JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Streamlined Synthesis of Polycyclic Conjugated Hydrocarbons Containing Cyclobutadienoids via C−H Activated Annulation and Aromatization

Zexin Jin, Yew Chin Teo, Nicolo G. Zulaybar, Matthew D. Smith, and Yan Xia*

Department of Chemistry, Stanford University, Stanford, California 94305, United States

Supporting Information

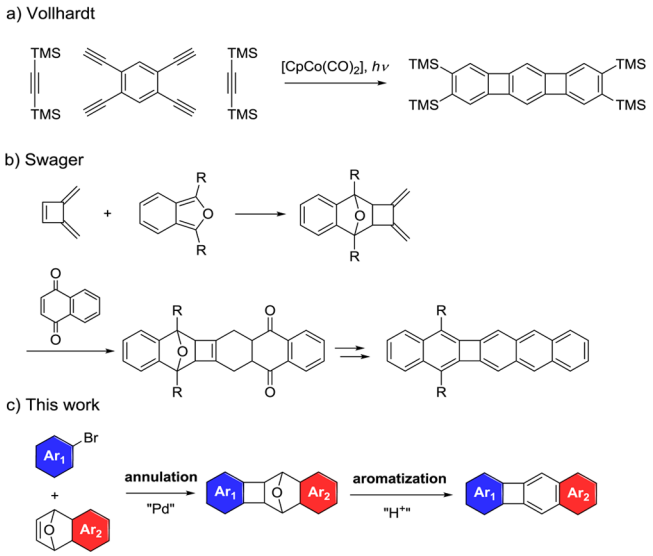
ABSTRACT: The juxtaposition of fused cyclobutadienoid (CBD) with benzenoid creates intriguing alternating antiaromatic and aromatic conjugation. Synthetic accessibility of such molecules, however, has been challenging and limited in scope. We report a modular and streamlined synthetic strategy to access a large variety of polycyclic conjugated hydrocarbons with fused CBD. Synthesis was achieved through efficient palladium-catalyzed C−H activated annulation between abundant aryl bromides and oxanorbornenes, followed by aromatization under acidic conditions. The influence of four-membered ring was examined using spectroscopy, crystallography, and computation. This strategy will facilitate exploration on the chemical, structural, and electronic properties of such conjugated systems containing CBD.

Nonbenzenoid structures with antiaromaticity have been much less explored with limited understanding of their electronic structures, chemical reactivity, and solid-state properties, compared to ubiquitous aromatic π-systems, largely due to their challenging synthesis and limited stability.[1] Opposite to aromaticity, antiaromaticity leads to strong destabilization, π-bond localization, and a paratropic current.[2] [*N*]Phenylene is an intriguing family of conjugated ladder structures with fused antiaromatic 4π-electron cyclobutadienoid (CBD) and aromatic 6π-electron benzenoid rings, two extremes of the aromaticity continuum.[3] As a result, the benzenoids fused with CBD are dearomatized to show significant bond alternation.[3] The most-established synthesis of [*N*]phenylenes was developed by Vollhardt and co-workers via cobalt-catalyzed [2 + 2 + 2] cycloaddition of appropriately designed phenylethynyl substrates under photolysis (Scheme 1a).[3,4] Their seminal work produced almost all known [*N*]phenylenes in literature. However, the cobalt-catalyzed cycloadditions form only benzenoid, thus phenylene structures, in moderate yields, and the synthesis of the required phenylethynyl precursors is multistep and time-consuming. Swager and co-workers recently extended [*N*]phenylene to phenylene-containing acenes (Scheme 1b), using 3,4-bis(methylene)cyclobutene as one of the starting materials, which is an air sensitive compound that needs to be synthesized via flash vacuum pyrolysis.[5] As a result of challenging synthesis, conjugated molecules containing four-membered rings remain rare but intriguing.[3,5,6]

A facile synthetic method to access a wide variety of phenylene or CBD containing structures will enable systematic investigation into the influence of their antiaromaticity and tuning of their optoelectronic properties. Transition-metal catalyzed C−H activation is emerging as powerful strategies for the synthesis of extended π-systems.[7] In powerful norbornene (NBE) mediated C−H functionalization of arenes, NBE fused benzocyclobutene may form as a byproduct following the *ortho*-C−H activation step.[8] We recently tuned this side reaction pathway into highly efficient catalytic arene-NBE annulation (CANAL) and used this chemistry to synthesize a series of shape-persistent, nonconjugated ladder polymers.[9] We envisioned that if NBE is replaced with oxanorbornene (oNBE), the CANAL chemistry may yield oNBE fused benzocyclobutene structures that can then be aromatized to form CBD subunits (Scheme 1c). Because a plethora of aryl bromides and oNBEs are readily accessible and widely used for many coupling reactions (especially aryl bromides are ubiquitously used for the synthesis of almost all conjugated structures), this strategy represents a versatile and step-economic synthesis of a wide range of conjugated structures containing CBD circuits.

