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Palladium-Catalyzed Direct Functionalization of Imidazolinone: Synthesis of Dibromophakellstatin

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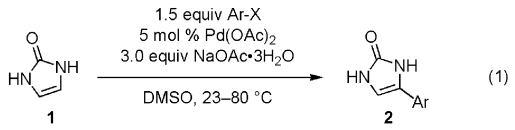
The popularity of transition metal-catalyzed C−H activation chemistry has grown rapidly in the recent years.[1] Both direct[2] and functional group-directed[3] C−H insertion reactions have been developed to form a C−X or a C−C bond using transition-metal catalysts. This reaction is particularly useful in heterocycle derivatization and several protocols have been reported.[4] Despite its potentials, the application to natural product synthesis is rare.[5] The limitation is partly due to the relatively harsh reaction conditions and limited functional group compatibility. We describe herein a C−H functionalization reaction of imidazolinone (**1**) under mild conditions (eq 1). We also demonstrate its synthetic utility with dibromophakellstatin synthesis.[6,7]



Our study started with the coupling of **1** and iodobenzene. We systematically studied the effects of palladium source, ligand, additive, and solvent.[8] The reaction proceeds most efficiently with 5 mol % $Pd(OAc)_2$ and 3 equiv $NaOAc{\cdot}3H_2O$ in DMSO at 80 °C (Table 1, entry 1). A small amount of water (<5% v/v) can be tolerated. The reaction can also be carried out with 2 mol % $Pd(OAc)_2$ (entry 2), 20 mol % Pd/C (entry 3), or at room temperature (entry 4).

The scope of this palladium-catalyzed imidazolinone *C*-arylation reaction is shown in Table 1. Substitution at the 2-position of aryl iodide does not affect the reaction (entry 5). Both electron-deficient (entry 6−8) and electron-rich (entry 9−13) aryl iodides can be used. However, electron-deficient aryl iodides are less reactive. Extending the reaction time leads to a small amount of bisarylation product. Notably, hydroxyl and phenol groups are tolerated (entry 11−13). Aryl bromides are also less reactive; however, good results can be obtained with electronic-deficient aryl bromides (entry 14−16).[8] Finally, the direct vinylation of **1** can also be achieved (entry 17).

We have carried out a series of mechanistic studies and found the C−H insertion pathway most consistent with the experimental data. If the reaction proceeds through the Heck-type mechanism, the migratory insertion intermediate **3** would bear no *syn*-β-H for the subsequent β-hydride elimination (Scheme 1).

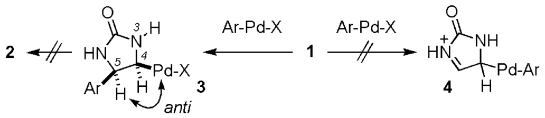
Although a β-H is present at the N-3 position in **3**, the reaction does not proceed through N−H β-hydride elimination, as **5** also reacts (Scheme 2). We next carried out the linear free-energy relationship (LFER) analysis to test if the reaction proceeds through the *anti*-β-H elimination pathway.[9] The *anti*-β-H elimination is believed to be promoted by base via an E2 or $E1_{cb}$ mechanism and a non-negative ρ value is expected with **3**. However, we have obtained a strongly negative ρ value ($\rho = -1.1$) in the LFER analysis.[8]

Table 1. Scope of the Direct Arylation of Imidazolinone[a]

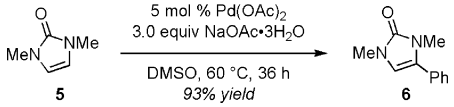
entry	Ar	X	catalyst loading	time	yield
1	Ph	I	5 mol %	6 h	78%
2	Ph	I	2 mol %	30 h	71%
3	Ph	I	20 mol % Pd/C	16 h	63%
4	Ph	I	10 mol % at 23 °C	5 d	68%
5	2-Me−Ph	I	5 mol %	6 h	75%
6	4-F−Ph	I	5 mol %	12 h	62%
7	4-Cl−Ph	I	5 mol %	12 h	61%
8	4-Br−Ph	I	5 mol %	12 h	52%
9	3-MeO−Ph	I	5 mol %	6 h	77%
10	4-MeO−Ph	I	5 mol %	6 h	85%
11	2-$HOCH_2$-Ph	I	5 mol %	6 h	62%
12	3-$HOCH_2$-Ph	I	5 mol %	6 h	87%
13	4-HO−Ph	I	5 mol %	6 h	85%
14	2-NO_2-Ph	Br	10 mol %	24 h	68%
15	3-MeCO−Ph	Br	10 mol %	36 h	62%
16	4-CF_3-Ph	Br	10 mol %	36 h	64%
17	Ph−CH=CHBr		10 mol %	36 h	68%

[a] Conditions: 1.5 equiv Ar−X, catalyst $Pd(OAc)_2$, 3.0 equiv $NaOAc{\cdot}3H_2O$, degassed DMSO, 80 °C.

