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Cascade Reaction to Synthesis of Carbolines from *O*-Methylketoximes and Styrenes via Palladium-Catalyzed C–H bond Activation and Sequential Annulation

Xiao-Pan Fu,[+a] Shi-Biao Tang,[+a] Jin-Yue Yang, [a] Li-Li Zhang,[a] Cheng-Cai Xia[*b] and Ya-Fei Ji[*a]

Abstract: A novel cascade reaction has been described for synthesis of Carbolines via palladium-catalyzed successive C–C/C–N formation from O-methylketoximes and styrenes. The oxime ether auxiliary not only serve as a traceless directing group, but also be partly transformed into the value-added pharmacophore in a two-step, one-pot fashion.

Introduction

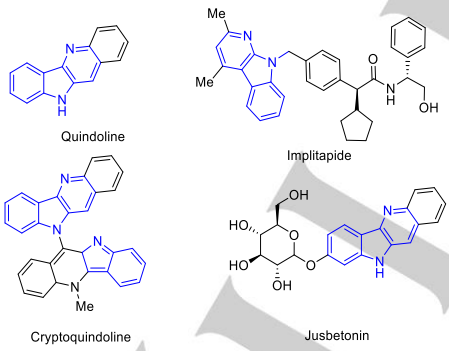
Carbolines are important structural motifs in numerous natural products and bioactive molecules.[1] Carboline derivatives have a wide range of applications not only in the pharmaceutical chemistry,[2,3a-e] but also in the materials.[3f,3g] (Figure 1) Therefore, many methods have been established for synthesis of carbolines derivatives, including Graebe-Ullmann, Fischer indolization, Bischler-Napieralski, and Pictet-Spengler reactions. However, the reactions are required to assemble the carboline frameworks.[4] Therefore, the development of simple and efficient method for construction of the carbolines has attracted significant attention.

Over the past few decades, transition-metal-catalyzed C–H bond functionalization assisted by DG (directing groups) has become an efficient method for C-C and C-X bond formation.[5] Especially in recent years, the *ortho* alkenylation directed by DG provides an atom- and step-economic fashion in contrast to the traditional transformations, such as Heck reaction.[6] Significant progress with the help of various DG such as pyridine,[7] ester,[8] amide,[9] carboxyl [10]and others[11] has been accomplished.

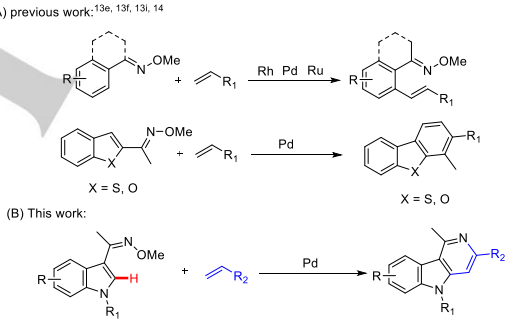
Oxime ethers as heteroatom-containing directing group, have a superior directing ability to assist the C–H bond functionalization.[12] The oxime ethers directed *ortho* C(sp^2)–H functionalization such as acyloxylation,[13h,13d] arylation,[13a,13c] hydroxylation [13g] arylation,[13a,13c] which generally go through a five-membered endo-palladacycle intermediate.[13] Apart from these reactions, Ellman,[13e] Sun[13f] and Jeganmohan[13i] groups respectively reported the *ortho* olefination assisted by oxime ethers via different catalysts There are several reports for metal-catalyzed annulation reactions starting from oxime ethers.[14] (Scheme 1A). Despite tremendous efforts have been made, these reports are limited in the intermolecular alkenylation.[14] Therefore, oxime ethers serve as a traceless directing group, go through a tandem, 2-fold C-H bond functionalization in a one pot fashion with sole catalyst would be of great significance.

To continue our interest,[14h] we here report the palladium-catalyzed the protected Indol-*O*-methyloxime-directed 2-fold C−H bond functionalization with substituted styrenes, providing carbolines in good yields (Scheme 1B). The newly dual functionalization strategy can not only make the step concise and efficient but also could be applied in the synthesis of key functional units.

