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Pd-Catalyzed Cyclization and Carbene Migratory Insertion: New Approach to 3-Vinylindoles and 3-Vinylbenzofurans

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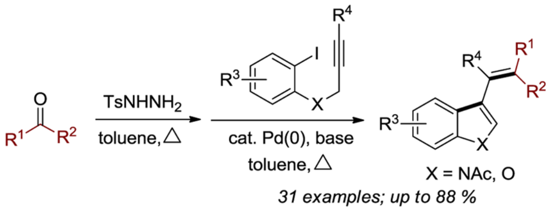
ABSTRACT



A Pd-catalyzed stereoselective synthesis of 3-vinylindoles and 3-vinylbenzofurans has been developed. The reaction merges the alkyne-based Pd-catalyzed cyclization and Pd carbene migratory insertion in a single catalytic cycle, generating a C−C single bond and a C═C double bond in one operation.

Indoles and benzofurans represent privileged structure motifs in many areas, and numerous synthetic methods have been developed related to those structures.[1,2] In particular, 3-vinylindoles and 3-vinylbenzofurans are versatile building blocks in organic synthesis.[3] Moreover, they have been reported to show interesting biological properties.[4] During the past decades, many effective methods have been developed to construct these structures, particularly Pd-catalyzed reactions which have attracted great attention. As summarized in the retrosynthetic representation shown in Scheme 1, the most common approach is the functionalization of a preformed indole system by Pd-catalyzed Heck coupling reactions using 3-halo or 3-OTf indoles with alkenes (Scheme 1, ***a***). One of the drawbacks of this approach is that the *N*-unprotected 3-haloindoles are usually not stable. More recently, direct alkenylation of indoles with alkenes through C−H bond functionalization has emerged as an alternative approach (Scheme 1, ***a′***).[5,6] In 2005, Gaunt and co-workers reported a Pd(II)-catalyzed solvent-controlled Fujiwara−Moritani−Heck coupling of free indoles and alkenes using $Cu(OAc)_2$ as the oxidant.[5] The reaction affords 3-vinylindoles when a DMF−DMSO mixture is used as the solvent. However,

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(1) Selected reviews on indoles, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9644. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215–PR218. (d) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489–4497. (e) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508–3549. (f) Bandini, M. *Org. Biomol. Chem.* **2013**, *11*, 5206–5212.

(2) For a recent review on benzofurans, see: Yeung, K.-S. *Top. Heterocycl. Chem.* **2012**, *29*, 47–76.

(3) For reviews, see: (a) Sundberg, R. J. *Indoles*; Academic: New York, 1996. (b) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303–4427. (c) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193–3328.

(4) (a) Kumar, D.; Kumar, N. M.; Akamatsu, K.; Kusaka, E.; Harada, H.; Ito, T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3916–3919. (b) Robinson, M. W.; Overmeyer, J. H.; Young, A. M.; Erhardt, P. W.; Maltese, W. A. *J. Med. Chem.* **2012**, *55*, 1940–1956. (c) Venkatesan, P.; Sumathi, S. *J. Heterocycl. Chem.* **2010**, *47*, 81–84.

(5) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125–3129.

(6) (a) Djakovitch, L.; Rouge, P. *J. Mol. Catal. A: Chem.* **2007**, *273*, 230–239. (b) Maehara, A.; Tsurugi, H.; Tsurugi, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159–1162. (c) Djakovitch, L.; Rouge, P. *Catal. Today* **2009**, *140*, 90–99. (d) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706–708. (e) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 3024–3033. (f) Chen, W.-L.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Wang, Y.-F.; Wang, Y.-Q. *Org. Lett.* **2012**, *14*, 5920–5923.

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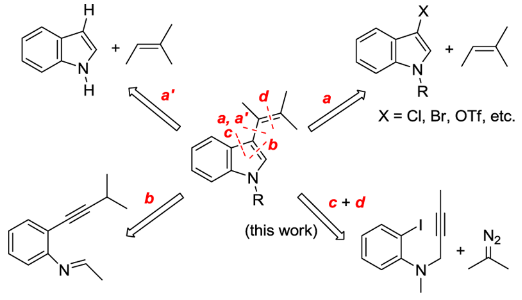
the direct vinylation of benzofuran by this method is always at the 2-position, since the electrophilic palladation of benzofuran is more favored at the 2-position.

