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Efficient Synthesis of C−N-Coupled Heterobiaryls by Sequential N−H Functionalization Reactions

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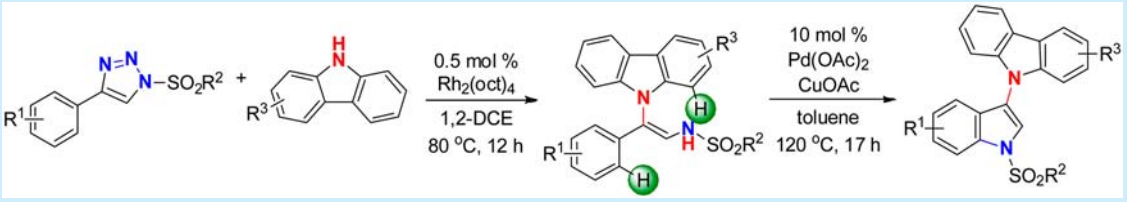
Supporting Information



ABSTRACT: C−N-coupled heterobiaryls were synthesized by sequential N−H functionalization reactions: stereoselective rhodium-catalyzed N−H insertion, followed by regioselective palladium-catalyzed C−H amination. Because of the good substrate scope and excellent selectivity, the developed method presents a novel approach for the synthesis of heterobiaryls, which are potent antibiotics.

Nitrogen-containing heterocycles such as pyrroles, indoles, and carbazoles are very common structural units in biologically active natural and unnatural compounds as well as in other functional materials.[1] Similar to monomeric heterocycles, heterobiaryls are interesting not only because they have unique structures but also because they exhibit a wide range of biological activities (e.g., antitumor, antibiotic, psychotropic, anti-inflammatory, and antihistaminic activities).[2−5] Since the 1990s, naturally occurring C−N-coupled heterobiaryls have consistently received increasing attention. Furukawa et al. have reported the isolation of the biscarbazole alkaloid murrastifoline-A from the root bark of *Murraya euchrestifolia* Hayata (Figure 1).[3] One of the C−N-coupled bispyrrole antibiotics,

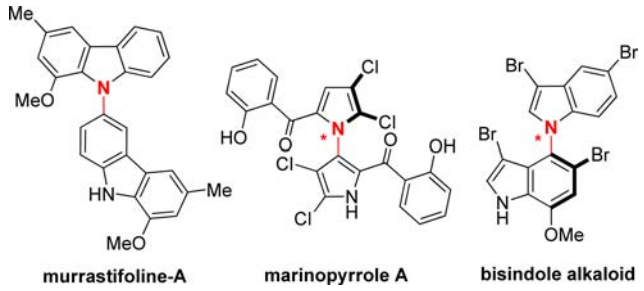


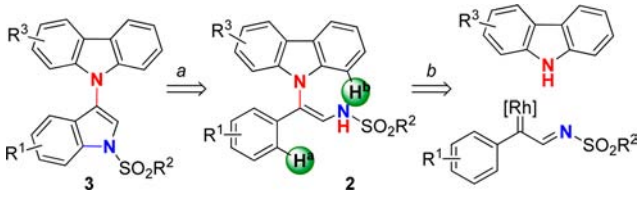
Figure 1. C−N-coupled heterobiaryl natural products.

marinopyrrole-A, was discovered and synthesized in 2008.[4] A series of bisindole alkaloids isolated from blue-green alga 25 *Rivularia firma* were also reported.[5]

Although natural products such as bis(heterobiaryls) have inspired the development of numerous amination reactions, studies of *N*-aryl-linked heterocycles are still limited.[2] Moreover, in most cases, the synthetic routes to such heterocycles are complicated because they require the use of prefunctionalized starting materials for the Ullmann reaction or the Buchwald−Hartwig amination. Therefore, the development of a method to synthesize C−N-bonded heterobiaryls in a straightforward manner from simple, easily available precursors is invaluable, especially for the discovery of new antibiotics.

