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Palladium-Catalyzed Redox-Neutral N–O/C(sp^3)–H Functionalization of Aryl Oximes with Isocyanides

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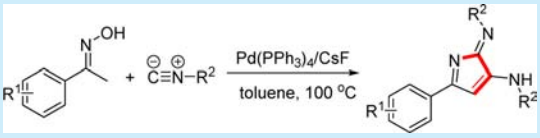
Supporting Information

ABSTRACT: A redox-neutral palladium-catalyzed N–O/C(sp^3)–H functionalization of aryl oximes with isocyanides has been developed. Various pyrrole derivatives were prepared in good to excellent yields through oxime carbamate as a key intermediate and internal oxidant in this process. Furthermore, this transformation also features readily available starting materials, good functional group tolerance, and excellent regioselectivity.



Transition-metal-catalyzed functionalization of the C–H bond has emerged as an efficient tool for the formation of C–C and C–heteroatom bonds over the past decades.[1] However, the use of stoichiometric or excess amounts of external oxidants are usually necessary in these reactions, which has provided a driving force for chemists to overcome this challenge. Recently, much attention has been shifted to redox-neutral coupling reactions. For example, the development of C–H bond activation transformations using N–N,[2] N–O,[3] and N–S[4] bond cleavages has been demonstrated by Pd, Rh, Ru, Co, etc. Furthermore, a Rh-catalyzed alkyne annulation of perester with an O–O bond as an internal oxidant has been reported by Cui.[5] Among the most investigated oxidative directing groups (DG^{ox}), the N–O bond in oximes is the most common (Scheme 1a). On the other hand, in these processes, the coupling partners are largely limited to alkynes or alkenes and the DG^{ox}-containing substrates also need to be prepared in advance. To the best of our knowledge, redox-neutral C(sp^3)–H bond functionalization has not been reported to date. Thus, the development of innovative internal oxidants is still meaningful and highly desirable.

Isocyanides are highly versatile reagents that have found widespread applications in organic synthesis.[6] Especially, palladium-catalyzed redox-neutral isocyanide insertion reactions from aryl halides and different nucleophiles to amidines,[7] (thio)imidates,[8] amides,[9] and various heterocycles[10] have been widely investigated (Scheme 1b). Despite the substantial advances that have been achieved, transition-metal-catalyzed isocyanide multiple insertion reactions have been less explored.[11] On the basis of our previous studies of oximes[12] and isocyanides,[13] herein we disclose an efficient method for the synthesis of pyrrole derivatives via palladium-catalyzed redox-neutral N–O/C(sp^3)–H functionalization of aromatic oximes with isocyanides (Scheme 1c). In this transformation, oxime carbamate is a key intermediate and internal oxidant, and thus, additional oxidants are unnecessary.

Our investigation was initiated by examining the reactions of acetophenone oxime (**1a**) with *tert*-butyl isocyanide (**2a**) in the presence of $Pd(PPh_3)_4$ as the catalyst (Table 1). Fortunately, product **3aa** and the unexpected product **4aa** were observed in low yields in toluene at 80 °C for 3 h (entry 1). Encouraged by this result, various bases, such as Cs_2CO_3, K_2CO_3, NaOAc, and CsF, were examined (entries 2–5). To our delight, **3aa** as a single product was obtained in 72% yield with NaOAc as the base (condition A). Furthermore, we were excited that the yield of **4aa** increased to 56% by when the amount of water was decreased to 1 equiv at 100 °C (entry 6). Toluene is the best solvent (entries 7–9). Further optimization revealed that 3 equiv of CsF as a base (condition B) gave the highest yield of **4aa** (entry 10). Finally, control experiments demonstrated that

Scheme 1. Transition-Metal-Catalyzed Coupling Reaction under Redox-Neutral Conditions

