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Ligand Enabled Palladium-Catalysed Through-Space C-H Bond Activation *via* a Carbopalladation/1,4-Pd Migration/C-H Functionalization Sequence

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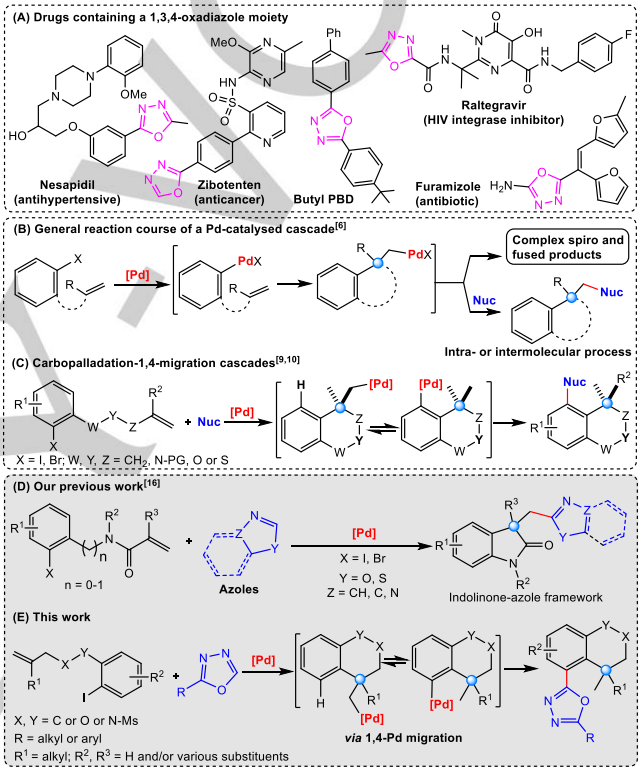
Abstract: We report, herein, a palladium-catalysed cascade comprising carbopalladation, 1,4-Pd-migration and C(sp^2)-C(sp^2) bond formation to construct a variety of bis-heterocyclic frameworks in a single operational step. The methodology provides a direct approach to introduce an oxadiazole core at a remote location without any functional group obligation, with moderate to good yields.

Palladium-catalysed cross coupling has remained in the forefront of organometallic chemistry to form C-C, C-O and C-N bonds and is characterized by versatility, extensive scope, and high tolerance to many functional groups.[1,2] Among this class of reactions, the Heck-Mizoroki reaction[3a] has been particularly well studied for forming carbo- and heterocyclic scaffolds such as indoles, benzofurans, and oxindoles.[3b] The *σ*–alkyl palladium intermediates lacking a *syn*-*β*-hydrogen, generated after an intramolecular insertion reaction (scheme 1B), are often termed as living species and have been extensively explored in domino processes with a variety of nucleophiles[4] following the early work by Grigg *et al*.[5] The whole concept revolves around designing substrates where *β*-hydride elimination is blocked to promote the development of both intra- as well as intermolecular cascades to form complex molecular architectures especially involving C-H activation as key step (scheme 1B).[6]

Recent advances in C-H functionalization of (hetero)arenes *via* transition-metal catalysis have transformed the way organic chemists execute the synthesis of complex structures[7] as it circumvents the need for pre-functionalization of the starting materials. One such interesting approach is the incorporation of palladium-migration to its neighbouring position *via* activating a C(sp^2)-H or C(sp^3)-H bond and followed by functionalization with another C-H bond, thus mimicking a dehydrogenative coupling pathway at a remote location.[8] Larock and co-workers[9] pioneered the study on palladium catalyzed through-space C(sp^2)-H bond activation by 1,4-alkyl to aryl palladium migration.



Scheme 1: Background on σ–alkyl palladium intermediates and the oxadiazole framework.

