fact that there is less than 100% deuterium incorporation in the product.

To better understand the mechanism of these reactions, we decided to examine the reaction of aldehyde **9** in the absence of an alcohol nucleophile. If the reaction proceeds through the mechanism described in Scheme 3, then an acylpalladium intermediate analogous to **6** should be formed.

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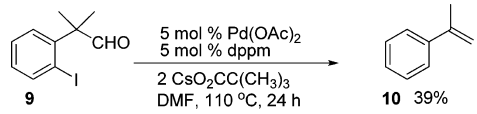
In the absence of a nucleophile, the acylpalladium intermediate should undergo decarbonylation, followed by β-hydride elimination, to give the corresponding styrene derivative **10** (Scheme 6). Indeed, we were pleased to see the formation

Scheme 6



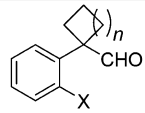
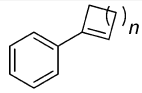
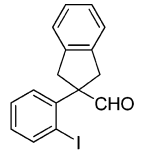
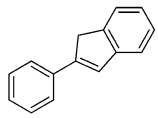
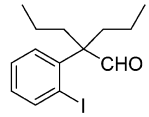
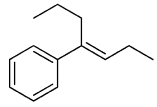
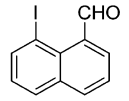
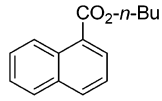
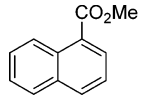
of styrene **10** in a 39% yield. This strongly suggests the formation of an acylpalladium species, which in turn implies the migration of palladium from an aryl position to an acyl position.

We have found that aryl bromide **11** undergoes an analogous migration/decarbonylation reaction producing **12** in a 33% yield (Table 1, entry 1). The corresponding aryl iodide affords olefin **12** in a 47% yield (entry 2). Other cyclic carboxaldehydes also afford modest yields of decarbonylation products. Thus, we obtained olefins **15**, **17**, and **19** in 42, 41, and 35% yields, respectively, from the corresponding aldehydes (entries 3−5). Acyclic carboxaldehyde **20** gave only one stereoisomer **21** in a 33% overall yield (entry 6).

When aldehyde **22** was subjected to our standard reaction conditions along with 20 equiv of *n*-BuOH, ester **23** was formed in 38% yield (entry 7). When **22** was subjected to reaction conditions developed by Wei and co-workers,[11] methyl ester **24** was obtained in a much higher yield of 76% (entry 8).

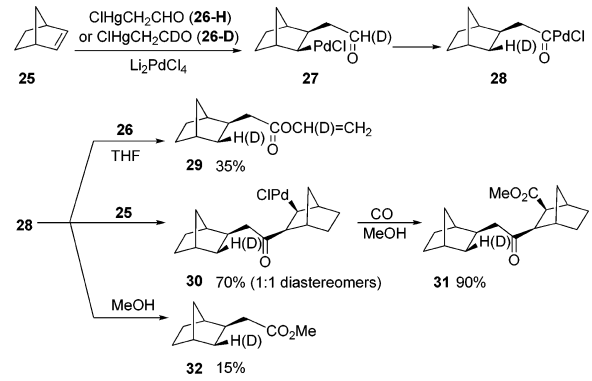
These acyl C−H activation processes appear to be quite general. For example, the reaction of norbornene, $ClHgCH_2CHO$, and Li_2PdCl_4 affords products most consistent with rearrangement of an initially formed aldehyde-containing norbornylpalladium species to an acylpalladium species, which can be trapped by reaction with the starting organomercurial, an excess of norbornene, or an alcohol (Scheme 7). Deuterium-labeling experiments are consistent with an alkyl- to acylpalladium rearrangement.

Table 1. Scope of the Aryl- to Acylpalladium Migration[a]

entry	aryl halide		product		% yield
1	 *n* = 2, X = Br	**11**		**12**	33
2	*n* = 2, X = I	**13**		**12**	47
3	*n* = 3, X = I	**14**		**15**	42
4	*n* = 1, X = I	**16**		**17**	41
5		**18**		**19**	35
6		**20**		**21**	33
7		**22**		**23**	38[b]
8		**22**		**24**	76[c]

[a] Unless otherwise stated, all reactions were performed using 0.5 mmol of aldehyde, 5 mol % of $Pd(OAc)_2$, 5 mol % of dppm, and 2 equiv of cesium pivalate in 6 mL of DMF at 110 °C for 12 h. [b] 20 equiv of *n*-BuOH was added under the above-mentioned reaction conditions. [c] These reactions were performed using 0.5 mmol of aldehyde, 5 mol % of $Pd(PPh_3)_4$, and 1.5 equiv of K_2CO_3 in 8 mL of MeOH at 65 °C for 24 h.

Scheme 7



In summary, we have found a unique way of activating an acyl C−H bond. "Through space" migration of palladium from an aryl or alkyl position to an acyl position by a five-membered ring palladacycle results in an acylpalladium species. The acylpalladium species can be trapped by an alcohol or in the absence of an alcohol, olefin products result from decarbonylation, followed by β-hydride elimination.

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Supporting Information Available: ^1H and ^{13}C NMR spectra and experimental preparations for all previously unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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