Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Palladium-Catalyzed [2 + 2 + 2] Annulation via Transformations of Multiple C−H Bonds: One-Pot Synthesis of Diverse Indolo[3,2-*a*]carbazoles

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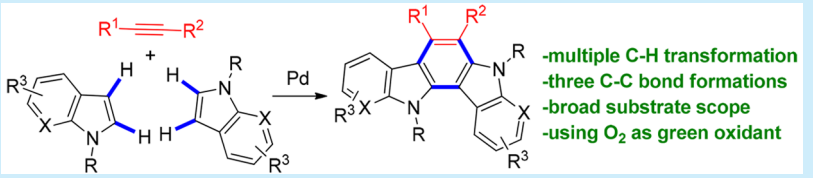
Supporting Information



ABSTRACT: A Pd-catalyzed novel cascade reaction has been developed for the synthesis of indolo[3,2*a*]carbazoles involving multiple C−H transformation−annulations between the indoles and alkynes. The method involves molecular oxygen as the sole oxidant and is an effective and step-economic process.

In recent years, transition-metal-catalyzed organic reactions via C−H bond activation[1] and functionalization[2] have been a highly intriguing research area. The main advantage of the C−H activation/functionalization approach lies in its atom- and step-economic process.[3] Among the various versions of C−H bond activations, double C−H bond activation of arene/heteroarene−annulation of alkyne has been rapidly developed in recent years.[4] Catalysts such as Rh and Pd have been well-investigated for this purpose by Jiao et al.,[5] Dong et al.,[6] Miura, Satoh, and co-workers,[7] Cheng et al.,[8] Li et al.,[9] and others.[4c,10] However, to date, the multiple C−H transformation−annulations of alkynes remain limited.[11] As part of our ongoing studies on the development of newer methodologies for functionalized heteroaromatics[12] and fused indoles[13] and in continuation of our interest, we investigated multiple Pd-catalyzed C−H transformation−annulations between indoles and alkynes for the first time. In the cascade reaction, three new C−C bonds are rapidly formed to build the molecular complexity, such as indolo[3,2-*a*]carbazoles.

The indolocarbazole framework has been found to be an integral part of several natural products, bioactive molecules, and drugs.[14] Among those, Asteropusazle A (**1**), Asteropusazle B (**2**), and Recemosin B (**3**) are notable examples for indolo[3,2-*a*]carbazoles (see Figure 1). In addition, carbazole scaffolds has been used extensively in the application of optical and solar cells.[15] Because of the isomeric forms of indolocarbazoles,[16] the [3,2-*a*]carbazole framework has not been thoroughly studied. Consequently, various methods have been developed for the synthesis of functionalized indolo[3,2-*a*]carbazoles during the past several years.

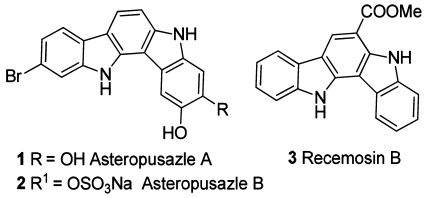
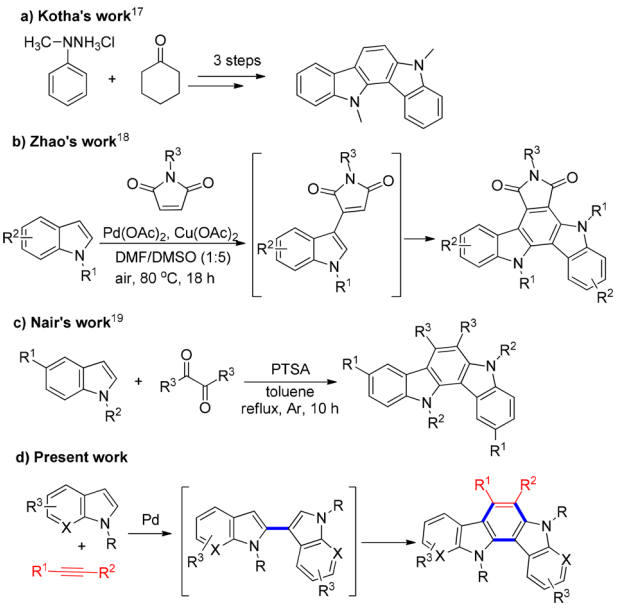


Figure 1. Representative compounds with an indolo[3,2-*a*]carbazoles structural motif.