Such 1,4-palladium migration after a usual carbopalladation step, is able to trigger a domino reaction from a simple starting material, allowing the rapid generation of molecular diversity and complexity in a minimum number of steps (Scheme 1C).[10]

The (hetero)aryl or alkyl 1,3,4-oxadiazole skeleton is a key structural unit in various biologically active compounds and finds profound applications in medicinal chemistry as well as in material sciences.[11] In addition, oxadiazoles are known as bioisosteres of amides and esters with superior hydrolytic and metabolic stability, improved pharmacokinetics as well as *in vivo* performance.[12] Raltegravir,[13] is an antiretroviral drug for the treatment of HIV infection containing the 1,3,4-oxadiazole moiety (Figure 1A).[14] Some other significant molecules possessing the 1,3,4-oxadiazole core include butyl PBD or ß-PBD (2-(4-*tert*-butylphenyl)-5-(4-biphenyl)-1,3,4-oxadiazole) which is used in the liquid scintillator neutrino detector (LSND).[15]

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In continuation of our previous work on C-H bond functionalization of (hetero)arenes (Scheme 1D),[16] we wondered if such transient alkylpalladium(II) species could activate the C(sp^2)-H bond of the neighbouring benzene ring *via* 1,4-Pd-migration. This could be followed by trapping the nascent Pd-intermediate *via* another intermolecular C-H functionalization step with an oxadiazole. Herein we report a Pd-catalysed cascade comprising of carbopalladation, 1,4-Pd-migration, C(sp^2)-C(sp^2) bond formation to construct bis-heterocyclic frameworks in a single operational step.

Table 1: Optimization of the reaction conditions.[a]

1a 2a 3a 3a'

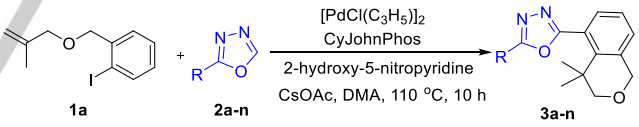
Entry	Catalyst	Base	Ligand	Yield 3a:3a' (%)
1	$Pd(OAc)_2$	CsOPiv	CyJohnPhos	37:24
2[b]	$Pd(OAc)_2$	CsOPiv	JohnPhos	30:35
3[b]	$Pd(OAc)_2$	CsOPiv	MePhos	20:35
4[b]	$Pd(OAc)_2$	CsOPiv	XPhos	15:35
5[b]	$Pd(OAc)_2$	CsOPiv	dppb	30:40
6[b]	$Pd(OAc)_2$	CsOPiv	DPEPhos	20:25
7	$Pd(OAc)_2$	CsOAc	CyJohnPhos	49:34
8[c]	$Pd(OAc)_2$	CsOAc	CyJohnPhos	58:30
9[c]	$Pd_2(dba)_3$	CsOAc	CyJohnPhos	40:17
10[c]	$[PdCl(C_3H_5)]_2$	CsOAc	CyJohnPhos	60:25
11[c]	$Pd(OAc)_2(PPh_3)_2$	CsOAc	CyJohnPhos	45:20
12[c,d]	$[PdCl(C_3H_5)]_2$	CsOAc	CyJohnPhos	62:13
13[c,d,e]	**$[PdCl(C_3H_5)]_2$**	**CsOAc**	**CyJohnPhos**	**72:11**
14[c,d,f]	$[PdCl(C_3H_5)]_2$	CsOAc	CyJohnPhos	60:17

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), and catalyst (10 mol %), ligand (20 mol %), base (2 equiv), Ac-Leu-OH additive (30 mol %) in DMA (1.5 mL) under N_2 for 10h at 110°C, isolated yield. [b]Determined by 1H NMR using 2,4,6-trimethoxybenzaldehyde as an internal standard. [c]2 equiv of **1a**. [d]30 mol % CyJohnPhos. [e]30 mol % 2-hydroxy-5-nitropyridine additive, [f]30 mol % 5-(trifluoromethyl)-2-pyridinol additive.