Scheme 1. Retrosynthetic Representation of the Pd-Catalyzed Synthesis of 3-Vinylindoles



Pd-catalyzed cyclization represents another powerful approach for the construction of an indole structure, among which the alkyne-based Pd-catalyzed synthesis of indoles has been extensively investigated.[7] In 2000, Yamamoto and co-workers reported an efficient synthesis of 3-vinylindoles by Pd-catalyzed intramolecular cyclization of alkynylimines (Scheme 1, ***b***).[8] Since the imine moiety can be generated *in situ* from the corresponding amine and aldehyde, this reaction has also been extended to a three-component coupling for 3-vinylindole synthesis.

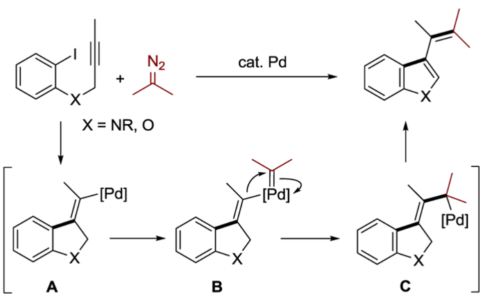
Although significant progress has been made for the synthesis of 3-vinylindoles, some drawbacks exist for the existing methods. For example, the alkene substrates used in the coupling reactions are often limited to those containing electron-withdrawing substituents, and the 3-vinylindole products obtained are usually limited to those bearing a disubstituted alkene moiety. Moreover, little attention has been paid to the synthesis of 3-vinylbenzofurans. Therefore, it is desirable to further develop novel methods for the synthesis of 3-vinylindoles and 3-vinylbenzofurans.

In recent years, we and several other groups have reported a series of Pd-catalyzed C=C bond forming reactions based on a Pd carbene migratory insertion process.[9]

We conceived that, in combination with Pd-catalyzed cyclization of alkynes, such a type of C=C bond forming reaction may be applied to the synthesis of 3-vinylindoles and 3-vinylbenzofurans (Scheme 1, ***c*** + ***d***).

As demonstrated in Scheme 2, the key step involved in this approach is the migratory insertion of the Pd carbene **B** to form intermediate **C**, which is followed by β-hydride elimination. Notably, in this transformation, C–C single bond formation (the cyclization) and C=C double bond formation (carbene coupling) are achieved in a single catalytic cycle.

Scheme 2. Synthesis of 3-Vinylindoles and 3-Vinylbenzofurans Based on Pd Carbene Reaction



At the outset of this investigation, we employed the *N*-tosylhydrazone **2** as the precursor for *in situ* generation of a nonstabilized diazo compound (Bamford–Stevens reaction).[10] We examined the reaction of *N*-acetyl-*N*-(3-phenylprop-2-ynyl)-2-iodoaniline **1a** with *N*-tosylhydrazone **2** in the presence of the Pd(PPh$_3$)$_4$ catalyst and Cs$_2$CO$_3$ in toluene at 80 °C. The reaction worked well to afford the desired 3-vinylindole **3a** in good yield (eq 1). To further simplify the reaction, we attempted a one-pot reaction starting directly from benzadehyde **4a**. Thus, the benzadehyde **4a** was heated with TsNHNH$_2$ at 60 °C in toluene for 10 min, and then *N*-acetyl-*N*-(3-phenylprop-2-ynyl)-2-iodoaniline **1a**, Pd(PPh$_3$)$_4$ catalyst, and Cs$_2$CO$_3$ were added and heating was continued for another 3 h. To our delight, the one-pot reaction afforded the desired 3-vinylindole **3a** in slightly improved yield (eq 2).

The one-pot reaction was then applied to a series of aromatic aldehydes/ketones **4a**–**k** and 2-iodoanilines **1a**–**e** (Scheme 3). The reaction is not markedly affected by the substituents on the aromatic aldehydes. The aromatic aldehydes including those bearing an electron-donating group (**4b**,**c**) and electron-withdrawing group (**4d**–**f**), as well as those sterically hindered aldehydes (**4h**) and heteroaromatic aldehyde (**4i**), all gave the corresponding 3-vinylindoles in moderate to good yields. However, ketones (**4j**, **k**) gave relatively lower yields, which may be attributed to the lower reactivity of the corresponding *N*-tosylhydrazones than these derived from the corresponding aldehydes. The other reaction component, the 2-iodoanilines **1a**–**e**, were then examined. It turned out