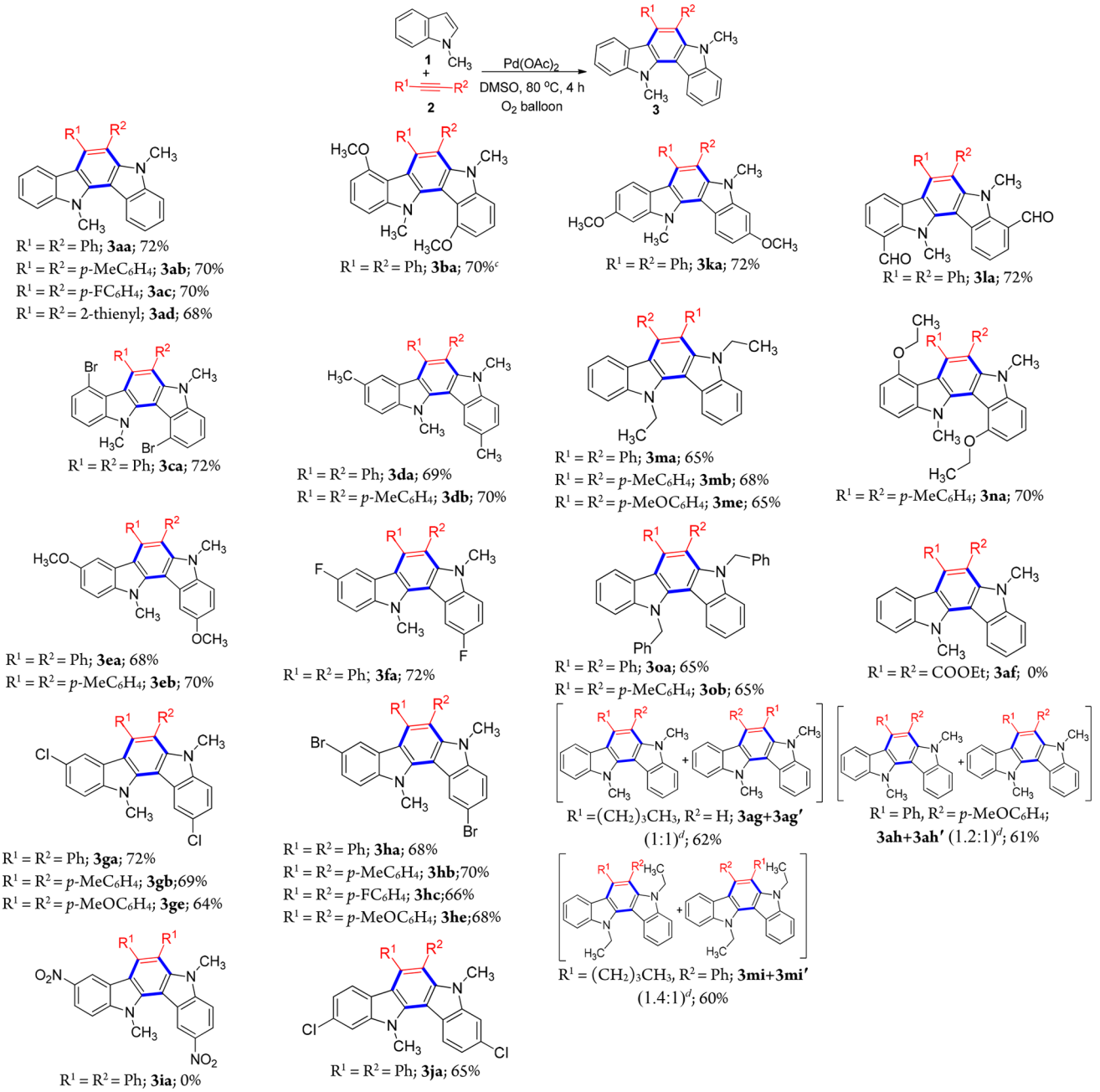
Scheme 1. Approaches to Synthesis of Indolo[3,2-*a*]carbazoles



Received: August 2, 2018

DOI: 10.1021/acs.orglett.8b02465
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Cascade Multiple C−H Transformations−Annulation of Indoles 1 with Alkynes 2[a,b]



[a]Reaction conditions: indole **1** (0.763 mmol), alkyne **2** (0.381 mmol), $Pd(OAc)_2$(0.076 mmol), DMSO (2 mL), 80 °C, 4 h under O_2. [b]Yields of isolated products are given. [c]Reaction performed on 1 mmol scale. [d]Ratio of the regioisomers was determined by ^1H NMR.

