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Palladium-Catalyzed Cyclization Reaction of Oxime Acetates and Aryl Iodides: Syntheses of 2-Imidazolines

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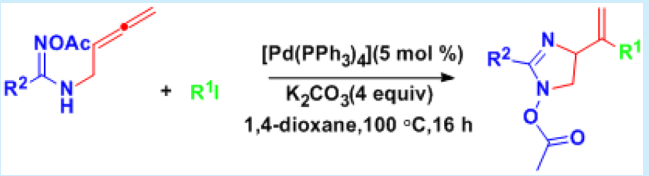
Supporting Information

ABSTRACT: A novel and versatile method for the synthesis of 2-imidazolines has been developed via the Pd-catalyzed cyclization reaction of readily available homoallenyl oxime acetates with aryl iodides. This protocol is performed under mild reaction conditions and needs no additives or ligands.



N-Heterocycles are some of the most important building blocks in organic chemistry.[1] Among them, 2-imidazolines are particularly significant, in both catalysis and biology,[2] but are also useful chiral organocatalysts in modern organic synthesis.[3] Because of the wide spectrum of fascinating applications, the synthesis of imidazoline derivatives has long been of interest, and a number of different methods have been devised for their preparation.[4] However, challenges still remain in the scope of group tolerance. Therefore, the development of methodologies for a more direct and efficient access to different substituted and specifically functionalized frameworks is always welcome.

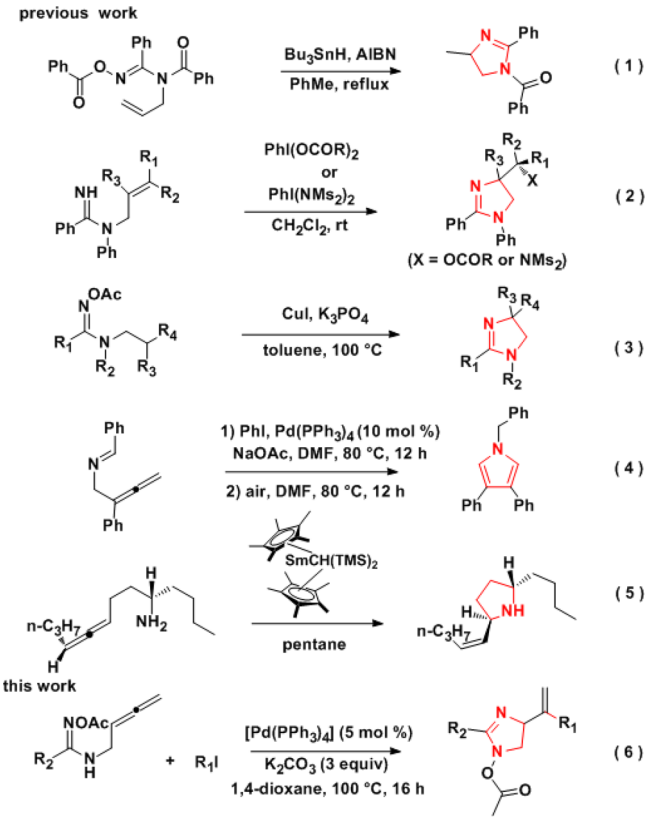
Zhang's group explored a new organocatalytic strategy for the synthesis of imidazolines based on amidinyl radical cyclization (Scheme 1, eq 1).[5] The Chiba group reported diastereoselective aminooxygenation and diamination of alkenes with amidines mediated by hypervalent iodine(III) reagents (Scheme 1, eq 2).[6] Afterward, they reported copper-catalyzed redox-neutral C−H amination with amidoximes to synthesize imidazolines (Scheme 1, eq 3).[7]

Recently, much research effort has been focused on the coupling/cyclization reactions of organic halides with functionalized allenes for the synthesis of potentially important carbocyclic and heterocyclic compounds.[8−10] For example, an internal N attack on an allene unit also gives pyrroles (Scheme 1, eq 4),[11] and cyclizations of N nucleophiles onto an allene give fused pyrroldines (Scheme 1, eq 5).[12] In this area, Pd-catalyzed reactions of functionalized allenes to form polysubstituted 2-imidazolines still remain a challenge.

In this paper, we envisioned a Pd-catalyzed cyclization reaction for the synthesis of polysubstituted 2-imidazoline derivatives from amidoximes and aryl iodides (Scheme 1, eq 6).

