OL | Organic Letters

Letter

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

pubs.acs.org/OrgLett

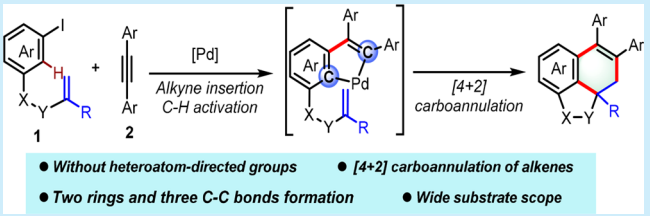
Pd-Catalyzed Alkyne Insertion/C−H Activation/[4 + 2] Carboannulation of Alkenes to the Synthesis of Polycyclics

Songjin Guo, Panpan Li, Zhe Guan, Libo Cai, Siwei Chen, Aijun Lin,* and Hequan Yao*

State Key Laboratory of Natural Medicines (SKLNM) and Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing 210009, P. R. China

Supporting Information

ABSTRACT: An unprecedented Pd-catalyzed alkyne insertion/C−H activation/intramolecular [4 + 2] carboannulation of alkenes has been reported. In this transformation, the C−H activation was triggered by an *in situ* generated alkenylpalladium species via the Pd-catalyzed cross-coupling reaction of aryl iodides and alkynes. Subsequently, the resulting five-membered C, C−palladacycle intermediates were added across the alkenes, providing a unique approach to access diversified polycyclics in good efficiency. Two new rings and three C−C bonds were formed in one pot.



Downloaded from pubs.acs.org by IOWA STATE UNIV on 01/29/19. For personal use only.

Org. Lett.

Transition-metal-catalyzed C−H activation/[4 + 2] heteroannulation of alkenes has emerged as an efficient synthetic tool for the rapid construction of functional six-membered heterocycles.[1] By using amides as the directing groups, Glorius,[2] Guimond,[3] Rovis,[4] Cramer,[5] and Wang[6] have disclosed the intermolecular C−H activation/alkene insertion to the synthesis of dihydroisoquinolones via rhodium or ruthenium catalysis (Figure 1a). Besides, with imines as the directing groups, Rovis described a rhodium-catalyzed C−H activation/alkene insertion to construct 2,3-dihydropyridines (Figure 1a).[7] Very recently, Daugulis reported a cobalt-catalyzed oxidative annulation of benzoic acids with alkenes to synthesize 1-isochromanons (Figure 1a).[8] Intramolecular rhodium-catalyzed C−H activation/[4 + 2] annulation of benzamides with a tethered alkene for the construction of fused oligocycle lactam skeletons has been reported by Rovis[9] and Glorius,[10] independently (Figure 1b). However, all of these elegant works relied on heteroatom-directed groups (N or O) to assist the C−H activation, forming stable five-membered C, X-metallacycle complexes (X = heteroatom) to enable the annulation process. Herein, we disclosed a Pd-catalyzed alkyne insertion/C−H activation/intramolecular [4 + 2] carboannulation of alkenes. In this reaction, the C−H activation was triggered by an *in situ* generated alkenylpalladium species via the Pd-catalyzed cross-coupling reaction of aryl iodides and alkynes. Subsequently, the resulting five-membered C, C-palladacycle species[11] were added across the alkenes, providing a unique approach to access diversified polycyclics in good efficiency (Figure 1c). Setting the potentially competitive benzannulation between the five-membered C, C-palladacycles and alkynes[12] or aryl halides[13] is a key to the success of this tandem reaction.

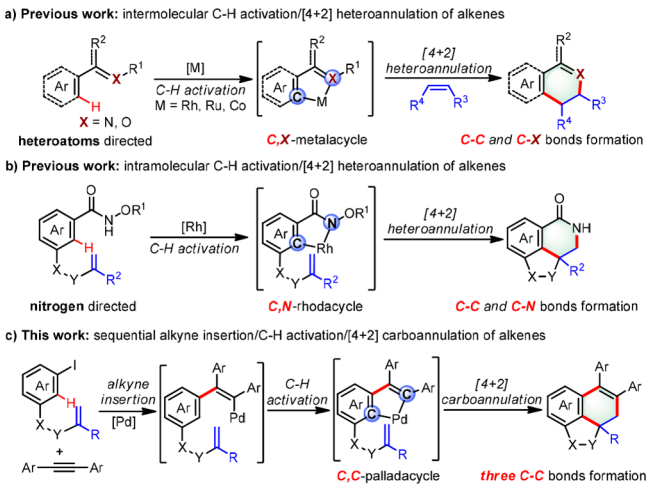


Figure 1. Transition-metal-catalyzed C−H activation/[4 + 2] annulation of alkenes.