In 2016, Kotha's group developed synthetic strategies to prepare indolocarbazoles via a 2-fold Fischer indolization in three steps (see Scheme 1a).[17] Zhao and co-workers successively demonstrated the formation of indolopyrrolocarbazoles from indoles and maleimides via double successive oxidative Heck reactions and thermal electrocyclization (see Scheme 1b).[18] Acid catalyzed synthesis of indolo[3,2-*a*]-carbazoles starting from indoles and diaryl-1,2-diones was reported by Nair in 2008 (see Scheme 1c).[19] While many of these methods are effective, they require a multistep process and/or prefunctionalized starting materials, excess usage of metal oxidant, long reaction time, and limited functional group tolerance.

However, these reports prompted us to envision the possibility of Pd-catalyzed [2 + 2 + 2] annulation of indoles with alkynes in a single pot, leading to indolo[3,2-*a*]carbazoles under metal−oxidant free conditions. Synthesis of 2,3-linked bi-indoles via Pd-catalyzed oxidative cross dimerization of indoles has been explored by different groups.[20]

We started our optimization studies by using indole **1a** and diphenylacetylene **2a** as the model substrates to give indolocarbazole (**3a**). After optimization of the conditions (see the Supporting Information for details), we found that the following reaction conditions were established for the best results: $Pd(OAc)_2$ (10 mol %), O_2 atm at 80 °C in DMSO (see Table S1, entry 6, in the Supporting Information). The

DOI: 10.1021/acs.orglett.8b02465
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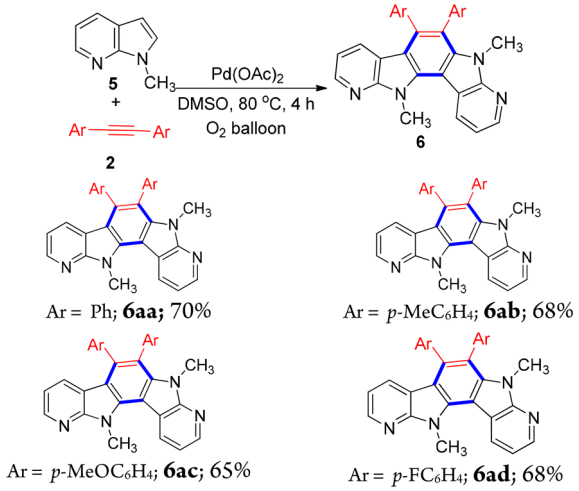
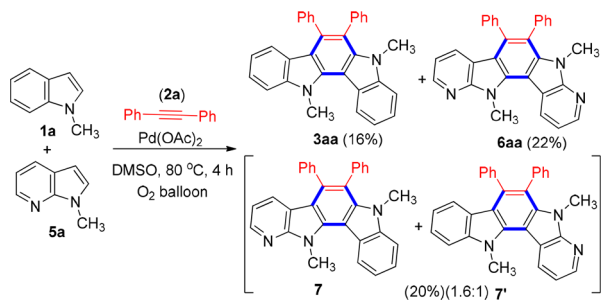
Scheme 3. Cascade Multiple C−H Transformations−Annulations of Azaindoles 5 with Alkynes 2[a,b]

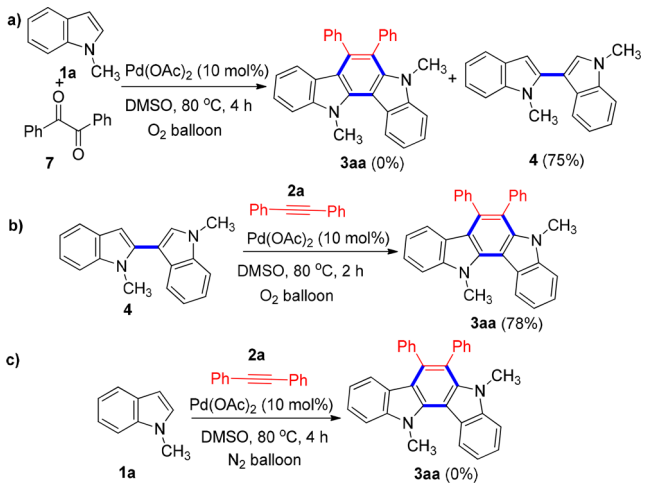


[a]Reaction conditions: azaindole **5** (0.763 mmol), alkyne **2** (0.381 mmol), $Pd(OAc)_2$ (0.076 mmol), DMSO (2 mL), 80 °C, 4 h under O_2. [b]Yields of isolated products are given.