At the outset, we examined the tandem cyclization reaction of *N*′-acetoxy-*N*-(buta-2,3-dien-1-yl)benzimidamide (**1a**) with iodobenzene (**2a**) as standard reaction partners using Pd-$(PPh_3)_2Cl_2$ as the catalyst (Table 1). During screening, the reaction of **1a**, **2a** in THF, with K_2CO_3 as the base, afforded 2-imidazoline **3aa** in 34% isolated yield (Table 1, entry 1). The product was carefully characterized by ^{1}H NMR, ^{13}C NMR, and

Scheme 1. Strategies for the Synthesis of Imidazolines



mass spectral data. ITo improve the yield, different catalysts were screened. Catalysts $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(CF_3COO)_2$ were investigated (Table 1, entries 2−5), with no reaction occurring in the absence of a catalyst (Table 1, entry 6). Significantly, $Pd(PPh_3)_4$ (5 mol %) improved the yield

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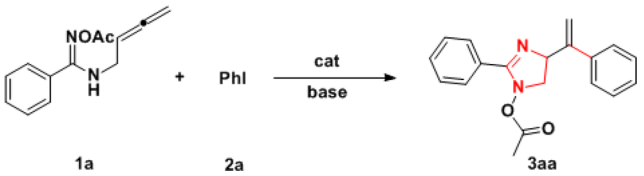
Table 1. Optimization of Reaction Conditions[a]



entry	cat	base	additive[b]	solvent	yield[c] (%)
1	$Pd(PPh_3)_2Cl_2$	K_2CO_3		THF	34
2	$Pd(PPh_3)_4$	K_2CO_3		THF	61
3	$Pd(OAc)_2$	K_2CO_3	PPh_3	THF	46
4	$Pd_2(dba)_3$	K_2CO_3	PPh_3	THF	48
5	$Pd(CF_3COO)_2$	K_2CO_3	PPh_3	THF	55
6		K_2CO_3		THF	nd[d]
7	$Pd(PPh_3)_4$	Na_2CO_3		THF	23
8	$Pd(PPh_3)_4$	CsF		THF	31
9	$Pd(PPh_3)_4$	Cs_2CO_3		THF	35
10	$Pd(PPh_3)_4$	NaH		THF	trace
11	$Pd(PPh_3)_4$	NaOH		THF	nd
12	$Pd(PPh_3)_4$	K_2CO_3	nBu_4NBr	THF	56
13	$Pd(PPh_3)_4$	K_2CO_3	$Cu(OTf)_2$	THF	53
14[e]	$Pd(PPh_3)_4$	K_2CO_3		THF	37
15	$Pd(PPh_3)_4$			THF	trace
16	$Pd(PPh_3)_4$	K_2CO_3		DMF	53
17	$Pd(PPh_3)_4$	K_2CO_3		CH_3CN	45
18	$Pd(PPh_3)_4$	K_2CO_3		toluene	63
19	$Pd(PPh_3)_4$	K_2CO_3		DMSO	43
20	$Pd(PPh_3)_4$	K_2CO_3		CH_3OH	nd
21[f]	$Pd(PPh_3)_4$	K_2CO_3		1,4-dioxane	72
22[g]	$Pd(PPh_3)_4$	K_2CO_3		1,4-dioxane	76
23[h]	$Pd(PPh_3)_4$	K_2CO_3		1,4-dioxane	31

