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Palladium-Catalyzed C−C Triple Bond Cleavage: Efficient Synthesis of 4*H*-Benzo[*d*][1,3]oxazin-4-ones

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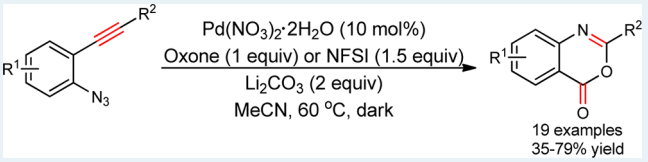
Supporting Information

ABSTRACT: Described herein is a new transformation of azidoalkynes by using a palladium catalyst, which involves a tandem process of aminopalladation of the alkyne and oxidative rearrangement. The reaction affords a variety of 4*H*-benzo[*d*][1,3]oxazin-4-ones. Mechanism studies support a Pd-catalyzed aminopalladation/oxidation/Baeyer−Villiger fragmentary sequence.



KEYWORDS: *Pd catalyst, azidoalkyne, aminocyclization, C−C triple bond cleavage, oxidation*

INTRODUCTION

The moiety of 4H-benzo[*d*][1,3]oxazin-4-ones represents an important skeleton existing in compounds that exhibit a variety of bioactivities, such as antifungal, antibacterial, herbicidal, HSV-1 protease inhibition, serine proteases inhibition, and others.[1−4] Furthermore, it is a key pharmacophore in Cetilistat (a phase III clinical trial drug), which showed promising market prospect as an antiobesity remedy (Figure 1).[5−8] Therefore, its syntheses has received intensive attention.[9−12]

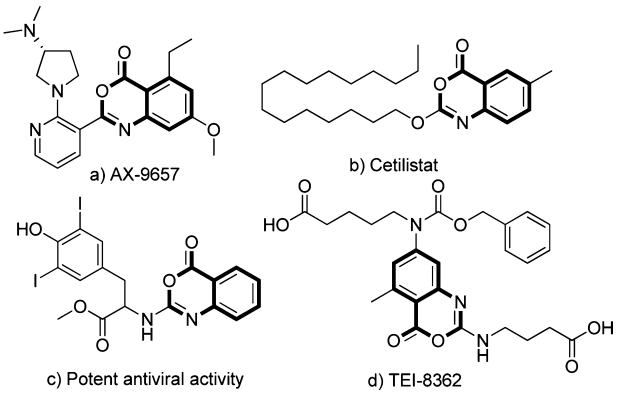
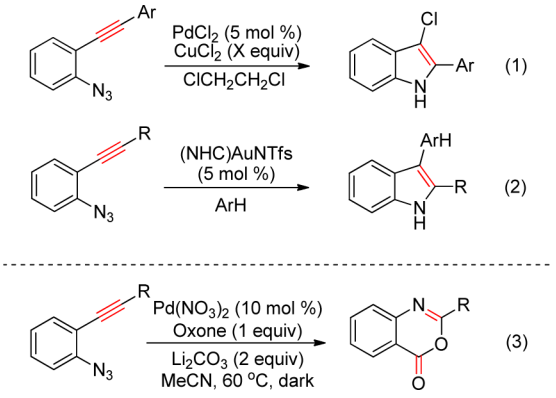


Figure 1. Some bioactive compounds.

Transition metal-catalyzed cleavage of carbon−carbon bonds is one of the most challenging areas in organic reactions. Among them, cleavage of the C−C triple bond is particularly difficult owing to its extraordinarily large bond dissociation energy (>200 kcal mol^{-1}).[13,14] Alkynes are important building blocks in organic transformations for the synthesis of more valuable compounds.[15] Apart from alkyne metathesis,[16] most early works on the cleavage of C−C triple bond operated in a stoichiometric manner.[17−19] Later on, some transition metal-catalyzed cleavage of C−C triple bonds was reported, including Au,[20,21] Pd,[22] Ru,[23,24] and Rh,[25,26] which to a large extent enriched the arsenal of organic synthesis.

Very recently, transition metal-catalyzed cyclization of 2-azidoalkynylbenzenes was reported to yield a variety of indole derivatives. For instance, Li[27] reported a Pd-catalyzed chloroamination of alkynes to give 3-chloroindole (eq 1).



