



## **Accepted Article**

**Title:** Pd-Catalyzed Dearomatization of Indole Derivatives via Intermolecular Heck Reactions

Authors: Ping Yang, Ren-Qi Xu, Chao Zheng,\* and Shu-Li You\*

This manuscript has been accepted and appears as an Accepted Article online.

This work may now be cited as: *Chin. J. Chem.* **2020**, *38*, 10.1002/cjoc.201900509.

The final Version of Record (VoR) of it with formal page numbers will soon be published online in Early View: http://dx.doi.org/10.1002/cjoc.201900509.

# WILEY-VCH SIOC CCS

ISSN 1001-604X • CN 31-1547/O6 mc.manuscriptcentral.com/cjoc www.cjc.wiley-vch.de

### Pd-Catalyzed Dearomatization of Indole Derivatives via Intermolecular Heck Reactions

Ping Yang,<sup>+,a</sup> Ren-Qi Xu,<sup>+,a</sup> Chao Zheng,<sup>\*,a</sup> and Shu-Li You<sup>\*,a</sup>

State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China \*These authors contributed equally.

Cite this paper: Chin. J. Chem. 2019, 37, XXX—XXX. DOI: 10.1002/cjoc.201900XXX

Summary of main observation and conclusion Pd-catalyzed intermolecular dearomative Heck reaction of indoles with aryl iodides is described. The chalinges on both reactivity and regioselectivity are addressed by the judicious regulation of the geometric and electronic properties of the substrates. An array of indoline derivatives bearing C2-quaternary center is obtained in good to excellent yields (up to 93%) with exclusive regioselectivity under operaonally simple conditions. The mechanistic proposal is supported by detailed DFT calculations.

#### **Background and Originality Content**

Indolines serve as vital structural cores of numerous natural products and pharmaceutically-relevant molecules. Their efficient and convenient syntheses have attracted considerable attention of the synthetic chemistry community.<sup>1</sup> In this regard, dearomatization of indole derivatives has been widely recognized as a straightforward approach to access diverse indolines.<sup>2,3</sup> Over the ast decades, transition-metal-catalyzed Heck reactions<sup>4,5</sup> have been applied in the dearomatization of indoles.<sup>6</sup> as exemplified by .ne elegant contributions from the groups of Yao and Wu,<sup>7</sup> Jia,<sup>8</sup> Lautens,<sup>9</sup> Jing and Liang,<sup>10</sup> Zhou,<sup>11</sup> and Wu<sup>12</sup> (Scheme 1(a)). Notaly, Kitamura and Fukuyama completed the total synthesis of +)-hinckdentine A with the dearomative Heck reaction as a key step.<sup>13</sup> In all the known examples, an indole-tethered aryl halides irst underwent oxidative addition to a Pd- or Ni-catalyst. Subsequently, the regioselective insertion of the corresponding aryl-Pd r aryl-Ni species into the C2=C3 double bond of the indole ring afforded the C3-Pd or C3-Ni intermediate which subsequently underwent  $\beta$ -hydride elimination or received external nucleophilic attack. However, the intramolecular reaction design was crucial to uarantee both the reactivity and the regioselectivity via the structurally well-organized precursors of the dearomatization step. Although intriguing polycyclic scaffolds could be readily assemled in this way, yet additional synthetic elaborations were generally required. To be noted, the intermolecular C2-arylative dearomatization of indoles have been realized via the cross oupling reactions under oxidative conditions.14

Apparently, formidable challenges would be encountered for the corresponding *intermolecular* dearomative Heck reactions. The key issues to be addressed include (i) how to enhance the reactivity of the indole ring toward the intermolecular Heck reaction, and (ii) how to control the regioselectivity of the insertion across the C2=C3 double bond.<sup>15</sup> We envisioned that tetrahydrocyclopenta[b]indole derivatives might serve as suitable candidates for this purpose (Scheme 1(b)). The desired isomerization of the olefinic bond in the 5,5-bicyclic ring system might somewhat release the ring strain, which could probably compensate to some extent the energetic uphill required for the dearomatization process, and thus facilitate the proposed intermolecular Heck reaction. In addition, an appropriate electron-withdrawing N-protecting group might regulate the distribution of the electron density of the indole ring, and direct the regioselectivity of the Heck reaction. Recently, we successfully executed this design plan and realized the first Pd-catalyzed intermolecular dearomative Heck reaction of indoles with aryl iodides. Herein, we report the results from this study.

Scheme 1 Pd-Catalyzed dearomatization of indole derivatives via Heck reaction.



This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cjoc.201900509

#### **Reaction Development**

We began our investigation by testing the model reactions of N-acyl tetrahydrocyclopenta[b]indole 1a and iodobenzene 2a (1.5 equiv) (Table 1). With Pd(OAc)<sub>2</sub> (10 mol%) as a palladium precursor, AgOAc (1.0 equiv) as an additive and Na<sub>2</sub>HPO<sub>4</sub>•12H<sub>2</sub>O (2.0 equiv) as a base, the effects of different ligands were initially examined in DMF at 80 °C. When monophosphine ligands (Q-Phos, PPh<sub>3</sub>, XPhos) were utilized, the desired product **3aa** (confirmed by X-ray crystallographic analysis) was obtained in moderate NMR y elds (45-48%), while 1a could be recovered with good mass alance (entries 1-3). However, the reaction with rac-BINAP provided **3aa** in a lower NMR yield (35%) (entry 4). Notably, when . e reaction proceeded without phosphine ligand, product 3aa could still be afforded in 49% NMR yield (entry 5), comparable v th that obtained with monophosphine ligands. Subsequently, me effect of additives was tested in the absence of phosphine ligand (entries 6-10). It was revealed that the reaction tolerated various Ag salts (AgSbF<sub>6</sub>, AgBF<sub>4</sub>, AgOTf or AgNTf<sub>2</sub>) as an additive. AgNTf<sub>2</sub> was identified as the optimal one, which afforded **3aa** in 5% NMR yield and 82% isolated yield (entry 9). Interestingly, the desired reaction was prohibited significantly when Ag<sub>2</sub>CO<sub>3</sub> was employed (92% of 1a recovered, entry 10). Screening of solvents solowed a clear connection between the reaction outcomes and the polarity of the solvent. When non-polar solvent like toluene as employed, the reaction was quite sluggish, and only 17% NMR yield of 3aa was observed. Alcoholic solvents including MeOH and tBuOH provided 3aa in moderate NMR yields (51-79%). To our delight, when DMA was applied, the NMR yield of **3aa** was further improved to 91% (entry 11). Surprisingly, the judicious choice of a base was quite critical to this reaction. Among tested, 32HPO4•12H2O was the optimal one. Other commonly used b ses including K<sub>2</sub>CO<sub>3</sub>, Et<sub>3</sub>N, K<sub>3</sub>PO<sub>4</sub>, and *t*BuOK were ineffective (entries 15-18). Finally, the optimal results (3aa, 97% NMR yield, 91% isolated yield) were obtained when the loading of AgNTf2 as increased to 1.2 equiv (entry 19). Of particular note, the desired reaction was hampered without Ag salt (entry 20), and could not proceed without Pd(OAc)<sub>2</sub> (entry 21). rable 1 Optimization of the reaction conditions.<sup>a</sup>



