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Palladium-Catalyzed Triple Successive C−H Functionalization: Direct Synthesis of Functionalized Carbazoles from Indoles

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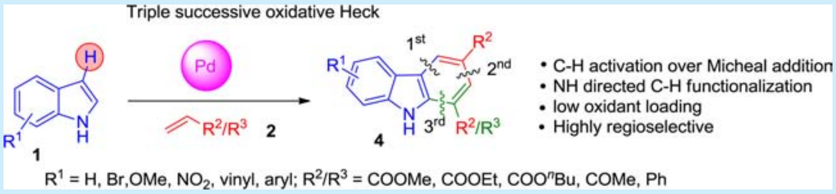
S *Supporting Information*



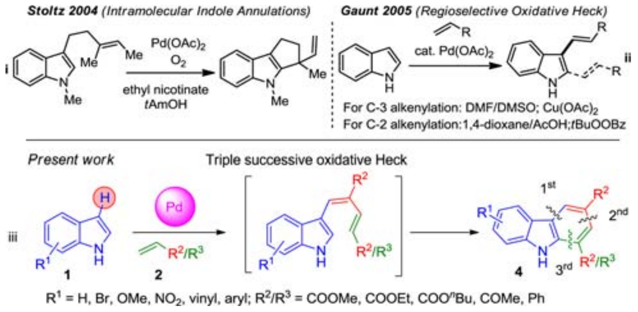
ABSTRACT: A novel Pd(II)-catalyzed approach for the direct synthesis of differentially substituted carbazoles from free (NH) indoles via regioselective triple successive oxidative Heck (Fujiwara−Moritani reaction) has been achieved. It is demonstrated that both electron-deficient and electron-rich alkenes could be used successively for the incorporation of two different functional groups into the product. The proposed mechanistic pathway was well supported by isolating the first and second successive oxidative Heck intermediates as well as by trapping with styrene-d_3.

Direct C−H bond functionalization and cross-coupling reactions are considered to be among the most valuable and powerful tools for constructing C−C bonds in the synthesis of complex molecules.[1] The Fujiwara−Moritani (oxidative Heck)[2] reaction was discovered in 1967; however, it was unnoticed for a long time because of the lack of regioselective control. Significant progress has been made in recent years on intermolecular alkenylations using arenes possessing either high electron density or directing groups.[3]

Carbazoles are among the most important nitrogen heterocycles present in a wide range of natural products, pharmaceuticals, and functional materials.[4] Owing to the significant biological activities[5] and applications as functional organic materials,[6] several methods are available in the literature for the synthesis of carbazoles.[7] In the past decade Buchwald,[8a] Gaunt,[8b] Chang,[8c] and Miura[8d] reported carbazole syntheses using Pd/Cu-catalyzed intramolecular C−H amination of anilides. Recently, Itami[9a] and Yu[9b] demonstrated the formation of carbazoles from *N*-protected indoles via a Diels−Alder reaction using trimetallic and bimetallic systems of Pd−Cu−Ag and Pd−Cu, respectively. They have used 4.0−6.0 equiv of oxidant for the oxidation of dihydrocarbazole into carbazole. Most of the carbazole syntheses are successful with *N*-protected indoles and remain challenging with free (NH) indole.

Pioneering work by Stoltz on intramolecular annulations of indoles (Scheme 1i),[10a,b] using electron-rich arenes constitutes a striking development on the Fujiwara−Moritani reaction. An elegant work on regioselective functionalization of indole was later reported by Gaunt and co-workers in 2005 (Scheme 1ii).[11a] A literature survey revealed that the intramolecular oxidative Heck reaction has not been well explored. *Also, to the best of our knowledge, successive oxidative-Heck reactions have not been reported and still remain a challenge.* Inspired by the Stoltz and Gaunt work and in continuation of efforts in this laboratory,[12] we envisioned that the carbazoles could be synthesized directly from free (NH) indoles via three successive oxidative Heck reactions (Scheme 1iii).

