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ARTICLE TYPE

Synthesis of 6-Aminophenanthridines via Palladium-Catalyzed Insertion of Isocyanides into *N*-Sulfonyl-2-aminobiaryls

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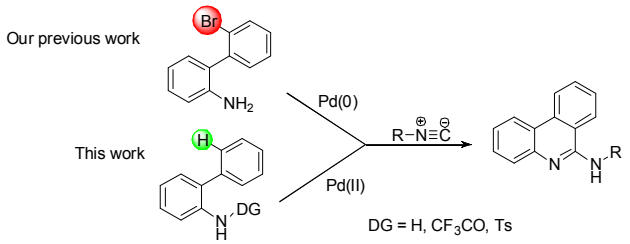
A robust route to a diverse set of 6-aminophenanthridines via palladium-catalyzed C–H activation of *N*-sulfonyl-2-aminobiaryls and isocyanides insertion is reported. This transformation could also provide an important approach for building core framework of conjugated organic polymer materials.

The phenanthridine core is an important structural unit present in a variety of natural products with wide-ranging biological activities and pharmacological properties.[1] Moreover, they are also important frameworks in materials science because of their optoelectronic properties.[2] In view of this, numerous methods used for the preparation of phenanthridines have been developed.[3-5] Despite numerous processes reported to construct these molecular scaffolds, the preparation of 6-aminophenanthridines (6APs) bearing diverse substituents at specific positions remains an attractive research area. Unfortunately, only a few examples were developed for constructing 6-aminophenanthridines.[6] Meanwhile, they are widely known effective inhibitors of yeast prions and successfully used as drugs against mammalian prions.[7] Thus, the development of new methodologies for the synthesis of 6-aminophenanthridines is highly desirable.

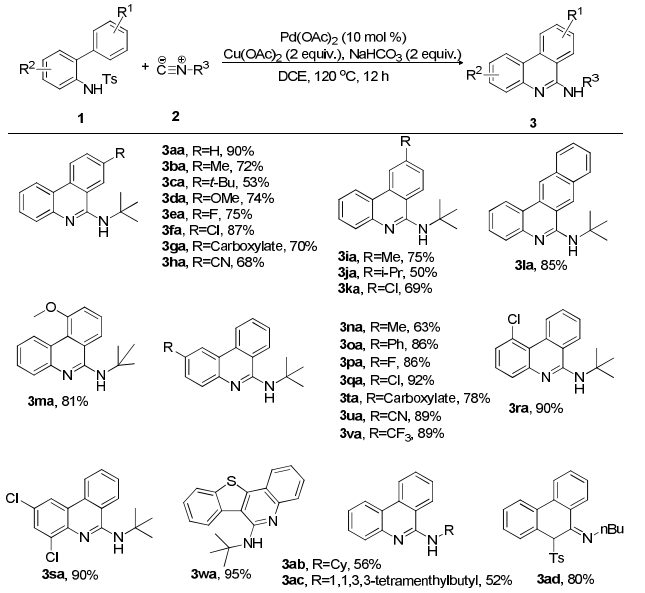
Isocyanides are powerful synthons in the formation of structurally appealing heteroarenes due to their amphoteric property.[8] Very recently, Studer and Yu et al. exploited a novel strategy to prepare 6-substituted phenanthridines via C-radical addition to 2-isocyanobiphenyls.[9] While we were preparing this manuscript, Ji's group reported a $Co(acac)_2$-catalyzed isocyanide insertion with 2-aryl anilines via homolytic aromatic substitution (HAS) type to 6-amino phenanthridine derivatives.[9h] In addition, the reactions of transition metal-catalyzed one-pot cyclization combined with isocyanides for the construction of various heterocycles have also become very attractive in modern organic synthesis.[10] Our group has also discovered that 6-aminophenanthridines could be prepared from 2'-bromo-[1,1'-biphenyl]-2-amine and isocyanides (Scheme 1).[11] However, the major limitation of this method is that the starting material should be prefunctionalized as *ortho*-halogenated anilines. In contrast, the C–H functionalization approach is more economical and environmental. And palladium-catalyzed functionalization of C–H bonds to prepare useful *N*-containing heterocyclics is valuable and more applicable to industrial catalysis.[12] Thus, we decided to investigate the synthesis of 6-aminophenanthridines (6APs) via Pd-catalyzed intramolecular C–H activation and isocyanide insertion (Scheme 1).