Our laboratory and other research groups have reported reactions of rhodium(II) azavinyl carbene, which is generated from 1-sulfonyl-1,2,3-triazole, with N-containing heterocycles.[6] Given the recent interest in the characteristics exhibited by this carbene species, we envisioned their application to synthesize C−N-coupled heterobiaryls (Scheme 1). Building on the

Scheme 1. Synthetic Strategy for Unnatural C−N-Bonded Heterobiaryls



modified N−H insertion of rhodium(II) azavinyl carbene (Scheme 1, step b),[6e,7] a unified approach facilitated by regioselective C−H amination (step a)[8] would yield C−N-coupled carbazole−indoles **3**.

Although electrophilic reactions are predominant between carbenes and pyrroles (indoles),[6b,9] the desired N−H insertion between 1-sulfonyl-1,2,3-triazoles **1** and 9*H*-carbazole using 0.5 mol % of $Rh_2(oct)_4$ as the catalyst at 80 °C was successfully

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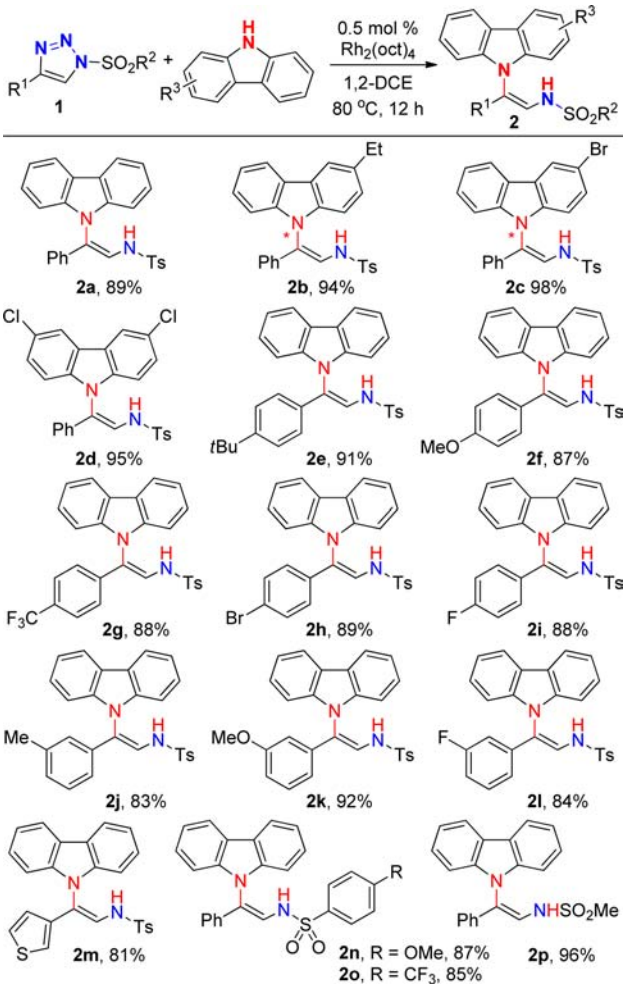
accomplished, affording products in good to excellent yield (Scheme 2).

Scheme 2. Stereoselective N−H Insertion Reactions[a,b]



[a]Reaction conditions: 1-sulfonyl-1,2,3-triazole (**1**, 1.2 equiv), carbazole (0.2 mmol), $Rh_2(oct)_4$ (0.5 mol %), and 1,2-DCE (0.5 mL) at 80 °C for 12 h. [b]Isolated yield.

Figure 2 shows the single-crystal analysis of the carbazolated enamide **2**; a geometrical single isomer, (*Z*)-form, was observed.

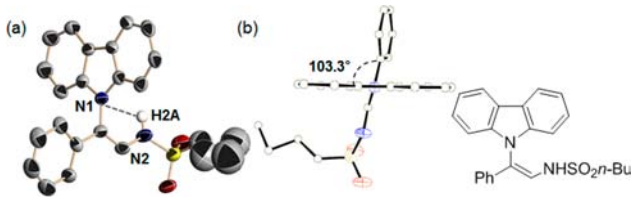


Figure 2. (a) Crystal structure of N-carbazolated enamide. (b) Dihedral angle between carbazole and enamide is 103.3°.

