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Substituent-Guided Palladium-Ene Reaction for the Synthesis of Carbazoles and Cyclopenta[*b*]indoles

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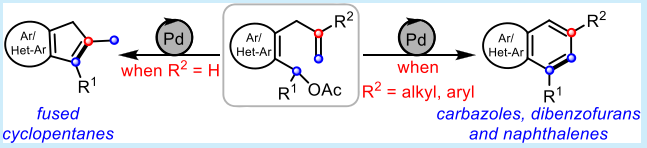
Supporting Information

ABSTRACT: An efficient palladium-catalyzed intramolecular Trost−Oppolzer type Alder-ene strategy was developed for the synthesis of carbazoles and cyclopenta[*b*]indoles from easily accessible(3-allyl-1*H*-indol-2-yl)methyl acetates. This strategy was extended for the synthesis of naphthalenes and dibenzobenzofurans as well. In addition, a short synthesis of antibacterial and antifungal natural product glycozoline and its analogues was also achieved.



Carbazoles are an important class of nitrogen-containing heterocycles, which are frequently encountered in several bioactive compounds.[1] In addition, carbazoles exhibit interesting properties for application as optoelectronic materials and conducting polymers.[2] Recently, carbazole-based synthetic dyes have been developed[3] and carbazole derivatives also have been employed as ligands for sensing applications.[4] A few representative carbazole natural products, medicinally important compounds, and some optoelectronic materials are depicted in Figure 1.[5]

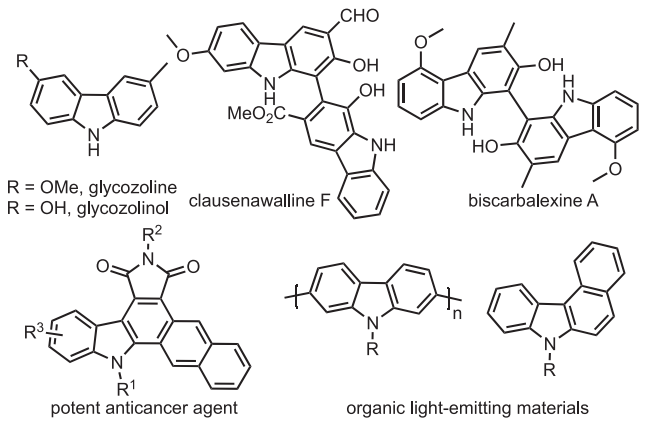
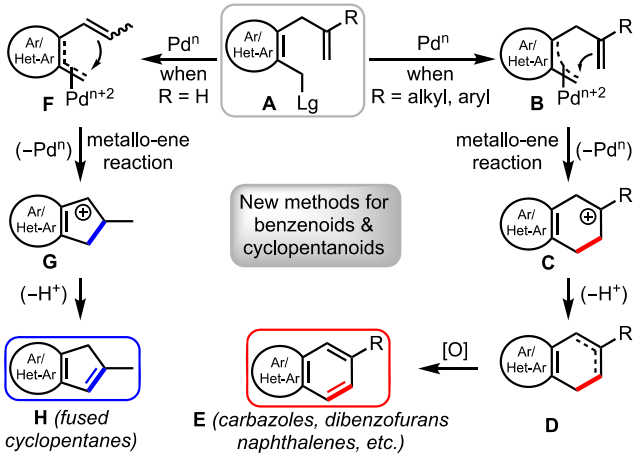


Figure 1. A few important carbazoles.

Due to their various applications, numerous methods for the synthesis of functionalized carbazoles have been developed, which include the classical Borsche−Drechsel cyclization[6] and the Graebe−Ullmann synthesis,[7] to mention only a few among many other outstanding approaches.[8] Despite these advancements, the development of modular and efficient approaches for the synthesis of carbazoles is of considerable interest. Herein, we wish to report a general and practical strategy for the synthesis of carbazoles **E** from easily accessible (3-allyl-1*H*-indol-2-yl)methyl acetates **A** (Scheme 1). A serendipitous observation made during the evaluation of substrate scope led to the discovery of a new method for the synthesis of cyclopenta[*b*]indoles **H**.