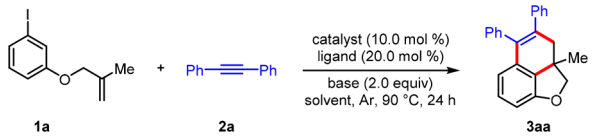
Initially, 1-iodo-3-((2-methylallyl)oxy)benzene **1a** and 1,2-diphenylethyne **2a** were chosen as the benchmark substrates to identify the systems capable of mediating this challenging transformation. Several palladium catalysts were first screened in the presence of NaOPiv·H_2O (2.0 equiv) in DMF (2.0 mL) at 90 °C (Table 1, entries 1−5), and $Pd(OAc)_2$ could offer the desired product **3aa** in 53% yield. Subsequent investigation of bases revealed that the use of CsOAc could increase the yield to 73%, whereas other bases such as NaOAc, K_2CO_3, Cs_2CO_3, and $KHCO_3$ led to a diminished yield (Table 1, entries 6−10). Screening of solvents indicated that the dipolar aprotic solvent DMF was optimal (Table 1, entries 7 and 11−14). Moreover, the addition of ligands was useless to improve the reaction effiency (Table 1, entries 15−19). In the absence of palladium catalyst, no desired product could be detected (Table 1, entry

Received: December 5, 2018

© XXXX American Chemical Society

DOI: 10.1021/acs.orglett.8b03884
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	catalyst	ligand	base	solvent	yield[b] (%)
1	$Pd(PPh)_4$	-	$NaOPiv·H_2O$	DMF	20
2	$Pd_2(dba)_3$	-	$NaOPiv·H_2O$	DMF	41
3	$Pd(PPh_3)_2Cl_2$	-	$NaOPiv·H_2O$	DMF	27
4	$Pd(CH_3CN)_2Cl_2$	-	$NaOPiv·H_2O$	DMF	34
5	$Pd(OAc)_2$	-	$NaOPiv·H_2O$	DMF	53
6	$Pd(OAc)_2$	-	NaOAc	DMF	22
7	$Pd(OAc)_2$	-	CsOAc	DMF	73 (70)[c]
8	$Pd(OAc)_2$	-	K_2CO_3	DMF	24
9	$Pd(OAc)_2$	-	Cs_2CO_3	DMF	ND[d]
10	$Pd(OAc)_2$	-	$KHCO_3$	DMF	45
11	$Pd(OAc)_2$	-	CsOAc	DMSO	49
12	$Pd(OAc)_2$	-	CsOAc	MeOH	ND
13	$Pd(OAc)_2$	-	CsOAc	DCE	ND
14	$Pd(OAc)_2$	-	CsOAc	toluene	ND
15	$Pd(OAc)_2$	BINAP	CsOAc	DMF	52
16	$Pd(OAc)_2$	PPh_3	CsOAc	DMF	62
17	$Pd(OAc)_2$	DavePhos	CsOAc	DMF	52
18	$Pd(OAc)_2$	bpy	CsOAc	DMF	43
19	$Pd(OAc)_2$	1,10-phen	CsOAc	DMF	46
20	-	-	CsOAc	DMF	NR[e]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (10.0 mol %), ligand (20.0 mol %), base (2.0 equiv), solvent (2.0 mL), at 90 °C under Ar atmosphere for 24 h, sealed tube. [b]The yields were determined from the crude reaction mixtures by ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard. [c]Isolated yields. [d]ND = not determined. [e]NR = no reaction.

20). We finally established the optimized conditions as **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (10.0 mol %), and CsOAc (2.0 equiv) in DMF (2.0 mL) at 90 °C under Ar atmosphere for 24 h.