Scheme 1. Fujiwara−Moritani Alkenylation of Indoles



To identify the optimal conditions for the reaction, a variety of reported Pd-catalysts, along with various combinations of organic solvents, were examined in the reaction of indole **1a** with methyl acrylate **2a** (Table 1). Using Gaunt conditions, the mono-oxidative Heck product **3a** was obtained in 80% yield along with a trace amount of product **4a** (Table 1, entry 1). Increasing the temperature from 70 to 100 °C provided the product **4a** only in 15% yields (Table 1, entry 2). When 15 mol

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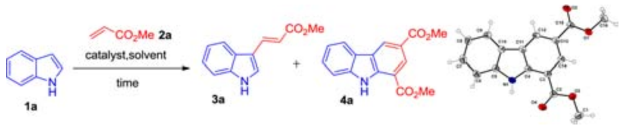
Table 1. Optimization of Reaction Conditions[a]



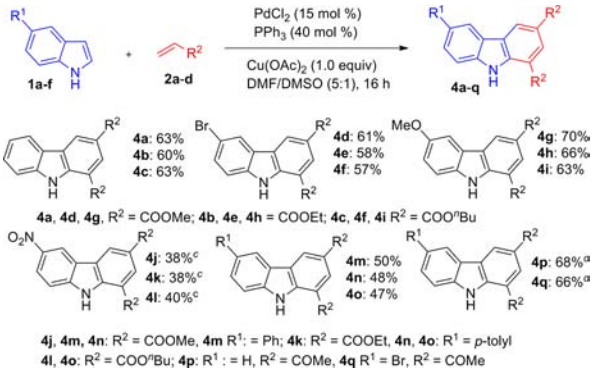
entry	catalyst (mol %)	solvent/oxidant[b]	temp (°C)/ time (h)	yield (%)[c] 3a	4a
1[11a]	$Pd(OAc)_2$/10	DMF/DMSO (9:1)/A[d]	70/18	80	2
2	$Pd(OAc)_2$/10	DMF/DMSO (9:1)/A[d]	100/18	70	15
3	$Pd(OAc)_2$/15	DMF/DMSO (7:1)/A[d]	100/18	60	30
4	$Pd(OAc)_2$/15	DMF/DMSO (5:1)/A[d]	100/18	40	41
5	$Pd(OAc)_2$/15	DMF/DMSO (5:1)/A[e]	100/18	40	42
6	**$PdCl_2$/15**	**DMF/DMSO (5:1)/A[e]**	**100/16**	**22**	**63**
7	$PdCl_2$/15	DMF/DMSO (5:1)/A[d]	100/16	20	59
8	$PdCl_2$/15	DMF/DMSO (5:1)/B[e]	100/16	5	0
9	$PdCl_2$/15	DMF/DMSO (5:1)/C[e]	100/16	35	0
10	$PdCl_2$/15	DMF/DMSO (5:1)/D[e]	100/16	5	0
11	$PdCl_2$/20	DMF/DMSO (5:1)/A[e]	100/16	18	62
12[8a]	$Pd(OAc)_2$/10	^{t}AmOH/AcOH (4:1)/E[f]	100/18	5	0
13[8a]	$PdCl_2$/15	^{t}AmOH/AcOH (5:1)/A[d]	100/18	0	0
14	$PdCl_2$/15	DMF/A[e]	100/16	65	15
15	$PdCl_2$/15	DMSO/A[e]	100/16	35	5

[a] Reactions were performed using 0.5 mmol of indole **1a**, acrylates **2a** (1.7 mmol), catalyst, and PPh_3 (40 mol %) in 2.0 mL of solvent. [b] A = $Cu(OAc)_2$; B = CuOAc; C = AgOAc; D = Ag_2O; E = O_2. [c] Isolated yield. [d] Oxidant (1.8 equiv). [e] Oxidant (1.0 equiv). [f] 1 atm.