Scheme 1. Hypothesis and the Present Work: Substitution-Dependent Alder-Ene Reaction for the Synthesis of Benzenoids and Cyclopentanoids



We commenced this study with the synthesis of carbazoles (Scheme 1). It was postulated that the allyl acetate **A** under the influence of an appropriate palladium complex could form the (π-allyl)palladium species **B**. An intramolecular ene-type reaction of the appropriately positioned olefin followed by deprotonation could then generate dihydrocarbazoles **D**, which, presumably via aerobic oxidation or in the presence of a suitable oxidizing agent, afford carbazoles and other related benzenoids. Thus, this hypothesis combines the electrophilic features of the Tsuji−Trost reaction[9] and the

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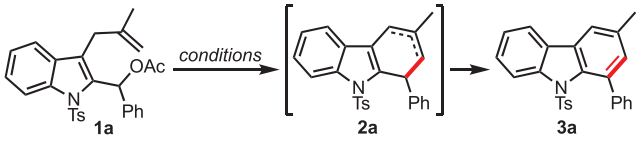
Org. Lett. XXXX, XXX, XXX−XXX

nucleophilic features of the ene reaction.[10] To our knowledge, this strategy also represents the first palladium-ene reaction-based approach for the synthesis of carbazoles.

With the intention to validate the hypothesis proposed in Scheme 1, the indolyl acetate **1a** was chosen as the model substrate (Table 1).[11] Various combinations of metal catalysts

Table 1. Optimization of the Reaction Parameters[a,b]



entry	catalyst (10 mol %)	solvent	t (h)	yield[c] (%)
1[d]	$Pd(PPh_3)_4$	toluene	72	–
2[d]	$Pd_2(dba)_3$	toluene	72	–
3	$Pd(OAc)_2$	toluene	72	20
4	$[Ir(cod)Cl]_2$	toluene	72	33
5[d]	$Ni(cod)_2$	toluene	72	–
6[d]	$Pd(PPh_3)_2Cl_2$	toluene	72	–
7	$[PdCl(allyl)]_2$	toluene	72	15
8	$PdCl_2$	toluene	26	74
9	$PdCl_2$	1,2-DCE	72	52
10[d]	$PdCl_2$	DMF	72	–
11	$PdCl_2$	CH_3CN	72	69
12[e]	$PdCl_2$	1,4-dioxane	24	83
13[f]	$PdCl_2$	1,4-dioxane	36	45
14[g]	$PdCl_2$	1,4-dioxane	18	85
15[h]	$PdCl_2$	1,4-dioxane	29	66

[a]Reaction conditions: See the Supporting Information for details. [b]Unless mentioned otherwise, all the reactions were performed at 80 °C. [c]Isolated yields after column chromatography. [d]**1a** remained as such even at 100 °C. [e]**1a** remained as such at rt–40 °C; a 1:1 mixture of **2a** and **3a** was observed at 60 °C and **1a** was obtained in 73% yield at 100 °C. [f]5 mol % $PdCl_2$ was employed; 35% of **2a** was also isolated. [g]20 mol % $PdCl_2$ was employed. [h]Reaction with **1a′** possessing OBoc group instead of OAc.

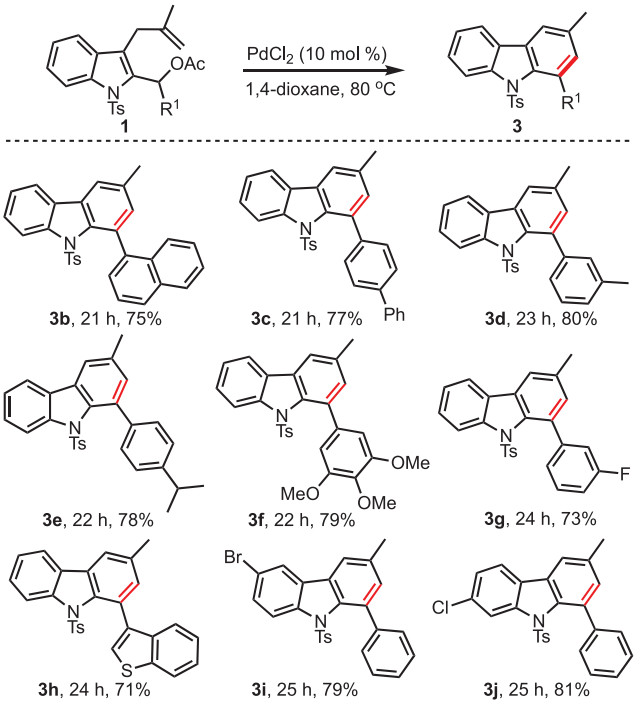
and solvents were evaluated, and the key results are summarized in Table 1. While the Pd(0) catalysts were unsuccessful, $Pd(OAc)_2$ straightaway provided **3a**, although in poor yield (entries 1–3). The structure of **3a** was readily deduced from the spectroscopic data and was eventually confirmed by X-ray diffraction analysis (CCDC 1590634).[12]