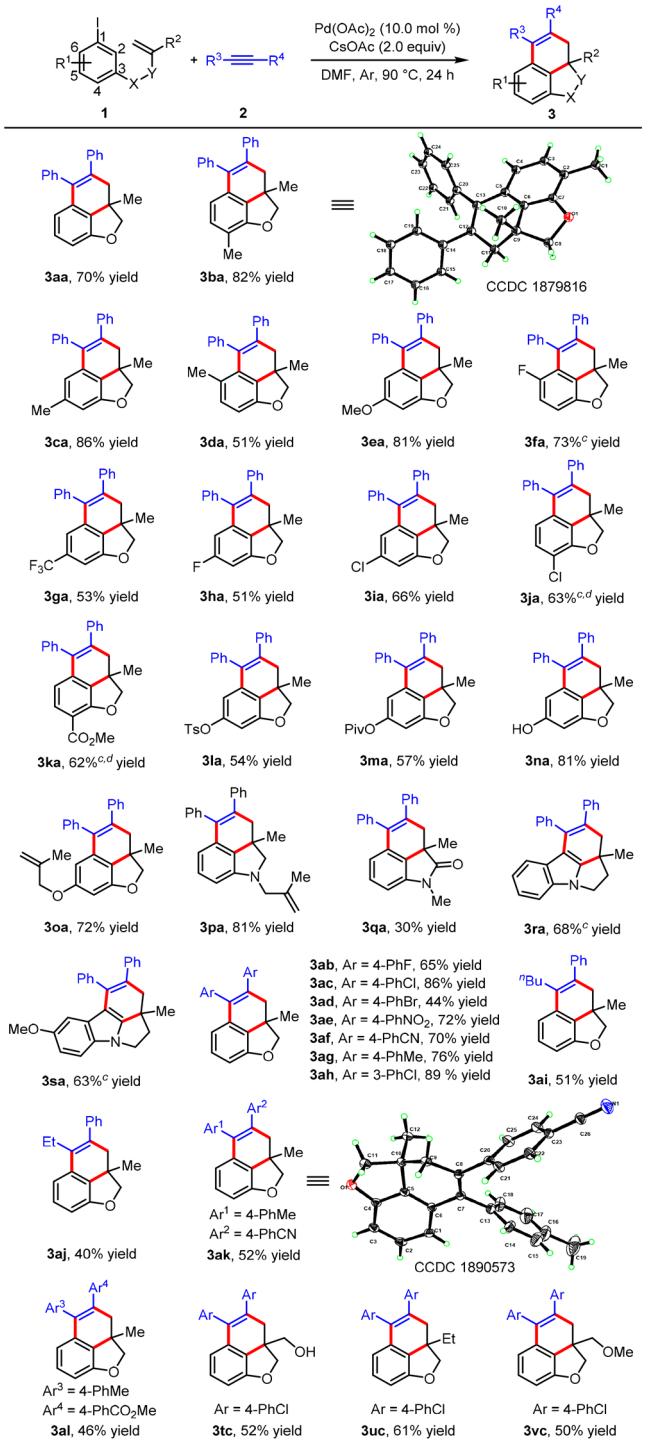
With the optimized reaction conditions in hand, we then probed the substrate scope and generality of the reaction (Scheme 1). Regarding the alkene-tethered aryl iodides **1**, we found that both electron-donating (**1b**−**e**) and electron-withdrawing (**1f**−**m**) groups could be well incorporated at the C4-, C5-, or C6-positions of the benzene ring, giving the corresponding products (**3ba**−**ma**) in moderate to good yields. The structure of **3ba** was confirmed by X-ray crystallography (see the Supporting Information for more details). The substrate **1n** with a transformable hydroxy group displayed good reactivity to offer **3na** in 81% yield. Substrates **1p** and **1q** with nitrogen atom as a linker could yield indoline (**3pa**) in 81% yield and oxindole (**3qa**) in 30% yield. Furthermore, the intriguing indole-fused tetracyclic compounds **3ra** and **3sa** could be well constructed in 68% and 63% yields. With respect to the diaryl acetylenes, which bear 4-fluoro (**2b**), 4-chloro (**2c**), 4-bromo (**2d**), 4-nitryl (**2e**), 4-cyano (**2f**), 4-methyl (**2g**), and 3-chloro (**2h**) groups, reaction occurred smoothly to deliver the desired products (**3ab**−**ah**) in 44−89% yields. The unsymmetrical alkynes, such as hex-1-yn-1-ylbenzene **2i** and but-1-yn-1-ylbenzene **2j**, could deliver the products **3ai** and **3aj** in moderate yields with good regioselectivities. The configuration of **3ai** and **3aj** was confirmed by the NOE spectra (see the SI for more details). When the unsymmetrical alkynes (**2k** and **2l**) with two different aryl groups were checked, products **3ak** and **3al** were achieved in good regioselectivities. The structures of **3ak** and **3al** were confirmed by X-ray crystallography (see the SI for more details). Changing the olefin substituents from methyl group to primary alcohol, ethyl, and methyl ether groups, the products (**3tc**−**vc**) could also be achieved in good yields. When mono- or trisubstituted alkenes were tested, no desired annulation products could be detected and replaced by formimg intramolecular Mizoroki−Heck coupling products (see the SI for more details).