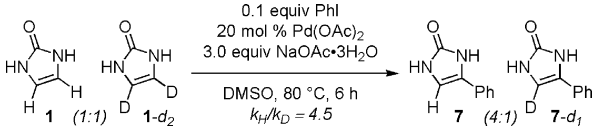
Scheme 1



Scheme 2



Scheme 3



We then considered the possibility of Pd(0)-mediated S_N2-inversion[10] of the C-4 stereogenic center in **3** followed by *syn*-β-hydride elimination to give **2**. While a secondary kinetic isotope effect (KIE) is expected for this sterically encumbered S_N2-inversion, we have observed a primary KIE ($k_H/k_D = 4.5$) in the competing experiment of **1** with 4,5-dideuterated **1** (94% D) (Scheme 3).

The Busacca−Farina mechanism, which involves an α-H elimination of **3** followed by a 1,2-H shift,[11] would be consistent with the experimental primary KIE; however, we did not observe significant amounts of H/D shift with 4-deuterated **8** (91% D) (Scheme 4).[12] The absence of crossover products further suggests

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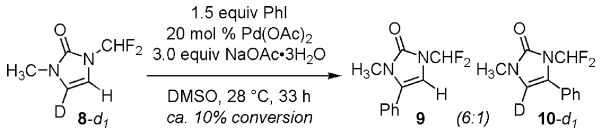
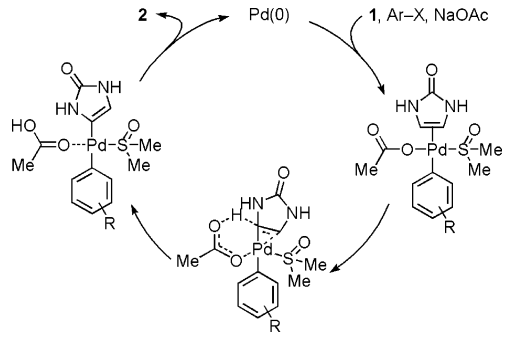
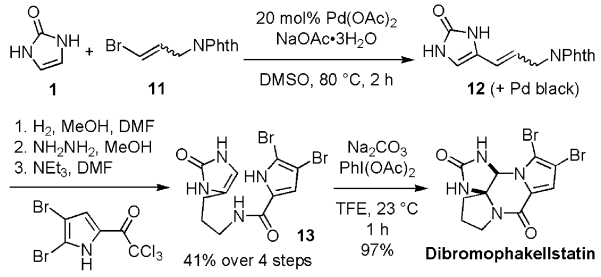
Scheme 4



Scheme 5



Scheme 6



that H-5 in **3** does not undergo a Wacker-type depalladative 1,2-H shift (C5 → C4)[13] to give **2** after losing a proton.

We have also ruled out the possibility of electrophilic palladation mechanism.[14] A secondary,[4f] instead of the observed primary KIE (Scheme 3) with **1** is expected for the electrophilic pathway. The regioselectivity of **8** (Scheme 4) is also opposite to that of the electrophilic reactions. Only the C−H insertion mechanism (Scheme 5) is consistent with all the experimental data. Our DFT calculations (B3LYP/LACVP**++)[15] support the acetate ligand-assisted C−H insertion pathway.

The synthetic utility of this catalytic C−H activation reaction is illustrated with the synthesis of dibromophakellstatin (Scheme 6). The direct coupling of **1** and vinyl bromide **11** proceeded smoothly. Imidazolinone **12**, together with the resultant palladium black, was subjected to hydrogenation, phthalimide deprotection, and acyl pyrrole installation to give **13**.[8] While the bromine oxidants were reported to promote the biomimetic oxidative cyclization[7a,f] of **13** with only modest efficiency, we have found that oxidation of **13** with $PhI(OAc)_2$ gave dibromophakellstatin in nearly quantitative yield.

In summary, we have developed a palladium catalyst system that allows the direct arylation and vinylation of imidazolinone under mild conditions. This method is proved useful in natural product synthesis. Dibromophakellstatin was synthesized with significantly improved efficiency (40% overall yield).

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

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