% of $Pd(OAc)_2$ was used in DMF/DMSO (7:1), product **3a** and **4a** were obtained in 60 and 30% yields, respectively (Table 1, entry 3). It is interesting to note that use of DMF/DMSO in a 5:1 ratio provided the product **4a** in improved yield (Table 1, entry 4 versus entry 3). No significant effect on the yield was observed by decreasing the oxidant from 1.8 equiv to 1.0 equiv (Table 1, entry 5). When $PdCl_2$ was used as catalyst, a significant improvement in the yield of product **4a** was observed (Table 1, entry 6). An increase of oxidant did not improve the yield of **4a** (Table 1, entry 7). The unprecedented role of DMSO as an oxidant has also been identified.[13] Inferior results were obtained when other oxidants such as CuOAc, AgOAc, and Ag_2O were used (Table 1, entries 8, 9, and 10, respectively). A further increase of catalyst loading gave no improvement in the yield of product **4a** (Table 1, entry 11). When the Stoltz conditions were applied, product **4a** was not observed (Table 1, entries 12 and 13). Examining different solvents did not provide the product **4a** in good yields (Table 1, entries 14 and 15). The product **4a** was fully characterized by ^{1}H and ^{13}C NMR, HRMS, and X-ray crystallographic studies.[14]

With the optimized reaction conditions in hand, the generality of the reaction was explored (Scheme 2). A variety of indoles (**1a**−**f**), bearing electron-neutral, electron-rich, and electron-deficient substituents reacted with alkene **2a**−**d** to provide functionalized carbazoles **4a**−**q** in 38−70% yield with excellent functional group tolerance. Reaction of indole **1a** with acrylate **2a**−**c** provided the desired product **4a**−**c** in 60−63% yields. When a bromo-group was used as R^1, then the reaction was well implemented to form the intriguing cyclized product **4d**−**f** in 57−61% yields. Reaction of the electron-rich substrate 5-methoxyindole **1c** with alkene **2a**−**c** provided the products **4g**−**i** in good yields (70%, 66%, and 63%); however, reaction of the electron-deficient substrate 5-nitroindole **1d** with **2a**−**c** provided the desired products **4j**−**l** in low yields. Aryl substituted indoles **1e**,**f** were found compatible and provided the products **4m**−**o** in 47−50% yields. Reaction of methyl vinyl ketone **2d** with substrates **1a**,**b** afforded the corresponding carbazoles **4p**,**q** in 68 and 66% yields (Scheme 2).

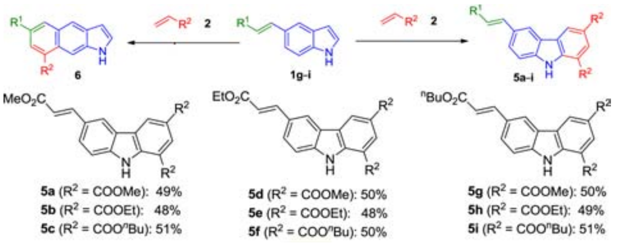
Scheme 2. Substrate Scope[a,b]



[a] Using optimized condition (entry 6, Table 1). [b] Isolated yield. [c] Time = 18 h. [d] Time = 12 h.

Encouraged by the above results, the regioselectivity of the reaction was investigated. The reaction of vinylindoles **1g**−**i** with acrylates **2a**−**c** was performed under optimized conditions. The reactions provided the carbazoles **5a**−**i** in 48−51% yields with excellent regioselectivity (Scheme 3). Formation of the benzoindole **6** was not observed, which suggests that C−H functionalization occurs over the Diels−Alder reaction.

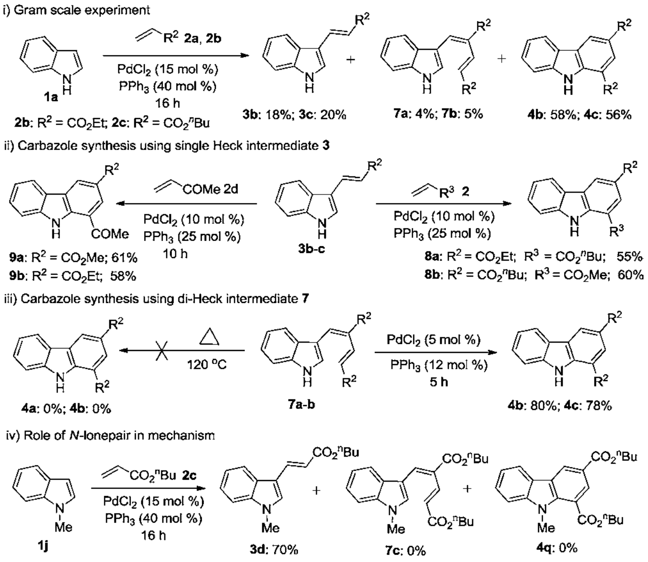
Scheme 3. Carbazole Synthesis by Regioselective Triple Successive Oxidative Heck Reaction[a,b]



[a] Using optimized conditions (entry 6, Table 1). [b] Isolated yield.

