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Efficient Synthesis of Heterocyle-Fused β-Naphthylamines via Intramolecular Addition to a Cyano Group Initiated by Nucleopalladation of Alkynes

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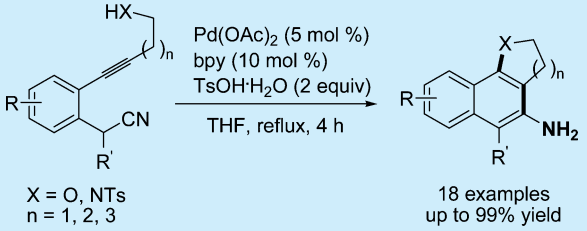
Supporting Information

ABSTRACT: A palladium(II)-catalyzed efficient synthesis of heterocycle-fused β-naphthylamines was accomplished via nucleophilic addition of a carbon−palladium bond to the intramolecular cyano group initiated by nucleopalladation (oxypalladation or aminopalladation) of alkynes.



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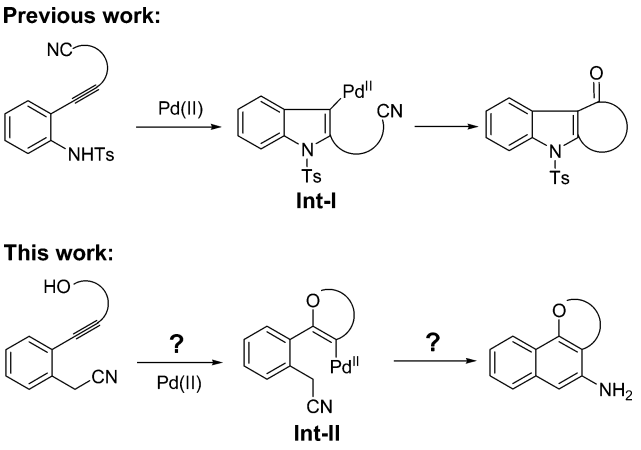
The carbon−palladium bond is generally considered to be electrophilic in traditional palladium chemistry and can undergo various carbon−carbon or carbon−heteroatom bond forming processes.[1] Early examples of the nucleophilic addition of a carbon−palladium bond to the carbonyl group were from the pioneer works of Heck[2] and Larock.[3] In 1996, Vicente's group first reported a direct stoichiometric nucleophilic addition of vinylpalladium species to benzaldehyde.[4] Since then, the nucleophilic addition reaction of the carbon−palladium bond to the carbon−heteroatom multiple bonds has become a new strategy for the carbon−carbon bond formation.[5]

The cyano group is one of the most accessible carbon−heteroatom multiple bonds, and it is widely used in synthetic organic chemistry. Generally, the cyano group is inert in palladium chemistry; e.g., acetonitrile could be used as a ligand or solvent in some palladium-catalyzed reactions. Nevertheless, several research groups have reported the nucleophilic addition of the carbon−palladium bond to the cyano group in the past decade.[6] We were interested in the nucleophilic addition of carbon−palladium bonds to carbon−heteroatom multiple bonds, including the cyano group.[7] From these works, it was demonstrated that the vinyl carbon−palladium bonds generated from nucleopalladation of alkynes could add to the cyano group conveniently.[7a,d] And very recently, a new strategy by exploring the tandem cyclization mode of this reaction to synthesize some heterocycle-fused indoles was also carried out successfully (Scheme 1).[8] Inspired by this result, we then changed the positions of nucleophiles and the cyano group to try to find a new tandem cyclization for the synthesis of heterocycle-fused β-naphthylamines (Scheme 1).

Furthermore, in our previous work, the nucleophiles used in the addition reactions to the nitriles were acetic acid and the NHTs group; we then wondered whether alcohols can also be used as the nucleophile due to its electromeric effect. Based on this consideration, we wish to investigate these kinds of reactions initiated by oxypalladation using an alcohol as the nucleophile to synthesize some heterocycle-fused β-naphthylamines. As we know, β-naphthylamines are widely used in dyestuff industry and are also found to have some applications in the synthesis of axial chiral ligands.[9] In addition, some of the derivatives of heterocycle-fused β-naphylamines were also target molecules in medicinal chemistry.[10] However, in general, these heterocycle-fused β-naphthylamines are not easily available.[10a,11] Thus, we wonder if these compounds could be prepared from some substituted benzenes via a tandem cyclization reaction developed by our group.