We first attempted the CANAL reaction using bromo-*p*-xylene and benzooxanorbornadiene as model substrates. Under the same conditions that we have used to achieve quantitative

Scheme 1. Syntheses of Phenylene Structures

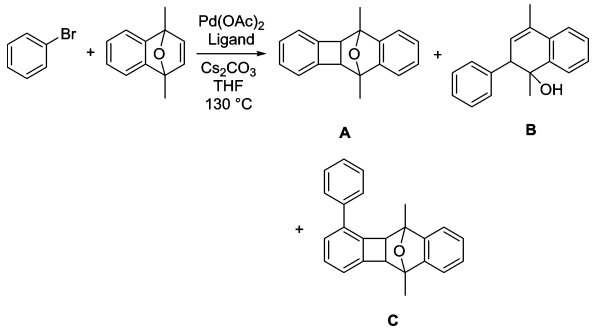


Received: December 22, 2016

DOI: 10.1021/jacs.6b12888
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

annulation between bromo-*p*-xylene and NBE, however, only (2-naphthyl)-*p*-xylene was obtained and no desired annulation product was observed (Figure S1). We rationalized that the naphthyl substituent was formed via Pd-assisted oNBE ring-opening followed by rapid aromatization from the aryl bromide-oNBE cross-coupled intermediate. This observation indicated that *β*-oxygen elimination of oNBE strongly competed with the annulation pathway. To suppress this undesired reaction pathway, we introduced two methyl groups to the bridge-head positions of oNBE, using 1,4-dimethyl-benzooxanorbornadiene as the substrate. Simple bromobenzene, instead of bromo-*p*-xylene, was used as the other coupling substrate, to avoid the otherwise high steric hindrance of the palladacycle intermediate. Delightfully, the selectivity was dramatically improved with the desired annulation product **A** formed in 87% yield using 5 mol % $Pd(OAc)_2$ and 10 mol % PPh_3 as ligand. Small amounts of two byproducts **B** and **C** were also detected (Table 1). The reaction mechanism is proposed to

Table 1. Optimization of Annulation between oNBE and Aryl Bromide[a]

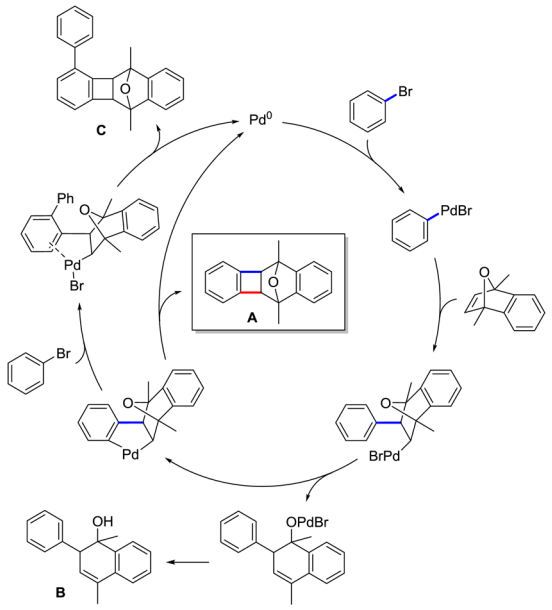


		conv. (%)[b]		
entry	ligand	A	B	C
1	PPh_3	87	9	4
2	$PtBu_3$	62	6	0
3	P(*o*-Tol)$_3$	72	7	0
4	P(2-furyl)$_3$	88	9	1
5	Johnphos	97 (91[c])	0	0

[a]Reactions were performed using 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 1 equiv Cs_2CO_3, at [substrate] = 0.25 M in THF at 130 °C for 24 h in a sealed pressure tube. [b]Conversions were determined by NMR spectroscopy using mesitylene as the internal standard. [c]Isolated yield.