Figure 1. Some Bioactive Compounds Containing Carboline Structures



Scheme 1. *O*-Methyloxime Directed Oxidative Heck Reaction



Results and Discussion

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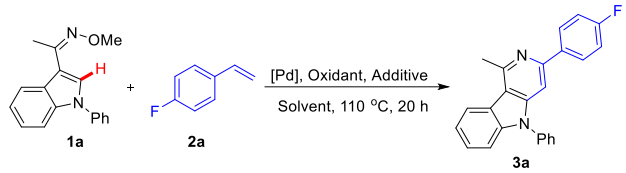
At the outset of the experiment, a variety of reaction conditions were examined. we initially tested the model substrate *O*-methyloxime ether **1a** and 4-fluorostyrene **2a** using the catalyst $Pd(OAc)_2$ (10 mol %), the oxidant AgTFA (1.5 equiv), the base pyridine (20.0 equiv) in AcOH at 110 °C under air (Table1). To our delight, the product **3a** was observed in the yield of 19%. Inspired by that result, different solvents were tested, the yield was improved significantly in HFIP (entries 1-4). Next, oxidants were screened, Ag_3PO_4 gave a better yield than other Ag salts including AgOAc, Ag_2CO_3 and Ag_2O (entries 5-8). When we tested the catalysts, $Pd(OAc)_2$ holding the best transformation other than Pd salts (entries 9-12). Base can improve the reaction[15a,15b] and the pyridine evidently facilitate the transformation (entries 13-19). Different amount of the pyridine was examined (entry 20). When increasing the temperature to 120 °C or decreasing to 100 °C, we observed that the yields were slightly decreased.

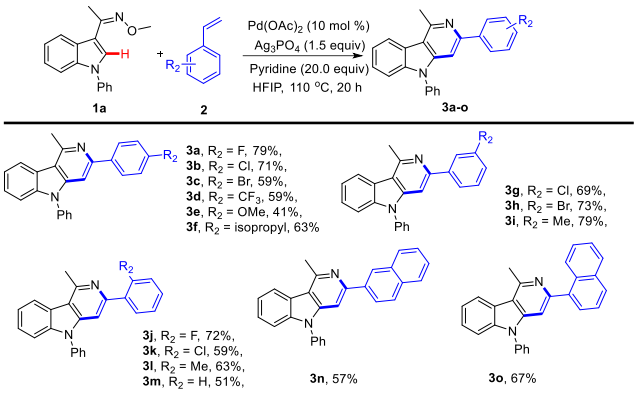
Table 1 Optimization of reaction conditions [a,b]



Entry	Catalyst	Oxidant	Additive	Yield [b](%)
1	$Pd(OAc)_2$	AgTFA	Pyridine	19[c]
2	$Pd(OAc)_2$	AgTFA	Pyridine	24[d]
3	$Pd(OAc)_2$	AgTFA	Pyridine	12[e]
4	$Pd(OAc)_2$	AgTFA	Pyridine	57[f](67)[g]
5	**$Pd(OAc)_2$**	**Ag_3PO_4**	**Pyridine**	**79**
6	$Pd(OAc)_2$	AgOAc	Pyridine	67
7	$Pd(OAc)_2$	Ag_2CO_3	Pyridine	54
8	$Pd(OAc)_2$	Ag_2O	Pyridine	37
9	$Pd(TFA)_2$	Ag_3PO_4	Pyridine	73
10	$PdCl_2$	Ag_3PO_4	Pyridine	70
11	$Pd(PPh_3)_2Cl_2$	Ag_3PO_4	Pyridine	68
12	$Pd(CH_3CN)_2Cl_2$	Ag_3PO_4	Pyridine	61
13	$Pd(OAc)_2$	Ag_3PO_4	NaOAc	<10
14	$Pd(OAc)_2$	Ag_3PO_4	CsOAc	<5
15	$Pd(OAc)_2$	Ag_3PO_4	$Cu(OAc)_2$	NR
16	$Pd(OAc)_2$	Ag_3PO_4	Et_3N	43
17	$Pd(OAc)_2$	Ag_3PO_4	DBU	68
18	$Pd(OAc)_2$	Ag_3PO_4	DABCO	trace
19	$Pd(OAc)_2$	Ag_3PO_4	/	<10
20	$Pd(OAc)_2$	Ag_3PO_4	Pyridine	54[h](66)[i](70)[j]
21	$Pd(OAc)_2$	Ag_3PO_4	Pyridine	77[k] (76)[l]

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), catalyst (10 mol %), oxidant (1.5 equiv), additive (20.0 equiv), HFIP (3.0 mL), 110 °C, 20 h. [b] Isolated yield of **3a**. [c] AcOH (3.0 mL). [d] DCE (3.0 mL). [e] Dioxane (3.0 mL). [f] HFIP (3.0 mL). [g] TFE (3.0 mL). [h] Pyridine (5.0 equiv). [i] Pyridine (10.0 equiv). [j] Pyridine (30.0 equiv). [k] 100 °C. [l] 120 °C.