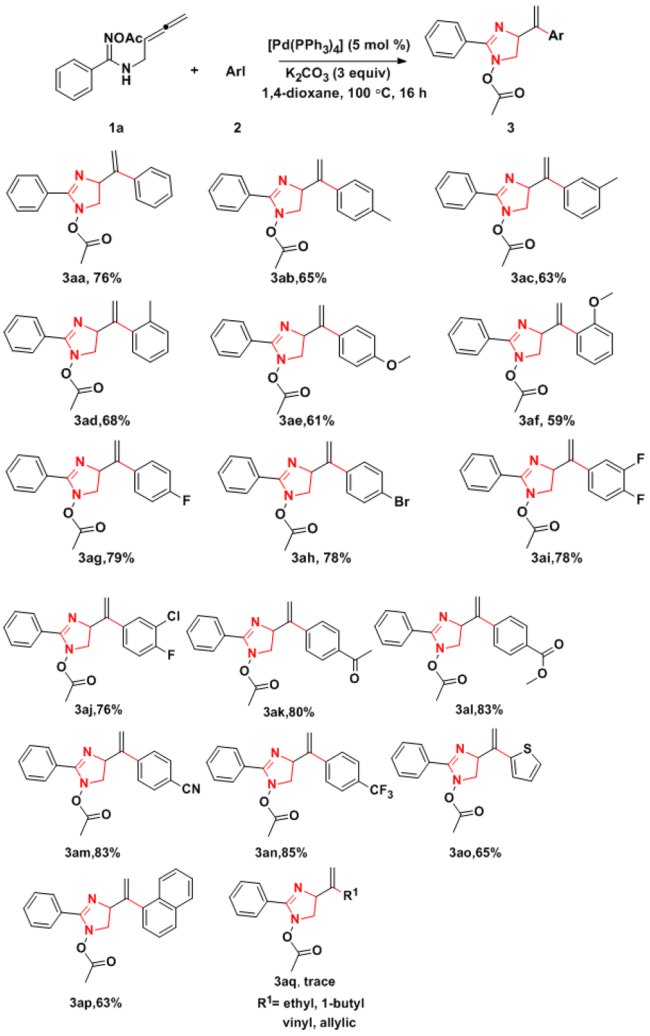
[a]Reaction conditions: under a N_2 atmosphere, **1a** (0.22 mmol, in 3 mL of THF), PhI (1.2 equiv), base (3 equiv), and [Pd^0] (5 mol %) at reflux. [b]*n*-Bu_4NBr (10 mol %), $Cu(OTf)_2$ (10 mol %). [c]Isolated yields. [d]nd = not detected. [e]K_2CO_3 (1 equiv) was used. [f]85 °C. [g]100 °C. [h]60 °C.

of **3aa** to 61% (Table 1, entry 2). To further improve reaction efficiency, several bases were evaluated (Table 1, entries 7–11). As shown, Na_2CO_3, CsF, or Cs_2CO_3 showed no improvement, compared with K_2CO_3. Stronger bases (e.g., NaH and NaOH) did not produce 2-imidazoline **3aa** (Table 1, entries 10 and 11). Based on a previous study,[13] different additives were tested (Table 1, entries 12 and 13). Using the phase-transfer catalyst *n*-Bu_4NBr (Table 1, entry 12) or the Lewis acid ($Cu(OTf)_2$) did not increase the yield (Table 1, entry 13). Reducing the equivalents of K_2CO_3 to 1 equiv reduced the yield of **3aa** to 37% (Table 1, entry 14), and in the absence of base, only a trace amount of product was observed (Table 1, entry 15).

The effects of the solvents and reaction temperature were also examined (Table 1, entries 16–23). Among all the solvents tested, dioxane was determined to be the most suitable one for the investigated transformation. When the reaction temperature was raised to 100 °C, the yield and reaction time were significantly affected (Table 1, entry 22). When the temperature was lowered to 60 °C, the conversion decreased and the yield did not increase, even if the reaction time was extended to 48 h (Table 1, entry 23). Thus, the standard reaction conditions used for further investigations were **1a** (1 equiv), **2a** (1.2 equiv) with K_2CO_3 (3 equiv) in 1,4-dioxane at 100 °C while using [$Pd(PPh_3)_4$] (5 mol %) as the catalyst.

Under the optimized conditions, the scope and limitations of the transformation were also evaluated for the reaction of **1a** with various aryl iodides **2** (Scheme 2). It was found that several aryl iodide derivatives were excellent reaction partners, producing the corresponding 2-imidazoline derivatives in good to excellent yields.

Scheme 2. Substrate Scope of Aryl Iodides[a,b]



[a]Reaction conditions: under a N_2 atmosphere, **1a** (0.22 mmol, in 3 mL of 1,4-dioxane), $Pd(PPh_3)_4$ (5 mol %), **2** (1.2 equiv), and K_2CO_3 (3 equiv). [b]Isolated yields.