Our efforts to enhance the efficiency of the reaction with Ir- or Ni-catalysts were not encouraging (Table 1, entries 4 and 5). Then, we turned our attention to Pd(II) catalysts. Among them, $PdCl_2$-promoted reaction generated **3a** in good yield (entry 8). A brief solvent screening was undertaken from where 1,4-dioxane was realized to be optimal for the conversion of **1a** to **3a** (entries 12). Whereas a 5 mol % loading of $PdCl_2$ lowered the conversion, the reaction with a higher catalyst loading (20 mol %) required less time for completion, but did not offer any significant improvement in the yield (entries 13 and 14). Interestingly, the reaction of **1a′** (**1a** with OBoc group instead of OAc) under the best yielding conditions afforded **3a** in 66% yield (entry 15).

Thus, 10 mol % of the cheap and readily available palladium chloride in a less toxic and environmentally benign dioxane medium were realized to be optimal for the transformation of **1a** to **3a**. Some other salient features of this method include the following: (i) unlike many Pd-catalyzed reactions, this reaction does not require any additives, reoxidants, bases, etc.; (ii) the overall reaction can be perceived to be a one-pot sequential Tsuji–Trost reaction, Alder-ene reaction, and an oxidative aromatization, all of them being promoted by the same catalyst in one pot.

To evaluate the scope and generality of the method, the optimized conditions were applied to a variety of substrates possessing diverse steric and electronic features (Scheme 2). A

Scheme 2. Substrate Scope for 1,3-Disubstituted Carbazoles 3[a,b]

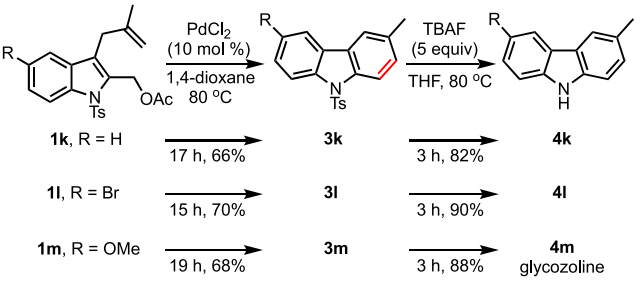


[a]Reaction conditions: See Supporting Information for details. [b]Chromatographic yields.

wide range of 1,3-disubstituted carbazoles possessing electron-donating and -withdrawing arenes, and heteroarenes at R^1, could be accessed in good yields (**3b**–**3h**). Even carbazoles substituted with bromo- and chloro-functionalities (such as **3i** and **3j**) could be conveniently prepared. These compounds are amenable for further synthetic elaborations; thereby, complex carbazole derivatives can be rapidly assembled.[13]

This method can be extended for the synthesis of monosubstituted carbazoles as well (Scheme 3). For example, unsubstituted indolyl acetates **1k**–**1m**, under the prototypical conditions, furnished the respective carbazoles **3k**–**3m** in good

Scheme 3. Synthesis of 3-Substituted Carbazoles and the Total Synthesis of the Natural Product Glycozoline



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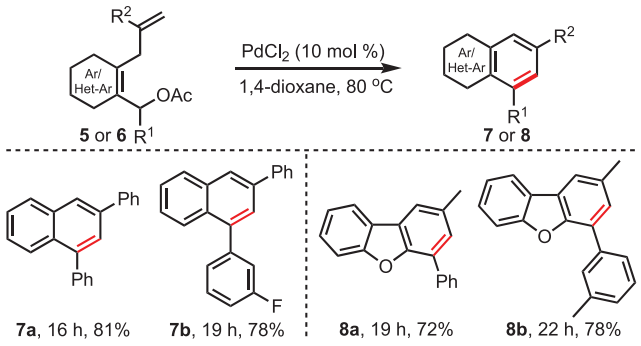
yields, thereby enhancing the scope of the present method. Further treatment of **3k**−**3m** with TBAF generated *NH*-carbazoles **4k**−**4m** in excellent yields.[8c] Among them, **4m** is the antibiotic and antifungal natural product glycozoline.[5a] The other analogues of glycozoline (**4k** and **4l**) are known to have prominent biological activity profiles.[14]