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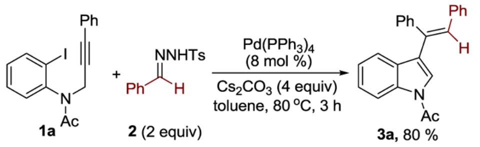
(7) For selected reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (c) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (d) Vlaar, T.; Ruijter, E.; Orru, R. V. A. *Adv. Synth. Catal.* **2011**, *353*, 809–841. (e) Abbiati, G.; Marinelli, F.; Rossi, E.; Arcadi, A. *Isr. J. Chem.* **2013**, *53*, DOI: 10.1002/ijch.201300040. For related approaches, see: (f) Le Strat, F.; Maddaluno, J. *Org. Lett.* **2002**, *4*, 2791–2793. (g) Fressigné, C.; Girard, A.; Durandetti, M.; Maddaluno, J. *Eur. J. Org. Chem.* **2009**, 721–729. (h) Durandetti, M.; Hardou, L.; Clément, M.; Maddaluno, J. *Chem. Commun.* **2009**, 4753–4755. (i) Durandetti, M.; Hardou, L.; Lhermet, R.; Rouen, M.; Maddaluno, J. *Chem. Eur. J.* **2011**, *17*, 12773–12783. (j) Arcadi, A.; Blesi, F.; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Marinelli, F. *J. Org. Chem.* **2013**, *78*, 4490–4498.

(8) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662–5663.

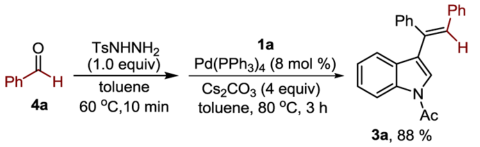
(9) For reviews, see: (a) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015–1026. (b) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486–7500. (c) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560–572. (d) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236–247. (e) Zhang, Y.; Wang, J. *Top. Curr. Chem.* **2012**, *327*, 239–269.

(10) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735–4740.

that a terminal alkyne (R^4 = H) was not a suitable substrate for the reaction, affording the product in low yield (**3l**). This is attributed to the side reactions of the terminal alkyne under the reaction conditions. In contrast, substitution on the aromatic ring does not markedly affect the reaction (**3m**–**o**).



(1)



(2)

Interestingly, this reaction shows excellent stereoselectivity. All the 3-vinylindole products were formed as a single isomer judged by ^{1}H and ^{13}C NMR spectra. For one of the products (**3e**), the *E* configuration was unambiguously confirmed by X-ray diffraction (Figure 1). We assume that all the products have the same *E* configuration based on the comparison of their NMR spectra.

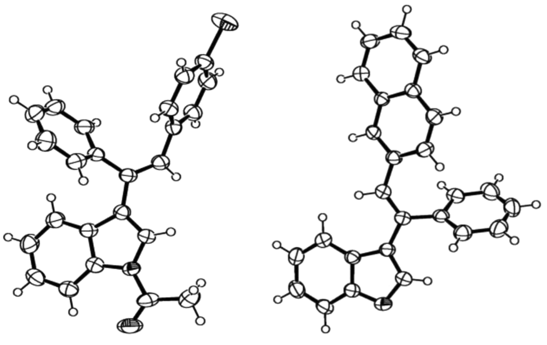
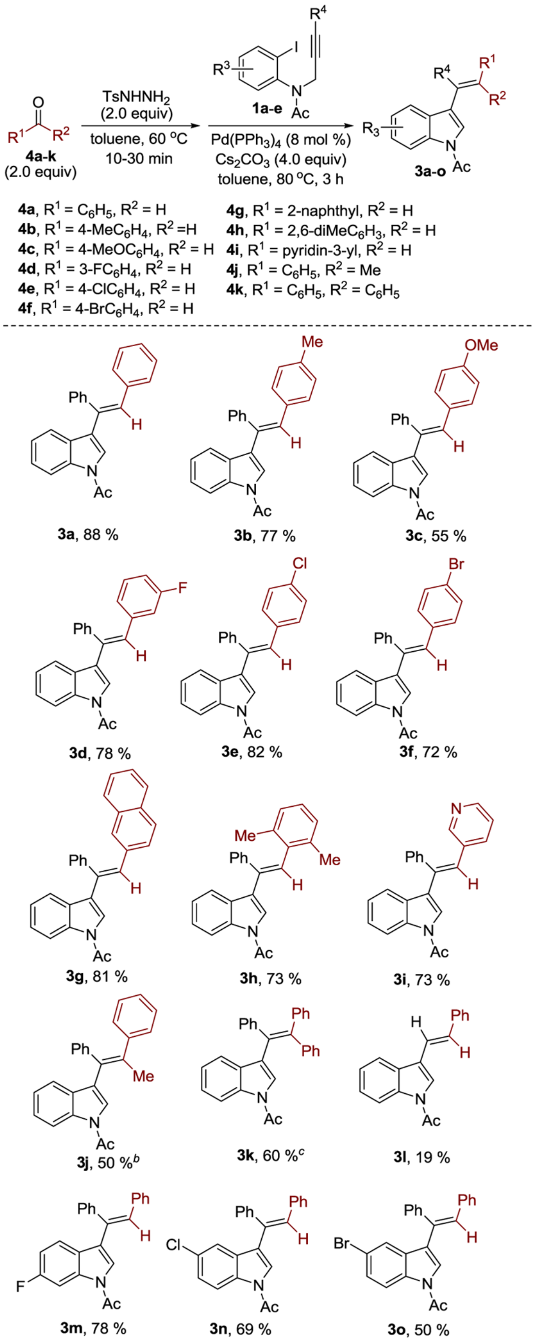

