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Water-Controlled Regioselectivity of Pd-Catalyzed Domino Reaction Involving a C−H Activation Process: Rapid Synthesis of Diverse Carbo- and Heterocyclic Skeletons

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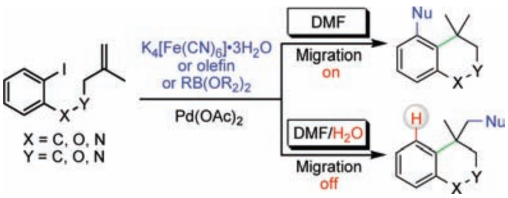
ABSTRACT



A palladium-catalyzed domino reaction involving a C−H activation process to synthesize diverse carbo- and heterocyclic skeletons was developed. H_2O (as cosolvent) is used to control the regioselectivity.

Domino reactions have proven to be of exceptional power for the construction of complex molecules through the formation of multiple bonds in one-pot reactions.[1] The importance and reliability of palladium-catalyzed transformations has made it an ideal basis for devising domino processes, and indeed, significant progress has been achieved in this regard.[2] In recent years, palladium-catalyzed C−H activation has received substantial attention because it can transform otherwise unreactive C−H bonds into carbon−carbon or carbon-heteroatom bonds.[3] Thus, the development of palladium-catalyzed domino reactions involving C−H activation represents an attractive research field of synthetic organic chemistry.

The cyclopalladation proceeding through alkyl/aryl palladacycles has proven to be a good model for C−H activation. Lautens,[4] Catellani,[2c,5] and others[6] have reported many interesting transformations employing norbornene-

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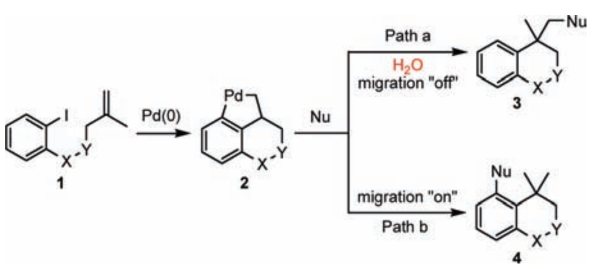
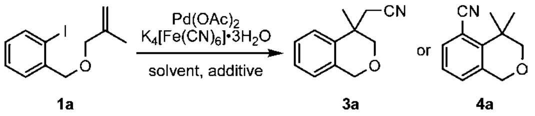
mediated chemistry. To date, only a few examples of complete alkyl to aryl palladium rearrangement via intramolecular C−H activation have been reported by Larock and others without using norbornene, and all reactions occurred on the aromatic site.[7] Moreover, regioselective attack at either the aromatic or alkyl site of palladacycle **2** remains a challenging task. Herein, we report for the first time that five-membered palladacycle **2** could be regioselectively trapped by Heck, as well as Suzuki cross-coupling or cyanation to give migration "off" product **3** (path a) or migration "on" product **4** (path b) by manipulating the reaction conditions (Scheme 1). Also of note is that these Pd-catalyzed domino reactions involving intramolecular C−H activation could be achieved under normal Heck reaction conditions without ligands. Another advantage of this method is that a diverse range of carbo- or heterocycles can be prepared starting from the same substrate, which is consistent with atom- and step-economy.[8]

Scheme 1. Condition-Controlled Pd-Catalyzed Domino Reactions from Iodobenzene Derivatives



In connection with a total synthesis project using the Heck-cyanation cascade reaction as key step, compound **1a** was employed as a model.[9] To our surprise, compound **4a**, an intramolecular C−H activation via 1,4-palladium migration product, was obtained in 42% yield.[10] This unexpected result promted us to obtain a clear picture of how various reaction variables affect the C−H activation. A wide variety of reaction conditions (bases, additives, solvents, and temperatures) were examined, and some of the representative results are shown in Table 1. Interestingly, when 18-crown-6 was added as an additive, only the normal Heck-cyanation product **3a** was obtained in 49% yield (entry 2). These results indicated clearly that the regioselectivity of the palladacycle could be controlled by manipulating the reaction conditions. When DMF/H_2O (95:5) was used as solvent the sole product **3a** was obtained in 52% yield (entry 3).[11] We have found that upon the addition of *tert*-butylammonium chloride (TBAC) described by Jeffery,[12] the yield of **4a** was increased to 52% (entry 4), along with 29% of **3a**. To our delight, simply lowering the reaction temperature to 60 °C led to an improvement and gave **4a** as an exclusive product in 78% yield (entry 6). Most interesting, the sole compound **3a** was obtained in 60% yield by using DMF/H_2O (95:5) as solvent (entry 7). *Thus, the regioselectivity of palladacycle could be controlled in the presence/absence of water.*[7c,11] It is noteworthy that TBAC is not essential to the C−H activation, but its presence could shorten the reaction time and minimize side reactions.