To demonstrate the utility of the reaction, the scale-up experiment and further transformations of **3na** were carried out as shown in Scheme 2. Product **3na** (841 mg) was achieved in 82% yield on 3.0 mmol scale under the standard reaction conditions (Scheme 2a). 2-Bromo-6-(trifluoromethyl)pyridine and trifluoromethylated vinyl bromide as significant fluorine-containing precursors could react with **3na** smoothly to provide compounds **4** and **5** in 75% and 52% yield, respectively. Moreover, **3na** could be readily converted into compound **6** in 91% yield, which served as a versatile intermediate for the further diversification. The subsequent coupling reactions of **6** rapidly constructed a variety of functionalized 3,4-fused dihydrobenzofurans via forming C−C, C−N, and C−P bonds. A novel indole derivative **11** could be obtained directly via a palladium-catalyzed tandem cross-coupling and cyclization of **6** and *o*-ethynylaniline.

To elucidate some mechanistic insight into this reaction, some control experiments were carried out. First, we examined the reaction in the presence of CH_3CO_2D (Scheme 3a). After 24 h, deuterium incorporation at the C6 position of D_1-**3a** was observed, as determined by ^{1}H NMR analysis. This result suggested that the process of the C−H activation triggered by the *in situ* generated alkenylpalladium species is reversible.

DOI: 10.1021/acs.orglett.8b03884
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Substrate Scope[a,b]

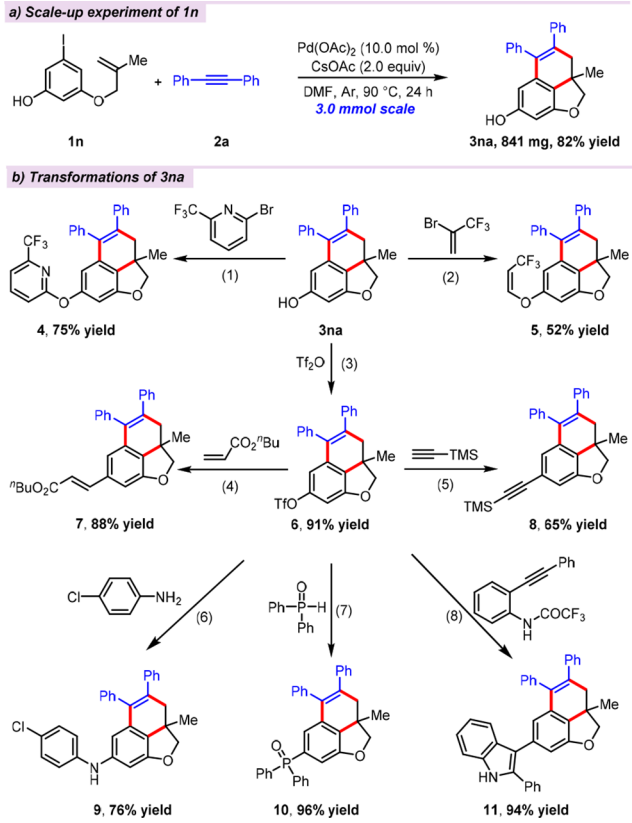


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (10.0 mol %), CsOAc (2.0 equiv), and DMF (2.0 mL), at 90 °C under Ar atmosphere for 24 h, sealed tube. [b]Isolated yields. [c]36 h. [d]HOAc (5.0 equiv).

Subsequently, the kinetic isotope effect (KIE) experiment was examined. When an equimolar mixture of **1o** and D_3-**1o** was checked at a low degree of conversion (Scheme 3b), a K_H/K_D ratio of 2.3 was obtained, which indicated that the C−H activation may be involved in the rate-determining step.