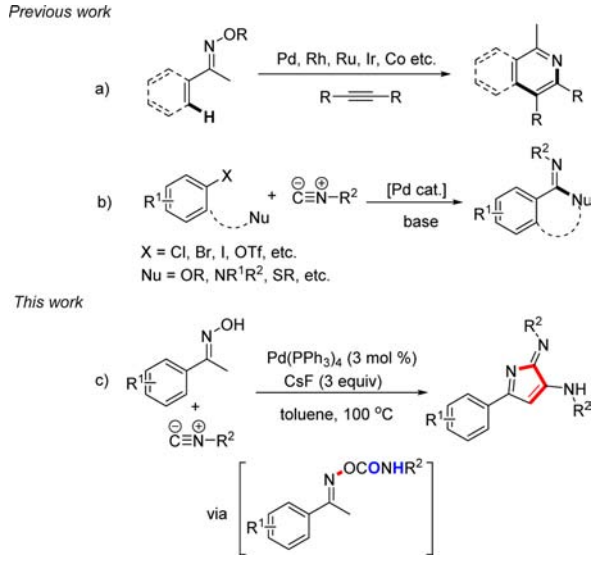


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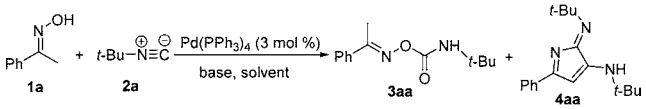
Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	yield of **3aa** (%)[b]	yield of **4aa** (%)[b]
1	–	toluene	28	20
2	Cs_2CO_3	toluene	18	10
3	K_2CO_3	toluene	32	16
4	**NaOAc**	**toluene**	**72 (68)**	**n.d.**
5	CsF	toluene	22	16
6[c]	CsF	toluene	20	56
7[c]	CsF	DMF	33	20
8[c]	CsF	THF	12	37
9[c]	CsF	dioxane	16	46
10[c,d]	**CsF**	**toluene**	**8**	**91 (86)**
11[c,d,e]	CsF	toluene	n.r.	n.r.

[a]Reaction conditions: unless otherwise noted, all of the reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol), base (0.2 mmol), $Pd(PPh_3)_4$ (3 mol %), and H_2O (3 equiv) in the solvent (2 mL) at 80 °C for 3 h. [b]Determined by GC using dodecane as an internal standard. Numbers in parentheses are yields of isolated products. n.d. = not detected. n.r. = no reaction [c]0.3 mmol of **2a** and 1 equiv of H_2O were added at 100 °C for 10 h. [d]3 equiv of CsF was added. [e]No $Pd(PPh_3)_4$.

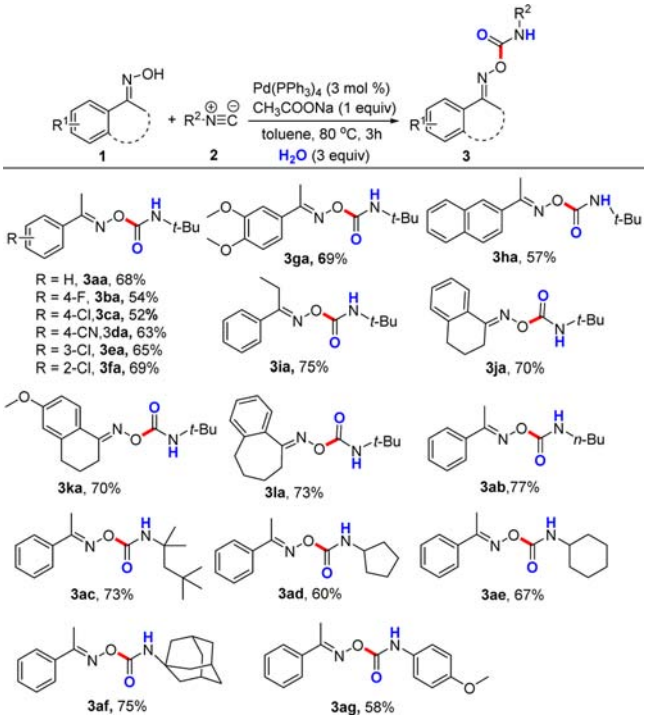
the palladium catalyst is crucial for this transformation (entry 11) (see the Supporting Information for details).

Oxime carbamates are crucial structural motifs for their antimicrobial activity[14] and inhibition of various enzymes.[15] Considering the importance of this skeleton, the scope of the substrates was first examined. As shown in Scheme 2, a variety of functional groups, such fluoro, chloro, cyano, and methoxy on the benzene ring were well-tolerated in this transformation (**3ba**–**ga**). It is worth mentioning that propiophenone and 2-acetylnaphthalene oximes were also found to be good substrates, delivering the corresponding oxime carbamates **3ha** and **3ia** in moderate yields. Notably, 3,4-dihydronaphthalen-1(2*H*)-one and 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one oximes also reacted smoothly to afford the desired products in satisfactory yields (**3ja**–**la**). Disappointedly, benzaldehyde and alkyl oximes failed to afford the corresponding products.

Moreover, the scope of isocyanides was also examined. Fortunately, alkyl isocyanides, such as *n*-butyl, 1,1,3,3-tetramethylbutyl, cyclopentyl, cyclohexyl, and adamantyl isocyanides, were found to effectively undergo insertion, and the corresponding products **3ab**–**af** were isolated in 60–77% yield. 1-Isocyano-4-methoxybenzene was also a suitable substrate, and the final product **3ag** was obtained in 58% yield.

