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Pd-Catalyzed C4-Olefination of Oxazoles via C−H Bond Activation: Divergent Synthesis of Functionalized Amino Alcohol and Amino Acid Derivatives

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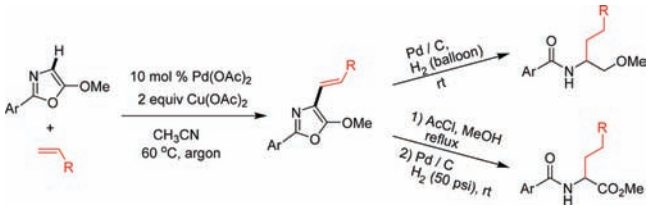
ABSTRACT



A Pd-catalyzed C4-olefination of oxazoles via C−H bond activation under mild conditions was achieved. The reaction was shown to be general over a range of substrates. New protocols for the divergent transformation of these products to provide functionalized amino alcohol and amino acid derivatives have also been established.

Transition-metal-catalyzed cross-coupling through C−H bond activation has emerged as one of the most powerful methods for the construction of C−C bonds.[1] These processes preclude the need for a prior functionalization step, making the overall chemical transformation highly efficient, thus allowing for widespread application toward the synthesis of various natural products and pharmaceuticals.[2,3] Recent reports on Pd-catalyzed C(aryl)−H olefination describe methods utilizing electrophilic metalation of aromatic and heteroaromatic C−H bonds.[4] This strategy encouraged us to develop a Pd-catalyzed olefination through C−H bond activation, and additionally demonstrate the synthetic utility of the reaction for the generation of compounds with useful molecular architecture.

Oxazoles are an important class of heterocycles that are found in a wide number of natural products, pharmaceuticals, polymeric materials, and fluorescent dyes.[5] To date, there have been numerous reported methods for the synthesis of oxazole derivatives.[6] In addition, the transition-metal-catalyzed functionalization of oxazoles has also

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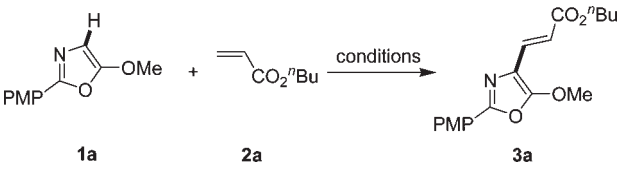
Table 1. Optimization for the Pd-Catalyzed Olefination of **1a** with **2a**[a]

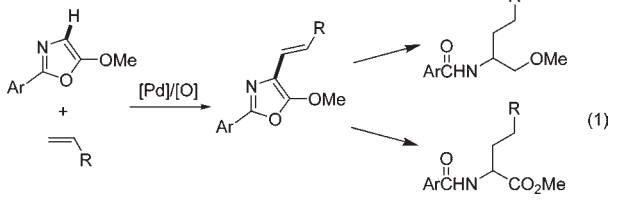


1a **2a** **3a**

entry	catalyst (10%)	oxidant (2 equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	70	12	30
2	$Pd(OAc)_2$	$Cu(OAc)_2$	CH_3CN	70	6	45
3[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	CH_3CN	60	6	84
4[c]	$Pd(OAc)_2$	AgOAc	CH_3CN	60	6	<5
5[c]	$Pd(OAc)_2$	BQ	CH_3CN	60	6	nd[d]
6[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	60	6	<5
7[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF- DMSO (1/1)	60	6	<5
8[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	60	6	nd
9[c,e]	$Pd(OAc)_2$	$Cu(OAc)_2$	CH_3CN	60	6	<5
10[c,f]	$Pd(OAc)_2$	$Cu(OAc)_2$	CH_3CN	60	6	51
11[c]	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	CH_3CN	60	6	nd
12[c]	$Pd(OAc)_2$	none	Acetone	70	20	10

[a] Conditions: molar ratio of **1a**/**2a** = 1:3 (equiv), with a concentration of **1a** being 0.25 M, PMP = *para*-methoxyphenyl. [b] Isolated yield. [c] Under argon atmosphere. [d] nd = not detected. [e] Pyridine (0.1 equiv) was added. [f] $NaHCO_3$ (2.2 equiv) was added.

been developed.[7] Recently, Miura reported a Pd-catalyzed oxidative C5-alkenylation of azoles.[8] Herein, we report a Pd-catalyzed C4-olefination of oxazoles via C−H bond activation under mild conditions and the divergent transformation of the products to functionalized amino alcohol and amino acid derivatives (eq 1).