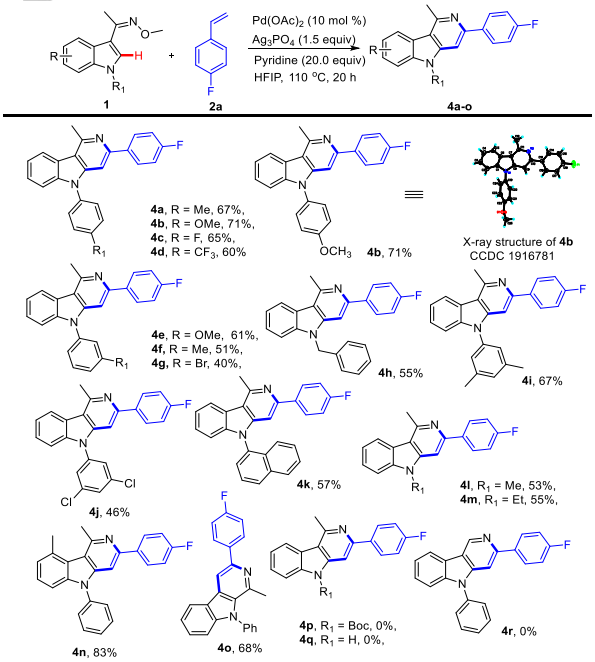
Table 2. Substrate scope of Styrenes.[a,b]



[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Ag_3PO_4 (1.5 equiv), Pyridine (20.0 equiv), HFIP (3.0 mL), 110 °C, 20 h. [b] Isolated yields of **3**.

Having the optimized reaction conditions, we continued to explore the scope of substrates in this reaction. First, a remarkably broad of the styrenes with 1-(1-phenyl-1*H*-indol-3-yl) ethan-1-one *O*-methyl oxime (**1a**) was achieved. As shown in Table 2. The styrenes with electron-withdrawing groups, such as F (**3a**), Cl (**3b**), Br (**3c**), CF_3 (**3d**) on the *para*-position of the phenyl ring, could afford the corresponding alkenylation-cyclization products in good yields. Notably, the DG was directly removed under basic conditions. Moreover, the introduced DG can not only assist the C–H bond functionalization but also be transformed into Carboline units. The electron-donating groups (**3e**, **3f**) gave the satisfactory yield. It is

Table 3. Substrate scope of various indoles.[a,b]



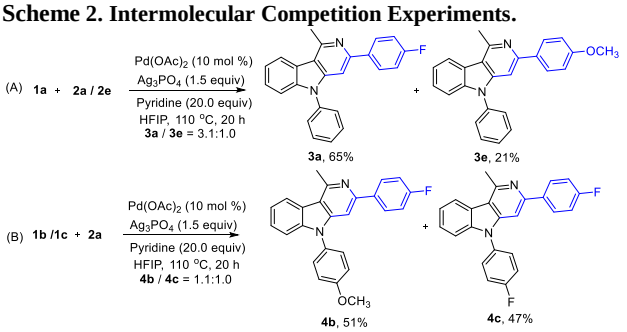
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Ag_3PO_4 (1.5 equiv), Pyridine (20.0 equiv), HFIP (3.0 mL), 110 °C, 20 h. [b] Isolated yields of **4**.

worth mentioning that electron-withdrawing groups on the *para*-position provide higher yield than those electron-donating groups. The substitution at the *meta*-position were also isolated (**3g-3i**). The *ortho*-substituted styrenes were also transformed into the cyclization products in good yields (**3j-3l**). In addition, 1-vinylnaphthalene and 2-vinylnaphthalene could be also delivered the desired product (**3n**, **3o**).

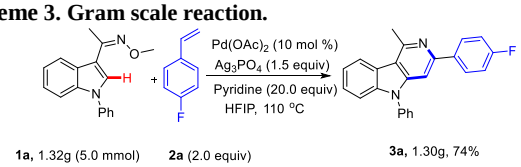
Next, we explored the substrates scope in the alkenylation-cyclization reaction. To our delight, a various of substituted substrates proved to be compatible in the transformation, obtaining the desired products in moderate to good yields (Table 3). The substrates with electron-donating groups (**4a**, **4b**) gave better yield than electron-withdrawing groups (**4c**, **4d**) on the *para*-position of the phenyl. Gratifyingly, the *meta*-substituted substrates (**4e**, **4f**, **4g**) are tolerated under the standard reaction conditions. As we all know, the Br group could be transformed into different functional groups via cross-coupling reaction. Benzyl (**4h**), multiply-substituted (**4i, 4j**), naphthalene (**4k**) were well reacted with **2a**, affording the desired products in good yields. The alkyl-protected indole derivatives offered the moderate yield (**4l, 4m**). Respectively, the phenyl protected indole is crucial for the transformation. Then, substituted on the indol afforded a good yield in 83% (**4n**). 2-Acetyl-indole was also obtained the corresponding product (**4o**). Unfortunately, removable protecting group such as *N*-Boc (**4p**) and the unprotecting group *N*-H (**4q**) were not suitable for reaction. In addition, 3-aldoximine (**4r**) was unable to afford any desired product.