Scheme 1. Strategy for the Synthesis of Heterocycle-Fused β-Naphthylamines



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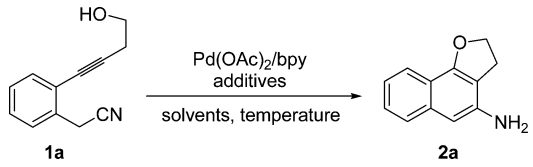
Initially, substrate **1a** was used to study the reaction conditions. It was found that only starting material was recovered using $Pd(OAc)_2$/bpy as the catalyst in dioxane at 100 °C (Table 1, entry 1). This preliminary result indicated that the oxypalladation probably could not occur under the neutral conditions. Several bases were then tried using the same catalyst, since some of the oxypalladations reported in literature were under basic conditions.[12] Unfortunately, none of these conditions worked and only starting material was recovered besides some unidentified products (Table 1, entries 2–4). In our previous works, it was found that the Brønsted acid could activate the cyano group and make it react with the carbon–palladium bond successfully.[8] Thus, we turned our attention to the acidic conditions. When acetic acid was used as the cosolvent, no expected product was detected (Table 1, entry 5).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

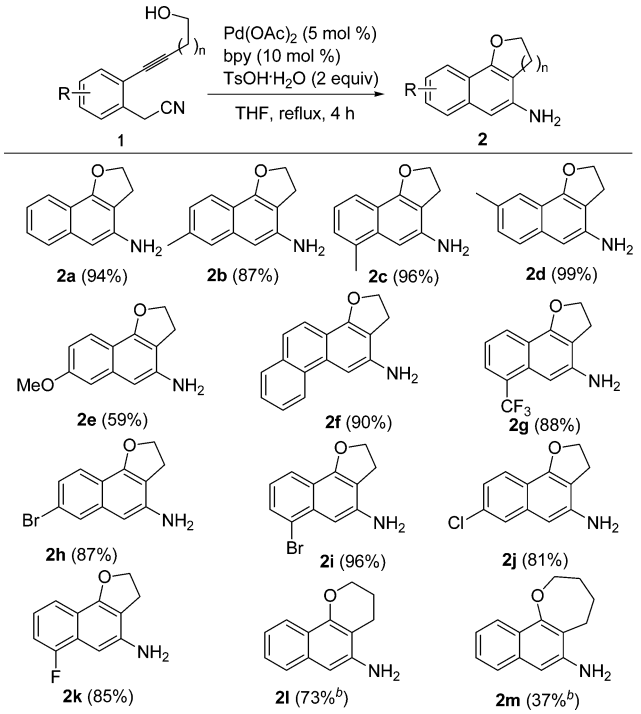
entry	additives	solvents	temp (°C)	yield (%)[b]
1	–	dioxane	100	0
2	Cs_2CO_3	dioxane	100	0
3	Et_3N	dioxane	100	0
4	K_2CO_3	DMF/H_2O (10:1)	100	0
5	–	dioxane/HOAc (4:1)	100	0
6	TsOH·H_2O	dioxane	100	83
7	TsOH·H_2O	dioxane	80	86
8	TsOH·H_2O	dioxane	60	82
9	TsOH·H_2O	THF	reflux	94
10[c]	TsOH·H_2O	THF	reflux	0
11[d]	TsOH·H_2O	THF	reflux	0
12[e]	TsOH·H_2O	THF	reflux	0
13[f]	TsOH·H_2O	THF	reflux	0

[a]Reaction conditions: $Pd(OAc)_2$ (5 mol %), bpy (10 mol %), **1a** (0.3 mmol), and additives (2 equiv) were dissolved in 2.0 mL of the indicated solvents, and then the reaction mixture was stirred for 4 h under the indicated temperature. [b]Isolated yield. [c]No $Pd(OAc)_2$ was added. [d]No bpy was added. [e]$Sc(OTf)_3$ was used as the catalyst. [f]$Cu(OTf)_2$ was used as the catalyst.

To our delight, when TsOH·H_2O was used, the *β*-naphthylamine **2a** was formed successfully in 83% yield (Table 1, entry 6), and the reaction could also proceed smoothly without a significant change in the yield even after decreasing the temperature from 100 to 60 °C (Table 1, entries 7 and 8). A higher yield (94%, Table 1, entry 9) could be given in THF. In the absence of palladium acetate or bpy, the reaction was completely blocked (Table 1, entries 10 and 11), indicating that the palladium(II) catalyst and bpy are crucial to the reaction. In addition, some Lewis acids such as $Sc(OTf)_3$ or $Cu(OTf)_2$ could not catalyze this reaction under the same conditions. Finally, the optimal conditions were chosen as follows: $Pd(OAc)_2$ (5 mol %), bpy (10 mol %), substrate (0.3 mmol), and TsOH·H_2O (2 equiv) were dissolved in 2.0 mL of THF, and the reaction mixture was refluxed for 4 h.