(1)

Inspired by the Suga-Ibata reaction of oxazole **1a** and aldehydes for the synthesis of oxazolines,[9] we envisioned that **1a** could be transformed to an electrophilic palladium species via C−H activation, which could then be used for further functionalization by reaction with olefins. The reaction of **1a** with butyl acrylate (**2a**) was used to optimize the reaction conditions (Table 1). With 10 mol % $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$ as oxidant, the reaction proceeded in *N*,*N*-dimethylformamide (DMF) for 12 h at 70 °C under an atmosphere of air, forming the desired product **3a** in 30% yield (Table 1, entry 1), while a 45% yield was obtained in CH_3CN at 70 °C (entry 2). There was a remarkable improvement when the reaction was conducted in CH_3CN at 60 °C under an argon atmosphere (84% yield, entry 3). Further optimization showed that AgOAc and *para*-benzoquinone (BQ) were much less efficient oxidants than $Cu(OAc)_2$ (entries 4 and 5), and the solvent screening showed that DMSO, DMF-DMSO cosolvent and HOAc all dramatically decreased the reaction efficiency (entries 6−8). Addition of either pyridine as a ligand or $NaHCO_3$ as a base deteriorated the yield (entries 9 and 10) and $PdCl_2(CH_3CN)_2$ could not catalyze the reaction (entry 11). Attempts to use acetone as solvent and a hydrogen acceptor to intercept the HPdOAc intermediate for the purpose of regenerating the Pd(II) without forming Pd(0) failed (Table 1, entry 12).[10] The argon atmosphere was crucial for this reaction because of the decomposition of the olefination product when heated in the presence of air.

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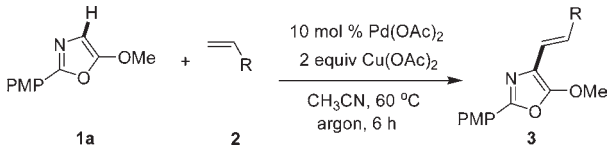
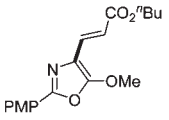
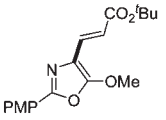
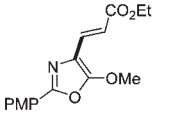
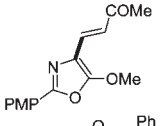
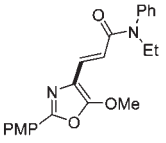
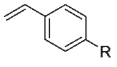
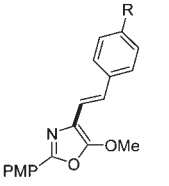
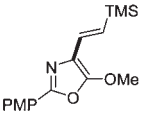
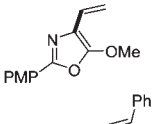
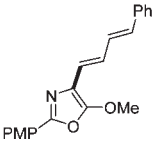
Table 2. Pd-Catalyzed Olefination of Oxazole **1a** via C−H Activation[a]



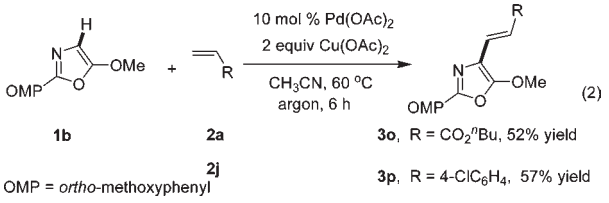
1a **2** **3**

entry	olefin		product		yield (%)[b]
1	$CO_2{}^nBu$	**2a**		**3a**	84
2	$CO_2{}^tBu$	**2b**		**3b**	79
3	CO_2Et	**2c**		**3c**	83
4	Me	**2d**		**3d**	52
5	Et, Ph	**2e**		**3e**	64
6					
	2f, R= H **2g**, R= Me **2h**, R= OMe **2i**, R= CO_2Me **2j**, R= Cl **2k**, R= NO_2			**3f** **3g** **3h** **3i** **3j** **3k**	73 78 65 77 72 87
7	TMS	**2l**		**3l**	84
8	OAc	**2m**		**3m**	26
9	Ph	**2n**		**3n**	52

[a] Conditions: **1a** (1 equiv), **2** (3 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2 equiv), CH_3CN (1.2 mL), 60 °C, argon, 6 h. [b] Isolated yield based on **1a**.

With the optimized reaction conditions in hand, we next examined the substrate scope. The reaction of **1a** with electron- deficient olefins, that is, alkyl acrylates (**2a**−**c**), methyl vinyl ketone (MVK) (**2d**), and *N*,*N*-ethylphenylacrylamide (**2e**), afforded the products **3a**−**e** in 52−84% yield (Table 2, entries 1−5). Treatment of **1a** with styrene (**2f**) generated the desired product **3f** in 73% yield (entry 6). Similarly, the reaction of **1a** with substituted styrenes (**2g**−**k**) furnished the corresponding products in 65−87% yield (entry 6). Vinyl trimethylsilane (**2l**), which is rarely employed in C−H olefination, could also be applied to this protocol, affording trimethylsilyl (TMS) substituted product **3l** in 84% yield (entry 7). Vinyl acetate (**2m**) only showed the moderate reactivity to furnish product **3m** in 26% yield with loss of the acetate group in the product (entry 8). The diene was also investigated and the coupling with 1-phenyl-1,3-diene proceeded at the terminal double bond to give the dienyl oxazole **3n** in 52% yield (entry 9).

