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Site-Selective Intermolecular Oxidative C-3 Alkenylation of 7-Azaindoles at Room Temperature

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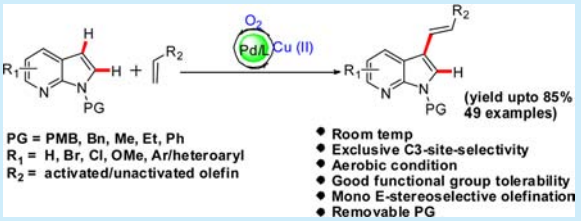
Supporting Information

ABSTRACT: A previously unexplored palladium-catalyzed C-3 selective alkenylation of 7-azaindoles, performed in the presence of $Pd(OAc)_2$ as the catalyst, PPh_3 as the ligand, $Cu(OTf)_2$ as an oxidative cocatalyst, and molecular oxygen (O_2) as the terminal oxidant at room temperature, has been reported. This direct alkenylation strategy offers a new approach in functionalizing pharmaceutically important 7-azaindoles.



Transition-metal-catalyzed direct C−H alkenylations of unfunctionalized arenes with simple alkenes, pioneered by Fujiwara−Moritani in 1967, have emerged as powerful variants of Heck reactions, featuring higher atom economy and efficiency.[1] However, a fundamental challenge intrinsic to these oxidative couplings lies with achieving high selectivity. Nevertheless, regioselective alkenylations have successfully been achieved largely on arenes,[2] electron-rich indoles,[3] and other heteroarenes.[4] Given the unique chemical reactivity and structural properties of 7-azaindoles that are structurally related to indoles/purines, regioselective arylations have been used as reaction tools to engender functionalized 7-azaindoles relevant to pharmaceutical interest.[5,6] Toward this endeavor, a significant effort has been directed to identify drug-like compounds by designing molecules that incorporate 7-azaindoles containing an alkenyl group. Therapeutically promising kinase inhibitors are illustrative examples of 7-azaindoles containing a C-3 alkenyl group (Figure 1).[7]

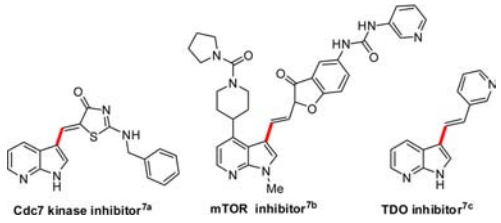
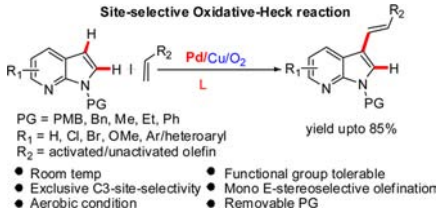


Figure 1. C3-Olefinated 7-azaindoles as anticancer agents.

While site-selective alkenylation of indoles and pyrroles merits extensive discussion,[3] alkenylations of 7-azaindoles have only been reported by classic intramolecular Heck reaction at the C-3 position to introduce desired molecular complexity into the target molecule in poor yield.[8] However, direct intermolecular C-3 regioselective alkenylation on 7-azaindoles, to the best of our knowledge, is unprecedented despite the potential in drug discovery.

During the late-stage preparation of this manuscript, a report on tandem synthesis of carbazoles has appeared that involves a sequential C-3 alkenylation/C-2 alkenylation/thermal electrocyclization. Only two examples of the preparation of α-carbolines from 7-azaindoles have been supplemented in this report.[9] Recently, we have demonstrated regioselective C-2 arylation of 7-azaindoles.[10] Based on our previous experiences and ongoing interest in functionalizing 7-azaindoles,[11] we embarked on an ambitious objective of achieving regioselective C-3 alkenylation on 7-azaindoles with alkenes as the other coupling partners. Herein, we describe, distinct from the previous report, C-3 selective alkenylations of 7-azaindoles with various activated/unactivated alkenes, affording C-3 alkenylated 7-azaindoles at room temperature in good to excellent yields (Scheme 1).

