ORGANIC
LETTERS

XXXX
Vol. XX, No. XX
000–000

# Nucleopalladation Triggering the Oxidative Heck Reaction: A General Strategy to Diverse β-Indole Ketones

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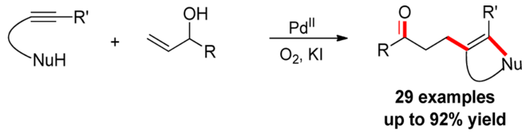
**Received September 24, 2013**

## ABSTRACT



**A simple and efficient palladium-catalyzed oxidative coupling between 2-alkynyl anilines and allylic alcohols is described by using cheap and green dioxygen as the oxidant. These cross-couplings have a large functional group tolerance and are of higher reactivity toward electron nonbaised allylic alcohols. The resultant *β*-indole ketones are readily converted to pharmaceutically significant *β*-indole alcohol/amine and pyrrolo[2,1-*a*]isoquinolines.**

In recent decades, the alkyne-directed transformations catalyzed by palladium have become a powerful tool to construct highly functionalized products.[1] In this regard, nucleopalladation of C−C triple bonds arguably represents one of the most attractive strategies to form multiple carbon−carbon and carbon−heteroatom bonds, thus leading to various significant organic molecules in one step.[2−5] Generally, different kinds of nucleophiles including halides,[2] acetates,[3] amines,[4] and electron-rich carbon nucleophiles[5] have attacked alkynes activated by $Pd^{II}$ to afford the vinyl-Pd species, which could be captured by CO and olefins.[3,6,7] However, olefins used to capture the vinyl-Pd species have usually been the electron-biased olefins, such as α,β-unsaturated olefins and styrenes [eq 1].[3,7] This has been due to electron nonbiased olefins having sluggish reactivity and facing the dilemma of selective β-H elimination.[8,9]

Lei and Kommu respectively reported the Pd-catalyzed oxidative coupling between benzoboric acid and allyic

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[†] These authors contributed equally.

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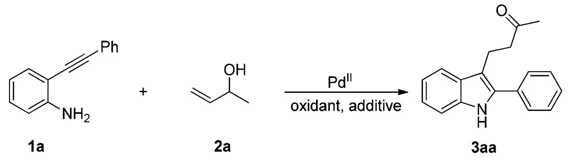
10.1021/ol4027683

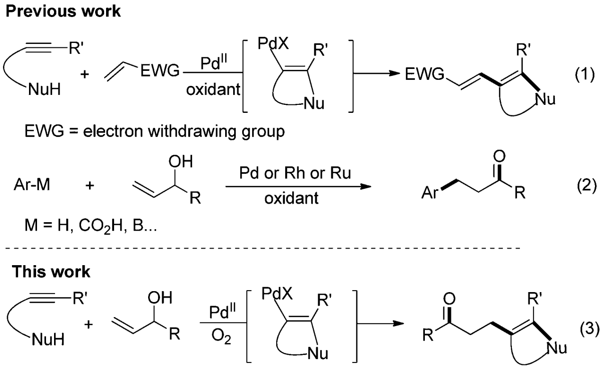
**Table 1.** Impact of Reaction Parameters[a]