Table 1. Optimization of Pd-Catalyzed Domino Reaction of **1a** and $K_4[Fe(CN)_6]{\cdot}3H_2O$[a]



entry	temp (°C)	solvent	additive	product (yield, %)[b]
1	120	DMF		**4a** (42)
2	120	DMF	18-C-6	**3a** (49)
3	120	DMF/H_2O (95:5)		**3a** (52)
4	120	DMF	TBAC	**3a** (29), **4a** (52)
5	90	DMF	TBAC	**3a** (22), **4a** (62)
6	**60**	**DMF**	TBAC	**4a** (78)
7	**60**	**DMF/H_2O (95:5)**	**TBAC**	**3a** (60)

[a] General reaction conditions: concentration 0.04 M in solvent, 0.05 equiv of $Pd(OAc)_2$, 1.0 equiv of **1a**, 0.22 equiv of $K_4[Fe(CN)_6]{\cdot}3H_2O$, 1.0 equiv of Na_2CO_3, and 1.0 equiv of additive. [b] Isolated yield.

Having established the optimal reaction conditions, the scope of the palladium migration "on" process was first examined. Aryl halides **1b**−**e**, representing different heterocyclic skeleton types, were smoothly transformed to the desired products (**4b**−**e**) in good to excellent yields (Figure 1).

An interesting question is whether the arylpalladium intermediates can be trapped by other traditional palladium-catalyzed chemistry which could broaden the scope and

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utility of this migration progress. To address this issue, aryl halides **1a−e** were allowed to react with methyl acrylate under the aforementioned optimized conditions. The desired products **4f−j** were generated in good to excellent yield (Figure 1). When styrene was used as a trapping reagent the desired products **4k** and **4l** were obtained in good yield.

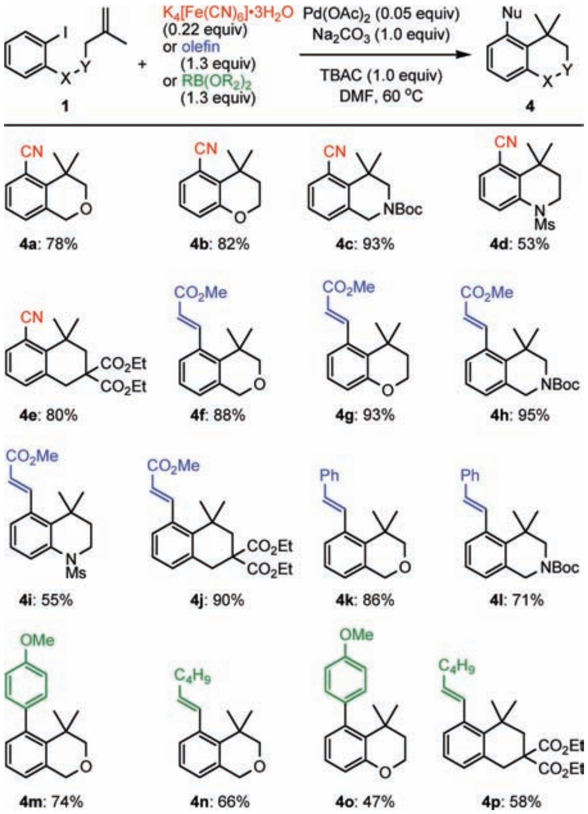


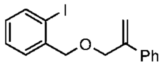
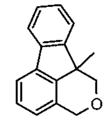
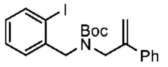
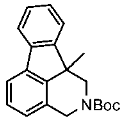
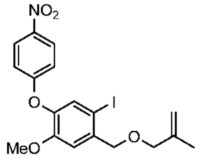
Figure 1. Scope of the Pd-catalyzed domino reaction involving intramolecular C−H activation process (migration "on").