Scheme 4. Cross-Over Experiment between 1a, 5, and 2a



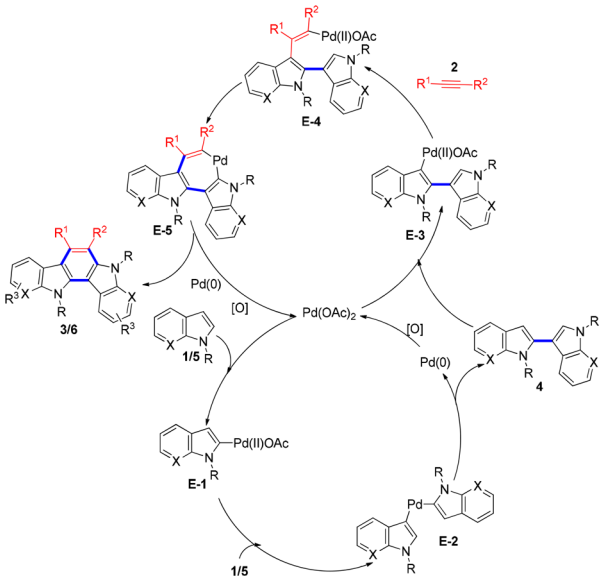
Scheme 5. Mechanistic Studies



structure of **3a** was confirmed by nuclear magnetic resonance (NMR), high-resolution mass spectroscopy (HRMS), and X-ray crystallography.[21]

These optimized reaction conditions were then tested for the multiple C−H transformation−annulation reactions of various substituents on indoles **1a−1o** with alkyne **2a−2i**, as summarized in Scheme 2. The indoles containing electron-donating substitutes such as methyl methoxy and ethoxy

Scheme 6. Proposed Reaction Mechanism



reacted smoothly to give indolo[3,2-*a*]carbazoles in high yields (see Scheme 2, entries **3aa−eb**). The presence of halogens on indole ring did not change the reaction pathway and generated the desired products in good yields (see Scheme 2, **3fa−3he** and **3ja**). The strong electron-withdrawing indoles failed to provide the desired product (**3ia**). A possible reason is that the presence of an electron-withdrawing group may affect the C−H transformation process significantly. Subsequently, *N*−ethyl and benzyl indole tolerated the reaction conditions well and generated the indolo[3,2-*a*]carbazoles products in good yields (see Scheme 2, **3ma−3ob**). Indoles having free NH, NAc, and NTs were also tested, but the reaction did not proceed in these cases.

We then evaluated the scope and limitations of the alkyne substrate. The reaction was compatible with substituents at the *para*-position on the benzene rings of internal alkynes, such as Me− (**3ab**, **3db**, **3eb**, **3gb**, **3hb**, **3mb**, and **3ob**), MeO− (**3ge**, **3he**, and **3me**), and F− groups (**3ac** and **3hc**), providing the corresponding products in good yields (64%−70%). Furthermore, a heterocyclic thiophene motif also served as a suitable substrate, as exemplified by the synthesis of **3ad**. Notably, strong electron-deficient alkynes were not compatible with this protocol (**3af**). The use of a terminal alkyne, e.g., hexyne (**2g**), afforded a mixture of two regioisomers in a 1:1 ratio (**3ag** + **3ag′**). The nonsymmetrical alkynes, **2h** and **2i**, reacted under these conditions to result a mixture of two isomeric products, **3ah** + **3ah′** and **3 mi** + **3 mi′** in ratios of 1.2:1 (61% yield) and 1.4:1 (60% yield). Since the R_f values were too close, the separation and isolation of individual isomers were rather difficult.

We further extended the scope of the developed chemistry for the synthesis of an important class of heterocyclic scaffolds. We successfully extended the multiple C−H transformation−annulations to 7-azaindoles and the corresponding products (**6aa−6ad**; see Scheme 3) were obtained in good yields (65%−70%).