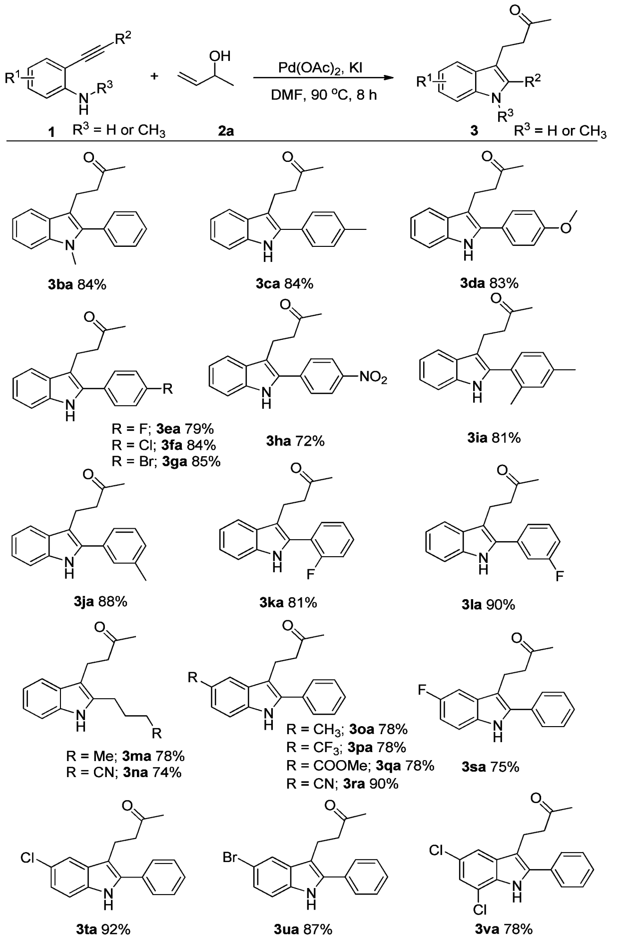
| entry | catalyst | additive | oxidant | yield [%][b] |
|---|---|---|---|---|
| 1 | $PdCl_2$ | KI | $O_2$ (1 atm) | 60 |
| 2 | $Pd(TFA)_2$ | KI | $O_2$ (1 atm) | 54 |
| 3 | $Pd(OAc)_2$ | KI | $O_2$ (1 atm) | 85 (80) |
| 4 | $Pd(OAc)_2$ | $Cs_2CO_3$ | $O_2$ (1 atm) | 13 |
| 5 | $Pd(OAc)_2$ | TBAI | $O_2$ (1 atm) | 34 |
| 6 | $Pd(OAc)_2$ | $K_2CO_3$ | $O_2$ (1 atm) | 55 |
| 7 | $Pd(OAc)_2$ | – | $O_2$ (1 atm) | 63 |
| 8 | $Pd(OAc)_2$ | KI | $Ag_2CO_3$ (1 equiv) | trace |
| 9 | $Pd(OAc)_2$ | KI | $CuBr_2$ (1 equiv) | 20 |
| 10 | – | KI | $O_2$ (1 atm) | n.r. |
| 11 | $Pd(OAc)_2$ | KI | – | n.d. |

[a] Reaction was carried out with **1a** (0.5 mmol), **2a** (1.0 mmol), additive (0.5 mmol), catalyst (0.025 mmol), DMF (1.5 mL), 90 °C for 8 h. [b] Determined by GC using dodecane as the internal standard. The value in parentheses is the yield of isolated product.

alcohols to afford β-aryl ketones and aldehydes [eq 2].[10] Very recently, Glorius and our group achieved the Rh- or Ru-catalyzed highly efficient C–H alkylation and a palladium-catalyzed decarbonxylative alkylation using allylic alcohols as the alkylation reagents.[11] And in continuation of our persistent focus on Pd-catalyzed alkynes–alkenes coupling initiated by nucleopalladation of alkynes,[12] we herein report the intramolecular nucleopalladation of alkynes, using oxygen as the sole oxidant,[13] followed by an oxidative Heck-type reaction with another allylic alcohol to afford the β-heterocycle ketones [eq 3].



**Scheme 1.** Scope of 2-Alkynyl Anilines[a,b]



[a] Reaction was carried with **1** (0.5 mmol), **2** (1.0 mmol), KI (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), DMF (1.5 mL), 90 °C for 8 h. [b] Isolated yield.

The effort was initiated by using 2-(phenylethynyl)-aniline (**1a**) and allyl alcohol (**2a**) as a model reaction in the presence of palladium catalyst under various conditions (Table 1). We briefly studied the solvent effects and results illustrated by the high performance of DMF in terms of yield and reaction time, and we found polar solvents displayed much better activity (see Supporting Information for details). Palladium-catalyst investigation revealed that $Pd(OAc)_2$ showed a higher reactivity (Table 1, entries 1–3). Then we explored the influence of several additives, and 1 equiv of KI gave the best result, which afforded the desired product **3aa** in 85% yield (Table 1, entries 3–6). Furthermore, **3aa** was also obtained in 63% yield when the reaction proceeded without KI (Table 1, entry 7), which suggested KI played a beneficial role in this process.[3c] Among the oxidants screened, metal oxidants showed a lower yield than that with only $O_2$. Only a trace