start with oxidative addition of Pd(0) to aryl bromide, followed by coupling with oNBE (Scheme 2). The *ortho* aryl C−H bond is then activated to form the palladacycle, followed by reductive elimination to give the desired product **A**. Competing with C−H activation, *β*-oxygen elimination[10] of the oNBE coupled Pd intermediate may occur to give ring-opened product **B**. The palladacycle intermediate may also undergo *ortho* coupling with another equivalent of aryl bromide before annulation occurs to give product **C**. To improve further the yield and the selectivity for the CANAL product, various phosphine-based ligands were examined. We found that bulky ligands eliminated the formation of *ortho* coupled product **C**. Gratifyingly, Johnphos ligand gave both high yield and high selectivity for the desired product **A** with 97% conversion (91% isolated yield). The relatively bulky Buchwald ligands are known to not only stabilize the Pd intermediate but also accelerate reductive elimination,[11] thus facilitating the annulation pathway. The stereochemistry of

Scheme 2. Proposed Mechanism

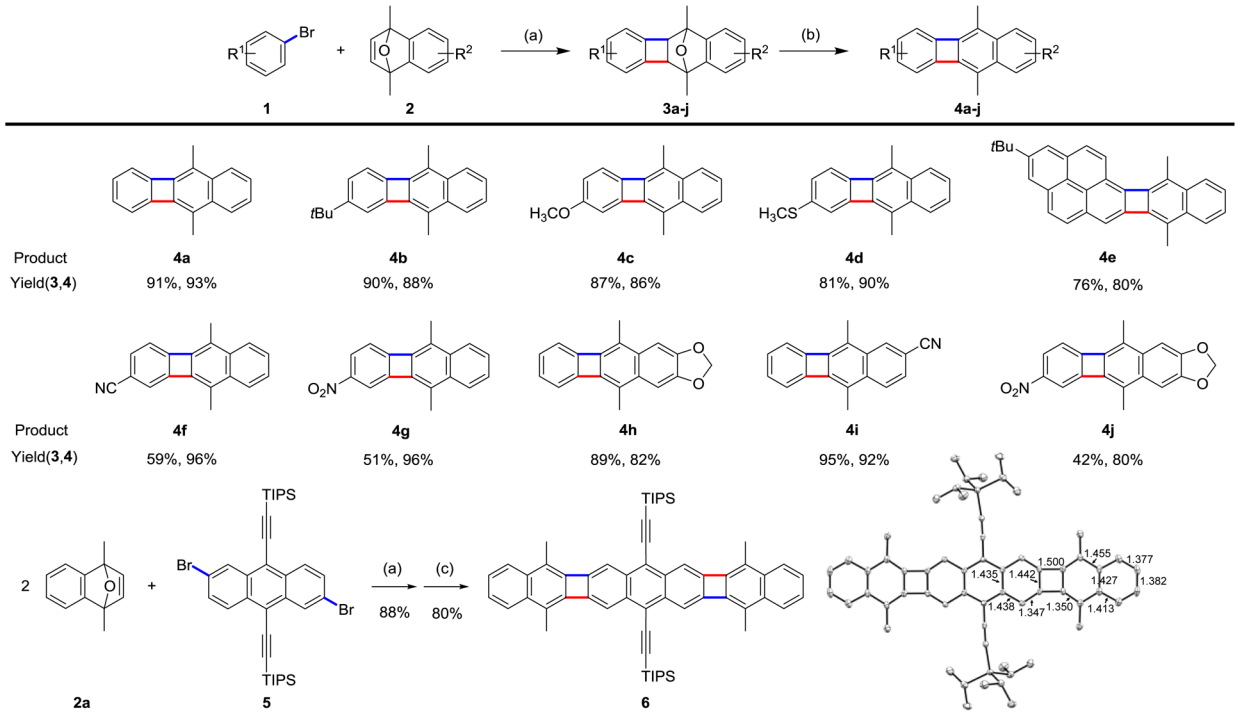


the annulation is unimportant for our goal of synthesizing novel *π*-systems since the fused oxanorbornyl ring will be aromatized in the next step, but 2D NMR spectroscopy of the product indicated that the *exo*-product was formed (Figure S2), in agreement with what we previously observed using NBEs as the substrates.[9]