The reaction proceeded smoothly when electron-donating substituents, such as methyl and methoxy, were present in the aryl iodide coupling partners (Scheme 2, **3ab–af**). Further, when iodo aryl halides were employed, the desired compounds could also be obtained in high yields (Scheme 2, **3ag–aj**). Notably, with strong electron-withdrawing substituents (−CN, $-CF_3$) on the aromatic ring, the transformation proceeded smoothly to afford the desired products (**3am**, **3an**). We also found that substitution at the *ortho*-, *meta*-, or *para*-position of the aromatic ring had a slight impact (**3ab–af**). The presence of a halogen group had a negligible effect on the reaction, thus offering the possibility for further transformation by aromatic substitution or coupling reactions. Moreover, heteroaromatic

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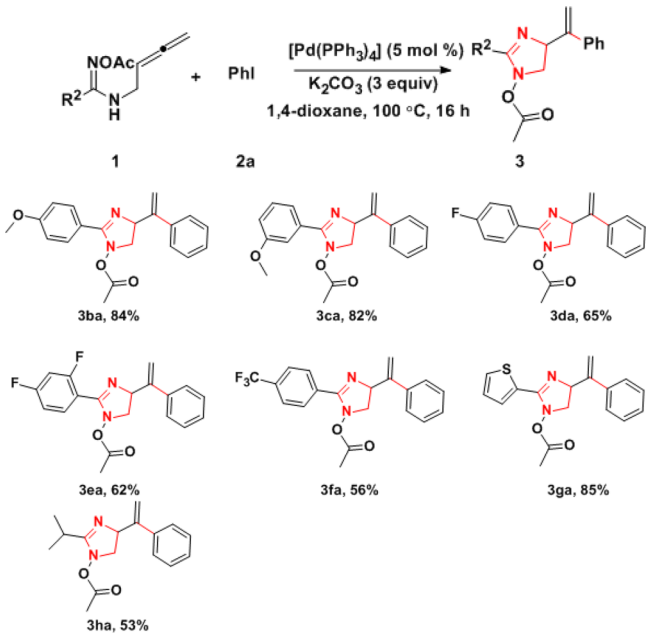
iodides also gave satisfactory results. 2-Iodothiophene and 1-iodonaphthalene reacted smoothly, affording the expected products **3ao** and **3ap** in 65% and 63% yields, respectively. Apart from aryl iodides, representative aliphatic iodides such as iodoethane, *n*-butyl iodide, vinyl iodides, and allylic iodides (Scheme 2, **3aq**) were tested, but the desired products **3aq** were not acquired. These tests suggested that the aliphatic iodides were unviable coupling partners.

Subsequently, we turned our attention toward the cycloaddition of different oxime acetates (**1**) with iodobenzene (**2a**) under optimal conditions (Scheme 3). In general, electron-donating substituents on the phenyl ring, such as methoxyl (Scheme 3, **3ba**, **3ca**), enhanced the yield, while electron-withdrawing substitutents such as fluoro (Scheme 3, **3da**, **3ea**) and CF_3 (Scheme 3, **3fa**) reduced the yield. Notably, when the phenyl ring was replaced by 2-thienyl (**3ga**, 85%), the yield was improved. Furthermore, isobutyraldehyde oxime acetate was also suited to this process, affording imidazolidine **3ha** in 53% yield.

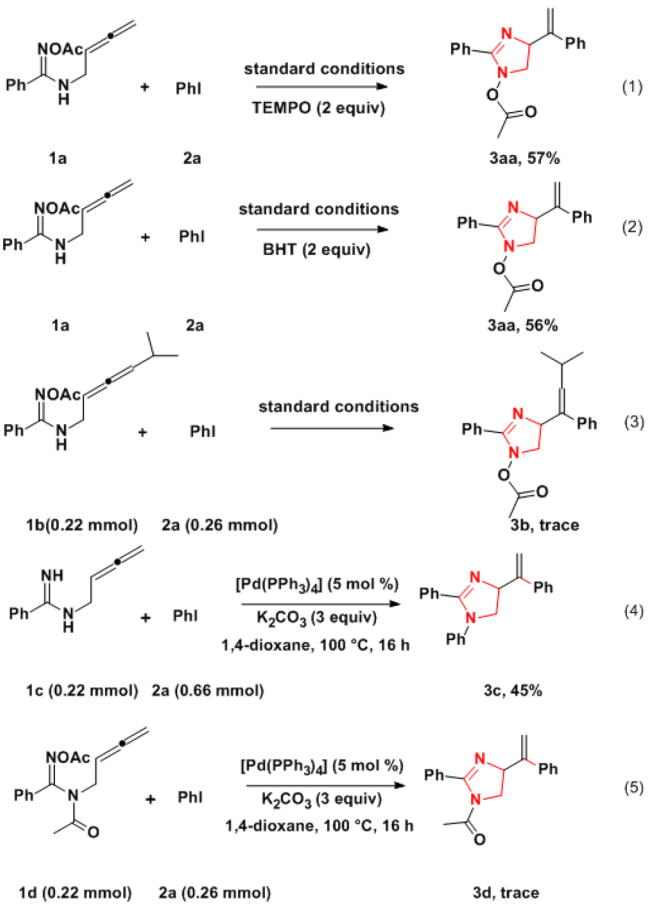
Scheme 3. Substrate Scope of Oxime Acetates[a,b]