Scheme 1. Schematic Representation of Site-Selective C−H Bond Functionalization of 7-Azaindole



While *N*-methyl azaindole is largely used as a successful coupling partner in the C-2-arylation,[12] we considered using 7-azaindoles with a *N*-protecting group that could be easily installed and subsequently removed after the desired operation. In our initial study, (*N*-Bn)-7-azaindole was considered as a coupling partner. However, we observed the formation of a mixture of C2:C3 (1:2) products with a combined 30% yield in the presence of $Pd(OAc)_2$ (10 mol %) as a catalyst, AcOH as an

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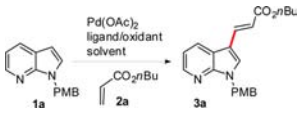
additive, and 1,4-dioxane as a solvent when O_2 was used as the terminal oxidant at 60 °C.[13] When we changed the protecting group from benzyl to the more electron-rich *p*-methoxy benzyl (PMB) group, we observed improvement in the selectivity (C2:C3 = 1:3) as well as in the isolated yield (55%). Thus, in our optimization study for an oxidative Heck-type coupling reaction, *p*-methoxy benzyl (*N*-PMB)-7-azaindole (**1a**) and *n*-butyl acrylate (**2a**) were chosen as model substrates. To achieve optimized conditions for the coupling, various ligand/oxidant combinations were explored, such as 1,10-Phen, bipy and Ag_2O, AgOAc, $AgNO_3$, Ag_2CO_3 under N_2 at 80 °C for 12 h (Table 1, entries 1−5). Reaction conditions including $Pd(OAc)_2$ (10 mol %), 1,10-Phen (20 mol %), and $AgNO_3$ (2.0 equiv) in DMSO under N_2 at 80 °C became beneficial, giving exclusively C3-alkenylated product in 55% isolated yield (Table 1, entry 3). Next we screened PPh_3, with different oxidants (1.0 equiv) [such as $Cu(OAc)_2$, $Cu(OAc)_2{\cdot}H_2O$, $Cu(OTf)_2$] in DMSO under air at 50 °C for 12 h (Table 1, entries 6−8), and the C3-alkenylated product was isolated in good yields (58−70%). Interestingly, a substoichiometric amount of oxidant $Cu(OTf)_2$ (50 mol %) under O_2 (balloon) at room temperature afforded the alkenylated product with improved yield (75%) in 6 h (Table 1, entry 9). Finally, we found the combination of $Pd(OAc)_2$ (10 mol %), $Cu(OTf)_2$ (50 mol %), PPh_3 (20 mol %), and O_2 (balloon) at room temperature in DMSO/1,4-dioxane (3:1) afforded the best yield of 80% in 6 h (Table 1, entry 10). Use of PPh_3 in combination with other oxidants [such as O_2, BQ, $PhI(OAc)_2$, $K_2S_2O_8$] in DMSO/1,4-dioxane at rt did not provide any improvement in the yield (Table 1, entries 11−14). Use of any other phosphine ligand [$(o\text{-Tol})_3P$] in the presence of oxidant $Cu(OTf)_2$ (50 mol %) in DMSO/1,4-dioxane (3:1) under O_2 at rt was less effective (Table 1, entry 15). *This reaction is completely selective for C3-alkenylation. In no case was any C2-alkenylated product detected.* This demonstrated that the regioselectivity of Pd-catalyzed 7-azaindole alkenylation could be controlled with the help of the ligand in combination with the proper solvent system. We investigated the scope of *N*-substitution on the azaindole moiety, using the optimized conditions and it was observed that only *N*-alkyl (*N*-Me, *N*-Et, *N*-PMB) substituted azaindoles proved to be suitable substrates. The *N*-Bn-7-azaindole furnished the corresponding C-3 alkenylated products in moderate yield (40%), while the *N*-Ar derivative afforded a poor yield (30%). The other derivatives such as *N*-Boc, *N*-Ts, and *N*-Ac 7-azaindoles remained inert under these cross-coupling conditions (Supporting Information Table S1). Addtional results of the reaction condtions (by varying the Pd-source, catalyst loading, and "oxygen activator" catechol) can be found in the Supporting Information (for details, see Tables S2 and S3).