As listed in Scheme 2, a number of carbazoles, including mono- and disubstituted carbazoles, efficiently underwent N−H insertion with **1**, affording **2a**−**2d** (89−98%). Notably, by using nonsymmetrical carbazoles, atropisomers of products **2b** and **2c** were formed because of the constricted rotation about the C−N axis.[10,11] We also examined the scope of 1-sulfonyl-1,2,3-triazoles; various functional groups were tolerated under the reaction conditions. Even by varying the electronic and steric character of the R^1 substituent in **1**, no effect was observed on the reaction efficiency of **2e**−**2l** (83−92%). Moreover, a substrate containing a heterocyclic group afforded the corresponding product **2m** (81%) in comparable yield. Furthermore, for a substrate containing an N1-aliphatic sulfonyl group, the reaction proceeded with the formation of **2p** in excellent yield (96%).

To complete the synthetic method of C−N-coupled heterobiaryls, we initiated our investigation of the regioselective Pd(II)-catalyzed C−H amination of the obtained product **2**. While remarkable progress has been made in the synthesis of indoles by transition-metal-catalyzed C−H amination, regioselective synthetic routes from enamines, rather than anilines, have been rarely explored (Figure 3, *a*).[12] Furthermore, the desired

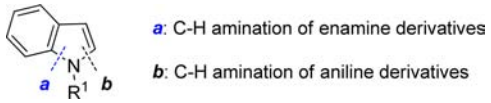
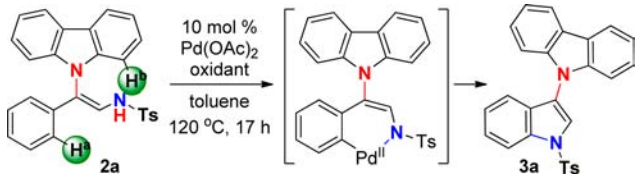


Figure 3. Possible C−H amination strategies of indole.

reaction is more challenging because regioselective cyclization requires an anti-orientation between carbazoles and the *N*-sulfonyl amino group, which is achieved by the palladium-catalyzed isomerization of the enamine double bond.

Preliminary studies show that the performance of the oxidant was crucial in the intramolecular C−H amination of **2a** (Table 1).[10] While a number of oxidants such as $PhI(OAc)_2$, $K_2S_2O_8$,

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant (equiv)	co-oxidant (equiv)	yield[b] (%)
1	$PhI(OAc)_2$ (1.2)		<1
2	$K_2S_2O_8$ (1.2)		15
3	BQ (1.2)		10
4	Ag_2CO_3 (1.2)		33
5	Ag_2CO_3 (2.0)		<1
6	Ag_2CO_3 (0.5)	Cu_2O (0.5)	47
7	Ag_2CO_3 (0.5)	CuOAc (0.5)	66
8	Ag_2CO_3 (0.5)	CuOAc (1.2)	85
9		CuOAc (3.0)	86

[a]Reaction conditions: **2a** (0.2 mmol), 10 mol % of $Pd(OAc)_2$, and oxidant and toluene (2.0 mL) at 120 °C for 17 h. [b]^{1}H NMR yields of **3a** using CH_2Br_2 as the internal standard.

and BQ were less effective, Ag_2CO_3 (1.2 equiv) was compatible and gave the desired C−N-coupled carbazole−indole **3a** in 33% yield (entries 1−4, respectively). Unexpectedly, the yield rather decreased for the reaction using more than 2.0 equiv of Ag_2CO_3 (entry 5). With further oxidant system screening, the addition of Ag_2CO_3−CuOAc (0.5 equiv each) was observed to improve the yield to 66% (entry 7). Moreover, the best yield of the desired product was obtained with the use of 0.5 equiv of Ag_2CO_3 and 1.2 equiv of CuOAc as the co-oxidant system (entry 8). Using an excess of CuOAc was another alternative for attaining full conversion (entry 9).