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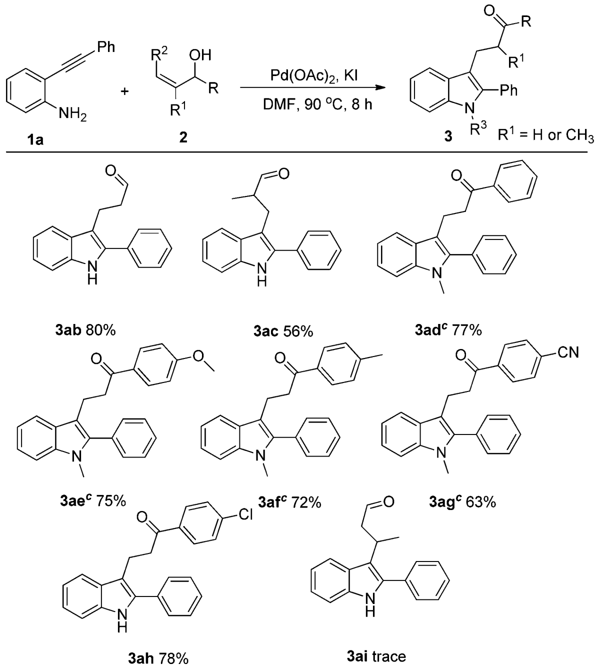
**Scheme 2.** Scope of Allylic Alcohols[a,b]



[a] Reaction was carried with **1** (0.5 mmol), **2** (1.0 mmol), KI (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), DMF (1.5 mL), 90 °C for 8 h. [b] Isolated yield. [c] Isolated yield after methylation.

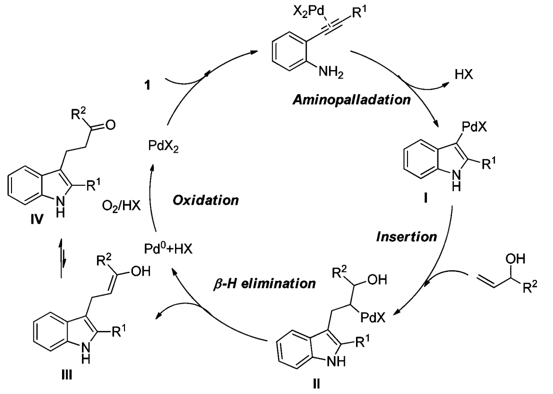
amount of product was obtained when using $Ag_2CO_3$ as the oxidant (Table 1, entries 8, 9). Additionally, control experiments showed that the reaction failed to give the desired product **3aa** without a Pd catalyst or $O_2$ (entries 10, 11).

With the optimal conditions in hand, we investigated the substrate scope of 2-alkynyl anilines for this transformation (Scheme 1). First, *N*-methyl-2-(phenylethynyl)aniline was treated with **2a**, and an 84% yield of **3ba** was obtained. To our delight, the substrates with electron-donating groups (R = Me, OMe), or electron-withdrawing groups (R = F, Cl, Br, $NO_2$), could proceed well in the reaction and afford the corresponding products in good isolated yields (**3ca**−**3ha**).

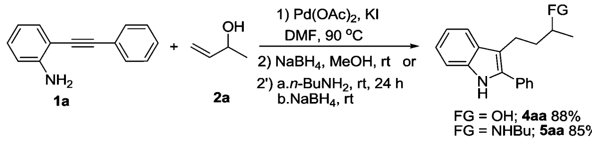
Encouraged by these promising results, some 2-alkynyl anilines containing meta- and ortho-substituted groups reacted with **2a** and gave a high yield of **3ia**−**3la**, respectively. Moreover, **3ma** and **3na** were also successfully formed, which greatly expanded the scope of the products. Besides, substrates **1o**−**1r** including electron-donating or -withdrawing groups on the benzene ring performed well in this transformation and gave the corresponding products **3oa**−**3ra** in moderate to excellent yields. In addition, the halide functional groups, such as −F, −Cl, −Br, were well tolerated in this reaction, which gave the expected products (**3sa**−**3va**) in excellent yields. It is noteworthy that the 2-alkynl anilines including functional groups of biological activity, such as $CF_3$ or COOMe, could be transformed to the desired products **3pa** and **3qa** in 90% and 78% yields, respectively.