To explore the scope of this migration progress, further trapping of the arylpalladium intermediates was tried by a Suzuki coupling. To the best of our knowledge, this type of domino reaction has never been reported in the literature.[13] Gratefully, all substrates indeed afforded the aryl functionalized products in good yields (**4m−p**, Figure 1).

Larock has reported that complex fused polycycles could be synthesized via a novel 1,4-palladium alkyl to aryl migration followed by intramolecular arylation under their usual palladium migration conditions.[7a] We envisioned that this type of domino reaction could similarly occur under our conditions to generate complex fused polycycles. Compounds **5**, **7**, and **9** reacted well to afford the corresponding fused ring systems **6**, **8**, and **10** in good yields (Table 2).

The scope of the palladium migration "off" process was also examined (Figure 2). The Heck-cyanation and Heck−Suzuki cascade reaction proceed well to afford the desired product under optimized conditions (**3a−c**, **3f−i**). However, the Heck−Heck cascade reaction proved to be problematic. The migration "on" product **4f** and migration "off" product **3d** were obtained in a ratio of 1 to 4. Fortunately, we raised the water amount in the reaction system to 20%, and then **3d** was obtained exclusively in 62% yield (Figure 2). Similarly, **3e** was obtained in 70% yield.

Table 2. Synthesis of Fused Polycycles via Pd-Catalyzed Heck/C−H Activation/Intramolecular Arylation Domino Process[a]

Entry	Substrate	Product	Yield(%)
1	 **5**	 **6**	56
2	 **7**	 **8**	85
3	 **9**	 **10**	88

[a] Concentration 0.04 M in DMF, 0.05 equiv of $Pd(OAc)_2$, 1.0 equiv of substrate, 1.0 equiv of Na_2CO_3, and 1.0 equiv of TBAC, 60 °C. Isolated yields.

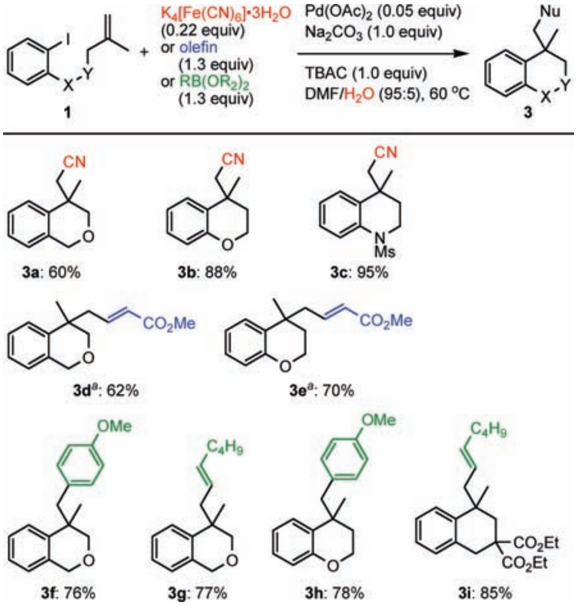


Figure 2. Scope of the Pd-catalyzed domino reaction involving intramolecular C−H activation process (migration "off"). [a]DMF/H_2O (80/20).

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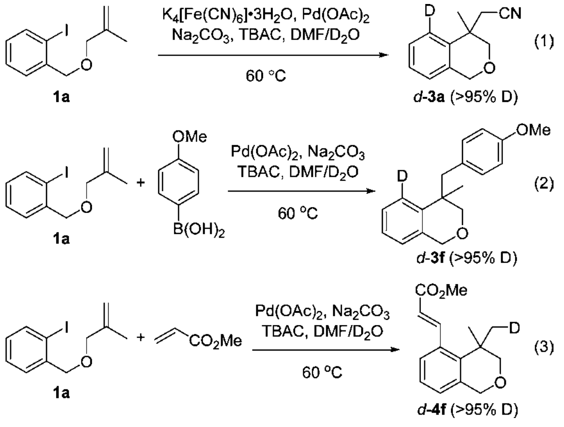
(13) A related domino reaction with a boronic acid was reported by Buchwald et al.; see ref 10i.