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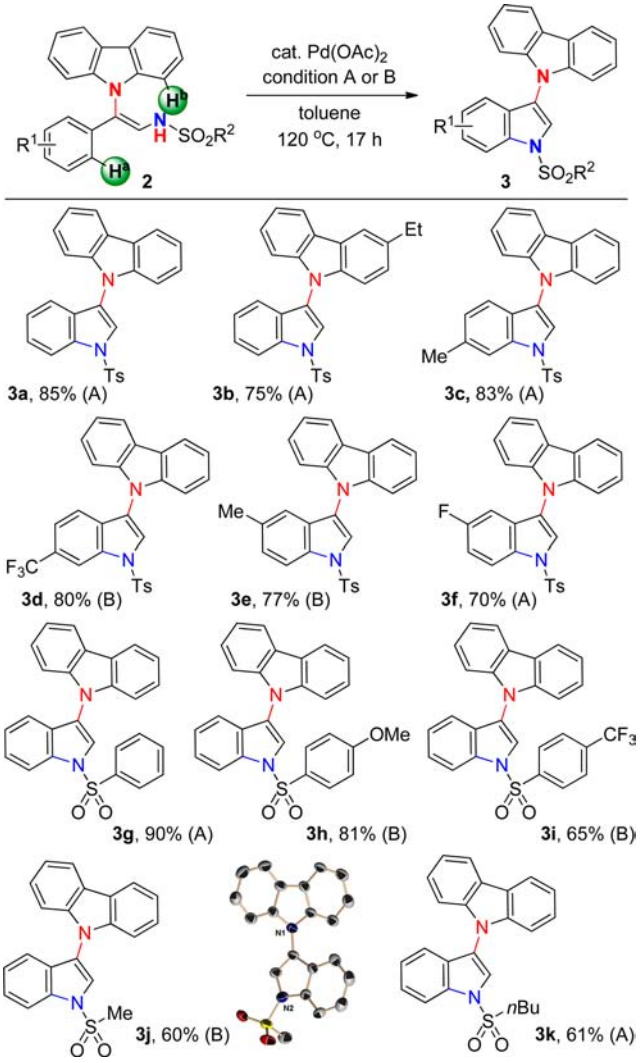
Having established the optimized conditions, we decided to test the scope of **2** to obtain various C−N-coupled carbazole−indoles (Scheme 3). A substrate bearing substituted carbazole

Scheme 3. Formation of Heterobiaryls by Regioselective C−H Amination[a,b]



[a]Condition A: **2** (0.2 mmol), 10 mol % of $Pd(OAc)_2$, CuOAc (3.0 equiv), toluene (2.0 mL) at 120 °C for 17 h. Condition B: **2** (0.2 mmol), 15 mol % of $Pd(OAc)_2$, Ag_2CO_3 (0.5 equiv), CuOAc (1.2 equiv), toluene (2.0 mL) at 120 °C for 17 h. [b]Isolated yield.

underwent C−H amination smoothly to afford the corresponding heterobiaryl **3b** in good yield (75%). Varying the electronic character (i.e., electron-donating and electron-withdrawing groups) on **2** did not significantly influence the reaction; as a result, the desired products **3c** and **3d** were obtained in 83 and 80% yields, respectively. Notably, high regioselectivity was observed even though the reaction was conducted with substrates having the R^1 substituent at the meta position under the optimized conditions, affording **3e** and **3f**. We were also pleased to observe that a series of substrates **2** bearing different electronic substituents on the sulfonyl group readily underwent the reaction to afford products **3g**−**3i** in high yields of 65−90%. Moreover, aliphatic sulfonyl groups were also tolerated, affording **3j** and **3k**, albeit in low yield.

In summary, C−N-coupled heterobiaryls are efficiently synthesized by sequential N−H functionalization reactions. Various 9*H*-carbazoles underwent insertion into the rhodium(II) azavinyl carbene species in a stereoselective manner to afford (*Z*)-ene-1,2-diamine, which cyclizes to indole by palladium-catalyzed C−H amination. Owing to the compatibility of this method with various substrates, the novel construction of unprecedented C−N-coupled heterobiaryls is possible.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new compounds and crystallographic data. 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) (a) *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Saxton, J. E., Eds.; Wiley-Interscience: New York, 1983 and 1994; Vol. 25. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (d) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193.