Additionally, we carried out the intermolecular competition experiments to probe the electronic effect of the alkenylation-cyclization reaction (Scheme 2). Firstly, different substituted styrenes **2a** and **2e** (1:1 equiv) with substrate **1a** was performed in 110 °C for 20 h. We isolated the products **3a** and **3e** with the ratio of 3.1/1.0, revealing that the electron-deficient styrene kinetically favored. In contrast, competition experiment between electronically biased *para*-substituted substrates **1b** and **1c** (1:1 equiv) reacted with styrene **2a**, showing the electron-rich substrate (**4b**) reacted preferentially. These observations have agreement with the mode of electrophilic activation.[9a] Moreover, the reaction of gram scale was also examined (Scheme 3).

Scheme 2. Intermolecular Competition Experiments.

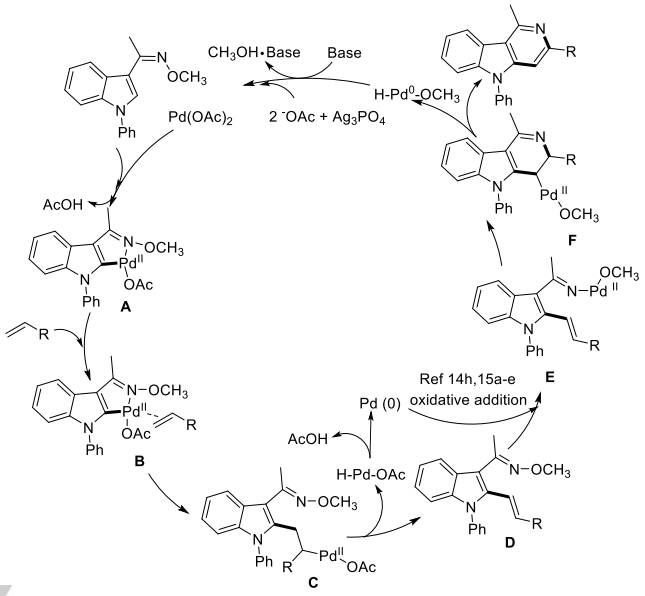


Scheme 3. Gram scale reaction.



Based on documented reports,[13f,14h,15] a plausible reaction pathway through CMD (concerted metalation-deprotonation) pathway[13f,14,16] or an agnostic intermediate[14h,17] was proposed in Schemes 4. Firstly, the substrate **1a** coordinates with $Pd(OAc)_2$ reversible to form endo-cyclopalladated (II) intermediate A. The ligand of the endo-cyclopalladated A interchanges with alkene to provide B, which followed by 1,2-migratory insertion, *β*-hydride elimination and reductive elimination to form the product D and liberation of Pd (0) species. After the oxidative addition, the N-O bond was cleaved and an alkenylpalladium species (II) was generated the key intermediate E.[14h,15a-e] Then C−N bond formation/N−O bond cleavage and β-hydride elimination provide the product.

Scheme 4. Postulated reaction mechanism



Conclusions

In conclusion, we have developed a novel method for synthesis of carbolines via palladium-catalyzed dual C–C/C–N formation and annulation with styrenes. This protocol provides a simple, direct, efficient method to construct diversified carbolines for the screening of the potential natural products and medicines.

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Keywords: carbolines • dual C–C/C–N formation • annulation • styrenes • palladium-catalyzed

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Layout 2:

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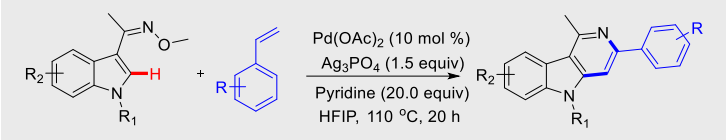

Text for Table of Contents: *Cascade reaction has been described for synthesis of Carbolines via palladium-catalyzed dual C–C/C–N formation and annulation with styrenes.*

Styrenation Annulation

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Title

Cascade Reaction to Synthesis of Carbolines from *O*-Methylketoximes and Styrenes via Palladium-Catalyzed C–H bond Activation and Sequential