With the optimized conditions in hand, the scope of this reaction was explored using various PMB-protected 7-azaindoles and different alkenes as the two coupling partners (Scheme 2). The reactivities of an array of acrylates were first examined. All the acrylates used in this reaction gave the corresponding *E*-products (**3a−d**) in excellent yields (70−80%). Besides acrylates, alkenes such as vinyl phosphonates, sulfonates, and acrylonitrile (**3e−g**) have been utilized as coupling partners to furnish the coupled product in moderate yields (40−55%). A series of differently substituted 7-azaindoles were subjected to alkenylation with different acrylates. Interestingly, halo substituted 7-azaindoles are also compatible with this catalytic system, affording the desired products (**3h−n**) in moderate to excellent yields (50−85%), amenable for molecular complexity. Azaindole aryl substituted at the C5-position coupled smoothly with methyl/butyl acrylates to furnish the desired *E*-alkenylated products (**3o−r**) in good yields (70−71%). A somewhat reduced yield (60%) was observed in the case of heteroaryl substituted azaindoles (**3s**). Notably, 7-azaindoles diversely substituted at both the C3- and C5-position are found in many pharmaceutically designed compounds.[14,6c] *N*-Bn and *N*-Ar 7-azindole

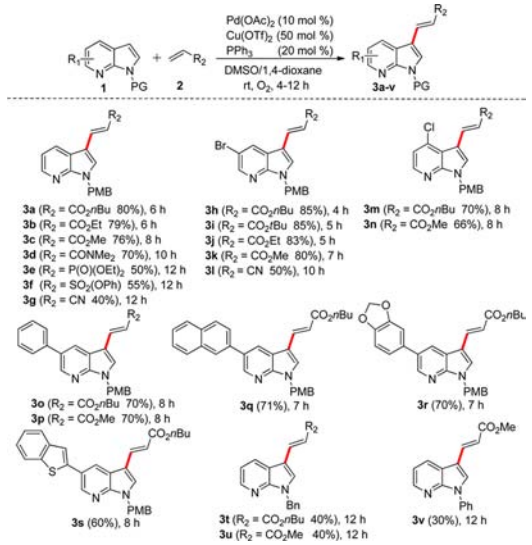
Table 1. Optimization of Reaction Conditions[a]



entry	ligand	oxidant	solvent	yield[b](%)
1[c]	1,10-Phen	Ag_2O	DMF	20
2[c]	1,10-Phen	AgOAc	DMSO	50
3[c]	1,10-Phen	$AgNO_3$	DMSO	55
4[c]	1,10-Phen	Ag_2CO_3	DMSO	40
5[c]	bipy	$AgNO_3$	DMSO	20
6[d]	PPh_3	$Cu(OAc)_2$	DMSO	65
7[d]	PPh_3	$Cu(OAc)_2{\cdot}H_2O$	DMSO	58
8[d]	PPh_3	$Cu(OTf)_2$	DMSO	70
9[e]	PPh_3	$Cu(OTf)_2$	DMSO	75
10[e]	**PPh_3**	**$Cu(OTf)_2$**	**DMSO/1,4-dioxane**	**80[10][f]**
11	PPh_3	O_2	DMSO/1,4-dioxane	10
12	PPh_3	BQ	DMSO/1,4-dioxane	20
13	PPh_3	$PhI(OAc)_2$	DMSO/1,4-dioxane	10
14	PPh_3	$K_2S_2O_8$	DMSO/1,4-dioxane	10
15[e]	$(o\text{-Tol})_3P$	$Cu(OTf)_2$	DMSO/1,4-dioxane	5

[a]Reaction conditions: **1a** (1.0 equiv), **2a** (2.0 equiv), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), oxidant, solvent (1 mL). [b]Isolated yield. [c]Oxidant (2.0 equiv) under N_2 at 80 °C. [d]Oxidant (1.0 equiv) under air at 50 °C. [e]$Cu(OTf)_2$ (50 mol %), O_2 (balloon) at rt. [f]Recovered starting material in brackets.