Next, we tried to further expand the scope of allylic alcohols for the indole synthesis (Scheme 2). The simplest allyl alcohol was first tested which gave a moderate yield of product **3ab**, and the hydroxy was successfully transformed into the more active aldehyde. And 2-methyl-2-propen-1-ol was tested, although only a 56% yield of **3ac** was isolated. To our disappiontment, nonterminal allylic alcohol reacted with 2-alkynyl aniline, giving the desired product of **3ai** in very low GC yield. In addition, the phenyl substituted allyl alcohols with electron-donating groups (−Me, −OMe), the halide functional group (−Cl), and the electron-withdrawing group (−CN) also proceeded well in this reaction system. All of them could be converted to 2,3-disubstituted indoles **3ad**−**3ah** in moderate yields. However, compounds **3ad**−**3ag** were isolated after methylation, except for **3ah**.

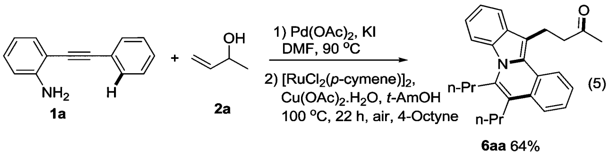
**Scheme 3.** Proposed Mechanism



Naturally occurring and synthetic indole rings are both biologically active. Our products have a similar framework to that of tryptamine.[14] So it greatly inspired us to synthesize the *β*-indole ketones. Then through a simple reduction or reductive amination, *β*-aryl alcohol (**4aa**) or amine (**5aa**) could be obtained in 88% and 85% yields, respectively [eq 4]. More importantly, the indole ring can be also used as a useful oriented functional group for C−H activation via the nucleopalladation process. Consequently, under Ackermann's conditions,[15] the corresponding 2-arylpyrrole **6aa**, which is a kind of bioactive compound and functional material, was successfully formed in 64% yield in two steps [eq 5].



(4)



(5)

On the basis of the above results, we proposed a mechanism for Pd-catalyzed oxidative couplings between 2-alkynyl anilines and allylic alcohols (Scheme 3). This transformation pathway was initiated by aminopalladation of 2-alkynyl

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anilines to afford vinyl palladium intermediate **I**. Subsequently allylic alcohols that were 1,2-migratory were inserted into the C–Pd bond to produce the intermediate **II**,[3c]which easily transformed to the alkyl palladium species **III** by $\beta$-H elimination. This selective $\beta$-H elimination occurred followed by an enol isomerization between **III** and **IV** and finally gave the $\beta$-indole ketones.[11a] In addtion, the $\mathrm{Pd}^{\mathrm{II}}$ active species was regenerated with $O_2$.

In conclusion, we have developed the vinyl-Pd species which were produced though nucleopalladation captured by allylic alcohols to obtain $\beta$-indole ketones. It is a simple and efficient method for constructing 2-substituted and 3-substituted indoles. Notable features of this transformation include the readily available materials, high reactivity, and broad functional group tolerance. Furthermore, molecular oxygen as the oxidant makes the reaction practical and environmentally friendly. Moreover, the products can also be converted into pyrrolo[2,1-*a*]isoquinolines. We believe that this method should provide a new and eco-friendly approach to functional indole synthesis.

**Acknowledgment.** We thank the National Basic Research Program of China (973 Program) (2011CB808600), the National Nature Science Foundation of China (20932002 and 21172076), the Guangdong Natural Science Foundation (10351064101000000), and the Fundamental Research Funds for the Central Universities (2010ZP0003) for financial support.

**Supporting Information Available.** Experimental procedure and characterization of compounds **3aa**–**3va**, **3ab**–**3ah**, **4aa**–**6aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.