AgOAc

DMF

38

48

4	rac-BINAP	AgOAc	DMF	46	35
5		AgOAc	DMF	42	49
6		AgSbF <sub>6</sub>	DMF	17	79
7		$AgBF_4$	DMF	15	81
8		AgOTf	DMF	11	82
9		AgNTf <sub>2</sub>	DMF	trace	85 (82 <sup>c</sup> )
10		$Ag_2CO_3$	DMF	92	7
11		AgNTf <sub>2</sub>	DMA	trace	91
12		AgNTf <sub>2</sub>	MeOH	11	79
13		AgNTf <sub>2</sub>	<i>t</i> BuOH	47	51
14		$AgNTf_2$	toluene	73	17
15 <sup>d</sup>		AgNTf <sub>2</sub>	DMA	94	trace
16 <sup>e</sup>		AgNTf <sub>2</sub>	DMA	82	17
17 <sup>f</sup>		AgNTf <sub>2</sub>	DMA	92	trace
18 <sup>g</sup>		AgNTf <sub>2</sub>	DMA	53	
19 <sup><i>h</i></sup>		$AgNTf_2$	DMA	trace	97 (91 <sup><i>c</i></sup> )
20 <sup><i>i</i></sup>			DMA	77	18
21 <sup><i>h,j</i></sup>		AgNTf <sub>2</sub>	DMA	quant.	

<sup>*a*</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), ligand (0.02 mmol), Na<sub>2</sub>HPO<sub>4</sub>•**1**2H<sub>2</sub>O (0.4 mmol), Ag salt (0.2 mmol) in solvent (1.0 mL) at 80 °C. <sup>*b*</sup> Yield determined by <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> (0.2 mmol) as an internal standard. <sup>*c*</sup> Isolated yield. <sup>*d*</sup> K<sub>2</sub>CO<sub>3</sub> as the base. <sup>*e*</sup> Et<sub>3</sub>N as the base. <sup>*f*</sup> K<sub>3</sub>PO<sub>4</sub> as the base. <sup>*g*</sup> tBuOK as the base. <sup>*h*</sup> AgNTf<sub>2</sub> (0.24 mmol), 5 h. <sup>*i*</sup> Without Ag salts. <sup>*j*</sup> Without Pd(OAc)<sub>2</sub>.

With the optimal conditions in hand, various indoles were allowed to react with iodobenzene to examine the generality of this reaction (Scheme 2(a)). Firstly, the effects of the protecting group on the nitrogen atom of indoles were investigated. Electron-withdrawing groups like Boc (3ab, 92% yield), CO2Me (3ac, 87% yield), and Bz (3ad, 63% yield) were well tolerated, while electron-donating ones (Me and Bn) were not (not shown). Notably, a large array of electronically and sterically varied substituents including alkyl (Me and tBu), alkoxyl (MeO), halogen (F, Cl and Br), ketone (Ac), and ester (CO<sub>2</sub>Me) were accommodated at the 4- to 7-positions of the indole ring. The corresponding products (3ae-3ap) were generally obtained in moderate to high yields (49-84%). In addition, benzo-fused indole substrates also underwent the dearomatization reactions smoothly, leading to desired products 3aq and 3ar in 88% and 61% yields, respectively. The structure of 3aq was also confirmed by X-ray crystallographic analysis. The reaction of 1a and 2a could proceed with the loading of the Pd-catalyst lowered to 5 mol%, affording **3aa** in a gram scale (1.20 g).

Next, the scope of aryl iodides was considered (Scheme 2(b)). Aryl iodides bearing substituents at the *para-* or *meta-*positions could participate the desired dearomatization reactions (**3ba-3na**, 41-93% yields). Particularly, the reaction efficiency was significantly influenced by the electronic property of *para-*substituted aryl iodides. Electron-rich benzene rings (*p*-OMe, *p-t*Bu, *etc.*) could be installed with excellent yields, while the

XPhos

3

reactions with electron-poor aryl iodides (*p*-NO<sub>2</sub>, *p*-CF<sub>3</sub>, *etc.*) were rather sluggish. This phenomenon provided useful clues for further mechanistic studies (*vide infra*). Probably due to the unfavorable steric congestion in the key transition state, *ortho*-substituted aryl iodides were relatively less reactive, leading to the corresponding products **3oa** (*o*-Me) and **3pa** (*o*-OMe) in moderate yields (51-53%). In addition, 2-iodothiophene was also a viable reaction partner. Desired product **3qa** could be delivered in 61% yield. Indeed, the 5,5-bicyclic ring system was crucial for the reactivity, In addition, 2-iodothiophene was also a viable reaction artner. Desired product **3qa** could be delivered in 61% yield. Indeed, the 5,5-bicyclic ring system was crucial for the reactivity,

In addition, several synthetic transformations were performed for dearomatized products **3** (Scheme 3). The newly formed double bond of **3aa** could be hydrogenated to obtain **4** in 94% ield with high diastereoselectivity (>20:1 dr). The relative configuration of **4** was determined by X-ray crystallographic nalysis. Besides, the N-Boc group of **3ab** could be removed smoothly by the treatment of TMSOTf, leading to **5** in 86% yield. <sup>1</sup> Moreover, **3am** could undergo Suzuki coupling reaction with PhB(OH)<sub>2</sub> to afford **6** in 96% yield.



Scheme 3 Product transformations.