3e **6g**

Figure 1. X-ray structure of **3e** and **6g**.

Furthermore, we applied this methodology to the synthesis of 3-vinylbenzofurans. To our delight, the reactions occurred smoothly under the similar reaction conditions, affording the corresponding 3-vinylbenzofurans **6a**–**p** in moderate to good yields (Scheme 4). The substrate scope is similar to the synthesis of 3-vinylindoles shown in Scheme 3.[11] Notably, 3-vinylfuro[3,2-*b*]pyridine (**6p**) could also be obtained in 74% yield. Again, in all the reactions the 3-vinylbenzofuran products were formed as a single isomer as indicated by their ^{1}H and ^{13}C NMR spectra. For one of the products (**6g**), the *E* configuration was unambiguously confirmed by X-ray diffraction (Figure 1).

Scheme 3. Pd-Catalyzed Synthesis of 3-Vinylindoles[a]



[a] The reaction was carried out in 0.25 mmol scale; the yields refer to the products after isolation by silica gel column. [b] For the second step, the reaction needed another 2 h at 110 °C after heating 3 h at 80 °C. [c] The reaction was carried out by isolating the tosylhydrazone and then submitting it to the second step.

Based on our knowledge of Pd-catalyzed cyclization and Pd carbene reactions, we proposed a reaction mechanism for this 3-vinylindole/3-vinylbenzofuran synthesis (Scheme 5). First, **1a** undergoes oxidative addition to Pd(0) to form Pd(II) species **A**, from which 5-*exo-dig* cyclization occurs to afford Pd(II) intermediate **B**.[7] Then **A** decomposes the in situ formed diazo compound to give Pd carbene **C**, which is followed by migratory insertion to produce intermediate **D**. As there is no *β*-H for palladium in **D**, the palladium