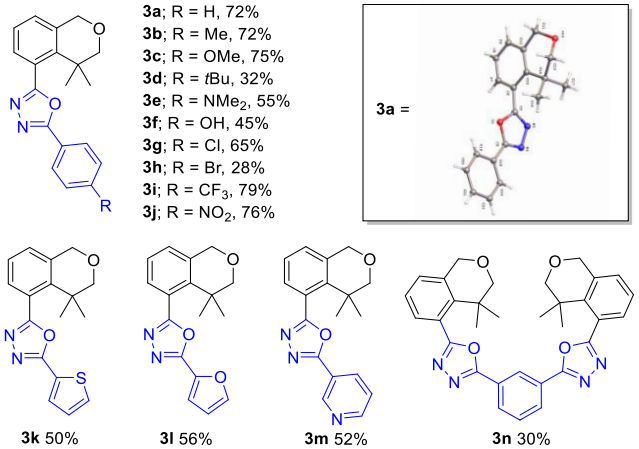
This reaction was first tested by applying 1-iodo-2-(((2-methylallyl)oxy)methyl)benzene (**1a**) and 2-phenyl-1,3,4-oxadiazole (**2a**) as model substrates (Table 1). Earlier attempts on the concept of 1,4-Pd-migration and trapping *via* thiophene forged the ground work for these initial optimization studies[17] but mostly resulted in 1:1 mixtures or reaction decomposition (for details, See table S1, SI). Attempts were performed in the presence of $Pd(OAc)_2$ (10 mol %), Ac-Leu-OH (30 mol %) and CsOPiv (2 equiv) as base in DMA at 110 °C affording 2-(4,4-dimethylisochroman-5-yl)-5-phenyl-1,3,4-oxadiazole (**3a**) further confirmed by X-ray crystal structure analysis (see the Supporting Information) in 37% yield (Table 1, entry 1), along with direct coupling (no 1,4-Pd shift) product 2-((4-methylisochroman-4-yl)methyl)-5-phenyl-1,3,4-oxadiazole (**3a'**) in 24% yield. Thereafter, several Pd-ligands were screened (Table 1, entries 2-6), but the reaction did not work well under these conditions. Among the choice of bases, different inorganic bases were screened (see entry 7 and Supporting Information, Scheme 3). CsOAc proved to be superior to CsOPiv with less side product (**3a'**) formation. Moreover, when the amount of **1a** was increased to 2 equiv (entry 8), the desired product **3a** was obtained in 58% yield. Screening of other palladium-catalysts, such as $Pd_2(dba)_3$, $[PdCl(C_3H_5)]_2$ and $Pd(OAc)_2(PPh_3)_2$ revealed that $[PdCl(C_3H_5)]_2$ was the best choice (entries 9-11). Slightly higher yields were obtained by increasing the amount of ligand JohnPhos to 30 mol% (entry 12). Inspired by the work of Yu's lab on C(sp^2)-H activation,[18] we decided to investigate the effect of 2-pyridone-based ligands on the desired C-H activation at remote location. Thus, when 30 mol% 2-hydroxy-5-nitropyridine was employed instead of 30 mol% Ac-Leu-OH, the desired product **3a** was obtained in 72% yield (entry 13). Other pyridone-based ligands displayed decreased activity (entry 14 and supporting information). We finally established the optimized conditions as **1a** (0.4 mmol), **2a** (0.2 mmol), $[PdCl(C_3H_5)]_2$ (10 mol%), CyJohnPhos (30 mol%), 2-hydroxy-5-nitropyridine (30 mol%) and CsOAc (2 equiv) in DMA at 110°C for 10h (entry 13).

With the optimized reaction conditions in hand, we then explored the substrate scope (table 2). First, various oxadiazoles were examined and most of the functional groups were well tolerated under the optimized conditions. With a methyl substituent on the phenyl ring of 2-phenyl-1,3,4-oxadiazole, the compound reacted efficiently to give the desired products **3b** in 72% yields. Electron donating functional groups (methoxy and *tert*-butyl) were also investigated whereby a methoxy group resulted in 75% yield (**3c**) contrary to only 32% yield with the bulkier *tert*-butyl group on the aromatic ring (**3d**). Potentially useful groups for further functionalization like an *N,N*-dimethyl amino and hydroxyl group on the phenyl ring were also examined, and the desired products **3e** and **3f** were obtained in moderate yields. In addition, a chloro-substituent resulted in a moderate yield of 65% for **3g**, while we observed a lower yield of 28% for **3h** bearing a bromine**,** due to the formation of some unidentified side products. Substrates bearing electron-withdrawing (CF_3 and NO_2) groups on the phenyl ring were also investigated and successfully converted into products **3i**−**3j** in good yields.

Table 2: Substrate scope for various oxadiazoles.[a]



1a 2a-n 3a-n



[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), $[PdCl(C_3H_5)]_2$ (10 mol %), CyJohnPhos (30 mol %), 2-hydroxy-5-nitropyridine (30 mol %) and CsOAc (2 equiv) in DMA (1.5 mL) under N_2 at 110°C for 10h.