Gagosz[28] and Zhang,[29] respectively, reported Au-catalyzed tandem cyclization/nucleophilic addition to afford 3-arylated indoles (eq 2). As part of our continued interest in metal-catalyzed fluorination of C−C multibond for the synthesis of fluorinated heterocycles,[30−35] we'd like to expand our oxidative fluorination system to the synthesis of 3-fluoroindoles. Instead of designed transformation, we disclose herein a serendipitous finding on the triple bond cleavage of 2-azidoalkynylbenzenes,

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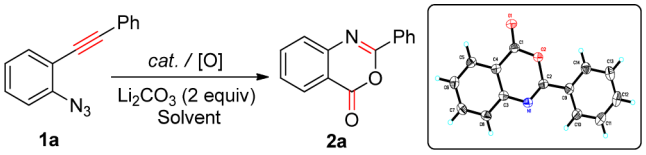
which affords a variety of 4H-benzo[*d*][1,3]oxazin-4-ones products (eq 3).

RESULTS AND DISCUSSION

In light of our ongoing program to synthesize 3-fluoroindoles, the initial studies were focused on the reaction of 2-phenylacetenylaniline using our previously developed silver catalyst system.[33,34] However, the reaction could not afford the desired product because of overoxidation. We then turned our attention to 2-azidoalkynylbenzenes **1a** as a prospect substrate.

As shown in Table 1, no reaction occurred with the silver catalyst system (entry 1); however, with a combination of

Table 1. Optimization of Reaction Conditions[a]



1a **2a**

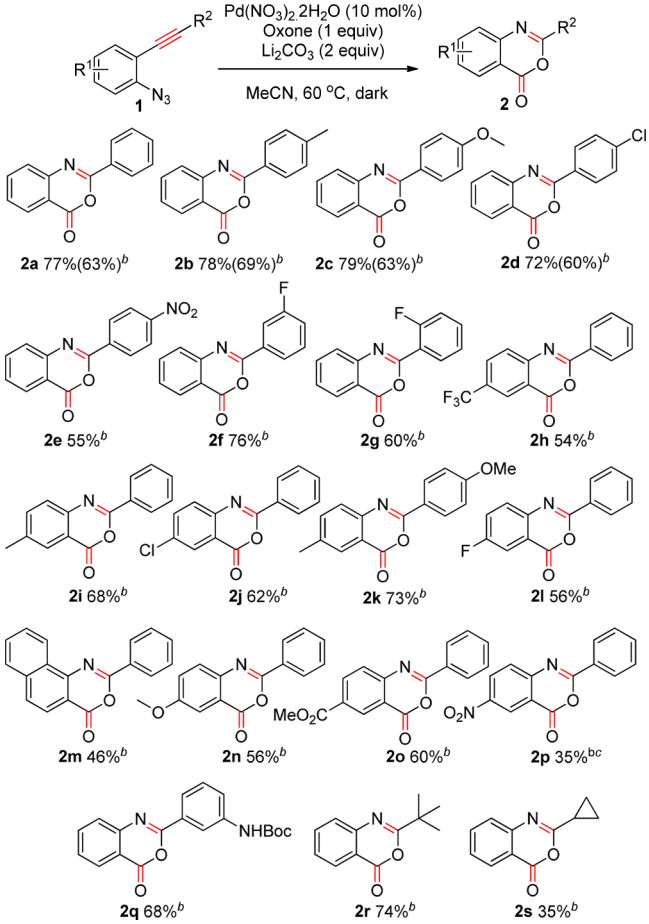
entry	catalyst (mol %)	oxidant	solvent	yield (%)[b]
1	$AgNO_3$ (20)	NFSI	DCE	0
2	$AgNO_3$ (20)/$PdCl_2$ (20)	NFSI	DCE	53
3	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	NFSI	DCE	60
4	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	$PhI(OAc)_2$	DCE	32
5	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	TBHP	DCE	38
6	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	oxone	DCE	70
7	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	oxone	MeCN	77
8[c]	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	oxone	MeCN	61
9[d]	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	oxone	MeCN	66
10[e]	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	oxone	MeCN	49
11	$Pd(OAc)_2$ (10)	oxone	MeCN	25
12	$Pd(TFA)_2$ (10)	oxone	MeCN	28
13	$PdCl_2$ (10)	oxone	MeCN	18
14		oxone	MeCN	0
15	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	oxone	MeCN	40[h]
16	$Pd(NO_3)_2{\cdot}2H_2O$ (10)		MeCN	0[i]
17[f]	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	oxone	MeCN	70
18[g]	$Pd(NO_3)_2{\cdot}2H_2O$ (10)	oxone	MeCN	60