We next examined the scope of the synthesis of pyrrole derivatives (Scheme 3). A variety of *ortho*-, *meta*-, and *para*-substituted acetophenone oximes participated well in this reaction and were converted into the corresponding products in good to excellent yields (**4aa**–**oa**). On the whole, electron-withdrawing substituents on the benzene ring showed higher reactivity than electron-donating ones. In addition, heteroaryl-bearing and 1- and 2-naphthyl-substituted acetophenone oximes also smoothly underwent cyclization to give the desired products in good yields (**4pa**–**ra**). Notably, thiophene oxime could be transformed to the desired product **4sa** in 50% yield. In contrast, propiophenone and 2-methyl-1-phenylpropan-1-one oximes were not converted to the corresponding products

Scheme 2. Synthesis of Oxime Carbamates from a Variety of Aryl Oximes and Isocyanides[a]



[a]Reaction conditions: **1** (0.4 mmol), **2** (0.4 mmol), H_2O (1.2 mol), $Pd(PPh_3)_4$ (3 mol %), and NaOAc (0.4 mmol) in toluene (2.0 mL) at 80 °C for 3 h. Isolated yields are shown.

under the optimized conditions. Most importantly, the strategy was suitable for 3,4-dihydronaphthalen-1(2*H*)-one oximes, and the corresponding tricyclic products (**4ta**–**wa**) were generated in good yields. The structure of **4wa** was unambiguously confirmed by single-crystal X-ray analysis (see the Supporting Information for details).[16] With regard to the isocyanide scope, only 1,1,3,3-tetramethylbutyl isocyanide underwent insertion, while 1-isocyano-4-methoxybenzene and cyclohexyl isocyanide failed to give the desired products (**4ab**–**ad**).

To gain more insight into the mechanism of this reaction, several experiments were performed (Scheme 4). We investigated the oxygen source by ^{18}O-labeling experiments and confirmed that the oxygen atom in the product **3** is attained from water (eq 1). Notably, when we coupled the oxime with 2 equiv of **2a** under condition A, the product **5** was formed in 60% yield (eq 2). Further experiments indicated that oxime carbamate **3aa** instead of ketazine could be converted into the target product **4aa** in 56% yield (eqs 3 and 4). When compound **5** was treated with **2a** under optimized reaction condition B, the desired product **4ca** was also produced in 89% yield (eq 5). Finally, a primary KIE value of 4.0 (eq 6) indicated that the C–H bond cleavage process is presumably involved in the turnover-limiting step.

On the basis of the above observations and related literature reports,[10d,11f] a plausible mechanism is illustrated in Scheme 5. The right pathway is initiated by insertion of Pd(0) into the O–H bond of **1** to generate intermediate **A** with the aid of base, followed by migratory insertion of **2** to afford intermediate **B**. With the assistance of H_2O in the reaction, intermediate **C** was formed. Subsequent reductive elimination leads to Pd(0) and compound **D**, which could be isomerized to