Scheme 2. Substrate Scope of C3-Alkenylation of *N*-PMB 7-Azaindoles[a]



[a]Reaction conditions: *N*-PMB-7-azaindole (1.0 equiv), alkene (2.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), $Cu(OTf)_2$ (50 mol %), O_2 (balloon), DMSO/1,4-dioxane (3:1, 1 mL), and rt.

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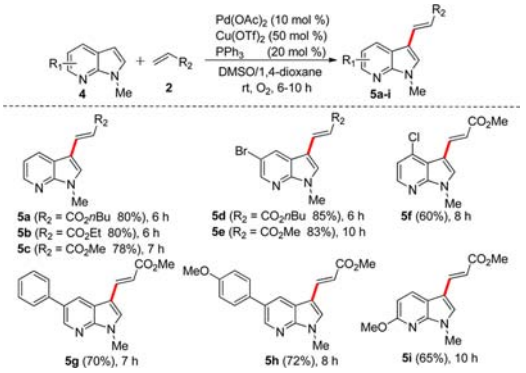
derivatives were also investigated. In the case of the *N*-Bn derivative the yield is 40% (**3t−u**), whereas the *N*-Ar derivative (**3v**) gave only a 30% yield. In the presence of C3-substitution (CHO, OAc, Ph), no alkenylation occurred at the C2-position.

Next, we focused on exploring the scope of different acrylates with *N*-methyl 7-azaindoles (Scheme 3). As expected, the

Scheme 3. Substrate Scope of C3-Alkenylation of *N*-Methyl 7-Azaindole[a]

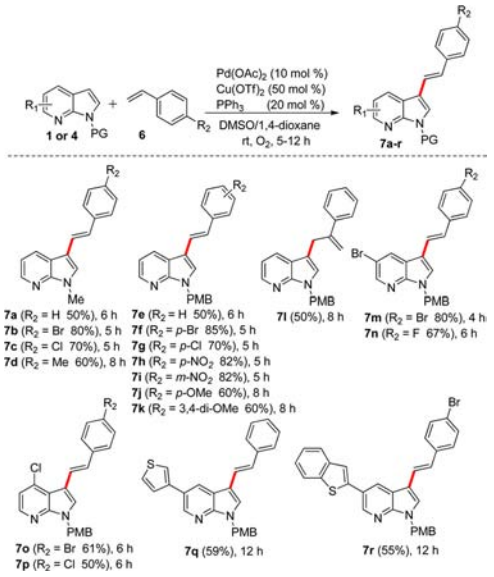


[a]Reaction conditions: *N*-methyl-7-azaindole (1.0 equiv), alkene (2.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), $Cu(OTf)_2$ (50 mol %), O_2 (balloon), DMSO/1,4-dioxane (3:1, 1 mL), and rt.

acrylates and acrylonitrile undergo smooth conversion to give the *E*-alkenylated products (**5a−i**). To make this coupling more general, we utilized differently substituted azaindoles (5-Br, 4-Cl, 5-Ar, 6-OMe), and the alkeynyaltion occurred exclusively at the C3-position. 5-Bromo and 4-chloro-7-azaindoles gave the olefinated products (**5d−f**) in good yields (60−85%). Two more 5-aryl substituted *N*-methyl substituted azaindoles have also been tested with methyl acrylate, and the products (**5g−h**) obtained in these reactions have been isolated in good yields (70−72%). The 6-OMe substituted 7-azaindole was smoothly converted into an alkenylated product (**5i**) in 65% yield. The nonactivated alkene allyl acetate, however, failed to give the coupled product.