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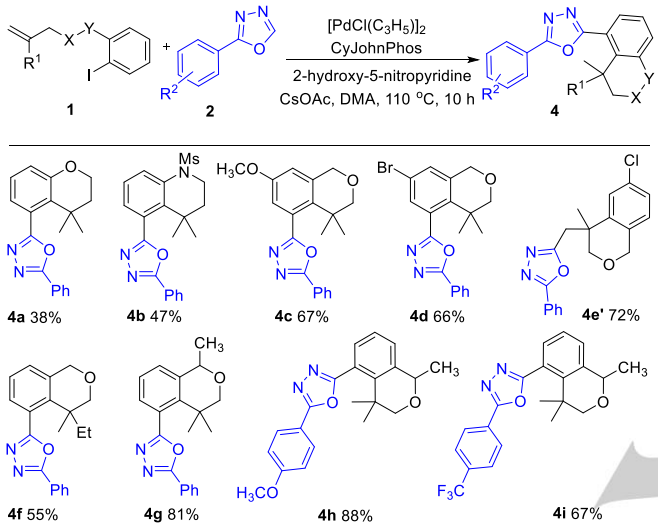
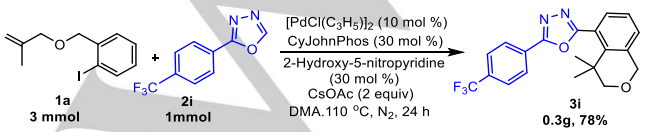
Interestingly, the replacement of the phenyl group in oxadiazole with more challenging heterocycles such as thiophene, furan or pyridine, delivered the expected products **3k**−**3m** in moderate yields. Moreover, the 1,3-di(1,3,4-oxadiazol-2-yl)benzene framework led to the desired product **3n** in satisfactory yield, providing the opportunity to generate complex scaffolds in minimal steps. Surprisingly, methyl oxadiazole did not result in the desired product.

Table 3: Substrate scope.[a]



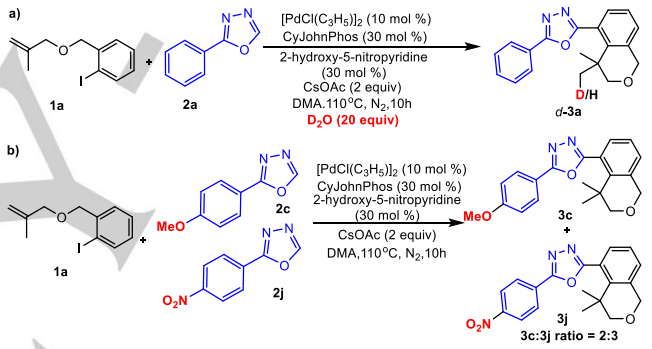
[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), $[PdCl(C_3H_5)]_2$ (10 mol %), CyJohnPhos (30 mol %), 2-hydroxy-5-nitropyridine (30 mol %) and CsOAc (2 equiv) in DMA (1.5 mL) under N_2 at 110°C for 10h.

Next, we turned our attention to explore various heterocyclic skeletons under standard conditions. First, 1-iodo-2-((3-methylbut-3-en-1-yl)oxy)benzene and N-(2-iodophenyl)- N-(3-methylbut-3-en-1-yl)methanesulfonamide were examined and provided the desired products **4a** and **4b** in 38% and 47% yield respectively. In addition, substrates with the phenyl group of the methallyl ether bearing a methoxy- or a bromo-substituent were also investigated. These compounds reacted efficiently to give the desired products **4c** and **4d** in 67% and 66% yield respectively. Unfortunately, the substrate bearing a chloro group at the meta-position of the aryl iodide did not afford the desired product, as solely the side product **4e'** (no 1,4-Pd-shift) was formed in 72% yield. This might be attributed to an increased steric hindrance for the C−H functionalization step. Additionally, substitution of the vinylic methyl group by a bulkier ethyl-group resulted in a slightly lower yield of **4f**. The flexibility of the reaction was further demonstrated by the synthesis of **4g**, **4h** and **4i** in 81%, 88% and 67% yield, respectively.