. **Scheme 1.** The reaction hypothesis.

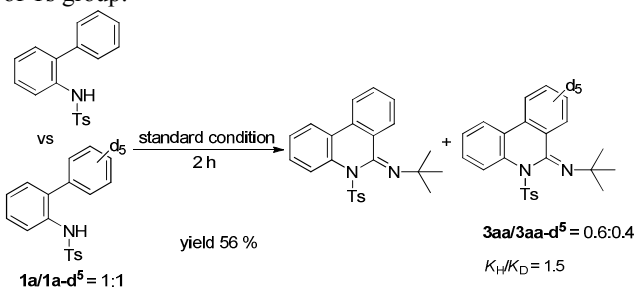
With the standard condition in hand (see ESI for details), various *N*-sulfonyl-2-aminobiaryls and isocyanides were employed to explore this method's functional group compatibility (Table 1). Substituent effect of the aniline moiety of 2-phenylanilines was first evaluated under the optimized conditions. It was shown that both electron-donating groups

Table 1. Substrate Scope of 6-Aminophenanthridines [a]



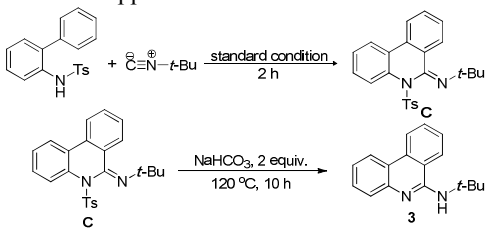
[a] Reaction conditions: All reactions were performed with **1a** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), $NaHCO_3$ (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), and H_2O (0.4 mmol) in DCE (2.0 mL) at 120 °C for 12 h

and electron-withdrawing groups on aryl rings reacted smoothly to afford the corresponding phenanthridinones **3aa-3ha** in good to excellent yields (53-90 %). At the same time, **3ia**, **3ja** and **3ka** were generated as the only product at the less hindered site when substrates bearing a *meta* substituent.[13] In addition to **3ja**, the yields of **3ia-3ma** were satisfying. It was the same with **3la** in good yield. When it came to the substituent effect of the 2-aryl moiety in *N*-sulfonyl-2-aminobiaryls, the process bore a diverse array of substituents on *ortho*, *meta* and *para* positions, including alkyl, aryl, halogen, ester, nitrile, and trifluoromethyl groups, which worked well and gave the desired products in good yields (**3na-3ua**). As expected, it is also applicable to heteroaromatic system such as benzothiophene, giving **3wa** in good yield. In terms of various isocyanides investigated, isocyanides (isocyanocyclohexane, 2-isocyano-2,4,4-trimethylpentane, 1-isocyanobutane) were found to successfully undergo insertion and cyclization, and **3ad** was obtained without the cleavage of Ts group.



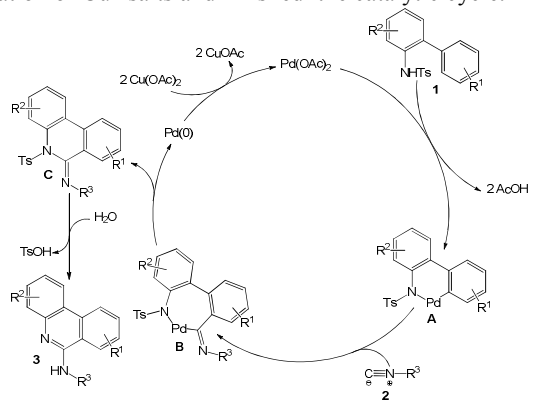
Scheme 2. Kinetic isotope experiments

In order to gain insight into this reaction, we have developed an intermolecular kinetic isotope experiment by the employment of equivalent *N*-sulfonyl-2-aminobiaryl (**1a**) and its deuterated analogues **1a–d^5** under the standard condition except the reaction time was reduced to 2 h (Scheme 2). Through the kinetic isotope effect of 1.5, the C–H activation mechanism was supported in our reaction.