To understand the mode of C−H transformation, a cross-over experiment was performed using a 1:1 mixture of **1a** and **5** under the optimized conditions. The cross-over products, i.e., **3aa** and **6aa**, along with the other two products, 7 and 7′, in a 1.6:1 ratio were isolated in this case (see Scheme 4). The R_f

DOI: 10.1021/acs.orglett.8b02465
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values were also too close for compound 7 and 7′; hence, their separation was difficult. The NMR data suggested the formation of two isomers (see the experiment and the Supporting Information) clearly indicating a nonconcerted process for the observed multiple C−H bonds transformations.

To understand the possible reaction pathway, some control experiments have been performed (see Scheme 5). First, *N*-methylindole **1a** was reacted with benzil **7** under the optimized conditions but 2,3-linked bi-indole was obtained in 75% yield instead of **3aa**. This suggested that the alkyne may not be converted to the 1,2-diketone during the reaction and the reaction did not proceed via a simple condensation reaction pathway (see Scheme 5a). This result also suggests that the presently developed methodology involve multiple C−H transformations−annulations with alkynes. As mentioned above, the formation of indolo[3,2-*a*]carbazoles is assumed to occur via the 2,3-linked bi-indole intermediate by a C−H transformation. To confirm this, we performed a reaction between 2,3-linked biindoles (**4**) and diphenylacetylene (**2a**). Satisfyingly, this reaction afforded indolo[3,2-*a*]carbazoles **3aa** in 78% yield (Scheme 5b). We further examined the reaction of **1a** with **2a** in the presence of 10 mol % $Pd(OAc)_2$ in DMSO at 80 °C for 4 h in the presence of nitrogen atmosphere, and the indolo[3,2-*a*]carbazoles **3aa** were not observed (see Scheme 5c). This clearly shows that the oxygen plays an essential role in the success of the present reaction.

Based on the literature precedents[4c,5,20] and our experimental observations, a plausible mechanism for this cascade reaction is outlined in Scheme 6. Initially, electrophilic palladiation occurs preferentially at the C3-position of indole, followed by a subsequent migration of the C3−PdX bond to the C-2 position of indole results in the formation of intermediate **E-1**,[22,20a] further electrophilic palladation of the second indole to form intermediate **E-2**, which, upon reductive elimination, generates the 2,3-dimer of bi-indole (**4**), and the formed Pd(0) is oxidized to Pd(II). The palladium diacetate reacted with a 2,3-dimer of indole through C−H activation to form intermediate **E-3**, and then **E-3** coordinated with the triple bond in alkyne (**2**) to produce a vinylic palladium(II) intermediate **E-4**. A seven-membered palladacycle **E-5** through C−H activation then was formed from **E-4** through a second C−H activation. Finally, the intermediate **E-5** afforded the corresponding indolo[3,2-*a*]carbazoles derivative via reductive elimination, along with the generation of Pd(0). Finally, palladium acetate was regenerated from Pd(0) under oxygen to complete the catalytic cycle.

In conclusion, a direct, one-pot and metal-based oxidant-free synthesis of indolo[3,2-*a*]carbazoles has been developed for the first time via the multiple Pd-catalyzed C−H transformation−annulations of readily available indoles with alkynes under O_2. The present methodology is also extended to azaindoles. The methodology may find broad applications in the construction of indolo[3,2-*a*]carbazole-based libraries for medicinal uses or natural product synthesis. Further studies and applications of this method are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02465.

Experimental procedures, characterization details and ^1H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

K.S.K. thanks University Grants Commission (UGC), New Delhi, India for the award of an Assistant Professorship under the FRP and CSIR, India, for financial support [No. 02(0234)/15/EMR-II].

■ REFERENCES

(1) For selected reviews on C−H activation, see: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744 and references cited therein. . (d) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (e) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (f) Bettadapur, K. R.; Kapanaiah, R.; Lanke, V.; Prabhu, K. R. *J. Org. Chem.* **2018**, *83*, 1810 and references cited therein. .

(2) For selected reviews on C−H bond functionalization, see: (a) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (b) Li, B.; Dixneuf, P. H. *Top. Organomet. Chem.* **2014**, *48*, 119. (c) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (d) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (e) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546 and references cited therein. .

(3) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548 and references cited therein. .

(4) (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (b) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13. (c) Qi, Z.; Yu, S.; Li, X. *J. Org. Chem.* **2015**, *80*, 3471. (d) Jin, T. N.; Zhao, J.; Asao, N.; Yamamoto, Y. *Chem. - Eur. J.* **2014**, *20*, 3554. (e) Le Bras, J.; Muzart, J. *Synthesis* **2014**, *46*, 1555.