To identify the possible reaction intermediates, a gram scale experiment was conducted using indole **1a** and alkenes **2b**,**c**; carbazole **4b** and **4c** were obtained in 58 and 56% yields, respectively, along with the mono-Heck products **3b** and **3c** in 18 and 20% yields, respectively. However; the di-Heck intermediates **7a** and **7b** were isolated in only 4 and 5% yields, respectively (Scheme 4i). Intermediate **3**, on reaction with acrylates **2c** and **2a**, fruitfully provided the corresponding carbazoles **8a** and **8b** in 55 and 60% yields, respectively. Furthermore, and much to our gratification, variation of the

Scheme 4. Preliminary Mechanistic Studies[a]

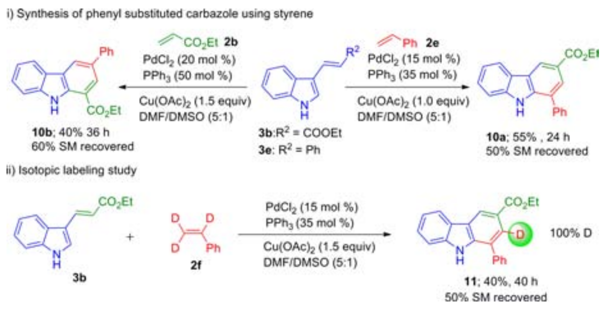


[a] All reactions were performed using 1.0 equiv of $Cu(OAc)_2$ in 2.0 mL of DMF/DMSO (5:1) at 100 °C.

carbazole backbone was possible with methyl vinyl ketone **2d**, which advantageously afforded the ester and keto-functionalized carbazoles **9a** and **9b** in 61 and 58% yields, respectively, in 10 h (Scheme 4ii). Relevance to the di-Heck intermediate **7** in the presence of $PdCl_2$ (5 mol %), PPh_3 (12 mol %), and $Cu(OAc)_2$ 1.0 equiv provided the consequent carbazoles **4b** and **4c** in 80 and 78% yields, respectively (Scheme 4iii). In the absence of Pd-catalyst applying the thermal conditions, the carbazole was not observed. These observations clearly support the formation of carbazoles via successive C−H activation (Scheme 4i−iii). Involvement of the *N*-lone pair in the mechanism is understood by invoking the C−H activation onto *N*-methylindole **1j**, wherein the reaction ceased at the formation of the mono-Heck product **3d** in 70% yield. This control reaction confirms that the presence of the free (NH) of indole is crucial for the reaction, possibly functioning as a directing group for the second and third successive oxidative Heck reaction (Scheme 4iv).