After successfully establishing a new method for the facile synthesis of carbazoles, we considered extending this concept to the synthesis of other prominent benzenoids. Accordingly, a variety of ε,ω-unsaturated acetates (**5** and **6**) were prepared and subjected to the optimized conditions (Scheme 4). An

Scheme 4. Synthesis of Naphthalenes (7) and Dibenzofurans (8)



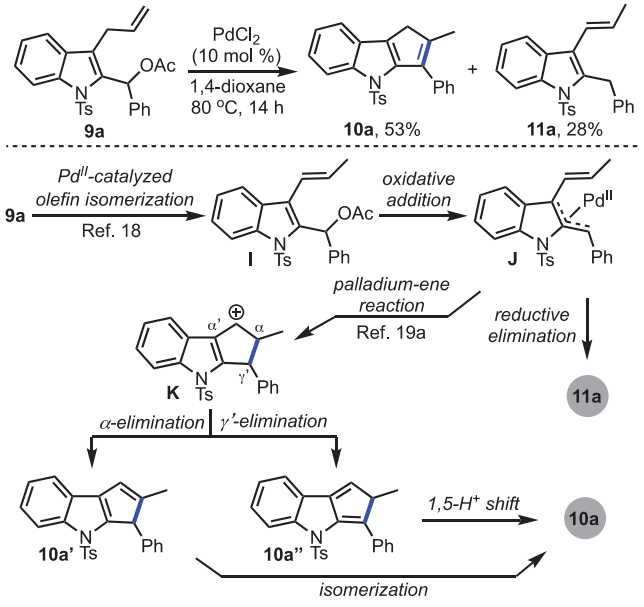
interesting range of 1,3-disubstituted naphthalenes (**7a** and **7b**) and dibenzofurans (**8a** and **8b**) were achieved in an efficient manner. It is worth mentioning that naphthalenes[15] and benzofuranoids[16] are the primary molecular architectures of many bioactive compounds and drug candidates and find important applications in materials chemistry as well.[17]

Next, as part of our efforts to evaluate the scope of the palladium-ene process, we made an interesting observation. When the acetate **9a** having no substitution at the vinylic position was subjected to the prototypical conditions described in Scheme 2, the cyclopenta[*b*]indole **10a** was isolated in 53% yield (Scheme 5). In addition, the 2-benzyl-3-vinyl-*N*-tosylindole **11a** was also isolated in 28% yield.

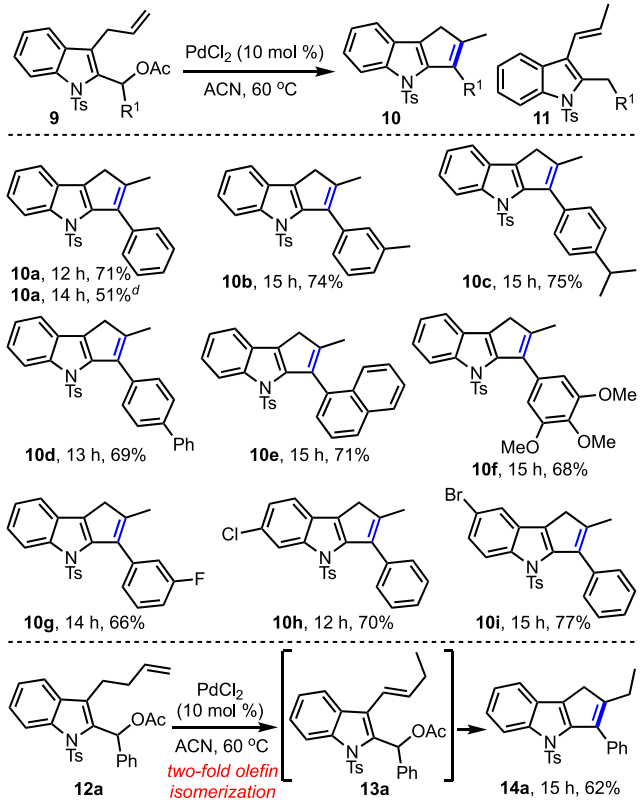
The formation of **10a** and **11a** can be explained as depicted in Scheme 5. The reaction presumably commences with a Pd-catalyzed isomerization of the unactivated terminal olefin[18] followed by the oxidative addition, to form **J**.[19] Although the mechanism leading to the formation of **11a** from **J** is not established at this stage, it can be surmised that the reductive elimination of **J** to **11a** is promoted by the presence of an adventitious amount of water.[20] While an intramolecular palladium ene reaction of **J** generates **K**,[19] which undergoes α-elimination to afford **10a′** (a regioisomer of **10a**), a γ'-elimination of **K** provides neutral but unstable intermediate **10a″**. Finally, the double bond isomerization of **10a′** or a [1,5]-sigmatropic hydrogen shift of **10a″** affords **10a**.[21]