#### Mechanistic studies

In order to shed light on the reaction mechanism, detailed FT calculations were performed. Initially, the thermodynamic aspect of the reaction was evaluated (Scheme 4(a)). As expected, t<sup>1</sup> e isomerization of the double bond of cyclic or acyclic \_,3-disubstituted indoles is generally endergonic. The energetic uphill of dihydrocyclobuta[b]indole, tetrahydrocarbazole (n = 4 nd 6), and 2,3-dimethylindole (acyclic) is about 9.4-9.6 kcal/mol. However, this value of tetrahydrocyclopenta[b]indole (n = 5) drops to 7.9 kcal/mol. We believe that this outlier implies the energy compensation gained from the strain release of the 5,5-bicyclic system during the dearomatization process.

Based on the literature reports, a plausible catalytic cycle was proposed (Scheme 4(b)). In the presence of AgNTf<sub>2</sub>, the oxidative addition of aryl iodide 2 to the Pd(0) catalyst delivers the aryl-Pd(II) species I. Subsequently, the coordination and insertion of I across the C2=C3 double bond of 1 provide intermediate II. Finally, base-assisted  $\beta$ -hydride elimination affords desired product **3**. Our calculations confirmed that the regioselectivity of the reaction was determined in the insertion step (vide infra). The optimized structures of the most stable insertion transition states leading to 3aa (TS-A-5-III) and the unobserved regioisomer (TS-A-5-II) are shown in Figure 1. The relative Gibbs free energy of the latter one is higher than that of the former one by 3.1 kcal/mol, which is in good agreement with the experimental results. Although the geometric features around the bond-forming/breaking area in the two structures (highlighted in green) are rather similar [B(Pd···C3) = 2.08 Å, B(C<sub>ipso</sub>…C2) = 2.16 Å, and B(Pd…C<sub>ipso</sub>) = 2.06 Å in TS-A-5-III; B(Pd···C2) = 2.10 Å, B(Cipso···C3) = 2.17 Å, and B(Pd···Cipso) = 2.05 Å in TS-A-5-II], natural population analysis (NPA) revealed that the preference of TS-A-5-III might stem from the electronic match of the bond-forming atom pairs [between Pd (0.308) and C3 (-0.072), and between Cipso (-0.120) and C2 (0.298)]. On the other hand, in TS-A-5-II the connection between two positively-charged atoms [Pd (0.308) and C2 (0.156)] makes the reversed insertion pathway energetically unfavorable.

Activation strain model (ASM) analysis<sup>16</sup> was performed on the systems derived from **1a** with phenyl iodide (**2a**), p-OMeC<sub>6</sub>H<sub>4</sub>I (**2d**), and p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>I (**2k**), respectively (Figure 2). As the electron density of the aryl group is getting lower (from p-OMe to p-NO<sub>2</sub>), the insertion transition state appeared at a later stage with a higher activation energy [ $\Delta E(act)$ ] (Figure 2(a)), which well reproduced the experimental results with **2a**, **2d**, and **2k** (Scheme 2(b)). Notably, a good superposition of the curves of the total

<sup>b</sup> Department, Institution, Address 2 E-mail: <sup>c</sup> Department, Institution, Address 3 E-mail:

© 2018 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

![](_page_4_Picture_13.jpeg)

This article is protected by copyright. All rights reserved.

<sup>&</sup>lt;sup>a</sup> Department, Institution, Address 1 E-mail:

distortion energy [ $\Delta E$ (dist)] was disclosed (Figure 2(b)). It suggested that when the aryl-Pd(II) species and 1a approached to each other, their respective geometric distortions were rather similar in the three systems. However, the interaction energy between the bended substrates  $[\Delta E(int)]$  varied significantly (Figure 2(c)). In addition, at any given point along the reaction coordinate, the interaction between indole and electron-rich aryl-Pd(II) species (R = OMe) was stronger compared with the parent system (R = H), and that between indole and electron-deficient aryl-Pd(II) species (R = NO<sub>2</sub>) was even weaker. Moreover, the alculated NPA charges (Figure 2(d)) corroborated that the avorable electronic match between the bond-forming atom pairs was reinforced for the case of electron-rich aryl-Pd(II) species between C<sub>ipso</sub> (-0.157) and C2 (0.316), R = OMe] but attenuated for the case of electron-deficient aryl-Pd(II) species [between Cipso 0.083) and C2 (0.279),  $R = NO_2$ ]. In this regard, the influence of the electronic property of substrates to the regioselectivity and the reactivity could be well understood.

**Scheme 4** (a) Thermodynamics of the dearomatization process and (b) The roposed catalytic cycle.

![](_page_5_Figure_3.jpeg)

**Figure 1** Optimized structures and relative Gibbs free energies ( $\Delta G$ ) of **TS-A-5-III** and **TS-A-5-II** in kcal/mol (relative to the direct precursor **.VT-A-5**, see Table 2 for details). Calculated at M06/SDD/6-31+G\*\* level of theory. Values in bold are bond distances in angstrom. Values in italic are NPA charges of the corresponding atoms.

![](_page_5_Figure_6.jpeg)

**Figure 2** (a) to (c) Diagrams of activation energy  $\Delta E(\text{act})$ , total distortion energy  $\Delta E(\text{dist})$ , and interaction energy  $\Delta E(\text{int})$  in kcal/mol relative to the bond length of forming C2–C<sub>ipso</sub> bond for the system derived from **1a** with **2a** (R = H), **2d** (R = *p*-OMe), and **2k** (R = *p*-NO<sub>2</sub>), respectively. Calculated based on the IRC plots of the insertion transition states obtained at M06/SDD/6-31G\*\* level of theory. (d) NPA charges on certain atoms in the corresponding insertion transition states. Calculated at M06/SDD/6-31+G\*\* level of theory.

Table 2 Energy profiles for indole substrates with varied ring sizes.<sup>a</sup>

![](_page_5_Figure_9.jpeg)

n	INT-A-n	TS-A-n	INT-B-n	TS-B-n	INT-C-n
4	0.0	3.1	-26.4	4.9	1.3
5	0.0	6.1	-15.2	2.6	-0.4
6	0.0	8.7	-12.6	0.6	-0.4
acyclic	0.0	8.2	-13.6	-2.5	-3.2

 $^{\it a}$  Relative Gibbs free energies (ΔG) in kcal/mol are listed. Calculated at M06/SDD/6-31+G\*\* level of theory.