Having established the optimal conditions, we then set out to investigate the substrate scope of this reaction. A series of substituted substrates were tested under the optimal conditions. The results showed that substrates with a methyl group on the benzene ring gave good to excellent yields, and the site of the substitution did not affect the yield obviously (Scheme 2, **2b**-**2d**). Surprisingly, the yield decreased dramatically when the substitution was a methoxy group, and we are unable to give a reasonable explanation for this at present (Scheme 2, **2e**). Substrates with an electron-withdrawing group such as CF_3 also gave a high yield (Scheme 2, **2g**), and this reaction was also suitable for the naphthalene-fused substrate (Scheme 2, **2f**). Substrates with halogen atoms such as Cl, Br, and F gave good to excellent yields (Scheme 2, **2h**–**2k**), and similarly the site of the halogen on the benzene ring did not affect the yields too much. Finally, we tried to extend the fused-heterocycle in the product from a five-membered to six-membered or even to a seven-membered ring system. Fortunately, it worked well for a six-membered ring when the corresponding substrate was reacted under similar conditions for 8 h (73% yield, Scheme 2, **2l**), but for a seven-membered ring, only a 37% yield was achieved under the same conditions (Scheme 2, **2m**).

Scheme 2. Substrate Scope of Oxypalladation-Initiated Tandem Cyclization Reaction[a]



[a]Reaction conditions: $Pd(OAc)_2$ (5 mol %), bpy (10 mol %), substrate (0.3 mmol), and TsOH·H_2O (2 equiv) were dissolved in 2.0 mL of THF, and the reaction mixture was refluxed for 4 h. [b] The reaction time was 8 h.

In our previous work, it was found that a nitrogen atom *α* to the vinyl C–Pd bond could also promote the nucleophilic addition to the cyano group.[8] So we continued to investigate this kind of reaction initiated by aminopalladation. With this purpose, substrates **3a**–**3c** were applied to the reaction and all of them gave the corresponding products in moderate to good yields (Scheme 3, **4a**–**4c**).

In addition, we also examined the reaction of substrate **5**, in which the *tert*-butyl ester could also be used for the oxypalladation reaction in literature.[13] To our delight, naphthylamine **6** was formed successfully in 98% yield. The

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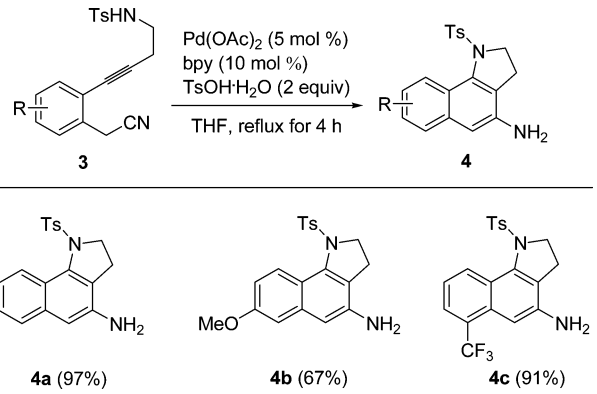
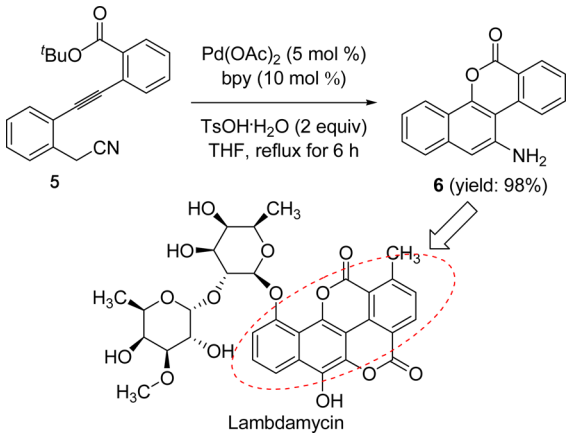
Scheme 3. Substrate Scope of Aminopalladation-Initiated Tandem Cyclization Reaction[a]