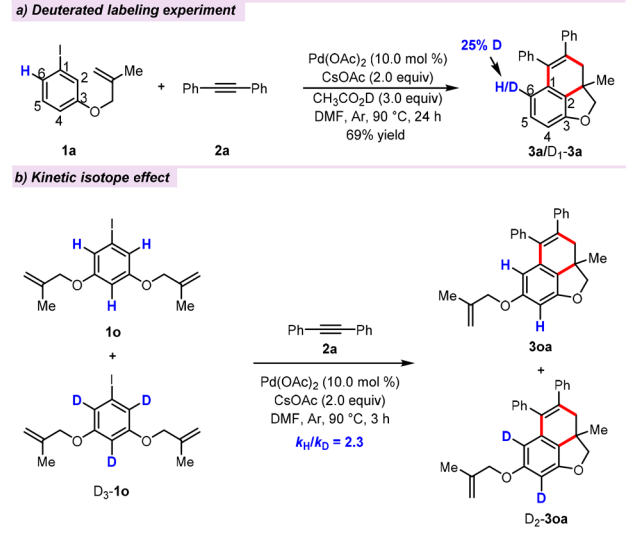
On the basis of the above mechanistic study and literature precedents,[11−13] a plausible catalytic cycle of this reaction was proposed and shown in Scheme 4. Initially, the oxidative addition of aryl iodide **1a** to the active Pd(0) generates the aryl Pd(II) species **A**, which inserts the diphenylacetylene **2a** to

Scheme 2. Scale-Up Experiment and Synthetic Transformations[a]



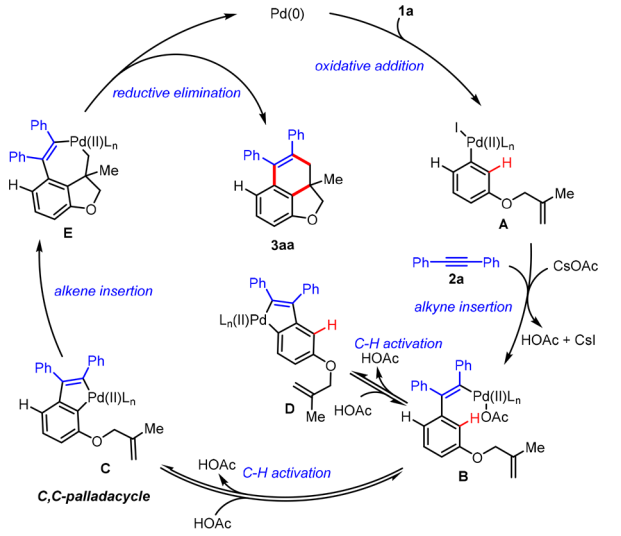
[a]Reaction conditions: (1) CuI, K_3PO_4, 2-carboxypyridine, DMSO, at 90 °C under Ar. (2) $K_3PO_4·3H_2O$, DMF, at 100 °C. (3) Et_3N, DCM, at −78 °C under Ar. (4) $Pd(OAc)_2$, PPh_3, K_2CO_3, toluene, at 110 °C under Ar. (5) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, at 80 °C under Ar. (6) $Pd(OAc)_2$, Xphos, Cs_2CO_3, toluene, at 100 °C under Ar. (7) $Pd_2(dba)_3$, DPPP, *i*-Pr_2NEt, toluene, at 110 °C under Ar. (8) $Pd(PPh)_4$, Cs_2CO_3, CH_3CN, at 100 °C under Ar.

Scheme 3. Mechanistic Experiments



DOI: 10.1021/acs.orglett.8b03884
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Proposed Reaction Mechanism



form the intermediate **B**. The resulting alkenylpalladium species **B** undergoes reversible C−H activation to afford the five-membered C, C-palladacycle intermediates **C** and **D**. Next, the intramolecular alkene coordination and insertion into the Pd−C bond of the species **C** generates a seven-membered C, C-palladacycle intermediate **E**. Finally, the C−C reductive elimination of species **E** results in the formation of the desired product **3aa** and releases Pd(0) to the next catalytic cycle.

In summary, we have developed an unprecedented Pd-catalyzed alkyne insertion/C−H activation/intramolecular [4 + 2] carboannulation of alkenes, providing an efficient and straightforward approach to prepare diversified polycyclics via the formation of two new rings and three C−C bonds. The *in situ* generated alkenylpalladium species via Pd-catalyzed cross-coupling between aryl iodides and alkynes could efficiently enable the C−H activation to form a five-membered C, C-palladacycle intermediate, which then successfully realized the alkene insertion process. A deuterium labeling experiment identified that the C−H activation triggered by the *in situ* generated alkenylpalladium species is reversible and could be involved in the rate-determining step. Further study on the asymmetrical process of this reaction is currently underway 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.8b03884.