Finally, the influence of ring size of indole substrates to the reaction outcomes was investigated (Table 2). The energy profiles of the key transition states and intermediates for both insertion and  $\beta$ -hydride elimination steps for N-Ac

www.cjc.wiley-vch.de

#### Report

tetrahydrocyclopenta[b]indole. dihydrocyclobuta[b]indole, tetrahydrocarbazole (n = 4-6), and 2,3-dimethylindole (acyclic) were calculated. In all cases, the insertion of aryl-Pd(II) species across the C2=C3 double bond of the indole substrate is an irreversible step. Notably, the energy barriers of this step for N-Ac tetrahydrocarbazole (TS-A-6, 8.7 kcal/mol) and 2,3-dimethylindole (TS-A-acyclic, 8.2 kcal/mol), respectively, are very similar. When the fused ring of the indole substrates became smaller, the corresponding barrier height decreased (TS-A-5, 6.1 kcal/mol and TS-A-4, 3.1 kcal/mol). Accordingly, the stability of the following ir termediates increased monotonously (INT-B-6, -12.6 kcal/mol; .NT-B-5, -15.2 kcal/mol and INT-B-4, -26.4 kcal/mol). These trends confirmed our initial conjecture about the strain release of the small-ring-fused indole substrates which was probably caused by the favorable shift of the hybridization scenarios of C2 and C3 for sp<sup>2</sup> to sp<sup>3</sup> during the insertion step. However, the extremely stable INT-B-4 hampered the subsequent  $\beta$ -hydride elimination tep (TS-B-4, 31.3 kcal/mol relative to INT-B-4). Whereas this step was feasible in all other cases (TS-B-n, 11.1-17.8 kcal/mol relative **INT-B-n**, n = 5, 6, and acyclic). Based on all these results, the uniqueness of tetrahydrocyclopenta[b]indole derivatives in the intermolecular dearomative Heck reactions became reasonable. The 5,5-bicyclic ring system was not only capable of releasing the ring-strain sufficiently for the dearomative intermolecular (not available for tetrahydrocarbazole ir sertion and 2,3-dimethylindole systems), but also suitable for promoting the following  $\beta$ -hydride elimination to furnish the final products (not available for dihydrocyclobuta[b]indole system).17

#### Conclusions

In summary, we have developed the first Pd-catalyzed i termolecular dearomatization of indoles via Heck reaction. A series of indolines bearing a quaternary center could be accessed efficiently under mild conditions in good to excellent yields (up to 3%) with exclusive regioselectivity. Detailed DFT calculations revealed that the successful execution of this unprecedented r action design relied on the judicious regulation of the geometric and electronic properties of the substrates. The unique 5.5-bicyclic ring system in tetrahydrocyclopenta[b]indole derivatives well balanced the feasibility of both insertion and ride elimination steps. On the other hand, the electronic match of the bond-forming atom pairs in the insertion step g ided the regioselectivity of the intermolecular Heck reaction. urther exploration on advancing the dearomatization of diverse aromatic systems via Heck reactions is currently underway in this la boratory.

#### Experimental

General procedure for intermolecular dearomative Heck reaction. A flame-dried Schlenk tube was cooled to room temperare under argon. To this tube were added indole derivative (0.2 mmol), Pd(OAc)<sub>2</sub> (4.5 mg, 0.02 mmol), Na<sub>2</sub>HPO<sub>4</sub>•12H<sub>2</sub>O (143.3 mg, 0.4 mmol), AgNTf<sub>2</sub> (93.1 mg, 0.24 mmol), DMA (1.0 mL) and aryl ic dide (0.3 mmol). The reaction mixture was stirred at 80 °C. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with ethyl acetate (3 mL). The mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE/EtOAc = 10/1) to afford the desired product.

The full experimental details can be found in the Supporting Information.

**Computational methods.** All the DFT calculations in this work were performed with Gaussian16.<sup>18</sup> The density functional theory (DFT) method was employed using the M06 functional.<sup>19</sup> The SDD basis set with the associated effective core potential was used for Pd, and the 6-31+G\*\* basis sets for all other atoms unless otherwise specified. Optimizations were conducted without any constraint using implicit solvation model (SMD)<sup>20</sup> in DMA ( $\epsilon =$  37.781). Frequency analyses were carried out to confirm each structure being a minimum (no imaginary frequency) or a transition state (only one imaginary frequency). The Gibbs free energies in DMA ( $\Delta G$ ) were discussed throughout this paper unless otherwise specified. The 3D images of the calculated structures were prepared using CYLview.<sup>21</sup>

The full computational details can be found in the Supporting Information.

#### **Supporting Information**

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

#### Acknowledgement

We thank MOST (2016YFA0202900), NSFC (21772219, 21821002, 91856201), Science and Technology Commission of Shanghai Municipality (18QA1404900), Chinese Academy of Sciences (XDB20000000, QYZDY-SSW-SLH012) and Youth Innovation Promotion Association (2017302) of CAS for generous financial support.

#### References

- (a) Bandini, M.; Eichholzer, A. Catalytic Functionalization of Indoles in a New Dimension. *Angew. Chem., Int. Ed.* 2009, *48*, 9608-9644. (b) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-b]indole. *Chem. - Eur. J.* 2011, *17*, 1388-1408. (c) Shiri, M. Indoles in multicomponent processes (MCPs). *Chem. Rev.* 2012, *112*, 3508-3549. (d) Stempel, E.; Gaich, T. Cyclohepta[b]indoles: A Privileged Structure Motif in Natural Products and Drug Design. *Acc. Chem. Res.* 2016, *49*, 2390-2402. (e) Song, J.; Chen, D.-F.; Gong, L.-Z. Recent progress in organocatalytic asymmetric total syntheses of complex indole alkaloids. *Natl. Sci. Rev.* 2017, *4*, 381-396.
- [2] For recent reviews of dearomative reaction: (a) Pape, A. R.; Kaiappan, K. P.; Kündig, E. P. Transition-Metal-Mediated Dearomatization Reactions. *Chem. Rev.* 2000, *100*, 2917-2940. (b) Quideau, S.; Pouységu, L.; Deffieux, D. Oxidative Dearomatization of Phenols: Why, How and What For? *Synlett* 2008, 467-495. (c) Pouységu, L.; Deffieux, D.; Quideau, S. Hypervalent iodine-mediated phenol dearomatization in natural product synthesis. *Tetrahedron* 2010, *66*, 2235-2261. (d) Pouységu, L.; Sylla, T.; Garnier, T.; Rojas, L. B.; Charris, J.; Deffieux, D.;

© 2019 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Chin. J. Chem. 2019, 37, XXX-XXX