[a]Reaction conditions: $Pd(OAc)_2$ (5 mol %), bpy (10 mol %), substrate (0.3 mmol), and $TsOH{\cdot}H_2O$ (2 equiv) were dissolved in 2.0 mL of THF, and then the reaction mixture was refluxed for 4 h.

similar skeleton of compound **6** was found to be the core structure in antibiotics such as the lambdamycin (Scheme 4).[14]

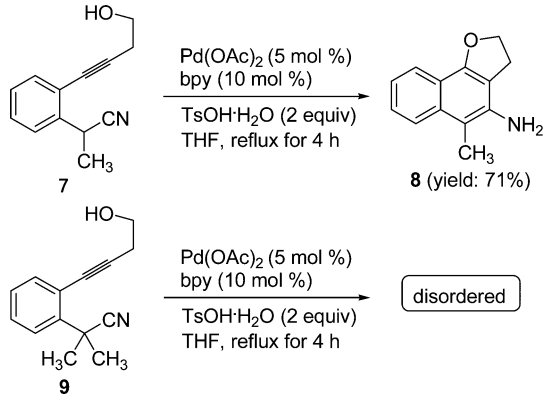
Scheme 4. Tandem Cyclization Using *tert*-Butyl Ester as the Nucleophile



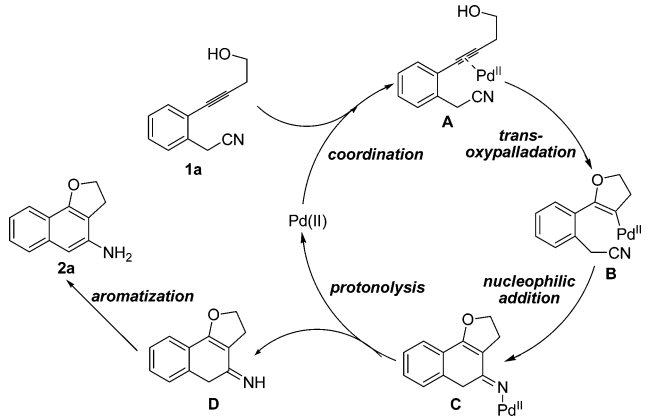
In this reaction, all the substrates bear the hydrogen atom α to the cyano group and it seems that it is indispensable for the formation of β-naphthylamines as seen from Scheme 1. In order to investigate the role of the hydrogen atom, compounds **7** and **9** were tested under the optimal conditions. Product **8** was formed successfully in 71% yield using **7** as the substrate, while the reaction became disordered and no expected product was detected when substrate **9** was used (Scheme 5). This result indicated that the existence of the hydrogen atom α to the cyano group is crucial to the success of this reaction.

Finally, a proposed mechanism is outlined in Scheme 6. Using substrate **1a** as an example, the carbon−carbon triple bond in the substrate coordinates with the palladium(II) catalyst in the first stage of the reaction, and then *trans*-oxypalladation occurs to generate the intermediate **B**. The nucleophilic addition to the cyano group generates **C**, and the protonolysis of **C** results in the formation of the imine **D**. Then **D** undergoes aromatization to generate the final product **2a**. From the mechanism, it can be seen that the existence of a hydrogen atom α to the cyano group can initiate the aromatization of intermediate **D** to β-naphthylamines (isomerization from imine to enamine), which may cause the tandem cyclization to occur successfully.

Scheme 5. Study for the Role of the α-H in the Reaction



Scheme 6. Proposed Mechanism



In conclusion, we have developed a new tandem cyclization mode for the synthesis of a series of heterocycle-fused β-naphthylamines via an intramolecular nucleophilic addition of a carbon−palladium bond to the cyano group. This is a reaction which can be initiated by either oxypalladation or aminopalladation of alkynes without the necessity of a redox system. The existence of the hydrogen atom α to the cyano group is crucial to the reaction, probably because it provides the potential to undergo aromatization. This reaction should have some applications in synthetic chemistry and pharmaceutics due to the special skeleton of the products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compounds characterization data, and copies of NMR spectra. 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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■ REFERENCES

(1) For reviews, see: (a) Negishi, E., de Meijere, A., Eds. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons, Inc.: New York, 2002; Vol. *1*, p 17. (b) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 5th ed.; John Wiley & Sons, Inc.: NJ, 2009; pp 252−254.

(2) Tao, W.; Silverberg, L. J.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1989**, *8*, 2550.