Having realized the significance of the aforementioned observation, we commenced to optimize various parameters influencing the reaction (see the Supporting Information for details). During the screening, it was realized that the selectivity toward the formation of **10a** could be significantly enhanced in the acetonitrile medium, in which case **10a** was isolated in 72% yield. Under these conditions, a wide range of 1,2-disubstituted cyclopenta-fused indoles were synthesized in a highly regioselective manner (Scheme 6, **10a**−**10i**).[22] It is evident that electronically distinct arenes, and heteroarenes,

Scheme 5. Unexpected Formation of Cyclopenta[*b*]indole 10a and a Plausible Mechanistic Rationale



Scheme 6. Substrate Scope for Cyclopenta[*b*]indoles 10[a,b,c]



[a]Reaction conditions: See the Supporting Information for details. [b]Isolated yields after column chromatography. [c]About 12−15% of **11** was also isolated in each case. [d]Reaction with **9a′** (**9a** with OBoc group instead of OAc).

were well-tolerated at R^1. The presence of chloro- and bromo-functionalities (**10h** and **10i**) on the arene moiety presents the opportunity for further elaborations. The significance of cyclopenta[*b*]indoles as the primary molecular architectures in several bioactive molecules and their relevance in medicinal

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Org. Lett. XXXX, XXX, XXX−XXX

chemistry as well as in materials science makes the present method an attractive alternative.[23]

Further, to our surprise, the butenyl acetate **12a** under the standard conditions furnished the cyclopetannulated indole **14a**, via the intermediacy of **13a**. It is interesting to note that Pd-catalyzed twofold olefin isomerizations are known,[18b,24] but not under such straightforward conditions as reported herein.

In summary, we presented a divergent approach for the synthesis of a variety of carbazoles, naphthalenes, dibenzofurans, and cyclopenta[*b*]indoles from easily accessible (3-allyl-1*H*-indol-2-yl)methyl acetates. Interesting substitution dependence on the product distribution was realized. Based on the mechanistic considerations, this phenomenon was efficiently crafted to yield the product of choice. The methodologies described herein have been realized to be practical and scalable[25] and demonstrated great potential for the synthesis of new heterocycles. We are currently involved in extending these strategies toward the total synthesis of complex carbazole and indole-based natural products, and the results will be communicated in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00410.

Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR) (PDF)

Accession Codes

CCDC 1590634 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Moody, C. J. *Synlett* **1994**, 681. (b) Choi, T. A.; Czerwonka, R.; Forke, R.; Jaeger, A.; Knoell, J.; Krahl, M. P.; Krause, T.; Reddy, K. R.; Franzblau, S. G.; Knoelker, H.-J. *Med. Chem. Res.* **2008**, *17*, 374. (c) Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron* **2012**, *68*, 6099.

(2) (a) Li, J.; Grimsdale, A. C. *Chem. Soc. Rev.* **2010**, *39*, 2399. (b) Lellouche, J.-P.; Koner, R. R.; Ghosh, S. *Rev. Chem. Eng.* **2013**, *29*, 413. (c) Liu, S.; Zhang, Z.; Chen, D.; Duan, C.; Lu, J.; Zhang, J.; Huang, F.; Su, S.; Chen, J.; Cao, Y. *Sci. China: Chem.* **2013**, *56*, 1119.