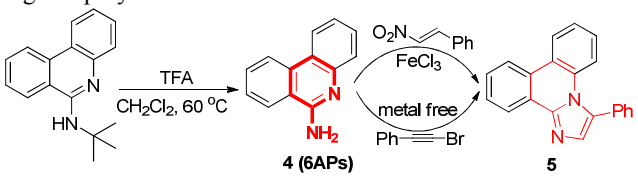
Scheme 3. Study of the intermediate **C**

A plausible mechanism for the synthesis of 6-aminophenanthridines is depicted in Scheme 4. The reaction is initiated by the reaction of Pd^{II} with **1** to form the palladacycle intermediate **A**,[14] followed by the migratory insertion of **2** into **A** to provide intermediate **B**.[15] Subsequent reductive elimination of intermediate **B** forms Pd^0 and intermediate **C**. And we were delightly to synthesize our intermediate **C** (Schem 3). Then with the aid of H_2O and base, Ts group is easily cleaved out of **C** to afford the desired product **3**. Finally, the active Pd^{II} species is regenerated by oxidation of Cu^{II} salts and finished the catalytic cycle.



Scheme 4. Possible Catalytic Cycle.

It is noteworthy that 6-aminophenanthridines which the nitrogen are substituented can be further transformed to free amine product (**4**) from the deprotection of TFA.[16] Moreover, the pyridin-2-amine skeleton derived from 6-aminophenanthridine is an important and reactive class of compound that it can enables rapid formation of the extended conjugated molecules (**5**) (Scheme 5).[17] And in addition, compound **5** was an important core framework of conjugated organic polymer materials.[18]



Scheme 5. Reaction with 6-aminophenanthridine

In summary, a novel C–H activation and isocyanide insertion of *N*-sulfonyl-2-aminobiaryls for the synthesis of the corresponding functionalized 6-aminophenanthridines has been developed. From a synthetic point of view, this protocol represents a simple, efficient and practical way to construct 6-aminophenanthridines with diverse functional groups in good yields with high regioselectivity. The application of this method to the synthesis of 6-aminophenanthridine derivatives and other heterocyclic compounds is ongoing in our laboratory.

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Supporting Information Available: Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

1 (a) S. Simeon, J. L. Rios, A. Villar, *Pharmazie.*, 1989, **44**, 593; (b) B. D. Krane, M. O. Fagbule, M. Shamma, *J. Nat. Prod.*, 1984, **47**, 1;

(c) O. B. Abdel-Halim, T. Morikawa, S. Ando, H. Matsuda, M. Yoshikawa, *J. Nat. Prod.*, 2004, **67**, 1119; (d) M. Blanchot, D. A. Candito, F. Larnaud, M. Lautens, *Org. Lett.*, 2011, **13**, 1486; (e) K. Merz, T. Muller, S. Vanderheiden, G. Eisenbrand, D. Marko, S. Bräse, *Synlett*, 2006, **20**, 3461; (f) A. A. Ali, H. M. El Sayed, O. M. Abdallah, W. Steglich, *Phytochemistry*, 1986, **25**, 2399; (g) S. D. Phillips, N. Castle, R. *J. Heterocycl. Chem.*, 1981, **18**, 223.

2 (a) N. Stevens, N. O'Connor, H. Vishwasrao, D. Samaroo, E. R. Kandel, D. L. Akins, C. M. Drain, N. J. Turro, *J. Am. Chem. Soc.*, 2008, **130**, 7182; (b) J. Zhang, J. R. Lakowicz, *J. Phys. Chem., B*, 2005, **109**, 8701; (c) S. L. Bondarev, V. N. Knyukshto, S. A. Tikhomirov, A. N. Pyrko, *Opt. Spectrosc.*, 2006, **100**, 386.