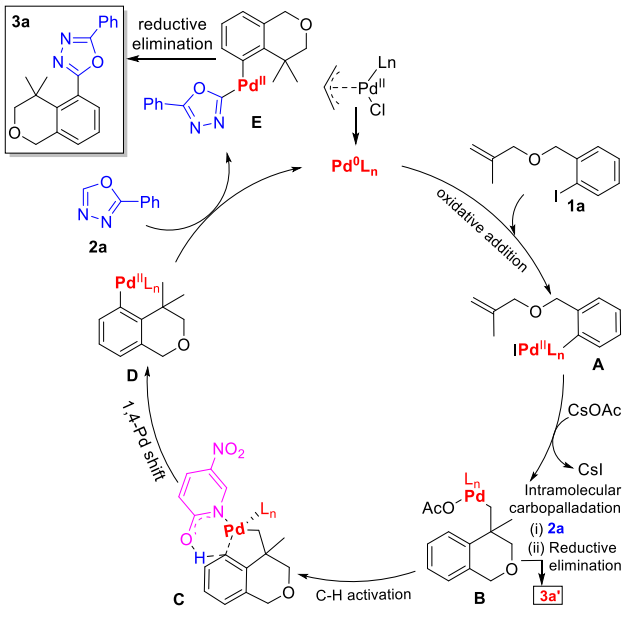


Scheme 2: Millimole scale synthesis of **3i**.

The practical applicability of the process for the synthesis of **3i** has been demonstrated by performing the reaction at 1 mmol scale, affording **3i** in 78% yield (Scheme 2). However, in order to fully consume the starting material **2i**, an additional equivalent of **1a** was added to the reaction after 12h. To gain more insight into the mechanism *via* deuterium-labelling studies, we employed 20 equiv of D_2O under our optimized conditions (Scheme 3a). Since the reaction undergoes Pd migration from the intermediate **B** to **C**, we expected deuteration at the terminal methyl group. To our delight, we observed 64% deuterium incorporation in *d*-**3a,** confirmed by ^{1}HNMR and ^{13}CNMR (see supporting information). This result is in line with the previous reports and supports the formation of a five-membered palladacycle intermediate towards intramolecular C-H activation *via* 1,4-Pd-migration.[19] A competition experiment with substituted oxadiazoles was also performed (Scheme 3b). The formation of **3c** and **3j** in a 2:3 ratio suggested that the oxadiazole bearing an electron withdrawing substituent reacts preferably with the 1,4-Pd-migration intermediate **D**, which could be accounted for preferential deprotonation as compared to electron-rich **3c**.[20]



Scheme 3: Control experiments.



Scheme 4: Proposed mechanism.

Based on the previous reports[21] and control experiments, a plausible catalytic cycle of this reaction is outlined in scheme 4. The reaction begins with the oxidative addition of Pd(0) to the C-I bond of 1-iodo-2-(((2-methylallyl)oxy)methyl)benzene **1a,** forming the arylpalladium species **A**, which undergoes intramolecular carbopalladation to generate intermediate **B.** The 2-hydroxy-5-nitropyridine could serve as a ligand or as an internal base[18] to assist a tandem intramolecular C−H activation and 1,4-Pd-shift to generate species **C** and **D**, respectively. Afterwards, the attack of 2-phenyl-1,3,4-oxadiazole **2a** generates intermediate **E**, which delivers the desired product **3a** after reductive elimination, and simultaneously liberates the Pd(0) species for the next catalytic cycle.

In summary, we have developed an efficient methodology involving carbopalladation, 1,4-Pd-migration, and C(sp^2)-C(sp^2) bond formation to construct a variety of bis-heterocyclic frameworks. Over 22 examples of structurally and functionally diverse products were successfully synthesized. The substrate scope along with relatively mild reaction conditions and the good yields make this method synthetically useful. This new azole activation method should enable the mild synthesis of these biologically relevant molecules in a more sustainable manner.

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Conflicts of interest

The authors declare no conflict of interest.

Keywords: 1,4-Pd migration • oxadiazoles • C-H activation • Pd-catalysis

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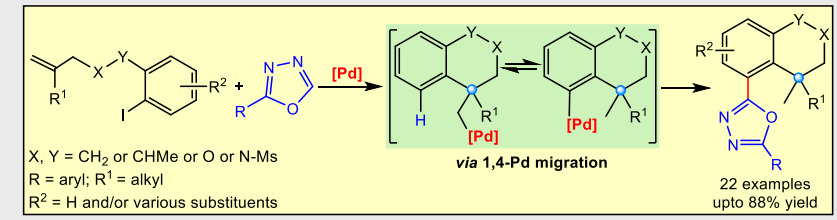

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