(3) Teng, C.; Yang, X.; Yuan, C.; Li, C.; Chen, R.; Tian, H.; Li, S.; Hagfeldt, A.; Sun, L. *Org. Lett.* **2009**, *11*, 5542 and references cited therein .

(4) (a) Curiel, D.; Cowley, A.; Beer, P. D. *Chem. Commun.* **2005**, 236. (b) Vetrichelvan, M.; Nagarajan, R.; Valiyaveettil, S. *Macromolecules* **2006**, *39*, 8303. (c) Gale, P. A. *Chem. Commun.* **2008**, *38*, 4525. (d) Kim, D. A.; Kang, P.; Choi, M.-G.; Jeong, K.-S. *Chem. Commun.* **2013**, *49*, 9743.

(5) (a) For glycozoline and glycozolinol, see: Forke, R.; Krahl, M. P.; Krause, T.; Schlechtingen, G.; Knoelker, H.-J. *Synlett* **2007**, 268. For clausenawalline F, see: (b) Maneerat, W.; Ritthiwigrom, T.; Cheenpracha, S.; Promgool, T.; Yossathera, K.; Deachathai, S.; Phakhodee, W.; Laphookhieo, S. *J. Nat. Prod.* **2012**, *75*, 741. For biscarbalexine A, see: (c) Bruetting, C.; Fritsche, R. F.; Kutz, S. K.; Boerger, C.; Schmidt, A. W.; Kataeva, O.; Knoelker, H.-J. *Chem. - Eur. J.* **2018**, *24*, 458.

(6) (a) Drechsel, E. *J. Prakt. Chem.* **1888**, *38*, 65. (b) Borsche, W. *Justus Liebigs Ann. Chem.* **1908**, *359*, 49.

(7) (a) Graebe, C.; Ullmann, F. *Justus Liebigs Ann. Chem.* **1896**, *291*, 16. (b) Ashton, B. W.; Suschitzky, H. *J. Chem. Soc.* **1957**, *0*, 4559.

(8) (a) Among the exceedingly large number of studies, only a few randomly selected works are cited here: Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 7342. (b) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605. (c) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738. (d) Sreenivas, D. K.; Nagarajan, R. *Synlett* **2012**, *23*, 1007. (e) Maeda, C.; Masuda, M.; Yoshioka, N. *Org. Biomol. Chem.* **2014**, *12*, 2656. (f) Saunthwal, R. K.; Patel, M.; Kumar, S.; Danodia, A. K.; Verma, A. K. *Chem. - Eur. J.* **2015**, *21*, 18601. (g) Sankar, E.; Karunakaran, J.; Dhivyapirabha, L.; Mohanakrishnan, A. K. *Chemistry Select* **2017**, *2*, 7899. (h) Konidena, R. K.; Thomas, K. R. J. *Chemistry Select* **2017**, *2*, 7514. (i) Lin, S.; He, X.; Meng, J.; Gu, H.; Zhang, P.; Wu, J. *Eur. J. Org. Chem.* **2017**, 443. (j) Chen, S.; Wang, L.; Zhang, J.; Hao, Z.; Huang, H.; Deng, G.-J. *J. Org. Chem.* **2017**, *82*, 11182. (k) Arae, S.; Beppu, S.; Kawatsu, T.; Igawa, K.; Tomooka, K.; Irie, R. *Org. Lett.* **2018**, *20*, 4796. (l) Kaufmann, J.; Jäckel, E.; Haak, E. *Angew. Chem., Int. Ed.* **2018**, *57*, 5908. (m) Bal, A.; Maiti, S.; Mal, P. *J. Org. Chem.* **2018**, *83*, 11278. (n) Mandal, T.; Chakraborti, G.; Karmakar, S.; Dash, J. *Org. Lett.* **2018**, *20*, 4759. (o) Men, Y.; Hu, Z.; Dong, J.; Xu, X.; Tang, B. *Org. Lett.* **2018**, *20*, 5348.

(9) (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387. (b) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292.

(10) (a) For seminal works on the Pd-catalyzed ene-type reaction, see: Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. (b) Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39.

(11) See the Supporting Information for the synthesis of **1a** and its analogues.