(3) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.

(4) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *Organometallics* **1996**, *15*, 3509.

(5) For reviews, see: (a) Yamamoto, Y.; Nakamura, I. *Top. Organomet. Chem.* **2005**, *14*, 211. (b) Solé, D.; Fernández, I. *Acc. Chem. Res.* **2014**, *47*, 168.

(6) (a) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302. (b) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3551. (c) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987. (d) Lindh, J.; Sjöberg, P. J. R.; Larhed, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7733. (e) Liu, J.; Zhou, X.; Rao, H.; Xiao, F.; Li, C.-J.; Deng, G.-J. *Chem.—Eur. J.* **2011**, *17*, 7996. (f) Ma, Y.; You, J.; Song, F. *Chem.—Eur. J.* **2013**, *19*, 1189. (g) Jiang, T.-S.; Wang, G.-W. *Org. Lett.* **2013**, *15*, 788. (h) Jiang, T.-S.; Wang, G.-W. *Adv. Synth. Catal.* **2014**, *356*, 369.

(7) (a) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343. (b) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987. (c) Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 6765. (d) Xia, G.; Han, X.; Lu, X. *Adv. Synth. Catal.* **2012**, *354*, 2701.

(8) Xia, G.; Han, X.; Lu, X. *Org. Lett.* **2014**, *16*, 2058.

(9) For reviews, see: (a) Kočovský, P.; Vykočil, Š.; Smrčina, M. *Chem. Rev.* **2003**, *103*, 3213. (b) Telfer, S. G.; Kuroda, R. *Coord. Chem. Rev.* **2003**, *242*, 33.

(10) For some examples, see: (a) Alvarez-Fitz, P.; Alvarez, L.; Marquina, S.; Luna-Herrera, J.; Navarro-Garcia, V. M. *Molecules* **2012**, *17*, 8464. (b) Ferreira, S. B.; Salomão, K.; De Carvalho Da Silva, F.; Pinto, A. V.; Kaiser, C. R.; Pinto, A. C.; Ferreira, V. F.; De Castro, S. L. *Eur. J. Med. Chem.* **2011**, *46*, 3071. (c) Silva, R. S. F.; Pinto, F. R.; Goulart, M. O. F.; De Souza Filho, J. D.; Neves, I., Jr.; Lourenco, M. C. S.; Pinto, A. V. *Eur. J. Med. Chem.* **2009**, *44*, 2334. (d) Perez-Sacau, E.; Diaz-Penate, R. G.; Estevez-Braun, A.; Ravelo, A. G.; Garcia-Castellano, J. M.; Pardo, L.; Campillo, M. *J. Med. Chem.* **2007**, *50*, 696. (e) Don, M. J.; Shen, C. C.; Lin, Y. L.; Syu, W. J.; Ding, Y. H.; Sun, C. M. *J. Nat. Prod.* **2005**, *68*, 1066.

(11) (a) Pan, C.; Abdukader, A.; Han, J.; Cheng, Y.; Zhu, C. *Chem.—Eur. J.* **2014**, *20*, 3606. (b) Sallenave, X.; Delbaere, S.; Vermeersch, G.; Pozzo, J.-L. *J. Phys. Org. Chem.* **2007**, *20*, 872. (c) Tominaga, Y.; Castle, L. W.; Raymond, N. *J. Heterocycl. Chem.* **1993**, *30*, 845. (d) Kamel, M.; Allam, M. A.; Abou-Zeid, N. Y. *Tetrahedron* **1967**, *23*, 1863.

(12) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Tetrahedron* **2003**, *59*, 4661. (b) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2002**, *56*, 613. (c) Hosokawa, T.; Murahashi, S.-I. *Heterocycles* **1992**, *33*, 1079.

(13) (a) Wang, H.; Han, X.; Lu, X. *Tetrahedron* **2013**, *69*, 8626. (b) Zhao, P.; Chen, D.; Song, G.; Han, K.; Li, X. *J. Org. Chem.* **2012**, *77*, 1579. (c) Speranca, A.; Godoi, B.; Pinton, S.; Back, D. F.; Menezes, P. H.; Costa, M. D.; Zeni, G. *J. Org. Chem.* **2011**, *76*, 6789. (d) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936.

(14) Fleck, W.; Strauss, D.; Prauser, H.; Jungstand, W.; Heinecke, H.; Gutsche, W.; Wohlrabe, K. *Z. Allg. Mikrobiol.* **1976**, *16*, 521.