Running title

Quideau, S. Hypervalent iodine-mediated oxygenative phenol dearomatization reactions. Tetrahedron 2010, 66, 5908-5917. (e) Roche, S. P.; Porco, J. A. Jr. Dearomatization Strategies in the Synthesis of Complex Natural Products. Angew. Chem., Int. Ed. 2011, 50, 4068-4093. (f) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. Asymmetric Hydrogenation of Heteroarenes and Arenes. Chem. Rev. 2012, 112, 2557-2590. (g) Zhuo, C.-X.; Zhang, W.; You, S.-L. Catalytic Asymmetric Dearomatization Reactions. Angew. Chem., Int. Ed. 2012, 51, 12662-12686. (h) Zhuo, C.-X.; Zheng, C.; You, S.-L. Transition-Metal-Catalyzed Asymmetric Allylic Dearomatization Reactions. Acc. Chem. Res. 2014, 47, 2558-2573. (i) Ding, Q.; Zhou, X.; Fan, R. Recent advances in dearomatization of heteroaromatic compounds. Org. Biomol. Chem. 2014, 12, 4807-4815. (j) Roche, S. P.; Youte Tendoung, J.-J.; Tréguier, B. Advances in dearomatization strategies of indoles. Tetrahedron 2015, 71, 3549-3591. (k) Wu, W.-T.; Zhang, L.; You, S.-L. Catalytic asymmetric dearomatization (CADA) reactions of phenol and aniline derivatives. Chem. Soc. Rev. 2016, 45, 1570-1580. (I) Zheng, C.; You, S.-L. Catalytic Asymmetric Dearomatization (CADA) by Transition-Metal-Catalysis: A Method for Transformations of Aromatic Compounds. Chem 2016, 1, 830-857. (m) James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Synthesis of Spirocyclic Indolenines. Chem. Eur. J. 2016, 22, 2856-2881. (n) Sun, W.; Li, G.; Hong, L.; Wang, R. Asymmetric dearomatization of phenols. Org. Biomol. Chem. 2016, 14, 2164-2176. (o) Chen, J.-B.; Jia, Y.-X. Recent progress in transition-metal-catalyzed enantioselective indole functionalizations. Org. Biomol. Chem. 2017, 15, 3550-3567. (p) Wu, W.-T.; Zhang, L.; You, S.-L. Recent Progress on Gold-catalyzed Dearomatization Reactions. Acta Chim. Sinica 2017, 75, 419-438. (q) Bariwal, J.: Voskressensky, L. G.: Van der Evcken, E. V. Recent advances in spirocyclization of indole derivatives. Chem. Soc. Rev. 2018, 47, 3831-3848. (r) Wertjes, W. C.; Southgate, E. H.; Sarlah, D. Recent advances in chemical dearomatization of nonactivated arenes. Chem. Soc. Rev. 2018, 47, 7996-8017. (s) An, J.; Bandini, M. Gold-catalyzed Dearomatization Reactions. Chimia 2018, 72, 610-613. (t) Cheng, Y.-Z.; Zhang, X.; You, S.-L. Visible-light-mediated photocatalysis as a new tool for catalytic asymmetric dearomatization (CADA) reactions. Sci. Bull. 2018, 63, 809-811. (u) Huang, G.; Yin, B. Recent Developments in Transition Metal-Catalyzed Dearomative Cyclizations of Indoles as Dipolarophiles for the Construction of Indolines. Adv. Synth. Catal. 2019, 361, 405-425. For a book: (v) You, S.-L. Asymmetric Dearomatization Reactions. Wiley-VCH, Weinheim, 2016.

[3] For selected examples: (a) Xu, H.; Li, Y.-P.; Cai, Y.; Wang, G.-P.; Zhu, S.-F.; Zhou, Q.-L. Highly Enantioselective Copper- and Iron-Catalyzed Intramolecular Cyclopropanation of Indoles. J. Am. Chem. Soc. 2017, 139, 7697-7700. (b) Niemeyer, Z. L.; Pindi, S.; Khrakovsky, D. A.; Kuzniewski, C. N.; Hong, C. M.; Joyce, L. A.; Sigman, M. S.; Toste, F. D. Parameterization of Acyclic Diaminocarbene Ligands Applied to a Gold(I)-Catalyzed Enantioselective Tandem Rearrangement/Cyclization. J. Am. Chem. Soc. 2017, 139, 12943-12946. (c) Tu, H.-F.; Zhang, X.; Zheng, C.; Zhu, M.; You, S.-L. Enantioselective dearomative prenylation of indole derivatives. Nature Catal. 2018, 1, 601-608. (d) Panda, S.; Ready, J. M. Tandem Allylation/1,2-Boronate Rearrangement for the Asymmetric Synthesis of Indolines with Adjacent Quaternary Stereocenters. J. Am. Chem. Soc. 2018, 140, 13242-13252. (e) Cheng, Q.; Zhang, F.; Cai, Y.; Guo, Y.-L.; You, S.-L. Stereodivergent Synthesis of Tetrahydrofuroindoles via Pd-Catalyzed