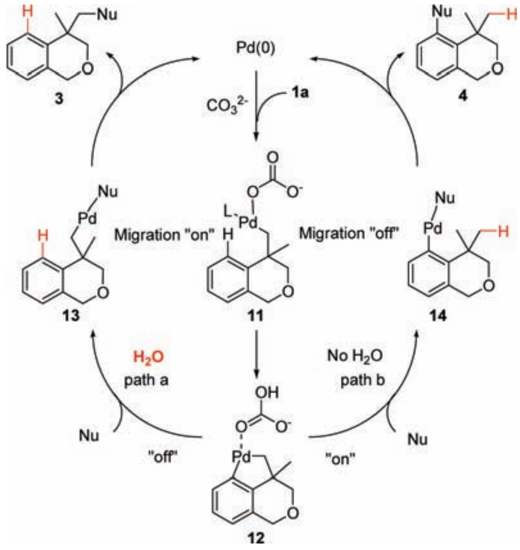
To study the mechanism in detail, we carried out the reaction of **1a** and K$_4$[Fe(CN)$_6$]·3H$_2$O using DMF/D$_2$O (95/5) as solvent (Scheme 2, eq 1), the condition which gives the alkyl-functionalized product **3a** (Table 1, entry 7). Proton NMR spectroscopic analysis of the product showed that incorporation of the deuterium occurs only in the aryl position, and no deuterium incorporation in the methylene or methyl position was observed. A similar result was obtained by the reaction of **1a** and 4-methoxyphenylboronic acid in DMF/D$_2$O (95/5) (Scheme 2, eq 2). To understand this process better, the reaction shown in eq 3 (Scheme 2) was conducted in the presence of 20 equiv of D$_2$O.[14] The isolated product **4f** contained >95% deuterium in one of the methyl groups (see the Supporting Information). These results provide strong evidence that the five-membered palladacycle was formed via intramolecular C−H activation under both palladium migration "on" and "off" reaction conditions before being trapped. The two types of products, **3a** and **4a**, were formed by direct regioselective cleavage of the carbon−palladium bond of the resulting palladacycle by cyanation, Heck, or Suzuki reactions or direct arylation.[7c] These results also indicate the palladium migration occurs inreversibly between the aryl and alkyl positions in the present cases since incorporation of the deuterium occurs only in either the aryl or alkyl position.[10h]

Scheme 2. Deuterium-Labeling Experiments



On the basis of these preliminary results, the mechanism of these transformations was hypothesized as shown in Scheme 3. The Pd(0) catalyst undergoes oxidative addition to the aryl iodide **1** to generate an organopalladium(II) intermediate, which undergoes 6-*exo-trig* cyclization to afford the σ-alkylpalladium complex **11**. The resulting intermediate **11** can insert into the neighboring C−H bond to form a palladium(II) intermediate or a palladium(IV) intermediate **12**. Palladacycle **12** could be regioselectively protonated and transmetalated to afford the Pd^{II} species **13a** or **14a**, which then would give either **3a** or **4a** upon reductive elimination.[15] Alternatively, palladacycle **12** could be also regioselectively trapped by cyanation, Heck, Suzuki reactions, or direct arylation by varying reaction conditions to provide either **3a** or **4a**.

Scheme 3. Proposed Mechanism for the Transformations



In conclusion, we have reported an efficient palladium-catalyzed domino reaction involving a C−H activation process. The palladacycle intermediate was successfully trapped by cyanation, Heck reaction, secondary C−H activation and Suzuki coupling. The regioselectivity was controlled by manipulating the reaction conditions to give either an aryl-functionalized product with yields in the 47−95% range or alkyl-functionalized product with yields in the 60−95% range. Moreover, our conditions avoided using expensive bases, which are usually employed in C−H activation, and phosphorus ligands, which are usually not friendly to the environment. Diverse products can be prepared starting from the same substrate by using this method.

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

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[14] Reaction of **1a** with methyl acrylate using DMF as solvent in the presence of 20 equiv of D$_2$O gave the sole 1,4-palladium migration product.

[15] This mechanism was proposed by one of the reviewers; we are grateful for this suggestion.