(12) (a) The structure of **3a** was also confirmed by comparing the data of structurally related compounds. See: Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281. (b) James, M. J.; Clubley, R. E.; Palate, K. Y.; Procter, T. J.; Wyton, A. C.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Org. Lett.* **2015**, *17*, 4372.

(13) (a) Jacquemard, U.; Routier, S.; Tatibouet, A.; Kluza, J.; Laine, W.; Bal, C.; Bailly, C.; Merour, J.-Y. *Org. Biomol. Chem.* **2004**, *2*, 1476. (b) Huang, Y.; Guo, Z.; Song, H.; Liu, Y.; Wang, Q. *Chem. Commun.* **2018**, *54*, 7143.

(14) (a) Furukawa, H.; Wu, T. S.; Ohta, T.; Kuoh, C. S. *Chem. Pharm. Bull.* **1985**, *33*, 4132. (b) Momin, A. A.; Urmode, T. D.; Bhosale, S. M.; Kusurkar, R. S. *Synth. Commun.* **2016**, *46*, 1292.

(15) (a) De Koning, C. B.; Rousseau, A. L.; Van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7. (b) Hein, S. J.; Lehnherr, D.; Arslan, H.; Uribe-Romo, F. J.; Dichtel, W. R. *Acc. Chem. Res.* **2017**, *50*, 2776.

(16) (a) Zhang, M. *Adv. Synth. Catal.* **2009**, *351*, 2243. (b) Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. *Org. Lett.* **2011**, *13*, 5628. (c) Hagimori, M.; Temma, T.; Kudo, S.; Sano, K.; Kondo, N.; Mukai, T. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 193.

DOI: 10.1021/acs.orglett.9b00410
Org. Lett. XXXX, XXX, XXX−XXX

(17) (a) Vecchi, P. A.; Padmaperuma, A. B.; Qiao, H.; Sapochak, L. S.; Burrows, P. E. *Org. Lett.* **2006**, *8*, 4211. (b) Jeong, S. H.; Lee, J. Y. *Org. Electron.* **2012**, *13*, 1141.
(18) (a) Sen, A.; Lai, T. W. *Inorg. Chem.* **1984**, *23*, 3257. (b) Murai, M.; Nishimura, K.; Takai, K. *Chem. Commun.* **2019**, *55*, 2769.
(19) (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) For Pd-catalyzed ene-type process, see: Bankar, S. K.; Singh, B.; Tung, P.; Ramasastry, S. S. V. *Angew. Chem., Int. Ed.* **2018**, *57*, 1678. (c) Bharadwaj, S. K.; Bankar, S. K.; Ramasastry, S. S. V. *Synlett* **2018**, *29*, 2456.
(20) The reaction of **9a** in the presence of D_2O provided **11a** with ~50% deuterium incorporation at the benzylic position. See the Supporting Information for details.
(21) For a similar mechanistic pathway, see: Satpathi, B.; Dhiman, S.; Ramasastry, S. S. V. *Eur. J. Org. Chem.* **2014**, 2022.
(22) Surprisingly, under the same conditions, cyclopenta-fused benzofurans or benzothiophenes could not be obtained.
(23) (a) For recent reviews, see: Vivekanand, T.; Satpathi, B.; Bankar, S. K.; Ramasastry, S. S. V. *RSC Adv.* **2018**, *8*, 18576. (b) Satpathi, B.; Mondal, A.; Ramasastry, S. S. V. *Chem. - Asian J.* **2018**, *13*, 1642.
(24) (a) Kochi, T.; Hamasaki, T.; Aoyama, Y.; Kawasaki, J.; Kakiuchi, F. *J. Am. Chem. Soc.* **2012**, *134*, 16544. (b) Kocen, L.; Brookhart, M.; Daugulis, O. *Chem. Commun.* **2017**, *53*, 10010. (c) Chuc, L. T. N.; Chen, C.-S.; Lo, W.-S.; Shen, P.-C.; Hsuan, Y.-C.; Tsai, H.-H. G.; Shieh, F.-K.; Hou, D.-R. *ACS Omega* **2017**, *2*, 698. (d) Ahn, H.; Son, I.; Lee, J.; Lim, H. J. *Asian J. Org. Chem.* **2017**, *6*, 335.
(25) See the Supporting Information for details.

DOI: 10.1021/acs.orglett.9b00410
Org. Lett. XXXX, XXX, XXX−XXX