(2) (a) Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfarth, M.; Lobin, W. *J. Am. Chem. Soc.* **2001**, *123*, 2703 and references cited therein. For a review, see: (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563. For recent examples, see: (c) Kitawaki, T.; Hayashi, Y.; Chida, N. *Heterocycles* **2005**, *65*, 1561. (d) Kitawaki, T.; Hayashi, Y.; Ueno, A.; Chida, N. *Tetrahedron* **2006**, *62*, 6792. (e) Börger, C.; Kataeva, O.; Knölker, H.-J. *Org. Biomol. Chem.* **2012**, *10*, 7269. (f) Hung, T. Q.; Thang, N. N.; Hoang, D. H.; Dang, T. T.; Villinger, A.; Langer, P. *Org. Biomol. Chem.* **2014**, *12*, 2596.

(3) Ito, C.; Wu, T.-S.; Furukawa, H. *Chem. Pharm. Bull.* **1990**, *38*, 1143.

(4) Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629.

(5) Norton, R. S.; Wells, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 3628.

(6) (a) Zibinsky, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1507. (b) Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6802. (c) Chuprakov, S.; Worrell, B. T.; Selander, N.; Sti, R. K.; Fokin, V. V. *J. Am. Chem. Soc.* **2014**, *136*, 195. (d) Xing, Y.; Sheng, G.; Wang, J.; Lu, P.; Wang, Y. *Org. Lett.* **2014**, *16*, 1244. (e) Sheng, G.; Huang, K.; Chi, Z.; Ding, H.; Xing, Y.; Lu, P.; Wang, Y. *Org. Lett.* **2014**, *16*, 5096. (f) Lee, D. J.; Han, H. S.; Shin, J.; Yoo, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 11606. (g) Ryu, T.; Baek, Y.; Lee, P. H. *J. Org. Chem.* **2015**, *80*, 2376. For the recent review, see: (g) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151.

(7) For an overview of catalyzed insertions of diazo compounds into N−H bonds, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998; Chapter 8.2. (b) Gillingham, D.; Fei, N. *Chem. Soc. Rev.* **2013**, *42*, 4918.

DOI: 10.1021/acs.orglett.5b00625
Org. Lett. 2015, 17, 1830−1833

(8) For the recent reviews of C−H amination, see: (a) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (c) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* **2012**, *44*, 1778. (d) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901.

(9) (a) Gibe, R.; Kerr, M. A. *J. Org. Chem.* **2002**, *67*, 6247. (b) Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 604. (c) Alford, J. S.; Davis, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 10266. For recent examples on the reaction of metal carbenes with electron-rich heterocycles, see: (d) Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 440. (e) Yu, Z.; DeAngelis, A.; Cai, Y.; Zhu, S.; Wang, G.; Zhou, Q. *Adv. Synth. Catal.* **2011**, *353*, 2939. (f) Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 11035. (g) Ma, B.; Qui, H. Q.; Li, M.; Jiang, L.; Lv, F.; Zan, L.; Zhai, C.; Doyle, M. P.; Hu, W. *Nat. Chem.* **2012**, *4*, 733. (h) Chen, M.; Wu, H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904. (i) Xing, Y.; Sheng, G.; Wang, J.; Lu, P.; Wang, Y. *Org. Lett.* **2014**, *16*, 1244.

(10) See the Supporting Information for details.

(11) Louillat, M.-L.; Biafora, A.; Legros, F.; Patureau, F. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 3505.

(12) For the recent review, see: (a) Yoshikai, N.; Wei, Y. *Asian J. Org. Chem.* **2013**, *2*, 466. For recent examples of a synthetic method for indoles, see: (b) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (c) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, *134*, 9098. (d) Nanjo, T.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2012**, *14*, 4270. (e) Gogoi, A.; Guin, S.; Rout, S. K.; Patel, B. K. *Org. Lett.* **2013**, *15*, 1802. (f) Feng, X.; Wang, H.; Yang, B.; Fan, R. *Org. Lett.* **2014**, *16*, 3600. (g) Jang, Y. H.; Youn, S. W. *Org. Lett.* **2014**, *16*, 3720.

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Org. Lett. 2015, 17, 1830−1833