3 (a) M. E. Budén, V. B. Dorn, M. Gamba, A. B. Pierini, R. A. Rossi, *J. Org. Chem.*, 2010, **75**, 2206; (b) V. A. Vaillard, M. E. Budén, S. E. Martín, R. A. Rossi, *Tetrahedron Lett.*, 2009, **50**, 3829; (c) S. M. Barolo, X. Teng, G. D. Cuny, R. A. Rossi, *J. Org. Chem.*, 2006, **71**, 8493; (d) J. K. Laha, S. M. Barolo, R. A. Rossi, G. D. Cuny, *J. Org. Chem.*, 2011, **76**, 6421.

4 (a) S. De, S. Mishra, B N. Kakde, D. Dey, A. Bisai, *J. Org. Chem.*, 2013, **78**, 7823; (b) L. Anna M, C M. Williams, B. Stefan, *J. Org. Chem.*, 2011, **76**, 9127.

5 (a) T. Gerfaud, L. Neuville, J. P. Zhu, *Angew. Chem. Int. Ed.*, 2009, **48**, 572.

6 (a) F. Gug, S. Bach, M. Blondel, J.-M. Vierfond, A-S. Martin, H. Galons, *Tetrahedron*, 2004, **60**, 4705; (b) F. Gug, N. Oumata, D. Tribouillard-Tanvier, C. Voisset, S. N. Bach, M. Blondel, H. Galons, *Bioconjugate Chem.*, 2010, **21**, 279; (c) F. Gug, M. Blondel, N. Desban, S. Bouaziz, J-M. Vierfond, H. Galons, *Tetrahedron Lett.*, 2005, **46**, 3725.

7 S. Bach, N. Talarek, J.-M. Vierfond, Y. Mettey, H. Galons, L. Meijer, C. Cullin, M. Blondel, *Nat. Biotechnol.*, 2003, **21**, 1075 .

8 (a) A. D□mling, *Chem. Rev.*, 2006 , **106**, 17; (b) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.*, 2010, **110**, 5235; (c) A. V. Lygin, A. de Meijere, *Angew. Chem., Int. Ed.*, 2010, **49**, 9094; (d) A. D□mling, I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (e) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem., Res.*, 2003, **36** , 899.

9 (a) B. Zhang, C. Mück-Lichtenfeld, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.*, 2013 , **52** , 10792; (b) Y. Cheng, H. Jiang, Y. Zhang, S. Y. Yu, *Org. Lett.*, 2013, **15**, 5520; (c) Q. L. Wang, X. C. Dong, T. B. Xiao, L. Zhou, *Org. Lett.*, 2013, **15**, 4846; (d) M. Tobisu, K. Koh, T. Furukawa, N. Chatani, *Angew. Chem., Int. Ed.*, 2012, **51**, 11363; (e) D. Leifert, C. G. Daniliuc, A. Studer, *Org. Lett.*, 2013, **15**, 6286; (f) H. Jiang, Y. Z. Cheng, R. Z. Wang, M. M. Zheng, Y. Zhang, S. Y. Yu, *Angew. Chem. Int. Ed.*, 2013, **52** , 13289; (g) B. Zhang, C. G. Daniliuc, A. Studer, *Org. Lett.*, 2014, **16**, 250; (h) T.-H. Zhu, S.-Y. Wang, Y.-Q. Tao, T.-Q. Wei, and S.-J. Ji, *Org. Lett.*, 2014, **16**, 1260.

10 (a) P. J. Boissarie, Z. E. Hamilton, S. Lang, J. A. Murphy, C. Suckling, J. *Org. Lett.*, 2011, **13**, 6256; (b) J. Vicente, I. Saura-Llamas, J. García-López, *Organometallics*, 2009, **28**, 448; (c) J. Vicente, M. T. Chicote, A. J. Martínez-Martínez, A. Abellán-López, *Organometallics*, 2010, **29**, 5693; (d) G. V. Baelen, S. Kuijer, L. Rýček, S. Sergeyev, E. J. J. Janssen, F. U. W. de Kanter, B. Maes, E. V. A. Ruijter, R. Orru, *Chem. Eur. J.*, 2011, **17**, 15039.