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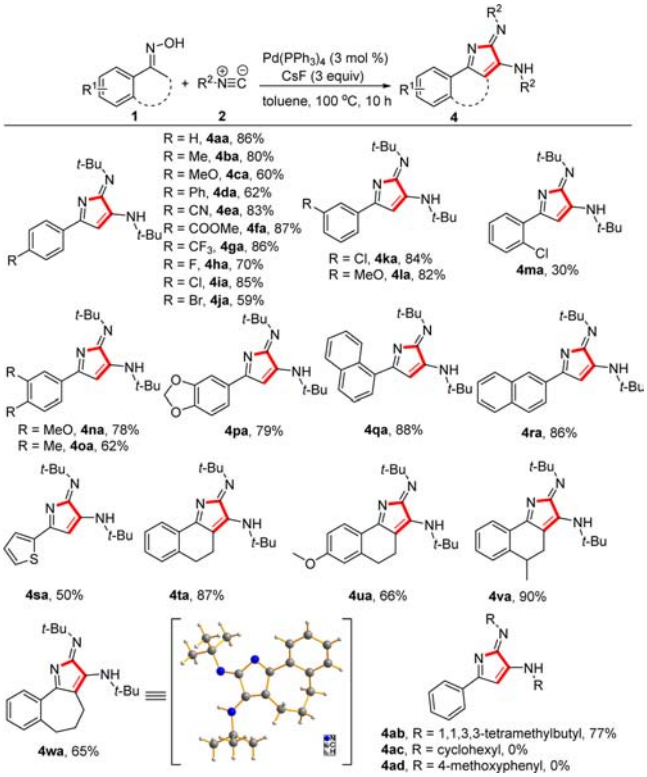
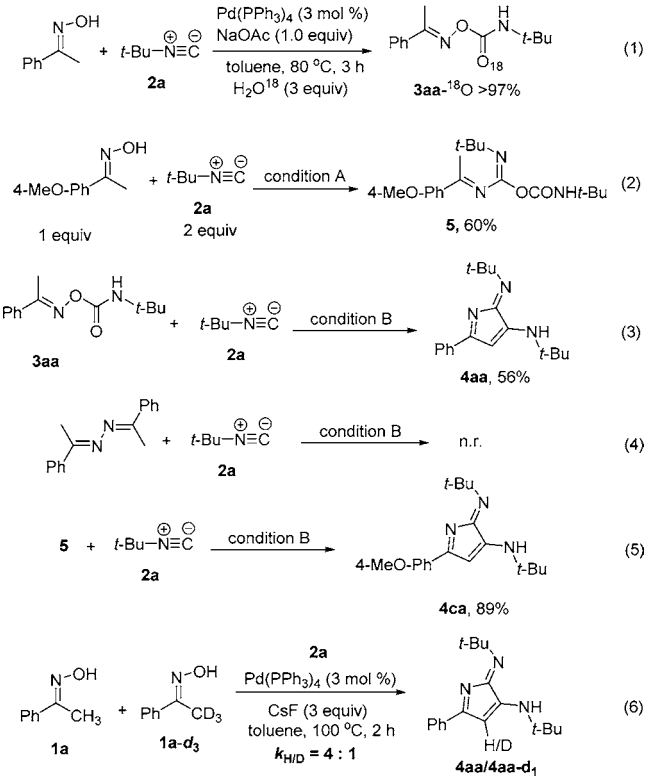
Scheme 3. Synthesis of Pyrrole Derivatives from a Range of Aryl Oximes and Isocyanides[a]

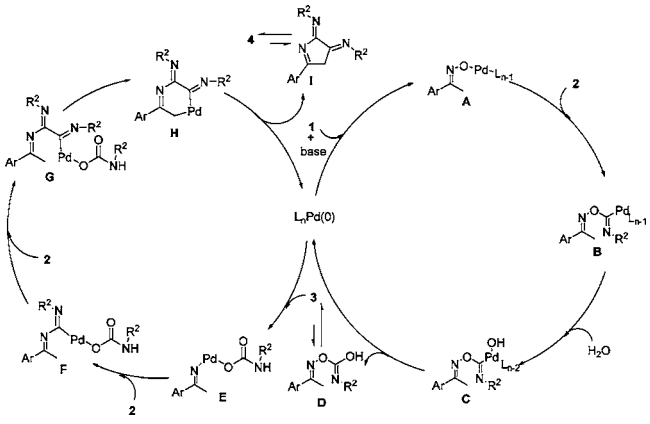


[a]Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), H_2O (0.5 mmol), $Pd(PPh_3)_4$ (3 mol %), and CsF (1.5 mmol) in toluene (2.0 mL) at 100 °C for 10 h. Isolated yields are shown.

Scheme 4. Control Experiments



Scheme 5. Proposed Mechanism



afford the product **3**. For the left pathway, the oxidative addition of Pd(0) species to the N−O bond of **3** affords imino-Pd intermediate **E**, which could undergo migratory insertion of **2** to generate intermediate **F**. Intermediate **G** would be obtained after the insertion of another molecule of **2**. Subsequently, the C(sp^3)−H cleavage results in the formation of palladacyclic complex **H**. Finally, reductive elimination affords **I**, regenerating the Pd(0) species for the next catalytic cycle. Immediately, the unstable product **I** would be isomerized to give the final product **4**.

In summary, we have developed a novel and efficient palladium-catalyzed redox-neutral N−O/C(sp^3)−H functionalization of aromatic oximes with isocyanides to afford pyrrole derivatives. In addition, this transformation also features good functional group tolerance, no use of oxidants, and excellent regioselectivity. Oxime carbamate is demonstrated to be a key intermediate and an internal oxidant in this reaction. Further applications of this strategy to the cleavages of other unactivated chemical bonds are currently 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.6b03852.

Experimental procedures, condition screening table, characterization data, and copies of NMR spectra for all products (PDF)

Crystallographic data for **4wa** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1440842 contains the supplementary crystallographic data for **4wa**. These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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