We next explored the scope of CANAL using phenyl bromides with variable electronic properties and extending the conjugation to pyrenyl bromides (Scheme 3). All the electron-rich and -neutral aryl bromides gave >80% isolated yields of the desired products (**3a**−**e**) using 5 mol % $Pd(OAc)_2$ and 10 mol % JohnPhos. Electron-deficient aryl bromides gave slower reactions and moderate yields (50−60%) (**3f**−**g**). We suspected that the C−H activation step may be rate-determining and is slowed for electron-deficient arenes. We also varied the oNBE structures. Varying the substituents on benzo-oNBEs did not affect the reaction efficiency or selectivity, and high yields (>89%) were obtained (**3h**−**i**). Therefore, aryl bromide and oNBE can be independently varied to yield precursors for a wide range of asymmetric CBD-containing polycyclic conjugated hydrocarbons (PCHs), and the tolerance to a range of functional groups allows tuning of the energy levels of PCHs and their further manipulation using substitutions. We further illustrated the synthetic flexibility by synthesizing a donor-bridge-acceptor type of compound (**4j**), which is useful to tune the optoelectronic properties and understand electron transfer across the four-membered ring in the future.[12] Subsequent aromatization of all the CANAL products was achieved using pyridinium *p*-toluenesulfonate (PPTS) in toluene at 120 °C to afford the corresponding CBD-containing PCHs. Pure PCHs were obtained in >80% isolated yields after simple aqueous and MeOH washes of the crude products without column chromatography. We also synthesized an acene-like molecule **6** containing two four-membered rings, using dibromo-bis-(triisopropylsilylethynyl)-anthracene **5** and oNBE **2a**, in 88% and 80% yields for the CANAL and aromatization steps, respectively (Scheme 3). Exclusive regioselectivity for C−H activation and annulation at 3 and 7 positions of anthracene was observed. Stronger acids, such as HCl, were required for aromatization to produce **6**. The generated antiaromaticity and increased strain

DOI: 10.1021/jacs.6b12888
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of CBD-Containing PCHs from Various Aryl Bromides and oNBEs



All yields are isolated yields. The first yield is for the CANAL step and the second yield is for the aromatization step. (a) 5 mol % $Pd(OAc)_2$, 10 mol % JohnPhos, 1.0 equiv. Cs_2CO_3, in THF at 130 °C for 24 h in a sealed pressure tube; (b) PPTS, toluene, 120 °C; (c) HCl, *i*PrOH/$CHCl_3$, 80 °C.

upon aromatization may reduce the favorable aromatic stabilization energy.

NMR spectroscopy of the resulting compounds showed shielding of arene protons adjacent to four-membered ring. This indicated reduced diatropicity in the arenes or the presence of paratropicity from the CBD or both. Upon aromatization, the NMR signals of the protons on the benzenoids adjacent to four-membered ring shifted upfield. For instance, the α-proton of the benzenoid in **4a** had shifted upfield to 6.93 ppm from 7.25 ppm in **3a**; anthracenoid in **6** has upfield shifted to 8.02 ppm from 8.43 ppm in the CANAL product (all δ in $CDCl_3$). The same trend of upfield shifting was observed in all the compounds regardless of the electronic properties of the substituents and conjugation length, revealing the universal paratropicity from fused CBD.

The same magnetic features can be captured from nucleus independent chemical shifts (NICS) calculation,[13] which computes the magnetic shielding in a space of interest of a molecule as a means to determine diatropicity and paratropicity. Negative NICS values denote aromatic rings and positive values denote antiaromatic rings. NICS-XY scan of **6** at the GIAO-B3LYP/6-311+G* level of theory showed small positive NICS values for the four-membered rings, indicating the presence of antiaromaticity (Figure 1). Their neighboring fused rings have significantly reduced aromaticity, indicated by the small negative NICS values; while the benzenoids that are not directly fused with CBDs are not as affected by the paratropicity, indicated by the large negative NICS values, similar to that of normal benzenoids.

All the PCHs exhibited bathochromic shifts in their UV−vis absorption upon aromatization, supporting the electron delocalization across four-membered rings (Figure S4). A strongly electron-withdrawing nitro substituent led to broad and more red-shifted absorption as a result of intramolecular charge transfer. Electron delocalization was also illustrated by the electronic structures calculated using density functional theory (DFT) at the B3LYP/6-311+G* level of theory, which showed that the HOMO and LUMO occupy the entire conjugated structures across four-membered rings (Figure S5). All the synthesized PCHs were stable under ambient conditions with no change in absorption after 10 days in solution under air.