Oxidative Heck-type reactions have been reported using styrenes, but with low yields or with a poor substrate scope.[15] To the best of our knowledge it has never been exercised with azaindole systems. Therefore, the C3-alkenylation was further investigated with various styrenes (**6**) bearing electron-withdrawing or -donating groups on the phenyl ring to afford the Heck-type product in moderate to good yields as illustrated in Scheme 4. When subjected for oxidative coupling with *N*-methyl-7-azaindole, the electron-neutral styrene gave the desired product (**7a**) in 50% yield. Styrenes containing halo substituents (*p*-Cl, *p*-Br) afforded the alkenylated product (**7b−c**) in excellent yields (70−80%). A styrene with an electron-donating group (*p*-Me) produced the coupled product (**7d**) in 60% yield. The *N*-PMB-protected 7-azaindoles also work well under the optimized conditions, as the desired products (**7e−k**) were isolated in moderate to excellent yields (50−85%); here the electron-deficient styrenes afforded higher yields (**7h−i**) than electron-rich styrenes (**7j−k**). It is worth mentioning that the *α*-substituted styrene provides the olefinated product (**7l**) through Pd−H insertion and immediately *β*-hydride elimination in moderate yield (50%).[16] In this context, 5-bromo and 4-chloro substituted 7-azaindoles also have been studied with different styrenes bearing halogen substitution (F, Cl, Br) in the aryl ring

Scheme 4. Substrate Scope with Styrenes[a]

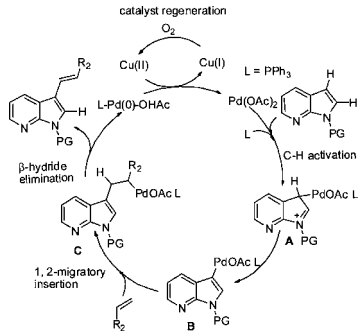


[a]Reaction conditions: *N*-methyl-7-azaindole (1.0 equiv), alkene (2.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), $Cu(OTf)_2$ (50 mol %), O_2 (balloon), DMSO/1,4-dioxane (3:1, 1 mL), and rt.

to afford exclusively the *E*-alkenylated products (**7m−p**) in good yields (50−80%). The 7-azaindole system bearing heteroaryl substitutions at the C5-position underwent smooth C3-alkenylation (**7q−r**) in moderate yields (55−59%).

To understand the reaction better, we propose a plausible mechanism (Scheme 5).[3] Electophilic palladation of 7-azaindole

Scheme 5. Plausible Reaction Mechanism



at the C3 position with a Pd(II) species is favorable due to the greater nucleophilicity of the C3 position, thereby generating palladated intermediate **B**. Then this undergoes alkene insertion to afford intermediate **C**. This is followed by *β*-hydride elimination to deliver the C3-alkenylated product. Pd(0) generated from the reductive elimination is then oxidized by Cu(II) to form the active Pd(II) catalyst, thus completing the catalytic cycle.

Finally, the *N*-PMB group of **3a** was deprotected by using boron trichloride[17] at rt to generate the free NH 7-azaindole (**8**), which led us to realize the synthetic utility of this method (Scheme 6).

In summary, we have demonstrated a Pd-catalyzed C3-selective alkenylation of 7-azaindole derivatives at rt. An easily removed protecting group (PMB) and mild reaction conditions offer significant flexibility in derivatizing these medicinally

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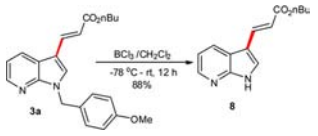
Scheme 6. Removal of the PMB Group



important heterocycles with an unexplored and/or a challenging substitution pattern. In view of the growing understanding in oxidative Heck-type coupling, the reaction described herein has a reactivity profile that is significantly different than those previously reported. Detailed mechanistic investigations and application in synthesizing designed internal alkene-substituted medicinally important compounds are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03429.

Complete experimental details and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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