[a]Reaction conditions: under a N_2 atmosphere, **1** (0.22 mmol, in 3 mL 1,4-dioxane), $Pd(PPh_3)_4$ (5 mol %), **2a** (1.2 equiv), and K_2CO_3 (3 equiv). [b]Isolated yields.

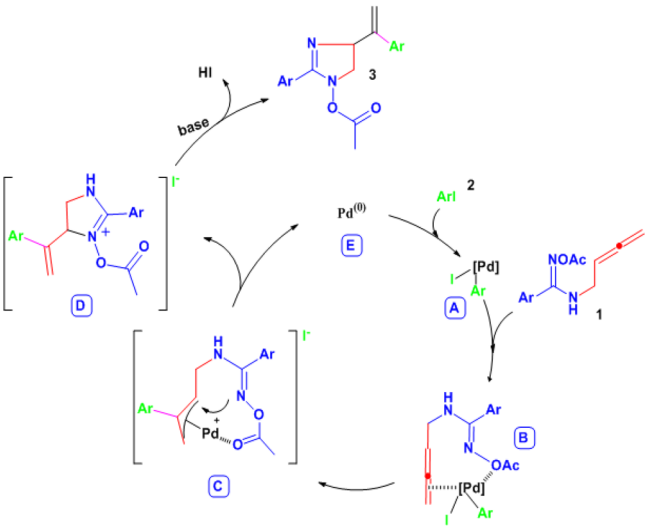
In order to explore the reaction mechanism, control experiments were conducted under the standard reaction conditions. When the radical scavengers 2,2,6,6-tetramethylpiperidine oxide (TEMPO) and butylated hydroxytoluene (BHT) were added to the mixture, the reaction proceeded smoothly and was not inhibited, which indicated that this reaction did not proceed via a radical mechanism (Scheme 4, eq 1 and eq 2). It was noteworthy that **1a** could be replaced by another oxime acetate, **1b**. As presented in Scheme 4 (eq 3), no product was observed, suggesting that the terminal substituent group of allenes has a pronounced effect on the two-component tandem reaction. Finally, the corresponding reaction of *N*-(buta-2,3-dien-1-yl)benzimidamide **1c**, which can be viewed as an oxime acetate-removed version of **1a**, with PhI (**2a**), the desired product could not be obtained, but instead gave a new 2-imidazoline compound **3c** was formed (Scheme 4, eq 4). When the substrate was changed to **1d**, the desired product was not obtained, and we could see the importance of retaining hydrogen on the nitrogen atom (Scheme 4, eq 5).

Scheme 4. Experiments for Mechanistic Study



On the basis of the above results and previous reports,[11,13,14] a tentative mechanism for the cross-coupling reaction is proposed (Scheme 5). We believe that, initially, an oxidative

Scheme 5. Proposed Mechanism



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addition of Pd^0 to the aryl iodide (**2**) affords the Pd^{II} intermediate **A**. Coordination of one of the allene double bonds to the electrophilic complex **B**, and subsequent carbopalladation affords the π-allyl species **C**. The π-allylpalladium intermediate **C** presumably undergoes the cyclization, initiated by an intramolecular attack of the electrophilic π-allyl moiety by the imine nitrogen affords the intermediate **D** with the active regeneration of palladium(0) catalyst for the next catalytic cycle. Finally, the intermediate **D** through intramolecular rearrangement under alkaline conditions affords the final product **3**. This process was supported by experiments in the presence of foreign anions (chloride, other acid anions; and aryl oxide ions),[15] which were not incorporated in the products.

In conclusion, we have developed a two-component tandem cyclization reaction that provides an efficient route to polysubstituted 2-imidazoline derivatives. This strategy offers significant advantages over classical step-by-step approaches by forming several bonds in a single synthetic operation. Further studies on the scope and synthetic applications of this reaction are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00696.

Experimental procedures, full spectroscopic data for all new compounds, and copies of ^1H, ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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