[a]Reaction conditions: **1a** (0.1 mmol), catalyst, oxidant (0.1 mmol), and base (0.2 mmol) in solvent (1 mL), 60 °C, in the dark. [b]GC yield using *n*-tetradecane as internal standard. [c]Li_2CO_3 (1 equiv). [d]$LiHCO_3$ (2 equiv) as base. [e]NaOAc (2 equiv) as base. [f]TEMPO (1 equiv) was added. [g]BHT (2,6-di-*tert*-butyl-4-methylphenol, 1 equiv) was added. [h]Without Li_2CO_3. [i]The reaction gave 40% 2-phenyl-3*H*-indol-3-one.

$AgNO_3$ and $PdCl_2$, the reaction afforded an unexpected 2-phenyl-4*H*-benzo[*d*][1,3]-oxazin-4-one (**2a**), which was confirmed by X-ray single crystal diffraction (entry 2). Since the cleavage of C−C triple bonds is still an underdeveloped area, this, together with the interesting reaction pattern, prompted us to optimize the reaction conditions. Considering the role of $AgNO_3$ as a halogen-scavenger, $Pd(NO_3)_2{\cdot}2H_2O$ was investigated and proven to be a superior catalyst to give product **2a** in 60% yield (entry 3). Further screening of solvent and oxidant followed. Oxone was demonstrated to be a better oxidant than NFSI and other oxidants (entries 4−6). The reaction in MeCN gave the best yield (entry 7). In addition, the base also played a pivotal role. Reducing the amount of base resulted in a lower yield (entry 8). Other weak bases, such as $LiHCO_3$ and NaOAc, gave slightly poor yields (entries 9−10). In contrast to $Pd(NO_3)_2{\cdot}2H_2O$, other palladium catalysts exhibited poor reactivity, and no reaction occurred in the absence of the palladium catalyst (entries 11−14). Control experiments confirmed that all reagents, including the Pd catalyst, oxidant, and base, were necessary to achieve a satisfactory yield (entries 14−16). Addition of free radical scavengers TEMPO and BHT did not cause a significant effect on the outcome (entries 17−18). Thus, the optimal reaction was carried out in the presence of $Pd(NO_3)_2{\cdot}2H_2O$ (10 mol %), oxone (1 equiv), and Li_2CO_3 (2 equiv) in MeCN.

With the optimal reaction conditions, the substrate scope was examined; the results are summarized in Table 2. Substrates

Table 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), $Pd(NO_3)_2{\cdot}2H_2O$ (0.02 mmol), Li_2CO_3 (0.4 mmol), oxone (0.2 mmol) in MeCN (2 mL), dark at 60 °C, 6 h. [b]Isolated yield (the yield in parentheses was obtained with NFSI (0.3 mmol) instead of oxone). [c]80% conversion, 48 h.

bearing both electron-rich and electron-poor aromatic groups on the terminal triple bond (R^2) gave the desired products in moderate to good yields (**2a**−**2g**). Similarly, electronic properties of R^1 have no significant effect on this transformation, and desired products were obtained in comparable yields (**2h**−**2o**, **2q**). What's more, functional groups such as ether, ester, halogen, and amide were well tolerated, although the substrate **1p** bearing a nitro group (R^1) delivered product **2p** in lower yield. In addition to an aryl substituent, the reaction of substrate **1r** with a *tert*-butyl group (R^2) also proceeded very well. For substrate **1s** with a cyclopropyl (R^2) substituent, the reaction gave the desired product in 35% yield. In contrast, when R^2 became a linear alkyl group, the reaction of **1u** could not deliver the desired product. Instead, a nitroalkene product **3**