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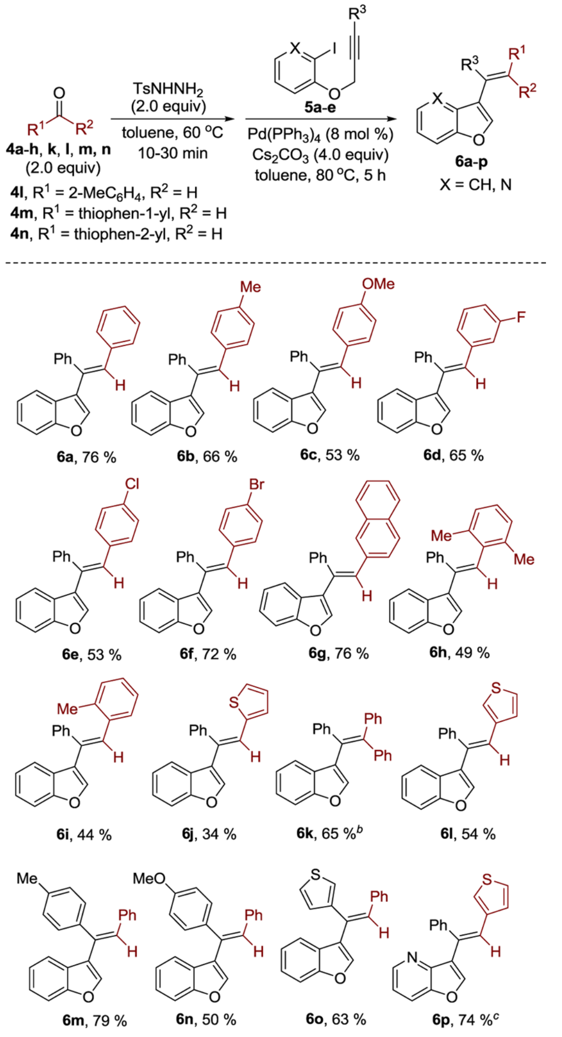
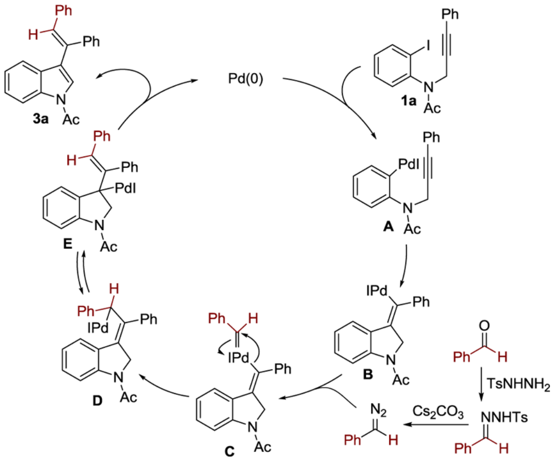
[11] Aliphatic aldehydes do not work under the current conditions. Substrates bearing a substituent on the propargylic position lead to a mixture of *E*/*Z* isomers.

Scheme 4. Pd-Catalyzed Synthesis of 3-Vinylbenzofurans[a]

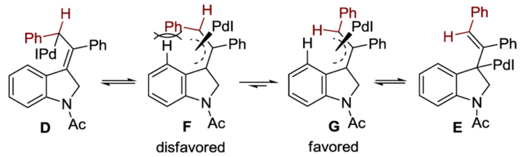


[a] The reaction was carried out in 0.25 mmol scale, and isolated yields are given. [b] The reaction was carried out by isolating the tosylhydrazone and then submitting it to the second step. [c] The reaction temperature was 100 °C.

Scheme 5. Proposed Reaction Mechanism



Scheme 6. Rationalization of Stereoselectivity



undergoes a 1,3-migration to form intermediate **E** through allylpalladium $\eta^1-\eta^3$ interconversion.[12] From **E**, β-H elimination occurs to afford the final product **3a**.

The excellent stereoselectivity observed for the C═C double bond formation in this reaction may be interpreted by the equilibrium shown in Scheme 6. In the allylpalladium $\eta^1-\eta^3$ interconversion, **G** is favored over **F** due to the A (1,3) interaction in the latter case.[13] **G** rearranges to η^1-allylpalladium complex **E**, which undergoes β-H elimination to afford the final product **3a** with *E* configuration in the formed C═C double bond.

In conclusion, we have developed a Pd-catalyzed synthesis of 3-vinylindoles and 3-vinylbenzofurans. This method combines alkyne-based Pd-catalyzed cyclization and Pd carbene chemistry and generates a C−C single bond and a C═C double bond in a single catalytic cycle.[14] This transformation further demonstrates the generality of the incorporation of Pd carbene migratory insertion in various Pd-catalyzed reactions. From the viewpoint of practical applications, the reaction uses easily available starting materials and tolerates various functional groups. Moreover, the reaction shows excellent stereoselectivity. With these features, we expect that this reaction will find applications in the synthesis of 3-vinylindoles and 3-vinylbenzofurans.

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Supporting Information Available. Experimental procedures, characterization data and NMR spectra of all products, X-ray crystallographic data of **3e** and **6g** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] For a similar carbene migration process involving π-allylpalladium intermediates, see: (a) Chen, S.; Wang, J. *Chem. Commun.* **2008**, 4198–4200. (b) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2010**, *352*, 3235–3240. (c) Xiao, Q.; Wang, B.; Tian, L.; Yang, Y.; Ma, J.; Zhang, Y.; Chen, S.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9305–9308.

[13] Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

[14] For a recent report on a similar Pd-catalyzed cascade reaction, see: Liu, X.; Ma, X.; Gu, Z. *Org. Lett.* **2013**, *15*, 4814–4817.

The authors declare no competing financial interest.