Detailed experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1879816 and 1890573−1890574 contain 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.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ajlin@cpu.edu.cn.
*E-mail: hyao@cpu.edu.cn, cpuhyao@126.com.

ORCID

Aijun Lin: 0000-0001-5786-4537
Hequan Yao: 0000-0003-4865-820X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support from the National Natural Science Foundation of China (NSFC21502232 and NSFC21572272), the Innovation Team of "the Double-First Class" Disciplines (CPU2018GY04 and CPU2018GY35), and the Foundation of The Open Project of State Key Laboratory of Natural Medicines (SKLNMZZCX201818) is gratefully acknowledged.

■ REFERENCES

(1) For selected reviews, see: (a) Huang, H.; Ji, X.; Wu, W.; Jiang, H. Transition metal-catalyzed C−H functionalization of *N*-oxyenamine internal oxidants. *Chem. Soc. Rev.* **2015**, *44*, 1155. (b) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. A Simple and Versatile Amide Directing Group for C−H Functionalizations. *Angew. Chem., Int. Ed.* **2016**, *55*, 10578.

(2) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. Rh(III)-Catalyzed Directed C−H Olefination Using an Oxidizing Directing Group: Mild, Efficient, and Versatile. *J. Am. Chem. Soc.* **2011**, *133*, 2350.

(3) Guimond, N.; Gorelsky, S. I.; Fagnou, K. Rhodium(III)-Catalyzed Heterocycle Synthesis Using an Internal Oxidant: Improved Reactivity and Mechanistic Studies. *J. Am. Chem. Soc.* **2011**, *133*, 6449.

(4) (a) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. Biotinylated Rh(III) Complexes in Engineered Streptavidin for Accelerated Asymmetric C−H Activation. *Science* **2012**, *338*, 500. (b) Hyster, T. K.; Dalton, D. M.; Rovis, T. Ligand design for Rh(III)-catalyzed C−H activation: an unsymmetrical cyclopentadienyl group enables a regioselective synthesis of dihydroisoquinolones. *Chem. Sci.* **2015**, *6*, 254. (c) Semakul, N.; Jackson, K. E.; Paton, R. S.; Rovis, T. Heptamethylindenyl (Ind*) enables diastereoselective benzamidation of cyclopropenes via Rh(III)-catalyzed C−H activation. *Chem. Sci.* **2017**, *8*, 1015. (d) Piou, T.; Romanov-Michailidis, F.; Romanova-Michaelides, M.; Jackson, K. E.; Semakul, N.; Taggart, T. D.; Newell, B. S.; Rithner, C. D.; Paton, R. S.; Rovis, T. Correlating Reactivity and Selectivity to Cyclopentadienyl Ligand Properties in Rh(III)-Catalyzed C−H Activation Reactions: An Experimental and Computational Study. *J. Am. Chem. Soc.* **2017**, *139*, 1296.

(5) (a) Ye, B.; Cramer, N. Chiral Cyclopentadienyl Ligands as Stereocontrolling Element in Asymmetric C−H Functionalization. *Science* **2012**, *338*, 504. (b) Wodrich, M. D.; Ye, B.; Gonthier, J. F.; Corminboeuf, C.; Cramer, N. Ligand-Controlled Regiodivergent Pathways of Rhodium(III)-Catalyzed Dihydroisoquinolone Synthesis: Experimental and Computational Studies of Different Cyclopentadienyl Ligands. *Chem. - Eur. J.* **2014**, *20*, 15409.

(6) (a) Wu, J.-Q.; Zhang, S.-S.; Gao, H.; Qi, Z.; Zhou, C.-J.; Ji, W.-W.; Liu, Y.; Chen, Y.; Li, Q.; Li, X.; Wang, H. Experimental and Theoretical Studies on Rhodium-Catalyzed Coupling of Benzamides with 2,2-Difluorovinyl Tosylate: Diverse Synthesis of Fluorinated Heterocycles. *J. Am. Chem. Soc.* **2017**, *139*, 3537. (b) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. Ruthenium-Catalyzed Oxidative C−H Bond Olefination of *N*-Methoxybenzamides Using an Oxidizing Directing Group. *Org. Lett.* **2012**, *14*, 736.