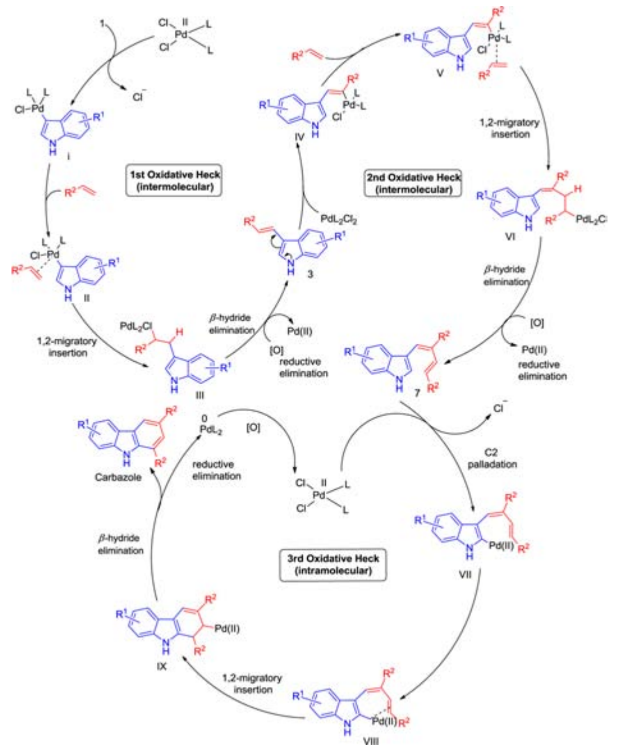
For the first time, we have provided an early example of ethyl 1-phenyl-9*H*-carbazole-3-carboxylate **10a** synthesized via Pd-catalyzed asymmetric intermolecular C−H functionalization of **3b** with styrene **2e**. Alternatively, the reaction of **3e** successfully provided the carbazole product **10b** in 40% yield along with the starting material (Scheme 5i). Isotopic labeling studies of **3b** with deuterated styrene **2f** provided the isotopic carbazole **11** in 40% yields. This evidence suggests that the second C−H activation is occurring exclusively onto the alkene fraction and that C−H activation is much faster than C−D activation (Scheme 5ii).

Scheme 5. Carbazole Syntheses Using Styrene and d_3-Styrene



Based on the evidence from the control experiments, a plausible reaction pathway was proposed, as outlined in Scheme 6. C-3 Alkenylation (**3**) of indole takes place via regioselective C-3 palladation (I), olefin insertion (II−III), and *syn* β-hydride elimination (first oxidative Heck).[15] The palladium(II)−hydrido complex is reduced to a Pd(0) complex, which is oxidized by $Cu(OAc)_2$ to regenerate Pd(II). Further regioselective palladation takes places on intermediate **3** at the α-position of R^2 and completes the second oxidative Heck cycle to form intermediate **7** via formation of palladium complexes IV−VI. The third catalytic cycle is then completed by C-2 palladation (VII) and followed by intramolecular oxidative Heck (rapid), leading to the carbazole formation via generation of complexes VIII and IX, respectively. To probe the mechanism, we have isolated the key intermediates **3** and **7**, and their structures were confirmed by the ^1H and ^{13}C NMR and HRMS spectral data as well as transformation of these intermediates into the carbazole product (Scheme 4i−iii). These results support the assertion that the proposed reaction mechanism proceeds through a triple successive oxidative Heck pathway, as shown in Scheme 6.

Scheme 6. Plausible Mechanism



In summary, a novel Pd(II)-catalyzed approach for the direct synthesis of highly functionalized carbazoles from free (NH) indoles via regioselective triple successive oxidative Heck reaction has been developed. For the first time, it was established that both electron-deficient and electron-rich alkenes can be used successively for the incorporation of two different functional groups in the product. Notably, mechanistic studies succeeded in the isolation of the single- and doubleoxidative Heck intermediates, which supports the proposed mechanism. A deuterium labeling experiment revealed that C−H activation is much faster than C−D activation. Owing to the great diversity of the substitution pattern, this developed chemistry provides a facile and atom economical route for the synthesis of highly functionalized carbazoles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, CIF information, and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01476.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (b) Yu, D.-G.; Azambuja, F. D.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 2754. (c) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700. Selected examples of direct C2-alkenylation of indoles: (d) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854. (e) García-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511. (f) García-Rubia, A.; Urones, B.; Arrayas, R. G.; Carretero, J. C. *Chem. - Eur. J.* **2010**, *16*, 9676. (g) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357. (h) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (i) Sharma, U.; Kancherla, R.; Naveen, T.; Agasti, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 11895 and references cited therein .