Under similar reaction conditions, oxazole **1b** was also employed to test this Pd-catalyzed oxidative olefination, giving the corresponding products in moderate yields (eq 2).



With this result in hand, we planned to transform the functionalized oxazole products to more synthetically interesting motifs. Initially, we attempted to perform a Pd/C hydrogenation to reduce the alkene in **3a** at room temperature with a hydrogen balloon. Gratifyingly, we found that an acyclic 1,2-amido ether (an amino alcohol derivative) product **4a** was formed in 67% yield. The hydrogenation was also efficient for other oxazole products and the results are shown in Scheme 1. The structure of the amido ether was confirmed by single crystal X-ray diffraction analysis of compound **4b** (see Supporting Information), in addition to standard characterization.

Amino alcohol derivatives are extensively used in medicinal chemistry,[11] representing a wide range of β-adrenergic blockers in the management of cardiovascular disorders.[12] This method for Pd-catalyzed olefination and subsequent Pd/C catalyzed reduction gives facile access to novel amino alcohol derivatives in a general and efficient manner. The hydrogenation also led to an unexpected ring-opening, which was previously unreported for Pd-catalyzed ring fragmentation of oxazoles. A control experiment employing $LiAlH_4$ as a reductant left the oxazole structure intact even in refluxing THF. While the ring-opening mechanism is

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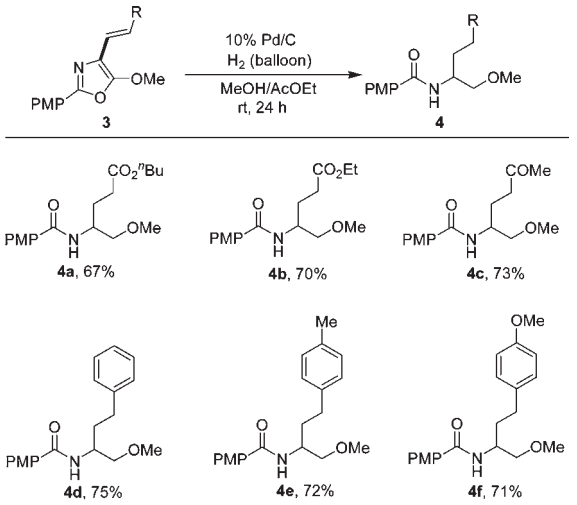
currently unclear, we hypothesize that Pd/C plays a key role in this process presumably by coordination to the oxazole nitrogen.[13]

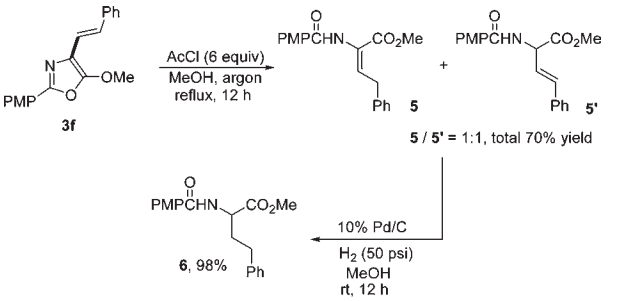
Scheme 1. Pd/C Catalyzed Ring-Opening of Oxazoles **3** to Functionalized Amino Alcohol Derivatives **4**[a,b]



[a] Conditions: **3** (100 mg), 10% Pd/C (100 mg), MeOH (10 mL), AcOEt (2 mL), H_2 (balloon), rt, 24 h. [b] Isolated yield.

This new methodology also provides a versatile and efficient approach to amino acid derivatives, and represents a concise synthesis of functionalized homophenylalanines as shown in Scheme 2. Hydrolysis of oxazole **3f** in AcCl–MeOH provided an inseparable 1:1 mixture of **5** and **5′**, and the subsequent hydrogenation furnished the homophenylalanine product **6**, which is an important synthon in many angiotensin-converting enzyme inhibitors.[14,15]

Scheme 2. Synthesis of Homophenylalanine Derivative **6**



In conclusion, we have developed a Pd-catalyzed oxidative C4-olefination of oxazoles through C−H bond activation under mild conditions. Protocols are provided for the transformation of these products to functionalized amino alcohol derivatives, and homophenylalanine derivatives have also been established.

Acknowledgment. We thank the University of South Florida for financial support.

Supporting Information Available. Detailed experimental procedures, characterization for products, NMR spectra and crystallographic information file for compound **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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