Asymmetric Dearomative Formal [3+2] Cycloaddition Reactions. Angew. Chem., Int. Ed. 2018, 57, 2134-2138. (f) Bai, L.; Liu, J.; Hu, W.; Li, K.; Wang, Y.; Luan, X. Palladium/Norbornene-Catalyzed C-H Alkylation/Alkyne Insertion/Indole Dearomatization Domino Reaction: Assembly of Spiroindolenine-Containing Pentacyclic Frameworks. Angew. Chem., Int. Ed. 2018, 57, 5151-5155. (g) Chen, L.; Shen, J.-J.; Gao, Q.; Xu, S. Synthesis of cyclic chiral  $\alpha$ -amino boronates by copper-catalyzed asymmetric dearomative borylation of indoles. Chem. Sci. 2018, 9, 5855-5859. (h) Xu, G.; Chen, L.; Sun, J. Rhodium-Catalyzed Asymmetric Dearomative [4 + 3]-Cycloaddition of Vinylindoles with Vinyldiazoacetates: Access to Cyclohepta[b]indoles. Org. Lett. 2018, 20, 3408-3412. (i) Liang, X.-W.; Cai, Y.; You, S.-L. Asymmetric Fluorinative Dearomatization of Tryptophol Derivatives by Chiral Anion Phase-Transfer Catalysis. Chin. J. Chem. 2018, 36, 925-928. (j) Ho, H. E.; Stephens, T. C.; Payne, T. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Merging π-Acid and Pd Catalysis: Dearomatizing Spirocyclization/Cross-Coupling Cascade Reactions of Alkyne-Tethered Aromatics. ACS Catal. 2019, 9, 504-510. (k) Zhu, M.; Zheng, C.; Zhang, X.; You, S.-L. Synthesis of Cyclobutane-Fused Angular Tetracyclic Spiroindolines via Visible-Light-Promoted Intramolecular Dearomatization of Indole Derivatives. J. Am. Chem. Soc. 2019, 141, 2636-2644. (I) Wu, J.; Dou, Y.; Guillot, R.; Kouklovsky, C.; Vincent, G. Electrochemical Dearomative 2,3-Difunctionalization of Indoles. J. Am. Chem. Soc. 2019, 141, 2832-2837. (m) Huang, L.; Cai, Y.; Zhang, H.-J.; Zheng, C.; You, S.-L. Highly Diastereo- and Enantioselective Synthesis of Quinuclidine Derivatives by an Iridium-Catalyzed Intramolecular Allylic Dearomatization Reaction. CCS Chem. 2019, 1, 106-116. (n) Bai, Z.; Tong, H.; H. Wang, H.; Chen, G.; He, G. Synthesis of 2.3-Fused Indoline Aminals via 4+2 Cycloaddition of NH-free Benzazetidines with Indoles. Chin. J. Chem. 2019, 37, 119-125.

- [4] For selected reviews: (a) Heck, R. F. Palladium-catalyzed reactions of organic halides with olefins. Acc. Chem. Res. 1979, 12, 146-151. (b) Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. Chem. Rev. 2000, 100, 3009-3066. (c) Dounay, A. B.; Overman, L. E. The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. Chem. Rev. 2003, 103, 2945-2964. (d) Tietze, L. F.; Ila, H.; Bell, H. P. Enantioselective Palladium-Catalyzed Transformations. Chem. Rev. 2004, 104, 3453-3516. (e) Mc Cartney, D.; Guiry, P. J. The asymmetric Heck and related reactions. Chem. Soc. Rev. 2011, 40, 5122-5150. (f) Li, H.; Ding, C.; Xu, B.; Hou, X. Recent Developments in Palladium-Catalyzed Asymmetric Intermolecular Heck Reaction. Acta Chim. Sinica 2014, 72, 765-770. (g) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. Pd Metal Catalysts for Cross-Couplings and Related Reactions in the 21st Century: A Critical Review. Chem. Rev. 2018, 118, 2249-2295. (h) Kurandina, D.; Chuentragool, P.; Gevorgyan, V. Transition-Metal-Catalyzed Alkyl Heck-Type Reactions. Synthesis 2019, 51, 985-1005.
- [5] For selected recent examples: (a) Shrestha, B.; Basnet, P.; Dhungana, R. K.; KC, S.; Thapa, S.; Sears, J. M.; Giri, R. Ni-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Olefins by Intercepting Heck Intermediates as Imine-Stabilized Transient Metallacycles. J. Am. Chem. Soc. 2017, 139, 10653-10656. (b) Orlandi, M.; Hilton, M. J.; Yamamoto, E.; Toste, F. D.; Sigman, M. S. Mechanistic Investigations of the Pd(0)-Catalyzed Enantioselective 1,1-Diarylation of Benzyl Acrylates. J. Am. Chem. Soc. 2017, 139, 12688-12695. (c) Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Fu, Y. Irradiation-Induced Heck Reaction of Unacti-

© 2019 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

www.cjc.wiley-vch.de

This article is protected by copyright. All rights reserved.

vated Alkyl Halides at Room Temperature. J. Am. Chem. Soc. 2017, 139, 18307-18312. (d) Bao, X.; Wang, Q.; Zhu, J. Palladium-Catalyzed Enantioselective Narasaka-Heck Reaction/Direct C-H Alkylation of Arenes: Iminoarylation of Alkenes. Angew. Chem., Int. Ed. 2017, 56, 9577-9581. (e) Ortega-Jiménez, F.; Penieres-Carrillo, J. G.; López-Cortés, J. G.; Ortega-Alfaro, M. C.; Lagunas-Rivera, S. Arylhydrazones Derivatives Containing a Benzothiazole Moiety, Efficient Ligands in the Palladium-Catalyzed Mizoroki-Heck and Suzuki-Miyaura Cross-coupling Reactions under IR Irradiation. Chin. J. Chem. 2017, 35, 1881-1888. (f) Patel, H. H.; Prater, M. B.; Squire, S. O.; Sigman, M. S. Formation of Chiral Allylic Ethers via an Enantioselective Palladium-Catalyzed Alkenylation of Acyclic Enol Ethers. J. Am. Chem. Soc. 2018, 140, 5895-5898. (g) Yuan, Q.; Sigman, M. S. Palladium-Catalyzed Enantioselective Relay Heck Arylation of Enelactams: Accessing α,β-Unsaturated δ-Lactams. J. Am. Chem. Soc. 2018, 140, 6527-6530. (h) Carmona, J. A.; Hornillos, V.; Ramírez-López, P.; Ros, A.; Iglesias-Sigüenza, J.; Gómez-Bengoa, E.; Fernández, R.; Lassaletta, J. M. Dynamic Kinetic Asymmetric Heck Reaction for the Simultaneous Generation of Central and Axial Chirality. J. Am. Chem. Soc. 2018, 140, 11067-11075. (i) McAlpine, N. J.; Wang, L.; Carrow, B. P. A Diverted Aerobic Heck Reaction Enables Selective 1,3-Diene and 1,3,5-Triene Synthesis through C-C Bond Scission. J. Am. Chem. Soc. 2018, 140, 13634-13639. (j) Tang, C.; Zhang, R.; Zhu, B.; Fu, J.; Deng, Y.; Tian, L.; Guan, W.; Bi, X. Directed Copper-Catalyzed Intermolecular Heck-Type Reaction of Unactivated Olefins and Alkyl Halides. J. Am. Chem. Soc. 2018, 140, 16929-16935. (k) Kwiatkowski, M. R.; Alexanian, E. J. Nickel-Catalyzed Mizoroki-Heck-Type Reactions of Unactivated Alkyl Bromides. Angew. Chem., Int. Ed. 2018, 57, 16857-16860. (I) Reddi. Y.: Tsai. C.-C.: Avila. C. M.: Toste. F. D.: Sunoi. R. B. Harnessing Noncovalent Interactions in Dual-Catalytic Enantioselective Heck-Matsuda Arylation. J. Am. Chem. Soc. 2019, 141, 998-1009. (m) Ma, X.; Hazelden, I. R.; Langer, T.; Munday, R. H.; Bower, J. F. Enantioselective Aza-Heck Cyclizations of N-(Tosyloxy)carbamates: Synthesis of Pyrrolidines and Piperidines. J. Am. Chem. Soc. 2019, 141, 3356-3360. (n) Yuan, Z.; Feng, Z.; Zeng, Y.; Zhao, X.; Lin, A.; Yao, H. Palladium-Catalyzed Asymmetric Intramolecular Reductive Heck Desymmetrization of Cyclopentenes: Access to Chiral Bicyclo[3.2.1]octanes. Angew. Chem., Int. Ed. 2019, 58, 2884-2888. (o) Race, N. J.; Yuan, Q.; Sigman, M. S. Enantioselective C2-Alkylation of Indoles through a Redox-Relay Heck Reaction of Indole Triflates. Chem. - Eur. J. 2019, 25, 512-515. (p) Wang, Y.; Y.; Wang, C. Rhenium-Catalyzed Decarboxylative Yang, Tri-/Difluoromethylation of Styrenes with Fluorinated Carboxylic Acid-Derived Hypervalent Iodine Reagents. Chin. J. Chem. 2019, 37, 1229-1233.