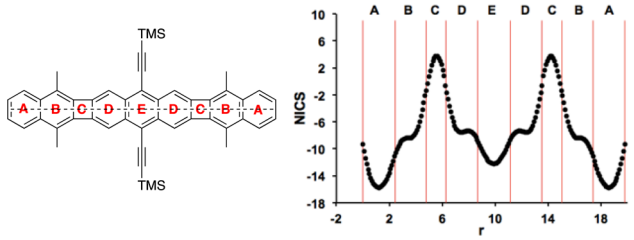


Figure 1. NICS-XY scans ($NICS_{\pi,ZZ}$ (σ-only)) of **6**. Dashed line on molecular structure indicates the trajectory of NICS scan.

Single-crystal X-ray crystallography and bond-distance analysis also revealed the influence of antiaromaticity on the bonding structures. Crystal structure of **6** showed its nearly planar geometry with small torsion angles along phenylene linkage (1.69°). The four-membered ring has a slightly rectangular geometry with long edge of 1.50 Å and short edge of 1.44 Å (Scheme 3 inset). The adjacent benzenoids exhibit alternating short bonds of 1.35 Å and long bonds of 1.44 Å, revealing increased π-bond localization in order to minimize the paratropicity of CBD. The peripheral and central benzenoid rings that are not directly fused with four-membered rings are less affected and have more delocalized π-bonds. The packing of **6** (Figure 2) reveals face-to-face slipped π stacking in two sets of columns, with an intersect angle of 67.3°, close inter-π-planar spacing of 3.40 Å, and 0.41 Å short-axis slip of the

DOI: 10.1021/jacs.6b12888
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

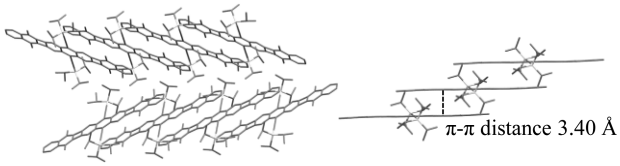


Figure 2. Crystal packing of **6**.

interacting molecules, which are favorable packing features for charge transport and encouraging for future study in transistor devices.

In summary, we report a modular and efficient strategy for the synthesis of a large variety of CBD-containing PCHs via CANAL followed by aromatization using easily accessible substrates, aryl halides and oNBEs. Because aryl bromides are ubiquitous in constructing almost all conjugated structures, this reported strategy can be potentially applied to and integrated with a large number of aromatic building blocks and chemistries to build more complex π-systems containing formally antiaromatic CBD circuits. Further understanding and facile accessibility to such intriguing and underexplored conjugated structures will facilitate control over their structural and electronic properties.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12888.

Experimental and computational details, UV−vis spectra, ^{1}H and ^{13}C NMR spectra (PDF)

Data for $C_{60}H_{66}Si_2$ (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*yanx@stanford.edu

ORCID

Zexin Jin: 0000-0002-4971-3656

Yan Xia: 0000-0002-5298-748X

Author Contributions

Z.J. and Y.C.T. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Stanford University start-up funding. We thank C. J. Galvin for setting up the aroma package, Dr. S. Liu for preliminary exploration, and Prof. H. I. Karunadasa for assistance with single-crystal data collection. Y.C.T. is supported by an A*STAR graduate fellowship. MDS is supported by a NSF graduate fellowship. Single-crystal X-ray diffraction experiments were performed at beamline 11.3.1 at the Advanced Light Source (ALS). The ALS is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under contract no. DE-AC02-05CH11231.