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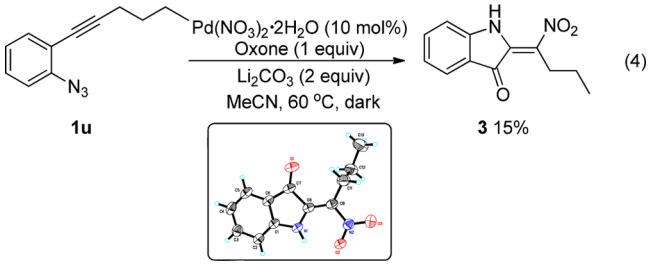
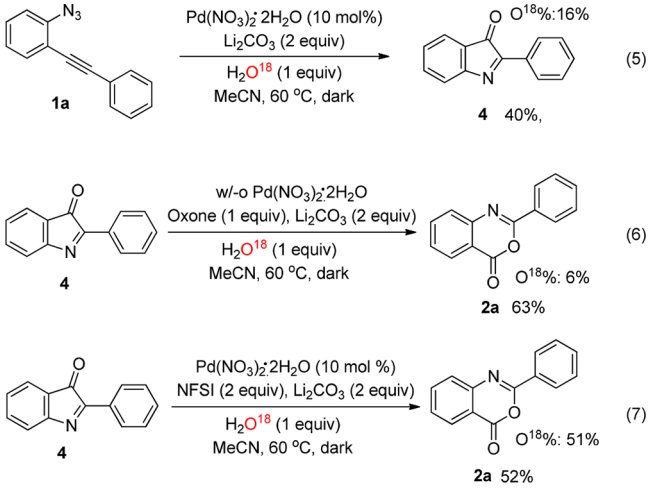
was isolated in 15% yield, which was characterized by X-ray crystallography (eq 4). It is noteworthy that NFSI could also act as a comparable oxidant to give the same products in slightly lower yields (**2a**–**2d**).



With the above results in hand, we turned our attention to address the mechanistic pathway of triple bond cleavage. During the reaction optimization process, a small amount of 2-phenyl-3*H*-indol-3-one (**4**) was detected as the side product. When the reaction was conducted in the absence of oxone, intermediate **4** was obtained as the only isolatable product and in 40% yield (entry 16, Table 1). In addition, compound **4** could be transformed to product **2** in 62% yield by oxone with or without $Pd(NO_3)_2{\cdot}2H_2O$; however, the palladium catalyst was necessary when NFSI was used as the oxidant (for details, see the Supporting Information).

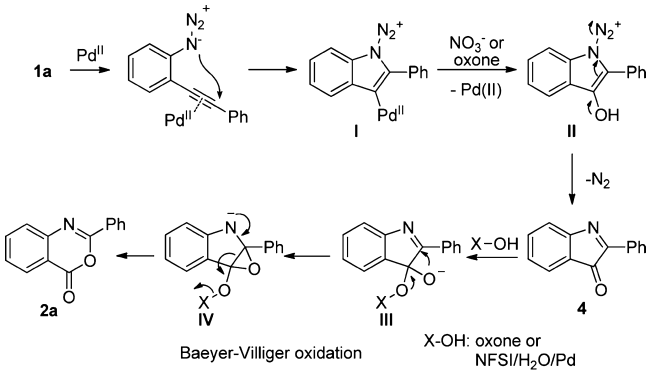
In addition, this reaction involved the incorporation of two oxygen atoms. To gain more detailed information, several experiments were conducted in the presence of $H_2{}^{18}O$: (1) substrate **1a** was treated by $Pd(NO_3)_2{\cdot}2H_2O$ in the absence of oxone, and the related product **4a**, with low ^{18}O atom incorporation, was isolated in 40% yield (eq 5);[36] (2) treatment



of **4a** with oxone afforded product **2a** containing a trace amount of ^{18}O atom (eq 6). However, the product **2a** with 51% ^{18}O atom was obtained when NFSI was used as the oxidant (eq 7).

On the basis of the above results, a proposed mechanism is listed in Scheme 1: The reaction was initiated by amino-palladation of alkynes to generate indolyl–Pd complex **I**, and then the C–Pd bond was oxidized by a nitrate ion or oxone to form 3-hydroxylindole **II**, which tautomerizes to give compound **4**. Following Baeyer–Villiger oxidation of **4** by oxone gave the final product **2**. NFSI as the oxidant had been reported previously,[37] but the exact oxidizing mechanism of **4** is

Scheme 1. The Proposed Mechanism



unclear at this moment. However, the palladium catalyst is necessary, and water is involved in this transformation.

CONCLUSIONS

In summary, a novel Pd-catalyzed cyclization of azidoalkynes/oxidative rearrangement was disclosed to afford a variety of 4*H*-benzo[*d*][1,3]-oxazin-4-ones products. Preliminary study supports a tandem aminopalladation of alkyne and oxidative rearrangement pathway to address the cleavage of the C–C triple bond. Further study of aminofluorination of alkyne continues.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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