- Zeidan, N.; Lautens, M. Migratory Insertion Strategies for Dearomatization. Synthesis 2019, 51, 4137-4146.
- [7] Zhao, L.; Li, Z.; Chang, L.; Xu, J.; Yao, H.; Wu, X. Efficient Construction of Fused Indolines with a 2-Quaternary Center via an Intramolecular Heck Reaction with a Low Catalyst Loading. *Org. Lett.* **2012**, *14*, 2066-2069.
- B] (a) Shen, C.; Liu, R.-R.; Fan, R.-J.; Li, Y.-L.; Xu, T.-F.; Gao, J.-R.; Jia, Y.-X. Enantioselective Arylative Dearomatization of Indoles via Pd-Catalyzed Intramolecular Reductive Heck Reactions. *J. Am. Chem. Soc.* 2015, 137, 4936-4939. (b) Liu, R.-R.; Xu, T.-F.; Wang, Y.-G.; Xiang, B.; Gao, J.-R.; Jia, Y.-X. Palladium-catalyzed dearomative arylalkynyla-

tion of indoles. Chem. Commun. 2016, 52, 13664-13667. (c) Liu, R.-R.; Wang, Y.-G.; Li, Y.-L.; Huang, B.-B.; Liang, R.-X.; Jia, Y.-X. Enantioselective Dearomative Difunctionalization of Indoles by Palladium-Catalyzed Heck/Sonogashira Sequence. Angew. Chem., Int. Ed. 2017, 56, 7475-7478. (d) Liu, R.-R.; Xu, Y.; Liang, R.-X.; Xiang, B.; Xie, H.-J.; Gao, J.-R.; Jia, Y.-X. Spirooxindole synthesis via palladium-catalyzed dearomative reductive-Heck reaction. Org. Biomol. Chem. 2017, 15, 2711-2715. (e) Wang, Y.; Liu, R.; Gao, J.; Jia, Y. Palladium-Catalyzed Dearomative Decarboxylative Alkynylation of Indoles with Acetylenecarboxylic Acids. Chin. J. Org. Chem. 2017, 37, 691-697. (f) Liang, R.-X.; Yang, R.-Z.; Liu, R.-R.; Jia, Y.-X. Palladium-catalyzed asymmetric dearomative alkenylation of indoles through a reductive-Heck reaction. Org. Chem. Front. 2018, 5, 1840-1843. (g) Li, X.; Zhou, B.; Yang, R.-Z.; Yang, F.-M.; Liang, R.-X.; Liu, R.-R.; Jia, Y.-X. Palladium-Catalyzed Enantioselective Intramolecular Dearomative Heck Reaction. J. Am. Chem. Soc. 2018, 140, 13945-13951. (h) Weng, J.-Q.; Xing, L.-L.; Hou, W.-R.; Liang, R.-X.; Jia, Y.-X. Palladium-catalyzed dearomative arylphosphorylation of indoles. Org. Chem. Front. 2019, 6, 1577-1580. (i) Liang, R.-X.; Wang, K.; Song, L.-J.; Sheng, W.-J.; Jia, Y.-X. Synthesis of tetracyclic indolin-3-ones through Pd-catalyzed intramolecular deacetylative dearomatization of 3-acetoxy-indoles. RSC Adv. 2019, 9, 13959-13967. (j) Liang, R.-X.; Wang, K.; Wu, Q.; Sheng, W.-J.; Jia, Y.-X. Palladium-Catalyzed Dearomative Arylvinylation Reaction of Indoles with N-Arylsulfonylhydrazones. Organometallics 2019, 38, 3927-3930.