(5) Shi, Z.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895.

(6) Li, S.; Wang, C.; Lin, H.; Zhang, X.; Dong, L. *Org. Lett.* **2015**, *17*, 3018.

(7) Iitsuka, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. - Eur. J.* **2014**, *20*, 385.

(8) Peng, H.; Yu, J.-T.; Jiang, Y.; Wang, L.; Cheng, J. *Org. Biomol. Chem.* **2015**, *13*, 5354.

(9) Qi, Z.; Yu, S.; Li, X. *J. Org. Chem.* **2015**, *80*, 3471.

(10) (a) Li, P.; Zhang, X.; Fan, X. *J. Org. Chem.* **2015**, *80*, 7508. (b) Ghosh, M.; Naskar, A.; Mishra, S.; Hajra, A. *Tetrahedron Lett.* **2015**, *56*, 4101.

(11) (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (b) Kianmehr, E.; Faghih, N.; Khan, K. M. *Org. Lett.* **2015**, *17*, 414.

(12) Kumar, K. S.; Rajesham, B.; Kumar, N. P.; Ramulu, M. S.; Dandela, R. *Chem. Select* **2018**, *3*, 4581.

(13) (a) Kumar, K. S.; Kumar, N. P.; Rajesham, B.; Kishan, G.; Akula, S.; Kancha, R. K. *New J. Chem.* **2018**, *42*, 34. (b) Kumar, K. S.; Bhaskar, B.; Ramulu, M. S.; Kumar, N. P.; Ashfaq, M. A.; Pal, M. *Org. Biomol. Chem.* **2017**, *15*, 82. (c) Kumar, K. S.; Ramulu, M. S.; Rajesham, B.; Kumar, N. P.; Voora, V.; Kancha, R. K. *Org. Biomol. Chem.* **2017**, *15*, 4468.

DOI: 10.1021/acs.orglett.8b02465
Org. Lett. XXXX, XXX, XXX−XXX

(14) (a) Markad, S. B.; Argade, N. P. *J. Org. Chem.* **2016**, *81*, 5222. (b) Markad, S. B.; Argade, N. P. *Org. Lett.* **2014**, *16*, 5470. (c) Samala, S.; Mandadapu, A. K.; Saifuddin, M.; Kundu, B. *J. Org. Chem.* **2013**, *78*, 6769. (d) Li, J. J. *Heterocyclic Chemistry in Drug Discovery*; John Wiley & Sons: Hoboken, NJ, 2013. (e) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (f) Merlic, C. A.; You, Y.; McInnes, D. M.; Zechman, A. L.; Miller, M. M.; Deng, Q. *Tetrahedron* **2001**, *57*, 5199.

(15) (a) Gong, P.; Sun, J.; Xue, P.; Qian, C.; Zhang, Z.; Sun, J.; Lu, R. *Dyes Pigm.* **2015**, *118*, 27. (b) Park, K. S.; Salunkhe, S. M.; Lim, I.; Cho, C. G.; Han, S. H.; Sung, M. M. *Adv. Mater.* **2013**, *25*, 3351. (c) Blouin, N.; Leclerc, M. *Acc. Chem. Res.* **2008**, *41*, 1110.

(16) For a comprehensive review on carbazoles, see: Knölker, H. J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.

(17) Kotha, S.; Saifuddin; Aswar, M. V. R. *Org. Biomol. Chem.* **2016**, *14*, 9868.

(18) An, Y.-L.; Yang, Z.-H.; Zhang, H.-H.; Zhao, S.-Y. *Org. Lett.* **2016**, *18*, 152.

(19) Nair, V.; Nandialath, V.; Abhilash, K. G.; Suresh, E. *Org. Biomol. Chem.* **2008**, *6*, 1738.

(20) (a) Liang, Z. J.; Zhao, J. L.; Zhang, Y. H. *J. Org. Chem.* **2010**, *75*, 170. (b) Guchhait, S. K.; Chaudhary, V.; Rana, V. A.; Priyadarshani, G.; Kandekar, S.; Kashyap, M. *Org. Lett.* **2016**, *18*, 1534.

(21) The molecular structure of compound **3a** was established based on single-crystal data analysis, which has been reported; see ref 19.

(22) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

DOI: 10.1021/acs.orglett.8b02465
Org. Lett. XXXX, XXX, XXX−XXX