(7) Romanov-Michailidis, F.; Sedillo, K. F.; Neely, J. M.; Rovis, T. Expedient Access to 2,3-Dihydropyridines from Unsaturated Oximes

DOI: 10.1021/acs.orglett.8b03884
Org. Lett. XXXX, XXX, XXX−XXX

by Rh(III)-Catalyzed C−H Activation. *J. Am. Chem. Soc.* **2015**, *137*, 8892.
(8) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed Coupling of Benzoic Acid C−H Bonds with Alkynes, Styrenes, and 1,3-Dienes. *Angew. Chem., Int. Ed.* **2018**, *57*, 1688.
(9) Davis, T. A.; Hyster, T. K.; Rovis, T. Rhodium(III)-Catalyzed Intramolecular Hydroarylation, Amidoarylation, and Heck-type Reaction: Three Distinct Pathways Determined by an Amide Directing Group. *Angew. Chem., Int. Ed.* **2013**, *52*, 14181.
(10) Shi, Z.; Boultadakis-Arapinis, M.; Koester, D. C.; Glorius, F. Rh(III)-Catalyzed intramolecular redox-neutral cyclization of alkenes via C−H activation. *Chem. Commun.* **2014**, *50*, 2650.
(11) For selected examples, see: (a) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. Cyclocarbopalladation Involving an Unusual 1,5-Palladium Vinyl to Aryl Shift as Termination Step: Theoretical Study of the Mechanism. *J. Am. Chem. Soc.* **2005**, *127*, 7171. (b) Bour, C.; Suffert, J. Cyclocarbopalladation: Sequential Cyclization and C−H Activation/Stille Cross-Coupling in the Pd-5-*Exo*-*Dig* Reaction. *Org. Lett.* **2005**, *7*, 653. (c) Zhao, J.; Larock, R. C. Synthesis of Substituted Carbazoles by a Vinylic to Aryl Palladium Migration Involving Domino C−H Activation Processes. *Org. Lett.* **2005**, *7*, 701. (d) Liu, Z.; Larock, R. C. Palladium-Catalyzed, Sequential, Three-Component Cross-Coupling of Aryl Halides, Alkynes, and Arynes. *Angew. Chem., Int. Ed.* **2007**, *46*, 2535. (e) Zhou, B.; Lu, A.; Shao, C.; Liang, X.; Zhang, Y. Palladium-catalyzed sequential three-component reactions to access vinylsilanes. *Chem. Commun.* **2018**, *54*, 10598. (f) Zhou, B.; Wu, Z.; Ma, D.; Ji, X.; Zhang, Y. Synthesis of Indoles through Palladium-Catalyzed Three-Component Reaction of Aryl Iodides, Alkynes, and Diaziridinone. *Org. Lett.* **2018**, *20*, 6440.
(12) For selected examples, see: (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. Fluorescent Naphthyl- and Anthrylazoles from the Catalytic Coupling of Phenylazoles with Internal Alkynes through the Cleavage of Multiple C−H Bonds. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (b) Zheng, J.; You, S.-L. Rhodium-catalyzed direct coupling of biaryl pyridine derivatives with internal alkynes. *Chem. Commun.* **2014**, *50*, 8204. (c) Pham, M. V.; Cramer, N. Aromatic Homologation by Non-Chelate-Assisted Rh^{III}-Catalyzed C−H Functionalization of Arenes with Alkynes. *Angew. Chem., Int. Ed.* **2014**, *53*, 3484. (d) Zhang, X.; Yu, X.; Ji, D.; Yamamoto, Y.; Almansour, A. I.; Arumugam, N.; Kumar, R. S.; Bao, M. Rhodium-Catalyzed Oxidative Benzannulation of *N*-Adamantyl-1-naphthylamines with Internal Alkynes via Dual C−H Bond Activation: Synthesis of Substituted Anthracenes. *Org. Lett.* **2016**, *18*, 4246.
(13) For selected examples, see: (a) Dyker, G.; Kellner, A. A palladium catalyzed domino coupling process to substituted phenanthrenes. *Tetrahedron Lett.* **1994**, *35*, 7633. (b) Sickert, M.; Weinstabl, H.; Peters, B.; Hou, X.; Lautens, M. Intermolecular Domino Reaction of Two Aryl Iodides Involving Two C−H Functionalizations. *Angew. Chem., Int. Ed.* **2014**, *53*, 5147.

DOI: 10.1021/acs.orglett.8b03884
Org. Lett. XXXX, XXX, XXX−XXX