- [9] (a) Petrone, D. A.; Yen, A.; Zeidan, N.; Lautens, M. Dearomative Indole Bisfunctionalization via a Diastereoselective Palladium-Catalyzed Arylcyanation. *Org. Lett.* 2015, *17*, 4838-4841. (b) Petrone, D. A.; Kondo, M.; Zeidan, N.; Lautens, M. Pd(0)-Catalyzed Dearomative Diarylation of Indoles. *Chem. Eur. J.* 2016, *22*, 5684-5691. (c) Zeidan, N.; Beisel, T.; Ross, R.; Lautens, M. Palladium-Catalyzed Arylation/Heteroarylation of Indoles: Access to 2,3-Functionalized Indolines. *Org. Lett.* 2018, *20*, 7332-7335. (d) Shen, C.; Zeidan, N.; Wu, Q.; Breuers, C. B. J.; Liu, R.-R.; Jia, Y.-X.; Lautens, M. Pd-catalyzed dearomative arylborylation of indoles. *Chem. Sci.* 2019, *10*, 3118-3122. (e) Marchese, A. D.; Lind, F.; Mahon, Á. E.; Yoon, H.; Lautens, M. Forming Benzylic Iodides via a Nickel Catalyzed Diastereoselective Dearomative Carboiodination Reaction of Indoles. *Angew. Chem., Int. Ed.* 2019, *58*, 5095-5099.
- [10] Chen, S.; Wu, X.-X.; Wang, J.; Hao, X.-H.; Xia, Y.; Shen, Y.; Jing, H.; Liang, Y.-M. Palladium-Catalyzed Intramolecular Dearomatization of Indoles via Decarboxylative Alkynyl Termination. *Org. Lett.* **2016**, *18*, 4016-4019.
- [11] Qin, X.; Lee, M. W. Y.; Zhou, J. S. Nickel-Catalyzed Asymmetric Reductive Heck Cyclization of Aryl Halides to Afford Indolines. *Angew. Chem., Int. Ed.* 2017, *56*, 12723-12726.
- [12] Wang, H.; Wu, X.-F. Palladium-Catalyzed Carbonylative Dearomatization of Indoles. Org. Lett. 2019, 21, 5264-5268.
- [13] Douki, K.; Ono, H.; Taniguchi, T.; Shimokawa, J.; Kitamura, M.; Fukuyama, T. Enantioselective Total Synthesis of (+)-Hinckdentine A via a Catalytic Dearomatization Approach. J. Am. Chem. Soc. 2016, 138, 14578-14581.
- [14] (a) Kirchberg, S.; Frçhlich, R.; Studer, A. Stereoselective Palladium-Catalyzed Carboaminoxylations of Indoles with Arylboronic Acids and TEMPO. Angew. Chem. Int. Ed. 2009, 48, 4235-4238. (b) Tomakinian, T.; Guillot, R.; Kouklovsky, C.; Vincent, G. Direct Oxida-

© 2019 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Chin. J. Chem. 2019, 37, XXX-XXX

tive Coupling of N-Acetyl Indoles and Phenols for the Synthesis of Benzofuroindolines Related to Phalarine, Angew. Chem. Int. Ed. 2014. 53, 11881-11885. (c) Ramella, V.; He, Z.; Daniliuc, C. G.; Studer, A. Palladium-Catalvzed Diastereoselective Oxvarvlation of 2-Alkylindoles. Org. Lett. 2015, 17, 664-667. (d) Morimoto, N.; Morioku, K.; Suzuki, H.; Takeuchi, Y.; Nishina, Y. Lewis Acid and Fluoroalcohol Mediated Nucleophilic Addition to the C2 Position of Indoles. Org. Lett. 2016, 18, 2020-2023. (e) Nandi, R. K.; Ratsch, F.; Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. Intermolecular dearomative C2-arylation of N-Ac indoles activated by FeCl<sub>3</sub>. Chem. Commun. 2016, 52, 5328-5331. (f) Liu, K.; Tang, S.; Huang, P.; Lei, A. External oxidant-free electrooxidative [3 + 2] annulation between phenol and indole derivatives. Nat. Commun. 2017, 8, 775-782. (g) Lai, Z.-W.; Liu, C.; Sun, H.; You, S.-L. Asymmetric Synthesis of 3-Allyloxindoles and 3-Allenyloxindoles by Scandium(III)-Catalyzed Claisen Rearrangement Reactions. Chin. J. Chem. 2017, 35, 1512-1516. (h) Li, L.; Yuan, K.; Jia, Q.; Jia, Y. Eight-Step Total Synthesis of Phalarine by Bioinspired Oxidative Coupling of Indole and Phenol. Angew. Chem. Int. Ed. 2019, 58, 6074-6078.

- [4] Lane, B. S.; Brown, M. A.; Sames, D. Direct Palladium-Catalyzed C-2 and C-3 Arylation of Indoles: A Mechanistic Rationale for Regioselectivity. J. Am. Chem. Soc. 2005, 127, 8050-8057. (b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. Room Temperature Palladium-Catalyzed 2-Arylation of Indoles. J. Am. Chem. Soc. 2006, 128, 4972-4973. (c) Stuart, D. R.; Villemure, E.; Fagnou, K. Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene Cross-Coupling. J. Am. Chem. Soc. 2007, 129, 12072-12073. (d) Gemoets, H. P. L.; Kalvet, I.; Nyuchev, A. V.; Erdmann, N.; Hessel, V.; Schoenebeck, F.; Noël, T. Mild and selective base-free C–H arylation of heteroarenes: experiment and computation. Chem. Sci. 2017, 8, 1046-1055. (e) Liu, C.; Fan, J.; Wu, M.; Chen, J.; Zhao, Y.; Xie, M. Metal Free Mono- and 2,3-Bis-sulfenylation of Indoles in Water with Sodium Sulfinates as a Sulfur Source. Chin. J. Chem. 2018, 36, 819-825.
- [16] For selected reviews: (a) van Zeist, W.-J.; Bickelhaupt, F. M. The activation strain model of chemical reactivity. Org. Biomol. Chem. 2010, 8, 3118-3127. (b) Fernández, I.; Bickelhaupt, F. M. The activation strain model and molecular orbital theory: understanding and designing chemical reactions. Chem. Soc. Rev. 2014, 43, 4953-4967. (c) Bickelhaupt, F. M.; Houk, K. N. Analyzing Reaction Rates with the

Distortion/Interaction-Activation Strain Model. Angew. Chem., Int. Ed. 2017, 56, 10070-10086.

- [17] N-Ac dihydrocyclobuta[b]indole is synthetically inaccessible at our hands. Our prediction about the reactivity of this substrate toward the intermolecular dearomative Heck reaction cannot be proved experimentally at present.
- [18] Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Jr. Montgomery, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.
- [19] Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* 2008, 120, 215-241.
- [20] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. J. Phys. Chem. B 2009, 113, 6378-6396.
- [21] Legault, C. Y. CYLView, 1.0b; Université de Sherbrooke, Montreal, Québec, Canada, 2009; http://www.cylview.org.

(The following will be filled in by the editorial staff) Manuscript received: XXXX, 2019 Manuscript revised: XXXX, 2019 Manuscript accepted: XXXX, 2019 Accepted manuscript online: XXXX, 2019 Version of record online: XXXX, 2019

www.cjc.wiley-vch.de

#### **Entry for the Table of Contents**

![](_page_10_Figure_1.jpeg)

<sup>a</sup> Department, Institution, Address 1 E-mail:

<sup>b</sup> Department, Institution, Address 2 E-mail: <sup>c</sup>Department, Institution, Address 3 E-mail:

© 2018 SIOC, CAS, Shanghai, & WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

![](_page_10_Picture_8.jpeg)

This article is protected by copyright. All rights reserved.