11 B. F. Liu, Y. B. Li, M. Z. Yin, H. W. Huang, H. F. Jiang, *Adv. Synth. Catal.*, 2012, **354**, 2288.

12 (a) T. Vlaar, E. Ruijter, A. Znabet, E. Janssen, F. J. J. de Kanter, B. U. W. Maes, R. V. A. Orru, *Org. Lett.*, 2011, **13**, 6496; (b) D. P. Curran, W. Du, *Org. Lett.*, 2002, **4** , 3215; (c) P. J. Z. Boissarie, E. Hamil-ton, S. Lang, J. A. Murphy, C. J. Suckling, *Org. Lett.*, 2011, **13**, 6256; (d) G. Qiu, G. Liu, S. Pu, J. Wu, *Chem. Commun.*, 2012, **48**, 2903; (e) G. Qiu, Y. He, J. Wu, *Chem. Commun.*, 2012, **48**, 3836; (f) T. Miura, Y. Nishida, M. Morimoto, M. Yamauchi, M. Murakami, *Org. Lett.*, 2011, **13**, 1429; (g) G. V. Baelen, S. Kuijer, L. Rycek, S. Sergeyev, E. Janssen, F. J. J. de Kanter, B. U. W. R Maes, E. R. uijter, V. A. Orru, *Chem. Eur. J.*, 2011, **17**, 15039; (h) Y. Wang, H. G. Wang, J. L. Peng and Q.Zhu, *Org. Lett.*, 2011, **13**, 4604.

13 In order to prove our inference, we did a NOE test of **3ia**, which the result was what we expected. As for the NOE spectrogram of **3ia**, see the supporting information.

14 (a) S. W. Youn, J. H. Bihn, B. S. Kim, *Org. Lett.*, 2011, **13**, 3738; (b) J. Vicente, I. Saura-Llamas, M.-J. Oliva-Madrid, and J.-A. García-López, *Organometallics*, 2011, **30**, 4624; (c) M.-J. Oliva-Madrid, J-A. García-López, I. Saura-Llamas, D. Bautista and J. Vicente, *Organometallics*, 2012, **31**, 3647.

15 (a) J. Vicente, J.-A. Abad and W. F□rtsch, *Organometallics*, 2001, **20**, 2704; (b) J. Vicente, J.-A. Abad, and J. López-Serrano, *Organometallics*, 2005, **24**, 5044; (c) J. Vicente, I. Saura-Llamas, J.-A. García-López and B. Calmuschi-Cula, *Organometallics*, 2007, **26**, 2768, (d) J. Vicente and I. Saura-Llamas, *Comments Inorg. Chem.*, 2007, **28**, 39.

16 P. P. Sharp, M. G. Banwell, J. Renner, K. Lohmann, A. C. Willis, *Org. Lett.*, 2013, **15**, 2616.

17 (a) H. Cao, X. H. Liu, L. M. Zhao, J. H. Cen, J. X. Lin, Q. X. Zhu, M. L. Fu, *Org. Lett.*, 2014, **16**, 146; (b) R.-L. Yan, H. Yan, C. Ma, Z.-Y. Ren, X.-A. Gao, G.-Sh. Huang, Y.-M. Liang, *J. Org. Chem.*, 2012, **77** , 2024; (c) J. Zeng, Y. J. Tan, M. L. Leow, X. W. Liu, *Org. Lett.*, 2012, **14**, 4386; (d) S. Santra, A. K. Bagdi, A. Majee, A. Hajra, *Adv. Synth. Catal.*, 2013, **355** , 1065; (e) Z. Q. Wu, Y. Y. Pan, X. G. Zhou, *Synthesis*, 2011, **14**, 2255; (f) Y. F. Zhang, Z. K. Chen, W. L. Wu, Y. H. Zhang, W. P. Su, *J. Org. Chem.*, 2013, **78**, 12494; (g) Y. Gao, M. Z. Yin, W. Q. Wu, H. W. Huang, H. F. Jiang, *Adv. Synth. Catal.*, 2013, **355**, 2263; (h) H. He, J. Hao, H. Xu, Y. P. Mo, H.Y. Liu, J. J. Han, A. W. Lei, *Chem. Commun.*, 2012, **48**, 11073.

18 W. Pisula, F. Dierschke, K. Müllen, *J. Mater. Chem.*, 2006, **16**, 4058.