■ REFERENCES

(1) Representative examples: (a) Iida, A.; Yamaguchi, S. *J. Am. Chem. Soc.* **2011**, *133*, 6952−6955. (b) Shimizu, A.; Kishi, R.; Nakano, M.; Shiomi, D.; Sato, K.; Takui, T.; Hisaki, I.; Miyata, M.; Tobe, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 6076−6079. (c) Parkhurst, R.; Swager, T. *Top. Curr. Chem.* **2014**, *350*, 141−175. (d) Cao, J.; London, G.; Dumele, O.; von Wantoch Rekowski, M.; Trapp, N.; Ruhlmann, L.; Boudon, C.; Stanger, A.; Diederich, F. *J. Am. Chem. Soc.* **2015**, *137*, 7178−7188. (e) Zeng, Z.; Shi, X.; Chi, C.; Lopez Navarrete, J. T.; Casado, J.; Wu, J. *Chem. Soc. Rev.* **2015**, *44*, 6578−6596. (f) Rudebusch, G. E.; Zafra, J. L.; Jorner, K.; Fukuda, K.; Marshall, J. L.; Arrechea-Marcos, I.; Espejo, G. L.; Ponce Ortiz, R.; Gómez-García, C. J.; Zakharov, L. N.; Nakano, M.; Ottosson, H.; Casado, J.; Haley, M. M. *Nat. Chem.* **2016**, *8*, 753−759.

(2) Minkin, V. I.; Glukhovtsev, M. N.; Simkin, B. Y. *Aromaticity and Antiaromaticity: Electronic and Structural Aspects*; Wiley: New York, 1994.

(3) Miljanić, O. Š.; Vollhardt, K. P. C. *Carbon-Rich Compounds: From Molecules to Materials*; Haley, M. M., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2006; pp 140−197.

(4) Representative examples of Vollhardt synthesis of [*N*]phenylenes: (a) Berris, B. C.; Hovakeemian, G. H.; Lai, Y. H.; Mestdagh, H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1985**, *107*, 5670−5687. (b) Schmidt-Radde, R. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1992**, *114*, 9713−9715. (c) Eickmeier, C.; Holmes, D.; Junga, H.; Matzger, A. J.; Scherhag, F.; Shim, M.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 800−804. (d) Han, S.; Bond, A. D.; Disch, R. L.; Holmes, D.; Schulman, J. M.; Teat, S. J.; Vollhardt, K. P. C.; Whitener, G. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 3223−3227.

(5) Parkhurst, R. R.; Swager, T. M. *J. Am. Chem. Soc.* **2012**, *134*, 15351−15356.

(6) (a) Fukazawa, A.; Oshima, H.; Shimizu, S.; Kobayashi, N.; Yamaguchi, S. *J. Am. Chem. Soc.* **2014**, *136*, 8738−8745. (b) Schlütter, F.; Nishiuchi, T.; Enkelmann, V.; Müllen, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 1538−1542. (c) Biegger, P.; Schaffroth, M.; Patze, C.; Tverskoy, O.; Rominger, F.; Bunz, U. H. F. *Chem.—Eur. J.* **2015**, *21*, 7048−7052. (d) Yang, S.; Shan, B.; Xu, X.; Miao, Q. *Chem. - Eur. J.* **2016**, *22*, 6637−6642. (e) Biegger, P.; Schaffroth, M.; Tverskoy, O.; Rominger, F.; Bunz, U. H. F. *Chem. - Eur. J.* **2016**, *22*, 15896−15901.

(7) Representative reviews on metal-catalyzed synthesis of conjugated polycycles: (a) Jin, T.; Zhao, J.; Asao, N.; Yamamoto, Y. *Chem. - Eur. J.* **2014**, *20*, 3554−3576. (b) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 66−81.

(8) (a) Ye, J.; Lautens, M. *Nat. Chem.* **2015**, *7*, 863−870. (b) Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res.* **2016**, *49*, 1389−1400. (c) Catellani, M.; Ferioli, L. *Synthesis* **1996**, *1996*, 769−772. (d) Wu, X.; Zhou, J. *Chem. Commun.* **2013**, *49*, 11035−11037.

(9) Liu, S.; Jin, Z.; Teo, Y. C.; Xia, Y. *J. Am. Chem. Soc.* **2014**, *136*, 17434−17437.

(10) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58.

(11) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461−1473.

(12) (a) Ricks, A. B.; Solomon, G. C.; Colvin, M. T.; Scott, A. M.; Chen, K.; Ratner, M. A.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2010**, *132*, 15427−15434. (b) Sukegawa, J.; Schubert, C.; Zhu, X.; Tsuji, H.; Guldi, D. M.; Nakamura, E. *Nat. Chem.* **2014**, *6*, 899−905.

(13) Gershoni-Poranne, R.; Stanger, A. *Chem. - Eur. J.* **2014**, *20*, 5673−5688.

DOI: 10.1021/jacs.6b12888
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX