ACS Catalysis

Research Article

Cite This: ACS Catal. 2019, 9, 3906–3912

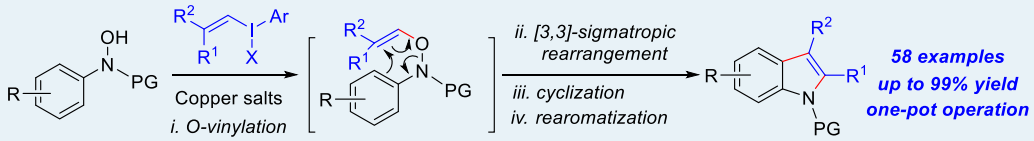
pubs.acs.org/acscatalysis

Copper-Catalyzed Tandem *O*-Vinylation of Arylhydroxylamines/[3,3]-Rearrangement/Cyclization: Synthesis of Highly Substituted Indoles and Benzoindoles

Hairui Yuan, Lirong Guo, Fengting Liu, Zechen Miao, Lei Feng, and Hongyin Gao*

School of Chemistry and Chemical Engineering, Key Laboratory of Colloid and Interface Chemistry, Ministry of Education, Shandong University, 27 South Shanda Road, Ji'nan 250100, Shandong, People's Republic of China

Supporting Information



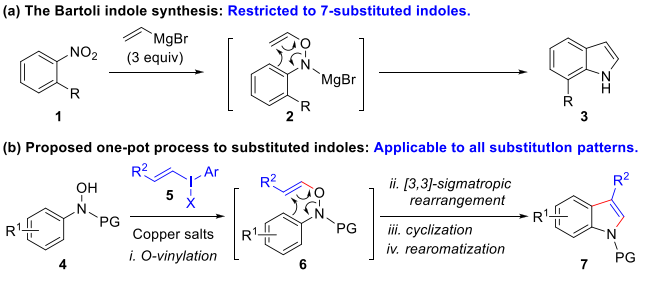
ABSTRACT: Herein, we developed a copper-catalyzed *O*-vinylation of arylhydroxylamine using vinyliodonium salts as vinylation reagents to generate a transient *O*-vinyl-*N*-arylhydroxylamine that rapidly undergoes a [3,3]-sigmatropic rearrangement and subsequent cyclization/rearomatization to form a substituted indole. A wide range of highly substituted indoles and benzoindoles can be afforded in good yields. This approach is readily scalable, and the scope and application of this process are presented.

KEYWORDS: *copper, arylhydroxylamines, vinyliodonium salts, rearrangement, indoles*

The indole nucleus is one of the most ubiquitous scaffolds because of its wide presence in a plethora of natural products, pharmaceuticals, and agrochemicals, as well as in materials science.[1] In particular, highly substituted indoles have been referred to as "privileged structures" because of their capability of binding to a variety of receptors with high affinity.[2] In view of the importance and abundance of the indole motif, it is not surprising that significant efforts have been devoted to develop new strategies for the generation of indole units, and numerous methods have been reported[1g,3] (for example, Fischer,[4] Madelung,[5] Hegedus,[6] Bartoli,[7] Larock,[3c,8] and Buchwald[9] indole synthesis and so on). However, via these methods, harsh conditions (for example, high temperature (>100 °C), low temperature (<−40 °C)), specific starting material availability, and low functional-group tolerance often hamper the versatility and utility of indole synthesis. Thus, the continuous development of alternative approaches that may allow for the straightforward construction of structurally diverse indoles (in particular, 3-substituted indoles) is still a field of increasing interest.

In 1989, Bartoli and co-workers described the reaction of *ortho*-substituted nitroarenes **1** with an excess (3 equiv or more) of vinyl Grignard reagents at low temperature to generate 7-substituted indoles **3** upon aqueous workup conditions.[7c] The presumably formed intermediate **2** from the addition of the second equivalent of Grignard reagent to the corresponding nitrosoarene, which was generated in situ by the addition of the first equivalent of Grignard reagent to the oxygen of the nitro group followed by the rapid elimination/decomposition of the *O*-alkenylated intermediate, could undergo a facile [3,3]-sigmatropic rearrangement, followed by an intramolecular nucleophilic addition and rearomatization to furnish the final indole products (Scheme 1a). This approach has been proven successful in a number of synthetic applications involving a series of bioactive molecules.[7e,10] While powerful, this method is inherently limited to substrates which have to possess a substituent *ortho* to the nitro group of the nitroarenes; otherwise, the reaction gives low or no yield of the desired indole product. In addition, 3 equiv of the alkenyl Grignard reagent and harsh conditions of low temperature (−78 to −20 °C) are necessary. The products of the Bartoli indole synthesis are restricted to 7-substituted indoles, and the yields are usually moderate (less than 70%). If such a process could be generalized for non-*ortho*-substituted nitroarene

Scheme 1. Proposed Indole Synthesis Inspired by the Bartoli Reaction



Received: January 30, 2019
Revised: March 19, 2019
Published: March 26, 2019

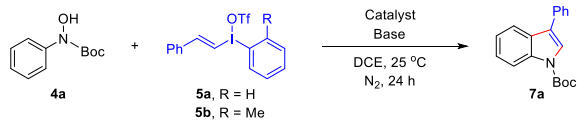
DOI: 10.1021/acscatal.9b00470
ACS Catal. 2019, 9, 3906–3912

substrates, the scope of the potential applications could be further expanded to a broader range of transformations.

Along this line and inspired by the Bartoli indole synthesis, we surmised that the direct *O*-vinylation of arylhydroxylamines **4** would occur using highly reactive vinyliodonium salts **5** as the vinylation reagent to form *O*-vinyl-*N*-arylhydroxylamines **6**, which would rapidly undergo a similar [3,3]-rearrangement/cyclization/rearomatization to afford indole products **7** (Scheme 1b). This approach utilizes *N*-protected arylhydroxylamines, which are readily prepared from nitroarenes,[11] as substrates to undergo a copper-catalyzed cross-coupling reaction[12] with vinyliodonium salts. Vinyliodonium salts are an environmentally benign electrophilic vinylation reagent with low toxicity, high reactivity, and moisture and air stability.[13] However, in comparison to the diverse utility of analogous diaryliodonium salts[14] in organic synthesis, vinyliodonium salts have been much less explored.

Initially, we chose *N*-Boc-phenylhydroxylamine (**4a**) and (*E*)-phenyl(styryl)iodonium trifluoromethanesulfonate (**5a**) as model substrates to optimize the reaction conditions (selected results are summarized in Table 1 and detailed optimization

Table 1. Optimization of the Reaction Conditions[a]



entry	5a/5b	base	catalyst	yield of 7a, %[b]
1	**5a**	Na_2CO_3		0
2	**5a**	*t*BuOK		0
3	**5a**	Na_2CO_3	$Cu(OTf)_2$	0
4	**5a**	Na_2CO_3	$Cu(OAc)_2$	0
5	**5a**	Na_2CO_3	CuI	trace
6	**5a**	Na_2CO_3	CuCl	34
7	**5a**	Na_2CO_3	CuBr	50
8	**5a**	K_2CO_3	CuBr	29
9	**5a**	Cs_2CO_3	CuBr	34
10	**5a**	DTBP	CuBr	0
11	**5b**	Na_2CO_3	CuBr	60
12[c]	**5b**	Na_2CO_3	CuBr	64
13[d]	**5b**	Na_2CO_3	CuBr	73
14[e]	**5b**	Na_2CO_3	CuBr	78

[a]Unless otherwise noted, all reactions were carried out under the following conditions: **4a** (0.2 mmol), **5a** or **5b** (1.1 equiv), base (1.5 equiv), catalyst (10 mol %), DCE (1 mL) at 25 °C under N_2 for 24 h. Abbreviations: Boc = *tert*-butyloxycarbonyl; DCE = 1,2-dichloroethane; DTBP = 2,6-di-*tert*-butylpyridine; Tf = trifluoromethanesulfonyl; Ac = acetyl. [b]Yields of isolated products. [c]1.5 equiv of **5b** was employed. [d]2.0 equiv of **5b** was employed. [e]1.2 equiv of base was employed.

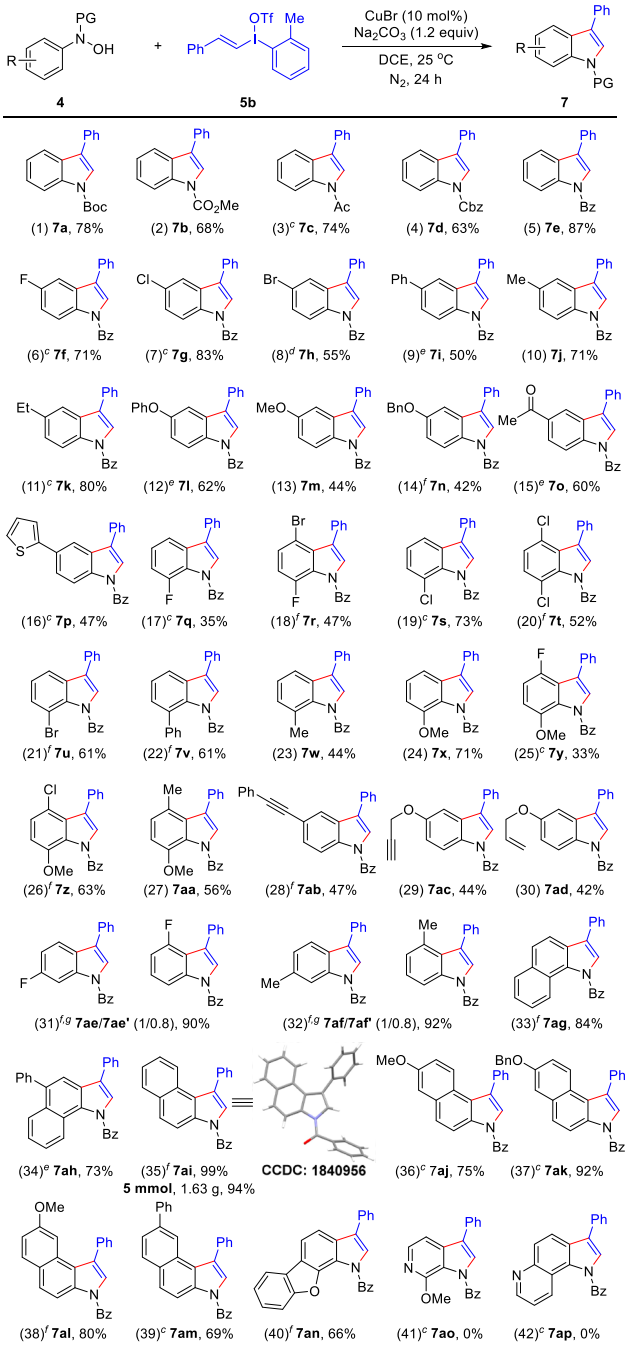
results are summarized in the Supporting Information). Without the employment of catalyst, the reaction did not occur (Table 1, entries 1 and 2). The screening of copper salt catalysts revealed that CuBr was an efficient catalyst to afford a 50% yield of the desired indole product in the presence of Na_2CO_3 (Table 1, entries 3−7). Various bases (K_2CO_3, Cs_2CO_3, DTBP) were also tested, and no higher yields were provided (Table 1, entries 8−10). To our delight, when (*E*)-styryl(*o*-tolyl)iodonium trifluoromethanesulfonate (**5b**) was used as the vinylation reagent, a higher yield was afforded (Table 1, entry 11). Further optimization screening showed that increasing the loading of iodonium salt **5b** had a positive effect on the reaction (Table 1, entries 12 and 13). The results revealed that 2.0 equiv of **5b**, 1.2 equiv of Na_2CO_3, and 10 mol % CuBr in DCE at 25 °C were optimal conditions (Table 1, entry 14).

With the optimized conditions in hand, we next turned our attention to assessing the scope and limitations of this transformation. We were pleased to find that the copper-catalyzed cascade *O*-vinylation[15]/rearrangement/cyclization works across a broad range of arylhydroxylamines, providing access to a diverse array of substituted indole motifs (Table 2). We first explored the scope of the protecting group on the nitrogen atom and found that the benzoyl group is the best option to give a good yield of the desired indole product (Table 2, entries 1−5). The variation of different substituents at the *para* position of the phenyl group was then examined. Both electron-withdrawing groups and electron-donating groups can be well tolerated in this transformation to afford the corresponding indole products in moderate to good yields (Table 2, entries 6−14). It is noteworthy that the acetyl and 2-thiophenyl groups are compatible with this reaction system (Table 2, entries 15 and 16). Meanwhile, various *ortho*-substituted arylhydroxylamines were amenable to the optimized reaction conditions to generate 7-substituted indoles (Table 2, entries 17−27). Notably, different disubstituted aromatic rings, in particular, dihalide-substituted substrates, were also well tolerated in this transformation (Table 2, entries 18, 20, and 25−27). Probably, the steric hindrance of the *ortho* substituents has a negative effect on the efficiency of the reaction and resulted in relatively lower yields in comparison to the *para*-substituted substrates (Table 2, entries 6 vs 17, 7 vs 19, 10 vs 23). To our delight, a series of substrates with redox-sensitive moieties, such as alkynes and olefins, can also be well tolerated (Table 2, entries 28−30). When *meta*-substituted arylhydroxylamines were used as substrates, low regioselectivities but good yields were observed (Table 2, entries 31 and 32). Furthermore, this methodology is applicable to more complex aromatic rings, such as the naphthalene system (Table 2, entries 33−39) and dibenzofuran system (Table 2, entry 40); especially noteworthy are the excellent regioselectivities and high isolated yields of benzoindoles when 2-substituted naphthylhydroxylamines were employed as substrates (Table 2, entries 35−39). The structure of the product was unambiguously confirmed by the single crystal X-ray diffraction study of compound **7ai** (Table 2, entry 35).[16] However, this method is not suitable to pyridine- and quinoline-containing substrates, due to the favored coordination of nitrogen atom to copper preventing the formation of the highly electrophilic vinyl copper complex which was generated in situ between vinyliodonium salts and the copper catalyst (Table 2, entries 41 and 42).

Further investigation with respect to the scope of vinyliodonium salts was conducted (Table 3). As shown in Table 3, these optimized conditions are amenable to a wide range of alkenyliodonium triflates. Both electron-rich and electron-poor styrenes (Table 3, entries 43−45) as well as alkylvinyl groups (Table 3, entries 46−54) are efficiently transferred onto the indole motif with good to excellent yields. Notably, 2,3-disubstituted benzoindoles **7aac**−**aae** can also be synthesized in moderate yields employing (2,2-diphenylvinyl)(*o*-tolyl)-λ^3-iodanyl trifluoromethanesulfonate (**5i**) and (2-methoxyphenyl)(2-phenylprop-1-en-1-yl)-λ^3-iodanyl trifluoromethanesulfonate (**5j**) as electrophiles under standard

DOI: 10.1021/acscatal.9b00470
ACS Catal. 2019, 9, 3906−3912

Table 2. Substrate Scope of Arylhydroxylamines[a,b]

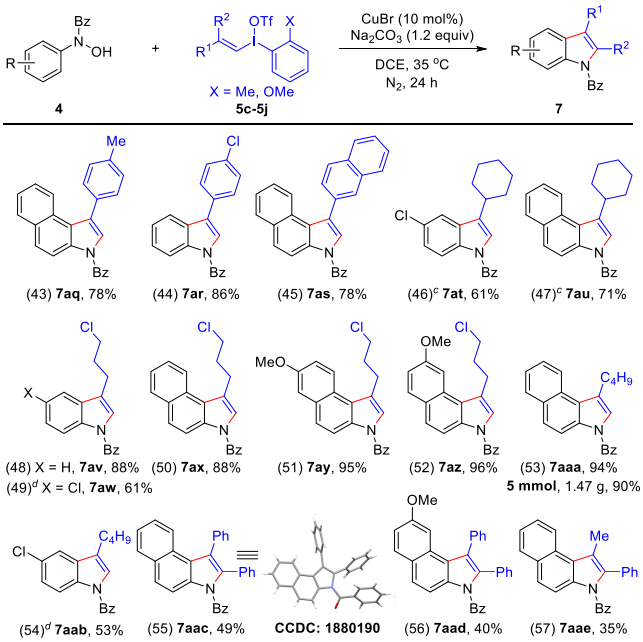


[a]Reaction conditions unless specified otherwise: **4** (0.2 mmol), **5b** (0.4 mmol), CuBr (10 mol %), Na_2CO_3 (0.24 mmol), DCE (1 mL) at 25 °C under N_2 for 24 h. Abbreviations: Cbz = benzoxycarbonyl; Bz = benzoyl. [b]Yields of isolated products. [c]At 50 °C. [d]At 70 °C. [e]At 60 °C. [f]At 35 °C. [g]The regioselectivity was determined by ^1H NMR analysis of the crude reaction mixture; combined yield of the pure regioisomers.

conditions (Table 3, entries 55−57). The structure of the product **7aac** was also confirmed by the single-crystal structure, which was analyzed by X-ray diffraction.[16]

To demonstrate the synthetic utility of this one-pot (benzo)indole process on a multigram scale, we chose naphthylhydroxylamine **4ai** and vinyliodonium salts **5b**,**h** as substrates. We gratefully found that benzoindole **7ai**,**aaa** were

Table 3. Substrate Scope of Vinyliodonium Salts[a,b]

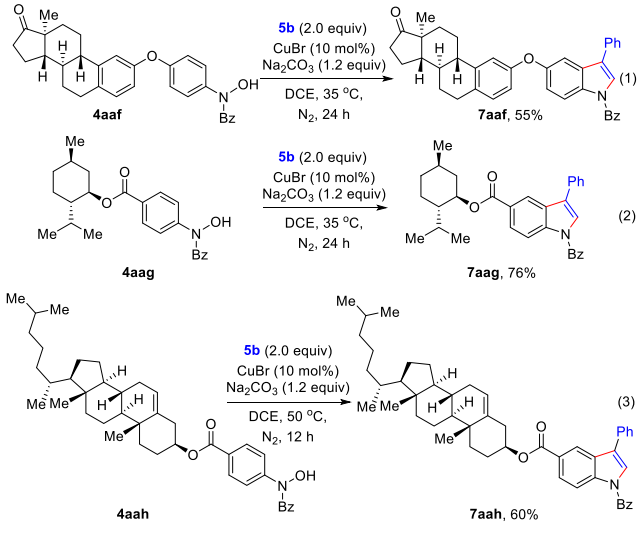


[a]Reaction conditions unless specified otherwise: **4** (0.2 mmol), **5** (0.4 mmol), CuBr (10 mol %), Na_2CO_3 (0.24 mmol), DCE (1 mL) at 35 °C under N_2 for 24 h. [b]Yields of isolated products. [c]At 60 °C. [d]At 50 °C.

afforded in 94% and 90% isolated yields with excellent regioselectivities, respectively (Table 2, entry 35 and Table 3, entry 53). This methodology can also be applied to the late-stage functionalization of pharmaceutically relevant and structurally complex intermediates, such as the estradiol derivative **7aaf** (Scheme 2, eq 1), the terpenoid derivative **7aag** (Scheme 2, eq 2), and the cholesterol derivative **7aah** (Scheme 2, eq 3).

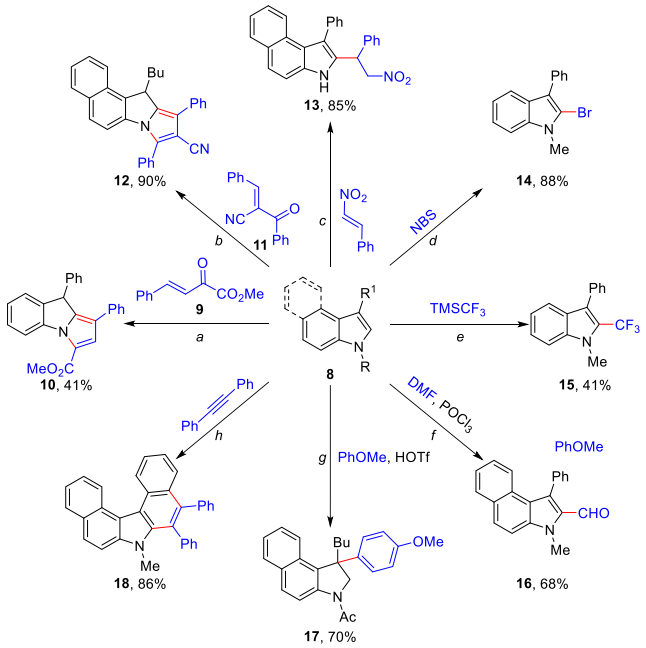
To further expand the synthetic applications of our indole products, we wished to demonstrate that the products of this reaction can be selectively manipulated to more complex functional molecules[17] (Scheme 3). For example, treatment of

Scheme 2. Late-Stage Functionalization of Pharmaceutically Relevant Compounds



DOI: 10.1021/acscatal.9b00470
ACS Catal. 2019, 9, 3906−3912

Scheme 3. Synthetic Applications of the Indole Products[a]

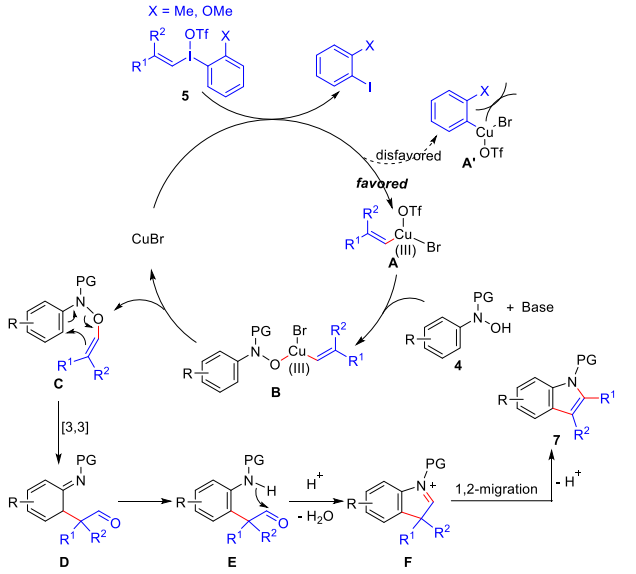


[a]Legend: (*a*) **9**, $Cu(OTf)_2$, 1,4-dioxane, 70 °C, 12 h; (*b*) **11**, $Cu(OTf)_2$, CH_3CN, 35 °C, 36 h; (*c*) nitrostyrene, $Zn(OTf)_2$, toluene, 80 °C, 12 h; (*d*) NBS, trifluorotoluene, 100 °C, 1 h; (*e*) $TMSCF_3$, $PhI(OAc)_2$, BQ, K_3PO_4, CH_3CN, 85 °C, 12 h; (*f*) $POCl_3$, DMF, toluene, reflux, 42 h; (*g*) anisole, TfOH, CH_2Cl_2, 25 °C, 1.5 h; (*h*) 1,2-diphenylethyne, $Pd(OAc)_2$, TBAB, $Cu(OAc)_2$, DMF, 100 °C, 12 h. Abbreviations: NBS = *N*-bromosuccinimide, BQ = benzoquinone, DMF = *N*,*N*-dimethylformamide, TBAB = tetrabutylammonium bromide.

3-phenyl-1*H*-indole (**8a**) or 1-butyl-3*H*-benzo[*e*]indole (**8aaa**) with $Cu(OTf)_2$ and methyl (*E*)-2-oxo-4-phenylbut-3-enoate (**9**) or (*E*)-2-benzoyl-3-phenylacrylonitrile (**11**) led to 9*H*-pyrrolo[1,2-*a*]indoles **10**[17a] and **12**[17b] in moderate to good yields, respectively (Scheme 3, paths *a* and *b*). A $Zn(OTf)_2$-catalyzed Friedel–Crafts C2-alkylation reaction of 3-substituted indole **8ai** with nitrostyrene as alkylating agent generated C2-alkylated product **13** in 85% yield[17c] (Scheme 3, path *c*). The C2 position of our indole products can be also readily converted into other important building blocks via various direct C2-functionalization reactions: for instance, bromination,[17d] trifluoromethylation,[17e] and formylation[17f] reactions (Scheme 3, paths *d*–*f*). A TfOH-promoted umpolung hydroarylation reaction of the indole **8aaa-Ac** with anisole was successfully accomplished to afford **17** in a good yield of 70%[17g] (Scheme 3, path *g*). Additionally, a palladium-catalyzed dehydro-genative annulation of 3-aryl-substituted indole **8ai-Me** with 1,2-diphenylethyne was conducted to produce dibenzo[*c*,*g*]carbazole **18** in good yield[17h] (Scheme 3, path *h*).

On the basis of our findings and the previous studies related to the combination of copper catalysts and iodonium salts which have been established by Gaunt,[14a,c,e,g,18] MacMillan,[14d,f,h] and others,[13g,19] we proposed a reaction pathway involving a vinyl–Cu^{III} species (Scheme 4). We postulated that CuBr will undergo chemoselective oxidative addition into the vinyl–iodine bond to form the highly electrophilic alkenyl–Cu^{III} complex **A** rather than aryl–Cu^{III} complex **A′** because of the *ortho* effect[13n,20] in the presence of vinyliodonium triflate **5**. The complexation/nucleophilic attack of arylhydroxylamine

Scheme 4. Proposed Mechanism of the One-Pot Process for Indole Synthesis



4 to alkenyl–Cu^{III} complex **A** is expected to generate intermediate **B**, which upon reductive elimination will afford the *O*-vinyl-*N*-arylhydroxylamine **C** and reconstitute the active CuBr catalyst to complete the catalytic cycle. *O*-vinyl-*N*-arylhydroxylamine **C** will undergo a facile [3,3]-sigmatropic rearrangement process, which is similar to the Bartoli indole synthesis, followed by 1,3-proton migration/rearomatization to furnish intermediate **E**. The intramolecular condensation between aldehyde and amide will occur to generate iminium intermediate **F**, and the final indole product **7** will be formed by the 1,2-migration/dehydration/rearomatization of intermediate **F**.

In summary, we have developed a highly efficient copper-catalyzed tandem protocol for the synthesis of substituted indoles and benzoindoles using readily available arylhydroxylamines and vinyliodonium salts under mild conditions. This transformation is tolerant to a broad range of functional groups and provides ready access to a wide selection of indole products in high yield and with excellent regioselectivity. In addition, the indole products can be readily converted into more complex functionalized indoles or polycyclic heterocycles. We envision that this method will be instrumental for the late-stage functionalization of bioactive compounds and drug discovery. Further investigation and synthetic applications are undergoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b00470.

Experimental procedures, detailed optimization, compound characterization, and NMR spectra (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for H.G.: hygao@sdu.edu.cn.

DOI: 10.1021/acscatal.9b00470
ACS Catal. 2019, 9, 3906–3912

ORCID

Hongyin Gao: 0000-0003-4049-6832

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of Shandong University, the National Natural Science Foundation of China (21702122), and the Natural Science Foundation of Shandong Province (ZR2017MB002). We thank Prof. Di Sun at Shandong University for the X-ray diffraction and data analysis.

■ REFERENCES

(1) (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. Methods for drug discovery: development of potent, selective, orally effective cholecystokinin antagonists. *J. Med. Chem.* **1988**, *31*, 2235−2246. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. Natural Product-like Combinatorial Libraries Based on Privileged Structures. 1. General Principles and Solid-Phase Synthesis of Benzopyrans. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953. (c) Somei, M.; Yamada, F. Simple indole alkaloids and those with a non-rearranged monoterpenoid unit. *Nat. Prod. Rep.* **2005**, *22*, 73−103. (d) Kawasaki, T.; Higuchi, K. Simple indole alkaloids and those with a nonrearranged monoterpenoid unit. *Nat. Prod. Rep.* **2005**, *22*, 761−793. (e) Ertl, P.; Jelfs, S.; Muehlbacher, J.; Schuffenhauer, A.; Selzer, P. Quest for the Rings. In Silico Exploration of Ring Universe To Identify Novel Bioactive Heteroaromatic Scaffolds. *J. Med. Chem.* **2006**, *49*, 4568−4573. (f) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety. *Chem. Rev.* **2010**, *110*, 4489−4497. (g) Vicente, R. Recent advances in indole syntheses: New routes for a classic target. *Org. Biomol. Chem.* **2011**, *9*, 6469−06480. (h) Lal, S.; Snape, T. J. 2-arylindoles: a privileged molecular scaffold with potent, broad-ranging pharmacological activity. *Curr. Med. Chem.* **2012**, *19*, 4828−4837. (i) Patil, S. A.; Patil, R.; Miller, D. D. Indole molecules as inhibitors of tubulin polymerization: potential new anticancer agents. *Future Med. Chem.* **2012**, *4*, 2085−2115. (j) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. The combinatorial synthesis of bicyclic privileged structures or privileged substructures. *Chem. Rev.* **2003**, *103*, 893−930.

(3) (a) Pindur, U.; Adam, R. Synthetically attractive indolization processes and newer methods for the preparation of selectively substituted indoles. *J. Heterocycl. Chem.* **1988**, *25*, 1−8. (b) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. Radical cyclization of 2-alkenylthioanilides: a novel synthesis of 2,3-disubstituted indoles. *J. Am. Chem. Soc.* **1999**, *121*, 3791−3792. (c) Gribble, G. W. Recent developments in indole ring synthesis-methodology and applications. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075. (d) Gilchrist, T. L. Synthesis of aromatic heterocycles. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491−2515. (e) Cacchi, S.; Fabrizi, G. Synthesis and Functionalization of Indoles Through Palladium-catalyzed Reactions. *Chem. Rev.* **2005**, *105*, 2873−2920. (f) Humphrey, G. R.; Kuethe, J. T. Practical Methodologies for the Synthesis of Indoles. *Chem. Rev.* **2006**, *106*, 2875−2911. (g) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Joergensen, M. Palladium-catalyzed aryl amination-Heck cyclization cascade: a one-flask approach to 3-substituted indoles. *Angew. Chem., Int. Ed.* **2008**, *47*, 888−890. (h) Bandini, M.; Eichholzer, A. Catalytic Functionalization of Indoles in a New Dimension. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608−9644. (i) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. Copper-catalyzed C-C bond formation through C-H functionalization: synthesis of multisubstituted indoles from *N*-aryl enaminones. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078−8081. (j) Barluenga, J.; Jimenez-Aquino, A.; Aznar, F.; Valdes, C. Modular Synthesis of Indoles from Imines and *o*-Dihaloarenes or *o*-Chlorosulfonates by a Pd-Catalyzed Cascade Process. *J. Am. Chem. Soc.* **2009**, *131*, 4031−4041. (k) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. Rhodium(III)-Catalyzed Arene and Alkene C-H Bond Functionalization Leading to Indoles and Pyrroles. *J. Am. Chem. Soc.* **2010**, *132*, 18326−18339. (l) Wang, Y.-Z.; Ye, L.-W.; Zhang, L.-M. Au-catalyzed synthesis of 2-alkylindoles from *N*-arylhydroxylamines and terminal alkynes. *Chem. Commun.* **2011**, *47*, 7815−7817. (m) Wang, Y.; Liu, L.; Zhang, L. Combining Zn ion catalysis with homogeneous gold catalysis: an efficient annulation approach to *N*-protected indoles. *Chem. Sci.* **2013**, *4*, 739−746. (n) Breazzano, S. P.; Poudel, Y. B.; Boger, D. L. A Pd(0)-Mediated Indole (Macro)cyclization Reaction. *J. Am. Chem. Soc.* **2013**, *135*, 1600−1606. (o) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C-H/Het-H Bond Functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281−295.

(4) (a) Fischer, E.; Hess, O. Synthesis of indole-derivatives. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559−568. (b) Robinson, B. The Fischer Indole Synthesis. *Chem. Rev.* **1963**, *63*, 373−401. (c) Robinson, B. Studies on the Fischer indole synthesis. *Chem. Rev.* **1969**, *69*, 227−250. (d) Robinson, B. *The Fischer Indole Synthesis*; Wiley: Chichester and New York, 1982. (e) Downing, R. S.; Kunkeler, P. J. In *Fine Chemicals Through Heterogenous Catalysis*; Sheldon, R. A., Bekkum, H., Eds.; Wiley-VCH: Weinheim and New York, 2001; p 178. (f) Müller, S.; Webber, M. J.; List, B. The Catalytic Asymmetric Fischer Indolization. *J. Am. Chem. Soc.* **2011**, *133*, 18534−18537.

(5) (a) Houlihan, W. J.; Parrino, V. A.; Uike, Y. Lithiation of N-(2-alkylphenyl)alkanamides and related compounds. A modified Madelung indole synthesis. *J. Org. Chem.* **1981**, *46*, 4511−4515. (b) Verboom, W.; Orlemans, E. O. M.; Berga, H. J.; Scheltinga, M. W.; Reinhoudt, D. N. Synthesis of dihydro-1*H*-pyrrolo- and tetrahydropyrido[1,2-*a*]indoles via a modified Madelung reaction. *Tetrahedron* **1986**, *42*, 5053−5064. (c) Orlemans, E. O. M.; Schreuder, A. H.; Conti, P. G. M.; Verboom, W.; Reinhoudt, D. N. Synthesis of 3-substituted indoles via a modified Madelung reaction. *Tetrahedron* **1987**, *43*, 3817−3826. (d) Wacker, D. A.; Kasireddy, P. Efficient solid-phase synthesis of 2,3-substituted indoles. *Tetrahedron Lett.* **2002**, *43*, 5189−5191.

(6) (a) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. Palladium assisted intramolecular amination of olefins. A new synthesis of indoles. *J. Am. Chem. Soc.* **1976**, *98*, 2674−2676. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. Palladium-assisted intramolecular amination of olefins. Synthesis of nitrogen heterocycles. *J. Am. Chem. Soc.* **1978**, *100*, 5800−5807. (c) Bozell, J. J.; Hegedus, L. S. Palladium-assisted functionalization of olefins: a new amination of electron-deficient olefins. *J. Org. Chem.* **1981**, *46*, 2561−2563. (d) Hegedus, L. S.; Winton, P. M.; Varaprath, S. Palladium-assisted *N*-alkylation of indoles: attempted application to polycyclization. *J. Org. Chem.* **1981**, *46*, 2215−2221. (e) Harrington, P. J.; Hegedus, L. S. Palladium-catalyzed reactions in the synthesis of 3- and 4-substituted indoles. Approaches to ergot alkaloids. *J. Org. Chem.* **1984**, *49*, 2657−2662. (f) Hegedus, L. S. Transition Metals in the Synthesis and Functionalization of Indoles [New Synthesis Methods (72)]. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113−1126.

(7) (a) Bartoli, G.; Leardini, R.; Medici, A.; Rosini, G. Reactions of nitroarenes with Grignard reagents. General method of synthesis of alkyl-nitroso-substituted bicyclic aromatic systems. *J. Chem. Soc., Perkin Trans. 1* **1978**, 692−696. (b) Bartoli, G. Conjugate addition of alkyl Grignard reagents to mononitroarenes. *Acc. Chem. Res.* **1984**, *17*, 109−115. (c) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. The reaction of vinyl Grignard reagents with 2-substituted nitroarenes: a new approach to the synthesis of 7-substituted indoles. *Tetrahedron Lett.* **1989**, *30*, 2129−2132. (d) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E. Reactivity of nitro- and nitrosoarenes with vinyl Grignard reagents: synthesis of 2-(trimethylsilyl)indoles. *J.*

DOI: 10.1021/acscatal.9b00470
ACS Catal. 2019, 9, 3906−3912

Chem. Soc., Perkin Trans. 1 **1991**, 2757−2761. (e) Dalpozzo, R.; Bartoli, G. Bartoli indole synthesis. *Curr. Org. Chem.* **2005**, *9*, 163−178. (f) Bartoli, G.; Dalpozzo, R.; Nardi, M. Applications of Bartoli indole synthesis. *Chem. Soc. Rev.* **2014**, *43*, 4728−4750.

(8) (a) Larock, R. C.; Yum, E. K. Synthesis of indoles via palladium-catalyzed heteroannulation of internal alkynes. *J. Am. Chem. Soc.* **1991**, *113*, 6689−6690. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. Synthesis of 2,3-Disubstituted Indoles via Palladium-Catalyzed Annulation of Internal Alkynes. *J. Org. Chem.* **1998**, *63*, 7652−7662. (c) Poli, G.; Giambastiani, G.; Heumann, A. Palladium in Organic Synthesis: Fundamental Transformations and Domino Processes. *Tetrahedron* **2000**, *56*, 5959−5989. (d) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. The aminopalladation/reductive elimination domino reaction in the construction of functionalized indole rings. *Eur. J. Org. Chem.* **2002**, *2002*, 2671−2681. (e) Alonso, F.; Beletskaya, I. P.; Yus, M. Transition-metal-catalyzed addition of heteroatom-hydrogen bonds to alkynes. *Chem. Rev.* **2004**, *104*, 3079−3159.

(9) (a) Wagaw, S.; Yang, B. H.; Buchwald, S. L. A Palladium-Catalyzed Strategy for the Preparation of Indoles: A Novel Entry into the Fischer Indole Synthesis. *J. Am. Chem. Soc.* **1998**, *120*, 6621−6622. (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. A palladium-catalyzed method for the preparation of indoles via the Fischer indole synthesis. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263. (c) Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. An Annulative Approach to Highly Substituted Indoles: Unusual Effect of Phenolic Additives on the Success of the Arylation of Ketone Enolates. *J. Am. Chem. Soc.* **2002**, *124*, 15168−15169.

(10) (a) Harrowven, D. C.; Lai, D.; Lucas, M. C. A short synthesis of hippadine. *Synthesis* **1999**, *1999*, 1300−1302. (b) Dobbs, A. Total Synthesis of Indoles from Tricholoma Species via Bartoli/Heteroaryl Radical Methodologies. *J. Org. Chem.* **2001**, *66*, 638−641. (c) Zhang, Z.; Yang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. A General Method for the Preparation of 4- and 6-Azaindoles. *J. Org. Chem.* **2002**, *67*, 2345−2347. (d) Garg, N. K.; Sarpong, R.; Stoltz, B. M. The First Total Synthesis of Dragmacidin D. *J. Am. Chem. Soc.* **2002**, *124*, 13179−13184. (e) Engler, T. A.; Henry, J. R.; Malhotra, S.; Cunningham, B.; Furness, K.; Brozinick, J.; Burkholder, T. P.; Clay, M. P.; Clayton, J.; Diefenbacher, C.; Hawkins, E.; Iversen, P. W.; Li, Y.; Lindstrom, T. D.; Marquart, A. L.; McLean, J.; Mendel, D.; Misener, E.; Briere, D.; O'Toole, J. C.; Porter, W. J.; Queener, S.; Reel, J. K.; Owens, R. A.; Brier, R. A.; Eessalu, T. E.; Wagner, J. R.; Campbell, R. M.; Vaughn, R. Substituted 3-Imidazo[1,2-*a*]pyridin-3-yl-4-(1,2,3,4-tetrahydro-[1,4]diazepino-[6,7,1-hi]indol-7-yl)pyrrole-2,5-diones as Highly Selective and Potent Inhibitors of Glycogen Synthase Kinase-3. *J. Med. Chem.* **2004**, *47*, 3934−3937. (f) Fonseca, T.; Gigante, B.; Marques, M. M.; Gilchrist, T. L.; De Clercq, E. Synthesis and antiviral evaluation of benzimidazoles, quinoxalines and indoles from dehydroabietic acid. *Bioorg. Med. Chem.* **2004**, *12*, 103−112. (g) Huleatt, P. B.; Choo, S. S.; Chua, S.; Chai, C. L. L. Expedient routes to valuable bromo-5,6-dimethoxyindole building blocks. *Tetrahedron Lett.* **2008**, *49*, 5309−5311. (h) Buszek, K. R.; Brown, N.; Luo, D. Concise Total Synthesis of (±)-cis-Trikentrin A and (±)-Herbindole A via Intermolecular Indole Aryne Cycloaddition. *Org. Lett.* **2009**, *11*, 201−204.

(11) (a) Evans, D. A.; Song, H.-J.; Fandrick, K. R. Enantioselective Nitrone Cycloadditions of *α,β*-Unsaturated 2-Acyl Imidazoles Catalyzed by Bis(oxazolinyl)pyridine-Cerium(IV) Triflate Complexes. *Org. Lett.* **2006**, *8*, 3351−3354. (b) Celebi-Olcum, N.; Lam, Y.-h.; Richmond, E.; Ling, K. B.; Smith, A. D.; Houk, K. N. Pericyclic Cascade with Chirality Transfer: Reaction Pathway and Origin of Enantioselectivity of the Hetero-Claisen Approach to Oxindoles. *Angew. Chem., Int. Ed.* **2011**, *50*, 11478−11482. (c) Richmond, E.; Duguet, N.; Slawin, A. M. Z.; Lebl, T.; Smith, A. D. Asymmetric Pericyclic Cascade Approach to Spirocyclic Oxindoles. *Org. Lett.* **2012**, *14*, 2762−2765. (d) Hojczyk, K. N.; Feng, P.; Zhan, C.; Ngai, M.-Y. Trifluoromethoxylation of Arenes: Synthesis of ortho-Trifluoromethoxylated Aniline Derivatives by OCF_3 Migration. *Angew. Chem., Int. Ed.* **2014**, *53*, 14559−14563.

(12) For selected reviews on Cu-catalyzed or -mediated coupling reactions, see: (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl-aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.* **2002**, *102*, 1359−1469. (b) Evano, G.; Blanchard, N.; Toumi, M. Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis. *Chem. Rev.* **2008**, *108*, 3054−3131. (c) Monnier, F.; Taillefer, M. Catalytic C-C, C-N, and C-O Ullmann-Type Coupling Reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954−6971. (d) Surry, D. S.; Buchwald, S. L. Diamine ligands in copper-catalyzed reactions. *Chem. Sci.* **2010**, *1*, 13−31. (e) Casitas, A.; Ribas, X. The role of organometallic copper(III) complexes in homogeneous catalysis. *Chem. Sci.* **2013**, *4*, 2301−2318. (f) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Copper catalysed Ullmann type chemistry: from mechanistic aspects to modern development. *Chem. Soc. Rev.* **2014**, *43*, 3525−3550. (g) Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. Selected Copper-Based Reactions for C-N, C-O, C-S, and C-C Bond Formation. *Angew. Chem., Int. Ed.* **2017**, *56*, 16136−16179.

(13) (a) Moriarty, R. M.; Epa, W. R.; Awasthi, A. K. Palladium-catalyzed coupling of alkenyl iodonium salts with olefins: a mild and stereoselective Heck-type reaction using hypervalent iodine. *J. Am. Chem. Soc.* **1991**, *113*, 6315−6317. (b) Ochiai, M.; Yamamoto, S.; Suefuji, T.; Chen, D. W. Stereoselective synthesis of (*Z*)-enethiols and their derivatives: vinylic S_N2 reaction of (*E*)-alkenyl(phenyl)-λ^3-iodanes with thioamides. *Org. Lett.* **2001**, *3*, 2753−2756. (c) Thielges, S.; Bisseret, P.; Eustache, J. Copper-mediated cross-coupling of H-phosphonates with vinyliodonium salts: a novel very mild synthesis of 2-arylvinylphosphonates. *Org. Lett.* **2005**, *7*, 681−684. (d) Hara, S.; Guan, T.; Yoshida, M. Stereoselective Generation of (*E*)- and (*Z*)-2-Fluoroalkylidene-Type Carbenoids from (2-Fluoro-1-alkenyl)-iodonium Salts and Their Application for Stereoselective Synthesis of Fluoroalkenes. *Org. Lett.* **2006**, *8*, 2639−2641. (e) Zhdankin, V. V.; Stang, P. J. Chemistry of Polyvalent Iodine. *Chem. Rev.* **2008**, *108*, 5299−5358. (f) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. Iodonium salts in organic synthesis. *ARKIVOC* **2011**, 370−409. (g) Liu, C.; Zhang, W.; Dai, L.-X.; You, S.-L. Copper(I)-catalyzed cascade dearomatization of 2-substituted tryptophols with iodonium salts. *Org. Lett.* **2012**, *14*, 4525−4527. (h) Skucas, E.; MacMillan, D. W. C. Enantioselective *α*-Vinylation of Aldehydes via the Synergistic Combination of Copper and Amine Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 9090−9093. (i) Cahard, E.; Bremeyer, N.; Gaunt, M. J. Copper-Catalyzed Intramolecular Electrophilic Carbo-functionalization of Allylic Amides. *Angew. Chem., Int. Ed.* **2013**, *52*, 9284−9288. (j) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. Copper-Catalyzed Electrophilic Carbofunctionalization of Alkynes to Highly Functionalized Tetrasubstituted Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 5332−5335. (k) Holt, D.; Gaunt, M. J. Copper-catalyzed oxy-alkenylation of homoallylic alcohols to generate functional *syn*-1,3-diol derivatives. *Angew. Chem., Int. Ed.* **2015**, *54*, 7857−7861. (l) Liu, C.; Wang, Q. Arylation, Vinylation, and Alkynylation of Electron-Deficient (Hetero)arenes Using Iodonium Salts. *Org. Lett.* **2016**, *18*, 5118−5121. (m) Yoshimura, A.; Zhdankin, V. V. Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem. Rev.* **2016**, *116*, 3328−3435. (n) Sheng, J.; Wang, Y.; Su, X.; He, R.; Chen, C. Copper-Catalyzed [2+2+2] Modular Synthesis of Multi-substituted Pyridines: Alkenylation of Nitriles with Vinyliodonium Salts. *Angew. Chem., Int. Ed.* **2017**, *56*, 4824−4828. (o) Rajkiewicz, A. A.; Kalek, M. *N*-Heterocyclic Carbene-Catalyzed Olefination of Aldehydes with Vinyliodonium Salts To Generate *α,β*-Unsaturated Ketones. *Org. Lett.* **2018**, *20*, 1906−1909. (p) Liu, C.; Wang, Q. Alkenylation of $C(sp^3)$-H Bonds by Zincation/Copper-Catalyzed Cross-Coupling with Iodonium Salts. *Angew. Chem., Int. Ed.* **2018**, *57*, 4727−4731.

(14) (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. Cu(II)-Catalyzed Direct and Site-Selective Arylation of Indoles Under Mild Conditions. *J. Am. Chem. Soc.* **2008**, *130*, 8172−8174. (b) Merritt, E. A.; Olofsson, B. Diaryliodonium Salts: A Journey from Obscurity to Fame. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052−9070. (c) Phipps, R. J.;

DOI: 10.1021/acscatal.9b00470
ACS Catal. 2019, 9, 3906−3912

Gaunt, M. J. A Meta-Selective Copper-Catalyzed C-H Bond Arylation. *Science* **2009**, *323*, 1593−1597. (d) Allen, A. E.; MacMillan, D. W. C. Enantioselective α-Arylation of Aldehydes via the Productive Merger of Iodonium Salts and Organocatalysis. *J. Am. Chem. Soc.* **2011**, *133*, 4260−4263. (e) Bigot, A.; Williamson, A. E.; Gaunt, M. J. Enantioselective α-Arylation of N-Acyloxazolidinones with Copper(II)-bisoxazoline Catalysts and Diaryliodonium Salts. *J. Am. Chem. Soc.* **2011**, *133*, 13778−13781. (f) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. Enantioselective α-Arylation of Carbonyls via Cu(I)-Bisoxazoline Catalysis. *J. Am. Chem. Soc.* **2011**, *133*, 13782−13785. (g) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. Copper-Catalyzed Alkene Arylation with Diaryliodonium Salts. *J. Am. Chem. Soc.* **2012**, *134*, 10773−10776. (h) Zhu, S.; MacMillan, D. W. C. Enantioselective Copper-Catalyzed Construction of Aryl Pyrroloindolines via an Arylation-Cyclization Cascade. *J. Am. Chem. Soc.* **2012**, *134*, 10815−10818. (i) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. Copper-Catalyzed Diastereoselective Arylation of Tryptophan Derivatives: Total Synthesis of (+)-Naseseazines A and B. *J. Am. Chem. Soc.* **2013**, *135*, 5557−5560. (j) Zhou, B.; Hou, W.; Yang, Y.; Feng, H.; Li, Y. Copper(I)-Catalyzed Aryl or Vinyl Addition to Electron-Deficient Alkenes Cascaded by Cationic Cyclization. *Org. Lett.* **2014**, *16*, 1322−1325. (k) Cahard, E.; Male, H. P. J.; Tissot, M.; Gaunt, M. J. Enantioselective and Regiodivergent Copper-Catalyzed Electrophilic Arylation of Allylic Amides with Diaryliodonium Salts. *J. Am. Chem. Soc.* **2015**, *137*, 7986−7989. (l) Jamison, C. R.; Badillo, J. J.; Lipshultz, J. M.; Comito, R. J.; MacMillan, D. W. C. Catalyst-controlled oligomerization for the collective synthesis of polypyrroloindoline natural products. *Nat. Chem.* **2017**, *9*, 1165−1169. (m) Lukamto, D. H.; Gaunt, M. J. Enantioselective Copper-Catalyzed Arylation-Driven Semipinacol Rearrangement of Tertiary Allylic Alcohols with Diaryliodonium Salts. *J. Am. Chem. Soc.* **2017**, *139*, 9160−9163. (n) Wu, H.; Wang, Q.; Zhu, J. Copper-Catalyzed Enantioselective Domino Arylation/Semipinacol Rearrangement of Allylic Alcohols with Diaryliodonium Salts. *Chem. - Eur. J.* **2017**, *23*, 13037−13041. (o) Wu, H.; Wang, Q.; Zhu, J. Copper-Catalyzed Enantioselective Arylative Desymmetrization of Prochiral Cyclopentenes with Diaryliodonium Salts. *Angew. Chem., Int. Ed.* **2018**, *57*, 2721−2725.

(15) For selected examples of Cu-catalyzed/-mediated *O*-vinylation reactions, see: (a) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. Copper-catalyzed general C-N and C-O bond cross-coupling with arylboronic acid. *Tetrahedron Lett.* **2001**, *42*, 3415−3418. (b) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. Copper-promoted/catalyzed C-N and C-O bond cross-coupling with vinylboronic acid and its utilities. *Tetrahedron Lett.* **2003**, *44*, 4927−4931. (c) Fang, Y.; Li, C. CuI-catalyzed intramolecular *O*-vinylation of carbonyl compounds. *Chem. Commun.* **2005**, 3574−3576. (d) Taillefer, M.; Ouali, A.; Renard, B.; Spindler, J.-F. Mild copper-catalyzed vinylation reactions of azoles and phenols with vinyl bromides. *Chem. - Eur. J.* **2006**, *12*, 5301−5313. (e) Kabir, M. S.; Lorenz, M.; Namjoshi, O. A.; Cook, J. M. First Application of an Efficient and Versatile Ligand for Copper-Catalyzed Cross-Coupling Reactions of Vinyl Halides with *N*-Heterocycles and Phenols. *Org. Lett.* **2010**, *12*, 464−467. (f) Patil, A. S.; Mo, D.-L.; Wang, H.-Y.; Mueller, D. S.; Anderson, L. L. Preparation of α-Oxygenated Ketones by the Dioxygenation of Alkenyl Boronic Acids. *Angew. Chem., Int. Ed.* **2012**, *51*, 7799−7803. (g) Wang, H.-Y.; Anderson, L. L. Interrupted Fischer-Indole Intermediates via Oxyarylation of Alkenyl Boronic Acids. *Org. Lett.* **2013**, *15*, 3362−3365. (h) Kundu, D.; Maity, P.; Ranu, B. C. Copper-Assisted Nickel Catalyzed Ligand-Free C(sp^2)-O Cross-Coupling of Vinyl Halides and Phenols. *Org. Lett.* **2014**, *16*, 1040−1043.

(16) CCDC 1840956 (**7ai**) and CCDC 1880190 (**7aac**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

(17) (a) Sun, Y.; Qiao, Y.; Zhao, H.; Li, B.; Chen, S. Construction of 9H-Pyrrolo[1,2-*a*]indoles by a Copper-Catalyzed Friedel-Crafts Alkylation/Annulation Cascade Reaction. *J. Org. Chem.* **2016**, *81*, 11987−11993. (b) Zhu, Y. S.; Yuan, B. B.; Guo, J. M.; Jin, S. J.; Dong, H. H.; Wang, Q. L.; Bu, Z. W. A Copper-Catalyzed Friedel-Crafts Alkylation/Cyclization Sequence: an Approach to Functionalized Pyrrolo[1,2-*a*]indole Spirooxindoles and 9*H*-Pyrrolo[1,2-*a*]indoles. *J. Org. Chem.* **2017**, *82*, 5669−5677. (c) Weng, J. Q.; Fan, R. J.; Deng, Q. M.; Liu, R. R.; Gao, J. R.; Jia, Y. X. Enantioselective Friedel-Crafts Alkylation Reactions of 3-Substituted Indoles with Electron-Deficient Alkenes. *J. Org. Chem.* **2016**, *81*, 3023−3030. (d) Bedford, R. B.; Fey, N.; Haddow, M. F.; Sankey, R. F. Remarkably reactive dihydroindoloindoles via palladium-catalysed dearomatisation. *Chem. Commun.* **2011**, *47*, 3649−3651. (e) Wu, X.; Chu, L.; Qing, F.-L. PhI(OAc)$_2$-mediated oxidative trifluoromethylation of arenes with CF_3SiMe_3 under metal-free conditions. *Tetrahedron Lett.* **2013**, *54*, 249−251. (f) Pathak, R.; Nhlapo, J. M.; Govender, S.; Michael, J. P.; van Otterlo, W. A. L.; de Koning, C. B. A concise synthesis of novel naphtho[*a*]carbazoles and benzo[*c*]carbazoles. *Tetrahedron* **2006**, *62*, 2820−2830. (g) Nandi, R. K.; Perez-Luna, A.; Gori, D.; Beaud, R.; Guillot, R.; Kouklovsky, C.; Gandon, V.; Vincent, G. Triflic Acid as an Efficient Brønsted Acid Promoter for the Umpolung of *N*-Ac Indoles in Hydroarylation Reactions. *Adv. Synth. Catal.* **2018**, *360*, 161−172. (h) Ghosh, S. K.; Kuo, B.-C.; Chen, H.-Y.; Li, J.-Y.; Liu, S.-D.; Lee, H. M. Double C-H Functionalization to Construct Polycyclic Heteroarenes Catalyzed by an Ionic Salt of a Pd Complex with an N-Heterocyclic Carbene Ligand. *Eur. J. Org. Chem.* **2015**, *2015*, 4131−4142.

(18) (a) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. A Highly Para-Selective Copper(II)-Catalyzed Direct Arylation of Aniline and Phenol Derivatives. *Angew. Chem., Int. Ed.* **2011**, *50*, 458−462. (b) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. Copper(II)-catalyzed meta-selective direct arylation of α-aryl carbonyl compounds. *Angew. Chem., Int. Ed.* **2011**, *50*, 463−466.

(19) (a) King, A. E.; Brunold, T. C.; Stahl, S. S. Mechanistic study of copper-catalyzed aerobic oxidative coupling of arylboronic esters and methanol: insights into an organometallic oxidase reaction. *J. Am. Chem. Soc.* **2009**, *131*, 5044−5045. (b) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. Direct observation of CuI/CuIII redox steps relevant to Ullmann-type coupling reactions. *Chem. Sci.* **2010**, *1*, 326−330. (c) Chen, B.; Hou, X.-L.; Li, Y.-X.; Wu, Y.-D. Mechanistic Understanding of the Unexpected Meta Selectivity in Copper-Catalyzed Anilide C-H Bond Arylation. *J. Am. Chem. Soc.* **2011**, *133*, 7668−7671. (d) Hickman, A. J.; Sanford, M. S. High-valent organometallic copper and palladium in catalysis. *Nature* **2012**, *484*, 177−185. (e) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. A copper-catalyzed arylation of tryptamines for the direct synthesis of aryl pyrroloindolines. *Chem. Sci.* **2012**, *3*, 3170−3174.

(20) (a) Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. Solvolysis of Cyclohexenyliodonium Salt, a New Precursor for the Vinyl Cation: Remarkable Nucleofugality of the Phenyliodonio Group and Evidence for Internal Return from an Intimate Ion−Molecule Pair. *J. Am. Chem. Soc.* **1995**, *117*, 3360−3367. (b) Okuyama, T. Solvolysis of Vinyl Iodonium Salts. New Insights into Vinyl Cation Intermediates. *Acc. Chem. Res.* **2002**, *35*, 12−18.

DOI: 10.1021/acscatal.9b00470
ACS Catal. 2019, 9, 3906−3912