(2) (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. (b) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968**, *9*, 3863. (c) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. (d) Fujiwara, Y.; Asano, R.; Moritani, I.; Teranishi, S. *J. Org. Chem.* **1976**, *41*, 1681. (e) Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851. (f) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (g) Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851. Reviews on Pd-catalyzed directed C−H activation: (h) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (i) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (j) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(3) Intermolecular alkenylation (a) Liu, W.; Zell, D.; John, M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 4092. (b) Wang, H.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5386. (c) Gandeepan, P.; Cheng, C.-H. *J. Am. Chem. Soc.* **2012**, *134*, 5738. (d) Ying, C.-H.; Yan, S.-B.; Duan, W.-L. *Org. Lett.* **2014**, *16*, 500. (e) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. *J. Am. Chem. Soc.* **2014**, *136*, 13602. (f) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuween, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (g) Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822 and references cited therein .

(4) (a) Knolker, H. J.; Frohner, W.; Reddy, K. R. *Eur. J. Org. Chem.* **2003**, *2003*, 740. (b) Hagiwara, H.; Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. A. *Tetrahedron* **2000**, *56*, 5807. (c) Cuong, N. M.; Wilhelm, H.; Porzel, A.; Arnold, N.; Wessjohann, L. *Nat. Prod. Res.* **2008**, *22*, 1428.

(5) (a) Knolker, H. J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (b) Zhang, F. F.; Gan, L. L.; Zho, C. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1881.

(6) (a) Diaz, J. L.; Dobarro, A.; Villacampa, B.; Velasco, D. *Chem. Mater.* **2001**, *13*, 2528. (b) Thomas, K. R. J.; Lin, J. T.; Tao, Y. T.; Ko, C. W. *J. Am. Chem. Soc.* **2001**, *123*, 9404. (c) Zhang, Y.; Wada, T.; Sasabe, H. *J. Mater. Chem.* **1998**, *8*, 809.

(7) (a) Qiu, Y.; Kong, W.; Fu, C.; Ma, S. *Org. Lett.* **2012**, *14*, 6198. (b) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310. (c) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 701. (d) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (e) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738. (f) Markad, S. B.; Argade, N. P. *Org. Lett.* **2014**, *16*, 5470 for a recent carbazole synthesis, references cited therein. .

(8) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (c) Cho, S. H.; Yoon, C. J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996. (d) Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 2892.

(9) (a) Ozaki, K.; Zhang, H.; Ito, H.; Lei, A.; Itami, K. *Chem. Sci.* **2013**, *4*, 3416. (b) Guo, T.; Jiang, Q.; Huang, F.; Chen, J.; Yu, Z. *Org. Chem. Front.* **2014**, *1*, 707.

(10) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (b) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144. (c) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987.

(11) (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C.R. A.; Gaunt, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528.

(12) (a) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138. (b) Aggarwal, T.; Jha, R. R.; Tiwari, R. K.; Kumar, S.; Kotla, S. K. R.; Kumar, S.; Verma, A. K. *Org. Lett.* **2012**, *14*, 5184. (c) Saunthwal, R. K.; Patel, M.; Danodia, A. K.; Verma, A. K. *Org. Biomol. Chem.* **2015**, *13*, 1521. (d) Saunthwal, R. K.; Patel, M.; Tiwari, R. K.; Parang, K.; Verma, A. K. *Green Chem.* **2015**, *17*, 1434. (e) Verma, A. K.; Jha, R. R.; Chaudhary, R.; Tiwari, R. K.; Danodia, A. K. *Adv. Synth. Catal.* **2013**, *355*, 421.

(13) (a) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (b) Chen, M. S.; White, C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.

(14) CCDC 889590 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) Selected examples of direct C3-alkenylation of indoles: (a) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097. (b) Xiang, S.-K.; Zhang, B.; Zhang, L.-H.; Cui, Y.; Jiao, N. *Chem. Commun.* **2011**, *47*, 8097. (c) Chen, W.-L.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Wang, Y.-F.; Wang, Y.-Q. *Org. Lett.* **2012**, *14*, 5920. (d) Xiang, S.-K.; Wu, G.; Zhang, B.; Cui, Y.; Jiao, N. *Tetrahedron Lett.* **2012**, *53*, 3802. (e) Young, P. C.; Hadfield, M. S.; Arrowsmith, L.; Macleod, K. M.; Mudd, R. J.; Jordan-Hore, J. A.; Lee, A.-L. *Org. Lett.* **2012**, *14*, 898.